Asymmetric Addition of Cyanide to Aldehydes and Imines

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PhD Thesis

Declaration

The work submitted in this thesis was carried out in the chemistry departments of King's College London and the University of Newcastle upon Tyne between October 2003 and October 2007. The work contains no material which has been accepted for the award of any other degree or diplomas 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 reference has been made in the text. The thesis is being submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

Acknowledgement

Firstly, I would like to thank Professor North for giving me the opportunity of this PhD, and guiding me through the years I have spent on this. I would also like to thank Jamie for being a fantastic friend and flatmate, Lisa and Paola for teaching me the basics of this cyanohydrin chemistry, Elisabetta for going to the conference in Nagoya with me, and Thierry, Carl and Dmitry for being good friends and colleagues for the years I have spent in the lab. And finally but not least, I would like to thank my parents for the moral support they gave me.

Abstract

Cyanohydrins are a group of compounds that are widely used in industry as common building blocks for asymmetric synthesis. In this thesis, novel methods of synthesizing chiral cyanohydrins are investigated using complexes of transition metals complexed to salen ligands. To start the project, alternative sources of cyanide were investigated. Unfortunately, this investigation could not uncover a new cyanide source that was more effective than trimethylsilyl cyanide as a substrate for titanium(salen) based catalysts. However, this research has led to the finding that KCN / 18-Crown-6 can be used as a co-catalyst in the addition of ethyl cyanoformate to various aldehydes. This has led to a huge reduction in the amount of catalyst that is required to achieve the same enantiomeric excess. In addition, the diastereoselective synthesis of cyanohydrin derivatives using chiral cyanoformates was made possible for the first time. Some of the cyanohydrins synthesized by the new ethyl cyanoformate route were taken a step further, and their use as chiral building blocks was also studied. By using a palladium based catalyst, α,β,-unsaturated cyanohydrins were converted into amides via a two-step reaction.

Research into the Strecker reaction was also carried out using vanadium(V)(salen) complexes as catalysts. In this field, the use of phenols as co-catalysts was discovered, and this has led to a world leading enantiomeric excess.

Abbreviations

aq	Aqueous
br	broad
^{o}C	Degrees centigrade
^{13}C-NMR	Carbon 13 NMR spectrum
cat	catalyst
CI	Chemical ionization
d	doublet
DMSO	Dimethylsulphoxide
ee	Enantiomeric Excess
EI	Electron ionization
ESI	Electrospray ionization
FT-IR	Fourier Transform infrared
g	gram
(g)	Gas
GC	Gas chromatography
h	hours
^{1}H-NMR	Proton NMR Spectrum
High res	High resolution
HPLC	high performance liquid chromatography
I	Iso
IR	Infrared / Infrared spectrum
Lit.	Literature
Low res	Low resolution

M	Moles per decimeter cubed
m	meta
m	multiplet （NMR） / medium (IR)
M^+	Molecular ion
Mass spec	Mass spectrometry
mg	milligram
min	minutes
ml	milliliter
mp	melting point
NMR	Nuclear magnetic resonance
o	ortho
p	para
q	quartet
RT	room temperature
s	singlet (NMR) / strong (IR)
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
tms	Trimethylsilyl
w	weak

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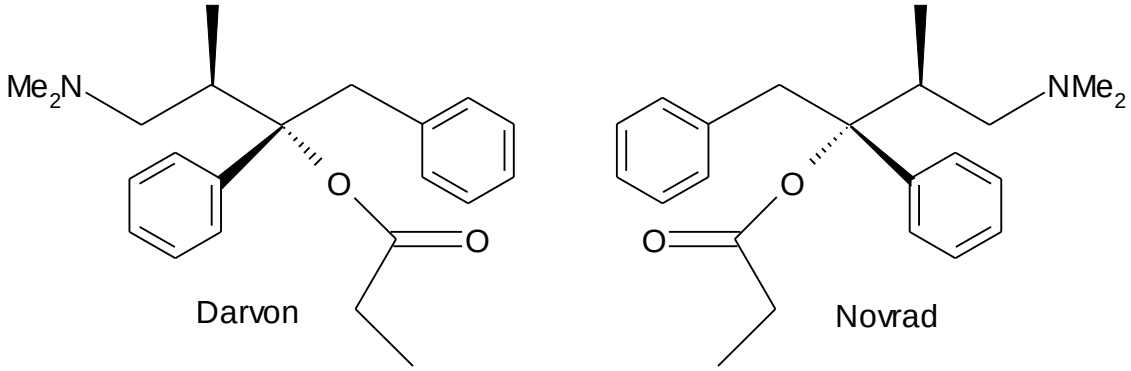
Introduction

Chapter 1

Chiral Synthesis

Chiral molecules exist in two non-superimposable mirror image forms. These mirror images are called enantiomers, and have identical chemical activity and physical properties, and so are difficult to separate. In classical chemistry, there is no need to separate these enantiomers, but it is getting increasingly more important to synthesize optically pure compounds, as enantiomers can have a totally different effect when used as drugs. One example of this is shown below. Darvon is a painkiller, whereas its enantiomer, Novrad, is an anticough agent.[1]

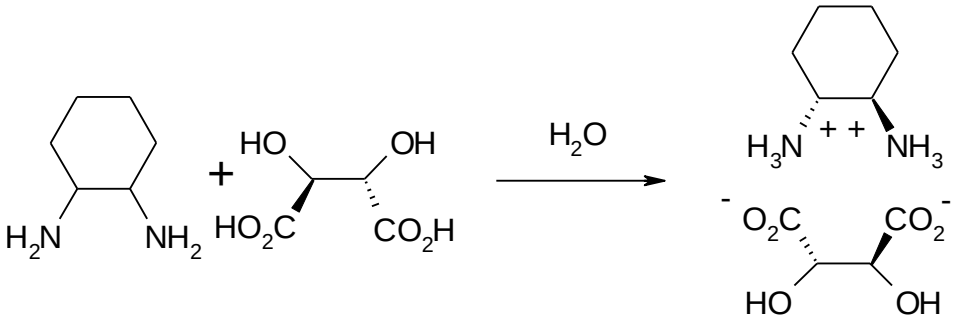


In this case, the two enantiomers only have a different therapeutic effect, but there are cases in which the other enantiomer of a pharmaceutical has a negative effect on the human body. Therefore, it is always desirable to synthesize drugs as a single enantiomer, so that side effects induced by the unwanted enantiomer can be avoided. There are several ways to achieve this.

The first method is to start with the chiral pool. Most compounds in nature

come as single enantiomers. If a compound can easily be isolated from a natural source, then it can be used as a starting point in the synthesis. Amino acids are one group of compounds that are easily mass produced and commercially available.[2] The benefit of this method is that some compounds that are very difficult to synthesize can be prepared simply from a compound that is abundant in nature. The major drawback is that only a selected number of compounds can be obtained from natural sources in large quantities, and quite often only one enantiomer can be obtained from natural sources.

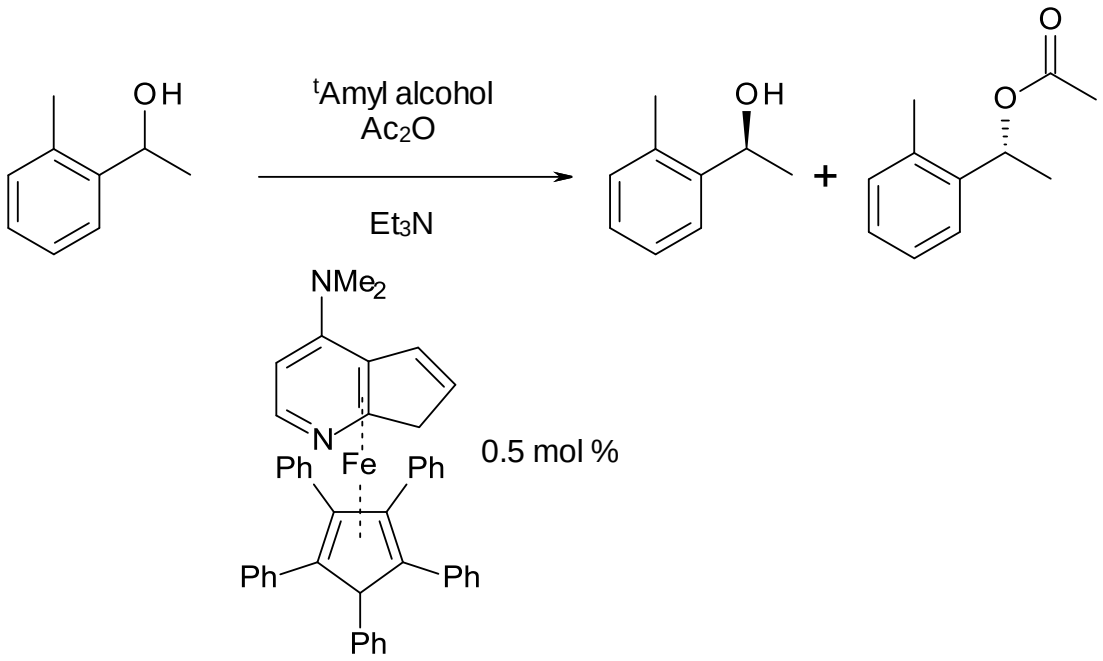
The second method is resolution. There are three main pathways in which this can be achieved, the first of which is the classical resolution. A racemic compound is reacted with a chiral compound, to form two diastereomeric compounds which can easily be separated. An example of this is the resolution of cyclohexanediamine, using (L)-tartaric acid.[3] (Scheme 1)



Scheme 1

Both enantiomers of cyclohexanediamine complex to the (*L*)-tartaric acid, but the (*R,R*)-enantiomer precipitates out of the solution. It can then be recrystallized, and treated with potassium carbonate to remove the tartaric acid to give the cyclohexanediamine in greater than 99% enantiomeric excess. If (D)-tartaric acid is used, then the other enantiomer of cyclohexanediamine can be

prepared as easily. The second resolution method is using chiral chromatography. This method is only useful on a small scale though, due to the high cost of a chiral column, so it is not a synthetically viable option in most cases. The last method is kinetic resolution, in which a chiral catalyst is used to selectively react with one enantiomer of a racemic reagent. An example is shown in Scheme 2.[4]

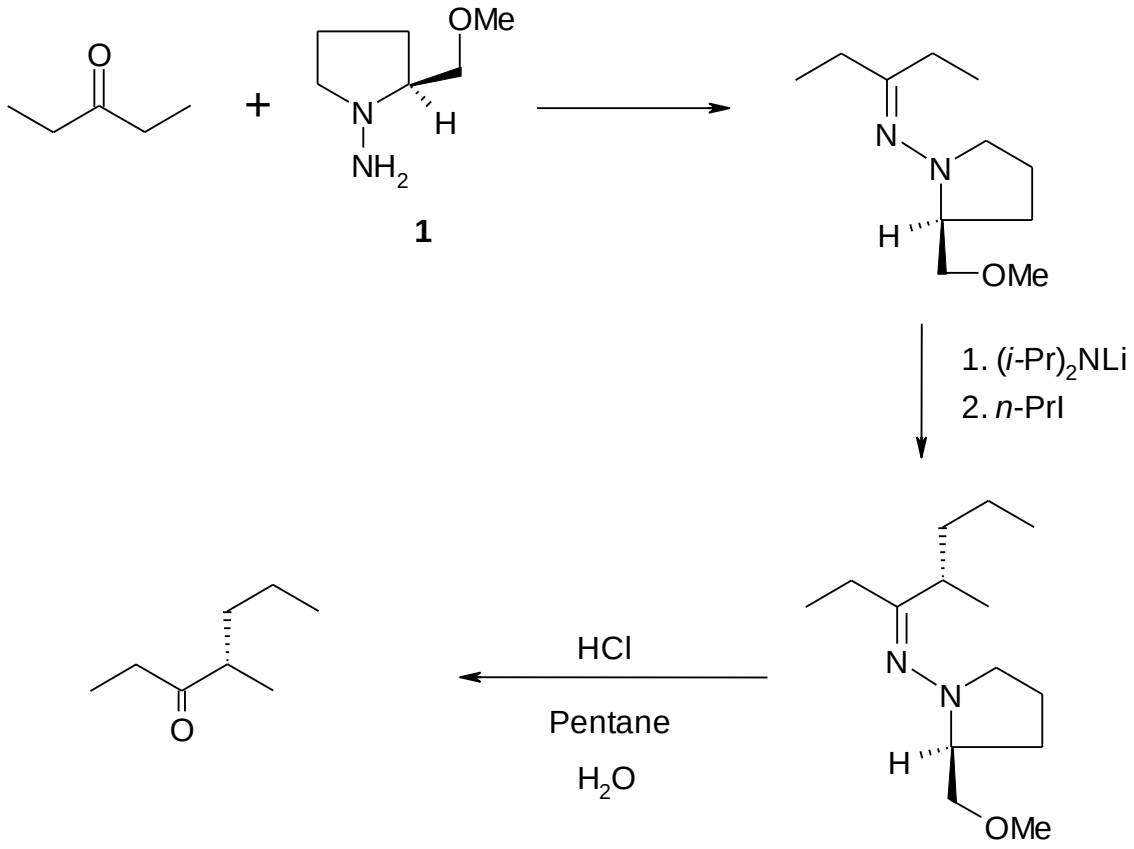


Scheme 2

Although resolution can provide an effective route for the synthesis of enantiomerically pure compounds, it has a major drawback; the product can usually only be formed with 50% chemical yield, so half of the starting material is wasted.[5] In favourable cases it may be possible to racemize and recycle the unwanted enantiomer of the starting material, and in the most desirable cases this racemization of the starting material occurs *in situ.* In this case, the racemic starting material can be converted into an enantiomerically pure product with up

to 100% enantioselectivity and in up to 100% chemical yield. This is referred to as a dynamic kinetic resolution.

The last method for the synthesis of enantiomerically pure compounds is chiral synthesis. This method converts an achiral starting material into a chiral compound using either a chiral auxiliary or a chiral catalyst. A chiral auxiliary is a chiral compound that can be attached to a functional group in the starting material, so that the main step of the reaction can be carried out in an asymmetrical manner. The chiral auxiliary is then cleaved after the reaction to regenerate the original functional group. An example of this is shown in Scheme 3, the conversion of 3-pentanone to 4-methyl-3-heptanone.[5]

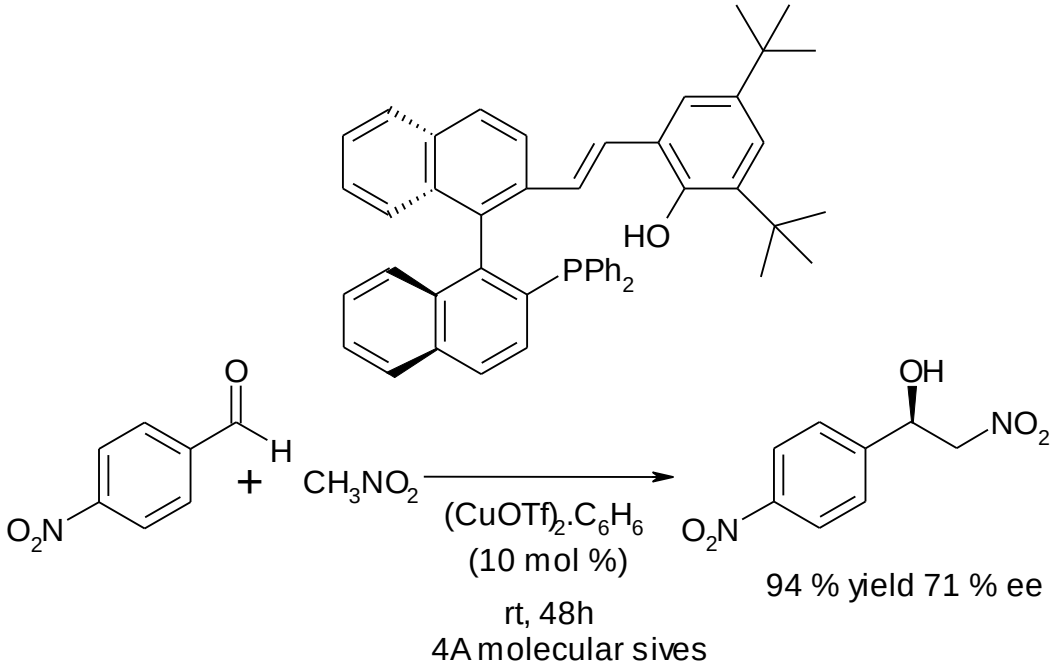


Scheme 3

In the first step, chiral molecule **1** is attached to 3-pentanone. This bulky, chiral group makes one face of 3-pentanone more hindered than the other face, thus inducing the addition of propyl iodide to occur exclusively on one face of the molecule. Although the two faces seem equal as there is free rotation around the N-N bond, they are not as the lithium chelates with both the oxygen and the nitrogen of this molecule. In this particular reaction, an enantiomeric excess exceeding 99% has been observed. The unwanted chiral auxiliary is then cleaved using HCl. Although this is a very effective way of making chiral molecules, there are several drawbacks using this method. Firstly, this process needs two extra steps in the reaction. As reactions rarely provide 100% yield, this means that the efficiency of the reaction decreases, normally by a substantial amount. This results in a higher cost of synthesis which is not favourable from an industrial point of view. Secondly, the chiral auxiliary has to be cleaved at the end. This is not so much of a problem if the compound is small, but if a stereoselective reaction has to be carried out on a large molecule, this can be a huge problem. Cleavage is normally achieved either by acid as in the case of Scheme 3, or under basic conditions. As the number of functional groups increases, a molecule is more likely to be acid or base sensitive, so cleaving the chiral auxiliary becomes more and more difficult.

All three methods can provide high enantiomeric excesses, but they all have their downsides. This is why a new method has been investigated. This is chiral catalysis. Chiral catalysts act in a similar way to chiral auxiliaries, that is the catalyst binds to an already existing functional group and differentiates two sides of the achiral reagent. However, as no covalent bond is formed between the catalyst and the reagent, no extra step to cleave it off is required. Also catalysts

are only required in small quantities, sometimes as little as 1/1000 of the amount of substrate is required. This means that the cost of the reaction is minimal compared to the other types of reactions. One example of chiral catalysis is the asymmetric Henry reaction, summarized in Scheme 4.[6]



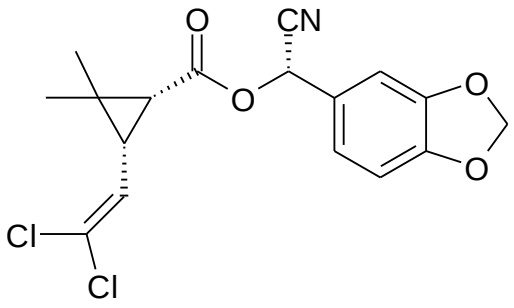
Scheme 4

Although in terms of cost, chiral catalysis is by far the best method, this is not always easy. The catalyst is quite often only active in one particular reaction, so for each reaction that needs to be done, a new catalyst has to be found. This is easier said than done, as a small change in one functional group may have a dramatic change in the yield and / or the enantiomeric excess. For example, replacing the ^{t}Bu groups of the catalyst in Scheme 4 with hydrogens completely removes any asymmetric induction.

Chapter 2

Cyanohydrin synthesis

Cyanohydrins are a group of compounds that have an oxygen and a cyanide group directly attached to the same carbon. Synthesis of cyanohydrins was first published by Winkler in 1832,[7] using hydrogen cyanide as the cyanide source. After this report, these compounds quickly became the subject of great interest for two major reasons. The first is that this functionality is included in many natural molecules and drugs, such as cypermethrin **2**, phenothiazines **3** and fluvalinate **4**. As can be expected from their completely different molecular structures, these compounds have very different uses. Cypermethrin **2** and fluvalinate **4** are insecticides, while phenothiazines **3** are tranquilizers.



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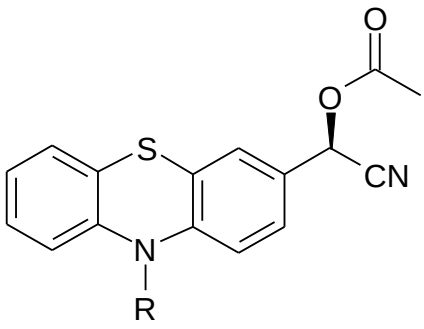

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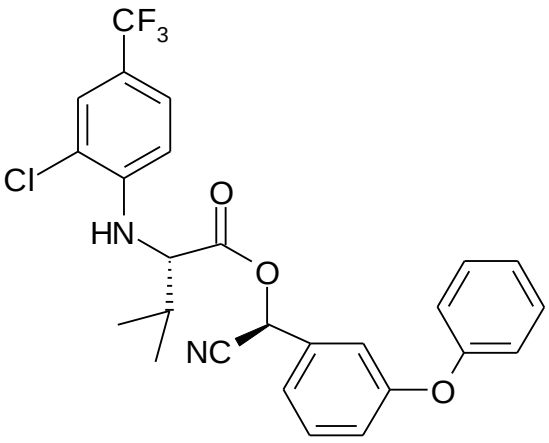

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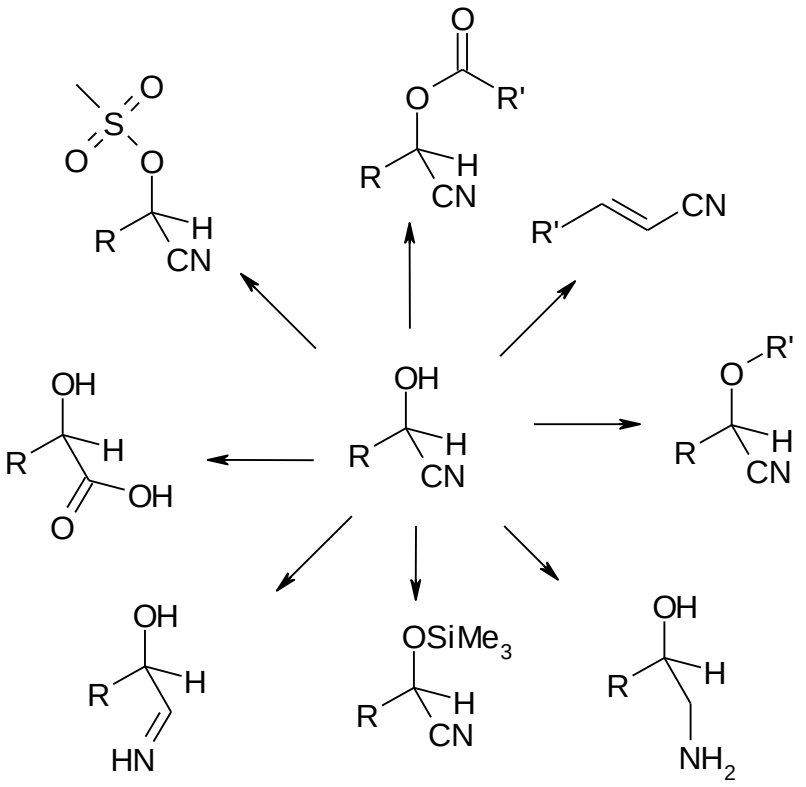
The second reason is that cyanohydrins have two functional groups that are easily converted into other functionalities.[9-19] This property has led to cyanohydrins being used as building blocks for other large molecules. Some examples of their uses are summarized in Scheme 5.



Scheme 5

In 1837, an enzyme was identified by Wohler to break down cyanohydrins into the corresponding aldehyde and hydrogen cyanide.[20] This enzyme, called oxynitrilase, is synthetically more useful when used in the reverse direction, i.e. in the synthesis of the cyanohydrins. When a non-racemic method for cyanohydrin synthesis using an oxynitrilases enzyme was reported in 1908,[21] the importance of cyanohydrin synthesis grew dramatically.

At the same time, various synthetic routes to achiral cyanohydrins were

also reported.[22-88] As the large number of references shows, cyanohydrin synthesis was a widely investigated topic. Novel uses of cyanohydrins were also researched, such as forming fluorescent cyanohydrins as soon as any cyanide ion becomes present, as a means of cyanide detection.[89] Fast detection of cyanide is important in industry, as cyanide binds extremely quickly to the haeme in red blood cells, and causes death by suffocation within minutes.[90] Another example is the use of cyanohydrins as insecticides.[91] When some plants are damaged by insects, they give off hydrogen cyanide to repel the insects. The cyanide is often stored as a cyanohydrin in this type of plant, so researchers investigated whether cyanohydrins could act as insecticides. Liquid crystalline cyanohydrins were also found to be of industrial interest. Some ferroelectric liquid crystals exhibited very fast polarization, which was ideal for high-speed switching devices.[92,93] For this investigation, a series of cyanohydrins of the type shown in Figure 1 were synthesized and investigated.[94]

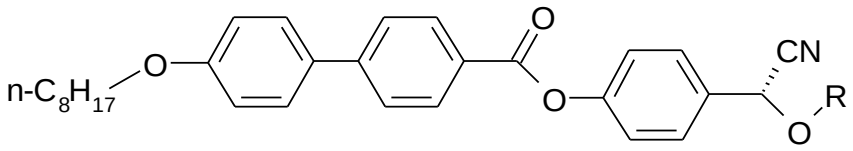


Figure 1

However, chiral synthesis of cyanohydrins turned out to be challenging, due to the planar structure of the carbonyl starting material. In most cases, the synthesis cannot start from the chiral pool, rather chirality has to be inserted by asymmetric catalysis. A range of catalysts have been developed, and some of them have become established methods for cyanohydrin synthesis. These include transition metal complexes, non-transition metal complexes, organocatalysts, and enzymes.

2.1 Transition metal based catalysts

Transition metal complexes are one of the most recently developed branches of catalysts out of the four categories. The importance of their use has increased rapidly in recent years, as these catalysts can be synthesized at a far lower cost compared to other forms of catalysts, and tend to have high turn over numbers.[95,96] For these reasons, there is a huge variety of catalysts in this category. The complexes tend to have multi-dentate ligands.[97] Some of these catalysts are shown below in Figure 2.[98,99]

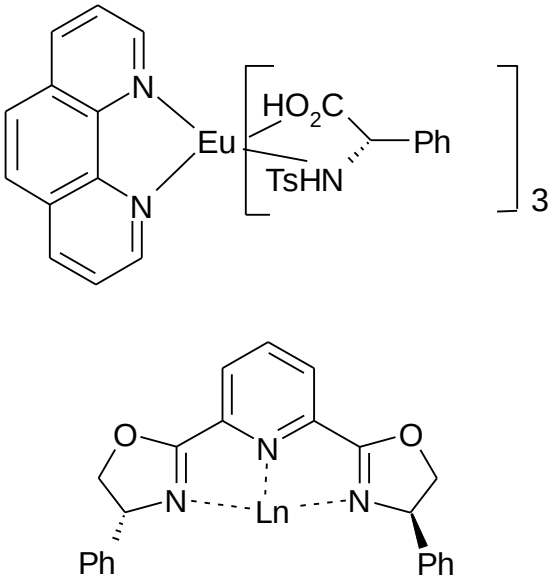


Figure 2

These catalysts all work in essentially the same way. The metal core of the catalyst binds to the aldehyde, which activates the carbonyl group, whilst at the same time making the two faces of the aldehyde diastereotopic. This is illustrated in Figure 3.

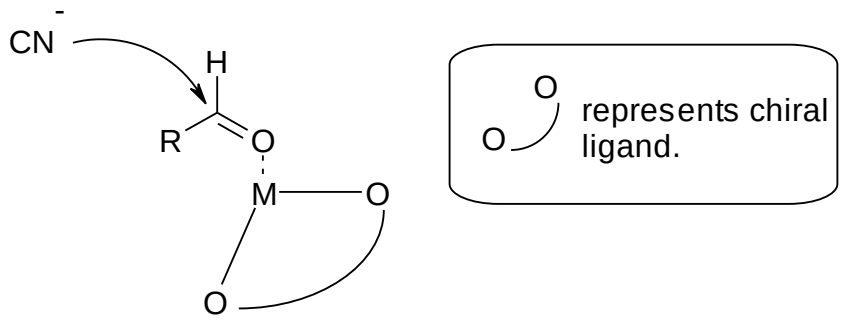
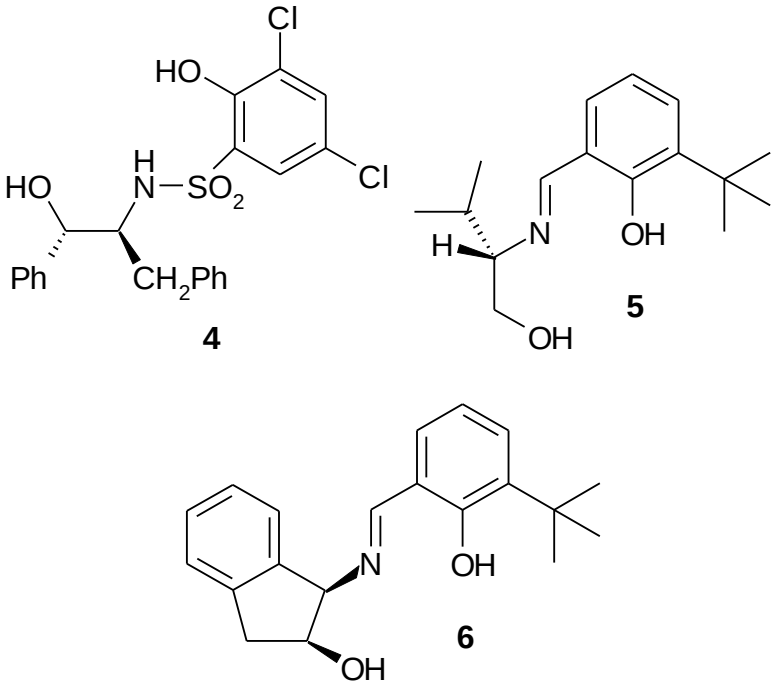


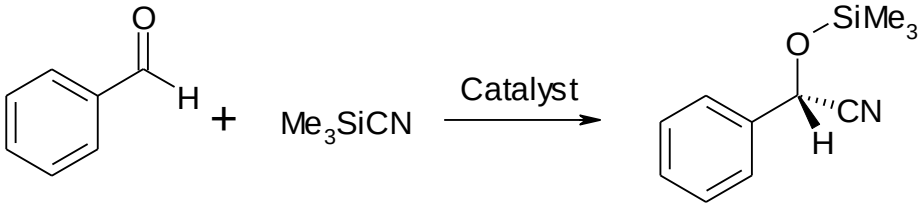
Figure 3

As research progressed, it was found that the titanium isopropoxide complex of ß-sulfonamido alcohol **4** was an effective catalyst for this kind of reaction. The best results (77-96% enantiomeric excess) were obtained using 10 mol% of this catalyst at -65 ^{o}C.[100] Subsequently, a series of Schiff-base type ligands were discovered,[101,102] two of which (**5** and **6**) are shown below.

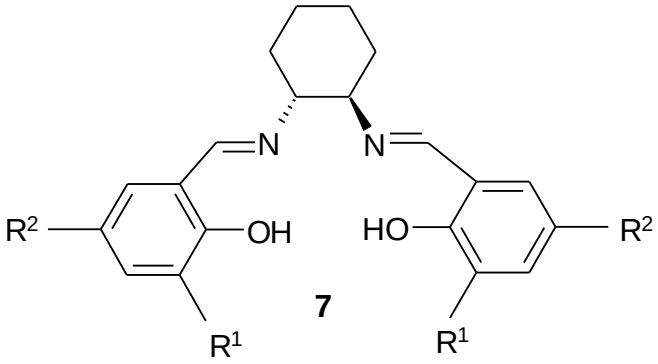


The use of 20 mol% of the titanium complex of ligand **6** gave a cyanohydrin trimethylsilyl ether with 85% enantiomeric excess using benzaldehyde and trimethylsilylcyanide as substrates (Scheme 6). Removing the ^{t}Bu group in ligand

6 reduced the enantioselectivity. Somanathan, Walsh and co-workers argued that if a smaller group was placed on that position on the benzene ring, then the complex changed from a favourable, penta-coodinated state to an inactive, octahedral complex. By using a substituent larger than ^{t}Bu, the coordination remains penta-coordinate, but now the binding of the substrate is hindered, and the catalyst becomes less active.[103]



Scheme 6



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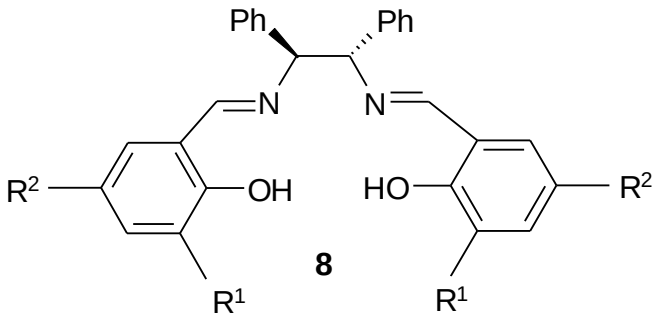
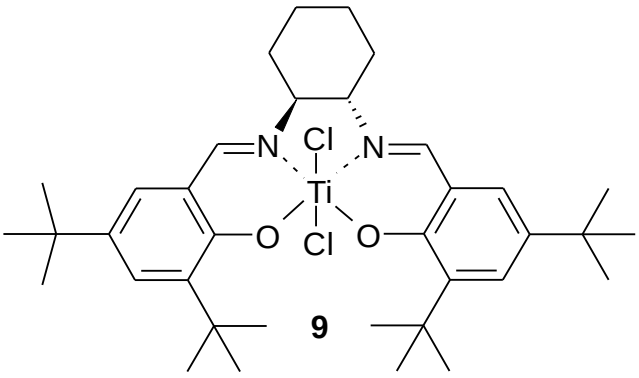


8

With the success of the tridentate Schiff base ligands, it was natural that tetradentate salen ligands were tried as the next series of catalysts for

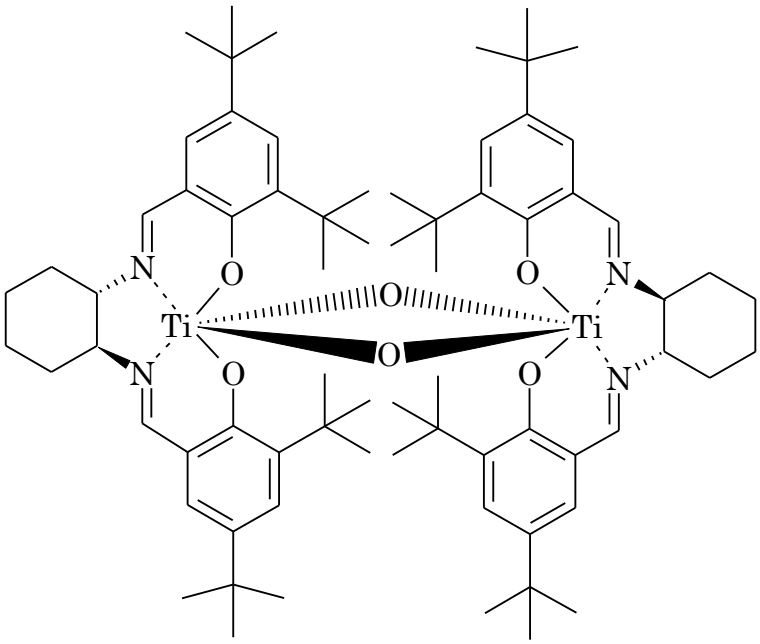
asymmetric cyanohydrin synthesis. In 1996, the use of two salen ligands complexed to titanium were simultaneously reported.[104,105] In this early work, both ligands **7** and **8** were complexed to titanium tetraisopropoxide *in situ*, and trimethylsilyl cyanide and benzaldehyde were used as the substrates. With ligand **8**, it was found that R^1=R^2=H gave the best enantioselectivity. Also, the amount of catalyst was found to be crucial in this case, with 10 mol% being the optimal amount of catalyst. Under these conditions, at -78 °C, (*R*)-mandelonitrile was formed with 87% enantiomeric excess.

Ligand **7** on the other hand, was found to be best when R^1=R^2=^{t}Bu, and replacing either of these groups reduced the enantioselectivity significantly. However, this required 20 mol% of the complex, and so was not really an effective synthetic method, although cyanohydrin product with 92% enantiomeric excess could be obtained using this catalyst. The main problem was the *in situ* complexation, and a major breakthrough was achieved when an isolable, crystalline form of the catalyst was found, using titanium tetrachloride instead of titanium tetraisopropoxide. The new catalyst, **9**, was found to give (*S*)-mandelonitrile with 87% enantiomeric excess at room temperature, using just 0.1 mol% of the catalyst.[106]



9

Replacing the ^{t}Bu groups with other groups was tried, and a series of catalysts were formed, but this did not improve the enantiomeric excesses obtained.[107] It was also discovered that the actual active species in this reaction was not **9**, but a dimeric complex **10**, shown below.[107]



10

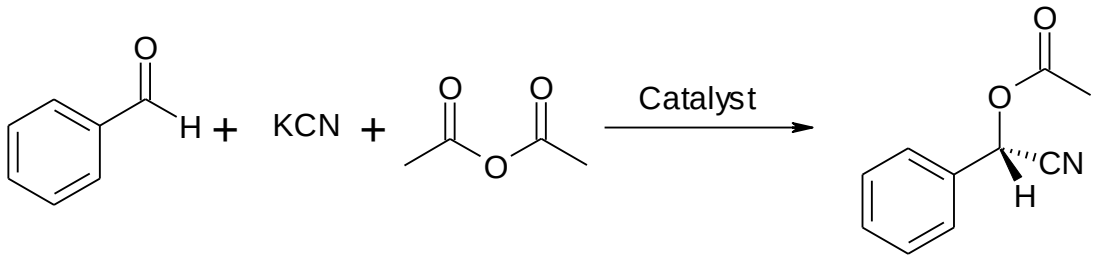
Complex **10** was found to be isolable, by treating monomeric titanium complex **9** with either a buffer solution derived from a combination of phosphates, or aqueous triethylamine. Catalyst **10** was used to convert a series of aldehydes and trimethylsilyl cyanide to (*S*)-cyanohydrins, and gave 76-92% enantiomeric excess with aromatic aldehydes, and 52-66% enantiomeric excess using aliphatic aldehydes. These results are summarized in Table 1.[108]

Table 1 Reaction of carbonyls R^1OR^2 with TMS cyanide

R^1	R^2	Amount of catalyst required	Yield /%	Enantiomeric excess /%	Time
Ph	H	0.1	100	86	24 h
2-MeC_6H_4	H	0.1	100	62	24 h
3-MeC_6H_4	H	0.1	100	74	24 h
4-MeC_6H_4	H	0.1	100	72	24 h
2-$MeOC_6H_4$	H	0.1	100	72	24 h
3-$MeOC_6H_4$	H	0.1	100	78	24 h
4-$MeOC_6H_4$	H	0.1	100	84	24 h
2,4-$(MeO)_2C_6H_4$	H	0.1	100	86	24 h
3,4-$(MeO)_2C_6H_4$	H	0.1	100	80	24 h
3,5-$(MeO)_2C_6H_4$	H	0.1	100	84	24 h
4-$CF_3C_6H_4$	H	0.1	100	50	24 h
4-$NO_2C_6H_4$	H	0.1	100	30	24 h
Me_3C	H	0.1	100	46	24 h
Me_2CH	H	0.1	100	44	24 h
Ph	Me	0.1	38	70	24 h
Ph	Me	0.5	100	66	24 h
Ph	Me	1.0	100	62	24 h
Ph	Et	0.1	41	32	2 weeks
Ph	Et	0.5	64	32	4 days
Ph	Et	1.0	100	30	4 days
Ph	*i*Pr	0.5	0	N/A	N/A
Ph	*t*Bu	0.5	0	N/A	N/A
4-MeC_6H_4	Me	0.1	100	52	4 days
4-MeC_6H_4	Me	0.5	100	66	24 h
2-$MeOC_6H_4$	Me	0.1	27	64	4 days
2-$MeOC_6H_4$	Me	0.5	100	72	2 days
3-$MeOC_6H_4$	Me	0.1	82	54	4 days
3-$MeOC_6H_4$	Me	0.5	100	56	24 h
4-$MeOC_6H_4$	Me	0.1	54	54	4 days
4-$MeOC_6H_4$	Me	0.5	100	60	24 h
4-$F_3CC_6H_4$	Me	0.1	78	60	4 days
4-$F_3CC_6H_4$	Me	0.5	100	56	24 h

Catalyst **10** is such an active catalyst that it was found to accept some ketones as substrates as well as aldehydes. This was the first catalyst to be able to convert ketones to cyanohydrins at atmospheric pressure, and a series of ketones were converted into the corresponding cyanohydrins with enantiomeric excesses of 56-72%. This however is a more difficult process, and requires more catalyst (0.5-1 mol%) and a longer reaction time (1-4 days)

A kinetic study of asymmetric cyanohydrin synthesis catalysed by complex **10** was carried out, and this led to the conclusion that more than one titanium atom must be taking part in the rate determining step.[109,110] It is now believed that one titanium atom complexes to the aldehyde, while the other one complexes to the cyanide, thus activating both components in this reaction.



Scheme 7

Later studies have also shown that catalyst **10** can be used with potassium cyanide as well as trimethylsilyl cyanide (Scheme 7). This is a great advancement from an industrial point of view, as potassium cyanide is far less volatile compared to trimethylsilyl cyanide, and thus a lot less hazardous. Also potassium cyanide has the benefit that it is far less costly than trimethylsilyl cyanide. Using 1 mol% of catalyst **10**, acetic anhydride and potassium cyanide, a group of aldehydes were successfully converted into the corresponding (*S*)-cyanohydrins. The enantiomeric

excesses ranged from 85-93% for aromatic aldehydes, and 62-84% with aliphatic aldehydes as substrates when the reaction was carried out at -40 °C. The result of this work is summarized in Table 2.[111]

Table 2: Reaction of aldehydes with acetic anhydride and potassium cyanide at -40 °C

Aldehyde	ee / %
PhCHO	89
4-$CF_3C_6H_4CHO$	76
4-FC_6H_4CHO	90
2-FC_6H_4CHO	86
$PhCH_2CH_2CHO$	82

As the results show, catalyst **10** was found to be a very effective catalyst, which accepts a variety of aldehydes as substrate. When used with aromatic aldehydes, the enantiomeric excess is consistently over 80%. The enantiomeric excess is lower for aliphatic aldehydes, but this was not surprising as the same trend was observed when trimethylsilyl cyanide was used as the cyanide source. Unfortunately, to obtain consistent results, effective stirring was essential. This is due to the fact that potassium cyanide is totally insoluble in dichloromethane which was the solvent of choice. This meant that the reaction could only occur on the surface of potassium cyanide in the reaction mixture, and without effective stirring the rate of the reaction would be controlled by the rate of diffusion, which is extremely slow.

Unfortunately, although the enantiomeric excesses obtained in this reaction were world leading, the reaction rate had scope for improvement. After 10 h, only 20% conversion could be achieved in each case. A series of additives were tested in

an attempt to increase the rate of the reaction. As the active cyanating agent was thought to be hydrogen cyanide, a series of acids were first tested. However, this led to a reduction of yield, especially in the case of ethanoic acid. Replacing the potassium cyanide with hydrogen cyanide also resulted in the loss of optical purity. This meant that the active cyanating agent in the reaction was not hydrogen cyanide. Further research revealed that addition of imidazole, water or *t*-butanol led to a marked increase in reactivity without a loss in either enantioselectivity or yield. This acceleration is believed to be due to the fact that the small amount of the additive allows potassium cyanide to dissolve in the solvent system, liberating cyanide ions into the solution where they can react with the aldehyde. A combination of water and *t*-butanol was found to be the best additive in this reaction. The results are summarized in Table 3 which shows that a variety of aldehydes were converted into the corresponding cyanohydrins.[111,113]

Table 3 reaction of aldehydes with KCN/Ac_2O in the presence of catalyst **10** and *t*BuOH/H_2O mixture

Aldehyde	ee / %	Yield / %
PhCHO	89	92
4-$MeOC_6H_4CHO$	93	74
3-$MeOC_6H_4CHO$	93	99
3-$PhOC_6H_4CHO$	89	99
4-FC_6H_4CHO	93	99
3-FC_6H_4CHO	89	99
2-FC_6H_4CHO	82	86
2-ClC_6H_4CHO	88	89
$PhCH_2CH_2CHO$	82	79
Me_2CHCHO	72	62
Me_3CCHO	60	40
PhCOMe	no reaction	no reaction

Belokon and North carried out extensive kinetic studies on asymmetric cyanohydrin synthesis using trimethylsilyl cyanide catalysed by bimetallic complex **10**. These studies have revealed that the reaction was first order with respect to trimethylsilyl cyanide concentration, and zero order with respect to the concentration of the aldehyde. The order with respect to the catalyst concentration was 1.3 in this particular reaction, although similar catalysts with different substituents on the aromatic ring showed different values between 1 and 2. This meant that at least two titanium ions were taking part in the catalytic cycle. The results led to the following rate equation.[109,110]

$$\text{Rate}=654[\text{catalyst } \mathbf{10}]^{1.3}[Me_3SiCN]^{1.0}[PhCHO]^{0}$$

A similar study was carried out using acetophenone as substrate, and the rate equation was determined to be:

$$\text{Rate}=0.013[\text{catalyst } \mathbf{10}]^{1.1}[Me_3SiCN]^{1.0}[PhCOMe]^{0}$$

This result highlighted two important factors. The first is that the nature of the substrate changed the rate order with respect to catalyst concentration. This means that the substrate is involved in converting catalyst **10** into the active species, without getting involved in the actual catalytic cycle until after the rate determining step. The second point is that the rate constant for the reaction with a ketone substrate is far smaller than when benzaldehyde is used as the substrate. This is not surprising though, considering the extremely slow rate of reaction. At the same time, it was found that catalyst **10** reacts with hexafluoroacetone, forming a monomeric complex (Figure 4).[110]

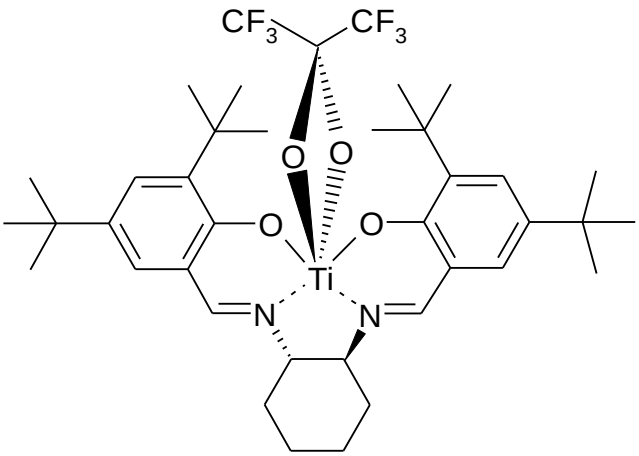
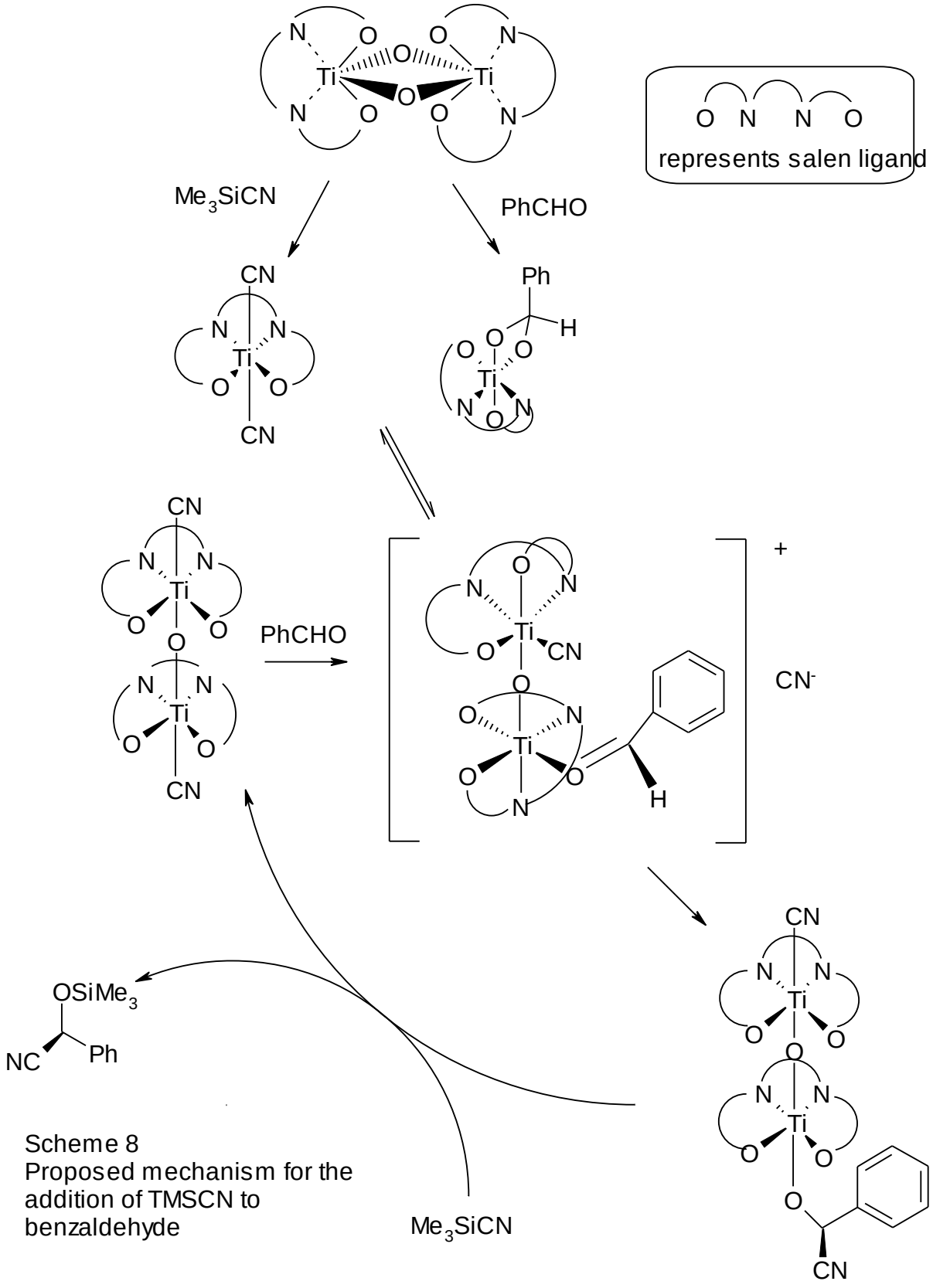


Figure 4

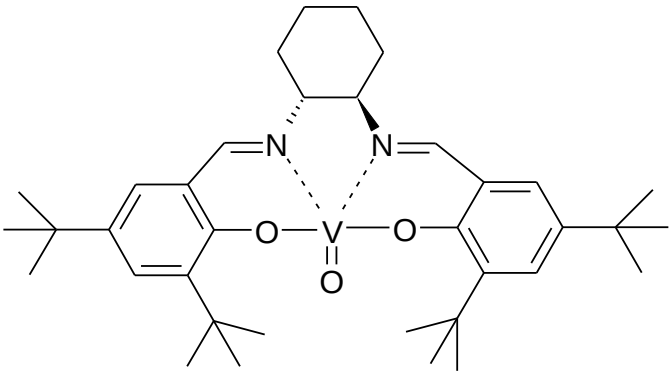
Based on these results, a mechanism for the asymmetric addition of trimethylsilyl cyanide to benzaldehyde was proposed. This is shown in Scheme 8.[114] Catalyst **10** reacts with the aldehyde and trimethylsilyl cyanide to form two monomeric species, which exist in equilibrium with another dimer that delivers the cyanide to benzaldehyde. The active species is then regenerated on reaction with another benzaldehyde and trimethylsilyl cyanide molecule.

The actual catalytic cycle is simple, containing just three complexes, which are all bimetallic. However, to create the active species, the aldehyde is involved. This system can thus explain how the substrate can influence the reaction order with respect to the catalyst, without its concentration affecting the rate.

Following on from this work, Belokon' and North have studied a series of other metal salen complexes. The first to be studied was the vanadium(IV) complex **11**. This was chosen as there was literature precedent which suggested that VO(salen) complexes can also exist as monomeric and polymeric species. Catalyst **11** was prepared, and tested in the reaction using trimethylsilyl cyanide.



Scheme 8
Proposed mechanism for the addition of TMSCN to benzaldehyde



Catalyst **11**

This complex was found to be an even better catalyst than titanium complex **10**. Complex **11** was tested in the reaction under identical condition as the titanium-based catalyst **10** using eight different aldehydes, and produced the O-TMS protected cyanohydrins with 2-25% higher enantiomeric excess than those obtained using complex **10**. In the case of electron rich aromatic aldehydes, this catalyst was able to synthesize the cyanohydrins with consistently greater than 90% enantiomeric excess, as summarized in Table 4.[110,111]

Table 4: Reactions of aldehydes with trimethylsilyl cyanide using catalyst **11**

Aldehyde	Enantiomeric Excess /%
PHCHO	94
4-$MeOC_6H_4CHO$	90
2-MeC_6H_4CHO	90
3-MeC_6H_4CHO	95
4-MeC_6H_4CHO	94
4-$O_2NC_6H_4CHO$	73
CH_3CH_2CHO	77
Me_3CCHO	68

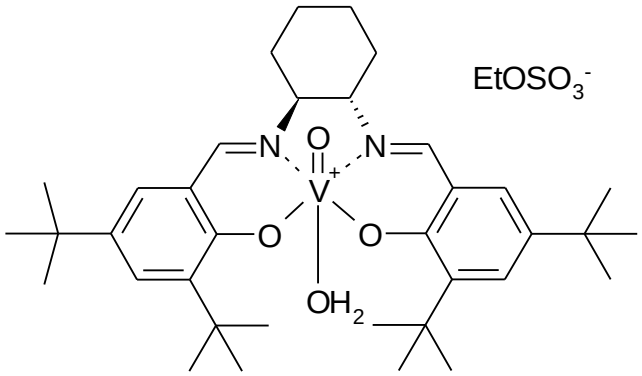
The kinetics of this reaction were also studied, and the rate equation was determined as:

$$\text{Rate} = 76[\text{catalyst } \mathbf{11}]^{1.45}[\text{benzaldehyde}]^{0}[Me_3SiCN]^{1}$$

This rate equation is in exactly the same form as the rate equation for the reaction using catalyst **10**. This means that the mechanism for this reaction is likely to be the same as in the case of titanium-based catalyst **10**. The rate constant is also a lot lower in this case, which is also consistent with the observed behavior, in that asymmetric cyanohydrin synthesis with catalyst **10** requires 30 minutes, while the vanadium catalysed reaction requires 24 hours. The order with respect to catalyst is higher for the vanadium complex, and this shows that the equilibrium needed to form the active species is more favourable for catalyst **11** than for catalyst **10**. This is due to the fact that for titanium-based catalyst **10**, the equilibrium between the monomer and dimer is more inclined towards the dimer than for the vanadium-based catalyst **11**, hence the active species, which requires the monomers to be present in solution first, is harder to form. The higher enantioselectivity is believed to be due to the greater Lewis acidity of the central metal. Vanadium based catalyst **11** is believed to form a vanadium(V) species as the active complex, and as vanadium(V) is more Lewis-acidic than titanium(IV), the substrate is bound more tightly to the metal centre, and so the substrate is closer to the chiral ligand. This means that the effect of the chirality of the catalyst is greater, which is reflected in the higher enantiomeric excess of the product.

Interestingly though, vanadium-based catalyst **11** was totally inactive when

tested in the reaction between potassium cyanide and benzaldehyde (Scheme 7). However, a very similar catalyst, vanadium(V) salen complex **12** was active in this reaction.[111]



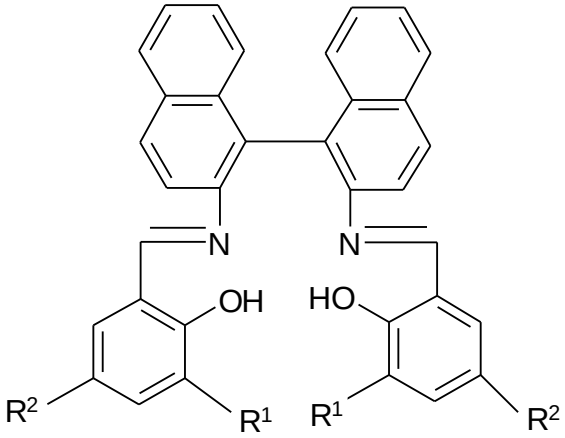
Catalyst **12**

At -42 °C, catalyst **12** catalysed the addition of potassium cyanide to benzaldehyde, *ortho*-chlorobenzaldehyde and *meta*-chlorobenzaldehyde to give cyanohydrin acetates with 78-90% enantiomeric excess. This trend is consistent with the results previously obtained with titanium based catalyst **10**. Vanadium(IV), with the lowest Lewis acidity, does not bond as strongly to the substrate, and so cyanohydrin acetate synthesis cannot occur. However, vanadium(V) is a stronger Lewis acid, and is capable of bonding to the aldehyde, resulting in good catalytic behaviour.

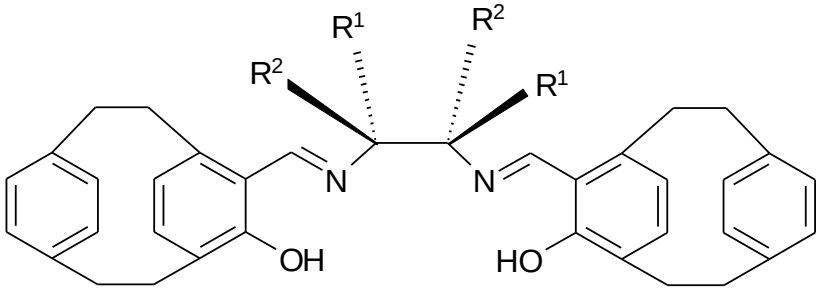
Meanwhile, Holmes and Kagan demonstrated that it was not just transition metal complexes that could catalyse the asymmetric addition of cyanide to aldehydes.[115] A mono-lithium salt of ligand **7** was synthesized with R = *tert*-butyl, and this was shown to be active in the addition of trimethylsilyl cyanide to a variety of aromatic aldehydes (Scheme 6). At -78 °C in diethyl ether, this catalyst is able to catalyse the reaction with up to 97% enantiomeric excess, with reaction

times of less than one hour. This catalyst however has one significant difference from catalysts **10** and **11**; the (*R*)-enantiomers of **10** and **11** give the (*S*) enantiomer of the *O*-protected trimethylsilyl cyanohydrin, whereas the (*R*) enantiomer of the lithium catalyst favours the formation of the (*R*) cyanohydrin. The reason for this is as yet unknown, and research in this area still continues.

Following these results, salen based catalysts were looked at in closer detail than before. A variety of catalysts were synthesized and tested for the addition of trimethylsilyl cyanide to aldehydes. Below are some examples of such catalysts.[116,117]



13



14 a $R^1=R^2=H$

b $R^1=H$ $R^2=(CH_2)_4$

c $R^2=H$ $R^1=(CH_2)_4$

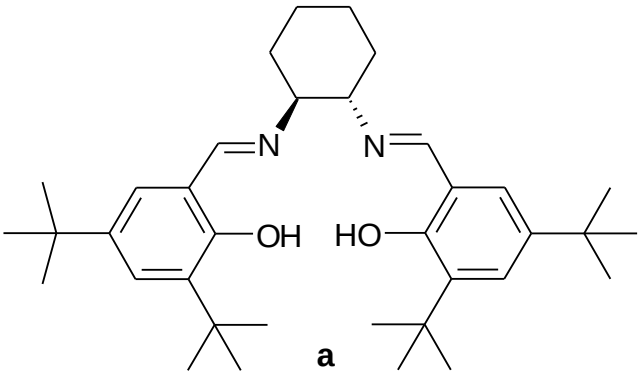
Ligand **13** was prepared by Che *et al*, and was complexed to titanium tetraisopropoxide *in situ* to catalyse the addition of trimethylsilyl cyanide to aldehydes. A series of R groups were tested, and it was found that the best results were obtained when R^1=R^2=*tert*-butyl. This result is consistent with results obtained when catalyst **10** was investigated so this came as no surprise. A range of aldehydes were successfully converted into the trimethylsilyl protected cyanohydrins, with enantiomeric excesses ranging from 42 to 96%, with electron rich aromatic aldehydes giving best results. This too is the same trend as catalyst **10**, so it is assumed that this catalyst reacts in a similar catalytic cycle as catalyst **10**.

Catalyst **14** was prepared by Belokon' and Rozenberg, and this produced an interesting result. When complexed to titanium tetraisopropoxide *in situ*, catalyst **14a** was found to be more active than the diastereomeric catalysts **14b** or **14c**. At -78 ^{o}C, 10 mol% of catalyst **14a** was able to convert benzaldehyde into the corresponding trimethylsilyl protected cyanohydrin with 82% enantiomeric excess and 90% yield, but the reaction time required was 120 hours.

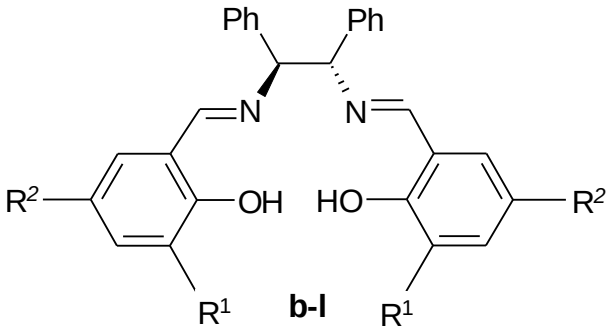
Although a series of catalysts have been demonstrated to have good selectivity in forming cyanohydrins, most of these require trimethylsilyl cyanide as the cyanating agent. This is a huge advancement, but from the industrial point of view, the volatility, toxicity and expense of trimethylsilyl cyanide is still a problem. The potassium cyanide / acetic anhydride system is a step forward, but this system now requires a lowered temperature, and still adds cost to this process. If a cheaper alternative can be discovered, this would become a much more useful process.

2.2 Non-Transition metal Complexes

This area of research is mostly dominated by aluminium chemistry, which can be divided into three major categories. The first one is the reaction using aluminium salen complexes, which is analogous to the reaction using catalyst **9**.[118] Complexes of triethylaluminium with the ligands listed below were prepared, and the reaction shown in Scheme 9 was carried out using all these complexes to investigate the catalytic activity of these complexes. The results are summarized in Table 5.



a



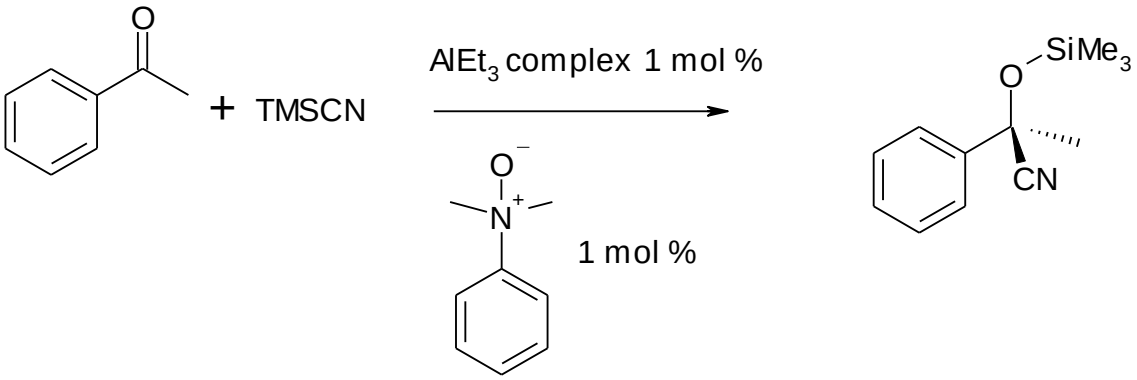
b-l

b $R^1=R^2=tBu$ **c** $R^1=tBu$ $R^2=Me$ **d** $R^1=R^2=Cl$

e $R^1=$adamantyl, $R^2=tBu$ **f** $R^1=R^2=H$ **g** $R^1=H$ $R^2=Me$

h $R^1=H$ $R^2=MeO$ **i** $R^1=H$ $R^2=tBu$ **j** $R^1=H$ $R^2=Ph$

k $R^1=H$ $R^2=Cl$ **l** $R^1=H$ $R^2=Br$



Scheme 9

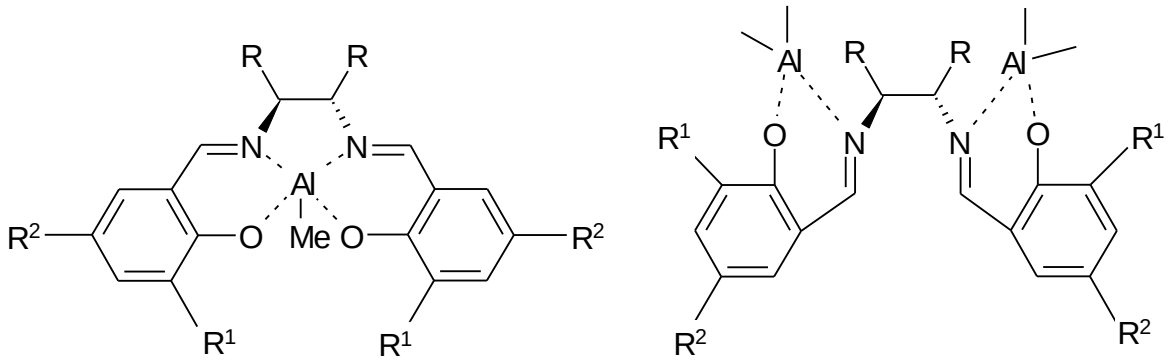
Table 5: Effect of the ligand structure of aluminium salen complexes on the enantioselectivity

Ligand	Yield / %	ee / %
a	45	51
b	45	83
c	99	70
d	99	53
e	trace	0
f	52	81
g	94	75
h	73	82
i	99	81
j	50	83
k	99	51
l	96	0
(*R*)-binol	trace	0
L-taddol	12	0

The data suggested that a small H group on the 3'-position of the phenyl ring was beneficial, while a large adamantyl group in this position completely destroyed the catalytic activity. At the 5'-position, having an electron withdrawing group gave the best results. This is of no surprise, as having an electron

withdrawing group on the 5'-position would make the aluminium ion more electropositive, which would allow the acetophenone to bind more strongly to the catalyst, thus making the carbonyl more reactive towards a nucleophilic attack.

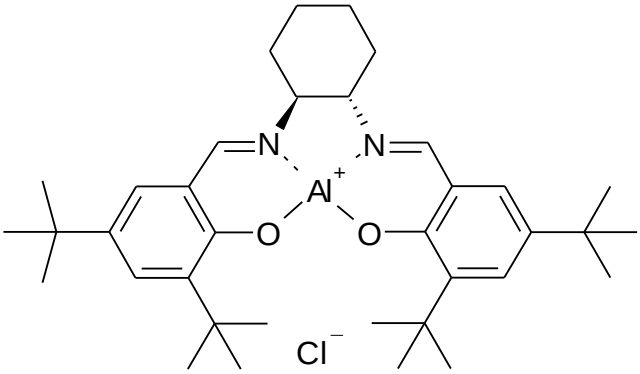
Interestingly, the aluminium salen catalyst exists in two forms.[119] In the case of titanium, the salen complex was in equilibrium with a dimer, but in the case of this aluminium catalyst, the two forms are not in equilibrium, and they can both be isolated by recrystallization. The two forms are shown in Figure 5.



15 16

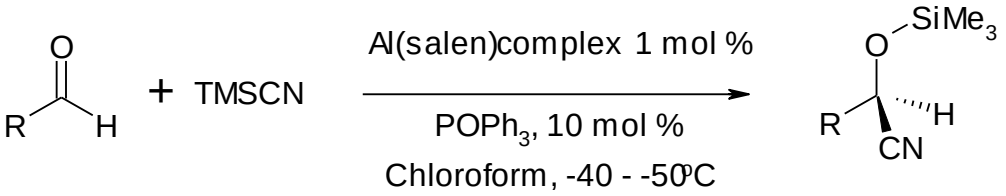
Figure 5

In general, the monometallic species gave slightly better results (70-86% ee) than the bimetallic species (66-81% ee), but neither gave particularly good results. A similar catalyst (Figure 6) was also tested for the addition of trimethylsilyl cyanide to various aldehydes[120] (Scheme 10). The results are summarized in Table 7.



17

Figure 6

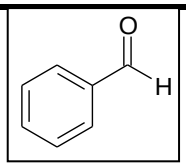
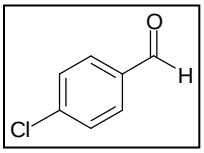
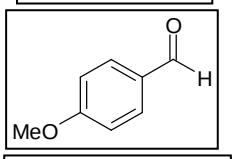
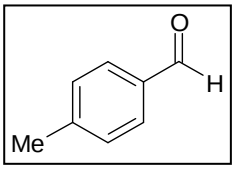
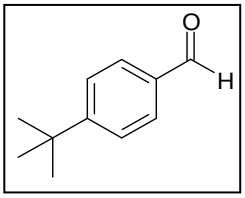
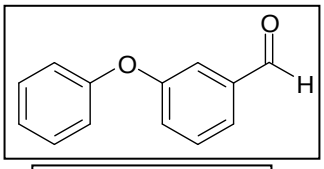
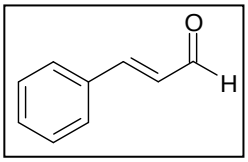
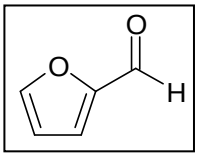
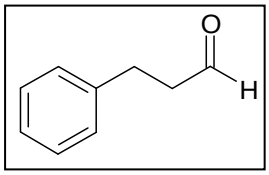
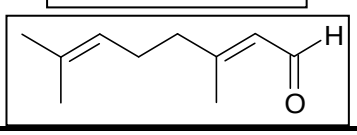


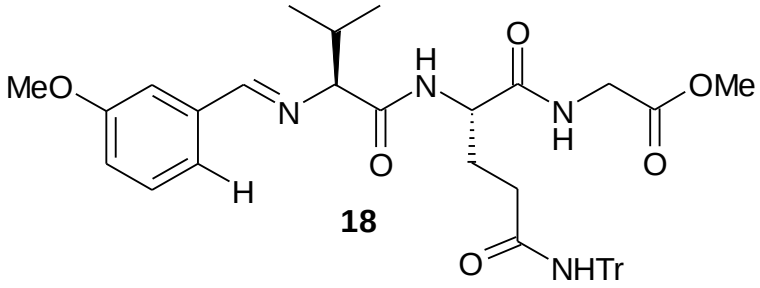
Scheme 10

Using the same system, addition of trimethylsilyl cyanide to ketones was also investigated. The reaction temperature was raised to 25 °C, and the amount of $POPh_3$ was also increased to 30 mol% to drive the reaction to completion. By this method, acetophenone was successfully converted to the corresponding cyanohydrin in 93% yield and with 78% enantiomeric excess.

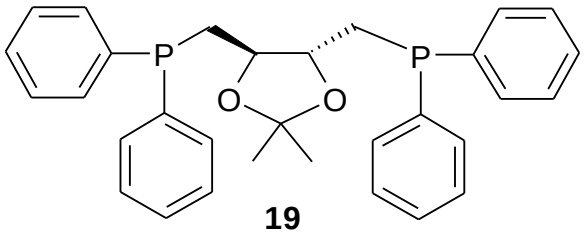
The second type of reaction is that catalysed by non-salen aluminium complexes. Some of these ligands are shown in Figure 7.

Table 7, Addition of TMSCN to aldehydes using Al(salen) catalyst

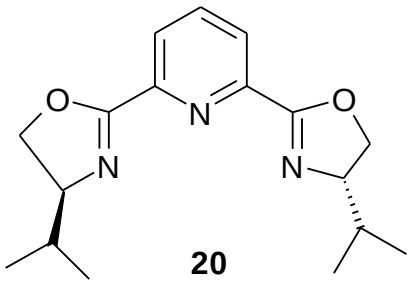
Substrate	Time / h	Temp / °C	Yield / %	ee / %
	18	−50	95	83
	18	−50	96	86
	18	−50	92	82
	22	−45	94	72
	21	−45	93	73
	20	−50	93	81
	26	−40	91	78
	18	−50	93	78
	21	−50	93	79
	24	−50	93	72



18



19

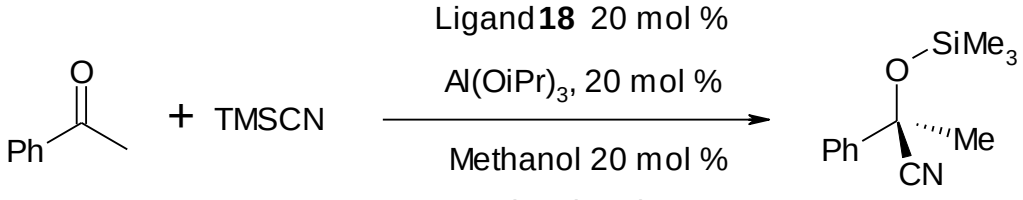


20

Pybox

Figure 7

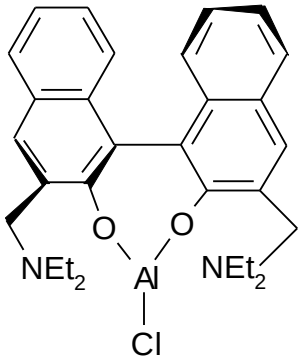
Ligand **18** was investigated by Hoveyda *et al.*[121] The ligand is bound to $Al(O^iPr)_3$ *in situ* and was found to catalyse the addition of trimethylsilyl cyanide to acetophenone effectively, as 98% yield and 88% ee could be achieved in the reaction shown in Scheme 11.



Scheme 11

Although a large quantity of catalyst is required, this process is not as inefficient as it seems. The ligand can be recovered from the reaction mixture by silica gel chromatography in very good yield (>98%), and can be recycled without loss of activity or enantioselectivity.

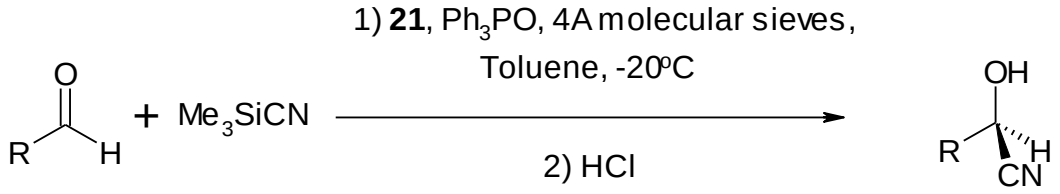
Ligands **19** and **20** were both investigated by Iovel *et al.*[122] These ligands were complexed to $AlCl_3$, and both were found to catalyse the addition of trimethylsilyl cyanide to benzaldehyde at room temperature. However, the complex of ligand **19** only gave the product with 6% ee, so the research on this ligand was abandoned. The aluminium complex of ligand **20** was more promising giving the product with 44% ee, so the conditions were optimized. At 0-10 ^{o}C, 20 mol% of $AlCl_3$ and 20 mol% of ligand **20** were added to the reaction mixture to form the catalyst *in situ*, and benzaldehyde and trimethylsilyl cyanide were then added and the reaction left for 22 hours. In this way, the cyanohydrin was produced in 92% yield and with 90% ee.



21

Another ligand that is widely used in asymmetric catalysis is the binolam ligand.[123-127] One of the best results was achieved by Najera *et al*, using catalyst **21**.[128] This catalyst is very effective in asymmetric cyanohydrin synthesis when 10 mol% of the catalyst is used (Scheme 12), as the catalyst has both Lewis acid and

basic site within the same molecule. The NEt_2 group is the Lewis base part which activates the trimethylsilyl cyanide, while the Lewis acid part, the aluminium ion, binds to the aldehyde. Thus, both reagents are activated and so the catalysis becomes very efficient. The results are summarized in Table 8.



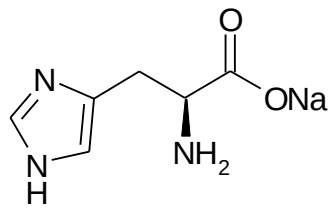
Scheme 12

Table 8: Addition of TMSCN to various aldehydes using catalyst **21**

Aldehyde	Temperature / °C	Time / h	Yield / %	ee / %
PhCHO	-20	6	99	>99
4-(MeO)C_6H_4CHO	-20	20	99	>99
2-ClC_6H_4CHO	-20	8	99	96
4-ClC_6H_4CHO	-20	21	99	>99
4-(PhO)C_6H_4CHO	-20	48	70	70
4-(PhO)C_6H_4CHO	-40	48	99	78
2-FurylCHO	-20	5	99	76
2-FurylCHO	-40	12	99	92
PhCH=CHCHO	-20	6	99	82
PhCH=CHCHO	-40	12	99	>99
$PhCH_2CH_2CHO$	-20	4.5	99	88
$CH_3(CH_2)_5CHO$	-20	3.5	99	66

The last category is asymmetric cyanohydrin synthesis using non-transition metals complexed to non-salen based ligands. A first example of this is the sodium salt of L-histidine, **22**.[129] This compound was found to catalyse the addition of trimethylsilyl cyanide to benzaldehyde in tetrahydrofuran. Although the reaction

was driven to completion in just 25 minutes, the enantioselectivity was disappointing. A variety of 3- and 4-substituted benzaldehydes were tested as substrates, but the best ee obtained was just 24%, using p-nitrobenzaldehyde.



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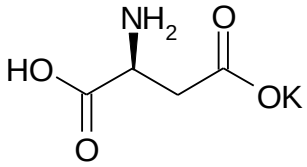

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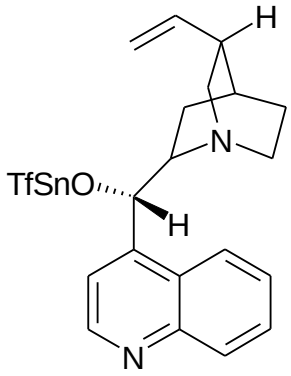
The potassium salt of L-aspartic acid was also tested as a catalyst for the same reaction. This too gave a good yield of 98%, but again the enantiomeric excess was poor, at just 3%.[130]



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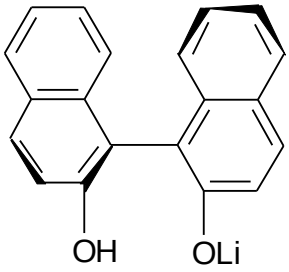

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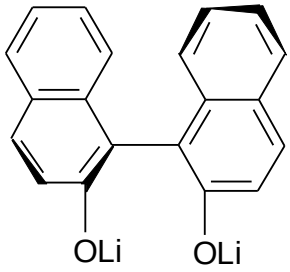
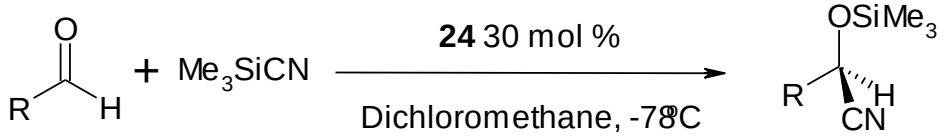


26

Tin triflate **24** was investigated by Kobayashi *et al.*, and was found to be an active catalyst for the addition of trimethylsilyl cyanide to aliphatic aldehydes.[131] This catalyst was tested in the reaction shown in Scheme 13. The results are summarized in Table 9.



Scheme 13

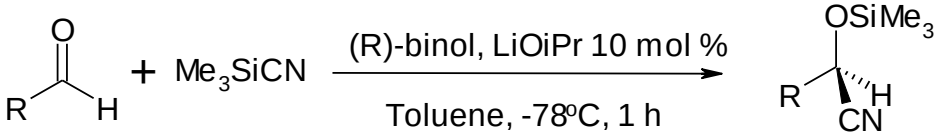
Table 9: Addition of trimethylsilyl cyanide to various aliphatic aldehydes using catalyst 24

Aldehyde	Yield / %	ee / %
n–C_8H_{17}CHO	89	72
c–C_6H_{11}CHO	79	96
i–PrCHO	67	95
t–BuCHO	49	83
CH_2=$CHCH_2C(CH_3)_2$CHO	27	93

Catalysts **25** and **26** were both studied by Ishihara *et al.*[132] The two binol based catalysts were prepared *in situ* using a 1:1 or 1:2 ratio of (*R*)-binol and LiO*i*Pr. Initial tests showed that the mono-lithium complex gave better results than bimetallic complex **26** with two lithium ions, so optimization was carried out on catalyst **25**. The results are summarized in Scheme 14 and Table 10.

Table 10: Addition of trimethylsilyl cyanide using catalyst **25**

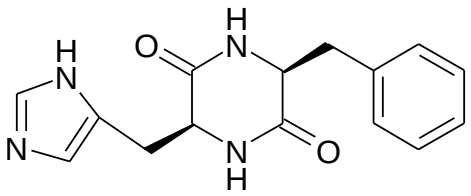
R	Yield / %	ee / %
Ph	>99	97
p-FC_6H_4	92	96
m-FC_6H_4	97	93
p-ClC_6H_4	98	92
m-ClC_6H_4	83	91
p-BrC_6H_4	98	93
m-BrC_6H_4	96	87
p-$CF_3C_6H_4$	97	82
m-$CF_3C_6H_4$	99	86
m-MeC_6H_4	96	95
m-$MeOC_6H_4$	93	97
3,5-$(MeO)_2$-C_6H_3	99	97
α-naphthyl	95	81
ß-naphthyl	96	95
3-furyl	96	98



Scheme 14

2.3 Organocatalysts

This section concentrates mainly on the use of diketopiperazine **26** as a catalyst for the addition of cyanide to carbonyl compounds. This compound was first reported by Inoue to have a catalytic activity in 1981.[133] Diketopiperazine **26** was reported to catalyse the addition of hydrogen cyanide to benzaldehyde in 97% yield and 97% enantiomeric excess (Scheme 14)



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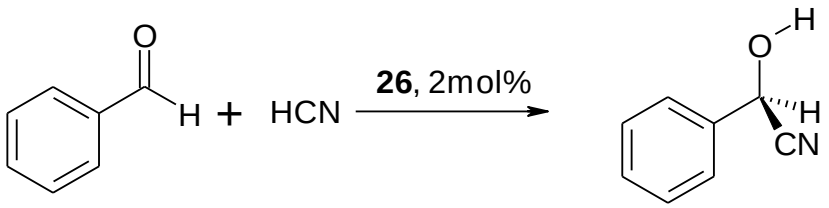


Scheme 14

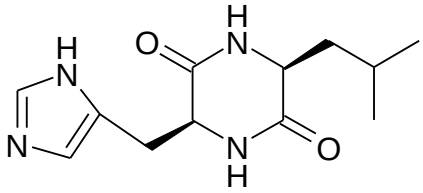
Table 11: Reactions of various aldehydes with hydrogen cyanide catalysed by diketopiperazine **26**

Aldehyde	Yield /%	ee /%
2-Methoxybenzaldehyde	45	84
3-Methoxybenzaldehyde	97	90
4-Methoxybenzaldehyde	85	83
2-Methylbenzldehyde	67	70
3-Methylbenzaldehyde	95	91
4-Methylbenzaldehyde	91	92
2-Nitrobenzaldehyde	100	50
3-Nitrobenzaldehyde	87	4
4-Nitrobenzaldehyde	99	53
2-Hydroxybenzaldehyde	78	32
3-Hydroxybenzaldehyde	75	67
4-Hydroxybenzaldehyde	86	35
2-Chlorobenzaldehyde	86	67
3-Chlorobenzaldehyde	88	57
4-Chlorobenzaldehyde	96	66
3-Cyanobenzaldehyde	91	32
4-Cyanobenzaldehyde	100	32
Ethanal	100	9
Butanal	100	37
Pentanal	100	27
Hexanal	90	56
Decanal	100	26
Phenyletahnal	100	14
2-Methylpropanal	79	27
3-Methylbutanal	44	18
2,2-Dimethylpropanal	60	58
Cyclohexanecarboxaldehyde	96	58
But-2-enal	44	11
Butanone	31	19
Acetophenone	0	0
Phenylethylketone	55	17

The advantage of this catalyst is that it can be cheaply and easily prepared from two readily available amino acids, (*S*)-histidine and (*S*)-phenylalanine. The reaction was repeated using a series of aldehydes and these were converted into the corresponding (*R*)-cyanohydrins in good yield and enantiomeric excess, as demonstrated in Table 11.[134] Following this breakthrough, research in this area investigated the synthesis and catalytic activity of similar diketopiperazines with different functional groups. Thus, Noe *et al* reported the use of catalysts **27**-**32**.[135]

Diketopiperazine **27** gave similar results to diketopiperazine **26**, but the enantiomeric excesses were not as good as those obtained when compound **26** was used as the catalyst, giving products with 61-81% enantiomeric excess. The N-methylated diketopiperazines, **29**, **30**, and **32**, were all totally inactive. The reason for this is unclear, but all the active catalysts form a gel in the reaction mixture, which is a mixture of toluene and benzaldehyde, and these three diketopiperazines were totally soluble in this mixture. Of these three compounds, **32** gave the maximum yield of just 20%. Compounds **33** and **34** also gave very low yields of 10-20%, combined with low enantioselectivity (20 and 36%). Catalyst **31** gave the best yield of 50%, but the enantiomeric excess was extremely low at 16%. The sulfonated catalyst **28** was totally inactive and gave no product.

However, Thoen and Lipton also worked on catalysts **33** and **34**, and obtained contradictory results.[136] Their study showed that these catalysts could give mandelonitrile with up to 99% yield, although the enantiomeric excess was negligible.



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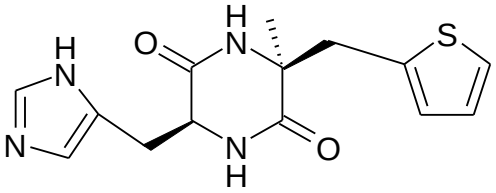

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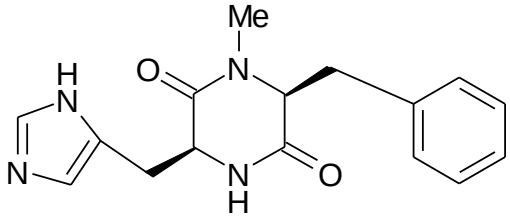

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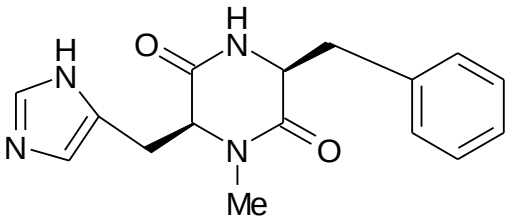

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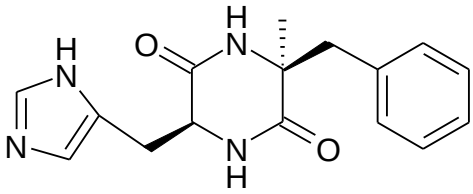

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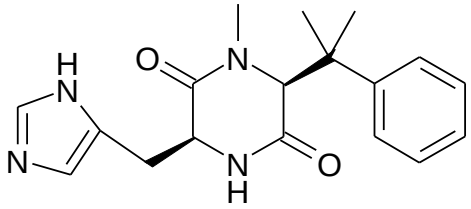

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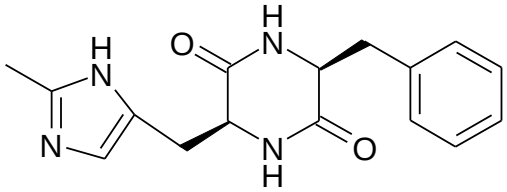

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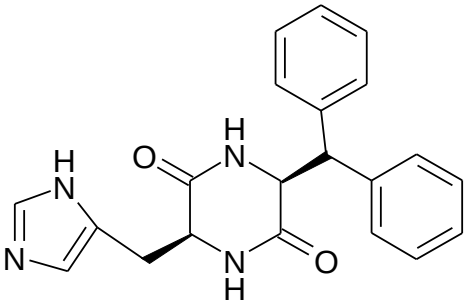

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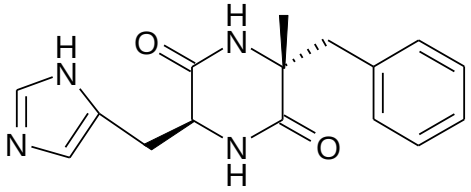


35

Also simultaneously with these works, Broxterman *et al.* studied catalyst **31** and its diastereomer, **35**. Their results disagreed with Noe's results, in that at -40

°C, diketopiperazine **31** could produce mandelonitrile with 98% yield and 99% enantiomeric excess. Their research also showed that *p*-methoxybenzaldehyde was a substrate for catalyst **31**, and gave the corresponding cyanohydrin with 93% yield and with 89% enantiomeric excess. Surprisingly, the diastereomer, **35**, was also an active catalyst in this reaction. The result was not as good as diketopiperazine **31** though, and the enantiomeric excess was only in the range of 23-32%.[137]

The difference in the results obtained by various groups using the same diketopiperazine is thought to be caused by differences in the formation of these compounds. This highlights the fact that the structure of the catalyst is not the only important factor in the reaction, but also its supramolecular structure.

In order to synthesize a more effective catalyst, the reaction mechanism was investigated. The first major step forward was the success of Shvo *et al* in 1996, who managed to carry out gel-phase kinetics on this reaction. The results showed that the reaction was second order with respect to the catalyst, which meant that two diketopiperazine molecules are involved in the catalytic cycle. Up to this point, mechanisms which involved only one molecule of diketopiperazine were suggested, and all these hypotheses were hence nullified.[138]

Another key feature which gave mechanistic information was the fact that this reaction exhibits enantioselective autoinduction. This means that the enantioselectivity of the reaction increases as the reaction progresses. This peculiar effect was first observed by Danda *et al*,[139] and Lipton *et al* have expanded on this and shown that this is a general effect observed in reactions using diketopiperazine **26**.[140] Interestingly, this effect is also observed in the presence of the cyanohydrins other than the product cyanohydrin, and it is not

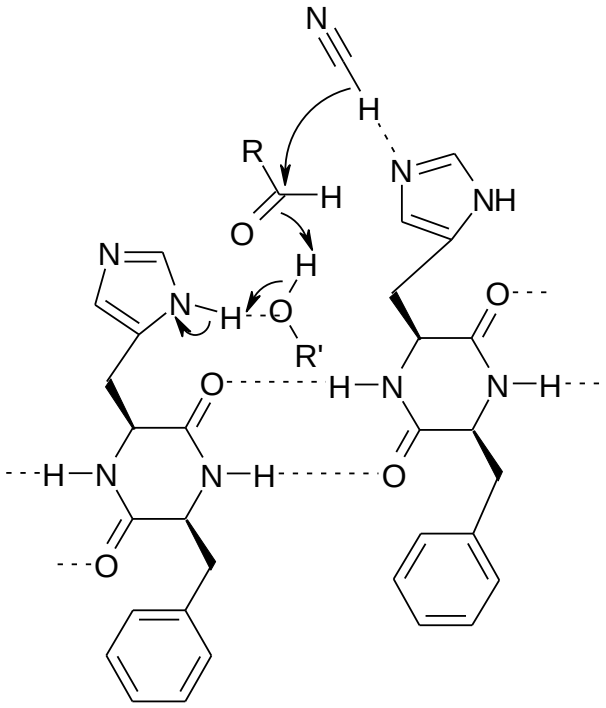
necessary that the added cyanohydrin is chiral. This implies that a complex of a cyanohydrin and diketopiperazine **26** is a more effective catalyst than diketopiperazine **26** alone. By adding a sample of a cyanohydrin to the reaction mixture at the beginning of the reaction, it should be possible to improve on the asymmetric induction of this reaction. An example of this is the addition of hydrogen cyanide to furfural, catalysed by diketopiperazine **26**. Without an added cyanohydrin, this reaction occurs in 92% yield and gives 53% enantiomeric excess, but when 8 mol% of (*S*)-mandelonitrile is added, it gives the desired cyanohydrin in 95% yield and with 81% enantiomeric excess. Interestingly, addition of (*R*)-mandelonitrile lowers the enantiomeric excess of the product to 50%. Similarly, when 8 mol% of acetone cyanohydrin is added to the reaction, the enantiomeric excess is raised to 71%. Several other additives were tried, and the results are summarized in Table 12.

Table 12: Effect of additives on the addition of hydrogen cyanide to benzaldehyde catalysed by diketopiperazine **26**

Additive	Enantiomeric Excess / %
None	53
(*S*)-mandelonitrile	81
(*R*)-mandelonitrile	50
Acetone cyanohydrin	73
(*S*)-pivaldehyde cyanohydrin	55
(*S*)-1-phenylethanol	72
(*R*)-1-phenylethanol	58
Methanol	58

With these results in mind, a mechanism for this reaction has been proposed. This is shown in Scheme 15. The catalyst is held in place by a hydrogen bonded

network. This explains why the N-methylated diketopiperazine lost their catalytic activity in polar solvents, as the hydrogen-bonded network would be disrupted in solution. Hydrogen cyanide is delivered from the diketopiperazine molecule that is not coordinated to the aldehyde, and this accounts for the second order kinetics that are observed.



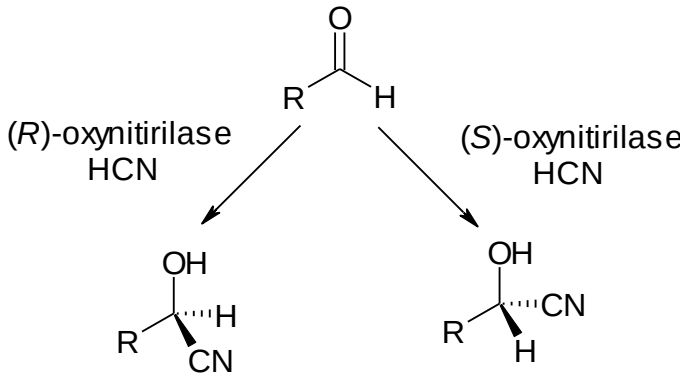
Scheme 15

Although a significant step forward has been achieved, and this model can explain all the observed features of the reaction, there is still a lot of scope for research in this area. For example, this model is not enough on it's own to explain the magnitude of change in asymmetric induction when a part of the catalyst is changed. The asymmetric induction also has room for improvement. However, interest in this area is diminishing for several reasons. Firstly, this system only accepts hydrogen cyanide as the cyanide source. This makes the reaction difficult to carry out. More data is needed to work out the mechanism in greater detail so

that a model can be constructed to allow the structure of the catalyst to be optimized, but this is also troublesome as the reaction only occurs under heterogeneous conditions. This means that it is difficult to find a better catalyst than the original structure **26**, and for this reason, interest in this area is rapidly diminishing.

2.4 Enzymes

Enzymes that catalyse the addition of cyanide to aldehydes are called oxynitrilases. (*R*)-oxynitrilases are readily available from plants, and whilst (*S*)-oxynitrilases are less common, they have been cloned and over-expressed, and are also commercially available.



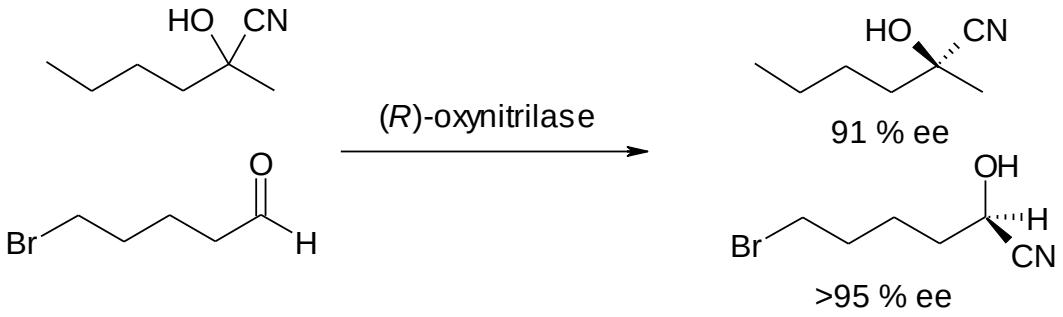
Scheme 16

The most common form of oxynitrilase is the (*R*)-oxynitrilase isolated from bitter almonds. This enzyme can readily be isolated from this source, but defatted almond meal can be used directly in reactions too. The latter method is a lot easier, as this requires no special biological equipment.[141] Both purified and crude

enzymes show similar enantioselectivity towards a range of substrates. The enzyme can be used in a variety of mixed aqueous organic solvents, but the best results are obtained when a wet organic solvent such as ethyl acetate or diisopropyl ether is used.[141] This is because in a wet solvent, the background reaction is suppressed, and most of the material is reacted via the catalysed route. This reaction can be carried out in a flow reactor, in which a pre-mixed solution of hydrogen cyanide and aldehyde in wet diisopropyl ether is pumped through a column of defatted almond meal. This gave the cyanohydrins with enantiomeric excesses greater than 97% using four different aromatic and heteroaromatic aldehydes. 4-Fluorobenzaldehyde is also accepted as a substrate, but the enantiomeric excess was lower at 84%.

Although this system is highly effective for aldehydes that are suitable for the enzyme, more difficult substrates need more precisely controlled conditions to obtain good catalytic activity.[142] For unsaturated aliphatic aldehydes, cinnamaldehyde and hydroxybenzaldehydes the use an aqueous-organic solvent system, comprising a mixture of citrate buffer and *tert*-butyl ether is recommended, along with precise temperature control. Hydrogen cyanide can either be added directly, or created *in situ* by the decomposition of acetone cyanohydrin. Using this method, even some ketones were shown to be substrates for this enzyme. Effenberger and Heid have converted four methyl ketones into cyanohydrins, with enantiomeric excesses ranging from 95 to 98%. The yield was not as good though, ranging from 40 to 94%. Ethyl ketones are also accepted, and three ketones gave 66-90% enantiomeric excess, but with only 7-33% chemical yield, which shows that these are at the limit of substrate tolerance for this enzyme.[143]

Utilizing the fact that aldehyde cyanohydrins are more thermodynamically stable than ketone cyanohydrins and that reactions using enzymes are always in a thermodynamic equilibrium, an ingenious reaction has been demonstrated. This is the enantioselective transfer of hydrogen cyanide from a ketone cyanohydrin to an aldehyde cyanohydrin. An example is shown in Scheme 17. The (*R*)-enantiomer of the ketone cyanohydrin is converted into the corresponding ketone and hydrogen cyanide, and the hydrogen cyanide is taken up by the aldehyde to give the corresponding (*R*)-cyanohydrin. As only the (*R*)-cyanohydrin of the ketone is converted back to the ketone, the (*S*)-ketone cyanohydrin is left with a high enantiomeric excess, along with the (*R*)-cyanohydrin of the aldehyde.[144]



Scheme 17

So far, only the (*R*)-oxynitrilase from bitter almonds has been discussed, but other enzymes are also available. One example of this is the (*R*)-oxynitrilase isolated from flax. This has a completely different substrate specificity to (*R*)-oxynitrilase isolated from almonds. The natural substrate for the almond (*R*)-oxynitrilase is benzaldehyde, but for the flax (*R*)-oxynitrilase, the natural substrate is acetone. This means that aliphatic aldehydes and a few aliphatic

ketones react well using this enzyme, but it shows poor reactivity towards aromatic aldehydes. The enzyme has been cloned and a range of substrates were converted into the corresponding (*R*)-cyanohydrins. In general, the results were better when smaller substrates were used, both in terms of yield and enantiomeric excess. Propanal, butanal, isobutanal, crotonaldehyde, methacrolein, butanone and pentan-2-one all gave the corresponding cyanohydrins with greater than 90% enantiomeric excess. However, bigger substrates such as hexanal and cinnamaldehyde gave the products with less than 10% enantiomeric excess.[145,146]

Other (*R*)-oxynitrilases, such as those from apples, apricots, cherries, plums loquats and peaches have also been studied. Most of these were not as good as the (*R*)-oxynitrilase isolated from almonds, but the enzyme from apples was superior to almond (*R*)-oxynitrilase in the case of sterically hindered substrates, such as trimethylacetaldehyde.[147] This substrate was converted into the corresponding cyanohydrin with 99% yield and 90% enantiomeric excess with apple oxynitrilase, while the almond (*R*)-oxynitrilase could only achieve 73% yield and 70% enantiomeric excess. Peach (*R*)-oxynitrilase had similar substrate tolerance to almond (*R*)-oxynitrilase, and in most cases gave lower enantiomeric excesses, but in the case of cinnamaldehyde it was found to have higher enantioselectivity, thus the peach (*R*)-oxynitrilase gave the cyanohydrin product with 69% enantiomeric excess, while the almond (*R*)-oxynitrilase could only achieve 51%.

(*S*)-Oxynitrilases are less common in the natural world, and only three of these have been obtained in large enough amounts to be investigated as catalysts. The first is the (*S*)-oxynitrilase from millet. This (*S*)-oxynitrilase does not need to be isolated, and ground, lyophilized and acetone washed shoots of millet can be used directly in reactions. By this method, this (*S*)-oxynitrilase was able to

transfer hydrogen cyanide produced *in situ* from acetone cyanohydrin to benzaldehyde, producing (*S*)-mandelonitrile in 90% yield and with 91% enantiomeric excess though the reaction took ten days. The reaction time can be shortened if hydrogen cyanide is used directly, instead of making it *in situ*. A series of aromatic aldehydes were reacted by this method, and were found to give cyanohydrins with enantiomeric excesses greater than 90% and in high yield, unless a large group is attached in the para-position of the aromatic ring.[147]

The second (*S*)-oxynitrilase to be studied was isolated from cassava. This has been cloned and over-expressed in *E. coli*, and the recombinant enzyme exhibited 25 times the specific activity of the natural enzyme.[148] This enzyme can also accept a broad range of aldehydes as substrates. Fifteen aldehydes, which were a mixture of aromatic, heteroaromatic, aliphatic and α,ß-unsaturated aldehydes, were studied, and only acrolein gave product with less than 85% enantiomeric excess. The best results were obtained when the enzyme was supported on nitrocellulose, with hydrogen cyanide as cyanide source, and diisopropyl ether as solvent. The use of this enzyme to add hydrogen cyanide to O-protected glycolaldehydes and lactaldehydes was investigated, and it was found that the catalytic activity was heavily dependent on the nature of the protecting groups. Allyl and 2-methylallyl protecting groups gave the best results. Methyl ketones were also investigated as substrates, but the results were rather varied. 4-Methyl pentan-2-one was converted into the corresponding cyanohydrin in 69% yield and with 91% enantiomeric excess, but butan-2-one and 3,3-dimethyl butan-2-one gave products with high yield but a low enantiomeric excess, while others such as acetophenone and heptan-2-one gave the desired cyanohydrin with a high enantiomeric excess, but in low chemical yields.[149]

The third (*S*)-oxynitrilase enzyme has been isolated from the leaves of the rubber tree plant. This enzyme is well suited to deliver hydrogen cyanide from acetone cyanohydrin to aliphatic aldehydes to give the corresponding (*S*)-cyanohydrins with 67-85% enantiomeric excess. Aromatic aldehydes can also be accepted as substrates, but the result depends heavily on the aldehyde used. For example, benzaldehyde can be converted into (*S*)-mandelonitrile with 97% enantiomeric excess, but 3-phenoxy benzaldehyde can only be converted into the corresponding cyanohydrin with 20% enantiomeric excess. It was later discovered that α,ß-unsaturated aldehydes were also substrates for this enzyme, when hydrogen cyanide was used directly as the cyanide source, allowing the conversion of a variety of aldehydes to cyanohydrins with 80-95% enantiomeric excess. Cinnamaldehyde was at first thought to be unacceptable for the enzyme, but it was later discovered that this substrate requires a careful control of the reaction conditions. The reaction has to be done in a citrate buffer solution, with the pH maintained at 4 and at 0 ^{o}C, and using potassium cyanide as the cyanide source, which is converted *in situ* into hydrogen cyanide. By this method, the desired product can be obtained with greater than 93% enantiomeric excess. The only aldehydes that were not accepted were heteroaromatic aldehydes containing nitrogen, and aromatic aldehydes with substituents on the ortho-position which gave products with a lower enantiomeric excess.[150,151,152]

This (*S*)-oxynitrilase enzyme has been cloned and over-expressed in *P. pastoris*. The cloned enzyme works best in a biphasic solvent system, comprised of citrate buffer and methyl *tert*-butyl ether. In this solvent system, a variety of aldehydes were converted into the corresponding cyanohydrin with greater than 98% enantiomeric excess. The only aldehyde that did not give a good result was

benzyloxyethanal, which gave a high yield but the cyanohydrin had only 12% enantiomeric excess. Methyl ketones also were accepted by this enzyme, giving products with 75-89% enantiomeric excess, but only a moderate yield of 13-49% could be achieved.[153]

As so far discussed, use of an oxynitrilase enzyme is a very useful method that can easily be used to convert aldehydes and ketones into cyanohydrins. In this particular case, the usual problem that is common in enzymes does not apply; that is, lack of one enantiomer of the enzyme. So, both enantiomers of the cyanohydrins can readily be produced. However, this method is not without problems. Although high enantiomeric excesses can already be achieved, there is still scope for improvement, but modification of an enzyme is not an easy process. The enzyme needs to be genetically modified, cloned and then tested. To achieve an effective modification, a detailed structure of the active site and the mechanism are a great help, but although both have been suggested, neither of them are actually known for oxynitrilases. This makes modification a difficult task. Also, although some ketones are accepted as substrates, not all of them can be converted into cyanohydrins. All of these enzymes struggle with ketones bearing a group that is bigger than methyl. This is another field where improvement is desired, but this too is not an easy task.

Chapter 3

Use of other Cyanide Sources with Complex **10**

3.1 Reactions with Ethyl Cyanoformate

Cyanoformate esters are known to react with aldehydes and ketones to give the corresponding cyanohydrin carbonates.[154,155] The asymmetric synthesis of cyanohydrin carbonates was reported in 2001 by Tian and Deng,[156] but their method required up to 30 mol% of an alkaloid catalyst, and still required reaction times of up to seven days. Shibasaki also showed that a heterobimetallic system with three binol units, three lithium ions and a yttrium ion catalyses the addition of ethyl cyanoformate to aldehydes with enantiomeric excesses of up to 98%.[157] However, this could only be achieved with 10 mol% of this catalyst, and three other additives, making the reaction rather ineffective in terms of cost. Najera *et al.* showed that an aluminium binol complex could catalyse the addition of methyl cyanoformate to aldehydes at room temperature, but only 80% enantiomeric excess could be achieved.[158]

Scheme 18

Scheme 18 shows the addition of ethyl cyanoformate to aldehydes. There are three main advantages of this reaction over the addition of trimethylsilyl cyanide.

The first is the lower cost of the reagent. Secondly, this reaction does not give any by-products, so the purification process is easy. Finally, cyanohydrin carbonates are more stable to hydrolysis than the silyl ethers, thus facilitating the purification and storage of the product.

Initial results with catalyst **10** showed that when 1 mol% of the catalyst was used with benzaldehyde at -85 ^{o}C, no reaction occurred, but when the temperature was raised to -73 ^{o}C, the reaction proceeded to completion in 48 hours, giving mandelonitrile ethyl carbonate with 94% enantiomeric excess.[159] Raising the temperature to -40 ^{o}C resulted in the enantiomeric excess dropping to 83%. Reduction of the amount of catalyst was also attempted, but with 0.1 mol% of catalyst, the reaction only went to 3% completion. Although the first result was encouraging, the long reaction times were thought to be impractical, so the effect of increasing the amount of catalyst was investigated. Increasing the catalyst loading to 5 mol% gave product with 95% ee after just 18 hours. These conditions were then used to screen a range of aldehydes with ethyl cyanoformate, and the results are summarized in Table 13.

Although the yields obtained using 4-methylbenzaldehyde, cinnamaldehyde and dimethyl acetaldehyde as substrates seem very low, this is only because of the loss during purification. The conversions in all three cases were around 90%, but a lot of the product was lost during distillation.

As Table 13 shows, all electron rich aromatic aldehydes gave excellent results. The electron deficient aldehyde, 4-trifluoromethylbenzaldehyde, gave a much lower enantiomeric excess than the other substrates, but this is of no surprise. As the reaction time shows, this aldehyde is far more reactive than the other aldehydes, as the electron withdrawing effect makes the carbonyl carbon

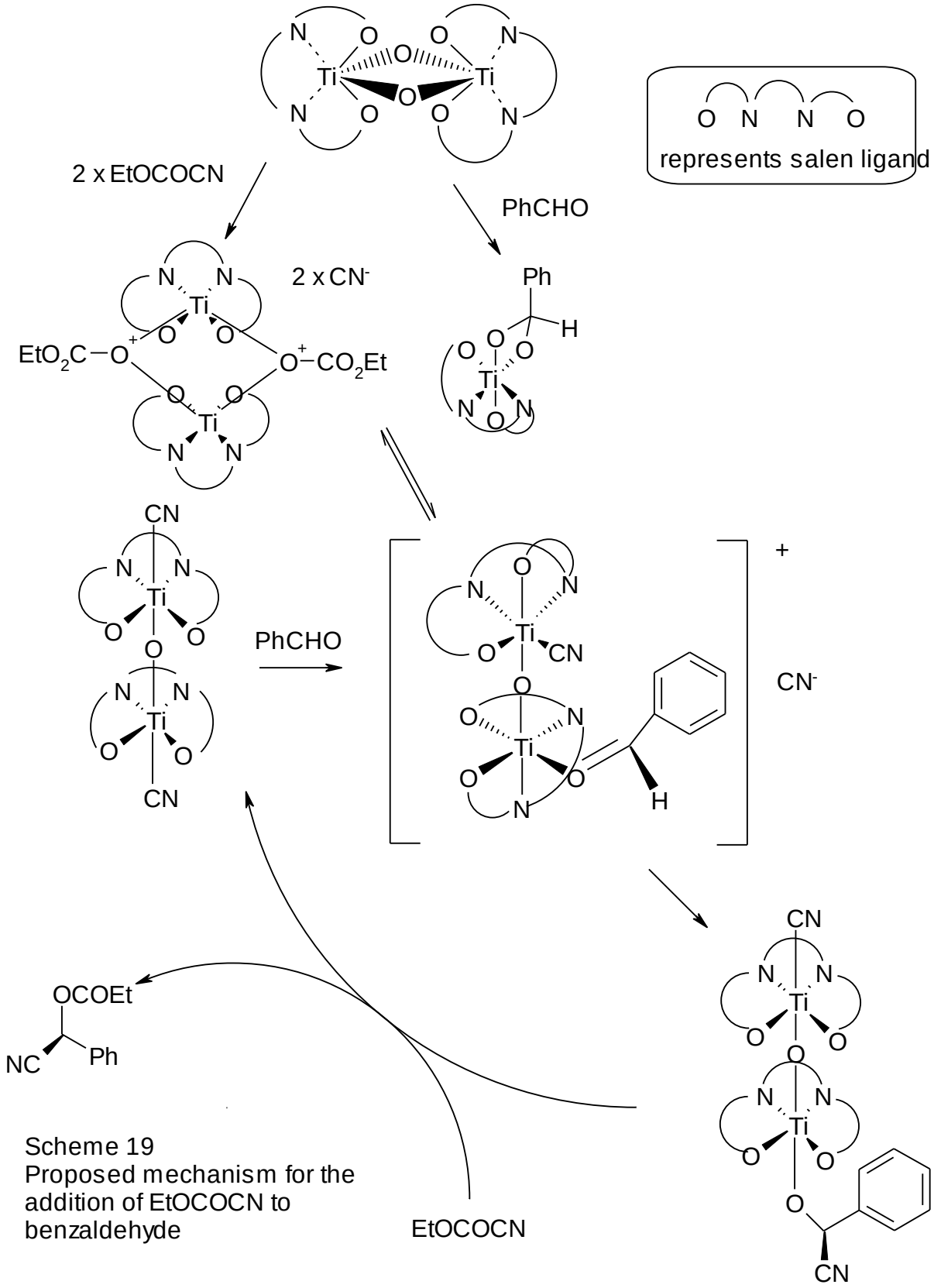
more electropositive. This probably facilitated a non-catalysed reaction, allowing more substrate to react via the uncatalysed background reaction.

Table 13: Reaction of various aldehydes with ethyl cyanoformate using 5 mol% of catalyst **10**

Aldehyde	Time / h	Ethyl cyanoformate / equiv	Yield / %	ee / %
PhCHO	18	2	90	95
4-$MeOC_6H_4CHO$	18	2	92	95
3-$MeOC_6H_4CHO$	17	2	94	99
2-$MeOC_6H_4CHO$	48	1.2	95	98
4-MeC_6H_4CHO	48	1.2	67	94
4-$CF_3C_6H_4CHO$	6	2	84	76
4-ClC_6H_4CHO	68	1.2	96	94
PhCH=CHCHO	45	1.2	47	94
$C_8H_{17}CHO$	22	2	54	84
Me_2CHCHO	20	1.2	23	79
CyCHO	18	1.2	82	79
Me_3CCHO	48	1.2	69	76

The aliphatic aldehydes gave slightly lower enantiomeric excesses, but the reason for this is as yet unknown. The primary aldehyde was the most effective substrate, but there were no significant differences observed between the secondary and tertiary aldehydes. The reaction time for the tertiary aldehyde was longer, which is assumed to be due to steric reasons.

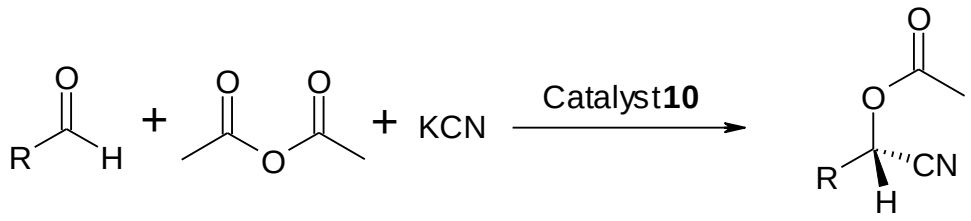
The mechanism of cyanohydrin synthesis using ethyl cyanoformate was also studied.[160] The mechanism seems to be analogous to that determined for reactions using trimethylsilyl cyanide, which is of no surprise. This is summarized in Scheme 19.



Scheme 19
Proposed mechanism for the addition of EtOCOCN to benzaldehyde

3.2 Reactions using Acetic Anhydride and Potassium Cyanide

Scheme 20 shows the general reaction of the addition of acetic anhydride and potassium cyanide to aldehydes. This reaction occurs smoothly at -42 °C with 1 mol% of catalyst **10** in dichloromethane, without any side reactions.[161] The reaction is greatly accelerated when water or t-butyl alcohol is added to the reaction mixture. At room temperature, the two additives had a similar effect, but when the reaction temperature was reduced to -42 °C, t-butyl alcohol was better at accelerating the reaction, even though both additives were as effective as each other in terms of the enantiomeric excess of the products. However, addition of organic acids greatly reduced the reaction speed, and the addition of hydrogen cyanide resulted in a reduction in optical purity of the product. Efficient stirring is necessary in this reaction, as potassium cyanide is totally insoluble in dichloromethane, and the reaction occurs under heterogeneous conditions. Table 14 summarizes the results obtained for the synthesis of various O-acetyl cyanohydrins produced by this method.



Scheme 20

Table 14: Addition of Acetic Anhydride and Potassium Cyanide using Catalyst **10**

Aldehyde	Yield / %	ee / %
PhCHO	93	90
4-$MeOC_6H_4CHO$	74	93
3-$MeOC_6H_4CHO$	99	93
3-$PhOC_6H_4CHO$	99	90
4-$CF_3C_6H_4CHO$	87	85
3-$CF_3C_6H_4CHO$	99	89
4-ClC_6H_4CHO	89	88
$PhCH_2CH_2CHO$	80	84
Me_2CHCHO	62	72
Me_3CCHO	40	62
PhCOMe	No reaction	0

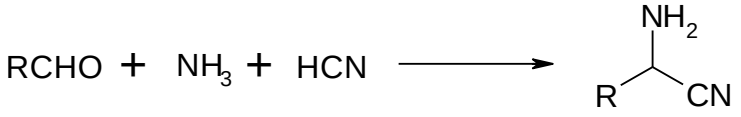
As the addition of hydrogen cyanide greatly reduces the enantiomeric excess, any mechanism involving hydrogen cyanide can be ruled out. This is why the mechanism is thought to go in a very similar way to the trimethylsilyl cyanide and ethyl cyanoformate chemistry. The fact that (*S*)-cyanohydrin is produced using (*R,R*)-catalyst **10** also supports this hypothesis.

This chemistry has resulted in a cyanohydrin synthesis starting from inexpensive non-volatile starting materials with good yields and enantiomeric excesses. However, this process is still not perfect from an industrial point of view, as a large excess (four equivalents) of highly toxic potassium cyanide has to be used. An even safer source of cyanide is preferable.

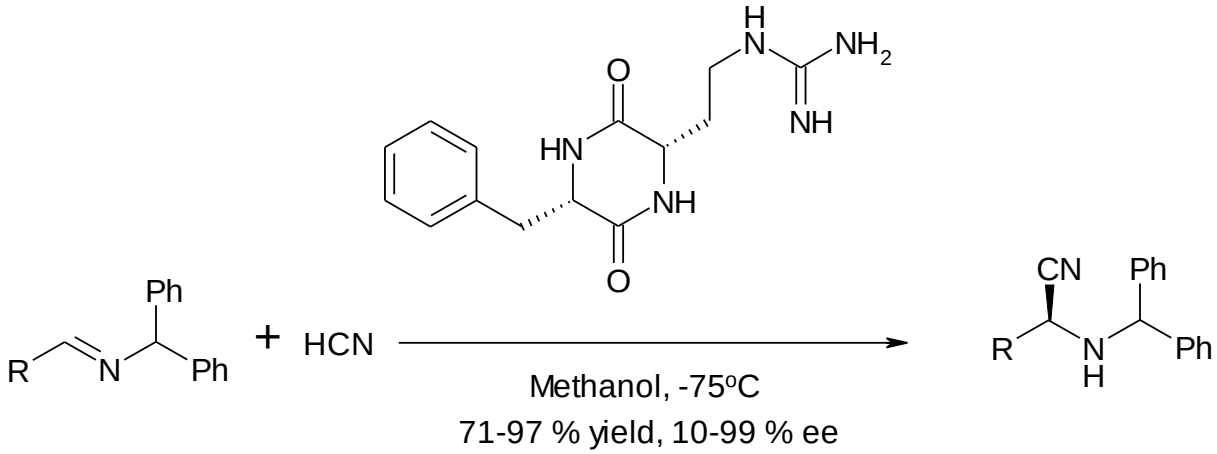
Chapter 4

The Strecker Reaction

The classical Strecker reaction was first reported as early as 1850.[162] The α-aminonitrile product is produced by the method shown in Scheme 21, then hydrolysed in the original paper, allowing an easy preparation of amino acids. This process has been carried out on an industrial scale for the mass production of α-amino acids, but more recently this type of reaction has been investigated again as a possible way of producing optically pure amino acids.[163] The first chiral Strecker reaction was reported by Lipton *et al.*, and was achieved using a guanidine containing dipeptide catalyst as, shown in Scheme 22.[164]



Scheme 21

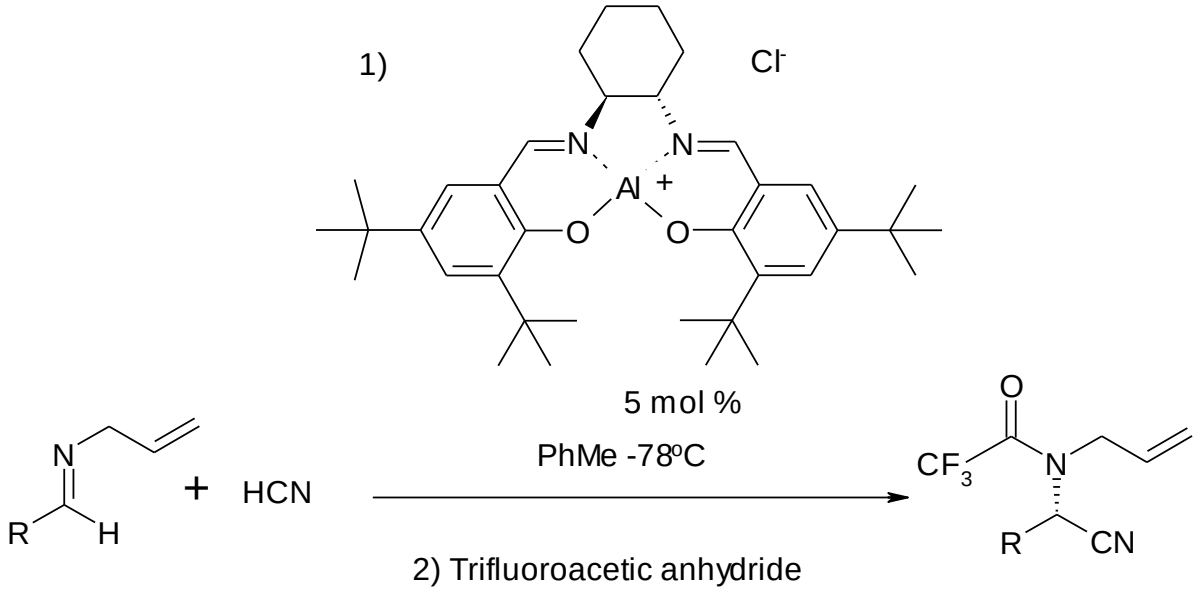


Scheme 22

Although this process only required 2 mol% of the catalyst and resulted in high enantiomeric excesses for electron rich aromatic aldehydes, this system did

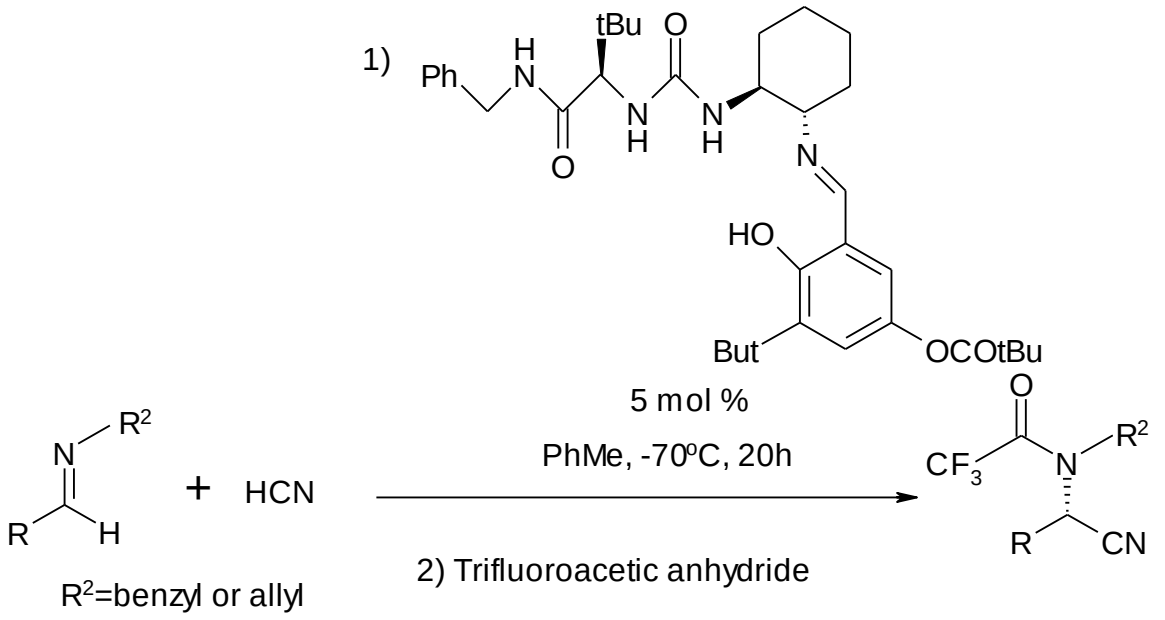
not give good results for electron deficient and aliphatic systems.

Scheme 23 shows the first example of an asymmetric Strecker reaction catalysed by a metal complex. This was reported by Sigman and Jacobson[165] and gave good yields for all the substrates that were tested. Unfortunately the enantiomeric excesses were not as great, and varied between 37 and 95%. Aryl imines in general provided the best enantiomeric excesses, while alkyl substituted imines were not as effective substrates.



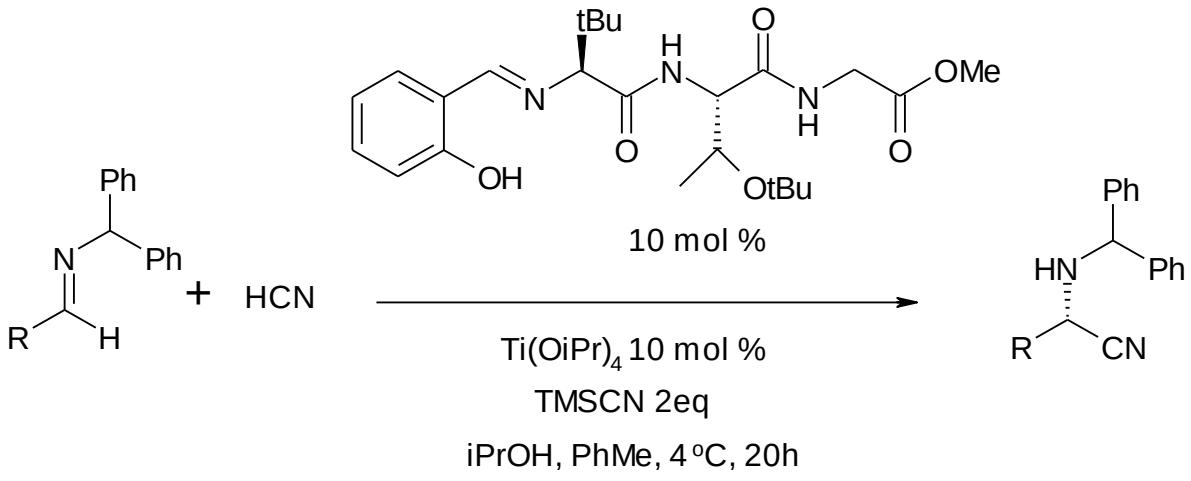
Scheme 23

Following the previous result, Jacobsen has reported a new catalyst that gives better results.[166] This new system is summarized in Scheme 24. A range of both aromatic and aliphatic substrates were screened, and gave α-aminonitriles with 77-97% enantiomeric excess. This enantioselectivity is achieved due to the two tertiary butyl groups on the imine part of the catalyst. Binding the catalyst onto a polystyrene support allowed the product to be easily separated by filtration, and the catalyst could be recycled indefinitely without apparent loss in either the yield or optical purity of the α-aminonitrile product.



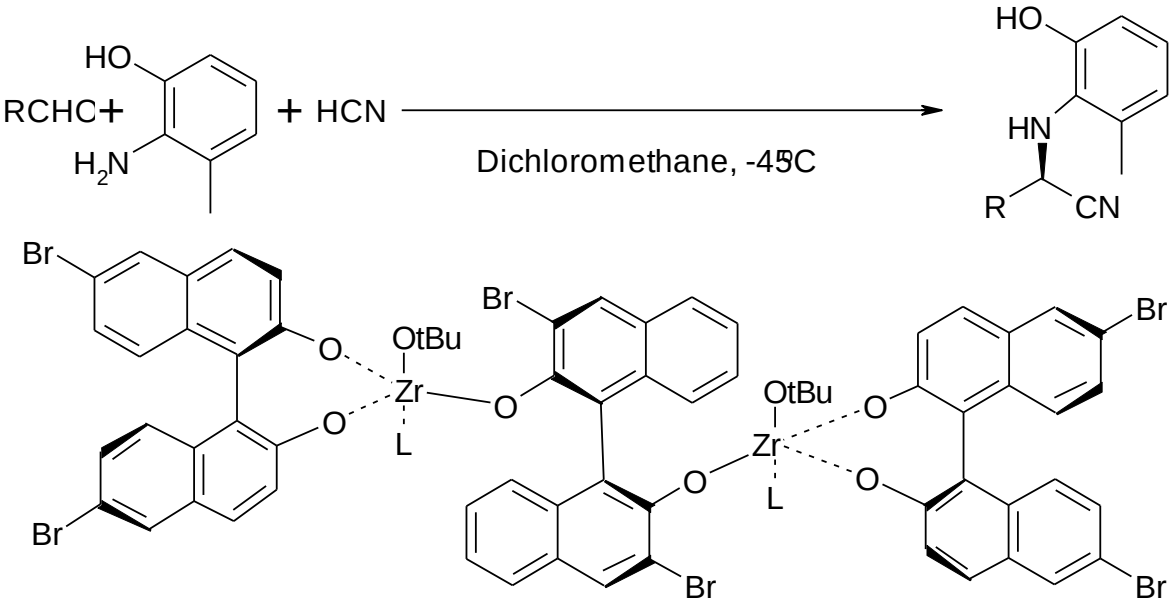
Scheme 24

Snapper, Hoveyda and co-workers developed a similar Schiff base ligand shown in Scheme 25. This system, when complexed to titanium, gave excellent results, with yields of 80-97% and ee's of 85-99%.[167] The N-benzhydryl α-aminonitriles prepared using this system also had the advantage that they could be easily purified by silica gel chromatography, so the acylation step was unnecessary.



Scheme 25

Scheme 26 summarizes the work by Kobayashi and co-workers.[168] This method resulted in 76-100% yield and 84-94% enantiomeric excesses. This is by far the best results that have been obtained in the Strecker reaction. Although the results are excellent and the process could be applied on an industrial scale, this system still has a problem, since it requires hydrogen cyanide which is a very toxic gas. A system that can use a safer source of cyanide would be far safer.[169]



1 - 5 mol %

Scheme 26

Chapter 5

Aim of the project

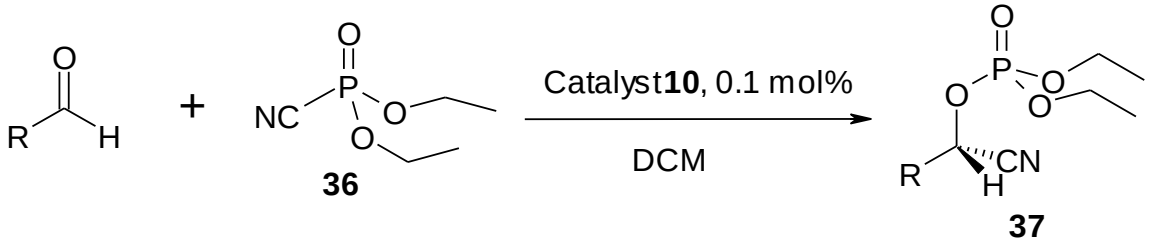
In the previous section, ways of synthesizing cyanohydrins have been discussed. Although some of these gave promising results, none of them are perfect, and there is still room for improvement. In this project, cyanohydrin synthesis using catalysts **10** and **12** are studied in detail, in an attempt to either find an alternative cyanide source that could produce cyanohydrins more effectively, or a more effective modification of previously known methods. Also, the cyanohydrins are taken a step further and ways of utilizing them in synthesis are investigated.

Results and Discussion

Chapter 1

Use of Novel Cyanide Sources

As mentioned in the introduction, the search for a new effective cyanohydrin synthesis started by investigating alternative sources of cyanide. The best place to start was thought to be diethyl cyanophosphonate **36**, which is known to react with aldehydes to form cyanohydrin phosphonates **37** as shown in Scheme 27.[170]



Scheme 27

This was thought to be a good starting point, as this reagent has been used by other groups[180] who commonly use reagents that are compatible with our titanium salen catalyst. Initial reactions using benzaldehyde as substrate gave promising results, with the reaction proceeding to 100% conversion overnight, and at room temperature when using 0.1 mol% of catalyst **10** in dichloromethane. There was no background reaction when diethyl cyanophosphonate was stirred with benzaldehyde under these conditions. Following this result, a series of aldehydes were converted into the corresponding cyanohydrin phosphonates, as shown in Table 15. However, determining the enantiomeric excess of these

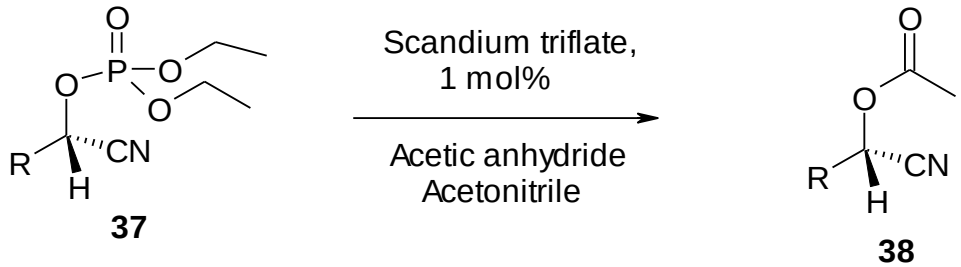
cyanohydrin phosphonates turned out to be a problem. Using the available GC facilities, the two enantiomers of the benzaldehyde cyanohydrin phosphonates could only be separated after a 16 hour run, which by itself was enough reason not to analyse these compounds by this method. In addition, this separation was not reproducible. This was a real problem, as it was not possible to be sure if the results were reliable or not. Therefore, an alternative method of determining the enantiomeric excess had to be found.

Table 15: Yields for the addition of diethyl cyanophosphonate to various aldehydes using 0.1mol% of catalyst **10**

Aldehyde	Yield (%)	Time (h)
Benzaldehyde	98	20
2-Methyl benzaldehyde	57	20
3-Methyl benzaldehyde	78	20
4-Methyl benzaldehyde	71	20
4-Methoxy benzaldehyde	22	20
4-Trifluoromethyl benzaldehyde	46	20
Cinnamaldehyde	92	20
Crotonaldehyde	63	20
Cyclohexanaldehyde	84	20
2,2,2-Trimethyl ethanal	99	20
2,2-Dimethyl ethanal	100	20
Nonanal	100	20

The first attempt was to convert cyanophosphonates **37** into a series of compounds that had previously been prepared and analysed within the group, such as cyanohydrin acetates **38**. This was achieved by reacting the cyanophosphonates with acetic anhydride and scandium triflate (Scheme 28). This method has been routinely used in our group to convert *O*-trimethylsilyl cyanohydrins into acetates, without causing racemization,[171] but has not

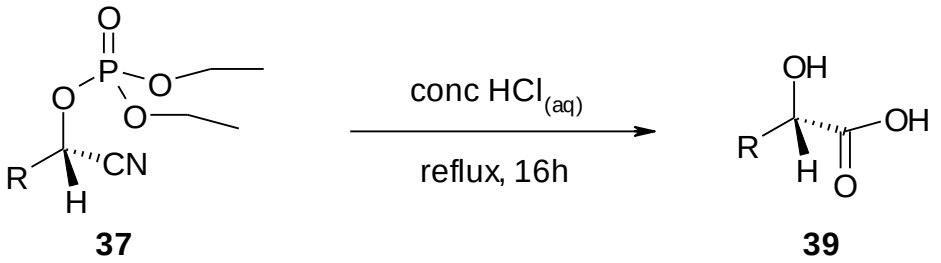
previously been applied to cyanohydrin phosphonates.



Scheme 28

This reaction using the benzaldehyde cyanohydrin phosphonate was successful, and enough material was obtained to be analysed by chiral GC. Unfortunately however, acetate **38** was found to be racemic. It was not clear if the racemization was occurring during the formation of acetate **38**, or if cyanohydrin phosphate **37** was actually racemic. Therefore, another analysis was required to clarify this uncertainty. Hence, the conversion of phosphonate **37** into other chemicals was investigated.

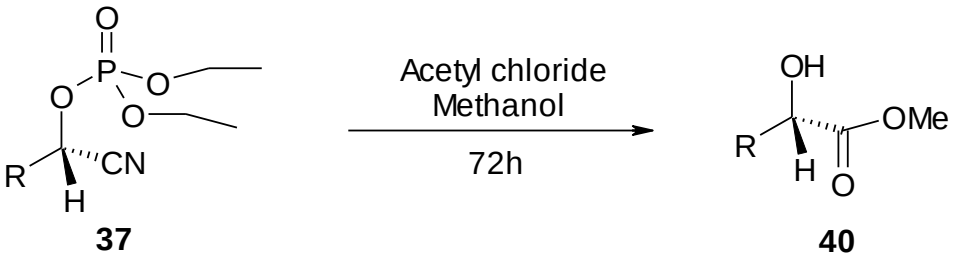
The first transformation to be carried out was acid hydrolysis of compound **37**. By this simple transformation, it was hoped that the phosphonate would be converted into a known α-hydroxy acid **39** that would be easier to analyse.



Scheme 29

The process shown in Scheme 29 gave racemic product with benzaldehyde cyanohydrin phosphonate. A chiral shift reagent, europium tris [3-heptafluoropropylhydroxymethylene-(+)-camphorate] was used for the analysis of this product. However, there was still uncertainty that the acid could be causing

the racemization, as harsh conditions had to be used to accomplish the transformation shown in Scheme 29. A milder, but similar transformation was therefore tried next (Scheme 30).

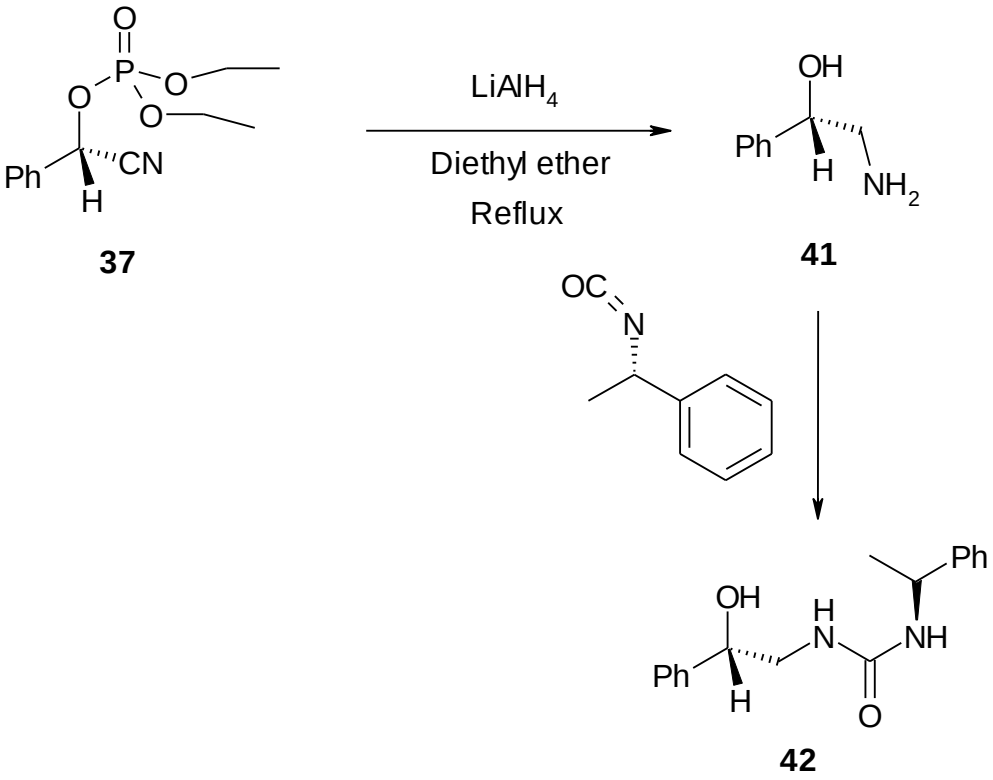


37 **40**

Scheme 30

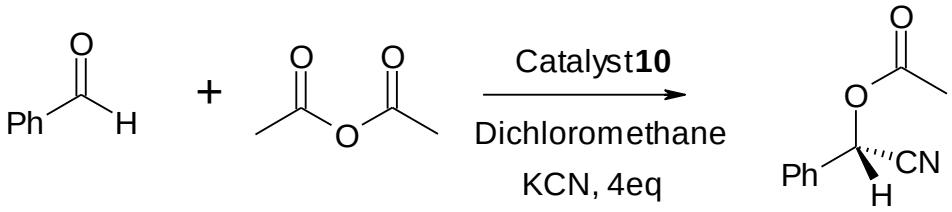
This reaction was tried with two compounds (R=Ph and R=*t*Bu), and found not to be reliable. In most cases, the reaction produced a green mess which did not have any sensible peaks when analysed by NMR spectroscopy. When it did finally work, the product was again found to be racemic (analysed by chiral shift reagent as discussed above). Since all the hydrolysis methods failed, a reduction was tried next on cyanohydrin phosphonate **37** with R=Ph, as shown in Scheme 31. The reaction smoothly gave the desired product, and the amine was then reacted with (*S*)-phenylethylisocyanate in a NMR tube to give diastereomeric ureas **42** which were again found to be racemic.

All these transformations had given racemic product. At this point, chiral HPLC became available, and cyanohydrin phosphates **37** were analysed by this technique. Cyanohydrin phosphonates **37** with R=Ph, 3-MePh, 3-MeOPh, Me_3C and C_9H_{19} were analysed by this technique, using a hexane and isopropanol mixture as eluant. This confirmed that cyanohydrin phosphonates **37** were all racemic. This came as a surprise, as this was the first reaction in which titanium salen catalyst **10** catalysed the addition of a cyanide source to aldehydes without inducing any asymmetry during the reaction.



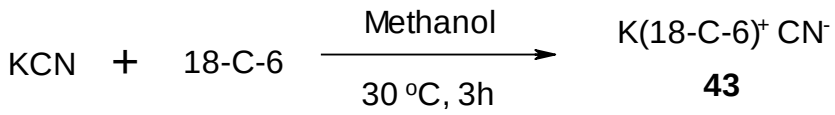
Scheme 31

Following this unfortunate result, attempts were made to improve the reaction. The first attempt was to add solid potassium cyanide as a co-catalyst to the reaction. It was already known that potassium cyanide could be used with titanium salen catalyst **10**, and the catalyst could be used as a phase transfer catalyst to deliver the cyanide to the aldehyde. This is demonstrated by the reaction of benzaldehyde with potassium cyanide and acetic anhydride, shown in Scheme 32.



Scheme 32

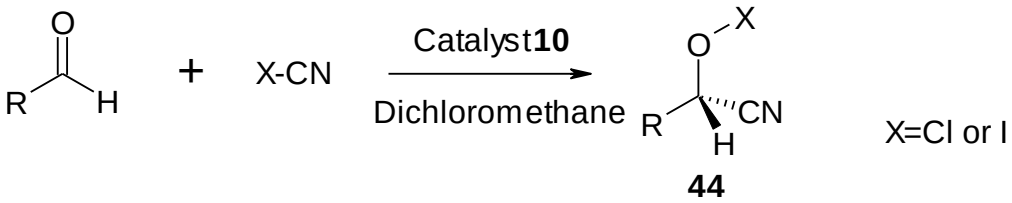
With this in mind, the diethyl cyanophosphonate reaction was tried again, with various amounts of potassium cyanide, ranging from 0.1 mol% to 10 mol%, added to the reaction. However, potassium cyanide is totally insoluble in dichloromethane, and a significant increase in either the rate of the reaction or the enantiomeric excess was not observed. To overcome this problem, a "soluble" potassium cyanide was sought, and literature precedent suggested that by complexing the potassium cyanide to 18-crown-6, it is possible to obtain a cyanide source **43** that is soluble in most organic solvents[172] as shown in Scheme 33.



Scheme 33

When complex **43** was used instead of solid potassium cyanide, the reaction did indeed go much quicker. Instead of taking overnight, the reaction proceeded to completion in just six hours when more than 10 mol% of the KCN/18-C-6 complex was used. However, this did not improve the enantiomeric excess. In fact, there was enough cyanide ion present in the reaction mixture, that significant reaction was occurring without the presence of the catalyst. This was proven when the reaction was repeated under the same conditions without catalyst **10**, and the reaction still proceeded to approximately 90% completion in six hours. As this path of investigation was getting nowhere, it was concluded that diethyl cyanophosphonate should not be pursued further, and alternative cyanide sources should be investigated.

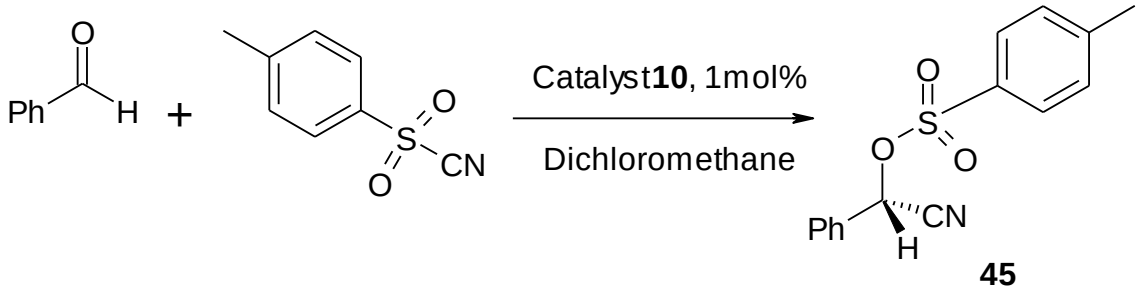
The next sources of cyanide that were investigated were cyanogen chloride and cyanogen iodide (Scheme 34). These two compounds were interesting to study, as the polarity of the cyanide-X bond is reversed from the normal. The chloride and iodide species are sufficiently electron-withdrawing, to give the cyanide unit a δ+ charge. Unfortunately though, this reaction did not proceed when stirred with benzaldehyde or trimethyl acetaldehyde, even after three days with as much as 20 mol% of catalyst **10** in the reaction mixture.



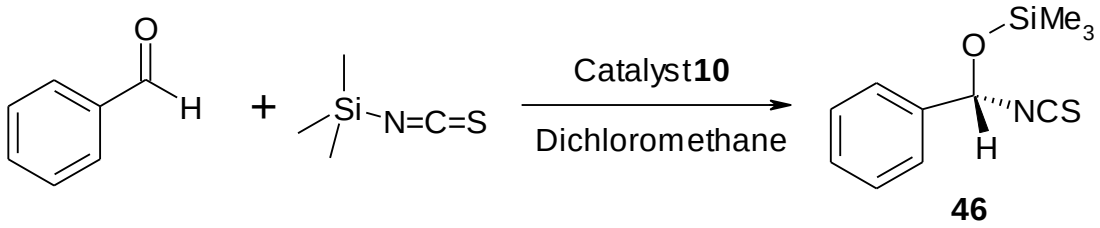
44

Scheme 34

The next cyanide source to be investigated was tosyl cyanide. This was chosen, as the tosyl group is very labile, and the cyanide ion can easily be liberated. This reaction unfortunately also did not proceed, even when the amount of catalyst was increased to 5 mol%. Another reaction was attempted, using KCN as co-catalyst, but this change still did not give any product. Finally, the use of trimethylsilyl isothiocyanate was investigated (Scheme 36). Unfortunately, this reaction did not work either.



Scheme 35



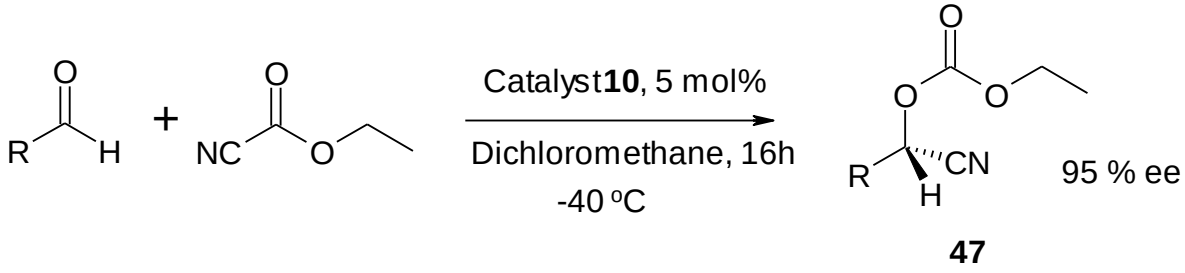
Scheme 36

So far, there has been no positive result in the search for an alternative cyanide source to be used with titanium(salen) catalyst **10**. However, a new promising reagent has been found. The KCN/18-C-6 complex is active as a co-catalyst. Therefore, it was decided to investigate the use of this co-catalyst with ethyl cyanoformate.

Chapter 2

2.1: Synthesis of cyanohydrin ethyl carbonates revisited

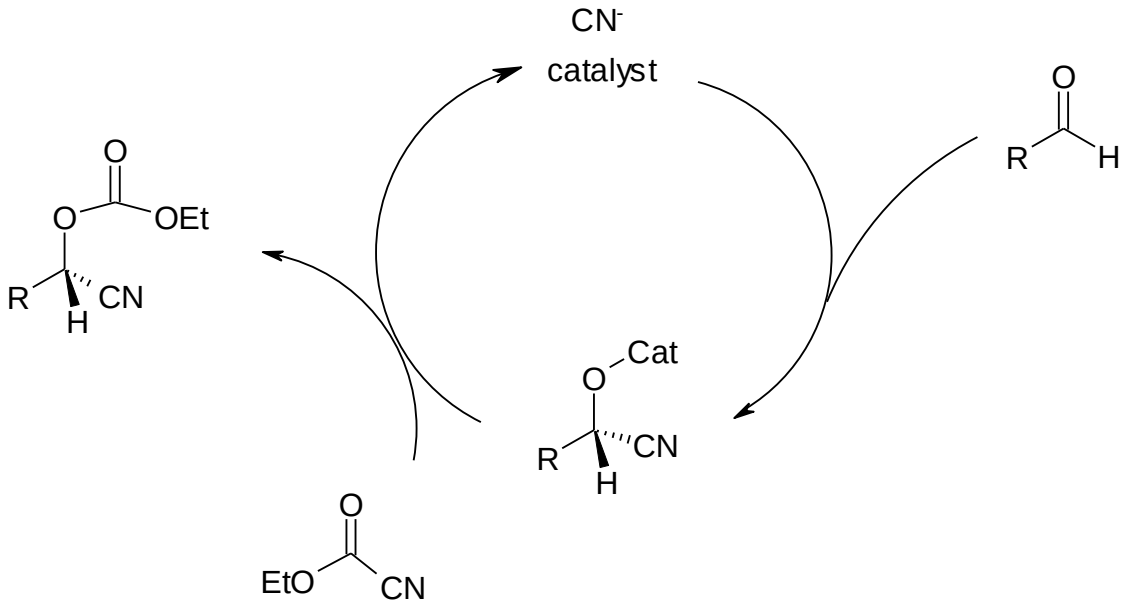
At the beginning of this project, the best conditions developed for the asymmetric addition of ethyl cyanoformate to aldehydes were as shown in Scheme 37.[173] The drawback of the reaction is that it requires 5 mol% catalyst and a low temperature to obtain a high enantiomeric excess, which makes this procedure rather too costly. If asymmetric induction could be achieved at a lower catalyst loading than has been possible so far, then one of these two drawbacks can be removed, and the synthesis could be carried out at a much lower cost.



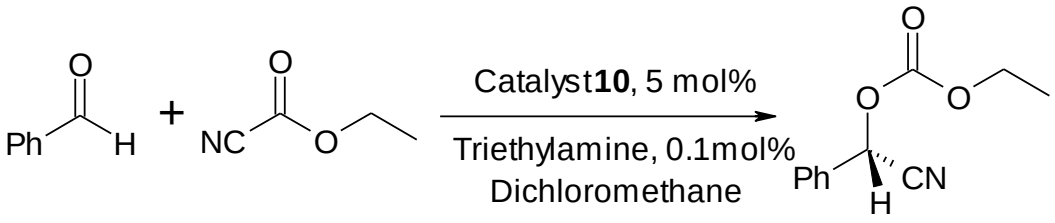
Scheme 37

The reaction is thought to go by the catalytic cycle shown in Scheme 38. From this cycle, it was thought that by increasing the concentration of cyanide ions in the solution, a significant increase in rate could be achieved, allowing the amount of catalyst **10** to be reduced. Initially, addition of a nucleophile was investigated. The research started by adding 0.1 mol% of triethylamine to the reaction mixture, as shown in Scheme 39. The reaction had gone to completion in just 3 hours when benzaldehyde was used as the substrate. Unfortunately though, the enantiomeric excess was only 71%, a lot lower than the product obtained from the standard conditions. This was probably because triethylamine is a base as well as a nucleophile, and it has deprotonated the α-proton of the product. So

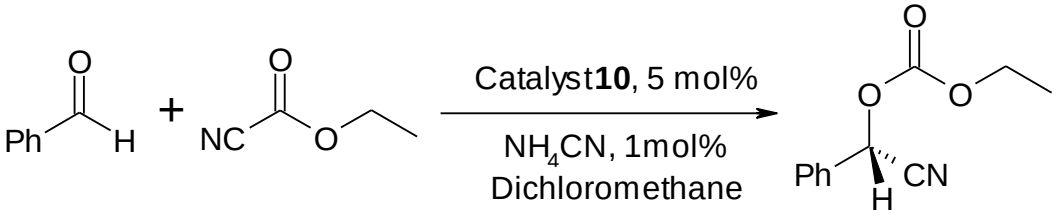
instead of trying to liberate cyanide ions from ethyl cyanoformate, several sources of cyanide were investigated to introduce cyanide ions separately into solution.



Scheme 38



Scheme 39

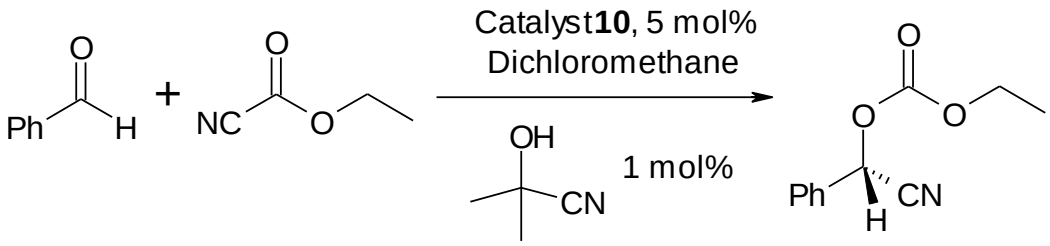


Scheme 40

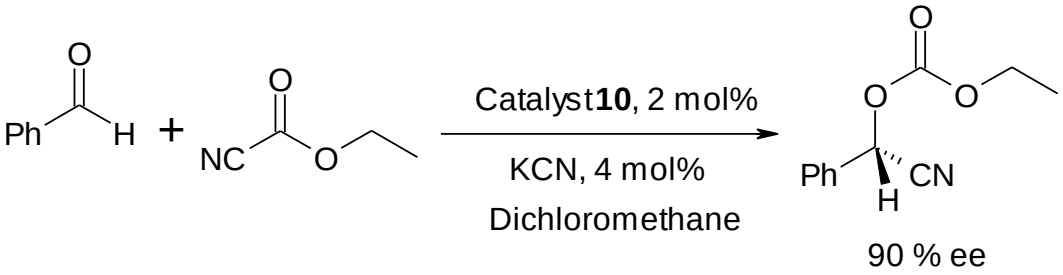
Ammonium cyanide was found to be an effective catalyst. The reaction had gone to completion after five hours, but the concentration of cyanide seemed to be

too high even when only 1 mol% of ammonium cyanide was added, and only racemic product could be obtained (Scheme 40). Since ammonium cyanide melts at room temperature, and handling small quantities of this compound was rather tricky as it freezes in a syringe, and molten cyanide has to be handled using a spatula, this route was not investigated any further.

The second source of cyanide studied was acetone cyanohydrin (Scheme 41). Unfortunately, this reaction did not give any product. Acetone cyanohydrin exists in equilibrium with hydrogen cyanide and acetone, but there seemed to have been not enough hydrogen cyanide present at -40 °C for it to exhibit a catalytic effect. Use of higher concentrations of acetone cyanohydrin was not investigated, as acetone and dichloromethane form an explosive mixture, and it was feared that increasing the concentration of acetone cyanohydrin might lead to a build up of acetone in the reaction mixture and hence an explosion. After the failure of the first two attempts, the use of potassium cyanide as an additive was investigated (Scheme 42).



Scheme 41



Scheme 42

This time, a reduction in the amount of catalyst **10** required was successfully achieved. This did not come as a surprise, as it was known that potassium cyanide and catalyst **10** can be used together and our group routinely use this combination in this synthesis of cyanohydrin acetates, as mentioned previously. The conditions were then optimized. Increasing the amount of catalyst did not increase the enantiomeric excess. Reducing the amount of catalyst did not affect the enantiomeric excess significantly either, but the reaction did not reach completion overnight. Increasing the amount of potassium cyanide to 3 mol% reduced the enantiomeric excess significantly, presumably because it catalyses the background reaction too, and this racemic catalysis became significant when the amount of potassium cyanide was increased to this level. When the amount of potassium cyanide was reduced, the addition of ethyl cyanoformate failed to reach completion in 18 hours. The results of the optimization process are summarized in Table 16.

Table 16: Optimization process for the addition of ethyl cyanoformate to benzaldehyde using potassium cyanide at -40 °C

Catalyst / mol%	KCN / mol%	Conversion / %	ee / %	Time / h
2	4	100	95	18
5	4	100	95	18
1.5	4	82	90	18
2	5	100	81	18
2	3	89	92	18

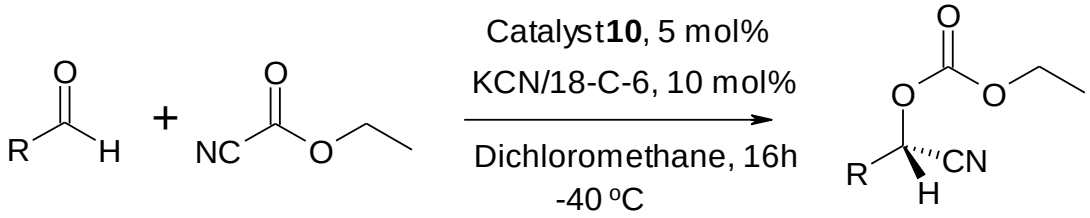
The use of 4 mol% of potassium cyanide along with 2 mol% of catalyst **10** was taken as standard conditions and applied to several substrates. However, it was felt that the amount of catalyst **10** could be cut even further in the case of the

more reactive aldehydes, so the reactions were repeated using just 1 mol% of catalyst **10**. Unfortunately, the reaction only went to completion with two of the aldehydes investigated. The results are summarized in Table 17.

Table17: Cyanohydrin ethyl carbonates prepared via the KCN method

Substrate	catalyst **10** / mol%	Yield / %	ee / %
Benzaldehyde	2	100	95
4-Methoxybenzaldehyde	2	98	97
4-Trifluoromethylbenzaldehyde	1	100	69
Cinnamaldehyde	2	94	95
Nonanal	2	90	79
Cyclohexanaldehyde	1	86	74
Trimethylacetaldehyde	2	79	68

Although a reduction in the amount of catalyst was successfully achieved, it was felt that more could be done to make the reaction even more efficient. The KCN/18-C-6 complex **43** which was discussed in the previous section was thought to be the perfect additive for this reaction, as it is soluble in dichloromethane, so the reaction can be carried out in one phase.



Scheme 43

The reaction was initially carried out under the standard conditions, but introducing 10 mol% of the KCN/18-C-6 complex **43** to the reaction mixture as shown in Scheme 43. This reaction worked, but gave totally racemic product. It

was believed that 10 mol% of the KCN complex introduced too much cyanide ion into the solution so that it was forming the product totally via the background reaction. However, this proved the crucial point; the KCN/18-C-6 complex **43** is indeed effective at catalysing the reaction.

Once the complex was found to be active, a set of conditions had to be found to maximize the activity. These conditions had to fulfil several important conditions. The first was that the product must have more than 90% ee. Secondly, the reaction must be complete overnight, otherwise it would be of no interest to industry. Thirdly, the amount of 18-C-6 and catalyst **10** that needs to be used must be minimized to reduce the cost of the process. With these conditions in mind, a series of experiments were carried out to find the optimized conditions for this reaction. The results of this study are summarized in Table 18.

Table 18: conditions investigated for the optimization process

Catalyst **10**, mol%	KCN/18-C-6, mol%	Temperature, °C	Yield, %	ee, %
2	0.1	-40	0	N/A
0.1	1	-40	0	N/A
0.1	1	25	0	N/A
3	1	-40	87	89
2	2	-40	100	86
1	3	-40	100	17
1	2	-40	100	85
1	0.1	-40	0	N/A
1	1	-40	0	N/A
1.5	2	-40	100	88
1.5	0.5	-40	0	N/A
1.5	1	-80	0	N/A
1.5	1	-65	0	N/A
1.5	1	-50	10	89
1.5	1	-40	100	88

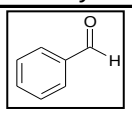
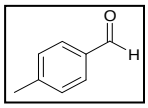
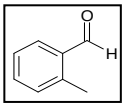
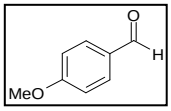
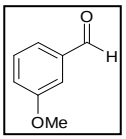
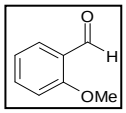
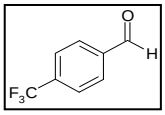
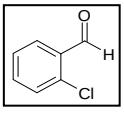
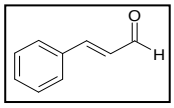
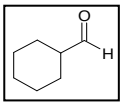
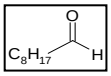
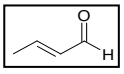
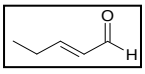
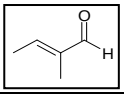
As Table 18 shows, the best conditions for this reaction are 1.5 mol% of catalyst **10** and 1 mol% of the KCN/18-C-6 complex **43**. Compared to the 5 mol% of catalyst **10** that was required for previous work, this is a significant improvement.

Once the optimized conditions had been found, a series of aldehydes were tested as substrates for this reaction. This study is summarized in Table 19. The reactions were carried out at least twice, and the enantiomeric excesses given are the averages of all values obtained by chiral GC. As Table 19 shows, the new method provides products with enantiomeric excesses that are usually either as good or better than those obtained by the old method. There are however three exceptions. The *para*-trifluoromethyl benzaldehyde derivative is easy to explain. The product racemizes on standing, so it is difficult to get the enantiomeric excess accurately.

The enantiomeric excess of the 2-methylpropanal product is also rather low. This is often observed when synthesizing cyanohydrins, whether it is via salen catalysts or using other catalysts. The reason for this is not yet known, however, it can be speculated that this is due to the interaction between the catalyst and the aldehyde. 2-Methylpropanal is a particularly small aldehyde, so it is probably less influenced by the chirality of the salen catalyst.

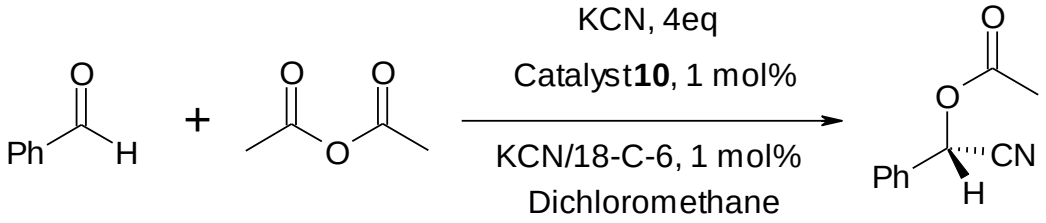
The last exception to the rule is *para*-tolualdehyde. This is the one that is out of the trend and the reason for this is unknown. It is rather strange that a very similar compound, *meta*-tolualdehyde, works particularly well for this system, yet *para*-tolualdehyde is such a poor substrate.

Table 19: Conversions and ee's of cyanohydrin carbonates obtained using KCN/18-C-6 as a cocatalyst

Aldehyde	Conversion after 24h (%)	Previously reported ee (%)	Enantiomeric excess (%)
	100	95	88
	100	94	59
	100		97
	100	95	90
	100	99	90
	100	98	100
	100	76	51
	100		93
	56	94	90
	100	79	55
	100	73	71
	100	79	78
	98	88	81
	100		93
	100		91
	45		89

The two reactions in Table 19 which did not go to completion were repeated, and it was shown that a reaction time of two days instead of 18 hours, does give complete reaction, and gives enantiomeric excesses that are as high as those indicated in Table 19.

Following this success, the synthesis of cyanohydrin acetates was investigated, as shown in Scheme 44.



42

Scheme 44

Although compound **42** had 95% enantiomeric excess, this was the same as the original method without the KCN/18-C-6 complex, and the reaction took the same length of time. When the amount of either potassium cyanide or the catalyst was reduced from the standard conditions while keeping the amount of complex **10** at 1 mol%, the reaction failed to go to completion overnight. Although the enantiomeric excess was still as high, this fails to meet the target that was set at the beginning of the research. Use of a higher concentration of the KCN/18-C-6 complex **43** was not investigated, as the cost of this complex would exceed the beneficial reduction in cost from the lower amount of the other materials used for the reaction.

To find out how the KCN/18-C-6 complex **43** was acting in the synthesis of cyanohydrin carbonates, a kinetic study was carried out. Although synthetic

reactions are carried out at -40 °C, kinetics were done at 20 °C, using 2 mol% of catalyst **10** and benzaldehyde as substrate to reduce the reaction time. 5 mol% of catalyst **10** was used for the reaction without KCN, as this was the minimum amount of catalyst required for the reaction to occur. The progress of the reaction was monitored by taking a very small sample from the reaction mixture, which was then passed through a plug of silica to remove catalyst **10** and potassium cyanide complex **43**, and the relative amounts of benzaldehyde and the product cyanohydrin ethyl carbonates were determined by proton NMR.

Initially, a run with no KCN complex added was carried out, as shown in Figure 8. The reaction was very slow, and was only 10% complete after 3 hours. There seems to be two parts to this trace, with the initial stage of the reaction being extremely slow, then the reaction suddenly speeding up. Not surprisingly, the kinetics could not be fitted to zero, first, second or third order. This is because the reaction is catalysed by cyanide ions which are produced by the slow, *in situ* hydrolysis of ethyl cyanoformate. Thus, the reaction accelerates over time as more ethyl cyanoformate is hydrolysed by adventitious moisture.

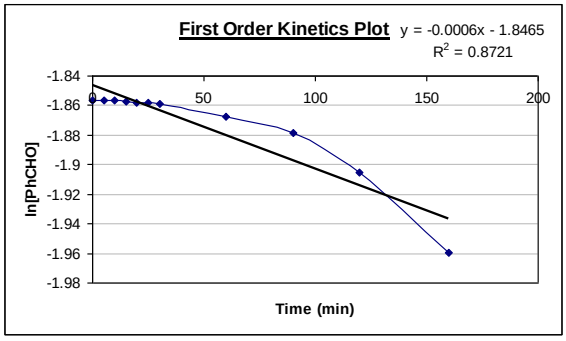


Figure 8: No KCN/18-C-6 complex, 5 mol% cat

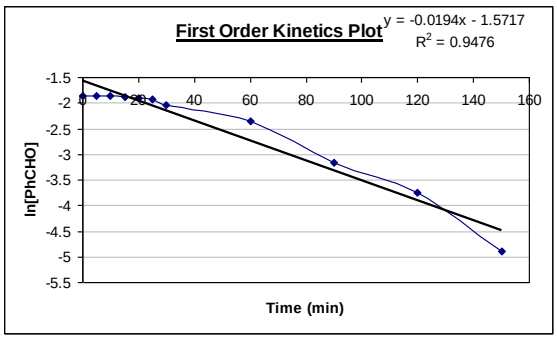


Figure 9: 0.5 mol% KCM/18C6 complex

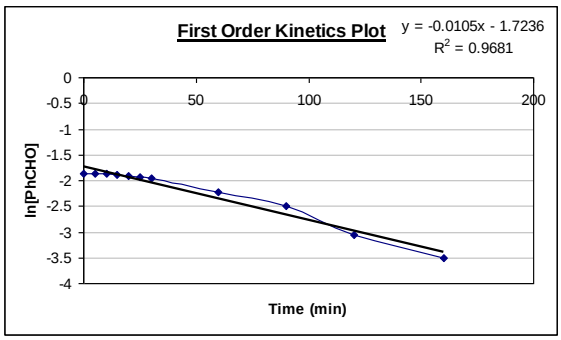


Figure 10: 1 mol% KCN/18-C-6 complex

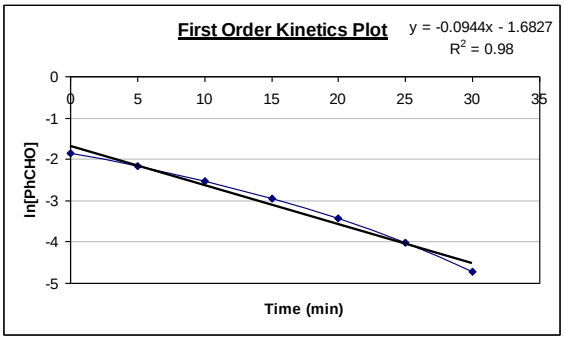


Figure 11: 2 mol% KCN/18-C-6 complex

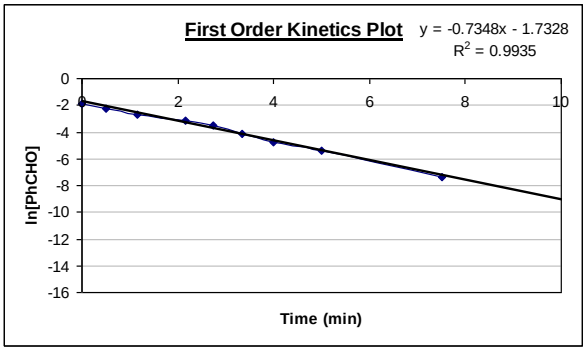
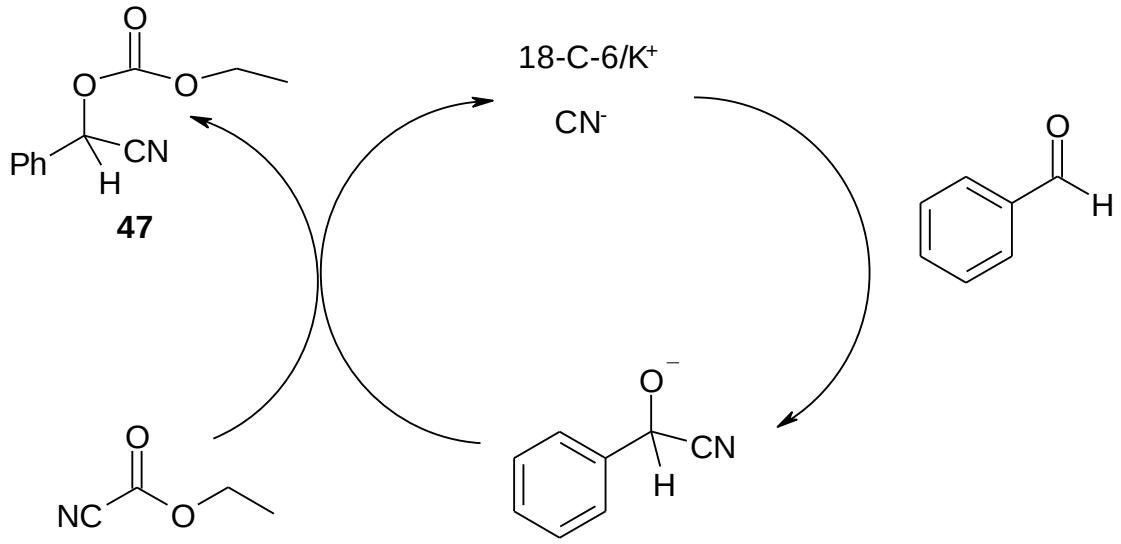


Figure 12: 4 mol% KCN/18-C-6 complex

By introducing a small amount of the KCN/18-C-6, this induction period can be reduced as shown in Figures 9-12. With as little as 1 mol% of the complex added this effect can be seen, and the induction period is cut to approximately 20 minutes, allowing the reaction to be complete after approximately 3 hours, as shown in Figure 10. When the concentration of the KCN complex is increased to 2 mol%, the induction period is down to about a minute, and the reaction is complete in just 30 minutes (Figure 11). When the amount of the KCN complex is increased to 4 mol%, the reaction is over in just 15 minutes (Figure 12). The kinetics trace by this stage has become a reasonable fit to first order kinetics with respect to benzaldehyde, which is consistent with previous results on the addition of TMSCN to aldehydes catalysed by complex **10**. This trend is observed, as up to

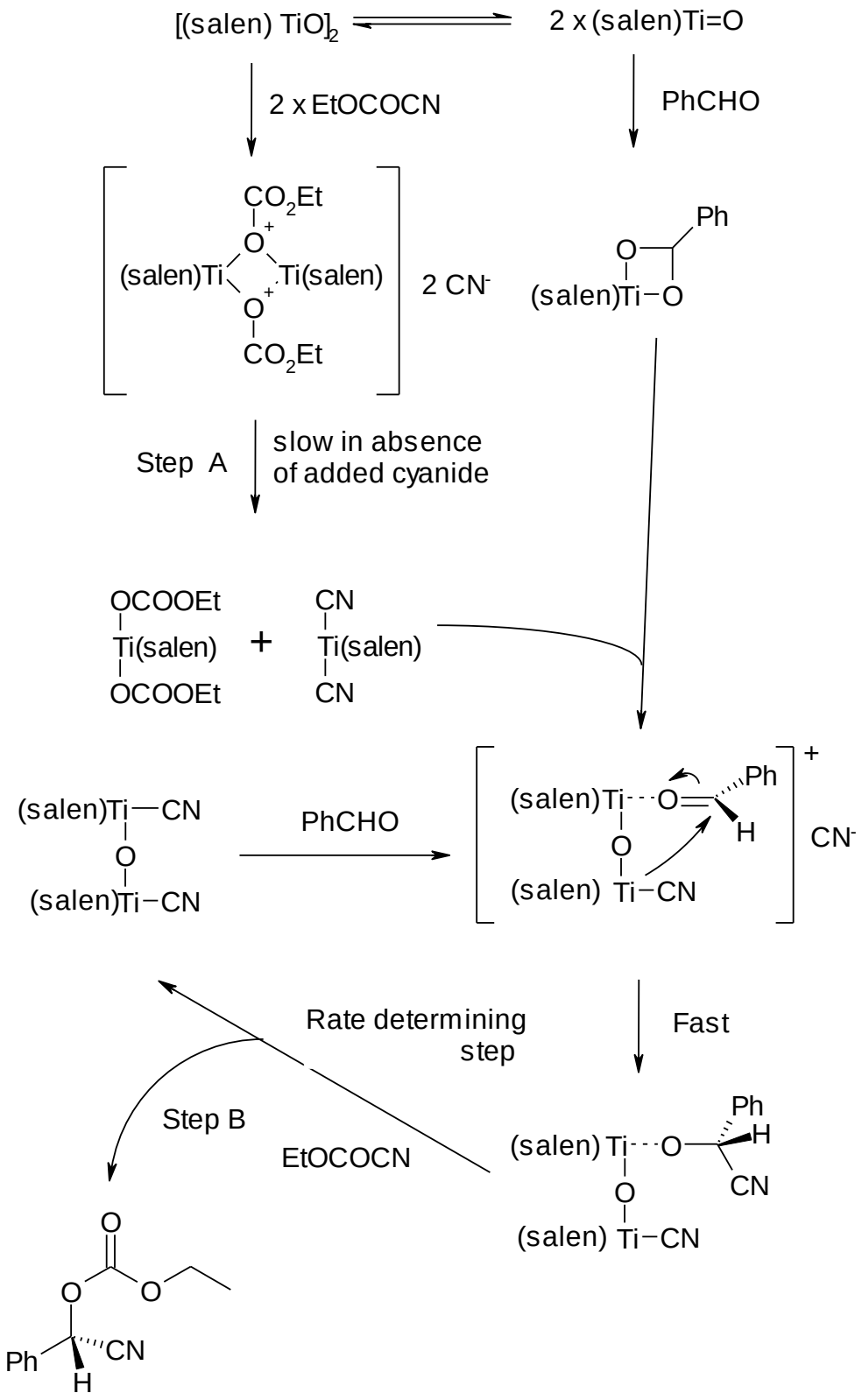
1 mol%, KCN/18-Crown-6 **43** is acting just as a co-catalyst, speeding the reaction up. However, when its concentration is increased to 2 mol%, it starts to catalyse the reaction independently of complex **10**. The reaction pathway is now closer to that shown in Scheme 45.



Scheme 45

This proposed mechanism is consistent with the enantiomeric excesses that were observed. When no KCN/18-C-6 complex is added to the reaction, product **47** is obtained with 67% ee. With 1 mol% of KCN/18-C-6, the enantiomeric excess is 70%, and the reaction is still going via the catalysed pathway. However, with 2 mol% of KCN/18-C-6 the ee drops to 49% as the route without catalyst **10** gets more pronounced. By the time the concentration of KCN/18-6 is increased to 4 mol%, the ee drops to just 11%. By this time, most of the reaction is proceeding via the uncatalysed path.

This result, together with the knowledge of the mechanism of the trimethylsilyl cyanide reaction, leads to a proposed mechanism for the asymmetric addition of ethyl cyanoformate to aldehydes catalysed by complex **10**. This proposed mechanism is summarized in Scheme 46.

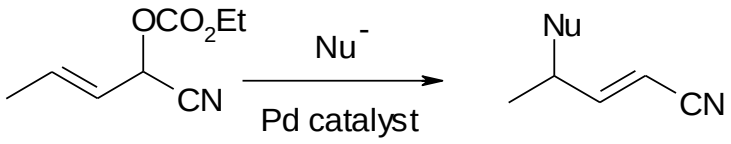

[(salen) TiO]2
2 x (salen)Ti=O
2 x EtOCOCN
PhCHO
CO2Et
(salen)Ti
Ti(salen)
2 CN-
CO2Et
Ph
(salen)Ti−O
Step A
slow in absence
of added cyanide
OCOOEt
Ti(salen)
OCOOEt
+
CN
Ti(salen)
CN
(salen)Ti—CN
O
(salen)Ti−CN
PhCHO
(salen)Ti
O
Ph
H
(salen) Ti−CN
CN-
Rate determining
step
Fast
Step B
EtOCOCN
(salen) Ti
O
Ph
H
CN
(salen) Ti−CN
O
O
O
Ph
CN
H

Scheme 46

When there is no added source of cyanide, step A is very slow. This is the rate determining step, and so it does not fit into any understandable kinetic trace, as this would rely on a small amount of moisture that is present in the reaction mixture. However, when KCN/18-C-6 complex **43** is added, the rate of step A is increased. In this case, step B becomes the rate determining step. As the concentration of the intermediate complex is directly proportional to the concentration of benzaldehyde in the solution, the reaction now follows first order kinetics.

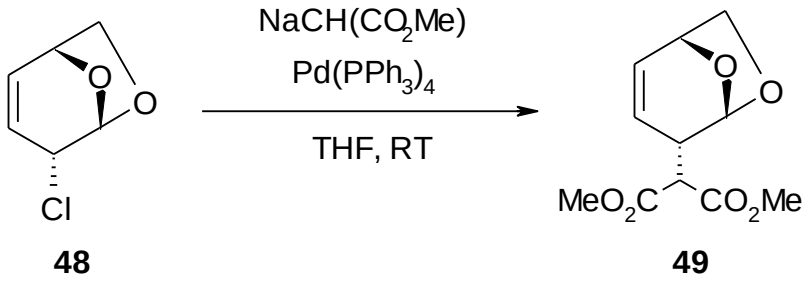
2.2: Reactions of the cyanohydrins

To demonstrate the usefulness of the cyanohydrins prepared in this project, a new set of reactions that would be able to utilize the chiral centre of the cyanohydrins were investigated. In particular, palladium catalysed allylic rearrangement[174] of cyanohydrins derived from α,β-unsaturated aldehydes was investigated, as shown in Scheme 47



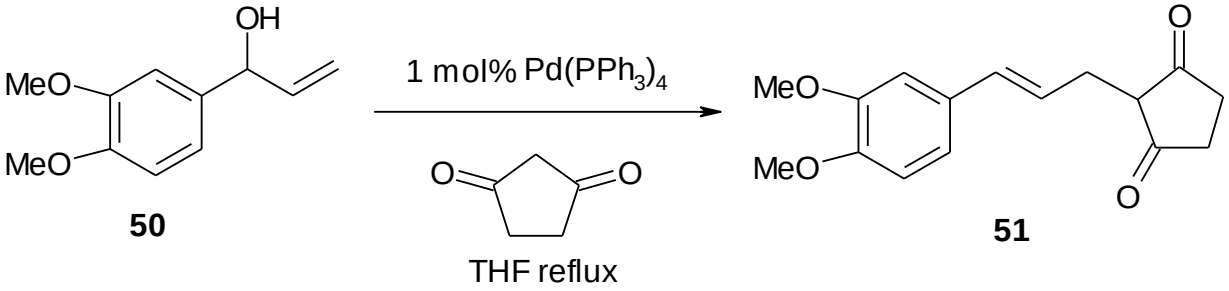
Scheme 47

Tetrakis(triphenylphosphine)palladium was chosen as the catalyst to be used with the cyanohydrins. This was because this catalyst was known to be compatible with a wide variety of nucleophiles and alkenes as its substrate.[174] Schemes 48-50 show a few examples.



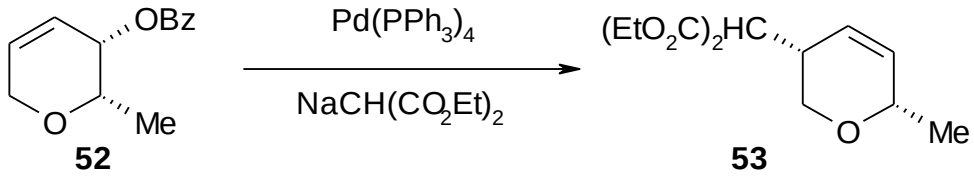
48 **49**

Scheme 48



50 **51**

Scheme 49

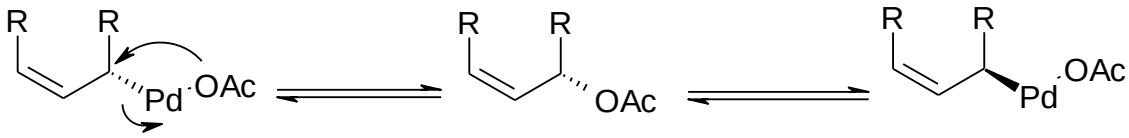


52 **53**

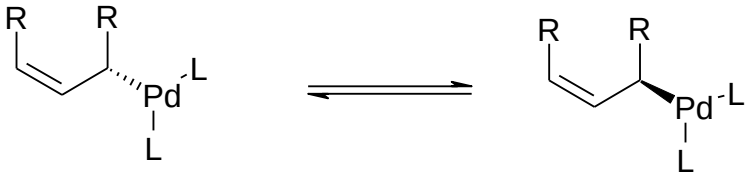
Scheme 50

There are two things that need to be considered; the regiochemistry and the stereochemistry of these reactions. The regiochemistry is fairly simple. The nucleophile will attack the least hindered end of the system, unless there is a strong electronic effect that favours reaction at the other end. The stereochemistry of the reaction is normally retention of configuration. This is because the reaction occurs in two steps. In the first step, the palladium catalyst complexes to the double bond, eliminating the leaving group as it complexes and

inverting the stereochemistry. The nucleophile then attacks the double bond, displacing the catalyst, and inverting the stereochemistry once more. Hence the overall effect is retention of the stereochemistry, although there are some exceptions to the rule. In particular, racemization can occur via two main pathways,[175] racemization by acetate (Scheme 51) and racemization by palladium (Scheme 52)



Scheme 51



Scheme 52

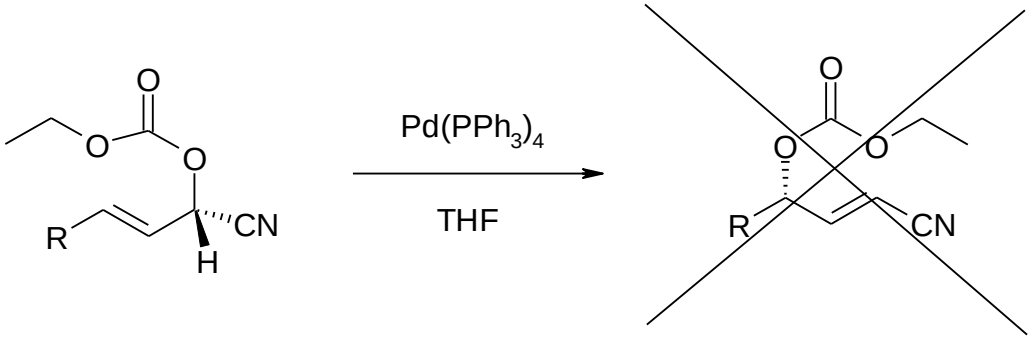
Racemization by acetate can be prevented by drying the glassware carefully before using it. However, racemization by palladium cannot be prevented. Fortunately, this racemization process is very slow,[174] so as long as the nucleophilic substitution is a lot faster than this process, racemization can be kept to a negligible level.

For this project, two cyanohydrin ethyl carbonates were chosen. They are the ones derived from crotonaldehyde **55** and cinnamaldehyde **54**, both synthesized by the KCN/18-C-6 pathway and obtained with enantiomeric excesses of 93% and 90% respectively.

Scheme 53

These two substrates were chosen as they have a double bond adjacent to the chiral centre, so attempts can be made to transfer the chiral centre to another carbon atom, which would widen the range of compounds that can be synthesized from these cyanohydrins.

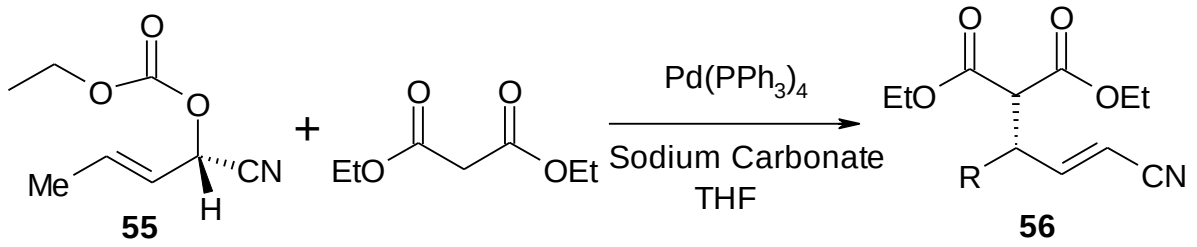
Initially, the cyanohydrin ethyl carbonate was stirred with the palladium catalyst in tetrahydrofuran to check if a rearrangement reaction would take place, as shown in Scheme 54. This reaction however did not take place, which was good news, as this rearrangement would lead to racemization once another nucleophile is added to this reaction, which would destroy the object of this research.



Scheme 54

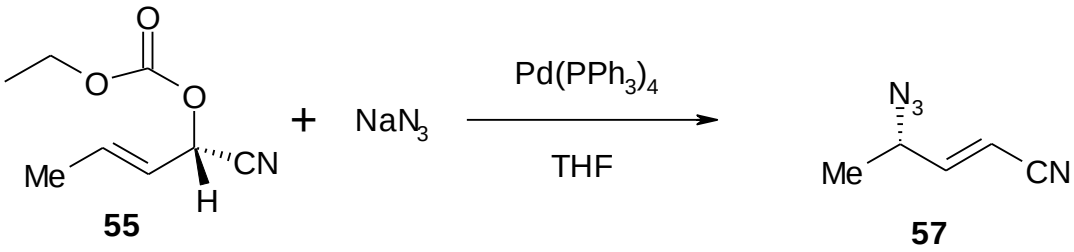
Initially, substrate **55** was used rather than the cinnamaldehyde derived cyanohydrin **54**. This was because the aromatic group adjacent to the double bond

could affect the regiochemistry of the reaction and addition might take place on the original chiral centre. Thus, it was thought that a simpler molecule should be chosen as the starting point for this chemistry. The first nucleophile used was diethyl malonate. This was chosen as it is one of the most widely used nucleophiles with the palladium(tetrakis)triphenylphosphine catalyst.[174] The proposed chemistry is shown in scheme 55.



Scheme 55

Under these conditions however, the reaction did not take place. This was probably because there wasn't a strong enough base present to deprotonate the diethyl malonate to initiate the reaction. This reaction was not carried out with the enolate of the diethyl malonate, as it was feared that the strong base required for this may be strong enough to deprotonate the hydrogen on the chiral centre in the cyanohydrin, racemizing the reactant. Therefore another nucleophile (azide) was chosen instead, as shown in Scheme 56.



93% ee

91% ee

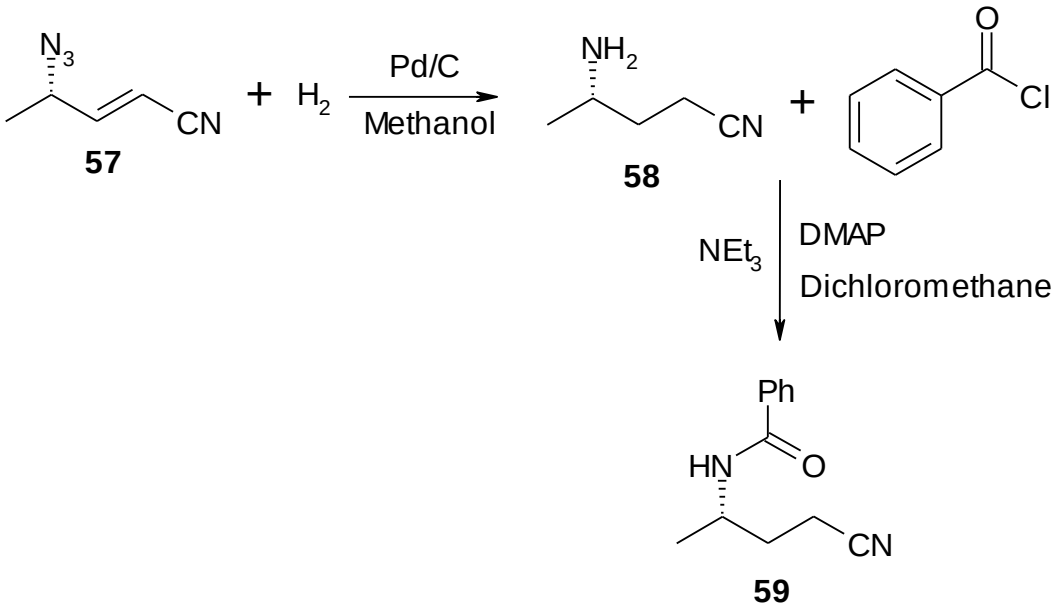
Scheme 56

This reaction occurred smoothly overnight. The chirality of the product was checked by chiral HPLC, and it was shown that the reaction was successfully carried out without a loss of enantiomeric excess. The overall conversion has occurred with retention of configuration, which was as expected. The enantiomeric excess has changed from 93% to 91%, but it is not possible to say that there was a loss in chirality as the HPLC has an error of 2%, so this small difference in values is within the experimental error.

To demonstrate the usefulness of this transformation, compound **57** was reacted further to produce a more versatile group on the chiral centre. Amine **58** is a versatile group, but it has a major set back; this amine decomposes over several hours, before full characterization can be carried out. As the enantiomeric excess of the final product is needed for this project, it had to be converted further into a more stable compound. Amide **59** was chosen, as the benzoyl group acts as a protecting group. It is easily cleaved by acid hydrolysis if the free amine is required. Azide **57** was stirred in an atmospheric pressure hydrogenator with palladium on activated charcoal for 4 days. The crude material was then purified by silica gel chromatography in methanol, and the product was then redissolved in dichloromethane, and immediately reacted with an excess of benzoyl chloride, triethylamine, and a catalytic amount of DMAP at room temperature overnight. The final product was purified again by silica gel chromatography, using chloroform as eluant. The process is summarized in Scheme 57.

Product **59** was analysed by chiral HPLC, and was found to have 80% ee. At this point, a paper was published by Najera,[176] which contained exactly the same chemistry. So although there was scope for more research in this area, such as using the various unsaturated cyanohydrin carbonates that have been

synthesized by the KCN/18-C6 method, this research project was abandoned.



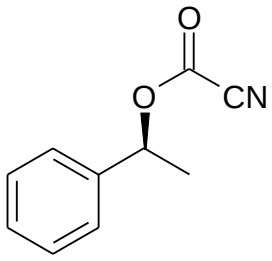
Scheme 57

Chapter 3

Diastereomeric synthesis of cyanohydrin carbonates

Catalyst **10** has been extensively used in the synthesis of chiral products from achiral starting materials. However, its use in conjunction with chiral starting materials has not been investigated. Since the aldehydes that react best in the presence of catalyst **10** are aromatic aldehydes, the chirality was thought to be best placed in the cyanoformate.

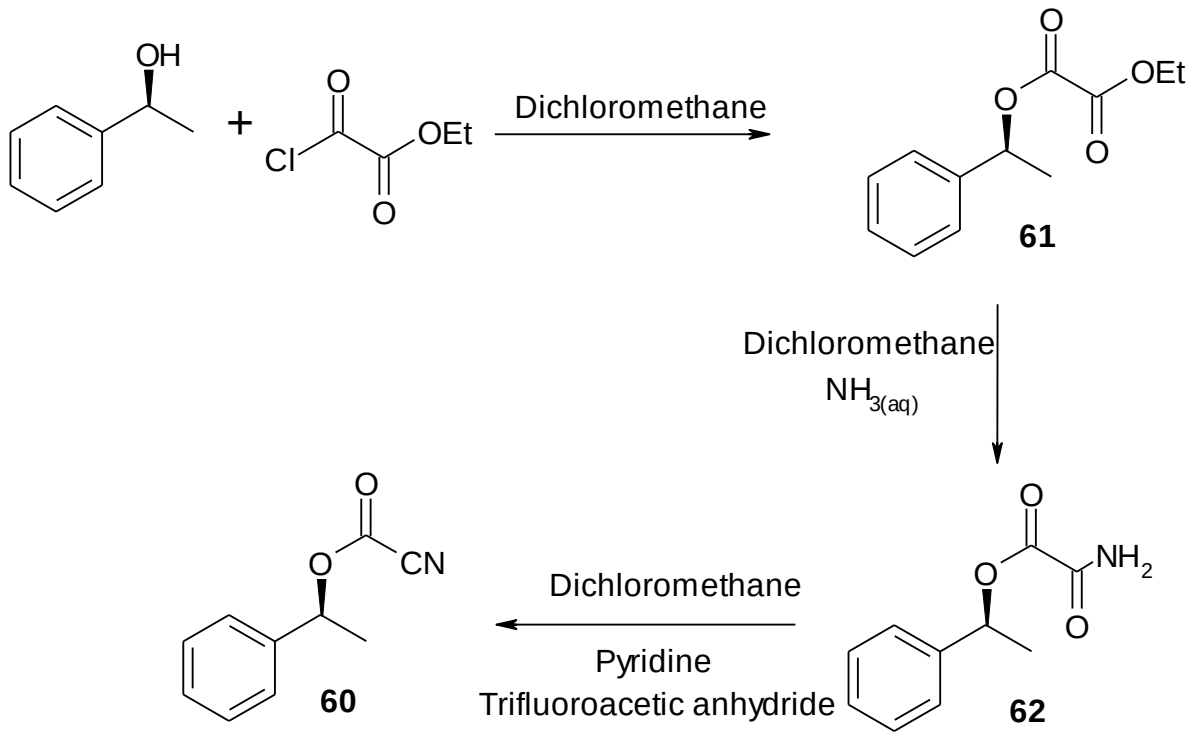
The initial candidate for this chemistry was the 1-phenylethanol derived cyanoformate **60**. This compound was chosen, as it is similar to ethyl cyanoformate which is known to react well with catalyst **10**. It was also known that benzyl cyanoformate reacts in a very similar way to ethyl cyanoformate,[181] and the extra methyl group could make the molecule chiral, without affecting its chemical properties too much. Compound **60** was not commercially available, so the research started with the synthesis of this chiral cyanoformate.



60

Initially, compound **60** was synthesized following a literature procedure for the synthesis of a similar compound,[177] as shown in Scheme 58. 1-Phenylethanol, a commercially available starting material, was reacted with ethyl chloro-oxalate to form ester **61**, which was then reacted with ammonia to form oxamate **62**.

Compound **62** was then dehydrated to give the desired cyanoformate product **60**, as shown in Scheme 58.

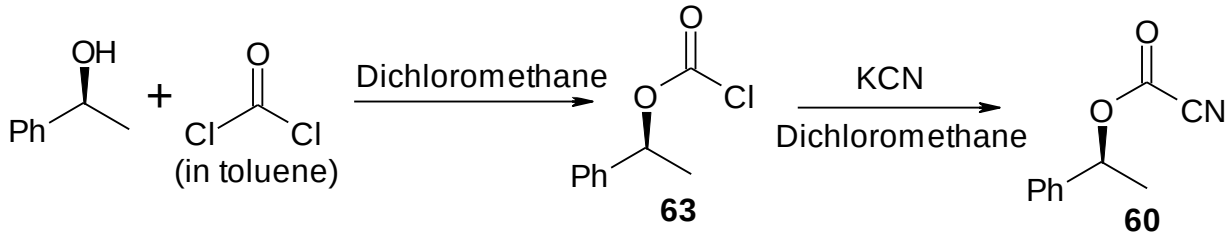


Scheme 58

This synthesis did give the desired product, but it had several flaws. Firstly, the initial reaction was rather temperamental. It is done at room temperature, but on a warm day a lot of the alcohol reacted at both the acid chloride and ester groups of ethyl chloro-oxalate, whilst on a cold day the reaction did not go to completion. The second step was also tricky, as it quite often just regenerated starting alcohol. As fairly large amounts of cyanoformate **60** would be required for this research, a better, more reliable route to this compound was needed.

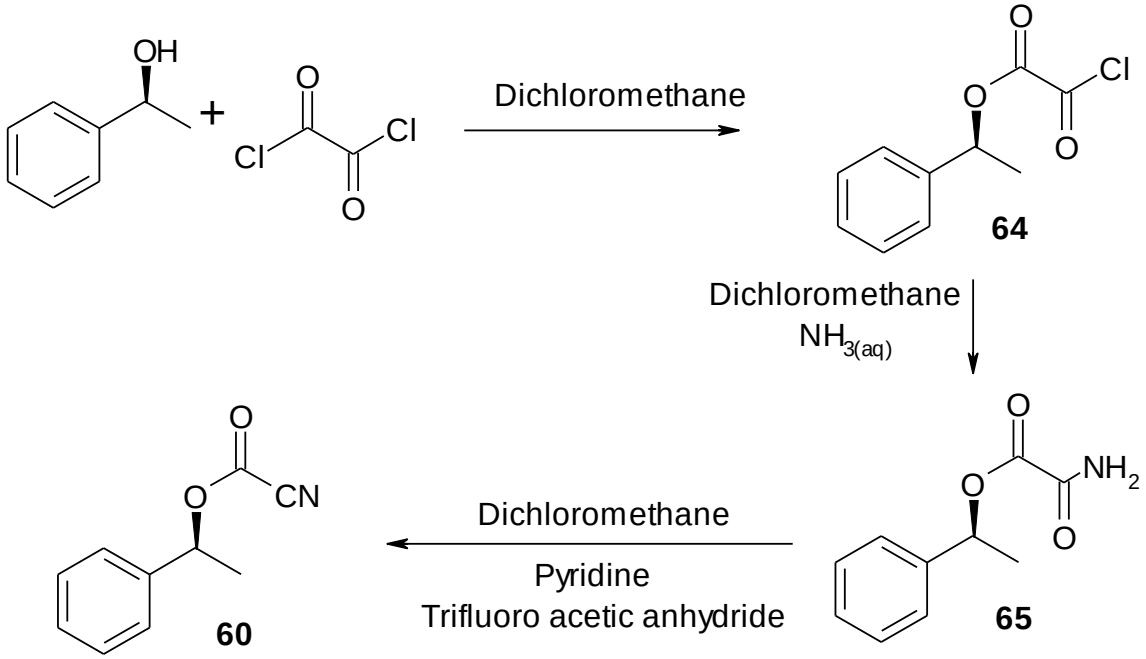
The second route that was investigated was using phosgene in a two step synthesis, as shown in Scheme 59. In the previous synthesis, the main problem was that the ethoxy group was not a good enough leaving group, and ammonia

was attacking the compound unselectively at both carbonyl positions. To prevent this, phosgene, which would leave an acid chloride free for attack, was chosen as the substrate. Also, by changing the nucleophile from ammonia to potassium cyanide, the synthesis required only two steps, which should be more efficient than the previous three step synthesis. There was literature precedent for the preparation of cyanoformates via this route.[178]



Scheme 59

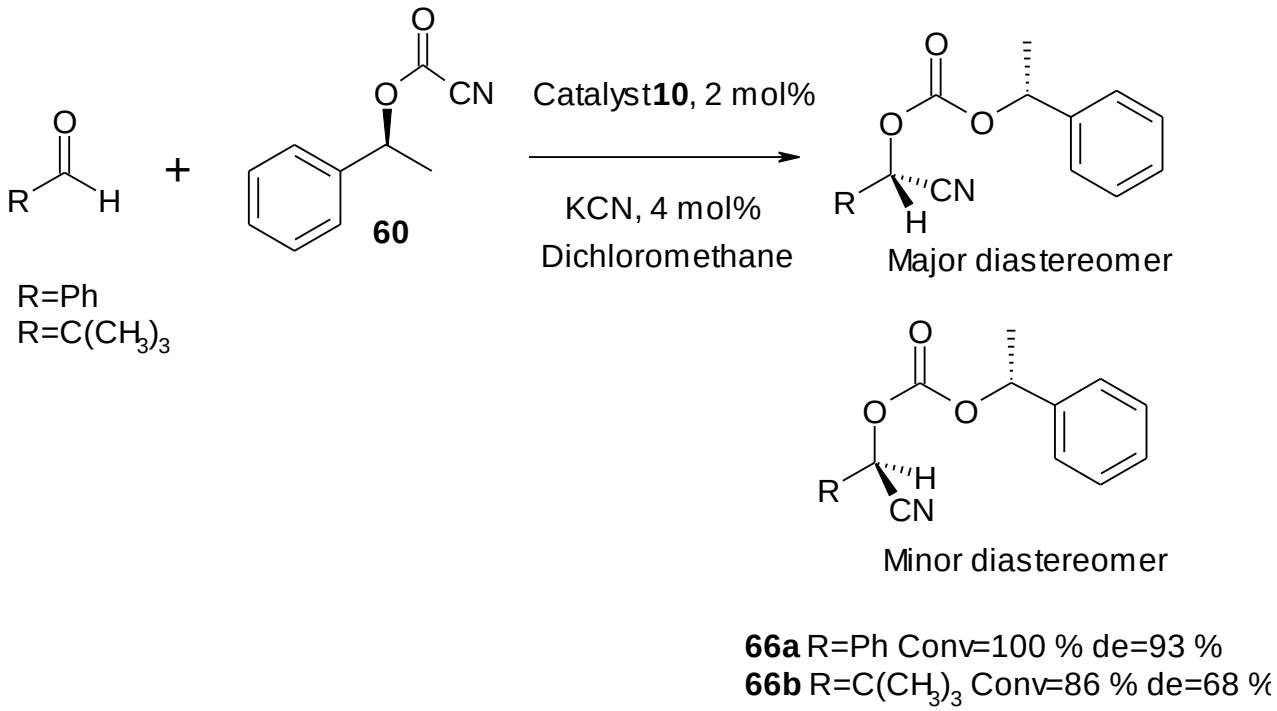
This route did give the desired product **60**, but was still not satisfactory. There are two reasons for this. The first step requires phosgene, which is highly toxic. So, this reaction needs to be done with care, and also the reaction has to be done on a scale that would give the minimum amount of product that is required for safety reasons. However, the second step is a low yielding process. This is not surprising, as potassium cyanide is totally insoluble in dichloromethane, but other polar solvents that would dissolve the potassium cyanide are more likely to react with the acid chloride. Furthermore, the acid chloride intermediate **63** eliminates carbon dioxide and gives 1-chlorophenylethane on standing, so the two steps have to be done consecutively. Rather than repeating the reaction many times to produce enough material for the research, it was felt that investigating a third method would be quicker and easier.



Scheme 60

The third route (Scheme 60) is actually a modification of the first route. By using oxalyl chloride rather than ethyl chloro-oxalate, the reaction is a lot more vigorous. This means the reaction has to be cooled down, but because the temperature is now fixed, the reaction is under more control. The second step is higher yielding, as the chloride is far more reactive than the ester, so the ammonia selectively reacts at the desired site of compound **64**, forming almost exclusively the desired product, oxamide **65**. Subsequent dehydration of oxamide **65** to cyanoformate **60** was straight forward using trifluoroacetic anhydride as dehydrating agent.

Once a route to cyanoformate **60** had been established, the cyanoformate was reacted with two aldehydes in the presence of catalyst **10**, as shown in Scheme 61. Benzaldehyde and trimethylacetaldehyde were chosen for this study, as they were thought to be good representatives of aromatic and aliphatic substrates.



Scheme 61

This reaction was carried out with the (*R,R*) and (*S,S*) versions of catalyst **10**. When the reaction was carried out using benzaldehyde, both the (*R,R*) and the (*S,S*) catalyst showed as good an activity as each other. However when trimethylacetaldehyde was used as substrate, the (*S,S*) catalyst did not give as good a yield or an enantiomeric excess as the (*R,R*) catalyst. The results of this study are summarized in Table 20.

Table 20: Diastereoselective synthesis using cyanoformate **60**

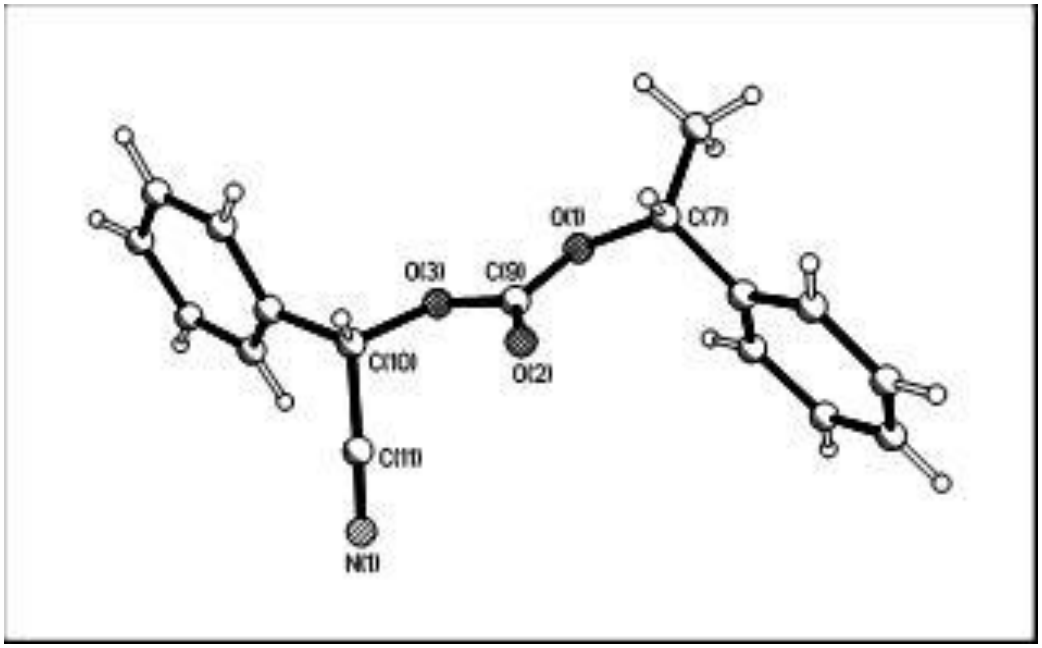
Aldehyde	Catalyst	Conversion / %	Diastereomeric excess / %
Benzaldehyde	(R,R)	100	93
Trimethylacetaldehyde	(R,R)	88	68
Benzaldehyde	(S,S)	100	89
Trimethylacetaldehyde	(S,S)	68	57

To determine the relative stereochemistry of the products of this reaction, the two products **66a** and **66b** derived from the (*R,R*)-catalyst were crystallized from dichloromethane and analysed by X-ray crystallography. Ortep diagrams of the resulting X-ray structures are shown in Figures 13 and 14. Although this only gives the relative configurations of the two compounds, compounds **66a** and **66b** were synthesized from a cyanoformate with a known configuration, as it was derived from an enantiomerically pure, commercially available starting material. Thus by determining the relative configuration, it is possible to deduce the absolute configuration as well.

An NMR study showed that the major diastereomer obtained using the (*R,R*)-catalyst is the minor diastereomer when the opposite enantiomer of the catalyst is used. Now the absolute configuration of the major diastereomer obtained from the (*R,R*)-catalyst has been established, the major diastereomer from the (*S,S*)-catalyst can be deduced. The absolute configuration of the newly

formed chiral centre of products **66** was found to be the same as that formed by the catalysts if achiral cyanoformates were used. This means that the stereochemistry of the products is primarily dependent on the chirality of the catalyst, rather than on the chirality of the cyanoformate used. This is important, as it shows tha, a predictable chirality can be induced in the product, regardless of the structure and stereochemistry of the cyanoformate.

Following the success obtained with cyanoformate **60**, several other cyanoformates were prepared. A slight modification has been made in each of the reaction pathways, since as the alcohols became bulkier, the yield dropped if the method used for phenylethanol derived cyanoformate **60** was employed



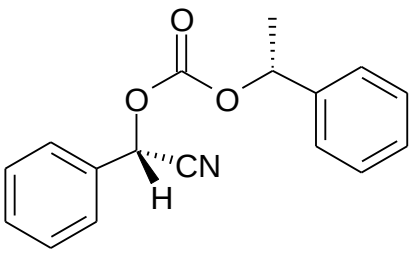
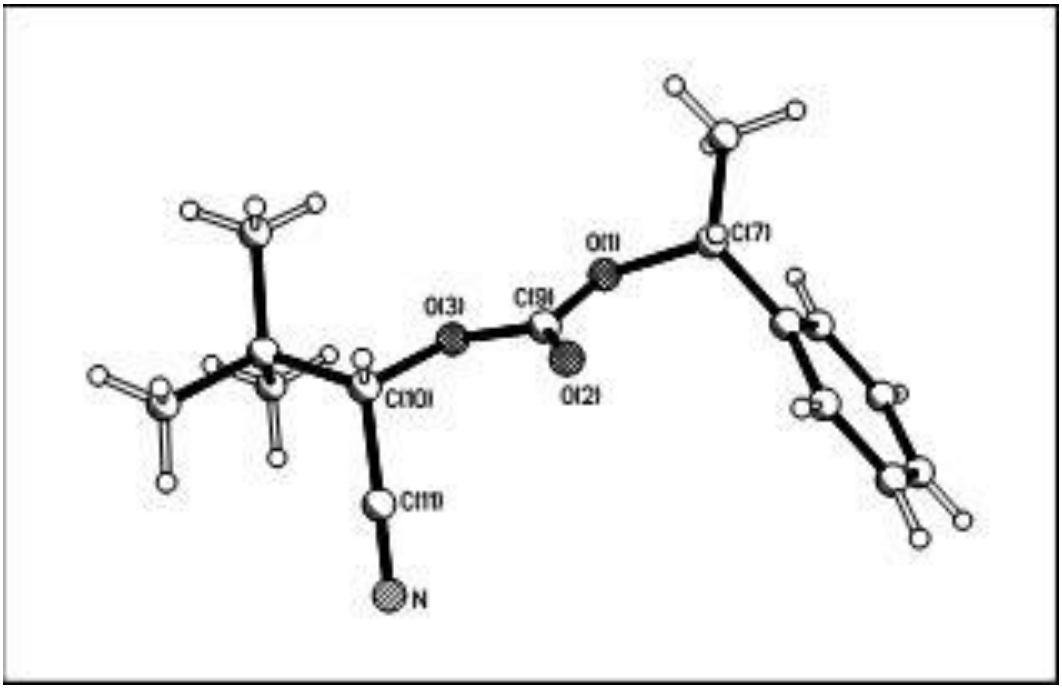


Figure 13: The major product of benzaldehyde and phenylethanol cyanoformate



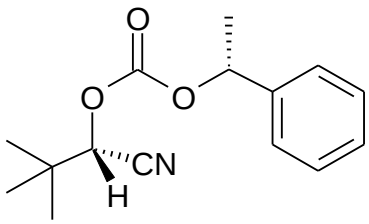
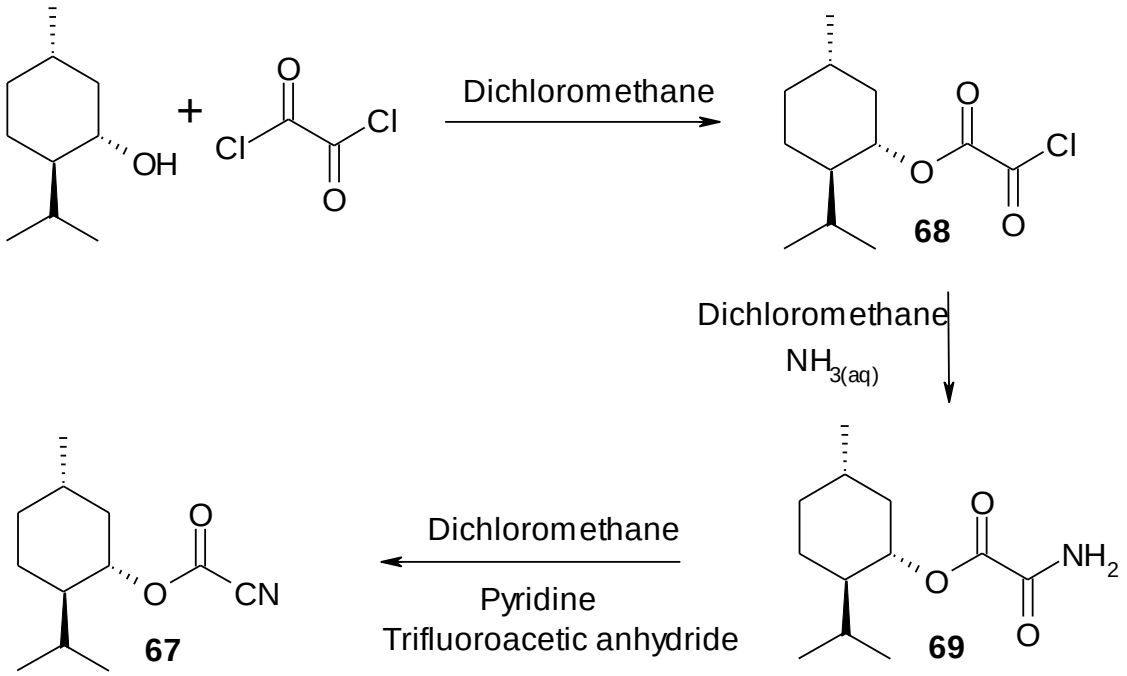


Figure 14: The major product of trimethylacetaldehyde and phenylethanol cyanoformate

First, menthol derived cyanoformate **67** was prepared, as shown in Scheme 62. With this compound, the only modification was that the amount of ammonia solution used in the second step was reduced to 1.2 equivalents. Cyanoformate **67** was then formed as easily as the phenylethanol cyanoformate **60**.

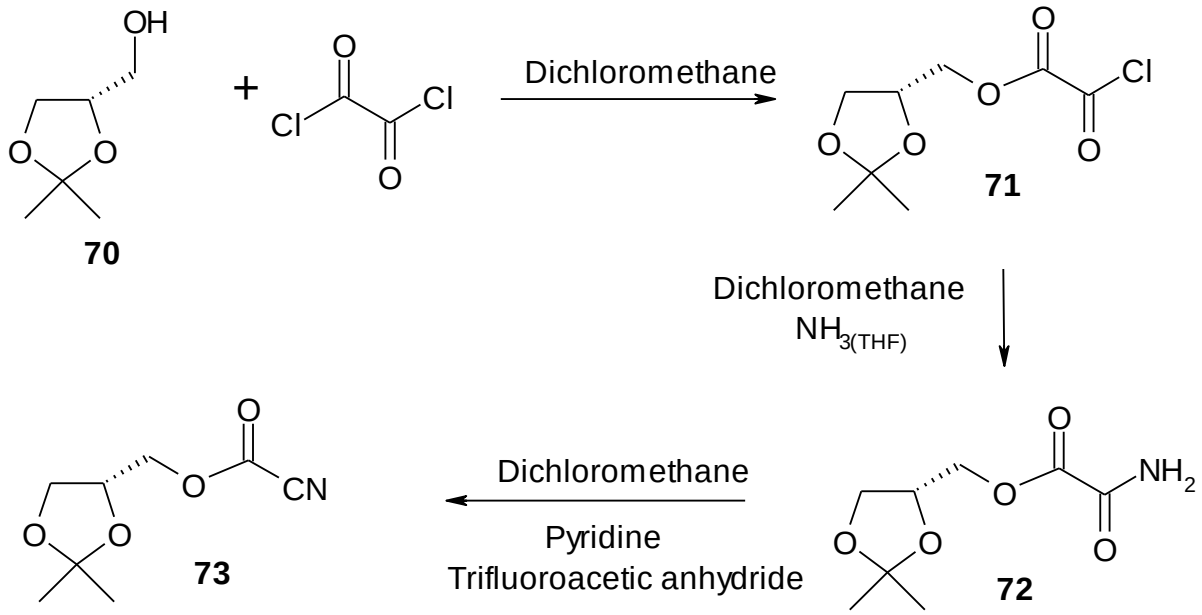


Scheme 62

Cyanoformate **67** was stirred in dichloromethane with catalyst **10**, benzaldehyde and potassium cyanide, but no reaction took place, even when the reaction was stirred for up to 2 weeks in dichloromethane at room temperature. This is believed to be because of the steric bulk of the cyanoformate, which prevented this molecule from reacting with the aldehyde when it is bound to the catalyst.

Subsequently, cyanoformate **73** was prepared from alcohol **70** as shown in Scheme 63. This cyanoformate was one of the hardest to synthesize. There were two problems; oxamate **72** is so soluble in water that if aqueous ammonia was used, then the product could never be recovered from the aqueous layer. To overcome this problem, a saturated solution of ammonia in tetrahydrofuran was used instead, and the solvent was removed *in vacuo* instead of the workup used for the other two compounds. The second problem was that cyanoformate **73** was

unstable in acid, so the product could not be washed with dilute hydrochloric acid to remove the pyridine residue. Copper(II) sulfate solution was used instead to remove the pyridine, but the wash had to be repeated many times to remove all the pyridine.

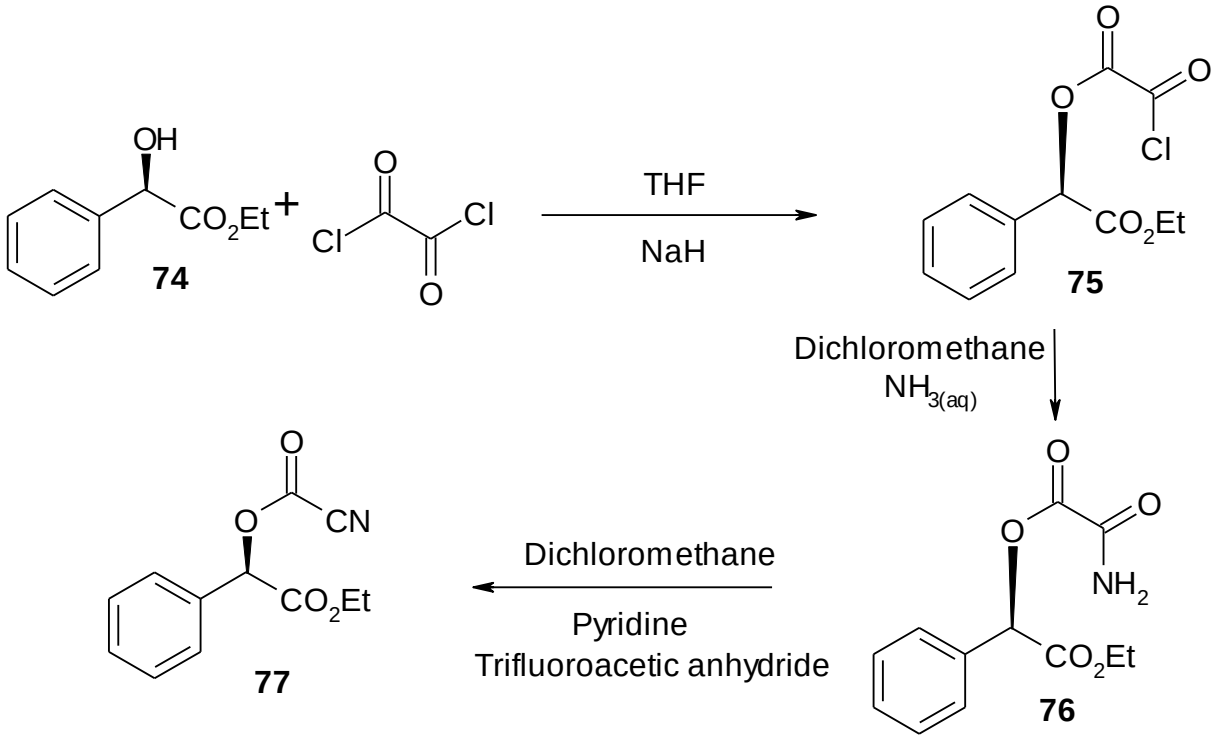


Scheme 63

After all these synthetic problems that had to be overcome, it was very disappointing that cyanoformate **73** did not react with either benzaldehyde or trimethylacetaldehyde, when stirred in dichloromethane at room temperature for up to 3 weeks. This came as a surprise, as this compound is far less sterically hindered compared to menthyl cyanoformate **67**. It is possible that the oxygens in this cyanoformate somehow bind to the catalyst, thus preventing the aldehyde from coordinating to the catalyst, but there is no evidence to support this.

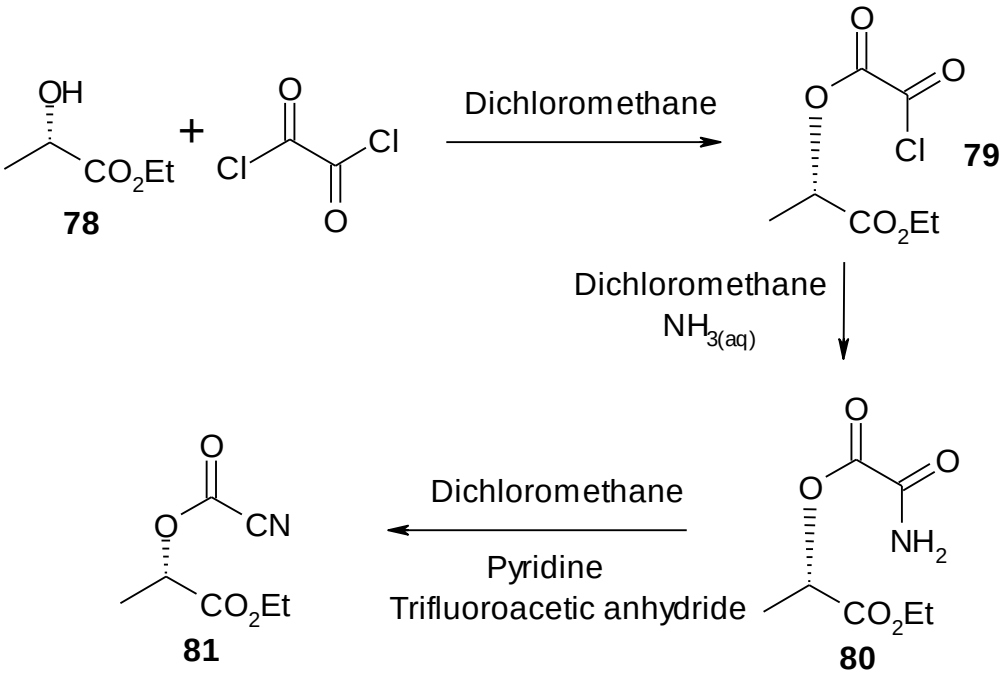
Next, ethyl mandelate derived cyanoformate **77** was prepared, as shown in Scheme 64. In this system, modification was required in the first step. Without the presence of sodium hydride, oxalyl chloride would not react with ethyl

mandelate. This is probably because steric effects prevent the oxygen from being sufficiently nucleophilic. For the reaction to be compatible with sodium hydride, the solvent was also changed from dichloromethane to tetrahydrofuran.



Scheme 64

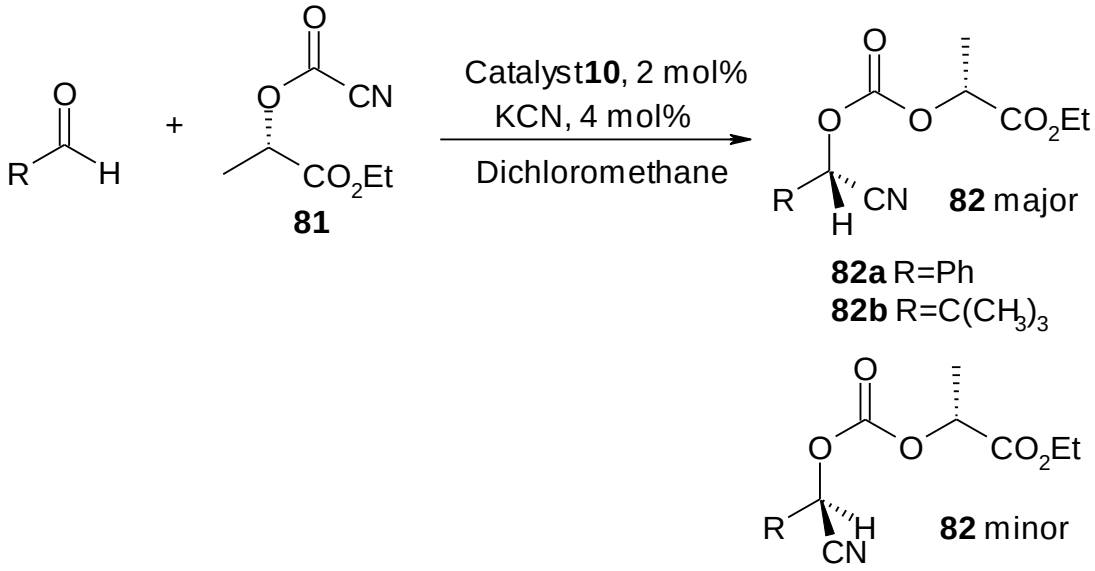
Considering that the reactivity of the chiral alcohol was so low, it was not too surprising that the corresponding cyanoformate **77** was totally unreactive when subjected to the standard reaction conditions. Having both the phenyl group and ethyl ester seems to inhibit the reactivity of cyanoformate **77**, so finally a species without the phenyl group was investigated, as shown in Scheme 65.



Scheme 65

The reaction between ethyl lactate and oxalyl chloride went a lot more smoothly than the other chiral alcohols. The synthesis proceeded smoothly, except for the amide forming step. In the case of phenylethanol, the amount of aqueous ammonia was not important, and a large excess could be used. Compound **80** was rather more delicate, and when an excess of ammonia was used, it regenerated ethyl lactate. The reaction went smoothly though, when the amount of ammonia was reduced to 1.2 equivalents.

Now that the steric bulk has been significantly reduced, cyanoformate **81** reacted smoothly with both benzaldehyde and trimethylacetaldehyde, as shown in Scheme 66. The results of this study are summarized in Table 21.



Scheme 66

Table 21: Reaction of cyanoformate **81** with aldehydes

Aldehyde	Catalyst	Conversion / %	de / %
Benzaldehyde	(R,R)	32	85
Trimethylacetaldehyde	(R,R)	28	83
Benzaldehyde	(S,S)	54	80
Trimethylacetaldehyde	(S,S)	46	86

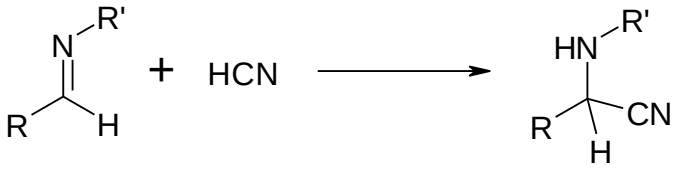
As Table 21 shows, both enantiomers of the catalysts react equally well with this substrate. Although X-ray crystallography could not be carried out as these products were all oils, it is probably safe to assume that the chirality is determined solely by the catalyst used, rather than the chirality of the cyanoformate given the similarities in the structure of the molecules.

What these results have shown is that catalyst **10** is a useful and predictable catalyst for the synthesis of large as well as small molecules, and its use can be extended to the synthesis of molecules which need a specific stereochemistry of the product, such as in the synthesis of natural products or drugs.

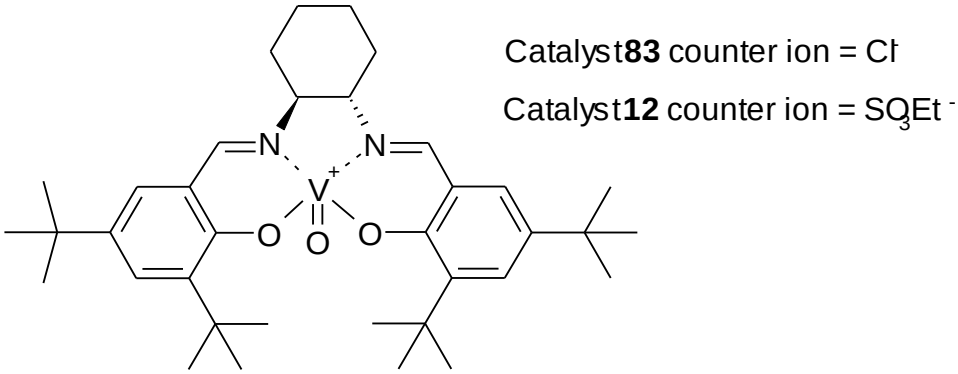
Chapter 4

The Strecker reaction

Another reaction our group has been interested in is the Strecker reaction. This reaction, in general, is the addition of hydrogen cyanide to an imine as shown in Scheme 67. Although this reaction is similar to the addition of cyanide to aldehydes, catalyst **10** is known to be inactive for asymmetric Strecker reactions. Catalyst **83** or catalyst **12**, both vanadium(V) complexes, are however useful for this reaction.

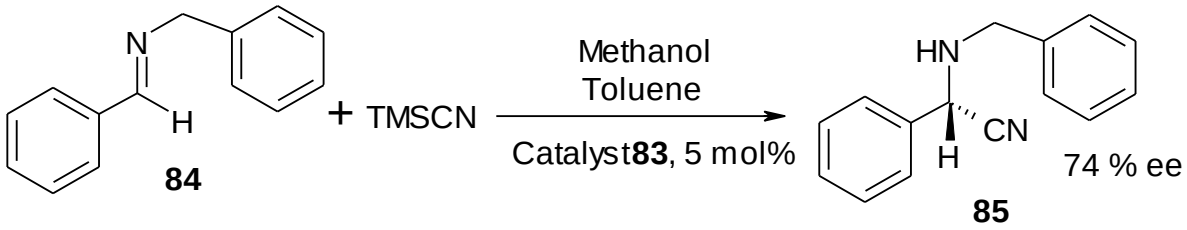


Scheme 67



At the start of my research in this area, catalyst **12** was the only catalyst used for the Strecker reaction. Unfortunately the synthesis of catalyst **12** is rather inefficient, as a lot of the corresponding vanadium(IV) complex **11** is also produced. Vanadium(IV) complexes are totally inactive in these reactions, and a new method of preparing the catalyst was sought for. Just after I started my research on the Strecker reaction, the synthesis of catalyst **83** by oxidation of a mixture of complex

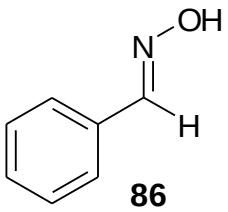
12 and the corresponding vanadium(IV) complex using cerium ammonium nitrate followed by treatment with hydrochloric acid was developed to avoid the problems associated with vanadium(IV) complexes. Catalyst **83** reacts slightly more quickly than catalyst **12**, but both the enantiomeric excess and the reaction time are similar. The best reaction conditions which had been developed are shown in Scheme 68.

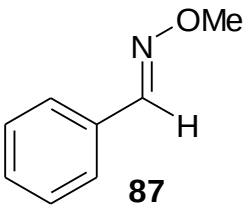


Scheme 68

Although trimethylsilyl cyanide is used, it is believed that the actual cyanating agent is hydrogen cyanide. This is produced *in situ* by the reaction of trimethylsilyl cyanide with methanol. For this reason, the reaction mixture is left to stir for one hour before the imine is added to the reaction.

The research into the Strecker reaction started with trying to find an alternative substrate for the vanadium catalyst. Two substrates **86** and **87** were prepared as a starting point.

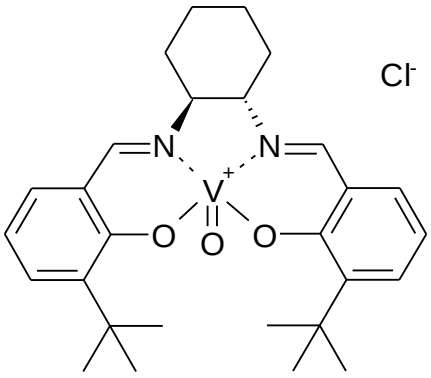




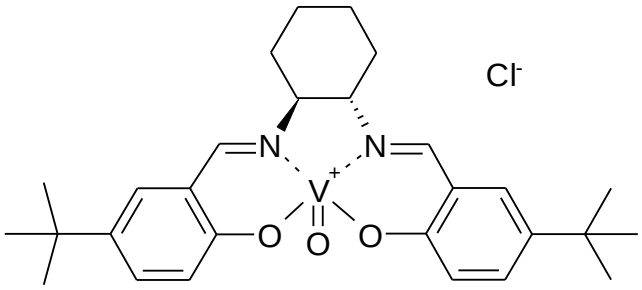
These two compounds were used under the standard reaction conditions instead of α-benzylidene benzylamine. However, these two compounds were

totally inactive under these conditions. The reason for this is not clear, but it is suspected that the catalyst does not bind to these two substrates in the usual manner. The vanadium catalyst binds to the imine through the nitrogen atom, but in this case, the oxygen on the substrate is more nucleophilic than the nitrogen, and that is probably where the substrates are bound to the catalyst. This form of binding is too far away from where the reaction should be taking place, so the reaction does not happen.

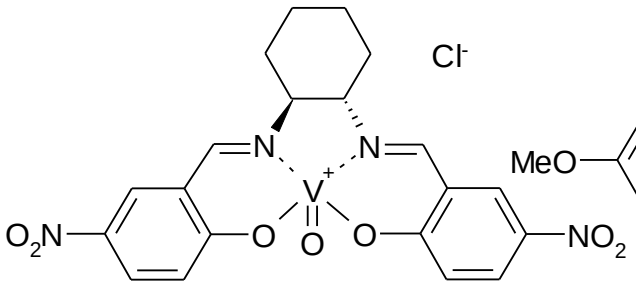
While this investigation was progressing, the catalyst for the reaction was also investigated. Several complexes with minor differences to catalyst **83** were prepared by a colleague.[183]



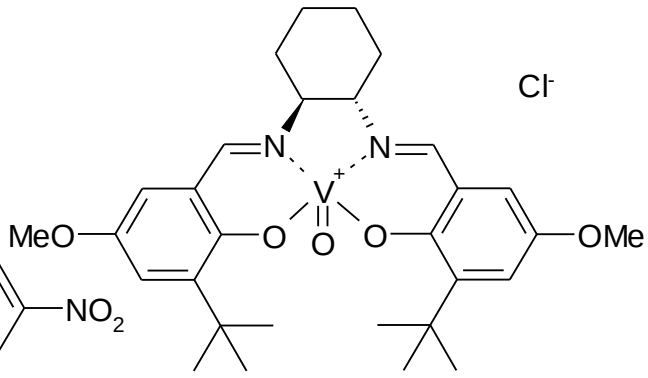
Catalyst**88**



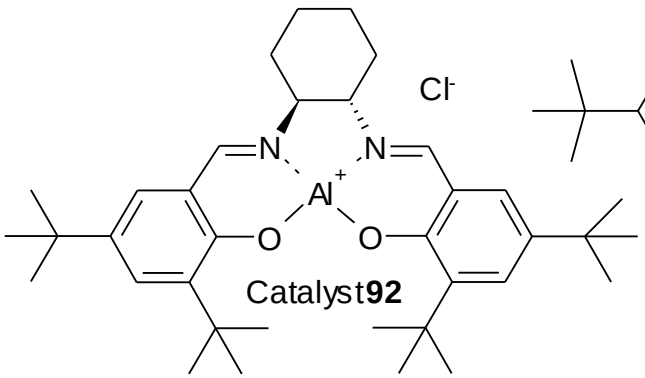
Catalyst **89**



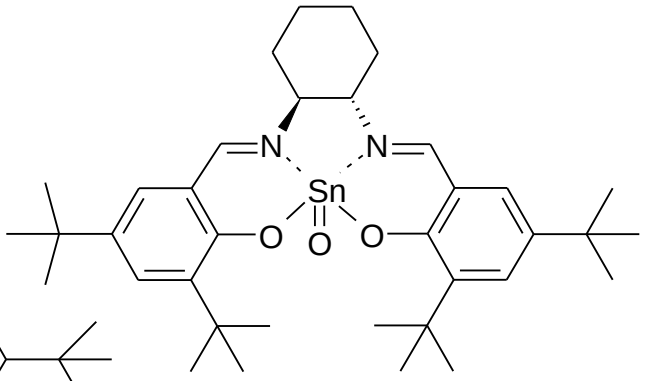
Catalyst**90**



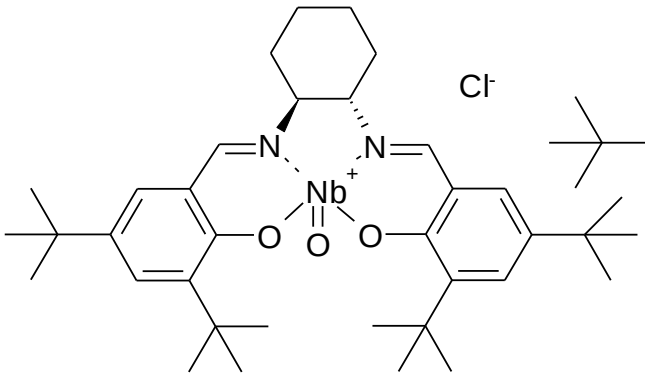
Catalyst**91**



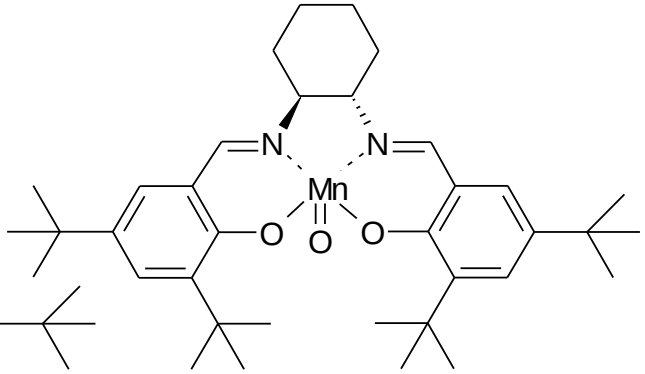
Catalyst**92**



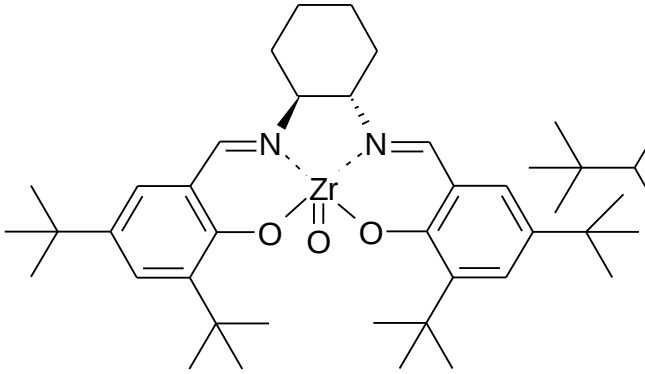
Catalyst**93**



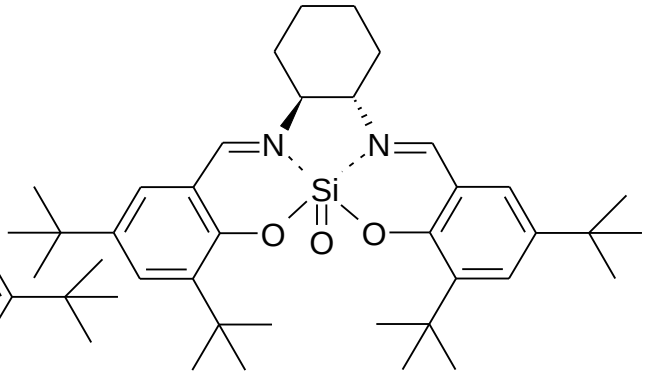
Catalyst**94**



Catalyst**95**

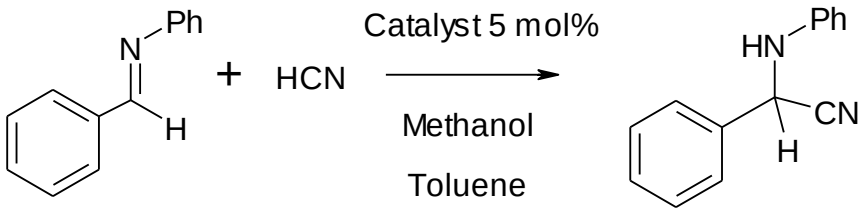


Catalyst**96**



Catalyst**97**

Catalysts **88-97** were used in the Strecker reaction under the standard conditions as shown in Scheme 69. The results are summarized in Table 22. As Table 22 shows, none of these catalysts could improve on the enantiomeric excess obtained by using catalyst **83**.



Scheme 69

Table 22: Products obtained in Strecker reactions using various catalysts

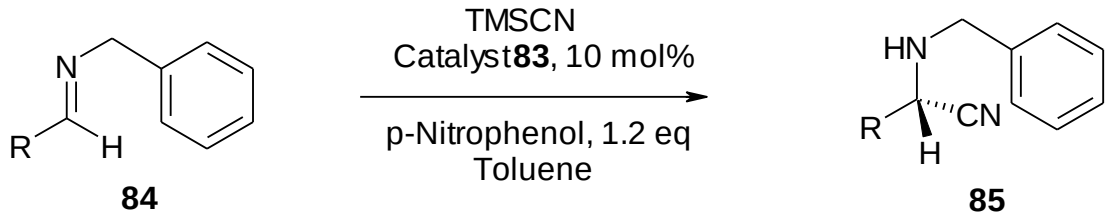
Catalyst	Conversion / %	Enantiomeric Excess / %
88	97	56
89	100	67
90	0	N/A
91	100	55
92	82	0
93	0	N/A
94	84	3
95	100	2
96	74	4
97	86	2

At this point, a report was published showing that addition of phenols to Strecker reactions, catalysed by a different catalyst, enhanced the enantioselectivity.[182] Therefore, the effect of adding a phenol to Strecker reactions of imine **84** catalysed by complex **83** was investigated. A series of alcohols and phenols were used, and added to the reaction instead of methanol, and the

enantiomeric excess of product **85** was determined. As Table 23 shows, a remarkably high enantiomeric excess was observed using p-nitrophenol and p-methoxyphenol. It was a surprise that both of these phenols gave a higher enantiomeric excess compared to phenol itself, as the two substituents have a completely opposite electronic effect; one is electron donating, whilst the other is strongly electron withdrawing. As such a high enantiomeric excess has never been observed in the Strecker reaction catalysed by complex **83**, this was a major breakthrough.

Table 23: Addition of various alcohols to the Strecker reaction using catalyst **83**

Additive	Conversion / %	Enantiomeric excess / %
Phenol	100	79
p-Nitrophenol	100	98
p-Methoxyphenol	100	92
o-tert-Butylphenol	100	88
2,3-Dimethyl-1,3-diphenol	100	89
Salicylaldehyde	100	87
3,5-Di tert-butyl 2-hydroxy benzaldehyd	62	53
Di-tert-butyl ligand x	100	76
Ethanol	100	75
tert-Butanol	100	74
Ethanoic acid	92	98
Trifluoroacetic acid	0	N/A



84 **85**

Scheme 69

This new route was used with a series of substrates (Scheme 69) to confirm that this is a general improvement to the previous method and the results are

shown in Table 24. These reactions were repeated twice each, and average values have been recorded. The results are remarkable; with most substrates the new method gives significantly higher enantiomeric excesses, with just the one exception, which had an unusually high ee with the older method. This is the point that the project had reached at the end of my research.

Table 24: Strecker reaction with p-nitrophenol and catalyst **83**

R	With PNP		With methanol	
	Conversion / %	Enantiomeric excess / %	Conversion / %	Enantiomeric excess /%
Ph	100	98	100	74
2-MePh	85	65	95	30
4-MePh	79	93	98	81
3-MeOPh	70	78	29	96
4-MeOPh	19	2	23	1
4-ClPh	37	80	51	45

Chapter 5

Conclusions

In the course of my research, several things have been successfully achieved. Two previously known reactions, the addition of ethyl cyanoformate to aldehydes and the Strecker reaction were studied and new variations of them have been discovered. The ethyl cyanoformate reaction especially was significantly improved, with the amount of catalyst minimised. Although with the Strecker reaction, an insight to how this reaction could be improved was obtained, it was unfortunate that the new method was not reliable, and I did not have time to find out why this was the case. I would have liked to spend more time on this reaction, and produce a reliable, reproducible method. The use of catalyst **10** has also been developed and used with chiral cyanoformates, to create a variety of diastereomeric cyanohydrin derivatives, giving an even wider scope for the use of catalyst **10**. What this reaction showed was that regardless of the chirality of the reagents, the newly formed chirality of the cyanoformate depends solely on the nature of the catalyst used. As both *S* and *R* catalysts are readily available, this means that a whole range of diastereomeric cyanohydrins can be synthesized using catalyst **10**, which gives even broader possibilities for the use of this catalyst, especially in drug and natural product synthesis.

Experimental

General Methods

^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance 300 or 360 spectrometers, (^{1}H 300 / 360 MHz, ^{13}C 75 / 90 MHz). The solvent for a particular spectrum is given in parentheses. Spectra were referenced to TMS and chemical-shift (δ) values, expressed in parts per million (ppm), are reported downfield of TMS. The multiplicity of signals is reported as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br) or a combination of any of these. For ^{13}C NMR spectra, the peak assignments were made with the assistance of DEPT experiments.

Infrared spectra were recorded on a Perkin-Elmer FT-IR Paragon 1000 spectrometer, as a thin film between NaCl plates or on the pure solid using ATR. The characteristic absorption is reported as broad (br), strong (s), medium (m) or weak (w). Low and high resolution mass spectra were recorded at the EPSRC national service at the University of Wales, Swansea, or on a Bruker Apex III FTMS or Jeol AX505W spectrometer within the chemistry department at King's College. The sample was ionized by electron ionization (EI), chemical ionization (CI), fast atom bombardment (FAB) or electrospray ionization (ESI). The major fragment ions are reported and only the molecular ions are assigned.

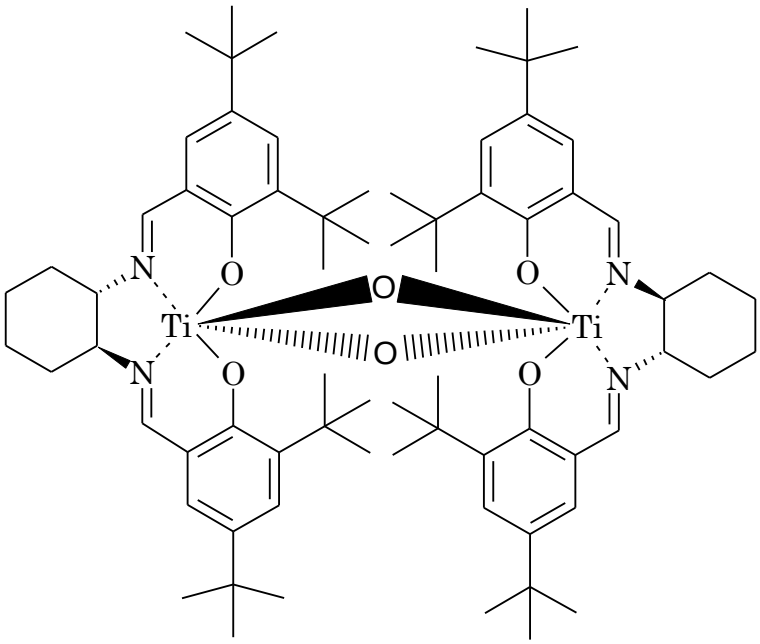
Optical rotations were recorded on a Perkin-Elmer 343 polarimeter or a Polaar 2001 Optical Activity automatic polarimeter in a thermostated cell of length 1 dm at 20 °C using the sodium D-line, and a suitable solvent that is reported along with the concentration (in g / 100 ml). Melting points are

uncorrected and were recorded on a Barnstead Electrothermal 9100 melting point apparatus.

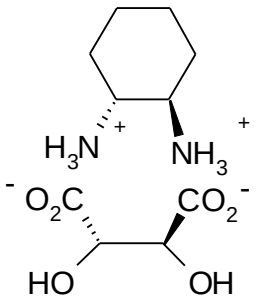
Chromatographic separations were performed with silica gel 60 (230-400 mesh) and thin–layer chromatography was performed on polyester backed sheets coated with silica gel 60 F254, both supplied by Merck. Chiral GC was carried out on a Hewlett Packard 5890 gas chromatograph fitted with a thermal conductivity detector, using a γ-CD butyryl, fused silica capillary column (30m x 0.25 mm) and hydrogen as the carrier gas.

Experimental details

Synthesis of Catalyst **10**



Synthesis of (1*R*,2*R*)-(-)-1,2-Diaminocyclohexane L-tartrate[187]

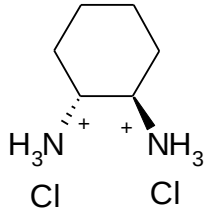


(L)-Tartaric acid (150 g, 1.0 mol) was added to water (400 ml). The mixture was stirred until complete dissolution occurred, and diaminocyclohexane (233 ml, 2.0 mol) was added dropwise at 65 °C. The reaction mixture was allowed to cool to room temperature over 2 hours, then left at 0 °C for a further 20 hours. The crude product was filtered, washed with water (2 × 100 ml) and methanol (2 × 100 ml). A second crop of product was obtained by acidification of the filtrate with glacial

acetic acid (100 ml, 1.75 mol), followed by cooling to 0 °C. The solid was filtered and washed with water (2 × 100 ml) and methanol (2 × 100 ml). The two crops were combined and recrystallized from water (2 l) to give the pure (1*R*,2*R*)-(-)-1,2-diaminocyclohexane L-tartrate (264 g, 41%) as a white solid. $[\alpha]^{D}_{20}$ (H_2O) = +12.4° (c=0.10g / 100ml), Lit[187]=+12.5

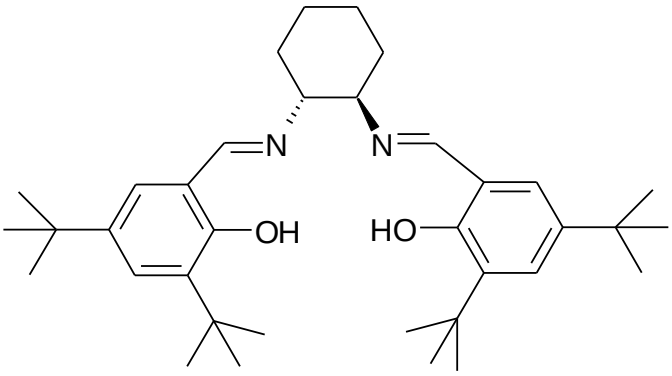
Route 1

Synthesis of (1*R*,2*R*)-(-)-1,2-Diaminocyclohexane dihydrochloride[183]



A cold solution of acetyl chloride (8.94 ml, 0.14 mol) in methanol (25 ml) was added to a suspension of (1*R*,2*R*)-(-)-1,2-diaminocyclohexane L-tartrate (5.0 g, 0.019 mol) in methanol (25 ml), and stirred for 48 hours. The precipitate was filtered and washed with a very small amount of diethyl ether. The filtrate was diluted with diethyl ether (150 ml) and cooled to 0 °C. The resulting precipitate was filtered to give the pure (1*R*,2*R*)-(-)-1,2-diaminocyclohexane dihydrochloride (3.54 g, 90%) as a white solid.

Synthesis of the ligand[183]



A solution of sodium methoxide (1.7 g, 32.0 mmol) and (1*R*,2*R*)-(-)-1,2-diaminocyclohexane dihydrochloride (3.0 g, 16.0 mmol) in methanol (200 ml) was added to a solution of 2-hydroxy-3,5-di-tert-butylbenzaldehyde (7.5 g, 0.032 mol) in methanol (300 ml). The reaction was heated under reflux for 150 minutes. The solvent was removed *in vacuo* and the residue redissolved in CH_2Cl_2. The solid residue was filtered off, and the solution was washed with water (2 × 100 ml) and brine (100 ml). The solution was dried ($MgSO_4$), and the solvent was removed *in vacuo* to yield the pure ligand ((-)-(*R,R*)-*N,N'*-bis(3,5-di-*tert*-butyl)salicylidene-1,2-cyclohexanediamine) (8.75 g, 96%) as a yellow solid. $\delta_H(CDCl_3)$ 13.74 (2H, s, OH), 8.33 (2H, s, N=CH), 7.31 (2H, d, J=2.1 Hz, ArH), 7.02 (2H, d, J=2.1Hz, ArH), 3.7-3.3 (2H, m, NCH), 2.0-1.3 (8H, m, $(CH_2)_4$), 1.45 (18H, s, ^{t}Bu), 1.25 (18H, s, ^{t}Bu).

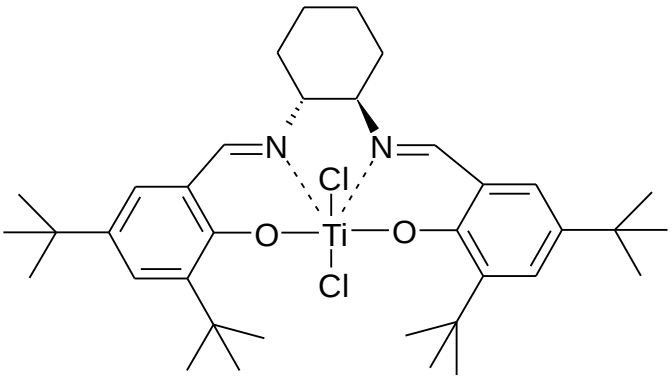
Route 2

Synthesis of the ligand directly from the tartrate salt[188]

To a stirred suspension of 2,4-di-*tert*-butyl phenol (4.12 g, 20 mmol) and anhydrous $MgCl_2$ (3.81 g, 40 mmol) in dry THF (80 ml) was added dropwise dry triethylamine (5.58 ml, 40 mmol). The solution was then heated at gentle reflux

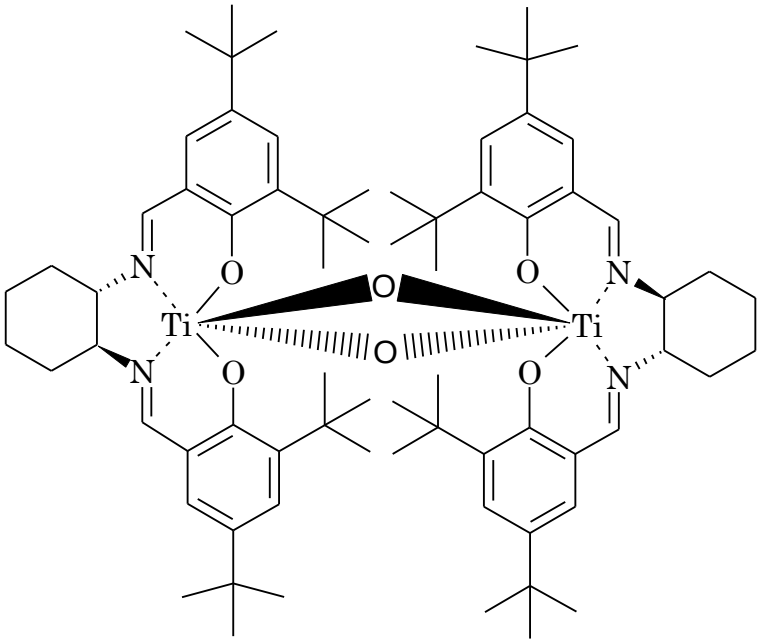
for 2 hours. A solution of the tartrate salt (2.65 g, 10 mmol) and K_2CO_3 (3.12 g, 22.5 mmol) in a 1:1 mixture of ethanol and water (30 ml) was added dropwise at room temperature. The reaction mixture was heated under reflux for 4 hours. The solution was cooled, and water was added to the reaction mixture. The product was extracted with CH_2Cl_2 (3 x 100 ml), and the combined organic layers were washed with water (100 ml) and brine (2 x 100 ml). The organic layer was then dried ($MgSO_4$), and the solvent was removed *in vacuo* to leave the crude product which was recrystallized from acetone to give the pure ligand (5.03 g, 92%) as a yellow solid.

Synthesis of the titanium dichloride complex[107] **9**



A 1M solution of $TiCl_4$ (11 ml, 0.011 mol) was diluted with CH_2Cl_2 (50 ml). A solution of the ligand (6.0 g, 0.011 mol) was added dropwise to the titanium chloride solution. The reaction mixture was stirred for 3 hours and the solvent was removed *in vacuo* to give the product (5.51 g, 75% yield) as a brown powder. $\delta_H(CDCl_3)$ 8.31 (2H, s, N=CH), 7.62 (2H, s, ArH), 7.35 (2H, s, ArH), 4.1-4.0 (2H, m, NCH), 2.6-2.5 (4H, m, $(CH_2)_2$), 2.1-2.0 (4H, m, $(CH_2)_2$), 1.47 (18H, s, ^{t}Bu), 1.35 (18H, s, ^{t}Bu).

Synthesis of catalyst **10**[107]



A buffer solution was prepared by dissolving $Na_2HPO_4.7H_2O$ (14.18 g) and $NaH_2PO_4.2H_2O$ (4.89 g) in water (800 ml). A solution of the titanium dichloride complex (2.00 g, 0.0030 mol) in CH_2Cl_2 (150 ml) was added to the buffer solution (200 ml) and the reaction was stirred for 2 hours. The buffer solution was decanted, fresh buffer (200 ml) added and the reaction mixture was stirred for 20 minutes. The buffer solution was changed again, and stirred for a further 10 minutes. The organic layer was separated, washed with water (150 ml) and dried ($MgSO_4$). The solvent was removed *in vacuo* to leave the pure catalyst (1.09 g, 60%). $\delta_H(CDCl_3)$ 11.57 (s), 8.53 (s), 8.33 (s), 8.11 (s), 8.11 (s), 7.74 (s), 7.52 (s), 7.52 (s), 7.49 (s), 7.41 (s), 7.41 (s), 7.28 (s), 7.21 (s), 7.25 (s), 7.25 (s), 7.19 (s), 7.07 (s), 7.07 (s), 6.97 (s), 6.96 (s), 4.09 (t, J=9 Hz), 2.65-2.62 (m), 2.34-2.32 (m), 2.10-2.07 (m), 1.79 (d, J=10.8 Hz), 1.61 (br) 1.57 (br), 1.52 (br), 1.49 (s), 1.41 (s), 1.36 (s), 1.31 (s), 1.28 (s), 1.26 (s), 1.26 (s), 1.23 (s), 1.20 (s) 1.20 (s) 1.19 (s) 1.17 (s) 1.16 (s) 1.09 (s) Exists as a mixture of monomer and dimer in solution.[179]

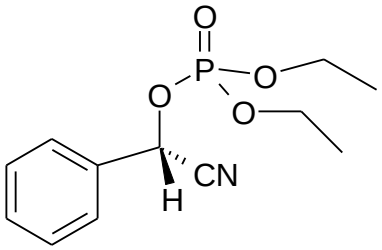
General method for the synthesis of racemic cyanophosphonates,[189] Scheme 27

A solution of n-butyl lithium (0.12 ml of 2.5M solution in tetrahydrofuran, 0.3 mmol) was added dropwise to a stirred solution of diisopropylamine (0.04 ml, 0.3 mmol) in dry tetrahydrofuran (4 ml) at -10 °C. The reaction mixture was left to stir for 20 minutes. Aldehyde (3.0 mmol) dissolved in tetrahydrofuran (4 ml) was added, and the reaction was stirred for a further 20 minutes. Diethyl cyanophosphonate (0.50 ml, 3.3 mmol) was added dropwise, and after 10 minutes the reaction was allowed to reach room temperature, then left to stir for one hour. To this, a small amount of water was added and the solution concentrated *in vacuo*, then dissolved in CH_2Cl_2 (50 ml). The organic layer was washed with water (3 × 10 ml) then solvent was removed *in vacuo*. The crude material was purified by chromatography through a plug of silica eluting with CH_2Cl_2 (400 ml) followed by ethyl acetate (200 ml). NMR data is not shown here, as all these compounds had identical NMR to the chirally synthesized cyanohydrin phosphonates listed below.

General method for the synthesis of chiral cyanophosphonates, Scheme 27

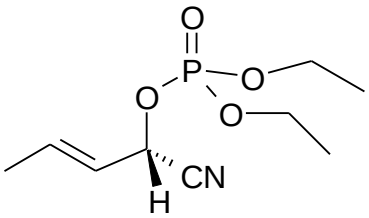
Aldehyde (2.0 mmol) was added to a stirred mixture of catalyst **10** (2 mg, 0.02 mmol) and potassium cyanide (1 mg, approx 0.002 mmol) in CH_2Cl_2 (5 ml). Diethyl cyanophosphonate (0.30 ml, 0.02 mmol) was added, and the solution was left for 20 hours, then the solvent was removed *in vacuo*. The crude material was purified by passing through a plug of silica eluting with CH_2Cl_2 (400 ml) followed by ethyl acetate (200 ml).

Benzaldehyde cyanohydrin-O-phosphonate[185] **37a**



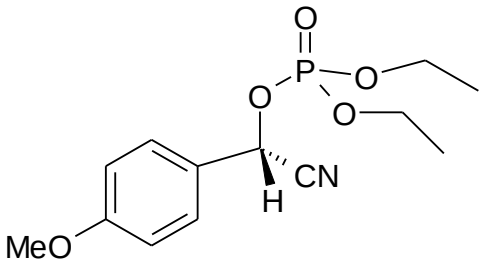
Obtained as a yellow oil in 98% yield. $\delta_H(CDCl_3)$ 7.64-7.28 (5H, m, ArH), 6.08 (1H, d, J=6 Hz, C<u>H</u>CN), 4.30-4.18 (2H, m, POC<u>H</u>$_2$CH$_3$), 4.09-3.98 (2H, m, POC<u>H</u>$_2$CH$_3$), 1.40 (3H, t, J=6 Hz, POCH$_2$C<u>H</u>$_3$) 1.29 (3H, t, J=6 Hz, POCH$_2$C<u>H</u>$_3$); $\delta_C(CDCl_3)$ 132.81, 130.98, 129.66, 127.92, 116.57, 66.94, 65.24, 65.10, 16.44, 16.27; ν_{max}(neat) 2986 m (CH), 2360 w (CN), 1269 m (P=O) and 1024 cm^{-1} s (C-O); $[\alpha]_D^{20}$ -0.85 (c 0.1, $CHCl_3$); m/z(EI) 269 (M^+); Found(ESI) 292.07026; $C_{12}H_{16}NO_4PNa$ ($M+Na^+$) requires 292.07092.

Crotonaldehyde cyanohydrin-O-phosphonate[185] **37b**



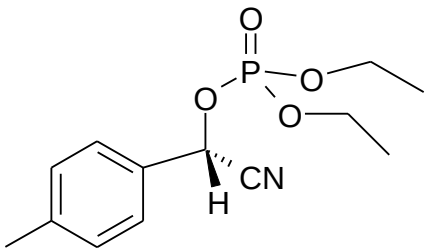
Obtained as a yellow oil in 63% yield. $\delta_H(CDCl_3)$ 6.15-6.06 (1H, m, C<u>H</u>CN), 5.5-5.6 (1H, m, CH$_3$C<u>H</u>=CHCH), 5.3-5.4 (1H, m, CH$_3$CH=C<u>H</u>), 4.23-4.00 (4H, m, POC<u>H</u>$_2$CH$_3$), 1.75 (3H, d, J=7 Hz, C<u>H</u>$_3$CH), 1.33-1.27 (6H, m, POCH$_2$C<u>H</u>$_3$); $\delta_C(CDCl_3)$ 136.0, 122.8, 116.1, 65.4, 65.3, 65.2, 18.0, 16.4, 16.3; ν_{max}(neat) 2986 s (CH), 2333 w (CN), 1262 m (P=O) and 1030 cm^{-1} s (C-O).

p-Methoxybenzaldehyde cyanohydrin-O-phosphonate[185] **37c**



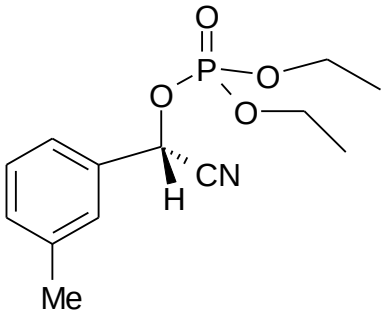
Obtained as a yellow oil in 22% yield. $\delta_H(CDCl_3)$ 7.44-7.40 (2H, m, ArH), 6.95-6.88 (2H, m, ArH), 5.93 (1H, d, J=8.6 Hz, C<u>H</u>CN), 4.19-3.88 (4H, m, POC<u>H</u>$_2$CH$_3$), 3.77 (3H, s, OCH$_3$), 1.32 (3H, t, J=7 Hz, POCH$_2$C<u>H</u>$_3$), 1.16 (3H, t, J=7 Hz, POCH$_2$C<u>H</u>$_3$); $\delta_C(CDCl_3)$ 132.5, 129.8, 128.6, 114.9, 114.6, 66.8, 65.3, 64.2, 63.5, 16.5, 16.4; ν_{max}(neat) 2984 m (C-H), 2293 w (CN), 1254 m (P=O) and 1027 cm^{-1} s (C-O); m/z(EI) 299 (M^+); Found(ESI) 298.11847; $C_{13}H_{17}NO_5P$ ($M\text{-}H^-$) requires 298.08498.

4-Methylbenzaldehyde cyanohydrin-O-phosphonate[190] **37d**



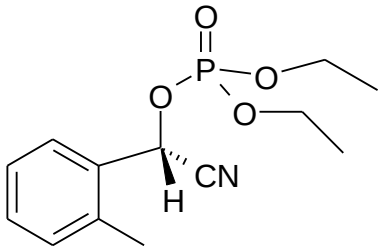
Obtained as a yellow oil in 71% yield. $\delta_H(CDCl_3)$ 7.37 (2H, d, J=8 Hz, ArH), 7.20 (2H, d, J=8 Hz, ArH), 5.93 (1H, d, J=8 Hz, C<u>H</u>CN), 4.10-3.89 (4H, m, POC<u>H</u>$_2$CH$_3$), 2.32 (3H, s, CH$_3$Ar), 1.32 (3H, t, J=7 Hz, POCH$_2$C<u>H</u>$_3$), 1.18 (3H, t, J=7 Hz, POCH$_2$C<u>H</u>$_3$); $\delta_C(CDCl_3)$ 141.24, 130.26, 129.96, 127.93, 116.68, 66.83, 65.23, 65.16, 21.66, 16.52, 16.40; ν_{max}(neat) 2986 m (C-H), 1269 s (P=O) and 1028 cm^{-1} s (C-O); m/z(EI) 283 (M^+); Found(ESI) 306.15429; $C_{13}H_{18}NO_4PNa$ ($M+Na^+$) requires 306.08657.

3-Methylbenzaldehyde cyanohydrin-O-phosphonate **37e**



Obtained as a yellow oil in 78% yield. $\delta_H(CDCl_3)$ 7.43-7.28 (4H, m, ArH), 6.02 (1H, d, J=8.8 Hz, CHCN), 4.26-4,12 (2H, m, POC$\underline{H}_2CH_3$), 4.00-3.98 (2H, m, POC$\underline{H}_2CH_3$), 2.41 (3H, s, CH_3Ar), 1.41 (3H, t, J=8 Hz, $POCH_2C\underline{H}_3$), 1.25 (3H, t, J=8 Hz, $POCH_2C\underline{H}_3$); $\delta_C(CDCl_3)$ 140.24, 130.46, 129.92, 127.96, 126.95, 115.68, 115.61, 66.82, 65.22, 65.21, 21.46, 16.22, 16.20; ν_{max}(neat) 2987 m (C-H), 2360 w (CN), 1269 s (P=O) and 1026 cm^{-1} s (C-O); m/z(EI) 283 (M^+); Found(ESI) 306.15422; $C_{13}H_{18}NO_4PNa$ ($M+Na^+$) requires 306.08657.

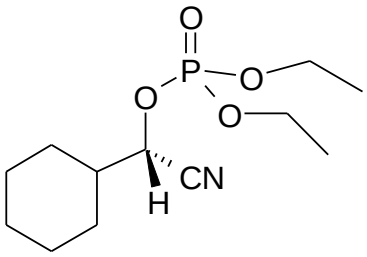
2-Methylbenzaldehyde cyanohydrin-O-phosphonate[191] **37f**



Obtained as a yellow oil, in 57% yield. $\delta_H(CDCl_3)$ 7.82 (1H, d, J=9 Hz, ArH), 7.64-7.26 (3H, m, ArH), 6.16 (1H, d, J=9 Hz, CHCN), 4.28-3.99 (4H, m, POC$\underline{H}_2CH_3$), 2.51 (3H, s, C$\underline{H}_3$Ar), 1.41 (3H, t, J=10 Hz, $POCH_2C\underline{H}_3$), 1.25 (3H, t, J=10 Hz, $POCH_2C\underline{H}_3$); $\delta_C(CDCl_3)$ 140.24, 132.42, 130.62, 128.16, 126.95, 115.44, 114.22, 66.62, 65.42, 65.20, 21.41, 16.21, 16.14; ν_{max}(neat) 2986 m (C-H), 2360 w (CN), 1268 s (P=O) and 1030 cm^{-1} s (C-O); m/z(EI) 283 (M^+); Found(ESI)

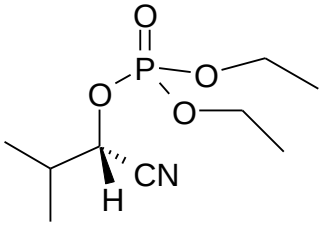
306.15745; $C_{13}H_{18}NO_4PNa$ ($M+Na^+$) requires 306.08657.

Cyclohexanecarboxaldehyde cyanohydrin-O-phosphonate[192] **37g**



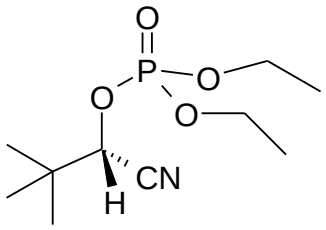
Obtained as a yellow oil in 84% yield. $\delta_H(CDCl_3)$ 4.83-4.79 (1H, dd, J=6, 5 Hz, C<u>H</u>CN), 4.24-4.09 (4H, m, POC<u>H</u>$_2$CH$_3$), 2.05-1.82 (6H, m, $(CH_2)_3$), 1.42-1.32 (6H, m, POCH$_2$C<u>H</u>$_3$), 1.13-1.08 (5H, m, CH$(CH_2)_2$); ν_{max}(neat) 2933 s (C-H), 2360 w (CN), 1271 s (P=O) and 1024 cm^{-1} s (C-O); m/z(CI) 276 (MH^+); Found(ESI) 276.13539; $C_{12}H_{24}NO_4P$ (MH^+) requires 276.13592.

Dimethylacetaldehyde cyanohydrin-O-phosphonate[170,190] **37h**



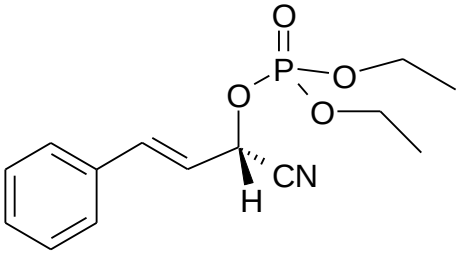
Obtained as a yellow oil in 100% yield. $\delta_H(CDCl_3)$ 4.84-4.80 (1H, dd, J=8, 5 Hz, CHCN), 4.27-4.10 (4H, m, POC<u>H</u>$_2$CH$_3$), 2.23-2.01 (1H, m, C<u>H</u>$(CH_3)_2$), 1.42-1.33 (6H, m, POCH$_2$C<u>H</u>$_3$), 1.13 (6H, t, J=7 Hz, $(CH_3)_2$); ν_{max}(neat) 2976 m (C-H), 2245 w (CN), 1270 s (P=O) and 1018 cm^{-1} s (C-O); m/z(CI) 236 (MH^+); Found(ESI) 236.10407; $C_9H_{19}NO_4P$ (MH^+) requires 236.10462.

Trimethylacetaldehyde cyanohydrin-O-phosphonate[185] **37i**



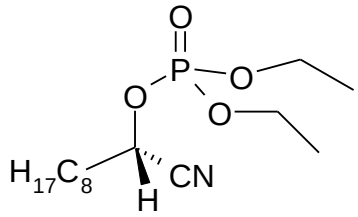
Obtained as a yellow oil in 99% yield. $\delta_H(CDCl_3)$ 4.65 (1H, d, J=8 Hz, CHCN), 4.24-4.17 (4H, m, POC<u>H</u>$_2$CH$_3$), 1.41-1.36 (6H, m, POCH$_2$C<u>H</u>$_3$), 1.11 (9H, s, (CH$_3$)$_3$C); ν_{max}(neat) 2981 m (C-H), 2360 br w (CN), 1267 m (P=O) and 1026 cm^{-1} m (C-O); m/z(CI) 250 (MH^+); Found(ESI) 250.08615; $C_{10}H_{21}NO_4P$ (MH^+) requires 250.12027.

Cinnamaldehyde cyanohydrin-O-phosphonate[185] **37j**



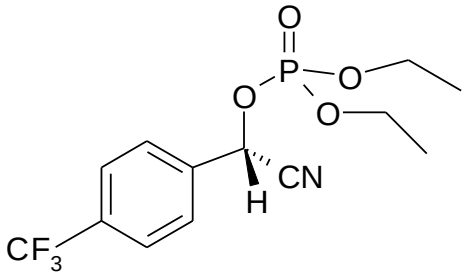
Obtained as a yellow oil in 92% yield. $\delta_H(CDCl_3)$ 7.47-7.34 (5H, m, ArH), 7.98 (1H, d, J=16 Hz, PhC<u>H</u>=CH), 6.26 (1H, dd, J=16, 7 Hz, PhCH=C<u>H</u>), 5.72-5.67 (1H, m, CHCN), 4.28-3.92 (4H, m, POC<u>H</u>$_2$CH$_3$), 1.43-1.23 (6H, m, POCH$_2$C<u>H</u>$_3$); m/z(EI) 295 (M^+); Found(ESI) 318.08657; $C_{14}H_{18}NO_4PNa$ ($M+Na^+$) requires 318.08711.

Nonanal cyanohydrin-O-phosphonate **37k**



Obtained as a yellow oil in 100% yield. $\delta_H(CDCl_3)$ 5.02-4.99 (1H, m, C<u>H</u>CN), 4.24-4.10 (4H, m, POC<u>H</u>$_2$CH$_3$), 2.05-1.82 (2H, m, C<u>H</u>$_2$CHCN), 1.57-1.52 (2H, m, C<u>H</u>$_2$CH$_2$CHCN), 1.48-1.41 (6H, m, POCH$_2$C<u>H</u>$_3$), 0.90-0.71, (15H, m, CH$_3$(CH$_2$)$_6$); $\delta_H(CDCl_3)$ 117.3, 65.2, 65.1, 65.0, 34.6, 32.1, 29.6, 29.4, 29.1, 24.5, 23.0, 16.5, 16.4, 14.4; ν_{max}(neat) 2929 s (C-H), 2312 w (CN), 1271 s (P=O) and 1037 cm^{-1} s (C-O); m/z(CI) 306 (MH^+); Found(ESI) 306.18273; $C_{14}H_{29}NO_4P$ (MH^+) requires 306.18287.

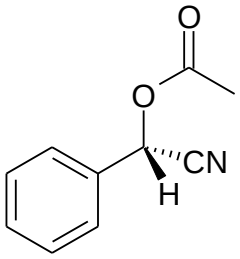
Trifluoromethylbenzaldehyde cyanohydrin-O-phosphonate **37l**



Obtained as a yellow oil in 46% yield. $\delta_H(CDCl_3)$ 7.78-7.55 (4H, m, ArH), 6.06 (1H, d, J=9 Hz, CHCN), 4.20-3.96 (4H, m, POC<u>H</u>$_2$CH$_3$), 1.32 (3H, t, J=7 Hz, POCH$_2$C<u>H</u>$_3$), 1.19 (3H, t, J=7 Hz, POCH$_2$C<u>H</u>$_3$); ν_{max}(neat) 2989 m (C-H), 2360 w (CN), 1269 m (P=O) and 1029 cm^{-1} s (C-O); m/z(EI) 337 (M^+); Found(ESI) 360.05876; $C_{13}H_{15}NO_4F_3PNa$ ($M+Na^+$) requires 360.05885.

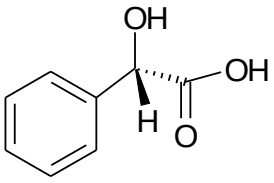
Attempts to determine the enantiomeric excesses of cyanohydrin phosphonates

Transformation into O-acetyl mandelonitrile



A solution of trimethylsilyl bromide (0.22 ml, 1.69 mmol) and benzaldehyde cyanohydrin phosphonate (0.11 g, 0.42 mmol) in dry CH_2Cl_2 (5 ml) was stirred for 20 hours. The solvent was removed *in vacuo*, and the compound was dried under vacuum for 2 hours. The residue was taken up in acetonitrile (2 ml) and scandium tiflate (2.1 mg, 0.42 mmol) and acetic anhydride (0.08 ml, 8.48 mmol) were added. The reaction mixture was stirred for 30 minutes, and the mixture was purified by passing through a plug of silica eluting with CH_2Cl_2. The crude material was analysed by chiral GC without further purification. The product was found to be racemic by chiral GC.

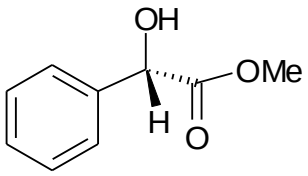
Conversion into mandelic acid



Benzaldehyde cyanohydrin phosphonate (0.160 g, 0.595 mmol) was dissolved in concentrated hydrochloric acid (40 ml) and the reaction mixture was heated under reflux for 16 hours. The solvent was removed *in vacuo* to give mandelic acid which was analysed without purification. This was found to be racemic by ^1H NMR

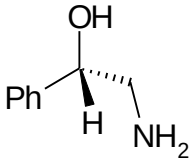
analysis in the presence of the chiral shift reagent, europium tris [3-heptafluoropropylhydroxymethylene-(+)-camphorate]. δ_H(DMSO) 7.48-7.24 (5H, m, ArH) 5.06 (1H, s, PhCH) 2.50 (1H, s, OH).

Conversion into methyl mandelate



Benzaldehyde cyanohydrin phosphonate (0.250 g, 0.929 mmol) was stirred for 72 hours in a saturated solution of acetyl chloride in methanol (10 ml). NMR showed that the desired product was present in the mixture, but this proved impossible to purify, as it decomposed on silica, or on heating.

Conversion to aminomethyl benzyl alcohol



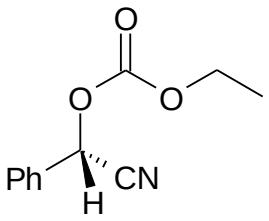
To a stirred solution of phenyl cyanohydrin-O-phosphonate (0.10 g, 0.37 mmol) in dry ether (100 ml), lithium aluminium hydride (0.01 g, 0.37 mmol) was added. The solution was heated under reflux for 16 hours. The solution was cooled to room temperature, and quenched with a small amount of water. The organic layer was separated, the aqueous layer was washed with diethyl ether (10 x 20 ml) and the combined organic layers were dried ($MgSO_4$). The solvent was removed *in vacuo* to leave the crude material. This was then purified by silica gel chromatography using ethyl acetate, followed by a 3:1 mixture of ethyl acetate and ethanol as the

eluent to give the pure product (0.09 g, 18% yield) as a yellow oil. $\delta_H(CDCl_3)$ 7.36-7.26 (5H, m, ArH) 5.18-4.96 (1H, m, PhC<u>H</u>) 2.95-2.65 (2H, m, C<u>H</u>$_2$NH$_2$) 2.58 (2H, br, NH$_2$).

<u>Complexation of KCN and 18-Crown-6, **43**</u>[172]

Potassium cyanide (0.652 g, 0.010 mol) was dissolved in methanol (45 ml). 18-Crown-6 (2.640 g, 0.010 mol) was added, and the solution was stirred at 30 °C for 3 hours. The solvent was removed *in vacuo* to give the pure complex (3.292 g, 100%) as a white crystalline solid.

<u>Attempts to improve the addition of ethyl cyanoformate to benzaldehyde</u>[160]



1. Using triethylamine as a co-catalyst

To a stirred solution of benzaldehyde (0.20 ml, 2.0 mmol) and catalyst **10** (0.11 g, 0.10 mmol) in CH_2Cl_2 (10 ml), ethyl cyanoformate (0.24 ml, 2.4 mmol), then triethylamine (0.029 ml, 0.002 mmol) were added at -40 °C under argon. The reaction mixture was allowed to stir for 3 hours. The reaction was allowed to warm to room temperature, and passed through a plug of silica using CH_2Cl_2 as eluent. The solvent was removed *in vacuo* to leave the product (0.410 g, 100%) as a yellow oil. $\delta_H(CDCl_3)$ 7.60-7.44 (5H, m, ArH), 6.29 (1H, s, CHCN), 4.39-4.23 (2H, m, OC<u>H</u>$_2$CH$_3$), 1.36 (3H, t, J=15 Hz, OCH$_2$C<u>H</u>$_3$); ee = 71% (chiral GC, Supelco Gamma DEX 120 fused silica capillary column (30m x 0.25 mm) with hydrogen as carrier

gas, initial temperature=100°C, ramp rate=0.2°C/min, T_R=121.8min (minor) and 124.2 min (major))

2. Using ammonium cyanide as a co-catalyst

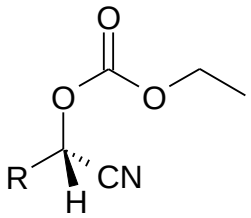
To a stirred solution of benzaldehyde (0.20 ml, 2.0 mmol), ammonium cyanide (0.88 mg, 0.02 mmol) and catalyst **10** (0.11 g, 0.10 mmol) in CH_2Cl_2 (10 ml), ethyl cyanoformate (0.24 ml, 2.4 mmol) was added at -40 °C under argon. The reaction mixture was allowed to stir for 5 hours. The reaction was allowed to warm to room temperature, and passed through a plug of silica using CH_2Cl_2 as eluent. The solvent was removed *in vacuo* to leave the product (0.410 g, 100%) as a yellow oil. $\delta_H(CDCl_3)$ 7.60-7.44 (5H, m, ArH), 6.29 (1H, s, CHCN), 4.39-4.23 (2H, m, $OC\underline{H}_2CH_3$), 1.36 (3H, t, J=15 Hz, $OCH_2C\underline{H}_3$); ee = 0% (chiral GC. Supelco Gamma DEX 120 fused silica capillary column (30m x 0.25 mm) with hydrogen as carrier gas, initial temperature=100°C, ramp rate=0.2°C/min, T_R=121.8min (minor) and 124.2 min (major))

3. Using acetone cyanohydrin as a co-catalyst

To a stirred solution of benzaldehyde (0.20 ml, 2.0 mmol), acetone cyanohydrin (1.82 ml, 2.0 mmol) and catalyst **10** (0.11 g, 0.10 mmol) in CH_2Cl_2 (10 ml), ethyl cyanoformate (0.24 ml, 2.4 mmol) was added at -40 °C under argon. The reaction mixture was allowed to stir for 5 hours. The reaction was allowed to warm to room temperature, and passed through a plug of silica using CH_2Cl_2 as eluent. No product was obtained.

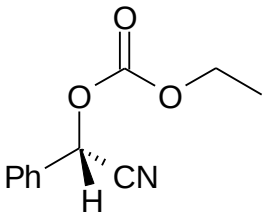
Addition of ethyl cyanoformate via the KCN method

General method



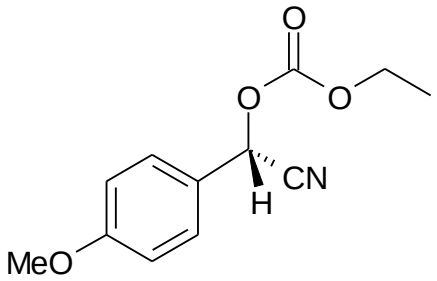
To a stirred solution of aldehyde (2.0 mmol), potassium cyanide (2.9 mg, 0.08 mmol) and catalyst **10** (0.045 g, 0.04 mmol) in CH_2Cl_2 (10 ml), ethyl cyanoformate (0.24 ml, 2.4 mmol) was added at -40 °C under argon. The reaction mixture was allowed to stir for 5 hours. The reaction was allowed to warm to room temperature, and passed through a plug of silica using CH_2Cl_2 as eluent. The solvent was removed *in vacuo* to leave the product as a yellow oil.

1. *O*-Ethoxycarbonyl (*S*)-2-hydroxy-2-phenyl-acetonitrile[160] **37a**



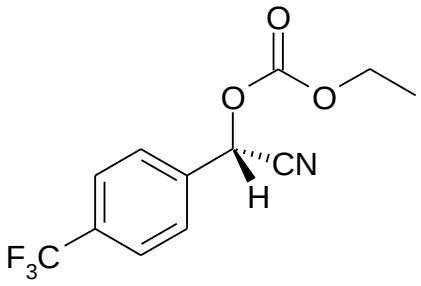
Obtained in quantitative yield and with 95% ee. $\delta_H(CDCl_3)$ 7.60-7.44 (5H, m, ArH), 6.29 (1H, s, CHCN), 4.39-4.23 (2H, m, $OC\underline{H}_2CH_3$), 1.36 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$); $[\alpha]_D^{20}$ -16.5 (c 1.0, $CHCl_3$) [lit.[184] $[\alpha]_D^{20}$ +16.2 (c 2.8, $CHCl_3$) for (*R*)-enantiomer with 94% ee]. Chiral GC conditions: flow rate 1 ml / minute, initial temperature 100 °C, hold at initial temperature for 2 minutes then ramp rate 0.2 °C / minute; t_R=117.2 and 119.5 minutes.

2. *O*-Ethoxycarbonyl (*S*)-2-hydroxy-2-(4-methoxyphenyl)acetonitrile[160] **37c**



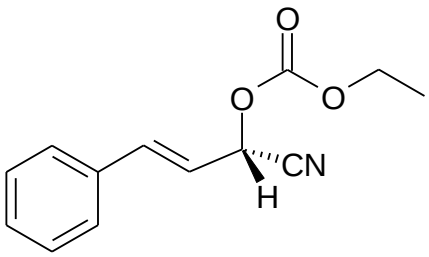
Obtained in 98% yield and with 97% ee. $[\alpha]_D^{20}$ +1.8 (c 1.35, $CHCl_3$) [lit.[184] $]_D^{20}$ +1.8 (c 1.8, $CHCl_3$) for (*S*)-enantiomer with 95% ee]. $\delta_H(CDCl_3)$ 7.51 (2H, d, J=3 Hz, ArH), 7.47 (2H, d, J=3 Hz, ArH), 6.22 (1H, s, CHCN), 4.37-4.21 (2H, m, OCH_2), 1.31 (3H, t, J=5 Hz, $OCH_2C\underline{H}_3$).Chiral GC conditions: flow rate 1 ml / minute, initial temperature 100 ^oC, hold at initial temperature for 2 minutes then ramp rate 0.2 ^oC / minute; t_R = 242.2 and 245.7 minutes.

3. *O*-Ethoxycarbonyl (*S*)-2-hydroxy-2-(4-trifluoromethylphenyl)acetonitrile[160] **37l**



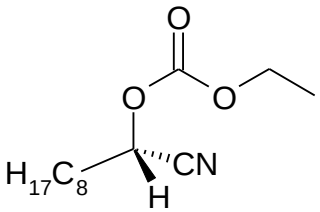
Obtained in quantitative yield and with 69% ee. $[\alpha]_D^{20}$ -9.9 (c 1.4, $CHCl_3$). $\delta_H(CDCl_3)$ 7.66,(2H, d, J=7 Hz, ArH), 7.64 (2H, d, J=7 Hz, ArH), 6.25 (1H, s, CHCN), 4.34-4.16 (2H, m, OCH_2), 1.33 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$). Chiral GC conditions: flow rate 1 ml / minute, initial temperature 100 ^oC, hold at initial temperature for 2 minutes then ramp rate 0.4 ^oC / minute; t_R = 79.4 and 82.6 minutes.

4. *O*-Ethoxycarbonyl (*S*)-2-hydroxy-4-phenyl-but-3-enonitrile[160] **37j**



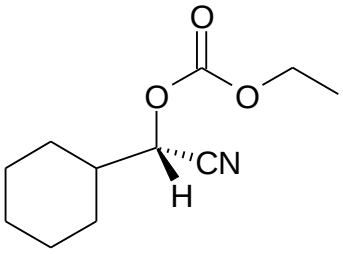
Obtained in 94% yield and with 95% ee. $[\alpha]_D^{20}$ +21.9 (c 1.1, $CHCl_3$) [lit.[160] $[\alpha]_D^{20}$ -23.4 (c 1.9, $CHCl_3$) for (*S*)-enantiomer with 94% ee.] Chiral GC conditions: flow rate 1 ml / minute, initial temperature 100 °C, hold at initial temperature for 2 minutes then ramp rate 0.2 °C / minute; t_R = 250.1 and 254.2 minutes.

5. *O*-Ethoxycarbonyl (*S*)-2-hydroxy-decanonitrile[160] **37k**



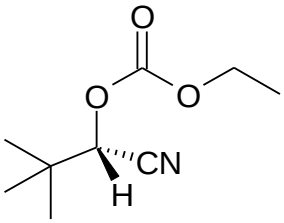
Obtained in 90% yield and with 79% ee. $[\alpha]_D^{20}$ -42.8 (c 1.05 $CHCl_3$). δ_H($CDCl_3$) 5.22 (1H, t, J=6 Hz, CHCN), 4.33-4.23 (2H, m, OCH_2), 1.98-1.91 (2H, m, $C\underline{H}_2CHCN$), 1.61-1.48 (2H, m, $C\underline{H}_2CH_2CHCN$), 1.41 (3H, t, J=3 Hz, $OCH_2C\underline{H}_3$), 1.38-1.33 (10H, m, $Me(CH_2)_5$), 0.88 (3H, t, J=3 Hz, CH_3). Chiral GC conditions: flow rate 1 ml / minute, initial temperature 100 °C, hold at initial temperature for 2 minutes then ramp rate 0.2 °C / minute; t_R = 140.6 and 143.3 minutes.

6. *O*-Ethoxycarbonyl (*S*)-2-hydroxy-2-cyclohexyl-acetonitrile[160] **37g**



Obtained in 86% yield and with 74% ee. $[\alpha]_D^{20}$ -42.1 (c 1.05 $CHCl_3$) [lit. [184] $[\alpha]_D^{20}$ +53.4 (c 2.0, $CHCl_3$) for (*R*)-enantiomer with 96% ee]. $\delta_H(CDCl_3)$ 5.19 (1H, d, J=6 Hz, $C_6H_{11}C\underline{H}CN$), 4.43-4.32 (2H, m, OCH_2), 2.06-1.71 (6H, m, $(CH_2)_3$), 1.57 (3H, t, J=6 Hz, $OCH_2C\underline{H}_3$), 1.47-1.24 (5H, m, CH_2CHCH_2). Chiral GC conditions: flow rate 1 ml / minute, initial temperature 100 °C, hold at initial temperature for 2 minutes then ramp rate 0.2 °C / minute; t_R = 97.8 and 99.1 minutes.

7. *O*-Ethoxycarbonyl (*S*)-2-hydroxy-3,3-dimethyl-butanonitrile[160] **37i**



Obtained in 79% yield and with 68% ee. $[\alpha]_D^{20}$ -68.0 (c 1.35 $CHCl_3$) [lit.[184] $[\alpha]_D^{20}$ +75.6 (c 2.2, $CHCl_3$) for (*R*)-enantiomer with 87% ee]. $\delta_H(CDCl_3)$ 4.90 (1H, s, $(CH_3)_3CC\underline{H}CN$), 4.40-4.20 (2H, m, $OC\underline{H}_2CH_3$), 1.35 (3H, t, J=5.5 Hz, $OCH_2C\underline{H}_3$), 1.12 (9H, s, $(CH_3)_3$). Chiral GC conditions: flow rate 1 ml / minute, initial temperature 50 °C, hold at initial temperature for 2 minutes then ramp rate 0.1 °C / minute; t_R = 150.7 and 157.7 minutes.

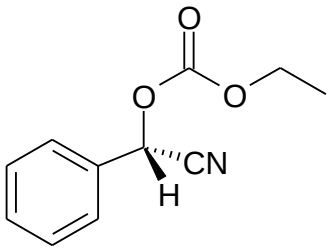
Optimization process for the KCN/18-C-6 route to O-Ethoxycarbonyl (S)-2-hydroxy-2-phenylacetonitrile

To a stirred solution of benzaldehyde (0.2 ml, 2.0 mmol), KCN/18-C-6 complex (0.1-3 mol%) and catalyst **10** (0.1-3 mol%) in CH_2Cl_2 (10 ml), ethyl cyanoformate (0.24 ml, 2.4 mmol) was added at -40 ^oC under argon. The reaction mixture was allowed to stir for 16 hours. The reaction was allowed to warm to room temperature, and passed through a plug of silica using CH_2Cl_2 as eluent. The solvent was removed *in vacuo* to give the product as a yellow oil.

Asymmetric addition of ethyl cyanoformate to aldehydes in the presence of potassium cyanide / 18-crown-6 complex.

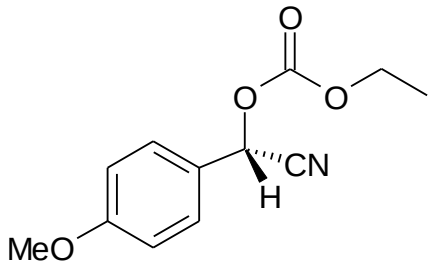
KCN/18-crown-6 complex (6.6 mg, 0.02 mmol) and catalyst **10** (36 mg, 0.03 mmol) were dissolved in CH_2Cl_2 (5 ml). The solution was cooled to -40 ^oC, then aldehyde (2.0 mmol) and ethyl cyanoformate (0.24 ml, 2.4 mmol) were added. The resulting solution was allowed to stir for 24 hours (or 48 hours when specified) at -40 ^oC. The reaction was warmed to room temperature and passed through a plug of silica gel, eluting with CH_2Cl_2. The solvent was removed *in vacuo* to give the product as a yellow oil.

O-Ethoxycarbonyl (*S*)-2-hydroxy-2-phenyl-acetonitrile[160]



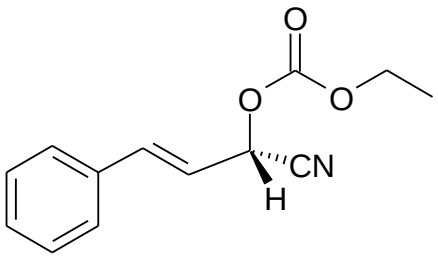
Obtained in quantitative yield and with 88% ee. Analytical data as reported in the previous section.

O-Ethoxycarbonyl (*S*)-2-hydroxy-2-(4-methoxyphenyl)acetonitrile[160]



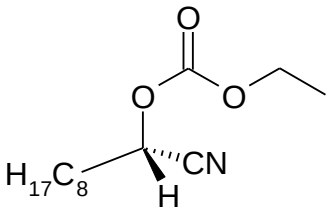
Obtained in quantitative yield and with 90% ee. Analytical data as reported in the previous section

O-Ethoxycarbonyl (*S*)-2-hydroxy-4-phenyl-but-3-enonitrile[160]



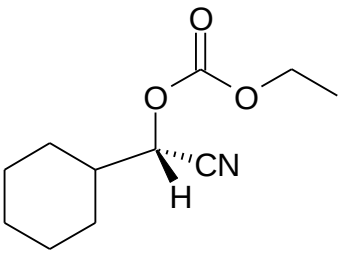
Obtained in quantitative yield and with 90% ee after a reaction time of 48 hours. Analytical data as reported in the previous section.

O-Ethoxycarbonyl (*S*)-2-hydroxy-decanonitrile[160]



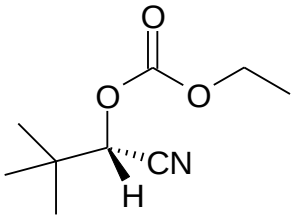
Obtained in 98% yield and with 81% ee. Analytical data as reported in the previous section.

O-Ethoxycarbonyl (*S*)-2-hydroxy-2-cyclohexylacetonitrile[160]



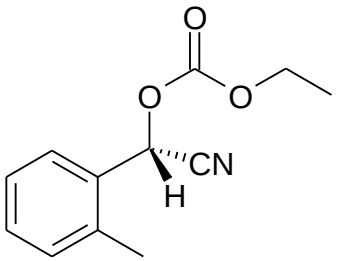
Obtained in quantitative yield and with 78% ee. Analytical data as reported in the previous section.

O-Ethoxycarbonyl (*S*)-2-hydroxy-3,3-dimethylbutanonitrile[160]



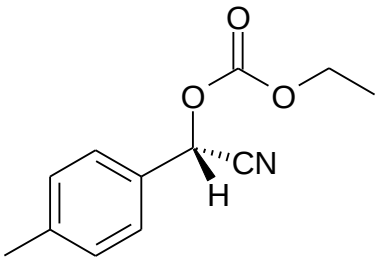
Obtained in quantitative yield and with 71% ee. Analytical data as reported in the previous section.

O-Ethoxycarbonyl (*S*)-2-hydroxy-2-(2-methylphenyl)acetonitrile[193] **37f**



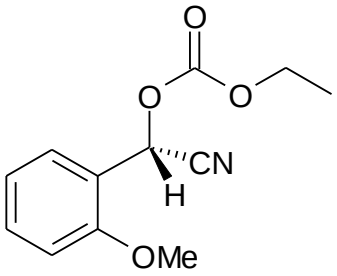
Obtained in quantitative yield and with 97% ee. $\delta_H(CDCl_3)$ 7.56 (1H, dd, J=7.5, 1.3 Hz, ArH), 7.2-7.4 (3H, m, ArH), 6.38 (1H, s, CHCN), 4.2-4.4 (2H, m, OCH_2), 2.44 (3H, s, $ArCH_3$), 1.34 (3H, t, J=7.1 Hz, $C\underline{H}_3CH_2$). $\delta_C(CDCl_3)$ 153.8 (CO_3), 137.1 (ArC), 131.7 (ArCH), 130.9 (ArCH), 130.1 (ArC), 128.9 (ArCH), 127.1 (ArCH), 115.9 (CN), 65.8 (CHCN), 65.0 (CH_2O), 19.1 (CH_3), 14.4 (CH_3); ν_{max}(neat) 2986 m, 1756 s and 1697 cm^{-1} w; $[\alpha]_D^{20}$ -21.5 (c 1.0, $CHCl_3$); m/z(EI) 219 (M^+, 5%), 130 (40), 129 (100); Found(EI) 219.0813; $C_{12}H_{13}NO_3$ (M^+) requires 219.0890. Chiral GC conditions: flow rate 1.6 ml / minute, initial temperature 100 °C, hold at initial temperature for 2 minutes then ramp rate 0.2 °C / minute; t_R = 146.7 and 147.0 minutes.

O-Ethoxycarbonyl (*S*)-2-hydroxy-2-(4-methylphenyl)acetonitrile[160] **37d**



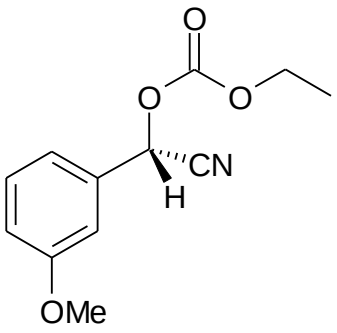
Obtained in quantitative yield and with 59% ee. $[\alpha]_D^{20}$ -1.9 (c 1.55, $CHCl_3$). Chiral GC conditions: flow rate 1.6 ml / minute, initial temperature 100 °C, hold at initial temperature for 2 minutes then ramp rate 0.2 °C / minute; t_R = 118.7 and 121.3 minutes.

O-Ethoxycarbonyl (*S*)-2-hydroxy-2-(2-methoxyphenyl)acetonitrile[160] **37m**



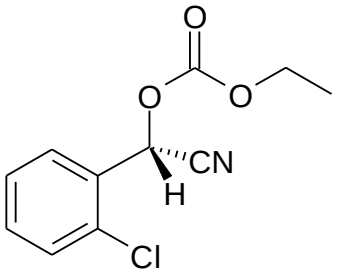
Obtained in quantitative yield and with greater than 99% ee. $[\alpha]_D^{20}$ +2.8 (c 1.0, $CHCl_3$). Chiral GC conditions: flow rate 1.6 ml / minute, initial temperature 100 °C, hold at initial temperature for 2 minutes then ramp rate 0.2 °C / minute; t_R = 207.6 and 224.9 minutes.

O-Ethoxycarbonyl (*S*)-2-hydroxy-2-(3-methoxyphenyl)acetonitrile[160] **37n**



Obtained in quantitative yield and with 90% ee. $[\alpha]_D^{20}$ -4.9 (c 1.65, $CHCl_3$). Chiral GC conditions: flow rate 1.6 ml / minute, initial temperature 100 °C, hold at initial temperature for 2 minutes then ramp rate 0.2 °C / minute; t_R = 223.4 and 227.9 minutes.

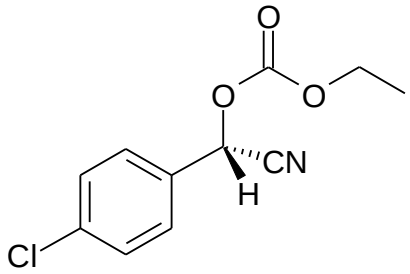
O-Ethoxycarbonyl (*S*)-2-hydroxy-2-(2-chlorophenyl)acetonitrile[194] **37o**



Obtained in quantitative yield and with 90% ee. $\delta_H(CDCl_3)$ 7.7-7.8 (1H, m, ArH), 7.3-7.5 (3H, m, ArH), 6.62 (1H, s, CHCN), 4.2-4.4 (2H, m, OCH_2), 1.35 (3H, t, J=7.2 Hz, $C\underline{H}_3CH_2$); δ_C ($CDCl_3$) 153.5 (CO_3), 133.9 (ArC), 132.1 (ArCH), 130.6 (ArCH), 129.9 (ArCH), 129.8 (ArC), 128.0 (ArCH), 115.3 (CN), 66.0 (OCH_2), 64.0 (CHO), 14.4 (CH_3); $[\alpha]_D^{20}$ -10.1 (c 1.05, $CHCl_3$); ν_{max}(neat) 3074 s, 2986 s, 2941 s, 2868 s and 1763 cm^{-1} s; m/z(CI) 259 ($(^{37}Cl)M+NH_4^+$, 35%), 257 ($(^{35}Cl)M+NH_4^+$, 100%), 171

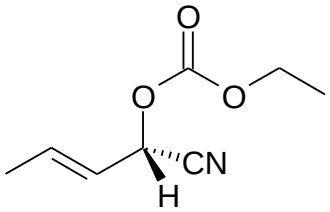
(20), 169 (60); Found(CI) 257.0687; $C_{11}H_{14}N_2O_3(^{35}Cl)$ $(M+NH_4)^+$ requires 257.0687. Chiral GC conditions: flow rate 1.6 ml / minute, initial temperature 100 °C, hold at initial temperature for 2 minutes then ramp rate 2 °C / minute; t_R = 41.0 and 42.0 minutes.

O-Ethoxycarbonyl (*S*)-2-hydroxy-2-(4-chlorophenyl)acetonitrile[160] **37p**



Obtained in quantitative yield and with 93% ee. $[\alpha]_D^{20}$ -2.6 (c 0.94, $CHCl_3$) [lit.[160] $[\alpha]_D^{20}$ -2.9 (c 1.3, $CHCl_3$)]. Chiral GC conditions: flow rate 1.6 ml / minute, initial temperature 100 °C, hold at initial temperature for 2 minutes then ramp rate 0.2 °C / minute; t_R = 123.4 and 124.2 minutes.

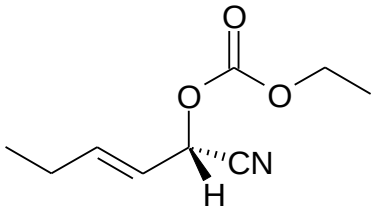
O-Ethoxycarbonyl (*S,E*)-2-hydroxy-pent-3-enonitrile[195] **37b**



Obtained in quantitative yield and with 93% ee. $[\alpha]_D^{20}$ +6.6 (c 1.0, $CHCl_3$) [lit.[195] $[\alpha]_D^{25}$ -7 (c 1.4, $CHCl_3$) for (R)-enantiomer]. m/z(CI) 187 ($M+NH_4^+$, 100%);

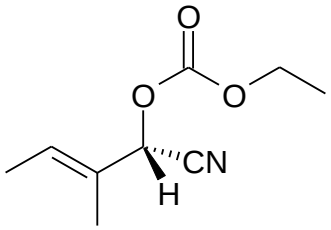
Found(CI) 187.1077; $C_8H_{15}N_2O_3$ $(M+NH_4)^+$ requires 187.1077. Chiral GC conditions: flow rate 1.6 ml / minute, initial temperature 100 °C, hold at initial temperature for 2 minutes then ramp rate 0.2 °C / minute; t_R = 22.6 and 24.4 minutes.

O-Ethoxycarbonyl (*S,E*)-2-hydroxy-hex-3-enonitrile[195] **37q**



Obtained in quantitative yield and with 91% ee. $\delta_H(CDCl_3)$ 6.18 (1H, dt, J=15.3, 6.3 Hz, =C<u>H</u>CH_2), 5.4-5.6 (2H, m, =C<u>H</u>C<u>H</u>CN), 4.19 (2H, q, J=7.3 Hz, OCH_2), 2.0-2.2 (2H, m, $CH_3C\underline{H}_2CH$=), 1.27 (3H, t, J=7.3 Hz, $C\underline{H}_3CH_2O$), 1.06 (3H, t, J=7.4 Hz, $C\underline{H}_3CH_2$); $\delta_C(CDCl_3)$ 152.5 (CO_3), 141.4 (=CH), 118.3 (=CH), 114.4 (CN), 64.3 (OCH_2), 64.0 (OCH), 24.1 (=$CHCH_2$), 13.1 (CH_3), 11.5 (CH_3); $[\alpha]_D^{20}$ +8.6 (c 4.5, $CHCl_3$); ν_{max}(neat) 2971 w, 2879 w and 1758 cm^{-1} s; m/z(CI) 201 ($M+NH_4^+$, 60%), 113 (100), 102 (50); Found(ESI) 206.0789; $C_9H_{13}NO_3Na$ $(M+Na)^+$ requires 206.0787. Chiral GC conditions: flow rate 1.6 ml / minute, initial temperature 100 °C, hold at initial temperature for 2 minutes then ramp rate 0.2 °C / minute; t_R = 36.2 and 37.4 minutes.

O-Ethoxycarbonyl (*S,E*)-2-hydroxy-3-methyl-pent-3-enonitrile **37r**



Obtained in quantitative yield after a 48 hour reaction and with 89% ee. $\delta_H(CDCl_3)$ 5.87 (1H, q, J=7.0 Hz, =C<u>H</u>CH_3) 5.55 (1H, s, CHCN), 4.1-4.3 (2H, m, OCH_2), 1.76 (3H, s, CH_3C=), 1.66 (3H, d, J=7.0 Hz, C<u>H</u>$_3$CH=), 1.29 (3H, t, J=7.1 Hz, C<u>H</u>$_3CH_2$); $\delta_C(CDCl_3)$ 153.6 (CO_3), 130.2 (=CH), 127.1 (=C), 115.6 (CN), 70.1 (CHCN), 64.5 (OCH_2), 14.2 (CH_3), 13.7 (CH_3), 12.3 (CH_3); $[\alpha]_D^{20}$ +7.7 (c 1.8, $CHCl_3$); ν_{max}(neat) 2986 s, 2950 s, 2921 s, 2484 w, 1756 s and 1670 cm^{-1} s; m/z(CI) 201 ($M+NH_4^+$, 70%), 113 (100); Found(CI) 201.1233; $C_9H_{17}N_2O_3$ $(M+NH_4)^+$ requires 201.1234. Chiral GC conditions: flow rate 1.6 ml / minute, initial temperature 100 ^oC, hold at initial temperature for 2 minutes then ramp rate 0.2 ^oC / minute; t_R = 32.2 and 33.6 minutes.

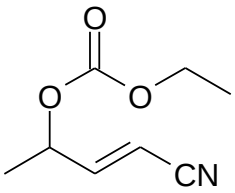
Kinetics of the addition of ethyl cyanoformate to benzaldehyde catalysed by complex 1 and potassium cyanide / 18-crown-6

To a stirred solution of catalyst **10**, KCN/18-crown-6 complex and ethyl cyanoformate (0.2 g, 2.0 mmol) in CH_2Cl_2 (5 ml) at 20 ^oC, benzaldehyde (0.11 g, 1.0 mmol) was added. Samples (0.5 ml) were taken at regular intervals and passed through a plug of silica. The solvent was evaporated *in vacuo*, and the residue redissolved in $CDCl_3$ and analysed by ^1H NMR spectroscopy. The extent of

reaction was determined from the relative integrals of the PhC*H*O signals of unreacted benzaldehyde and mandelonitrile ethyl carbonate.

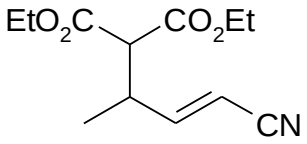
Conversion of (*S*)-cyanohydrin carbonates into γ-substituted α,β-unsaturated nitriles.

O-Ethoxycarbonyl 4-hydroxy-pent-2-enonitrile



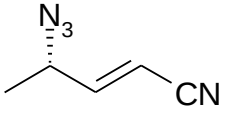
A solution of cyanohydrin carbonate **55** (2.0 g, 11.8 mmol) in THF (30 ml) was cooled in an ice bath and stirred under a nitrogen atmosphere. Tetrakis(triphenylphosphine) palladium(0) (0.28 g, 0.28 mmol) was added, then the solution was allowed to warm to room temperature and stirred for 16 hours. Et_2O (100 ml) was added, the organic layer was separated and the aqueous layer was extracted with Et_2O (2 x 100 ml). The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated *in vacuo*. The residue was passed through a plug of silica topped with $MgSO_4$, eluting with Et_2O. The solvent was evaporated *in vacuo.* No product was obtained, and the starting material was recovered.

(4-Diethyl malonyl)pent-2-enonitrile **56**



A solution of cyanohydrin carbonate **55** (2.0 g, 11.8 mmol), diethyl malonate (0.18 ml, 11.8 mmol) and sodium carbonate (0.2 g, 17.6 mmol) in THF (10 ml) and water (10 ml) was cooled in an ice bath and stirred under a nitrogen atmosphere. Tetrakis(triphenylphosphine) palladium(0) (0.28 g, 0.28 mmol) was added, then the solution was allowed to warm to room temperature and stirred for 16 hours. Et_2O (100 ml) was added, the organic layer was separated and the aqueous layer was extracted with Et_2O (2 x 100 ml). The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated *in vacuo*. The residue was passed through a plug of silica topped with $MgSO_4$, eluting with Et_2O. The solvent was evaporated *in vacuo.* No product was obtained, and the starting material was recovered.

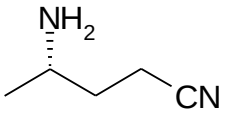
(*S*)-4-Azido-pent-2-enonitrile **57**[176]



A solution of cyanohydrin carbonate **55** (2.0 g, 11.8 mmol) and sodium azide (1.5 g, 23.6 mmol) in THF (30 ml) and water (30 ml) was cooled in an ice bath and stirred under a nitrogen atmosphere. Tetrakis(triphenylphosphine) palladium(0) (0.28 g, 0.28 mmol) was added, then the solution was allowed to warm to room

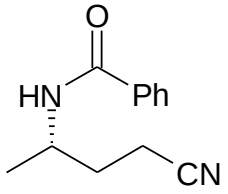
temperature and stirred for 16 hours. Et_2O (100 ml) was added, the organic layer was separated and the aqueous layer was extracted with Et_2O (2 x 100 ml). The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated *in vacuo*. The residue was passed through a plug of silica topped with $MgSO_4$, eluting with Et_2O. The eluent was evaporated *in vacuo*, and the residue was purified by silica gel chromatography ($CHCl_3$) to give compound **57** (1.17 g, 81%) as a colourless oil. $[\alpha]_D^{20}$ -38.5 (c 1.05, $CHCl_3$) [lit.[195] $[\alpha]_D^{20}$ -38.7 (c 1.9, $CHCl_3$) for (*R*)-enantiomer with 81% ee].

(*S*)-4-Amino-pentanonitrile **58.**[196]



Azide **57** (0.25 g, 2.0 mmol) was dissolved in dry methanol (150 ml) and 10% Pd/C (0.04 g) was added. The reaction was stirred under a hydrogen atmosphere for four days, then filtered through a plug of silica and the solvent evaporated *in vacuo*. The residue was purified by silica gel chromatography (MeOH) to give compound **58** (0.05 g, 17%) as a colourless oil. Compound **58** was found to be unstable and so was characterized as its *N*-benzoyl derivative.

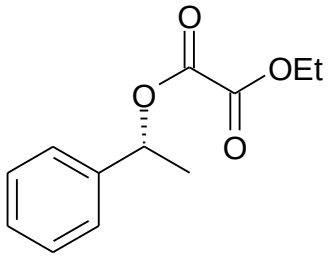
N-Benzoyl (*S*)-4-amino-pentanonitrile **59.**[196]



To a stirred solution of amine **58** (0.05 g, 0.6 mmol) in CH_2Cl_2 (10 ml), was added triethylamine (0.12 g, 1.2 mmol) and benzoyl chloride (0.17 g, 1.2mmol). The reaction was stirred at room temperature for 16 hours, then the solvent was evaporated *in vacuo*, and the residue purified by silica gel chromatography ($CHCl_3$) to give compound **59** (0.09 g, 81%) as a yellow oil. $\delta_H(CDCl_3)$ 7.3-7.8 (5H, m, ArH), 6.67 (1H, br, NH), 4.1-4.3 (1H, m, C<u>H</u>NH), 2.39 (2H, t, J=7.5 Hz, CH_2CN), 1.8-1.9 (2H, m, C<u>H</u>$_2$CH$_2$CN), 1.42 (3H, d, J=6.7 Hz, C<u>H</u>$_3$CH); Chiral GC conditions: flow rate 1.6 ml / minute, initial temperature 100 ^oC, ramp rate 2 ^oC / minute; t_R = 9.6 and 12.3 minutes.

<u>Synthesis of chiral cyanoformates</u>

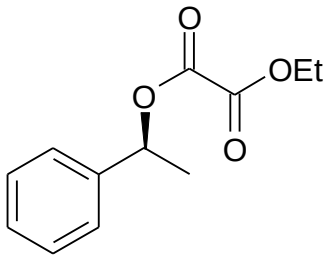
Ethyl (*R*)-1-phenylethyl oxalate *R*-**61.**[197]



A stirred solution of (*R*)-1-phenylethanol (6.9 g, 56.5 mmol) and pyridine (4.5 g, 57.0 mmol) in CH_2Cl_2 (24 ml) was cooled in an ice-bath and ethyl oxalyl chloride

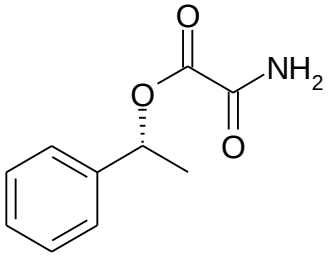
(7.8 g, 57.0 mmol) was added over 1 hour. The mixture was stirred in an ice-bath for 4 hours, then at room temperature overnight. The reaction was washed with water (2 x 6 ml), dried ($MgSO_4$) and solvent evaporated *in vacuo* to leave diester **61** (12.2 g, 97%) as a colourless liquid. $\delta_H(CDCl_3)$ 7.3-7.4 (5H, m, ArH), 6.03 (1H, q, J=6.6 Hz, CH), 4.35 (2H, q, J=7.1 Hz, CH_2), 1.68 (3H, d, J=6.6 Hz, CH_3), 1.38 (3H, t, J=7.1 Hz, CH_3); $\delta_C(CDCl_3)$ 158.3 (C=O), 157.7 (C=O), 140.4 (ArC), 128.9 (ArCH), 128.8 (ArCH), 126.6 (ArCH), 75.9 (OCH), 63.4 (OCH_2), 22.2 (CH_3), 14.2 (CH_3); $[\alpha]_D^{20}$ +60.0 (c 1.25, $CHCl_3$); ν_{max}(neat) 2985 s and 1740 cm^{-1} s; m/z(CI) 223 (MH^+, 24), 209 (52), 131 (35), 106 (67), 105 (100), 104 (46), 77 (48), 51 (15); Found(ESI) 245.0783; $C_{12}H_{14}O_4Na$ $(M+Na)^+$ requires 245.0784.

Ethyl (*S*)-1-phenylethyl oxalate ***S*-61.**[197]



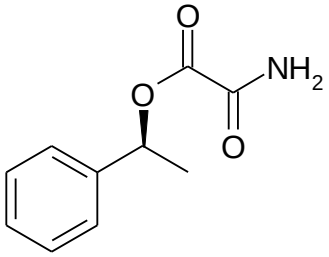
Prepared from (*S*)-1-phenylethanol (5.0 g, 40.9 mmol) as described for the (*R*)-enantiomer ***R*-61** to give compound ***S*-61** (9.0 g, 97%) as a colourless liquid. $[\alpha]_D^{20}$ -60.0 (c 1.1, $CHCl_3$). Other analytical data as reported for the (*R*)-enantiomer ***R*-61**.

(*R*)-1-phenylethyl oxamide ***R*-62** from diester ***R*-61.**[197]



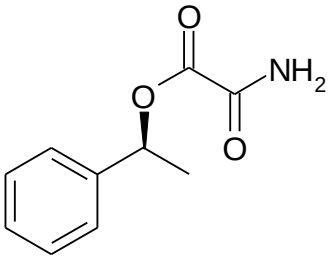
To a solution of compound ***R*-61** (17.3 g, 78.2 mmol) in ethanol (9 ml) was added 0.88 ammonia (5.4 ml) in 4-5 portions with swirling over 3-5 minutes. The solution was allowed to stand at room temperature for 3 days, then diluted with CH_2Cl_2 (34 ml). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (25 ml). The combined organic layers were dried ($MgSO_4$) and evaporated *in vacuo* to leave an oil which solidified on standing. The solid was washed with 40-60 petroleum ether, recrystallized from toluene (50 ml) and washed again with 40-60 petroleum ether. Further recrystallization from toluene / methanol (9:1) gave compound ***R*-62** (3.0 g, 20%) as white crystals. Mp 89.5-90.5°C (from benzene / 60-90 petroleum ether); $\delta_H(CDCl_3)$ 7.3-7.4 (5H, m, ArH), 6.98 (1H, br, NH), 6.61 (1H, br, NH), 5.99 (1H, q, J=6.6 Hz, CH), 1.68 (3H, d, J=6.6 Hz, CH_3); $\delta_C(CDCl_3)$ 159.9 (C=O), 159.1 (C=O), 140.4 (ArC), 129.1 (ArCH), 128.9 (ArCH), 126.7 (ArCH), 76.4 (OCH), 22.3 (CH_3); $[\alpha]_D^{20}$ +109.1 (c 0.5, $CHCl_3$); ν_{max}(neat) 3403 s, 3234 s, 1736 s and 1688 cm^{-1} s; m/z(CI) 211 ($M+NH_4^+$, 100); Found(ESI) 216.0628; $C_{10}H_{11}NO_3Na$ $(M+Na)^+$ requires 216.0631.

(*S*)-1-phenylethyl oxamide ***S*-62** from diester ***S*-61.**[197]



Prepared from compound ***S*-61** (9.0 g, 40.7 mmol) as described for the (*R*)-enantiomer ***R*-62** to give compound ***S*-62** (2.9 g, 37%) as white crystals. $[\alpha]_D^{20}$ -109.3 (c 0.45, $CHCl_3$). Other analytical data as reported for the (*R*)-enantiomer ***R*-62**.

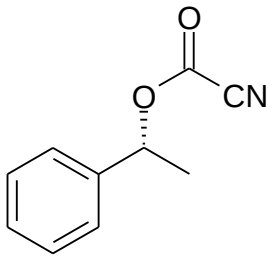
(*S*)-1-phenylethyl oxamide ***S*-62** from (*S*)-phenylethanol.[198]



A solution of (*S*)-phenylethanol (1.0 g, 8.2 mmol) in CH_2Cl_2 (10ml) was stirred and cooled in an ice bath. Oxalyl chloride (2.1 g, 16.4 mmol) was added dropwise and the resulting mixture was stirred for 1 hour at room temperature. The solvent and excess oxalyl chloride were removed *in vacuo*. The residue was dissolved in CH_2Cl_2 (50 ml) and cooled to 0 °C in an ice bath. A saturated solution of ammonia in THF (0.2 ml, excess) was added dropwise, and the resulting mixture was stirred for 15 minutes. The reaction was washed with water (40 ml), the aqueous

layer was extracted with CH_2Cl_2 (40 ml) and the combined organic layers were washed with water (40 ml). The organic layer was dried ($MgSO_4$) and evaporated *in vacuo*. The residue was recrystallized from a toluene/hexane mixture to give oxamide ***S*-62** (0.90g, 98%) as a white solid.

(*R*)-1-phenylethyl cyanoformate ***R*-60.**[197]



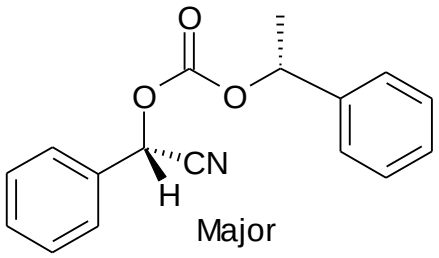
To a stirred mixture of oxamide ***R*-62** (2.9 g, 15.0 mmol) and pyridine (4.6 g, 57.8 mmol) in CH_2Cl_2 (27 ml), in an ice-bath, trifluoroacetic anhydride (3.8 g, 17.9 mmol) was added dropwise over 10 minutes. The ice-bath was removed and the thick reaction mixture was allowed to stir at room temperature for 2 hours. Water (58 ml) was added, the organic layer was separated, washed with water (43 ml), and the aqueous layer extracted with CH_2Cl_2 (2 x 30 ml). The combined CH_2Cl_2 layers were again washed with water (50 ml), dried ($MgSO_4$) and evaporated *in vacuo* to leave an oil which was subjected to bulb to bulb distillation (120-170 °C at 150 mmHg) to give compound ***R* -60** (1.9 g, 71%) as a colourless oil. $\delta_H(CDCl_3)$ 7.3-7.4 (5H, m, ArH), 6.06 (1H, q, J=6.5 Hz, CH), 1.71 (3H, d, J=6.5 Hz, CH_3); $\delta_C(CDCl_3)$ 144.0 (C=O), 138.8 (ArC), 129.6 (ArCH), 129.3 (ArCH), 126.8 (ArCH), 109.8 (CN), 78.8 (OCH), 21.9 (CH_3); $[\alpha]_D^{20}$ +95.6 (c 1.65, $CHCl_3$); ν_{max}(neat) 2244 s and 1744 cm^{-1} s; m/z(EI) 175 (M^+, 38), 159 (12), 132 (11), 121 (11), 105 (100), 77

(24); Found(ESI) 293.1147; $C_{17}H_{18}O_3Na$ $(2M\text{-}CO(CN)_2+Na)^+$ requires 293.1148. Compound reacts with water under electrospray mass spectrometry conditions to form $(PhCHMeO)_2CO$ *in situ*.

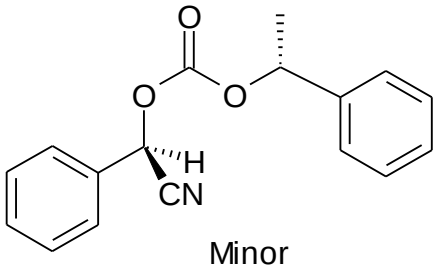
Diastereoselective synthesis of cyanoformates derived from chiral cyanoformate 60.

To a stirred solution of aldehyde (benzaldehyde or trimethylacetaldehyde) (2.4 mmol) and catalyst **10** ((*R,R*)- or (*S,S*)-enantiomer) (57.8 mg, 0.05 mmol) in CH_2Cl_2 (6 ml) was added KCN (7.7 mg, 0.1 mmol). The mixture was cooled to -78 °C, then cyanoformate **60** (0.5 g, 2.9 mmol) was added and the reaction stirred vigorously at -40 °C for 24 hours. If after this time, the reaction had not reached completion an additional batch of KCN (7.7 mg, 0.1 mmol) and catalyst **10** (57.8 mg, 0.05 mmol) was added and the reaction stirred at -40 °C for a further 48 hours. The reaction was warmed to room temperature and passed through a plug of silica gel, eluting with CH_2Cl_2. The solvent was removed *in vacuo* to give the product.

Compound **66a** (major) and (minor) from (*R,R*) catalyst



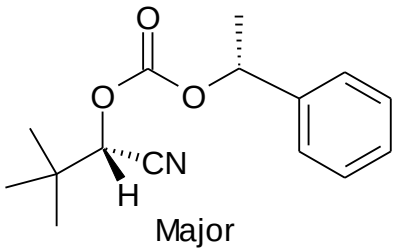
Major



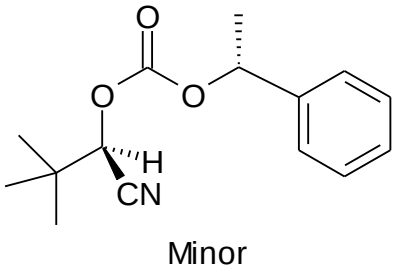
Minor

Obtained as a colourless, crystalline solid (0.48 g, 88% conversion from benzaldehyde). To obtain crystals suitable for X-ray analysis, the white solid was first further purified by flash chromatography (CH_2Cl_2) and then recrystallized from CH_2Cl_2. $\delta_H(CDCl_3)$ **major:** 7.2-7.8 (10H, m, ArH), 6.15 (1H, s, CHCN), 5.68 (1H, q, J=6.7 Hz, CHMe), 1.51 (3H, d, J=6.7 Hz, CH_3); **minor** (not all peaks visible) 6.10 (1H, s, CH); $\delta_C(CDCl_3)$ **major** 153.3 (CO_3), 140.5 (ArC), 131.8 (ArC), 131.1 (ArCH), 129.7 (ArCH), 129.2 (ArCH), 129.0 (ArCH), 128.4 (ArCH), 126.5 (ArCH), 116.23 (CN), 78.9 (Ph*C*HCN), 66.9 (PhCHO), 22.6 (CH_3); $[\alpha]_D^{20}$ +36.8 (c 1.45, $CHCl_3$); ν_{max}(neat) 2985 m, 2346 w and 1762 cm^{-1} s; m/z(CI) 282 (MH^+, 2%), 238 (7), 193 (10), 105 (100); Found(ESI) 304.0945; $C_{17}H_{15}NO_3Na$ $(M+Na)^+$ requires 304.0944.

Compound **66b** (major) and (minor) from (*R,R*) catalyst



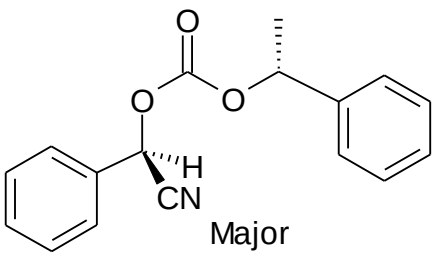
Major



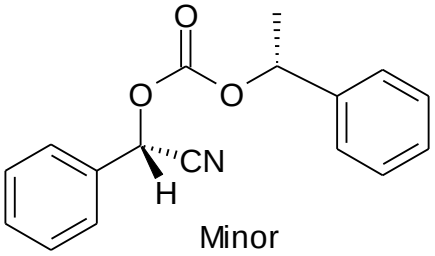
Minor

Obtained as a white solid. (0.59 g, 100% conversion from trimethylacetaldehyde). To obtain crystals suitable for X-ray analysis, the white solid was first further purified by flash chromatography (CH_2Cl_2) and then recrystallized from CH_2Cl_2. $\delta_H(CDCl_3)$ **major:** 7.2-7.4 (5H, m, ArH), 5.69 (1H, q, J=6.6 Hz, CHMe), 4.85 (1H, s, CHCN), 1.55 (3H, d, J=6.6 Hz, CH_3), 1.02 (9H, s, $(CH_3)_3$); **minor:** (not all peaks visible) 4.79 (1H, s, CH); $\delta_C(CDCl_3)$ 153.8 (CO_3), 140.4 (ArC), 129.1 (ArCH), 128.9 (ArCH), 126.4 (ArCH), 115.9 (CN), 78.5 (CHCN), 73.6 (CHMe), 35.4 (CMe_3), 25.5 ($(CH_3)_3$), 22.5 (CH_3); $[\alpha]_D^{20}$ +33.3 (c 1.15, $CHCl_3$); ν_{max}(KBr) 2973 s, 2244 w and 1754 cm^{-1} s; m/z(EI) 261 (M^+, 27%), 121 (41), 105 (100); Found(ESI) 284.1257; $C_{15}H_{19}NO_3Na$ $(M+Na)^+$ requires 284.1257.

Compound **66a**(*S*) (major) and (minor) from (*S,S*) catalyst



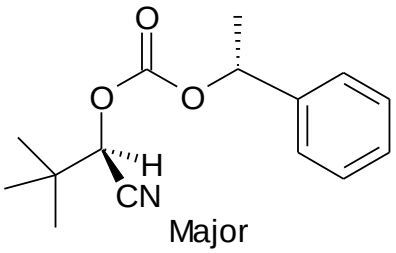
Major



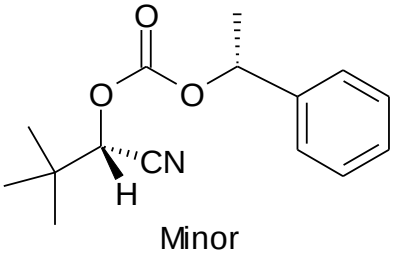
Minor

Obtained as a yellow oil (0.53 g, 66% conversion from benzaldehyde). $\delta_H(CDCl_3)$ **major:** 7.2-7.8 (10H, m, ArH), 6.11 (1H, s, CHCN), 5.70 (1H, q, J=6.5 Hz, CHMe), 1.52 (3H, d, J=6.5 Hz, CH_3); **minor:** (not all peaks visible) 6.15 (1H, s, CH); $\delta_C(CDCl_3)$ 153.3 (CO_3), 140.4 (ArC), 131.5 (ArC), 131.0 (ArCH), 129.6 (ArCH), 129.1 (ArCH), 129.0 (ArCH), 128.2 (ArCH), 126.5 (ArCH), 116.2 (CN), 78.9 (CHCN), 66.8 (CHPh), 22.6 (CH_3); $[\alpha]_D^{20}$ -40.1 (c 2.75, $CHCl_3$); ν_{max}(neat) 2986 m, 2348 w and 1761 cm^{-1} s; m/z(CI) 282 (MH^+, 4%), 105 (100); Found(ESI) 304.0956; $C_{17}H_{15}NO_3Na$ $(M+Na)^+$ requires 304.0944.

Compound **66b**(*S*) (major) and (minor) from (*S,S*) catalyst



Major

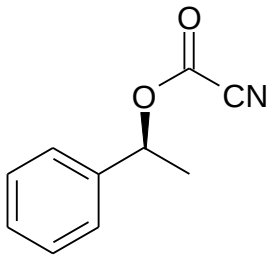


Minor

Obtained as a yellow oil (0.37 g, 100% conversion from pivaldehyde). $\delta_H(CDCl_3)$ **major:** 7.3-7.4 (5H, m, ArH), 5.79 (1H, q, J=6.6 Hz, CHMe), 4.89 (1H, s, CHCN), 1.65 (3H, d, J=6.6 Hz, CH_3), 1.10 (9H, s, $(CH_3)_3$); **minor:** 4.96 (1H, s, CH);

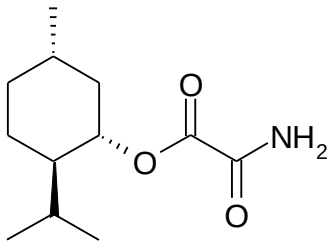
$\delta_C(CDCl_3)$ 153.8 (CO_3), 140.8 (ArC), 129.1 (ArCH), 128.9 (ArCH), 126.4 (ArCH), 116.2 (CN), 78.5 (CHCN), 73.6 (CHMe), 25.5 ($(CH_3)_3$), 22.6 (CH_3); $[\alpha]_D^{20}$ -115.2 (c 1.25, $CHCl_3$); ν_{max}(neat) 2972 s, 2227 w and 1753 cm^{-1} s; m/z(EI) 261 (M^+, 16%), 121 (33), 105 (100); Found(ESI) 284.1251; $C_{15}H_{19}NO_3Na$ $(M+Na)^+$ requires 284.1257.

(*S*)-1-phenylethyl cyanoformate ***S-60***.[197]



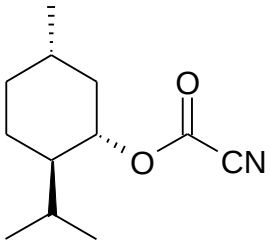
Prepared from compound ***S-62*** (1.1 g, 5.7 mmol) as described for the (*R*)-enantiomer ***R-60*** to give compound ***S-60*** (0.85 g, 85%) as a colourless oil. $[\alpha]_D^{20}$ -95.6 (c 1.35, $CHCl_3$). Other analytical data as reported for the (*R*)-enantiomer ***R-60***.

(+)-Menthyl oxamide **69**



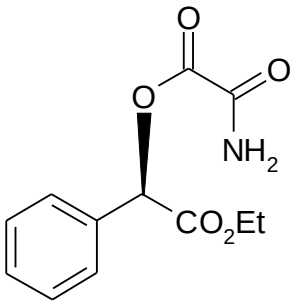
To a stirred solution of (+)-menthol (1.0 g, 7.7 mmol) in CH_2Cl_2 (20 ml) at 0 °C, oxalyl chloride (1.95 g, 15.4 mmol) was added dropwise. The ice bath was removed and the mixture was stirred for 1 hour at room temperature. The solvent was then removed *in vacuo*, and the residue was dried on a vacuum line. The crude oxalic ester was redissolved in CH_2Cl_2 (50 ml), and concentrated aqueous ammonia (0.46 ml excess) was added at 0 °C. The mixture was stirred for 30 minutes, then water was added, and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 20ml) and the combined organic layers were washed with water. The organic layer was dried ($MgSO_4$), and the solvent was removed *in vacuo*. The residue was recrystallized from CH_2Cl_2 to give compound **69** (1.7 g, 97%) as a white solid. Mp=148-148.5 °C; $\delta_H(CDCl_3)$ 6.95 (1H, br, NH_2), 5.84 (1H, br, NH_2), 4.84 (1H, td, J=11.0, 4.5 Hz, CHO), 1.4-2.1 (8H, m, 3 x CH_2, 2 x CH), 1.0-1.3 (1H, m, CH), 0.92 (3H, d, J=6.5 Hz, CH_3), 0.90 (3H, d, J=7.0 Hz, CH_3), 0.76 (3H, d, J=7.0 Hz, CH_3); $\delta_C(CDCl_3)$ 160.0 (C=O), 158.9 (C=O), 78.5 (CHO), 47.2 (CH), 40.7 (CH_2), 34.4 (CH_2), 31.9 (CH), 26.7 (CH), 24.0 (CH_2), 22.1 (CH_3), 20.9 (CH_3), 16.6 (CH_3); $[\alpha]_D^{20}$ +87.4 (c 0.95, $CHCl_3$); ν_{max}(ATR) 3404 m, 3234 m, 2957 m, 2921 m, 2872 m, 1733 s, 1682 s and 1651 cm^{-1} m; m/z(ESI) 245 ($M+NH_4^+$, 30), 139 (20), 122 (18); Found(ESI) 245.1864, $C_{12}H_{25}N_2O_3$ ($M+NH_4^+$) requires 245.1864.

(+)-Menthyl cyanoformate **67**.



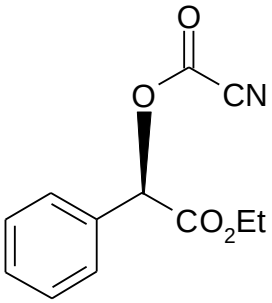
To a solution of oxamide **69** (0.5 g, 2.2 mmol) and pyridine (0.7 g, 8.8 mmol) in CH_2Cl_2 (8 ml), trifluoroacetic acid (0.55 g, 2.6 mmol) was added dropwise at 0 °C. The ice bath was removed, and the solution was stirred for 2 hours at room temperature. Water was added, and the layers were separated. The organic layer was washed with water (20 ml), then with dilute hydrochloric acid (20 ml). The organic layer was dried ($MgSO_4$), and the solvent was removed *in vacuo* to leave compound **67** (0.44 g, 96%) as a yellow oil. $\delta_H(CDCl_3)$ 4.80 (1H, td, J=11.0, 4.5 Hz, CHO), 1.9-2.0 (1H, m, CyCH), 1.7-1.9 (1H, m, CyCH), 1.6-1.7 (2H, m, 2 x CyCH), 1.3-1.5 (2H, m, 2 x CyCH), 0.9-1.2 (3H, m, 3 x CyCH), 0.87 (3H, d, J=6.5 Hz, CH_3), 0.86 (3H, d, J=7.0 Hz, CH_3), 0.70 (3H, d, J=7.0 Hz, CH_3); $\delta_C(CDCl_3)$ 144.3 (CO), 109.9 (CN), 81.2 (OCH), 47.1 (CH), 40.6 (CH_2), 34.4 (CH_2), 31.9 (CH), 26.8 (CH), 23.9 (CH_2), 22.0 (CH_3), 20.8 (CH_3), 16.5 (CH_3); $[\alpha]_D^{20}$ +78.5 (c 1.0, $CHCl_3$); ν_{max}(neat) 2960 s, 2873 s, 2244 m and 1744 cm^{-1} s; m/z(CI) 232 (M-CN+OMe+NH_4^+, 30), 172 (100), 155 (40), 137 (50), 95 (60); Found(ESI) 384.3110, $C_{22}H_{42}NO_4$ (2M-2CN+NH_4^+) requires 384.3108.

(*R*)-1-(carboxyethyl)benzyl oxamide **76**.



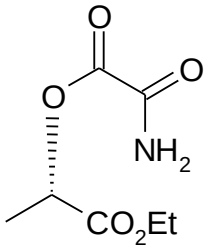
Sodium hydride (22 mg of a 60% dispersion in mineral oil) was washed with petrol, suspended in THF (20 ml) and cooled in an ice bath. Ethyl mandelate (0.10 g, 0.56 mmol) was added, followed by dropwise addition of oxalyl chloride (0.14 g, 1.12 mmol). The ice bath was removed and the mixture was stirred for 16 hours. The solvent was removed *in vacuo*, and the residue was dried on a vacuum line. The crude mono-ester was redissolved in CH_2Cl_2, and concentrated aqueous ammonia (0.20 ml, excess) was added at 0 °C. The mixture was stirred for 30 minutes, then water was added, and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 20 ml) and the combined organic layers were washed with water (20 ml). The organic layer was dried ($MgSO_4$) and evaporated *in vacuo* to give compound **76** (0.15 g, 97%) as a white solid. $\delta_H(CDCl_3)$ 7.2-7.5 (5H, m, ArH), 7.0-7.1 (1H, br, NH), 6.5-6.6 (1H, br, NH), 5.91 (1H, s, PhCHO), 4.0-4.3 (2H, m, OC$\underline{H}_2$CH$_3$), 1.12 (3H, t, J=7.1 Hz, C$\underline{H}_3$CH$_2$); $\delta_C(CDCl_3)$ 167.8 (C=O), 159.6 (C=O), 157.7 (C=O), 133.2 (ArC), 129.9 (ArCH), 129.2 (ArCH), 128.1 (ArCH), 73.4 (OCH), 62.4 (OCH_2), 14.2 (CH_3); Mp 190-200 °C (decomp.); $[\alpha]_D^{20}$ +4.7 (c 0.3, $CHCl_3$); ν_{max}(ATR) 3445 br, 2983 m, 1748 s and 1601 cm^{-1} m; m/z(CI) 269 ($M+NH_4^+$, 30%), 198 (70), 182 (100); Found(ESI) 269.1130, $C_{12}H_{17}N_2O_5$ ($M+NH_4^+$) requires 269.1132.

(*R*)-1-(carboxyethyl)benzyl cyanoformate **77**.



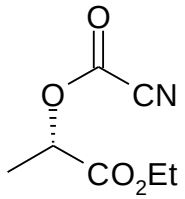
To a solution of oxamide **76** (1.1 g, 4.2 mmol) and pyridine (1.4 ml, 16.9 mmol) in CH_2Cl_2 (15 ml), trifluoroacetic anhydride (0.7 ml, 5.0 mmol) was added dropwise at 0 °C. The ice bath was removed, and the solution was stirred for 2 hours at room temperature. Water was added, and the layers were separated. The organic layer was washed with water (20 ml), then with dilute hydrochloric acid (20 ml). The organic layer was dried ($MgSO_4$), and the solvent was removed *in vacuo* to leave compound **77** (0.87 g, 87%) as a yellow oil. $\delta_H(CDCl_3)$ 7.3-7.5 (5H, m, ArH), 6.05 (1H, s, PhCHO), 4.1-4.3 (2H, m, OCH_2), 1.23 (3H, t, J=7.1 Hz, $C\underline{H}_3CH_2$); $\delta_C(CDCl_3)$ 166.6 (C=O), 143.8 (C=O), 138.8 (ArC), 129.6 (ArCH), 128.1 (ArCH), 126.9 (ArCH), 109.1 (CN), 78.3 (OCH), 62.8 (OCH_2), 14.2 (CH_3); $[\alpha]_D^{20}$ -8.4 (c 0.5, $CHCl_3$); ν_{max}(neat) 3069 s, 3038 w, 2986 m, 2943 m, 2908 w, 2249 m, 1791 s and 1748 cm^{-1} s; m/z(EI) 233 (M^+, 1%), 160 (90), 105 (100); Found(EI) 233.0685, $C_{12}H_{11}NO_4$ (M^+) requires 233.0683.

(*R*)-1-(carboxyethyl)ethyl oxamide **80**.



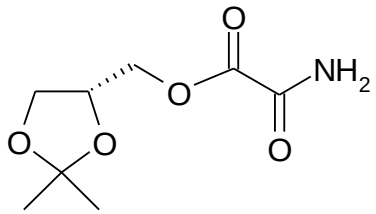
To a stirred solution of ethyl lactate (1.0 g, 7.7 mmol) in CH_2Cl_2 (20 ml) at 0 °C, oxalyl chloride (2.0 g, 15.4 mmol) was added dropwise. The ice bath was removed and the mixture was stirred for 1 hour, after which the solvent was removed *in vacuo* and the residue dried on a vacuum line. The resulting crude mono-ester was redissolved in CH_2Cl_2, cooled to 0 °C, and concentrated aqueous ammonia (0.46 ml, 1.2eq.) was added. The mixture was stirred for 30 minutes, then water was added, and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 20 ml) and the combined organic layers were washed with water. The organic layer was dried ($MgSO_4$) and evaporated *in vacuo*. The residue was recrystallized from CH_2Cl_2 to give oxamide **80** (0.44 g, 27%) as a white solid. $\delta_H(CDCl_3)$ 6.92 (1H, br, NH_2), 6.00 (1H, br, NH_2), 5.18 (1H, q, J=7.0 Hz, $CH_3C\underline{H}O$), 4.21 (2H, q, J=7.1 Hz, OCH_2), 1.61 (3H, d, J=7.0 Hz, $C\underline{H}_3CH$), 1.26 (3H, t, J=7.1 Hz, $C\underline{H}_3CH_2$); $\delta_C(CDCl_3)$ 169.5 (C=O), 159.6 (C=O), 157.8 (C=O), 71.5 (OCH), 62.1 (OCH_2), 17.0 (CH_3), 14.3 (CH_3); Mp 77-79 °C; $[\alpha]_D^{20}$ -36.5 (c 0.26, $CHCl_3$); $\nu_{max}(CH_2Cl_2)$ 3349 w, 3239 w, 3222 w, 1733 s, 1676 s and 1667 cm^{-1} s; m/z(ESI) 207 ($M+NH_4^+$, 80%), 180 (100); Found(ESI) 207.0978, $C_7H_{15}N_2O_5$ ($M+NH_4^+$) requires 207.0975.

(*R*)-1-(carboxyethyl)ethyl cyanoformate **81**.



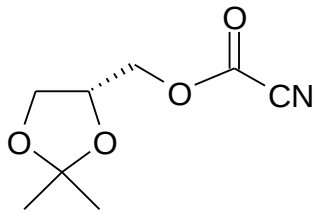
To a solution of oxamide **80** (0.8 g, 4.2 mmol) and pyridine (1.4 ml, 16.9 mmol) in CH_2Cl_2 (15 ml), trifluoroacetic anhydride (0.7 ml, 5.0 mmol) was added dropwise at 0 ^oC. The ice bath was removed, and the solution was stirred for 2 hours at room temperature. Water was added, and the layers were separated. The organic layer was washed with water (20 ml), then with dilute hydrochloric acid (20 ml). The organic layer was dried ($MgSO_4$), and the solvent was removed *in vacuo* to leave compound **81** (0.57 g, 78%) as a yellow oil. $\delta_H(CDCl_3)$ 5.20 (1H, q, J=7.1 Hz, $CH_3C\underline{H}O$), 4.21 (2H, q, J=7.1 Hz, OCH_2), 1.58 (3H, d, J=7.1 Hz, $C\underline{H}_3CH$), 1.27 (3H, t, J=7.1 Hz, $C\underline{H}_3CH_2$); $\delta_C(CDCl_3)$ 168.1 (C=O), 143.8 (C=O), 109.3 (CN), 73.0 (OCH), 62.6 (OCH_2), 16.8 (CH_3), 14.3 (CH_3); $[\alpha]_D^{20}$ -40.3 (c 1.2, $CHCl_3$); $\nu_{max}(CH_2Cl_2)$ 2989 s, 2945 m, 2249 m and 1748 cm^{-1} s; m/z(EI) 171 (M^+, 55%), 98 (50), 73 (60), 54 (90), 43 (100); Found(ESI) 285.0948 and 263.1111, $C_{11}H_{18}O_7Na$ $(2M\text{-}2CN\text{-}CO+Na)^+$ requires 285.0950 and $C_{11}H_{19}O_7$ $(2M\text{-}2CN\text{-}CO+H)^+$ requires 263.1131.

(*S*)-Glycerolacetonide oxamide **72**.



To a stirred mixture of sodium hydride in mineral oil (0.02 g, 0.56 mmol) and (*S*)-glycerol acetonide (0.10 g, 0.56 mmol) in THF (20 ml) at 0 °C, oxalyl chloride (0.14 g, 1.12 mmol) was added dropwise. The ice bath was removed and the mixture was stirred at room temperature for 16 hours. The solvent was removed *in vacuo*, and the residue dried on a vacuum line. The crude oxalic ester was redissolved in CH_2Cl_2 (2 ml), and concentrated aqueous ammonia (0.20 ml, excess) was added at 0 °C. The mixture was stirred for 30 minutes, then water was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 20 ml) and the combined organic layers were washed with water. The organic layer was dried ($MgSO_4$), and the solvent was removed *in vacuo* to give compound **72** (82 mg, 72%) as a white solid. $\delta_H(CDCl_3)$ 7.00 (1H, br, NH_2), 6.32 (1H, br, NH_2), 4.2-4.5 (3H, m, OCH), 4.08 (1H, dd, J=8.7, 6.4 Hz, OCH_2), 3.80 (1H, dd, J=8.7, 5.4 Hz, OCH_2), 1.41 (3H, s, CH_3), 1.33 (3H, s, CH_3); $\delta_C(CDCl_3)$ 160.0 (C=O), 158.3 (C=O), 110.2 ($OCMe_2$), 73.0 (OCH), 67.0 (OCH_2), 66.3 (OCH_2), 26.7 (CH_3), 25.3 (CH_3); Mp 184-186 °C (decomp.); $[\alpha]_D^{20}$ -18.0 (c 0.05, $CHCl_3$); ν_{max}(ATR) 3391 m, 3131 s, 3043 s, 1737 m, 1690 s and 1607 cm^{-1} m; m/z(ESI) 221 ($M+NH_4^+$, 30), 204 (MH^+, 100), 163 (70), 146 (50), 101 (95); Found(ESI) 221.1133, $C_8H_{17}N_2O_5$ ($M+NH_4^+$) requires 221.1132.

(*S*)-Glycerolacetonide cyanoformate **73**.



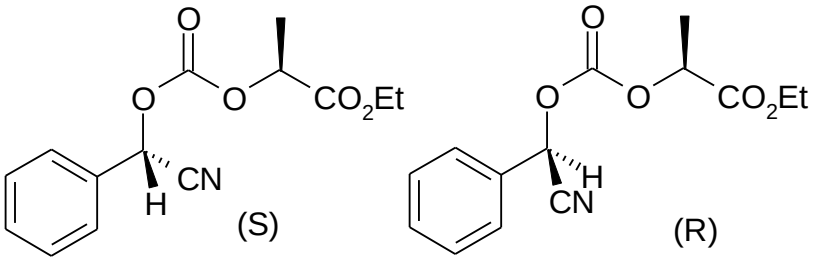
To a solution of oxamide **72** (0.86 g, 4.2 mmol) and pyridine (1.4 ml, 16.9 mmol) in CH_2Cl_2 (15ml), trifluoroacetic anhydride (0.7 ml, 5.0 mmol) was added dropwise at 0 ^oC. The ice bath was removed, and the solution was stirred for 2 hours at room temperature. Water was added, and the layers were separated. The organic layer was washed with water (20 ml), then with dilute hydrochloric acid (20 ml). The organic layer was dried ($MgSO_4$), and the solvent was removed *in vacuo* to leave compound **73** (0.16 g, 21%) as a yellow oil. $\delta_H(CDCl_3)$ 4.2-4.4 (3H, m, OCH + OCH_2), 4.08 (1H, dd, J=8.6, 6.1 Hz, OCH_2), 3.76 (1H, dd, J=8.6, 4.9 Hz, OCH_2), 1.41 (3H, s, CH_3), 1.34 (3H, s, CH_3); $\delta_C(CDCl_3)$ 144.3 (CO_2), 110.8 (CMe_2), 109.3 (CN), 73.1 (OCH), 68.7 (OCH_2), 64.8 (OCH_2), 26.9 (CH_3), 25.5 (CH_3); $[\alpha]_D^{20}$ +1.4 (c 1.15, $CHCl_3$); ν_{max}(neat) 2991 w, 2248 w, 1791 m and 1755 cm^{-1} s; m/z(CI) 336 (2M-2CN+NH_4^+, 20), 294 (100), 277 (50), 232 (70); Found(ESI) 336.1651, $C_{14}H_{26}NO_8$ (2M-2CN+NH_4^+) requires 336.1653.

Diastereoselective synthesis of cyanoformates derived from chiral cyanoformates 67-81.

To a stirred solution of KCN (3.3 mg, 0.06 mmol) and catalyst **10** (31.2 mg, 0.027 mmol) at -40 ^oC was added aldehyde (1.28 mmol) and cyanoformate **67**, **73**, **77**, or

81 (1.54 mmol). The reaction was stirred at -40 °C for 24 hours and if no reaction occurred, was allowed to warm to room temperature and stir for an additional two weeks. The reaction was passed through a plug of silica gel, eluting with CH_2Cl_2. A sample was purified by flash chromatography (CH_2Cl_2) to give compounds **82a,b** or **83a,b** as white solids.

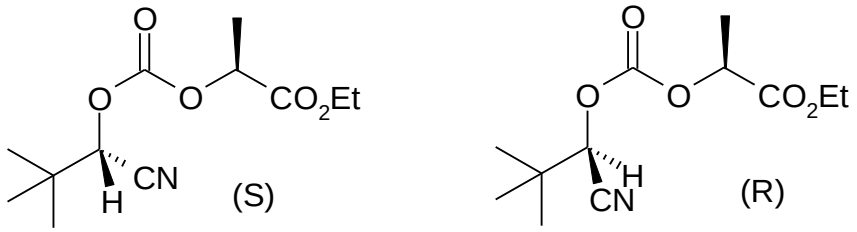
Compounds 82a (major and minor).



Obtained in a 12.3 : 1 ratio in favour of (S) using the (*R,R*)-enantiomer of catalyst **10** and in a 9 : 1 ratio in favour of (*R*) using the (*S,S*)-enantiomer of catalyst **10**. $\delta_H(CDCl_3)$ **82a**(S): 7.4-7.7 (5H, m, ArH), 6.28 (1H, s, CHCN), 5.07 (1H, q, J=7.2 Hz, $CH_3C\underline{H}O$), 4.19 (2H, q, J=7.1 Hz, $CH_3C\underline{H}_2O$), 1.56 (3H, d, J=7.2 Hz, $C\underline{H}_3CH$), 1.22 (3H, t, J=7.1 Hz, $C\underline{H}_3CH_2$); **82a**(R): 7.4-7.6 (5H, m, ArH), 6.25 (1H, s, CHCN), 5.01 (1H, q, J=7.1 Hz, $CH_3C\underline{H}O$), 4.1-4.3 (2H, m, $CH_3C\underline{H}_2O$), 1.51 (3H, d, J=7.1 Hz, $C\underline{H}_3CH$), 1.27 (3H, t, J=7.1 Hz, $C\underline{H}_3CH_2$); $\delta_C(CDCl_3)$ **82a**(S): 169.5 (CO_2), 153.1 (CO_3), 131.5 (ArC), 130.7 (ArCH), 129.5 (ArCH), 125.9 (ArCH), 115.4 (CN), 73.2 (OCH), 66.9 (OCH), 61.7 (OCH_2), 16.8 (CH_3), 13.9 (CH_3); **82a**(R): 169.4 (CO_2), 152.9 (CO_3), 131.6 (ArC), 130.8 (ArCH), 129.6 (ArCH), 126.1 (ArCH), 115.3 (CN), 73.3 (OCH), 67.0 (OCH), 61.8 (OCH_2), 16.8 (CH_3), 14.0 (CH_3); $[\alpha]_D^{20}$ **82a**(S): +112 (c 0.05, $CHCl_3$), **82a**(R): -12.5 (c 0.8, $CHCl_3$); ν_{max}(neat) 2988 m and 1748 cm^{-1} s;

m/z(CI) 295 ($M+NH_4^+$, 40), 136 (100); Found(ESI) 295.1292; $C_{14}H_{19}N_2O_5$ $(M+NH_4)^+$ requires 295.1288.

Compounds 82b (major) and (minor).

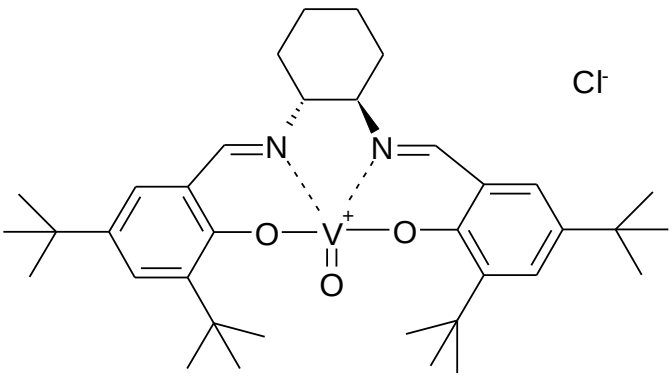


Obtained in a 10.8 : 1 ratio in favour of (S) using the (*R,R*)-enantiomer of catalyst **10** and in a 13.3 : 1 ratio in favour of (R) using the (*S,S*)-enantiomer of catalyst **10**. $\delta_H(CDCl_3)$ **82b**(S): 5.02 (1H, q, J=7.1 Hz, $CH_3C\underline{H}O$), 4.98 (1H, s, CHCN), 4.19 (2H, q, J=7.1 Hz, $CH_3C\underline{H}_2O$), 1.54 (3H, d, J=7.1 Hz, $C\underline{H}_3CH$), 1.26 (3H, t, J=7.1 Hz, $C\underline{H}_3CH_2$), 1.13 (9H, s, $(CH_3)_3$); **82b**(R): 5.05 (1H, q, J=7.1 Hz, $CH_3C\underline{H}O$), 4.92 (1H, s, CHCN), 4.1-4.3 (2H, m, $CH_3C\mathbf{H}_2O$), 1.57 (3H, d, J=7.1 Hz, $C\underline{H}_3CH$), 1.30 (3H, t, J=7.1 Hz, $C\underline{H}_3CH_2$), 1.12 (9H, s, $(CH_3)_3$); $\delta_C(CDCl_3)$ **71b**(S): 169.7 (CO_2), 153.5 (CO_3), 115.4 (CN), 73.8 (CHO), 73.1 (CHO), 62.0 (OCH_2), 35.1 (CMe_3), 25.2 (CH_3), 17.0 (CH_3), 14.1 (CH_3); **82b**(R): 169.4 (CO_2), 153.4 (CO_3), 115.3 (CN), 73.9 (CHO), 73.2 (CHO), 61.8 (OCH_2), 35.0 (CMe_3), 25.1 (CH_3), 16.8 (CH_3), 14.0 (CH_3); Mp **82b**(S): 82-84 °C, **82b**(R): 89-91 °C; $[\alpha]_D^{20}$ **71b**(S): +34.0 (c 0.1, $CHCl_3$), **82b(R)**: +100 (c 0.05, $CHCl_3$); ν_{max}(ATR) 2988 m, 1761 m, 1744 and 1633 cm^{-1} s; m/z(ESI) 280 ($M+Na^+$, 80%), 275 ($M+NH_4^+$, 100), 258 (MH^+, 10), 241 (20); Found(ESI) 275.1600; $C_{12}H_{23}N_2O_5$ $(M+NH_4)^+$ requires 275.1601.

General method for the synthesis of vanadium catalysts.[183]

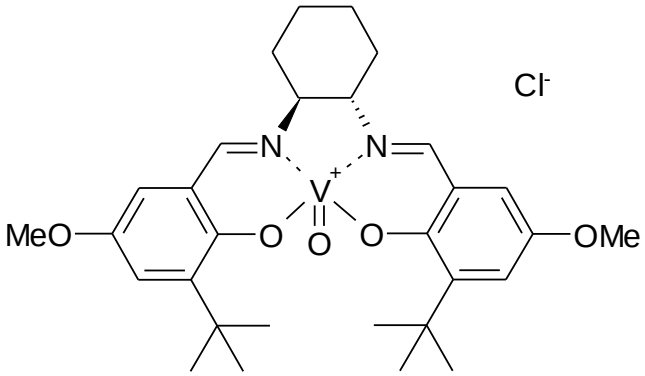
A solution of vanadyl sulphate (0.3 g, 2.2 mmol) in ethanol (30 ml) was added to a stirred solution of ligand (2.0 mmol) in THF (20 ml). The solution was heated under reflux for 3 hours, and the solvent was removed *in vacuo*. The green solid (mixture of V(IV) and V(V)) was redissolved in acetonitrile (200 ml) and ceric ammonium nitrate (1.3 g, 2.4 mmol) was added. The reaction was allowed to stir for 10 minutes, then the solvent was removed *in vacuo*. The residue was redissolved in CH_2Cl_2 (120 ml), and washed with 1M $HCl_{(aq)}$ (40 ml). The organic layer was dried over $MgSO_4$, the solvent removed *in vacuo*, and the crude product was purified by silica gel chromatography, using CH_2Cl_2 followed by a 2:1 mixture of EtOAc and MeOH as eluent.

Catalyst **83**, the standard vanadium catalyst



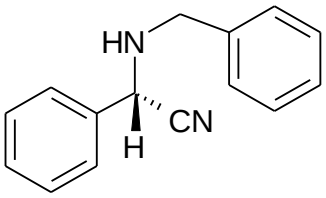
Obtained as a green solid (0.45 g, 37%). $\delta_H(CDCl_3)$: 8.79 (1H, s, N=CH), 8.58 (1H, s, N=CH), 7.82 (1H, s, ArH), 7.73 (1H, s, ArH), 7.62 (1H, s, ArH), 7.52 (1H, s, ArH), 4.16-4.11 (2H, m, CHN), 2.19-1.26 (44H, m, $4x(CH_2)_2$ + $4x(CH_3)_3$).

p-Methoxy, o-^{t}Bu catalyst (catalyst **90**)[199]



Obtained as a green solid (0.38 g, 30%). $\delta_H(CDCl_3)$: 8.65 (1H, s, N=CH), 8.44 (1H, s, N=CH), 7.29 (1H, s, ArH), 7.28 (1H, s, ArH), 7.03 (1H, s, ArH), 6.97 (1H, s, ArH), 4.35-4.26 (2H, m, CHN), 3.88 (3H, s, OMe), 2.54-1.82 (8H, m, $(CH_2)_4$), 1.51 (18H, s, $2x(CH_3)_3$).

General procedure for the Strecker reaction[183]



To a stirred solution of catalyst (0.026 mmol) in toluene (5ml) was added trimethylsilyl cyanide (0.041 ml, 0.307 mmol) and alcohol (0.321 mmol) under argon at -40 °C. The reaction mixture was allowed to stir at -40 °C for 1 hour. Benzilydene benzylamine (0.048 ml, 0.26 mmol) was added, and the reaction was stirred for a further 3 hours. The reaction mixture was passed through a plug of silica using CH_2Cl_2 as eluent, and the solvent was removed *in vacuo*. The

enantiomeric excess was determined by reacting the product with camphor-(+)-sulphonic acid inside a nmr tube.

$\delta_H(CDCl_3)$: 7.55-7.05 (10H, m, ArH), 4.66 (1H, s, CHCN), 3.98 (1H, d, J=15 Hz, $PhCH_2$), 3.87 (1H, d, J=15 Hz, $PhCH_2$), 1.79 (br, 1H, NH).

Genral procedure for the Strecker reaction with p-nitrophenol (Table 24, Scheme 69)

To a stirred solution of catalyst (0.026 mmol) in toluene (5ml) was added trimethylsilyl cyanide (0.041 ml, 0.307 mmol) and para-nitrophenol (0.321 mmol) under argon at -40 ^oC. The reaction mixture was allowed to stir at -40 ^oC for 1 hour. Benzilydene benzylamine (0.048 ml, 0.26 mmol) was added, and the reaction was stirred for a further 3 hours. The reaction mixture was passed through a plug of silica using CH_2Cl_2 as eluent, and the solvent was removed *in vacuo*. The enantiomeric excess was determined by reacting the product with camphor-(+)-sulphonic acid inside a nmr tube.

$\delta_H(CDCl_3)$: 7.55-7.05 (10H, m, ArH), 4.66 (1H, s, CHCN), 3.98 (1H, d, J=15 Hz, $PhCH_2$), 3.87 (1H, d, J=15 Hz, $PhCH_2$), 1.79 (br, 1H, NH).

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