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Synthesis and applications of non-racemic cyanohydrins

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Abstract—Methods for the catalytic asymmetric synthesis of cyanohydrins derived from both aldehydes and ketones are reviewed. Successful catalysts based on enzymes, peptides and transitional metal complexes are included, and mechanistic detail is included where appropriate. Illustrations of the many synthetic applications of non-racemic cyanohydrins are given.

Contents

1. Introduction

In 1993 I wrote a comprehensive review on catalytic asymmetric cyanohydrin synthesis.[1] At that time, the relative importance of the three main classes of catalysts for the asymmetric addition of cyanide to carbonyl compounds appeared to be: cyclic dipeptides > enzymes > transition metal complexes. Since then this order has completely reversed, so the purpose of this review is to provide an update on the current situation. Two other reviews dealing with the synthesis and applications of non-racemic cyanohydrins have also been published in the last 10 years.[2,3]

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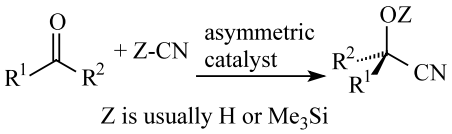
This review will first discuss the various asymmetric catalysts that are available for inducing the asymmetric addition of cyanide to carbonyl compounds (Scheme 1), and will then discuss other methods for the synthesis of non-racemic cyanohydrins. Within each section, the applications of the non-racemic cyanohydrins are illustrated to show the versatility of these readily available, bifunctional, chiral starting materials.

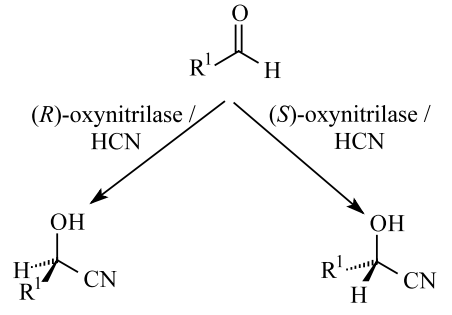


Scheme 1.

2. Enzyme-catalysed addition of cyanide to carbonyl compounds

In addition to the general reviews on asymmetric cyanohydrin synthesis,[1–3] four additional reviews dealing only with enzyme-catalysed asymmetric cyanohydrin synthesis have been published.[4–7] These reviews (along with the more general review of Gregory[3]) give more detail of the biological and biochemical aspects of these enzymes than is appropriate here.

Enzymes that catalyse the addition of hydrogen cyanide to carbonyl compounds are referred to as oxynitrilases or hydroxynitrile lyases (Scheme 2) and have been isolated from a wide variety of plant sources. The most readily available and hence most often used oxynitrilase enzyme is the (*R*)-oxynitrilase isolated from almonds. (*S*)-Oxynitrilase enzymes are less readily available from their natural sources, but have recently been cloned and over-expressed.



Scheme 2.

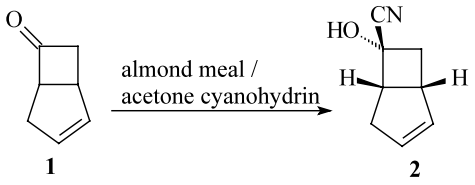
2.1. The (*R*)-oxynitrilase obtained from almonds

Bitter almonds (*Prunus amygdalus*) are the most abundant source of an oxynitrilase enzyme. As discussed in the previous review,[1] pure enzyme can be obtained readily from this source, or it is possible to use defatted almond meal as a crude source of the enzyme.[8] The preparation of the latter is particularly straightforward and requires no biochemical equipment. Both purified and crude enzyme extracts exhibit similar enantioselectivities towards a range of substrates. The entrapment of almond oxynitrilase in lens-shaped gels derived from poly(vinyl alcohol) has also been reported and the enzyme in this form was found to exhibit similar activity to the free enzyme.[9] The enzyme can be used in a mixed aqueous–organic solvent system, but better enantioselectivities are generally obtained when a wet organic solvent such as ethyl acetate[10] or diisopropyl ether[8,10–13] is used due to the selective suppression of the uncatalysed addition reaction in a non-aqueous solvent. This system has also been adapted to a continuous flow reactor, allowing a pre-mixed solution of an aldehyde and hydrogen cyanide in wet diisopropyl ether to be pumped through a column of almond meal. In this way, four aromatic and heteroaromatic aldehydes were converted into cyanohydrins with enantiomeric excesses of >97%. Only 4-fluorobenzaldehyde gave a product with a lower enantiomeric purity of 84%. A column composed of 15 g of defatted almond meal could convert at least 2 mol of aldehyde into its cyanohydrin without any decrease in yield or enantioselectivity during the reaction.[14]

The use of a mixed aqueous–organic solvent system comprised of citrate buffer and methyl *tert*-butyl ether combined with precise temperature control (±1°C) has however been recommended in the case of difficult substrates for almond oxynitrilase, such as unsaturated aliphatic aldehydes, cinnamaldehyde, and hydroxy benzaldehydes.[15] The hydrogen cyanide required by the enzyme can be added directly or can be generated in situ by the decomposition of acetone cyanohydrin.[8,16–18]

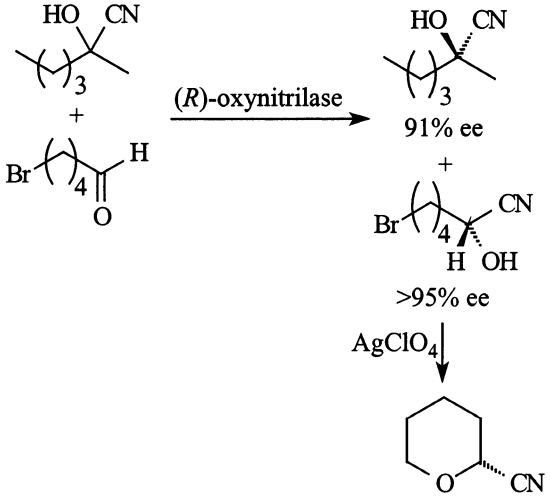
The natural substrate for the almond oxynitrilase is benzaldehyde, however the enzyme has a very broad substrate tolerance and a wide range of aliphatic and aromatic aldehydes are converted into cyanohydrins with high enantiomeric excesses. Effenberger and Heid have shown that some aliphatic ketones are also substrates for the enzyme.[19] Four methyl ketones were converted into (*R*)-cyanohydrins with 95–98% enantiomeric excess and in 40–94% chemical yield using the almond oxynitrilase in citrate buffer. Similarly, three ethyl ketones were converted to (*R*)-cyanohydrins with 66–90% enantiomeric excess by the same enzyme in diisopropyl ether. However, the chemical yields for the ethyl ketone products were only 7–33% indicating that these substrates are at the limit of the enzyme's tolerance. Similar results were obtained by Kiljun and Kanerva using almond meal in diisopropyl ether.[20] The only complex ketone that has been demonstrated to be a substrate for almond oxynitrilase is racemic bicyclo[3.2.0]hept-2-en-6-one **1**, which upon treatment with oxynitrilase and acetone cyanohydrin for five days gave the enantiomerically pure cyanohydrin **2** in 26% yield as shown in Scheme 3.[21]

An ingenious application of (*R*)-oxynitrilase, which takes advantage of the facts that both aldehydes and ketones are substrates and that the cyanohydrins of aldehydes are thermodynamically more stable than those of ketones, is the enantioselective transfer of



Scheme 3.

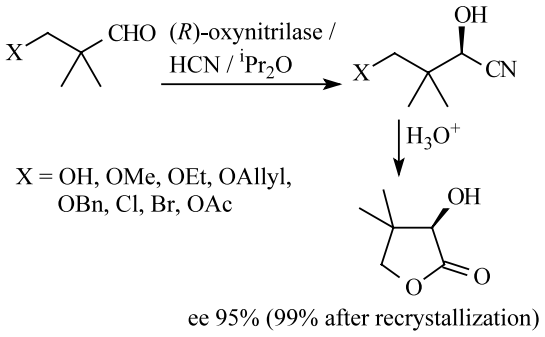
hydrogen cyanide from a ketone cyanohydrin to an aldehyde. An example of this process is shown in Scheme 4, and both the aldehyde cyanohydrin and the residual ketone cyanohydrin are obtained with greater than 90% enantiomeric excess, the former as the (*R*)-enantiomer and the latter as the (*S*)-enantiomer. Treatment of the ω-bromo-cyanohydrin with silver perchlorate gave the corresponding (*R*)-2-cyanotetrahydropyran without any racemisation.[20,22]



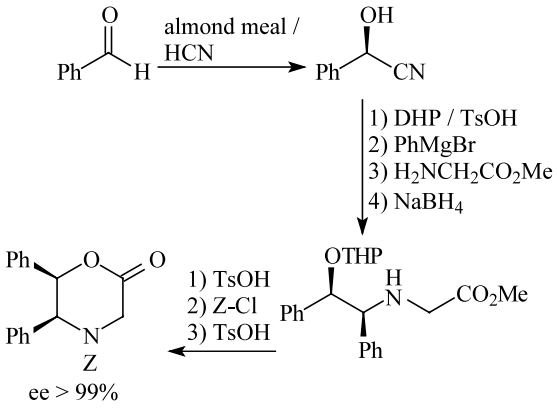
Scheme 4.

The enantiomerically enriched cyanohydrins obtained using (*R*)-oxynitrilase have been used as starting materials for a number of important chemical intermediates. Effenberger has shown that acid hydrolysis of the cyanohydrins derived from a number of substituted pivaldehydes (optimally X = OMe) leads directly to (*R*)-pantolactone (Scheme 5).[23] Another application is the asymmetric synthesis of Williams' template for asymmetric amino acid synthesis developed by Brussee et al. and outlined in Scheme 6.[24] A key step in this synthesis is the diastereoselective, chelation-controlled reduction of the imine formed after the reaction with glycine methyl ester, and many similar chelation-controlled additions have also been reported.

The reaction of a nitrile with a Reformatsky reagent is known as the Blaise reaction and when applied to *O*-trimethylsilyl cyanohydrins leads to the formation of tetronic acids with high enantiomeric excess as shown in Scheme 7.[25] By working-up the Blaise reaction with ammonium chloride it is possible to isolate acyclic γ-trimethylsilyloxy-β-amino-α,β-didehydro esters from this reaction. These compounds can subsequently be cyclised to the amino analogues of tetronic acids.[26]

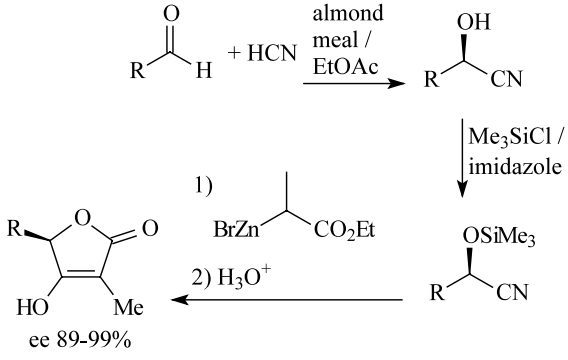


Scheme 5.

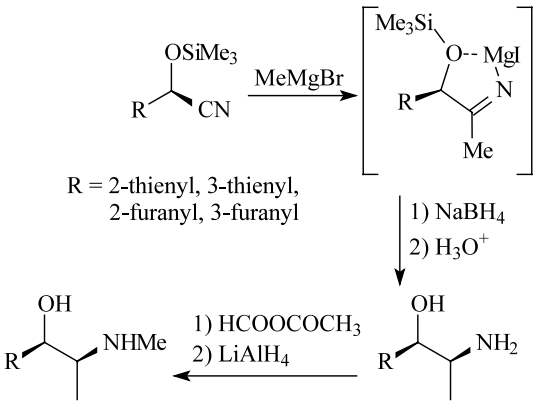


Scheme 6.

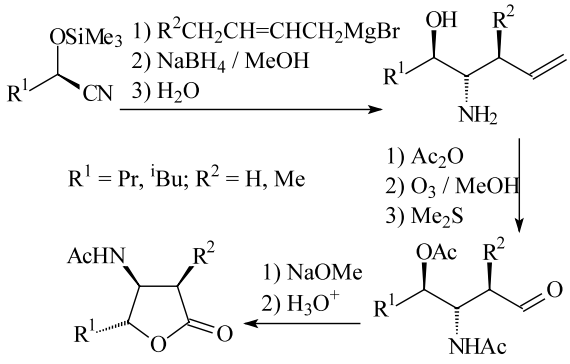
Grignard reagents also add to the nitrile group of a cyanohydrin trimethylsilyl ether and this has been employed in a synthesis of heterocyclic analogues of ephedrine (Scheme 8),[27] and β-amino-γ-butyrolactones (Scheme 9).[28] Again, a key step in these syntheses is the diastereoselective reduction of a magnesium iminate. A similar diastereoselective reduction of a magnesium iminate was employed in a synthesis of *N*-acetyl-L-daunosamine **3**, as well as its isobutyryl analogue **4** (Scheme 10). Whilst the aldehyde **5** (needed for the preparation of **3**) was readily available from lactaldehyde, the isobutyryl analogue **6** was itself prepared by the oxynitrilase-catalysed addition of hydrogen cyanide to isobutyraldehyde.[29] A general synthesis of (2*S*,3*S*)-β-amino-α-hydroxy acids starting from 2-furaldehyde and



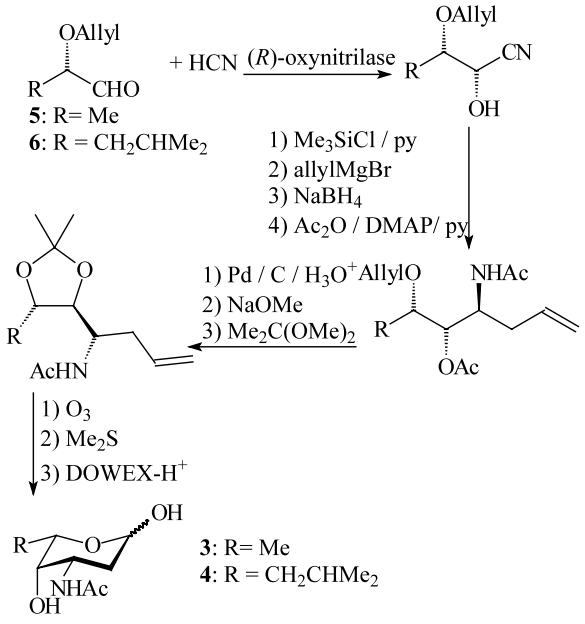
Scheme 7.



Scheme 8.

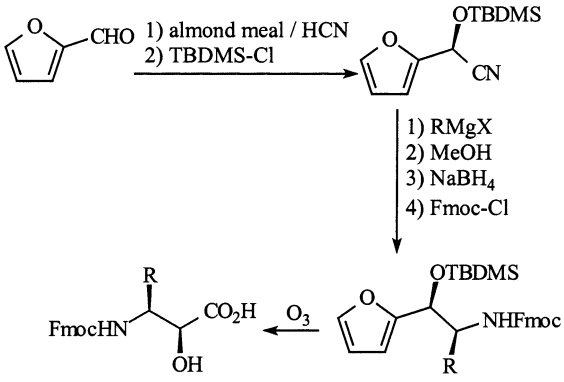


Scheme 9.

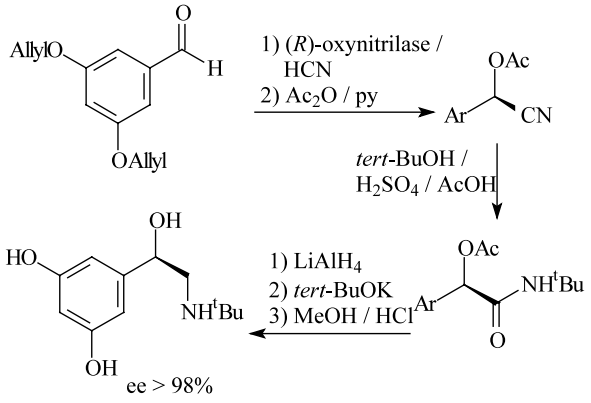


Scheme 10.

employing a similar sequence of hydrocyanation, Grignard addition and diastereoselective reduction of the resulting imine has also been reported as shown in Scheme 11.[30] A Ritter reaction to convert a protected cyanohydrin into the corresponding α-acetoxy *tert*-butylamide was a key step in an asymmetric synthesis of the bronchodilator (*R*)-terbutaline as shown in Scheme 12.[31]

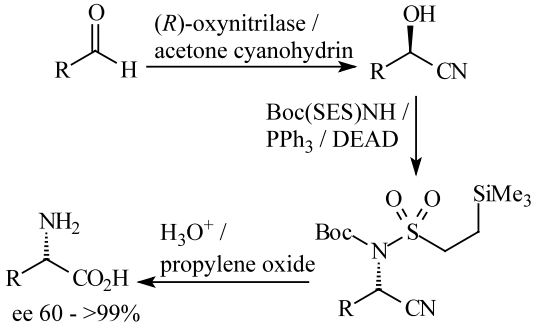


Scheme 11.



Scheme 12.

Whilst most transformations of non-racemic cyanohydrins have concentrated on the derivatisation of the nitrile group, reactions at the alcohol functionality can also be effective. Decicco and Grover have shown that (*R*)-cyanohydrins undergo a Mitsunobu reaction when treated with a suitable nitrogen source, triphenylphosphine and diethyl azodicarboxylate to give, after acidic hydrolysis, (*S*)-α-amino acids as shown in Scheme 13.[32] (*R*)-Cyanohydrins react with toluenesulfonyl chloride, methanesulfonyl chloride or 4-nitrobenzenesulfonyl chloride without loss of stereochemical purity and the sulfonyloxy nitriles react with a variety of sulfur-based



Scheme 13.

nucleophiles such as thioacetate or thiocyanate to give (*S*)-α-thionitriles without racemisation.[33]

2.2. Other (*R*)-oxynitrilases

An (*R*)-oxynitrilase enzyme has also been isolated and purified from flax (*Linum usitatissimum*). This enzyme has a completely different substrate specificity to the enzyme obtained from almonds; the natural substrate for the flax enzyme is acetone, and aliphatic aldehydes and some aliphatic ketones were also found to be substrates, whilst aromatic aldehydes were not processed by this enzyme. Using immobilised flax enzyme in methyl *tert*-butyl ether, butan-2-one could be converted into (*R*)-2-hydroxy-2-methyl butyronitrile with 87% enantiomeric excess.[34] This enzyme has subsequently been cloned and over-expressed in *Pichia pastoris*, a process which is simpler for the flax enzyme than the almond enzyme as the latter requires a flavin cofactor whilst the flax enzyme only requires zinc ions as cofactors. The cloned enzyme was used to catalyse the addition of hydrogen cyanide to a range of aliphatic aldehydes and ketones. In general, small substrates gave the best results (in terms of yields and enantiomeric excess), with propanal, butanal, isobutanal, crotonaldehyde, methacrolein, butanone and pentan-2-one all giving high yields of the corresponding (*R*)-cyanohydrins with enantiomeric excesses >90%. By contrast, large substrates such as hexanal, 3-phenylpropanal, and cinnamaldehyde gave low yields of cyanohydrins with <10% enantiomeric excess.[35]

Kiljunen and Kanerva have investigated the use of (*R*)-oxynitrilases obtained from apples, apricots, cherries and plums. In each case, the enzymes were used as a crude 'meal' and the results were compared with the use of almond meal. Apple meal was the most active of the fruit (*R*)-oxynitrilases and was superior to almond meal in the case of sterically hindered substrates. For example, pivaldehyde was converted into its (*R*)-cyanohydrin in 99% yield and with 90% enantiomeric excess by apple meal, compared to just 73% yield and 70% enantiomeric excess for almond meal.[36] The oxynitrilase in apple meal was subsequently found to accept methyl ketones as substrates and where a direct comparison with almond oxynitrilase was carried out, the apple enzyme gave slightly higher (3–5%) enantiomeric excesses.[20]

Oxynitrilase-containing extracts have also been obtained from peaches and loquats and their activity compared with that of almond meal. The loquat-derived enzyme was found to have a rather narrow substrate tolerance, restricted to aromatic and heteroaromatic aldehydes, and gave lower enantiomeric excesses than those obtained using almond oxynitrilase. In contrast, peach meal was found to have a very similar substrate tolerance to almond meal and in some cases gave products with superior enantiomeric excesses. Thus, cinnamaldehyde was converted into its (*R*)-cyanohydrin with 69% enantiomeric excess by peach meal, whilst under the same conditions almond meal gave the product with only 51% enantiomeric excess.[11]

2.3. (*S*)-Oxynitrilases

The isolation and application of (*S*)-oxynitrilases has always been more problematic than the use of the corresponding (*R*)-oxynitrilases. In the 1993 review, only one (*S*)-oxynitrilase had found synthetic application; the enzyme isolated from millet (*Sorghum bicolour*).[1] Even this enzyme was difficult to isolate compared to almond oxynitrilase, especially in quantities suitable for synthetic work. This situation has completely changed over the last 10 years due to advances in biotechnology that have allowed two (*S*)-oxynitrilases to be cloned and over-expressed, thus making large quantities of these enzymes available for the first time.

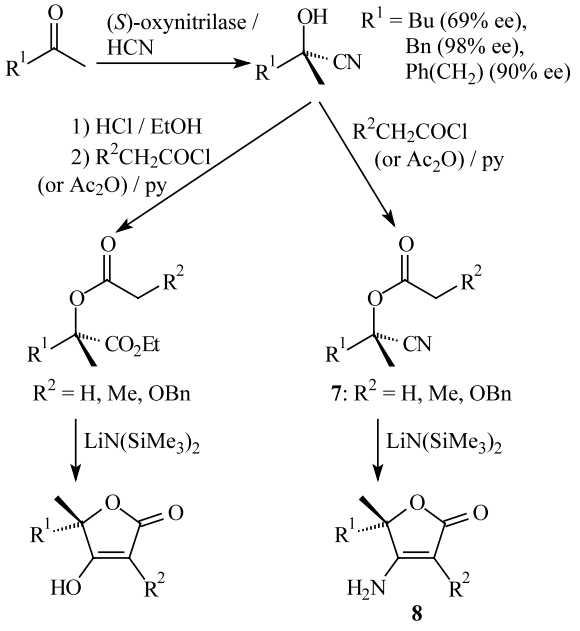
Rather than isolate pure enzyme, Kiljunen and Kanerva showed that it was possible to use ground, lyophilised and acetone washed shoots of *S. bicolour* as a source of (*S*)-oxynitrilase enzyme. This enzyme extract was capable of transferring hydrogen cyanide from acetone cyanohydrin to benzaldehyde, giving (*S*)-mandelonitrile with 90% enantiomeric excess and in 91% yield, all be it after 10 days reaction.[37] By using hydrogen cyanide as the cyanide source, the reaction times could be considerably shortened, and a range of aromatic aldehydes were converted into the corresponding (*S*)-cyanohydrins using *S. bicolour* shoots. High conversions and enantiomeric excesses (>90%) were observed unless the substrate contained a large substituent in the *para*-position of the aromatic ring.[8] The (*S*)-oxynitrilase obtained from *S. bicolour* was employed by Effenberger and Eichhorn to prepare the (*S*)-enantiomers of heterocyclic ephedrine analogues (see Scheme 8 for the synthesis of the (*R*)-enantiomers).[27]

Thus far it has not proven possible to clone the (*S*)-oxynitrilase enzyme present in *S. bicolour* due to the complex post-translational modifications made to this enzyme. However, a second (*S*)-oxynitrilase enzyme could be isolated from cassava (*Manihot esculenta*),[38] and in 1996 the coning and over-expression of this enzyme into *E. coli* was reported.[39] The recombinant enzyme had 25 times the specific activity of the natural enzyme and was found to have a very broad substrate tolerance. Of 15 assorted (aromatic, heteroaromatic, aliphatic and α,β-unsaturated) aldehydes studied, only acrolein (56% ee) gave a product with less than 85% enantiomeric excess. The best results were obtained using the enzyme supported on nitrocellulose, with hydrogen cyanide and diisopropyl ether. Subsequently, the use of this enzyme to add hydrogen cyanide to *O*-protected glycolaldehydes and lactaldehydes was investigated. The enantioselectivity and chemical yield were found to be very dependent on the nature of the *O*-protecting group, with allyl and 2-methylallyl groups giving best results.[12] Methyl ketones were also found to be substrates for the recombinant enzyme, though the range of good substrates was rather narrow in this case. Thus, whilst 4-methyl pentan-2-one was converted into its (*S*)-cyanohydrin in 69% yield and 91% enantiomeric excess, some other substrates such as butan-2-one and

3,3-dimethyl butan-2-one gave products in high yield (81 and 91%, respectively), but with low (28 and 18%) enantiomeric excess. Other substrates such as acetophenone and heptan-2-one gave cyanohydrins with high (78, 92%) enantiomeric excess but in low yields (13, 39%).[39] Recently, the use of both the almond and cassava oxynitrilases to catalyse the addition of hydrogen cyanide to cyclohexan-4-ones has been reported. Whilst the products of this reaction are achiral, it was found that, unlike the chemical reaction, the enzymatic reactions were diastereoselective and complementary. Thus, the almond enzyme gave, in all cases, predominantly (>90%) the *trans*-isomer of the product whilst the cassava enzyme gave very high *cis*-selectivity (>96%) unless the substituent at the 4-position of the cyclohexane ring was a methyl or ethyl group.[40,41]

The crystal structures of the cloned enzyme in the presence of either acetone or chloroacetone have been obtained at 2.2 Å resolution and show that the carbonyl compound is hydrogen bonded to threonine and serine residues within the active site. A histidine residue is also available in the active site and it is suggested that this residue deprotonates the hydrogen cyanide, thus giving a base-catalysed cyanohydrin formation reminiscent of the standard, achiral chemical method for cyanohydrin synthesis.[42]

Effenberger et al. have utilised the tolerance of methyl ketones by the recombinant enzyme to develop an alternative synthesis of tetronic acids and their amino derivatives as shown in Scheme 14. Thus, three methyl ketones were converted into their (*S*)-cyanohydrins with 69–98% enantiomeric excess and then acylated to give *O*-acyl cyanohydrins **7**. Treatment of compounds **7** with lithium disilazide resulted in base induced ring-closure to amino tetronic acid derivatives **8**. When R^2 was



Scheme 14.

a benzyloxy group, these could be hydrogenated to the corresponding hydroxy derivatives. Alternatively, the cyanohydrins could be converted to α-hydroxy esters prior to acylation, and the same base-induced cyclisation then led to tetronic acid derivatives.[43]

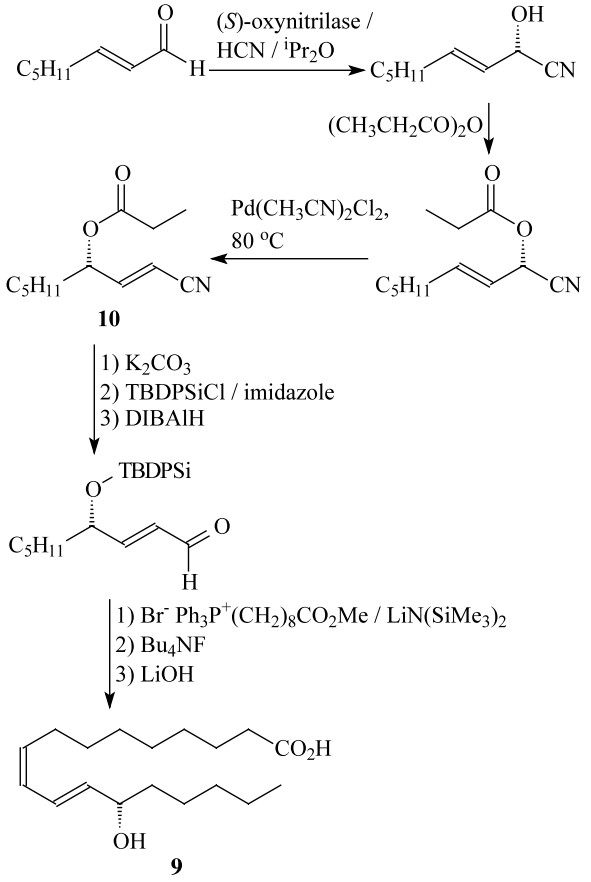
A third (*S*)-oxynitrilase enzyme has been isolated from the leaves of the rubber tree plant (*Hevea brasiliensis*) and exploited by the group of Griengl. This enzyme is capable of transferring hydrogen cyanide from acetone cyanohydrin to aliphatic aldehydes, giving (*S*)-cyanohydrins with enantiomeric excesses of 67–85%. Aromatic aldehydes are also substrates for the enzyme, but the enantioselectivity is more variable in this case. Thus, whilst benzaldehyde was converted into (*S*)-mandelonitrile with 94% enantiomeric excess, 3-phenoxy-benzaldehyde gave the corresponding cyanohydrin with only 20% enantiomeric excess.[44]

It was subsequently shown that a range of α,β-unsaturated aliphatic aldehydes were also substrates for this enzyme when hydrogen cyanide was used as the cyanide donor, giving allylic (*S*)-cyanohydrins with 80–95% enantiomeric excess.[45] Cinnamaldehyde was initially reported not to be a substrate for the rubber tree enzyme. However, it was later shown that under carefully controlled conditions (reaction in citrate buffer at 0°C at pH 4 using potassium cyanide to generate hydrogen cyanide in situ), cinnamaldehyde, aromatic aldehydes and heteroaromatic aldehydes were all good substrates, giving products with enantiomeric excesses >93%. The only exceptions were nitrogenous heteroaromatic aldehydes, which were not substrates for the enzyme, and *ortho*-substituted benzaldehydes, which gave products with lower enantiomeric excess (77% in the case of 2-methoxybenzaldehyde).[46]

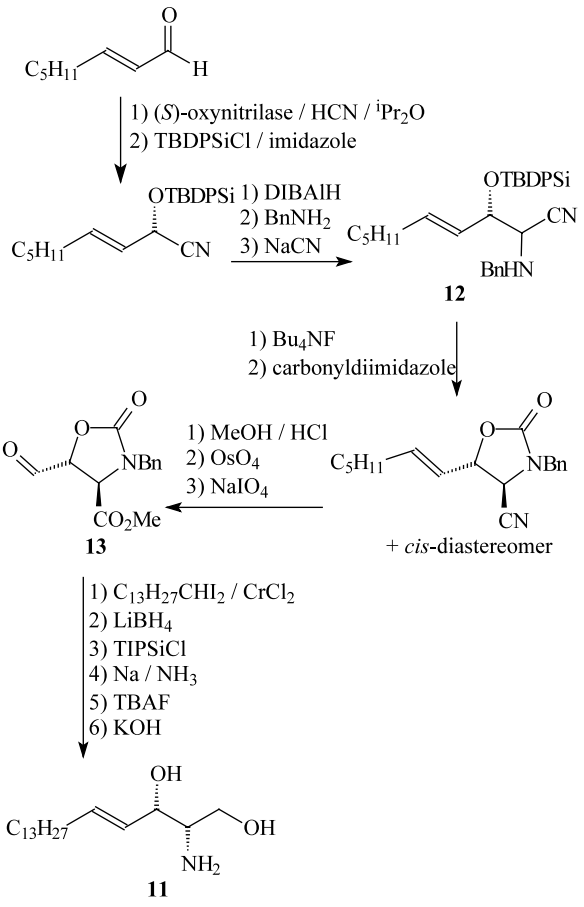
The rubber tree oxynitrilase has been cloned and overexpressed in *P. pastoris*. The optimal conditions for use of the cloned enzyme involve the use of a biphasic solvent system composed of citrate buffer and methyl *tert*-butyl ether. Under these conditions, eleven aliphatic, aromatic and heteroaromatic aldehydes were converted into their (*S*)-cyanohydrins with at least 98% enantiomeric excess. The only poor substrate observed under these conditions was benzyloxyethanal, which gave the corresponding cyanohydrin in high yield, but with only 12% enantiomeric excess. Aliphatic methyl ketones were also substrates for this oxynitrilase under these conditions, giving (*S*)-cyanohydrins with 75–89% enantiomeric excess, though in only moderate yields (13–49%).[47]

Given the poor results obtained with benzyloxyethanal, Griengl et al. subsequently investigated the use of a variety of chiral α-oxygenated and α,β-dioxygenated substrates and found that these are generally not good substrates for the rubber tree oxynitrilase.[18] Most recently, Griengl et al. have shown that whilst non-oxygenated chiral α-substituted aldehydes are generally substrates for the enzyme, no kinetic resolution occurs during reactions employing racemic α-substituted aldehydes, so the cyanohydrins are obtained as a mixture of diastereomers.[48]

The fact that α,β-unsaturated aldehydes are good substrates for the rubber tree oxynitrilase has been exploited in the synthesis of natural products. Thus Johnson and Griengl developed a nine-step synthesis of (*S*)-coriolic acid **9** starting from oct-2-enal as shown in Scheme 15. The addition of hydrogen cyanide to this aldehyde gave the (*S*)-cyanohydrin with 99% enantiomeric excess. Esterification of the cyanohydrin, followed by palladium-catalysed [3,3]-sigmatropic rearrangement gave α,β-unsaturated nitrile **10** with complete retention of configuration. The remainder of the synthesis involved standard protection, reduction, Wittig reaction and deprotection steps.[49] Subsequently, the authors reported a synthesis of the Sphingosines **11** starting from the same aldehyde (Scheme 16). In this case, the (*S*)-cyanohydrin was first protected, then reduced to an imine, condensed with benzylamine to give a benzyl imine and reacted again with cyanide to give amino nitrile **12** as an almost 1:1 mixture of diastereomers. Deprotection of the silyl ether of compound **12** followed by oxazolidinone formation allowed the two diastereomers to be separated by chromatography. Conversion of the nitrile of the *trans*-diastereomer to a methyl ester followed by oxidative cleavage of the alkene gave aldehyde **13**. Thereafter, a Schlosser modified Wittig reaction established the *cis*-double bond, and reduction of the ester established the required 2-amino-1,3-diol unit. Removal of the protecting groups then provided L-*threo*-sphingosine. Similarly, the *cis*-diastereomer of the oxazolidinone could



Scheme 15.



Scheme 16.

be used to prepare L-*erythro*-sphingosine, and the D-enantiomers could be prepared using almond (*R*)-oxynitrilase.[50]

2.4. Summary of the use of oxynitrilases

Oxynitrilase-catalysed asymmetric cyanohydrin synthesis is a field that has developed and matured rapidly over the last decade. The almond (*R*)-oxynitrilase is both commercially available and easily isolated; and both (*R*)- and (*S*)-oxynitrilases have been cloned and over-expressed into suitable organisms which are now commercially available. The oxynitrilases from almonds and the rubber tree have very broad substrate tolerances, generally give products with high enantiomeric excesses and are in many ways enantio-complementary to one another. The substrate ranges for these enzymes have been well documented, and the enzymes have been employed in a number of total syntheses.

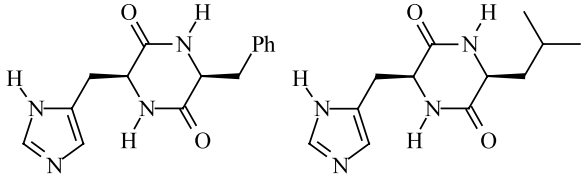
Looking to the future, reports of the site-directed mutagenesis of oxynitrilase enzymes are already starting to appear. At present, these studies are aimed at identifying key residues within the active site of the enzyme, but eventually they could be used to change the shape of the active site to enhance the enantioselectivity and/or alter the substrate range accepted by the enzyme. For example, only methyl and to some degree ethyl ketones are currently accepted as substrates for some

oxynitrilase enzymes. The mechanism of action of the enzymes is only now being determined due to the poor resolution of earlier X-ray crystal structures. Now that cloned enzymes are readily available, this situation should change and X-ray structures of the enzymes, mutated enzymes and enzyme/transition-state analogue should allow the mechanism of these enzymes to be fully understood.

3. Diketopiperazine-catalysed addition of cyanide to carbonyl compounds

In 1981, Inoue reported that diketopiperazine **14**, which is readily available from (*S*)-phenylalanine and (*S*)-histidine, would catalyse the asymmetric addition of hydrogen cyanide to aldehydes, giving (*R*)-cyanohydrins.[51] In the following years, it was shown that a wide range of aldehydes was substrates for catalyst **14**, with best enantioselectivities generally being observed for electron-rich aromatic aldehydes. For example, benzaldehyde is converted into (*R*)-mandelonitrile in 97% yield and with 97% enantiomeric excess using just 2 mol% of catalyst **14**. This work is covered in detail in my earlier review where the enantioselectivities observed with various substrates are tabulated.[1]

Inoue subsequently reported that diketopiperazine **15** catalyses the asymmetric addition of hydrogen cyanide to aldehydes to give (*S*)-cyanohydrins, despite the fact that both catalysts **14** and **15** are derived only from (*S*)-amino acids. Diketopiperazine **15** is not as enantioselective as catalyst **14**, giving cyanohydrins with 61–81% enantiomeric excess and unlike catalyst **14**, best results are obtained using aliphatic aldehydes as substrates.[52] Diketopiperazines **14** and **15** are two rare examples of synthetic asymmetric catalysts which do not contain a metal ion. The following sections will first discuss synthetic studies using catalyst **14**, and will then survey the mechanistic work that has been carried out to determine the mode of action and the origin of the asymmetric induction observed using these asymmetric catalysts.

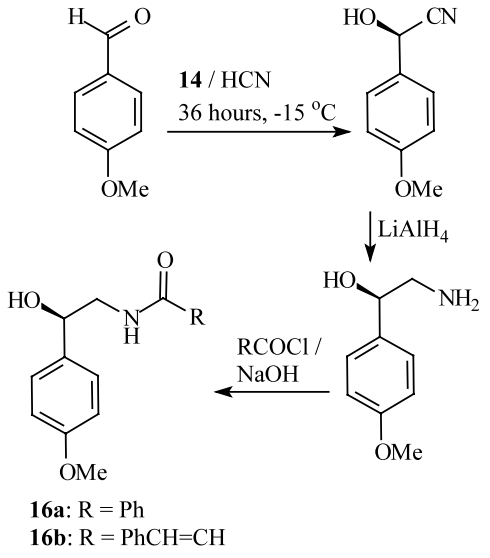


14 **15**

3.1. Synthetic studies employing diketopiperazine 14

Only one paper studying the substrate specificity of catalyst **14** has appeared since 1993. Kim and Jackson investigated the use of a range of *O*-substituted *para*-hydroxy-benzaldehydes as substrates. They found that substrates with a small group attached to the phenol were excellent substrates; thus *para*-allyloxy-benzaldehyde was converted into its (*R*)-cyanohydrin in 88% yield and with >98% enantiomeric excess. In contrast, substrates with a large group in the *para*-position (e.g. MEM or trimethylsilyl protected *para*-hydroxy-benzaldehydes) were very poor substrates for catalyst **14** giving cyanohydrins in less than 50% yield and with less than 5% enantiomeric excess.[53]

Jackson's group have also prepared a number of small natural products from cyanohydrins generated using catalyst **14**. Thus, *para*-methoxybenzaldehyde was converted into its (*R*)-cyanohydrin in 98% yield and with >99% enantiomeric excess as shown in Scheme 17. Subsequent reduction of the nitrile generated a β-amino alcohol which could be acylated with benzoyl chloride to give (−)-tembamide **16a**, or with cinnamoyl chloride to give (−)-aegeline **16b**.[54,55] Similarly, starting from *para*-allyloxy-benzaldehyde, the (*R*)-cyanohydrin could be prepared with >98% enantiomeric excess in 96% yield. Protection of the cyanohydrin followed by reduction with diisobutylaluminium hydride gave an imine which could be transiminated, reduced to the secondary amine with sodium borohydride and deprotected to give (−)-denopamine **17** as shown in Scheme 18.[55,56]

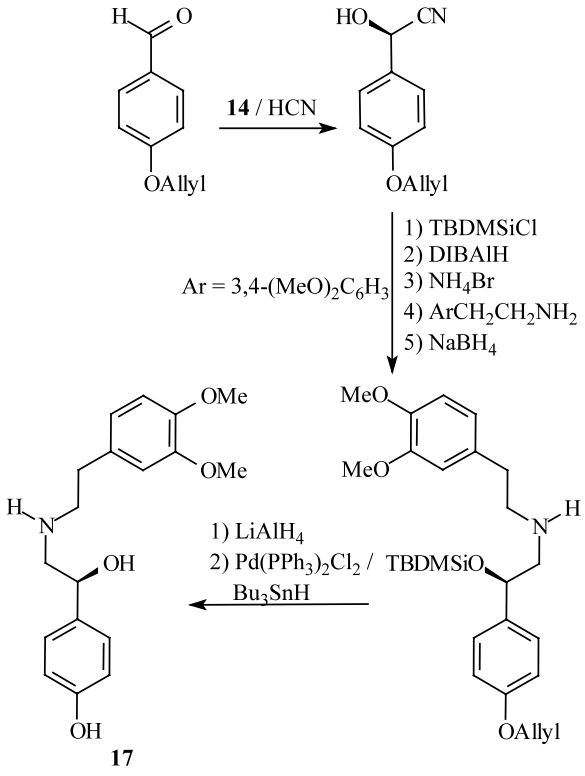


Scheme 17.

There have been two attempts to prepare matrix-supported versions of catalyst **14**. An attempt to attach the catalyst to Merrifield resin through one of the nitrogen atoms of the imidazole ring was unsuccessful as the resulting polymers converted *meta*-phenoxybenzaldehyde into its cyanohydrin with less than 20% enantiomeric excess.[57] The encapsulation of catalyst **14** within a sol–gel glass matrix was more successful as the resulting catalyst converted benzaldehyde into (*R*)-mandelonitrile with up to 98% enantiomeric excess, though the enantioselectivity decreased if the catalyst was reused.[58]

3.2. Mechanistic studies on diketopiperazine-catalysed asymmetric cyanohydrin synthesis

There have been a number of studies aimed at investigating the mode of action of catalyst **14** and hence



Scheme 18.

designing new catalysts with improved activity published since 1993. Before these are discussed however, a number of key features, known prior to 1993, associated with the use of catalyst **14** need to be appreciated:

1. The catalyst is only active under heterogeneous conditions. If reactions are carried out in benzene or toluene, then the catalyst forms a gel during the reaction. Gel formation is not essential however, since high catalytic activity can also be observed in ether, a solvent in which catalyst **14** is totally insoluble throughout the reaction.[59]
2. The active form of the catalyst is amorphous, so any attempt to purify the catalyst by recrystallisation gives inactive material.[60]
3. A proton source, such as water or methanol is required within the solid-state structure of the amorphous catalyst in order to observe catalytic activity.[61]

In view of these features, it is not surprising that the method of purification of catalyst **14** has a significant effect on its activity.[62] The most widely used method for purification/activation is to dissolve the catalyst in methanol and then precipitate it rapidly by pouring the solution into ether.

The conformations of catalysts **14** and **15** have been investigated by NMR techniques by a number of groups.[1] In 1994, North et al. published a direct comparison of the solution state conformations of the two catalysts based on NMR and molecular modelling studies. It was shown that the two catalysts had different minimum-energy conformations in DMSO, and that this resulted in different faces of the imidazole ring being shielded by the rest of the molecule (Fig. 1). It was speculated that this could be responsible for the opposite sense of asymmetric induction observed using these two catalysts.[63] A limitation of this work and of similar previous studies was that the solution state conformation might not have any relevance to the catalytically active conformation present in the amorphous solid state. However, North et al. were subsequently able to show by solid state ^{1}H NMR spectroscopy that the catalytically active, solid state conformation of catalyst **14** was the same as the solution state conformation.[64]

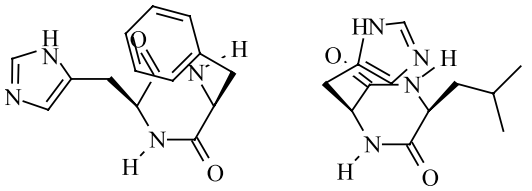


Figure 1.

There have been a number of attempts to modify the structure of catalyst **14** both to increase its catalytic activity, and to determine the important features for efficient catalysis. Noe et al. first prepared a range of analogues of catalyst **14** in which the phenylalanine residue had been replaced by an alternative aromatic or heteroaromatic residue (Fig. 2). Of these seven analogues, only the 2-thienyl derivative showed any catalytic activity for the asymmetric addition of hydrogen cyanide to benzaldehyde, and both the conversion and enantioselectivity were lower than those observed for catalyst **14** under the same conditions. The preferred conformation of each of these catalysts (in DMSO solution) was also determined, and all except the 9-anthracenyl derivative had the same conformation as that determined for catalyst **14**.[65]

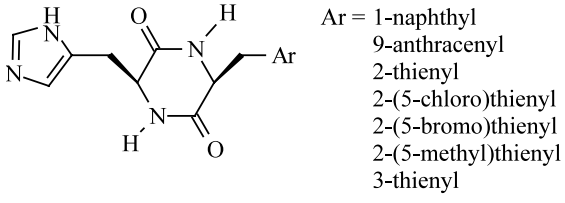


Figure 2.

In a subsequent paper, Noe et al. studied the use of methylated analogues **18**–**23** (Fig. 3) of diketopiperazine **14** as well as benzhydryl derivative **24** as catalysts for the asymmetric addition of hydrogen cyanide to benzaldehyde. The two *N*-methylated derivates **19** and **20** were found to be completely inactive, and this could be related to the fact that they were completely soluble in the reaction mixture. The other five analogues all formed a gel in a benzaldehyde/toluene mixture. The most active of the remaining catalysts was the dimethylphenylalanine derivative **22** which gave (*R*)-mandelonitrile with 60% enantiomeric excess but in

only 20% yield. The methylimidazole **23** and benzhydryl derivatives **24** also gave low chemical yields (10–20%) of mandelonitrile but with low enantiomeric excesses (22 and 36%, respectively) and in favour of the (*S*)-enantiomer. Catalyst **21** gave a 50% yield of (*R*)-mandelonitrile but with very low enantiomeric excess (15%), and the thienyl analogue **18** was completely inactive.[66]

Simultaneously with Noe's work, Thoen and Lipton prepared and studied the enantiomers of catalysts **19** and **20**, and found that whilst under some conditions the catalysts gave high yields of mandelonitrile, the enantiomeric excess of the product was always negligible.[67] Also simultaneously with Noe's work, Broxterman et al. studied diketopiperazine **21** and its diastereomer **25** (Fig. 3). In contrast to Noe's results, it was found that at –40°C, compound **21** was an excellent catalyst for the asymmetric addition of hydrogen cyanide to both benzaldehyde (98% yield, 99% enantiomeric excess) and *para*-methoxybenzaldehyde (93% yield, 89% enantiomeric excess). Surprisingly, diketopiperazine **25** was also found to be an active catalyst, though it gave products with only 23–32% enantiomeric excess.[68]

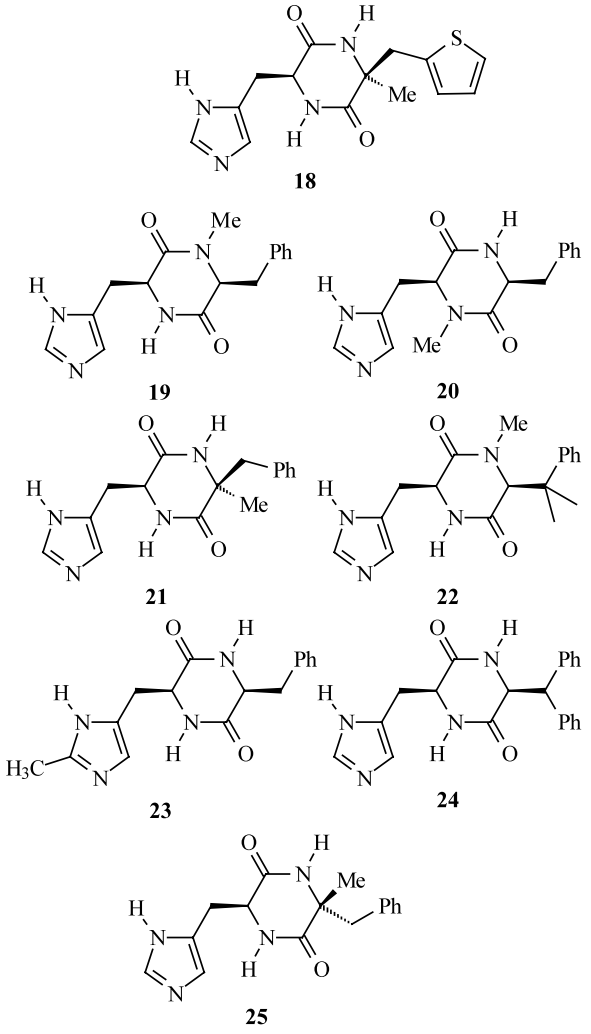


Figure 3.

The differing results obtained for diketopiperazines **19**–**21** and **25** by different groups are probably related to the different reaction conditions and methods of purifying/activating the catalyst used by different workers. This highlights again, that the catalytic activity of the diketopiperazines is very dependent on both the molecular structure of the catalyst and its supramolecular, solid-state structure.

Since catalyst **14** was first discovered, various transition state models have been proposed to explain the catalysis and the origin of the asymmetric induction. These models were all based on a single molecule of catalyst **14** being involved in the catalytic cycle.[53,59–61,68] In 1996 however, Shvo et al. carried out gel-phase kinetics studies on asymmetric cyanohydrin forming reactions catalysed by diketopiperazine **14**. The kinetics showed that the reactions were second order with respect to the catalyst and hence that two molecules of the catalyst were involved in the catalysis.[62] This result effectively nullified all previous mechanistic hypotheses.

Another unusual feature of catalysis using diketopiperazine **14** is that the reactions exhibit enantioselective autoinduction; that is the enantiomeric excess of the product increases as the reaction progresses. This phenomenon was first noted by Danda et al. for reactions involving 3-phenoxybenzaldehyde as substrate.[69] More recently, Lipton et al. have shown that this a general feature of reactions using catalyst **14** and that it can be exploited to enhance the enantioselectivity of the reactions. The implication of the enantioselective autoinduction is that a catalytic species derived from a complex of compound **14** and a cyanohydrin is a more effective catalyst than compound **14** alone. Hence, by adding a sample of a cyanohydrin to the reaction mixture at the start of the reaction, it should be possible to enhance the enantiomeric excess of the product. This process does not require that the added cyanohydrin is the same as the cyanohydrin being prepared during the catalytic reaction, or even that the added cyanohydrin is chiral. Thus, the addition of hydrogen cyanide to furfural catalysed by 2 mol% of *ent*-**14** gives the (*S*)-cyanohydrin in 92% yield, but with only 53% enantiomeric excess. However, if 8 mol% of (*S*)-mandelonitrile is also added at the start of the reaction, then the furfural cyanohydrin is formed in 95% yield and with 81% enantiomeric excess. Addition of the same amount of (*R*)-mandelonitrile however, lowers the enantiomeric excess of the product to 50%. Similarly, addition of acetone cyanohydrin (8 mol%) raises the enantiomeric excess of the furfural cyanohydrin to 73%. Even some non-cyanohydrin species can exhibit the same effect, thus (*S*)-1-phenyl-ethanol (8 mol%) raises the enantiomeric excess of the product to 72%, whilst (*R*)-1-phenyl-ethanol (8 mol%) raises the enantiomeric excess of the product by a much smaller amount to 58%. However, not all cyanohydrins or alcohols exhibit such a pronounced effect, (*S*)-pivaldehyde cyanohydrin (8 mol%) raises the enantiomeric excess of furfural cyanohydrin by only 2%, to 55%, and methanol (8–20 mol%) by only 4–5% to 57–58%.[70]

Based on the above results, Hua et al. have proposed a new model for the asymmetric addition of hydrogen cyanide to benzaldehyde catalysed by diketopiperazine **14** and a chiral cyanohydrin (Fig. 4).[71] This model involves two molecules of catalyst **14** (which is consistent with the kinetics results) each of which is bound to a cyanohydrin molecule (thus providing an explanation of the enantioselective autoinduction). In the early stages of the reaction, these cyanohydrins would have to be replaced by other hydrogen bonding species such as methanol or water unless a cyanohydrin additive was specifically introduced at the start of the reaction. The model is also consistent with the lack of catalytic activity observed for *N*-methylated analogues of catalyst **14** since the amide NH's are required for the formation of the hydrogen bonds which hold the supramolecular framework together. Similarly, catalysis by this model would only be effective in the solid-state since the hydrogen bonded network would be disrupted in solution. Cyanide would presumably be delivered to the *si*-face of the coordinated aldehyde from one of the imidazolium cyanides.

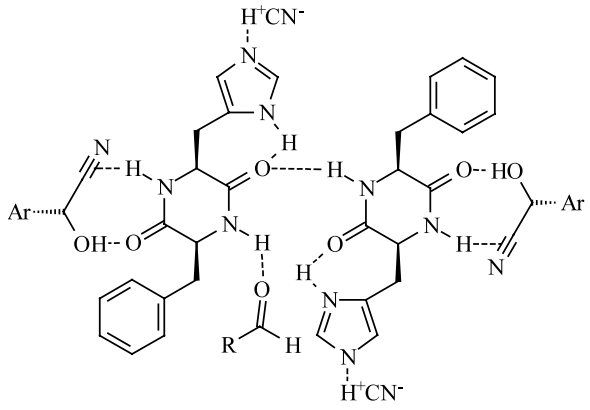


Figure 4.

Whilst the model of Hua et al. is a significant advance on previously proposed transition-state models, it does not explain all of the observed features of the reaction, and in particular the cyanohydrins appear to be coordinated some distance from the aldehyde and so would not be expected to be able to exert a significant effect on the enantioselectivity of the catalytic complex. An alternative transition state structure which includes all of the positive features of the Hua model but which involves the cyanohydrin (or another proton donor) in a more active role, closer to the prochiral centre of the aldehydes is suggested in Fig. 5.

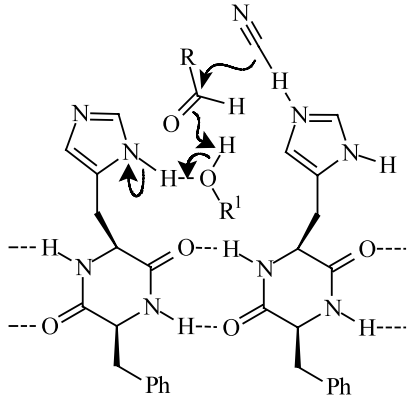


Figure 5.

3.3. Summary of the use of diketopiperazines as catalysts for asymmetric cyanohydrin synthesis

During the period of this review, most work in this area has concentrated on studying mechanistic aspects of the reaction and attempting to prepare analogous catalysts with even higher catalytic activity. Little if any progress has been made in the latter case, but thanks to the work of Shvo and Lipton, much more is now known about the mechanism of this reaction and new transition state structures, which are compatible with all of the observed features of the catalysis, can be proposed. Neither of the structures shown in Fig. 4 and Fig. 5 however, yet has the detail necessary to predict the magnitude and sense of the asymmetric induction during cyanohydrin formation. Hence, there is scope for further work (synthetic and modelling) to refine and optimise these possible transition state structures.

Interest in asymmetric cyanohydrin synthesis using diketopiperazines as catalysts has diminished somewhat over the last 10 years. This may be due to a number of factors including: the lack of success in developing new variants of the catalyst; the necessity to use hydrogen cyanide as the cyanide source since the diketopiperazines give poor results with acetone cyanohydrin as an in situ source of hydrogen cyanide;[1] and the lack of a viable mechanism combined with the difficulty of obtaining mechanistic information from a heterogeneous catalyst system.

4. Metal-catalysed addition of cyanide to carbonyl compounds

There has been an explosion of interest in the design of (mostly) transition metal complexes as catalysts for the asymmetric addition of cyanide to carbonyl compounds; the 1993 review of asymmetric cyanohydrin synthesis had just 14 references on metal-catalysed systems. In the following sections I have classified the various catalysts according to the nature of the chiral ligand(s), starting with bidentate ligands and progressing to tetradentate ligands, followed by a miscellaneous section covering ligands whose coordination number is not obvious. This is appropriate since increasingly, the same ligand is being complexed to more than one metal to give active catalysts, and this classification allows a direct comparison of the various metals.

4.1. Use of complexes containing bidentate ligands

In 1993, Corey and Wang reported that the *simultaneous* use of magnesium bisoxazoline complex **26** (20 mol%) and uncomplexed bisoxazoline **27** (12 mol%)

generated a catalytically active system for the asymmetric addition of trimethylsilyl cyanide to aldehydes. Best results (63–95% enantiomeric excess) were obtained with aliphatic and α,β-unsaturated aldehydes. Benzaldehyde was converted into (*S*)-mandelonitrile trimethylsilyl ether with a somewhat lower enantioselectivity (52%), and this order of reactivity is the reverse of that which is generally observed for asymmetric cyanohydrin synthesis. The authors postulate that the magnesium complex acts as a chiral Lewis acid and activates the aldehydes, whilst bisoxazoline **27** acts as a Lewis base to activate the hydrogen cyanide, which is generated in situ adventitiously from trimethylsilyl cyanide by moisture.[72] This dual activation of both components of the reaction is illustrated in Fig. 6 and is a recurring theme amongst many of the most enantioselective metal-based catalysts for asymmetric cyanohydrin synthesis.

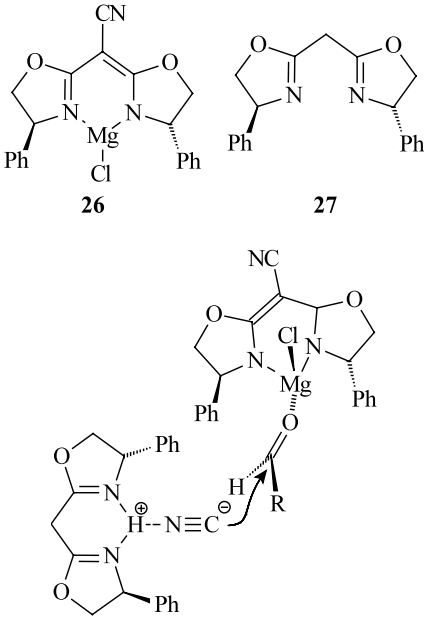
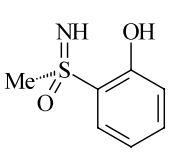


Figure 6.

Bolm and Müller have developed sulfoximines as chiral ligands for asymmetric cyanohydrin synthesis, and have shown that in the presence of stoichiometric amounts of ligand **28** and titanium tetraisopropoxide, aldehydes and trimethylsilyl cyanide were converted into (*S*)-cyanohydrins with 37–91% enantiomeric excess. Attempts to develop a catalytic version of this reaction were unsuccessful as reducing the amount of catalyst resulted in low enantioselectivities and longer reaction times.[73,74] Another unusual ligand structure which has been successfully employed in asymmetric cyanohydrin synthesis is the planar-chiral 1,3-diketone **29**. Complexation of this ligand to yttrium generated a highly catalytically active species; just 1 mol% of which could convert aldehydes and trimethylsilyl cyanide into cyanohydrin trimethylsilyl ethers with 30–91% enantiomeric excess.[75] The results were however, very dependent upon the nature of the yttrium source, with best results being obtained using $Y_5(O)(O^iPr)_{13}$.[76] Diethyl tartrate is a widely used chiral ligand, and Wada et al. have shown that the complex formed from diethyl tartrate and bismuth trichloride will catalyse the asymmetric addition of trimethylsilyl cyanide to aldehydes. The best results were obtained at −23°C using 20 mol% of the catalyst and under these conditions, (*S*)-cyanohydrins with 20–72% enantiomeric excess were obtained.[77]

Buono et al. have prepared diastereomerically pure phosphine oxide **30** (as well as diastereomeric ligands and ligands derived from other amino acids) and investigated the use of the titanium complexes of these ligands as chiral catalysts for the asymmetric addition of trimethylsilyl cyanide to aldehydes. Best results were obtained using 10 mol% of ligand **30** and titanium tetraisopropoxide at room temperature, and under these conditions 4-methoxybenzaldehyde was converted into its (*S*)-cyanohydrin in 86% yield and with 98% enantiomeric excess. Other aromatic aldehydes gave mixed results ranging from 94% enantiomeric excess with benzaldehyde as substrate to just 3% enantiomeric excess for the cyanohydrin derived from furfural. The configuration of the cyanohydrin was determined by the configuration at the phosphorus atom of the ligand, since the epimer at phosphorus of ligand **30** catalysed the formation of (*R*)-mandelonitrile with 98% enantiomeric excess.[78]

Complexation of TADDOL **31** to zirconium tetraisopropoxide forms a catalyst which will transfer cyanide enantioselectively from acetone cyanohydrin to aldehydes. Best results were obtained using stoichiometric amounts of the zirconium complex at −40°C in dichloromethane, and under these conditions (*R*)-cyanohydrins with 29–85% enantiomeric excess could be obtained from both aromatic and aliphatic aldehydes. It was also possible to use a catalytic amount (20 mol%) of the zirconium complex by adding 4 Å molecular sieves to the reaction mixture, though the enantiomeric excess was lower using this methodology. The authors suggest that the mechanism of this reaction is analogous to the Meerwein–Ponndorf–Verley reaction, though no mechanistic detail has been obtained.[79]



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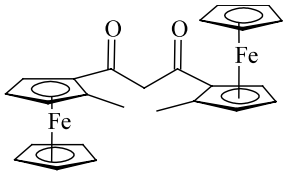

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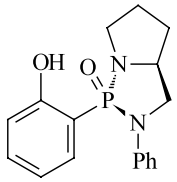

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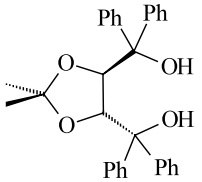

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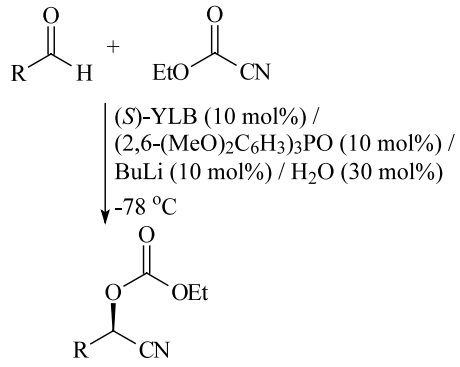
Binol and its derivatives have been extensively used to form asymmetric catalysts for a variety of organic reactions, and asymmetric cyanohydrin synthesis is no exception. Nakai et al. have shown that at 0°C, 20 mol% of a complex formed from binol and titanium tetraisopropoxide would catalyse the asymmetric addition of trimethylsilyl cyanide to aldehydes with up to 75% enantiomeric excess. Unusually, the best substrates are the aliphatic aldehydes nonal and pivaldehyde (giving products with 72 and 75% enantiomeric excess, respectively), whilst isobutanal and cyclohexanal gave products with much lower enantiomeric excesses (34%) and propanal and all aromatic aldehydes gave essentially racemic cyanohydrins (enantiomeric excess less than 10%).[80] Seebach et al. subsequently prepared a polymeric binol analogue by radical copolymerisation of styrene and a dendritic binol derivative containing styrenyl units. The titanium complex of the resulting polymer was found to catalyse the asymmetric addition of trimethylsilyl cyanide to pivaldehyde. Initially, the enantiomeric excess of the product was between 72–75%; exactly the same as that observed for the homogeneous catalyst by Nakai. However, the polymeric catalyst could be recycled and in subsequent runs the enantioselectivity was found to increase to a maximum of 83% after five runs. Thereafter, the enantioselectivity started to decrease, but product with 65% enantiomeric excess was still obtained in the 15th reaction carried out using the polymeric catalyst.[81]

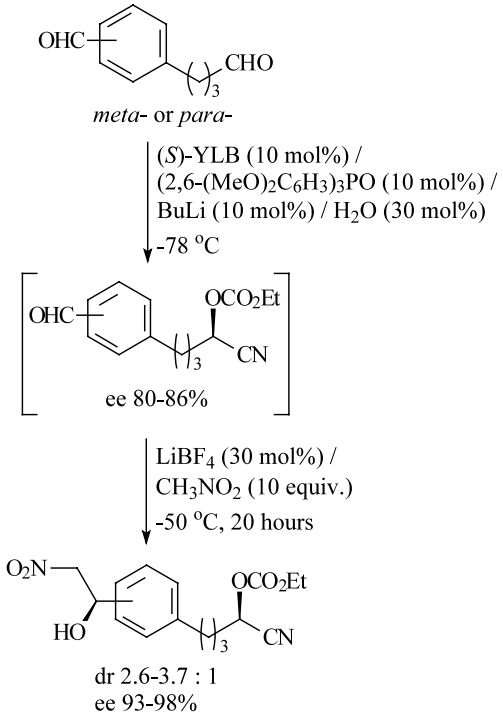
Holmes and Kagan also used binol complexes as catalysts for asymmetric cyanohydrin synthesis. In their case however, the mono-lithium salt of binol was found to catalyse the asymmetric addition of trimethylsilyl cyanide to aldehydes. Best results were obtained using 1 mol% of the catalyst at −78°C in ethereal solvent and under these conditions, cyanohydrin trimethylsilyl ethers were formed in high yield and with up to 59% enantiomeric excess in the case of the product derived from *para*-tolualdehyde. Mechanistically, the reaction is thought to proceed through a hypervalent silicon complex in which the chiral binolate, aldehyde and cyanide are all coordinated to the same trimethylsilyl group.[82]

Recently, Shibasaki et al. have reported that a heterobimetallic complex ((*S*)-YLB) derived from three (*S*)-binol molecules, three lithium ions and a yttrium ion would catalyse the asymmetric addition of ethyl cyanoformate to aldehydes, thus producing non-racemic (*R*)-cyanohydrin carbonates as shown in Scheme 19. Optimal results were obtained at −78°C using 10 mol% of the catalyst, in the presence of three additives: water (30 mol%); *n*-butyllithium (10 mol%) and tri(2,6-dimethoxyphenyl)phosphine oxide (10 mol%). Under these conditions, both aromatic and aliphatic aldehydes were converted into cyanohydrin carbonates in high yield with enantiomeric excesses of 87–98%. The reaction times were 2–3 h.[83]

The same basic catalyst system was also found to catalyse the nitro-aldol reaction, though in this case the phosphine oxide additive was found to inhibit the enantioselective catalysis. However, by adding lithium tetrafluoroborate to complex to the phosphine oxide after formation of the cyanohydrin derivative, it was possible to carry out asymmetric cyanohydrin formation and asymmetric nitro-aldol reactions in tandem as shown in Scheme 20. A feature of this chemistry is the preferential reaction of the aliphatic aldehyde during the asymmetric cyanohydrin forming reaction.[83] The mechanism of this catalysis has not yet been elucidated, and it remains to be seen how (if at all) it relates to Shibasaki's work on Lewis acid/Lewis base-catalysed asymmetric addition of trimethylsilyl cyanide to aldehydes (discussed below), and to the work of Tian and Deng on the cinchona alkaloid catalysed addition of ethyl cyanoformate to ketones discussed in Section 6.



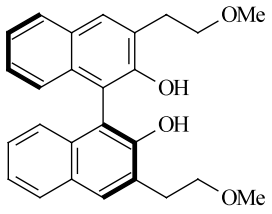
Scheme 19.



Scheme 20.

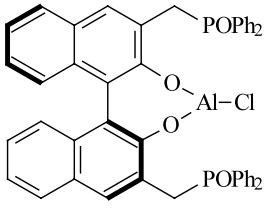
Qian et al. prepared lanthanum complexes of binol and 3,3′-bis substituted binol derivatives including ligand **32**. When used as a catalyst for the asymmetric addition

of trimethylsilyl cyanide to aldehydes at −78°C, 10 mol% of the binol complex gave cyanohydrins with 23–58% enantiomeric excess whilst ligand **32** under the same conditions gave products with 48–73% enantiomeric excess. In contrast, binol analogues with bulky substituents (Ph or $SiMe_3$) in the 3- and 3′-positions gave cyanohydrins with lower enantiomeric excesses than binol.[84] The role of the methoxyethyl substituents of ligand **32** is not clear; they may function as additional metal coordinating sites giving a tetradentate ligand, or they may be involved as Lewis bases binding to trimethylsilyl cyanide as discussed below for other binol derivatives.



32

By far the most successful use of binol complexes in asymmetric cyanohydrin synthesis is the combined Lewis acid/Lewis base derivative developed by Shibasaki et al.[85] Thus, aluminium complex **33** was found to catalyse the asymmetric addition of trimethylsilyl cyanide to aldehydes, giving cyanohydrins with 83–98% enantiomeric excess. Best results were obtained using 9 mol% of the catalyst at −40°C with slow addition of trimethylsilyl cyanide (over 10 h) and in the presence of 36 mol% of an additional phosphine oxide additive. For aliphatic aldehydes, the best additive was tributylphosphine oxide, whilst for aromatic aldehydes methyl(diphenyl)phosphine oxide gave best results.[86,87]



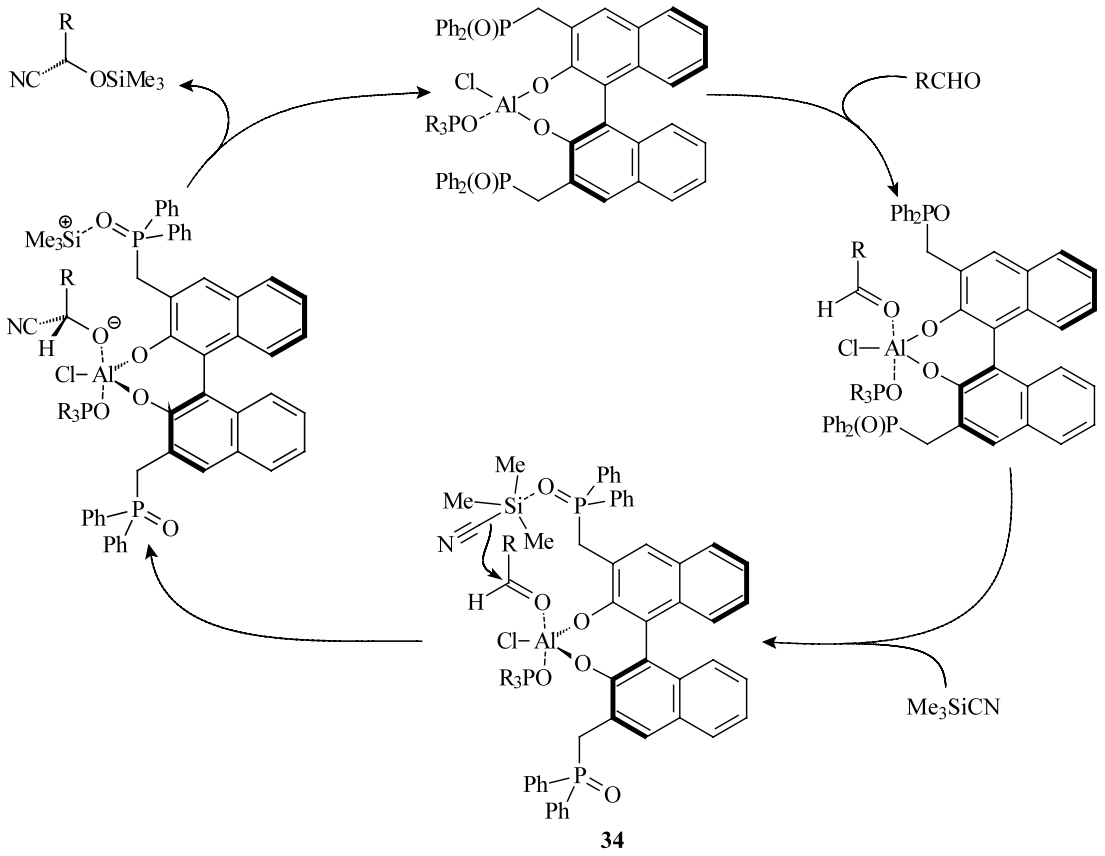
33

Catalyst **33** was designed to simultaneously bind and active the aldehyde (by coordination to the Lewis acidic aluminium) and the trimethylsilyl cyanide (by coordination to the Lewis basic phosphine oxides). Evidence that this mechanism is in fact operating was obtained by replacing the $POPh_2$ groups of complex **33** with $CHPh_2$ groups, since the resulting aluminium complex was a very poor catalyst for the addition of trimethylsilyl cyanide to benzaldehyde, giving the product in just 50% yield and with 12% enantiomeric excess. Additionally, the introduction of an extra CH_2 group between the binol and phosphine oxides gave a complex in which the phosphine oxides were able to coordinate intramolecularly to the aluminium, and this complex displayed essentially no catalytic activity. The role of the additional phosphine oxide additive required for optimal activity by complex **33** is postulated to be coordination to the aluminium to change the geometry of the metal in the transition state from tetrahedral to trigonal bipyramidal, the latter allowing a more optimal arrangement of the catalyst and coordinated reactants. Shibasaki has proposed the catalytic cycle shown in Scheme 21 and involving transition state structure **34** to account for all of the features of the reaction and explain the origin of the asymmetric induction.

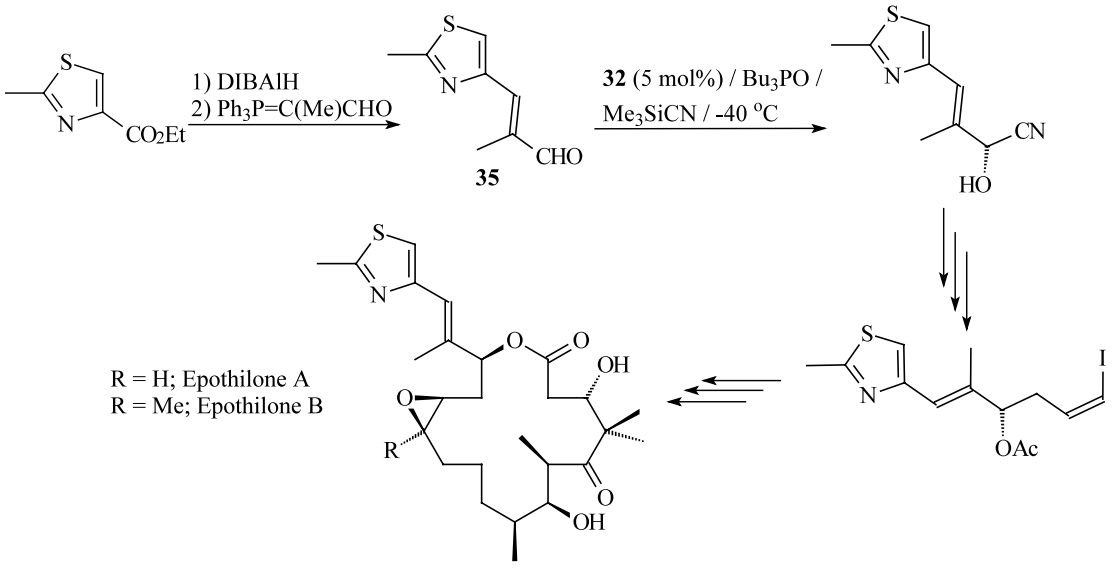
Shibasaki has demonstrated the utility of catalyst **33** with an asymmetric synthesis of the antitumour agents Epothilone A and B. A key step in the syntheses was the asymmetric addition of trimethylsilyl cyanide to α,β-unsaturated aldehyde **35** which was achieved in 97% yield to give cyanohydrin with 99% enantiomeric excess by using 5 mol% of catalyst **33** and 80 mol% of tributyl phosphine at −40°C as shown in Scheme 22. This established the north-western part of the Epothilone structure, which was combined with a fragment corresponding to the remainder of the macrocyclic ring to prepare the two natural products.[88,89]

A limitation of the Shibasaki catalyst system is the need for slow addition of trimethylsilyl cyanide in order to obtain optimal enantioselectivities. Nájera et al. have prepared binol complex **36** in which the phosphine oxides of Shibasaki's catalyst **33** have been replaced by diethylamino groups. Complex **36** was found to catalyse the asymmetric addition of trimethylsilyl cyanide to aldehydes, and again an external phosphine oxide additive (triphenylphosphine oxide) was required for optimal asymmetric induction. It was also necessary to add 4 Å molecular sieves to the reaction, which the authors suggest act as a limited water source. In contrast to the Shibasaki system however, all the reagents could be added at the start of the reaction and the binol ligand could be recovered and reused by a simple acid–base work-up. The enantioselectivities observed using catalyst **36** range from >98% for benzaldehyde down to 66% for heptanal. Reactions involving aromatic aldehydes could be carried out at −20°C, whilst reactions involving aliphatic aldehydes required a lower reaction temperature (−40°C) to obtain optimal asymmetric induction.[90]

Shibasaki has extended the concept of joint Lewis acid/Lewis base catalysts to systems other than binol. Thus, the C_1-symmetric ligand **37** was synthesised and complexed to aluminium. The resulting complex was found to catalyse the asymmetric addition of trimethylsilyl cyanide to aldehydes with 7–80% enantiomeric excess. Although these enantioselectivities are lower than those observed using binol derivative **33**, reactions using catalyst **37** have a number of advantages. Thus, no phosphine oxide additives are required, it is not necessary to add trimethylsilyl cya-

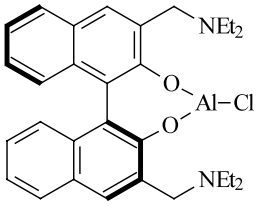


Scheme 21.

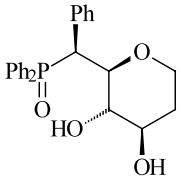


Scheme 22.

nide slowly to the reaction mixture and only 5 mol% of the catalyst is required in most cases. Catalyst **37** was also found to catalyse the asymmetric addition of trimethylsilyl cyanide to acetophenone, though the product was obtained with just 20% enantiomeric excess after 64 h at −10°C from a reaction using 20 mol% of catalyst **37**.[91]



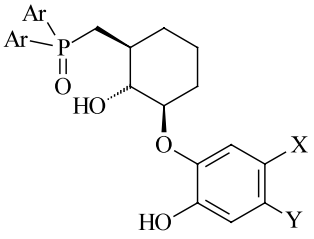
36



37

4.2. Use of complexes containing tridentate ligands

Building on the successful use of the aluminium complex of bidentate ligand **37** as a catalyst for the asymmetric addition of trimethylsilyl cyanide to acetophenone, all be it with low enantioselectivity, Shibasaki et al. modified the structure by the introduction of a catechol unit to give tridentate ligand **38**. Whilst the aluminium complex of ligand **38** was catalytically inactive, the corresponding titanium complex was found to be a good catalyst for the synthesis of (*R*)-cyanohydrins derived from ketones. Thus, using 10 mol% of ligand **38** and 10 mol% of titanium tetraisopropoxide at temperatures of between −50 and −20°C, in THF as solvent, both aliphatic and aromatic ketones were converted into cyanohydrin trimethylsilyl ethers with 69–95% enantiomeric excess.[92] Subsequent optimisation of the structure of the chiral ligand resulted in the discovery of ligand **39** which forms an even more active catalyst for the asymmetric addition of trimethylsilyl cyanide to ketones. Thus, only 1–2.5 mol% of the titanium complex of ligand **39** was required to convert ketones into (*R*)-cyanohydrins with 82–94% enantiomeric excess. The method of catalyst preparation is however important to obtain optimal catalytic activity. Thus, optimal catalytic activity was obtained when the ligand dissolved in toluene was treated with an equimolar amount of titanium tetraisopropoxide at room temperature followed by heating at 70°C for 1 h. The solution was then cooled to 0°C and 2 equiv. of trimethylsilyl cyanide were added after which the solution was stirred at room temperature for a further hour. The solvent was then evaporated in vacuo for 1 h, after which time THF was added to generate the active catalyst in solution.[93]



38: X = Y = H; Ar = Ph
39: X = COPh; Y = H; Ar = Ph
44: X = Y = F; Ar = *para*-MeC_6H_4
48: X = Y = F; Ar = Ph

The mode of action of catalysts derived from ligands **38** and **39** has been investigated by a combination of kinetic studies and labelling experiments with ^{13}C labelled trimethylsilyl cyanide. Based on these studies, Shibasaki has proposed the transition state structure shown in Fig. 7 to explain the origin of the asymmetric induction. The key features of this transition state structure are the simultaneous activation of both reaction components through the combined Lewis acid/Lewis base activity of the catalyst, and the transfer of cyanide directly from activated trimethylsilyl cyanide, not from cyanide coordinated to titanium.

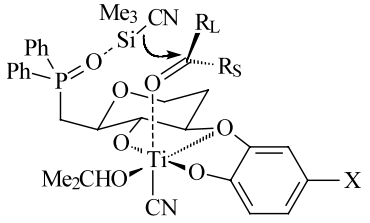


Figure 7.

Shibasaki subsequently showed that by complexing ligand **38** to gadolinium rather than titanium, it was possible to synthesise (*S*)-cyanohydrins, thus allowing either enantiomer of a cyanohydrin to be prepared from the same enantiomer of a chiral ligand. For the gadolinium system, best results were obtained with a ligand/metal ratio of about 1.5:1, suggesting that the active catalyst is composed of two gadolinium ions and three molecules of ligand. By using 5–15 mol% of the resulting catalyst at −60°C, a range of methyl and ethyl ketones were converted into (*S*)-cyanohydrin trimethylsilyl ethers with 62–92% enantiomeric excess. Based on the optimal ligand/metal ratio and electrospray mass spectrometry studies, Shibasaki has proposed the transition state shown in Fig. 8 to explain the catalysis and asymmetric induction. In this structure, two of the ligands act as tridentate ligands whilst the bridging ligand is tetracoordinate. Interestingly, the cyanide ion is now activated by coordination to one of the metal ions rather than by the Lewis basic phosphine oxides.[94]

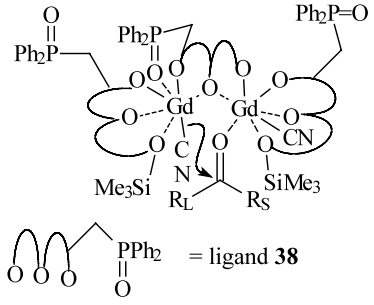
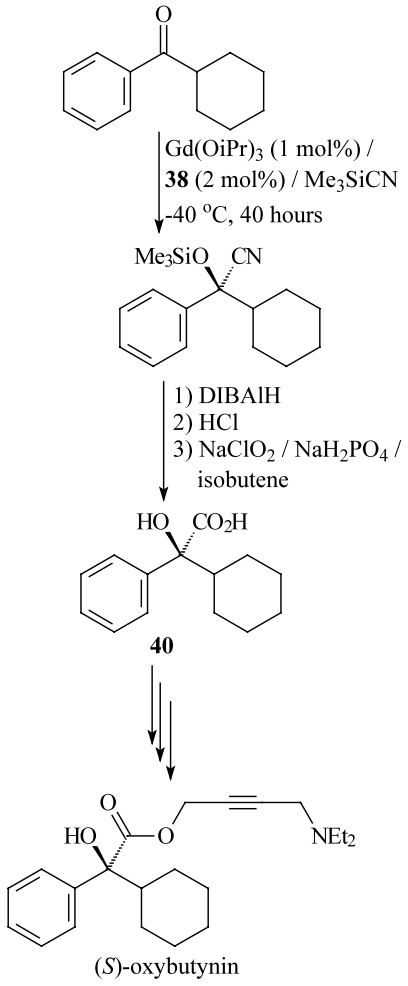


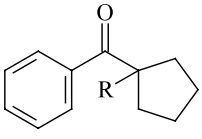
Figure 8.

Recently, Shibasaki has used the gadolinium complex of ligand **38** in a formal synthesis of (*S*)-oxybutynin as shown in Scheme 23. The asymmetric trimethylsilyl cyanation of phenyl cyclohexyl ketone proceeded remarkably well considering the small difference in size between the two substituents attached to the carbonyl. Thus, the (*S*)-cyanohydrin trimethylsilyl ether was obtained in 100% yield and with 95% enantiomeric excess on 100 g scale. However, subsequent hydrolysis of the sterically hindered nitrile turned out to be problematic, so the authors resorted to reduction of the nitrile to the corresponding aldehyde followed by re-oxidation to give acid **40** which has previously been converted into (*S*)-oxybutynin. In the same paper, the authors also studied the addition of trimethylsilyl cyanide to other aryl-cycloalkyl ketones catalysed by the



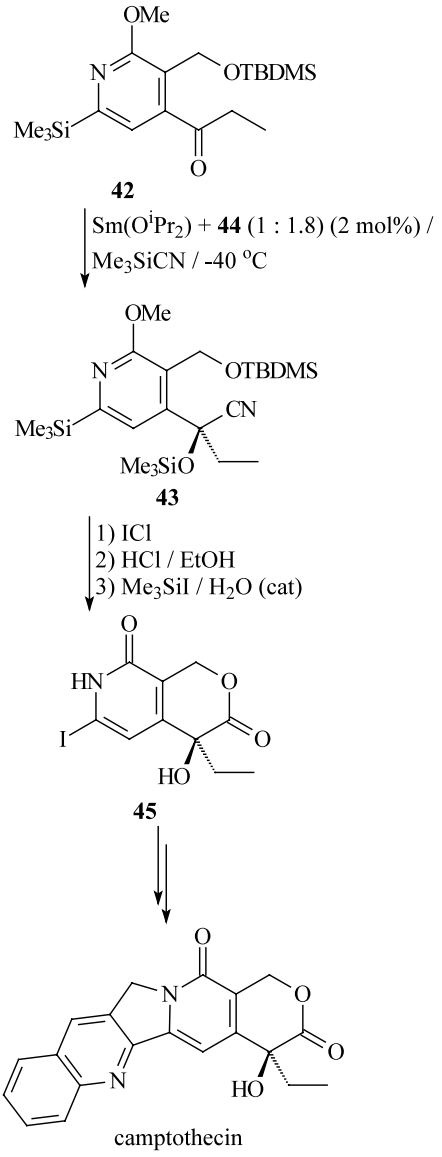
Scheme 23.

gadolinium complex of ligand **38**. All cycloalkyl ring sizes between three and six gave excellent results except for phenyl cyclopentyl ketone **41a** which gave the corresponding cyanohydrin trimethylsilyl ether with only 22% enantiomeric excess. The authors suggested that this was due to competitive deprotonation of the ketone due to the gadolinium complex acting as a base. The enolate could then coordinate to the gadolinium/**38** complex, formed a less enantioselective catalyst. Consistent with this, use of deuterated ketone **41b**, which should be less prone to enolate formation due to the deuterium isotope effect, resulted in the formation of a cyanohydrin trimethylsilyl ether with 95% enantiomeric excess.[95]

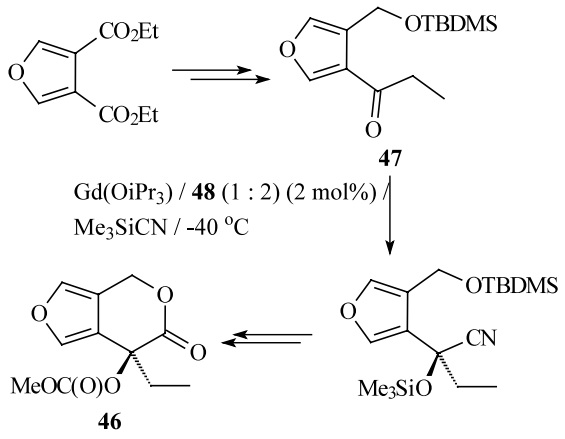


41 a: R = H
b: R = D

Shibasaki and Curran have teamed-up to use ligand **38** in the synthesis of (20*S*)-camptothecins. The key step of the synthesis is the asymmetric addition of trimethylsilyl cyanide to ethyl ketone **42** to give (*S*)-cyanohydrin trimethylsilyl ether **43** as shown in Scheme 24. In this particular case, the samarium complex of ligand **38** gave better results (98% yield; 84% enantiomeric excess) than the gadolinium complex, and the introduction of fluorine atoms onto the catechol to give ligand **44** produced an even more enantioselective catalyst (93% yield and 90% enantiomeric excess using 2 mol% of the catalyst). Cyanohydrin ether **43** was subsequently converted into hydroxy lactone **45** which is an established intermediate for the synthesis of camptothecin.[94,96] In the same paper, the authors also report the synthesis of Corey's intermediate **46** for camptothecin synthesis. In this case the key step is the asymmetric addition of trimethylsilyl cyanide to ethyl ketone **47** and the best results were obtained using the gadolinium complex of ligand **48** (100% yield and 94% enantiomeric excess using 2 mol% of the catalyst). Subsequent manipulations gave lactone **46** as shown in Scheme 25.



Scheme 24.

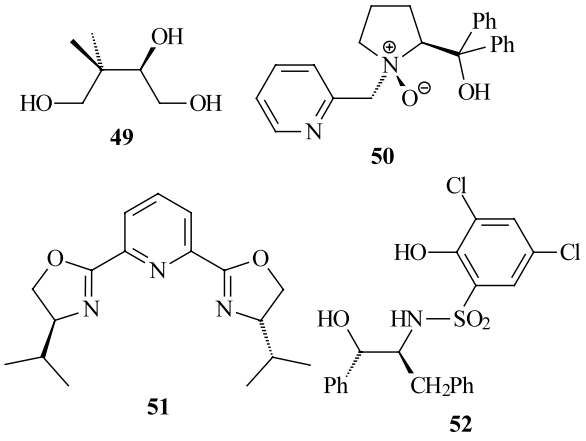


Scheme 25.

One of the earliest tridentate ligands used in asymmetric cyanohydrin synthesis is triol **49** which is obtained by reduction of (*R*)-pantolactone. When complexed to titanium tetraisopropoxide, triol **49** forms a catalyst for the asymmetric addition of trimethylsilyl cyanide to benzaldehyde, forming mandelonitrile with up to 76% enantiomeric excess. However, the reaction requires stoichiometric amounts of the titanium complex.[97] The real interest in this ligand is that it formed the first metal-based catalyst ever reported for the asymmetric addition of trimethylsilyl cyanide to ketones. Thus, by employing high pressures (0.8 GPa), Choi et al. showed that 1 mol% of the titanium tetraisopropoxide complex of ligand **49** would catalyse the addition of trimethylsilyl cyanide to acetophenone and 4-substituted acetophenones, to give cyanohydrins with 2–60% enantiomeric excess.[98]

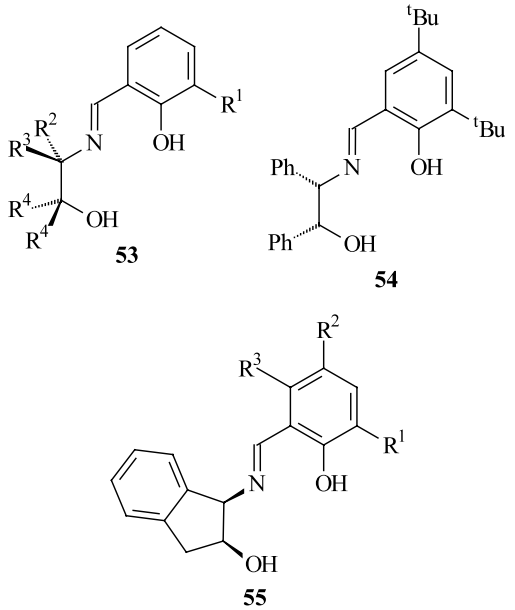
It has recently been reported that amine–oxide **50** can also be complexed to titanium tetraisopropoxide to form a catalyst for the asymmetric addition of trimethylsilyl cyanide to ketones. In this case however, reaction occurs at atmospheric pressure and a wider range of ketones can be used as substrates, giving cyanohydrin trimethylsilyl ethers with 25–69% enantiomeric excess when 20 mol% of the catalyst are employed.[99]

The pybox ligand **51** has been employed by two different groups to prepare catalysts for asymmetric cyanohydrin synthesis. Iovel et al. showed that ligand **51** could be complexed to aluminium trichloride and that the resulting complex (20 mol%) catalysed the addition of trimethylsilyl cyanide to aromatic and heteroaromatic aldehydes. Only in the case of benzaldehyde was the enantiomeric excess of the product determined and found to be >90% in favour of the (*S*)-enantiomer for a reaction carried out at 0°C.[100] Aspinall et al. subsequently showed that ligand **51** formed complexes with a range of lanthanide metal ions, and that these were active catalysts for the asymmetric trimethylsilyl cyanation of benzaldehyde. In the case of the ytterbium trichloride complex, 10 mol% of the catalyst converted ten aromatic and aliphatic aldehydes into the corresponding cyanohydrins with 45–75% enantiomeric excess.[101]



The titanium tetraisopropoxide complex of β-amino alcohol **52** has been shown to catalyse the asymmetric addition of trimethylsilyl cyanide to a range of both aromatic and aliphatic aldehydes. Best results were obtained at −65°C using 10 mol% of the catalyst and under these conditions, (*R*)-cyanohydrins were obtained with 77–96% enantiomeric excess.[102]

Schiff bases of salicylaldehyde derivatives make excellent ligands for titanium(IV) and the resulting complexes have been used by a number of groups as catalysts for the asymmetric addition of trimethylsilyl cyanide to carbonyl compounds. In 1993, Oguni et al. reported the synthesis and catalytic activity of complexes formed from Schiff bases of structure **53** and titanium tetraisopropoxide. Best results were obtained using 20 mol% of the complex derived from ligand **53** ($R^1 = {}^t$Bu; $R^2 = {}^i$Pr; $R^3 = R^4 = H$) at −80°C in dichloromethane. Under these conditions, 21 aromatic and aliphatic aldehydes were converted into the corresponding (*R*)-cyanohydrins with 20–96% enantiomeric excess. In general, electron-rich aromatic aldehydes and α,β-unsaturated aldehydes gave products with the highest enantiomeric excesses.[103,104] Subsequently, Jiang et al. showed that the titanium complex of Schiff base **54** would catalyse the conversion of aromatic aldehydes and cinnamaldehyde into (*S*)-cyanohydrins

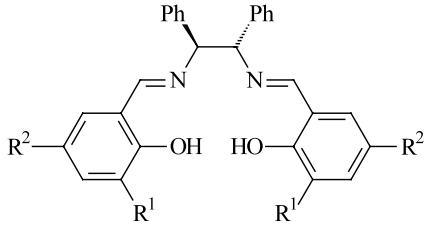


with 48–92% enantiomeric excess under the same conditions used by Oguni. Interestingly however, in this case the enantioselectivity of the reaction was influenced by the ligand: titanium ratio, with optimal results being obtained using 1.5–2 equiv. of ligand for each titanium ion.[105,106] This is in contrast to Oguni's system where use of a 2:1 ligand to titanium ratio gave an inactive complex.[103,104]

More recently, Somanathan, Walsh and co-workers have studied the use of Schiff bases **55** derived from *cis*-1-amino-2-indanol as ligands for titanium-based catalysts for asymmetric cyanohydrin synthesis. Using ligand **55** ($R^1 = {}^t$Bu; $R^2 = R^3 = H$) under Oguni's reaction conditions, benzaldehyde was converted into (*R*)-mandelonitrile with 85% enantiomeric excess. The authors carried out extensive NMR studies to show that provided R^1 was large (^{t}Bu), then the titanium complex formed from ligand **55** was a pentacoordinate species of structure [(**55**)Ti(O^{i}Pr)$_2$]. However, with smaller R^1 substituents significant amounts of catalytically inactive octahedral [(**55**)$_2$Ti] complexes were formed, one of which could be isolated and characterised by X-ray crystallography. Consistent with this, the optimal ligand: titanium ratio for reactions carried out using ligand **55** was 1:1 and use of a 2:1 ratio resulted in a significant reduction in the enantiomeric excess of the product (from 85 to 19%).[107] In addition to explaining the results obtained using ligand **55**, these NMR studies are also entirely consistent with Oguni's findings using ligand **53**.[103,104] They do not however, explain the results of Jiang using ligand **54**,[106] though the latter could be explained by the formation of polymetallic species. Somanathan and Walsh followed up this work by preparing ligands **55** in which R^1 is larger than *tert*-butyl. The ligands in which R^1 was adamantyl, *tert*-pentyl and dimethylbenzyl were prepared, but all were less enantioselective than the corresponding *tert*-butyl ligand. By changing the conformationally constrained indanol backbone to an acyclic amino alcohol, more enantioselective catalysts were obtained; with $R^1 =$ adamantyl giving best results, though still not as good as for ligand **55** $R^1 = {}^t$Bu. These results are suggested to be due to the ligand becoming so bulky that coordination of benzaldehyde to the remaining coordination site of the titanium complex is hindered. In the same paper, the use of the titanium complex of ligand **55** ($R^1 = {}^t$Bu) to catalyse the addition of trimethylsilyl cyanide to five additional electron-rich aromatic aldehydes is reported. Only 4-methoxybenzaldehyde gave a cyanohydrin with high (95%) enantiomeric excess, the other four aldehydes gave products with 48–62% enantiomeric excess.[108]

4.3. Use of complexes containing tetradentate ligands

Given the success encountered using tridentate Schiff bases as ligands for the preparation of chiral titanium-based catalysts for asymmetric cyanohydrin synthesis, it is not surprising that in early 1996, two groups simultaneously reported the use of the corresponding tetradentate, salen, ligands for the same purpose. These ligands have subsequently become the basis of some of the most effective and versatile asymmetric catalysts for the synthesis of cyanohydrin derivatives. Jiang et al. studied the use of salen ligands **56** derived from 1,2-diphenylethylenediamine. The ligand was complexed to titanium tetraisopropoxide in situ, and the resulting complex was found to induce the addition of trimethylsilyl cyanide to benzaldehyde. Best results were obtained at −78°C using ligand **56** with $R^1 = R^2 = H$, a result which contrasts sharply with both the results obtained using tridentate Schiff base ligands and with the results of Belokon'/North discussed below. Interestingly, the amount of catalyst used was also critical, with 10 mol% being optimal (giving mandelonitrile with 87% enantiomeric excess) and higher or lower amounts of the catalyst resulting in the formation of mandelonitrile with a lower enantiomeric excess.[109] In a subsequent paper, the authors extended the study to include other aromatic and aliphatic aldehydes and obtained (*R*)-cyanohydrins with 22–87% enantiomeric excess.[110]



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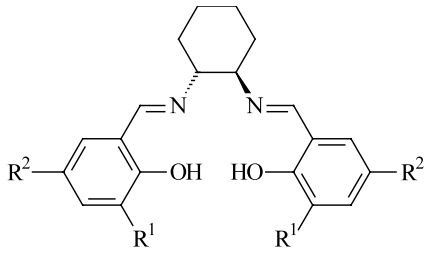
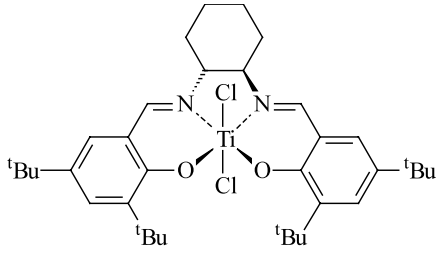


57

Simultaneously with Jiang's work, the partnership of Belokon' and North were studying the titanium complexes of salen ligand **57**, derived from (*R*,*R*)-cyclohexane diamine as catalysts for asymmetric cyanohydrin synthesis. In early work, ligand **57** was complexed in situ to titanium tetraisopropoxide and 20 mol% of the resulting catalyst used to catalyse the asymmetric addition of trimethylsilyl cyanide to aldehydes at −78°C. It was found that the ligand with $R^1 =$ *tert*-butyl and $R^2 = H$ was significantly more enantioselective than the ligand in which $R^1 = R^2 = H$, and converted benzaldehyde, *para*-methoxybenzaldehyde, cinnamaldehyde and pivaldehyde to their corresponding (*S*)-cyanohydrin trimethylsilyl ethers with 62–77% enantiomeric excess.[111] In a subsequent paper, the authors showed that the catalyst derived from ligand **57** $R^1 = R^2 =$ *tert*-butyl was even more enantioselective, and could convert 3-methylbenzaldehyde into its (*S*)-cyanohydrin with 92% enantiomeric excess.[112] Recently, Liang and Bu prepared the even more sterically hindered ligand **57** in which R^1 and $R^2 =$ *tert*-pentyl. When complexed to titanium tetraisopropoxide, 5 mol% of the resulting complex catalysed the asymmetric addition of trimethylsilyl cyanide to aromatic aldehydes to give (*S*)-cyanohydrins with 92–97% enantiomeric excess at −78°C.[113] The results are not directly comparable with those of Belokon' and North however, since a different

procedure was used to prepare the titanium isopropoxide complex, including the removal of isopropanol in vacuo.

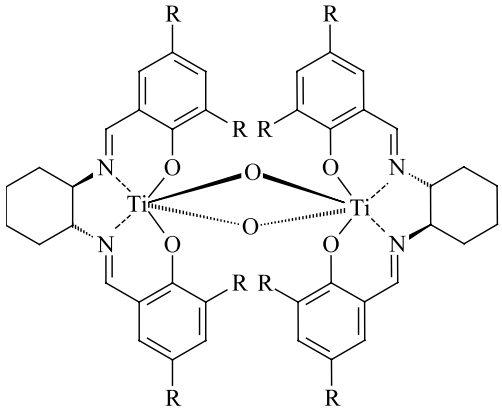
A major limitation of the titanium tetraisopropoxide complexes of ligands **56** and **57** is the in situ formation of the complex. NMR studies showed that in the case of ligand **57**, at three distinct complexes were generated and it is likely that these will have differing and possibly opposing enantioselectivities. This also makes mechanistic studies on the catalysis difficult to carry out. A major advance was therefore made in 1998 when it was found that treatment of ligand **57** ($R^1 = R^2 =$ *tert*-butyl) with titanium tetrachloride instead of titanium tetraisopropoxide resulted in the formation of complex **58**. Compound **58** is an easily isolable crystalline solid and its structure was unambiguously determined by X-ray crystallography. The X-ray structure showed that the two chlorine atoms were *trans* to one another within the octahedral complex, thus allowing the salen ligand to occupy four coplanar coordination sites. Complex **58** was also found to be a far more active catalyst for the asymmetric addition of trimethylsilyl cyanide to benzaldehyde than the in situ generated species. Thus, just 0.1 mol% of catalyst **58** was required to convert benzaldehyde into (*S*)-mandelonitrile trimethylsilyl ether with 86% enantiomeric excess at room temperature after 24 h.[114] Nine other electron-rich aromatic aldehydes were also converted into (*S*)-cyanohydrin trimethylsilyl ethers with 62–86% enantiomeric excess, whilst electron-deficient aromatic aldehydes and aliphatic aldehydes gave products with lower enantiomeric excesses (30–50%).[115] To obtain similar results with the in situ catalysts derived from ligands **56** or **57** requires 10–20 mol% of the ligand and titanium tetraisopropoxide at −78°C.



58

A number of analogues of compound **58** with different substituents on the aromatic rings were also prepared and tested as catalysts for asymmetric cyanohydrin synthesis. Amongst these was the catalyst in which the substituent adjacent to the phenols was a very large triphenylmethyl group with a *tert*-butyl group still present in the position *para* to the phenols.[115] The poor enantioselectivity (58% with benzaldehyde) displayed by this catalyst suggests that the results of Liang and Bu[113] with the catalyst derived from ligand **57** (R = *tert*-pentyl) may be due to the method of catalyst preparation rather than the bulky nature of the substituents.

Further studies on asymmetric cyanohydrin synthesis using titanium complexes of ligands **57** and preformed complex **58**, showed that under the reaction conditions both the titanium tetraisopropoxide complexes and complex **58** were converted into bimetallic complex **59**, and it is complex **59** which is the actual pre-catalyst formed in both systems. The water needed for the formation of complex **59** comes from adventitious moisture present in the reaction. It is also possible to prepare and isolate complex **59** by treatment of the titanium tetraisopropoxide complex or complex **58** with aqueous triethylamine. The structure of complex **59** (R = H) was determined by X-ray crystallography, and in this case the salen ligands have to adopt a non-planar (*cis*-β) conformation to allow the two bridging oxygens to occupy adjacent coordination sites. This destroys the C_2-symmetry of each salen ligand, though the complex as a whole retains C_2-symmetry. The most active catalyst was again found to be the complex in which R = *tert*-butyl. Thus, 0.1 mol% of catalyst **59** (R = *tert*-butyl) was found to convert aromatic aldehydes to the corresponding (*S*)-cyanohydrin trimethylsilyl ethers with 76–92% enantiomeric excess in the case of electron-rich substrates and 50–86% enantiomeric excess in the case of electron deficient aldehydes. Aliphatic aldehydes were also substrates, giving products with 52–66% enantiomeric excess. In all cases, these reactions were complete in less than 1 h, a significant rate enhancement compared to catalyst **58**.[115]



59

Catalyst **59** (R = *tert*-butyl) was found to be such an active catalyst for asymmetric cyanohydrin synthesis that it would even accept some ketones as substrates. As such, it was the first metal-based catalyst ever reported for the asymmetric addition of trimethylsilyl cyanide to ketones at atmospheric pressure. For reactions with ketones, it is necessary to use a larger amount of the catalyst (0.5–1 mol%) and the reactions are much slower (1–4 days). Only aryl methyl ketones are effective substrates, though both electron-donating and electron-withdrawing substituents on the aryl ring are accepted, and the (*S*)-cyanohydrin trimethylsilyl ethers are obtained with enantiomeric excesses of 56–72%.[116,117]

Belokon' and North have carried out extensive kinetic studies on asymmetric cyanohydrin forming reactions using bimetallic complexes **59**. These studies have shown that the reaction rate has a first order dependence on trimethylsilyl cyanide concentration and is independent of the aldehyde concentration. The order with respect to the catalyst concentration varies depending upon the

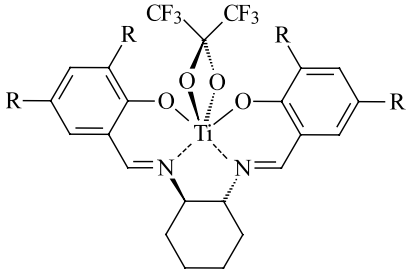
nature of the substituents on the aromatic rings, but is always between 1.0 and 2.0, and in the case of catalyst **59** (R = *tert*-butyl), the order is 1.3, and the rate constant is 634 when benzaldehyde is the substrate, so that:

$$\text{Rate} = 634[\mathbf{59}(\text{R} = \textit{tert}\text{-butyl})]^{1.3}[\text{Me}_3\text{SiCN}]^1[\text{PhCHO}]^0$$

The fact that the order with respect to the catalyst is between 1.0 and 2.0 indicates that at least two titanium ions are involved in the catalytic cycle, presumably as part of a bimetallic complex.[118] When the kinetics were repeated using acetophenone as substrate,[117] the following rate equation was observed:

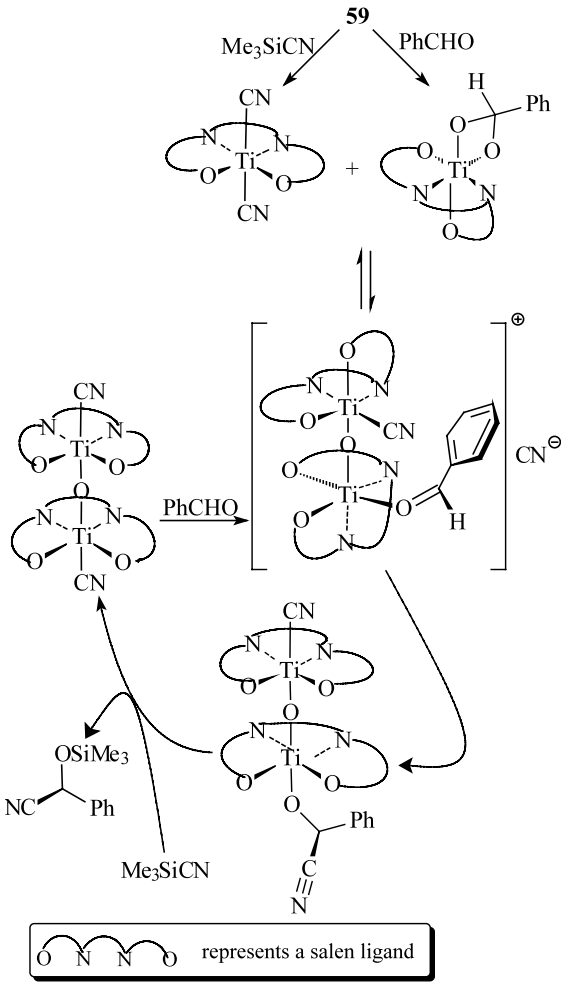
$$\text{Rate} = 0.013[\mathbf{59}\ (\text{R} = t\text{-butyl})]^{1.1}[\text{Me}_3\text{SiCN}]^1[\text{PhCOMe}]^0$$

There are two differences between the two rate equations. First, the rate constant is much smaller in the case of reactions using acetophenone as substrate and this is consistent with the much slower rate of reaction observed when ketones are used as substrates. Secondly, and more significantly, the order with respect to the catalyst changes from 1.3 when benzaldehyde is the substrate to 1.1 for reactions carried out using acetophenone as substrate. This indicates that the carbonyl compound is involved in the catalysis before the rate-determining step since otherwise the order with respect to the catalyst would be the same for both catalysts. However, the carbonyl compound cannot be involved in the catalytic cycle before the rate determining step or it would have a non-zero order in the rate equation. Hence, the carbonyl compound must be involved in the steps between complex **59** and the start of the catalytic cycle. Consistent with this, it was found that reaction of complex **59** with hexafluoroacetone led to the formation of metalloacetal **60**, and it is assumed that similar metalloacetals are formed with other carbonyl compounds.[118] It should be noted that complex **60** is a mononuclear species, so in the process of reaching the catalytic cycle from complex **59**, it is necessary to first break the bimetallic complex, and then to reform a new bimetallic species from metalloacetal **60**.



60 (R = H or *tert*-butyl)

Based on these results, Belokon' and North have proposed the mechanism shown in Scheme 26 to account for the nature of the catalysis using catalyst **59**. The catalytic cycle of this mechanism consists of just three complexes, all of which are bimetallic. However, formation of the species in the catalytic cycle involves the initial conversion of **59** into monometallic metalloacetal and cyanide complexes, thus both the carbonyl compound and trimethylsilyl cyanide are involved in the mechanism before the start of the catalytic cycle. The catalyst simultaneously



Scheme 26.

activates both the carbonyl compound and the trimethylsilyl cyanide, and the key step in this mechanism is the intramolecular transfer of cyanide to the coordinated aldehyde. This transition state is illustrated in Fig. 9, which illustrates how, to avoid unfavourable interactions between one of the cyclohexyl rings and its aryl ring, benzaldehyde is coordinated so that the cyanide has to

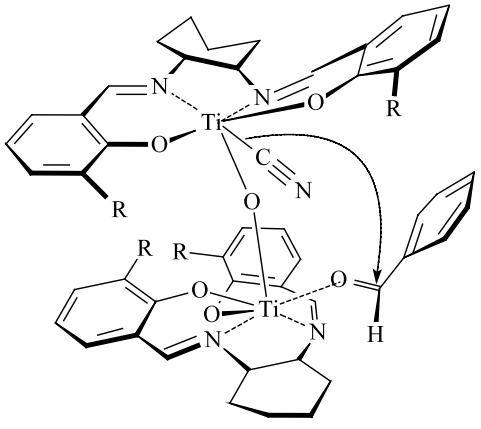
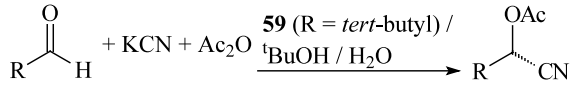


Figure 9.

attack the *re*-face, thus leading to the (*S*)-enantiomer of the product. This transition state also explains why only methyl ketones are substrates, since a larger substituent on the ketone would not fit into the space available around the cyclohexyl ring.[118]

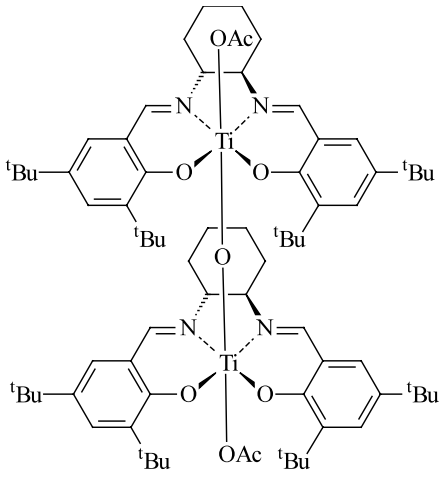
The most recent development in the use of catalyst **59** (R = *tert*-butyl) in asymmetric cyanohydrin synthesis is the demonstration that the catalyst can utilise potassium cyanide rather than trimethylsilyl cyanide as the cyanide source. This unique reactivity has not been demonstrated with any other catalyst system and has significant commercial implications since potassium cyanide is significantly less expensive than trimethylsilyl cyanide and is also less volatile and therefore less hazardous. Reactions using potassium cyanide are carried out in the presence of 1 mol% of the catalyst and acetic anhydride, and lead to non-racemic cyanohydrin acetates as shown in Scheme 27. The reaction occurs under heterogeneous conditions and requires additives such as water and *tert*-butanol for optimal enantioselectivity. Eleven aromatic and aliphatic aldehydes were converted into (*S*)-cyanohydrin acetates with 85–93% enantiomeric excess in the case of aromatic substrates and 62–84% enantiomeric excess with aliphatic aldehydes in reactions carried out at −42°C.[119] The mechanism of this reaction and the role of the additives are still under active investigation. It has recently been demonstrated that under the reaction conditions, complex **59** is converted into the diacetate complex **61**, the structure of which was proven by X-ray crystallography, and which is catalytically active. In contrast, reaction of complex **59** with trifluoroacetic anhydride leads to the catalytically inactive mononuclear complex **62**.[120]



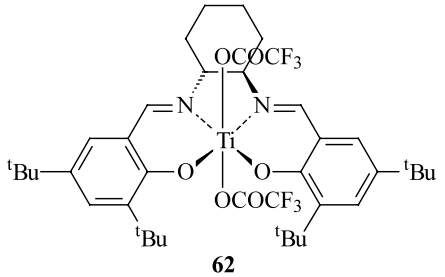
Scheme 27.

Building on the above work with titanium–salen complexes, Belokon' and North studied other metal–salen complexes. Literature precedent suggested that vanadium(IV)(salen) complexes could also exist as monometallic or polymetallic species, and consistent with this, complex **63** was found to be a more enantioselective catalyst for the addition of trimethylsilyl cyanide to aldehydes than the titanium complex **59**. For eight aliphatic and aromatic aldehydes, complex **63** gave products with enantiomeric excesses 2–25% higher than when complex **59** was used as a catalyst under identical conditions. For electron-rich aromatic aldehydes, complex **63** consistently gives cyanohydrin trimethylsilyl ethers with enantiomeric excesses >90%.[121] Reactions using catalyst **63** are much slower than those using catalyst **59**, requiring a reaction time of 24 h for complete reaction. A kinetics study showed that the reactions follow the rate equation:

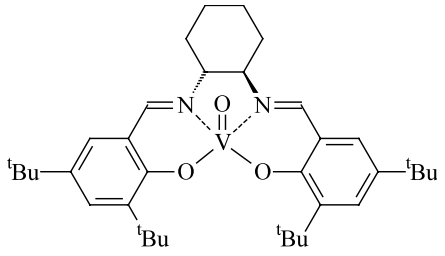
$$\text{Rate} = 76[\mathbf{63}]^{1.45}[\text{Me}_3\text{SiCN}]^{1}[\text{PhCHO}]^{0}$$



61



62

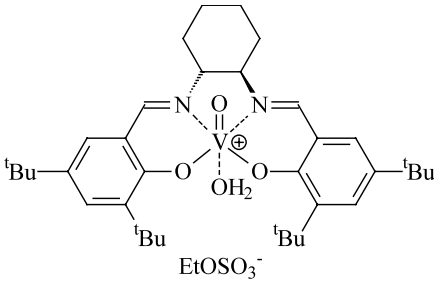


63

When compared with the corresponding rate equation for catalyst **59** (R = *tert*-butyl), the rate equations have the same general form which is consistent with a common mechanism, but two differences are apparent. Firstly, the rate constant is almost a factor of ten lower for catalyst **63**, which is consistent with the extended reaction times. Secondly, the order with respect to the catalyst is higher in the case of vanadium complex **63** than titanium complex **59**. This order is determined by the equilibrium between monometallic and bimetallic species (Scheme 26) and an increase in its magnitude suggests an increase in the concentration of monometallic species in the case of complex **63** compared to complex **59**.[117] The higher enantioselectivity observed with catalyst **63** may be related to the lower Lewis acidity of vanadium(IV) compared to titanium(IV) which would lower the reactivity of the coordinated aldehyde and hence increase the selectivity with which it reacts.

The use of vanadium-based catalysts to induce the asymmetric addition of potassium cyanide to aldehydes

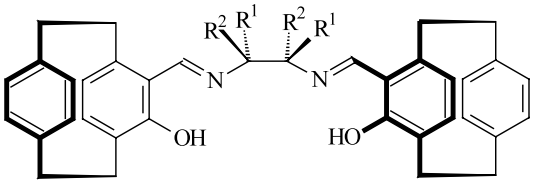
as shown in Scheme 27 has also been investigated. Interestingly, vanadium(IV) complex **63** was found to be completely inactive whilst the corresponding vanadium(V) complex **64** was an active catalyst. At −42°C, 1 mol% of catalyst **64** catalysed the asymmetric addition of potassium cyanide to benzaldehyde, *ortho*-chlorobenzaldehyde and *meta*-methoxybenzaldehyde to give cyanohydrin acetates with 78–90% enantiomeric excess.[120]



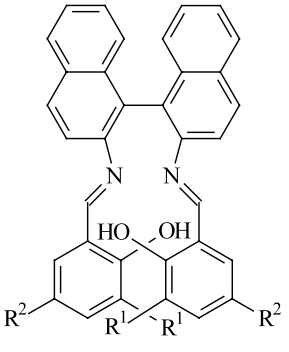
64

Holmes and Kagan have shown that it is not necessary to complex ligand **57**(R = *tert*-butyl) to a transition metal to obtain a catalyst for asymmetric cyanohydrin synthesis. Thus, the mono-lithium salt of ligand **57**(R = *tert*-butyl) catalysed the asymmetric addition of trimethylsilyl cyanide to a variety of aromatic aldehydes. Best results were obtained using 1 mol% of the lithium salt in diethyl ether at −78°C, and under these conditions (*R*)-cyanohydrin trimethylsilyl ethers with up to 97% enantiomeric excess could be obtained, usually with reaction times of less than 1 h.[122] It is notable that the lithium salt of ligand **57** catalyses the preferential formation of (*R*)-cyanohydrins, whilst the titanium and vanadium complexes of the same ligand preferentially form (*S*)-cyanohydrins.

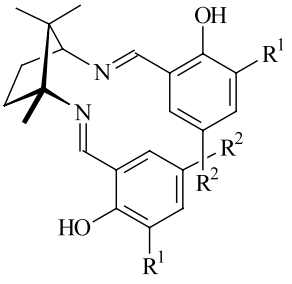
Other types of salen ligand have also been investigated as catalyst precursors for asymmetric cyanohydrin synthesis. Thus, Belokon' and Rozenberg prepared paracyclophane analogues **65a–c** which contain planar-chiral aromatic rings instead of or as well as a chiral diamine. Surprisingly, when the ligands were complexed in situ to titanium tetraisopropoxide, the complex derived from ligand **65a** was found to be more enantioselective than either of the diastereomeric catalysts **65b** or **65c**. In the presence of 10 mol% of the catalyst derived from ligand **65a**, at −78°C, benzaldehyde was converted into mandelonitrile trimethylsilyl ether with 82% enantiomeric excess and in 90% yield with a reaction time of 120 h.[123]



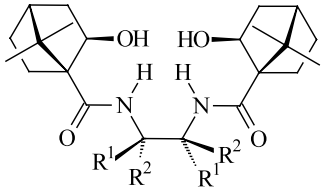
65a: $R^1 = R^2 = H$
b: $R^1 = H$; R^2-$R^2 = (CH_2)_4$
c: $R^2 = H$; R^1-$R^1 = (CH_2)_4$



66

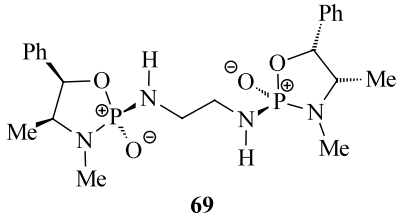


67

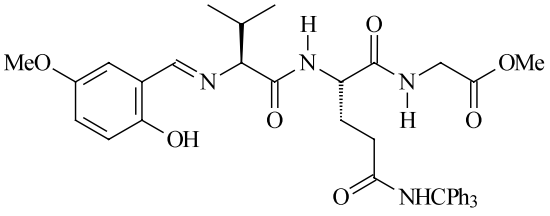


68a: R^1-$R^1 = (CH_2)_4$; $R^2 = H$
b: R^2-$R^2 = (CH_2)_4$; $R^1 = H$

Che et al. have prepared salen analogues **66** derived from BINAM. These were complexed in situ to titanium tetraisopropoxide and used to catalyse the asymmetric addition of trimethylsilyl cyanide to a range of aldehydes under Oguni's conditions (20 mol% catalyst, dichloromethane, −78°C, 36 h). Consistent with the results of Belokon' and North, the most enantioselective catalyst was that in which $R^1 = R^2 = tert$-butyl, and the titanium complex of this ligand converted aromatic, α,β-unsaturated, and aliphatic aldehydes into cyanohydrins with 42–96% enantiomeric excess, best results being obtained with electron-rich aromatic aldehydes.[124]



69



70

All of the salen ligands discussed so far in this section have possessed C_2-symmetry. However, Tang et al. have prepared C_1-symmetric ligands **67** from (*R*)-camphor. The ligands were again complexed in situ to titanium tetraisopropoxide and 20 mol% of the resulting complex used to catalyse the asymmetric addition of trimethylsilyl cyanide to aromatic aldehydes. Best results (33–73% enantiomeric excess) were obtained at −40°C with a reaction time of 24 h. Curiously, in this case the catalyst in which $R^1 = R^2 = H$ was found to be more enantioselective than the catalysts with halogenated or alkylated aromatic rings.[125,126]

There is only one example of a non-salen type tetradentate ligand being used in asymmetric cyanohydrin synthesis. Uang et al. prepared diastereomeric ligands **68a**,**b**, and showed that they could be complexed in situ to titanium tetraisopropoxide to form catalysts for asymmetric cyanohydrin synthesis. Best results were obtained at −78°C in the presence of powdered 4 Å molecular sieves. Under these conditions, 16.5 mol% of the complex derived from **68a** catalysed the addition of trimethylsilyl cyanide to a range of aromatic, aliphatic, and α,β-unsaturated aldehydes with excellent enantioselectivities (87–98% in favour of the *S*-enantiomer) and good to excellent yields after reaction times of 36–120 h. In contrast, under identical conditions, the complex derived from ligand **68b** converted benzaldehyde into (*R*)-mandelonitrile with only 4% enantiomeric excess, thus providing a clear example of matched and mismatched stereochemical features within the catalyst.[127]

4.4. Use of complexes containing ligands of unknown coordination number

Yang and Fang have investigated the use of samarium(III) complexes of phosphamidates as catalysts for asymmetric cyanohydrin synthesis. The most effective ligand was bis-phosphamidate **69**, and best results were obtained using 0.3 mol% of this ligand and 0.1 mol% of samarium trichloride. At temperatures between −70 and −15°C, the resulting complex catalysed the asymmetric addition of trimethylsilyl cyanide to aromatic aldehydes to give (*R*)-cyanohydrin trimethylsilyl ethers with 29–90% enantiomeric excess, with electron-rich substrates generally giving best results.[128]

Snapper, Hoveyda et al. have developed peptide-derived ligand **70** and shown that when complexed to aluminium tri-isopropoxide in the presence of methanol and 3 Å molecular sieves, a catalyst for the asymmetric addition of trimethylsilyl cyanide to ketones is formed. The optimal conditions require 20 mol% of the catalyst at −78°C for 2 days. Under these conditions, aliphatic, aryl-alkyl, and α,β-unsaturated-methyl ketones were all converted into (*R*)-cyanohydrins with 8–95% enantiomeric excess.[129]

4.5. Summary of the use of metal complexes for asymmetric cyanohydrin synthesis

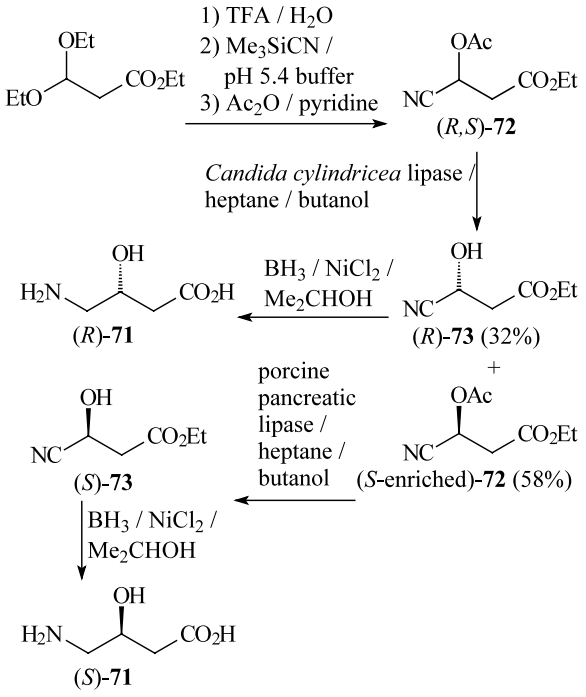
The asymmetric addition of trimethylsilyl cyanide to aldehydes is an area in which enormous progress has been made over the last 10 years. When I last reviewed this area, it was necessary to use 10–20 mol% of catalysts at low temperatures for long periods of time to obtain good chemical yields and high levels of asymmetric induction. The catalysts were prepared in situ, were ill defined and only speculation as to the mechanisms of catalysis and asymmetric induction were available. We now have well defined catalysts that are active at substrate: catalyst ratios of 1000:1, at room temperature and for which reactions are complete in just a few minutes. Detailed mechanistic studies have been carried out on a number of systems, and these have shown that for the best catalysts, both the carbonyl compound and trimethylsilyl cyanide should be simultaneously activated. This can be achieved by the use of a catalyst containing both Lewis acid and Lewis base sites (as in the Shibasaki catalysts) or by use of a bimetallic complex as developed by Belokon' and North. The corresponding addition to ketones was unknown 10 years ago, but again significant progress has been made in recent years. This is however, an area where there is still scope for further improvement in catalyst structure to obtain catalysts which will accept a wider range of substrates and are active at higher substrate:catalyst ratios.

Almost all of the work in this section has used trimethylsilyl cyanide as the cyanide source; however, the expense and volatility of this reagent mean that it is far from ideal, especially when working on large scale. In this respect, the discovery by the Belokon' and North groups of a catalytic system which utilises potassium cyanide holds great promise. It will be interesting to see how, if at all, the mechanism of this reaction compares with the corresponding reaction using trimethylsilyl cyanide, and whether the combined use of potassium cyanide/acetic anhydride has general applicability or is restricted to the Belokon'/North salen-type catalysts.

5. Enzymatic resolution of cyanohydrin derivatives

The use of lipase enzymes to enantioselectively hydrolyse cyanohydrin esters is a well-established process for the asymmetric synthesis of both free cyanohydrins and their esters. Compared to the catalytic asymmetric synthesis of cyanohydrins from prochiral precursors, this methodology suffers from disadvantages associated with low yields (50% maximum for a resolution under non-equilibrating conditions) and the large number of steps required. Nevertheless, the process is of synthetic utility.

Kunesch et al. have prepared both enantiomers of GABOB **71** from the racemic cyanohydrin acetate **72** as shown in Scheme 28. Thus, treatment of compound **72** with the lipase from *Candida cylindracea* selectively hydrolysed the (*R*)-enantiomer of the substrate, giving (*R*)-cyanohydrin **73** along with partially resolved (*S*)-cyanohydrin acetate **72**. The partially resolved substrate was then treated with porcine pancreatic lipase, which is known to selectively hydrolyse the (*S*)-enantiomers of cyanohydrin acetates. This resulted in the formation of the (*S*)-enantiomer of cyanohydrin **73**. Treatment of either enantiomer of **73** with borane in the presence of nickel(II) chloride and isopropanol then gave the two

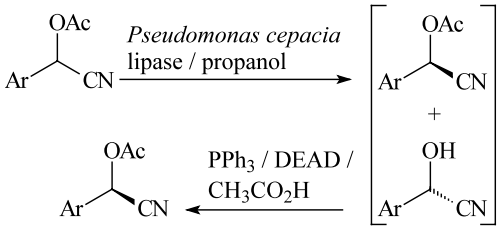


Scheme 28.

enantiomers of GABOB.[130] The same approach was used by Sakai et al. to obtain cyanohydrin derivatives from pentafluorobenzaldehyde. In this case, the lipase obtained from *Pseudomonas aeruginosa* was found to selectively hydrolyse the (*S*)-enantiomer of the propionate ester of the cyanohydrin, giving the (*S*)-cyanohydrin in 38% yield and with 97% enantiomeric excess as well as unreacted (*R*)-cyanohydrin propionate in 46% yield and with 92% enantiomeric excess.[131]

The racemic cyanohydrin acetate derived from 3-phenoxybenzaldehyde can be resolved by the lipase from *Pseudomonas* sp., giving the (*S*)-cyanohydrin and (*R*)-cyanohydrin acetate. The enantiomeric excess of the cyanohydrin was >96% after 46% conversion, and the (*R*)-cyanohydrin acetate could be racemised by treatment with triethylamine at 65°C and resubjected to enzymatic hydrolysis.[132] Lipase B from *Candida antarctica* has been used for the kinetic resolution of a series of substituted benzaldehyde cyanohydrin acetates at 60°C in propanol. The enzyme selectively hydrolyses the (*S*)-enantiomer of the cyanohydrin acetate, giving (*S*)-cyanohydrins with enantiomeric excesses >90% after 3–5 h reaction times.[133] In a later modification to the procedure, the resolution was carried out in the presence of vinyl butyrate to allow a second enzyme catalysed reaction: the enantioselective esterification of the cyanohydrin to the corresponding butyrate. In this way, (*S*)-cyanohydrin butyrates with enantiomeric excesses >96% were obtained.[134] The resolution of the cyanohydrin acetate of 2-naphthaldehyde has been achieved using the lipase from *Burkholderia cepacia* which selectively hydrolysed the (*S*)-enantiomer, leaving the (*R*)-cyanohydrin acetate with an enantiomeric excess of >99.9%.[135]

One way to avoid the 50% maximum yield in a traditional resolution is to combine the enzymatic hydrolysis of a cyanohydrin ester with a Mitsunobu reaction to reesterify the cyanohydrin product with inversion of configuration as shown in Scheme 29. The two processes can be carried out in the same pot, giving cyanohydrin acetates with 61–97% enantiomeric excess in 60–92% chemical yields. The lowest enantiomeric excess are obtained with aromatic cyanohydrins bearing electron donating substituents as these allow the Mitsunobu reaction to proceed by an S_N1 as well as an S_N2 mechanism.[136]

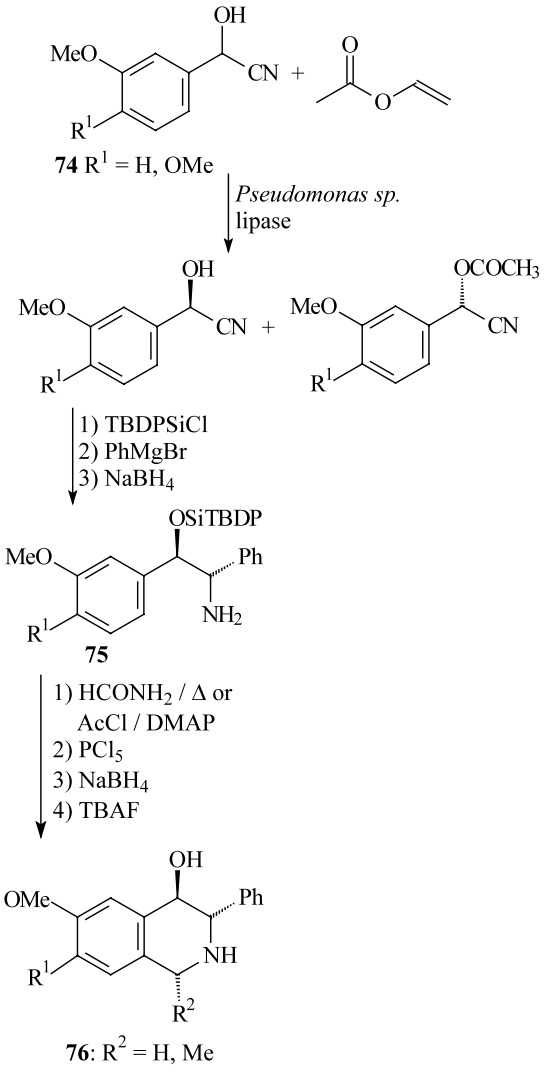


Scheme 29.

It also possible to use a lipase to resolve the esters of ketone derived cyanohydrins. In one example of this, esters of 1,1,1-trifluoroacetone and 1,1,1-trifluorobutan-2-one derived cyanohydrins were resolved using the lipase obtained from *Candida rugosa*. The best results were obtained with the butyrate esters of the cyanohydrins which could be resolved in ca. 40% yield to leave (*R*)-cyanohydrin esters with >98% enantiomeric excess from a reaction carried out on a 700 g scale.[137]

An alternative strategy is to use a lipase to enantioselectively esterify a cyanohydrin rather than to enantioselectively hydrolyse a cyanohydrin ester. This approach was utilised by Domínguez et al. in the synthesis of (3*S*,4*R*)-4-hydroxy-3-phenyltetrahydroisoquinolines as shown in Scheme 30. Thus, treatment of racemic cyanohydrins **74** with vinyl acetate in the presence of the lipase from *Pseudomonas* sp. gave the resolved (*R*)-cyanohydrins with >97% enantiomeric excess as well as the (*S*)-cyanohydrin acetates. Protection of the resolved cyanohydrins followed by Grignard addition and diastereoselective reduction (see Section 2.1 for related examples) gave β-amino alcohol derivatives **75**. Compounds **75** could be formylated or acetylated to give amides, which were cyclised to dihydroisoquinolines by treatment with phosphorus pentachloride, reduced to tetrahydroisoquinolines with sodium borohydride and deprotected to give the desired derivatives **76**.[138] The same approach using the lipase from *Pseudomonas cepacia* and vinyl acetate was used by Danieli et al. to prepare enantiomerically pure cyanohydrin derivatives derived from 2-phenyl-propanal.[16]

If conditions can be found where the cyanohydrin undergoes racemisation faster than the rate of enzymatic esterification, then a dynamic kinetic resolution can in principle be established that can proceed in >50% yield whilst still giving cyanohydrin esters with high enantiomeric excesses. This process has been investigated by Hanefeld et al., using alkaline Amberlite to

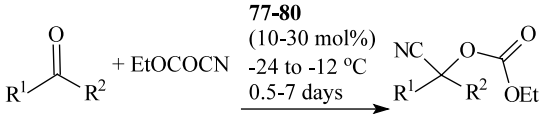


Scheme 30.

catalyse the racemisation of mandelonitrile, and *C. antarctica* Lipase B for the resolution. Unfortunately, whilst both processes work well in isolation, the acetic acid by-product formed during the reaction was found to inhibit the enzyme, and attempts to avoid this by ensuring that the reaction was kept basic were not successful due to polymerisation of the hydrogen cyanide formed during the racemisation step.[139]

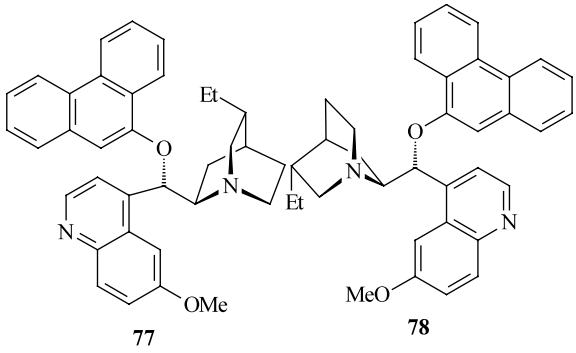
6. Miscellaneous methods

Tian and Deng have shown that cinchona alkaloid derivatives **77**–**80** will catalyse the asymmetric addition of ethyl cyanoformate to aliphatic ketones, including cyclic ketones as shown in Scheme 31. The best catalyst varies from substrate to substrate, but the catalysts form two *pseudo*-enantiomeric pairs (**77**/**78** and **79**/**80**), which give products with opposite absolute configurations. Under the optimal reaction conditions, ten ketones were converted into cyanohydrin carbonates with 59–97% enantiomeric excess, and only hepatan-2-one gave a product with less than 80% enantiomeric excess.[140] This unique reaction has significant potential and is worthy of further investigation to determine the mechanism and origin of the asymmetric induction.

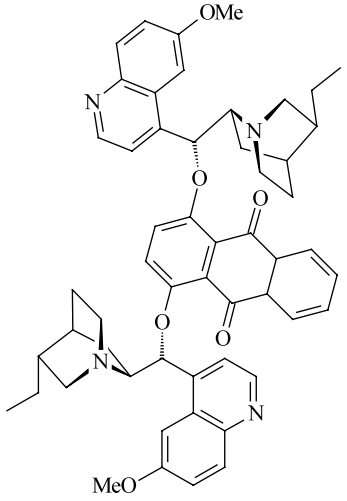


Scheme 31.

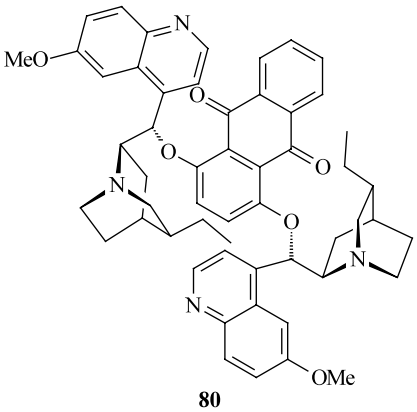
There have been two chiral auxiliary approaches to asymmetric cyanohydrin synthesis. Thus, Cativiela et al. have shown that treatment of cyanoacetate **81** with methyl iodide and potassium carbonate leads to a 77:23 ratio of diastereomeric cyanohydrin acetates of which **82** is the major stereoisomer. Subsequent manipulations



77 **78**

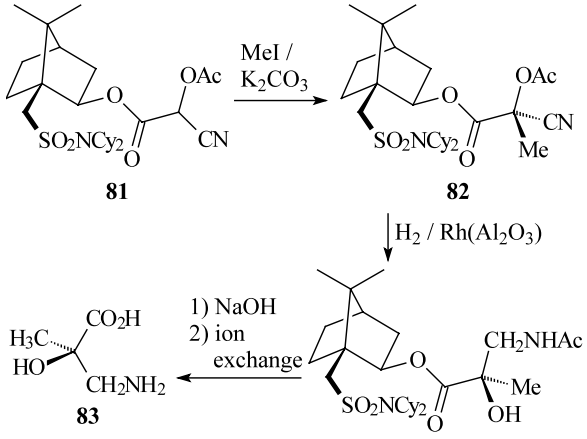


79

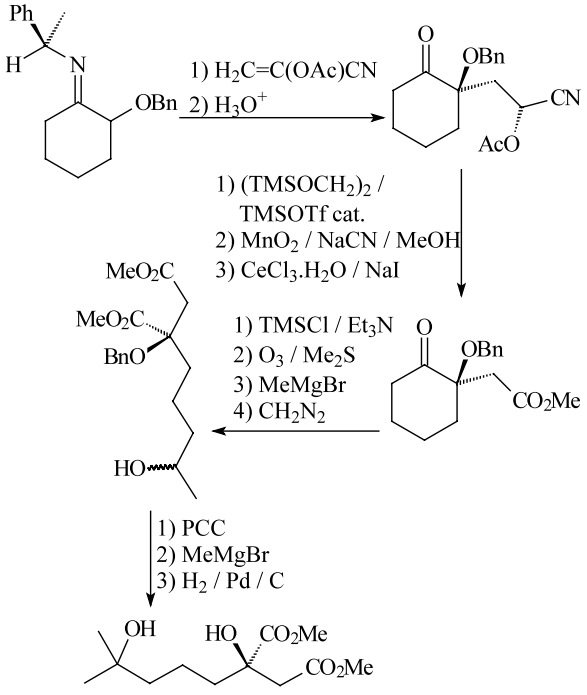


80

provided (*R*)-α-methyl isoserine **83** as shown in Scheme 32.[141] Imines derived from cyclic ketones and α-methyl benzylamine undergo a diastereoselective Michael addition when treated with 2-acetoxyacrylonitrile to give stereoisomerically pure cyanohydrin acetates.[142] This chemistry was used in a synthesis of the ester side chain of homoharringtonine as shown in Scheme 33.[143]

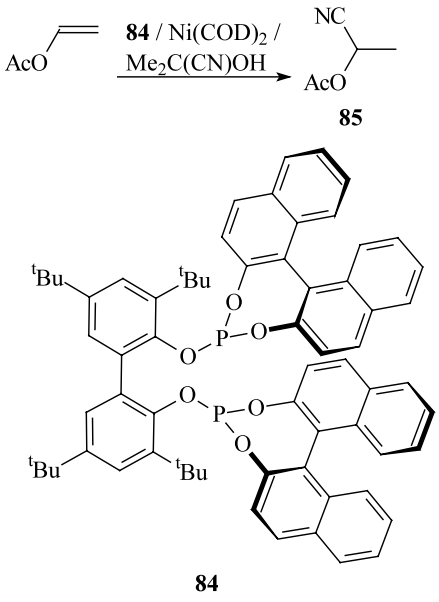


Scheme 32.



Scheme 33.

The asymmetric addition of hydrogen cyanide to alkenes is an established method for the synthesis of chiral nitriles. There is one example of vinyl acetate being used as the alkene in this process, leading to a cyanohydrin acetate as shown in Scheme 34. Thus, treatment of ligand **84** (7 mol%) with bis(cyclooctadiene)nickel (1 mol%) in the presence of vinyl acetate and acetone cyanohydrin gave cyanohydrin **85** with 73% enantiomeric excess (absolute configuration not determined), though in only 24% yield.[144]



Scheme 34.

7. Conclusions

Over the last 10 years there has been an explosion of interest in asymmetric cyanohydrin synthesis. The review that I wrote[1] in 1993 contained just 65 references, while the present manuscript cites more than double that number of papers. Much of this increased interest has been due to the discovery and development of effective catalysts derived from a metal and a chiral ligand. Ten years ago, this field was in its infancy, now it is arguably the method of choice for asymmetric cyanohydrin synthesis. In contrast, interest in peptide-catalysed asymmetric cyanohydrin synthesis has waned, probably due to the necessity to use hydrogen cyanide as the cyanide source and the failure to find catalysts with improved catalytic properties. Enzymatic cyanohydrin synthesis continues to be a thriving field, though contributions are increasingly coming from biological chemists studying the nature of the enzymes rather than synthetic groups seeking to exploit the catalysts.

There remains however, much progress left to make, especially with regard to the use of ketones as substrates and the development of catalytic systems that are compatible with non-volatile cyanide sources. It is a reasonable prediction that work on asymmetric cyanohydrin synthesis over the next 10 years will concentrate on overcoming these remaining difficulties, and that the search for solutions to these problems will exercise the minds and experimental abilities of synthetic and mechanistic chemists for the foreseeable future.

8. Note added in proof

After this review was submitted, the asymmetric addition of methyl cyanoformate to aldehydes catalysed by complex **36** was reported.[145] Use of 10 mol% of the catalyst at room temperature in the presence of 4 Å molecular sieves converted ten aldehydes into the corresponding cyanohydrin carbonates with 0–80% enantiomeric excess.

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