Review

Lewis Acid Catalyzed Asymmetric Cyanohydrin Synthesis

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1. Introduction

1.1. Historical Perspective

The addition of cyanide to a carbonyl compound to form a cyanohydrin is one of the fundamental carbon−carbon bond forming reactions in organic chemistry[1] and has frequently been at the forefront of advances in chemical transformations. Cyanohydrin synthesis was first reported by Winkler in 1832 using hydrogen cyanide as the cyanide source.[2] Just five years later, Wohler identified an oxynitrilase enzyme (this class of enzymes is also called hydroxynitrile lyases) as being present in almonds.[3] The natural role of this enzyme is to decompose mandelonitrile (2-hydroxyphenylacetonitrile) to benzaldehyde and hydrogen cyanide: the reverse of the synthetically more useful synthesis of cyanohydrins from aldehydes and hydrogen cyanide. Exactly 100 years ago in 1908, Rosenthaler successfully used an extract of almonds to catalyze the asymmetric addition of hydrogen cyanide to benzaldehyde.[4] This was one of the first asymmetric syntheses ever reported and the first to be catalyzed by an enzyme, thus placing asymmetric cyanohydrin synthesis at the leading edge of asymmetric organic synthesis. In 1903, Lapworth had carried out early mechanistic studies on cyanohydrin synthesis and demonstrated that the reaction was base catalyzed, with the role of the base being to convert hydrogen cyanide into the nucleophilic cyanide ion.[5] The reaction is also known to be reversible, with the position of equilibrium being determined by a combination of steric and electronic factors (Scheme 1).[6]

Early work on cyanohydrin synthesis was all carried out with hydrogen cyanide as the cyanide source. The volatility and extreme toxicity of this reagent cause obvious difficulties, and numerous alternative cyanide-based reagents have since been developed.[1] The structures of the more important of these reagents and the cyanohydrin derivatives that they produce are summarized in Scheme 2. Since the addition reaction is base catalyzed, the simplest approach is to use a metal cyanide salt as the cyanide source in the presence of a slightly less than stoichiometric amount of acid. However, this illustrates a common feature of many systems: that the

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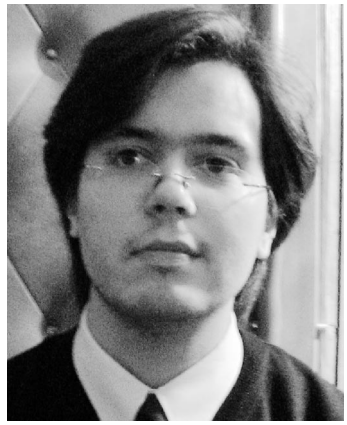
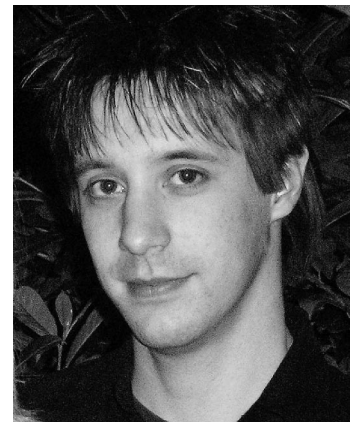
Michael North was born in Blackburn, England, in 1964. He obtained his B.Sc. in 1985 from the University of Durham and his D.Phil. in 1988 from the University of Oxford for work on the synthesis of nonracemic amino acids carried out in the group of Professor Sir J. E. Baldwin. After a two-year postdoctoral position in Professor G. Pattenden's research group at the University of Nottingham, he was appointed to his first academic post at the University of Wales at Bangor. In 1999 he moved to King's College London and was promoted to Professor of synthetic organic chemistry in 2001. In 2004, he moved to his current position as Professor of organic chemistry and joint director of the University Research Centre in Catalysis and Intensified Processing at the University of Newcastle upon Tyne. Professor North has published over 100 original papers and also holds five patents. His research interests are centered on the design and mechanistic study of new catalysts with applications including asymmetric carbon−carbon bond formation, carbon dioxide chemistry, and polymer chemistry. In 2001 he was awarded the Descartes Prize by the European Commission for his work on asymmetric cyanohydrin synthesis using metal(salen) complexes.



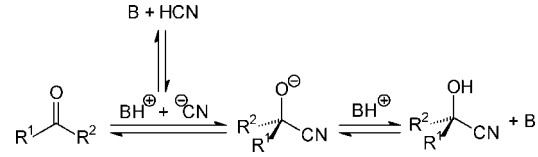
Dmitry L. Usanov was born in 1986 in Moscow, Russia. After entering The Moscow Chemical Lyceum high school in 2000, he joined Professor Yuri N. Belokon's group in the Nesmeyanov Institute of Organoelement compounds RAS in 2001. In 2002 he entered the Higher Chemical College of the Russian Academy of Sciences, from where he was awarded a Bachelor's Degree equivalent in 2006 and a Specialist Diploma in 2007 (Summa Cum Laude). During his undergraduate years, he was involved in a number of research projects in Poland (IChO PAS), the U.K. (Newcastle University), and the U.S.A. (University of Pennsylvania) as a visiting researcher. In 2007 Dmitry obtained an M.Phil. Degree from Newcastle University under the supervision of Professor Michael North. Since 2007 he has been a Ph.D. student at The University of Chicago in Professor Hisashi Yamamoto's group. He is a coauthor of five papers and has been awarded an Overseas Research Student Award, a Gerhard Closs Award, and a McCormick Fellowship.

alternative reagent is not a truly different reagent but rather is just a different precursor to the same hydrogen cyanide/cyanide used in the early work. Acetone cyanohydrin[7] may function as an *in situ* source of hydrogen cyanide or transfer cyanide directly to an aldehyde through a Meerwein−Ponndorf−

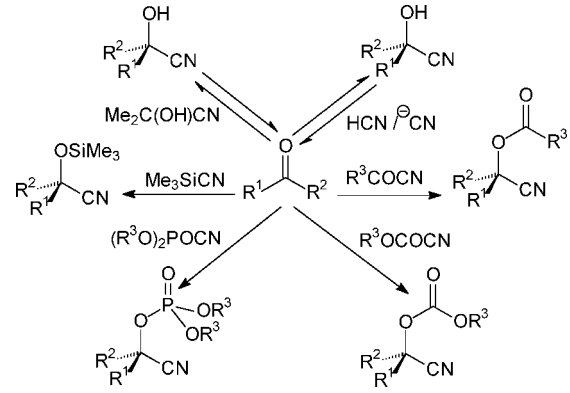


Carl Young was born in Carlisle, England, in 1982. In 2000 he began studies in medicinal chemistry at Newcastle University, and he received his M.Chem. in 2004. The following year, he started his doctoral studies under the supervision of Professor Michael North. Currently in the final stages of completing his Ph.D., his work has focused mainly on the investigation of salen-based catalysts for the asymmetric synthesis of cyanohydrins, with particular attention to the structural and mechanistic aspects of heterobimetallic systems involving the use of titanium and vanadium. His work has been published in two papers.

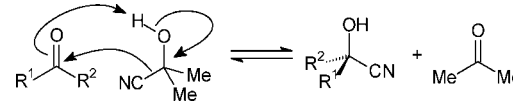
Scheme 1



Scheme 2



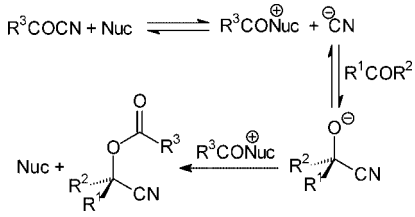
Scheme 3



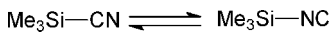
Verley type transition state[8] (Scheme 3). The use of acetone cyanohydrin as a cyanide source takes advantage of both the reversibility of cyanohydrin synthesis and the steric influence on the position of the equilibrium, which is generally more favorable for addition to aldehydes than to ketones.

Acyl cyanides,[9] cyanoformates,[10] and cyanophosphonates[11] can also be used as cyanating agents and have the major advantage of producing *O*-protected cyanohydrins which do not revert to carbonyl compounds; thus, the cyanohydrin formation becomes irreversible, and even substrates for which the equilibrium between carbonyl compound and cyanohydrin is unfavorable can be prepared

Scheme 4



Scheme 5



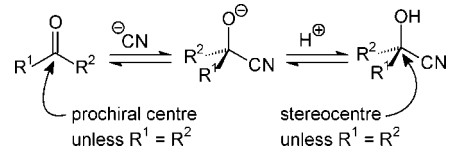
in this way. These addition reactions are also 100% atom economical.[12] However, the addition of these reagents to carbonyl compounds requires a nucleophilic catalyst or solvent, so they may not be true cyanating agents. Rather, they may be converted into cyanide *in situ* by the catalyst. The *in situ* formed cyanide can add to the carbonyl compound to form an unprotected cyanohydrin alkoxide which can react with the cyanating agent to form the *O*-protected derivative and generate another cyanide ion. Thus, only a catalytic amount of nucleophile is required to initiate the process (Scheme 4).

By far the most commonly used alternative cyanide source, however, is trimethylsilyl cyanide.[13] The synthesis of cyanohydrin trimethylsilyl ethers (*O*-trimethylsilyl cyanohydrins) from aldehydes or ketones[14] and trimethylsilyl cyanide was first reported in 1973, simultaneously by the groups of Evans[15] and Lidy[16] (Scheme 2). With aldehydes as substrates, the reaction will occur just by mixing the two reactants in the absence of a solvent. Reaction can also be induced thermally or by an enormous range of catalysts including Lewis acids, bases, and nucleophiles.[1] Mechanistically, the reaction has a number of complications. Trimethylsilyl cyanide is readily hydrolyzed to hydrogen cyanide by water or alcohols,[17] so it may act as a precursor to hydrogen cyanide, which may be the real cyanating agent. Since trimethylsilyl cyanide is also a good silylating agent,[17] it would silylate the initially formed cyanohydrin, leading to the formation of the cyanohydrin trimethylsilyl ether and regenerating the hydrogen cyanide. A second complication with trimethylsilyl cyanide is that the reagent exists as an equilibrium mixture of cyanide and isocyanide forms (Scheme 5).[18] Whilst the cyanide form dominates (typically >98%), reaction through the isocyanide form cannot be discounted.

Trimethylsilyl cyanide is only the simplest example of a family of silyl cyanides, and there are reports of the addition of other silyl cyanides to carbonyl compounds.[19] In general, the other silyl cyanides are less reactive than trimethylsilyl cyanide but have the advantage of producing cyanohydrin silyl ethers which are more stable with respect to hydrolysis.

Whilst detailed knowledge of the nature of the cyanating agent is not necessary for non-stereocontrolled cyanohydrin synthesis, it is clearly essential for stereoselective cyanohydrin synthesis, since the cyanide source will almost certainly be involved in the stereodetermining transition state. This situation is further complicated, since the initial cyanide source may react with any additives prior to formation of a cyanohydrin. For example, if a metal-based catalyst is used, then *in situ* formation of a metal cyanide must be considered.

Scheme 6



1.2. Principles of Stereoselective Cyanohydrin Synthesis

With the exception of additions to formaldehyde and symmetrical ketones, during the addition of cyanide to a carbonyl compound, a prochiral center is converted into a new stereocenter (Scheme 6). The reaction can therefore be stereocontrolled in a number of ways:

1. If the carbonyl compound contains one or more stereocenters, then reaction with achiral cyanide sources can lead to a diastereospecific reaction in which only one of the two possible diastereomeric cyanohydrins is formed.[20]

2. The carbonyl compound can be converted into a chiral acetal which can undergo Lewis acid catalyzed addition of cyanide followed by cleavage of the remaining carbon−oxygen bond, resulting in overall enantioselective addition of cyanide to the carbonyl compound by a chiral auxiliary approach.[21]

3. A chiral cyanide source can in principle react with the carbonyl compound in a diastereospecific reaction to form diastereomeric cyanohydrin derivatives.[22]

4. A stoichiometric or catalytic amount of a chiral additive can be used to induce the enantioselective addition of achiral cyanide sources to achiral carbonyl compounds.

The last of these four approaches is by far the most versatile and can be achieved with the aid of a wide range of chiral catalysts[23] or additives including enzymes (section 1.4), organic catalysts (section 1.5), and chiral metal-based catalysts (sections 2 and 3). However, the reversibility of cyanohydrin synthesis causes a potential problem for asymmetric cyanohydrin synthesis, since the products are prone to racemize by elimination and readdition of hydrogen cyanide. Reagents such as trimethylsilyl cyanide, acyl cyanide, and cyanoformates have a major advantage in this respect, since they produce *O*-protected cyanohydrins which are not prone to racemization by this mechanism. That does not mean, however, that asymmetric cyanohydrin synthesis cannot be achieved using hydrogen cyanide as the cyanide source. The rate of equilibration between a cyanohydrin and a carbonyl compound is highly pH and solvent dependent. As part of the development of the use of oxynitrilase enzymes in asymmetric cyanohydrin synthesis, much effort was devoted to developing conditions where the uncatalyzed addition and elimination reaction of hydrogen cyanide occurred at negligible rates. It was found that, by the use of nonaqueous solvents and nonbasic reaction conditions, the uncatalyzed reactions could be effectively suppressed. Nevertheless, an unprotected, enantiomerically enriched cyanohydrin will racemize on standing, so they are usually protected or converted to a more stable functionality immediately after their preparation.

Aldehyde derived cyanohydrin derivatives can also racemize by a second mechanism, since they possess an acidic proton adjacent to the nitrile and attached to the stereocenter. Thus, in the presence of base, reversible deprotonation can occur leading to racemization. This racemization mechanism is only significant for *O*-protected cyanohydrins in which the protecting group is electron withdrawing. It can be

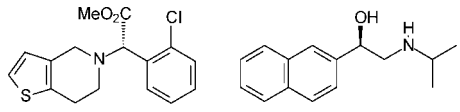
significant therefore for cyanohydrin esters and phosphonates, particularly if the cyanohydrin is also derived from an electron deficient aldehyde.

Another factor which needs to be considered is the nature of the stereodetermining step. Whilst in many cases this will be the addition of cyanide to the prochiral carbonyl, this is not necessarily the case. As Scheme 4 illustrates, if the mechanism involves a reversible addition of cyanide followed by irreversible protection of the cyanohydrin alkoxide (under the influence of the chiral catalyst), then a dynamic kinetic resolution[24] may occur, with the second step determining the overall stereochemistry of the process. Under these conditions, the cyanide containing reagent may not be involved in the stereodetermining step of the mechanism.

1.3. Synthetic Applications of Chiral Cyanohydrins

Cyanohydrins contain two functional groups: a nitrile and an alcohol (which may be prepared in protected form). These two functional groups can be readily manipulated to produce a diverse range of 1,2-difunctional compounds, including many which are often found as components of pharmaceuticals.[25] Methodology has been developed to allow these transformations to be achieved whilst preserving the stereochemistry associated with the cyanohydrin and, where new stereocenters are created, to allow the configuration of these to be controlled.

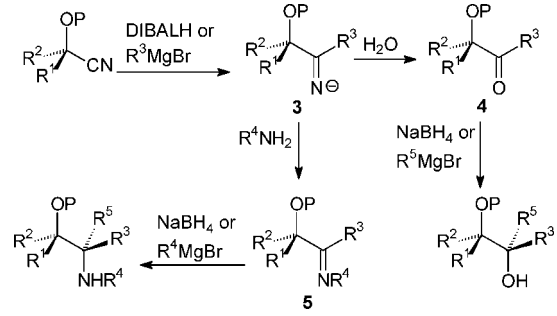
Commercially, currently the most important transformation of cyanohydrins is their conversion into α-hydroxy acids. This reaction can be achieved without causing any racemization simply by treating a cyanohydrin or any of the protected cyanohydrins shown in Scheme 2 with aqueous acid at ambient or elevated temperature.[26] Not only does this process not cause racemization, but recrystallization during the purification of the usually crystalline α-hydroxy acid can be used to raise the enantiomeric excess of the product above that of the cyanohydrin from which it was prepared. This process has been used industrially by a number of companies for the synthesis of 2-chloromandelic acid, which is a key component of Clopidogrel (**1**).[25,27] Clopidogrel is the fourth ranked pharmaceutical in terms of global sales and is used as an antidepressant and a platelet-aggregation inhibitor in the treatment of coronary artery disease as well as peripheral vascular and cerebrovascular diseases.



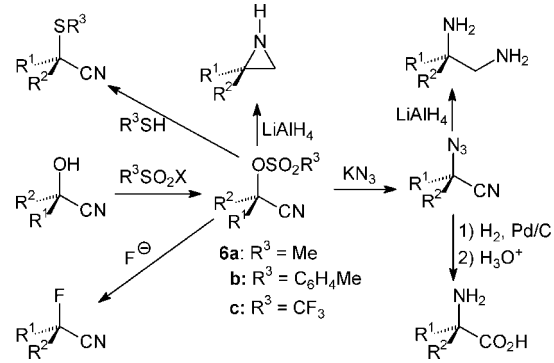
1 **2**

Another reaction of potential commercial importance[27] is the reduction of the nitrile group to provide β-amino alcohols related to adrenaline. This reduction can be achieved without racemization by treatment of either a free cyanohydrin or an *O*-protected derivative with lithium aluminum hydride.[26a,28,29] An example of this approach is the synthesis of the β-blocker pronethalol (**2**) in just three steps from 2-napththaldehyde. The synthesis gave compound **2** with an enantiomeric excess of 66%; however, the methodology available at the time for the asymmetric cyanation gave the cyanohydrin of 2-naphthaldehyde with just 70% enantiomeric excess.[28a] Cyanohydrin esters can also be hydrogenated over nickel supported on alumina, and under these conditions the intermediate

Scheme 7



Scheme 8



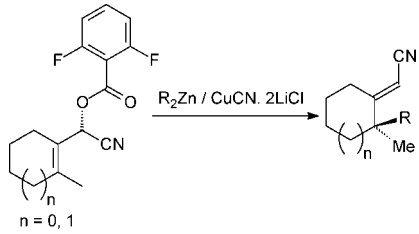
amino esters undergo spontaneous *O*- to *N*-acyl migration, leading to pharmaceutically relevant *N*-acyl β-amino alcohols.[30]

With less reactive nucleophiles (DIBALH and Grignard reagents), suitably protected cyanohydrins undergo a single addition reaction, leading initially to iminates **3**, as shown in Scheme 7.[28] Subsequent hydrolysis of the iminates gives α-hydroxy aldehydes and ketones **4**, whilst transimination gives imines **5**. Compounds **3**−**5** will all undergo a second nucleophilic addition (with sodium borohydride or a Grignard reagent), leading to a diverse range of 1,2-diols and β-amino alcohols with two consecutive stereocenters. The second nucleophilic addition occurs in a stereoselective manner due to the formation of a chelated intermediate and has been used to prepare a range of ephedrine analogues.[28]

Another class of transformation which cyanohydrins undergo is S_N2 type reactions on the alcohol group. Cyanohydrins can be converted into sulfonate esters **6a**−**c**, and the latter undergo S_N2 reactions with a range of nucleophiles and with inversion of configuration, as shown in Scheme 8. For aliphatic cyanohydrins, all of the sulfonate derivatives **6a**−**c** are stable, whilst for aromatic cyanohydrins only the mesylate **6a** could be isolated.[31] This approach has been used to prepare α-azido nitriles,[32] α-amino nitriles,[32,33] aziridines,[34] α-thionitriles,[35] and α-fluoronitriles[36] and to invert the stereochemistry of cyanohydrins.[31] The α-azido nitriles are particularly versatile intermediates for the synthesis of both α-amino acids and 1,2-diamines.[32] In related chemistry, both free cyanohydrins and their trimethylsilyl ethers react with DAST to produce α-fluoronitriles with inversion of configuration.[36] Mitsunobu chemistry has also been used to convert cyanohydrins into α-amino acids with inversion of configuration.[37]

Cyanohydrin derivatives derived from α,β-unsaturated carbonyl compounds can also undergo S_N2' reactions under appropriate conditions. Until recently, this was a rather neglected potential application of chiral cyanohydrins which

Scheme 9



transfers the chirality of the cyanohydrin to the γ-position and creates a synthetically useful α,β-unsaturated nitrile group for further manipulation. Knochel has recently shown that *O*-acylated-β,γ-unsaturated cyanohydrins derived from cyclohexenal and cyclopentenal react with organozinc reagents in the presence of a copper(I) catalyst to give γ-alkylated products (Scheme 9). There is no loss of stereochemical purity during the alkylation which also creates a new quaternary center and a stereochemically pure alkene.[38] Related chemistry using Grignard reagents and cyanohydrin phosphonates has also been reported by Nájera.[39]

Palladium catalyzed allylic transpositions of cyanohydrin derivatives are known to occur on the acetate,[40] carbonate,[41] and phosphonate[42] derivatives with a range of nucleophiles including azide, acetate, and malonate. The stereochemistry of these processes can be complex, as either retention or inversion of configuration can be obtained, and this can differ depending upon the configuration of the alkene in the substrate. In general, however, if a single stereoisomer (at the cyanohydrin and alkene) of the cyanohydrin derivative is employed, then the α,β-unsaturated nitrile product will be obtained as a single enantiomer, but as a 1:1 mixture of *E* and *Z* isomers.

1.4. Enzyme Catalyzed Asymmetric Cyanohydrin Synthesis

Nature makes wide use of the reversible addition of cyanide to carbonyl compounds, and cyanohydrin derivatives are found in a wide variety of plant sources where they are used as antifeedants and a source of other nitrogen containing metabolites.[43,44] Since the first oxynitrilase catalyzed asymmetric cyanohydrin synthesis in 1908,[4] oxynitrilases have been isolated from many different sources and have been used to catalyze the asymmetric addition of hydrogen cyanide to both aldehydes and ketones.[44,45] Over the last 100 years, enzyme catalyzed cyanohydrin synthesis has developed into a commercial process for the synthesis of cyanohydrins[25] and has been covered in numerous reviews,[43–45] so only a brief overview to put Lewis acid catalyzed asymmetric cyanohydrin synthesis in context is given here.

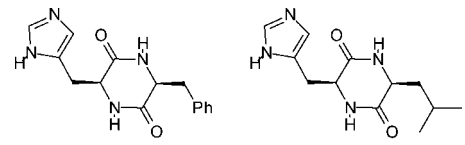
Enzymes which catalyze the addition of cyanide to either the *re*- or *si*-face of a carbonyl compound have been isolated, as have enzymes which will accept either aldehydes or ketones as substrates. The most versatile enzymes have been cloned and overexpressed, and crystal structures have been determined. Site directed mutagenesis experiments have been carried out to determine the key residues involved in the catalytic cycle. In addition it has been shown that oxynitrilases can control the diastereoselective as well as enantioselective addition of hydrogen cyanide to suitable substrates[46] and that the oxynitrilase enzyme obtained from *Hevea brasiliensis* can be used in conjunction with TEMPO/$PhI(OAc)_2$ to carry out a one pot conversion of alcohols into cyanohydrins.[47] The same oxynitrilase enzyme has also been shown to accept nitromethane as a hydrogen cyanide substitute, thus leading to an enzyme catalyzed asymmetric Henry reaction.[48]

Almost all work on asymmetric cyanohydrin synthesis using oxynitrilase enzymes uses hydrogen cyanide as the cyanide source, which is inconvenient from a research perspective. However, it has also been shown that oxynitrilases will catalyze transcyanation reactions to aldehydes using acetone cyanohydrin[49] or a racemic ketone derived cyanohydrin[50] as the cyanide source. The latter process is particularly interesting, as both the aldehyde and ketone derived cyanohydrins can be obtained enantiomerically enriched from a single enzyme catalyzed reaction. Ethyl cyanoformate has also been employed as the cyanide source in oxynitrilase catalyzed reactions carried out under organic−aqueous biphasic conditions and leading to (*R*)-cyanohydrin ethyl carbonates. It was shown however that, under the reaction conditions, the ethyl cyanoformate is hydrolyzed to hydrogen cyanide, which is the true cyanating agent.[51]

1.5. Organocatalyzed Asymmetric Cyanohydrin Synthesis

The history of organocatalyzed asymmetric cyanohydrin synthesis is almost as long as that of enzyme catalyzed cyanohydrin synthesis.[52] In 1912, Bredig and Fiske first reported the use of alkaloids to catalyze the asymmetric addition of hydrogen cyanide to aldehydes.[53,54] Other organic catalysts studied for this reaction include chiral polyamines[55] and linear peptides.[56] However, whilst these early reports indicated the potential for organocatalysis in this area, they all gave very low enantioselectivities (<20%).

The real breakthrough in this area came in 1979, when Inoue discovered that cyclic dipeptide (diketopiperazine) **7** derived from phenylalanine and histidine would catalyze the asymmetric addition of hydrogen cyanide to benzaldehyde to form (*R*)-mandelonitrile in 97% chemical yield and with 97% enantioselectivity.[56,57] Catalyst **7** was subsequently shown to be a general catalyst for the asymmetric addition of hydrogen cyanide to aromatic aldehydes.[58] Aliphatic aldehydes are also accepted as substrates, but with much lower enantioselectivity. Subsequently, Inoue reported diketopiperazine **8**, which despite still being derived from (*S*)-amino acids catalyzes the formation of (*S*)-cyanohydrins and gives higher enantioselectivities with aliphatic aldehydes than with aromatic substrates.[59]



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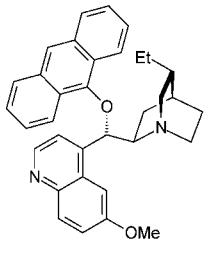
The discovery of catalyst **7** was a remarkable achievement, since it predated the development of the first metal-based catalyst for asymmetric cyanohydrin synthesis by eight years (see section 2.2) and it took 20 years for metal-based catalyst systems with activities and enantioselectivities similar to those of diketopiperazine **7** to be developed (section 2). It should also be noted that catalyst **7** was developed at a time when the conventional wisdom was that effective asymmetric catalysis could only be achieved within the coordination sphere of a metal. Diketopiperazine **7** can also be considered as a biomimetic catalyst, since there is an excellent correla-

tion between the activity of catalyst **7** and that of the readily available oxynitrilase enzyme obtained from almonds. Both the chemical yields and the enantioselectivities obtained with a wide range of aromatic aldehydes are highly comparable between the two systems.[23a] It is also known that both catalyst systems are compatible with the use of acetone cyanohydrin as the cyanide source, though this significantly reduces the reaction rate.[49,60]

The mechanism of action of catalysts **7** and **8** remains elusive. Extensive spectroscopic studies have determined the conformations of the catalysts,[61] and a kinetics study has shown that two catalyst molecules are involved in the catalysis.[62] It is also known that the reaction exhibits enantioselective autocatalysis[63] and that the reaction mixture is heterogeneous, with reaction often occurring in the gel phase.[64] A number of models have been proposed to account for the catalytic activity of diketopiperazine **7**,[23b,62,65] though there is no conclusive evidence in favor of any of them, and attempts to improve the enantioselectivity and/or substrate tolerance of the catalyst by modifying its structure have not led to catalysts with improved activity.[66]

There has been almost no activity related to catalyst **7** for the last decade. However, with the recent upsurge in interest in asymmetric organocatalysis in general,[52] a number of other systems have been developed for asymmetric cyanohydrin synthesis. In 2001, Deng reported that monomeric and dimeric *O*-arylated cinchona alkaloids **9** and **10** were excellent catalysts for the asymmetric addition of ethyl cyanoformate to aliphatic ketones,[67] achieving enantioselectivities and conversions of up to 97%. This is an example of a reaction where the asymmetric induction is thought to be due to a dynamic kinetic resolution of the cyanohydrin alkoxide rather than enantioselective cyanide addition (see Scheme 4 and section 1.2). Recently, Nájera has used dimeric cinchona alkaloid derived ammonium salts in the presence of triethylamine to catalyze the same reaction,[68] and Feng has shown that monomeric cinchona alkaloid derived ammonium salts will catalyze the cyanoformylation of aromatic aldehydes with enantioselectivities of 61−72%.[69] Deng has also shown that trimethylsilyl cyanide could be used as the cyanide source,[70] and in this case the best substrates were the monoacetals of 1,2-diketones which gave products in >80% yield and with enantioselectivities >90%. This chemistry was utilized in the total synthesis of bisorbicillinolide, bisorbicillinol, and bisorbibutenolide.[71]



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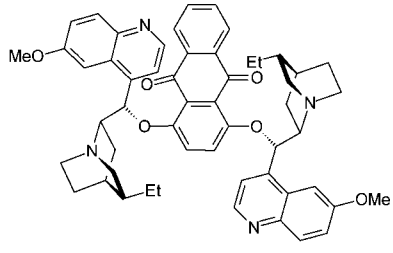

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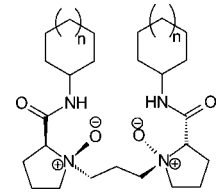
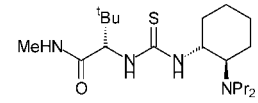
Feng has reported extensively on the use of chiral and achiral[72] *N*-oxides as catalysts for both racemic and asymmetric cyanohydrin synthesis. Much of this work involved the simultaneous use of an *N*-oxide and a metal-based catalyst and is discussed in sections 2 and 3. However, bis-*N*-oxides **11a**,**b** were found to function as effective organocatalysts for the asymmetric addition of trimethylsilyl cyanide to aromatic aldehydes[73] and the monoacetals of 1,2-diketones.[74] Interestingly, much higher enantioselectivities (85−93% using catalyst **11a**) were obtained with the ketone substrates than with aldehydes (53−73% using catalyst **11b**). Thioureas have been widely used as organocatalysts for a number of different reactions,[75] and Jacobsen has developed bifunctional thiourea **12** as a catalyst for the asymmetric addition of trimethylsilyl cyanide to ketones.[76] Under the optimized conditions, very high enantioselectivities (86−97%) and chemical yields (>80%) were obtained from a range of aromatic and α,β-unsaturated ketones. The reactions are carried out in the presence of trifluoroethanol, which suggests that hydrogen cyanide is the actual cyanating agent.[17] This was confirmed by a mechanistic study[76b] which also indicated that both the thiourea and tertiary amine are involved in the catalysis. The mechanistic study also allowed the structure of the catalyst to be optimized to give high enantioselectivities with aliphatic ketones by tuning the steric properties of the secondary amide within catalyst **12**. Gennari and coworkers have used similar thioureas as catalysts for the asymmetric addition of trimethylsilyl cyanide to aldehydes, though with much lower enantioselectivities (45−69%).[77]



11a) n = 0
b) n = 1



12

Without doubt, the main feature of effective organocatalysts for asymmetric cyanohydrin synthesis is the need for multifunctional catalysts either within a single molecule or within a supramolecular assembly. The diketopiperazines **7** and **8** self assemble into a gelatinous network, and catalysis takes place within this environment. Dimeric cinchona alkaloid derivatives are much more effective catalysts than their monomeric analogues, and both the *N*-oxide- and thiourea-based catalysts contain two catalytically active functional groups. This illustrates one of the key features of asymmetric cyanohydrin synthesis: catalysts which can activate both the carbonyl compound and the cyanide source form much more effective catalysts than species which can only activate one of the components of the reaction. This theme will also be apparent in the catalyst systems discussed in the main part of this review (sections 2 and 3), where catalysts based around one or more metal ions are discussed.

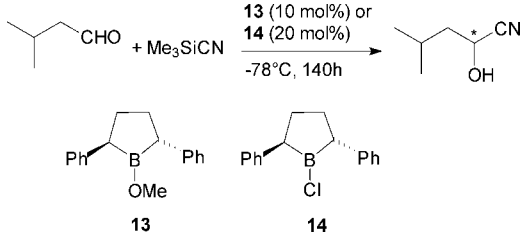
2. Chiral Lewis Acid-Based Systems for the Asymmetric Cyanation of Aldehydes

Within sections 2 and 3, the various Lewis acid-based catalytic systems for the asymmetric synthesis of cyanohydrins are discussed.[78] Each section is divided first by the Lewis acidic element and then by the nature of the chiral ligand(s) if appropriate.

2.1. Boron-Based Catalytic Systems

In 1986 Reetz described the first example[79] of the enantioselective addition of trimethylsilyl cyanide to aldehydes catalyzed by a chiral Lewis acid. Thus, in the presence of boron-containing heterocycles **13** (10 mol %) or **14** (20 mol %), isobutanal reacted with trimethylsilyl cyanide (Scheme 10), to give, after hydrolysis, 2-hydroxy-4-meth-

Scheme 10



Scheme 11

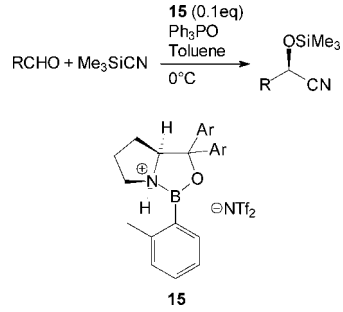


Table 1. Synthesis of Cyanohydrin Trimethylsilyl Ethers Using Catalyst 15[a]

aldehyde	time (h)	yield (%)	ee[b] (%)
PhCHO	40	94	95
2-MeC_6H_4CHO	72	95	91
4-$MeOC_6H_4CHO$	40	91	90
4-NCC_6H_4CHO	144	98	97
CyCHO	40	97	90
Me_3CCHO	40	96	91
$CH_3(CH_2)_5CHO$	48[c]	96	91

[a] Using 0.2 equiv of triphenylphosphine oxide. [b] Enantioselectivities determined by GC or ^1H NMR analysis of the cyanohydrins. [c] Reaction temperature = −20 °C.

ylpentanonitrile in 45−55% yield. The reaction was conducted at −78 °C for 140 h and showed some stereoselectivity (12−16% asymmetric induction). However, the absolute configuration of the product was not determined. Despite the low yields, extended reaction time, and poor enantioselectivity, this work was important, as it was the first demonstration of the use of chiral Lewis acids in asymmetric cyanohydrin synthesis.

For the next 18 years, there were no reports concerning applications of boron-based systems in cyanosilylation reactions. However, in 2004, Corey described compound **15** (Ar = 3,5-dimethylphenyl), which was catalytically active in the presence of 20 mol % of triphenylphosphine oxide (Scheme 11).[80] As shown in Table 1, a series of silylated cyanohydrins were obtained in 91−98% yield and with 90−97% enantioselectivity, from reactions employing 10 mol % of catalyst **15** and carried out in toluene at 0 °C for 40−144 h. It was found that similar asymmetric induction could be obtained for both aromatic (electron rich and electron deficient) and aliphatic substrates, with the best result being with 4-cyanobenzaldehyde, albeit after a reaction time of 144 h. Alongside the excellent stereoselectivity, this system is notable for the ability to reuse the chiral ligand connected to boron.

2.2. Titanium-Based Catalytic Systems

After the work of Reetz,[79] the use of chiral Lewis acids in cyanohydrin synthesis attracted significant attention.

Scheme 12

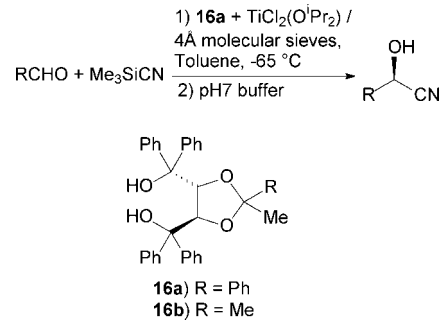


Table 2. Synthesis of Cyanohydrins Using the Titanium Complex of TADDOL 16a

aldehyde	time (h)	yield (%)	ee (%)
$PhCH_2CH_2CHO$	12	89	74
$PhCH_2CHO$	12	66	77
$CH_3(CH_2)_7CHO$	24	66	76
CyCHO	48	77	68
PhCHO	12	79	96

Undoubtedly, catalytic systems based on titanium complexes have been the most extensively studied in this field.[81] Most of the complexes were prepared by treatment of the ligand with titanium tetraisopropoxide and were used *in situ* without isolation and characterization of the precatalyst. This has important consequences for the nature of the cyanating agent since trimethylsilyl cyanide will react with the liberated isopropanol to form hydrogen cyanide *in situ*.

2.2.1. Complexes of Chiral Diols

The first example of a titanium-based reagent for asymmetric cyanosilylation was reported by Narasaka and coworkers in 1987.[82] The authors investigated the reaction between a range of aromatic and aliphatic aldehydes and trimethylsilyl cyanide in the presence of 4 Å molecular sieves and the complex formed *in situ* from $TiCl_2(O^iPr)_2$ and TADDOL[83] (**16a**) (Scheme 12). Cyanohydrins were obtained in 66−89% yield and with 73−96% enantioselectivity, as detailed in Table 2. The best result achieved in terms of enantioselectivity was with benzaldehyde, which was the only aromatic aldehyde included in the study.[84]

Use of stoichiometric quantities of the titanium complex was found to be pivotal, since attempted use of lower amounts gave a direct correlation of the cyanohydrin yield with the amount of titanium complex used. Reactions were mostly carried out in toluene at −78 °C and took 12−48 h to achieve an adequate conversion of aldehyde into cyanohydrin. Under these conditions, the authors showed that cyanohydrin synthesis was irreversible. It was also observed that the enantioselectivity was dependent on the temperature used for chiral reagent generation; when this was carried out at ambient temperature, only 10% asymmetric induction was observed. A hydrolysis step using a pH 7 buffer solution was required to release the free cyanohydrin from the complex. Although this protocol was not catalytic, it demonstrated that high enantioselectivities are achievable in asymmetric cyanohydrin synthesis by using chiral titanium-based Lewis acids.

The titanium dichloride complex of ligand **16a** was used by Hiyama, Takehara, *et al.* for asymmetric cyanosilylation of an aldehyde as part of the synthesis of chiral dopants for ferroelectric liquid crystals (Scheme 13).[85] In this case the

Scheme 13

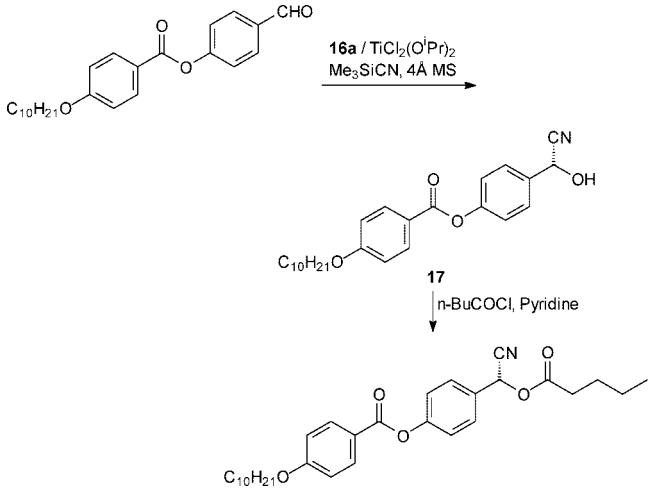


Table 3. Asymmetric Cyanosilylation of Aldehydes Catalyzed by the Titanium Complex of Ligand 16b[a]

aldehyde	yield (%)	ee (%) (*R*)
PhCHO	95	50
4-MeC_6H_4CHO	97	57
4-$MeOC_6H_4CHO$	94	40
4-$^tBuC_6H_4CHO$	96	60
3-F,4-$MeOC_6H_3CHO$	91	42
2-naphthaldehyde	87	52
3-$PhOC_6H_4CHO$	92	40
furan-2-carboxaldehyde	65	40
PhCH=CHCHO	92	44
$PhCH_2CH_2CHO$	95	59

[a] Reaction used 10 mol % of both **16b**-$Ti(O^iPr)_2$ and triphenylphosphine oxide at −10 °C in chloroform for 20 h.

asymmetric cyanation reaction proceeded in 88% yield and gave cyanohydrin **17** with 91% enantiomeric excess. Ward *et al.* also studied the use of the titanium dichloride complex of ligand **16a** for the asymmetric cyanation of chiral α-alkoxy aldehydes. These substrates gave only low enantio- and diastereoselectivities, but the authors were able to conclude that the stereochemistry of the reagent was more important than that of the substrate in controlling the overall stereochemistry of the process.[86]

More recently, Kim and co-workers prepared the titanium diisopropoxy complex of TADDOL **16b** and showed that in the presence of triphenylphosphine oxide as a cocatalyst it would catalyze the asymmetric addition of trimethylsilyl cyanide to aldehydes.[87] A number of reactions were carried out to determine the optimal conditions, which were found to require 10 mol % of the titanium complex of ligand **16b** and 10 mol % of triphenylphosphine oxide at −10 °C for 20 h in chloroform. Under these conditions, with benzaldehyde as substrate, the best result was the production of mandelonitrile trimethylsilyl ether in 95% yield with 50% enantiomeric excess. Using these conditions, nine other aldehydes were screened and a moderate asymmetric induction was observed in all cases (Table 3). The best substrates were *p*-tolualdehyde, *p-tert*-Bu-benzaldehyde, and 3-phenylpropanal, which gave enantiomeric excesses of 57, 60, and 60%, respectively. Yields were high for all substrates after a 20 h reaction time, with the exception of the cyanohydrin derivative obtained from furan-2-carboxaldehyde, which was produced in a moderate 65% yield.

The first report on the use of substoichiometric amounts of titanium complexes for the synthesis of enantiomerically

Scheme 14

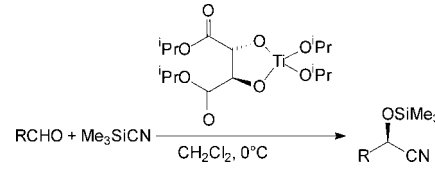


Table 4. Synthesis of Cyanohydrin Trimethylsilyl Ethers Using a Titanium−DIPT Catalyst System

	equimolar reaction		catalytic reaction	
aldehyde	yield (%)	ee (%) (*R*)	yield (%)	ee (%) (*R*)
4-MeC_6H_4CHO	89	77	79	65
4-$MeOC_6H_4CHO$	90	81	88	77
2-naphthaldehyde	89	73	80	60
thiophene-2-carboxaldehyde	92	81	84	83
PhCHO	63	88	84	91

Table 5. Effect of Solvent on Asymmetric Cyanohydrin Synthesis Catalyzed by the Ti-DIPT Complex

solvent	temp (°C)	time (h)	yield (%)	ee (%) (*R*)
hexane	0	24	79	5
toluene	27	24	86	23
diethyl ether	27	24	80	75
dichloromethane	0	18	81	91
chloroform	0	18	84	86
acetonitrile	29	48	83	17

enriched cyanohydrins was developed on the basis of the Sharpless system for asymmetric epoxidation.[88] Oguni *et al.* studied the reaction of aromatic aldehydes with trimethylsilyl cyanide in the presence of 20 mol % of the complex formed *in situ* from diisopropyl tartrate (DIPT) and titanium tetraisopropoxide.[89] It was shown that conducting the reaction in dichloromethane at 0 °C with 2 equiv of isopropanol present gave optimal results.[90] By using this protocol (Scheme 14), five aromatic silylated cyanohydrins were obtained in 79−88% yield and with enantiomeric excesses of 60−91% after a reaction time of 18 h (Table 4). This catalytic system suffers, however, from low substrate tolerance, as subtle changes in the aldehyde structure resulted in considerably inferior results. For example, with *p*-tolualdehyde as substrate, the enantioselectivity falls to 65% compared to the 91% obtained when benzaldehyde was the substrate.

The reactions were also carried out using an equimolar amount of titanium complex with respect to the aldehyde, and under these conditions, less variability of results was observed between substrates, with enantioselectivities of 73−88% being obtained. The effect of solvent was also investigated; using benzaldehyde, 20 mol % titanium tetraisopropoxide, and L-(+)-DIPT, polar solvents generally gave better enantioselectivities, with the exception of acetonitrile, as shown in Table 5. Chloroform and dichloromethane gave the best enantioselectivities (86 and 91%, respectively) and also gave moderately high yields. It was also found that treating the catalyst with a range of alcohol additives could greatly influence the enantioselectivity (Table 6). The addition of trimethylsilyl cyanide to benzaldehyde was studied for reactions conducted in dichloromethane at 0 °C for 18 h. The best result obtained in terms of enantioselectivity was that using isopropanol as an additive which gave mandelonitrile trimethylsilyl ether in 84% yield and with 91% enantiomeric excess.

Table 6. Effect of Additives on Asymmetric Cyanohydrin Synthesis Catalyzed by the Ti-DIPT Complex

additive	yield (%)	ee (%) (*R*)
H_2O	79	2
MeOH	86	68
EtOH	80	86
PrOH	81	68
^{i}PrOH	84	91
BuOH	83	70
^{i}BuOH	78	54
^{t}BuOH	40	13
CH_2=$CHCH_2OH$	82	75

Scheme 15

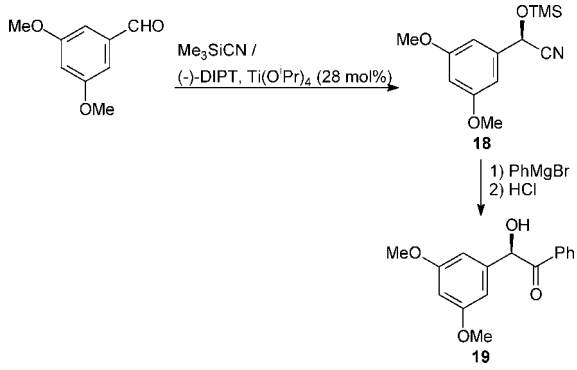
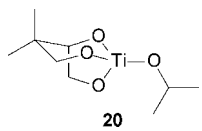


Table 7. Asymmetric Addition of Trimethylsilyl Cyanide to Benzaldehyde Catalyzed by Complex 20

solvent[a]	time (h)	yield (%)	ee (%)
toluene	1	92	60
dichloromethane	1	95	65
diethyl ether	1.25	93	54
tetrahydrofuran	1	92	66
hexane[b]	1.5	90	52
diphenyl ether	1	95	56
diisopropyl ether	1.5	90	40
dichloromethane, 4 Å molecular sieves	1	98	72
dichloromethane, 4 Å molecular sieves, −20 °C	2	92	76

[a] Reaction carried out at 0 °C with equimolar amounts of benzaldehyde, trimethylsilyl cyanide, and complex **20**. [b] Catalyst remained largely undissolved.

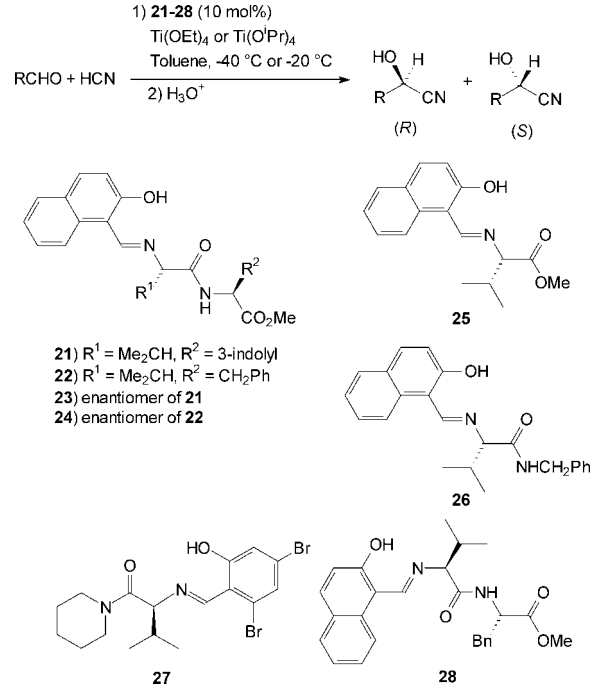
Oguni's diisopropyl tartrate/titanium tetraisopropoxide catalyst system[89] has been used by Pirrung for the asymmetric addition of trimethylsilyl cyanide to 3,5-dimethoxybenzaldehyde (Scheme 15) as part of a synthetic route to dimethoxybenzoin phosphotriesters.[91] Cyanohydrin derivative **18** was obtained in 95% yield and with 82% enantiomeric excess from a reaction carried out on a 180 mmol scale. After conversion to dimethoxybenzoin **19**, the enantiomeric excess could be raised to >97% by recrystallization.



20

In order to develop a system with industrial applicability, de Vries and co-workers attempted to find a complex which, unlike the protocols described above, was compatible with hydrogen cyanide.[92] They tested *in situ* formed complex **20** as a catalyst for the reaction of aldehydes with hydrogen cyanide. The main assumption was that triol complex **20** would be less prone to alkoxide-to-cyanide substitution than the previously studied titanium diol complexes. Unfortunately, no reaction of benzaldehyde with hydrogen cyanide was observed even using stoichiometric amounts of complex **20**. However, the authors did succeed in applying complex **20** in stereoselective cyanosilylation using trimethylsilyl cyanide as the cyanide source. With benzaldehyde as substrate, 66% enantioselectivity was achieved at 0 °C. Conducting the reaction in dichloromethane at −20 °C for 2 h using 4 Å molecular sieves and stoichiometric quantities of complex **20** proved to be the optimized conditions, giving mandelonitrile trimethylsilyl ether in 92% chemical yield and with 76% enantiomeric excess. Attempts to develop substoichiometric variants of this procedure (10 mol % of catalyst) resulted in a considerable increase of the reaction time (to 12 h) as well as a lower yield (70%) and poor enantioselectivity (10%). The use of 2 equiv of the complex with respect to benzaldehyde also gave inferior results. The effect of solvent was investigated (Table 7), and although the yield remained high (90−98%) in all solvents studied, there was some variation in the enantioselectivity, with dichloromethane giving the best result, increased further by reducing the temperature to −20 °C. Although this system did not compare favorably with the diol systems described above, it was important because of its subsequent successful application in cyanosilylation of ketones (see section 3.2).

Scheme 16



2.2.2. Complexes of C_1-Symmetric Schiff Bases and Related Ligands

Hydrocyanation and cyanosilylation of aldehydes mediated by titanium complexes of Schiff bases have been extensively studied. The groups of Inoue and Oguni reported pioneering work in this area, describing ligands possessing C_1-symmetry. Having previously found that some cyclic peptides were able to catalyze the asymmetric addition of HCN to aldehydes,[56,57] Inoue and co-workers prepared amino acid or peptide-derived Schiff bases (**21**−**28**) in order to test their titanium complexes as catalysts for asymmetric cyanohydrin synthesis (Scheme 16).[93]

Table 8. Asymmetric Cyanohydrin Synthesis Catalyzed by Titanium Complexes of Schiff Bases 21−26

aldehyde	Schiff base	Ti source	temp (°C)	time (h)	yield (%)	ee (%)
PhCHO	**21**	$Ti(OEt)_4$	−40	3	88	88 (*R*)
	22	$Ti(OEt)_4$	−40	4	85	86 (*R*)
	22	$Ti(OEt)_4$	−20	4	91	82 (*R*)
	22	$Ti(O^iPr)_4$	−20	4	94	78 (*R*)
	23	$Ti(OEt)_4$	−40	7	86	84 (*S*)
	24	$Ti(O^iPr)_4$	−20	4	84	38 (*S*)
	none	$Ti(O^iPr)_4$	−20	4	43	0
	25	$Ti(O^iPr)_4$	−20	4	17	0
	26	$Ti(O^iPr)_4$	−20	2	99	30 (*R*)
2-naphthaldehyde	**21**	$Ti(OEt)_4$	−40	7.5	88	90 (*R*)
furan-2-carboxaldehyde	**21**	$Ti(OEt)_4$	−40	7.5	74	86 (*R*)
3-$PhOC_6H_4CHO$	**23**	$Ti(OEt)_4$	*a*	*a*	85	86 (*S*)
CyCHO	**22**	$Ti(OEt)_4$	−40	1.5	99	54 (*R*)
$CH_3(CH_2)_5CHO$	**22**	$Ti(OEt)_4$	−40	1.5	99	74 (*R*)

[a] At −40 °C for 11 h followed by −20 °C for 11 h.

Table 9. Asymmetric Hydrocyanation of α,β-Unsaturated Aldehydes Catalyzed by $Ti(OEt)_4$−28[a]

aldehyde[b]	temp (°C)	time (h)	conversion (%)	ee (%)
n-$C_5H_{11}CH$=CHCHO	−60	119	83	89 (*R*)
n-C_3H_7CH=CHCHO	−20	22	93	85 (*R*)
PhCH=CHCHO	−40	18	82	81 (*R*)
$(Me)_2C$=CHCHO	−60	71	74	70
H_2C=C(Me)CHO	−60	46	90	72
MeCH=C(Me)CHO	−60	20	22	37
n-C_3H_7CH=C(Et)CHO	−60	143	28	60
MeCH=CHCH=CHCHO	−60	143	78	60
n-BuC≡CCHO	−40	2	57	68

[a] Reactions carried out with 10 mol % of the catalyst formed from $Ti(OEt)_4$ and ligand **28** in toluene under a nitrogen atmosphere. [b] All double bonds have *trans*-stereochemistry.

The best results were achieved using peptide derived Schiff base **21** at −40 °C, which gave respectable enantioselectivities, using aromatic aldehydes in particular (Table 8). After screening a diverse range of ligands, it was concluded that, in general, dipeptide derivatives gave better results than Schiff bases derived from a single amino acid, provided that both residues were of the same absolute configuration. The *C*-terminal residue was found to be responsible for the enantioselectivity, whereas the *N*-terminal residue influenced the absolute configuration of the product. Straightforward ligand modifications resulted in inversion of the product configuration, which enabled the authors to obtain both enantiomers of a cyanohydrin using only natural amino acids.[94]

Some of the complexes proved to be highly effective catalysts for the addition of hydrogen cyanide to aldehydes. In particular, the titanium complex of Nap-(*S*)-Val-(*S*)-Trp-OMe **21** gave enantioselectivities of up to 90%, whereas use of the Dbs-(*S*)-Val-Pip complex **27** led to products with the opposite configuration and enantiomeric excesses of up to 97%. The titanium complex of Nap-(*S*)-Val-(*S*)-Phe-OMe **28** performed reasonably well for α,β-unsaturated substrates, giving yields of 22−93% and enantioselectivities of 37−89% (Table 9).[40] The protocol required use of 10 mol % of the catalyst in toluene in a temperature range between −40 and −60 °C. The reaction times varied considerably (2−143 h) with the structure of the substrate. The best enantioselectivity (89%) was observed using 2-octenal as substrate after a reaction time of 119 h at −60 °C, although a good enantioselectivity (85%) and high conversion (93%) was also obtained at −20 °C after 22 h of reaction using 2-hexenal as substrate.

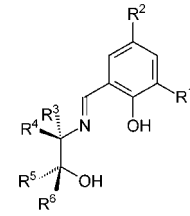
Table 10. Asymmetric Addition of Trimethylsilyl Cyanide to Benzaldehyde Using $Ti(O^iPr)_4$ Complexes of Schiff Bases 29−40

Schiff base[a]	temp (°C)	time (h)	yield (%)	ee (%) (configuration)
29	0	20	69	22 (*S*)
30	0	20	70	41 (*R*)
30	−30	44	90	67 (*R*)
30	−80	24	67	85 (*R*)
31	−78	24	64	64 (*R*)
32	−78	36	61	67 (*R*)
33	−78	36	40	40 (*S*)
34	−80	36	60	60 (*R*)
35	−80	36	72	80 (*S*)
36	−78	36	51	63 (*R*)
37	−80	36	41	40 (*S*)
38	−78	36	61	67 (*S*)
39	−80	36	45	76 (*R*)
40	−80	36	38	67 (*S*)

[a] All reactions were carried out in dichloromethane; Schiff bases have (*S*)-configuration.

In contrast to the high enantioselectivity when hydrogen cyanide was used as the cyanide source, titanium-based systems **21** and **27**−**28** gave poor results for the reaction of aldehydes with trimethylsilyl cyanide. Nevertheless, highly enantioselective cyanosilylations were accomplished with the aluminum complexes of these ligands[95] (see section 2.5.1).

Another system based on C_1-symmetric Schiff bases was elaborated by the Oguni group and subsequently gained much attention. Thus, β-iminoalcohol derivatives **29**−**40** were prepared and studied as ligands for the synthesis of titanium-based catalysts for the asymmetric cyanosilylation of benzaldehyde (Table 10) and six other aromatic and aliphatic aldehydes.[96,97] The optimal ligand within this series was **30**, which gave an enantioselectivity of 85% with benzaldehyde as substrate. Use of the complex formed *in situ* from ligand **30** and titanium tetraisopropoxide was subsequently found to catalyze the formation of aromatic and aliphatic cyanohydrin silyl ethers with 65−96% enantioselectivity and in 58−85% chemical yield after a reaction time of 36 h (Table 11). The process was carried out in dichloromethane at −80 °C, employing 20 mol % of the catalyst.



29) R^1 = H, R^2 = H, R^3 = ^{i}Pr, R^4 = R^5 = R^6 = H
30) R^1 = ^{t}Bu, R^2 = H, R^3 = ^{i}Pr, R^4 = R^5 = R^6 = H
31) R^1 = ^{t}Bu, R^2 = H, R^3 = ^{i}Pr, R^4 = H, R^5 = R^6 = Ph
32) R^1 = ^{t}Bu, R^2 = H, R^3 = ^{i}Bu, R^4 = R^5 = R^6 = H
33) R^1 = R^2 = H, R^3 = ^{t}Bu, R^4 = R^5 = R^6 = H
34) R^1 = ^{t}Bu, R^2 = H, R^3 = Me, R^4 = R^5 = R^6 = H
35) R^1 = ^{t}Bu, R^2 = R^3 = H, R^4 = Et, R^5 = R^6 = H
36) R^1 = ^{t}Bu, R^2 = H, R^3 = ^{t}Bu, R^4 = R^5 = R^6 = H
37) R^1 = ^{t}Bu, R^2 = R^3 = H, R^4 = Ph, R^5 = R^6 = H
38) R^1 = ^{t}Bu, R^2 = R^3 = R^4 = H, R^5 = ^{t}Bu, R^6 = H
39) R^1 = ^{t}Bu, R^2 = Me, R^3 = ^{i}Pr, R^4 = R^5 = R^6 = H
40) R^1 = R^2 = ^{t}Bu, R^3 = ^{i}Pr, R^4 = R^5 = R^6 = H

The titanium isopropoxide complex of ligand **40** was employed by Shiori *et al.* as part of an attempted synthesis of the trypsin inhibitor, radiosumin **41** (Scheme 17).[98] The

Table 11. Asymmetric cyanohydrin synthesis catalyzed by the Ti(O^{i}Pr)$_4$ complex of Schiff base 30

aldehyde[a]	yield (%)	ee (%) (*R*)
4-MeC$_6$H$_4$CHO	68	71
4-MeOC$_6$H$_4$CHO	62	91
3-PhOC$_6$H$_4$CHO	67	79
4-NCC$_6$H$_4$CHO	60	20
2-naphthaldehyde	76	73
thiophene-2-carboxaldehyde	60	79
H$_2$C=CHCHO	54	63
H$_2$C=C(Me)CHO	62	85
(*E*)-MeCH=CHCHO	70	89
Me$_2$C=CHCHO	63	89
(*E*)-MeCH=C(Me)CHO	68	96
PhCH=CHCHO	81	72
PhCH$_2$CH$_2$CHO	85	40
CH$_3$(CH$_2$)$_2$CHO	73	57
Me$_2$CHCHO	70	34
CH$_3$(CH$_2$)$_{10}$CHO	48	66
CyCHO	72	65

[a] All reactions carried out in dichloromethane for 36 h at −78 °C using 20 mol % catalyst.

Scheme 17

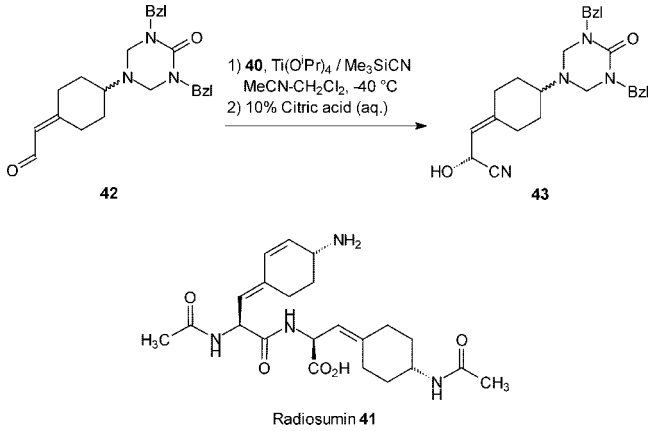


Table 12. Asymmetric Trimethylsilylation of Benzaldehyde Catalyzed by the Ti(O^{i}Pr)$_4$ Complexes of Ligands 44−48

ligand	temp (°C)	time (h)	yield (%)	ee (%)
44	0	20	95	0
44	−80	60	88	26 (*S*)
45	15	48	92	14 (*S*)
45	0	48	96	39 (*S*)
45	−80	60	85	53 (*S*)
45[a]	−80	60	84	50 (*R*)
46	−80	60	82	9 (*S*)
47	−80	60	88	9 (*S*)
48	−80	60	88	31 (*S*)

[a] Using (1*S*,2*R*)-**45** instead of the (1*R*-2*S*) enantiomer used in all other cases.

synthesis of cyanohydrins **43** from the highly functionalized, racemic α,β-unsaturated aldehyde **42** was achieved in 94% yield and gave cyanohydrins **43** as a 2:1 mixture of diastereomers, with 66−76% enantiomeric excess, though it subsequently proved impossible to convert cyanohydrins **43** into radiosumin.

A similar system (ligands **44**−**47**: based on 2-amino-1,2-diphenylethanol and a salicylaldehyde) was developed by Jiang and co-workers and was used in almost identical conditions to those employed by Oguni. The authors initially obtained silylated cyanohydrins in 82−96% yield (after 60 h) and with enantioselectivities up to 53% (Table 12).[99] The titanium complex of ligand **44** gave a high yield of racemic

Table 13. Asymmetric Trimethylsilylation of Benzaldehyde Catalyzed by the Ti(O^{i}Pr)$_4$ Complex of ligand 45[a]

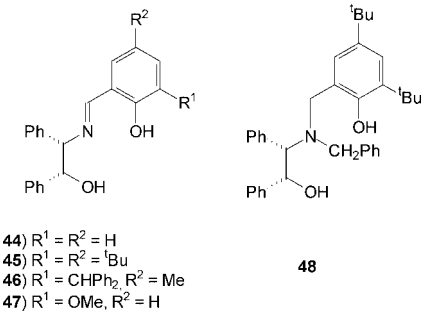
Schiff base **45**:Ti	time (h)	yield (%)	ee (%)
1.1:1	60	85	52 (*S*)
1.3:1	56	87	80 (*S*)
1.5:1	56	89	89 (*S*)
2.0:1	60	72	92 (*S*)

[a] Reactions carried out in dichloromethane using 20 mol % of the Ti(O^{i}Pr)$_4$ complex.

Table 14. Asymmetric Cyanohydrin Synthesis from Aromatic Aldehydes Catalyzed by the 45−Ti(O^{i}Pr)$_4$ Complex

aldehyde	yield (%)	ee (%)
3-PhOC$_6$H$_4$CHO	58	49 (*S*)
3-ClC$_6$H$_4$CHO	76	91 (*S*)
PhCH=CHCHO	60	54 (*S*)
4-MeOC$_6$H$_4$CHO	31	48 (*S*)

cyanohydrin product at 0 °C. Reducing the temperature to −80 °C and increasing the reaction time to 60 h raised the enantioselectivity to 26%. A similar effect was seen in the case of the titanium complex of ligand **45**, where lowering the temperature from 15 °C to −80 °C raised the enantioselectivity from 14% to 53%. Titanium complexes of ligands **46** and **47** performed poorly, giving product with only 9% ee, and the reduced ligand **48** was only slightly better, exhibiting 31% enantioselectivity. Subsequently, Jiang reported the effect of changing the amount of Schiff base with respect to titanium. It was found that a 2:1 ratio of ligand **45** to titanium tetraisopropoxide gave the highest enantioselectivity of 92%, although with slightly reduced yield (Table 13).[100] Four other aromatic aldehydes were studied using a ligand **45** to titanium ratio of 1.5:1, with 3-chlorobenzaldehyde proving to be a much better substrate than the other examples, giving the cyanohydrin trimethylsilyl ether with 91% ee and in 76% yield (Table 14). Reactions were carried out in dichloromethane at −80 °C for 60 h.



Walsh and Somanathan described a library of ligands derived from *cis*-1-amino-2-indanol (**49**−**54**) and a range of other amino alcohols (**55**−**64**).[101] By using 20 mol % of the titanium isopropoxide complex formed from ligand **50**, benzaldehyde was trimethylsilylated in a yield of 64% and with 85% enantioselectivity. This ligand appeared to be the most enantioselective of ligands **49**−**54**, as shown in Table 15. Since the titanium complex of ligand **50** gave the best enantioselectivity for cyanosilylation of benzaldehyde, this system was also screened on a series of aromatic aldehydes, which gave the corresponding cyanohydrin trimethylsilyl ethers in 50−77% yield and with enantioselectivities of 20−95%. The best substrate in terms of both yield and enantioselectivity was 4-methoxybenzaldehyde (Table 16).

Table 15. Enantioselective Addition of Trimethylsilyl Cyanide to Benzaldehyde Promoted by Ti(O^{i}Pr)$_4$ Complexes of Ligands 49−64[a]

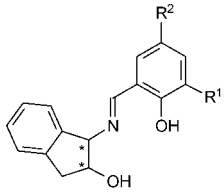
ligand (configuration)	yield (%)	ee (%) (configuration)
49 (*R*,*S*)	62	70 (*R*)
50 (*R*,*S*)	64	85 (*R*)
51 (*R*,*S*)	72	59 (*R*)
52 (*R*,*S*)	25	44 (*S*)
53 (*R*,*S*)	36	27 (*R*)
54 (*R*,*S*)	17	12 (*R*)
55 (*S*)	52	68 (*S*)
56 (*S*)	38	55 (*R*)
57 (*S*)	18	17 (*R*)
58 (*R*)	50	55 (*S*)
59 (*R*)	39	52 (*R*)
60 (*R*)	20	15 (*R*)
61 (*S*,*R*)	50	66 (*S*)
62 (*S*,*R*)	40	54 (*R*)
63 (*S*,*R*)	15	12 (*R*)
64 (*S*)	60	65 (*S*)

[a] All reactions carried out using 20 mol % of Ti(O^{i}Pr)$_4$ in dichloromethane at −78 °C for 36 h.

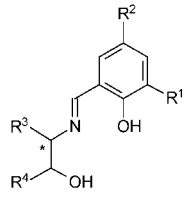
Table 16. Enantioselective Trimethylsilylation of Aldehydes Catalyzed by a Ti(O^{i}Pr)$_4$ Complex of Ligand 50[a]

aldehyde	yield (%)	ee (%) (configuration)
4-MeC$_6$H$_4$CHO	62	50 (*R*)
2,4-Me$_2$C$_6$H$_3$CHO	48	21[b]
4-(MeO)C$_6$H$_4$CHO	77	95 (*R*)
3-(MeO)C$_6$H$_4$CHO	52	56 (*R*)
2-(MeO)C$_6$H$_4$CHO	50	20 (*R*)

[a] Reactions were performed in dichloromethane at −78 °C for 36 h with 20 mol % Ti(O^{i}Pr)$_4$−**50**. [b] Absolute configuration not determined.



49) R^1 = ^{t}Bu, R^2 = ^{t}Bu
50) R^1 = ^{t}Bu, R^2 = H
51) R^1 = ^{t}Bu, R^2 = CH$_3$
52) R^1 = Adamantyl, R^2 = Me
53) R^1 = R^2 = C(Me)$_2$Et
54) R^1 = R^2 = C(Me)$_2$Ph



55) R^1 = Adamantyl, R^2 = Me, R^3 = ^{t}Bu, R^4 = H
56) R^1 = R^2 = C(Me)$_2$Et, R^3 = ^{t}Bu, R^4 = H
57) R^1 = R^2 = C(Me)$_2$Ph, R^3 = ^{t}Bu, R^4 = H
58) R^1 = Adamantyl, R^2 = Me, R^3 = Ph, R^4 = H
59) R^1 = R^2 = C(Me)$_2$Et, R^3 = Ph, R^4 = H
60) R^1 = R^2 = C(Me)$_2$Ph, R^3 = Ph, R^4 = H
61) R^1 = Adamantyl, R^2 = Me, R^3 = R^4 = Ph
62) R^1 = R^2 = C(Me)$_2$Et, R^3 = R^4 = Ph
63) R^1 = R^2 = C(Me)$_2$Ph, R^3 = R^4 = Ph
64) R^1 = Adamantyl, R^2 = Me, R^3 = CH(Me)$_2$, R^4 = H

Somanathan and Cole studied the influence of substituents in Oguni's ligand on the cyanosilylation reaction. They prepared a range of Schiff bases **30**, **31**, **34**, **37**, and **65**−**89** with varying substituents on positions R$_1$−R$_5$, which were subsequently tested as complexes with titanium tetraisopropoxide in a model reaction using benzaldehyde as a substrate (Tables 17 and 18).[102] Unfortunately, attempts to improve the existing system were not particularly successful. By use of ligands **30**, **31**, **34**, **37**, and **65**−**72**, it was shown that the asymmetric induction is highly susceptible to steric factors (Table 17). The best enantioselectivity was achieved using ligand **30**, which gave an enantioselectivity of 85% and chemical yield of 67%. The highest yield obtained (85%) was achieved using ligand **72**. In contrast, use of ligands **73**−**89** indicated that the influence of electronic factors was largely insignificant; thus, electron-donating

Table 17. Investigation of Steric Effects Using Ligands 30, 31, 34, 37, and 65−72[a]

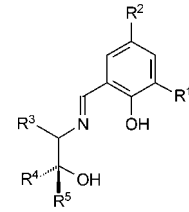
ligand	R^1	R^2	R^3	R^4	R^5	yield (%)	ee (%)
30	^{t}Bu	H	^{i}Pr	H	H	67	85 (*R*)
31	^{t}Bu	H	^{i}Pr	Ph	Ph	54	64 (*R*)
34	^{t}Bu	H	Me	H	H	60	60 (*R*)
37	^{t}Bu	H	Ph	H	H	41	40 (*S*)
65	^{t}Bu	H	Me	Ph	H	30	34 (*R*)
66	^{t}Bu	H	H	Me	H	60	63 (*S*)
67	^{t}Bu	^{t}Bu	H	Me	H	60	58 (*S*)
68	^{t}Bu	^{t}Bu	Me	Ph	H	35	35 (*R*)
69	^{t}Bu	H	Me	Ph	Ph	20	18 (*R*)
70	^{t}Bu	H	Ph	Ph	H	30	36 (*R*)
71	^{t}Bu	^{t}Bu	Ph	H	H	40	45 (*S*)
72	^{t}Bu	^{t}Bu	Ph	Ph	H	85	53 (*S*)

[a] Reactions carried out with 20 mol % of the Ti(O^{i}Pr)$_4$ complex of ligands **30**, **31**, **34**, **37**, and **65**−**72** in dichloromethane at −78 °C for 36 h.

Table 18. Investigation of Steric Effects Using Ligands 73−89[a]

ligand	R^1	R^2	R^3	R^4	R^5	yield (%)	ee (%)
73	^{t}Bu	NO$_2$	$CH_2C_6H_4$		H	52	39 (*S*)
74	^{t}Bu	Br	$CH_2C_6H_4$		H	59	56 (*R*)
75	^{t}Bu	OMe	$CH_2C_6H_4$		H	58	48 (*R*)
76	OCH_3	H	$CH_2C_6H_4$		H	73	38 (*R*)
77	Br	Br	$CH_2C_6H_4$		H	16	12 (*R*)
78	^{t}Bu	NO$_2$	^{t}Bu	H	H	29	44 (*R*)
79	^{t}Bu	Br	^{t}Bu	H	H	52	77 (*R*)
80	^{t}Bu	OMe	^{t}Bu	H	H	49	67 (*R*)
81	^{t}Bu	NO$_2$	Ph	H	H	60	22 (*S*)
82	^{t}Bu	Br	Ph	H	H	50	48 (*S*)
83	^{t}Bu	OMe	Ph	H	H	54	46 (*S*)
84	^{t}Bu	NO$_2$	Ph	Ph	H	55	24 (*S*)
85	^{t}Bu	Br	Ph	Ph	H	47	53 (*S*)
86	^{t}Bu	OMe	Ph	Ph	H	48	58 (*S*)
87	^{t}Bu	NO$_2$	^{i}Pr	H	H	25	40 (*R*)
88	^{t}Bu	Br	^{i}Pr	H	H	60	53 (*R*)
89	^{t}Bu	OMe	^{i}Pr	H	H	65	56 (*R*)

[a] Reactions carried out with 20 mol % of the Ti(O^{i}Pr)$_4$ complex of ligands **73**−**89** in dichloromethane at −78 °C for 36 h.

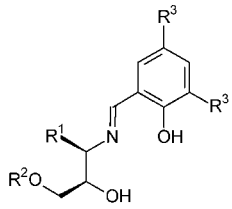


30, 31, 34, 37, 65-89
for the structures of
R^1-R^5 see
Tables 17 and 18

and electron-withdrawing substituents within R^2 had little effect on the reaction outcome (Table 18). Calculations indicated a crucial influence of the R^3 substituent on the reaction enantioselectivity, and the best yields and enantioselectivities were achieved when R^3 = *tert*-butyl or *iso*-propyl along with isopropoxy groups on the titanium ion (Table 18). This is believed to be due to steric factors where a bulky R^3 group blocks the *re*-face of the coordinated aldehyde, resulting in a higher selectivity for attack on the *si*-face.

Hu *et al.* carried out theoretical studies (B3LYP/ONIOM) on a selection of Oguni's ligands.[103] A simulation of enantioselective cyanation of benzaldehyde using the titanium isopropoxide complexes of ligands **30**, **31**, **34**, **37**, and **50** was made to calculate thermodynamic parameters. These

Scheme 18



R^1 = Ph, R^3 = H
90) R^2 = H
91) R^2 = Me
92) R^2 = CH_2Ph
93) R^2 = CH_2Ph
94) R^2 = CPh_3
95) R^2 = $SiⁱPr_3$

R^1 = Ph, R^3 = ^{t}Bu
96) R^2 = H
97) R^2 = Me
98) R^2 = CH_2Ph
99) R^2 = CH_2Ph
10) R^2 = CPh_3
101) R^2 = $SiⁱPr_3$

R^1 = ^{n}Pr
102) R^2 = CH_2Ph, R^3 = H
103) R^2 = CPh_3, R^3 = H
104) R^2 = CH_2Ph, R^3 = ^{t}Bu
105) R^2 = CPh_3, R^3 = ^{t}Bu

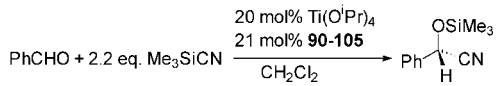


Table 19. Catalytic Asymmetric Addition of Trimethylsilyl Cyanide to Aldehydes Catalyzed by 97−Ti(O^{i}Pr)$_4$[a]

aldehyde	yield (%)	ee (%)[b]
PhCHO	87	75
2-MeC_6H_4CHO	100	73
2-$MeOC_6H_4CHO$	100	52
4-$MeOC_6H_4CHO$	96	48
4-NCC_6H_4CHO	98	40
2-ClC_6H_4CHO	98	77
4-ClC_6H_4CHO	99	53
2-FC_6H_4CHO	100	68
4-FC_6H_4CHO	99	66
3-FC_6H_4CHO	100	68
$PhCH_2CHO$	97	67
Me_3CCHO	77	28

[a] Reaction carried out using 20 mol % of Ti(O^{i}Pr)$_4$ and 20 mol % of ligand **97**, in dichloromethane at −40 °C for 4 days. [b] Cyanohydrin products have *S* configuration.

results were compared with actual experimental data, and a qualitative linear relationship was found between $\Delta\Delta G^{\ddagger}$ values for ligands containing one chiral center (i.e. all except ligand **50**). The calculations predicted that the rate determining step of the reaction is the attack of cyanide on the coordinated aldehyde and that the stereochemistry is controlled not only by the direction from which cyanide approaches but also by the binding mode of benzaldehyde to titanium.

Pericàs and co-workers screened another range of substituents based on Oguni's ligand.[104] The *in situ* formed titanium isopropoxide complexes of ligands **90**−**105** were tested for their activity for the cyanosilylation, firstly, of benzaldehyde (Scheme 18) in order to optimize the conditions. The best catalyst in the series was found to be the titanium complex of ligand **97**, which gave the *O*-silylated cyanohydrin product with 87% conversion and 75% enantiomeric excess. This complex was then tested with a range of other aromatic and aliphatic aldehydes (Table 19). All yields were high throughout the series of aldehydes used, with the best enantioselectivities being observed with 2-methyl and 2-chloro benzaldehydes (73% and 77%, respectively). Although pivaldehyde gave only a modest enantiomeric excess (28%), the other nonaromatic substrate, phenylethanal, was converted into its cyanohydrin trimethylsilyl ether with 67% enantiomeric excess and in 97% yield. The transition state shown in Figure 1 was proposed to explain the results. The key feature of this transition state model is that the oxygen linked to the

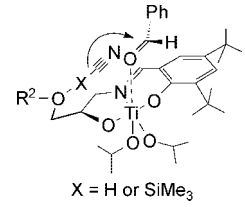
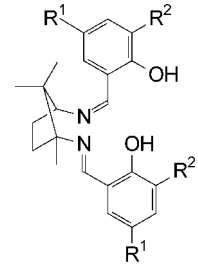


Figure 1.

R^2 group participates in the cyanide binding process whilst the metal ion acts as a Lewis acid and binds to the aldehyde. This transition state would probably look more reasonable if the silyl cyanide was presented in its isocyanide form.[18]

Along with modifications of Oguni's ligand, some other original systems have been developed. The Tang group described a series of ligands **106**−**108** obtained from camphor.[105] The titanium complex prepared by treatment of ligand **106** with titanium tetraisopropoxide was found to be a stereoselective catalyst for the addition of trimethylsilyl cyanide to benzaldehyde. Under optimized conditions (20 mol % of the catalyst, dichloromethane, −40 °C, 24 h), silylated mandelonitrile was obtained in 98% yield and with an enantioselectivity of 66%. This system was also tested on four other substituted aromatic aldehydes, and similar results were obtained (Table 20).

The introduction of substituents at positions R^1 and R^2 on the ligand was shown to drastically reduce the enantiomeric excess of the cyanohydrin product. Thus, ligands **107** and **108** gave only 9% and 28% enantioselectivity, respectively, for the addition of trimethylsilyl cyanide to benzaldehyde in comparison to the 48% enantioselectivity obtained with ligand **106** using half the catalyst loading. In general, lower temperatures and higher catalyst loadings were found to give better results, as illustrated by use of 20 mol % of complex **106** at −40 °C, where an enantioselectivity of 66% was achieved. Increasing the catalyst loading further to 50 mol % reduced the enantioselectivity to 48%. Electron rich, methoxy-substituted benzaldehydes gave higher enantioselectivities (72−73%), whilst 4-chlorobenzaldehyde gave a much lower enantioselectivity (30%). Thus, the aldehyde appears to have an electronic effect on the enantioselectivity of the reaction.



106) R^1 = R^2 = H
107) R^1 = R^2 = Cl
108) R^1 = Me, R^2 = ^{t}Bu

Moyano *et al.* synthesized a library of C_1-symmetric ligands **109**−**116** derived from ferrocene and tested the complexes formed by treatment of the ligands with titanium tetraisopropoxide in the addition of trimethylsilyl cyanide to aldehydes.[106] The titanium complex of ligand **112** was found to be the most enantioselective, producing silylated mandelonitrile in 91% yield and with 86% enantiomeric excess (Table 21). In contrast, the analogous non-ferrocene derived ligand **117** gave a cyanohydrin derivative with just

Table 20. Asymmetric Cyanosilylation of Aromatic Aldehydes Catalyzed by Ti(O^{i}Pr)$_4$ Complexes of Ligands 106−108[a]

ligand	aldehyde	Ti(O^{i}Pr)$_4$ (mol %)	temp (°C)	yield (%)	ee (%) (configuration)
106	PhCHO	10	−20	94	48 (*R*)
107	PhCHO	20	−20	94	9 (*R*)
108	PhCHO	20	−20	75	28 (*R*)
106	PhCHO	20	0	98	46 (*R*)
106[b]	PhCHO	20	0	98	19 (*R*)
106	PhCHO	5	−30	84	30 (*R*)
106	PhCHO	10	−30	100	61 (*R*)
106	PhCHO	20	−30	98	66 (*R*)
106	PhCHO	20	−40	98	66 (*R*)
106	PhCHO	50	−30	94	48 (*R*)
106	PhCHO	10	−30	94	58 (*R*)
106	4-ClC$_6$H$_4$CHO	20	−40 to −50	93	30 (*R*)
106	4-MeC$_6$H$_4$CHO	20	−40 to −50	92	65 (*R*)
106	2-MeOC$_6$H$_4$CHO	20	−40 to −50	92	72 (*R*)
106	4-MeOC$_6$H$_4$CHO	20	−40 to −50	89	73 (*R*)

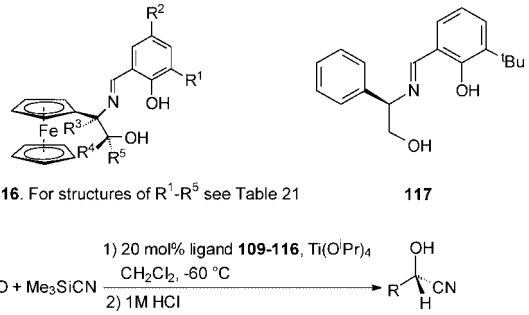
[a] All reactions carried out in dichloromethane followed by an acidic workup. [b] 20 mol % isopropanol was added.

Table 21. Structures and Catalytic Activities of Ferrocene-Based Ligands 109−116[a]

ligand	R^1	R^2	R^3	R^4	R^5	yield (%)	ee (%)[b]
109	H	H	H	Me	Me	85	18
110	^{t}Bu	H	H	H	H	83	70
111	^{t}Bu	H	H	H	Me	72	60
112	^{t}Bu	H	Me	H	H	91	86
113	^{t}Bu	H	H	Me	Me	85	8 (*R*)
114	^{t}Bu	H	H	H	Ph	27	24
115	1-adamantyl	Me	H	H	H	32	50
116	1-adamantyl	Me	Me	H	H	65	52

[a] 20 mol % of catalyst used in dichloromethane at −60 °C for 64−68 h. [b] Absolute configuration is *S* unless otherwise stated.

Scheme 19



50% enantiomeric excess under the same reaction conditions. Six aromatic and two α,β-unsaturated aldehydes were tested in asymmetric cyanosilylation reactions using the titanium isopropoxide complexes of ligands **110** and **111** as shown in Scheme 19. The corresponding products were obtained with 14−64% enantiomeric excess and in 47−85% yield (Table 22). The best results were obtained with ligand **110** using *o*-methoxybenzaldehyde and *p*-tolualdehyde, which gave products with 60 and 64% enantiomeric excess, respectively, and with 2-methyl-2-propanal, which gave an enantioselectivity of 62%.

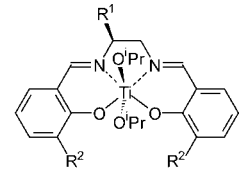
Belokon and North described the use of titanium isopropoxide complexes **118**−**121**, in which amino acids (methionine, valine, and leucine) were used to prepare the C_1-symmetric salen ligands, as catalysts for the asymmetric addition of trimethylsilyl cyanide to aldehydes.[107] Using a range of aromatic and aliphatic aldehydes, silylated cyanohydrins were obtained in 60−85% yield and with 25−76% enantioselectivity, the highest of which was achieved from

Table 22. Asymmetric Addition of Trimethylsilyl Cyanide to Aldehydes Catalyzed by Ti(O^{i}Pr)$_4$−110 and 111[a]

aldehyde	ligand	time (h)	yield (%)	ee (%)[b]
2-MeOC$_6$H$_4$CHO	**110**	70	60	60
2-MeOC$_6$H$_4$CHO	**111**	62	85	54
3-MeOC$_6$H$_4$CHO	**110**	70	85	42
4-MeOC$_6$H$_4$CHO	**110**	63	47	24
4-MeC$_6$H$_4$CHO	**110**	64	69	64
4-MeC$_6$H$_4$CHO	**111**	62	55	58
4-NCC$_6$H$_4$CHO	**110**	64	77	14
4-FC$_6$H$_4$CHO	**110**	64	70	46
(*E*)-MeCH=CHCHO	**110**	41	73	44
H$_2$C=C(Me)CHO	**110**	41	63	62

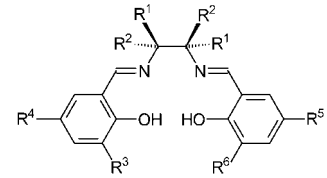
[a] Reactions carried out using 20 mol % of ligand−Ti complex in dichloromethane at −60 °C. [b] All products have *S* absolute configuration.

addition of trimethylsilyl cyanide to anisaldehyde catalyzed by 20 mol % of complex **119** (Table 23). Catalyst **119** also gave the best results overall, with reasonable enantioselectivities obtained for aromatic and aliphatic aldehydes, although pivaldehyde gave a lower enantioselectivity (45%) when compared with the other substrates studied.



118) R^1 = MeS(CH$_2$)$_2$, R^2 = H
119) R^1 = MeS(CH$_2$)$_2$, R^2 = ^{t}Bu
120) R^1 = ^{n}Pr, R^2 = ^{t}Bu
121) R^1 = Me$_2$CHCH$_2$, R^2 = ^{t}Bu

Kim reported a series of unsymmetrical salen-based ligands **122**−**126** used as titanium complexes for the asymmetric addition of trimethylsilyl cyanide to aromatic aldehydes (Table 24).[108] The best enantioselectivities were achieved using the titanium isopropoxide complex of ligand **122**, with the highest result derived from the catalyst supported on MCM-41 (94%). Increasing the reaction temperature (in the case of system **126**) increased the yield of reaction as expected but also reduced the enantioselectivity from 72% at −80 °C to 30% at −5 °C. A series of C_2-symmetric salen ligands were reported in the same paper, but gave no improvement in terms of enantioselectivity when compared with ligands **122**−**126**.



122) R^1 = -(CH$_2$)$_4$-, R^2 = R^3 = R^4 = H, R^5 = R^6 = ^{t}Bu
123) R^1 = Ph, R^2 = H, R^3 = R^4 = H, R^5 = R^6 = ^{t}Bu
124) R^1 = -(CH$_2$)$_4$-, R^2 = H, R^3 = OMe, R^4 = H, R^5 = R^6 = ^{t}Bu
125) R^1 = -(CH$_2$)$_4$-, R^2 = R^3 = R^4 = R^5 = H, R^6 = OMe
126) R^1 = Ph, R^2 = R^3 = R^4 = R^5 = H, R^6 = OMe

In summary, the systems elaborated by Choi and Feng are apparently the most effective amongst the C_1-symmetric Ti-based catalysts published so far. These systems have advantages such as the ability to invert the product configuration by a subtle change of the ligand structure, the ability to use HCN instead of trimethylsilyl cyanide, or good substrate tolerance. However, all these systems suffer from a number of fundamental problems, since relatively low

Table 23. Asymmetric Addition of Trimethylsilyl Cyanide to Aldehydes Catalyzed by Ti(O^{i}Pr)$_4$−118−121[a]

aldehyde	catalyst	yield (%)	ee (%)[b]
PhCHO	**118**	80	36
PhCHO	**119**	80	65
4-MeOC$_6$H$_4$CHO	**119**	60	76
(*E*)-MeCH=CHCHO	**119**	75	75
4-F$_3$CC$_6$H$_4$CHO	**119**	60	68
CH$_3$CH$_2$CH$_2$CHO	**119**	71	60
Me$_3$CCHO	**119**	70	45
PhCHO	**120**	80	25
PhCHO	**121**	85	64

[a] Reactions carried out for 120 h using 20 mol % of ligand−Ti complex in dichloromethane at −78 °C. [b] All products have *S* configuration.

Table 24. Asymmetric Addition of Trimethylsilyl Cyanide to Aldehydes Catalyzed by Ti(O^{i}Pr)$_4$−122−126[a]

catalyst	aldehyde	yield (%)	ee (%)[b]
122	PhCHO	65	90
122[c]	PhCHO	59	94
122[d]	PhCHO	72	87
122	4-MeOC$_6$H$_4$CHO	63	73
122	2-ClC$_6$H$_4$CHO	80	87
123	PhCHO	63	80
124	PhCHO	63	68
125	PhCHO	50	66
125[c]	PhCHO	44	67
126	PhCHO	51	72
126[e]	PhCHO	73	51
126[f]	PhCHO	89	30

[a] Reactions carried out for 24 h using 10 mol % of ligand−Ti complex in dichloromethane at −80 °C unless stated otherwise. [b] Products have *R* absolute configuration. [c] Catalyst supported on MCM-41. [d] Used 20 mol % catalyst. [e] Reaction carried out at −25 °C. [f] Reaction carried out at −5 °C.

temperatures, extended reaction times, and high catalytic loadings are often required. Although these protocols are suitable for laboratory scale syntheses of enantioenriched cyanohydrins, they are not commercially viable.

2.2.3. Complexes of C_2-Symmetric Schiff Bases and Related Ligands

2.2.3.1. Work Leading to the Development of Catalyst 161. The preferential utilization of C_2-symmetric ligands was a concept developed in the early stages of asymmetric catalysis.[109] Due to the symmetry axis in the catalytically active species, the number of possible transition states is decreased by a factor of 2 compared to a hypothetical C_1-symmetric equivalent, which may result in greater enantioselectivity. Amongst the C_2-symmetric Schiff base derived ligands, some precursors of highly enantioselective catalysts for cyanohydrin synthesis have been found.

In 1996, Jiang and co-workers studied a number of C_2-symmetric Schiff base complexes in asymmetric cyanosilylation reactions. Building on the fact that salen complexes had been effectively used in other enantioselective reactions,[110] they synthesized a series of ligands derived from 1,2-diphenylethylenediamine and salicylaldehydes.[111] Using conditions shown in Scheme 20, the titanium complexes of ligands **127**−**130** were found to be stereoselective cyanosilylation catalysts (Table 25). By far the most stereoselective catalyst was that derived from ligand **130**, which resulted in an 82% yield and 84% enantiomeric excess of the cyanohydrin product. This indicated unexpectedly that the least sterically hindered ligand gave the highest selectivity, in

Scheme 20

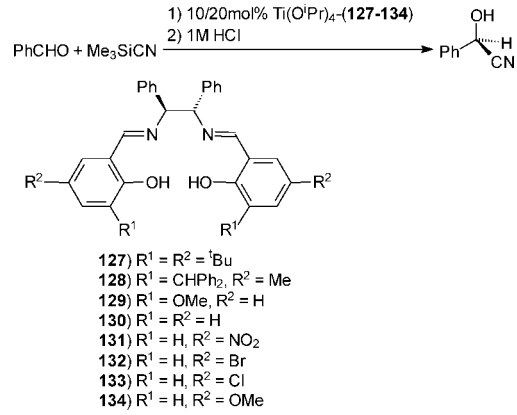


Table 25. Asymmetric Cyanosilylation of Benzaldehyde Catalyzed by Ti(O^{i}Pr)$_4$−127−130[a]

ligand	time (h)	yield (%)	ee (%)[b]
127	24	70	39
128	24	30	5
129	24	50	24
130	24	82	84

[a] Reactions used 20 mol % of ligand with 1.1 equiv of Ti(O^{i}Pr)$_4$ in dichloromethane at −78 °C. [b] Absolute configuration of the products is *R*.

Table 26. Effect of Changing the Ligand 130:Ti(O^{i}Pr)$_4$ Ratio on the Enantioselective Addition of Trimethylsilyl Cyanide to Benzaldehyde[a]

130:Ti(O^{i}Pr)$_4$	yield (%)	ee (%)[b]
0.5:1	48	78
1:1	71	78
1.1:1	82	87
1.25:1	76	83
1.5:1	58	83
2:1	66	81

[a] 10 mol % of ligand **130** was used at a concentration of 0.1 mol/L. [b] Absolute configuration of product is *R* in each case.

contrast to many other reactions catalyzed by salen ligands.[110] A further study into the effect of changing the ratio of ligand **130** to metal was also conducted, and it was found that a 1.1:1 ligand to titanium ratio gave both the highest yield and enantioselectivity (Table 26).

The amount of catalyst used in the reaction was also varied, and the optimal loading in terms of enantioselectivity was shown to be 10 mol % (87% ee), although the yield was lower than that achieved using stoichiometric quantities of the titanium tetraisopropoxide−**130** complex (72% compared with 97%) (Table 27). Concentration effects were also investigated, and it was found that, in dichloromethane, using a lower concentration of catalyst increased the enantioselectivity from 37% at 0.33 M to 80% at 0.1 M. However, when tetrahydrofuran was used as solvent, a higher enantioselectivity (85%) was obtained at a concentration of 0.33 M.

Using the optimal conditions, four other ligands (**131**−**134**) were subsequently synthesized in order to investigate the influence of electronic effects within the aromatic rings of the salen ligands (Table 28). None of these were an improvement over catalyst **130**, although a reasonable enantioselectivity was achieved with the complex of ligand **133** (78%), indicating that stronger electron donating groups were beneficial for both the yield and enantioselectivity. This

Table 27. Effect of Changing the Amount of Catalyst Ti(O^{i}Pr)$_4$−130[a]

catalyst (mol %)	yield (%)	ee (%)[b]
100[c]	92	37
100[d]	91	53
100[e]	90	80
100[f]	97	85
50	93	59
20	82	84
10	72	87
5	70	81

[a] Reaction carried out over a period of 24 h at −78 °C. [b] Absolute configurations are *R*. [c] Catalyst concentration was 0.33 M. [d] Isopropanol was removed and concentration was 0.33 M. [e] Concentration was 0.1 M. [f] THF used as the solvent at 0.33 M concentration.

Table 28. Asymmetric Cyanosilylation of Benzaldehyde Catalyzed by Ti(O^{i}Pr)$_4$ Complexes of Ligands 131−134[a]

ligand	yield (%)	ee (%)[b]
131	21	6
132	26	30
133	31	39
134	73	78

[a] Reactions used 10 mol % of ligand with 1.1 equiv of Ti(O^{i}Pr)$_4$ in dichloromethane at −78 °C. [b] Absolute configuration of the products is *R*.

Table 29. Asymmetric Cyanosilylation of Aldehydes Catalyzed by Ti(O^{i}Pr)$_4$−130[a]

aldehyde	time (h)	yield (%)	ee (%)[b]
PhCHO	24	72	87
4-ClC$_6$H$_4$CHO	36	76	84
3-ClC$_6$H$_4$CHO	36	69	62
2-ClC$_6$H$_4$CHO	22	80	66
4-MeC$_6$H$_4$CHO	36	60	82
3-MeC$_6$H$_4$CHO	36	69	76
4-MeOC$_6$H$_4$CHO	36	68	74
PhCH=CHCHO	36	73	75
(*E*)-MeCH=CHCHO	36	70	72
CH$_3$(CH$_2$)$_6$CHO	36	58	22
Me$_2$CHCHO	36	61	78
Me$_3$CCHO	36	85	73
CyCHO	36	86	41

[a] Reactions used 10 mol % of ligand with 1.1 equiv of Ti(O^{i}Pr)$_4$ in dichloromethane at −78 °C for the stated time period. [b] Absolute configuration of the products is *R*.

contrasted with the poor result (6% asymmetric induction) obtained with the complex of electron-withdrawing nitro-containing ligand **131**.

Having optimized the reaction conditions and ligand structure, the authors screened a range of aldehydes as substrates (Table 29). In general, for aromatic aldehydes, *para*-substituted substrates gave marginally higher enantioselectivities than the equivalent *ortho*- and *meta*-compounds. With the exception of 1-nonanal and cyclohexanecarboxaldehyde, all tested aldehydes gave moderate to good yields and enantioselectivities. To study the influence of the alkoxide ancillary ligand, seven other complexes were prepared by the treatment of titanium tetraisopropoxide−**130** with various alcohols in toluene (Scheme 21). There was little difference in the enantioselectivities, which remained between 80 and 85%, though the yields were improved by using aromatic-based counterions and also with the succinate dianion (Table 30).

At the same time, Belokon and North were studying titanium complexes of the salen ligands **135**−**136** based on

Scheme 21

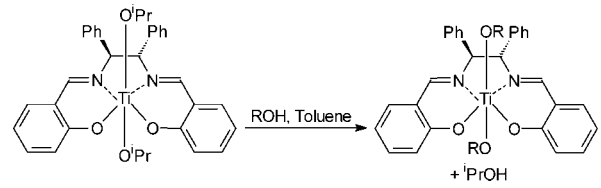
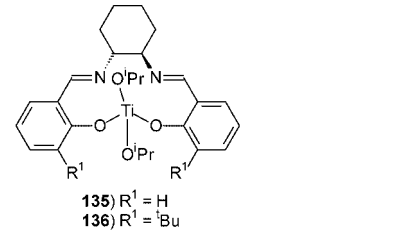


Table 30. Asymmetric Addition of Trimethylsilyl Cyanide to Aldehydes Catalyzed by Ti(OR)$_2$−130[a]

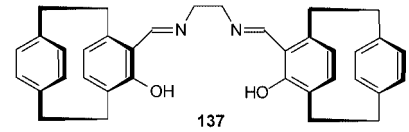
R	counterion/catalyst	time (h)	yield (%)	ee (%)[b]
α-naphthylO$^-$	1:1	18	91	83
	2:1	18	90	83
4-O$_2$NC$_6$H$_4$O$^-$	1:1	18		83
	2:1	18		83
2-(CO$_2^-$)C$_6$H$_4$O$^-$	1:1	12	78	80
1,2-di(CO$_2^-$)$_2$C$_6$H$_4$	1:1	12	80	82
(CH$_2$CO$_2^-$)$_2$	1:1	12	95	82
EtO$^-$	2:1	36	75	85
n-BuO$^-$	2:1	36	70	83

[a] Reactions carried out using 10 mol % of **130**−Ti complex with appropriate ancillary ligand in dichloromethane at −78 °C. [b] All products have *R*-configuration.

1,2-cyclohexanediamine. In contrast to Jiang's work, this system showed a positive influence of substituents in the salicylidene moiety on the enantioselectivity of cyanosilylation.[112] Complex **136** was shown to be the more effective of the two catalysts for the asymmetric addition of trimethylsilyl cyanide to four different aldehydes, with results between 55−70% yield and with 62−77% enantioselectivity (Table 31). The enantioselectivity was moderately high for all four aldehydes, indicating a good substrate tolerance.



135) R^1 = H
136) R^1 = ^{t}Bu



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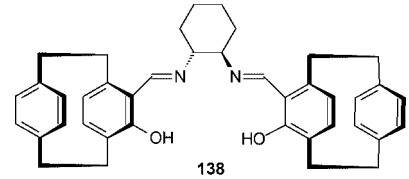

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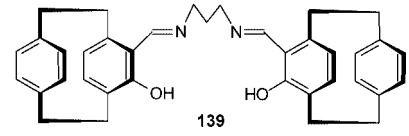


139

Building on the results obtained with complexes **135** and **136**, Belokon and Rozenberg developed salen ligands **137**−**139** based on planar-chiral 5-formyl-4-hydroxy-[2.2]paracyclophane (FHPC) and diamines.[113] The titanium complex of ligand **137** was found to be the optimum catalyst

Table 31. Asymmetric Cyanosilylation of Aldehydes Catalyzed by Titanium Complexes 135−136[a]

catalyst	aldehyde	yield (%)	ee (%)[c]
135[d]	PhCHO	70	0
135	PhCHO	98[b]	40[b]
135[e]	PhCHO	90	51
135	PhCHO	60	68
135	4-$MeOC_6H_4CHO$	40	60
135	PhCH=CHCHO	70	70
135	Me_3CCHO	86	16
136	PhCHO	68	75
136	4-$MeOC_6H_4CHO$	70	62
136	PhCH=CHCHO	60	71−77
136	Me_3CCHO	55	77

[a] Reactions used 20 mol % of catalyst in dichloromethane at −78 °C for 24−120 h. [b] Results from analysis of the free cyanohydrin. [c] Absolute configuration of the products is *S*. [d] Free ligand used as a catalyst in the absence of titanium. [e] 1:1.3 ratio of ligand to titanium used.

Table 32. Asymmetric Addition of Trimethylsilyl Cyanide to Benzaldehyde Catalyzed by $Ti(O^iPr)_4$−137−138[a]

catalyst	temp (°C)	time (h)	yield (%)	ee (%) (configuration)
S-(FHPC)-**137**	−78	120	90	82 (*R*)
R-(FHPC)-**137**	−78	120	90	84 (*S*)
S-(FHPC)-**137**	−5	72	90	48 (*R*)
S-(FHPC)-**137**	+25	4	80	22 (*R*)
S-(FHPC)-**137**	−5	72	80	49 (*R*)
R-(FHPC)-**137**	−78	120	73	73 (*S*)
S-(FHPC)-**138**	−78	120	0	0
R-(FHPC)-**138**	−78	120	0	0
R-(FHPC)-**138**	+25	35	80	0
S-(FHPC)-**138**[b]	−78	24	0	0
S-(FHPC)-**138**[b]	−78	120	50	17 (*R*)
S-(FHPC)-**138**[b]	−78	168	70	23 (*R*)
S-(FHPC)-**138**[b]	+25	3	90	0
R-(FHPC)-**138**[b]	−78	24	90	35 (*S*)
R-(FHPC)-**138**[b]	−78	120	90	48 (*S*)
R-(FHPC)-**138**[b]	−78	120	90	49 (*S*)
R-(FHPC)-**138**[b]	+25	1	90	44 (*S*)

[a] Reactions were conducted with 10 mol % ligand−Ti complex in dichloromethane with a benzaldehyde concentration of 0.7 M. [b] The cyclohexanediamine unit was always of *R*,*R* configuration.

within this series for the cyanosilylation of benzaldehyde, giving product with 84% enantioselectivity and in 90% yield using 10 mol % of the complex in dichloromethane at −78 °C after a reaction time of 120 h. Taking into account the lack of temperature dependence of catalyst **136**, the influence of temperature on the enantioselectivity of reactions catalyzed by the titanium complex of ligand **137** was investigated. However, conducting the reaction at room temperature resulted in a considerable loss of enantioselectivity.

Ligand **138** exhibited matched and mismatched pair effects involving the chirality of the backbone and the planar-chiral aromatic unit. Thus, the planar-*R*-isomer exhibited poor enantioselectivity and gave low yields even after long reaction times. In contrast, the planar-*S*-isomer was considerably better, giving 90% yield and 35−49% enantioselectivity even after a reaction time of just 1 h at ambient temperature. It is noteworthy that the complex of the less selective diastereomer of ligand **138** was found to be significantly less temperature-dependent than the more active diastereomer, showing only a 5% decrease in enantioselectivity when the reaction was carried out at ambient temperature instead of −78 °C (Table 32). It was also shown that the introduction of a further methylene group within the diamine, to give ligand **139**, resulted in loss of catalytic activity.

To further optimize the structure of complex **136**, Belokon and North screened various substituted salen ligands

Scheme 22

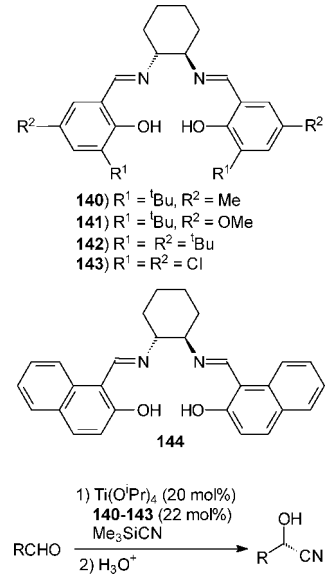


Table 33. Asymmetric Cyanosilylation of Aldehydes Catalyzed by Titanium Complexes of Ligands 140−143[a]

complex	aldehyde	yield (%)	ee (%)[b]
140	PhCHO	84	60
141	PhCHO	95	76
142	PhCHO	89	72
143	PhCHO	30	69
140	4-MeC_6H_4CHO	50	76
141	4-MeC_6H_4CHO	98	46
142	4-MeC_6H_4CHO	40	88
140	4-$MeOC_6H_4CHO$	20	60
141	4-$MeOC_6H_4CHO$	31	94
142	4-$MeOC_6H_4CHO$	40	84
140	4-$O_2NC_6H_4CHO$	42	0
141	4-$O_2NC_6H_4CHO$	43	0
142	4-$O_2NC_6H_4CHO$	60	10

[a] Reactions carried out as shown in Scheme 22 in dichloromethane at −80 °C for 24−100 h. [b] Absolute configuration determined as *S*.

(**140**−**144**), and compound **142** was found to give the highest consistent enantioselectivities for the cyanosilylation of various aldehydes. Thus, the complex obtained by treatment of ligand **142** with titanium tetraisopropoxide gave enantioselectivities of up to 88% in the cyanosilylation reaction (Scheme 22), the best of which was achieved using *p*-tolualdehyde as substrate (Table 33).[114] However, the highest recorded enantiomeric excess (94%) was achieved using ligand **141** with *p*-anisaldehyde as substrate, though this complex was significantly less selective for *p*-tolualdehyde. The complex of ligand **144** was found to be insoluble and was unable to function effectively as a catalyst.

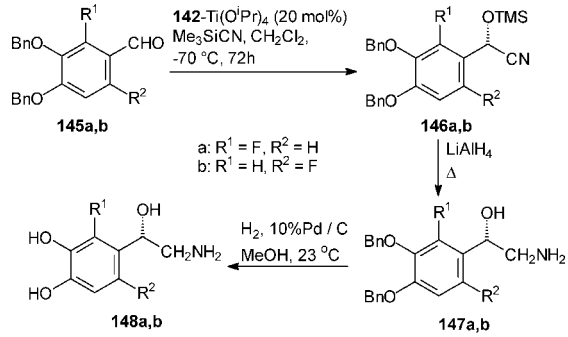
The use of electron rich aromatic substrates with complexes obtained from ligands **140**−**142** resulted in high enantioselectivities (72−94%), whilst electron deficient aldehydes gave inferior results, as illustrated by the use of *p*-nitrobenzaldehyde, which gave a maximum of 10% enantiomeric excess with the complex of ligand **142**. The titanium complex of ligand **142** was then used with a range of other aldehydes (Table 34) under the reaction conditions previously employed for catalyst **136**. Enantiomeric excesses for cyanohydrins obtained from *o*- and *m*-tolualdehyde were found to be high and comparable with those of the cyanohydrin obtained from *p*-tolualdehyde. Aliphatic cyanohydrins were obtained with enantioselectivities of 36−54% and full

Table 34. Asymmetric Cyanosilylation of Aldehydes Catalyzed by the Titanium Complex of Ligand 142[a]

aldehyde	yield (%)	ee (%) (configuration)[b]
3-MeC_6H_4CHO	81	92
2-MeC_6H_4CHO	90	80
PhCH=CHCHO	100	54
4-$MeO_2CC_6H_4CHO$	43	7
4-$F_3CC_6H_4CHO$	58	3
CH_3CH_2CHO	100	58
$(Me)_2CHCHO$	100	48
Me_3CCHO	100	36
PhCOMe	0	
$MeCOCH_2CH_2CH_3$	0	
$CH_3(CH_2)_4COMe$	0	

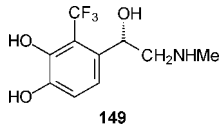
[a] Reactions carried out as shown in Scheme 22 in dichloromethane at −80 °C for 24−100 h. [b] Absolute configuration determined as *S*.

Scheme 23



conversion, in contrast to the lower conversions (40−90%) obtained for aromatic aldehydes. Three ketones were tested but were all found to yield no product.

The titanium isopropoxide complex of ligand **142** was employed by Kirk as part of a synthetic route to fluorinated norepinephrines (Scheme 23).[29] Thus, fluorinated aromatic aldehydes **145a**,**b** underwent asymmetric addition of trimethylsilyl cyanide catalyzed by 20 mol % of $Ti(O^iPr)_4$−**142** to give cyanohydrin derivatives **146a**,**b**, which were reduced with lithium aluminum hydride to give β-aminoalcohols **147a**,**b**. Compounds **147a**,**b** could be recrystallized to >95% enantiomeric excess, and subsequent hydrogenolysis of the benzyl protecting groups gave the desired fluorinated norepinephrines **148a**,**b**. The same synthetic route was used by Ammann *et al.* to prepare 2-trifluoromethylepinephrine **149**.[115] In this case, the asymmetric cyanation was conducted at −50 °C for five days and gave a cyanohydrin derivative with 80% enantiomeric excess, though again this could be increased to >99% by recrystallization of the β-amino alcohol.



149

The complexes formed *in situ* from titanium tetraisopropoxide suffered from a major disadvantage, since they could not be isolated or characterized. In particular, NMR studies showed at least three different species present in solution. A significant breakthrough took place in 1998 when Belokon and North isolated and characterized (salen)titanium dichloride complexes **150**−**155**. X-ray analysis showed that, in the crystal lattice, these complexes were monomeric and C_2-symmetric with a slight distortion of the octahedral geometry

Table 35. Enantiomeric Excesses from the Asymmetric Cyanosilylation of Benzaldehyde Using Complexes 150−155[a]

complex	ee (%) (*S*)
150	18
151	63
152	67
153	86
154	58
155	21

[a] All reactions gave 100% conversion within 24 h.

Scheme 24

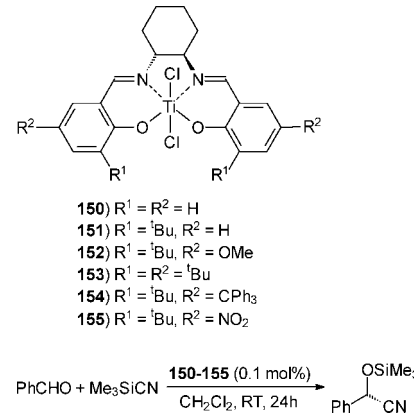


Table 36. Influence of Catalyst 153 Concentration on the Asymmetric Cyanosilylation of Benzaldehyde

catalyst amount (mol %)	conversion (%)	ee (%) (configuration)[a]
12	100	66
3	100	68
1	100	78
0.5	100	82
0.1	100	86
0.01	80	86

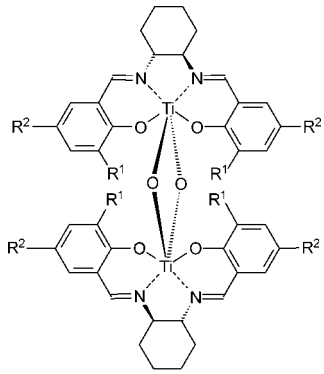
[a] All products had *S* configuration.

of the titanium ion.[116] In the cyanosilylation of benzaldehyde, complexes **150**−**155** gave enantioselectivities in the range of 18−86% (Table 35) with complete conversion after a reaction time of 24 h (Scheme 24). These reactions required only 0.1 mol % of the catalyst in dichloromethane at ambient temperature. Therefore, the catalytic activity of this system considerably surpassed those of all of the titanium complexes published at that time, most of which required low temperatures, long reaction times, and high catalytic loadings to achieve comparable asymmetric induction.

Complex **153** was found to be most stereoselective catalyst, giving silylated mandelonitrile with 86% enantiomeric excess.[117] Variation of the amount of catalyst **153** used in the cyanosilylation of benzaldehyde was investigated, and it was shown that as little as 0.1 mol % of the catalyst could be used before the conversion after 24 h was adversely affected; using just 0.01 mol % of complex **153** still gave 80% conversion after 24 h. Interestingly, using a lower catalyst loading resulted in higher enantioselectivities (Table 36). Decreasing the reaction temperature did not result in a significant enhancement of the enantioselectivity (90% enantiomeric excess at −80 °C as opposed to 86% enantiomeric excess at ambient temperature). Complex **153** was also tested on other substrates and gave enantioselectivities of 30−86% for aromatic aldehydes and 44−46% for aliphatic aldehydes (Table 37).

It was observed that the presence of additives, such as water, was crucial for reproducibly, obtaining high-yielding reactions when complex **153** was used as the catalyst. This led the authors to conduct experiments in rigorously anhydrous conditions, which showed that neither the titanium-tetraisopropoxide complex of ligand **142** nor the dichloride complex **153** were active in cyanosilylation reactions under these conditions. Titanium isopropoxide complex **136** and titanium chloride complexes **151** and **153** were further tested under a variety of conditions using water and triethylamine as additives with benzaldehyde as substrate. Again, it was found that using anhydrous conditions negatively affected the enantioselectivity, which fell to 40%. Using 1 equiv of water and 2 equiv of triethylamine resulted in the highest enantioselectivity (80%) when used with complex **153** (Table 38).

Based on these results, the authors deduced that complexes **136** and **151** were precatalysts to identical catalytically active species formed in the reaction by a hydrolysis reaction involving residual water from reagents and solvents. Therefore, Belokon and North reacted complexes **150**, **153**, and **155** with 1 equiv of water and isolated the bimetallic complexes **156**−**158**, whose structure was confirmed by X-ray analysis in the case of complex **156**.[117,118] It was found that compound **157** was also formed on addition of water to the titanium-isopropoxide complex of ligand **142**.



156) $R^1 = R^2 = H$
157) $R^1 = R^2 = {}^tBu$
158) $R^1 = {}^tBu$, $R^2 = NO_2$

Complex **157** was exceptionally active in the asymmetric cyanosilylation of aldehydes, giving full conversion in most cases after just 1 h (about 5 min for benzaldehyde) when only 0.1 mol % of catalyst was employed. In view of the inactivity of complexes **142**−$Ti(O^iPr)_2$ and **153** in strictly anhydrous conditions, these results led to the hypothesis that it was compound **157** which was the actual catalyst in the systems previously discussed. Enantioselectivities in reactions mediated by complex **157** were found to be very close to those obtained using catalyst **153** (50−88% for aromatic and 52−66% for aliphatic substrates), which also supported this theory (Table 39).[117]

Comparison of the results using dimeric complex **157** with those obtained from complex **153** (Tables 37 and 39) shows that a higher enantiomeric excess was obtained with complex **157** in all cases except for benzaldehyde and *p*-anisaldehyde, which gave the same level of asymmetric induction with both catalysts. In some cases, a significant improvement was noted; for example, with *m*-anisaldehyde and *m*-tolualdehyde, the enantioselectivity was increased from 78% and 74% to 92% and 90%, respectively, when complex **157** was used instead of catalyst **153**.

Table 37. Enantiomeric Excesses from the Asymmetric Cyanosilylation of Aldehydes Catalyzed by Complex 153[a]

aldehyde	cyanohydrin product ee (%) (*S*)
PhCHO	86
2-MeC_6H_4CHO	62
3-MeC_6H_4CHO	74
4-MeC_6H_4CHO	72
2-$MeOC_6H_4CHO$	72
3-$MeOC_6H_4CHO$	78
4-$MeOC_6H_4CHO$	84
2,4-$(MeO)_2C_6H_3CHO$	86
3,4-$(MeO)_2C_6H_3CHO$	80
3,5-$(MeO)_2C_6H_3CHO$	84
4-$F_3CC_6H_4CHO$	50
4-$O_2NC_6H_4CHO$	30
Me_3CCHO	46
CH_3CH_2CHO	44

[a] All reactions gave 100% conversion within 24 h using 0.1 mol % of catalyst **153** at ambient temperature.

Table 38. Asymmetric Cyanosilylation of Benzaldehyde Catalyzed by Complexes 136, 151, and 153 with Water and Triethylamine as Additives

catalyst	additive(s)	time (h)	conversion (%)	ee (%)[a]
136	0.007% H_2O	223	100	56
136	0.12% H_2O	24	100	70
136	1 equiv H_2O	24	100	74
151	anhydrous	24	80	62
151	1 equiv H_2O and Et_3N	24	100	80
153	anhydrous	24	42	40
153	1 equiv H_2O, 2 equiv Et_3N	24	100	86

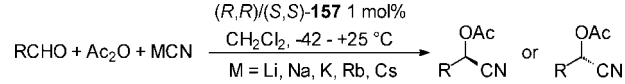
[a] Products were obtained with *S* configuration.

Table 39. Enantiomeric Excesses from the Asymmetric Cyanosilylation of Aldehydes Catalyzed by Complex 157[a]

aldehyde	cyanohydrin product ee (%) (*S*)
PhCHO	86
2-MeC_6H_4CHO	76
3-MeC_6H_4CHO	90
4-MeC_6H_4CHO	87
2-$MeOC_6H_4CHO$	88
3-$MeOC_6H_4CHO$	92
4-$MeOC_6H_4CHO$	84
2,4-$(MeO)_2C_6H_3CHO$	88
3,4-$(MeO)_2C_6H_3CHO$	85
3,5-$(MeO)_2C_6H_3CHO$	90
4-$F_3CC_6H_4CHO$	86
4-$O_2NC_6H_4CHO$	50
Me_3CCHO	66
Me_2CHCHO	64
CH_3CH_2CHO	52

[a] All reactions gave 100% conversion within 1 h using 0.1 mol % of complex **157** at ambient temperature.

Scheme 25



2.2.3.2. Asymmetric Synthesis of Cyanohydrin Esters Using Complex 157. To enhance the industrial applicability of catalyst **157**, Belokon, North, and co-workers investigated the use of alternative cyanide sources with this catalyst, including the use of a metal cyanide and acetic anhydride to form cyanohydrin acetates (Scheme 25).[119,120] It was found that this reaction produced enantiomerically enriched cyanohydrin acetates, but the enantioselectivity was strongly influenced by the nature of the cyanide counterion. A series of alkali metal cyanide salts were screened for the asym-

Table 40. Asymmetric Cyanation of Dihydrocinnamaldehyde Catalyzed by Catalyst 157, Metal Cyanide/Ac_2O[a]

metal cation	ee (%) (*R*)
Li	4
Na	56
K	82
Rb	76
Cs	54

[a] 1 mol % *(S,S)*-**157** in dichloromethane with vigorous stirring for 8 h at −42 °C.

Table 41. Asymmetric Cyanation of Benzaldehyde Catalyzed by Catalyst 157, Potassium Cyanide/Ac_2O[a]

solvent	ee (%) (*S*)
1,2-dichloroethane	90
dichloromethane	88
toluene	78
hexane	58

[a] 1 mol % (*R,R*)-**157** with vigorous stirring for 8 h at −20 °C.

Table 42. Asymmetric Cyanation of Aldehydes Catalyzed by Catalyst 157 and Potassium Cyanide[a]

	ee (%)				
aldehyde	+20 °C [b]	−20 °C [c]	−30 °C [d]	−42 °C [e]	−78 °C [f]
PhCHO	74	88	88	89	85
$PhCH_2CH_2CHO$	49		80	82	
4-$F_3CC_6H_4CHO$	60			76	54
4-FC_6H_4CHO	65			90	84
2-FC_6H_4CHO	45			86	88

[a] All reactions carried out with 1 mol % (*S,S*)-**157** in dichloromethane. [b] Stirred for 4 h, conversion of aldehyde >90%. [c] Stirred for 10 h, conversion of aldehyde *ca.* 40%. [d] Stirred for 10 h, conversion of aldehyde *ca.* 30%. [e] Stirred for 10 h, conversion of aldehyde *ca.* 20%. [f] Stirred for 2 days, conversion of aldehyde *ca.* 30%.

metric cyanation of dihydrocinnamaldehyde (Table 40), and potassium cyanide was found to give the best results (82% asymmetric induction). The solvent and temperature were also found to be important factors in the enantioselectivity of the reaction between potassium cyanide and benzaldehyde in the presence of acetic anhydride using catalyst **157**. The best results were obtained from reactions in 1,2-dichloroethane and dichloromethane (Table 41).

Four aromatic aldehydes and dihydrocinnamaldehyde were screened in this reaction at various temperatures (Table 42). The asymmetric induction was consistently high, between 80 and 90%, for all reactions carried out at −20 °C or below, with the exception of reactions involving *p*-trifluoromethylbenzaldehyde at −78 °C (54% ee) and −42 °C (76% ee). At +20 °C the enantioselectivities were significantly lower (maximum 74% using benzaldehyde) than those at the other temperatures studied. Under the optimized conditions, catalyst **157** was used to produce a series of *O*-acetylated cyanohydrins in 40−99% yield and with 60−93% enantioselectivity. These reactions used a catalyst loading of 1 mol % with 100 mol % of *tert*-butanol and 10 mol % of water added to the dichloromethane to improve the solubility of potassium cyanide (Table 43). Aromatic aldehydes again gave superior results compared to aliphatic substrates in terms of both chemical yield and asymmetric induction; however, dihydrocinnamaldehyde gave good results with an enantioselectivity of 82−84% and a yield of 79−80%.

Other carboxylic acid anhydrides were also studied in this reaction,[121] which revealed their influence on the reaction enantioselectivity (Scheme 26). All the acid anhydrides

Table 43. Asymmetric Cyanation of Aldehydes and Acetophenone with KCN/Ac_2O Catalyzed by Catalyst 157[a]

	(*R,R*)-**157**		(*S,S*)-**157**	
aldehyde	yield (%)	ee (%) (*S*)	yield (%)	ee (%) (*R*)
PhCHO	93	90	92	89
4-$MeOC_6H_4CHO$			74	93
3-$MeOC_6H_4CHO$			99	93
3-$PhOC_6H_4CHO$	99	90	99	89
4-FC_6H_4CHO	98	92	99	93
2-FC_6H_4CHO	87	85	86	82
3-FC_6H_4CHO			99	89
2-ClC_6H_4CHO	87	86	89	88
$PhCH_2CH_2CHO$	80	84	79	82
Me_2CHCHO	64	69	62	72
Me_3CCHO	40	62	40	60
PhCOMe	no reaction		no reaction	0

[a] Reactions stirred for 10 h using aldehyde (at 0.37−0.4 M concentration), KCN, and acetic anhydride in a ratio of 1:4:4 promoted by 1 mol % of catalyst **157** at −42 °C in dichloromethane, ^{t}BuOH, and water in a ratio of 2500:10:1.

Scheme 26

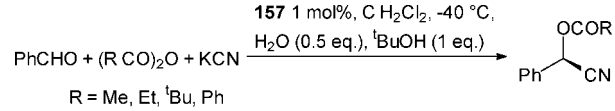


Table 44. Asymmetric Cyanation of Benzaldehyde Induced by Catalyst 157 with KCN and Various Anhydrides

anhydride	time (h)	conversion (%)	ee (%) (*S*)
acetic	10	93	90
propionic	48	100	92
pivalic	48	85	82
benzoic	72	95	56

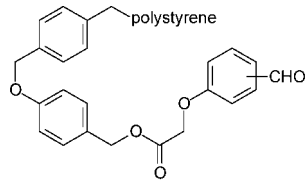
except benzoic anhydride gave similar levels of asymmetric induction (Table 44). Benzoic anhydride gave an enantioselectivity of only 56% and required 72 h to obtain 95% yield. This observation was explained by differences in the reactivity of precatalyst **157** with the acid anhydrides leading to formation of the active catalyst. Steric effects were thought to be the reason for the observed differences in enantioselectivity obtained when using different acid anhydrides, with linear anhydrides giving better results than those which were bulky or branched.

Although use of different anhydrides did not result in any enhancement of the enantioselectivity for the addition of potassium cyanide to benzaldehyde, it was thought that this would not necessarily be the case for other aldehydes. Therefore, a range of substrates were tested under the conditions given in Scheme 25 using the anhydrides from Table 44, with the exception of the less active benzoic anhydride. This gave the results shown in Table 45. Propionic anhydride gave enhanced yields in all cases and better enantioselectivities in all experiments except that using 2-methylpropanal as substrate, where acetic anhydride gave much better asymmetric induction (72% versus 17%). Aromatic aldehydes were generally better substrates for the asymmetric addition of potassium cyanide (81−95% enantioselectivity using propionic anhydride) than aliphatic aldehydes, although cinnamaldehyde gave 95% enantioselectivity when used with propionic anhydride. Enantioselectivities with aliphatic aldehydes ranged from mediocre to good. For example, a cyanohydrin product with 41% enantiomeric excess was obtained using cyclohexanecarboxaldehyde whereas a much greater enantioselectivity (82%) was achieved from nonanal.

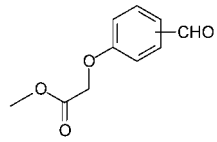
Table 45. Asymmetric Cyanation of Aldehydes Catalyzed by Complex 157 with KCN and Various Acid Anhydrides[a]

aldehyde	anhydride	time (h)	conversion (%)	ee (%) (*S*)
PhCH=CHCHO	propionic	48	73	95
	pivalic	72	50	75
4-$F_3CC_6H_4CHO$	propionic	50	100	94
	pivalic	50	100	62
3-$MeOC_6H_4CHO$	acetic	10	99	93
	propionic	48	100	90
4-$MeOC_6H_4CHO$	acetic	10	74	93
	propionic	48	100	91
Me_2CHCHO	acetic	10	62	72
	propionic	62	100	17
Me_3CCHO	acetic	10	40	62
	propionic	48	100	78
2-MeC_6H_4CHO	propionic	28	100	81
3-MeC_6H_4CHO	propionic	36	98	95
4-MeC_6H_4CHO	propionic	36	98	89
4-ClC_6H_4CHO	propionic	16	100	90
$CH_3(CH_2)_7CHO$	propionic	50	74	82
CyCHO	propionic	72	95	41

[a] All reactions carried out at −40 °C in dichloromethane using 1 mol % of catalyst **157**.



Polymer supported aldehyde



Analagous non-polymer supported aldehyde

Figure 2.

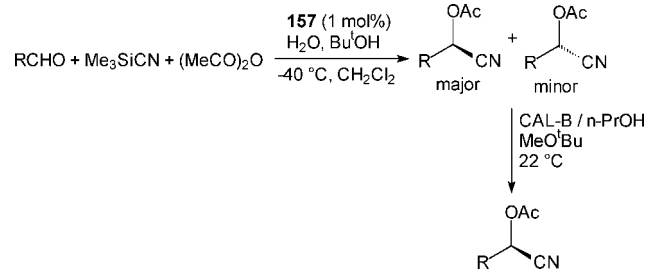
Table 46. Asymmetric Cyanation of Polymer Supported Aldehydes Catalyzed by Complex 157[a]

aldehyde (from Figure 2)	ee (%) [homogeneous]	ee (%) [supported]
para-CHO	81	91
ortho-CHO[b]		
meta-CHO	94	75
para-CHO; *ortho,ortho*-dimethyl	80	50

[a] Reaction carried out with KCN (8 equiv), propionic anhydride (8 equiv), **157** (2 mol %), ^{t}BuOH (2 equiv), and water (1 equiv), at 0 °C for 12 h in dichloromethane. [b] Not determined.

Further work from the same group described the use of catalyst **157** for the synthesis of propionate esters of cyanohydrins starting from aldehydes connected to Wang resin by an ester bond that could be cleaved after the reaction (Figure 2).[122] The polymer supported aldehydes, along with nonpolymer supported analogues, were selectively cyanated using potassium cyanide with propionic anhydride catalyzed by 2 mol % of complex **157** (Table 46). The polymer supported cyanohydrin esters were then cleaved from the resin and their enantiomeric excesses determined by chiral GC. In the case of the *para*-substituted aldehyde, 91% enantioselectivity was obtained from the polymer supported substrate whereas the reaction of the nonlinked aldehyde gave an asymmetric induction of just 81%. The opposite effect was seen when using the *meta*-substituted aldehyde, where the homogeneous reaction yielded the higher enantioselectivity (94%), compared to 75% obtained for the polymer supported aldehyde. Another *para*-substituted aldehyde with two *ortho*-methyl groups was also used, and similarly to the *meta*-substituted aldehyde, the higher asymmetric induction (80%) was observed for the homogeneous reaction whereas the supported version of the aldehyde gave an enantioselectivity of only 50%.

Scheme 27



North also developed a chemoenzymatic modification of the reaction of aldehydes with potassium cyanide and Ac_2O catalyzed by complex **157**. After carrying out the standard cyanosilylation step, the product was treated with a lipase enzyme; this resulted in hydrolysis of the minor enantiomer, leaving the highly enantioenriched product (Scheme 27).[123] The enzymes studied were *Candida antarctica* lipase-B (CAL-B), *Alcaligenes sp.* lipase (ASL), *Pseudomonas stutzeri* lipase (PSL), *Pseudomonas cepacia* lipase (PCL), and *Candida rugosa* esterase (CRE). These enzymes were tested for their ability to selectively hydrolyze racemic *O*-acetylmandelonitrile under a variety of conditions, and it was determined that CAL-B, ASL, and PSL showed enough activity to justify further investigation. Methyl *tert*-butyl ether was the best solvent for the enzymatic reaction, with toluene also being suitable, but reactions in dichloromethane were very slow. The selected lipase enzymes were then tested for their ability to resolve a nonracemic sample of *O*-acetylmandelonitrile (starting at 77% ee). CAL-B was selected as the optimal enzyme to be used for further study due to its ability to increase the enantiomeric excess to >99% in 5 h whereas the other enzymes required reaction times of almost 24 h.

The complex **157** catalyzed step required dichloromethane as solvent in order to achieve optimal enantioselectivity, but the enzymatic resolution was less effective in this solvent; therefore, a two stage reaction was required in which the solvent was changed to methyl *tert*-butyl ether before introducing the enzyme (Scheme 27). A range of aldehyde substrates were screened for the two step chemo-enzymatic procedure: *O*-acetylcyanohydrins were obtained with 47−87% enantiomeric excess after the catalyst stage and 63−99% enantiomeric excess following the enzymatic resolution. Benzaldehyde, *m*-anisaldehyde, and *m*-tolualdehyde gave the best enantioselectivities with catalyst **157** (84%, 87%, 87%, respectively) and in general, aromatic aldehyde substrates were better in terms of both conversion and enantioselectivity. Selectivities obtained from the enzyme resolution step were high for all substrates (88−99%), except for the moderate results achieved when using 2-methylpropanal (74%), cyclohexanecarboxaldehyde (68%), and pivaldehyde (63%) as substrates (Table 47). In the majority of cases, the enantiomeric excess of the final product was substantially higher than that obtained after a single-step chemically catalyzed reaction without a major reduction in the chemical yield.

Table 47. Asymmetric Addition of Potassium Cyanide to Aldehydes Using Catalyst 157 and CAL-B

aldehyde	ee (%) (after **157**)[a]	ee (%) (after CAL-B)[b]	time (h)[d]	overall yield (%)
PhCHO	84	99	7	81
4-ClC_6H_4CHO	80	97	8	81
2-ClC_6H_4CHO	79	90	5	74
3-$MeOC_6H_4CHO$	87	94	5	84
2-MeC_6H_4CHO	72	90	27	69
3-MeC_6H_4CHO[c]	87	98	192	61
4-MeC_6H_4CHO[c]	81	97	168	50
furan-2-carboxaldehyde	77	98	6	78
thiophene-2-carboxaldehyde	61	88	6.5	72
pyridine-3-carboxaldehyde	67	94	4	77
PhCH=CHCHO	75	95	5	80
$Me(CH_2)_7CHO$	77	92	7	66
Me_2CHCHO	47	74	23.5	46
CyCHO	60	68	21	65
Me_3CCHO	63	63	23	60

[a] Reaction used 1:4:4 aldehyde/potassium cyanide/acetic anhydride with 1 mol % catalyst **157** in CH_2Cl_2, ^{t}BuOH, and water at −40 °C. [b] Reaction used CAL-B (125 mg/mmol) with 1 equiv of isopropanol in MeO^tBu. [c] Reaction carried out in toluene using the isolated and purified *O*-acetyl mandelonitrile. [d] Time for the enzyme catalyzed reaction.

Table 48. One Pot Asymmetric Cyanation of Aldehydes Catalyzed by Complex 157 and CAL-B

aldehyde	ee (%) (with **157**)[a]	ee (%) (with CAL-B)[b]	time (h)[c]	overall yield (%)
PhCHO	76	97	26	84
4-ClC_6H_4CHO	89	99	7	94
2-ClC_6H_4CHO	75	89	22	89
3-$MeOC_6H_4CHO$	93	97	23	96
2-MeC_6H_4CHO	64	80	22	90
PhCH=CHCHO	67	90	23.5	85
furan-2-carboxaldehyde	76	99	23	86
thiophene-2-carboxaldehyde	70	95	8	83
pyridine-3-carboxaldehyde	61	92	7.5	82
$Me(CH_2)_7CHO$	69	92	22	75

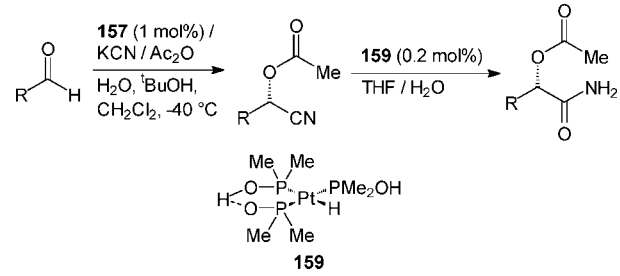
[a] Reaction used 1:4:4 aldehyde/potassium cyanide/acetic anhydride with 1 mol % catalyst **157** in CH_2Cl_2, ^{t}BuOH, and water at −40 °C. [b] CAL-B (125 mg/mmol) with 1 equiv of isopropanol in MeO^tBu added to the CH_2Cl_2 solution. [c] Time for the enzyme catalyzed reaction.

The procedure was refined by developing a one-pot variant in which the enzymatic reaction was carried out in a mixture of dichloromethane and methyl *tert*-butyl ether for which a series of substrates gave the cyanohydrin products in 75−96% yields and with 80−99% enantiomeric excess (Table 48). It was shown that in the one pot process CAL-B retained similar enantioselectivity to the two stage process, though the enzymatic resolution required a longer reaction time.

Catalyst **157** was also used as part of a study by Belokon *et al.* to investigate a phase transfer system for the asymmetric addition of potassium cyanide and acetic anhydride to benzaldehyde using a biphasic solvent mixture of toluene and water.[124] When 1 mol % of **157** was used in 9:1 toluene/water at −10 °C, a 75% yield of *O*-acetyl mandelonitrile was obtained with 20% enantiomeric excess. Using toluene as the only solvent, a much lower chemical yield of 20% was achieved, but the enantioselectivity was higher (52%).

To illustrate the synthetic utility of enantiomerically pure cyanohydrin acetates, North *et al.* demonstrated the selective hydrolysis of the nitrile group within *O*-acetyl cyanohydrins

Scheme 28



Scheme 29

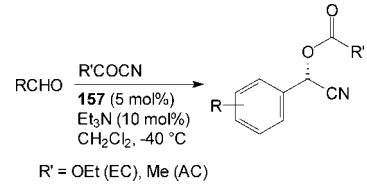


Table 49. Asymmetric Addition of Acetyl Cyanide to Benzaldehyde Catalyzed by 5 mol % 157 and Lewis Bases

Lewis base (mol %)	acetyl cyanide (equiv)	temp (°C)	time (h)	conv (%)	ee (%) (*S*)
none	2	−40	24	0	
none	2	25	24	30	53
DMAP (10)	2	−40	6	57	94
DMAP (15)	2	−40	6	67	91
DMAP (20)	2	−40	6	76	91
DMAP (10)	2	−10	6	78	89
DMAP (10)	2	25	4	97	67
DMAP (10)	1	−10	6	63	90
DABCO (10)	2	−40	9	67	92
Et_3N (10)	2	−40	8	96	94
DIEA (10)	2	−40	8	97	81
sparteine (10)	2	−40	8	93	65
cinchonidine (10)	2	−40	9	78	96
quinine (10)	2	−40	9	80	92
sparteine (10)	2	−40	8	96	67 (*R*)[a]
cinchonidine (10)	2	−40	9	75	92 (*R*)[a]
quinine (10)	2	−40	9	73	95 (*R*)[a]

[a] The *S*,*S*-enantiomer of complex **157** was used.

prepared by the complex **157** catalyzed addition of potassium cyanide to aldehydes.[125] Thus, platinum catalyst **159** was used to convert the nitrile into an amide (Scheme 28), and it was shown (by dehydration of the amide back to the *O*-acetyl cyanohydrin) that no racemization occurred during the hydrolysis reaction.

In a different approach to the synthesis of *O*-acetyl cyanohydrins, Moberg *et al.* found that, in the presence of Lewis bases, complex **157** is able to catalyze the asymmetric addition of acetyl cyanide to aldehydes as shown in Scheme 29. This was the first example of the use of this cyanating agent in asymmetric catalysis. The authors screened a variety of bases including triethylamine, DABCO, DMAP, and cinchona alkaloids in the acetyl cyanation of benzaldehyde.[126] The highest enantioselectivities were obtained using DMAP at −40 °C (91−94%), triethylamine (94%), cinchonidine (96%), and quinine (95%) with (*S*,*S*)-**157** (Table 49). Without a Lewis base catalyst, conversion and enantioselectivity were both greatly reduced. Control reactions using Lewis bases without catalyst **157** were carried out, resulting in low yields in most cases, but there was some asymmetric induction (up to 40%) using cinchonidine.

Under the conditions shown in Scheme 29, aromatic and aliphatic acetylated cyanohydrins were obtained in 64−90% yield and with 76−96% enantiomeric excess after reaction

Table 50. Asymmetric Addition of Acetyl Cyanide (AC) and Ethyl Cyanoformate (EC) to Aldehydes Catalyzed by Complex 157 (5 mol %) and Triethylamine (10 mol %)

aldehyde	cyanide source	time (h)	yield (%)	ee (%) (*S*)
PhCHO	EC	4	95	92
PhCHO	AC	10	89	94
4-MeC_6H_4CHO	EC	6	88	94
4-MeC_6H_4CHO	AC	10	90	96
4-$MeOC_6H_4CHO$	EC	6	79	94
4-$MeOC_6H_4CHO$	AC	12	72	94
4-ClC_6H_4CHO	EC	4	90	93
4-ClC_6H_4CHO	AC	8	89	95
PhCH=CHCHO	EC	7	97	93
PhCH=CHCHO	AC	23	64	93
Me_3CCHO	EC	5	81	73
Me_3CCHO	AC	6	84	76
furan-2-carboxaldehyde	AC	12	93	89 (*R*)
3-$PhOC_6H_4CHO$	AC	48	84	85
3-pyridine carboxaldehyde	AC	12	91	86
2-pyridine carboxaldehyde	AC	12	87	20
$CH_3(CH_2)_4CHO$	EC	5	83	89
$CH_3(CH_2)_4CHO$	AC	6	89	90

times of 4−12 h (Table 50). With the exception of pivaldehyde, all other aldehyde substrates gave very good enantioselectivities with both acetyl cyanide and ethyl cyanoformate (see section 2.2.3.3) as the cyanating agent. There was little difference in the yield or asymmetric induction between the two cyanide sources, though the reaction time for acetyl cyanide addition was somewhat longer (6−12 h) than that required for ethyl cyanoformate addition (4−7 h). A range of other cyanoformates and acyl cyanides were also studied, but it was found that they all gave very similar results (92−94% enantioselectivities) with the exceptions of 3,3-dimethyl-2-oxobutanenitrile and benzoyl cyanide, which gave lower enantioselectivities (79 and 75%, respectively).

Moberg has also reported a high throughput enzymatic method for the determination of the conversion and enantiomeric excess of *O*-acetylated cyanohydrins derived from the addition of acetyl cyanide to benzaldehyde in the presence of catalyst **157** and amine cocatalyst.[127] The principle involves using two different enzymes, the first of which reduces any remaining benzaldehyde to benzyl alcohol. A combination of horse liver alcohol dehydrogenase (HLADH) and NADH is used to achieve this; NADH absorbs in the UV region, but NAD^+ does not, and therefore, the amount of unreacted benzaldehyde can be calculated by the change in UV absorbance. The second enzyme selectively converts either (*R*)- or (*S*)-mandelonitrile acetate to benzaldehyde, and this can be achieved using pig liver esterase or *Candida antarctica* lipase B, respectively. The resulting aldehyde is then reduced by the NADH/HLADH system, and by comparing the results obtained using HLADH alone and the combination of enzymes, both the conversion and enantioselectivity can be calculated. The method allows the rapid evaluation of many reactions, but carefully controlled concentrations and volumes are required for accurate measurements. Since the UV measurements are recorded from the concentration of NADH, the protocol could also be applied to aldehydes other than benzaldehyde.

2.2.3.3. Asymmetric Synthesis of Cyanohydrin Carbonates Using Complex 157. Belokon and North also showed that complex **157** would catalyze the asymmetric addition of ethyl cyanoformate to aldehydes. By employing catalyst **157** with benzaldehyde and EtOCOCN in dichloromethane,

Scheme 30

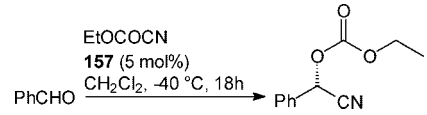


Table 51. Addition of Ethyl Cyanoformate to Benzaldehyde Catalyzed by Complex 157

temp (°C)	**157** (mol %)	time (h)	conversion (%)	ee (%) (*S*)
−85	1	19	<3	
−73	1	48	100	94
−40	1	19	100	83
−40	0.1	72	<3	
25	0.1	148	<3	
−40	5	18	100	95
−40	10	51	100	93

Table 52. Asymmetric Addition of Ethyl Cyanoformate to Aldehydes Catalyzed by Complex 157

aldehyde	time (h)	EtOCOCN (equiv)	yield (%)[a]	ee (%) (*S*)
PhCHO	18	2	90	95
4-$MeOC_6H_4CHO$	18	2	92	95
3-$MeOC_6H_4CHO$	17	2	94	99
2-$MeOC_6H_4CHO$	48	1.2	95	98
4-MeC_6H_4CHO	48	1.2	67 (95)	94
4-$CF_3C_6H_4CHO$	6	2	84	76
4-ClC_6H_4CHO	68	1.2	96	94
PhCH=CHCHO	45	1.2	47 (99)	94
$CH_3(CH_2)_7CHO$	22	2	54	84
Me_2CHCHO	20	1.2	23 (88)	79
CyCHO	18	1.2	82	79
Me_3CCHO	48	1.2	69	76

[a] After purification by distillation. Figures in brackets indicate yield before distillation.

mandelonitrile ethyl carbonate could be obtained with very good enantioselectivity (Scheme 30).[128] The optimal conditions were determined to be 5 mol % catalyst loading, at −40 °C, which gave 100% yield and 95% enantioselectivity after a reaction time of 18 h (Table 51). Using lower amounts of catalyst led to reduced enantioselectivity, which could be remedied by lowering the temperature to −78 °C, but the reaction then required 48 h for completion. Further reduction in catalyst loading or reaction temperature resulted in very low conversion. Under the optimized conditions, a range of aromatic and aliphatic aldehydes was converted into the corresponding ethyl carbonates using catalyst **157** with either 1.2 or 2 equiv of ethyl cyanoformate (Table 52). The best results were achieved with electron rich aromatic aldehydes (94−99% enantioselectivity), with a somewhat lower enantioselectivity of 76% being obtained for the electron deficient 4-trifluoromethylbenzaldehyde. Aliphatic substrates generally showed inferior yields and enantioselectivities of 76−84%. However, cinnamaldehyde was a reasonably good substrate, giving 94% enantioselectivity.

It was subsequently found that potassium cyanide or the KCN/18-crown-6 complex[129] had a beneficial effect on the activity and enantioselectivity of complex **157** catalyzed addition of ethyl cyanoformate to benzaldehyde.[130] The best result obtained for the potassium cyanide cocatalyzed cyanoformylation of benzaldehyde was 100% conversion using 2 mol % of complex **157** at −40 °C after a reaction time of 26 h (Table 53). Using 1 mol % of catalyst **157** without any potassium cyanide results in a poor conversion even after 90 h, though with a high level of asymmetric induction (89%). However, the introduction of 1 mol % of potassium

Table 53. Asymmetric Addition of Ethyl Cyanoformate to Benzaldehyde Catalyzed by 157 and KCN

157 (mol %)	KCN (mol %)	temp (°C)	time (h)	conv (%)	ee (%) (*S*)
1	0	25	90	5	89
1	1	25	48	100	51
1	10	25	48	98	68
1	10	−40	19	87	81
2	10	−40	26	100	95
1	10	−70	24	0	

Table 54. Asymmetric Addition of Ethyl Cyanoformate to Benzaldehyde Catalyzed by Complex 157 and Potassium Cyanide/18-Crown-6 as Cocatalyst[a]

aldehyde[b]	ee (%) (*S*)	previous ee (%) (*S*)[c]
PhCHO	91	95
2-MeC_6H_4CHO	97	
4-MeC_6H_4CHO	99	94
2-$MeOC_6H_4CHO$	100	98
3-$MeOC_6H_4CHO$	97	99
4-$MeOC_6H_4CHO$	90	97
2-ClC_6H_4CHO	93	
4-ClC_6H_4CHO	100	94
PhCH=CHCHO	90	95
(*E*)-MeCH=CHCHO	93	
(*E*)-EtCH=CHCHO	91	
(*E*)-MeCH=C(Me)CHO	89	
$CH_3(CH_2)_7CHO$	81	84
CyCHO	78	79
Me_3CCHO	71	76

[a] Reaction was carried out for 48 h with 1 mol % **157** and 1.5 mol % KCN/18-crown-6 in dichloromethane. [b] All reactions gave 100% conversion except nonanal (98%). [c] Results obtained with KCN but without the use of 18-crown-6.

cyanide boosts the conversion to 100% in only 48 h, though the enantioselectivity is adversely affected (51%). Using 10 mol % of potassium cyanide increases the selectivity to 68%, but the best improvements were made by reducing the reaction temperature to −40 °C, where 81% enantioselectivity was obtained using 1 mol % of catalyst **157** and 95% asymmetric induction was obtained with 2 mol % of complex **157**. This system is an improvement, as the loading of catalyst **157** can be significantly reduced from 5 to 2 mol %. Three other cyanoformates were studied including methyl, benzyl, and *tert*-butyl cyanoformate, but they did not show any improvement over ethyl cyanoformate. Six aldehydes were screened using 1−2 mol % of catalyst **157** and gave similar enantioselectivities to those obtained in the absence of potassium cyanide and at a higher loading of catalyst **157**.[128]

To improve the solubility of the cyanide cocatalyst in dichloromethane, the complex[129] of KCN/18-crown-6 can be used. The use of 1 mol % of this complex as well as 1.5 mol % of catalyst **157** resulted in enantioselectivities of 71−100% (Table 54).[130] The enantioselectivities were generally high for all substrates, in particular for aromatic aldehydes, with 4-methylbenzaldehyde, 2-anisaldehyde, and 4-chlorobenzaldehyde giving enantioselectivities of at least 99%. There is no significant improvement in enantioselectivity compared to the results obtained without 18-crown-6, but a further reduction in catalyst and cocatalyst loading was achieved.

The effect of the cyanoformate structure on the enantioselectivity of complex **157**/KCN catalyzed cyanohydrin carbonate synthesis has also been studied.[131] Using benzaldehyde as substrate, addition of methyl cyanoformate catalyzed by 2 mol % of **157** and 10 mol % of KCN gave

Table 55. Asymmetric Addition of Ethyl Cyanoformate to Aldehydes Catalyzed by $Ti(O^iPr)_4$−142[a]

aldehyde	time (h)	yield (%)	ee (%) (*S*)
PhCHO	16	99	91
3-MeC_6H_4CHO	40	99	91
4-MeC_6H_4CHO	55	99	87
4-$MeOC_6H_4CHO$	14	99	91
4-ClC_6H_4CHO	92	89	88
2-naphthaldehyde	16	91	90
3-$PhOC_6H_4CHO$	10	90	90
PhCH=CHCHO	40	87	81
4-FC_6H_4CHO	114	93	87
3,4-$(OCH_2O)C_6H_3CHO$	10	85	86
$CH_3(CH_2)_4CHO$	54	92	86
Me_2CHCHO	60	59	76

[a] All reactions performed in 1:4 $^iPrOH/CHCl_3$ at −20 °C using a 5 mol % catalyst loading.

equal enantioselectivity (95%) to that obtained with ethyl cyanoformate, with only a marginally lower yield (92%). Benzyl and *tert*-butyl cyanoformates also gave optically active products in 100% chemical yield, though the enantioselectivities were not determined in these cases. Using pivaldehyde as substrate, similar enantioselectivity (62−68%) was observed using methyl, ethyl, and *tert*-butyl cyanoformates with the highest chemical yields (100%) achieved *using tert*-butyl and benzyl cyanoformates, though the enantioselectivity was not determined in the latter case. Reactions were carried out in dichloromethane at −40 °C for a period of 24 h. The use of potassium cyanide as a cocatalyst did not increase the enantioselectivity of the reactions but allowed a decrease in catalyst loading from 5 to 2 mol %. Thus, the structure of the cyanoformate does not seem to influence the enantioselectivity in reactions catalyzed by complex **157**.

Feng screened a number of C_2-symmetric cyclohexanediamine derived salen ligands to form complexes of titanium isopropoxide *in situ* which were used for the asymmetric addition of ethyl cyanoformate to aldehydes.[132] After testing the complexes under a variety of conditions, it was shown that $Ti(O^iPr)_4$−**142** was the optimal catalyst. With benzaldehyde as substrate, use of 5 mol % of the titanium complex of ligand **142** in 1:4 isopropanol/chloroform at −20 °C gave mandelonitrile ethyl carbonate in 99% yield and with 91% enantiomeric excess. Using the same approach with other aldehydes, a range of cyanohydrin carbonates were obtained with 76−91% enantiomeric excess (Table 55). Enantioselectivities were good for all substrates including both aromatic and aliphatic aldehydes. Yields were excellent throughout, with the exception of 2-methylpropanal, which gave a yield of just 59%. The amount of ethyl cyanoformate used in the reaction was also investigated, but similar results were obtained for all tested concentrations. It seems likely that, under the reaction conditions, complex **157** is generated *in situ* and that some of the ethyl cyanoformate reacts with isopropanol to generate cyanide, which catalyzes the reaction.

Moberg investigated the combined use of catalyst **157** and a Lewis base for the addition of ethyl cyanoformate to aldehydes and found that this also had a beneficial effect on the reaction rate.[126] The best results were obtained by using either triethylamine (see Table 50) or DMAP (10 mol %) as the Lewis base, and with benzaldehyde as substrate under the same conditions used in Belokon and North's work,[128] this enabled the authors to decrease the reaction time from 18 to 4 h.

Table 56. Addition of Cyanoformate 160 to Benzaldehyde Catalyzed by Complex 157[a]

aldehyde	cyanoformate	conversion (%)	diastereomeric ratio (*lk*/*ul*)
PhCHO	(*R*)-**160**	88	28:1 (93% de)
PhCHO	(*S*)-**160**	66	1:18 (89% de)
Me_3CCHO	(*R*)-**160**	100	5.3:1 (68% de)
Me_3CCHO	(*S*)-**160**	100	1:3.6 (57% de)

[a] Reactions carried out in dichloromethane at −40 °C for 24 h using 2 mol % of catalyst **157** with 4 mol % KCN.

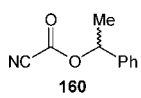
Table 57. Addition of Cyanoformate 161 to Benzaldehyde Catalyzed by Complex 157[a]

aldehyde	catalyst	conversion (%)	diastereomeric ratio
PhCHO	(*R*,*R*)-**157**	32	1:12.3 (85% de)
PhCHO	(*S*,*S*)-**157**	54	9:1 (80% de)
Me_3CCHO	(*R*,*R*)-**157**	28	1:10.8 (83% de)
Me_3CCHO	(*S*,*S*)-**157**	46	13.3:1 (86% de)

[a] Reactions carried out in dichloromethane at −40 °C for 24 h using 2 mol % of catalyst **157** with 4 mol % KCN.

North also demonstrated that chiral cyanoformates **160**−**164** could be used in conjunction with complex **157** and potassium cyanide, thus allowing diastereoselective cyanohydrin synthesis to be carried out on achiral aldehydes for the first time.[131] In this study, benzaldehyde and pivaldehyde were used as representative aromatic and aliphatic aldehyde substrates respectively. It was found that the asymmetric addition of (*R*)-**160** catalyzed by (*R*,*R*)-**157** constituted a matched pair, giving the cyanohydrin carbonate with a much higher diastereomeric excess than that obtained from the mismatched pair of (*S*)-**160** and (*R*,*R*)-**157** (Table 56). The matched pairs gave the *lk*-diastereomer of the cyanohydrin carbonate as the major product, whilst the mismatched pair gave the *ul*-diastereomer in excess, which indicates that the chirality of the catalyst is more important than the chirality of the cyanoformate in determining the stereochemistry of the newly created stereocenter within the cyanohydrin carbonate product.

Similar results were obtained using both enantiomers of complex **157** to catalyze the addition of cyanoformate **161** to aldehydes. It was shown that the product obtained with catalyst (*R*,*R*)-**157** was diastereomeric to that obtained using (*S*,*S*)-**157**, again indicating that the catalyst has more influence than the cyanoformate on the product stereochemistry (Table 57). Unfortunately, cyanoformates **162**−**164** failed to react with the aldehydes even after a reaction time of 2 weeks.



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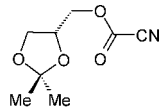

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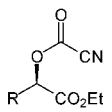
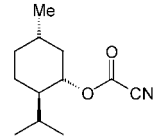


161) R = Me
162) R = Ph



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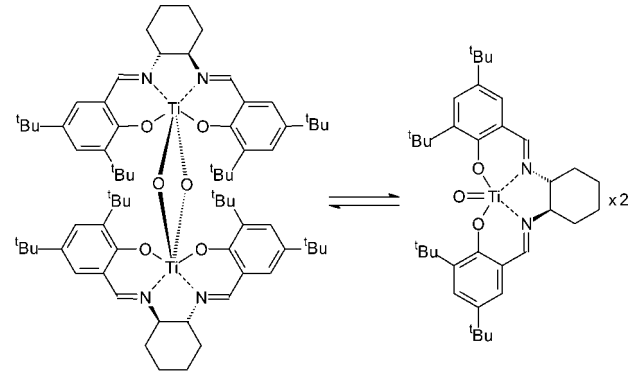
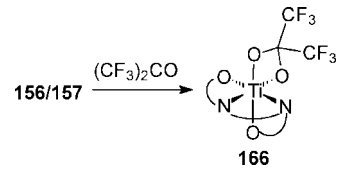
2.2.3.4. Mechanistic Studies on [(salen)TiO]$_2$ Complexes. In view of the significant synthetic advantages associated with complex **157**, Belokon and North have studied its mode of action in detail to understand the nature of the catalysis and asymmetric induction and allow catalysts with further improved catalytic properties to be developed. Ultracentrifugation techniques showed that the molecular weight of complex **157** in solution corresponded to the dimeric form of the complex.[133] However, no appreciable nonlinear effect[134] was detected in catalysis using partially racemic catalyst **157**, which indicated that there was no preferential formation of heterochiral dimers.



157 **165**

Figure 3.

Scheme 31



166

Subsequently it was shown by ^{1}H NMR spectroscopy that complex **157** existed in dichloromethane and chloroform solutions as a concentration-dependent equilibrium between dimeric **157** and monomeric **165** species, as shown in Figure 3.[135] In deuterated benzene, however, no dissociation of bimetallic complex **157** could be detected. Complex **165** is a key intermediate in the conversion of complex **157** into species on the catalytic cycle (*vide infra*), and the need to form complexes such as **165** *in situ* may explain why titanium(salen) complexes generally show the highest catalytic activity in chlorinated solvents such as dichloromethane.

Kinetic studies revealed that the reaction was first order with respect to trimethylsilyl cyanide and independent of the concentration of benzaldehyde, thus implying that benzaldehyde is only involved in the catalytic cycle after the rate determining step. By varying the concentration of catalyst in the reaction, it was possible to determine the order with respect to the catalyst and thus determine whether the active catalyst exists as a mononuclear or dinuclear species. The results gave a catalyst order of 1.6 for complex **156**, 1.3 for complex **157**, and 1.8 for complex **158**, indicating that more than one metal center is involved in the catalysis.[133]

Treatment of complexes **156** and **157** with hexafluoroacetone resulted in the formation of metalloacetals **166** (Scheme 31), whilst reaction of complex **157** with excess trimethylsilyl cyanide resulted in silylation of both bridging oxygens to give complex **167** (Figure 4). On the basis of these results, the authors were able to postulate the catalytic cycle shown in Figure 4 to account for the high level of catalytic activity displayed by complexes **156**−**158**.[133,135]

The key features of this catalytic cycle are that complex **157** first reacts separately with the aldehyde and with trimethylsilyl cyanide to generate mononuclear complexes

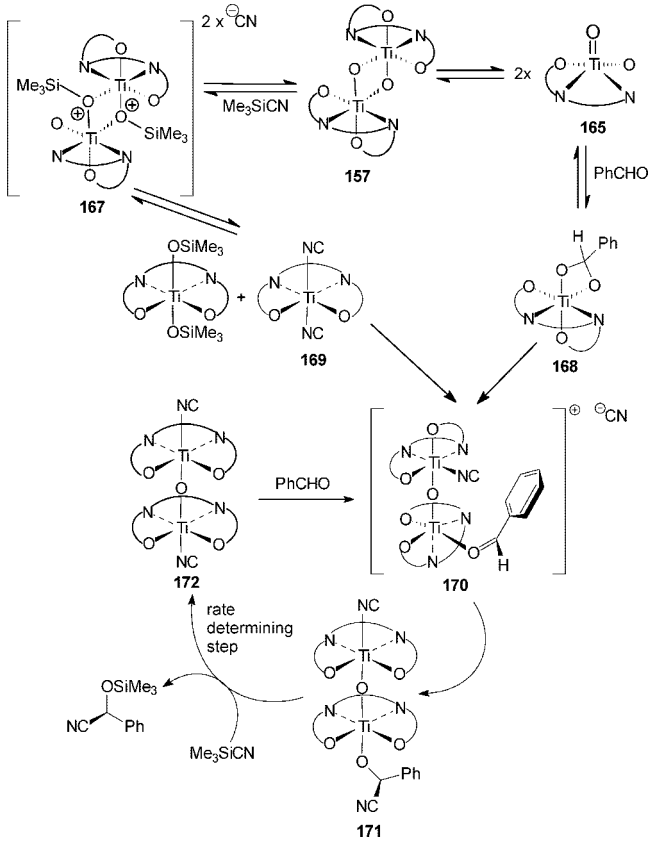


Figure 4.

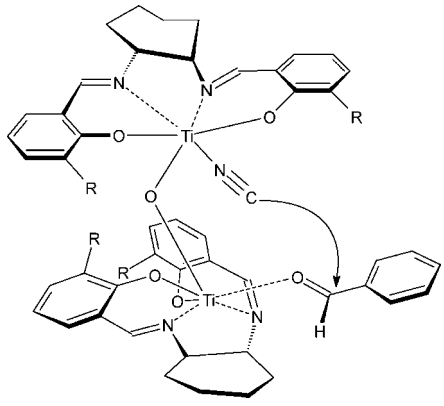
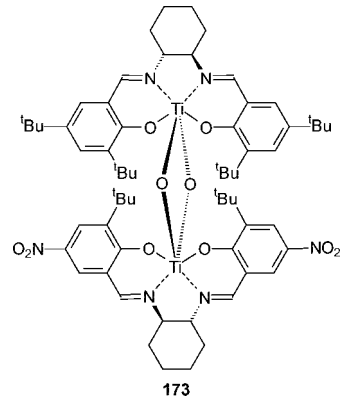


Figure 5.

168 and **169**, respectively. Recombination of complexes **168** and **169** generates the key bimetallic complex **170**, in which one metal ion acts as a chiral Lewis acid, activating the aldehyde whilst the other activates the cyanide. This preorganizes the two components of the reaction to undergo an intramolecular transfer of cyanide onto the *re*-face of the aldehyde (assuming the catalyst is derived from (*R,R*)-cyclohexanediamine) to form titanium bound cyanohydrin **171**, as highlighted in Figure 5. The structure of this transition state also explains why complex **157** will catalyze the asymmetric addition of trimethylsilyl cyanide to some but not all ketones (see section 3.2), as there is sufficient space to accommodate a methyl or ethyl group in place of the aldehyde hydrogen, but not a larger substituent. The rate determining step of the mechanism is then the silylation of complex **171** to form the silylated cyanohydrin product and C_2-symmetric bis-cyanide complex **172**, which can react with the aldehyde to re-form complex **170**. Thus, the catalytic cycle consists of just three complexes **170**−**172**, each of which is bimetallic.

Further evidence for the dinuclear catalyst system was obtained by the mixing of complexes **157** and **158**, which resulted in the formation of complex **173**, as indicated by ^{1}H NMR spectroscopy. Reactions catalyzed by complex **173** had an order with respect to catalyst of 1.9, and the observed rate of catalysis for the mixture was much greater than that observed using catalyst **158** alone but not as fast as that for catalyst **157**. If monomeric species had been responsible for the catalysis, the rate of catalysis of the mixture would have been expected to be similar to that obtained using catalyst **157** alone, as the same species would have been present in solution.[133]



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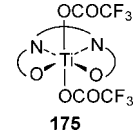
The mechanism shown in Figure 4 can easily be adapted to accommodate other cyanating agents.[131,135] Thus, treatment of complex **157** with acetic anhydride is known to produce bimetallic bis-acetate **174**.[120] Displacement of the acetate groups from complex **174** by cyanide and the aldehyde would generate the key complex **170** (but with an acetate counterion) on the catalytic cycle. After formation of the titanium bound cyanohydrin, acetic anhydride could acetylate the cyanohydrin and re-form complex **174** as shown in Figure 6. Other anhydrides and cyanoformates could react in exactly the same way. Whilst complex **157** is compatible with many different anhydrides (see section 2.2.3.2), it is not possible to use trifluoroacetic anhydride, as this more reactive acylating agent converts complex **157** into the catalytically inactive mononuclear complex **175**.[120] For reactions involving the use of Lewis bases[126,132] or cyanide as a cocatalyst along with an acyl cyanide or cyanoformate, the role of the Lewis base can be explained by its reaction with the acyl cyanide to generate cyanide ions and/or a more reactive acylating agent.[131] Since cyanide is needed to form complex **170** and the acylating agent is involved in the rate determining step of the catalytic cycle shown in Figure 6, this accounts for the role of these cocatalysts.



175

The important advantages of catalyst **157** are high enantioselectivity, very low catalyst loading, high reaction rate, simple and cheap synthesis of the complex, and the ability to use many different cyanide sources. This has resulted in the industrial application[136] of complex **157** by NPIL Pharma Ltd. under the trademark CACHy.

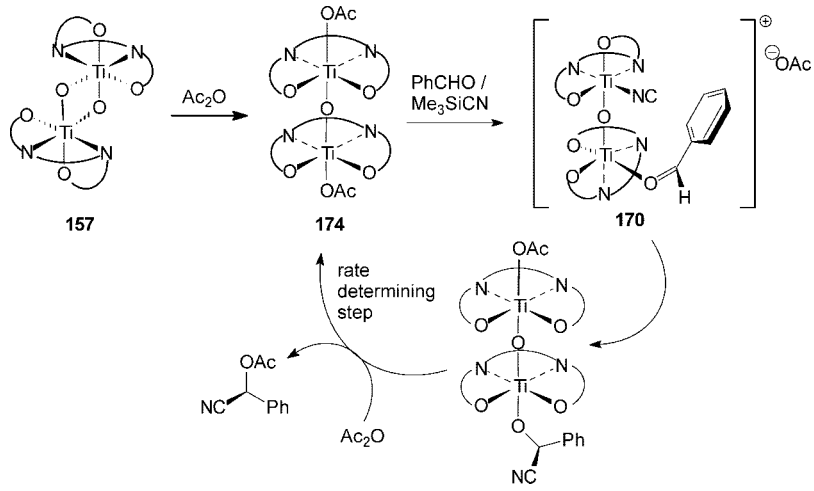
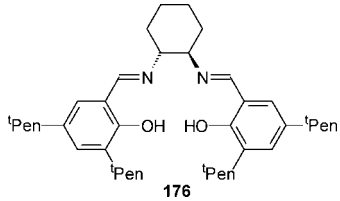


Figure 6.

Table 58. Asymmetric Cyanosilylation of Aldehydes Catalyzed by the Titanium Complex of Ligand 176

aldehyde	yield (%)	ee (%) (*S*-configuration)
PhCHO	92	97
3-MeC_6H_4CHO	85	92
4-MeC_6H_4CHO	96	94
4-EtC_6H_4CHO	84	94
4-$^{i}PrC_6H_4CHO$	93	93
4-$^{t}BuC_6H_4CHO$	94	95
4-ClC_6H_4CHO	89	97
3-ClC_6H_4CHO	87	97
4-FC_6H_4CHO	92	96
2-naphthaldehyde	93	>97

2.2.3.5. Other C_2-Symmetric Schiff Base Complexes. A number of alternative C_2-symmetric salen-based systems for asymmetric trimethylsilylcyanation have also been described. Bu and Liang slightly modified the structure of ligand **142** by introducing *tert*-pentyl groups onto the aromatic ring of the salen ligand in place of the *tert*-butyl groups to give ligand **176**.[137] The titanium complex obtained by treating ligand **176** with titanium tetraisopropoxide gave higher levels of asymmetric induction than complex **157**; for aromatic aldehydes, consistently high enantioselectivities of 92−97% and chemical yields of 84−93% were achieved (Table 58). The reaction was however conducted using 5 mol % of the complex in dichloromethane at −78 °C for 12 h (compared to 0.1 mol % of catalyst **157** at ambient temperature for 1 h). A significant temperature dependence was observed for cyanosilylations catalyzed by the complex derived from ligand **176.** For the cyanosilylation of benzaldehyde, there was only a marginal loss in enantioselectivity when raising temperature from −78 to −10 °C (97% to 90%); however, a further increase in the reaction temperature to 20 °C gave a significantly reduced enantioselectivity of only 56%, much lower than the 86% asymmetric induction obtained with catalyst **157** at 20 °C.[117]



176

North investigated the use of different chiral diamines to synthesize C_1- and C_2-symmetric salen ligands (**177a**−**e** and **178a**−**d**) to generate both titanium dichloride and vanadium-oxo (see section 2.3) complexes for the asymmetric addition of trimethylsilyl cyanide to benzaldehyde.[138] The titanium dichloride complexes of ligands **177** and **178** gave far lower enantioselectivities than the 72% asymmetric induction achieved using cyclohexyl containing complex **153**. The lower enantioselectivity obtained using salen ligands derived from acyclic diamines could be traced to the conformation of the salen ligand, which can exist as gauche and anti conformations (Figure 7). Salen ligands derived from cyclic diamines (such as ligand **142**) are locked into the gauche conformation, whilst salen ligands derived from acyclic diamines (such as **177a**−**e** and **178a**−**d**) can adopt both conformations, with the anti-conformation usually being preferred, as it minimizes steric interactions within the ligand.

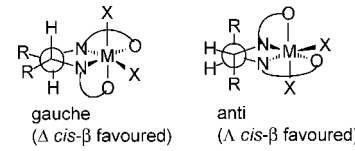
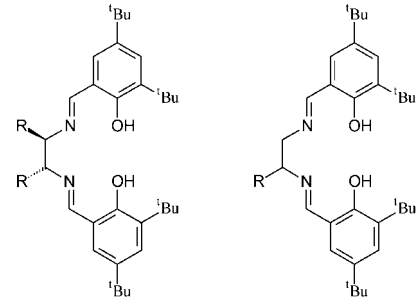


Figure 7.



For the cyclohexanediamine derived salen complexes, the configuration of the cyanohydrin products is always the opposite to that of the ligand; that is, *R*,*R* salen complexes give *S*-cyanohydrins. However, with the exception of ligand **177a**, titanium complexes of ligands **177** and **178** catalyzed the cyanosilylation of benzaldehyde to give mandelonitrile trimethylsilyl ether with the same configuration as that of the ligand. It was proposed that this was due to the increased

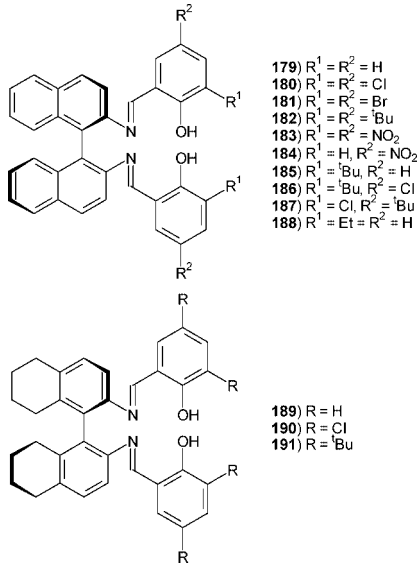
Table 59. Enantioselective Trimethylsilylation of Benzaldehyde Catalyzed by Titanium Complexes of BINAM Derived Schiff Bases 179−191[a]

ligand (configuration)	yield[b] (%)	ee (%) (configuration)
179(*R*)	76	38 (*S*)
180(*R*)	53	47 (*S*)
181(*R*)	60	81 (*S*)
182(*R*)	92	93 (*S*)
182(*S*)	94	93 (*R*)
183(*R*)	0	
184(*R*)	53	35 (*S*)
185(*R*)	82	86 (*S*)
186(*R*)	73	75 (*S*)
187(*R*)	63	51 (*S*)
188(*R*)	85	75 (*S*)
189(*R*)	54	24 (*S*)
190(*S*)	75	38 (*S*)
191(*S*)	68	29 (*S*)

[a] All reactions carried out in dichloromethane at −78 °C for 120 h. [b] Yield of mandelonitrile obtained after hydrolysis of the trimethylsilyl ether.

ligand flexibility which changes the preferred configuration (ΔΛ rather than ΔΔ) of the dimeric titanium complexes formed *in situ*. This in turn leads to a different conformation of the salen ligand which induces the opposite stereochemistry in the cyanohydrin to that obtained when using complex **157**.

Che and co-workers elaborated a new ligand system based on BINAM, which was used for the preparation of both titanium and ruthenium complexes.[139] Use of 20 mol % of the catalyst formed *in situ* from ligands **179**−**191** and titanium tetraisopropoxide in the cyanosilylation of benzaldehyde with trimethylsilyl cyanide in dichloromethane at −78 °C gave, after hydrolysis, mandelonitrile in 53−94% yield and with an enantiomeric excess of 24−93% after a reaction time of 120 h (Table 59). The best results were obtained with the titanium complex of ligand **182**, which gave an enantioselectivity of 93% and a yield of 94%.



The titanium isopropoxide complex of ligand **182** was then used to screen a range of four aromatic aldehydes as well as 2-methylpropenal and phenylethanal (Table 60). Good results were obtained from experiments using the methylbenzaldehydes as substrates, particularly in the case of *o*- and *m*-methylbenzaldehyde, where the corresponding cyanohydrins were obtained in 87 and 75% yield and with 95 and 96% enantiomeric excess, respectively.

Table 60. Enantioselective Trimethylsilylation of Aldehydes Catalyzed by Ti(O^{i}Pr)$_4$−182

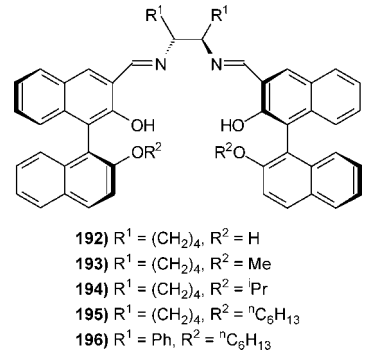
aldehyde	yield[a] (%)	ee (%) (*S*)
CH_2=C(Me)CHO	75	42
2-ClC_6H_4CHO	82	51
2-MeC_6H_4CHO	87	95
4-MeC_6H_4CHO	82	88
3-MeC_6H_4CHO	75	96
$PhCH_2CHO$	63	71

[a] Yield of cyanohydrin obtained after hydrolysis of the trimethylsilyl ether.

Table 61. Asymmetric Trimethylsilylation of Benzaldehyde Catalyzed by Titanium Complexes of 192−196[a]

ligand (mol %)	Ti (mol %)	solvent	time (h)	ee (%) (*S*)
192 (20)	Ti(O^{i}Pr)$_4$ (20)	dichloromethane	22	46
192 (20)	Ti(O^{i}Pr)$_4$ (20)	toluene	22	14
192 (20)	Ti(O^{i}Pr)$_4$ (20)	THF	22	14
192 (20)	Ti(O^{i}Pr)$_4$ (20)	ether	22	15
192 (10)	Ti(O^{i}Pr)$_4$ (10)	dichloromethane	22	66
192 (0.5)	Ti(O^{i}Pr)$_4$ (0.5)	dichloromethane	36	69
192 (0.05)	Ti(O^{i}Pr)$_4$ (0.05)	dichloromethane	60	26
192 (10)	$TiCl_4$ (10)	dichloromethane	22	45
192 (0.5)	$TiCl_4$ (0.5)	dichloromethane	36	34
193 (10)	Ti(O^{i}Pr)$_4$ (10)	dichloromethane	22	52
194 (10)	Ti(O^{i}Pr)$_4$ (10)	dichloromethane	4	66
195 (10)	Ti(O^{i}Pr)$_4$ (10)	dichloromethane	4	84
195 (10)[d]	Ti(O^{i}Pr)$_4$ (10)	dichloromethane	4	84
195 (12)	Ti(O^{i}Pr)$_4$ (10)	dichloromethane	3	86
195 (12)[b,f]	Ti(O^{i}Pr)$_4$ (10)	dichloromethane	4	85
195 (12)[b,c,e]	Ti(O^{i}Pr)$_4$ (10)	dichloromethane	4	89
196 (10)	Ti(O^{i}Pr)$_4$ (10)	dichloromethane	4	32

[a] Reactions were conducted at room temperature with 4 equiv of Me_3SiCN unless otherwise stated. [b] Reaction used 2 equiv of Me_3SiCN. [c] Reaction conducted at −20 °C. [d] Isolated complex of ligand **195** and Ti(O^{i}Pr)$_4$ was used. [e] 10 mol % Ph_3P=O was added. [f] 4 Å molecular sieves were used.



Pu *et al.* developed ligands **192**−**196** for the catalytic addition of alkynes to aldehydes.[140] Subsequently, these ligands were complexed *in situ* to titanium tetraisopropoxide or titanium tetrachloride and tested for the asymmetric trimethylsilylcyanation of benzaldehyde.[141] In order to find the ideal reaction conditions, titanium complexes of ligand **192**−**196** were studied using different catalyst loadings and solvents. Interestingly, decreasing the catalyst loading was shown to improve the enantioselectivity but resulted in a lower conversion, a result which is again consistent with *in situ* formation of bimetallic complexes.[117,133] Dichloromethane was found to be the optimal solvent, and the best

Table 62. Enantioselective Trimethylsilylation of Aldehydes Catalyzed by Ti(O^{i}Pr)$_4$−195

aldehyde	yield (%)	ee (%) (*R*)
PhCHO	78	85
4-MeOC$_6$H$_4$CHO	68	80
4-MeC$_6$H$_4$CHO	70	85
CH$_3$(CH$_2$)$_6$CHO	64	75

Scheme 32

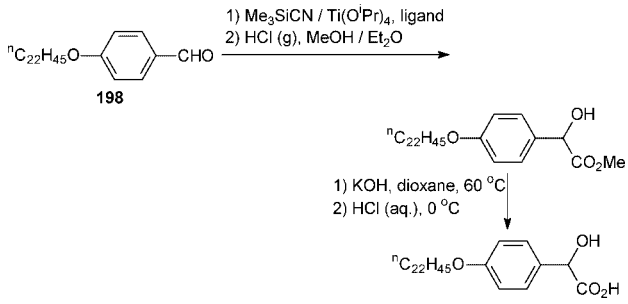
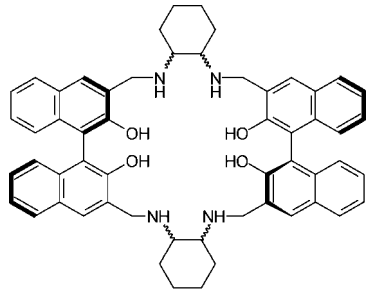


Table 63. Enantioselective Trimethylsilylation of 198 Catalyzed by Ti(O^{i}Pr)$_4$−DIPT or Ti(O^{i}Pr)$_4$−192

ligand (mol %)	solvent	Ti(O^{i}Pr)$_4$ (mol %)	ee (%)
(+)-DIPT (40)	dichloromethane	40	79 (*R*)
(−)-DIPT (40)	dichloromethane	40	77 (*S*)
(S)-**192** (10)	dichloromethane	8	84 (*R*)
(S)-**192** (10)	dichloromethane	10	54 (*R*)
(S)-**192** (10)	dichloromethane	12	14 (*R*)
(S)-**192** (10)	THF	10	39 (*R*)
(S)-**192** (10)	ether	10	3 (*R*)
(S)-**192** (10)	toluene	10	38 (*R*)
(R)-**192** (10)	dichloromethane	10	54 (*S*)
(R)-**192** (10)	dichloromethane	2	56 (*S*)



197

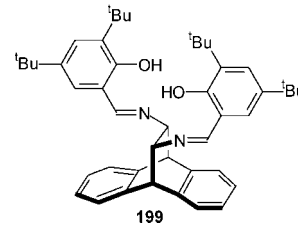
result was 89% asymmetric induction after a reaction time of 4 h, obtained using 12 mol % of ligand **195** with 10 mol % of titanium isopropoxide at −20 °C in dichloromethane (Table 61).

By treating ligand **195** with titanium tetraisopropoxide, the authors prepared a complex that was able to catalyze the reaction between two other aromatic aldehydes and trimethylsilyl cyanide in 64−70% yield and with 75−85% enantioselectivity. The best results were obtained with benzaldehyde and *p*-tolualdehyde (both gave enantioselectivities of 85%) (Table 62). The reaction was carried out at room temperature in dichloromethane for 4 h with a 10 mol % loading of the catalyst. The analogous catalyst derived from 1,2-diphenylethylenediamine (**196**−Ti(O^{i}Pr)$_4$) gave comparable results with benzaldehyde as substrate.

The titanium complex of BINOL Schiff base ligand **192** was also used in a separate study to develop a new system for chiral catalyst screening.[142] It was found that the *R* or *S* forms of the bisnaphthyl macrocycle **197** could be used as an enantioselective sensor for mandelic acid derivatives, which could be formed by the asymmetric cyanosilylation of aromatic aldehydes followed by treatment with anhydrous hydrogen chloride and hydrolysis to the carboxylic acid (Scheme 32). A number of aldehydes and their mandelic acid derivatives were screened on the basis of their solubility properties, and the most appropriate reagent for the experiments was benzaldehyde derivative **198** with a *para*-positioned 22-carbon alkyl chain ether. The authors used this substituted benzaldehyde derivative as a substrate for asymmetric cyanohydrin synthesis, followed by hydrolysis of the cyanohydrin to the corresponding mandelic acid. The enantiomeric excess of the mandelic acid was then determined by fluorescence measurements in the presence of macrocycle **197**. The titanium complexes of both DIPT (see section 2.2.1) and ligand **192** were used to test the system (Table 63), and the fluorescence results were roughly consistent with those from HPLC analysis (±12%). The best result (84% asymmetric induction) was obtained using 10 mol % of ligand **192** with 8 mol % of titanium tetraisopropoxide in dichloromethane at room temperature. The system was clearly quite sensitive to the conditions; changing the solvent or the loading of titanium by even a small amount resulted in much lower enantioselectivities.

Table 64. Enantioselective Trimethylsilylation of Aldehydes Catalyzed by Ti(O^{i}Pr)$_4$−199

aldehyde	yield (%)	ee (%) (*R*)
PhCHO	89	68
4-ClC$_6$H$_4$CHO	89	48
2-MeOC$_6$H$_4$CHO	97	61
4-MeOC$_6$H$_4$CHO	75	59
2-MeC$_6$H$_4$CHO	93	76
3-MeC$_6$H$_4$CHO	92	56
4-MeC$_6$H$_4$CHO	86	60
2-naphthaldehyde	97	56
PhCH$_2$CH$_2$CHO	91	55
thiophene-2-carboxaldehyde	88	61
furan-2-carboxaldehyde	76	53



199

Zhou *et al.* recently reported the use of the titanium tetraisopropoxide complex of C_2-symmetric Schiff base ligand **199**, based on an anthracene-derived diamine and di-*tert*-butylsalicylaldehyde, in the asymmetric cyanosilylation of aldehydes.[143] The optimal reaction conditions were achieved using 20 mol % of the catalyst at −20 °C in dichloromethane. A range of aldehydes were screened as substrates, and cyanohydrin products were obtained in 75−97% yield and with 48−76% enantiomeric excess (Table 64). Comparable enantioselectivities were obtained for both aromatic and aliphatic aldehydes. The best enantioselectivity was obtained from the trimethylsilylcyanation of *o*-chlorobenzaldehyde.

2.2.3.6. Immobilized C_2-Symmetric Salen Derived Catalysts. In view of the high catalytic activity shown by C_2-symmetric salen-based catalysts (especially complex **157**), there have been a number of efforts to polymerize or

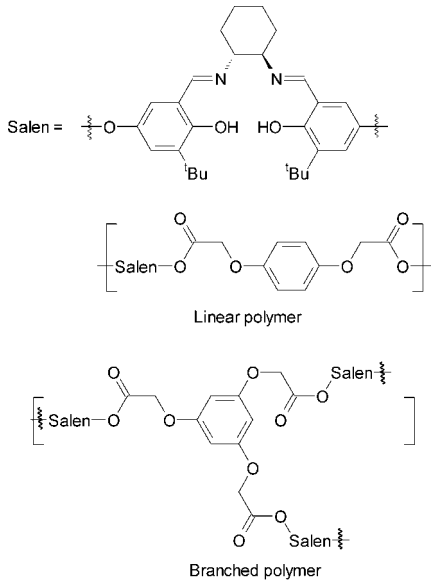


Figure 8.

Table 65. Asymmetric Cyanation of Benzaldehyde with KCN/Ac_2O Catalyzed by Complex 157 and the $Ti(O^iPr)_4$ Complexes of Polymers 200−204[a]

	20 °C		−20 °C	
catalyst[b]	conversion (%)	ee (%) (*S*)	conversion (%)	ee (%) (*S*)
157	90	74		88
200 (100:0)	72	62	58 (83)[c]	89 (89)[c]
201 (100:0.5)	83	78	91	89
201 (100:1)	88	78	89	88
201 (100:2)	92	78	85 (99)[c]	87 (87)[c]
201 (100:6)	95	75	84	85
201 (100:14)	86	63	79	81
201 (100:18)	87	59	60	77
201 (25:100)	92	56	60 (99)[c]	79 (79)[c]
201 (50:100)			39	70
202 (0:100)	35	44	13	55
203	77	47	52	68
204			68 (96)[c]	86 (83)[c]

[a] Reactions used benzaldehyde 1 mmol, potassium cyanide (4 equiv), acetic anhydride (4 equiv), in dichloromethane (5 mL) with *tert*-BuOH and water in the presence of 2 mol % ligand and 2 mol % $Ti(O^iPr)_4$ stirred for 4 h. [b] Bracketed figures indicate the ratio of linear to branched linked polymers. [c] Bracketed figures after 16 h reaction time.

Table 66. Asymmetric Cyanation of Benzaldehyde Catalyzed by $Ti(O^iPr)_4$−201

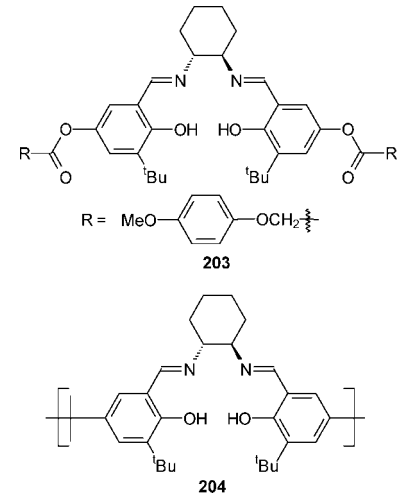
catalyst (mol %)	KCN (equiv)	solvent	temp (°C)	time (h)	conversion (%)	ee (%)
1	4	dichloromethane	−30	16	99	89
1	4	dichloromethane	−42	16	99	89
1	1.5	dichloromethane	−20	20	96	89
0.5	4	dichloromethane	−20	16	84	47
0.25	4	dichloromethane	−20	16	74	35
0.1	4	dichloromethane	−20	16	17	12
1	4	toluene	−20	27	14	61
1	4	ether	−20	4	8	43
1	4	THF	−20	4	31	18
1	4	hexane	−20	4	16	39

immobilize these complexes to enhance their recyclability. Zheng reported utilization of salen-based, covalently immobilized, cross-linked polymers for the addition of potassium cyanide and acetic anhydride to aldehydes.[144,145] The polymers were obtained in linear and branched forms (Figure 8, **200**−**202**), and the use of 1 mol % of the titanium tetraisopropoxide complexed polymer at −20 °C resulted in the formation of a range of silylated cyanohydrins with 55−89% enantioselectivity and in 13−99% conversion after a reaction time of 4−16 h (Table 65). The monomeric equivalent **203** and linear polymer **204** were also prepared for comparison.

Table 67. Asymmetric Cyanation of Aldehydes Catalyzed by $Ti(O^iPr)_4$−201 and 204[a]

		$Ti(O^iPr)_4$−**201**[b]		$Ti(O^iPr)_4$−**204**	
aldehyde	time (h)	conv (%)	ee (%) (*S*)	conv (%)	ee (%) (*R*)
PhCHO	16	100	89	79	64
2-MeC_6H_4CHO	16	99	88		
3-MeC_6H_4CHO	16	98	86		
4-MeC_6H_4CHO	16	95	89		
4-FC_6H_4CHO	16	99	91	89	63
4-ClC_6H_4CHO	16	99	85		
4-BrC_6H_4CHO	16	99	81		
4-$CF_3C_6H_4CHO$	4	99	70		
4-$MeOC_6H_4CHO$	40	57	87		
3-$PhOC_6H_4CHO$	16	98	84	80	48
$PhCH_2CH_2CHO$	16	99	83	90	41
CyCHO	16	97	81	87	41
Me_2CHCH_2CHO	20	62	86		
Me_2CHCHO	20	61	67		
furan-2-carboxaldehyde	16	99	66	81	27
thiophene-2-carboxaldehyde	16	62	78		
pyridine-2-carboxaldehyde	16	100	6.4		

[a] Reaction conditions as for Table 65 at −20 °C. [b] Used a 100:0.5 ratio of linear to branched polymer.



Scheme 33

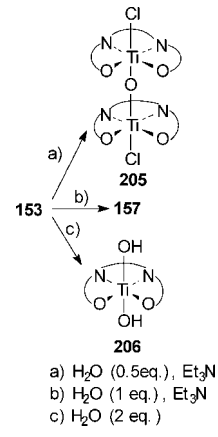


Table 68. Asymmetric Cyanosilylation of Aldehydes Induced by Homogeneous Catalysts 153, 157, 205, and 206[a]

aldehyde	catalyst	conversion (%)	ee (%) (*S*)
PhCHO	**153**	100	75
4-$MeOC_6H_4CHO$	**153**	100	58
2-ClC_6H_4CHO	**153**	100	69
PhCHO	**157**	100	86
PhCHO	**205**	100	72
PhCHO	**205**[b]	100	75
PhCHO	**206**	100	78

[a] Reaction time was 24 h using 10 mol % of catalyst at ambient temperature in dichloromethane. [b] Catalyst **205** was treated with 2 equiv of water.

Table 69. Asymmetric Cyanosilylation of Aldehydes Induced by Homogeneous Catalysts 153, 157, and 205[a]

aldehyde	catalyst	temp (°C)	conversion (%)	ee (%) (*S*)
PhCHO	**153**	−80	53	82
4-MeC_6H_4CHO	**153**	−80	48	65
2-ClC_6H_4CHO	**153**	−80	78	76
PhCHO	**157**	−80	44	93
PhCHO	**157**	0	72	89
PhCHO	**205**	−80	48	88
PhCHO	**205**	0	76	81

[a] Reaction time was 24 h using 10 mol % of catalyst in CH_2Cl_2.

The highest enantioselectivities were achieved at −20 °C using the titanium complexes of: polymer **201** (at the greatest ratios of linear/branched polymer) (85−89), **200** (89%), and **204** (86%). A range of conditions were also studied with the optimal method using 1 mol % of the titanium complex of ligand **201** (linear/branched 100:0.5) at −20 °C stirred for 20 h in dichloromethane using 1.5:1 potassium cyanide to benzaldehyde, which resulted in 96% conversion and 89% enantioselectivity. Using a lower catalyst loading or changing the solvent resulted in a significant loss of asymmetric induction (Table 66).

In every case, the reactions carried out using the titanium complex of ligand **201** gave better yields and enantioselectivities than the corresponding complex of ligand **204**. Enantioselectivities were generally good to very good across the whole range of aldehydes including both aromatic and aliphatic substrates. The best result was 91% asymmetric induction achieved using *p*-fluorobenzaldehyde as substrate, whilst the worst result was the heteroaromatic substrate pyridine-2-carboxaldehyde, which gave just 6.4% asymmetric induction. *iso*-Butyraldehyde and furan-2-carboxaldehyde gave moderate enantioselectivities of 67 and 66%, respectively (Table 67). Reusability of the titanium complex of **201** was also studied by conducting six consecutive runs, which resulted in a gradual decrease in activity, whereas enantioselectivity remained at approximately the same level. In conclusion, it was shown that a greater extent of branching of the polymer resulted in a better outcome compared with the case of linear polymers.

Another attempt to immobilize catalysts based around complex **157** was made by Kim's group, who synthesized modifications of the titanium catalyst linked covalently to the surface of mesoporous silica MCM-41 and standard silica gel.[146] Firstly, for comparison, the equivalent homogeneous systems were tested with the complexes prepared by the treatment of titanium dichloride complex **153** with different amounts of water and triethylamine to give complexes **157** and **205**−**206** (Scheme 33). All reactions involving complexes **153**, **157**, **205**, and **206** gave 100% conversion for

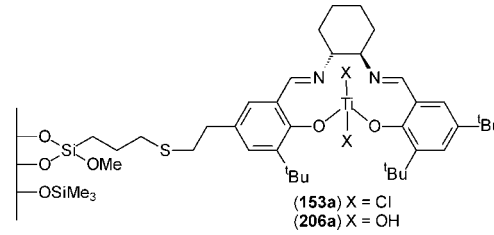
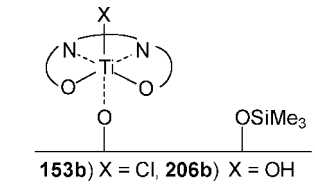
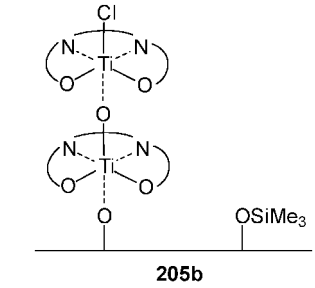


Figure 9.





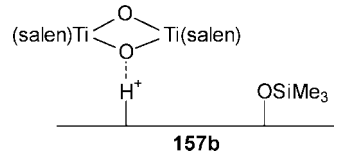


Figure 10. Titanium salen complexes bound to MCM-41 and Al-MCM-41 (via the direct anchoring method).

Table 70. Asymmetric Cyanosilylation of Benzaldehyde Induced by Heterogeneous Catalysts 153a,b, 157, 205a,b, and 206a,b[a]

catalyst	conversion (%)	ee (%) (*S*)
153a/MCM-41	23	87
153b/MCM-41	36	60
153/silica gel	34	52
205b/MCM-41	39	59
205/silica gel	31	48
157/MCM-41	38	43
206a/MCM-41	28	89
206b/MCM-41	40	64

[a] Reaction time was 24 h at ambient temperature in dichloromethane.

the asymmetric cyanosilylation of aromatic aldehydes after 24 h, though all of the modified catalysts gave lower enantioselectivities than complex **157** (Table 68). The effect of varying the temperature was also investigated for the complexes **153**, **157**, and **206**. It was found that reducing the temperature from +20 to 0 °C and again to −80 °C had a positive effect on the enantioselectivity, although the yields were adversely affected (Table 69).

The catalysts were immobilized onto MCM-41 (and Al-MCM-41 in the case of complex **157**) in two ways, the first of which involved formation of a covalent bond at the 5-position of the salen aromatic ring instead of a *tert*-butyl group to give complexes **153a** and **206a** (multigrafted method, Figure 9). The second set of complexes were anchored through the oxygen atoms linked to titanium, and the bridging oxygen for **157** to give complexes **153b**, **157b**,

Scheme 34

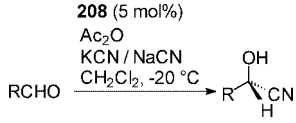


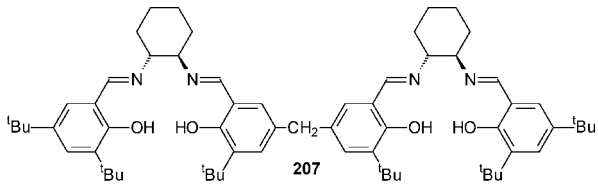
Table 71. Asymmetric Addition of Cyanide to Aldehydes Catalyzed by Complex 208[a]

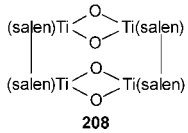
aldehyde	conversion (%) (KCN, NaCN)	ee (%) (*S*) (KCN, NaCN)
PhCHO	99, 99	92, 89
4-$MeOC_6H_4CHO$	91, 90	88, 87
3-$MeOC_6H_4CHO$	92, 91	89, 86
2-$MeOC_6H_4CHO$	90, 90	89, 85
4-ClC_6H_4CHO	99, 98	90, 89
4-BrC_6H_4CHO	99, 99	90, 88
4-FC_6H_4CHO	99, 98	91, 90
2-FC_6H_4CHO	99, 98	95, 91

[a] Reaction was carried out for 8−10 h at −20 °C in dichloromethane.

205b, and **206b** (Figure 10). The immobilized catalysts were used for the cyanosilylation of benzaldehyde to obtain mandelonitrile trimethylsilyl ether with 23−40% conversion and with 43−89% enantioselectivity (Table 70). The best enantioselectivity obtained was with catalyst **205a** (89%) although the yield was only 28% after a reaction time of 24 h. The reaction could be conducted at room temperature over a period of 24 h; however, the yields were generally poor for all systems with a maximum of 40% for catalyst system **205b**. Silica gel was also used as a support for comparison, although this offered no enhancement to enantioselectivity or yield.

The system of Belokon and North was also modified by Khan and co-workers, who prepared ligand **207** for the synthesis of a *bis*-dimeric titanium complex **208**. This complex was able to catalyze the reaction of aromatic aldehydes with KCN/NaCN and acetic anhydride to give the corresponding *O*-acetylated cyanohydrins in 90−99% yield and with enantioselectivities of 85−95%.[147] Catalyst **208** was prepared from ligand **207** and titanium tetraisopropoxide followed by treatment with 2 equiv of water to give the proposed dimeric species **208**. The cyanation reaction was carried out using 5 mol % of catalyst **208** at −20 °C for 8−10 h (Scheme 34). The catalyst was used for the asymmetric addition of both potassium and sodium cyanide to eight different aromatic aldehydes, giving high conversions (90−99%) and enantioselectivities of 85−95% (Table 71). Enantioselectivities were good for all tested aldehyde substrates, with the highest asymmetric induction obtained with benzaldehyde and potassium cyanide (92%). Using sodium cyanide gave marginally lower enantioselectivities but had little effect on the yield.





208

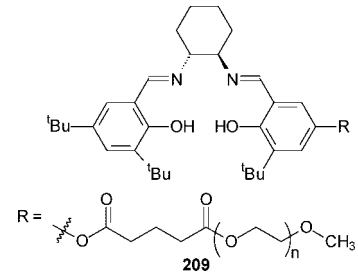
Table 72. Asymmetric Addition of Potassium Cyanide to Benzaldehyde Catalyzed by Complex 208[a]

catalyst loading (mol %)	solvent	temp (°C)	conversion (%)	ee (%) (*S*)
5	dichloromethane	−20	99	92
5	1,2-dichloroethane	−20	80	85
5	toluene	−20	40	70
5	tetrahydrofuran	−20	50	67
2	dichloromethane	−20	90	91
1	dichloromethane	−20	78	90
5	dichloromethane	−8	88	70
5	dichloromethane	ambient	89	60

[a] Reaction was carried out for 8−10 h.

Variation of the reaction conditions was also investigated; catalyst **208** showed a great preference for chlorinated solvents over hydrocarbon or higher polarity solvents. Both the yield and enantioselectivity were reduced significantly in toluene and tetrahydrofuran to 40−50% and 70−67%, respectively (Table 72). The effect of catalyst loading and temperature was also studied, and it was found that the optimal conditions involved use of 5 mol % of complex **208** at −20 °C. Reducing the loading to 1 mol % did not noticeably decrease the enantioselectivity, although the yield was reduced to 78%. Surprisingly, at ambient temperature, the yield was lower (89%) than that at −20 °C (99%) although the enantioselectivity was affected more greatly, being lowered to 60% at ambient temperature from 92% at −20 °C (Table 72). One of the advantages of this system is the opportunity to recover the complex after the reaction by adding hexane to the reaction mixture, which results in precipitation of complex **208**. The filtered catalyst could then be reused; this led to a gradual decrease in conversion (from 99% to 88% after four runs for benzaldehyde), but the enantioselectivity remained the same throughout the four runs.

Another investigation into the recyclability of systems based on catalyst **153** was reported by Venkataraman.[148] He and co-workers changed one of the *tert*-butyl groups in the *para*-positions of the salen ligand to polymeric fragments (polyethylene glycol) with relatively low molecular weight (∼5000 Da) to give ligand **209**. Treatment of ligand **209** with titanium tetrachloride gave a soluble complex that could be separated from the cyanosilylation products by Soxhlet dialysis techniques. The modified catalyst was able to catalyze trimethylsilyl cyanide addition to benzaldehyde up to 5 times without any loss in activity or enantioselectivity. The process was carried out using 0.1 mol % of the titanium complex of ligand **209** in dichloromethane at room temperature for 24 h, which gave mandelonitrile trimethylsilyl ether with >95% conversion and an enantioselectivity of 86%. The yield of regenerated catalyst after each run was 98−99%.



209

Table 73. Asymmetric Cyanosilylation of Nonanal Catalyzed by Complex 211

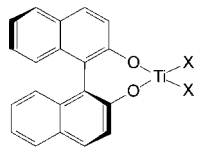
ligand (mol %)	solvent	time (h)	temp (°C)	yield (%)	ee (%) (*S*)
100	toluene	18	−30	72	78
100	toluene	24	0	80	32
100	dichloromethane	18	−30	71	64
20	toluene	96	ambient	43	0
20	dichloromethane	18	0	92	72
20	dichloromethane	16	ambient	98	63
20	propionitrile	16	0	93	23

Table 74. Asymmetric Cyanosilylation of Aldehydes Catalyzed by Complex 211

aldehyde	ee (*S*)
Me_3CCHO	75
$CH_3(CH_2)_7CHO$	72
Me_2CHCHO	34
CyCHO	33
CH_3CH_2CHO	<10
PhCHO	<10
4-$MeOC_6H_4CHO$	<10
4-ClC_6H_4CHO	<10

2.2.4. BINOL-Based Titanium Complexes

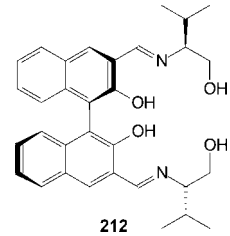
The pioneering work in the area of BINOL-derived titanium complexes in asymmetric cyanosilylation was published by Reetz in 1986.[149] It was found that, in the presence of 20 mol % of complex **210**, isobutanal could be converted into the corresponding silylated cyanohydrin in 85% chemical yield and with 82% enantiomeric excess when the reaction was carried out in toluene at −78 °C for 10 h. However, the absolute configuration of the product was not determined.



210) X = Cl
211) X = O^{i}Pr

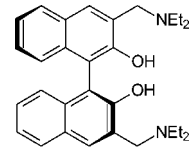
A similar catalytic system was developed by Nakai *et al.* Thus, the use of complex **211** for the asymmetric cyanosilylation of nonanal under a variety of conditions resulted in the formation of the cyanohydrin silyl ether with 0−78% enantioselectivity and in 43−98% yield.[150] The best result of 78% enantiomeric excess was obtained from a reaction in toluene at −30 °C for 18 h using 100 mol % of complex **211**. In contrast, using 20 mol % of the catalyst in toluene at ambient temperature produced only a 43% yield of the racemic cyanohydrin after 4 days reaction time (Table 73). It is notable that the catalytic version of this process was possible only above −30 °C, since at lower temperatures the reaction required a stoichiometric quantity of complex **211**. One of the peculiarities of the reaction was that aliphatic aldehydes gave high enantioselectivities, whilst aromatic substrates gave unsatisfactory results (less than 10% asymmetric induction), as shown in Table 74. In particular, pivaldehyde was a reasonably good substrate, giving the corresponding cyanohydrin with 75% enantiomeric excess.

Seebach modified the BINOL ligand system described previously by developing a polymer-immobilized analogue of complex **211** which could be easily separated from the reaction products.[151] By the use of 20 mol % of the supported catalyst, 72% enantioselectivity was achieved using pivaldehyde as substrate, which was comparable with the results of the homogeneous reaction. A remarkable feature of this system is that the enantioselectivity of the polymer supported catalyst actually increased to 83% when used over several runs. This suggests that the initial complex may be being slowly hydrolyzed to a more enantioselective catalyst.



212

The use of binuclear metal complexes in asymmetric catalysis has been attracting increasing attention.[152] Recently, Belokon and co-workers developed ligand **212** containing (*S*)-valinol moieties, which was obtained from (*R*)-BINOL in four steps. The complex formed by treatment of ligand **212** with 2 equiv of titanium tetraisopropoxide was tested in the cyanosilylation of benzaldehyde. The process was carried out with 20 mol % of the catalyst in dichloromethane at 6 °C for 4 h, which led to formation of mandelonitrile trimethylsilyl ether with 86% enantiomeric excess.[153] The diastereomeric complex derived from (*S*)-BINOL and (*S*)-valinol showed significantly inferior results (23−28% enantioselectivity), which indicated that the geometries of both chiral moieties were crucial for the asymmetric induction. It was also shown that the ligand to titanium ratio was an important factor in determining the enantioselectivity of the cyanosilylation of benzaldehyde; using a 1:2 ratio of ligand/titanium tetraisopropoxide resulted in the best recorded enantiomeric excess (86%), whereas using lower amounts of metal significantly reduced the enantioselectivity, to 15% in the case of a 1:1 ratio. This indicated that the active catalyst contains two titanium ions. The catalyst appears to have a preference for aromatic aldehydes, as the cyanosilylation of 2-chlorobenzaldehyde gave an enantioselectivity of 74% under the same reaction conditions. However, use of pivaldehyde as substrate gave only 27% enantioselectivity after a 7 h reaction time. Ketones were also shown not to be good substrates for the catalyst derived from ligand **212**, as acetophenone gave just 36% yield and 15% asymmetric induction after 24 h.



(*S*)-**213**

Ligand **213**, developed by Nájera and Saá, has been used to form aluminum complexes for various cyanation processes (see section 2.5.3). It was also possible to coordinate ligand **213** to titanium tetraisopropoxide, and the resulting complex catalyzed the cyanobenzoylation (Scheme 35) of aromatic, heteroaromatic, and aliphatic aldehydes in 76−93% yield and with 38−68% enantioselectivity (Table 75).[154] This work was the first example of catalytic asymmetric cyanobenzoy-

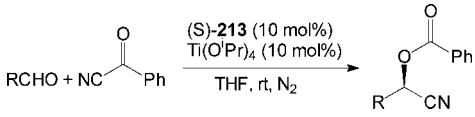
Table 75. Asymmetric Addition of Benzoyl Cyanide to Aldehydes Catalyzed by the Ti(O^{i}Pr)$_4$ Complex of Ligand 213

aldehyde	time (h)	yield (%)	ee (%) (*R*)
PhCHO	6	91	68
PhCHO[a]	6	90	68[c]
PhCHO[b]	6	90	68
4-MeOC$_6$H$_4$CHO	21	76	58
4-ClC$_6$H$_4$CHO	18	85	58
furan-2-carboxaldehyde	7	89	56[c]
pyridine-3-carboxaldehyde	22	93	38
(*E*)-CH$_3$(CH$_2$)$_4$CH=CHCHO	6	87	68
CyCHO	12	80	56
PhCH$_2$CH$_2$CHO	3	93	66

[a] (*R*)-BINOLAM−**213** was used. [b] Using recovered ligand **213**. [c] Cyanohydrin product had (*S*)-configuration.

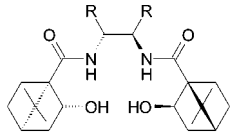
lation using benzoyl cyanide as the cyanide source. A simple workup enabled ligand **213** to be recovered after the reaction and the ligand could be recycled with consistent yield and enantioselectivity.

Scheme 35

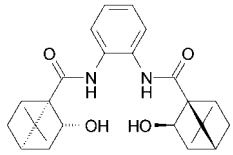


2.2.5. Complexes of Other C_2-Symmetric Ligands

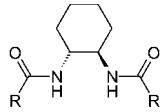
Uang's group developed a system based on complexes prepared by the treatment of C_2-symmetric camphor-based ligands **214**−**216** or cyclohexane-1,2-diamides **217**−**220** with titanium tetraisopropoxide.[155,156] The cyanosilylation reactions were carried out under a range of conditions, and the optimal system for benzaldehyde was found to work most efficiently when conducted in dichloromethane at −78 °C in the presence of 15 mol % of the catalyst and 4 Å molecular sieves. When screening other aldehydes using the titanium complex of ligand **214** (Scheme 36), it was noteworthy that excellent enantioselectivities were obtained for both aromatic and aliphatic substrates (Table 76).



214) R-R = $(CH_2)_4$
215) R = Ph



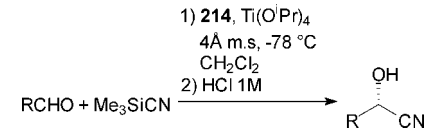
216



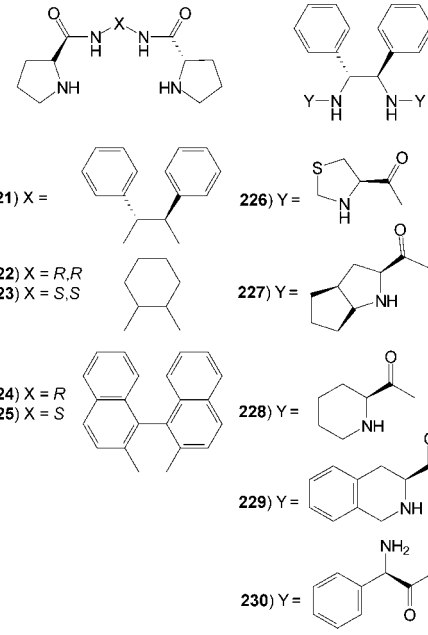
217) R = ^{t}Bu
218) R = Me
219) R = CF_3
220) R = CH(Ph)OH

Building on these results, the authors showed that enhancement in stereoselectivity could be achieved by using

Scheme 36



the modified ligand **215** but that the asymmetric induction was severely diminished when ligand **216** derived from an achiral diamine was used. Thus, the titanium complex derived from ligand **215** afforded the same range of cyanohydrin silyl ethers in 72−92% yield (after 48−120 h reaction times) and with 93−99% enantiomeric excess (Table 77).[155,156] Ligands **217**−**220** lacking the camphor group were also synthesized and showed that the geometries of both chiral moieties were responsible for the enantioselectivity (Table 77).[157] The same effect is illustrated in Table 76 by comparing the result obtained with ligand **214** derived from (*R*,*R*)-cyclohexane diamine (94% asymmetric induction) with that of the corresponding ligand derived from (*S*,*S*)-cyclohexane diamine (4% asymmetric induction).



Feng used the titanium tetraisopropoxide complexes of ligands **221**−**230** for the asymmetric cyanosilylation of aldehydes.[158] Using benzaldehyde as substrate, the best result was obtained using 10 mol % of ligand **229** with 20 mol % of titanium isopropoxide, which gave the cyanohydrin product in 98% yield and with 84% enantiomeric excess (Table 78). A further enhancement to the enantioselectivity was observed on the addition of 7.5 mol % of *p*-nitrobenzoic acid, which raised the enantioselectivity when using benzaldehyde as substrate to 88%. A range of aromatic and aliphatic aldehydes were then screened using the optimized conditions (Table 79). The highest enantioselectivities were obtained for electron rich aromatic aldehydes.

Belda, Moberg, and co-workers developed *bis*-pyridylamide ligand **231**, which was tested in the asymmetric cyanosilylation of benzaldehyde after complexation to titanium tetraisopropoxide.[159] Reactions were carried out under a variety of conditions, changing catalyst loading, solvent, and reagent concentrations. The optimized conditions involved the use of 1−2.5 mol % of the complex at room

Table 76. Asymmetric Cyanosilylation of Aldehydes Catalyzed by (*R*,*R*)-214−Ti(O^{i}Pr)$_4$

ligand (mol %)	aldehyde	Ti(O^{i}Pr)$_4$ (mol %)	temp (°C)	time (h)	yield (%)	ee (%) (*S*)
214 (22)[a]	PhCHO	20	0	10	78	20
214 (22)[a]	PhCHO	20	−30	24	0	
214 (11)	PhCHO	10	+30	6	78	48
214 (11)	PhCHO	10	−30	24	74	55
214 (22)	PhCHO	20	−30	18	75	71
214 (16.5)	PhCHO	15	−78	48	79	94
214 (16.5)[c]	PhCHO	15	−78	48	77	4[b]
214 (16.5)	3-PhOC$_6$H$_4$CHO	15	−78	120	57	97
214 (16.5)	4-MeOC$_6$H$_4$CHO	15	−78	120	53	97
214 (16.5)	2-naphthaldehyde	15	−78	120	76	96
214 (16.5)	PhCH=CHCHO	15	−78	120	51	95
214 (16.5)	PhCH$_2$CH$_2$CHO	15	−78	120	62	98
214 (16.5)	2-MeC$_6$H$_4$CHO	15	−78	120	68	97
214 (16.5)	CyCHO	15	−78	60	94	87
214 (16.5)	CH$_3$(CH$_2$)$_3$CHO	15	−78	36	96	89

[a] Molecular sieves not used. [b] Product was 4% (*R*)-configuration. [c] **214** derived from (*S*,*S*)-cyclohexanediamine was used.

Table 77. Asymmetric Cyanosilylation of Aldehydes Catalyzed by (*R*,*R*)-215−220−Ti(O^{i}Pr)$_4$[a]

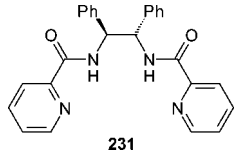
ligand	aldehyde	time (h)	yield (%)	ee (%) (*S*)
215	PhCHO	48	87	93
215	3-PhOC$_6$H$_4$CHO	120	54	95
215	4-MeOC$_6$H$_4$CHO	120	47	99
215	2-naphthaldehyde	120	67	99
215	PhCH=CHCHO	120	49	97
215	PhCH$_2$CH$_2$CHO	120	61	97
215	2-MeC$_6$H$_4$CHO	120	56	94
215	CyCHO	48	90	>99
215	CH$_3$(CH$_2$)$_3$CHO	36	92	97
216	PhCHO	60	89	61
217[c]	PhCHO	36	70	0[b]
218[c]	PhCHO	36	61	0[b]
219[c]	PhCHO	36	72	0[b]
220	PhCHO	24	76	13[b]
220[d]	PhCHO	24	73	4[b]

[a] Reactions performed in dichloromethane at −70 °C unless otherwise stated. [b] Reaction carried out at −30 °C. [c] 33 mol % ligand was used. [d] Catalyzed by ligand **220** using (*S*)-CH(Ph)OH.

Table 78. Enantioselective Trimethylsilylation of Benzaldehyde Catalyzed by Ti(O^{i}Pr)$_4$−221−230[a]

ligand	yield (%)	ee (%)
221	86	55
222	51	35
223	61	36
224	49	18
225	61	21
226	94	64
227	63	25
228	76	16
229	93	76
229[b]	98	84
230	95	27

[a] The reactions were carried out in dichloromethane for 14 h at 0 °C using 10 mol % of ligand and Ti(O^{i}Pr)$_4$. [b] 20 mol % Ti(O^{i}Pr)$_4$ used.



231

temperature for 5 h in dichloromethane. The best results came from using benzaldehyde with 1 or 2.5 mol % of both titanium tetraisopropoxide and ligand **231**, which gave *O*-trimethylsilyl mandelonitrile in over 95% yield and with 70% enantiomeric excess. It was shown that the enantioselectivity increased as the reaction progressed, with the maximum enantioselectivities reached after 3−5 h. The use of other aldehydes resulted in inferior enantioselectivity (11−47%) and in some cases required considerably longer reaction times (5−66 h) to reach >95% conversion (Table 80). Application of this system to acetophenone gave product with only 8% enantiomeric excess after a reaction time of

Table 79. Enantioselective Trimethylsilylation of Aldehydes Catalyzed by Ti(O^{i}Pr)$_4$−229[a]

aldehyde	yield (%)	ee (%) (*S*)
PhCHO	98	88
4-MeC$_6$H$_4$CHO	94	80
3-MeC$_6$H$_4$CHO	90	82
4-MeOC$_6$H$_4$CHO	96	85
3-MeOC$_6$H$_4$CHO	91	81
3-PhOC$_6$H$_4$CHO	73	76
4-FC$_6$H$_4$CHO	90	92
3-ClC$_6$H$_4$CHO	91	76
4-ClC$_6$H$_4$CHO	88	81
2-naphthaldehyde	82	84
furan-2-carboxaldehyde	86	84
PhCH=CHCHO	93	85
(*E*)-MeCH=CHCHO	49	74

[a] The reactions were carried out in dichloromethane for 17 h at 0 °C using 10 mol % of ligand and 15 mol % of Ti(O^{i}Pr)$_4$.

Table 80. Asymmetric Cyanosilylation of Carbonyl Compounds Catalyzed by 231−Ti(O^{i}Pr)$_4$[a]

aldehyde	time (h)	ee (%) (*S*)
PhCHO	6	70
4-MeOC$_6$H$_4$CHO	16	47
4-F$_3$CC$_6$H$_4$CHO	66	11
2-BrC$_6$H$_4$CHO	25	24
CH$_3$(CH$_2$)$_3$CHO	5	41
Me$_3$CCHO	5	12
PhCOMe	119	8

[a] Reactions performed in dichloromethane at ambient temperature using 1 mol % of ligand **231** and Ti(O^{i}Pr)$_4$. All yields were ≥95%.

Scheme 37

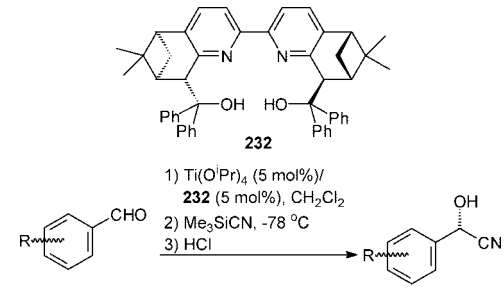


Table 81. Asymmetric Cyanosilylation of Benzaldehydes Catalyzed by 232−Ti(O^{i}Pr)$_4$

aldehyde	yield (%)	ee (%) (*S*)
PhCHO	86	59
2-MeOC$_6$H$_4$CHO	45	39
3-MeOC$_6$H$_4$CHO	53	57
4-MeOC$_6$H$_4$CHO	83	71
2-MeC$_6$H$_4$CHO	80	98
3-MeC$_6$H$_4$CHO	45	69
4-MeC$_6$H$_4$CHO	88	70
2-ClC$_6$H$_4$CHO	84	3
3-ClC$_6$H$_4$CHO	35	15
4-ClC$_6$H$_4$CHO	11	9
3-NCC$_6$H$_4$CHO	54	8
4-NCC$_6$H$_4$CHO	62	2

Scheme 38

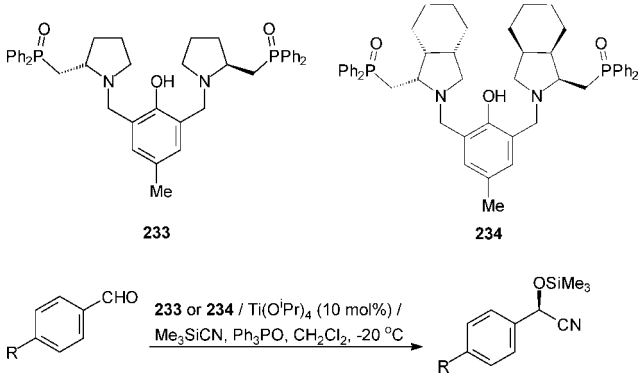


Table 82. Asymmetric Cyanosilylation of Aldehydes Catalyzed by (233−234)−Ti(O^{i}Pr)$_4$

ligand−Ti(O^{i}Pr)$_4$	aldehyde	yield (%)	ee (%) (*R*)
233	PhCHO	82	87
234	PhCHO	74	93
233	4-MeC$_6$H$_4$CHO	79	91
234	4-MeC$_6$H$_4$CHO	74	95
233	4-MeOC$_6$H$_4$CHO	65	81
233	4-BrC$_6$H$_4$CHO	63	72
233	4-NCC$_6$H$_4$CHO	60	70

Table 83. Asymmetric Cyanosilylation of Benzaldehyde Catalyzed by (235−243)−Ti(O^{i}Pr)$_4$[a]

ligand−Ti(O^{i}Pr)$_4$	yield (%)	ee (%) (*R*)
235	90	38
236	91	39
237	86	63
237[b]	10	36
237[c]	17	43
238	64	37
239	80	36
240	84	36
241	86	44
242	76	36
243	83	63

[a] Reactions were carried out using 5 mol % catalyst at −20 °C in dichloromethane for 36 h. [b] Used 1:2 ratio of **237**/Ti(O^{i}Pr)$_4$. [c] Used 1.25:1 ratio of **237**/Ti(O^{i}Pr)$_4$.

119 h. The authors found that mixing just the ligand and titanium tetraisopropoxide did not lead to any complex formation, and evidence from NMR studies showed that trimethylsilyl cyanide addition was necessary for the formation of the catalytically active species. In addition to titanium tetraisopropoxide, metal alkoxides of zirconium, ytterbium, scandium, and copper were tested for the asymmetric cyanation of benzaldehyde; however, these all gave inferior levels of asymmetric induction.

Table 84. Asymmetric Cyanosilylation of Aldehydes Catalyzed by 237−Ti(O^{i}Pr)$_4$[a]

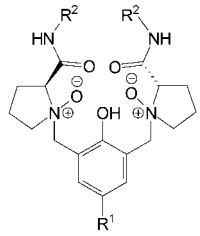
aldehyde	yield (%)	ee (%) (*R*)
PhCHO	88	86
4-MeC$_6$H$_4$CHO	86	84
2-MeC$_6$H$_4$CHO	92	86
4-MeOC$_6$H$_4$CHO	83	82
3-MeOC$_6$H$_4$CHO	93	80
2-MeOC$_6$H$_4$CHO	91	86
3-PhOC$_6$H$_4$CHO	92	88
4-FC$_6$H$_4$CHO	88	83
2-naphthaldehyde	82	90
PhCH=CHCHO	83	62
CyCHO	81	68

[a] Reactions were carried out using 10 mol % catalyst at −45 °C in dichloromethane for 48 h in the presence of 4 Å molecular sieves.

Chen's group developed ligand **232** derived from (+)-α-pinene and successfully applied it in asymmetric diethylzinc additions to aldehydes.[160] Based on these results, the authors used the titanium isopropoxide complex of ligand **232** in asymmetric cyanosilylation reactions.[161] The complex was tested for the asymmetric cyanation of a range of substituted benzaldehydes under optimized conditions involving the use of dichloromethane as solvent at −78 °C, with 5 mol % of the catalyst for 40 h (Scheme 37). This led to the isolation of a range of mandelonitriles in 35−88% yield and with 2−98% enantiomeric excess (Table 81). A significant influence of electronic effects due to substituents within the aldehyde on the enantioselectivity was observed; the best results were obtained for electron rich substrates, with *o*-tolualdehyde giving 2-methylmandelonitrile with 98% enantiomeric excess.

Kim's group synthesized the bifunctional ligands **233** and **234**, which were found to be precursors of enantioselective titanium complexes for the cyanosilylation of aldehydes.[162] By utilizing the titanium isopropoxide complex of ligand **233**, the authors converted benzaldehyde into mandelonitrile *O*-trimethylsilyl ether in 82% yield and with 87% enantiomeric excess after a reaction time of 24 h. The optimal conditions involved the use of 10 mol % of the titanium−ligand complex with triphenylphosphine oxide as cocatalyst in dichloromethane at −20 °C. It was necessary to add 2 equiv of the cocatalyst for the best results; use of lower amounts, or other additives such as molecular sieves or isopropanol, resulted in inferior enantioselectivities. Under the same conditions with benzaldehyde as substrate, modified ligand **234** demonstrated somewhat greater enantioselectivity (93%) and gave a 74% chemical yield of the cyanohydrin product. To explore the scope of the reaction, ligands **233** and **234** were screened on a range of *para*-substituted benzaldehydes under the conditions shown in Scheme 38, to produce cyanohydrin trimethylsilyl ethers in 70−91% yield and with enantioselectivities of 60−82%. The best results were obtained with electron rich aldehydes (Table 82). Ligand **233** was also complexed to titanium tetrachloride, which gave a marginally reduced 80% enantioselectivity in the asymmetric cyanosilylation of benzaldehyde. Aluminum and magnesium ions were also used as Lewis acids complexed to ligand **233** and gave respectable enantioselectivities (70% and 53%, respectively) but were less effective than the titanium complexes.

Feng investigated the use of *N,N′*-dioxide containing



235) R^1 = Me, R^2 = Cy
236) R^1 = Me, R^2 = *o*-Tolyl
237) R^1 = Me, R^2 = 2-*tert*-butylphenyl
238) R^1 = Me, R^2 = 2,6-diisopropylphenyl
239) R^1 = Me, R^2 = 1-Adamantyl
240) R^1 = Me, R^2 = Diphenylmethyl
241) R^1 = ^{t}Bu, R^2 = 2-*tert*-butylphenyl
242) R^1 = Cl, R^2 = 2-*tert*-butylphenyl
243) Enantiomer of **237**

ligands **235**−**243** for the addition of ethyl cyanoformate to aldehydes.[163] It was found that the nature of the group attached to the prolinamide moiety was an important factor influencing the enantioselectivity of the reaction. Using 5 mol % of the appropriate ligand/titanium tetraisopropoxide complex to catalyze the addition of ethyl cyanoformate to benzaldehyde at −20 °C, mandelonitrile ethyl carbonate was obtained with 27−63% enantiomeric excess. The best result (63% asymmetric induction) was obtained by the use of ligand **237** (Table 83). The ligand equivalent to **237** but with a neutral nitrogen (i.e. with no *N*-oxide) gave a much lower enantioselectivity of just 27%. Conducting the reactions at −45 °C increased the enantioselectivity to 86%, although 10 mol % of the catalyst was required. Further increasing the catalyst loading did not result in higher asymmetric induction. Lowering the temperature further gave no further advantage. Toluene and ether were also used as reaction solvents but were shown to give lower enantioselectivities than dichloromethane.

A number of aromatic aldehydes along with cinnamaldehyde and cyclohexanecarboxaldehyde were used under the optimized conditions as substrates for the addition of ethyl cyanoformate using the catalyst obtained from titanium tetraisopropoxide and ligand **237**. 2-Naphthaldehyde gave the best enantioselectivity of 90%, and it appeared that aromatic aldehydes were better substrates than aliphatic ones, since enantioselectivities of just 62% and 68%, respectively, were obtained from cinnamaldehyde and cyclohexanecarboxaldehyde (Table 84). Yields for all substrates were good (81−92%).

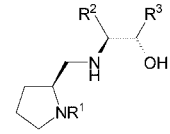
2.2.6. Complexes of Ligands Based on Amino Acids, β-Amino Alcohols, and Derivatives

In the same paper which discussed the use of ligands **233** and **234**, Kim and co-workers also reported the use of ligands **244**−**248** derived from (*S*)-proline.[162] The complexes formed by treatment of the ligands with titanium tetraisopropoxide could be used as catalysts for the asymmetric addition of trimethylsilyl cyanide to benzaldehyde, giving mandelonitrile trimethylsilyl ether in 54−80% yield and with 34−84% enantioselectivity. The best results (80% yield and 84% enantiomeric excess) were obtained using ligand **248**, though very similar results (78% yield, 80% enantiomeric excess) were achieved with ligand **247**. Ligands **244**−**246** gave lower levels of asymmetric induction, which was presumed to be due to the lower rigidity of the ligands (Table 85). Conducting the reaction in dichloromethane at −20 °C for 24−36 h

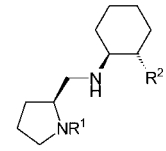
Table 85. Asymmetric Cyanosilylation of Benzaldehyde Catalyzed by (244−248)−Ti(O^{i}Pr)$_4$[a]

ligand	solvent	time (h)	temp (°C)	yield (%)	ee (%)[b]
244	dichloromethane	24	−20	76	34
245	dichloromethane	24	−20	70	67
246	dichloromethane	24	−20	68	57
246	dichloromethane	24	−10	72	48
247	dichloromethane	24	−20	78	80
247	dichloromethane	24	−10	80	71
247	toluene	36	−20	54	71
248	dichloromethane	24	−20	80	84
248	toluene	36	−20	65	68

[a] All reactions used 2 equiv of Me_3SiCN and 2 equiv of triphenylphosphine oxide. [b] Absolute configuration is *S*.

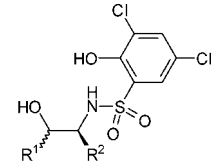


244) R^1 = H, R^2 = CPh_2OH, R^3 = H
245) R^1 = H, R^2 = Ph, R^3 = Ph
246) R^1 = Me, R^2 = Ph, R^3 = Ph



247) R^1 = H, R^2 = OH
248) R^1 = Me, R^2 = PPh_2

gave the optimum conditions, and it was necessary to use 10 mol % of the catalyst with 2 equiv of trimethylsilyl cyanide and triphenylphosphine oxide.



249) R^1 = Ph, R^2 = CH_2Ph
250) R^1 = Ph, R^2 = Ph
251) R^1 = ^{t}Bu, R^2 = CH_2Ph

Choi and co-workers developed *N*-sulfonated derivatives of *β*-amino alcohols in the form of ligands **249**−**251**, which were successfully utilized in the trimethylsilylcyanation of aldehydes.[164] The titanium complex generated from (*R,S*)-**249** and titanium tetraisopropoxide produced a range of silylated cyanohydrins in 90−100% yield and with high enantioselectivity (77−96%) when used with 4 Å molecular sieves. It is notable that excellent levels of enantioselectivity were obtained for both aromatic and aliphatic substrates. The best results achieved were with benzaldehyde and 2-naphthaldehyde at −65 °C, both of which gave cyanohydrin derivatives with 96% enantiomeric excess (Table 86).

Feng's group described the use of reduced Oguni ligands (see section 2.2.2) in the cyanosilylation of aldehydes.[165] Initially, they reported the use of ligand **252** complexed to three aluminum sources: $AlEt_3$, $AlEt_2Cl$, and Al(O^{i}Pr)$_3$, all of which catalyzed the addition of trimethylsilyl cyanide to benzaldehyde in dichloromethane at −20 °C (using 10 mol % catalyst) but gave poor enantioselectivities, with the highest being only 19% in favor of the *R*-enantiomer after a reaction time of 42 h. However, using the same ligand with

Table 86. Enantioselective Addition of Trimethylsilyl Cyanide to Aldehydes Catalyzed by *in Situ*-Formed (249−251)−Ti(O^{i}Pr)$_4$ Complexes[a]

ligand	aldehyde	yield (%)	ee (%) (configuration)
(*R*,*S*)-**249**[b]	PhCHO	100	68 (*R*)
(*R*,*S*)-**249**[c]	PhCHO	100	79 (*R*)
(*R*,*S*)-**249**	PhCHO	100	96 (*R*)
(*R*,*S*)-**249**[d]	PhCHO	52	77 (*R*)
(*R*,*S*)-**249**	PhCHO	90	94 (*R*)
(*R*,*S*)-**250**	PhCHO	82	62 (*R*)
(*R*,*S*)-**251**	PhCHO	85	38 (*R*)
(*S*,*S*)-**249**	PhCHO	51	8 (*S*)
(*R*,*S*)-**249**	4-ClC$_6$H$_4$CHO	93	90 (*R*)
(*R*,*S*)-**249**	4-MeOC$_6$H$_4$CHO	100	94 (*R*)
(*R*,*S*)-**249**	2-MeOC$_6$H$_4$CHO	100	86 (*R*)
(*R*,*S*)-**249**	2-naphthaldehdye	95	96 (*R*)
(*R*,*S*)-**249**	1-naphthaldehyde	100	77 (*R*)
(*R*,*S*)-**249**	PhCH=CHCHO	100	93 (*R*)
(*R*,*S*)-**249**	Me$_2$CHCHO	100	95 (*R*)

[a] 10 mol % ligand used in dichloromethane at −65 °C with powdered 4 Å molecular sieves, for 48 h. [b] Reaction at 0 °C. [c] Reaction at −40 °C. [d] No molecular sieves used.

Table 87. Asymmetric Cyanosilylation of Benzaldehyde Catalyzed by Ti(O^{i}Pr)$_4$ Complexes of Amino Alcohol-Based Ligands 252−264[a]

ligand	solvent	yield (%)	ee (%) (configuration)
252	dichloromethane	94	85 (*S*)
253	dichloromethane	99	76 (*S*)
254	dichloromethane	23	3 (*R*)
255	dichloromethane	88	69 (*S*)
256	dichloromethane	26	68 (*S*)
257	dichloromethane	47	61 (*S*)
258	dichloromethane	62	66 (*S*)
259	dichloromethane	28	4 (*R*)
260	dichloromethane	none detected	
261	dichloromethane	none detected	
262	dichloromethane	98	12 (*S*)
263	dichloromethane	99	10 (*R*)
264	dichloromethane	96	6 (*R*)
252	chloroform	95	72 (*S*)
252	diethyl ether	76	77 (*S*)
252	THF	28	83 (*S*)
252	toluene	83	64 (*S*)
252[b]	dichloromethane	99	92 (*S*)
252[c]	dichloromethane	99	81 (*S*)
252[d]	dichloromethane	98	90 (*S*)
252[e]	dichloromethane	64	87 (*S*)

[a] Using 10 mol % of catalyst at −20 °C with 0.2 M concentration of benzaldehyde unless otherwise stated. [b] 0.5 M benzaldehyde. [c] 1.0 M benzaldehyde. [d] Reaction at 0 °C with 0.5 M benzaldehyde. [e] Reaction at −40 °C with 0.5 M benzaldehyde.

Table 88. Effect of Varying the Amount of Catalyst 252−Ti(O^{i}Pr)$_4$

catalyst loading (mol %)	time (h)	yield (%)	ee (%) (configuration)
20	20	94	88 (*S*)
10	22	99	92 (*S*)
5	20	98	94 (*S*)
1	44	33	80 (*S*)

titanium tetraisopropoxide gave mandelonitrile trimethylsilyl ether in 94% yield after a reaction time of only 23 h with an enantiomeric excess of 85% in favor of the *S*-enantiomer. Following this lead, the titanium complexes of a range of substituted ligands **253**−**264** were screened in the same reaction (Table 87).

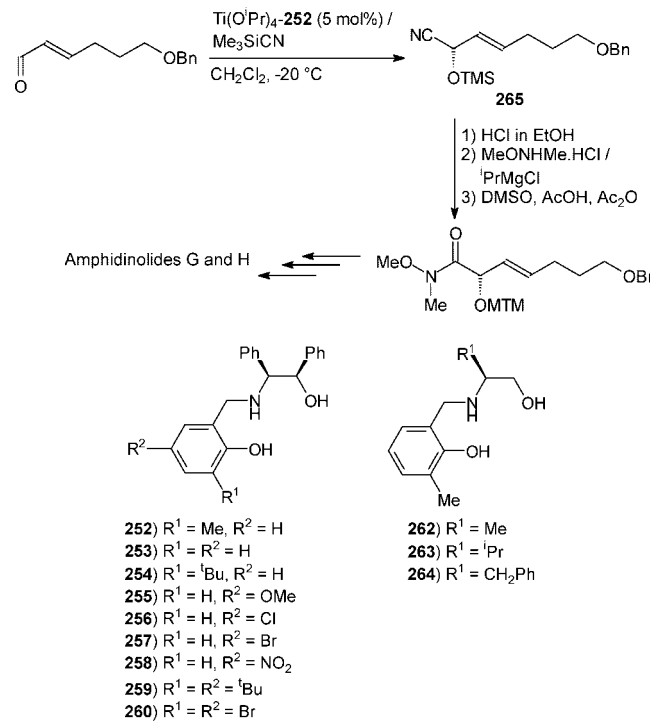
Ligand **252** was found to give the best results in terms of enantioselectivity (85%), combined with a yield of 94%, with

Table 89. Asymmetric Cyanosilylation of Aldehydes Catalyzed by 252−Ti(O^{i}Pr)$_4$[a]

aldehyde	time (h)	yield (%)	ee (%)[b]
PhCHO	22	99	94
3-MeC$_6$H$_4$CHO	15	90	93
4-MeC$_6$H$_4$CHO	16	99	88
4-MeOC$_6$H$_4$CHO	14	98	93
3-MeOC$_6$H$_4$CHO	16	99	90
4-FC$_6$H$_4$CHO	14	94	92
2-ClC$_6$H$_4$CHO	15	99	76
3-ClC$_6$H$_4$CHO	20	98	90
4-ClC$_6$H$_4$CHO	15	98	87
2-NCC$_6$H$_4$CHO	20	93	80
1-naphthaldehdye	16	99	82
2-naphthaldehyde	20	98	75
furan-2-carboxaldehyde	16	98	89
(*E*)-MeCH=CHCHO	16	99	82
CH$_3$(CH$_2$)$_3$CHO	16	99	57
PhCH$_2$CHO	14	98	72
Me$_2$CHCHO	16	99	60

[a] All reactions carried out with 5 mol % catalyst with 2.0 equiv of trimethylsilyl cyanide at 0.5 M concentration in dichloromethane at −20 °C. [b] Cyanohydrin products all have *S* absolute configuration except for the product derived from furan-2-carboxaldehyde.

Scheme 39

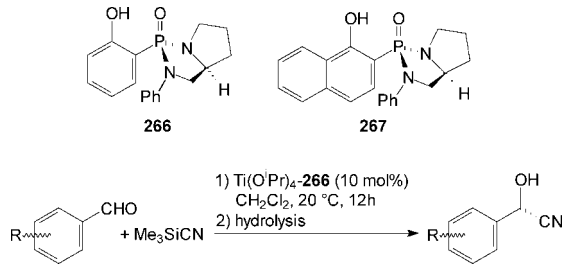


the latter bettered only by ligand **253** (99%). The influence of the solvent was also investigated, though all those tested gave inferior results to the use of dichloromethane, although THF gave a similar enantioselectivity. Reducing the concentration of benzaldehyde to 0.5 M increased the enantiomeric excess to 92%; however, higher and lower temperatures were shown to adversely affect the enantioselectivity. Further work was carried out to optimize the reaction conditions (Table 88), and it was shown that employing 5 mol % of the catalyst formed *in situ* from ligand **252** and titanium tetraisopropoxide for the addition of trimethylsilyl cyanide to benzaldehyde gave the silylated cyanohydrin product in 98% yield and with 94% enantiomeric excess after a reaction time of 20 h. Using these optimized conditions, a range of aromatic aldehydes and five aliphatic substrates were tested as substrates (Table 89). The substituted benzalde-

Table 90. Asymmetric Cyanosilylation of Aldehydes Catalyzed by the Complex Derived from a 1:4 Ratio of Ti(O^{i}Pr)$_4$ and Ligand 266

aldehyde	yield (%)	ee (%) (*S*)
PhCHO	95	94
3,4,5-(MeO)$_3$C$_6$H$_2$CHO	85	33
2-(PhCH$_2$O)C$_6$H$_4$CHO	75	42
1-naphthaldehyde	92	90
4-MeOC$_6$H$_4$CHO	86	98
furan-2-carboxaldehyde	79	3
3-F$_3$CC$_6$H$_4$CHO	70	15

Scheme 40



hydes, in general, gave slightly better enantioselectivities (76−94%) although all the tested aldehydes gave consistently high yields (90−99%).

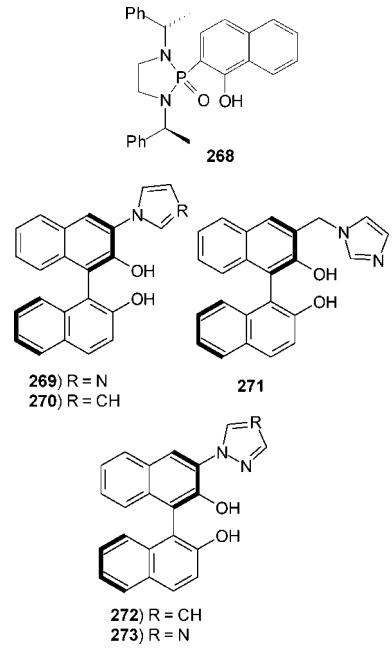
The titanium tetraisopropoxide complex of ligand **252** has also been used in a natural product synthesis by Crews *et al.* to create part of the macrocycles Amphidinolide G and H.[166] The complex was used to prepare the fragment containing carbons 3−9 as shown in Scheme 39. The key cyanohydrin derivative **265** was obtained in 75% yield and with 80% enantiomeric excess, with the latter determined by the Mosher ester method after conversion of cyanohydrin **265** into the corresponding α-hydroxy ethyl ester.

2.2.7. Bifunctional Catalysts

An important development in catalytic trimethylsilylcyanation was the discovery of bifunctional ligands, combining both Lewis acid and Lewis base properties. The first examples of such systems were reported in 1999 by Buono and Shibasaki (see section 2.5.3), who initiated extensive studies resulting in the development of a wide range of bifunctional catalysts. Thus, Buono and co-workers synthesized ligand **266**, the titanium complex of which was able to catalyze the addition of trimethylsilyl cyanide to a range of aromatic aldehydes in 70−95% yield and with 3−98% enantioselectivity (Scheme 40). It was shown that the best enantioselectivities were achieved with the catalyst obtained by using a 1:4 ratio of titanium to ligand **266** in the presence of 2 equiv of isopropanol.[167] Excellent enantioselectivities were achieved using *p*-methoxybenzaldehyde, benzaldehyde, and 1-naphthaldehyde, with somewhat lower asymmetric induction obtained for the other substrates (Table 90). Use of the diastereomer of ligand **266** with *R*-configuration at phosphorous with benzaldehyde as substrate resulted in the formation of (*R*)-mandelonitrile with 98% enantiomeric excess, thus showing that the configuration of this stereocenter within ligand **266** was principally responsible for the asymmetric induction. The titanium tetraisopropoxide complex of naphthol derived ligand **267** also gave high enantioselectivities for the asymmetric cyanosilylation of benzaldehyde, with 93% asymmetric induction obtained under the conditions shown in Scheme 40.

Table 91. Asymmetric Cyanosilylation of Aldehydes Catalyzed by the Ti(O^{i}Pr)$_4$ Complex of Ligand 268

aldehyde	ligand **268** (mol %)	Ti(O^{i}Pr)$_4$ (mol %)	temp (°C)	yield (%)	ee (%) (*R*)
PhCHO	20	10	0	90	38
PhCHO	40	10	0	98	43
PhCHO	40	20	0	90	41
PhCHO	40	40	0	98	35
2-MeOC$_6$H$_4$CHO	40	10	0	92	90
2-MeOC$_6$H$_4$CHO	40	10	20	86	73
4-MeOC$_6$H$_4$CHO	40	10	0	92	50
2-MeC$_6$H$_4$CHO	40	10	0	80	72
4-MeC$_6$H$_4$CHO	40	10	0	95	41
4-ClC$_6$H$_4$CHO	40	10	10	96	15
2-O$_2$NC$_6$H$_4$CHO	40	10	10	96	8
2-naphthaldehyde	40	10	0	90	76



Tang and co-workers studied the utilization of a similar ligand (**268**) for the asymmetric cyanosilylation of aromatic aldehydes.[168] Cyanohydrin products were obtained with 8−90% enantioselectivity and in high yield (80−98%) (Table 91). The level of asymmetric induction was affected both by electronic effects and by the location of substituents within the aldehyde. Thus, *o*-anisaldehyde gave an enantioselectivity of 90% whilst the cyanohydrin derived from *p*-anisaldehyde was obtained with a more moderate 50% enantiomeric excess. Electron deficient aldehydes, such as *o*-nitrobenzaldehyde, gave poor enantioselectivities (8%) though in high yield (96%).

Gau reported BINOL-based ligands **269**−**273** containing an attached heterocyclic Lewis base which could be complexed to titanium tetraisopropoxide. These complexes were used as catalysts for the asymmetric addition of trimethylsilyl cyanide to aldehydes (Table 92).[169] It was found that the titanium complex of ligand **269** was by far the best in the series, giving 97% yield with 98% enantioselectivity for the addition of trimethylsilyl cyanide to benzaldehyde. The same catalytic system was used with a range of aromatic and aliphatic aldehydes and produced cyanohydrin products with excellent enantioselectivities (90−98%). The system is notable because of the high enantioselectivities obtained for both aliphatic and aromatic substrates.

Table 92. Asymmetric Cyanosilylation of Aldehydes Catalyzed by the Ti(O^{i}Pr)$_4$ Complex of Ligands 269−273[a]

ligand (mol %)	aldehyde	yield (%)	ee (%) (*S*)
269 (10)[b]	PhCHO	52	7
269 (10)	PhCHO	97	98
270 (10)	PhCHO	21	50
270 (10)	PhCHO	44	51
271 (10)	PhCHO	7	20
272 (10)	PhCHO	trace	
273 (10)	PhCHO	19	32 (*R*)
269 (10)	4-ClC$_6$H$_4$CHO	92	92
269 (10)	2-MeOC$_6$H$_4$CHO	94	91
269 (10)	4-MeC$_6$H$_4$CHO	87	92
269 (10)	3-MeC$_6$H$_4$CHO	93	93
269 (5)	3-MeC$_6$H$_4$CHO	86	93
269 (10)	2-naphthaldehyde	94	94
269 (10)	furan-2-carboxaldehyde	88	91
269 (10)	PhCH$_2$CH$_2$CHO	98	97
269 (10)	CyCHO	99	95
269 (10)	(Me)$_2$CHCHO	93	98
269 (10)	CH$_3$(CH$_2$)$_4$CHO	97	97
269 (10)	Me$_2$CHCH$_2$CHO	91	97
269 (5)	Me$_2$CHCH$_2$CHO	90	97
269 (2)	Me$_2$CHCH$_2$CHO	64	91
269 (10)	CH$_3$(CH$_2$)$_6$CHO	95	96
269 (5)	CH$_3$(CH$_2$)$_6$CHO	93	91
269 (10)	(*E*)-MeCH=C(Me)CHO	85	90

[a] Reactions were performed in dichloromethane at −40 °C for 48 h. [b] In the absence of Ti(O^{i}Pr)$_4$.

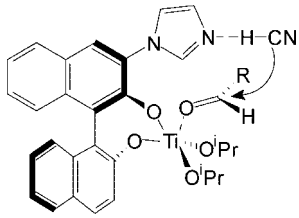
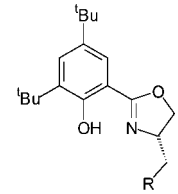


Figure 11.

The authors presented a catalytic cycle featuring a transition state which demonstrated how the complex was able to activate both aldehyde and cyanide simultaneously in a chiral environment (Figure 11). The titanium ion acts as a Lewis acid, whilst the heterocyclic group coordinates to hydrogen cyanide (generated *in situ* from trimethylsilyl cyanide and the isopropanol liberated by formation of the titanium complex). An intramolecular transfer of cyanide to the *re*-face of the coordinated aldehyde introduces the chirality into the cyanohydrin product.

Rowlands prepared ligands **274**−**278** containing oxazoline and sulfoxide moieties and complexed them to titanium tetraisopropoxide to form catalysts for the cyanosilylation of benzaldehyde.[170] The best results were obtained using the complex of ligand **275** with *S*-configuration at the sulfur atom, and this gave mandelonitrile with up to 60% enantiomeric excess and in greater than 95% yield, though this required a stoichiometric quantity of the complex (Table 93). Reducing the catalyst loading to 9 mol % of the complex derived from ligand **275** resulted in formation of product with only a marginally reduced enantiomeric excess of 54%.

Using ligand **275**, a range of aromatic and aliphatic *O*-silylated cyanohydrins were also prepared from the corresponding aldehydes with enantioselectivities of 10−61% and in 26−85% yield when 9 mol % of titanium tetraisopropoxide-**275** was employed as catalyst (Table 94). In general, aliphatic and electron deficient aromatic aldehydes gave products with lower enantiomeric excesses than those obtained from electron rich aromatic aldehydes. The reaction



274) R = SOCH$_3$
275) R = SO^{t}Bu
276) R = Ph
277) R = ^{i}Pr
278) R = SO$_2$^{t}Bu

was carried out in dichloromethane at −84 °C for 60 h, and the highest enantioselectivity (61%) was achieved using the electron rich substrate, 3,5-dimethoxybenzaldehyde. It was also shown that the sulfoxide moiety, a weak Lewis acid, was crucial for the catalytic activity of the system.

Feng's group elaborated a multicomponent bifunctional catalytic system, which included titanium tetraisopropoxide and derivatives of binaphthol (**279**−**286**), cinchonine (**287**−**290**), and *N*-methylephedrine (**291**−**293**).[171] The use of 10 mol % of each component enabled the authors to carry out the asymmetric addition of ethyl cyanoformate to aldehydes. The individual components were first screened for activity using 10 mol % of ligand and titanium tetraisopropoxide; all BINOL derivatives were inactive with the exception of ligands **284** and **285**, which gave good yields but low enantioselectivities. The cinchonine derivatives were all good catalysts, giving 99% yields of cyanohydrin product, but again the enantioselectivities were very low (<12%). The *N*-methylephedrine component also gave poor enantioselectivities, but again, yields were 99%. Using two components simultaneously, BINOL (**279**−**286**) and any other component, gave better results with high yields in most cases and enantioselectivities ranging from 12 to 69%. The highest of these was obtained using ligands **283** and **287** although 68% asymmetric induction was also achieved with the combination of ligands **283** and **288**. The best results, however, came when using all three components: 75% asymmetric induction was obtained when using ligands **283**, **287**, and **292** (Table 95).

Using the combination of **283**, **287**, and **292**, the effect of changing concentration and temperature was also investigated. The best results were obtained using a benzaldehyde concentration of 0.5 M and at lower temperatures (−40 °C and lower), though the yields were lowered and longer reaction times were required at temperatures below −40 °C, which also offered no improvement in enantioselectivity. A 95% yield and 90% asymmetric induction was achieved when conducting the reaction at −45 °C over a period of 48 h. The enantioselectivities were considerably reduced by omission of β-amino alcohol **292** from the catalytic system. The authors proposed that the titanium complex of BINOL worked as a Lewis acidic activator, whereas the cinchonine and methylephedrine components served as Lewis bases to activate the ethyl cyanoformate. Zinc and aluminum were also used as Lewis acids but failed to produce enantioselectivities as high as those obtained using titanium. A range of aldehydes were reacted with ethyl cyanoformate catalyzed by the titanium complex of ligand **283** in the presence of **287** and **292** (Table 96). Good enantioselectivities were achieved, particularly with aromatic aldehydes. Satisfactory yields were also obtained, though all reactions required long reaction times (48−100 h). The best aldehyde substrate was 2-naphthaldehyde, which gave a cyanohydrin ethyl carbonate

Table 93. Asymmetric Cyanosilylation of Benzaldehyde Catalyzed by Ti(O^{i}Pr)$_4$−274−278[a]

ligand (mol %)	time (h)	temp (°C)	yield (%)	ee (%)[b]
274 (9)	12	−35	>90	40
274 (9)[d]	12	−35	20	10
274 (9)[e]	12	−35	60	20
274 (9)	8	0	76	20
274 (9)	48	−84	52	49
274 (4.5)	48	−35	71	33
274 (100)	12	−35	79	49
274[c] (9)	12	−35	78	12 (*S*)
275[c] (9)	12	−35	72	47
275[c] (9)	60	−84	>95	54
275[c] (100)	60	−84	>95	60
275[c] (9)	24	−84	>95	54
275 (9)	12	−35	63	22 (*S*)
276 (9)	12	−35	40	7
276 (9)	96	−84	0	
277 (9)	168	−84	40	27
278 (9)	66	−84	0	
278 (9)	12	−35	27	26

[a] Chirality at the sulfur atom was *R* and solvent used was dichloromethane unless stated otherwise. [b] Absolute configuration of the cyanohydrin product was *R* unless stated otherwise. [c] Configuration at the sulfur atom was *S*. [d] Used toluene as solvent. [e] Used tetrahydrofuran as solvent.

Table 94. Asymmetric Cyanosilylation of Aldehydes Catalyzed by Ti(O^{i}Pr)$_4$−275

aldehyde	yield (%)	ee (%)[a]
PhCHO	85	54
4-MeOC$_6$H$_4$CHO	80	57
2-O$_2$NC$_6$H$_4$CHO	48	10
2,4,6-Me$_3$C$_6$H$_2$CHO	15	15
4-O$_2$NC$_6$H$_4$CHO	51	0
3,5-(MeO)$_2$C$_6$H$_3$CHO	72	61
2-naphthaldehyde	80	40
PhCH=CHCHO	78	50
Me$_3$CCHO	26	40
Me$_2$CHCHO	87	37[b]
CH$_3$(CH$_2$)$_5$CHO	62	37[b]

[a] Configuration of the cyanohydrin products was *R* unless stated otherwise. [b] Product had *S*-configuration.

Table 95. Asymmetric Addition of Ethyl Cyanoformate to Benzaldehyde Catalyzed by the Three Ligand System of Ti(O^{i}Pr)$_4$−283, 287, and a Third Ligand[a]

third ligand	time (h)	yield (%)	ee (%)
none	48	99	69
287	40	99	68
288	40	99	65
291	10	99	58
292	10	99	74
292	30	99	65
293	10	99	47

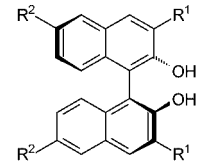
[a] 10 mol % of each component was used in dichloromethane with a 0.25 M concentration of benzaldehyde and 1.2 equiv of ethyl cyanoformate at −20 °C.

with 94% enantiomeric excess, though 4-methylbenzaldehyde and 4-methoxybenzaldehyde also gave 93% asymmetric induction.

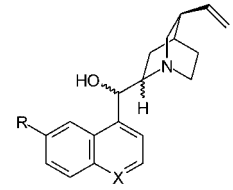
A more recent study by Feng[172] presented an expanded set of BINOL and ephedrine-based ligands **294**−**301** for the same reaction. BINOL ligands **294**−**297** were completely inactive when used alone whilst ligand **300** was found to give a moderate asymmetric induction (55%), and this was increased considerably to 87% when the catalyst loading was reduced by half to 5 mol % at −15 °C. A marginal improvement to 91% enantioselectivity was achieved using

Table 96. Asymmetric Addition of Ethyl Cyanoformate to Aldehydes Catalyzed by the Three Component System of Ti(O^{i}Pr)$_4$−283, 287, and 292

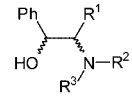
aldehyde	time (h)	yield (%)	ee (%) (configuration)
PhCHO	48	95	90 (*R*)
2-MeC$_6$H$_4$CHO	50	78	83 (*S*)
3-MeC$_6$H$_4$CHO	72	82	90 (*S*)
4-MeC$_6$H$_4$CHO	55	81	93 (*R*)
2-MeOC$_6$H$_4$CHO	72	75	74 (*R*)
3-MeOC$_6$H$_4$CHO	72	81	82 (*R*)
4-MeOC$_6$H$_4$CHO	90	88	93 (*R*)
3-PhOC$_6$H$_4$CHO	72	85	87 (*S*)
1-naphthaldehdye	50	83	84 (*R*)
2-naphthaldehyde	55	82	94 (*S*)
4-FC$_6$H$_4$CHO	100	78	82 (*S*)
4-ClC$_6$H$_4$CHO	96	81	58 (*R*)
3,4-(OCH$_2$O)C$_6$H$_3$CHO	48	87	76 (*S*)
PhCH=CHCHO	80	83	82 (*R*)
CH$_3$(CH$_2$)$_4$CHO	72	88	45 (*R*)
CyCHO	72	75	70 (*R*)



279) $R^1 = R^2 = H$
280) $R^1 = Br$, $R^2 = H$
281) $R^1 = I$, $R^2 = H$
282) $R^1 = H$, $R^2 = I$
283) $R^1 = H$, $R^2 = Br$
284) $R^1 = CH_2NHCH_2Ph$, $R^2 = H$
285) $R^1 = (S)$-$CH_2NHCH(Me)Ph$, $R^2 = H$
286) $R^1 = H$, $R^2 = Br$ (*R*-BINOL)
294) $R^1 = P(O)Ph_2$, $R^2 = H$
295) $R^1 = SiPh_3$, $R^2 = H$
296) $R^1 = CH_2$-Morpholine, $R^2 = H$
297) $R^1 = Quinoline$, $R^2 = H$
298) $R^1 = NHBn$, $R^2 = H$
299) $R^1 = NMeBn$, $R^2 = H$
300) $R^1 = (S)$-$CH_2N(Me)C(CH_3)Ph$, $R^2 = H$



287) (*S*,*S*) R = H, X = N
288) (*S*,*S*) R = OMe, X = N
289) (*R*,*R*) R = H, X = CH
290) (*R*,*R*) R = OMe, X = CH



291) (*R*,*S*) $R^1 = Me$, $R^2 = H$, $R^3 = Me$
292) (*R*,*S*) $R^1 = R^2 = R^3 = Me$
293) (*S*,*R*) $R^1 = Ph$, $R^2 = R^3 = Me$
301) (*R*,*S*) $R^1 = Ph$, $R^2 = H$, $R^3 = MeCO$
302) (*R*,*S*) $R^1 = Ph$, $R^2 = H$, $R^3 = Ts$
303) (*S*,*R*) $R^1 = Me$, $R^2 = H$, $R^3 = Me$

BINOL−**300** with chiral activator **301**, though none of the other chiral activators gave the same level of asymmetric induction. It was also found that using the cinchonine derivatives in place of the ephedrine chiral activators resulted in much lower enantioselectivities of 7−26%.

A range of aromatic and aliphatic aldehydes were used as substrates for ethyl cyanoformate addition catalyzed by the combination of ligands **300** and **301** with titanium tetraisopropoxide. In all cases, better enantioselectivities and yields

Table 97. Asymmetric Addition of Ethyl Cyanoformate to Aldehydes Catalyzed by the Three Component System of Ti(O^{i}Pr)$_4$−300 and −301[a]

aldehyde	time (h)	yield (%)	ee (%) (S)
PhCHO	24 (48)	88 (87)	91 (87)
4-MeC$_6$H$_4$CHO	96 (168)	76 (68)	83 (75)
2-MeOC$_6$H$_4$CHO	48 (96)	82 (71)	92 (87)
3-MeOC$_6$H$_4$CHO	48 (96)	84 (70)	90 (83)
4-MeOC$_6$H$_4$CHO	60 (120)	81 (65)	91 (84)
3-PhOC$_6$H$_4$CHO	24 (48)	95 (77)	89 (81)
2-naphthaldehyde	24 (48)	91 (78)	81 (76)
4-FC$_6$H$_4$CHO	48 (90)	81 (73)	92 (83)
PhCH=CHCHO	48 (96)	83 (70)	91 (84)
CH$_3$(CH$_2$)$_4$CHO	24 (48)	88 (76)	78 (67)
CH$_3$(CH$_2$)$_4$CHO[b]	96	64	85
CyCHO	24 (48)	86 (79)	75 (70)
CH$_3$CH$_2$CHO	24 (48)	84 (74)	76 (61)
Me$_2$CHCHO	24 (48)	81 (70)	62 (58)
Me$_3$CCHO	24 (48)	83 (76)	74 (69)

[a] Reactions used 5 mol % of ligand, activator, and Ti(O^{i}Pr)$_4$ in dichloromethane at −15 °C. Figures in parentheses are results using only **300**−Ti(O^{i}Pr)$_4$. [b] Reaction was carried out at −45 °C.

Table 98. Asymmetric Cyanosilylation of Benzaldehyde Catalyzed by Titanium Isopropoxide Complexes of Ligands 71 and 304−311 with 287−288[a]

ligand	cinchonine	time (h)	yield (%)	ee (%) (*R*)
304	(1*S*,2*R*)-**287**	12	90	47
305	none	48	0	
none	(1*S*,2*R*)-**287**	36	79	19
305	(1*S*,2*R*)-**287**	6	99	80
306	(1*S*,2*R*)-**287**	8.5	92	35
71	(1*S*,2*R*)-**287**	24	93	11
307	(1*S*,2*R*)-**287**	6	99	20
308	(1*S*,2*R*)-**287**	7	99	33
309	(1*S*,2*R*)-**287**	7	89	23
310	(1*S*,2*R*)-**287**	9	99	37
311	(1*S*,2*R*)-**287**	9	99	16
305	(1*S*,2*R*)-**288**	5	99	15
305	(1*R*,2*S*)-**287**	5	99	37 (*S*)
305	(1*R*,2*S*)-**288**	5	99	11
305[b]	(1*S*,2*R*)-**287**	20	99	49
305[c]	(1*S*,2*R*)-**287**	6	99	57
305[d]	(1*S*,2*R*)-**287**	6	99	77
305[e]	(1*S*,2*R*)-**287**	7	99	73

[a] Reactions carried out in dichloromethane at −20 °C using 5 mol % of ligand, **287**/**288**, and Ti(O^{i}Pr)$_4$ unless stated otherwise. [b] Used 10 mol % of each reagent. [c] Used 2.5 mol % of each reagent. [d] Used 6 mol % of **305** (with 5 mol % of titanium and **287**). [e] Used 4 mol % of **305** (with 5 mol % of titanium and **287**).

were observed when using both components rather than the titanium complex of the BINOL ligand only (Table 97). The best results were achieved with aromatic aldehydes, although a significant asymmetric induction was also observed for aliphatic substrates, especially in the case of hexanal when lowering the temperature to −45 °C.

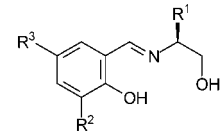
With the knowledge that high enantioselectivities could be achieved using two components, a further study was made of the asymmetric addition of ethyl cyanoformate to aldehydes. Thus, Feng used a two component system involving C_1-symmetric Schiff bases **71, 304−311** (see section 2.2.2 for the use of the titanium complexes of related Schiff bases as single component catalysts) in place of BINOL along with previously used cinchonine alkaloids **287−288**.[173] The best result (80% asymmetric induction) was obtained by the use of 5 mol % of the titanium complex of ligand **305** and (1*S*,2*R*)-**287** (Table 98). All other ligands gave inferior results (11−47% asymmetric induction), but unusually, a higher or lower amount of each reagent (10 and 2.5 mol %) gave lower

Table 99. Asymmetric Cyanosilylation of Aldehydes Catalyzed by Ti(O^{i}Pr)$_4$−305 with (1*S*,2*R*)-287[a]

aldehyde	yield (%)	ee (%) (*R*)
PhCHO	99	90
2-MeC$_6$H$_4$CHO	99	87
3-MeC$_6$H$_4$CHO	96	84
4-MeC$_6$H$_4$CHO	87	91
2-MeOC$_6$H$_4$CHO	99	83
3-MeOC$_6$H$_4$CHO	99	84
4-MeOC$_6$H$_4$CHO	89	84
4-FC$_6$H$_4$CHO	80	79
4-ClC$_6$H$_4$CHO	83	66
1-naphthaldehyde	99	82
2-naphthaldehyde	99	81
3,4-(OCH$_2$O)C$_6$H$_3$CHO	99	85
(E)-MeCH=CHCHO	73	91
CH$_3$(CH$_2$)$_4$CHO	82	68

[a] Reactions were carried out in dichloromethane at −20 °C using 5 mol % of ligand, **287**, and Ti(O^{i}Pr)$_4$ for 2.5 h.

enantioselectivities of 49% and 57%, respectively, and in the case of 10 mol % a longer reaction time of 20 h was required to obtain 99% yield. It was found that increasing the concentration of benzaldehyde from 0.5 to 2.0 M increased the rate of reaction (99% yield after 2.5 h instead of 6 h) and also increased the enantioselectivity of the reaction to 90%. Increasing the temperature increased the reaction rate as expected but reduced the enantioselectivity to only 70%. A further increase in enantioselectivity to 94% was observed by lowering the temperature to −45 °C, but the reaction was then significantly slower with only a 15% yield obtained after a reaction time of 50 h.



71) R^1 = Ph, R^2 = R^3 = ^{t}Bu
304) R^1 = Me, R^2 = R^3 = ^{t}Bu
305) R^1 = ^{i}Pr, R^2 = R^3 = ^{t}Bu
306) R^1 = Bn, R^2 = R^3 = ^{t}Bu
307) R^1 = H, R^2 = R^3 = ^{t}Bu
308) R^1 = ^{i}Pr, R^2 = R^3 = H
309) R^1 = ^{i}Pr, R^2 = H, R^3 = NO$_2$
310) R^1 = ^{i}Pr, R^2 = H, R^3 = ^{t}Bu
311) R^1 = ^{i}Pr, R^2 = Adamantyl, R^3 = ^{t}Bu

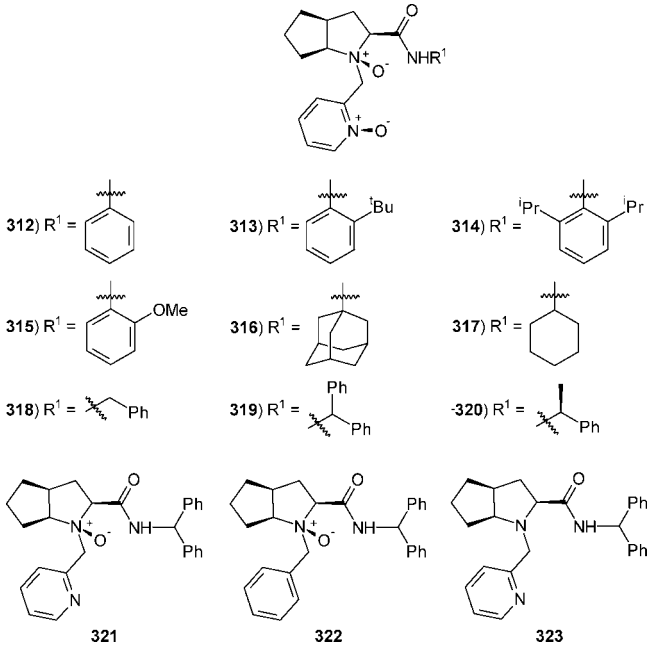
A range of aldehydes were used as substrates for the asymmetric addition of ethyl cyanoformate catalyzed by the titanium isopropoxide complex of ligand **305** and cinchona alkaloid (1*S*,2*R*)-**287**. Enantiomerically enriched cyanohydrin carbonates were obtained in good to excellent yields (70−99%) and with 66−94% enantiomeric excess (Table 99). The results obtained for all substrates were similar, indicating that this catalyst system has no preference for either aromatic or aliphatic substrates.

Feng also used *N*-oxide containing bifunctional ligands **312−323** as the corresponding titanium isopropoxide complexes formed *in situ* to catalyze the asymmetric addition of trimethylsilyl cyanide to aldehydes.[174] Using benzaldehyde as substrate, *O*-trimethylsilylated mandelonitrile was obtained in 34−88% yield and with 37−67% enantiomeric excess after a reaction time of 48−52 h. The highest enantioselectivity came from the reaction using ligand **315**; however, a yield of just 40% was obtained. In contrast, ligand **319** gave a comparably high level of asymmetric induction (65%) but

Table 100. Asymmetric Cyanosilylation of Benzaldehyde Catalyzed by Titanium Isopropoxide Complexes of Ligands 312−323[a]

ligand	time (h)	yield (%)	ee (%) (*R*)
312	48	86	55
313	48	78	40
314	48	88	47
315	48	40	66
316	52	87	50
317	52	85	55
318	52	67	37
319	52	83	65
320	52	72	47
321	48	62	48
322	48	34	47
323	48	0	

[a] Reactions were carried out using 10 mol % ligand with 5 mol % titanium tetraisopropoxide in dichloromethane at −78 °C using a 0.2 M benzaldehyde concentration.



a much higher yield of 83% (Table 100). Ligand **323** gave no conversion after 48 h, and ligand **322** gave a yield of just 34%, thus demonstrating the importance of the pyridyl group and the pyrrolidine *N*-oxide.

It was found that, through the use of an additive, the enantioselectivities and yields could be enhanced. After screening a number of potential additive compounds, mostly benzoic acid derivatives, 4-methylbenzoic acid (10 mol %) in conjunction with titanium tetraisopropoxide and **319** was shown to improve the enantioselectivity for the cyanosilylation of benzaldehyde from 65% to 77% and gave the product in 99% yield after a reaction time of just 20 h. Further increases in the amount of additive to 20 mol % boosted the enantioselectivity to 80%; however, adding more 4-methylbenzoic acid did not improve this further. Using these optimized conditions, different metal sources ($Al(O^iPr)_3$, Et_3Al, and $Zr(O^iPr)_4$) were tested. However, although these gave some asymmetric induction, none was as high as the 80% achieved using titanium tetraisopropoxide in dichloromethane. The use of THF, ether, and toluene as solvents also gave inferior results. It was also shown that variations in the reaction temperature and reagent concentrations did not offer any improvement in yield or enantioselectivity, nor did they offer scope for reducing the catalyst loading.

Table 101. Asymmetric Cyanosilylation of Aldehydes Catalyzed by the Titanium Isopropoxide Complex of Ligand 319[a]

aldehyde	time (h)	yield (%)	ee (%) (*R*)
PhCHO	20	99	80
4-MeC_6H_4CHO	20	99	77
3-MeC_6H_4CHO	20	99	79
4-ClC_6H_4CHO	20	90	73
3-ClC_6H_4CHO	20	99	71
2-ClC_6H_4CHO	20	98	73
4-FC_6H_4CHO	20	95	71
4-$MeOC_6H_4CHO$	28	91	70
1-naphthaldehyde	28	93	70
$CH_3(CH_2)_4CHO$	25	90	59
$PhCH_2CHO$	25	93	46
furan-2-carboxaldehyde	28	80	55
PhCH=CHCHO	28	83	45

[a] Reactions were carried out using 10 mol % of **319** with 5 mol % titanium tetraisopropoxide in dichloromethane at −78 °C using a 0.2 M benzaldehyde concentration in the presence of 20 mol % of 4-methylbenzoic acid.

A range of aldehydes were used as substrates under the optimized conditions, and aromatic aldehydes made better substrates than aliphatic ones, as 70−80% asymmetric induction and 90−99% yield were obtained using benzaldehyde derivatives and 1-naphthaldehyde (Table 101). There was no great variation in the enantioselectivities obtained using aromatic aldehydes, indicating that electronic effects were only weakly influential. Aliphatic aldehydes gave reduced enantioselectivities (45−59%), though the yields remained reasonably high (80−93%).

A catalytic cycle was formulated to explain the results in which it was proposed that the aldehyde binds to the titanium metal center in the most sterically favorable orientation and the cyanide is delivered to one face of the aldehyde intramolecularly from an *N*-oxide bound trimethylsilyl cyanide molecule as shown in Figure 12.

Zhou *et al.* reported bifunctional titanium complexes of camphor-based ligands **324**−**325** as catalysts for aromatic aldehyde cyanosilylation.[175] The reaction was conducted in dichloromethane at ambient temperature in the presence of 10−20 mol % of isopropanol for 24 h. For benzaldehyde, the best results were obtained by employing 40 mol % of the ligand; decreasing of the catalyst loading to 20 mol % resulted in inferior yields and stereoselectivity. A 4:1 ligand/titanium tetraisopropoxide ratio proved to be optimal with 20 mol % of isopropanol at 20 °C. A number of other aldehydes were used with the titanium catalyst derived from ligand **324**, with the most successful being *o*-methoxybenzaldehyde, which formed a cyanohydrin with 98% enantiomeric excess when reacted under the same optimized conditions as those for benzaldehyde (Table 102). Contrasting with the results of the methoxybenzaldehydes, the electron

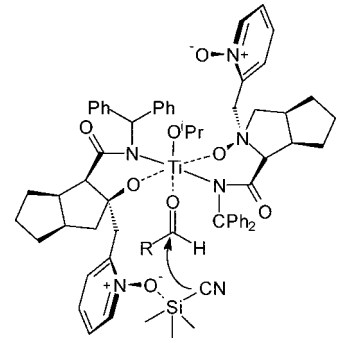
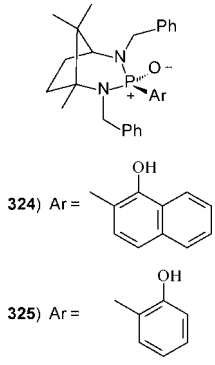


Figure 12.

Table 102. Asymmetric Cyanosilylation of Aldehydes Catalyzed by 324−Ti(O^{i}Pr)$_4$

aldehyde	**324** (mol %)	Ti(O^{i}Pr)$_4$ (mol %)	^{i}PrOH (mol %)	temp (°C)	yield (%)	ee (%)
PhCHO	40	10	20	20	84	54
PhCHO	20	5	10	20	74	44
PhCHO	40	10	20	0	90	34
PhCHO	40	10		20	90	28
PhCHO	40	40	20	20	96	47
2-MeOC$_6$H$_4$CHO	40	10	20	20	87	98
4-MeOC$_6$H$_4$CHO	40	10	20	20	64	54
3-MeOC$_6$H$_4$CHO	40	10	20	20	78	84
2-MeC$_6$H$_4$CHO	40	10	20	20	75	78
1-naphthaldehyde	40	10	20	20	66	84
4-MeC$_6$H$_4$CHO	40	10	20	20	81	78
4-ClC$_6$H$_4$CHO	40	10	20	20	71	55
4-O$_2$NC$_6$H$_4$CHO	40	10	20	20	73	35

deficient *p*-nitrobenzaldehyde substrate gave much lower asymmetric induction. Due to the need for a considerable catalytic loading under the optimal conditions, the authors developed a procedure to reisolate ligand **324** at the end of the reaction. Recovered ligand was then used again, showing no loss in activity or stereoselectivity. The titanium isopropoxide complex of ligand **325** was also tested under a variety of conditions using benzaldehyde and 2-methoxybenzaldehyde (Table 103), but it gave inferior enantioselectivities compared to ligand **324**, thus indicating the importance of the bulky naphthyl group.



The systems described in this section suffer from a number of disadvantages; despite the high enantioselectivities observed for some aldehydes and the reasonable reaction temperatures, Buono, Tang, and Zhou's catalysts require 40 mol % of the ligand, a considerable amount compared with the majority of other systems. Low substrate tolerance in terms of enantioselectivity should also be noted, with aromatic aldehydes being generally the best substrates. Rowland's system demonstrates only moderate enantioselectivity and requires very low temperatures. Feng's work is interesting from a mechanistic point of view but requires complex optimization of a multicomponent system.

2.2.8. Sulfoximine Ligands

In 1995, Bolm and Müller studied the possibility of using chiral sulfoximines as ligands for titanium complexes in asymmetric trimethylsilylcyanation. The chiral reagent (Figure 13) was prepared by the reaction of ligand **326** with titanium tetraisopropoxide and was used in stoichiometric amounts.[176] Silylated cyanohydrins were obtained from a selection of aromatic and aliphatic aldehydes in 60−92% yield and with 76−91% enantioselectivity (Table 104). The best asymmetric induction was obtained from the addition

Table 103. Asymmetric Cyanosilylation of Aldehydes Catalyzed by 325−Ti(O^{i}Pr)$_4$

aldehyde	**325** (mol %)	Ti(O^{i}Pr)$_4$ (mol %)	^{i}PrOH (mol %)	temp (°C)	yield (%)	ee (%)
PhCHO	40	10	20	20	84	44
PhCHO	40	10		20	90	12
PhCHO	40	10	20	0	84	34
PhCHO	20	10	20	20	73	53
PhCHO	40	40	20	20	96	47
2-MeOC$_6$H$_4$CHO	40	10	20	20	64	57
2-MeOC$_6$H$_4$CHO	40	10		20	82	41
2-MeOC$_6$H$_4$CHO	40	10	20	0	73	70

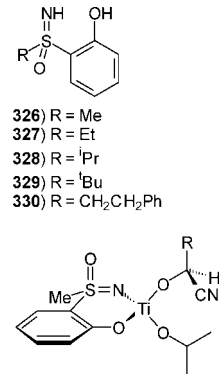


Figure 13.

of trimethylsilyl cyanide to benzaldehyde. One notable feature of this system is that comparable enantioselectivities were obtained using aliphatic aldehydes such as hexanal and cyclohexanecarboxaldehyde (both 89%) to those obtained with aromatic substrates. The use of substoichiometric quantities of titanium tetraisopropoxide−**326** led to more moderate results. For example, using 20 mol % of the catalyst at −45 °C produced only a 28% yield with 44% asymmetric induction after 20 h. After 60 h, the yield was higher (79%), but the enantioselectivity was further reduced to 23%.

Variations of ligand **326** were prepared (**327**−**330**) and were used catalytically (20 mol %) with titanium tetraisopropoxide for the cyanosilylation of benzaldehyde (Table 105).[177] The *N*-methylated version of ligand **326** gave a good yield (60%) but no asymmetric induction, indicating the importance of the nitrogen atom coordination to titanium (Figure 13). Using catalytic quantities of the complexes was largely ineffective compared with the stoichiometric system and gave at best 47% asymmetric induction along with low yields, unless extended reaction times were employed.

To summarize the use of titanium-based catalysts, the more enantioselective systems for cyanosilylation (those of Che, Bu and Liang, Uang, Chen) suffer from the need to use very low temperatures (−78 °C) and prolonged reaction times (greater than 12 h). Furthermore, in these cases, reactions require 5−20 mol % of catalysts, some of which are synthetically difficult to prepare. Catalyst **157** is especially notable, as it demonstrates high conversions and enantioselectivities (up to 86%) after a very short time (usually within 1 h) when exceptionally low catalytic loadings are used (0.1 mol %). Amongst other advantages of catalyst **157** are its simple synthesis from cheap and available chemicals as well as the possibility to use alternative cyanide sources. The mode of action of the catalyst and the origin of the asymmetric induction are also well understood. Khan's and Moberg's modifications of this system are also noteworthy. The latter is especially interesting as the first example of acetyl cyanide utilization in asymmetric cyanohydrin synthesis.

Table 104. Asymmetric Cyanosilylation of Aldehydes Promoted by Stoichiometric Quantities of Ti(O^{i}Pr)$_4$−326

aldehyde	yield (%)[a]	ee (%) (*S*)
PhCHO	72 (96)	91
4-MeOC$_6$H$_4$CHO	60	87
2-MeOC$_6$H$_4$CHO	72 (92)	74
1-naphthaldehyde	92 (97)	76
CH$_3$(CH$_2$)$_4$CHO	64	89
CyCHO	70 (97)	89
Me$_3$CCHO	70	81
PhCH=CHCHO	63	79

[a] Isolated yields after column chromatography; figures in parentheses indicate conversions determined by NMR.

Table 105. Asymmetric Cyanosilylation of Benzaldehyde Promoted by Ti(O^{i}Pr)$_4$−326−330[a]

ligand	yield (%)	ee (%) (*S*)
326	29	43
327	25	40
327	72[b]	<5
328	27	43
328	60[b]	18
329	26	40
330	32	47

[a] Used 20 mol % titanium with 22 mol % of ligand in dichloromethane at −45 °C for 20 h. [b] Reaction time was 60 h.

Table 106. Asymmetric Cyanosilylation of Aldehydes Promoted by Catalyst 331[a]

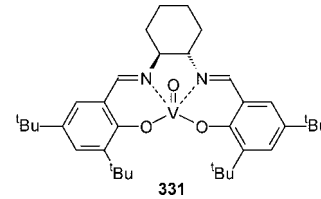
aldehyde	ee (%) (*S*)
PhCHO	94
4-MeOC$_6$H$_4$CHO	90
2-MeC$_6$H$_4$CHO	90
3-MeC$_6$H$_4$CHO	95
4-MeC$_6$H$_4$CHO	94
4-O$_2$NC$_6$H$_4$CHO	73
CH$_3$CH$_2$CHO	77
Me$_3$CCHO	68

[a] 0.1 mol % of catalyst was employed at ambient temperature in dichloromethane for 24 h, after which time all reactions gave 100% conversion.

2.3. Vanadium-Based Catalytic Systems

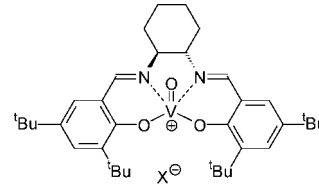
In 2000, Belokon and North described a catalytic system based on a vanadium salen complex.[178] The synthesis of the catalyst was accomplished by reaction of Schiff base **142** with VOSO$_4$; therefore, the authors supposed that the formed complex was vanadium(IV) derivative **331**. This system was able to convert aromatic aldehydes into cyanohydrin silyl ethers with enantioselectivities of 90−95% and full conversion after 24 h; a very low catalyst loading of 0.1 mol % was employed, and the reaction could be carried out in dichloromethane at ambient temperature (Table 106).

Compared to the analogous titanium-based system **157**, reactions catalyzed by complex **331** were somewhat slower but gave better enantioselectivities for all aldehyde substrates. Aliphatic aldehydes have more moderate levels of asymmetric induction (68−77%) than aromatic aldehydes (90−95%), and this catalytic system failed to give satisfactory results for the cyanosilylation of ketones. Thus, the use of acetophenone as a substrate resulted in 22% enantioselectivity and only 16% conversion after a reaction time of one week.



331

Further investigations[120] revealed that vanadium(V) complex **332a** was the real precatalyst and was formed by oxidation of vanadium(IV) complex **331** by air. The ethyl sulfate counterion was formed from the ethanol used as a solvent during the synthesis of the complex. X-ray analysis showed that in the crystal lattice the complex is monomeric; five coordination places are occupied by the V=O bond and distorted planar salen ligand. The sixth coordination place is taken by a water molecule so that the counterion, in the case of ethyl sulfate at least, is outside the coordination sphere of vanadium.



332a) X = EtOSO$_3$
b) X = CF$_3$SO$_3$
c) X = Cl
d) X = F
e) X = Br
f) X = BF$_4$
g) X = CN

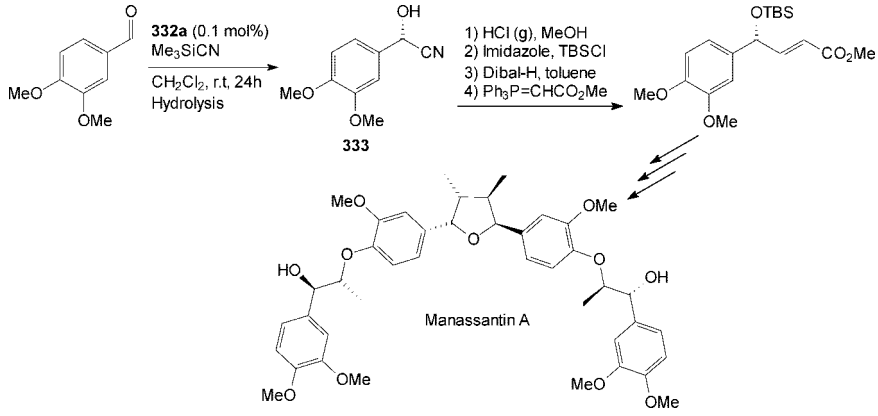
In addition to its activity in the cyanosilylation reaction, complex **332a** was an effective catalyst for the synthesis of *O*-acetyl cyanohydrins of aldehydes using the KCN/Ac$_2$O system previously developed by Belokon and North (see section 2.2.3.3).[120,179] Thus, acetylated cyanohydrins were obtained from benzaldehyde, 3-methoxybenzaldehyde, and 2-chlorobenzaldehyde, with enantioselectivities of 90%, 85%, and 78%, respectively. The reactions were carried out at −40 °C in a dichloromethane−*tert*-butanol−water (2500:10:1) mixture for 10 h using 1 mol % of catalyst **332a**. Complex **332a**, as well as a number of other complexes, was also tested under phase-transfer catalysis conditions in a toluene−water system; however, this resulted in a significant loss in enantioselectivity (25% asymmetric induction for benzaldehyde).[124]

Vanadium salen catalyst **332a** was used as part of the total synthesis of Manassantin A, B and B$_1$ reported by Hanessian in 2006.[180] The terminal aromatic groups were derived from a nonracemic cyanohydrin prepared using catalyst **332a** as shown in Scheme 41. Cyanohydrin **333** was obtained with 99% enantiomeric excess after recrystallization.

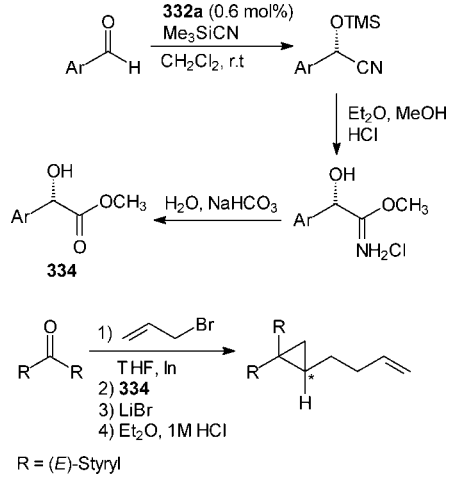
Lloyd-Jones *et al.* investigated the asymmetric homoallylcyclopropanation of dibenzylideneacetone using an allylindium halide reagent in which the enantioselectivity could be enhanced by using a modifier, in particular β-amino alcohols and methyl mandelate analogues **334**.[181] In order to obtain these chiral modifiers, catalyst **332a** was employed to convert a range of aromatic aldehydes into mandelate esters **334** as shown in Scheme 42.

The high levels of asymmetric induction obtained with catalyst **332a** have prompted the synthesis of a number

Scheme 41



Scheme 42



of immobilized versions of the complex. Gigante and Corma covalently linked the Schiff base of complex **332a** to the surface of various zeolites and to silica (Figure 14).[182] When bound to silica, various tether lengths were employed, and it was found that enantioselectivity in the cyanosilylation of benzaldehyde increased marginally with chain length (52% for $n = 3$ and 63% for $n = 11$). Silica was shown to be the best solid support from the three studied, giving 63% asymmetric induction compared to the 58% and 49% obtained using ITQ-2 and MCM-41 supports. Although the homogeneous system gave higher enantioselectivities and conversions, after optimization of conditions, the authors managed to achieve 68−85% enantioselectivity for various aldehydes (Table 107) with the silica bound catalyst in chloroform, which was comparable with the results obtained

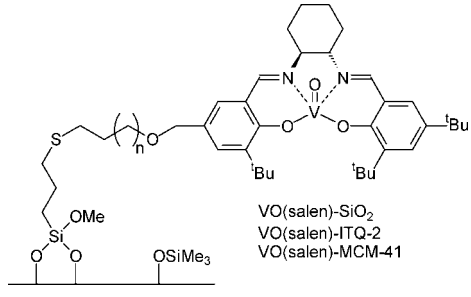


Figure 14.

Table 107. Asymmetric Cyanosilylation of Aldehydes Using Silica Supported 331[a]

aldehyde	conversion (%)	ee (%) (*S*)
PhCHO	78	85
PhCHO[b]	70	74
4-FC_6H_4CHO	80	75
4-$MeOC_6H_4CHO$	70	78
4-MeC_6H_4CHO	88	85
$Me_2C{=}CH(CH_2)_2CH(Me)CH_2CHO$	90	68

[a] Reactions carried out in chloroform at 0 °C under nitrogen atmosphere for 120 h with 100 mg of catalyst and 3 equiv of trimethylsilyl cyanide. [b] VO/ITQ-2 was used as catalyst.

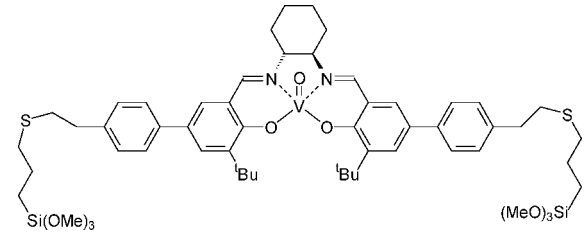


Figure 15.

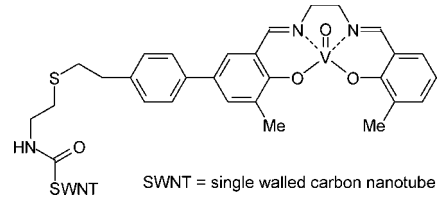


Figure 16.

using homogeneous catalyst **332a**. The activity of the heterogeneous system was however much lower; cyanosilylation of benzaldehyde in chloroform at 0 °C gave only 80% conversion after a reaction time of 120 h. Reusability studies showed that a considerable loss in enantioselectivity took place if the catalyst was reused more than four times.

Another solid supported system was investigated using a periodic mesoporous organosilica zeolite which was loaded with an analogue of complex **332a** (Figure 15).[183] The supported complex gave a good conversion (80%) but only 30% asymmetric induction when benzaldehyde was used as substrate. The same group subsequently reported immobilization of VO(salen) complexes on single wall carbon nanotubes (Figure 16).[184] For the cyanosilylation of

Table 108. Asymmetric Cyanosilylation of Aldehydes Catalyzed by 332a in (emim)−PF_6[a]

aldehyde	conversion (%)	ee (%) (*R*)
PhCHO	85	89
PhCH=CHCHO	76	98
2-FC_6H_4CHO	81	86
$CH_3(CH_2)_4CHO$	97	83

[a] Reactions carried out at ambient temperature for 24 h under a nitrogen atmosphere using 1 mol % of **332a**.

benzaldehyde, at 0 °C with 0.3 mol % of catalyst, an enantioselectivity of 66% was achieved after 72 h (67% conversion); however, this is lower than that observed with the homogeneous version of the reaction. At room temperature, the system could be recycled a number of times, maintaining a yield over 93% for five repetitions. Immobilization on silica gave the best results amongst the heterogeneous systems reported by Gigante and Corma.[185]

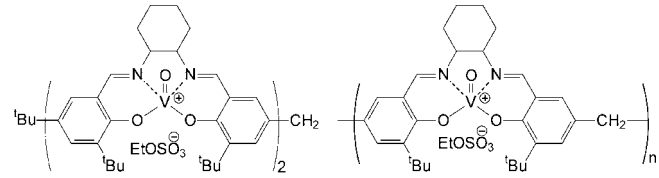
The same researchers described the use of ionic liquids as a medium for the cyanosilylation of aldehydes catalyzed by complex **332a**.[186] The main advantage of such a modification is the ability to simply extract the products from the ionic liquid by a solvent that is not capable of extracting the catalyst, for example hexane. Moreover, the compatibility of ionic liquids with the green chemistry[187] concept is also advantageous. Four ionic liquids were tested, and the best results in terms of yield and enantioselectivity were obtained by using 1-ethyl-3-methylimidazolium hexafluorophosphate (emim-PF_6) as a solvent, which for benzaldehyde enabled the authors to obtain an 85% yield and 89% enantioselectivity, figures which are comparable to the results obtained in dichloromethane. Three other aldehydes were used as substrates to produce the corresponding silylated cyanohydrins with enantioselectivities of 83−98% and conversions of 76−97% after 24 h at room temperature (Table 108). Good results were obtained for all substrates, with a particularly high asymmetric induction (98%) observed for cinnamaldehyde. The data was comparable to that obtained by Belokon and North, but it is notable that the use of an ionic liquid as solvent gave a better result for the aliphatic aldehyde hexanal (93% conversion and 83% enantioselectivity) although the catalytic loading was ten times larger in the ionic liquid compared to that used in dichloromethane. When used in the ionic liquid, catalyst **332** could be reused; after five consecutive runs with benzaldehyde, no decrease in conversion or enantioselectivity was observed.

Khan *et al.* developed dimeric[147] **335a** and polymeric **335b** versions of vanadium catalyst **332a** in order to improve the recyclability of Belokon and North's system whilst retaining the high enantioselectivity afforded by this catalyst for the addition of trimethylsilyl cyanide[188] and potassium cyanide/acetic anhydride[189] to aldehydes. The dimeric catalyst **335a** was used for the addition of potassium cyanide to a range of aromatic aldehydes for which excellent enantioselectivities (88−95%) and yields (90−99%) were obtained. The reactions were carried out at −20 °C in dichloromethane. For benzaldehyde, using between 1 and 5 mol % of the catalyst resulted in approximately the same enantioselectivity (92%) in each case. However, a reaction temperature of −20 °C was shown to be important for good asymmetric induction, as the asymmetric induction is reduced to 71% at −8 °C and to 61% at ambient temperature.

Table 109. Asymmetric Cyanosilylation of Benzaldehyde Catalyzed by Oxovanadium(salen) Complexes 332 with Various Counterions[a]

catalyst (counterion)	$t_{50\%}$ (min)	ee (%) (*S*)
332c (Cl)	8.6	93
332d (F)	7.6	91
332e (Br)	50.3	94
332f (BF_4)	78.2	90
332g (CN)	201.9	91
332a ($EtOSO_4$)	370.0	91
332b (CF_3SO_3)		

[a] Reactions carried out in dichloromethane at 0 °C using 0.2 mol % of catalyst.



335a **335b**

Using the polymeric version of the catalyst (**335b**), conversions and enantioselectivities comparable to those previously reported with catalyst **332a** were obtained. The polymeric catalyst retained the preference for aromatic aldehydes (82−96% asymmetric induction with 90−99% yield after 9 h) although good enantioselectivities were also achieved for aliphatic substrates (79−85%). The latter were higher than those reported with nonpolymeric catalyst **332a** but were obtained using a much larger catalyst loading (5 mol % instead of 0.1 mol %). It was shown that asymmetric induction and conversion could be preserved over at least four runs when catalyst **335b** was used to catalyze the addition of trimethylsilyl cyanide to benzaldehyde. The effect of including an additive was also investigated, and although no major improvement was made to the enantioselectivity, the reactions, in some cases, were faster when using *O*-coordinating additives such as triphenylphosphine oxide and pyridine *N*-oxide.

Catalyst **332a** was found to be a less effective catalyst in terms of reaction rate than the titanium analogue (**157**) but gave a higher level of asymmetric induction in cyanosilylation reactions. It was therefore highly desirable to find analogues of catalyst **332a** which retained its high level of asymmetric induction whilst increasing the rate of reaction. Further study of complexes **332** by Belokon and North revealed that the nature of the counterion had an unexpectedly significant influence on the activity of the catalyst.[190] The first reports of complex **332a** focused on the use of a catalyst containing an ethylsulfate counterion which was subsequently shown to be one of the least active members of a series of catalysts. A number of catalysts based on structure **332** with different anionic ligands (**332a**−**g**) were prepared and used for the asymmetric addition of trimethylsilyl cyanide to benzaldehyde. Belokon and North initially reasoned that a less coordinating counterion (such as triflate **332b**) would give a more Lewis acidic complex and hence a faster rate of catalysis. In the event, exactly the opposite was observed, with the most active of catalysts **332a**−**g** being those that possess coordinating counterions whilst complex **332b** was catalytically inactive.

As shown in Table 109, the nature of the counterion did not significantly affect the enantioselectivity of the cyanosi-

lylation of benzaldehyde, but it did have a significant influence on the rate of reaction. The most active catalyst was **332d**, which possessed a fluoride counterion. Through kinetics experiments, it was established that the counterion has a profound effect on the structure of the catalytically active species and thus on the reaction mechanism. At 293 K, all of complexes **332** displayed second order kinetics. This kinetic behavior distinguished VO(salen)X complexes **332** from titanium-based catalyst **157** and suggested that the two catalysts had different catalytic cycles, as complex **157** displayed first order kinetics with the rate being independent of the concentration of benzaldehyde.[133,135] Oxovanadium-(salen) complexes are known to exist in monomeric and oligomeric forms;[191,192] and in particular, fluoride containing complexes are known to be oligomeric, which may explain the high catalytic activity of this complex.[193]

Kinetics experiments were performed using catalysts **332** at different temperatures. Interestingly, complexes **332e**,**f** showed a change in overall reaction order from second to zero order as the reaction temperature was reduced from 293 to 263 K. The reaction atmosphere was also found to be an important factor influencing the catalyst activity.[190] Under an argon atmosphere, the complexes were either inactive or deactivated before the reaction was complete. This suggests that the initial vanadium(V) complexes are reduced to catalytically inactive vanadium(IV) complexes during the cyanohydrin synthesis and oxygen is needed to reoxidize the vanadium ions. This effect also explains the change to zero order kinetics observed at lower temperatures for some of the catalysts as the reoxidation becomes the rate determining step of the whole process.

North *et al.* prepared a series of VO(salen)Cl complexes **336**−**344** to investigate the influence of different chiral diamines within the salen unit on the catalytic activity of the complexes.[138] Complexes **336**−**344** were used as catalysts for the asymmetric addition of trimethylsilyl cyanide to benzaldehyde (Table 110). The best enantioselectivities 80% and 81% were achieved using 1 mol % of the 1,2-diphenyldiamine derived complex **336** and 0.1 mol % of the valine derived complex **344**, respectively. The lower activity of catalysts **336**−**340** compared to those of complexes **341**−**344** is probably due to the differing counterion, as complex **332c** is much more active than complex **332a** (Table 109). The results obtained were however inferior to that achieved using the corresponding cyclohexanediamine derived catalyst **332c** (93% asymmetric induction). Thus, variation of the diamine linker led to lower asymmetric induction, and this was reasoned to be due to the flexible nature of the ligand, as discussed in section 2.2.5 for the corresponding titanium complexes. The catalytic activity of complex **344** was tested with eight other aromatic and aliphatic aldehydes, and enantioselectivities of 45−78% were obtained (Table 111).

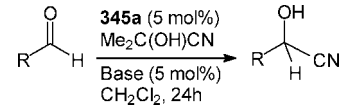
Oxovanadium(salen) complex **345a** was used by Katsuki for the enantioselective cyanation of aldehydes using acetone cyanohydrin as the cyanide source in the presence of a base (Scheme 43).[194] In order to determine the optimal conditions, 3-phenylpropanal was used as substrate with different bases and at various temperatures (Table 112). The highest enantioselectivity (90%) was achieved using 2,4,6-trimethylpyridine as base at 0 °C; however, under these conditions, the yield was low with only 25% conversion after 24 h. The conversion could be increased to 87% by leaving the reaction for 48 h at 10 °C, though at the expense of a slight reduction in the enantioselectivity to 82%.

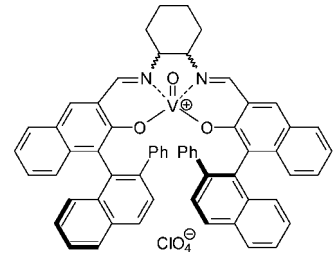
Table 110. Asymmetric Cyanosilylation of Benzaldehyde Catalyzed by Complexes 336−344[a]

catalyst (mol %)	conversion (%)	ee (%)
336 (0.1)	83	68 (*S*)
336 (1.0)	100	80 (*S*)
337 (0.1)	16	28 (*R*)
337 (1.0)	58	20 (*R*)
337 (2.0)	66	20 (*R*)
338 (0.1)	78	53 (*R*)
338 (1.0)	80	62 (*R*)
338 (2.0)	84	62 (*R*)
339 (0.1)	12	6 (*R*)
339 (1.0)	55	23 (*R*)
339 (2.0)	59	23 (*R*)
340 (0.1)	57	26 (*R*)
340 (1.0)	72	52 (*R*)
340 (2.0)	77	56 (*R*)
341 (0.1)	57	4 (*S*)
342 (0.1)	24	62 (*S*)
343 (0.1)	53	32 (*S*)
344 (0.1)	100	81 (*S*)

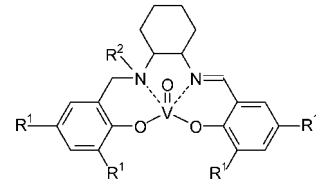
[a] Reactions carried out at ambient temperature in dichloromethane.

Scheme 43





345a



345b R^1 = ^{t}Bu, R^2 = Me; stereochemistry = (*S*,*S*)
c) R^1 = ^{t}Hex, R^2 = Me; stereochemistry = (*R*,*R*)
d) R^1 = ^{t}Bu, R^2 = Et; stereochemistry = (*R*,*R*)
e) R^1 = ^{t}Hex, R^2 = Et; stereochemistry = (*R*,*R*)

Using catalyst **345a** derived from (*S*,*S*)-diaminocyclohexane resulted in a lower enantioselectivity (48%) compared to that achieved with the *R*,*R*-complex (70%) under the same conditions, which indicates the importance of the axial chirality of the binaphthyl unit in this type of salen complex. The optimized catalytic system was also used for the asymmetric addition of acetone cyanohydrin to a range of aliphatic aldehydes and benzaldehyde (Table 113). This system gave moderate to good enantioselectivities for aliphatic substrates, but a lower asymmetric induction of just 45% was obtained for benzaldehyde.

Recently, Katsuki extended this study to the use of VO(salalen) complexes **345b**−**e**.[195] Salalen ligands are known to be more prone to forming cis-β configured

Table 111. Asymmetric Cyanosilylation of Aldehydes Catalyzed by Complex 344[a]

aldehyde	conversion (%)	ee (%) (*S*)
3-MeC_6H_4CHO	86	78
4-MeC_6H_4CHO	90	78
4-$MeOC_6H_4CHO$	100	45
4-$F_3CC_6H_4CHO$	100	77
CyCHO	91	73
$CH_3(CH_2)_7CHO$	93	73
Me_2CHCHO	85	73
Me_3CCHO	100	45

[a] Reactions carried out in dichloromethane for 16 h at room temperature using 0.1 mol % of catalyst.

Table 112. Asymmetric Addition of Acetone Cyanohydrin to 3-Phenylpropanal Catalyzed by Complex (*R*,*R*)-345a under Different Conditions[a]

base	temp (°C)	yield (%)	ee (%)
none	rt	13	84 (*R*)
Et_3N	rt	>99	65 (*R*)
pyridine	rt	34	85 (*R*)
2,4,6-trimethylpyridine	rt	99	70 (*R*)
2,6-dichloropyridine	rt	4	72 (*R*)
2,4,6-trimethylpyridine	10	57	86 (*R*)
2,4,6-trimethylpyridine [b]	10	87	82 (*R*)
2,4,6-trimethylpyridine [b]	0	25	90 (*R*)
2,4,6-trimethylpyridine [c]	rt	99	48 (*S*)

[a] 5 mol % of catalyst and base were used in dichloromethane for 24 h. [b] Reaction time was 48 h. [c] (*S*,*S*)-**345a** was used.

Table 113. Asymmetric Addition of Acetone Cyanohydrin to Aldehydes Catalyzed by (*R*,*R*)-345a−e[a]

catalyst	aldehyde	conversion (%)[b]	ee (%)
345a[a]	$CH_3(CH_2)_6CHO$	75 (65)	84 (*R*)
345a[a]	$PhO(CH_2)_5CHO$	61 (59)	79 (*R*)
345a[a]	CyCHO	79 (55)	76 (*R*)
345a[a]	Me_3CCHO	− (29)[d]	67 (*R*)
345a[a]	PhCHO[c]	13	45 (*R*)
345b[e]	$PhCH_2CH_2CHO$	>99	81 (*R*)[g]
345c[e]	$PhCH_2CH_2CHO$	>99	87 (*S*)
345d[e,f]	$PhCH_2CH_2CHO$	37	89 (*S*)
345e[e,f]	$PhCH_2CH_2CHO$	>99	92 (*S*)
345e[e,f]	$Me(CH_2)_6CHO$	83	94
345e[e,f]	CyCHO	>99	94 (*S*)
345e[e,f]	*cyclo*-C_5H_9CHO	75	95
345e[e,f]	^tBuCHO	92	94 (*S*)
345e[e,f]	EtCH(Me)CHO	66	94 (*S*)
345e[e,f]	$^tBuPh_2SiO(CH_2)_5$	>99	94
345e[e,f]	Ph	61	39

[a] Reactions carried out in dichloromethane for 48 h at 10 °C using 5 mol % of catalyst and 2,4,6-trimethylpyridine. [b] Figure in parentheses is the isolated yield. [c] Reaction time was 12 h. [d] Conversion not determined; isolated yield calculated as corresponding benzoate ester. [e] Reactions carried out in dichloromethane for 24 h at 0 °C using 10 mol % of catalyst in the presence of oxygen. [f] Reaction time was 36 h. [g] Catalyst had (*S*,*S*)-configuration.

complexes[196] than salen ligands, and Katsuki also showed that the catalytically active species is the corresponding V(V) species formed *in situ* by air oxidation of complexes **345b**−**e**. Optimal results were obtained with precatalyst **345e** at 0 °C, which for aliphatic aldehyde substrates gave enantioselectivities of 92−95% after a reaction time of 36 h using 10 mol % of the catalyst (Table 113). At 0 °C, racemization of the cyanohydrins of aliphatic aldehydes was suppressed under the reaction conditions, though benzaldehyde gave mandelonitrile with only 25−39% enantiomeric excess under these conditions, showing that racemization of aromatic cyanohydrins was still facile and thus that the methodology was limited to the synthesis of cyanohydrins of aliphatic aldehydes. Significantly, however, this contrasts with the Belokon/North system, which gave better results with aromatic aldehydes as substrates.

In general, most investigations of vanadium-catalyzed cyanation reactions are devoted to studies of complexes **332**. In addition to high enantioselectivity, amongst the advantages of this system are very low catalyst loading (0.1 mol %), ability to run reactions at room temperature, relatively easy synthesis of the catalysts, and the ability to use alternative cyanide sources. All these advantages have resulted in catalysts **332** being commercialized by NPIL Pharma Ltd. (CACHy) along with titanium complex **157**. Despite its generally higher enantioselectivity compared to that of titanium complex **157**, catalyst **332a** has considerably lower activity, which leads to an increase of the reaction time (up to 24 h) in comparison to the 15−20 min needed for reactions catalyzed by complex **157**, though this has been remedied somewhat with the recent development of complexes **332c**,**d** with different counterions. Very low activity in the cyanosilylation of ketones is another disadvantage of catalysts **332**. Nonetheless, vanadium complexes **332** appear to be the catalyst of choice to obtain the best enantioselectivities under mild reaction conditions (ambient temperature, low catalyst loading, no oxygen/moisture exclusion required).

2.4. Heterobimetallic Catalytic Systems of Vanadium and Titanium

The rapid rates of reaction obtained using titanium(salen) complex **157** and the high enantioselectivity achieved using vanadium catalysts **332** are attractive features for asymmetric cyanohydrin synthesis. Since the dimeric titanium complex **157** dissociates in solution,[135] it was felt that it might be possible to prepare a heterobimetallic complex which combines the favorable features of these two catalysts. In 2004, Belokon, North, *et al.* reported a study which used a mixture of vanadium complex **332a** and titanium complex **157** derived from opposite enantiomers of cyclohexanediamine.[197] In the absence of heterobimetallic complex formation, it was expected that combining the two systems would result in almost exclusive catalysis by titanium complex **157**; thus, the chirality of the cyanohydrin product would also be determined by the stereochemistry of the salen ligand attached to the titanium ion. A mixture of mononuclear vanadium complex (*S*,*S*)-**332a** and dimeric titanium complex (*R*,*R*)-**157** was used in a 2:1 ratio to catalyze the asymmetric addition of trimethylsilyl cyanide to benzaldehyde. Unexpectedly, (*R*)-mandelonitrile trimethylsilyl ether was obtained with 82% enantiomeric excess, indicating that the stereochemistry of the salen ligand attached to vanadium rather than that attached to titanium was determining the configuration of the product.

By running a series of experiments in which the ratio of (*S*,*S*)-**332a** to (*R*,*R*)-**157** was varied, it was found that as little as 10% of the vanadium complex (relative to complex **157**) was required to offset the stereochemical influence of the salen ligand attached to titanium and produce racemic mandelonitrile trimethylsilyl ether. When 20% of vanadium complex **332a** was used, the product enantioselectivity was already largely controlled by the vanadium, giving (*R*)-product with about 60% enantiomeric excess. Kinetics experiments revealed that the rate of reaction in these mixed systems was intermediate to that of the individual catalysts **157**and **332a**. The results suggested that catalysts **157** and **332a** combine *in situ* to create a catalytically active,

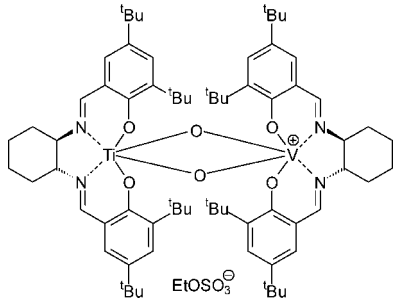


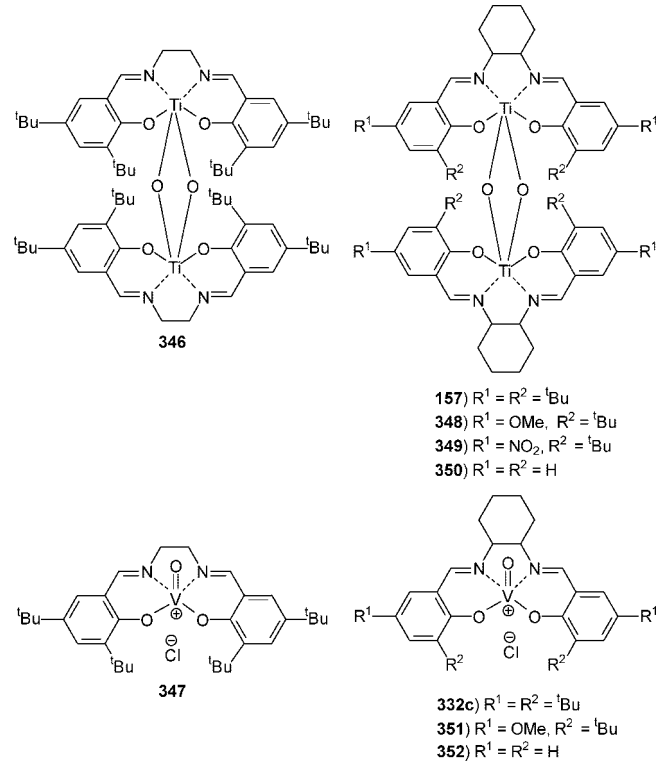
Figure 17.

heterobimetallic species containing both titanium and vanadium metal centers as shown in Figure 17. The results also suggest that, in the key stereodetermining transition state, the aldehyde binds to the more Lewis-acidic, positively charged vanadium ion (so that the stereochemistry of the salen ligand attached to vanadium predominantly determines the stereochemistry of the product) whilst cyanide is transferred intramolecularly from the titanium ion (see Figures 4 and 5).

Further investigations into heterobimetallic systems were made by the same group using combinations of chiral and achiral salen ligands to prepare titanium and vanadium catalysts.[198] To study the formation and catalytic properties of heterobimetallic complexes, achiral titanium **346** and vanadium **347** complexes were prepared and used in combination with chiral complexes **157**, **332c**, and **348**−**352** as catalysts for the asymmetric addition of cyanide sources to benzaldehyde.

Results again revealed that when a combination of vanadium and titanium catalysts were used together, the asymmetric induction depended largely on the nature of the vanadium catalyst. For example, use of chiral titanium complex (*R*,*R*)-**157** and achiral vanadium complex **347** in 1:2 ratio to catalyze the addition of trimethylsilyl cyanide to benzaldehyde resulted in the formation of mandelonitrile trimethylsilyl ether with just 18% enantiomeric excess, though with 100% conversion after a reaction time of 24 h. Complex **347** alone is a slightly less active catalyst, giving 89% conversion of benzaldehyde to racemic mandelonitrile trimethylsilyl ether in the same time period. Conversely, when achiral titanium complex **346** was used with vanadium complex (*R*,*R*-**332c**), (*S*)-mandelonitrile trimethylsilyl ether was formed with 92% enantiomeric excess. These results and those obtained using other combinations of complexes **157**, **332c**, and **346**−**352** indicate that the asymmetric induction is always principally determined by the salen ligand attached to the vanadium ion. Structural evidence to support the *in situ* formation of heterobimetallic complexes with the structure shown in Figure 17 was obtained during this study by a combination of ^{1}H NMR spectroscopy and high resolution electrospray mass spectrometry, with the latter being particularly diagnostic, as the characteristic isotope pattern associated with one titanium and one vanadium ion was readily detectable.[198b]

In addition to the titanium/vanadium mixtures, mixtures of two different titanium complexes were investigated. For example, when chiral complex **157** was combined with achiral complex **346**, the asymmetric induction was approximately half of that obtained when using complex **157** alone, but the conversion was much lower. Complex **346** is a much less active catalyst than complex **157**, a feature which can be traced to its formation of the thermodynamically more stable ΔΛ-configuration, whilst the chiral salen ligands in complex **157** force it to adopt the less stable ΔΔ-configuration.[198a] Once again, mass spectrometry clearly indicated that mixed bimetallic complexes were being formed *in situ*,[198b] and in this case, since both metal ions are titanium, they will have similar Lewis-acidity, so it is equally likely that the benzaldehyde will coordinate to the titanium bearing the chiral or the achiral ligand, which accounts for the observed asymmetric induction.



Salen ligands substituted with electron rich and withdrawing groups were also studied as catalysts for the asymmetric addition of trimethylsilyl cyanide to benzaldehyde. A moderate enantioselectivity of 58% was achieved using methoxy substituted titanium salen complex **348**, but the nitro substituted complex **349** gave just an 8% yield and 19% asymmetric induction. Mixtures of these titanium complexes again gave enantioselectivities approximately midway between those of the individual complexes. A good asymmetric induction (92%) was achieved using methoxy substituted vanadium salen complex **351**.

The use of other cyanide sources was also investigated. Previous results had shown that whilst titanium complex **157** will catalyze the asymmetric addition of ethyl cyanoformate to aldehydes (see section 2.2.3.3), vanadium-based complexes **332** would not catalyze this reaction. It was found that when any vanadium-based catalyst was mixed with any of the titanium-based catalysts, all catalytic activity was lost, a result which is again consistent with the *in situ* formation of a (catalytically inactive) heterobimetallic complex as shown in Figure 17. When a mixture of two different titanium-based complexes was used to catalyze the addition of ethyl cyanoformate to benzaldehyde, mandelonitrile ethyl carbonate was formed with an enantiomeric excess intermediate between those obtained using the two complexes individually.

The heterobimetallic system was also used to promote the asymmetric addition of potassium cyanide and acetic anhydride to aldehydes. However, for this reaction it was found

Table 114. Asymmetric Addition of Potassium Cyanide to Benzaldehyde Catalyzed by Titanium Complexes 157 and 346 and Vanadium Complexes 332c and 347[a]

catalyst(s)	conversion (%)	ee (%)
(*R*,*R*)-**157**	100	93 (*S*)
(*S*,*S*)-**332c**	70	94 (*R*)
(*R*,*R*)-**157** + (*S*,*S*)-**332c**	24	72 (*S*)
346	<10	0
347	<10	0
346[b]	27	0
347[b]	47	0
(*R*,*R*)-**157** + **347**	23	44 (*S*)
346 + (*S*,*S*)-**332c**	21	1 (*S*)
(*R*,*R*)-**157** + **346**	73	73 (*S*)
(*S*,*S*)-**332c** + **347**	40	46 (*R*)

[a] Reactions were carried out in dichloromethane at ambient temperature using a total of 1 mol % of catalyst relative to benzaldehyde. [b] Chloroform was used as solvent.

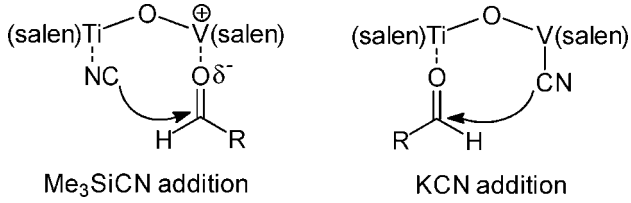


Figure 18.

that the salen ligand attached to titanium was responsible for the asymmetric induction rather than that attached to vanadium, which controlled the stereochemistry in the case of trimethylsilyl cyanide addition. Selected results for the enantioselective cyanation of benzaldehyde with a mixture of salen catalysts are shown in Table 114.

The reversal in product stereochemistry was explained by assuming that the ionic nature of the potassium cyanide means that the cyanide ion is strongly attracted to the positively charged vanadium metal center. The aldehyde would then have to bind to the titanium metal center, and thus, the addition of cyanide would occur within the chiral environment generated by the titanium bound ligand (Figure 18). In contrast, the most polar bond in the trimethylsilyl cyanide system is the aldehyde carbonyl bond, which will then have a preference for binding to the vanadium cation. This leads to asymmetric induction controlled by the ligand around the vanadium ion. As discussed above for trimethylsilyl cyanide addition, the potassium cyanide system using two titanium-based catalysts gives results which are intermediate to those of the individual catalysts, indicating no preference for binding of substrates to either metal center.

Conducting the reaction in chloroform resulted in a higher activity for the normally poorly active complexes **346** and **347**. On the basis of NMR studies, this was attributed to a greater amount of the catalytically active ΔΔ-stereoisomer of the dimer being present in chloroform solution than in dichloromethane. Kinetics experiments for trimethylsilyl cyanide addition to benzaldehyde also showed a faster rate of reaction for complex **346** in chloroform than in dichloromethane. However, the opposite effect was seen for catalyst **157**, for which the reaction rate in chloroform was slower than that observed in dichloromethane. This was also consistent with the ^{1}H NMR spectrum of catalyst **157**, since in dichloromethane only the catalytically active ΔΔ-stereoisomer was detected, whilst in chloroform a mixture of stereoisomers was present.

Table 115. Asymmetric Addition of Trimethylsilyl Cyanide to Aldehydes Catalyzed by $AlMe_3$−353[a]

aldehyde	time (h)	yield (%)	ee (%) (*R*)
PhCHO	5	66	71
PhCHO	24	95	69
2-MeC_6H_4CHO	3	75	58
3-$MeOC_6H_4CHO$	4	92	56
CyCHO	0.5	86	56
CyCHO	17	61	56
$CH_3(CH_2)_5CHO$	24	84	37

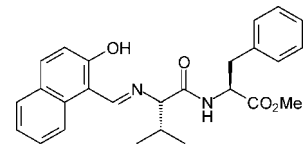
[a] Reactions were carried out in toluene at −78 °C.

Although there was no improvement in terms of enantioselectivity over the use of individual complexes **157** and **332c**, the study of heterobimetallic complexes provided important insight into the structure of the catalysts, the reaction mechanism, and the origin of the asymmetric induction. The results reinforce the mechanisms shown in Figures 4–6.

2.5. Aluminum-Based Catalytic Systems

2.5.1. Complexes of C_1-Symmetric Schiff Bases

Despite the absence of catalytic activity displayed by the titanium−peptide complexes developed by Inoue (see section 2.2.2), for the addition of trimethylsilyl cyanide to aldehydes, this process was catalyzed by the analogous aluminum complexes.[95] For example, the complex formed from peptide **22** and trimethylaluminum afforded silylated cyanohydrins from aromatic and aliphatic aldehydes in 66−92% yield and with 37−71% enantioselectivity. The highest enantioselectivity was achieved using ligand **353** for the addition of trimethylsilyl cyanide to benzaldehyde, which gave mandelonitrile trimethylsilyl ether with 71% enantiomeric excess in 66% yield after a reaction time of 5 h. Leaving the reaction for 24 h increased the yield to 95% whilst retaining an enantioselectivity of 69% (Table 115). This system has not proved to be of great synthetic importance but was interesting as the first example of asymmetric cyanosilylation of aldehydes catalyzed by aluminum complexes.



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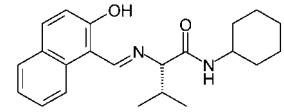


353

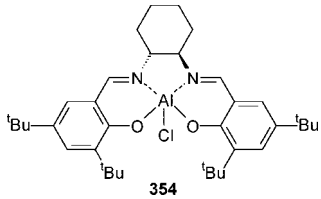
2.5.2. Complexes of C_2-Symmetric Schiff Bases

Kim and Song used the aluminum chloride complex **354** of ligand **142** with triphenylphosphine oxide as an additive for the cyanosilylation of aldehydes.[199] The reaction was optimized using benzaldehyde as substrate, and the best conditions were found using 1 mol % of catalyst **354** with 10 mol % of triphenylphosphine oxide at −50 °C in dichloromethane. This gave *O*-silylated mandelonitrile in 94% yield and with 86% enantiomeric excess after a reaction time of 18 h. A range of aliphatic and aromatic aldehydes

Table 116. Asymmetric Addition of Trimethylsilyl Cyanide to Aldehydes Catalyzed by Complex 354[a]

aldehyde	time (h)	temp (°C)	yield (%)	ee (%) (*R*)
PhCHO	18	−50	94	86
4-ClC_6H_4CHO	18	−50	96	86
4-$MeOC_6H_4CHO$	18	−50	92	82
4-MeC_6H_4CHO	22	−45	94	72
4-$^tBuC_6H_4CHO$	21	−45	93	73
4-$PhOC_6H_4CHO$	20	−50	93	81
PhCH=CHCHO	26	−40	91	78
furan-2-carboxaldehyde	18	−50	93	78
$PhCH_2CH_2CHO$	21	−50	93	79
$Me_2C=CH(CH_2)_2C(Me)=CHCHO$	24	−50	93	72

[a] Reactions were carried out in dichloromethane with 1 mol % of **354** and 10 mol % of Ph_3PO.



354

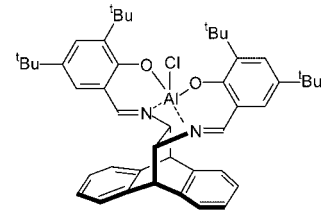
were used as substrates under the optimized conditions and afforded the corresponding cyanohydrin products in 91−96% yield and with 72−86% enantiomeric excesses (Table 116). Enantioselectivities and yields were consistently good for all substrates, with only a marginal preference apparent for aromatic aldehydes. Catalyst **354** was also used successfully by Kim for the asymmetric cyanosilylation of ketones (see section 3.3).

Zhou et al. developed aluminum complex **355** of ligand **199** for the asymmetric cyanosilylation of aldehydes.[200] Using trioctylphosphine oxide as a cocatalyst, an enantioselectivity of 86% was achieved using benzaldehyde as substrate during preliminary screening to optimize the reaction conditions. A number of aliphatic and aromatic aldehydes were then used as substrates under the optimized conditions (Table 117). Good enantioselectivities were obtained for all substrates, with the exception of 3-phenylpropanal, which gave only 42% asymmetric induction. Complex **355** was an improvement over the titanium complex of ligand **199** developed by the same authors (see section 2.2.3.5).

Table 117. Asymmetric Addition of Trimethylsilyl Cyanide to Aldehydes Catalyzed by Complex 355[a]

aldehyde	time (h)	yield (%)	ee (%)
PhCHO	16	93	86 (*S*)
4-ClC_6H_4CHO	14	86	70 (*S*)
2-$MeOC_6H_4CHO$	12	89	86 (*R*)
4-$MeOC_6H_4CHO$	12	90	81 (*S*)
2-MeC_6H_4CHO	12	94	80 (*S*)
3-MeC_6H_4CHO	12	92	88 (*S*)
4-MeC_6H_4CHO	12	90	92 (*S*)
1-naphthaldehyde	12	85	76 (*S*)
furan-2-carboxaldehyde	12	90	86 (*R*)
PhCH=CHCHO	12	89	78 (*S*)
$PhCH_2CH_2CHO$	12	89	42 (*R*)

[a] Reactions were carried out in dichloromethane at 10 °C using 1 mol % of catalyst **355** with 10 mol % of $nOct_3PO$.

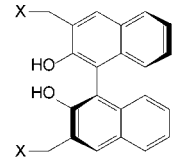


355

2.5.3. Complexes of BINOL-Based Ligands

An important area of catalysis by aluminum complexes was discovered by Shibasaki, who developed bifunctional ligand **356** based on BINOL, which combined the properties of both a Lewis acid and a Lewis base when complexed to a metal. The complex formed from ligand **356** and aluminum trichloride was found to give excellent results for the cyanosilylation of aldehydes.[201] Utilization of the catalyst under the conditions shown in Scheme 44 in the presence of an additive ($MeP(O)Ph_2$ or Bu_3PO) afforded cyanohydrin silyl ethers in 86−100% yield and with 90−98% enantiomeric excess (Table 118). It is notable that high enantioselectivities and yields were obtained for both aromatic and aliphatic substrates.

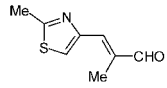
During the development of **356**-based catalysts, Shibasaki prepared a number of analogues **357a**−**e** of the ligand in which the phosphine oxide Lewis base was changed (**357a**−**d**) or the length of the linker between the phosphine oxide and the binol unit was modified (**357e**).[201] These modified ligands were complexed to aluminum, titanium, gallium, and zirconium, but in all cases except for the combination of aluminum and **357d**, only low levels of asymmetric induction (<35%) were observed. A kinetic study showed that the aluminum complex of ligand **357d** was a more active and more enantioselective catalyst than that of ligand **356**. These results indicated the critical role of the Lewis base in obtaining high enantioselectivity and also the importance of having the correct juxtaposition of the Lewis acidic and Lewis basic centers.



357a) X = PPh_2
b) X = SEt
c) X = $CHPh_2$
d) X = $PO(4\text{-}Me_2NC_6H_4)_2$
e) X = CH_2POPh_2

It was shown that the use of an additional, external phosphine oxide as an additive had a positive effect on the enantioselectivity of the cyanation reaction. This was proposed to be due to the formation of a pentacoordinated aluminum complex in which a bound trimethylsilyl cyanide molecule is delivered to one face of the aluminum-coordinated aldehyde without competing addition to the opposite face, which is hindered by the additive (Figure 19). In the absence of the additive, the two phosphine oxide units in ligand **356** would be able to deliver trimethylsilyl cyanide to opposite faces of the coordinated aldehyde within a tetrahedrally coordinated aluminum complex. On the basis of these kinetics and structure−activity studies, Shibasaki developed the catalytic cycle shown in Figure 20 to account for catalytic asymmetric cyanohydrin synthesis catalyzed by this class of catalysts.

Table 118. Asymmetric Addition of Trimethylsilyl Cyanide to Aldehydes Catalyzed by $AlCl_3$−356[a]

aldehyde	additive	time (h)	yield (%)	ee (%) (*S*)
$PhCH_2CH_2CHO$	$Bu_3P=O$	37	97	97
$CH_3(CH_2)_5CHO$	$Bu_3P=O$	58	100	98
$(Me)_2CHCHO$	$Bu_3P=O$	45	96	90
Et_2CHCHO	$Bu_3P=O$	60	98	83
(*E*)-$CH_3(CH_2)_3CH=CHCHO$	$Bu_3P=O$	58	94	97
$PhCH=CHCHO$	$Bu_3P=O$	40	99	98
	$Bu_3P=O$	36	91	97
$PhCHO$	$MeP(O)Ph_2$	96	98	96
4-MeC_6H_4CHO	$MeP(O)Ph_2$	79	87	90
Furan 2-carboxaldehyde	$MeP(O)Ph_2$	70	86	95

[a] Reactions were carried out in dichloromethane at −40 °C with dropwise addition of Me_3SiCN over a period of 10 h unless otherwise stated.

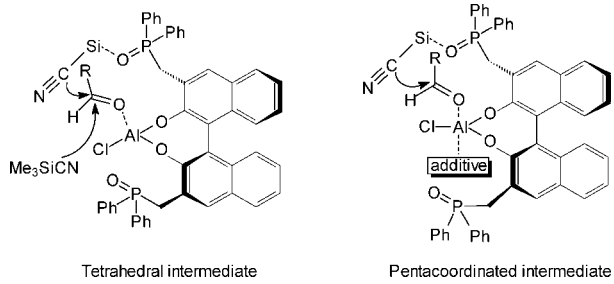
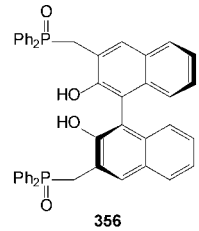
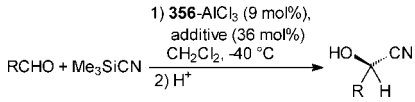


Figure 19.

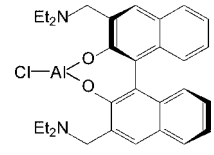
Scheme 44





The aluminum complex of ligand **356** has been used by Shibasaki in a number of total syntheses. Thus, Takamura and Shibasaki prepared cyanohydrin **358** in 85% yield and with 96% enantiomeric excess as part of a synthetic route to the antihyperglycaemic compound **359** (Scheme 45).[202] The aluminum complex of ligand **356** was also used by Nogami and Shibasaki to create chiral building blocks for the synthesis of the HIV protease inhibitor Atazanvir and a β_3-adenergic receptor agonist.[203] The diastereoselective addition of trimethylsilyl cyanide to *N*-protected 2-amino-3-phenylpropanal was carried out, and the resulting cyanohydrins were then reduced or hydrolyzed depending on the required product (Scheme 46). In the same paper, the use of the aluminum complex of ligand **356** in the asymmetric cyanosilylation of 3-chlorobenzaldehyde was described. An enantioselectivity of 90% was achieved in 98% yield with 9 mol % catalyst using methanol as solvent at −40 °C for 96 h. The resulting *O*-trimethylsilyl cyanohydrin could be reduced to 2-hydroxy-2-(3-chlorophenyl)ethylamine, which is a key component of a number of pharmaceuticals. In this work, Shibasaki also reported a work-up procedure which allows ligand **356** to be recovered and reused.

The aluminum complex of ligand **356** was also used by Shibasaki as part of a total synthesis of epothilones A and B, drug candidates with similar properties to taxol for cell nucleus microtubule binding.[204] The catalyst was used for the asymmetric cyanation of thiophene-containing α,β-unsaturated aldehyde **360** (Scheme 47). After screening a number of different conditions, the method was highly successful, with cyanohydrin intermediate **361** being obtained in 97% yield and with 99% enantiomeric excess, though slow addition of trimethylsilyl cyanide over 50 h at −40 °C was required to achieve this result.



Building on Shibasaki's work, Nájera, Saá, and co-workers synthesized BINOLAM-based aluminum complex **362** in order to obtain a reusable catalyst for the asymmetric addition of trimethylsilyl cyanide to aldehydes.[205,206] The use of 10 mol % of complex **362** formed *in situ* from the BINOLAM ligand and dimethylaluminum chloride in the presence of 4 Å molecular sieves and 40 mol % of triphenylphosphine oxide, followed by an acidic workup, afforded a series of cyanohydrins in 45−99% yield and with 66−98% enantioselectivity (Table 119). The best enantioselectivities were

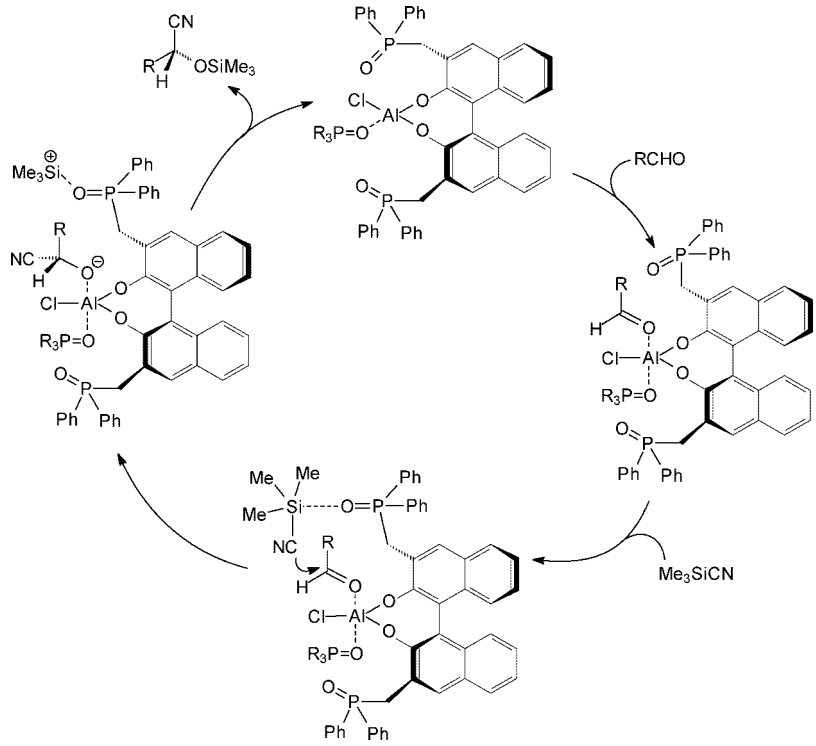
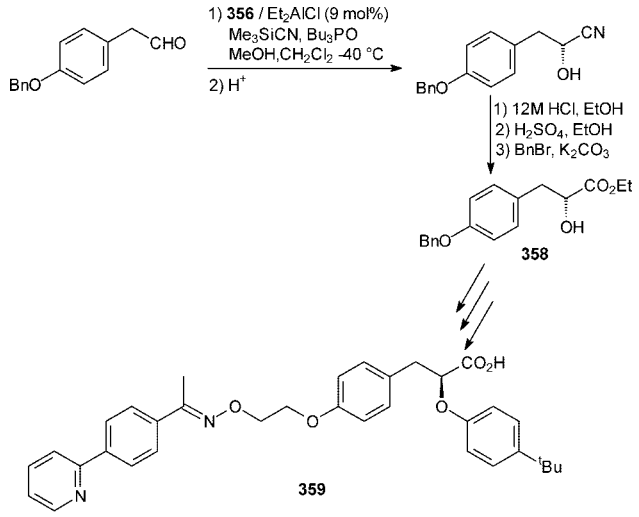
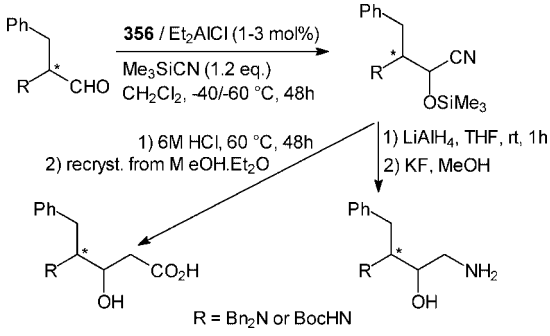


Figure 20.

Scheme 45

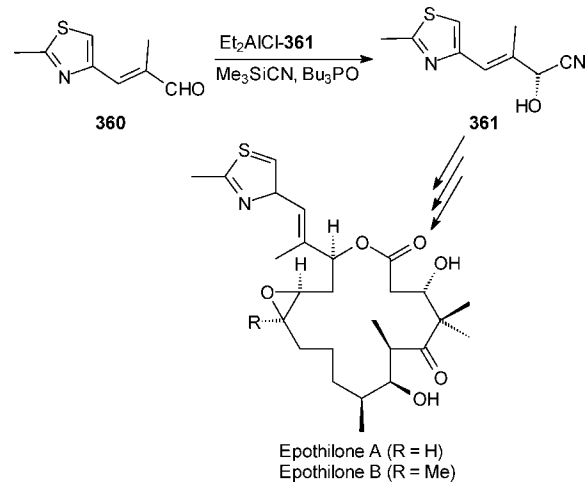


Scheme 46



obtained using benzaldehyde and its methoxy- and chloro-substituted derivatives, which gave 96−98% asymmetric induction. Of the aldehydes studied, only heptanal gave a relatively low enantioselectivity of 66%. A yield of 99% was obtained in all cases, except when 4-phenoxybenzaldehyde

Scheme 47



was used as the substrate. The ligand could be recovered by a simple acid−base workup, which allowed it to be reused without loss of catalytic activity.

Nájera and Saá also studied the use of complex **362** for the addition of alternative cyanide sources to aldehydes. Utilization of 10 mol % of the catalyst in the presence of 4 Å molecular sieves accomplished the asymmetric addition of methyl cyanoformate to aromatic and aliphatic aldehydes in 95−98% yield and with 54−82% enantioselectivity (Table 120).[42c,207] This modification did not require any phosphine-oxide additives, although 3−4 equiv of the cyanating agent was needed. On the basis of detailed mechanistic studies,[207] the authors proposed a catalytic cycle (Figure 21) in which complex **362** acts as a bifunctional catalyst with the diethylamino group acting as a base which coordinates to hydrogen cyanide generated *in situ* from the cyanoformate.

The same group also developed a novel process for the preparation of enantioenriched cyanohydrin *O*-phosphonates.[42] Thus, use of 10 mol % of aluminum complex **362**

Table 119. Asymmetric Addition of Trimethylsilyl Cyanide to Aldehydes Using Catalyst 362[a]

aldehyde	**362** config	temp (°C)	time (h)	yield (%)	ee (%)
PhCHO	*S*	−20	6	99	98 (*R*)
PhCHO	*R*	−20	6	99	98 (*S*)
PhCHO[b]	*S*	−20	6	99	98 (*R*)
4-$MeOC_6H_4CHO$	*S*	−20	20	99	98 (*R*)
2-ClC_6H_4CHO	*R*	−20	8	99	96 (*S*)
4-ClC_6H_4CHO	*S*	−20	21	99	98 (*R*)
4-$PhOC_6H_4CHO$	*S*	−20	48	70	70 (*R*)
4-$PhOC_6H_4CHO$	*S*	−40	48	45	78 (*R*)
furan-2-carboxaldehyde	*S*	−20	5	99	76 (*R*)
furan-2-carboxaldehyde	*S*	−40	12	99	92 (*R*)
PhCH=CHCHO	*S*	−20	6	99	82 (*R*)
PhCH=CHCHO	*R*	−40	12	99	98 (*S*)
$PhCH_2CH_2CHO$	*R*	−40	4.5	99	88 (*S*)
$CH_3(CH_2)_5CHO$	*R*	−40	3.5	99	66 (*S*)

[a] Reactions were carried out in toluene using 10 mol % of catalyst **362** with 40 mol % of triphenylphosphine oxide and 4 Å molecular sieves. [b] Result from using recovered catalyst.

Table 120. Asymmetric Addition of Methyl Cyanoformate to Aldehydes Using Catalyst 362[a]

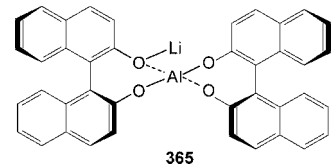
aldehyde	MeOCOCN (equiv)	time (h)	yield (%)	ee (%) (*R*)
PhCHO	3	28	>98	78
4-ClC_6H_4CHO	4	24	>98	80
4-$MeOC_6H_4CHO$	4	20	>98	78
2-naphthaldehyde	4	48	>98	70
pyridine-2-carboxaldehyde	4	20	96	0
PhCH=CHCHO	4	24	95	66
Me_2C=CHCHO	4	12	>98	82
(*E*)-MeCH=CHCHO	1.5	20	>98	54
$PhCH_2CH_2CHO$	4	20	>98	58
$CH_3(CH_2)_5CHO$	3	20	>98	68

[a] Reactions were carried out using 5 mol % of catalyst **362** under a nitrogen atmosphere in dry toluene at ambient temperature with 4 Å molecular sieves.

allowed the addition of diethyl cyanophosphonate to a range of aldehydes with chemical yields of 87−90% and enantioselectivities, in the best cases, of 88−98% (Table 121). Good results were obtained for aromatic, α,β-unsaturated, and aliphatic substrates, but electron deficient aromatic and heteroaromatic aldehydes were found to give lower enantioselectivities (4−26%). Benzaldehyde and hexanal both gave 98% enantioselectivity and similarly high yields, indicating good substrate tolerance for this catalytic system. As described previously, simple acid−base treatment again allowed regeneration of the chiral ligand in 93% yield.[42a] The bifunctional nature of the catalysis was proven by the fact that the analogous BINOL-based complex, lacking the diethylaminomethyl groups, showed low catalytic activity; furthermore, addition of a base such as triethylamine resulted in a considerable loss in enantioselectivity. For this system, a positive nonlinear effect[134] was observed, indicating apparent involvement of dimeric catalytic species in the catalytic cycle. Similar studies were also carried out for the asymmetric addition of trimethylsilyl cyanide to aldehydes catalyzed by complex **362**, which confirmed the bifunctional nature of the catalysis.[206] The same mechanism shown in Figure 21 was suggested to explain the catalysis with diethyl cyanophosphonate in place of methyl cyanoformate.

The use of enantioenriched cyanohydrin *O*-phosphates was illustrated by Nàjera[208] in the synthesis of tembamide **363** and aegeline **364**, which have been shown to have good hypoglycaemic activity.[209] They can be prepared by asymmetric addition of diethyl cyanophosphonate to *p*-methoxybenzaldehyde followed by reduction with lithium aluminum hydride and reaction with benzoyl or cinnamoyl chloride (Scheme 48). Nàjera also showed that cyanohydrin phosphonates were substrates for nucleophilic allylic substitution reactions, giving separable mixtures of enantiomerically enriched α,β-unsaturated nitriles (Scheme 49).[39,42c] The *E*/*Z* ratio of the products was dependent on the nature of the phosphine used. The same type of process could also be achieved by reaction of cyanohydrin phosphonates with Grignard reagents catalyzed by copper cyanide. This gave the opposite enantiomers of the products to those obtained using palladium catalysis.

Shibasaki developed bimetallic lithium−aluminum binol complex **365** as an asymmetric catalyst for Michael additions.[152] Feng's group subsequently reported that, in the presence of a cinchonine cocatalyst, complex **365** would also catalyze the asymmetric addition of ethyl cyanoformate to aldehydes[210] (for related work from the same group on the use of the Ti-binol/cinchonine systems, see section 2.2.7). After screening a number aluminum sources, it was found that use of 10 mol % of the catalyst derived from BINOL, aluminum triisopropoxide, and *n*-butyl lithium with 10 mol % of cinchonine **287** gave an enantioselectivity of 75% for the addition of ethyl cyanoformate to benzaldehyde. In fact, this was the only system that resulted in any degree of asymmetric induction. It was later found that evaporation of the solvent used to prepare the catalyst resulted in a complex which gave an improved 85% enantioselectivity. It was also shown that using triethylaluminum as the metal source along with a variety of alcohol additives gave catalysts which gave similar levels of asymmetric induction (between 74 and 86%, except for phenol, which gave just 52%). The use of 20 mol % of isopropanol gave an enantioselectivity of 86%, the same level of asymmetric induction as when using aluminum triisopropoxide. Changing the ligand by modifying the BINOL unit was shown to result in lower enantioselectivities.



365

A variety of additives, other than cinchonine **287**, were used, but all gave inferior enantioselectivities, with the best being 57% asymmetric induction, achieved using triphenylphosphine oxide, a common additive used alongside aluminum BINOL catalysts by Shibasaki.[152] By changing the concentration of the reagents, a maximum 90% enantioselectivity was achieved with 0.5 M benzaldehyde at −20 °C using 10 mol % of both Al-BINOL and cinchonine. Under these optimized conditions, a range of aromatic and aliphatic aldehydes were used as substrates for the synthesis of cyanohydrin ethyl carbonates (Table 122). Although good substrate tolerance was observed, the best enantioselectivities were achieved using electron rich aromatic aldehydes.

Pu and co-workers developed a one-step synthesis of ligand **366** starting from enantiomerically pure BINOL.[211] Treatment of ligand **366** with dimethylaluminum chloride afforded a highly stereoselective catalyst for cyanosilylation of aldehydes. Benzaldehyde and octanal were used as substrates

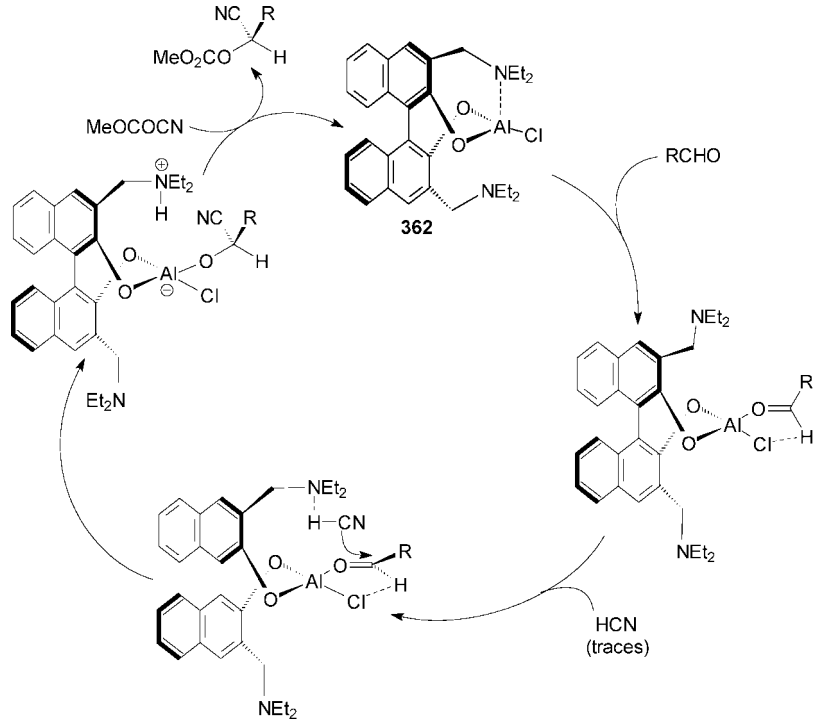
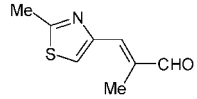


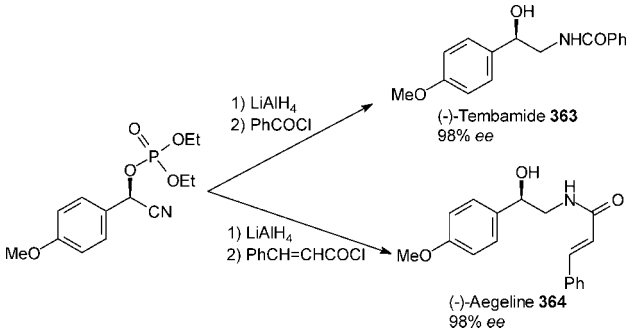
Figure 21.

Table 121. Asymmetric Addition of Diethyl Cyanophosphonate to Aldehydes Catalyzed by Complex 362[a]

aldehyde	time (h)	yield (%)	ee (%)
PhCHO	4	89	98
4-ClC_6H_4CHO	20	88	96
2-ClC_6H_4CHO	4	89	97
4-$MeOC_6H_4CHO$	10	87	98
4-$O_2NC_6H_4CHO$	50	87	26
Pyridine-2-carboxaldehyde	24	90	4
(*E*)-MeCH=CHCHO	2	89	88
PhCH=CHCHO	7	82	95
2-Naphthaldehyde	1.5	91	94
(*E*)-$CH_3(CH_2)_4CH$=CHCHO	6	90	94
	4	89	90
$PhCH_2CHO$	2	90	36
3-$PhOC_6H_4CHO$	2	90	97
$CH_3(CH_2)_5CHO$	3	90	98
$PhCH_2CH_2CHO$	2	90	92

[a] Reactions were carried out in toluene at ambient temperature using 10 mol % of **362**. Enantioselectivities reported for cyanohydrin *O*-phosphates after acidic hydrolysis and column chromatography.

Scheme 48



Scheme 49

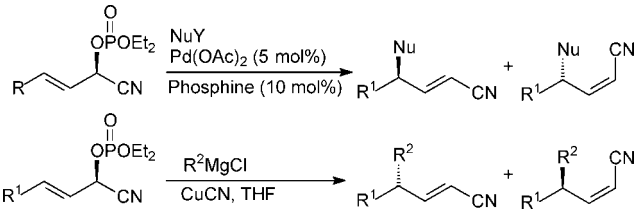


Table 122. Asymmetric Addition of Ethyl Cyanoformate to Aldehydes Catalyzed by (*S*)-Al-BINOL 365 and Cinchonine[a]

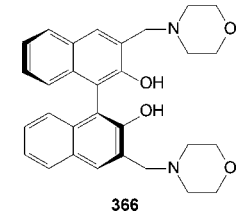
aldehyde	time (h)	yield (%)	ee (%) (*S*)
PhCHO	1.5	99	90
2-MeC_6H_4CHO	1.5	98	83
2-$MeOC_6H_4CHO$	2	96	95
3-$MeOC_6H_4CHO$	2	97	82
4-$MeOC_6H_4CHO$	10	89	85
3-$PhOC_6H_4CHO$	1.5	96	91
2-naphthaldehyde	1.5	97	86
2-naphthaldehyde[b]	24	88	90
4-FC_6H_4CHO	1.5	97	84
4-ClC_6H_4CHO	2	96	81
PhCH=CHCHO	2.5	90	80
CH_3CH_2CHO	1.5	94	80
Me_2CHCHO	1.5	95	78
$CH_3(CH_2)_4CHO$	1.5	95	81
CyCHO	2	96	74

[a] Reactions were carried out in dichloromethane at −20 °C using 10 mol % of **365** with 10 mol % of cinchonine. [b] Reaction was conducted at −45 °C.

for a number of experiments to establish the optimal conditions for the reaction. For octanal, it was found that using 10 mol % of the catalyst with ether as solvent and 5 mg of 4 Å molecular sieves and 40 mol % of HMPA as additives gave the best enantioselectivity of (97%) after a reaction time of 24 h. Leaving the reaction for only 3 h and using a higher amount of molecular sieves reduced the enantiomeric excess of the product significantly. A range of aromatic and aliphatic aldehydes were used as substrates and gave cyanohydrin silyl ethers in good yields (65−94%) and with 74−98% asymmetric induction (Table 123). It is noteworthy that excellent enantioselectivity was observed for aliphatic substrates (including linear, branched, α,β-unsaturated, and functionalized), which gave only moderate asymmetric induction with catalyst **362**. The reaction showed a strong positive nonlinear effect,[134] which indicated participation of dimeric catalytically active species in the process.

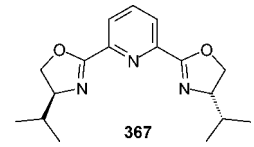
2.5.4. Complexes of Other C_2-Symmetric Ligands

Iovel and co-workers discovered a catalyst formed *in situ* from the PyBOX-based ligand **367** and aluminum trichloride for the asymmetric cyanosilylation of aromatic



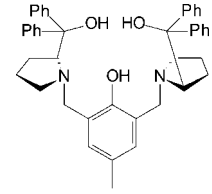
366

aldehydes.[212] In particular, the silyl ether of mandelonitrile was obtained in 92% yield and with 90% enantioselectivity after a reaction time of 4 h using 20 mol % of the complex. Use of other heterocyclic aldehydes (furancarboxaldehyde and thiophene carboxaldehyde derivatives) resulted in good isolated yields of 81−93%, but enantioselectivities were not determined. Despite the good results obtained, the scope of the reaction was not studied further.



367

Ligand **368** was developed by Trost and successfully applied in several asymmetric transformations, including the cyanosilylation of aldehydes.[213] Zinc, magnesium, titanium, and aluminum complexes were screened with benzaldehyde as a model substrate; the best result was obtained by use of the complex prepared by treatment of ligand **368** with 1 equiv of trimethylaluminum, which gave a 60% yield and 80% asymmetric induction. Using different solvents and temperatures to conduct the reaction revealed that the optimal conditions involved the use of 10 mol % of aluminum trichloride with 1.1 equiv of ligand **368** at 4 °C in chlorobenzene. Using the optimized system, asymmetric cyanosilylation was carried out with aromatic and heteroaromatic aldehydes as substrates, giving products in 50−80% yield and with 57−86% enantioselectivity (Table 124). For aliphatic substrates, only cyclohexanecarboxaldehyde was studied; and the cyanohydrin trimethylsilyl ether was obtained in 70% yield and with 54% enantiomeric excess.



368

A mechanism for the catalysis was suggested involving complexation of trimethylaluminum to ligand **368** to form complex **369** (Figure 22). The aluminum ion of complex **369** reacts with trimethylsilyl cyanide to form an aluminum cyanide species, and the aldehyde coordinates via hydrogen bonding to the free hydroxy group to give the key preassembled complex **370**. Complex **370** undergoes intramolecular transfer of cyanide to the aldehyde, giving the aluminum bound cyanohydrin, which is liberated by transfer of the trimethylsilyl group to regenerate complex **369**.

Table 123. Asymmetric Addition of Trimethylsilyl Cyanide to Aldehydes Catalyzed by Me_2AlCl−366[a]

aldehyde	yield (%)	ee (%)
PhCHO	92	94
3-MeC_6H_4CHO	90	93
3-ClC_6H_4CHO	77	94
3-BrC_6H_4CHO	88	82
3-$MeOC_6H_4CHO$	82	80
4-MeC_6H_4CHO	86	75
4-FC_6H_4CHO	85	90
4-$MeOC_6H_4CHO$	80	80
furan-2-carboxaldehyde	70	74
2-ClC_6H_4CHO	94	80
$CH_3(CH_2)_6CHO$	91	97
$CH_3(CH_2)_7CHO$	92	98
$CH_3(CH_2)_3CHO$	87	96
CyCHO	90	99
Me_2CHCHO	65	97
Me_2CHCH_2CHO	72	96
$PhCH_2CH_2CHO$	86	95
(*E*)-MeCH=C(Me)CHO	70	98
PhCH=CHCHO	74	94
H_2C=$CHCH_2CH_2CHO$	67	96
$MeO_2C(CH_2)_4CHO$	90	92

[a] Reactions were carried out using 10 mol % of ligand **366** with 10 mol % of Me_2AlCl in diethyl ether at ambient temperature with 5 mg of 4 Å molecular sieves and 40 mol % of HMPA additive. All aldehydes were freshly distilled.

2.5.5. Bifunctional Catalysts

Shibasaki's group elaborated a bifunctional ligand system based on glucose containing both Lewis-acidic and Lewis-basic centers; aluminum complex **371** was prepared to catalyze the asymmetric synthesis of cyanohydrins from aldehydes.[214] Complex **371** was used for the addition of trimethylsilyl cyanide to benzaldehyde and some aliphatic aldehydes (Table 125). An enantioselectivity of 80% was achieved with benzaldehyde and also with *n*-heptanal; thus, the catalyst showed no particular preference for aromatic or aliphatic aldehyde substrates. Despite the moderate enantioselectivity compared with BINOL derived systems (see section 2.5.3), use of complex **371** did not require any additives or slow addition of trimethylsilyl cyanide; it also tolerated lower catalyst loadings (5 mol %) for some substrates.

Table 124. Asymmetric Addition of Trimethylsilyl Cyanide to Aldehydes Catalyzed by $AlCl_3$−368[a]

aldehyde	yield (%)	ee (%) (*S*)
PhCHO	76	86
3-MeC_6H_4CHO	72	80
3,5-$Me_2C_6H_3CHO$	68	57
3-ClC_6H_4CHO	80	86
3-BrC_6H_4CHO	76	82
3,5-$Cl_2C_6H_3CHO$	78	80
3,5-$Br_2C_6H_3CHO$	74	85
3-(hex-1-ynyl)C_6H_4CHO	74	82
4-MeC_6H_4CHO	54	77
4-$MeOC_6H_4CHO$	68	62
4-PhC_6H_4CHO	56	60
2-naphthaldehyde	73	84
1-naphthaldehyde	68	73
furan-2-carboxaldehyde	50	60 (*R*)[b]
furan-3-carboxaldehyde	66	71
thiophene-3-carboxaldehyde	75	84

[a] Reactions were carried out in chlorobenzene at 4 °C using 11 mol % of ligand **368** with 10 mol % of trimethylaluminum. [b] Product derived from furan-2-carboxaldehyde is *R* configuration because of a change in substituent priority.

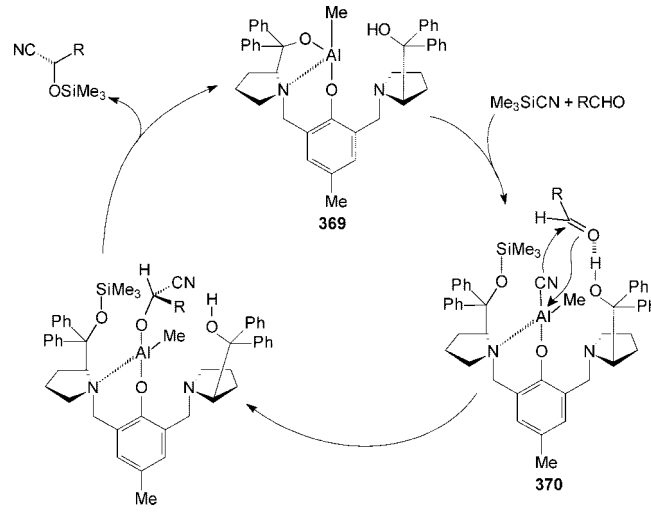
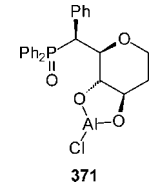


Figure 22.



371

As part of a study on the synthesis of HIV-protease inhibitors and bestatin, the use of complex **371** to catalyze the asymmetric addition of trimethylsilyl cyanide to chiral α-amino aldehydes derived from phenylalanine was investigated, and it was found that the diastereoselectivity obtained depended upon the nature of the amine protecting groups.[215] Thus, whilst the *N,N*-dibenzyl derivative gave the *syn*-diastereomer (86% diastereomeric excess) of the *β*-amino cyanohydrin, the anti-diastereomer (94% diastereomeric excess) was obtained from the *N*-Boc protected aldehyde. Moreover, complex **371** was found to have some activity (20% asymmetric induction) in the trimethylsilylcyanation of ketones, which led to the subsequent development of a related highly efficient system for this reaction (see section 3.3).

In summary, the most effective aluminum-based systems for cyanosilylation appear to be those developed by Shibasaki and Pu, which demonstrated high substrate tolerance (in particular, excellent stereoselectivities for aliphatic substrates). Although it gives marginally lower stereoselectivities on average, Nájera and Saá's catalyst has the important advantages of ligand recovery and the ability to use alternative cyanide sources. Utilization of this system in asymmetric cyanophosphorylation is especially notable, since this cyanide

Table 125. Asymmetric Addition of Trimethylsilyl Cyanide to Aldehydes Catalyzed by Complex 371[a]

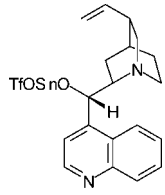
aldehyde	**371** (mol %)	time (h)	yield (%)	ee (%)
PhCHO	9	50	96	80
PhCH=CHCHO	5	76	82	76
(*E*)-$CH_3(CH_2)_3CH$=CHCHO	5	63	97	76
$PhCH_2CH_2CHO$	5	50	96	70
$CH_3(CH_2)_5CHO$	5	38	98	80

[a] Reactions were carried out in dichloromethane at −60 °C.

source has been little studied. The obvious merits of this protocol are its high enantioselectivity for aliphatic substrates as well as straightforward ligand regeneration.

2.6. Tin-Based Catalytic Systems

In 1991, Kobayashi developed catalyst **372** for the enantioselective addition of trimethylsilyl cyanide to aliphatic aldehydes.[216] Conducting the reaction in dichloromethane at −78 °C for 14 h gave cyanohydrin silyl ethers in 49−89% yield and with 72−96% stereoselectivity using a catalyst loading of 30 mol %. The highest levels of asymmetric induction were achieved using cyclohexanecarboxaldehyde (96%) and 2-methylpropanal (95%). Surprisingly, no product was detected when benzaldehyde was used as substrate. This process requires the use of 2 equiv of trimethylsilyl cyanide, high catalyst loadings, and low temperatures; nevertheless, it is interesting because of the unusual activity and selectivity profile. This remains the only tin-based catalyst for asymmetric cyanohydrin synthesis.



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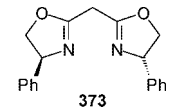
2.7. Magnesium-Based Catalytic Systems

In 1993, Corey and Wang reported an enantioselective procedure for the synthesis of silylated cyanohydrins in the presence of ligand **373** and magnesium complex **374** in a 3:5 ratio.[217] Chemical yields of 24−94% were obtained, whilst the enantioselectivity was between 52 and 95%. The reaction was carried out in a dichloromethane−propionitrile mixture at −78 °C for 5−30 h using 20 mol % of the catalyst and 2 equiv of trimethylsilyl cyanide. Aliphatic aldehydes gave higher enantioselectivities than aromatic substrates, as shown in Table 126. This work was the first report of the combined use of a Lewis-acid to activate the aldehyde and a Lewis-base to activate the trimethylsilyl cyanide. This concept was subsequently applied to generate many of the most effective systems currently known for asymmetric cyanohydrin synthesis with the Lewis-acid and -base either within the same catalyst or as part of a three-component catalyst system.

Table 126. Asymmetric Addition of Trimethylsilyl Cyanide to Aldehydes Catalyzed by 373 and 374[a]

aldehyde	time (h)	yield (%)	ee (%) (*S*)
$CH_3(CH_2)_5CHO$	10	88	95
Et_2CHCHO	6	86	91
CyCHO	<5	94	94
Me_3CCHO	30	57	90
(*E*)-$CH_3(CH_2)_2CH{=}CHCHO$	28	59	87
(*E,E*)-$CH_3CH{=}CH\text{-}CH{=}CHCHO$	24	24	84
$Me_2C{=}CH(CH_2)_2C(Me){=}CHCHO$	45	31	63
PhCHO	26	88	52

[a] Reactions were carried out in 3:1 acetonitrile/dichloromethane at −78 °C using 12 mol % of ligand **373** with 20 mol % of complex **374**.



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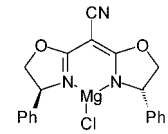

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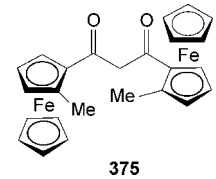
2.8. Yttrium-Based Catalytic Systems

The first example of the use of yttrium complexes in cyanohydrin synthesis was described by Abico and Wang, who discovered that the complex formed from ligand **375** and pentameric yttrium isopropoxide $Y_5(O)(O^iPr)_{13}$ was a stereoselective catalyst for trimethylsilyl cyanide addition to aldehydes.[218] A catalyst loading of 0.2 mol % was sufficient to obtain cyanohydrin silyl ethers in 95−98% yield after 2 h. The best enantioselectivities (81−90%) were obtained for aromatic aldehydes, which did not contain strongly electron-withdrawing substituents (Table 127). Electron deficient aromatic and aliphatic aldehydes gave inferior enantioselectivities of 30−49%. Remarkably, the absolute configuration of the aliphatic silylated cyanohydrins produced was the opposite of the cyanohydrins derived from aromatic aldehydes. Although the catalytically active species is unknown, the authors suggested a possible mechanism based on the available experimental data (Figure 23).



375

A highly effective system for ethyl cyanoformate addition to aldehydes was reported by Shibasaki *et al.* based on the bimetallic lithium−lanthanide binol complexes developed to catalyze a wide range of other reactions.[152] After optimization of the catalytic system, it was shown that the use of 10 mol % of catalyst **376** at −78 °C in tetrahydrofuran resulted in cyanoethoxycarbonylation of a wide range of substrates with enantioselectivities of 87−98% and yields of 79−100% (Table 128).[219] The reaction generally required reaction times of only 2−3 h (9 h in the case of 3-methylbutanal using 1 mol % of the catalyst) in the presence of 10 mol % of tris(2,6-dimethoxyphenyl)phosphine oxide. The substrate tolerance of catalyst **376** is one of the best reported so far for this reaction. Unlike the protocol of Nájera and Saá (see section 2.5.3), this system also requires only 1.2 equiv of ethyl cyanoformate. A unique feature of catalyst **376** is its ability to catalyze both asymmetric cyanohydrin synthesis and asymmetric Henry reactions. This, combined with the higher reactivity of aliphatic than that of aromatic aldehydes for asymmetric cyanohydrin synthesis was exploited by Shibasaki in a one-pot synthesis comprising both cyanohydrin synthesis and Henry reactions. Thus, treatment of an aromatic aliphatic aldehyde with 1 equiv of ethyl cyanoformate in the presence of catalyst **376** resulted in asymmetric cyanohydrin carbonate formation exclusively at the aliphatic aldehyde. Subsequent addition of lithium tetrafluoroborate transformed catalyst **376**

Table 127. Asymmetric Addition of Trimethylsilyl Cyanide to Aldehydes Catalyzed by the Yttrium Complex of Ligand 375[a]

aldehyde	ee (%)
PhCHO	90 (*S*)
PhCHO[b]	87 (*S*)
4-MeC_6H_4CHO	91 (*S*)
4-PhC_6H_4CHO	90 (*S*)
4-$MeOC_6H_4CHO$	84 (*S*)
4-$^tBuC_6H_4CHO$	72 (*S*)
4-FC_6H_4CHO	81 (*S*)
4-ClC_6H_4CHO	60 (*S*)
3-$PhOC_6H_4CHO$	79 (*S*)
4-NCC_6H_4CHO	30 (*S*)
4-$F_3CC_6H_4CHO$	10 (*S*)
2-$MeOC_6H_4CHO$	75 (*S*)
1-naphthaldehyde	58 (*S*)
2-naphthaldehyde	73 (*S*)
PhCH=CHCHO	68 (*S*)
Me_3CCHO	49 (*R*)
CyCHO	49 (*R*)

[a] Reactions were carried out using 1 mol % of catalyst $Y_5(O)(O^iPr)_{13}$−**375**. [b] 0.2 mol % of catalyst was used.

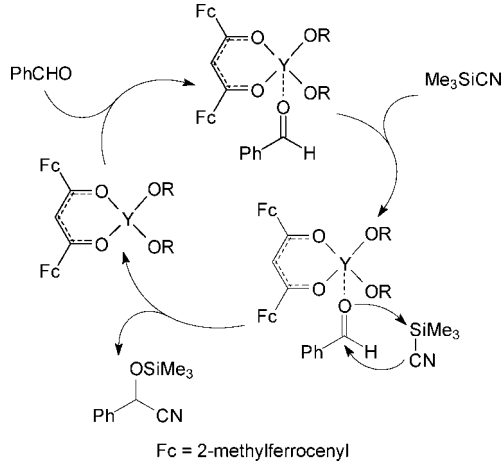
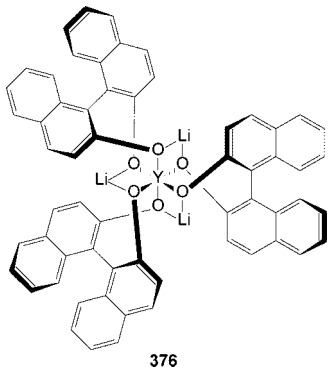


Figure 23.



into a catalyst for asymmetric Henry reactions, and addition of nitromethane gave the nitroaldol product at the aromatic aldehyde.

In a subsequent paper,[220] a number of phosphine oxide cocatalysts were screened in order to tune the enantioselectivity. For the addition of ethyl cyanoformate to 2-methylpropanal, without an additive, only 9% asymmetric induction was obtained. The highest enantioselectivity (89%) was achieved using tris(2,6-dimethoxyphenyl)phosphine oxide.

Table 128. Asymmetric Addition of Ethyl Cyanoformate to Aldehydes Catalyzed by Yttrium Complex 376[a]

aldehyde	time (h)	yield (%)	ee (%)
PhCHO	2	96	94
1-naphthaldehyde	2	97	90
(*E*)-$CH_3(CH_2)_2CH$=CHCHO	3	100	92
PhCH=CHCHO	3	100	91
$CH_3(CH_2)_4CHO$	3	93	94
CH_3CH_2CHO	2	79[b]	92
Me_2CHCHO	2	88[b]	98
Me_2CHCHO[c]	2	82[b]	96
Me_2CHCHO[d]	9	96	90
CyCHO	2	97	96
Me_3CCHO	3	93	87

[a] The reaction used 10 mol % of catalyst **376** unless stated otherwise with 1.2 equiv of EtOCOCN in THF at −78 °C. Water (30 mol %), BuLi (10 mol %), and $[2,6\text{-}(MeO)_2C_6H_3]_3P(O)$ (10 mol %) were used as additives. [b] Lower isolated yield due to product volatility. [c] Used 5 mol % of catalyst **376** with additives scaled down accordingly. [d] Used 1 mol % of catalyst **376** with additives scaled down accordingly.

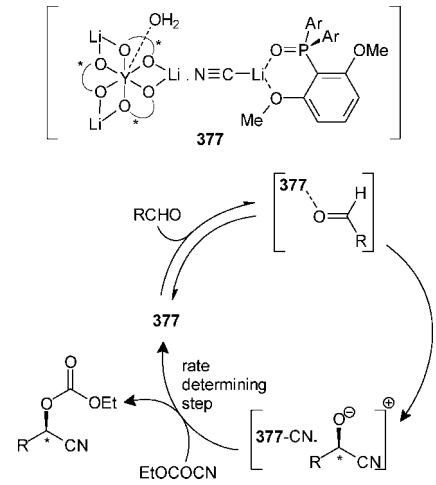


Figure 24.

A moderately high level of asymmetric induction (74%) was also obtained when using either tris(2,4,6-trimethoxyphenyl)phosphine oxide or (2,6-dimethoxyphenyl)diphenylphosphine oxide. Extensive kinetics experiments were carried out combined with *in situ* FTIR studies, and a catalytic cycle was postulated (Figure 24). The key feature of this catalytic cycle is the *in situ* formation of lithium cyanide, which then forms a cyanide bridged complex **377** between catalyst **376** and the phosphine oxide to form a supramolecular assembly which acts as both a chiral Lewis acid and a cyanide source, allowing cyanide to be transferred intramolecularly to the coordinated aldehyde. The initially formed cyanohydrin alkoxide then reacts with the ethyl cyanoformate to form the cyanohydrin carbonate product and regenerate complex **377**. The reaction was found to have an induction period, though this could be minimized by addition of acetone cyanohydrin, which generates lithium cyanide more efficiently than ethyl cyanoformate under the reaction conditions.

Catalyst **376** was also effectively used for the cyanophosphorylation of aldehydes.[221] A range of aromatic and aliphatic aldehydes were used as substrates for the asymmetric addition of ethyl cyanophosphonate (Scheme 50). Good to excellent enantioselectivities (76−97%) were obtained for all substrates, with the exception of cinnamaldehyde, which gave only 24% asymmetric induction (Table

Scheme 50

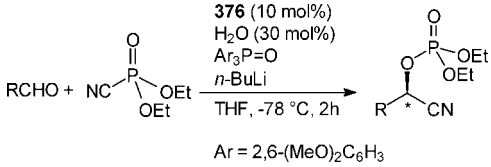
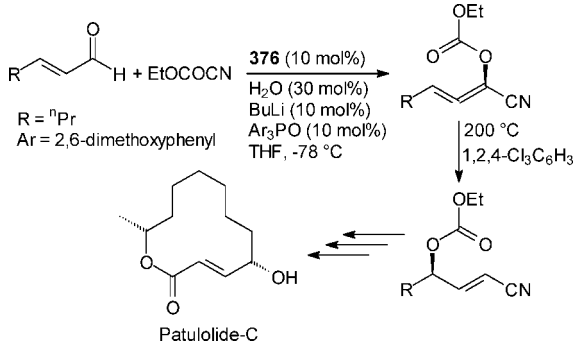


Table 129. Asymmetric Addition of Ethyl Cyanophosphonate to Aldehydes Catalyzed by Complex 376[a]

aldehyde	yield (%)	ee (%)
PhCHO	97	92
4-MeC_6H_4CHO	98	93
2-naphthaldehyde	98	81
1-naphthaldehyde[b]	95	89
$CH_3(CH_2)_5CHO$[b]	90	92
$PhCH_2CH_2CHO$	83	82
Me_2CHCHO	82	96
CyCHO	82	97
$PhCH_2C(Me)_2CHO$	81	76
PhCH=CHCHO	71	24

[a] Reactions were carried out under the conditions shown in Scheme 50. Ethyl cyanophosphonate (1.1 equiv) was added slowly over 1 h. [b] Tris-(2,4,6-trimethoxyphenyl)phosphine oxide was used as the phosphine oxide.

Scheme 51



129). Slow addition of ethyl cyanophosphonate was shown to be beneficial, raising the enantioselectivity observed with benzaldehyde as substrate from 86 to 92%. Mechanistic studies[221b] showed that at −78 °C the addition of cyanide to the aldehyde was irreversible and determined the overall stereochemistry of the process. The catalytic cycle is essentially the same as that shown in Figure 23 for ethyl cyanoformate addition, except that diethyl cyanophosphonate was proposed to inhibit the formation of complex **377**, thus explaining the need for slow addition of this reagent.

Shibasaki demonstrated the use of complex **376** for the asymmetric addition of ethyl cyanoformate to aldehydes as part of a total synthesis of the antifungal agent (+)-Patulolide C.[222] The initial addition of ethyl cyanoformate was achieved in 92−100% yield and with 87−93% enantioselectivity under a variety of conditions with four different α,β-unsaturated aldehydes. 92% Asymmetric induction was achieved with 2-hexenal, the aldehyde used in the synthetic sequence toward Patulolide C under the conditions shown in Scheme 51. The synthesis is notable for the thermal [3,3]-sigmatropic rearrangement of the β,γ-unsaturated cyanohydrin carbonate, which occurs with complete retention of configuration and

Table 130. Asymmetric Cyanosilylation of Aldehydes Catalyzed by La(O^{t}Bu)$_3$ Complexes of Ligands 279 and 378−380[a]

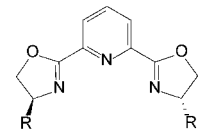
aldehyde	catalyst	yield (%)	ee (%) (*S*)
PhCHO	**279**	81	49
	378	86	36
	379	84	32
	380	77	71
4-MeC_6H_4CHO	**279**	79	58
	378	83	40
	379	82	34
	380	80	73
4-$MeOC_6H_4CHO$	**380**	56	63
$PhCH_2CH_2CHO$	**279**	82	52
	378	85	27
	379	87	19
	380	80	66
4-ClC_6H_4CHO	**279**	83	23
	378	92	7
	379	85	11
	380	82	48
CyCHO	**380**	76	54

[a] Reactions were all carried out for 10 h at −78 °C in dichloromethane using 10 mol % of ligand−La(O^{t}Bu)$_3$.

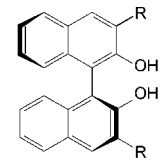
complements the metal catalyzed processes discussed in section 2.5.3.

2.9. Lanthanide-Based Catalytic Systems

Qian and co-workers found that complexes of BINOL-based ligands **279** and **378**−**380** with La(O^{t}Bu)$_3$ could carry out the asymmetric addition of trimethylsilyl cyanide to aromatic and aliphatic aldehydes (Table 130).[223] Use of ligand **380** (15 mol %) and La(O^{t}Bu)$_3$ (10 mol %) gave the highest enantioselectivities of 71% with benzaldehyde and 73% with *p*-tolualdehyde.



356) R = ^{i}Pr
381) R = Ph
382) R = Bn
383) R = ^{t}Bu



279) R = H
378) R = $SiMe_3$
379) R = Ph
380) R = $CH_2CH_2OCH_3$

Aspinall, Greeves, and co-workers described the lanthanide complexes of PyBOX ligands **356** and **381**−**383**, in particular the lanthanum, ytterbium, and europium complexes formed *in situ* from the ligand (20 mol %) and corresponding metal trichlorides (10 mol %). The complexes were used as catalysts in asymmetric cyanosilylation reactions.[224] Initial screening of the ligands with different metals showed that the best results were obtained using ytterbium with ligands **356** and **381** in acetonitrile. These complexes gave enanti-

Table 131. Asymmetric Cyanosilylation of Aldehydes Catalyzed by the Ytterbium Complex of Ligand 356[a]

aldehyde	yield (%)	ee (%) (*R*)
PhCHO	86 (96)	91 (71)
4-MeC_6H_4CHO	89 (22)	80 (64)
4-$O_2NC_6H_4CHO$	96 (95)	60 (32)
4-$^tBuC_6H_4CHO$	88 (56)	88 (0)
4-ClC_6H_4CHO	>99	80
3-$PhOC_6H_4CHO$	96	60
CyCHO	86	60
Me_3CCHO	83	49
MeCHO	61	45
$CH_3(CH_2)_4CHO$	96	46
(*E*)-$CH_3(CH_2)_2CH{=}CHCHO$	88	58

[a] Reactions were performed using 5 mol % of anhydrous catalyst in acetonitrile at 0 °C. Values in parentheses indicate results obtained using hydrated $YbCl_3$.

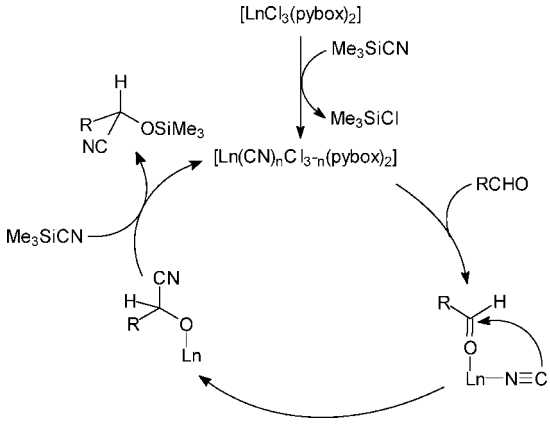


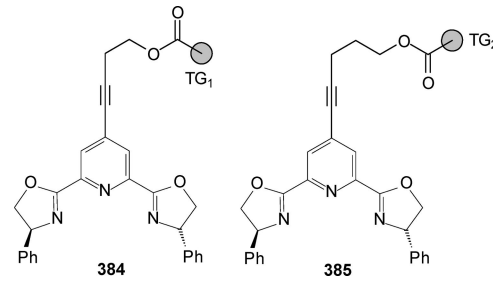
Figure 25.

oselectivities of 75 and 89%, respectively, for the asymmetric cyanosilylation of benzaldehyde at ambient temperature. Ytterbium complexes of ligands **382** and **383** gave inferior asymmetric inductions of 60 and 13%, respectively. Although it gave only 12% asymmetric induction, the La−**356** complex was notable in that the stereochemistry of the cyanohydrin product was reversed when compared to the use of other metal ions.

Subsequently, detailed studies of the influence of ligand substituents on the reaction outcome were carried out. The authors also found an almost linear dependence between the ionic radius of the complexed lanthanide and the enantioselectivity of the reaction. The best overall results were obtained for ytterbium complexed to ligand **356**, which gave 91% asymmetric induction using benzaldehyde as substrate under anhydrous conditions. It was found that using a hydrated complex resulted in reduced asymmetric induction. A range of aldehydes were used as substrates using 5 mol % of the complex formed *in situ* from $YbCl_3$ and ligand **356** (Table 131). There was a preference for electron rich aromatic aldehydes, which gave enantioselectivities at least 20% higher than those obtained with other substrates. The authors suggested a mechanism which involves intramolecular transfer of cyanide ion to the coordinated aldehyde in a mononuclear intermediate (Figure 25). This was consistent with the observed absence of nonlinear effects[134] for ytterbium and gadolinium complexes.

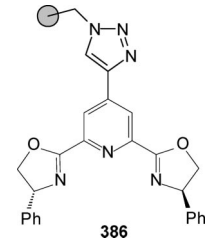
A variation of this system was also studied by Moberg's group, who described the use of a T-shaped borosilicate microreactor through which a voltage was applied, producing an electroosmotic flow of reagents; the voltage could be varied in order to optimize the reaction.[225] Using the ytterbium complex of ligand **356** for the asymmetric cyanosilylation of benzaldehyde, a maximum enantioselectivity of 53% was achieved with the microreactor, compared with 73% asymmetric induction obtained in a traditional batch reaction. It was found that use of the $LuCl_3$ complex of ligand **356** improved the enantioselectivity to 76% for the batch reaction, which was only slightly reduced to 73% when using the microreactor. A further improvement to 78% asymmetric induction was achieved by use of D-menthol as an additive.

Moberg also investigated the use of ytterbium complexes



of polymer supported PyBOX ligands **384** and **385**, based on Aspinall's ligand **381**, for the asymmetric cyanosilylation of aldehydes.[226] Using 10 mol % of $YbCl_3$ and 20 mol % of ligand for the addition of trimethylsilyl cyanide to benzaldehyde, an 88−89% yield was obtained with 81 and 80% asymmetric induction, respectively, for the complexes of ligands **384** and **385** after a reaction time of 30 min. The recyclability of the system was tested and the enantioselectivity was constant at 80−81% over four consecutive runs for both polymer supported ligands.

A similar system was later mentioned in an article by



Moberg on the preparation of the PyBOX ligands using "Click-Chemistry".[227] Thus, ligand **386** containing a 1,2,3-triazole linker in place of the alkyne featured in ligands **384** and **385** was complexed to ytterbium and lutetium. A maximum asymmetric induction of 78% was obtained for both $YbCl_3$−**386** and $LuCl_3$−**386** after four successive runs to test the catalyst recyclability. Interestingly, the enantioselectivity appeared to improve slightly after the first run from 67% to 73% in the case of $YbCl_3$−**386** and from 69% to 75% for $LuCl_3$−**386**.

Fang and Yang developed a catalytic system based on the complex formed *in situ* from samarium trichloride and phosphorus-containing ligand **387**.[228] They were able to carry out trimethylsilyl cyanide addition to a range of aromatic aldehydes with >95% yield and 29−90% enantioselectivity using very low loadings of metal and ligand (Table 132). However, whilst electron rich aromatic aldehydes gave good levels of asymmetric induction, electron deficient aldehydes

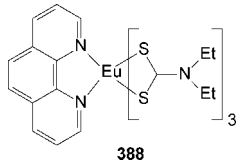
Table 132. Asymmetric Cyanosilylation of Aldehydes Catalyzed by the $SmCl_3$ Complex of Ligand 387[a]

aldehyde	$SmCl_3$/**387** (equiv)	temp (°C)	ee (%) (*R*)
PhCHO	0.001/0.003	−15 ± 5	84
4-$MeOC_6H_4CHO$	0.002/0.006	−15 ± 5	90
3-$MeOC_6H_4CHO$	0.002/0.006	−15 ± 5	83
2-$MeOC_6H_4CHO$	0.002/0.006	−15 ± 5	80
4-MeC_6H_4CHO	0.001/0.01	−15 ± 5	73
4-PhC_6H_4CHO	0.002/0.006	−15 ± 5	49
3-$PhOC_6H_4CHO$	0.002/0.006	−15 ± 5	45
4-FC_6H_4CHO	0.002/0.006	−15 ± 5	77
4-NCC_6H_4CHO	0.002/0.006	−15 ± 5	35
4-$O_2NC_6H_4CHO$	0.002/0.006	−70 ± 5	29

[a] Reactions were carried out in toluene for 15 h with a 1:2 ratio of aldehyde/trimethylsilyl cyanide. A variety of metal/ligand concentrations were used, but only the highest enantioselectivity achieved for each aldehyde is shown.

demonstrated significantly lower enantioselectivities (29−35%). The advantages of this system are the low catalyst loadings required and the fact that it was not necessary to conduct the reaction at very low temperatures in order to achieve good enantioselectivity.

Vale and co-workers elaborated a catalytic system for the asymmetric cyanosilylation of aldehydes involving the use of a europium complex.[229] It was found that, using 10 mol % of complex **388** in the presence of 30 mol % of *N*-tosylphenylalanine as a chiral ligand, it was possible to carry out the asymmetric addition of trimethylsilyl cyanide to benzaldehyde in 85% yield and with 85% enantioselectivity. The reaction was carried out in acetonitrile for 3 h at ambient temperature. A series of aromatic and aliphatic aldehydes were converted into the corresponding silylated cyanohydrins in 45−93% yield and with 30−99% enantioselectivity (Table 133). Remarkably, the best results were



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observed for electron deficient substrates, in particular the nitrobenzaldehydes, which gave products with an excellent 99% enantiomeric excess. A 1:3 ratio of complex to amino acid derivative appeared to be optimal, as decreasing the amount of amino acid resulted in a significant loss in stereoselectivity. The authors proposed that the actual catalyst had a supramolecular structure held together by hydrogen bonds between the *N*-tosylphenylalanine and **388**.

2.10. Manganese-Based Catalytic Systems

Kim and Lee reported a manganese-based catalytic system for asymmetric cyanosilylation in 2005. They found that complex **389** was able to catalyze trimethylsilyl cyanide addition to a range of aromatic and aliphatic aldehydes in 82−96% yield and with enantioselectivities of 44−62%.[230] A triphenylphosphine oxide cocatalyst was used to increase the rate of reaction; in dichloromethane, the enantioselectivity for benzaldehyde cyanosilylation was approximately the same in the absence of the cocatalyst (48%), although the rate of reaction was a factor of 5 slower. A small increase in the enantioselectivity to 59% was observed on reducing the reaction temperature from ambient to −10 °C, but the

Table 133. Asymmetric Cyanosilylation of Aldehydes Catalyzed by Complex 388 and *N*-Tosylphenylalanine[a]

aldehyde	time (h)	yield (%)	ee (%) (*S*)
PhCHO	3	85	85
naphthaldehyde	3	87	85
4-$O_2NC_6H_4CHO$	1	93	99
2-$O_2NC_6H_4CHO$	1	90	99
4-$EtOC_6H_4CHO$	3.5	89	89
4-BrC_6H_4CHO	12	45	44
$CH_3(CH_2)_5CHO$	7	60	30

[a] Reactions involved the use of 10 mol % of complex **388** and 30 mol % of *N*-tosylphenylalanine in acetonitrile at ambient temperature.

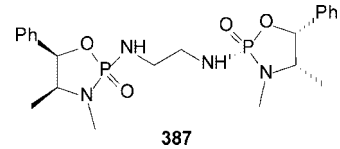

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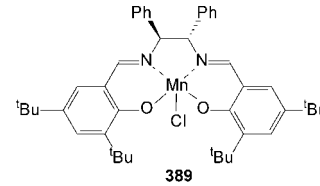
Table 134. Asymmetric Cyanosilylation of Aldehydes Catalyzed by Complex 389[a]

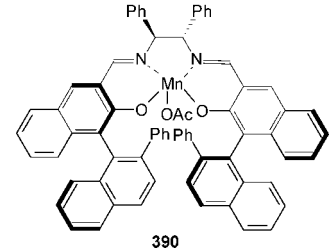
aldehyde	time (h)	yield (%)	ee (%) (*R*)
PhCHO	24	91	58
4-ClC_6H_4CHO	24	96	62
4-$MeOC_6H_4CHO$	48	87	54
4-MeC_6H_4CHO	20	93	52
4-$^tBuC_6H_4CHO$	35	92	48
4-$PhOC_6H_4CHO$	20	82	54
PhCH=CHCHO	20	93	55
furan-2-carboxaldehyde	18	91	47
$PhCH_2CH_2CHO$	20	90	52
$Me_2C=CH(CH_2)_2C(Me)=CHCHO$	24	86	44

[a] Reactions were all carried out at 0 °C in dichloromethane using 5 mol % of catalyst **389** and 10 mol % of triphenylphosphine oxide.

reaction was much slower under these conditions. A number of different aldehydes were used as substrates; the best result of 62% asymmetric induction and 96% yield was obtained with *p*-chlorobenzaldehyde. There was no large variation in enantioselectivity with the nature of the aldehyde; both aromatic and aliphatic substrates gave moderate enantioselectivities (Table 134).



389



390

The closely related complex **390**, previously developed by Katsuki *et al.* for the epoxidation of olefins,[231] was also used by Kim for asymmetric cyanosilylation of aldehydes.[232] By conducting the reaction in THF with 0.25 mol % of catalyst **390** with 10 mol % of triphenylphosphine oxide cocatalyst at 0 °C, *O*-trimethylsilyl mandelonitrile was

Table 135. Asymmetric Cyanosilylation of Aldehydes Catalyzed by Complex 390[a]

aldehyde	time (h)	yield (%)	ee (%) (*S*)
PhCHO	80	80	65
4-MeC_6H_4CHO	70	80	56
3-MeC_6H_4CHO	75	90	11
4-$MeOC_6H_4CHO$	75	75	53
4-$^tBuC_6H_4CHO$	60	93	45
4-FC_6H_4CHO	60	85	39
4-$O_2NC_6H_4CHO$	30	95	43
2-ClC_6H_4CHO	40	92	30
4-ClC_6H_4CHO	45	89	20
3-ClC_6H_4CHO	72	83	52
2-naphthaldehyde	45	80	67
$PhCH_2CH_2CHO$	35	84	67
PhCH=CHCHO	46	88	44

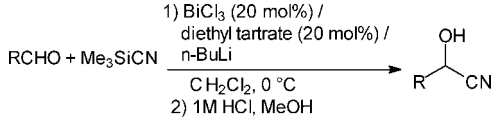
[a] Reactions were carried out at 0 °C in THF using 0.25 mol % of catalyst **390** and 10 mol % of triphenylphosphine oxide.

obtained with 65% enantiomeric excess after a reaction time of 80 h. A range of aromatic aldehydes (plus cinnamaldehyde and 3-phenylpropanal) were used as substrates (Table 135). Some substrates gave better results with catalyst **389**, whilst others gave better results with catalyst **390**. Notably however, whilst complexes **389** and **390** are both derived from (*S,S*)-1,2-diamino-1,2-diphenylamine, they give cyanohydrin silyl ethers with opposite absolute configurations (Tables 134 and 135). Thus, it appears that the axial chirality rather than the stereocenters present in complex **390** is principally responsible for the asymmetric induction.

2.11. Bismuth-Based Catalytic System

The only example of bismuth-catalyzed asymmetric cyanosilylation was reported by Wada and Smith. The complex obtained from bismuth trichloride and L-diethyl tartrate was used to catalyze the addition of trimethylsilyl cyanide to aromatic and aliphatic aldehydes (Scheme 52).[233] It was established that dichloromethane was the best solvent for the reaction, with 1,2-dichloroethane giving a similar result but other solvents resulting in much lower enantioselectivities. The highest enantioselectivity achieved was with

Scheme 52



benzaldehyde as substrate; other substrates showed moderate to poor asymmetric induction (Table 136). These results are inferior to Oguni's system derived from diisopropyl tartrate (see section 2.2.1), and utilization of toxic bismuth com-

Table 136. Asymmetric Cyanosilylation of Aldehydes Catalyzed by Diethyl Tartrate−$BiCl_3$[a]

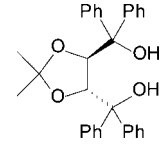
aldehyde	time (h)	yield (%)	ee (%)
PhCHO	0.5	100	73
$PhCH_2CH_2CHO$	0.5	100	52
$CH_3(CH_2)_7CHO$	0.5	100	28
CyCHO	3.5	87	58
3-$PhOC_6H_4CHO$	3.0	100	58
1-naphthaldehyde		0	
PhCH=CHCHO	20	100	20

[a] Reactions were all carried out using the conditions shown in Scheme 52.

Table 137. Asymmetric Addition of Acetone Cyanohydrin to Aldehydes Catalyzed by the TADDOL 16b Complex of $Zr(O^tBu)_4$[a]

aldehyde	time (h)	yield (%)	ee (%) (*R*)
$PhCH_2CH_2CHO$	7.5	63	85
$PhCH_2CH_2CHO$[b]	7.5	80	80
$PhCH_2CH_2CHO$	7.5	32	91
$CH_3(CH_2)_8CHO$	5	63	84
CyCHO	5	55	79
Me_3CCHO	5	36	72
PhCHO	18	45	63
furan-2-carboxaldehyde	18	30	61

[a] Reactions were carried out at −40 °C in dichloromethane. TADDOL **16b** and $Zr(O^tBu)_4$ were premixed with acetone cyanohydrin for 1 h prior to addition of aldehyde. [b] Four equivalents of acetone cyanohydrin were used.



16b

pounds also makes this protocol less competitive. The actual structure of the active catalyst was not determined.

2.12. Zirconium-Based Catalytic Systems

An interesting approach for asymmetric cyanohydrin synthesis was described by Maruoka, who developed a catalytic system for Meerwein−Ponndorf−Verley cyanation.[7e,234] The complex prepared from TADDOL **16b** and zirconium tetrakis(*tert*-butoxide) was found to be active in the cyanation of aldehydes. The main feature of this system is its use of acetone cyanohydrin as a cyanating agent, which is very uncommon for chemically catalyzed cyanohydrin synthesis (unlike enzymatic processes[44b]). Utilization of acetone cyanohydrin has a number of advantages, for example relatively low toxicity and cost. The use of stoichiometric amounts of the zirconium complex of **16b** resulted in the conversion of a range of aromatic and aliphatic aldehydes into the corresponding cyanohydrins in 30−63% yield and with 61−85% enantioselectivity (Table 137). It was shown that decreasing the temperature to −78 °C led to an increase in enantioselectivity, though at the cost of a reduction in the reaction rate. This system produced superior enantioselectivities when used with aliphatic aldehydes.

Attempts to develop a catalytic version of this reaction have also been made. In particular, the reaction with 3-phenylpropanal was performed using 20 mol % of the catalyst, giving 72% asymmetric induction and 51% chemical yield after 15 h. An important feature of this protocol is the use of 4 Å molecular sieves, which are crucial for obtaining optimal yields and enantioselectivities. Despite the relatively moderate enantioselectivity, this system is promising, as it demonstrates the use of acetone cyanohydrin in the asymmetric cyanation of aldehydes.

2.13. Cobalt-Based Catalytic Systems

Belokon and co-workers reported an original system involving the use of negatively-charged complex ions in asymmetric cyanosilylation.[235] Complex **391** prepared from tryptophan, salicylaldehyde, and $K_3[Co(CO_3)_3]$ was found

Table 138. Asymmetric Cyanosilylation of Aldehydes Catalyzed by Lithium Salt 392[a]

aldehyde	time (min)	yield (%)	ee (%) (*S*)
PhCHO	5	96	56
4-MeC_6H_4CHO	15	95	59
3-MeC_6H_4CHO	40	93	55
2-MeC_6H_4CHO	40	99	5
4-$MeOC_6H_4CHO$	4050	95	54
3-$MeOC_6H_4CHO$	30	89	52
2-$MeOC_6H_4CHO$	450	92	47
4-$O_2NC_6H_4CHO$		decomposition	
4-ClC_6H_4CHO	120	38	43
4-$F_3CC_6H_4CHO$	<5	73	0
2-naphthaldehyde	1440	93	6
PhCH=CHCHO	210	95	8
$CH_3(CH_2)_4CHO$	<5	82	9
CyCHO	20	94	30
Me_3CCHO	5	62	26

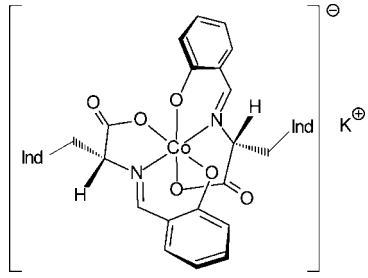
[a] 1 mol % of catalyst **392** was used, and the reaction was carried out in diethyl ether at −78 °C.

Table 139. Asymmetric Cyanosilylation of Aldehydes Catalyzed by the Monolithium Salt of Ligand 142[a]

aldehyde	time (min)	yield (%)	ee (%) (*R*)
PhCHO	15	98	86
4-MeC_6H_4CHO	45	96	93
3-MeC_6H_4CHO	20	88	97
2-MeC_6H_4CHO	40	96	45
4-$MeOC_6H_4CHO$	11 days	93	2
3-$MeOC_6H_4CHO$	45	96	77
2-$MeOC_6H_4CHO$	9 days	86	6
2-$MeOC_6H_4CHO$	180[b]	96	40
4-ClC_6H_4CHO	240	85	64
4-$F_3CC_6H_4CHO$	140	88	0
2-naphthaldehyde	120	64	6 (*S*)
4-EtC_6H_4CHO	120	99	61
4-$^iPrC_6H_4CHO$	40	99	82
4-$^tBuC_6H_4CHO$	140	99	53

[a] 1 mol % of catalyst was used, and the reaction was carried out in diethyl ether at −78 °C.

to be the best of a series of similar complexes studied. The octahedral nature of the cobalt ion leads to diastereomeric Λ- and Δ-complexes, which could be separated chromatographically. In the reaction between benzaldehyde and trimethylsilyl cyanide, the effect of additives, such as triphenylphosphine, indole, water, *tert*-butanol, etc. was also studied. It was demonstrated that the Δ-potassium salt **391** (2 mol %) gave optimum results in the presence of triphenylphosphine (0.1 mol %). Using catalyst **391**, *O*-silylated mandelonitrile was obtained in 85% yield and with 77% enantioselectivity when the reaction was conducted in dichloromethane at ambient temperature for a period of 20 min. It is notable that for the majority of other cations tested (H^+, Li^+, Na^+, Cs^+, NH_4^+) the reaction resulted in almost racemic product. Unfortunately, aldehydes other than benzaldehyde gave poor or no asymmetric induction, as did the attempted addition of potassium cyanide to benzaldehyde.

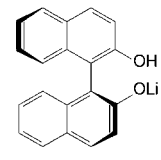


391

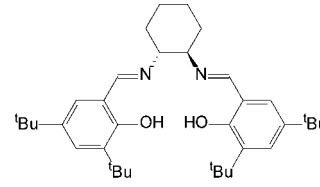
2.14. Group One Metal-Based Catalytic Systems

For use of bimetallic lithium−aluminum and lithium−yttrium complexes, see sections 2.5.3 and 2.8, respectively; for use of bimetallic cobalt−potassium complexes, see section 2.13. Kagan *et al.* reported examples of catalysis by lithium salts of chiral phenols; in particular, BINOL **279** and salen **142** were precursors of enantioselective cyanosilylation catalysts prepared by the reaction of the bis-phenol with 1 equiv of butyllithium.[236] The use of 1 mol % of the BINOL monolithium salt **392** resulted in cyanosilylation of a range of aromatic aldehydes in 73−99% yield (except *p*-chlorobenzaldehyde, which gave just 38% yield) and with 0−59% enantioselectivity. For aliphatic substrates, the enantioselectivity of the process did not exceed 30% (62−95% chemical yield). The rate of reaction was very dependent on the nature of the aldehyde used, and the reaction time required varied between 5 min and 68 h (Table 138).

The monolithium salt of ligand **142** gave greater enantioselectivities than those seen for BINOL salt **392**. A wide range of aromatic aldehydes was screened in the cyanosilylation reaction, which was conducted in diethyl ether at ambient temperature with 1 mol % catalyst loading. Cyanohydrin silyl ethers were obtained in 64−99% yield and with a broad range of enantioselectivities (0−97%). The reaction time again varied significantly depending on the aldehyde (from 15 min to 11 days) (Table 139). Kagan also reported a very simple and useful procedure for converting nonracemic cyanohydrin trimethylsilyl ethers into the corresponding cyanohydrin esters by treatment with scandium(III) triflate and the appropriate anhydride or acid chloride.[237] The method avoids aqueous hydrolysis and has been demonstrated not to cause any racemization except with *p*-nitrobenzaldehyde.



392



142

The low substrate tolerance and extended reaction times make Kagan's systems uncompetitive compared to some of the other protocols for asymmetric cyanohydrin synthesis. Nonetheless, these systems are interesting from a mechanistic point of view. The authors proposed that hypervalent silicon species coordinating substrate and cyanide ion simultaneously were involved in the catalytic cycle. An intramolecular attack of cyanide on the carbonyl group was suggested to be the stereodetermining step. An alternative mechanism considered the activation of the substrate by the lithium cation, serving as a Lewis acid.

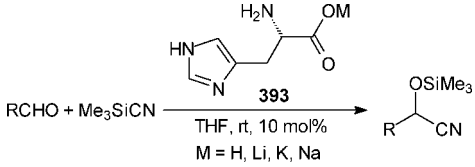
Kagan's system based on BINOL **279** was subsequently modified by Ishihara and co-workers.[238] They found that cyanosilylation of benzaldehyde catalyzed by 10 mol % of salt **392** (instead of the 1 mol % used by Kagan) resulted in enhanced enantioselectivity (58% compared with 23%) and also inverted the absolute configuration of the product. The authors suggested that the catalyst contained a certain amount of water; therefore, its utilization at higher loading resulted

Table 140. Asymmetric Cyanosilylation of Aldehydes Catalyzed by 10 mol % of 392[a]

aldehyde	yield (%)	*ee* (%) (*S*)
PhCHO	99 (98)[b]	97 (90)[b]
4-FC_6H_4CHO	92	96
3-FC_6H_4CHO	97	93
4-ClC_6H_4CHO	98 (99)[b]	92 (91)[b]
3-ClC_6H_4CHO	83	91
4-BrC_6H_4CHO	98 (95)[d]	93 (90)[d]
3-BrC_6H_4CHO	96	87
4-$F_3CC_6H_4CHO$	97	82
3-$F_3CC_6H_4CHO$	99	86
3-MeC_6H_4CHO	96 (97)[c]	95 (90)[c]
3-$MeOC_6H_4CHO$	93 (93)[d]	97 (95)[d]
3,5- $(MeO)_2C_6H_3CHO$	99 (92)[d]	97 (97)[d]
1-naphthaldehyde	95	81
2-naphthaldehyde	96	95
furan-3-carboxaldehyde	96 (93)[d]	98 (93)[d]
3-$(OHC)C_6H_4CHO$	85[e]	98[e]

[a] 10 mol % of both BINOL and LiO^iPr was used unless stated otherwise. [b] Figures in parentheses indicate the use of 1 mol % of BINOL and LiO^iPr. [c] Figures in parentheses indicate the use of 2 mol % of BINOL and LiO^iPr. [d] Figures in parentheses indicate the use of 3 mol % of BINOL and LiO^iPr. [e] Results show yield and enantiomeric excess of *dl*-product with the remaining product being the *meso*-compound.

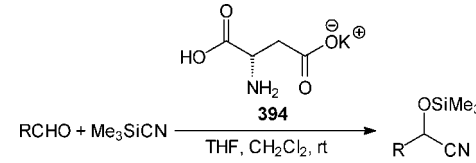
Scheme 53



in a greater percentage of water in the reaction mixture. This could change the equilibria between the catalytically active species present in solution. This assumption was supported by experiments which demonstrated the beneficial influence of added water on the stereoselectivity. For instance, the use of 10 mol % of **392** in the presence of 3 mol % of water resulted in an increase in the enantioselectivity to 95%. Also, an increase in the asymmetric induction was observed when lithium hydroxide was employed instead of butyllithium for the catalyst generation (since this introduced more water). Subsequently, it was found that lithium isopropoxide was the best choice of base, giving even higher asymmetric induction. A series of aromatic and heteroaromatic aldehydes gave the corresponding cyanohydrin trimethylsilyl ethers in 83−99% yield and with 81−98% enantiomeric excesses (Table 140). Based on nonlinear effect studies,[134] it was concluded that addition of water resulted in the formation of new catalytically active species. The authors assumed that the presence of proton donors caused dissociation of oligomeric complexes of low activity to give highly active monomers.

Kim used catalysts **393** based on histidine for the catalytic addition of trimethylsilyl cyanide to aldehydes, including the lithium, sodium, and potassium salts.[239] Initial screening with benzaldehyde gave up to 100% yield with a maximum enantioselectivity of 13% when using the sodium salt of histidine. Good conversions were obtained in all solvents tested, with the best yield achieved in the shortest time when using THF as solvent. Ten mole percent catalyst was used at ambient temperature for the addition of trimethylsilyl cyanide to a range of aldehydes with varied results (Scheme 53). The highest enantioselectivities were obtained using

Scheme 54



Scheme 55

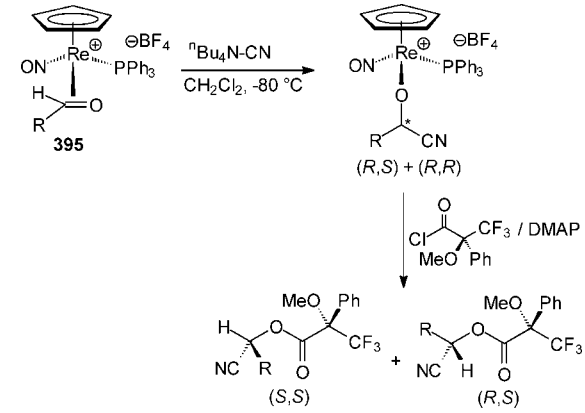


Table 141. Addition of Cyanide to Rhenium Aldehyde Complexes 395

aldehyde	rhenium alkoxide de (%)	yield (%)	cyanohydrin ester de (%)
MeCHO	53	96	56
CH_3CH_2CHO	80	93	80
Me_2CHCHO	83	94	83
$PhCH_2CHO$	71	85	68
PhCHO	89	87	90

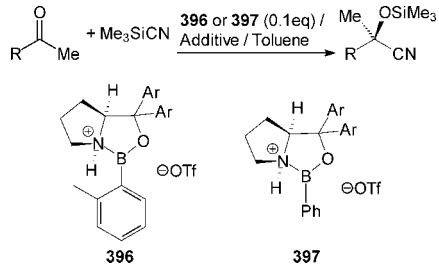
cyclohexanecarboxaldehyde (25%), *p*-nitrobenzaldehyde (24%), and 3,7-dimethyl hepta-2,6-diene (22%) as substrates.

Kim also investigated the use of potassium L-aspartate **394** to catalyze the addition of trimethylsilyl cyanide to aldehydes and two ketones (Scheme 54).[240] This system was an active catalyst, giving >90% conversion to cyanohydrin when using benzaldehyde. However, very little enantioselectivity was observed using 20 mol % of catalyst at various temperatures. A range of aldehydes were used as substrates for cyanosilylation, and although no enantioselectivity was recorded for most examples, *p*-anisaldehyde and 1-naphthaldehyde gave reasonable asymmetric inductions of 52% and 87%, respectively. Despite the generally poor asymmetric inductions produced by the amino acid salt catalysts derived from histidine and aspartic acid, they have been shown to effectively catalyze the racemic addition of trimethylsilyl cyanide to aldehydes and to give reasonable enantioselectivities in a few cases.

2.15. Rhenium-Based Systems

In 1989, Gladysz reported the use of chiral rhenium complexes in the asymmetric cyanosilylation of aldehydes.[241] It was found that rhenium complexes **395** in which the rhenium was coordinated to one of the enantiotopic faces of the aldehyde could be formed with 90−98% enantiomeric excess. Addition of tetrabutylammonium cyanide to the complexed aldehyde occurred diastereoselectively to give cyanohydrin alkoxides with diastereomeric excesses of 53−89%. The diastereomers could be separated by chromatography, and the cyanohydrins could be released from the rhenium as diastereomeric cyanohydrin esters by reaction

Scheme 56



with Mosher's acid chloride (Scheme 55). The diastereomeric excesses of the cyanohydrin Mosher esters were virtually identical to those of the cyanohydrin−alkoxide/rhenium complex from which they were prepared. The best result obtained was for benzaldehyde (90% *de*), whilst aliphatic aldehydes gave more moderate results (Table 141).

3. Chiral Lewis Acid-Based Systems for the Asymmetric Cyanation of Ketones

Asymmetric cyanation of ketones has always been a problematic area compared with the cyanation of aldehydes. The main difficulties are the greater steric hindrance to cyanide attack on the carbonyl group, the lower electrophilicity of the carbonyl group, and enhanced requirements for the stereodifferentiating properties of the catalyst due to the smaller difference in size between two alkyl/aryl groups than between hydrogen and alkyl/aryl groups. Nevertheless, this field attracts considerable interest due to the synthetic importance of enantiomerically pure cyanohydrins derived from ketones.

3.1. Boron-Based Catalytic Systems

Building on the successful application of boron-containing catalyst **15** for the cyanosilylation of aldehydes (see section 2.1), Corey studied the use of this system for cyanation of methyl ketones (Scheme 56).[242] After optimization of the reaction conditions, it was found that compound **396** with a triflate anion (10 mol %) was the optimum catalyst, used in toluene in the presence of triphenylphosphine oxide or methyl diphenylphosphine oxide (11−20 mol %). Analogue **397** with a phenyl group on the boron atom was also found to be an effective catalyst. The system was tested on some aliphatic (62−92% yields, 80−96% asymmetric induction) and aromatic (45−83% yields, 32−96% enantioselectivity) methyl ketones (Table 142). The main disadvantages of the system were the large amount of catalyst required and the long reaction times (2−14 days).

3.2. Titanium-Based Catalytic Systems

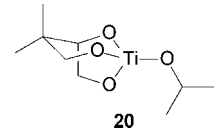
The first example of chemically catalyzed asymmetric cyanation of ketones was reported by Choi,[243] who based his work on De Vries' system for the cyanosilylation of aldehydes.[92] Reactions were carried out under high pressure to facilitate the addition reaction. The reaction of acetophenone with trimethylsilyl cyanide was carried out in dichloromethane at 0.8 GPa pressure in the presence of 1 mol % of catalyst **20** to give the cyanohydrin product in 93% yield and with 60% enantiomeric excess. After the reaction, the catalyst could be isolated and reused; this did not influence the stereoselectivity but did decrease the yield. Taking into account that at atmospheric pressure the reaction displayed

Table 142. Asymmetric Cyanosilylation of Methyl Ketones Catalyzed by the 396 and 397 Triflates[a]

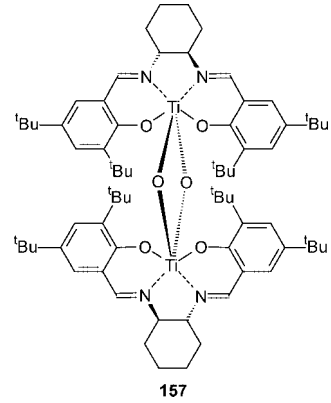
ketone	catalyst	additive	time (days)	yield (%)	ee (%) (*S*)
CyCOMe	**397**	Ph_3PO[b]	4	97	80
	397	$MePh_2PO$	3	62	88
	396	$MePh_2PO$	3	95	85
$(MeO)_2CHCOMe$	**397**	Ph_3PO	2	92	96
PhCOMe	**396**	Ph_3PO	4	49	65
	397	$MePh_2PO$	14	77	83
4-BrC_6H_4COMe[c]	**396**	$MePh_2PO$	10	73	81
4-$O_2NC_6H_4COMe$[c]	**396**	$MePh_2PO$	10	83	96
4-$TfOC_6H_4COMe$[c]	**396**	$MePh_2PO$	10	79	95
4-$MeOC_6H_4COMe$	**396**	$MePh_2PO$	7	45	32

[a] 10 mol % of catalyst was used, and the reaction was carried out in toluene at 25 °C with 0.11 equiv of phosphine oxide additive unless otherwise stated. [b] Used 0.2 equiv of phosphine additive. [c] Reaction was carried out at 45 °C.

only 7% enantioselectivity, the authors assumed that the role of the high pressure was to suppress the reverse reaction and hence suppress racemization. The protocol was extended to substituted aromatic methyl ketones, which, in contrast to acetophenone, gave low yields (24−39%) and enantioselectivities (32−45%), the best of which was achieved with 4-methylacetophenone. Thus, the harsh conditions and moderate results make this system of little utility. However, this work was important, having shown that it was possible to obtain asymmetric induction in the addition of trimethylsilyl cyanide to ketones.



Based on the excellent results obtained with bimetallic titanium catalyst **157** in the cyanosilylation of aldehydes,[117] Belokon and North described the first example of a catalytic

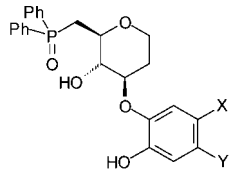


system for cyanation of ketones at atmospheric pressure.[244] It was shown that use of 0.5 mol % of catalyst **157** would induce the cyanosilylation of aromatic methyl and ethyl ketones, giving the corresponding cyanohydrin products in 64−100% yield and with enantioselectivities of 32−72% at ambient temperature. The best results were obtained from 2-methoxyacetophenone and acetophenone. When isopropyl or *tert*-butyl phenyl ketone were used, no product was detected. It is noteworthy that all the substrates required considerably longer reaction times (48−96 h) compared to the cyanation of aldehydes.

Table 143. Asymmetric Cyanosilylation of Ketones Using the Titanium Complex of Ligand 398[a]

ketone	temp (°C)	time (h)	yield (%)	ee (%) (*R*)
PhCOMe	−30	36	85	92
4-MeC_6H_4COMe	−30	84	80	90
4-ClC_6H_4COMe	−40	80	82	92
2-acetylnaphthalene	−40	80	82	95
1-indanone	−40	96	72	69
PhCOEt	−20	64	89	91
PhCH=CHCOMe	−50	88	72	91
CyCOMe	−50	36	86	90
$PhCH_2CH_2COMe$	−50	36	92	85
$CH_3(CH_2)_4COMe$	−50	36	88	76

[a] 10 mol % of the titanium complex of ligand **398** was used, and the reaction was carried out in THF.



398) X = Y = H
399) X = COPh, Y = H
400) X-Y = $(CH)_4$
401) X = Y = F

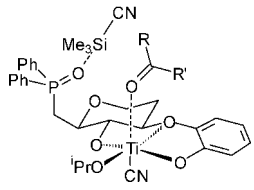
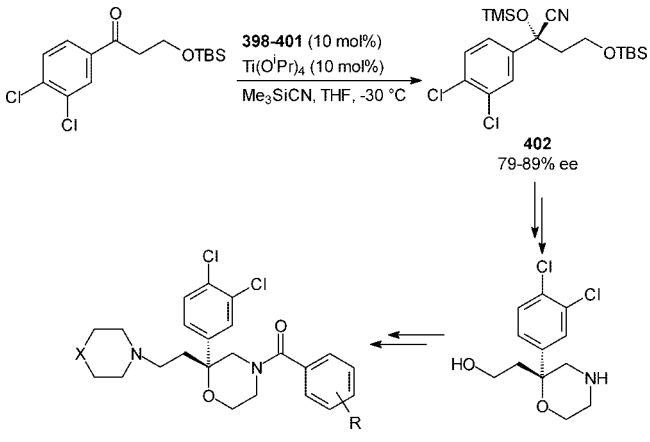


Figure 26.

Scheme 57



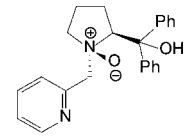
The first relatively universal system for the asymmetric addition of trimethylsilyl cyanide to ketones was developed by Shibasaki *et al.*, also on the basis of previous studies on the cyanation of aldehydes.[245] While studying aluminum complexes of bifunctional ligands, such as complex **360** (see section 2.5.5), they found that the titanium complex of ligand **398** was able to catalyze the reaction of ketones with trimethylsilyl cyanide in high yields (72−92%) and enantioselectivities (69−92%) (Table 143).[246] It is notable that high enantioselectivities were obtained for aromatic, aliphatic, and cyclic substrates. Further investigations showed that modification of the ligand structure[246] to give **399** led to enhancement of enantioselectivity (up to 97% in the case of acetophenone) and enabled the use of lower catalyst loadings. A transition state was proposed in which trimethylsilyl cyanide coordinates through silicon to the pendant phosphine oxide and transfers the cyanide intramolecularly to the titanium coordinated ketone (Figure 26). This work was a considerable contribution to this area, mostly because of the wide choice of substrates, including even sterically hindered and cyclic ketones, since cyanation of these substrates has always been a very difficult task.

Table 144. Asymmetric Cyanosilylation of Ketones Using the Titanium Complex of Ligand 403[a]

ketone	time (h)	yield (%)	ee (%) (*R*)
PhCOMe	96	78	54
2-acetylnaphthalene	96	73	69
PhCH=CHCOMe	96	77	25
$PhCH_2CH_2COMe$	120	87	68
1-tetralone	120	61	37
4-MeC_6H_4COMe	96	63	41
3-ClC_6H_4COMe	120	76	33
2-FC_6H_4COMe	96	47	55

[a] 10 mol % of $Ti(O^iPr)_4$−**403** was used, and the reaction was carried out in dichloromethane.

Shibasaki used the titanium complex of ligand **398**−**399**, and the related ligands **400**−**401**, for the asymmetric addition of trimethylsilyl cyanide to a ketone in order to prepare a key intermediate toward the synthesis of neurokinin receptor antagonists, potential drug targets for the treatment of



403

pulmonary diseases (Scheme 57).[247] The transformation was carried out in 67−100% yield and with 75−89% asymmetric induction. The titanium complex of ligand **398** gave a 91% yield of cyanohydrin derivative **402** with 79% enantiomeric excess, whilst use of ligand **399** gave just 65% yield and 75% enantioselectivity. Ligand **400** formed compound **402** in quantitative yield and with 86% enantiomeric excess, but the best result was achieved using the titanium complex of ligand **401**, which gave a quantitative yield and 89% asymmetric induction. The use of the gadolinium complexes of the same ligands gave silimar enantioselectivities but with opposite absolute configuration (see section 3.3.4).

Feng and Jiang also used bifunctional ligands in the asymmetric cyanation of ketones.[248] They prepared and tested titanium complexes of a range of ligands containing an *N*-oxide moiety, serving as a Lewis basic center. Use of the catalyst formed by treatment of ligand **403** with titanium tetraisopropoxide in a 1:1.2 ratio enabled the cyanosilylation of a series of ketones in 61−87% yield and with 25−69% enantioselectivity (Table 144). A catalytic cycle was devised in which the ketone coordinates to the titanium ion and trimethylsilyl cyanide binds through silicon to the *N*-oxide moiety. Delivery of cyanide could then take place intramolecularly, resulting in the enantiomerically enriched cyanohydrin (Figure 27).

In order to develop a more readily available system, Feng and co-workers investigated the cyanosilylation of ketones mediated by Lewis acidic complexes in the presence of additives with Lewis basic properties.[249] Titanium complexes of a number of substituted salen ligands were evaluated, and

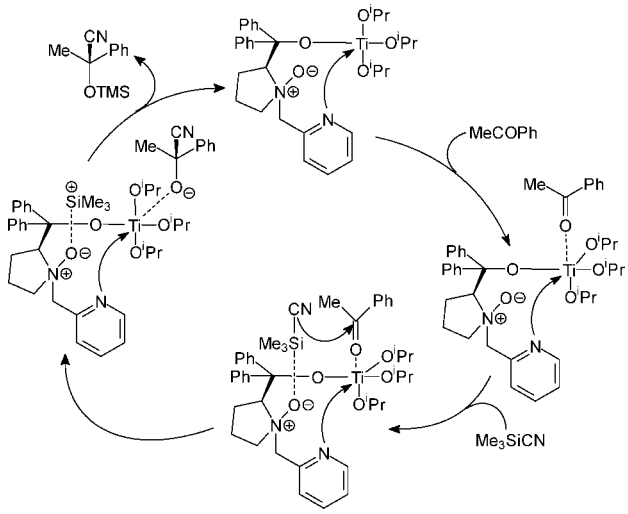
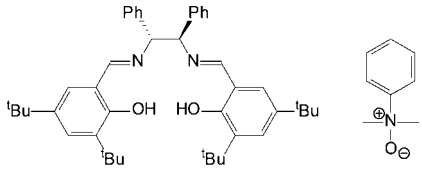


Figure 27.

Table 145. Asymmetric Cyanosilylation of Ketones Using the Titanium Isopropoxide Complex of Ligand 177a with Additive 404[a]

ketone	yield (%)	ee (%) (*S*)
PhCOMe	75	84
4-MeC$_6$H$_4$COMe	57	73
2-FC$_6$H$_4$COMe	80	76
4-FC$_6$H$_4$COMe	71	83
4-ClC$_6$H$_4$COMe	58	84
3-ClC$_6$H$_4$COMe	93	80
2-acetylnaphthalene	50	84
1-tetralone	37	81
PhCH$_2$CH$_2$COMe	85	84
PhCH=CHCOMe	79	64

[a] 2 mol % of Ti(O^{i}Pr)$_4$−**177a** and 1 mol % of **404** were used, and the reaction was carried out in dichloromethane at −20 °C for 120 h.



(*R*,*R*)-**177a**

404

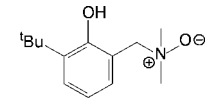
ligand **177a** was found to promote the highest levels of asymmetric induction. Thus, simultaneous utilization of the titanium complex of ligand **177a** (2 mol %) and *N*-oxide **404** (1 mol %) afforded cyanohydrin silyl ethers in 37−85% yield and with 64−84% enantioselectivity (Table 145). The best results of 83−84% asymmetric induction were obtained with acetophenone, *p*-chloroacetophenone, *p*-fluoroacetophenone, β-acetonaphthone, and benzylacetone. Respectably good enantioselectivities were also obtained for the other ketones used in the study.

Feng's group also studied combinations of titanium(salen) complexes and different achiral phenolic *N*-oxide additives.[250] A range of *N*-oxides were screened, and all gave similar enantioselectivities for the addition of trimethylsilyl cyanide to acetophenone (66−70%), with the exception of a molecule containing two *N*-oxide groups. Once again, salen ligand **177a** was shown to produce the best catalyst, so simultaneous use of the titanium complex of (*S*,*S*)-**177a** and *N*-oxide **405** proved to be optimal for the cyanosilylation of a range of aromatic, heteroaromatic, and aliphatic methyl ketones as well as for some cyclic and α,β-unsaturated substrates. Yields of 58−95% and enantioselectivities of 56−82% were obtained (Table 146), the highest of which were obtained using acetophenone and *m*-chloroacetophenone. Interestingly, better results were achieved for *p*-nitroacetophenone without using the *N*-oxide additive. A screening of other metal ions resulted in much lower enantioselectivities than those obtained using titanium complexes. On the basis of the

Table 146. Asymmetric Cyanosilylation of Ketones Using the Titanium Isopropoxide Complex of Ligand 177a with Additive 405[a]

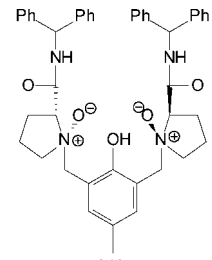
ketone	yield (%)	ee (%) (*R*)
PhCOMe	94	81
4-MeC$_6$H$_4$COMe	68	71
4-MeOC$_6$H$_4$COMe	81	74
4-ClC$_6$H$_4$COMe	75	67
4-FC$_6$H$_4$COMe	89	73
4-O$_2$NC$_6$H$_4$CHO[b]	23 (93)	15 (65)
3-ClC$_6$H$_4$COMe	93	82
1-tetralone	73	77
1-indanone	96	79
2-acetylthiophene	58	59
CH$_3$(CH$_2$)$_4$COMe	71	69
PhCH$_2$CH$_2$COMe	94	74
PhCH=CHCOMe	77	52

[a] 10 mol % of catalyst Ti(O^{i}Pr)$_4$−**177a** and 1 mol % of **405** were used, and the reaction was carried out in dichloromethane at −20 °C for 96 h. [b] Figures in parentheses indicate results obtained without the use of **405**.

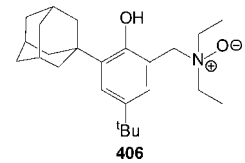


405

results, a mechanism was proposed in which the ketone coordinated to the titanium ion through the carbonyl oxygen with the *N*-oxide molecule also associating with the metal center through the phenol group. The *N*-oxide additive also activates the trimethylsilyl cyanide, resulting in intramolecular transfer of cyanide to the ketone (Figure 28).



240



406

Feng and co-workers also studied the use of the titanium complexes of *N*-oxide derived ligands for the asymmetric addition of trimethylsilyl cyanide to ketones.[251] The complex prepared from ligand **240**, previously used by the same group for the asymmetric cyanosilylation of aldehydes[163] (see section 2.2.3), appeared to be the most effective catalyst

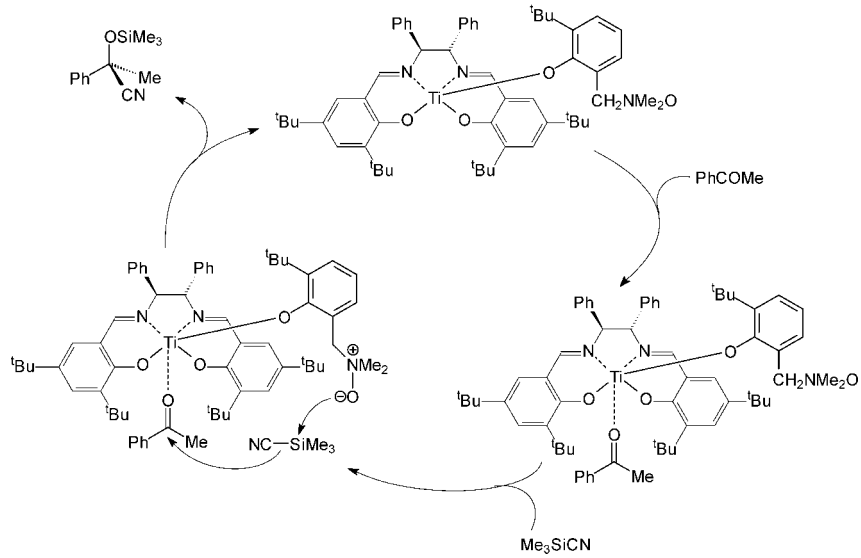


Figure 28.

Table 147. Asymmetric Cyanosilylation of Ketones Using the Titanium Isopropoxide Complex of Ligand 240 with Additive 406[a]

ketone	time (h)	yield (%)	ee (%) (*R*)
PhCOMe	48	96	90
2-FC_6H_4COMe	36	93	90
4-FC_6H_4COMe	36	90	90
3-ClC_6H_4COMe	36	93	94
4-ClC_6H_4COMe	48	90	89
4-MeC_6H_4COMe	60	91	86
4-$MeOC_6H_4COMe$	60	88	89
2-acetylthiophene	60	78	92
2-acetylnaphthalene	60	89	96
1-tetralone	60	80	85
PhCH=CHCOMe	36	92	91
$PhCH_2CH_2COMe$	48	92	89
$Me_2CHCOMe$	36	89	62
$CH_3(CH_2)_4COMe$	36	95	82
$CH_3(CH_2)_2COMe$	36	92	75
CyCOMe	36	90	71

[a] 2.5 mol % of $Ti(O^iPr)_4$/**240/406** was used (1:1:1 ratio), and the reaction was carried out in THF at −45 °C under an argon atmosphere.

Table 148. Asymmetric Cyanosilylation of Ketones Using the Titanium Isopropoxide Complex of Ligand 221[a]

ketone	yield (%)	ee (%) (*S*)
PhCOMe	77	92
4-MeC_6H_4COMe	60	90
4-$MeOC_6H_4COMe$	48	94
2-acetylnaphthalene	72	88
1-indanone	66	92
1-tetralone	63	87
4-ClC_6H_4COMe	82	74
3-ClC_6H_4COMe	90	61
4-FC_6H_4COMe	61	83
3-FC_6H_4COMe	87	66
2-acetylthiophene	56	88
PhCH=CHCOMe	65	64
$CH_3(CH_2)_4COMe$	89	51
$PhCH_2CH_2COCH_3$	84	51

[a] A 1:1 mixture of titanium tetraisopropoxide and ligand **221** was used (30 mol %) with 2.5 equiv of trimethylsilyl cyanide. The reaction was carried out in dichloromethane at −45 °C with a ketone concentration of 2.0 M.

within the series studied affording products from methyl ketones in 78−96% yield and with 62−96% enantioselectivity when used with phenolic *N*-oxide additive (**406**) (Table 147). In general, better results were obtained when using aromatic substrates, although 2-heptanone gave a good enantioselectivity of 82% and 95% yield after a reaction time of 36 h.

Table 149. Addition of Trimethylsilyl Cyanide to Ketones Using $Al(O^iPr)_3$−407[a]

ketone	**407**/$Al(O^iPr)_3$ (mol %)	yield (%)	ee (%)
PhCOMe	10	84	91
	20	93	88
4-$MeOC_6H_4COMe$	20	67	91
4-$O_2NC_6H_4COMe$	20	98	88
	10	92	90
2-ClC_6H_4COMe	20	87	85
2-acetylnaphthalene	20	83	94
PhCOEt	20	98	88
$PhCOCH_2Cl$	20	87	80
1-indanone	20	87	88
4-chromanone	20	85	88
$PhCH_2CH_2COMe$	20	93	80
	10	97	82
PhCH=CHCOMe	20	67	95
$CH_3(CH_2)_6COMe$	20	93	86
(*E*)-$CH_3(CH_2)_4C$=CHCOMe	20	98	95
	10	77	95
$CH_3(CH_2)_5C$≡CCOMe	20	78	90
	10	66	91

[a] The reactions were carried out at −78 °C in toluene using the indicated amounts of catalyst and ligand with 20 mol % of added methanol, 2 equiv of trimethylsilyl cyanide, and 3 Å molecular sieves.

Feng *et al.* also used titanium complexes of ligands **221**−**230**, previously developed for asymmetric cyanohydrin synthesis from aldehydes,[158] for the asymmetric cyanosilylation of ketones.[252] Initial screening of ligands showed that the best results (49−51% enantioselectivity) were obtained with ligands **221** and **222**−**223**. Optimization of the reaction conditions using the titanium tetraisopropoxide complex of ligand **221** for the addition of trimethylsilyl cyanide to acetophenone resulted in a maximum asymmetric induction of 92%. Titanium tetraisopropoxide−**221** was then used for the catalytic asymmetric cyanation of a range of ketones (Table 148), and moderate to good enantioselectivities were obtained for all substrates, with the best results derived from aromatic ketones.

Table 150. Addition of Trimethylsilyl Cyanide to Ketones Using Al−408 and *N*-Oxide 404

ketone	time (h/day)	yield (%)	ee (%) (*R*)
PhCOMe[a]	46 h	94	93
PhCOMe[b]	16 day	99	94
1-tetralone[a]	48 h	99	92
1-tetralone[b]	9.5 day	99	90
1-indanone[a]	28 h	98	92
2-acetylthiophene[a]	66 h	99	90
4-MeC_6H_4COMe[a]	24 h	99	92
4-FC_6H_4COMe[a]	32 h	99	88
4-FC_6H_4COMe[b]	9 day	99	92
4-ClC_6H_4COMe[a]	40 h	99	86
4-ClC_6H_4COMe[b]	7 day	99	90
3-ClC_6H_4COMe[a]	36 h	95	90
3-ClC_6H_4COMe[b]	9 day	95	90
PhCOEt[a]	40 h	92	84
PhCOEt[b]	13 day	99	87
2-acetylnaphthalene[a]	3 day	96	79
2-acetylnaphthalene[b]	16 day	99	81 (99)[c]
$CH_3(CH_2)_4COMe$[b]	36 h	99	79
$CH_3(CH_2)_2COMe$[b]	36 h	95	80
$Me_2CHCOMe$[b]	36 h	80	90

[a] Conditions: 5 mol % $AlEt_3$−**408**, 0.25 mol % **404**, Me_3SiCN 2 equiv, −20 °C, [ketone] = 1.5 M in THF. [b] Conditions: 0.1 mol % $AlEt_3$−**408**, 0.05 mol % **404**, Me_3SiCN 2 equiv, −20 °C, [ketone] = 2.4 M in THF. [c] Value in parentheses indicates enantiomeric excess after recrystallization from hexane.

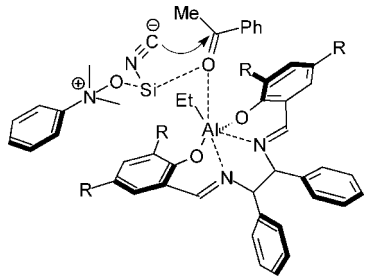
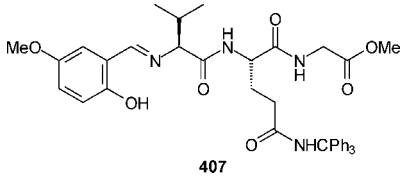


Figure 29.

In summary, the more enantioselective systems, **398**, **399**, and **240**, generally require low reaction temperatures (−20 to −50 °C) to achieve high levels of asymmetric induction. Shibasaki's system has an important advantage due to its broad substrate tolerance, though it is necessary to use 10 mol % of the catalyst.

3.3. Aluminum-Based Catalytic Systems

Snapper and Hoveyda reported the aluminum complex of peptide derivative **407**, which displayed wide substrate tolerance for the cyanosilylation of ketones.[253] The use of 10 mol % of ligand **407** in the presence of aluminum isopropoxide (10 mol %) and methanol (10 mol %) gave high yields (67−97%) and excellent enantioselectivities (82−95%) for aromatic and aliphatic (saturated and unsaturated) ketones (Table 149). The flexibility of this system and the opportunities for structure modification are important advantages of this catalyst. The ligand was also shown to be recoverable and could be reused in subsequent cyanation reactions.



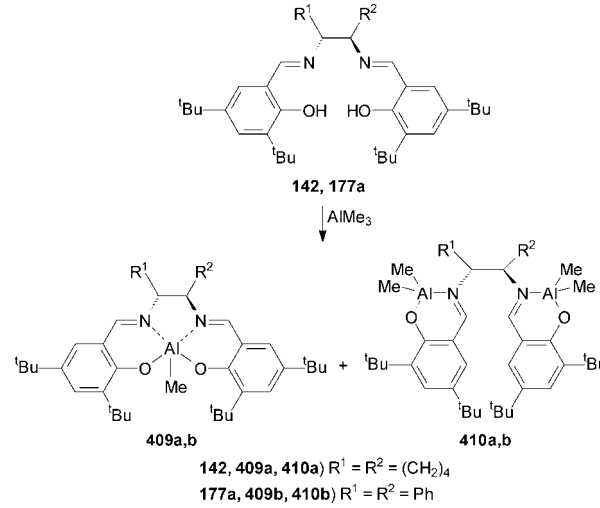
407

Table 151. Asymmetric Cyanosilylation of Ketones Using Aluminum Complex 354 with Triphenylphosphine Oxide

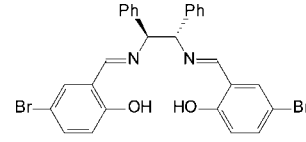
ketone	time (h)	yield (%)	ee (%) (*S*)
PhCOMe	19	93	78
4-ClC_6H_4COMe[b]	11	97	77
3-ClC_6H_4COMe	6	98	91
2-ClC_6H_4COMe	23	98	62
4-FC_6H_4COMe	7	95	73
4-BrC_6H_4COMe	5	96	73
4-$O_2NC_6H_4COMe$	2	95	72
4-MeC_6H_4COMe	21	90	66
4-$MeOC_6H_4COMe$	20	87	71
1-indanone	25	87	68
$PhCOCHMe_2$	40	80	92
4-$MeOC_6H_4CH_2COMe$	3	85	65
$PhCH_2CH_2COMe$	3	90	75
PhCH=CHCOMe	4	75	60

[a] The reactions were carried out in dichloromethane at ambient temperature with 1 mol % of catalyst **354** and 30 mol % of triphenylphosphine oxide unless stated otherwise. [b] 10 mol % of triphenylphosphine oxide was used.

Scheme 58



Feng's group conducted detailed studies of the influence of the metal atom, ligand substituents, and *N*-oxide additive in asymmetric cyanosilylation of ketones using salen ligands



408

related to **177a** (see section 3.2 for titanium-based catalysts). The aluminum complex formed from ligand **408** and triethylaluminum in the presence of *N*-oxide **404** proved to be the optimum catalyst for cyanosilylation of ketones.[254] For a series of aromatic and aliphatic methyl ketones (and also some cyclic ketones), yields of 80−99% and enantioselectivities of 79−94% were obtained under the optimized conditions (Table 150). The authors proposed a mechanism for the reaction in which the aluminum(salen) complex acts as a Lewis acid and activates the ketone whilst the *N*-oxide acts as a Lewis base to activate the trimethylsilyl cyanide as shown in Figure 29.

After successfully applying aluminum salen complex **354** in the asymmetric cyanosilylation of aldehydes[199] (see

Scheme 59

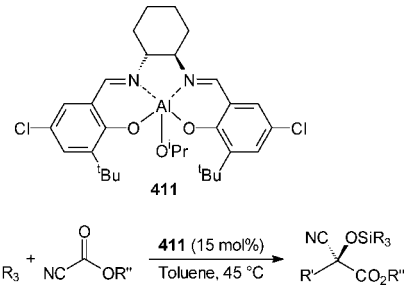


Table 152. Asymmetric Addition of Cyanoformates to Silyl Ketones Using the Aluminum Complex 411[a]

silyl ketone	cyanoformate	yield (%)	ee (%) (*S*)
$PhCOSiEt_3$	BnOCOCN	83	79
$PhCOSi^tBuMe_2$[b]	BnOCOCN	82	64
$PhCOSiEt_3$	EtOCOCN	93	77
$4\text{-}MeC_6H_4COSiEt_3$	BnOCOCN	79	80
2-naphthylCOSiEt$_3$	BnOCOCN	90	62
$4\text{-}MeOC_6H_4COSiEt_3$	BnOCOCN	84	82
$4\text{-}ClC_6H_4COSiEt_3$	BnOCOCN	87	64
$4\text{-}ClC_6H_4COSiEt_3$	EtOCOCN	87	61
$4\text{-}FC_6H_4COSiEt_3$	BnOCOCN	81	78
$4\text{-}NCC_6H_4COSiEt_3$	BnOCOCN	70	64

[a] The reactions were carried out as shown in Scheme 59 using 1 equiv of silyl ketone with 2 equiv of cyanoformate for 72 h unless stated otherwise. [b] 20 mol % catalyst was used.

section 2.5.2), Kim's group studied the use of the same complex in the addition of trimethylsilyl cyanide to ketones.[255] The reaction was carried out in dichloromethane at room temperature using 1 mol % of **354** and 30 mol % of triphenylphosphine oxide to give the cyanohydrin products for a range of substrates (aromatic, aliphatic, and α,β-unsaturated methyl ketones) in 75−98% yield and with 62−92% enantioselectivity (Table 151). The authors proposed the same transition state to explain the asymmetric induction as that suggested by Feng for the **408/404** catalyst system, but with triphenylphosphine oxide rather than an *N*-oxide acting as the Lewis base.

Carpentier *et al.* investigated aluminum complexes of salen-based ligands **142** and **177a** for the asymmetric cyanosilylation of ketones.[256] They focused particularly on the differences between catalysts formed *in situ* and the isolated complexes. It was shown that addition of the ligands to trimethylaluminum could result in formation of two types of complex **409a**,**b** and **410a**,**b** depending on the order of addition of reagents and the relative amounts used (Scheme 58). Preparing the catalyst at higher temperatures (110 °C) generally resulted in higher proportions of **409a**,**b**, (91:9 in the case of **409b**:**410b**), particularly when the reagents were preheated before mixing.

Complexes **409a**,**b** could be converted into the corresponding aluminum alkoxide salen complexes through reaction with the appropriate alcohol. A number of different alcohols were used and gave enantioselectivities of 66−83% for the addition of trimethylsilyl cyanide to acetophenone, with the highest of these derived from the aluminum isopropoxide salen catalyst. *N*,*N*-Dimethylaniline *N*-oxide **404** (1 mol %) was used as a cocatalyst in the reaction. The fastest reaction occurred when using the hexafluoro-2-propanol aluminum salen complex of ligand **142**, which gave a 90% conversion after 3 h (with 73% asymmetric induction) compared to a reaction time of 48 h required with all the other complexes to give similar results. In general, it was found that lower enantioselectivities were obtained when using catalysts formed *in situ* when compared to the isolated complexes. This was reasoned to be due to the influence of catalytically active species other than the aluminum salen complex, such as residual trimethylaluminum, being present in solution.

Johnson *et al.* reported the use of aluminum salen complexes for the asymmetric cyanation of silyl ketones using ethyl and benzyl cyanoformate.[257] The reaction proceeds with concomitant Brook rearrangement, leading to cyanohydrin trimethylsilyl ethers of α-keto esters (Scheme 59). Moderate to good enantioselectivities (61−82%) were obtained for a range of substrates (Table 152) when using complex **411**, the most active catalyst from a series of related ligands. As an example of the use of the cyanohydrins, the synthesis of α-hydroxy β-lactams **412** was developed by reduction of the nitrile followed by cyclization through treatment with a Grignard reagent (Scheme 60).

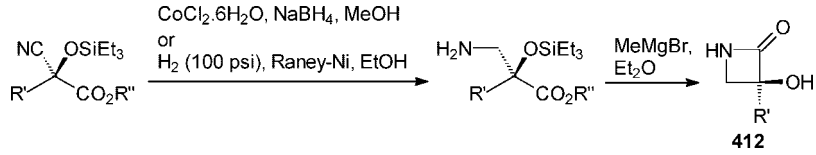
Thus, aluminum complexes generally demonstrate comparable or superior enantioselectivities in comparison with titanium-based systems for the asymmetric cyanation of ketones. However, the most stereoselective protocol, that of Snapper and Hoveyda, requires 10 mol % of the catalyst and a temperature of −78 °C. Kim's catalyst is convenient because of the relatively low catalyst loading (1 mol %) and the ability to conduct the reaction at ambient temperature. Feng's system, which allowed an even greater decrease of the catalyst loading, nonetheless requires lower temperatures (−20 °C) and extended reaction times.

3.4. Lanthanide-Based Catalytic Systems

Shibasaki used gadolinium complexes of sugar derived ligands[246] **398**, **401**, and **413**−**415** for the asymmetric addition of cyanide to ketones and illustrated the utility of the chemistry in a number of natural product syntheses. The catalyst formed from ligand **398** and gadolinium triisopropoxide showed excellent results in the cyanosilylation of aryl and alkyl ketones (Scheme 61), giving cyanohydrin trimethylsilyl ethers in 85−97% yield and with 62−97% enantiomeric excess (Table 153).[258] Enantioselectivities were high for all substrates with the exception of 4-phenylbutan-2-one (62%). Mass spectrometry studies revealed that the active precatalyst had a 2:3 metal/ligand ratio, although use of a 1:2 ratio of metal to ligand produced somewhat higher enantioselectivities. It is notable that this system gave products with opposite absolute configuration to the system based on the titanium complex of **398** (see section 3.2). On this basis, a catalytic transition state structure was proposed containing two metal centers each complexed to one ligand with a third ligand bridging between the two metals. Two equivalents of trimethylsilyl cyanide react with the catalyst to give cyanide ligands on both metal ions and trimethylsilyl groups coordinated to both phosphine oxides. Coordination of the ketone to one metal ion, followed by delivery of cyanide from the other then forms the cyanohydrin (Figure 30). The importance of the stabilizing ability of the phosphine oxide groups was shown through the use of ligand **413**, which lacks the phosphine oxide group and which catalyzed asymmetric cyanohydrin synthesis with a maximum enantioselectivity of just 7% after a reaction time of 10 h.

The same article illustrated the application of ligand **398** complexed to samarium triisopropoxide for the preparation of a key intermediate in the synthesis of Camptothecin (Scheme 62), a molecule related to the

Scheme 60



Scheme 61

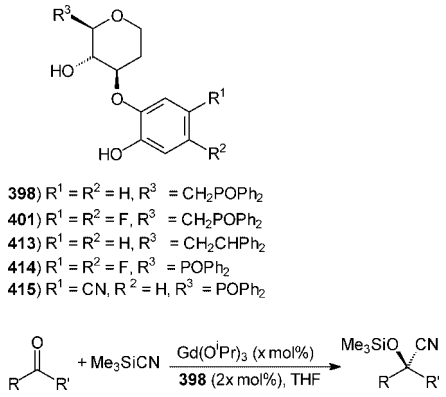


Table 153. Asymmetric Cyanosilylation of Ketones Catalyzed by Gd(O^{i}Pr)$_3$−398[a]

ketone	catalyst (mol %)	temp (°C)	time (h)	yield (%)	ee (%) (*S*)
PhCOMe	5	−40	2	95	92
4-ClC$_6$H$_4$COMe	5	−60	55	89	89
2-acetylnaphthalene	5	−60	24	95	87
PhCOEt	5	−60	14	93	97
PhCH=CHCOMe	10	−60	14	97	86
(*E*)-CH$_3$(CH$_2$)$_4$CH=CHCOMe	15	−60	18	87	80
1-acetylcyclohexene	15	−60	4	95	89
PhCH$_2$CH$_2$COMe	5	−60	1	90	62

[a] Reaction carried out as shown in Scheme 61.

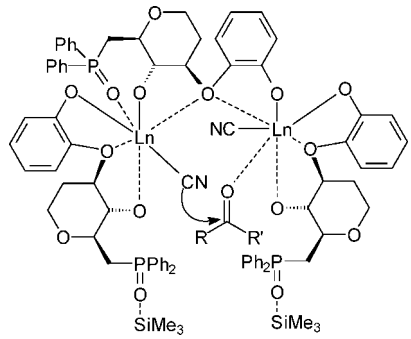
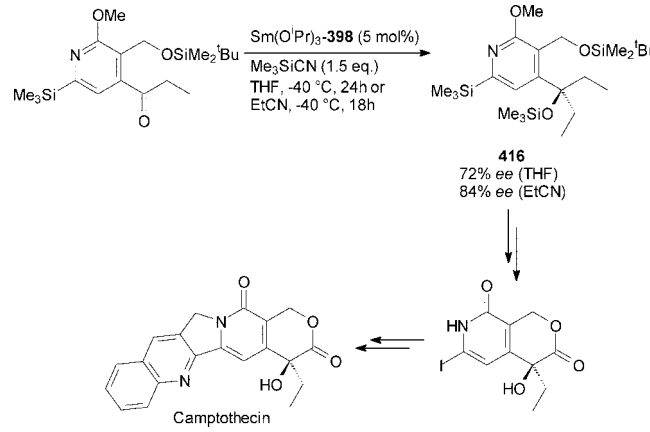


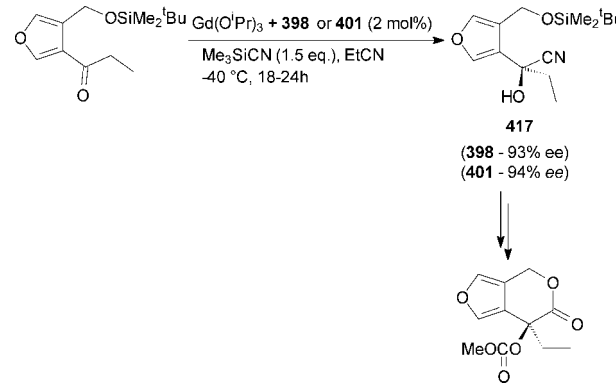
Figure 30.

approved anticancer drugs Topotecan and Irinotecan, which function by interfering with topoisomerase enzymes involved with the unwinding of coiled DNA. The required cyanohydrin intermediate **416** was prepared with 84% enantiomeric excess, and later synthetic intermediates could be purified by recrystallization to give a final enantiomeric excess of 99%. Further studies were carried out using samarium complexes of ligands related to **398** with variations made to the aromatic ring and the groups attached to the phosphine. It was found that 91% asymmetric induction could be achieved for the transformation shown in Scheme 62 using 5 mol % of Sm(O^{i}Pr)$_3$−**401**.[259]

Scheme 62



Scheme 63

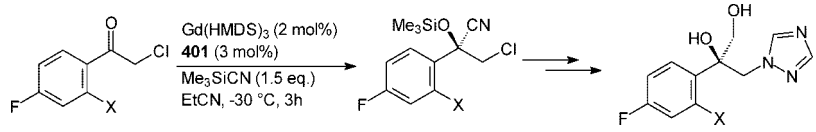


An alternative convergent synthesis of Camptothecin had been reported by Corey in 1975;[260] thus, Shibasaki's group also applied gadolinium complexes of ligands **398** and **401** for the synthesis of an intermediate in Corey's synthesis (Scheme 63). The synthesis of the furan containing cyanohydrin **417** was achieved in 94−100% yield and with 93−94% enantioselectivity.

Gadolinium complexes of ligands **398** and the fluorinated analogue **401** were also used in the synthesis of key intermediates for the production of triazole antifungal agents.[261] The catalysts were used to perform the cyanation shown in Scheme 64, which was accomplished with 96% asymmetric induction in the best case using 3 mol % of ligand **401** with 2 mol % of Gd(HMDS)$_3$ for 3 h in propionitrile.

The gadolinium complex of ligand **398** was used to prepare a chiral intermediate within the total synthesis of the muscarinic receptor antagonist Oxybutynin.[262] Using cyclohexyl phenyl ketone as substrate to prepare the cyanohydrin **418**, 95% asymmetric induction was achieved using 5 mol % of the catalyst (Scheme 65). The ability to obtain exceptionally high enantioselectivities (95%) from substrates such as cyclohexyl phenyl ketone in which there is only a small size difference between the two substituents attached

Scheme 64



Scheme 65

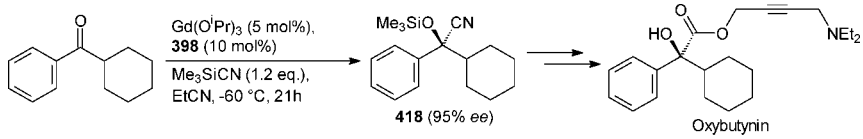
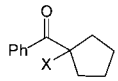


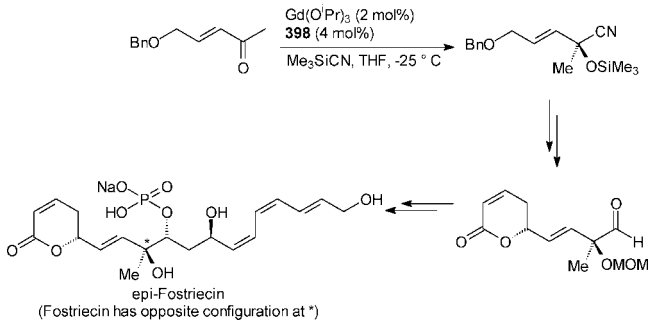
Table 154. Asymmetric Cyanosilylation of Ketones Catalyzed by Gd(O^{i}Pr)$_3$−398[a]

ketone	time (h)	yield (%)	ee (%) (S)
4-MeOC$_6$H$_4$CO*c*C$_6$H$_{11}$	22	99	94
4-F$_3$COC$_6$H$_4$CO*c*C$_6$H$_{11}$	1	96	83
PhCO*c*C$_7$H$_{13}$	5	99	94
	64	87	22
X = H			
X = D (85%)	1	99	95
X = D (65%)	1	99	95
X = D (21%)	18	99	78
PhCO*c*C$_4$H$_7$	2	99	97
PhCO*c*C$_3$H$_5$	48	97	82
PhCOMe	1	89	95
PhCOEt[b]	14	93	97
PhCOPr[b]	2.5	94	97
PhCOBu[b]	14	91	87
	20	99	38
X = H			
X = D (80%)	1	81	96
PhCO^{i}Bu[b]	2.5	90	80
MeCH=CHCOPr	1	87	85

[a] Reactions were carried out using 5 mol % of gadolinium triisopropoxide with 10 mol % of ligand **398** at −40 °C unless stated otherwise. [b] Reaction was carried out at −60 °C.

to the carbonyl is a remarkable feature of this catalyst. Shibasaki also used the gadolinium complex of **398** to catalyze the addition of trimethylsilyl cyanide to a range of related ketones to give cyanohydrins which could be used as intermediates for the preparation of Oxybutynin analogues (Table 154). Good enantioselectivities were obtained with all substrates except cyclopentyl phenyl ketone (22%) and isopropyl phenyl ketone (38%). The low enantioselectivities were explained by the lower pK_a of the CO−CH proton in these substrates. The authors suggested a mechanistic pathway in which the catalyst can also act as a Brönsted base and deprotonate the ketone. In order to study this further,

Scheme 66



Scheme 67

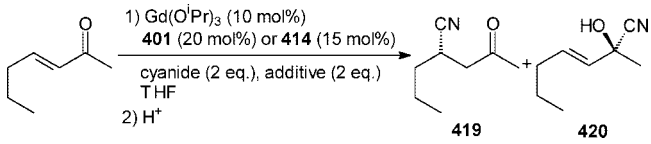


Table 155. Asymmetric Cyanation of 3-Hepten-2-one Using Catalysts 401 and 414[a]

ligand	conditions	yield (%)[b]	419/420	ee 420 (%) (*S*)
401	Me_3SiCN, rt, 15 min	63	19:81	15 (*R*)
414	1.5 equiv Me_3SiCN, rt, 18 h	62	52:48	40
414	1 equiv Me_3SiCN, 1equiv HCN, rt, 18 h	67	18:82	53
414	Me_3SiCN, DMP, rt, 1 h	70	100:0	84
414	Me_3SiCN, DMP, −20 °C, 24 h	40	72:28	90
414	Me_3SiCN, DMP, −40 °C, 45 h	44	27:73	93
414	HCN, −20 °C, 41 h	37	27:73	47
414	^{t}BuMe$_2$SiCN, DMP, −20 °C, 24 h	77	100:0	92

[a] Conditions used are illustrated in Scheme 66 unless stated otherwise. DMP = 2,6-dimethylphenol. [b] Yield is combined total of **419** and **420**.

a deuterium kinetic isotope effect was utilized and it was observed that the cyanosilylation reaction proceeded much faster and with vastly improved enantioselectivities (95% for cyclopentyl phenyl ketone and 96% for isopropyl phenyl ketone) for the deuterated substrates.

Shibasaki further used the gadolinium complex of ligand **398** for part of the synthesis of Fostriecin and 8-epi-Fostriecin, an antibiotic with cytotoxic properties toward cancer cells.[263] The (*S*)-enantiomer of the cyanohydrin, needed for the synthesis of epi-Fostriecin, was prepared in 95% yield and with 86% enantiomeric excess (Scheme 66). To synthesize Fostriecin, the (*R*)-enantiomer of the cyanohydrin could be prepared using the titanium complex of ligand **398** (see section 3.2) due to the reversal of asymmetric induction observed on changing the metal from gadolinium to titanium.

The gadolinium complexes of ligands **398**, **401**, and **413**−**415** were also used by Shibasaki for the asymmetric addition of cyanide to enones.[264] It was found that there were two competing reaction pathways: cyanation of the ketone and asymmetric conjugate addition of cyanide (Scheme 67). Complexes **401** and **414** were used to catalyze addition of cyanide sources (trimethylsilyl cyanide, hydrogen cyanide, and *tert*-butyldimethylsilyl cyanide) to hept-3-en-2-one under a variety of conditions (Table 155). The main focus of the work was to investigate the 1−4 addition to give cyano ketones rather than the synthesis of cyanohydrins. Thus, Gd(O^{i}Pr)$_3$−**414** catalyzed the addition of *tert*-butyldimethylsilyl cyanide, in the presence of dimethylphenol to give 100% of 1,4-adduct **419**. It was discovered that the same catalytic system was able to convert cyanohydrin **420** into **419**; even racemic **420** could be used, which resulted in formation of compound **419** with 85% enantiomeric excess as shown in Scheme 68.

Scheme 68

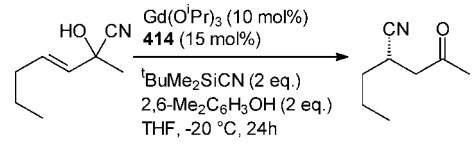


Table 156. Addition of Trimethylsilyl Cyanide to Ketones Using Catalyst 389[a]

ketone	time (h)	yield (%)	ee (%) (*R*)
PhCOMe	45	82	63
3-ClC_6H_4COMe	20	91	63
4-ClC_6H_4COMe	26	90	57
4-BrC_6H_4COMe	36	89	85
4-FC_6H_4COMe	50	82	60
3-$O_2NC_6H_4COMe$	10	93	46
4-$O_2NC_6H_4COMe$	6	89	50
4-$MeOC_6H_4COMe$	45	38	55
$PhCOCH_2CH(Me)_2$	38	75	57
4-$MeOC_6H_4CH_2COMe$	7	90	82
3,4-$(Cl)_2C_6H_3CH_2COMe$	5	95	75
$PhCH_2COEt$	32	94	72
$PhCH_2CH_2COMe$	10	89	60
1-indanone	70	56	58

[a] 5 mol % catalyst **389** was used with 50 mol % of triphenylphosphine oxide at ambient temperature in dichloromethane.

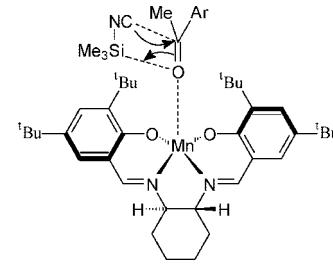


Figure 31.

3.5. Manganese-Based Catalytic Systems

In continuation of their work on the cyanosilylation of aldehydes (see section 2.10), Kim and co-workers studied the use of manganese complex **389** with ketones as substrates.[265] It was found that in the presence of triphenylphosphine oxide as a cocatalyst, complex **389** afforded a range of silylated cyanohydrins in 38−95% yield and with 46−82% enantioselectivity (Table 156). Aromatic methyl ketones were mostly used as substrates, and the best results were achieved using 4-bromoacetophenone (85% enantioselectivity) and 4-methoxyphenylacetone (82% enantioselectivity). A transition state was suggested in which the carbonyl bond is activated by coordination to the manganese ion and the silicon of trimethylsilyl cyanide simultaneously makes a bond with the carbonyl oxygen whilst transferring the cyanide to the carbonyl carbon atom (Figure 31).

3.6. Sodium-Based Catalytic Systems

Feng and co-workers reported the use of amino acid salts as catalysts for the asymmetric cyanation of ke-

Scheme 69

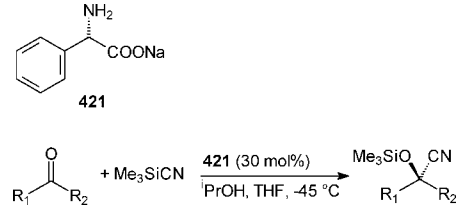


Table 157. Asymmetric Cyanation of Ketones Using Catalyst 421[a]

ketone	time (h)	yield (%)	ee (%) (*R*)
PhCOMe	24	96	94
4-MeOC$_6$H$_4$COMe	54	81	92
4-MeC$_6$H$_4$COMe	54	75	97
4-FC$_6$H$_4$COMe	27	90	92
4-ClC$_6$H$_4$COMe	40	83	90
3-ClC$_6$H$_4$COMe	54	80	96
2-FC$_6$H$_4$COMe	36	77	90
2-acetylthiophene	66	58	92
PhCH=CHCOMe	27	96	97
2-acetylnaphthalene	27	90	96
PhCH$_2$CH$_2$COMe	20	97	81
Me$_2$CHCOMe	20	92	55

[a] 30 mol % of catalyst **421** was used with 50 mol % of triphenylphosphine oxide at ambient temperature in dichloromethane.

tones.[266] Amongst the catalysts screened, the best results were obtained using the sodium salt of L-phenylglycine **421**. The authors conducted reactions with a range of substituted acetophenones as well as with some heteroaromatic and aliphatic methyl ketones, obtaining yields of 77−97% and enantioselectivities of 55−97% (Scheme 69). The best results were obtained when the catalyst was prepared *in situ* and left to stir with trimethylsilyl cyanide for 1 h before the addition of the ketone. Enantioselectivities were high for most of the substrates tested (81−97%), with the exception of 3-methylbutanone (55%) (Table 157). The authors assumed involvement of hypervalent silicon species, as proposed in Kagan's system for asymmetric cyanosilylation of aldehydes (see section 2.14).

4. Conclusions

Asymmetric cyanohydrin synthesis has come a long way over the last 100 years, with most progress having been made over the last decade. For aldehyde substrates, readily prepared catalysts are now available which will virtually guarantee to produce high levels of asymmetric induction for any substrate, with a range of different cyanide sources at high substrate to catalyst loadings. The titanium and vanadium salen complexes **157** and **332c** are particularly notable in this respect, as are the aluminum(binol) complexes **361** and **367**. The use of ketones as substrates is a less well developed field, with the first Lewis acid-based catalysts for their cyanosilylation having been reported only in the mid 1990s. Very high enantioselectivities can however be obtained using the titanium and lanthanide complexes of ligands **398** and **401**, but the synthesis of the ligands is itself a multistep process and high catalyst loadings are required. Nevertheless, as is illustrated throughout this review, asymmetric cyanohydrin synthesis using both aldehydes and ketones as substrates is now being used as a central part of the synthesis of natural products and pharmaceuticals, both in academia and in industry.

Mechanistically, asymmetric cyanohydrin synthesis is an interestingly complex area. It is now well established that all of the most effective and enantioselective catalysts work by activating *both* the carbonyl compound and the cyanide source. In most early catalyst systems, this was achieved more by accident than by design, though the magnesium-based system of Corey is a notable exception. More recently, catalysts have been specifically designed to activate both components of the reaction. Examples where this is accomplished by having two binding sites within the same catalyst have been demonstrated, as have examples of use of chiral Lewis acids in conjunction with chiral or achiral Lewis bases. Clearly, there is enormous scope for variation in this concept, and it is likely that many highly active systems remain to be discovered. Most postulated transition state structures then involve a supramolecular assembly in which cyanide is transferred intramolecularly, a process which is reminiscent of the mode of action of enzymes and which provides a reminder of the ability of oxynitrilase enzymes to catalyze asymmetric cyanohydrin synthesis. It should be borne in mind, however, that whilst most authors propose transition state structures, relatively few systems have been subjected to rigorous mechanistic studies to confirm the catalytic cycle and origin of the asymmetric induction.

It might seem from reading this review that any metal complexed to any chiral ligand will catalyze asymmetric cyanohydrin synthesis, especially when trimethylsilyl cyanide is used as the cyanide source. Certainly, it is true that over twenty different metals and many of the common "privileged" ligands have been demonstrated to display catalytic activity. However, there are also many, mostly unpublished, cases where a particular combination of metal and ligand provided no catalysis whatsoever. It will be apparent that the literature is currently dominated by catalysis by titanium complexes, and for aldehyde substrates, titanium complexes do seem to form the most active catalysts. For ketone substrates, however, the dominance of titanium is less apparent and the lanthanides, especially gadolinium, may currently be the metals of choice.

In summary, asymmetric cyanohydrin synthesis is now well established as a useful chemical transformation and the reaction is increasingly being routinely used in screens of new catalysts. However, sufficient detailed mechanistic information has recently become available that it should be possible to design highly active and enantioselective catalysts from first principles.

5. Note Added in Proof

Whilst this review was being typeset, a number of other reports of asymmetric cyanohydrin synthesis appeared in the literature. Ohkuma reported the use of a bimetallic ruthenium–lithium based system for the asymmetric addition of trimethylsilyl cyanide to aldehydes.[267] The ruthenium complex used was Ru((*S*)-binap)((*S*)Phg)$_2$, where Phg is phenylglycine. By itself this complex had negligible catalytic activity, but in the presence of lithium carbonate a highly active catalyst for asymmetric cyanosilylation was formed. Electrospray mass spectrometry suggested that the catalytically active species was a 1:1 complex of the ruthenium complex and lithium. A feature of this system is the exceptionally high substrate to catalyst ratios used (10,000:1 to 100,000:1), which are totally unprecedented in the area of asymmetric cyanohydrin synthesis. Good to excellent

levels of asymmetric induction (70–98%) were obtained for a wide range of aldehydes, and unusually the best results were obtained in ethereal solvents. The need to carry out reactions at –70 to –78 °C is however a limitation of the system. This system may be related to other heterobimetallic lithium containing catalysts (see sections 2.5.3 and 2.8, respectively) and to the use of the sodium salt of phenylglycine as a catalyst for the cyanosilylation of ketones (see section 3.6).

Ishihara reported the extension of the Li-binol chemistry initially developed by Kagan for the asymmetric cyanosilylation of aldehydes (see section 2.14) to the use of substates.[268] To obtain activity with ketones, the authors used binol-phosphoric acid instead of binol. Optimal results were obtained using 10 mol % of 3,3'diphenylbinol-phosphoric acid and BuLi in toluene at –40 °C. Under these conditions, aryl methylketones were converted into cyanohydrin trimethylsilul ethers with 37–86% enantiomeric excess when treated with trimethylsilyl cyanide. The authors propose a mechanism in which the trimethylsilyl cyanide coordinates to one oxygen of the lithium phosphonate and the ketone is coordinated to both the lithium and silicon. Cyanide is then transferred intramolecularly to the carbonyl group.

Khan showed that, in the presence of imidazole as a cocatalyst, vanadium(salen) complex **332a** (see section 2.3) would catalyze the asymmetric addition of ethyl cyanoformate to aldehydes.[269] Various other basic catlysts such as potassium cyanide, 2,6-litidine, and 2-methylimidazole could also be used, but in the absence of the basic cocatalyst no reaction occured (see section 2.2.3.3 for closely related results using titanium(salen) complex **157** as catalyst). Optimal results were obtained at –20 °C using 2.5 mol % of catalyst **332a** and 10 mol % of imidazole in dichloromethane as solvent. Under these conditions, 18 aldehydes were converted into cyanohydrin carbonates with enantioselectivities of 76–96% and in yields of 82–96% after reaction times of 18–60 h.

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