Asymmetric Synthesis of Pharmaceutically important Cyanohydrins through chiral catalytic route using chiral Lewis acid based metal complexes

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By

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March, 2009

Dedicated to my Bhaiya-Bhabhi

CANDIDATE'S STATEMENT

I hereby declare that the work incorporated in the present thesis is original and has not been submitted to any University / Institution for the award of a Diploma or a Degree. Further, I hereby declare that the results presented in this thesis and the considerations made therein, contribute in general to the advancement of knowledge in Chemistry and on particular topic, entitled **"*Asymmetric Synthesis of Pharmaceutically important Cyanohydrins through chiral catalytic route using chiral Lewis acid based metal complexes*"**

(Santosh Agrawal)

Signature of the candidate

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CERTIFICATE BY THE Ph. D. SUPERVISOR

This is to certify that the contents of this thesis entitled "***Asymmetric Synthesis of Pharmaceutically important Cyanohydrins through chiral catalytic route using chiral Lewis acid based metal complexes***" is the original research work of Mr. Santosh Agrawal, carried out under my supervision in the Discipline of Inorganic Materials and Catalysis at Central Salt and Marine Chemicals Research Institute, Bhavnagar 364 002 (Gujarat) INDIA.

Further, I hereby certify that the work has not been submitted either partly or fully to any other University or Institution for the award of any other Diploma or Degree.

(N. H. Khan)
Signature of Ph.D. Supervisor

PREFACE

The work embodied in the present thesis comprises of six chapters. In chapter 1 the brief introduction of chiral catalysis with special emphasis on Asymmetric synthesis of Cyanohydrins. This chapter also highlights with the scope and objectives of the present work.

Chapter 2 includes the synthesis and characterisation of dimeric chiral Ti(IV) and V(V) salen complexes as active catalysts for enantioselective synthesis of cyanoester of various aromatic and aliphatic aldehydes using alkali metal cyanide sources viz. NaCN and KCN.

Chapter 3 consists of synthesis and characterization of polymeric V(V) salen complexes, this chapter consist two section. In first section the polymeric V(V) salen complexes were used for the enantioselective cyanation of aldehydes using trimethylsilylcyanide as a source of cyanide, the kinetic study of reaction was also carried out by varying the various parameters. In the second section instead of trimethylsilylcyanide, KCN were used as source of cyanide for the cyanation of various aromatic and aliphatic aldehydes.

Chapter 4 consists the synthesis and characterization of dimeric and polymeric Mn(III) salen complexes as efficient catalysts for the enantioselective cyanosilylation of various aromatic and aliphatic ketones in presence of triphenylphosphine oxide as a additive.

Chapter 5 deals with synthesis and characterization of monomeric V(V) salen complex. This complex was used to catalyzed the cyantion of various aldehydes using ethylcyanoformate as a source of cyanide in the presence of imidazole as a co-catalyst. The role of the catalyst and co-catalyst were investigated through NMR spectroscopy.

Chapter 6 comprises the cyanoformylation of aldehydes using monomeric and polymeric V(V) salen complex in the presence of solid base like hydrotalcite and basic alumina as a co-

catalyst. References have been placed at the end of each chapters for the sake of convenience.

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With core of my heart, I am thankful to my dear respected Parents, beloved brothers, sisters and all my well wishers whose continuous encouragement and support have been a source of inspiration in completion of this tough task.

Last but not the least; I am thankful to the Almighty, who has provided me sound health and strength to complete this work. What I am and what I would be I owe to the Almighty for leading me the path of Light and Success.

March, 2009 (Santosh Agrawal)

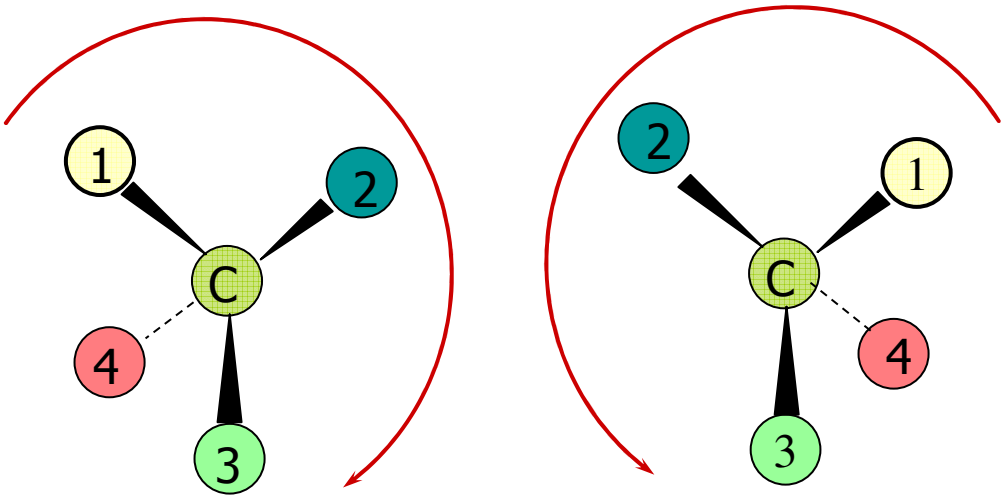
CONTENT OF THE THESIS

CONTENTS

List of Abbreviations

DCM	Dichloromethane
DDA	Dodecylamine
ee	Enantiomeric Excess
FSM	Folded Sheet Materials
FTIR	Fourier Transform Infrared
GC	Gas Chromatography
HT	Hydrotalcite
ICP-AES	Inductive Coupled Plasma – Atomic Emission Spectrometry
NMR	Nuclear Magnetic Resonance
Py*N*-O	Pyridine *N*-Oxide
SEM	Scanning Electron Microscopy
TEM	Transmission Electron Microscopy
TOF	Turnover Frequency
TON	Turnover Number
TMSCN	Trimethyl Silyl Cyanide
THF	Tetra Hydro Furon
UV-Vis	Ultraviolet-Visible
XRPD	Powder X-Ray Diffraction

Chapter 1



Rectus (*R*) **Sinister** (*S*)

Introduction

1.1 What is chirality?

Chirality, the molecular version of right- and left-handedness was first introduced by the French chemist Jean Baptiste Biot in 1815 when he discovered optical activity in nature[1]. One of his students, Louis Pasteur found that crystallization of sodium ammonium paratartrate, formed a mixture of tiny crystals of two types with structures which were mirror images of each other. On separating out the two types of crystals, one was found to be identical to ordinary sodium ammonium tartrate which was optically active and rotated the plane of polarized light. The other type of crystal rotated the plane of polarized light in the opposite direction.[2] This behavior was thought to be due to an asymmetric grouping of atoms in the optically active molecules. Since then, chirality has tremendous significance in our daily life.

A chiral object is one that possesses the property of "handedness". Thus a molecule can exist in two forms, which are non super imposable mirror images of each other, are called enantiomers (**Figure 1.1**), but possess identical physical properties and different chemical nature in an achiral environment.

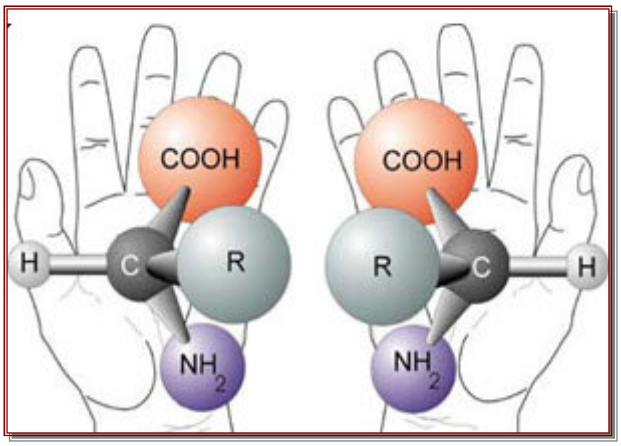


Figure 1.1 The two enantiomers of amino acid

1.2 Significance of chirality

Most of biological system are composed of chiral molecules e.g. the amino acids which are the building blocks of proteins are found only in the left-handed L-configuration whereas sugars are found in the right-handed D-configuration. The chemical processes in living cells depend on, and maintain, these asymmetries, since they are driven by enzyme catalysis. The enzymes are protein molecules which fold up into complex three dimensional structures, providing an active site into which reactants (drug) can fit. In the biological systems, only molecules of the drug with right shape provides the desire effect, while the other enantiomer is, at best, less or not active (**Figure 1.2**).

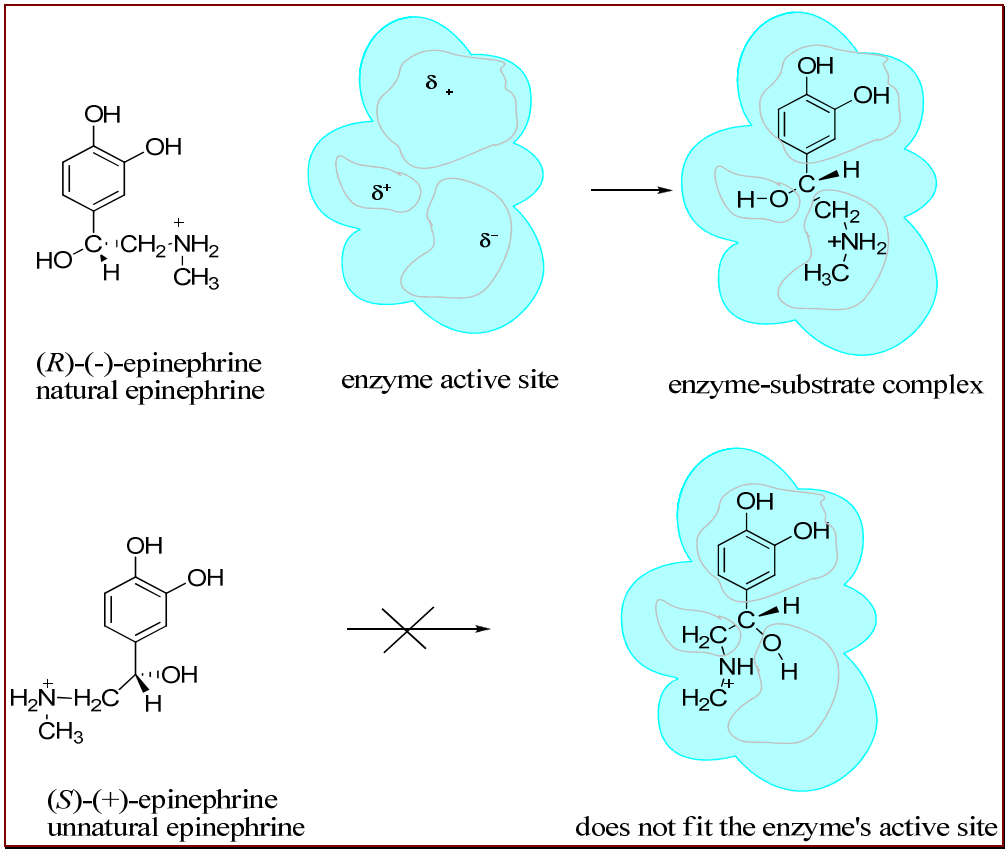


Figure 1.2 Model depicting drug-enzyme activity based on the chirality of the drug molecule

However, in some cases the undesired enantiomer can have severe side effects. The most infamous and tragic example is the drug thalidomide, prescribed to pregnant woman

during the year 1960s to lighten the symptom of morning sickness. The drug formulation contained racemic form of the thalidomide. It was later discovered that only one of the thalidomide enantiomer has the intended effect, while the other induces abnormalities in human embryos (**Figure 1.3**). Unfortunately, the situation is complicated by the racemization of the desired enantiomer in the body.

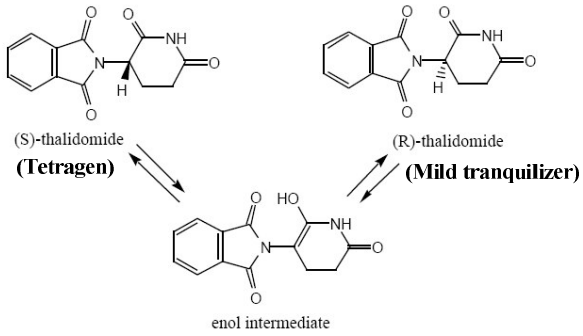


Figure 1.3 Racemization of two thalidomide enantiomers

Chiral molecules play distinct role not only in pharmaceutical industry but also in perfumery and food industry; as our senses for taste and smell also depend on chirality. One enantiomeric form of limonene is responsible for the odor of orange while the other enantiomer smells like lemon. Similarly, one enantiomer of the amino acid-asparagine tastes sweet while the other is bitter (**Figure 1.4**)

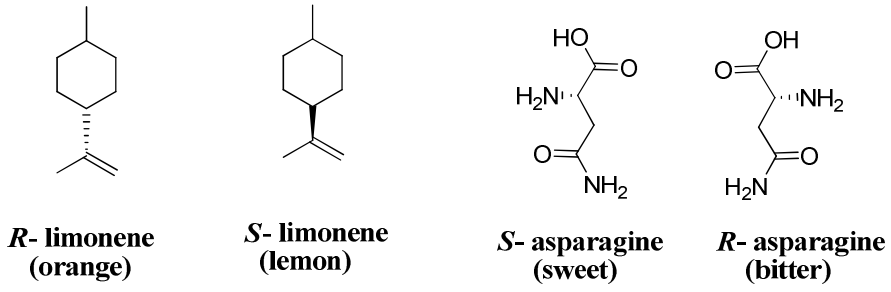


Figure 1.4 Example of enantiomers having different smell or taste

1.3 The quest for the single isomer

There are three main ways to synthesize an enantiomerically pure compound[3] (**Figure 1.5**). First racemates can be separated into their enantiomer by mean of resolution. This can be done by crystallization, classical resolution, chiral chromatography and kinetic resolution. Alternatively, primary resources of enantiomer, denoted as the chiral pool, can be used as starting materials in the synthesis of enantiopure compounds. Finally enantiomerically pure compounds can be obtained from prochiral substrates by asymmetric synthesis [4,5.]

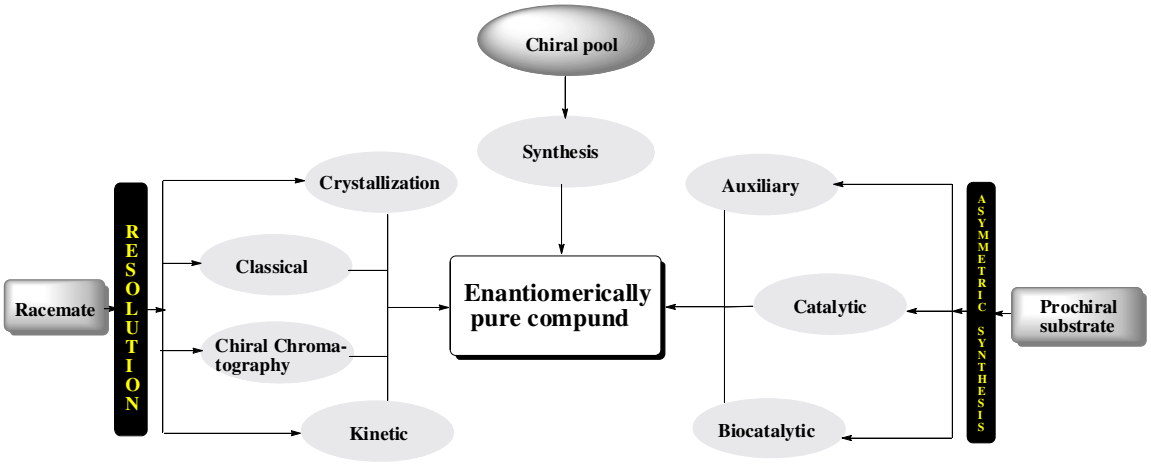


Figure 1.5 Routes to synthesize enantiomerically pure compounds

1.3.1 The chiral pool approach

Chiral pool synthesis is considered as easiest of all approaches, where a chiral starting material is manipulated through successive reactions to obtain the desired target molecule using achiral reagents with retention of chirality. This is especially attractive for target molecules having the similar chirality to a relatively inexpensive naturally occurring building block such as a sugar or amino acid, carbohydrates, terpenes or alkoloids (**Figure 1.6**). Chiral pool approach though very attractive has limitations such

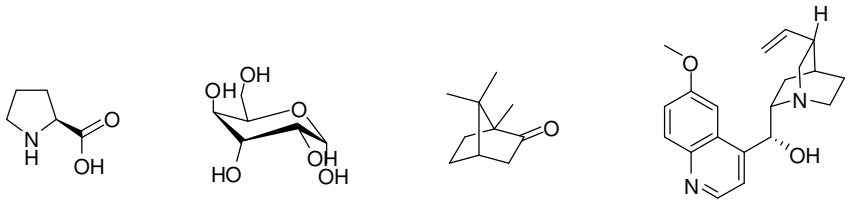


Figure 1.6 Examples of chiral molecules abundantly available in nature

as; only limited number of starting materials are available, only one enantiomer is present, sometimes quantity of the desired molecule is very small and difficult to isolate from the source. Hence, synthetic application of this strategy is limited.

1.3.2 Resolution of racemates

The resolution of racemates still constitutes the main method for the industrial synthesis of pure enantiomers.[6] It is done by the following strategies.

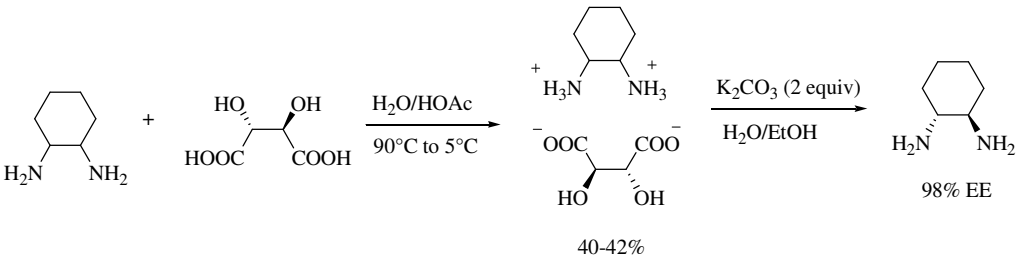
1.3.2.1 Crystallization

D**irect crystallization** is a useful technique[7] to resolve the racemates. In this method the two enantiomers are allowed to crystallize simultaneously in different vessels by the addition of seeds of the opposite enantiomers to a racemic supersaturated solution and the racemic filtrate is recycled after concentration. However, a prerequisite for this method is that the target molecule must exist as crystalline conglomerates (racemic mixture) rather than racemic compounds. In practice, not all chiral compounds exist in crystalline conglomerate form, making this method of limited utility.

1.3.2.2 Classical kinetic resolution

Classical resolutions involve the use of a stoichiometric amount of a chiral resolving agent. The resolving agent is associated to the substrate, either covalently or non-covalently, to generate a pair of diastereisomers. The diastereoisomers are separated through a separate

chemical transformation, the substrate is released from the resolving agent.[8]This approach has proven to be especially useful if salt formation is straightforward, as in the case of amines and carboxylic acids (**Scheme1.1**)



Scheme 1.1 Classical resolution of *trans*-1,2-cyclohexanediamin

1.3.2.3 Kinetic resolution

Kinetic resolution[9] is based on the principle that with the use of an optically active catalyst or reagent or a biocatalyst such as an enzyme or microorganism one of the two enantiomers of a racemic mixture is more rapidly transformed or metabolized to the product than the other. This is illustrated as follows: in which S and P refers to racemic substrate and product respectively.

$$\mathbf{S_R} \xrightarrow[\text{Chiral catalysis}]{K_R} \mathbf{P_R} \qquad \boldsymbol{K}_{\mathbf{rel}} = \frac{K_{Fast}}{K_{slow}} = e^{\Delta\Delta G\#/RT}$$

$$\mathbf{S_S} \xrightarrow[\text{Chiral catalysis}]{K_S} \mathbf{P_S}$$

The subscript points to the nature of the enantiomer. Kinetic resolution occurs when $K_R \neq Ks$, i.e. when the catalytic rate constants for both reaction are different. In a catalytic kinetic resolution, the relative rates of the reaction for the substrate enantiomer (typically expressed as K*rel*) are dictated by the magnitude of $\Delta\Delta G^{\#}$. This corresponds to the difference

in the energies between the diasterioisomeric transition states in selectivity determining step of catalytic reaction. (**Figure 1.7**).

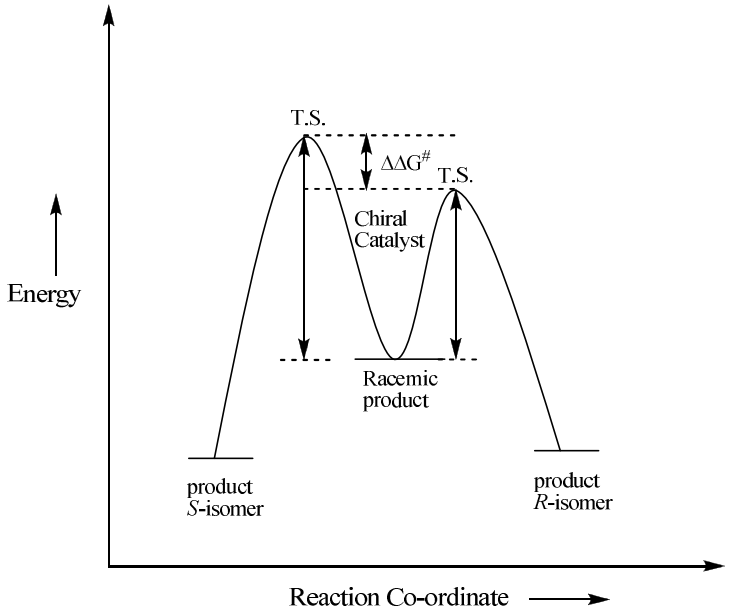


Figure 1.7 Relative rate constants in kinetic resolution

1.3.2.4 Chiral chromatography

This technique relies on the use of the stationary phase to resolve enantiomers contained in a mobile phase[10] (**Figure 1.8**). In principle it can be carried out on analytical or preparative scale. In reality, the large solvent volume, long separation times and relatively high cost of the chiral chromatographic supports often limit the scale at which chromatographic separations can be carried out.

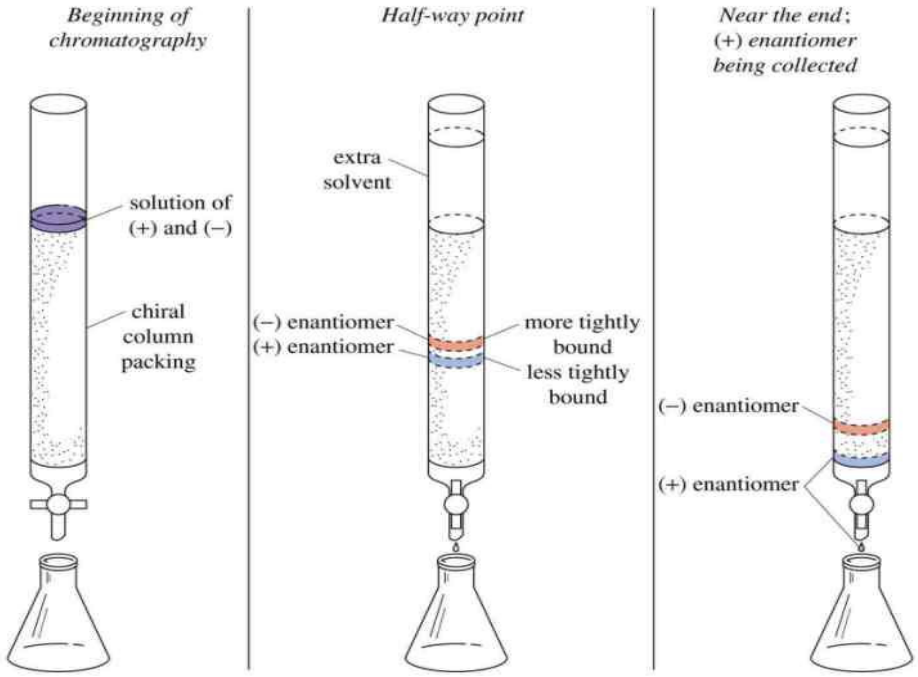


Figure 1.8 Schematic representation of resolution of racemic compound using chiral column

1.4 Asymmetric synthesis

Asymmetric synthesis, also called chiral synthesis or enantioselective synthesis is organic synthesis which introduces one or more new stereogenic centre under the influence of a chiral molecule. This is important in the field of pharmaceuticals because the different enantiomers or diastereomers of a molecule often have different biological activity.

Asymmetric synthesis can be further divided into four categories, depending of how the stereo-centre is formed:

- Substrate-controlled methods.
- Auxillary-controlled methods.
- Reagent-controlled methods.
- Catalyst-controlled methods.

In the substrate-controlled method the formation of a new chiral centre is directed by the presence of a stereogenic unit that already exists within the chiral substrate. While in the auxiliary-controlled method the asymmetric control of the reaction is achieved by a chiral group in the substrate. The advantage of this method is that the enantiomerically pure chiral auxiliary is attached to an achiral substrate in order to direct the enantioselective reaction. The chiral auxiliary can be removed once the transformation is achieved and often reused. This method usually offers high level of selectivity and has proven itself to be very useful. However, this methodology suffers from the need of two extra steps of attachment and removal of the chiral auxiliary.

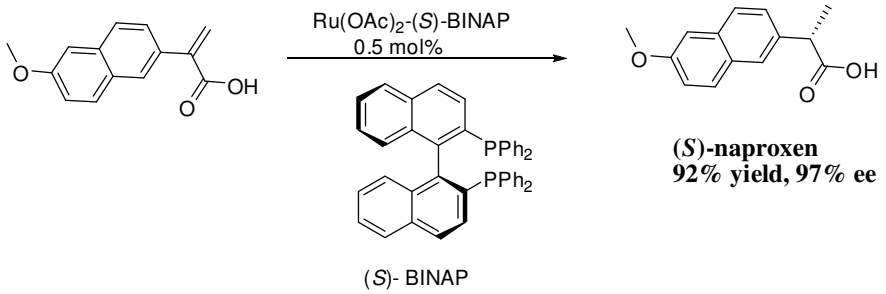
In the third method, an achiral substrate is directly transformed to a chiral product using an enantiomerically pure chiral reagent. However, the above three chiral transformations required at least one equivalent of an enantiomerically pure compound, which is not satisfactory from an economical and environmental perspective. Thus, the most significant advance in asymmetric synthesis, during the past three decades has been the development and application of chiral catalysts to induce the transformation of an achiral molecule to an enantioenriched chiral product.

1.5 Asymmetric catalysis

In asymmetric catalysis a small amount of a "*chiral catalyst*" can produce thousand of chiral compounds and speeds up a chemical process by decreasing the transition state energy. This process seems ideal for the preparation of chiral molecules since it only requires a small amount of chiral catalyst to transform an achiral molecule into an enantioeneriched chiral product or in other words "**asymmetric catalysis is a process where a chiral catalyst is used to transform a prochiral substrate into an enantiopure product".**

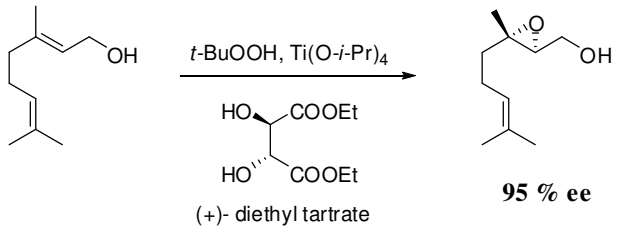
In 2001 the Nobel Prize in Chemistry was awarded to **Dr. William S. Knowles, Professor Ryoji Noyori**, and **Professor K. Barry Sharpless** for *their contributions in the development of catalytic asymmetric synthesis*.[11] Knowles and Noyori received half the prize for "*their work on catalytic chiral hydrogenation reactions*" and Sharpless was rewarded with the other half of the prize for *his work on catalytic chiral oxidation reactions*. The achievements of these three chemists are of great significance in academic research, industrial syntheses of pharmaceutical products and others biologically active substances[12].

An important example resulting from the work of Professor Noyori[13,14] and Dr. Knowles, is the synthesis of the anti-inflammmatory agent naproxen, involving a stereoselective catalytic hydrogenation reaction (**Scheme 1.2**) with organometallic complex obtained from ruthenium and a chiral organic ligand called *S*-BINAP. The reaction itself is truly remarkable because it produces the product with excellent enantiomeric excess (97%) in high yield (92%).



Scheme 1.2 Asymmetric synthesis of (*S*)-naproxen

While Sharpless has discovered highly enantioselective asymmetric epoxidation of allylic alcohols,[15] which is now widely used asymmetric organic transformation in the synthesis of complex chiral molecules (**Scheme 1.3**).



Scheme 1.3 Sharpless dihydroxylation of alkenes

1.5.1 Classification of asymmetric catalysis

Asymmetric catalysis can be classified in three broad classes (**Figure 1.9**)

1. Homogeneous asymmetric catalysis

2. Heterogeneous asymmetric catalysis

3. Biocatalysis

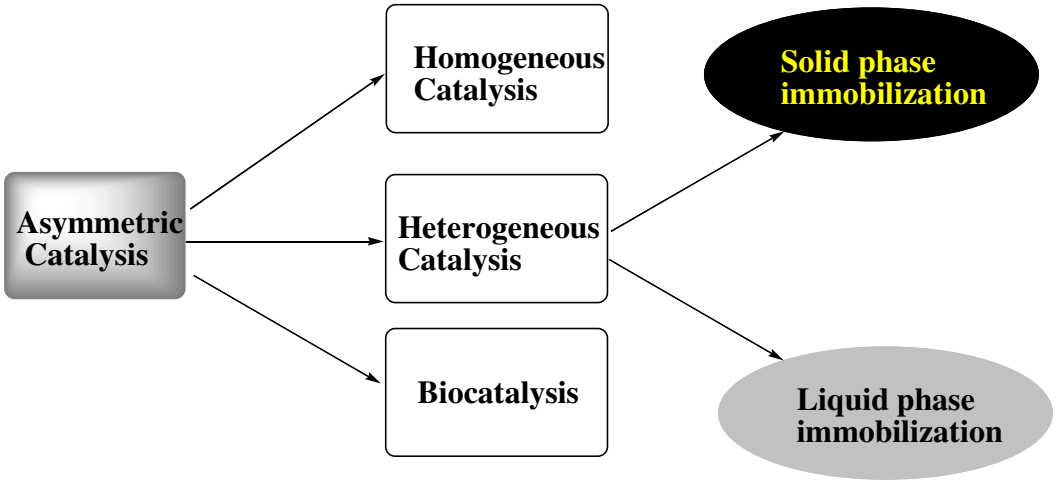


Figure 1.9 Classification of asymmetric catalysis

1.5.1.1 Homogenous asymmetric catalysis

Asymmetric catalysis using either chemical catalysis or enzyme catalysis is the most efficient method for the production of enantiomerically pure compounds on a large scale. In homogenous asymmetric catalysis, the catalyst and reactant are present in the same phase.

These catalysts can further be divided into nucleophile (Lewis bases[16], Brønsted bases[17], Biological[18]), electrophilic (Lewis acid[19], Brønsted acids[20]) and coordination catalysts[21] (transition metal complexes). Biocatalysis makes use of enzymes to affect high activity and stereoselectively, which is widely practiced in industries for the production of pharmaceuticals, bio-chemicals and fine chemicals. However, enzymes are substrate specific and often require different setups to which chemists and chemical engineers are not used to. This has led intense activity for developing homogeneous metal catalyzed asymmetric synthesis where reactions can be carried out in familiar reaction setups. These studies marked a new era in coordination chemistry, in which metal catalysts, due to their activity and selectivity, started to be considered as *chemists' enzymes*, thereby reducing the gap between chemo- and bio-catalysis.

The field of asymmetric catalysis has been dominated for a long time by homogeneous catalysis because of their key features, such as:

- Higher selectivity and activity.
- Operation under milder reaction conditions.
- Reaction reproducibility.
- Accessible mechanistic insight.
- Easier structural modification of the catalyst.

1.5.1.2 Heterogeneous Asymmetric Catalysis

In heterogeneous catalytic systems, the reactant and catalyst are present in different phases. In most of the cases, catalysts are in solid phase and reactants are in gas or liquid phase. In recent years, significant progress in the area of solid-phase chemistry has led

interdisciplinary research on stereoselective heterogeneous catalysis.[22] The potential advantages of heterogeneous catalysis lies in its easy separation, efficient recycling, minimization of metal traces in the product and an improved handling and process control. This eventually result in overall cost reduction in the target product. Furthermore, in some cases heterogeneous catalysts are even more selective than their homogeneous counterparts,[23] possibly due to the confinement effect of the support. The confinement effect essentially originates from the pore and surfaces of the support that are not inert thus might influence the active catalyst through various weak interactions to impart higher enantioselectivity during the catalytic process.[24] Heterogenization of homogeneous catalyst also takes into account of the principles of green chemistry where the industry requires to make all necessary efforts to minimize wastes, particularly those substances that contain noxious transition metals typically present in metallic catalysts.[25]

Two main strategies have been employed for the heterogenization of chiral homogeneous catalysts.

[1] *Solid phase immobilization*: The homogeneous catalyst is heterogenized by anchoring it onto a solid support (*e.g.,* inorganic material or organic polymer) *via*, (i) a covalent bonding; (ii) adsorption; (iii) ion-pair formation; (iv) encapsulation or (v) entrapment.

[2] *Liquid phase immobilization*: the homogeneous catalyst is confined in one of the liquid phase in a two-phase system (*e.g.,* aqueous phase, fluorous phase, supercritical carbon dioxide ($ScCO_2$) or ionic liquid) and the other phase is used for delivery and/or removal of reactants and products.

1.5.1.3 Biocatalysts

Enzymes are considered as a biocatalyst, which are working efficiently under homogeneous system due to their high activity and specificity. Enzymes are protein molecules of colloidal size [*e.g.,* poly (amino acids)] with a metal as the active center. Often the only difference to the industrial homogeneous catalysts is that the metal center is ligated by one or more proteins, resulting in a relatively high molecular mass. Some of the factors that account for the significance of enzymes are, (i) they are chemo-, regio-, and stereoselective, and environment friendly, (ii) Because of the mild conditions under which they operate, enzymatic reactions are affected to a lesser extent by side reactions (*viz.* isomerization, racemization, epimerization, and rearrangement of molecules) as compared to nonenzymatic processes.[18] Their disadvantage is that they are sensitive, unstable molecules which are destroyed by extreme reaction conditions. They generally function well only at physiological pH values in very dilute solutions of the substrate. Enzymes are expensive and difficult to obtain in pure form.

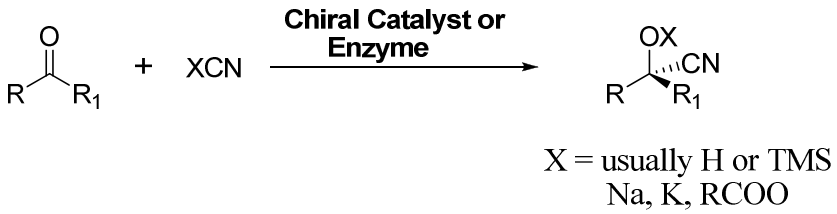
1.6 Asymmetric C-C bond forming reactions

Enantioselective catalytic reactions in which the chirality of an asymmetric catalyst induces the preferred formation of a given product enantiomer have been one of the most important achievements in chemistry in the 20th century. Among the numerous enantioselective catalytic reactions C-C bond forming reactions *viz.* Aldol reaction, Diels-Alder reaction, Cyclopropanation, alkylation, allylation of carbonyls, cyanation of carbonyl compounds have been discovered in recent years using various chiral catalysts[26, 27] whose Chiral products are important intermediates for pharmaceuticals, vitamins, agrochemicals, flavors, fragrances and functional materials.

Among the various C-C bond forming reactions, catalytic asymmetric is of current interest.

1.7 Enantioselective synthesis of cyanohydrins

Chiral cyanohydrins are well known natural products and versatile synthetic intermediates for pharmaceuticals and agrochemicals. They are present in over 3000 plants, bacteria, fungi, and many insects as antifeedants forming part of self-defense system.[28,29,30] Cyanohydrins also serve as source of nitrogen for the biosynthesis of amino acids.[31] For the synthetic organic chemists, chiral cyanohydrins offer an immense opportunity for synthesizing various chiral compounds. Different enantiomers of chiral compounds have different *in vivo* activity spectrum and metabolic transformations and/or degradation as the molecule-binding sites are chiral in nature. Therefore, chiral compounds for biological applications are required to be synthesized in all possible stereo-isomers in their high chiral purity. The development of straightforward synthetic procedures for such compounds, which also result in a high degree of stereoselectivity, therefore, has prime importance. To this effect chiral cyanohydrins may serve as stereochemically pure starting materials.[32-38] They can easily be prepared by the addition of cyanide to a carbonyl compound in the presence of a synthetic chiral catalyst or an enzyme (**Scheme 1.4**).



Scheme 1.4 Cyanide addition to carbonyl compound

The resulting cyanohydrins are readily transformed into a variety of compounds such as α-hydroxyacids[39], α-aminoacids[40-49], α-hydroxyaldehydes, α-hydroxyketones[50,51], β-aminoalcohols, among others[52-64] (**Figure 1.10**). Despite immense synthetic potential offered by chiral cyanohydrins in the synthesis of bio-active molecules, it is surprising that intensive research on this topic has started relatively recently.

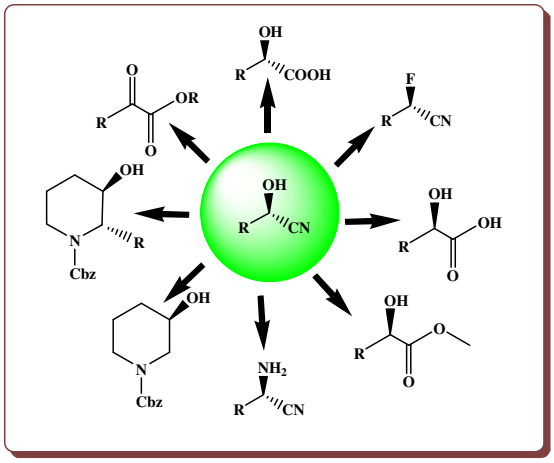


Figure 1.10 Synthetic transformations of cyanohydrins

Among the various methods, catalytic enantioselective cyanation of aldehydes and ketones by new generation of catalysts is increasingly finding application in the syntheses of bio-active natural and synthetic compounds. Although, many methods of asymmetric cyanohydrin synthesis using enzyme and peptide that give high yield are well known,[65-73] many synthetic chemists are apprehensive about using enzymatic procedures as they require the use of totally different laboratory set-up and reagents for which they are normally trained. Moreover, the flexibility of enzymatic process in term of accommodating different substrates and scale-up of the process to the economically viable scale are also limiting factors. Hence, recent advances in the field of metal complexes catalyzed asymmetric cyanation are about to

deliver the much desired breakthrough for process scale synthesis of chiral cyanohydrins in high yields and excellent enantioselectivity[42].

1.8 Sources of cyanide

The preparation of cyanohydrins utilizes a source of cyanide (**Figure 1.11**) which in most cases is trimethylsilylcyanide (TMSCN) (a). Although TMSCN is associated with several disadvantages, it is the most commonly used cyanide source in enantioselective cyanation of carbonyl compounds because it directly provides the TMS-protected cyanohydrin. The protecting group prevents racemization by checking the reverse reaction to occur. However, TMSCN is prohibitive for large scale production due to its high cost.; (b) HCN, KCN (c) and NaCN (d) are other sources of cyanide, which are often used on large scale production of enantioenriched compounds, e.g., production of mandelonitrile derivatives using enzyme catalysis uses HCN.[74] However, both TMSCN and HCN are highly volatile and extremely toxic. On the other hand KCN and NaCN are deadly toxic at the same time they slowly release toxic HCN gas when come in the contact on moisture. Therefore, efforts are being made to look for cyanation reaction using inexpensive and less toxic cyanide source that can easily be handled for the production of protected cyanohydrins e.g., alkyl cyanoformates (e), acetone cyanohydrin (f), acetyl cyanide (g) and alkyl cyanophosphorylates (h).

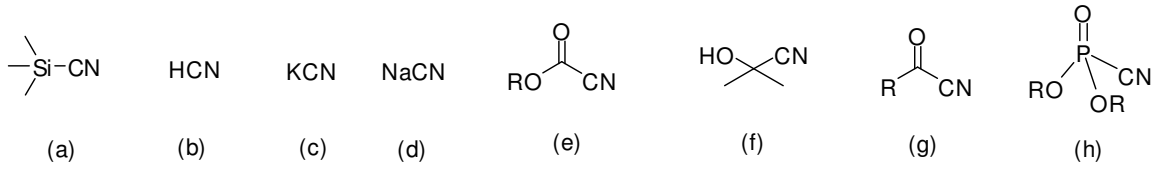
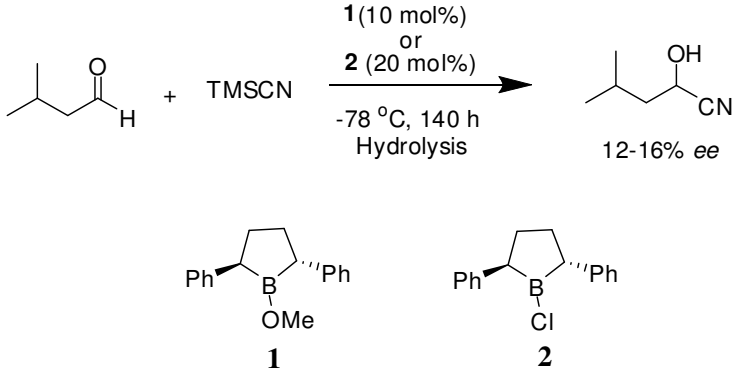


Figure 1.11 Examples of cyanide sources

1.8.1 Use of TMSCN in asymmetric cyanation of carbonyl compounds

Trimethylsilyl cyanide (TMSCN) in the presence of certain catalysts, such as $TiCl_4$[74], KCN/18-crown-6[75], ZnI_2[76], Me_3SiOTf[77] were reported to react with ketones to afford trimethylsilyl ether of cyanohydrin, which after aqueous work-up release the desired cyanohydrin. In 1986, Reetz et al. reported[78] the first enantioselective addition of TMSCN to an aldehyde (isobutanal) catalyzed by boron based optically active Lewis acid. Although, only moderate yields (45-55%) and poor enantioselectivity (12-16% ee) could be achieved at a very low temperature with prolonged reaction time, (**Scheme 1.5**). This report effectively demonstrated the potential use of a Lewis acid catalyst in asymmetric cyanohydrin synthesis.



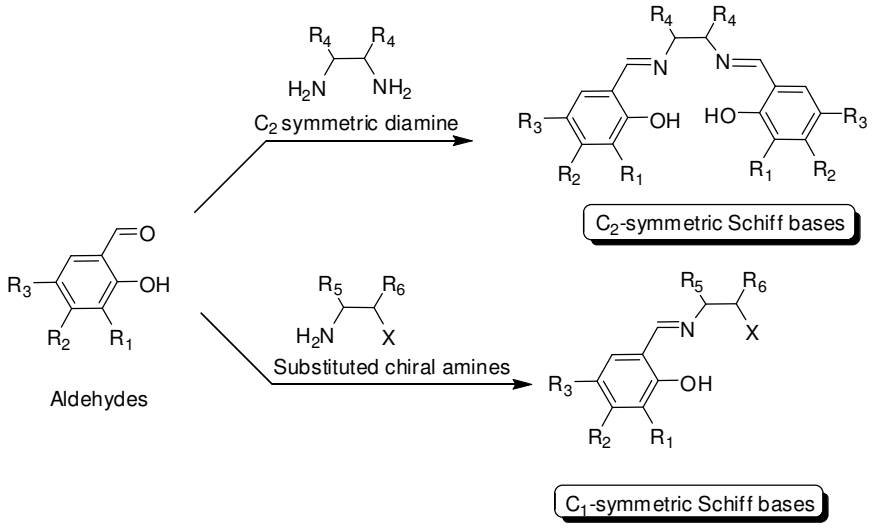
Scheme 1.5 Boron based catalysts for asymmetric cyanosilylation reaction

Subsequently, numerous other Lewis acid systems with different chiral ligands have been investigated for asymmetric cyanohydrin synthesis. The area that has received the most attention is without doubt that of titanium (IV) catalysis.

1.8.1.1 C_2 and C_1 symmetric chiral Schiff bases and related ligands

C_2 and C_1 symmetric chiral Schiff bases derived from the condensation of salicylaldehydes with suitable chiral amines are among the most successful types of ligands used in enantioselective addition of cyanide to ketones and aldehydes. They are easy to

synthesize and alter for their electronic and steric features as per the specific needs of the reaction (**Scheme 1.6**).

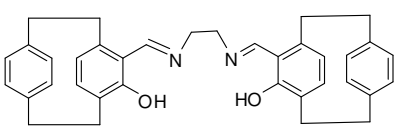


Scheme 1.6 Synthesis of C_2 and C_1 symmetric Schiff bases

Schiff base ligands became one of the most frequently employed structure entity after Inoue et al.,[45,79] used them for the first time for enantioselective addition of TMSCN to aldehydes.

1.8.1.2 C_2 symmetric Ti-Schiff bases for cyanosilylation (salen Based Complex)

A number of C_2 symmetric Schiff bases (**Figure 1.12**) derived from diamine and salicylaldehyde have been frequently used for the cyanosilylation of aldehydes with in situ generated Ti (IV) complex, although the 84% ee and 90% yield was achieved at very low reaction temperature[50-53] which in most of cases was -78 ^{o}C.



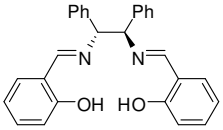
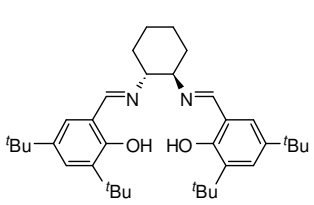
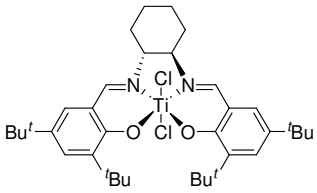


Figure 1.12 C_2 symmetric salen catalyst

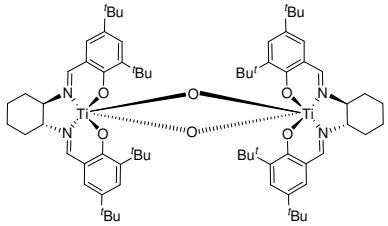
Later, Belokon et al. reported the C_2 symmetric salen monomeric (**10a**, **10b**) and dimeric (**10c**) complexes with cyclohexane collar and *t*-butyl group on 3,3' and 5,5' positions of the salicylaldehyde[80,81,82] for the cyanosilylation of aldehydes (**Figure 1.13**). In such systems, the dimeric form (**10c**) showed very high catalytic activity(Yield, >99%) at room temperature with enantioselectivity (92%) in 24-120h.



(**10a**)



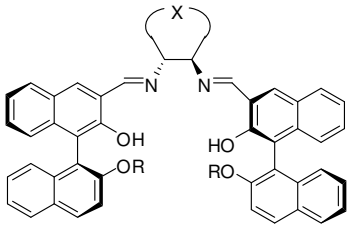
(**10b**)



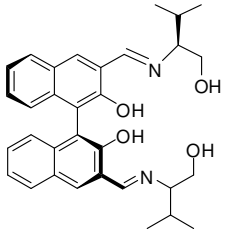
(**10c**)

Figure 1.13 Salen Catalysts

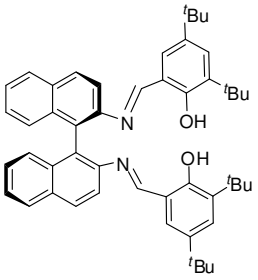
In order to decrease the reaction time and improvement in yield and enantioselectivity the other types of chiral ligands[83,-86](**11a-d**) were also explored by using their in situ generated Ti complexes (**Figure 1.14**). Among them, BINOL based salen complex **11b** gave 100% yield with 86% ee within 4h at room temperature. While the complexes **11c** and **11d** required very low temperatures in order to introduce high chiral induction in the desired products.



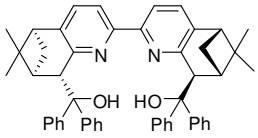
(**11a**)



(**11b**)



(**11c**)

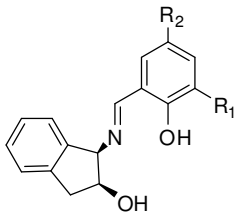


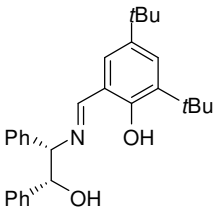
(**11d**)

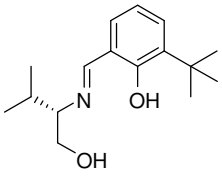
Figure 1.14 Some other C_2 symmetric salen ligands

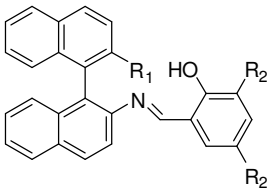
1.8.1.3 C_1 symmetric Ti-Schiff base complexes for cyanosilylation

C_1 symmetric chiral Schiff base ligands prepared by the reaction of a salicylaldehyde with a chiral aminoalcohol (**Figure 1.15**) were also used for the cyanosilylation of aldehydes. Catalysts prepared from this ligand system[87-94] could lead to enantioselectivity up to 92% for addition of TMSCN to aldehydes.

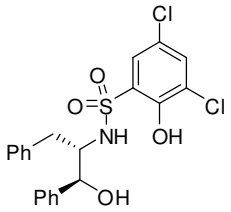


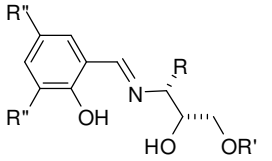






R_1 = NH_2, OH , R_2=*t*Bu, Cl





R=Ph, *n*-Pr,
R'=H, Me,CH_2Ph, CPh_3, SiiPr_3,
R''=H,*t*Bu,

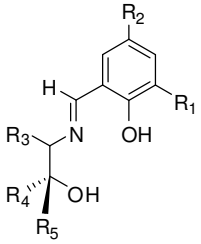
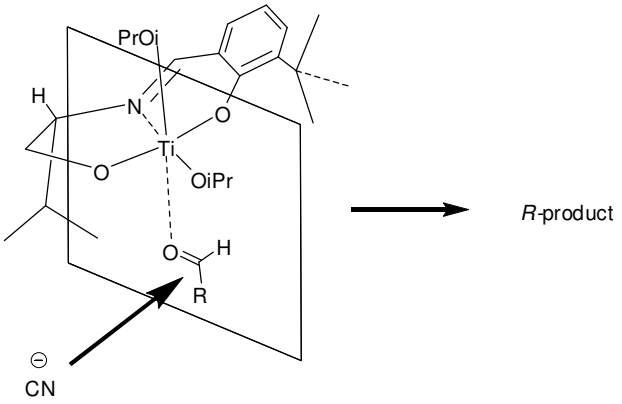
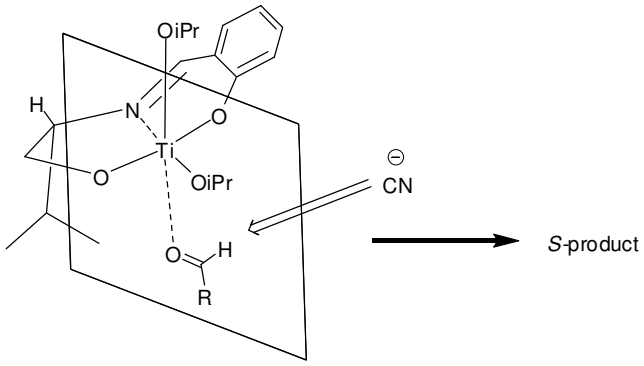


Figure 1.15 Representative C_1 Symmetric Schiff bases derived from amino alcohols

For such high enantioselective systems, Oguni and co-workers[88] suggested a mechanism based on the structural features of the catalyst where shielding of one face of the activated aldehyde occurred by the substituents on the ligand (**Scheme 1.7**).



si face attack of cyanide on activated aldehyde



re face attack of cyanide on activated aldehyde

Scheme 1.7 The proposed mechanism of cyanosilylation of an aldehyde using C_1 symmetric titanium complex for the *R* and *S* product formation

1.8.1.4 Amide based ligands with Titanium

The other most used ligands were observed to be C_2 symmetric amides derived from an enantiopure 1,2-diamine and an acid including pyridyl or pinene motif (**Figure 1.16**). These systems invariably required a very low temperature for extended time periods in order to give high enantioselectivity for the product in reasonably high yields.[95-98] However, both aromatic and aliphatic aldehydes were effectively cyanosilylated with very high ee values using this class of catalysts with TMSCN as a cyanide source.

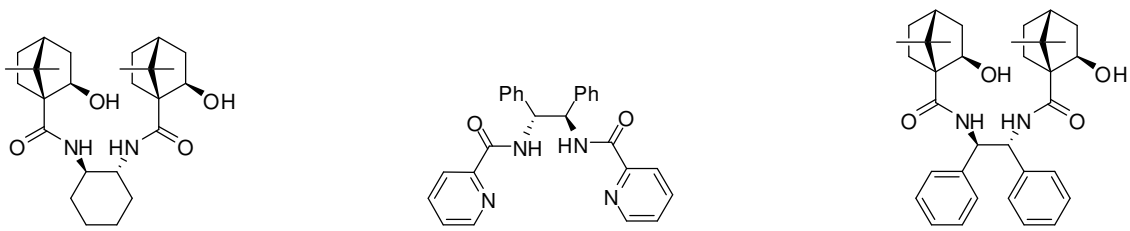


Figure 1.16 Amide based ligands for cyanosilylation of aldehydes with Ti metal

An additional class of proline based C_2-symmetric diamide ligand (**Figure 1.17**) was explored for the cyanosilylation of various aldehydes. Though there was no metal involved, this ligand system is included here to provide useful information on activation of TMSCN and substrate by the acidic and basic sites present on the ligand[99]

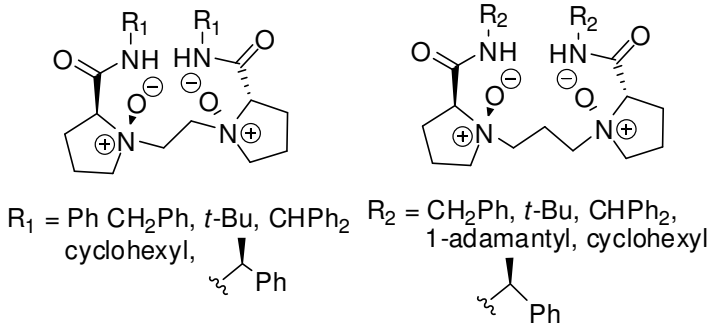
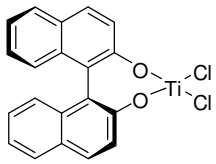


Figure 1.17 Proline based C2 symmetric diamide ligand

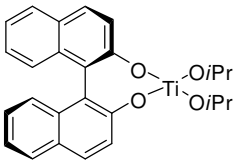
1.8.1.5 Binol-derived titanium complexes

Chiral binol-derived complexes have been investigation to catalyze the enantioselective cyanosilylation of various aldehydes with TMSCN.[100] Complex **12a** (**Figure 1.18**) was reported to give 85% yield with 82% ee for the cyanosilylation of isobutanal at -78 ^{o}C in 10 h[101] while the complex **12b** effected <10% ee (yield >90%) for aromatic aldehydes at 0 ^{o}C in 17 h.[102] However, complex **12b** gave moderate ee (33-75%) with >90% yield for

cyanosilylated products of aliphatic aldehydes. This is a rare example in the literature where much higher ee values were obtained with aliphatic aldehydes as compared to aromatic aldehydes.



Complex 12a



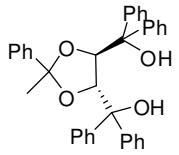
Complex 12b

Figure 1.18 Structure of chiral binol based Ti(IV) complexes

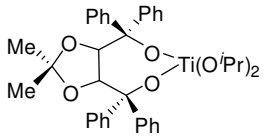
1.8.1.6 Chiral alcohol –Titanium complexes

The use of poly-hydroxy ligand with titanium to catalyze asymmetric formation of cyanohydrin using TMSCN as cyanide source is among the earliest reports on this topic. Among such system Taddol ligand 1**3a (Figure 1.19)** was used to give a maximum ee of 96% with 79% yield at –78 ^{o}C in 12 h for the cyanosilylation of benzaldehyde where stoichiometric quantity of the reagents was employed.[103] An attempt to reduce the quantity of the reagent decreased the yield concomitantly. A variant of titanium complex of Taddol **13b**, however, found to be catalytic but imparted only moderate enantioselectivity at 10 mol% catalysts loading. This system also required 10 mol% Ph_3P=O as an additive, in absence of which the reaction does not proceed.[104] Callant et al.,[105] used a stoichiometric quantity of titanium-chiral trialcohol complex **13c** to convert benzaldehyde to (*S*)-mandelonitrile in 92% yield with 76% ee after 2 h at -20 ^{o}C in the presence of molecular sieves (M.S.) 4A using TMSCN as a source of cyanide. Interestingly, Callant et al.[105], originally used **13c** as a catalyst with HCN as an inexpensive source of cyanide for the asymmetric cyanation of aldehydes but failed to get any conversion. Hayashi, et al.,[106] reported the use of Sharpless epoxidation catalyst (L-(+)-diisopropyl tartrate **13d** with $Ti(O^{i}Pr)_4$) in a substoichiometric

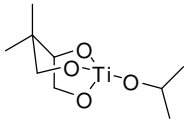
quantity for the preparation of enantioenriched cyanohydrins at 0 ^{o}C. The use of 40 mol% of propane-2-ol as an additive was found to be essential in order to obtain high enantioselectivity (ee, up to 91%). The role of the additive (propan-2-ol) as supported by mechanistic studies was found to hydrolyze TMSCN to generate HCN which eventually initiates the reaction.



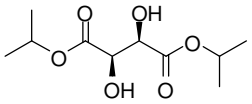
Ligand 13a



Ligand 13b



Ligand 13c

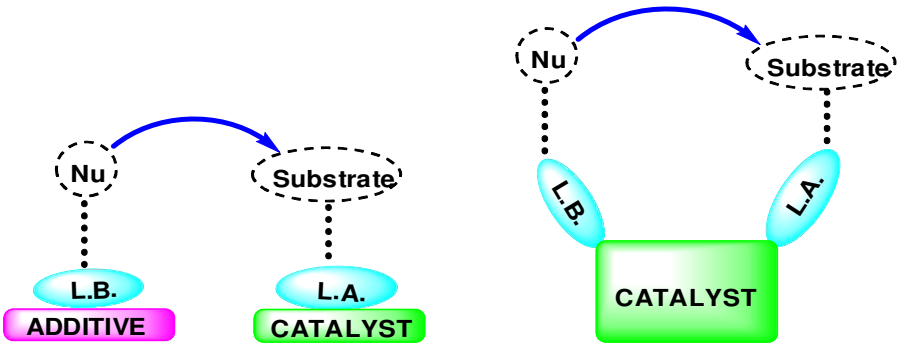


Ligand 13d

Figure 1.19 Structure of Taddol based Ti(IV) complexes

1.8.1.7 Bi-functional catalysts

The use of a base additive is well known in asymmetric catalysis to activate nucleophile while the substrate is activated by an acidic site of the catalyst (**Scheme 1.8, A**). This dual activation phenomenon has led many researchers to fabricate catalysts having built-in acid and base functionalities (**Scheme 1.8, B**). This class of catalysts is also known as bi-functional catalyst. Some of such catalysts used for the asymmetric cyanation of aldehydes using TMSCN as the source of cyanide[107-120] shown in **Figure 1.20.**



Scheme 1.8 Dual activation of reactants by (**A**) separate catalysts (**B**) a bifunctional catalysts

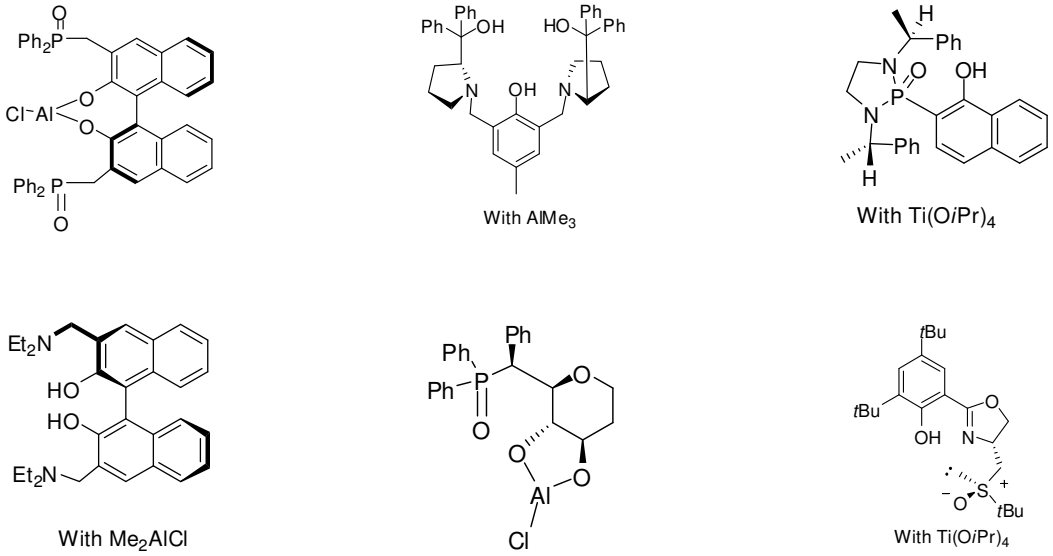


Figure 1.20 Some bi-functional catalyst for the cyanosilylation

Shibasaki and co-workers[114] in their efforts to develop multifunctional asymmetric catalyst conceptualized the ligand design, where activation of substrates and nucleophiles occurs simultaneously at the Lewis acid and the Brönsted base moiety in the catalyst, thus affording high enantioselectivity. Based on kinetic studies they have proposed a working model of the transition state (**Figure 1.21**) for the cyanosilylation of aldehydes using TMSCN as a source of cyanide. In this model, aldehyde positioned itself at the apical site of the penta-valent aluminum which is in close proximity to the internal phosphine oxide.

TMSCN, interacting with the internal phosphine oxide, could then transfer cyanide to the aldehyde thus giving the product in desired enantioselectivity.

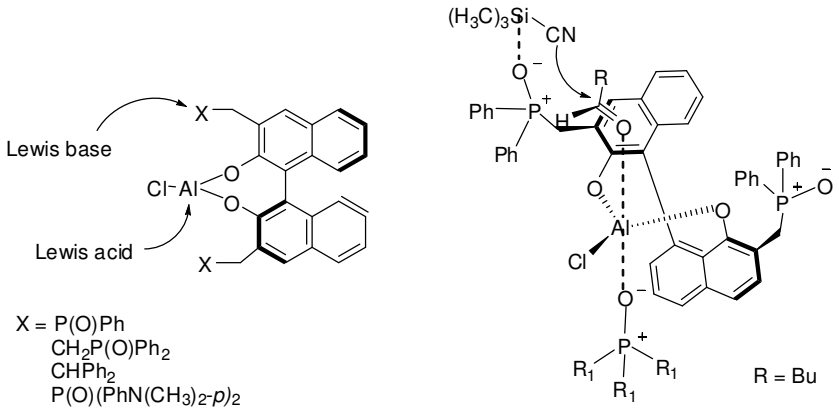
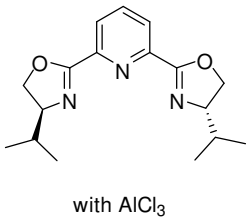


Figure 1.21 Structure for chiral Binol-Al complex as multifunctional asymmetric catalyst

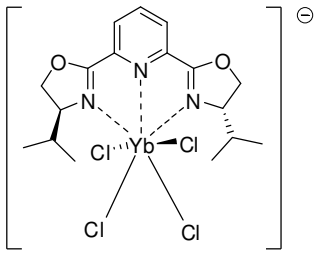
1.8.1.8 Pyridine-2,6-bisoxazoline (pybox) based complexes

Pyridine-2,6-bisoxazoline (pybox) is another versatile ligand (**Figure 1.22**) that can be used in a variety of enantioselective reactions. Although titanium is more frequently used with variety of ligand systems for enantioselective cyanation reaction, it is conspicuously absent with pybox ligand. Iovel and co-workers in 1997 for the first time used pybox ligand with $AlCl_3$ in enantioselective cyanosilylation of aldehydes (**14a**).[121] This catalyst afforded variety of cyanohydrins in high yields, but the ee obtained never went beyond 90%. Later on, Greeves et al.[122,123] used pybox ligand system with lanthanum metals (**14b**, **14C**) (Specifically ytterbium) as catalyst for cyanosilylation of aldehydes. This system was found to be quite active at moderate temperatures for a variety of aliphatic and aromatic aldehydes. Due to the congenial reaction conditions and short reaction time it has been suggested that this ligand system deserves more studies in terms of metal, additive and ligand design. Due to the close structural resemblance with pybox, bidentate ligands derived from bisoxazoline have been included here. Mg metal complex of these ligands found application as catalysts

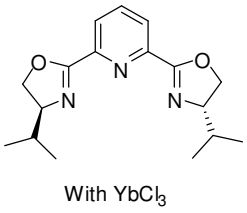
in the cyanosilylation of various aldehydes. Interestingly, the Mg complex **(14d**) with (**14e)** was found to be more enantioselective for cyanosilylation of aliphatic aldehydes (ee up to 94%) as compared to benzaldehyde (ee, 52%).[124]



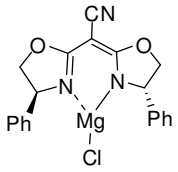
(**14a**)



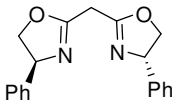
(**14b**)



(**14c**)



(**14d**)



(**14e**)

Figure 1.22 Structure of pybox based complexes

1.8.1.9 Vanadium based catalysts

Belokon et al.[125,126] while working on Ti-salen system for asymmetric cyanation reactions also prepared its oxo-vanadium(V) complex **15 (Figure 1.23)** and showed that this complex is far more active than its Ti-counterpart with a catalyst loading of 0.1 mol% is sufficient to catalyze aromatic and aliphatic aldehydes into corresponding *O*-trimethylsilyethers of cyanohydrins with 94 % ee and >95% yield in 24 h at ambient temperature.

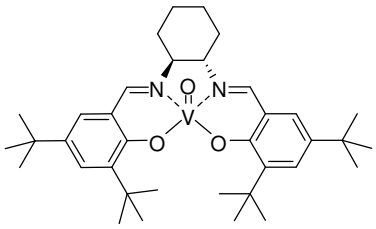


Figure 1.23 Structure of chiral V(V) salen complex **15**

1.8.1.10 Aluminum complexes for cyanosilylation

Recently, Kim and co-workers have reported[127] Al-salen complex **16** (**Figure 1.24**) at a catalyst loading of 1 mol% for the cyanosilylation of different aldehydes in the presence of $Ph_3P{=}O$ as an additive at -40 to -50 ^oC in CH_2Cl_2. Excellent yields (91-96%) with 72-86% ee was achieved in 18-26 h for *O*-TMS ether of respective cyanohydrins.

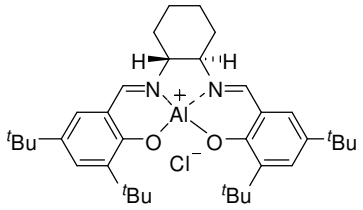


Figure 1.24 Structure of chiral Al based complex **16**

1.8.1.11 Tin complexes for cyanosilylation

The sole example of tin-complex **17** (**Figure 1.25**) catalyzed asymmetric cyanation of aldehydes was reported by Kobayashi as early as in 1991[128]. This complex at 30 mol% loading was able to catalyze the asymmetric addition of TMSCN to aldehydes at -78 ^oC in 14 h, however, only aliphatic aldehydes were found to be successful candidates to give up to 96% ee with 79% yield of *O*-TMS ether of cyanohydrins but this system failed to catalyze the formation of cyanohydrin from benzaldehyde.

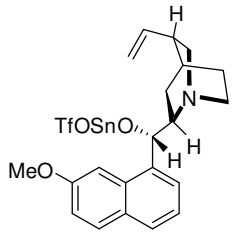
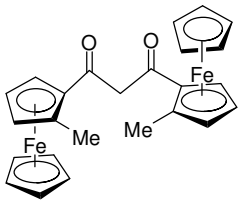


Figure 1.25 Structure of Tin based complex **17**

1.8.1.12 Yttrium complex for cyanosilylation

Abiko and Wang[129,130] have reported yttrium complex of the chiral acetoacetate analogue of 1,3-bis-(2-methylferrocenyl)propane-1,3-dione **18** (**Figure 1.26)** as an efficient catalyst for asymmetric addition of TMSCN to aldehydes. The reaction recipe required 1 mol% of **10** with 0.2 mol% of $[Y_5(O)(O\textit{i}Pr)_{13}]$ to give *O*-TMS ether of cyanohydrins in excellent yield (up to 98%) with ee up to 91% at -78 ^oC in 2 h.

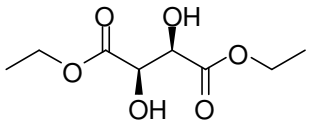


With $[Y_5(O)(O\textit{i}Pr)_{13}]$

Figure 1.26 Structure of Yttrium based complex **18**

1.8.1.13 Bismuth complex for cyanosilylation

Wada et al.,[131] have reported some of the interesting results on asymmetric cyanosilylation of aldehydes and ketones along with its non-chiral version using a bismuth complex (**Figure 1.27**) generated *in situ* by the interaction of *n*-BuLi and dialkyl ester of tartaric acid with $BiCl_3$. Their protocol gave quantitative yields of respective *O*-TMS cyanohydrins however, a maximum of 73% ee was achieved by the use of diethyl tartrate **19** with benzaldehyde as a substrate in CH_2Cl_2 at -23 ^oC

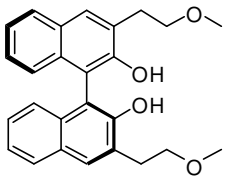


With $BiCl_3$

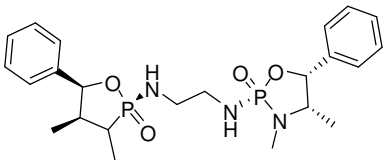
Figure 1.27 Structure of chiral Bismuth based complex **19**

1.8.1.14 Lanthanide complexes for cyanosilylation

The use of lanthanide metal ions was restricted to a substituted binol (*S*)-3,3'-bis(methoxyethyl)binol) **20**[132] and a bis-phosphoramidate **21** ligands[133] with La and Sm metal ion (**Figure 1.28)** for the cyanosilylation of various aldehydes. In binol based system the active catalyst was generated *in situ* using 15 mol% of **20** with 10 mol% of La(O*t*Bu)$_3$ and the cyanosilylation reaction was conducted at -78 ^{o}C for 10 h to give *O*-TMS of cyanohydrins in up to 82% yield with maximum 73% ee for the *p*-methylbenzaldehyde as substrate. On the other hand bis-phosphoramidate **21** derived Sm complex[133] was more active and enantioselective (ee up to 90%; Yield >95%) at relatively moderate reaction condition (-15 ^{o}C) at a very low catalyst loading (0.6mol%).



With (La(O*t*Bu)$_3$



With $SmCl_3$

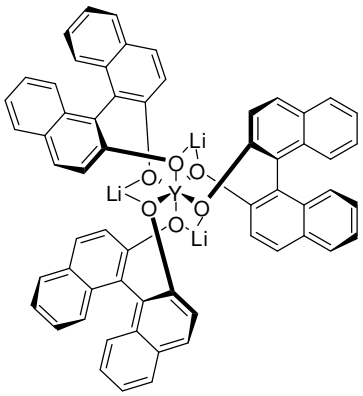
Complex 20 **Complex 21**

Figure 1.28 Structure of chiral lanthanide based complexes

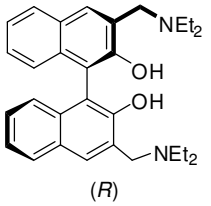
1.8.2 Alkyl Cyanoformate as a source of Cyanide

Alkyl cyanoformates are cheaper and less toxic source of cyanide. Moreover, alkyl carbonylated/phosphate cyanohydrins are stable and not easily hydrolyzed by moisture in air. They are useful synthetic intermediates and can be applied in the synthesis of β-amino alcohols and γ-substituted unsaturated nitriles from *O*-carbonylated allylic cyanohydrins. After the first report on the use of ethyl cyanoformates in the cyanation of ketones by Tian and Deng in 2001[134], it was Shibasaki and co-workers in 2002[135] who have used a binol-based heterobimetallic complex **22** (**Figure 1.29**) in combination with phosphine oxides for

the addition of ethyl cyanoformate to aldehydes. Using 10 mol% of catalyst **22** at –78 °C in THF, cyanohydrins were formed with up to 98% ee with high yield. Later on same group successfully employed this catalyst for the catalytic asymmetric cyanation-ethoxycarbonylation reactions of α,β-unsaturated aldehydes for the two-step synthesis of optically active γ-oxy-α -β-unsaturated nitriles[136]. Shibasaki et al. also complex **23** for cyanoethylation of aldehydes along with three achiral additives viz., H_2O, tris(2,6-dimethoxyphenyl)phosphine oxide and BuLi.[137].



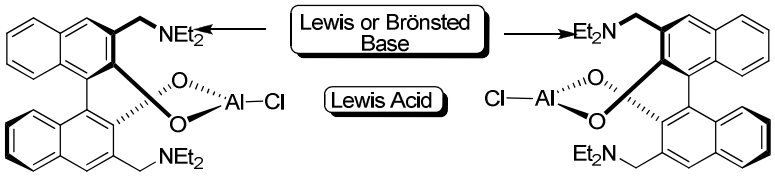
Complex 22



Complex 23

Figure 1.29 Structure of chiral binol based heterobimetallic complexes

Nájera et al.[138] have used a monometallic bifunctional complex **23** along with Me_2AlCl **(Figure 1.30)** for cyano-methoxycarbonylation of aldehydes using methyl cyanoformates as a source of cyanide giving methoxy carbonylated cyanohydrins in >98% yield and ee up to 82 % in 12-28 h. Same authors[139,140] have also reported cyanophosphorylation of aldehydes with commercially available diethyl cyanophosphonate as a source of cyanide with various Lewis acids[138]. the product cyanophosphate was achieved in high yields (up to 90%) with ee up to 98% using 10 mol% of **(*S*)-24** as catalyst in 2-50 h.



(*R*)-**24** (S)-**24**

Figure 1.30 Structure of chiral monometallic bifunctional complex

Various pioneer research groups reported the chiral Lewis acid catalyst for the cyanation of aldehydes using ethyl cyanoformate as a source of cyanide along with the various bases as a co-catalyst.[139-146]

1.8.3 Alkali metal cyanide source.

Sodium and potassium cyanides are the basic raw materials for all other cyanide sources. These are primarily used as bulk chemical in metallurgy and electrochemical based industries. These are highly toxic when contacted directly and also release highly toxic hydrogen cyanide gas when in contact with moister. Therefore, great care is required in handling these two sources of cyanide. Nevertheless, they are used as source of cyanide for the asymmetric cyanation of aldehydes. Belokon and co-workers for the first time reported the use of dimeric Ti-salen complex **10c** (**Figure 1.13**) and V-salen complex **15** (**Figure 1.23**) as catalysts (1 mol%) to induce the asymmetric addition of alkali cyanide and acetic anhydride to various aliphatic and aromatic aldehydes, giving enantiomerically enriched cyanohydrin esters in high yield (up to 99 %) and ee up to 92% in CH_2Cl_2 at -42 ^oC [147,148]. The best results were obtained with KCN as compared to other alkali cyanides, *e.g.*, NaCN, LiCN, CeCN and RbCN used by them.

1.9 Asymmetric cyanation of ketones

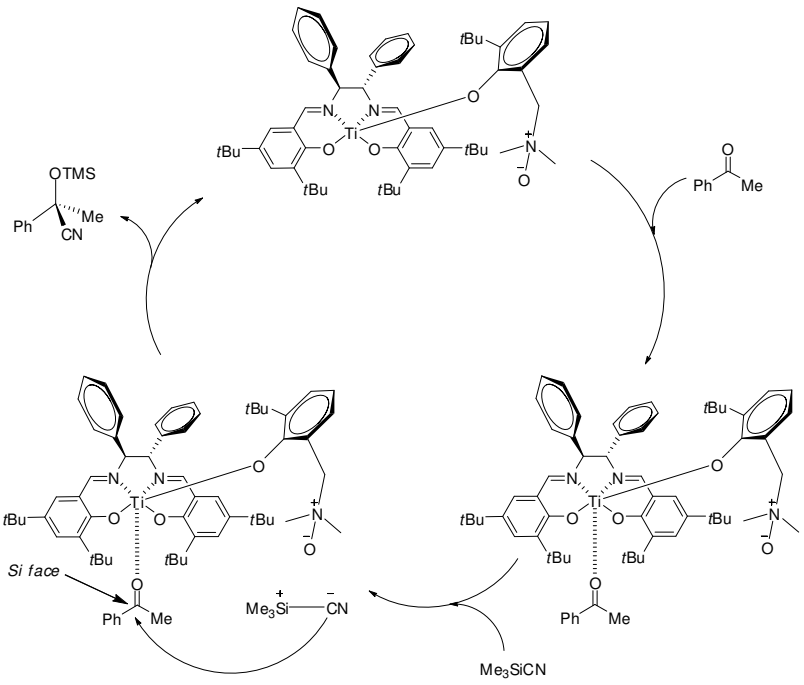
Reactivity of carbonyl group in ketones is affected by greater steric hindrance and lower electrophilicity as compared to aldehydes. Nevertheless, asymmetric addition of

cyanide to ketones did not go unchallenged. Choi et al. in 1997[149] published the first report on trimethylsilylcyanation of acetophenone catalyzed by a reusable complex **13c** (1 mol%) (**Figure 1.19**) derived from (*S*)-3,3-dimethyl-1,2,4-butanetriol and titanium isopropoxide under high pressure at 18 ^{o}C producing the corresponding cyanohydrin with ee up to 60% in 93% yield. However, reactions of 4'-substituted acetophenones to the corresponding cyanohydrins gave lower ee and yields.

Belokon et al.[150] however, were the first to report the asymmetric cyanation of aromatic-aliphatic ketones at room temperature and atmospheric pressure using 0.5 mol% of the Ti-bimetallic catalyst **10C** to yield corresponding cyanohydrinsilyl ethers in 27-100% yield with 30-72% ee.

Later on Feng and co-worker used diphenyl salen-Ti complex along with the various additive to improve the enantioselectivity and yield.[151-154] Feng et al.[155] studied in detail the effect of several reaction parameters viz., catalyst loading, temperature, solvents, and amount of additive (*N*-oxides) for the cyanosilylation of acetophenone. They also studied the effect of the various substituents in the salen ligand with variation in metal ions and substituents on *N*-oxides on the above reaction. Based on the analysis of the data collected they proposed a mechanism for the trimethylsilylcyanation of acetophenone (**Scheme 1.9**). The role of *N*-oxide was proposed to activate TMSCN, while the substrate was activated by the acidic center of the catalyst that is optimized for titanium. The catalytic cycle also predicts the sense of asymmetric induction; acetophenone is coordinated to the catalyst so as to minimize the interaction between the acetophenone and the phenyl groups of the ligand, which results in an orientation in which the *Si* face of the acetophenone is exposed to intermolecular attack by

the cyanide of the activated TMSCN to produce the *R* enantiomer of the *O*-TMS cyanohydrin.



Scheme 1.9 Catalytic cycle for the cyanosilylation of actophenone using Ti-salen as catalyst

Kim et al.[156] reported the use of Al-salen complex **16**[157] (**Figure 1.24**) and Mn-salen complex **25 (Figure 1.25)** as catalyst for the asymmetric cyanosilylation of various ketones at *RT* in DCM using triphenylphosphine oxide as base for double activation. While Mn(III) catalyst inducted a maximum of 85% ee with 89% yield (in 5-70 h) for the product *O*-TMS cyanohydrin, Al(III) was better catalyst both in terms of ee (up to 92%) and reaction time (3-40 h).

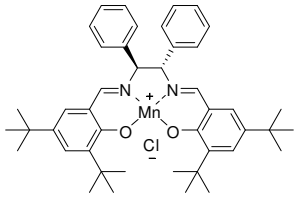
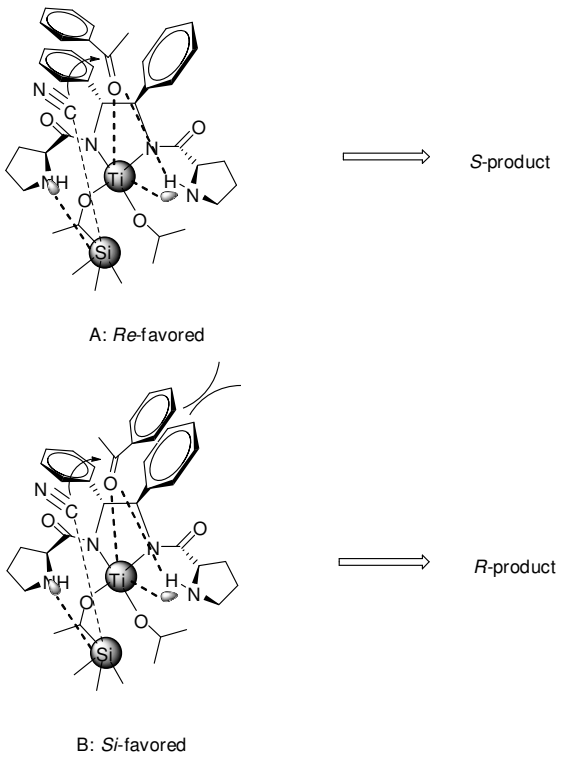


Figure 1.25 Structure of Mn(III) salen complex **25**

Feng et al. proposed a possible dual activation mechanism[158] (**Scheme 1.10**), in which the acidic titanium activated the ketone as a Lewis acid and the basic nitrogen atom of one of the pyrrolidinyl groups activated TMSCN as a Lewis base, respectively. On the basis of the observed absolute configuration of the product the transition state involved, during the catalytic cycle was proposed. Accordingly, in transition state A, the *Re* face of the carbonyl of acetophenone is more accessible to a nucleophilic group CN than *Si* face since the interaction of the *Si* face and the attacking group CN will strongly increase the repulsion between phenyl subunits as in transition state B. According to them, *S*-Proline also plays a vital role in inducing enantioselectivity, which causes a fit concave to define the position of the coordinated ketone at the *Re* face *syn* to the Lewis basic amine group of pyrrolidine. The activated nucleophile will attack the highly polarized C=O of acetophenone at the carbon atom from a less stereo-hindered direction

(*Re*) to give the *S*-configuration



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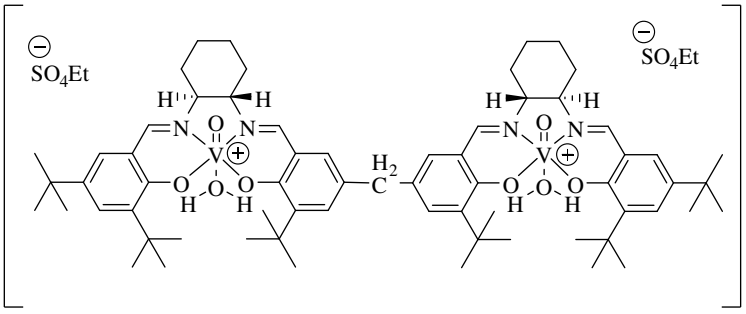
Scheme 1.10 The proposed dual activation model for the cyanation of acetophenone

1.10 Summary of the work done in the present thesis

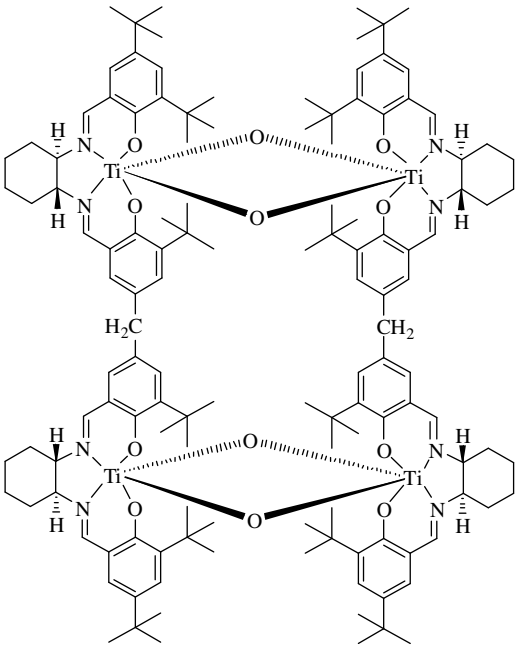
CHAPTER 2

With the state-of-the-art in asymmetric cyanation reaction the second chapter of the thesis deals with synthesis of dimeric Ti(IV)/V(V) salen complexes obtained from dimeric chiral salen ligand viz. 5,5-methylene di-[(*R,R*)-{*N*-(3-*tert*-butyl salicylidine)-*N*'-(3',5'-di-*tert*-butyl salicylidene)}-1,2-cyclohexanediaminate with Ti(IV) **2** and V(IV) metal ions followed by auto-oxidation to give dimeric V(V) salen complexes **1** (**Figure 1.26**) which carries two active catalytic metal centers. The characterization of the complexes was accomplished by microanalysis, IR-, UV Vis.-, molar conductance and optical rotation. These complexes have been investigated as catalysts for enantioselective cyanation of

aldehydes using inexpensive and non-volatile alkali metal cyanide source such as KCN, NaCN in the presence of acetic anhydride at –20 °C to give the *O*-protected chiral cyanohydrins. Excellent yield (90-99%) and ee (89-96%) of *O*-acetylcyanohydrin was achieved within 8-10 h. The results achieved with sodium cyanide are quite comparable with that of potassium cyanide. Besides, V(V) salen complex turned to be the most efficient recyclable system reported so far in the literature and is relatively better than Ti(IV) salen system. The interesting feature of these dimeric Ti(IV)/V(V) salen complexes lie in their inherent tendency to get precipitated in a non-polar solvent system like n-hexane due its higher molecular weight and lower solubility. We have recovered the catalysts, which worked well up to four cycles with marginal loss in reactivity due to some physical loss during post work up process with retention of enantioselectivity of *O*-acetylcyanohydrin.



Complex **1**



Complex **2**

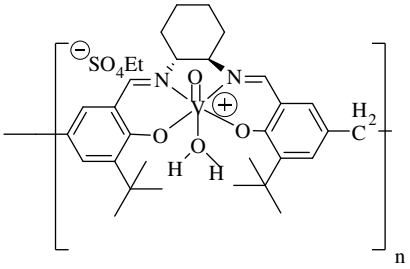
Figure 1.26 Structure of the chiral dimeric V(V) and Ti(IV) salen complexes **1** and **2**

CHAPTER 3

With our continuous effort to develop recyclable chiral catalysts novel polymeric chiral V(V) salen complex **3** derived from poly[(*R,R*)-*N,N'*-bis-{3-(1,1-dimethylethyl)-5-methylene salicylidene} cyclohexane 1,2-diamine] with vanadyl sulphate was synthesized (**Figure 1.27**). Number of repetitive units and molecular weight of the polymeric ligand was found to be 10 with M_n= ~5200 respectively by Vapour Pressure Osomometry. The recyclable polymeric V(V) salen complex was characterized by microanalysis, ^{1}H NMR, optical rotation, IR, and UV-Vis spectroscopy and effectively used as catalyst for the cyanation of various aromatic and aliphatic aldehydes using TMSCN as source, good to

excellent yield 76-97 % and high chiral induction 77-94% was achieved within 18 hours at room temperature.

In order to understand the mechanism of cyanosilylation reaction the kinetic investigations were carried out using benzaldehyde as a representative substrate. The kinetic data obtained showed the first order dependence with respect to the concentrations of the catalyst and the substrate. The rate of the cyanation was observed to be independent of concentration of the TMSCN. Based on kinetic, catalytic and experimental evidences, a probable mechanism of the cyanation reaction is suggested.



Complex **3**

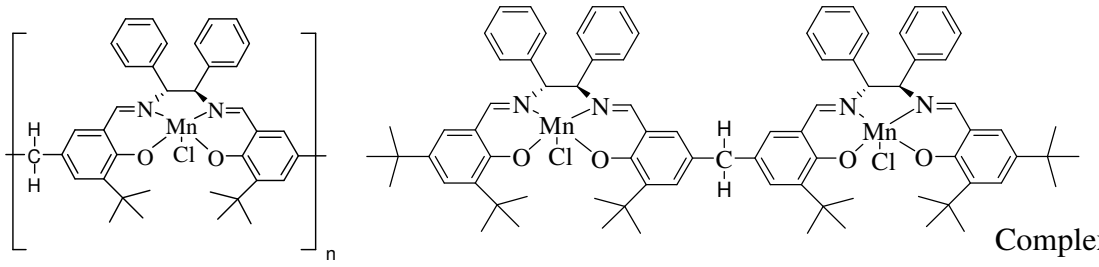
Figure 1.27 Structure of polymeric V(V) salen complex **3**

CHAPTER 4

This chapter deals with the synthesis of Dimeric and Polymeric Mn (III) salen complexes **4** and **5** respectively derived from 5,5-methylene di-[(*R,R*)-{*N*-(3-*tert*-butyl salicylidine)-*N*'-(3',5'-di-*tert*-butyl salicylidene)}-1,2-cyclohexanediaminate/poly[(*R,R*)-*N,N'*-bis-{3-(1,1-dimethylethyl)-5-methylene salicylidene} cyclohexane 1,2-diamine] with manganese acetate followed by auto oxidation in presence of LiCl (**Figure 1.28**). The characterization of the complexes was accomplished by microanalysis, IR-, UV/Vis. Spectroscopy and optical rotation. These complexes were used as catalysts for the cyanation of various aromatic and aliphatic ketones using TMSCN as a source of cyanide. To find the

optimum reaction condition the role of solvent, catalyst loading, and variation of temperature is investigated. As the additive play crucial role for the achieving high yield and ee, triphenyl phosphine oxide used as an effective additive for these reaction. The role of additive was also investigated where the optimum reaction condition for this reaction was found to be; 5 mol% catalyst loading, 40 mol% TPPO, dichloromethane as solvent at room temperature. At these optimum reaction conditions, excellent yield up to 98% with 86% ee of chiral cyanohydrintrimethylsilyl ether was achieved in 24h. Among the two polymeric and dimeric Mn (III) salen complex the polymeric complex showed better catalytic activity in terms of reactivity and enansioselctivity.

The mechanism of reaction was stabilized by using acetophenone as a modal substrate by the spectroscopic methods such as ^{1}H, ^{13}C NMR and IR. It was found out that neither catalyst nor TPPO on its own was efficient enough to expedite the addition of TMSCN to acetophenone. TPPO has played dual role. It acted as an axial ligand and also activated the polarized TMSCN.



Complex **4**

Complex **5**

Figure 1.28 Structure of chiral polymeric and dimeric Mn(III) salen complexes **4** and **5**

CHAPTER 5

This chapter deals with the synthesis of V(V) Salen complex **6** (**Figure 1.29**) derived from 1*R*, 2*R* -*N*-(3,5-di-*tert*-butyl salicylidene)-1,2-cyclohexanediamine with vanadyl sulphate followed by auto oxidation. The characterization of the complexes was done by microanalysis, IR-, UV/Vis. ^{1}HNMR and ^{13}CNMR Spectroscopy and optical rotation. These V(V) salen complexs were used as catalyst for the cyanoformyaltion of various aldehydes in the presence of various additives such as KCN, LiOH, 2,6-lutidine, pyridine, imidazole, 2-methyl imidazole and triethylamine where imidazole was found to the best to give excellent yield (97%) of the ethylcyanocarbonate with 97% ee at -20 ^{0}C. Ee of the product was further improved to >99% by a single re-crystallization step.

A probable mechanism for ethylcyanoformylation is proposed on the bases of ^{1}H and ^{13}C NMR spectroscopy.

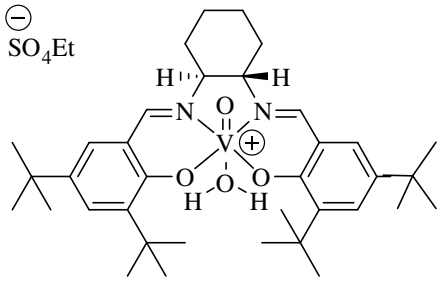


Figure 1.29 Structure of monomeric V(V) salen complex **6**

CHAPTER 6

Chapter 6 describes the synthesis of V(V) salen complexes derived from poly[(*R,R*)-*N,N'*-bis-{3-(1,1-dimethylethyl)-5-methylene salicylidene} cyclohexane 1,2-diamine] (**Figure 1.27**)/1*R*, 2*R* -*N*-(3,5-di-*tert*-butyl salicylidene)-1,2-cyclohexanediamine with vanadyl sulphate (**Figure 1.29**). These complexes were used as a effective catalyst for the cyanoformylation of aldehyde using solid bases such NaOH, KOH, Basic Al_2O_3 and

Hydrotalsite. Among these solid bases the inorganic bases (NaOH, KOH) promoted reaction very fast but the reaction bearing the non chiral path. Excellent yield (>95%) of chiral ethyl cyanohydrincarbonate with high enantioselectivity up to 93% was achieved in 24-36h when hydrotalcite was used as an additive. To find out the optimum reaction condition a series of experiment were carried out and according to results obtained we concluded that neither the catalyst nor the solid base alone sufficient enough to catalyzed the reaction the combination of catalyst and co-catalyst shows the cooperative manner to catalyzed the reaction.

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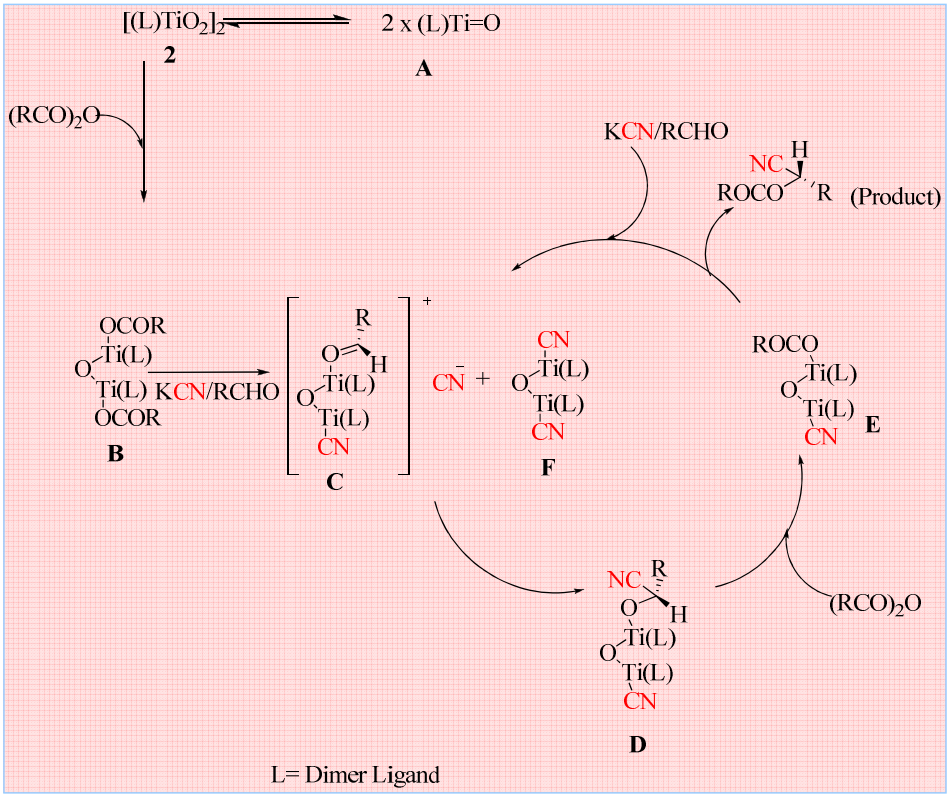
Chapter-2



Dimeric Ti(IV)/V(V) salen complex as a Recyclable Catalyst for the cyanation of aldehyde using NaCN and KCN as a source of cyanide.

2.1 Introduction

The transition metal catalyzed enantioselective cyanation of various carbonyl compounds is of utmost importance in synthetic applications as well as in biological transformation. Chiral cyanohydrins are versatile building blocks for pharmaceuticals, agrochemicals and specialty materials bearing optically active multifunctional groups such as amino hydroxyls, hydroxyl acids, and amino acids.[1-11] Since last decades metal complexes being the most widely used, at the same time significant advances have also been made towards enantioselective cyanation of carbonyl compounds employing enzymes,[12-15] synthetic peptides,[16,17] and organo-catalysts[18] by utilizing various cyanide sources. In this direction in 2002, Belokon and North group have developed a system based on the use of potassium cyanide (KCN) as cyanide source for the synthesis of acylated cyanohydrins[19,20] where the dimeric salen-Ti complex was used for the preparation of enantiomerically enriched acetylated cyanohydrins, with up to 95% ee at –40 °C, in the presence of acetic anhydride as a trapping agent. The advantages of cyanide salts (KCN, NaCN) are; they are easy to handle, cheap and non volatile. The catalysts used for the synthesis of cyanohydrin are often low-molecular weight organometallic compounds and are highly soluble in the reaction medium, hence difficult to recycle. As chiral ligands are expensive, the recycling of chiral catalyst is highly desirable. Recently, many efforts have been made to develop recyclable metal complexes using organic or inorganic supports[21,22] and ionic liquids[23,24] as reaction media.

In quest for the development of recyclable catalysts under homogeneous system,[25-27] one way is to increase the molecular weight of the catalyst so that it has lower solubility in some

of the non-polar solvents, facilitating product isolation and catalyst recovery, which in turn makes the post product work up much convenient.

In this Chapter we present the synthesis of new homochiral dimeric V(V) /Ti(IV) salen complexes (**1** and **2**) derived from chiral salen ligand *viz.*, 5,5-methylene di-[(*R,R*)-{*N*-(3-*tert*-butyl salicylidine)*N*-(3',5'-di-tert-butyl salicylidene)}-1,2-cyclohexanedi-amine] with V(V) and Ti(IV)metal ions were synthesized and used as catalysts for asymmetric cyanation of benzaldehyde and substituted benzaldehyde as substrate in the presence of acetic anhydride using NaCN and KCN as cyanide source.

2.2 Experimental

2.2.1 Materials and methods

Vanadyl sulphate hydrate (Loba Chemie, India), KCN, (Merck), NaCN (Robert Johnson), Paraformaldehyde (National Chemical India), $SnCl_4$ (S.D. fine Chem. India), titanium tetraisopropoxide, benzaldehyde, 4-methoxybenzaldehyde, 3-methoxybenzaldehyde, 2-methoxybenzaldehyde, 4-chlorobenzaldehyde, 4-bromobenzaldehyde, 4-fluorobenzaldehyde, 2-fluorobenzaldehyde, Isovaraldehyde, 2,6-lutidine, 2,4-di-*tert*-butyl phenol, 2-*tert*-butyl phenol, were purchased from Aldrich Chemicals and were used as received. The solvents were dried by standard procedure[28] distilled and stored under nitrogen. NMR spectra were obtained with a Bruker F113V spectrometer (200 MHz and 50 MHz for ^{1}H and ^{13}C respectively) and are referenced internally with TMS. FTIR spectra were recorded on Perkin Elmer Spectrum GX spectrophotometer in a KBr window. High-resolution mass spectra were obtained with a LC-MS (Q-TOF) LC (Waters), MS (Micromass) instruments. For the product purification flash chromatography was performed using silica gel 60-200 mesh purchased from s. d. Fine Chemicals Limited, Mumbai (India).

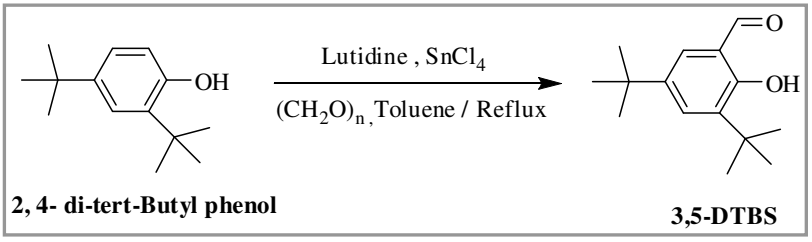
Enantiomeric excess (*ee*) were determined by HPLC (Shimadzu SCL-10AVP) using Daicel Chiralpak OD and AD chiral columns with 2-propanol/hexane as eluent. Optical rotations were measured with a Digipol 781 Automatic Polarimeter Rudolph Instruments.

2.3 Synthesis of chiral dimeric salen ligands (1')

The synthesis of chiral dimeric salen ligands and its precursor is described as follows.

2.3.1 3,5-di-*tert*-Butyl salicylaldehyde (3,5-DTBS)

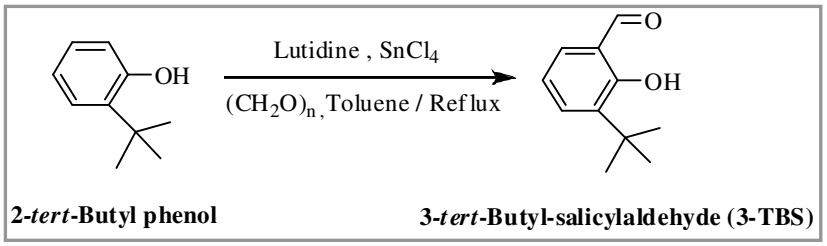
2, 6-lutidine (4.3 mL, 0.04 mol), $SnCl_4$ (5.2 mL, 0.02 mol), 2, 4- di-*tert*-butyl phenol (10 g, 0.67 mol) was taken in dry toluene (200 ml). The resulting mass was stirred at 25 °C under nitrogen for 1 h followed by the addition of paraformaldehyde (8.0 g, 0.26 mol). The mixture was heated under reflux for 8 h and the reaction progress was monitored by TLC. The reaction mixture was allowed to cool to 25 °C and water (200 ml) and diethyl ether (200 ml) was added. The resulting emulsion was filtered through a pad of celite and the layers were separated. The organic layer was washed with water, brine, and dried over anhydrous Na_2SO_4, and then concentrated. The crude product was purified by flash column chromatography on silica gel (Hexane: EtOAc = 95:05) to afford the title compound as a yellow solid (**Scheme 2.1**). IR (KBr): 2958, 1612, 1653 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 1.34 (s, 18H), 6.89 (t, 1H), 7.40 (d, 1H), 7.54 (d, 1H), 9.89 (s, 1H), 11.80 (s, 1H), ppm; Anal. Calcd. For ($C_{14}H_{19}O_2$): C, 76.68; H, 7.7, Found: C, 76.60; H, 7.79%.



Scheme 2.1 Synthesis of 3,5-di-*tert*-butyl salicylaldehyde (**3,5-DTBS**)

2.3.2 3-*tert*-Butyl-salicyaldehyde (3-TBS)

2,6-Lutidine (4.3 mL, 0.04 mol), $SnCl_4$ (5.2 mL, 0.02 mol), 2- *tert*-butyl phenol (10 g, 0.67 mol) was taken in dry toluene (200 ml). The resulting mass was stirred at 25 °C under nitrogen for 1 h followed by the addition of paraformaldehyde (8.0 g, 0.26mol). The mixture was heated under reflux for 8 h and the reaction progress was monitored by TLC. The reaction mixture was allowed to cool to 25 °C and water (200 ml) and diethyl ether (200 ml) was added. The resulting emulsion was filtered through a pad of celite and the layers were separated. The organic layer was washed with water, brine, and dried over anhydrous Na_2SO_4, and then concentrated. The crude product was purified by flash column chromatography on silica gel (Hexane: EtOAc.) to afford the title compound as a pale yellow oil[29] (**Scheme 2.2**) (10.6 g, 90% yield), IR (KBr): 2958, 1612, 1653, $cm.^{-1}$; ^1H NMR (200 MHz, $CDCl_3$): δ 1.33 (s, 9H), 6.87 (t, 1H), 7.38(d, 1H), 7.52 (d, 1H), 9.84(s, 1H), 11.77(s, 1H) ppm; Anal. Calcd. For ($C_{11}H_{14}O_2$): C, 74.15; H, 7.87, Found: C, 74.05; H, 7.79%.

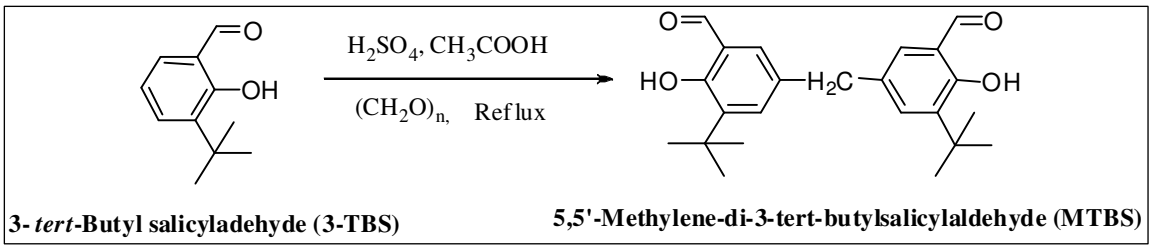


Scheme 2.2 Synthesis of 3-*tert*-Butyl-salicyaldehyde **(3-TBS)**

2.3.3 5,5'-Methylene-di-3-*tert*-butylsalicylaldehyde (MTBS)

3-*tert*-Butyl salicylaldehyde **(3-TBS)** (0. 12 mol) was treated with a solution of paraformaldehyde (0.06 mol) in glacial acetic acid (16 ml) and sulfuric acid (2 ml) under

nitrogen. The resulting solution was allowed to heat to 90°C with stirring for 24 h. The reaction mixture was poured into cold water and allowed to stand overnight. The deposited dark brown solid was extracted with petroleum ether (3×15 ml). The organic phase was dried over anhydrous sodium sulfate. The dark brown compound was purified by silica gel column chromatography using hexane–ethyl acetate as eluent to yield **MTBS** as a solid (**Scheme 2.3**) (30.9 g, 70%). M. P. 99-100°C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.40 (s, 9H, methyl), 3.93 (s, 2H, methylene), 7.14 (d, 2H, aromatic, *J*m = 2.14), 7.37 (d, 2H, aromatic *J*m = 2.14), 9.82 (s, 2H, HCO), 11.72 (s, 2H, OH) ppm; ^{13}C ($CDCl_3$, 50 MHz): δ 197.6, 160.3, 139.3, 135.1, 131.6, 121.1, 40.7, 35.3, 29.7 ppm; Anal. Calcd. for ($C_{23}H_{28}O_4$): C, 74.97; H, 7.66, Found: C, 74.80; H, 7.58%.

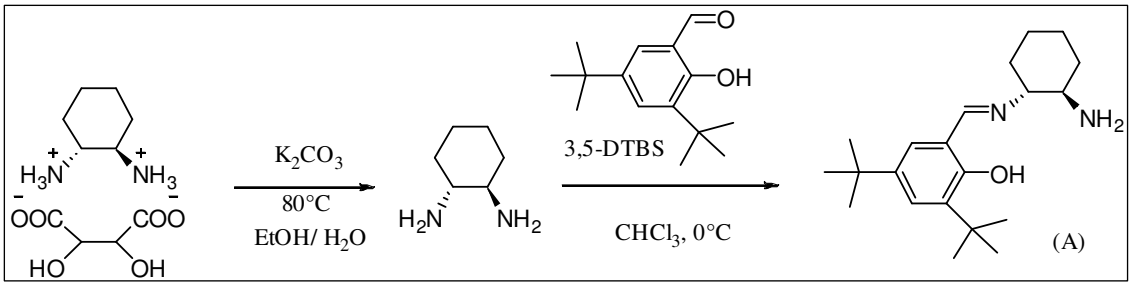


Scheme 2.3 5,5'-Methylene-di-3-*tert*-butylsalicylaldehyde **(MTBS)**

2.3.4*N*-2-Hydroxy-3,4-di-*tert*-butyl-benzaldehyde)-1-amino-2-yclohexeneimine (A)

The mono tartrate salt of (1*R,*2*R*)-(-)-cyclohexane diamine (0.01 mol) and anhydrous K_2CO_3 (0.02 mol) were dissolved in 15 ml of distilled water with stirring. Ethanol (6ml) was added and the resulting cloudy mixture was heated to reflux at 70-80 °C for 2 h. The solvent was removed completely and the liberated diamine was extracted with $CHCl_3$ (4x5ml). The free diamine thus obtained was stirred with **3,5-DTBS** (0.0022 mol in 20ml $CHCl_3$) for 48 h at 0 ^{o}C. Removal of the solvent gave yellow colored compound (**A**) (**Scheme 2.4**). ^{1}H NMR ($CDCl_3$, 200MHz): δ 1.24 (s, 9H),

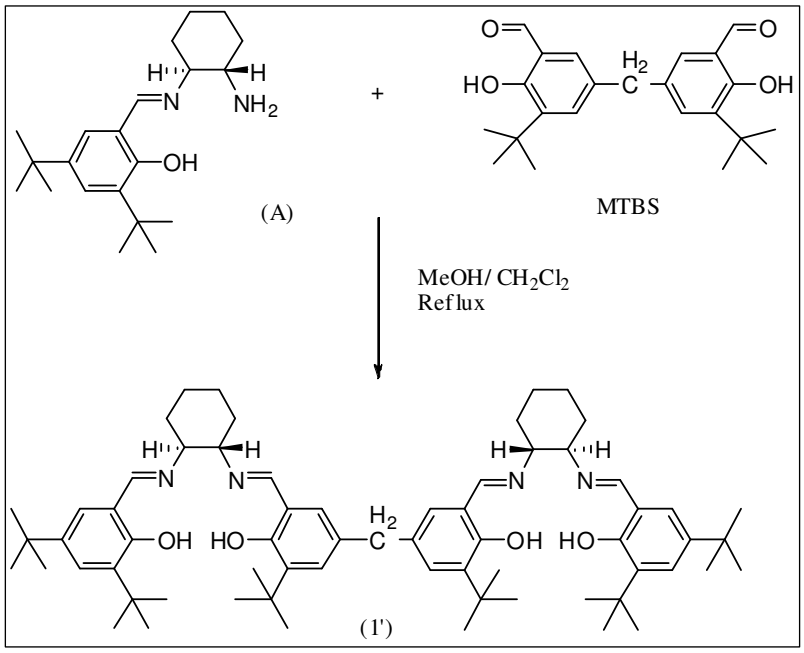
1.41 (s, 9H), 1.58-2.25 (m, 11H, 2H exchangeable with D_2O), 3.35 (1H), 6.89 (s, 1H), 7.26 (s, 1H), 8.42 (s, 1H), 13.73 (b, 1H, exchangeable with D_2O) ppm; ^{13}C NMR ($CDCl_3$, 50 MHz): δ 25.1 25.8, 26.0, 30.0, 31.0, 34.0, 35.2, 55.3, 77.3, 118.3, 126.5, 127.5, 140.0, 142.7, 158.63, 166.1 ppm; Anal. Calcd. for ($C_{21}H_{34}N_2O$): C, 76.31; H, 10.37; N, 8.48, Found: C, 76.26; H, 10.30; N, 8.40%; MS (ESI): *m/z* = 331.37 $[M+H]^+$.



Scheme2.4 Synthesis of *N*-2-Hydroxy-3,4-di-*tert*-butyl-benzaldehyde)-1-amino-2-cyclohexeneimine **(A)**

2.3.5 5,5-Methylene di-[(*R,R*)-{*N*-(3-*tert*-butyl salicylidine)-*N'*-(3',5'-di-*tert*-butyl salicylidene)]-1,2-cyclohexanediamine] (1')

Compound **A** (0.002 mol) in CH_2Cl_2 and 5,5-methylene-di-3-*tert*-butyl salicylaldehyde (**MTBS**) (0.001 mol) in ethanol were refluxed for 6-8 h. The resulting solution on concentration precipitated out the desired chiral ligand (**1'**) (**Scheme 2.5**).Yield 85%. IR (KBr): 1620 ν(H-C=N) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.23 (s, 18H), 1.40 (s, 36H), 1.54-2.0 (m, 16 H), 3.22 (s, 4H), 3.68 (s, 2H), 6.74 (s, 4H), 7.05 (s, 4H), 8.21 (s, 4H), 13.69 (bs, 4H exchangeable with D_2O) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ 23.3, 24.8, 28.3, 29.4, 31.6, 34.9, 35.4, 40.2, 42.2, 65.1, 69.4, 121.3, 125.0, 127.1, 128.4, 128.8, 137.1, 138.2, 139.2, 139.5, 157.3, 161.4 ppm; Anal. Calcd for ($C_{65}H_{92}O_4N_4$): C, 78.58; H, 9.34; N, 5.64, Found: C, 78.26; H, 9.30; N, 5.47%.

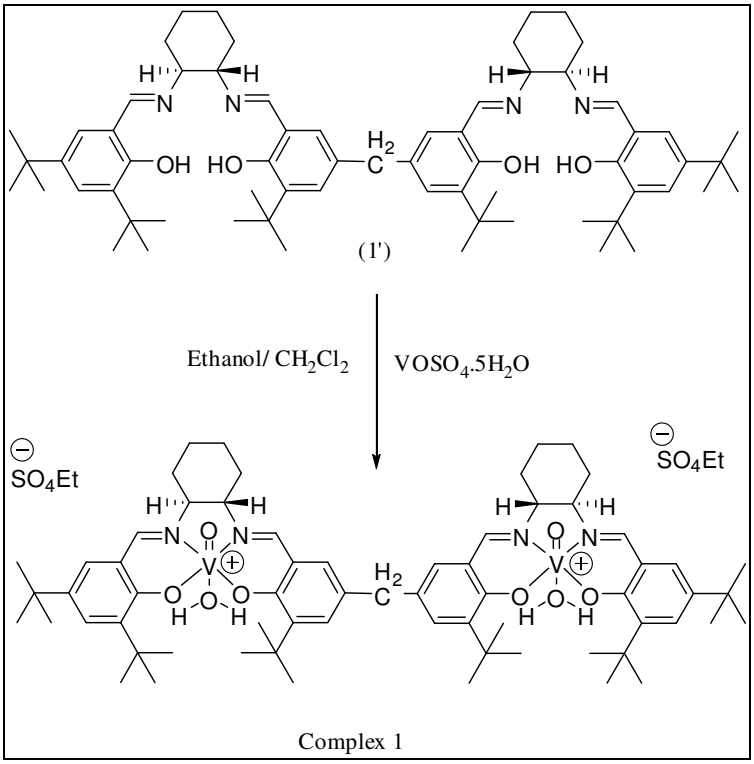


Scheme 2.5 Synthesis of 5,5-Methylene di-[(*R,R*)-{*N*-(3-*tert*-butyl salicylidine)-*N'*-(3',5'-di-*tert*-butyl salicylidene)]-1,2-cyclohexanediamine] **(1')**

2.3.6 Synthesis of complex 1

The ligand **1'** (0.499 g, 0.504mmol) was dissolved in mixed solvent ethanol:CH_2Cl_2 (3:2, 15 ml) to which an aqueous solution of vanadyl sulphate hydrate (0.255 g, 1.008 mmol in 2 ml water) was added drop wise under an inert atmosphere at RT. The resulting solution was refluxed for 4 h and then cooled to room temperature with an extended stirring for 2 h while opening the side arm of the reaction flask. Solvent was completely evaporated and the residue was dissolved in CH_2Cl_2 (10 ml), washed with water (3 x 5ml) and finally with brine. The organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated to give V(V) complex (**Scheme 2.6**). Yield, 0.385 g, 68%. Melting point: d. 200 °C. Data for catalyst **1**. ^{1}H NMR (200MHz, $CDCl_3$): δ = 0.82 (t, J = 7.2, 3 H), 1.33 (s, 18 H), 1.42 (s, 36H), 1.6-2.3 (m, 8 H), 3.41 (q, J = 7.2, 2 H), 3.81 (m, 1 H), 3.92 (s, 2H), 4.25 (m, 1H), 7.48 (s, 1 H), 7.53 (s,

1 H), 7.68 (s, 1 H), 7.73 (s, 1 H), 8.52 (s, 1 H), 8.73 (s, 1 H) ppm. IR: (KBr): $\bar{\nu}$ = 3435, 2958, 2868, 2359, 1650, 1613, 1538, 1465, 1437, 1389, 1361, 1317, 1269, 1253, 1227, 1171, 1028, 982, 929, 834, 770, 748, 711, 643, 563 cm^{-1}; Anal. Calcd. for $C_{69}H_{102}N_4O_{16}S_2V_2^{+2}$: C, 58.79; H, 7.29; N, 3.97. Found: C, 58.85; H, 7.32; N, 3.99. λ_{max} (ε): 252 (33915), 352 (12681), 421 (4114), 633 (1592); $[\alpha]_D^{27}$ = – 860 (c = 0.01, $CHCl_3$). TOF-MS (ESI+): *m/z* 1160.4 $[M+H]^+$.

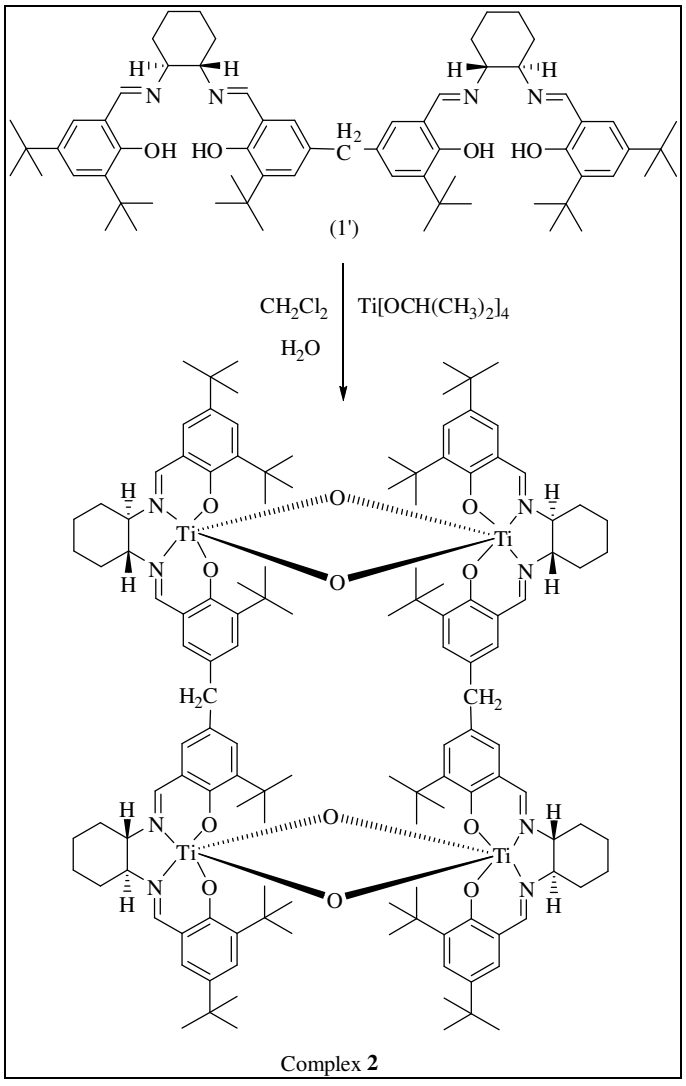


Scheme 2.6 Synthesis of Complex **1**

2.3.7 Synthesis of complex 2

Ligand **1'** (98.0 mg, 0.10 mmol) and titanium tetraisopropoxide (0.06 ml, 0.20 mmol) in dry CH_2Cl_2 (2 ml) was stirred at room temperature under nitrogen for 2 h. H_2O (0.004 µl, 0.20 mmol) was added to the above solution and the reaction mixture was again stirred at

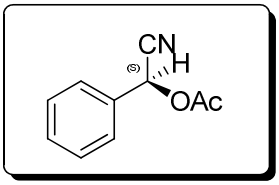
room temperature for 3 h (**Scheme 2.7**). ^{1}H NMR (200MHz, $CDCl_3$): δ = 1.05 (s, 18 H), 1.22 (s, 18 H), 1.31 (s, 18 H), 1.5–1.6 (m, 2 H), 2.5–2.6 (m, 2 H), 3.92 (s, 2 H), 4.0–4.1n(m, 2 H), 6.97 (s, 2H), 7.05 (s, 2 H), 7.24 (s, 2 H), 7.43 (s, 2 H), 7.80 (s, 2 H), 8.18 (s, 2 H). IR: (KBr): $\bar{\nu}$ = 1624, 702 cm^{-1}s $[\alpha]_D^{27}$ = – 320 (c = 0.01, $CHCl_3$). TOF–MS (ESI+): *m/z* 2235.8 $[M+H]^+$.



Scheme 2.7 Synthesis of Complex **2**

2.3.8 Procedure for asymmetric *O*-acetylcyanation of aldehyde catalyzed by Vanadium (V) dimeric salen complex

V(V)-salen complex **1** was dissolved in dry CH_2Cl_2 (3 ml) and the solution was cooled to –20 °C. CH_2Cl_2 (2 ml), *t*-BuOH (0.2 ml, 2.09 mmol), H_2O (0.020 ml, 1.11mmol), benzaldehyde (0.20 ml, 1.98 mmol) and Ac_2O (0.75 ml, 7.92 mmol) were then added to the solution in that order. The addition of KCN (0.51 g, 7.92 mmol) was done slowly during 2h followed by addition of dry CH_2Cl_2 (3 ml). After the reaction was completed (as detected by TLC), the reaction mass was washed with water (3 x 5 ml) followed by brine, the organic layer was separated, and dried over anhydrous Na_2SO_4. The solution was filtered, evaporated and compound was purified by flash column chromatography on silica gel (eluted with hexane/ethylacetate = 95:5). The enantiomeric excess of *O*-acetyl cyanohydrin was determined by HPLC analysis using OD and AD column.



Data for product: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.11 (s, 3 H), 6.38 (s, 1 H), 7.40–7.52 (m, 5 H). ^{13}C NMR (50 MHz, $CDCl_3$): 20.8, 63.3, 116.7, 128.3, 129.7, 130.8, 132.3, 169.4. $[\alpha]_D^{27}$ = – 30.5 (c = 1, CH_2Cl_2). TOF–MS (ESI+): *m/z* 160.2 $[M+H]^+$.

2.4 Results and discussion

The synthesis of dimeric salen ligand (**1'**) and its precursors was carried out as described in experimental section. The complexation of the dimeric salen ligand (**1'**) with $V(O)SO_4$. $5H_2O$ for the catalyst **1 (Scheme 2.6)** was carried out in ethanol while catalyst **2** was generated *in situ* by the interaction of equimolar quantities of chiral salen ligand with

$Ti(O^iPr)_4$ (**Scheme 2.7**). These catalysts **1** and **2** were characterized by ^1H NMR, optical rotation, IR, UV-Vis and microanalysis CHN (data given in experimental section). The formation of Ti-O-Ti complex **2** generated *in situ* was confirmed by recording the solution IR (Figure 1)of parent complex $TiL(O^iPr)_2$ and after interaction with 1 equiv. water which forms catalyst **2** or species **A** (**Scheme 2.8**). The emergence of a new band at 702 cm^{-1} indicates the formation of Ti-O-Ti complex. This band was absent in the complex $TiL(O^iPr)_2$ prior to the addition of water[30]

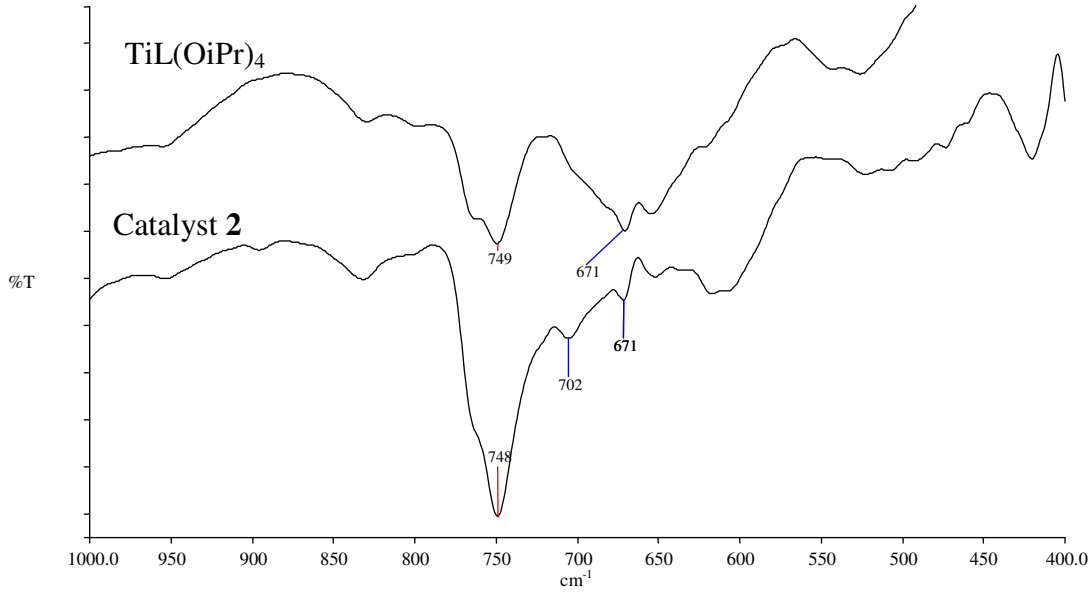


Figure 2.1 Solution IR spectra of Catalyst 2 recorded in dichloromethane

The catalysts **1** and **2** were used for the asymmetric addition of cyanide by using sodium cyanide and potassium cyanide as non-volatile and inexpensive cyanide source to various aldehydes namely, benzaldehyde (**3a**), 4-methoxybenzaldehyde (**3b**), 3-methoxybenzaldehyde (**3c**), 2-methoxybenzaldehyde (**3d**), 4-chlorobenzaldehyde (**3e**), 4-

bromobenzaldehyde (**3f**), 4-fluoro benzaldehyde (**3g**) and 2-fluorobenzaldehyde (**3h**) in the presence of acetic anhydride at –20 °C as shown in **Table 2.3 and 2. 4.**

It has been reported that the reactivity and enantioselectivity of *O*-acetylcyanohydrin formation using chiral Ti(IV) salen is solvent dependent.[31] In view of this the effect of solvent using the complexes **1** and **2** in asymmetric addition of KCN and acetic anhydride to benzaldehyde as representative substrate was carried out and results are shown in **Table 2.1**. Good conversion (80–82%) and high *ee* (85–87%) was achieved when 1,2-dichloroethane (Entries 3, 4) was used as solvent while in case of toluene and THF the conversion (40–53%) with (*ee*, 68–71%) was moderate (Entries 5–8). In all the solvents used dichloromethane found to be the solvent of choice (Entries 1, 2) and it showed better results than the previously reported chiral cross linked polymeric salen complexes with Ti(IV).

The complexes **1** and **2** were also used for examining the influence of catalyst loading and temperature variation on the formation of *O*-acetylcyanohydrin using benzaldehyde as a substrate and KCN as cyanide source. The results are given in **Table 2.2**, where best conversion (99%) and *ee* (92–93%) were achieved at –20 ºC with 5 mol% (with respect to salen unit) of the complexes **1** and **2** (Entries 1, 2). On reducing the catalyst loading from 5 mol% to 2 mol% there is a decrease in conversion 90–92

Table 2.1. Data for the effect of solvents on conversion and *ee* of *O*-acetylcyanohydrin using benzadehyde as representative substrate with catalysts **1** and **2** using KCN as cyanide source

Entry	Solvent	Conversion [%][a]	*ee* [%][b]
1 (2)	Dichloromethane	99(99)	92(93)[c]
3 (4)	1,2 Dichloroethane	80 (82)	85(87)
5 (6)	Toluene	40 (43)	70(71)
7 (8)	Tetrahydrofurane	50(53)	67(68)

[a] The conversion was determined based on G. C. integral area. [b] The *ee* was determined by using chiralpak HPLC OD column. [c] Results in parenthesis are for catalyst **1**.

(Entries 9, 10) with retention in *ee* 91–92%. On further decreasing the catalyst loading (1 mol%) there is a further decrease in the conversion and *ee* (Entries 11, 12). Furthermore, the increase in reaction temperature had an adverse effect on the yield and enantioselectivity of the product. These observations are in consonance to those reported earlier.[31]

It can be seen that the present catalytic protocol is quite general for a range of substrates used in the present study. However, the substituents on benzaldehyde derivative had some influence on the reactivity and enantioselectivity. While, excellent conversions to *O*-acetylcyanohydrin (yield up to 98–99%) (**Table 2.3**, Entries 1, 2, 23–30 and **Table 2.4**, Entries 31, 32, 39–46) were obtained for most of the aldehydes with both the catalysts in 8-10 h, methoxy substituted aldehydes (**Table 2.3**, Entries 17–22 and Table**2.4**, Entries 33–38) affected relatively lesser conversions to *O*-acetylcyanohydrin (conversion 90–93%). The lower conversions for 4-methoxy benzaldehyde was also

Table 2.2 Data for the effect of loading and temperature on conversion and *ee* of *O*-acetyl cyanohydrin using benzadehyde as representative substrate with catalysts **1** and **2** using KCN as cyanide source

Entry	**Catalyst loading [mol%]**	**Temp. [°C]**	**Conversion [%][a]**	***ee* [%][b]**
1 (2)	5	–20	99(99)	92(93)[c]
9 (10)	2	–20	90(92)	91(92)
11 (12)	1	–20	78(80)	90(92)
13 (14)	5	–8	88(89)	70(71)
15 (16)	5	RT	89(91)	60(61)

[a]The conversion was determined based on G. C. integral area. [b]The *ee* was determined by using chiralpak HPLC OD column. [c] Value in parenthesis was given for catalyst **1**.

Observed with BINOLAM-Ti(IV) complexes.[32] Best enantio-induction (*ee*, 96%) and quantitative yield of *O*-acetylcyanohydrin was obtained for 2-fluorobenzaldehyde using KCN as cyanide source with catalyst **1** (Entry 30). The chiral induction in *O*-acetylcyanohydrin utilizing the catalysts **1** and **2** followed the following order: F benzaldehyde > benzaldehyde > Cl benzaldehyde > Br benzaldehyde > MeO benzaldehyde as shown in **Figure 2.2**. Besides, the over all performance of the V(V) chiral salen complex **1** was found to be most efficient recyclable system so far reported in literature over Ti(IV) salen complex in term of reactivity and enantioselectivity. Further, the results obtained with sodium cyanide as cyanide source are fairly comparable with that of KCN in term of reactivity and enantioselectivity and is an important finding considering the fact that former is far less toxic than later.

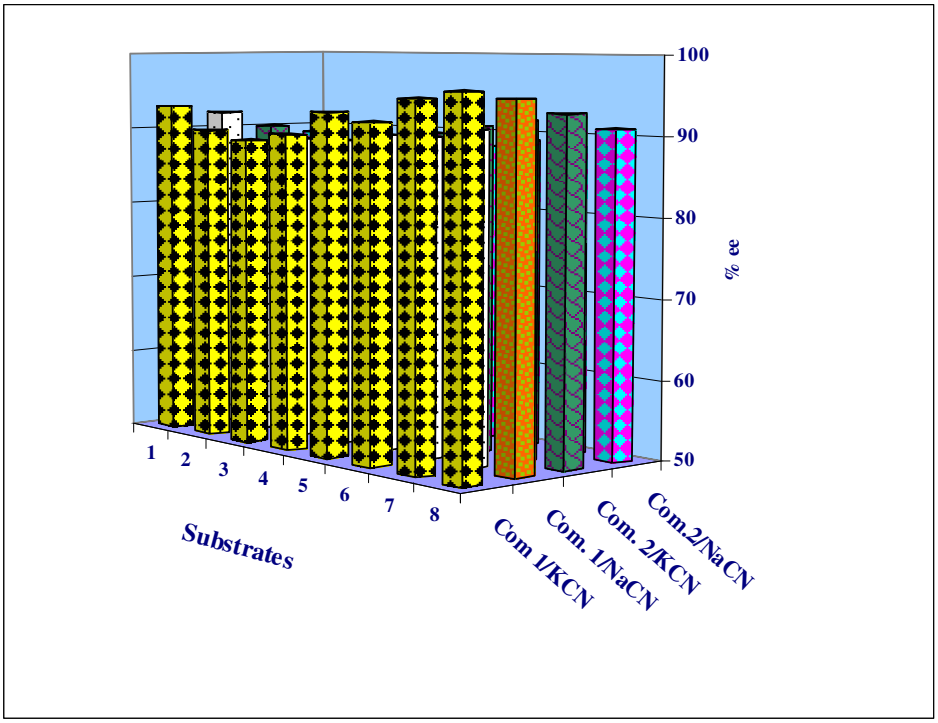


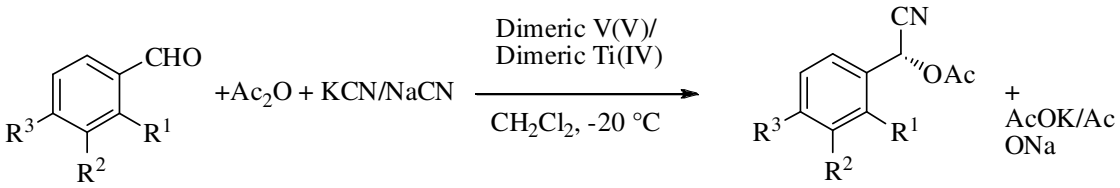
Figure 2.2 3D view showing % ee vs. aldehydes (1) **3a,** (2) **3b**, (3) **3c**, (4) **3d**, (5) **3e**, (6) **3f**, (7) **3g**, (8) **3h** using the catalysts **1**, **2** with KCN and NaCN.

2.4.1 Mechanism

A plausible mechanism for the formation of *O*-acetylcyanohydrin is shown in **Scheme 2.8** where catalyst **2** was activated by the addition of acetic anhydride to give bis acetate (**B**), which on reaction with KCN/NaCN in the presence of an aldehyde gives species (**C**). The nucleophilic attack by CN-group on partially coordinated aldehydic carbon to species (**D)** takes place which facilitates the acylation of titanium bound cyanohydrin to give product *O*-acetylcyanohydrin. This titanium complex (**E**) either reacts with cyanide to give bis cyanide species (**F**) or reacts with aldehyde to form species (**C**) which further continue the catalytic cycle. It has been reported[33,34] in the literature that the catalytic cycle in case of vanadium (V) salen complex proceed in an

intramolecular manner via the formation of *cis*-β vanadium(V)salen species in the same manner as reported[20,33,34] for Ti (salen) di-μ-oxo-complex.

Table 2.3 Enantioselective synthesis of the *O*-acetylcyanohydrin from various aldehydes, potassium cyanide and acetic anhydride catalyzed by dimeric chiral Ti(IV) and V(V) complexes



3a; R^1 = H, R^2 = H, R^3 = H
3b; R^1, R^2 = H, R^3 = OMe
3c; R^1 = H, R^2 = OMe, R^3 = H
3d; R^1 = OMe, R^2 = H, R^3 = H
3e; R^1 = H, R^2 = H, R^3 = Cl
3f; R^1 = H, R^2 = H, R^3 = Br
3g; R^1 = H, R^2 = H, R^3 = F
3h; R^1 = F, R^2 = H, R^3 = H

4a-h

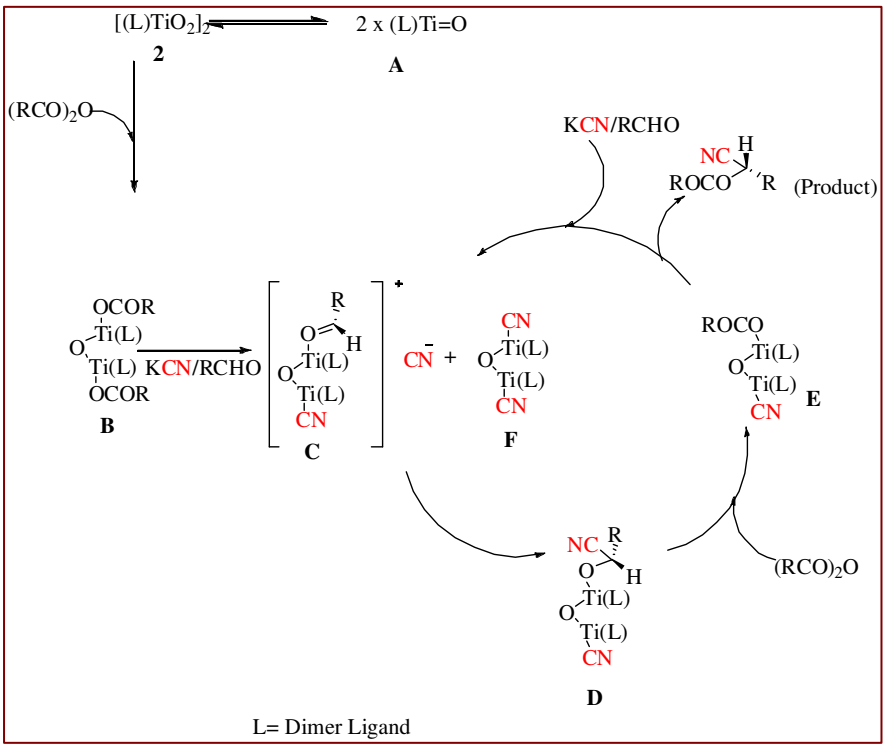
Entry	Substrate	Catalysts	Source of cyanide KCN	
			Conversion [%][a]	*ee* [%][b, d]
1(2)	**3a**	**2(1)**	99(99)	92(93)[c]
(17)18	**3b**	**2(1)**	91(90)	88(90)
(19)20	**3c**	**2(1)**	92(93)	89(89)
(21)22	**3d**	**2(1)**	90(92)	89(90)
(23)24	**3e**	**2(1)**	99(99)	90(93)
(25)26	**3f**	**2(1)**	99(99)	90(92)
27(28)	**3g**	**2(1)**	99(99)	91(94)
29(30)	**3h**	**2(1)**	99(99)	95(96)

[a] The conversion was determined based on G. C. integral area. [b] The *ee* was determined by using chiralpak HPLC OD and AD column. [c]Value in parenthesis was given for catalyst **2**. [d]The absolute configuration was assigned by comparison with literature data found to be *S*.[20]

Table 2.4. Enantioselective synthesis of the *O*-acetylcyanohydrin from various aldehydes, sodium cyanide and acetic anhydride catalyzed by dimeric complexes **1, 2**

Entry	Substrate	Catalysts	Source of cyanide NaCN Conversion [%][a]	*ee* [%][b, d]
31(32)	**3a**	**2(1)**	99(99)	89(90)[c]
33(34)	**3b**	**2(1)**	90(90)	87(88)
35(36)	**3c**	**2(1)**	91(93)	86(88)
37(38)	**3d**	**2(1)**	90(91)	85(87)
39(40)	**3e**	**2(1)**	98(99)	89(91)
41(42)	**3f**	**2(1)**	99(99)	88(90)
43(44)	**3g**	**2(1)**	98(99)	90(92)
45(46)	**3h**	**2(1)**	98(99)	91(93)

[a] The conversion was determined based on G. C. integral area. [b] The *ee* was determined by using chiralpak HPLC OD and AD column. [c] Value in parenthesis was given for catalyst **2**. [d] The absolute configuration was assigned by comparison with literature data found to be *S*.[20]



Scheme 2.8 Probable mechanism for catalytic cycle of asymmetric cyanation reaction

2.4.2 Recycling of the catalysts

Catalysts recycling studies were carried out by precipitating the catalysts by the addition of hexane to the post catalytic reaction mixture. To the recovered catalysts fresh substrates and reactants were supplied in the similar manner as in the case of fresh catalysts. The data of four-time use of the same catalysts is given in **Table2. 5**. The activity of the recycled catalysts gradually decreased upon successive use possibly due to some physical loss of the catalyst with retention of enantioselectivity.

Table 2.5 Data for enantioselective synthesis of the *O*-acetylcyanohydrin with benzaldehyde, potassium cyanide and acetic anhydride catalyzed by recovered dimeric chiral Ti(IV) and V(V) complexes

Run	1	2	3	4
Time (h)	8(8)	10(9)	12(10)	14(12)
Conversion [%][a]	99(99)[c]	98(99)	90(92)	88(90)
***ee* [%][b]**	92(93)	92(93)	92(93)	92(93)

[a] The conversion was determined based on G. C. integral area. [b] The *ee* was determined by using chiralpak HPLC OD column. [c] Value in parenthesis was given for catalyst **1**.

2.5 Conclusions

Chiral dimeric vanadium (V) and titanium (IV) salen complexes **1** and **2** were tested for the asymmetric addition of non-volatile and inexpensive sodium cyanide and potassium cyanide as cyanide source to various aldehydes in presence of acetic anhydride at –20 °C. Excellent yield (99%) of *O*-acetylcyanohydrin with high chiral induction was achieved (*ee,* up to 96%) in the case of 2-fluorobenzaldehyde both with sodium cyanide and potassium cyanide as a source of cyanide. Besides, V(V) salen complex turned out to be the most efficient recyclable system reported so far in the literature and is relatively better than Ti(IV)

salen system. Both the catalysts were recovered after first use and recycled four times effectively.

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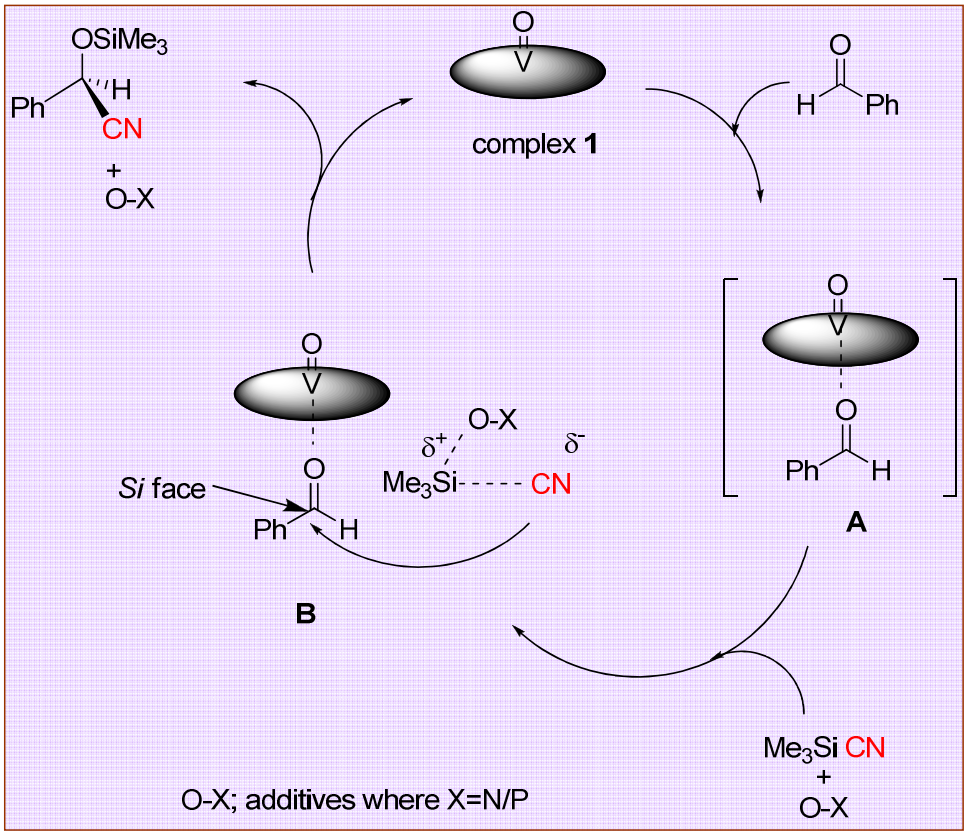
Chapter-3



Polymer V(V) salen complex as a Recyclable Catalyst for the cyanation of aldehyde

3.1 Introduction

Chiral cyanohydrins play an important role for the preparation of wide range of pharmaceuticals, agrochemicals and insecticides.[1] To achieve chiral cyanohydrins in high chiral purity, substantial progress has been made towards the development of efficient methods for the preparation of these compounds, with a growing emphasis on the identification of enantioselective catalytic approaches with practical potentials[2,3] in the presence of different cyanation reagents.[4-14] Among them trimethylsilylcyanide (TMSCN) is one of the most frequently used cyanation sources for nucleophilic addition to carbonyl compounds in the presence of chiral catalyst.[15-32]

Although impressive enantio-induction have been obtained in most of the cases, yet issues such as moderate temperature, reaction conditions and recycling of the expensive chiral catalyst need to be addressed for their practical application. Recently, many efforts have been made to develop recyclable metal complexes involving multi-step surface modification of the support and its binding with catalytically active complex using organic or inorganic supports[33,34] and ionic liquids[35,36] as reaction media.

After the successful utilization of chiral Dimeric V(V) and Ti(IV) salen complexes in the asymmetric cyanation of aldehydes using NaCN and KCN as a source of cyanide, this chapter describes the synthesis of polymeric V(V) salen complex **3** and **4** derived from the chiral polymeric ligands with vanadyl sulphate. These complexes were used for cyanation of various aldehydes with TMSCN and KCN as cyanide source in the sections **A** and **B** of this chapter respectively.

3.2Experimental

3.2.1 Materials & methods

Vanadyl sulphate hydrate (Loba Chemie, India), benzaldehyde, 4-methoxybenzaldehyde, 3-methoxybenzaldehyde, 2-methoxybenzaldehyde, 4-chlorobenzaldehyde, 4-bromobenzaldehyde, 4-fluorobenzaldehyde, *n*-butylaldehyde, *iso*-butylaldehyde, 3-methylbutarldehyde, 4-phenyl pyridine *N*-oxide, tri-phenylphosphane oxide (Aldrich), 2-methylbenzaldehyde, 4-methylbenzaldehyde, tri-phenylphosphane (Merck Chemicals), trimethysilylcyanide (Acros), pyridine *N*-oxide (Fluka), Triethylamine (S. D. Fine-Chem, India), pyridine (Qualigens Fine Chem, India) were purchased and used as received. Polymeric chiral salen ligands **3'** and **4'** were synthesized by earlier reported method.[37] All the solvents were dried by standard procedures,[38] distilled and stored under nitrogen.

3.3 Synthesis of chiral polymeric salen ligands

The synthesis of chiral polymeric salen ligands **3'** and **4'** is described as follows

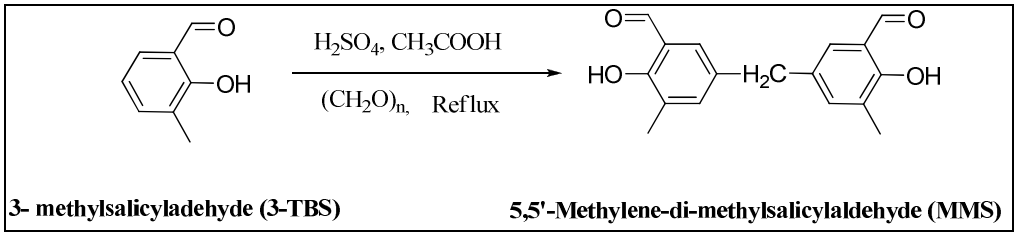
3.3.1 5,5'-Methylene-di-3-*tert*-butylsalicylaldehyde (MTBS)

The compound 5,5'-Methylene-di-3-*tert*-butylsalicylaldehyde was synthesized according to the procedure described in the chapter 2 in the experimental section

3.3.2 5,5'-Methylene-di-3-methylsalicylaldehyde (MMS)

3-methylsalicylaldehyde (0.12 mol) was treated with a solution of paraformaldehyde (0.06 mol) in glacial acetic acid (16 ml) and sulfuric acid (2 ml) under nitrogen. The resulting

solution was allowed to heat at 90°C with stirring for 24 h. The reaction mixture was poured into cold water and allowed to stand overnight. The deposited dark brown solid was extracted with petroleum ether (3×15 ml). The organic phase was dried over anhydrous sodium sulfate. The dark brown compound was purified by silica gel column chromatography using hexane–ethyl acetate as eluent to **MMS** as a solid (**Scheme 3.1**), yield 85%. M. P. 92-98°C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.15 (s, 3H, methyl), 3.93 (s, 2H, methylene), 7.14 (d, 2H, aromatic, *J*m = 2.14), 7.37 (d, 2H, aromatic J_m = 2.14), 9.82 (s, 2H, HCO), 11.64 (s, 2H, OH) ppm; ^{13}C ($CDCl_3$, 50 MHz): δ 197.6, 160.3, 139.3, 135.1, 131.6, 121.1, 40.7, 15.23 ppm; Anal. Calcd for ($C_{17}H_{16}O_4$): C,71.82 ; H, 5.67, Found: C, 71.78; H, 5.63%.



Scheme 3.1 Synthesis of 5,5'-methylene-di-methylsalicyladehyde (MMS)

3.3.3 Poly[(*R,R*)-*N,N'*-bis-{3-(1,1-dimethylethyl)-5-methylene salicylidine}- cyclohexane 1,2 -diamine] (3')

5,5'-methylene-di-3-*tert*-butylsalicylaldehyde (**MTBS**) (0.002 mol) was dissolved in methanol and 1*R,*2*R*-(-)-cyclohexanediamine (0.002 mol) was added under cold condition and the resulting mixture was refluxed for 6-8 h. After cooling a partial removal of the solvent from the reaction mixture precipitated out the desired chiral ligand **4'** in high yield. This ligand was re-crystallized with ethanol and characterized by micro analysis, IR, ^{1}H NMR and Vapour Pressure Osmometry (VPO). The number

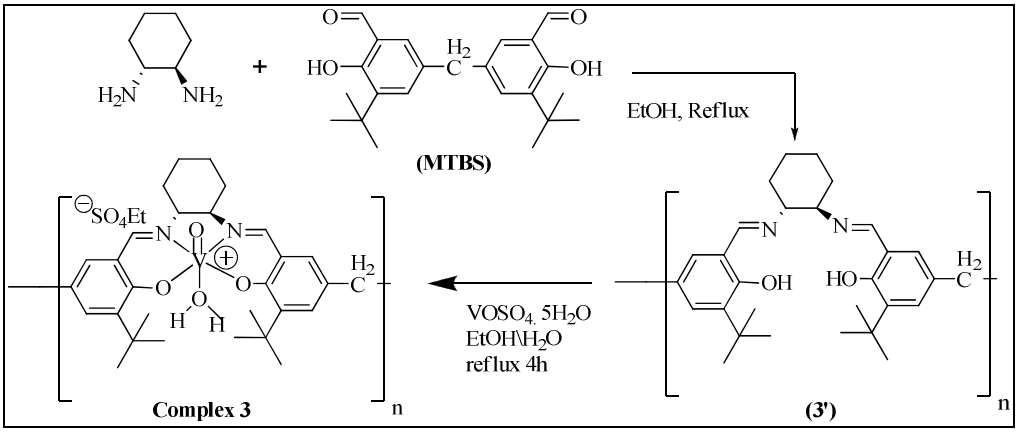
of repeating units and the approximate molecular weight was found to be n = ~12; M_n= ~5400; Yield. 84%; IR (KBr): 1620 ν(H-C=N) cm^{-1}; ^1H NMR ($CDCl_3$, 200MHz): δ 1.36 (s, 18H, *t*- butyl), 1.87 (m, 8H, cyclohexane), 3.29 (bm, 2H, asymmetric), 3.68 (s, 2H, methylene), 6.74 (d, 2H, aromatic, J_m = 2Hz), 7.05 (d, 2H, aromatic, J_m = 2Hz), 8.21 (s, 2H, azomethine), 13.77 (bs, 2H, OH) ppm. ^{13}C ($CDCl_3$, 50 MHz): δ 24.9, 30.0, 33.8, 35.4, 41.1, 73.0, 119.1, 130.1, 130.9, 137.7, 159.2, 166.1 ppm; Anal. Calcd. for ($C_{29}H_{40}N_2O_2$): C, 77.64; H, 8.98; N, 6.24, Found: C, 77.52; H, 8.93; N, 6.20%.

3.3.4 Poly[(*R,R*)-*N,N'*-bis-{3-methyl-5-methylene salicylidine} cyclohexane 1,2 -diamine] (4')

5,5'-methylene-di-methylsalicylaldehyde (**MMS**) (0.002 mol) was dissolved in methanol and 1*R,*2*R*-(-)-cyclohexanediamine (0.002 mol) was added under cold condition and the resulting mixture was refluxed for 6-8 h. After cooling a partial removal of the solvent from the reaction mixture precipitated out the desired chiral ligand in high yield. This ligand was re-crystallized with ethanol and characterized by micro analysis, IR, ^1H NMR and Vapour Pressure Osmometry (VPO). The number of repeating units and the approximate molecular weight was found to be n = ~12; M_n= ~4700; Yield. 84%; IR (KBr): 1620 ν(H-C=N) cm^{-1}; ^1H NMR ($CDCl_3$, 200MHz): δ 2.11 (s, 6H, methyl), 1.82 (m, 8H, cyclohexane), 3.32 (bm, 2H, asymmetric), 3.72 (s, 2H, methylene), 6.77 (d, 2H, aromatic, J_m = 2Hz), 7.15 (d, 2H, aromatic, J_m = 2Hz), 8.23 (s, 2H, azomethine), 13.81 (bs, 2H, OH) ppm. ^{13}C ($CDCl_3$, 50 MHz): δ 15.12, 41.1, 73.0, 119.1, 130.1, 130.9, 137.7, 159.2, 168.1 ppm; Anal. Calcd. for ($C_{24}H_{30}N_2O_2$): C, 76.16; H, 7.99; N, 7.40, Found: C, 76.12; H, 7.72; N, 7.38%.

3.3.5 Synthesis of polymeric Vanadium(V) salen complex 3

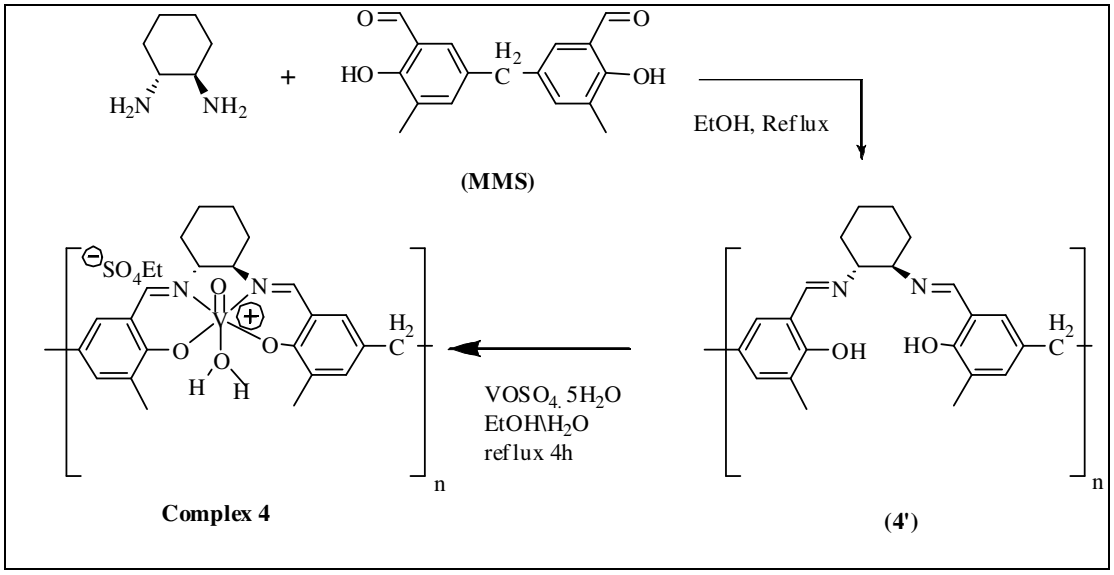
The ligand **3'** (0.80 g, 1.79 mmol) was dissolved in mixed solvent ethanol:CH_2Cl_2 (3:2, 15 ml) to which an aqueous solution of vanadyl sulphate hydrate (0.45 g, 1.79 mmol in 2 ml water) was added drop wise under an inert atmosphere at RT. The resulting solution was refluxed for 4 h and then cooled to room temperature with an extended stirring for 12 h while opening the side arm of the reaction flask. Solvent was completely evaporated and the residue was dissolved in CH_2Cl_2 (10 ml), washed with water (3 x 5ml) and finally with brine. The organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated to give polymeric V(V) salen complex **3**. (**Scheme 3.2**) Yield, 74%; m.p.: 204–210 °C; IR: (KBr): $\bar{\nu}$ = 3473, 2957, 2867, 1612, 1536, 1466, 1387, 1345, 1315, 216, 1177, 1030, 987, 887, 821, 789, 748, 714, 662, 567 $cm.^{-1}$; $[\alpha]_D^{27}$ = –204.6 (c = 0.05, CH_2Cl_2); λ_{max} (ε): 236 (45090), 404 (11680), 630 (2620); ^1H NMR (200 MHz, $CDCl_3$): δ = 0.85 (t, J = 7.2, 3H), 1.30 (s, 18H), 1.51–1.88 (m, 8H), 3.31 (q, J = 7.2, 2H), 3.39 (bs, 2H), 3.81 (m, 2H), 4.26 (m, 2H), 6.89–7.24 (m, 4H), 8.26 (bs, 2H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.4, 23.4, 26.2, 28.9, 30.0, 40.8, 63.6, 121.3, 126.4, 128.2, 132.0, 135.6, 160.6, 168.3. Anal. Calcd for $C_{31}H_{43}N_2O_8SV.^+$: C, 56.88, H, 6.57, N, 4.28. Found: C, 56. 92, H, 6.58, N, 4.30.



Scheme 3.2 Synthesis of the complex **3**

3.3.6 Synthesis of polymeric Vanadium(V) salen complex 4

The ligand **4'** (0.16 g, 0 .45mmol) was dissolved in mixed solvent ethanol:CH_2Cl_2 (3:2, 10 ml) to which an aqueous solution of vanadyl sulphate hydrate (0.12 g, 0.45mmol in 2 ml water) was added drop wise under an inert atmosphere at RT. The resulting solution was refluxed for 4 h and then cooled to room temperature with an extended stirring for 12 h while opening the side arm of the reaction flask. Solvent was completely evaporated and the residue was dissolved in CH_2Cl_2 (10 ml), washed with water (3 x 5ml) and finally with brine. The organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated to give polymeric V(V) salen complex **4**. Yield (**Scheme 3.3**), 69.5%; m.p.: 198–205°C; IR: (KBr): $\bar{\nu}$ =, 3398, 2924, 2853, 1617, 1561, 1466, 1381, 1312, 1262, 1163, 1031, 973, 934, 839, 746, 709, 626, 568, 462 $cm.^{-1}$; $[\alpha]_D^{27}$ = –591 (c = 0.05, CH_2Cl2); λ_{max} (ε): 248 (31512), 358 (10375), 650 (1138); ^1H NMR (200 MHz, $CDCl_3$): δ = 0.87 (t, J = 7.3, 3H), 1.25 (s, 6H), 1.60–1.85 (m, 8H), 3.30 (q, J = 7.1, 2H), 3.42 (m, 2H), 3.77 (bs, 2H), 4.26 (m, 2H), 6.76–7.24 (m, 4H), 8.22 (bs, 2H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.7, 24.8, 34.1, 28.9, 30.0, 40.8, 73.6, 118.8, 129.1, 132.3, 133.8, 135.5, 158.2, 165.1. Anal.Calcd for $C_{25}H_{31}N_2O_8SV.^+$: C, 52.63, H, 5.48, N, 4.91. Found: C, 52.60, H, 5.51, N, 4.89.



Scheme 3.3 Synthesis of the complex **4**

The polymeric V(V) salen complexes **3** and **4** were used for the enantioselective cyanation of aldehydes viz., using TMSCN and KCN as source of cyanide.

3.4 Procedure for Vanadium(V) polymeric salen complexes-catalyzed asymmetric

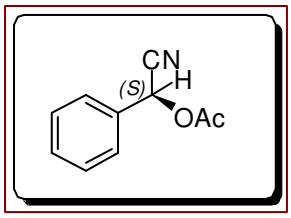
3.4.1 (A) Addition of Trimethylsilyl Cyanide to Aldehydes

Polymeric V(V) salen catalysts **3/4** (0.013 mmol) were dissolved in dry CH_2Cl_2 (3 ml) and the solution was stirred at room temperature under nitrogen atmosphere. To this solution benzaldehyde (0.12 ml, 1.25 mmol) was added, followed by the drop wise addition of TMSCN (0.33 ml, 2.50 mmol), the reaction was monitored by TLC, after the reaction was completed the mixture was concentrated and the product was purified by flash column chromatography on silica gel (eluted with hexane/ethylacetate = 95:5). The corresponding trimethylsilylether derivative of cyanohydrin was dissolved in MeOH (3 ml) and then 1N HCl (3 ml) was dropped to the mixture. The mixture was stirred vigorously at room

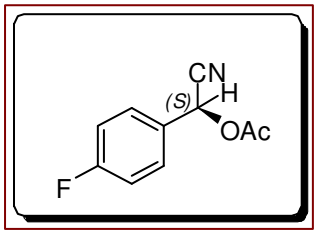
temperature for 4 h. The aqueous solution was then extracted with CH_2Cl_2, the combined organic layer was dried with anhydrous sodium sulfate. After evaporating the solvent, the corresponding cyanohydrins were obtained. The ee of the products was determined by using Chiralpak HPLC OD and AD column, after conversion to the corresponding acetate.

3.5 Characterization data of product

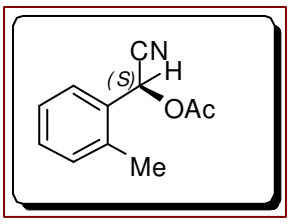
3.5.1 (*S*)**2-*O*-acetyl-2-phenyl acetonitrile (derived from 5a)** ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.11 (s, 3H), 6.38 (s, 1H), 7.40–7.52 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.8, 63.3, 116.7, 128.3, 129.7, 130.8, 132.3, 169.4; $[\alpha]_D^{27}$ = –31.5 (c = 1, CH_2Cl_2); TOF–MS (ESI+): *m/z* 160.2 $(M+H)^+$; HPLC analysis: Chiralpak OD column, hexane/isopropanol = 99:1, Flow rate 0.8 ml/min, Rt_1 =19.61 min (minor), Rt_2 = 21.88 min (major).



3.5.2 ***(S)-2-O*-acetyl-2-(4-flourophenyl) acetonitrile (derived from 5b)** ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.16 (s, 3H), 6.39 (s, 1H), 7.09–7.18 (m, 2H), 7.49–7.55 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.0, 68.8, 116.7, 117.2, 129.4, 130.6, 160.9, 169.5; $[\alpha]_D^{27}$ = –20.2 (c = 1, CH_2Cl_2); TOF–MS (ESI+): *m/z* 195.19 (M+H); HPLC analysis: Chiralpak AD column, hexane/isopropanol = 99:1, Flow rate 0.8 ml/min, Rt_1 = 19.68 min(minor), Rt_2 = 21.44 min (major).

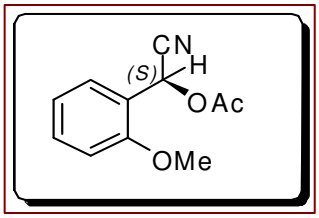


3.5.3 ***(S)-2-O*-acetyl-2-(2-methylphenyl) acetonitrile (derived from 5c)** ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.17 (s, 3 H), 2.43 (s, 3H), 6.51 (s, 1H), 7.23–7.58 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.6, 21.0, 61.7, 113.2, 127.5, 129.2, 130.8, 131.2, 132.0, 138.2,



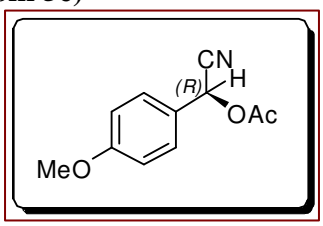
169.0; $[\alpha]_D^{27}$ = –26.2 (c = 1, CH_2Cl_2); TOF–MS (ESI+): *m/z* 191.03 $(M+H)^+$; HPLC analysis: Chiralpak AD column, hexane/isopropanol = 99:1, Flow rate 0.8 ml/min, Rt_1 = 17.48 min(major), Rt_2 = 22.13 min (minor).

3.5.4 *(S)*-2-*O*-acetyl-2-(2-methoxyphenyl) acetonitrile (derived from 5d)



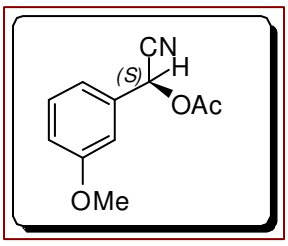
^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.13 (s, 3 H), 3.85 (s, 3H), 6.68 (s, 1H), 6.91–7.57 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.8, 56.2, 68.6, 111.7, 116.8, 121.2, 129.2, 132.3, 157.3, 169.3; $[\alpha]_D^{27}$ = –25.6 (c = 1, CH_2Cl_2); TOF–MS (ESI+): m/z 207.14 $(M+H)^+$; HPLC analysis: Chiralpak OD column, hexane/isopropanol = 99:1, Flow rate 0.8 ml/min, Rt_1 = 19.90 min(major), Rt_2 = 22.41 min(minor).

3.5.5 *(S)*-2-*O*-acetyl-2-(4-methoxyphenyl) acetonitrile (derived from 5e)



^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.14 (s, 3H), 3.83 (s, 3H), 6.35 (s, 1H), 6.94 (d, *J* = 8.75, 2H), 7.44 (d, *J* = 8.90, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.5, 56.1, 63.3, 115.1, 115.3, 130.3, 132.6, 161.9, 169.7; $[\alpha]_D^{27}$ = –24.4 (c = 1, CH_2Cl_2); TOF–MS (ESI+): *m/z* 207.18 $(M+H)^+$; HPLC analysis: Chiralpak OD column, hexane/isopropanol = 99:1, Flow rate 0.8 ml/min : Rt_1 = 28.41min(minor), Rt_2 = 32.71min (major).

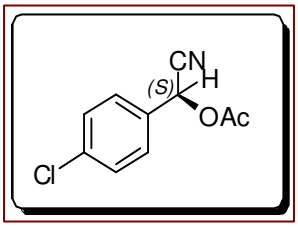
3.5.6 *(S)*-2-*O*-acetyl-2-(3-methoxyphenyl) acetonitrile (derived from 5f)



^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.16 (s, 3H), 3.83 (s, 3H), 6.37 (s, 1H), 6.96–7.39 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.0, 56.1, 63.3, 113.9, 116.6, 120.5, 130.9, 133.7, 160.8, 169.5; $[\alpha]_D^{27}$ = –23.1 (c = 1, CH_2Cl_2); TOF–MS (ESI+): *m/z* 207.38 $(M+H)^+$; HPLC analysis:

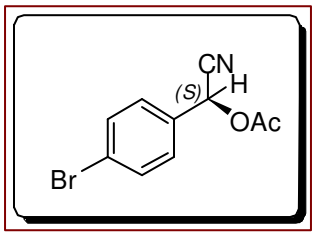
Chiralpak OD column, hexane/isopropanol = 99:1, Flow rate 0.8 ml/min : Rt_1 = 27.38 min(minor), Rt_2 = 35.05min (major).

3.5.7 *(S)-2-O*-acetyl-2-(4-cholophenyl) acetonitrile (derived from 5g)



^{1}H NMR (200 MHz, CDCl3): δ 2.15 (s, 3 H), 6.25 (s, 1 H), 7.39 (d, J = 8.70, 2H), 7.46 (d, J = 8.56, 2H); ^{13}C NMR (50 MHz, CDCl3): δ = 20.8, 62.6, 116.7, 129.7, 129.9, 130.9, 132.9, 169.2; $[\alpha]_D^{27}$ = –10.2 (c = 1, CH_2Cl_2); TOF–MS (ESI+): m/z 211.20 $(M+H)^+$; HPLC analysis: Chiralpak OD column, hexane/isopropanol = 99:1, Flow rate 0.8 ml/min, Rt_1 = 27.41 min(minor), Rt_2 = 31.91 min (major).

3.5.8 *(S)-2-O*-acetyl-2-(4-bromophenyl) acetonitrile (derived from 5h) ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.16 (s, 3H), 6.36 (s, 1H), 7.36 (d, J = 8.52, 2H), 7.58 (d, J = 8.38, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.0, 62.8, 116.3, 125.5, 129.4, 131.0, 133.1, 169.3; $[\alpha]_D^{27}$ = –11.6 (c = 1, CH_2Cl_2); TOF–MS (ESI+): m/z 153.10 $(M+H)^+$; HPLC analysis: Chiralpak OD column, hexane/isopropanol = 99:1, Flow rate 0.8 ml/min, Rt_1 = 31.33 min(minor), Rt_2 = 37.01 min (major).



3.5 Recycling of the catalyst

At the end of the catalytic run (checked on TLC) the solvent was completely removed under reduced pressure. The residue was extracted with hexane to remove the reactants. The remaining solid was further washed with hexane (10 ml), dried under reduced pressure at 50 $^{\circ}$C for 1–2h and was used as recovered catalyst for recycle experiments of cyanation of 2-methyl benzaldehyde.

3.6 Results and discussion

The catalytic asymmetric addition of trimethylsilyl cyanide to benzaldehyde **(3a),** 4-fluorobenzaldehyde (**3b**), 2-methylbenzaldehyde (**3c**) and 2-methoxybenzaldehyde (**3d**) as representative substrates was carried out at room temperature using the complexes **3** and **4** as catalysts **(**data given in **Table 3.1)**. ^{1}H and ^{13}C NMR data has shown the exclusive formation of the product **4a–d** with no detectable amount of enolized product (data given in experimental section). The data shown in **Table 3.1** revealed that the present catalytic protocol can be applied to a range of substrates. Both the catalysts gave excellent to good conversions with all substrates (Entries 1-8) with high enantiomeric excess for the substrate **3c** (Entries 5, 6) in 18 h as shown by their turn over frequency (TOF) values (**Table 3.1**). The overall performance of complex **3** is better than complex **4.** The complex **3** was further explored for catalytic asymmetric addition of trimethylsilyl cyanide to different aromatic aldehydes viz. 4-methoxybenzaldehyde (**3e**), 3-methoxybenzaldehyde (**3f**), 4-chlorobenzaldehyde (**3g**), 4-bromobenzaldehyde (**3h**), 4-methylbenzaldehyde (**3i**), *n*-butylaldehyde (**3j**), *t*-butylaldehyde (**3k**), *iso*-butylaldehyde (**3l**) in order to see the effect of the substituents and their position on benzaldehyde derivatives on the enantioselectivity at room temperature whereby the trimethylsilylether derivatives of the corresponding cyanohydrins (**4e-i**) are formed as shown in **Table 3.1.**

Electron withdrawing substituents such as F, Cl, Br on aromatic ring gave moderate enantioselectivity (**Table 3.1**, Entries 3, 11, 12) while electron donating groups such as MeO and Me favors the enantioselectivity (**Table 3.1**, Entries 5, 7, 9, 10, 13) as shown in **Figure 3.1**. Further, *o*-substituted (Me, MeO) gave high enantiomeric excess (**Table 3.1**, Entries 5, 6, 7) than that of *p*-substituted benzaldehydes (**Table 3.1**, Entries 9, 10). This finding

indicates that not only electronic effect but also the position of substituents has a decisive role on the enantioselectivity of the reaction. The best enantio-induction (ee, 96%) was obtained with *o*-methylbenzaldehyde (**Table 3.1,** Entry 5). On conducting the cyanation reaction with aliphatic aldehyde, viz., *n*-butylaldehyde (**3j**), *t*-butylaldehyde (**3k**), *iso*-butylaldehyde (**3l**) in presence of trimethylsilyl cyanide (**Table 3.1**, Entries 14–16) at room temperature, 94–99% conversion with 81–85% ee of respective cyanosilylether was achieved in the case of *n*-butylaldehyde and *t*-butylaldehyde (**Table 1,** Entries 14, 15) respectively in 18 h. While with 3-methylbutarldehyde as substrate only moderate conversion (76%) and ee (79%) was achieved (Entry 16). In all catalytic runs *R* form of polymeric V(V) salen complexes converted aldehydes into (*S*)-cyanohydrins. These results are in consonance with earlier reports in literature.[39]

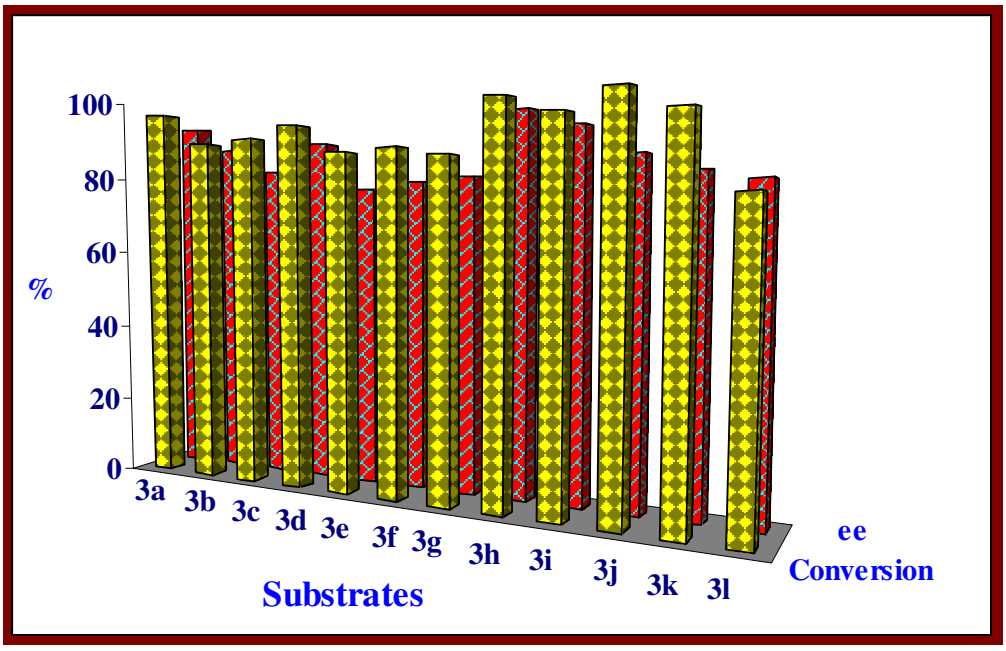
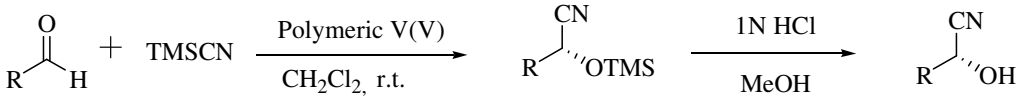


Figure 3.1 3D view showing the % conversion and % ee of trimethylsilylether derivatives of cyanohydrin of different aldehydes

The reactivity and enantioselectivity of cyanation reaction is strongly dependent on the nature of the solvent used.[21] Therefore, catalytic enantioselective cyanation reactions were conducted in different solvents such as dichloromethane, 1,2-dichloroethane, toluene and THF using benzaldehyde as representative substrate with catalyst **3** under identical reaction conditions.

Table 3.1 Enantioselective addition of trimethylsilyl cyanide to various aldehydes catalyzed by polymeric V(V) salen complexes **3** and **4**



3a-l **4a-l** **5a-l**

3a; R = phenyl **3b**; R = 4-fluoro phenyl **3c**; R = 2-methyl phenyl
3d; R = 2-methoxy phenyl **3e**; R = 4-methoxy phenyl **3f**; R = 3-methoxy phenyl
3g; R = 4-chloro phenyl **3h**; R = 4-bromo phenyl **3i**; R = 4- methyl phenyl
3j; R = n-butyl **3k**; R = *t*-butyl **3l**; R = *iso*-butyl

Entry	Substrate	Time [h]	Conversion [%][a]	ee [%][b]	TOF [h^{-1}][c]
1(2)[d]	**3a**	18	97(80)	94(58)	5.38(4.44)
3(4)	**3b**	18	85(70)	80(48)	4.72(3.88)
5(6)	**3c**	18	98(92)	96(89)	5.44(5.11)
7(8)	**3d**	18	93(88)	89(35)	5.16(4.88)
9	**3e**	18	85	86	4.72
10	**3f**	18	89	82	4.94
11	**3g**	18	86	77	4.77
12	**3h**	18	88	79	4.88
13	**3i**	18	94	92	5.22
14	**3j**	18	99	85	5.50
15	**3k**	18	94	81	5.22
16	**3l**	18	76	79	4.22

All the reactions were carried out at room temperature.
[a]The conversion was determined based on G. C. integral area. [b]The ee was determined by using Chiralpak HPLC OD and AD column, after conversion to the corresponding acetate. [c]TOF = [Product]/[Catalyst]x time (h).[d] Results in parenthesis are for catalyst **4.**

Good conversion (88%) with good enantioselectivity was obtained with 1,2-dichloroethane (**Table 3.2**, Entry 18) but on using THF and toluene as solvent the conversion was (78–65%) with ee (65–70%) (**Table 3.2**, Entries 19, 20). The best results of the model reaction was achieved in dichloromethane (**Table 3.2,** Entry 17) (**Figure 3.2**).

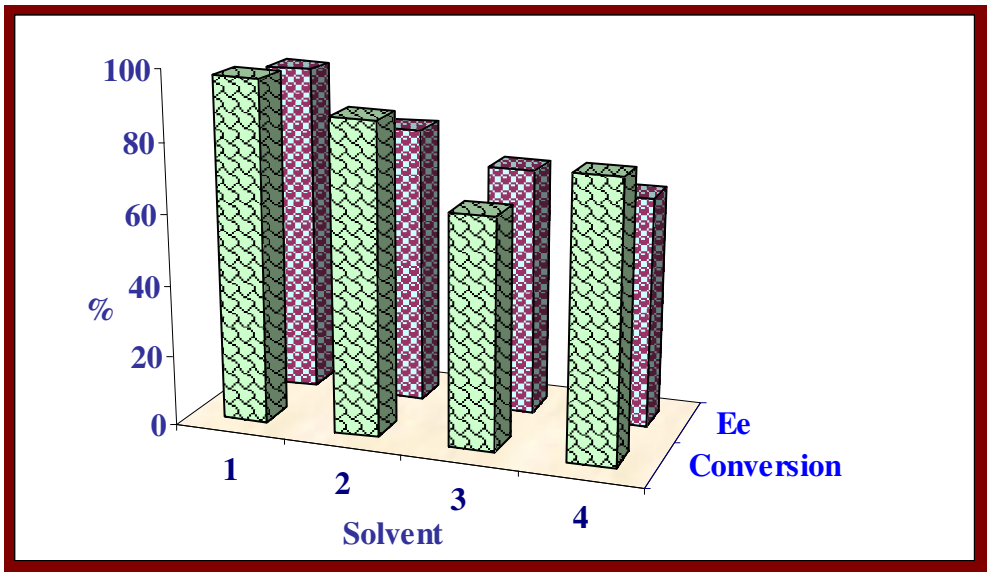


Figure 3.2 3D view showing % conversion and % ee of trimethylsilylether derivative of cyanohydrin in different solvents

Table 3.2 Data for the effect of solvents on conversion and ee of enantioselective addition of trimethylsilyl cyanide to benzaldehydes, catalyzed by recovered chiral polymeric V(V) salen complex **3**

Entry	Solvent	Conversion [%][a]	ee [%][b]
17	dichloromethane	97	94
18	1,2-dichloroethane	88	79
19	toluene	65	70
20	THF	78	65

All the reaction were carried out at room temperature.
[a]The conversion was determined based on G. C. integral area. [b]The ee was determined by using Chiralpak HPLC OD column, after conversion to the corresponding acetate.

It has been reported in the literature that the use of additive greatly influence the reactivity and enantioselectivity of asymmetric cyanation reaction.[40-46] Therefore, tri-phenylphosphine, tri-phenylphosphine oxide, tri-ethylamine, pyridine, pyridine *N*-oxide, 4-phenyl pyridine *N*-oxide (5 mol%) were tested as additive for their influence on asymmetric cyanation of benzaldehyde as representative substrate with catalyst **3** and the data are given in **Table 3.3**. The use of *O*-coordinating additives gave better results in term of reaction time with little improvement in conversion and retention of enantioselectivity (**Table 3.3**, Entries 22–24) than the above mentioned other additives viz., triphenylphosphine, triethyamine and pyridine (**Table 3.3,** Entries 21, 25, 26). The additive quantity was also varied using 4-phenyl pyridine *N*-oxide (1–10 mol%) as representative additive with benzaldehyde as substrate under identical condition and data are given in **Table 3.3.** On using 4-phenyl pyridine *N*-oxide (10 mol%) the catalytic reaction completes in 6h with slight improvement in ee (Entry 27). On the contrary, decreasing the amount of additive from 2.5 mol% to 1 mol% there was no improvement in the conversion and ee of trimethylsilylether derivative of cyanohydrin

(**Table 3.3**, Entries 28, 29). Thus, the use of 5 mol% additive is proved to be optimal (**Table 3.3**, Entry 24).

The reaction temperature and catalyst loading were also found to be crucial factors for the optimization of parameters for enantioselective cyanation reaction. The cyanation reaction at rt using benzaldehyde as representative substrate led to excellent conversion (97%) with 94% ee (**Table 3.4,** Entry 30). Lowering the temperature from rt

Table 3.3 Data for the effect of additives on conversion and ee of enantioselective addition of trimethylsilyl cyanide to benzaldehydes, catalyzed by polymeric chiral V(V) salen complex **3**

Entry	Additives	Mol[%]	Time [h]	Conversion [%][a]	ee [%][b]
21	triphenylphosphine	5	12	90	69
22	triphenylphosphine oxide	5	12	99	94
23	pyridine-*N*-oxide	5	12	99	94
24	4-phenyl pyridine-*N*-oxide	5	12	99	94
25	pyridine	5	12	75	78
26	triethylamine	5	12	85	36
27	4-phenyl pyridine-*N*-oxide	10	6	99	95
28	4-phenyl pyridine-*N*-oxide	2.5	17	96	94
29	4-phenyl pyridine-*N*-oxide	1	18	96	94

All the reactions were carried out at room temperature.
[a] The conversion was determined based on G. C. integral area.[b] The ee was determined by using Chiralpak HPLC OD column, after conversion to the corresponding acetate.

Table 3.4 Data for the effect of catalyst loading and temperature on conversion and ee of trimethylsilylether derivative of cyanohydrin using benzaldehyde as representative substrate with catalyst **1**

Entry	Catalyst loading [mol%]	Temp. [^{o}C]	Conversion [%][a]	ee [%][b]
30	5	RT	97	94
31	5	–20	71	95
32	1	45	58	63
33	1	RT	97	90
34	0.1	RT	89	88

All the reactions were carried out at room temperature.
[a] The conversion was determined based on G. C. integral area. [b] The ee was determined by using chiralpak HPLC OD, after conversion to the corresponding acetate.

to –20 ^{0}C, there was significant increase in the reaction time with lower yield (71%) (**Table 3.4,** Entry 31) and marginal increase in the ee (95%) of the product. An increase in reaction temperature to 45 $^{\circ}$C resulted in a detrimental effect to the reaction due to the instability of adduct trimethylsilylether (**Table 3.4,** Entry 32). Attempts to reduce the catalyst loading from 1 mol% to 0.1 mol% (Entries 33, 34) gave 89% conversion of trimethylsilylether with 88 % ee (**Table 3.4,** Entry 34).

Table 3.4 Data for the effect of catalyst loading and temperature on conversion and ee of trimethylsilylether derivative of cyanohydrin using benzaldehyde as representative substrate with catalyst **1**

Entry	Catalyst loading [mol%]	Temp. [^{o}C]	Conversion [%][a]	ee [%][b]
30	5	RT	97	94
31	5	–20	71	95

32	1	45	58	63
33	1	RT	97	90
34	0.1	RT	89	88

All the reactions were carried out at room temperature.
[a] The conversion was determined based on G. C. integral area. [b] The ee was determined by using chiralpak HPLC OD, after conversion to the corresponding acetate.

3.6.1 Kinetic studies

In order to understand the mechanism of cyanation reaction, kinetic experiments were performed with benzaldehyde as a representative substrate as a function of the concentrations of catalyst **3**, benzaldehyde and TMSCN. In all the kinetic runs the plots of formation of cyanosilylether from the cyanation of benzaldehyde with time was found to be linear in beginning of the reaction which attained saturation (conversion >99%) near completion (**Figure 3.3**). Based on this observation, the initial rate constants K_{obs} (up to the linear portion of the graph) were determined by directly estimating the amount of cyanosilylether formed up to completion of the reaction.

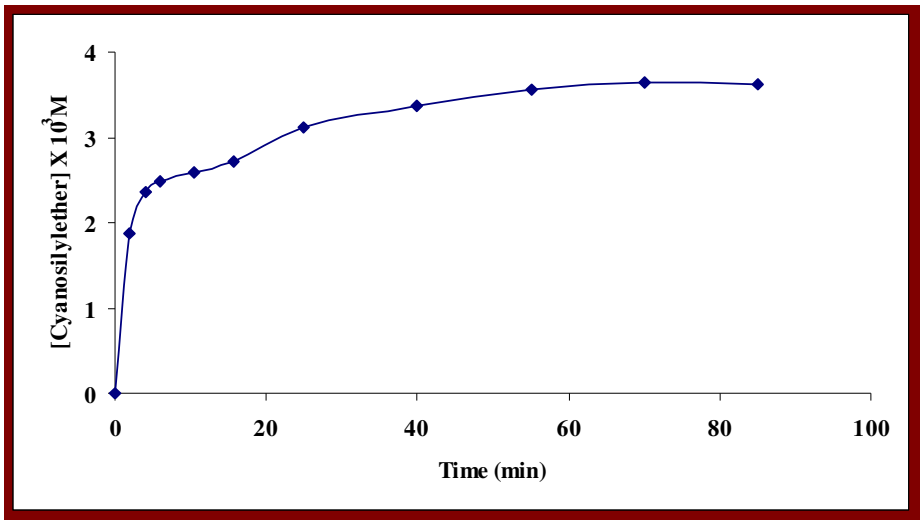


Figure 3.3 Time dependent plot of the formation of trimethylsilylether at room temperature, [catalyst **3**] = 3.0×10^{-3} M, [benzaldehyde] = 399.3×10^{-3}M, [TMSCN] = 1118.3×10^{-3}M

3.6.2 Dependence of the rate on catalyst concentration

The cyanation of benzaldehyde was studied at rt by conducting the kinetic experiments at different concentration of the catalyst **3** [1.5x10^{-3}M–12.2x10^{-3}M] at constant concentration of benzaldehyde [399.3x 10^{-3}M] and TMSCN [1118.3x 10^{-3}M]. From the kinetic data a linear plot of K_{obs} of the cyanosilylether formation versus log[catalyst] with unit slopes (*d* log K_{obs}/ *d* log [catalyst] = 1) was obtained which passes through the origin, indicating that the reaction is first order with respect to the concentration of the catalyst (**Figure 3.4**).

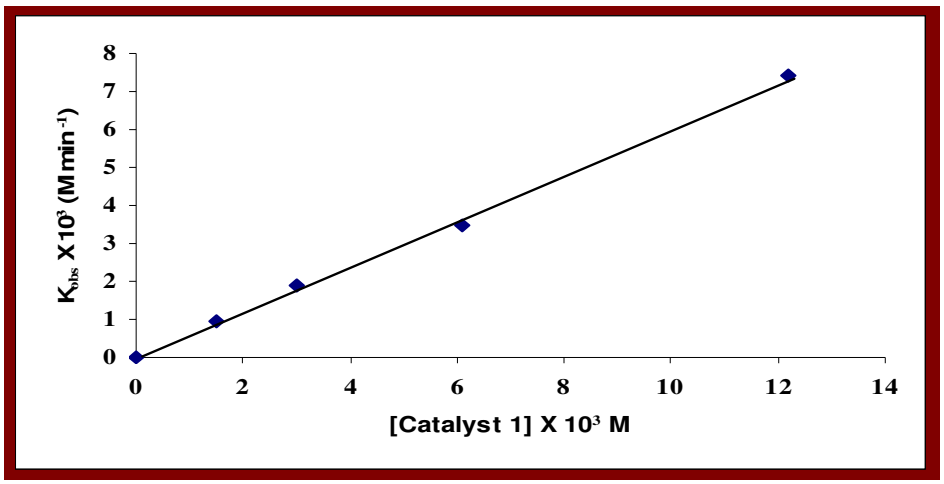


Figure 3.4 Plot of catalyst **3** versus K_{obs} at rt, [Benzaldehyde] = 399.3 x 10^{-3}M and [TMSCN] = 1118.3 x 10^{-3}M

3.6.3 Dependence of the rate on benzaldehyde concentration

Kinetic experiments were carried out at different initial concentration of benzaldehyde ranging from (198.1 x 10^{-3}M–1597.4 x 10^{-3}M) by keeping the concentration of other reactants and physical conditions constant from which the rate was calculated and the plot of rate constant (K_{obs}) versus the concentration of benzaldehyde (*d* log K_{obs}/ *d* log [benzaldehyde] ~1) also showed the first dependence of the reaction on the substrate concentration (**Figure 3.5**).

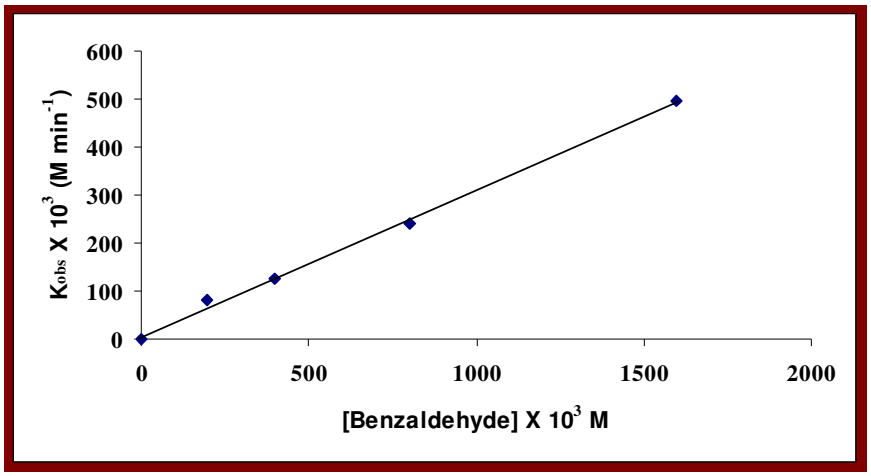


Figure 3.5 Plot of Benzaldehyde versus K_{obs} at rt, [Catalyst] = 3.0 x 10^{-3}M and [TMSCN] = 1118.3 x 10^{-3}M

3.6.4 Dependence of the rate on TMSCN concentration

The effect of concentration of the TMSCN over the range of (557.7 x 10^{-3}M–4475.3 x 10^{-3}M) on the rate of cyanation of the benzaldehyde were studied, keeping the catalyst [3.0 x 10^{-3}M] and benzaldehyde [399.3 x 10^{-3}M] concentration as constant which indicated a zero order dependence in terms of the concentrations of TMSCN. The zero order kinetics for cyanosilylation in term of concentration of TMSCN has been observed earlier[47] (**Figure 3.6**).

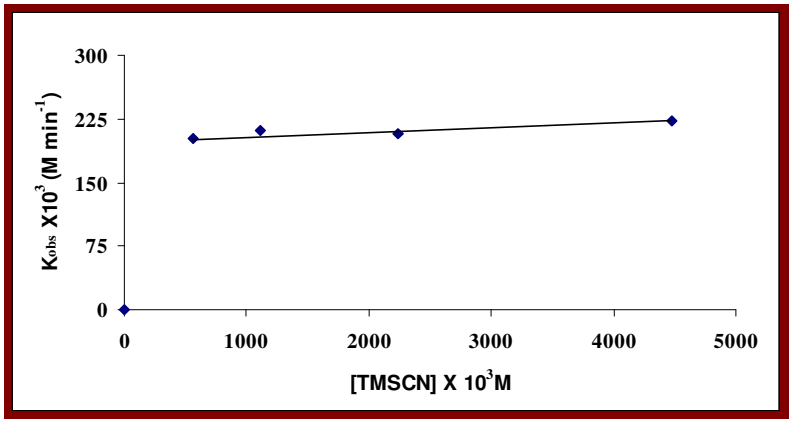
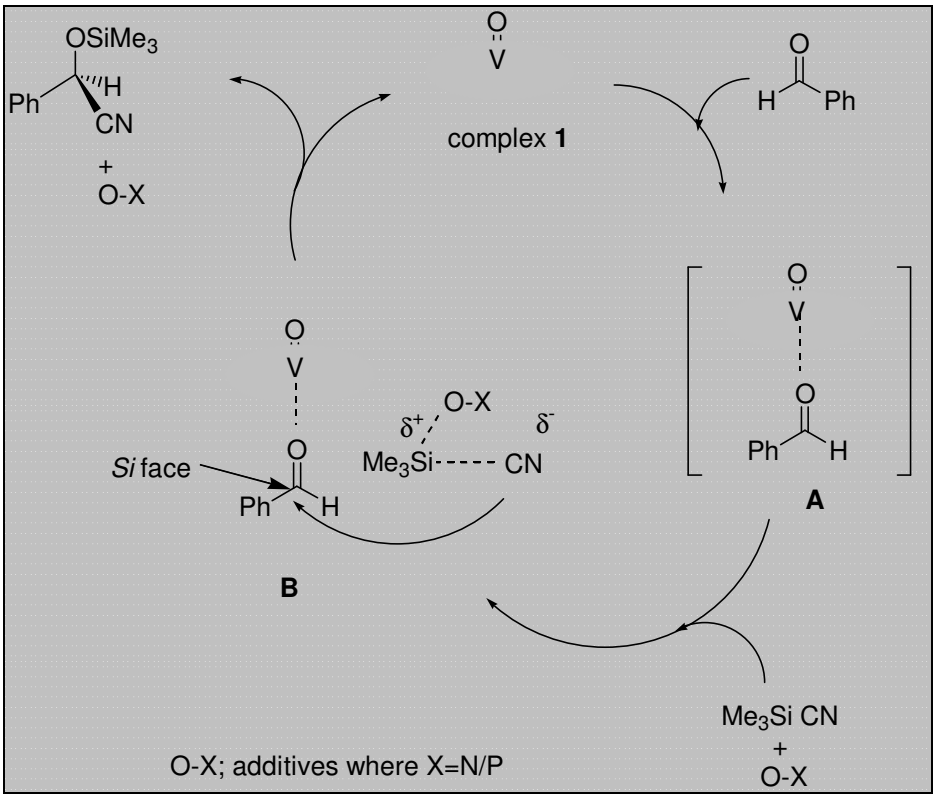


Figure 3.6 Plot of TMSCN versus K_{obs} at rt, [Catalyst] = 3.0 x 10^{-3}M and [Benzaldehyde] = 399.3 x 10^{-3}M

On the basis of kinetic data (**Table 3.5**) it is evident that the reaction is first order with respect to the complex and the substrate benzaldehyde and zero order with respect to TMSCN. A probable mechanism is shown in **Scheme 3.4** where in the presence of an Lewis acidic complex the activation of substrate, benzaldehyde takes place to form an intermediate **A** in a rate determining step. This intermediate reacted in a fast step with polarized TMSCN guided by the chiral environment of the catalyst **3** to produce trimethylsilyl ether of respective cyanohydrin.

Table 3.6 Concentration dependent kinetics data for the cyanation of benzaldehyde at RT

Reactants	**[concentration] x 10^3M**	**k_{obs} x 10^3M min^{-1}**
Catalyst	1.5	0.95
	3.0	1.89
	6.1	3.47
	12.2	7.44
Benzaldehyde	198.1	81
	399.3	127
	798.7	239
	1597.4	495
TMSCN	557.7	201
	1118.3	212
	2237.6	208
	4475.3	222



Scheme 3.4 Probable mechanism for cyanosilylation of aldehyde

The interesting feature of this novel polymeric V(V) salen complex **3** lies in its inherent tendency to precipitate in a non polar solvent like hexane due to its higher molecular weight and lower solubility in the reaction medium. After one catalytic cycle the polymeric catalyst was recovered and re-used for the subsequent runs of cyanosilylation of 2-methyl benzaldehyde as representative substrate by adding fresh reactants. From the data in **Table 3.7** it is evident that the catalyst **3** worked well up to four cycles with small decrease in reactivity due to some physical loss during post work up process with retained enantioselectivity of trimethylsilylether of cyanohydrin.

Table 3.7 Enantioselective addition of trimethylsilyl cyanide to 2-methylbenzaldehyde catalyzed by polymeric chiral V(V) salen complex.

Run	**1**	**2**	**3**	**4**

Time[h]	18	20	20	20
Conversion[%][a]	98	98	96	94
ee [%][b]	96	96	96	96

All the reactions were carried out at room temperature.
[a]The conversion was determined based on G. C. integral area. [b] The ee was determined by using Chiralpak HPLC OD column, after conversion to the corresponding acetate.

3.7 (B) KCN as a source of cyanide

In Chapter **2** the Dimeric V(V) and Ti(IV) salen complex were used as effective catalysts for the Cyanation of aldehydes using KCN and NaCN as source of Cyanide while in this Chapter we have used polymeric V(V) salen complex **3** for the cyanation of aldehydes using KCN as source of cyanide.

3.7.1 Procedure for vanadium (V) polymeric salen-catalyzed asymmetric *O*-acetylcyanation of aldehydes

V(V)-polymeric salen catalyst **3** (0.05 g, 0.10 mmol) (with respect to single salen unit) was dissolved in dry CH_2Cl_2 (3 ml) and the solution was cooled to –20 °C. Dry CH_2Cl_2 (2 ml), *t*-BuOH (0.2 ml, 2 mmol), H_2O (20 µl, 1.1mmol), appropriate aldehyde **2a-2i** (1.98 mmol) and Ac_2O (0.75 ml, 7.92 mmol) were then added to the solution in that order. The addition of KCN (0.56 g, 7.92 mmol) was done slowly during 2h followed by the addition of dry CH_2Cl_2 (3 ml). After the reaction was completed (as detected by TLC), the reaction mass was washed with water (3 x 5 ml) followed by brine, the organic layer was separated, and dried over anhydrous Na_2SO_4. The solution was filtered, evaporated and compound was purified by flash column chromatography on silica gel (eluted with hexane/ethylacetate = 95:5). The enantiomeric excess of the product *O*-acetylcyanohydrins was determined by HPLC using Chiralpak OD and AD column.

3.8 Results and discussion

The complex **3** was used as an active catalyst for the asymmetric addition of potassium cyanide in the presence of acetic anhydride at –20 °C to benzaldehyde as a model substrate using KCN as a source of cyanide that gave exclusively the product **3a** as confirmed by ^{1}H and ^{13}C NMR with no trace of enolized cyanohydrin (data given in experimental section). It has been reported in the literature that substituents on benzaldehyde derivatives had some influence on the reactivity and enantioselectivity of *O*-acetylcyanohydrin. Therefore, asymmetric addition of potassium cyanide to various aldehydes viz., benzaldehyde (**2a**), 4-methoxybenzaldehyde (**2b**), 3-methoxybenzaldehyde (**2c**), 2-methoxybenzaldehyde (**2d**), 4-chlorobenzaldehyde (**2e**), 4-bromobenzaldehyde (**2f**), 4-fluorobenzaldehyde (**2g**), 2-methylbenzaldehyde (**2h**), 4-methylbenzaldehyde (**2i**) was carried out and data are given in **Table 3.7**. Excellent conversions to *O*-acetylcyanohydrin (95–99%) (**Table 3.7**, Entries 1, 5–9) were obtained for most of the aldehydes in 9 h as shown by the turn over frequency (TOF) values. However, methoxy substituted aldehydes (**Table 3.7**, Entries 2–4) have shown relatively less conversions to *O*-acetylcyanohydrin (90%). The lower conversions for 4-methoxy benzaldehyde has also been reported with dimeric/non-recyclable ploymeric V(V) salen complexes.[11,48] On carrying out the cyanation reaction with aliphatic aldehyde such as valeraldehyde in the presence of KCN and acetic anhydride at −20 °C, 90% conversion with 90% ee of *O*-acetylcyanohydrin was achieved in 9 h.

In order to compare the reactivity of monomeric V(V) complex and polymeric V(V) salen complex **3,** we have conducted the kinetic reaction for cyanation of benzaldehyde as representative substrate using KCN as source of cyanide at −20 °C. At the beginning of cyanation reaction, the kinetic runs found to be fast (**Figure 3.7**). The initial rate constant k_{obs}

were determined by directly estimating the amount of *O*-acetylcyanohydrin formed up to completion of the reaction which gave the k_{obs} value $106.9x10^{-3}$ M/h for complex **3** while for monomeric V(V) salen complex this value was found to be $55.5x10^{-3}$ M/h suggesting that in polymeric V(V) salen complex the active catalytic sites do not operate in isolation but interact.

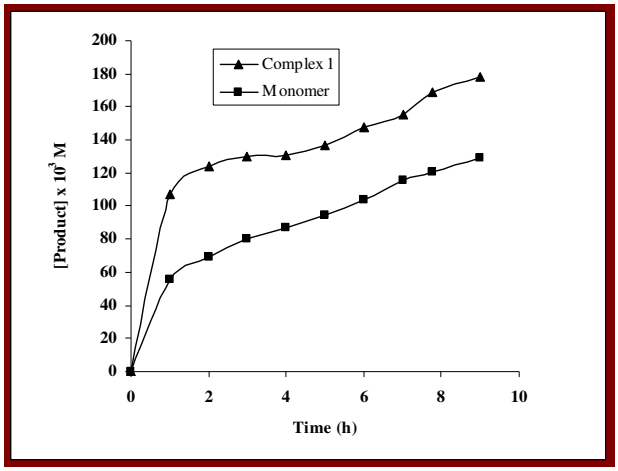
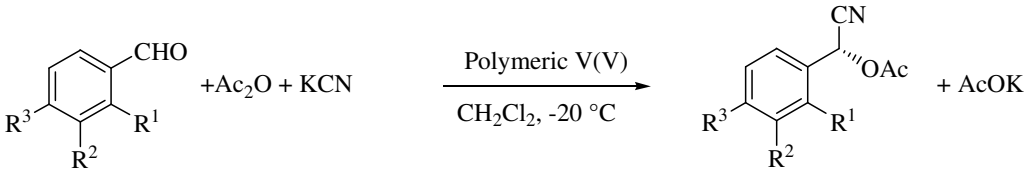


Figure 3.7 Time dependent plot of the formation of *O*- acetylcyanohydrin at –20 °C, [catalyst **3] =**$7.6x10^{-3}$ M, [benzaldehyde] = $198.1x10^{-3}$M, [KCN] = $789.4x10^{-3}$M

Table 3.7 Enantioselective synthesis of the *O*-acetylcyanohydrin from various aldehydes, potassium cyanide and acetic anhydride catalyzed by polymeric V(V) complex **3**



2a; R^1 = H, R^2 = H, R^3 = H
2b; R^1, R^2 = H, R^3 = OMe
2c; R^1 = H, R^2 = OMe, R^3 = H
2d; R^1 = OMe, R^2 = H, R^3 = H
2e; R^1 = H, R^2 = H, R^3 = Cl
2f; R^1 = H, R^2 = H, R^3 = Br
2g; R^1 = H, R^2 = H, R^3 = F
2h; R^1 = Me, R^2 = H, R^3 = H
2i;R^1 = H,R^2 = H,R^3 = Me

3a-i

Entry	Substrate	Time [h]	Conversion [%][a]	Ee [%][b]	TOF[c] [h-1]	Config.
1	2a	9	95	91	2.11	*S*
2	2b	9	90	82	2.00	*S*
3	2c	9	91	89	2.02	*S*
4	2d	9	91	88	2.02	*S*
5	2e	9	98	90	2.17	*S*
6	2f	9	99	89	2.20	*S*
7	2g	9	98	92	2.17	*S*
8	2h	9	99	96	2.20	*S*
9	2i	9	96	93	2.13	*S*

All the reactions were carried out at –20 °C.
[a] The conversion of *O*-acetylcyanohydrin was determined based on G. C. integral area.
[b] The ee was determined by using Chiralpak HPLC OD and AD column [c] TOF = [product]/[catalyst]x time(h^{-1}) TOF is based on monomeric salen unit.

The recovered catalyst **3** was reused by adding fresh substrates and reactants in the similar manner as in the case with fresh catalyst. After each use the catalyst was precipitated by the addition of hexane to the reaction mixture, the precipitated catalyst was dried in vacuum and was used without further purification. The data of four reuse experiments with complex **3** as catalyst is given in **Table 3.8**. The activity of the recycled catalysts gradually decreased upon successive use. As there was no observable loss in enantioselectivity the loss in activity can possibly due to some physical loss of the catalyst and not due to the degradation of the catalyst under the reaction conditions used in these experiments. The

recyclability of this catalytic system has clear edge over previously reported polymeric V(V) salen complexes[11].

Table 3.8 Data for enantioselective synthesis of the *O*-acetylcyanohydrin with benzaldehyde, KCN and acetic anhydride catalyzed by recovered polymeric chiral V(V) complex **3**

Run	**1**	**2**	**3**	**4**	**5**
Time[h]	9	9	9	9	9
Conversion[%][a]	95	90	88	86	84
Ee[%][b]	91	91	91	91	91

All the reactions were carried out at – 20 ^{o}C.
[a]The conversion of *O*-acetylcyanohydrin was determined based on G C integral area.
[b]The ee was determined by Chiralpak HPLC OD column and compared with literature.[4]

3.9 Conclusion

Chiral polymeric Vanadium (V) salen complexes **3** and **4** were tested for the asymmetric cyantion of various aromatic and aliphatic aldehydes using TMSCN and KCN as a source of cyanide at room temperature and -20 ^{0}C respectively. The catalyst 3 performed very well with 2-methyl benzaldehyde by giving excellent yield of trimethylsilylether of cyanohydrins up to (98%) with high chiral induction (96%) in 18h using TMSCN as a source of cyanide and in case of KCN as a source of cyanide 99% conversion and 96% ee of cyanoester of 2-methyl benzaldehyde were achieved within 9h. The system turned out to be an efficient recyclable system in term of reactivity and enantioselectivity. The catalyst was recovered after first use and recycled four times with retention of enantioselectivity.

3.10 References

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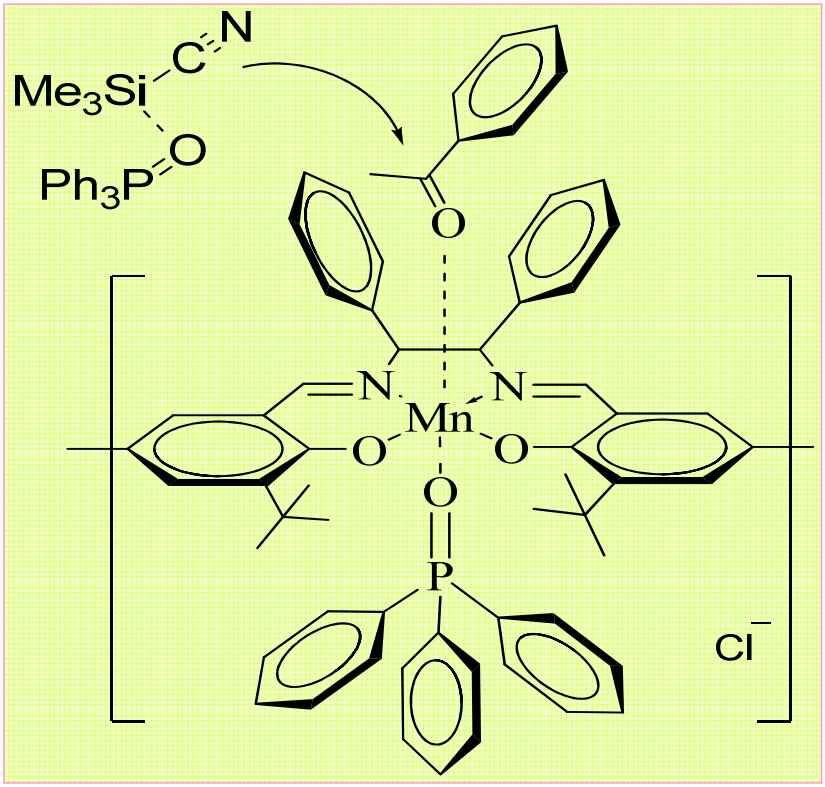
Chapter-4



Dimeric and Polymer Mn(III) salen complex as a Recyclable Catalyst for the cyanation of ketones using Trimethylsilylcyanide as source of cyanide.

4.1 Introduction

Unlike aldehydes, the reactivity of the carbonyl group in ketones is affected by greater steric hindrance and lower electrophilicity. Despite this inherent problem, the area has received considerable attention as a consequence of the synthetic utility of homochiral cyanohydrins of ketones. The first chemically catalyzed system for the asymmetric cyanation of ketones was described in 1997 by Choi and coworkers, who built on the work of de Vries.[1] After that, significant advances have been made for developing efficient catalysts for the synthesis of chiral cyanohydrins through ketones.[2-24] Recently, Kim et al. have reported the Al and Mn monomeric salen complexes for the cyanosilylation of ketones with triphenylphosphine oxide as an additive at room temperature[25,26]but none of the above works mentioned that the catalysts are recyclable.

In this chapter, the synthesis and the application of dimeric and polymeric Mn(III) salen complexes is described for the asymmetric addition of trimethylsilyl cyanide (TMSCN) to various ketones at room temperature.

4.2 Experimental

4.2.1 Materials and methods

TMSCN, Acetophenone, 4-fluoro acetophenone, 2-methyl acetophenone, 4-methyl acetophenone, propiophenone (Across organics), 2-fluoro acetophenone, 2-bromo acetophenone, 2-methoxy acetophenone, 3-methoxy acetophenone, *trans*-4-phenyl-3-butene-2-one, 2-acetonaphthone (Alfa Aesar), manganese acetate (SD Fine Chem. Ltd. India) were used as received. All the solvents were dried using standard procedures,[27] distilled and stored under nitrogen. NMR spectra were obtained with a Bruker F113V spectrometer (200 MHz and 50 MHz for ^{1}H and ^{13}C respectively) and are referenced internally with TMS. FTIR

spectra were recorded on Perkin Elmer Spectrum GX spectrophotometer in KBr window. Optical rotations were measured with a Digipol 781 Automatic Polarimeter Rudolph Instruments. Enantiomeric excess (*ee*) were determined by HPLC (Shimadzu SCL-10AVP) using Daicel Chiralpak OD-H and OJ-H chiral columns with 2-propanol/hexane as eluent. For the product purification, flash chromatography was performed using silica gel 60-200 mesh and purchased from s. d. Fine-Chem. Limited Mumbai (India). The conversions of cyanohydrintrimethylsilyl ethers were determined by using capillary GC column SPB-5 (60 meter) at 150 °C isotherm on Shimadzu GC 2010.

4.3 Synthesis of chiral dimeric and polymeric ligands

The synthesis of dimeric and polymeric ligand and its precursor is described as follows.

4.3.1 Synthesis of 5,5'-Methylene-di-3-*tert*-butylsalicylaldehyde (MTBS)

The compound 5,5'-Methylene-di-3-tert-butylsalicylaldehyde was synthesized according to the procedure described in the experimental part of chapter 2.

4.3.2 Synthesis of poly [(*R,R*)-*N,N'*-bis{3-(1,1-dimethylethyl)-5-methylene salicylidine} 1,2-diphenyl-1,2- ethylenediamine] (5')

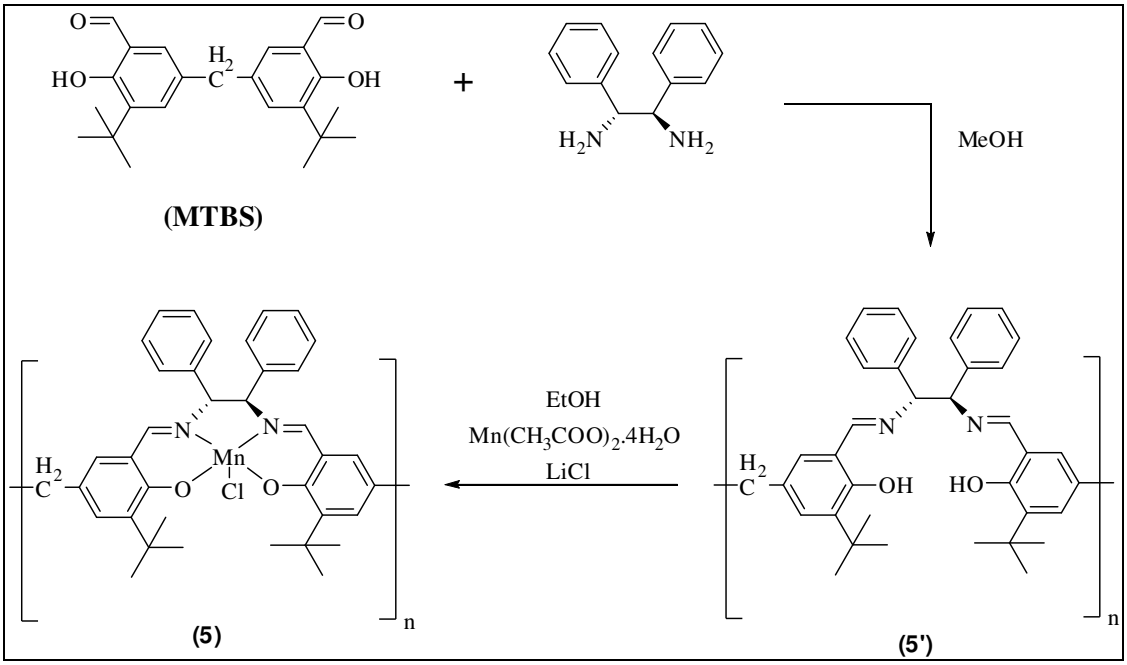
5,5'-methylene-di-3-*tert*-butylsalicylaldehyde **(MTBS)** (0.002 mol) was dissolved in methanol and 1*R,*2*R*-(+)-1,2-diphenyldiamine (0.002 mmol) was added under cold condition and the resulting mixture was refluxed for 6-8 h. Partial removal of the solvent and addition of hexane precipitated out the desired chiral ligand **5' (Scheme 4.1)** and was characterized by microanalysis, IR, ^{1}HNMR and Vapour Pressure Osmometry (VPO) and characterization data is as follows.

M_n= 5200, n = ~10. M. P. 220°C. Yield 85%. ^{1}H NMR ($CDCl_3$, 200MHz) δ: 13.56 (bs, 2H, OH), 8.22 (s, 2H, azomethine), 7.13 (bs, 10H, phenyl), 7.03 (d, 2H, aromatic), 6.67(d, 2H,

aromatic), 4.64 (s,2H, methylene), 3.66 (s, 2H, asymmetric), 1.34 (s, 18H, *t*-butyl) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 167.4, 159.2, 140.3, 137.7, 131.0, 130.8, 130.4, 128.9, 128.6, 128.1, 119.0, 80.6, 40.9, 35.4, 29.9 ppm. IR (KBr): ν(H-C=N) 1630 cm^{-1}. Anal. Calcd. for. $C_{37}H_{40}N_2O_2$: C, 82.83, H, 6.90, N, 4.82: Found: C, 82.75, H, 6.85, N, 4.76.

4.3.3 Synthesis of poly [(*R*,*R*)-N,N'-bis{3-(1,1-dimethylethyl)-5-methylene- salicylidine}1,2-diphenyl-1,2 ethane diaminato manganese(III) chloride] 5

Poly [(*R,R*)-*N,N'*-bis{3-(1,1-dimethylethyl)-5-methylene salicylidine} 1,2-diphenyl-1,2- ethylenediamine ligand (**5'**) (1.0 gm, 1.83 mmol) in CH_2Cl_2 (15 ml) was stirred under reflux with manganese acetate (0.89 gm, 3.66 mmol) in CH_3OH (5 ml) for 8–10 h under an inert atmosphere. The reaction mixture was cooled to room temperature and lithium chloride (0.46 gm, 10.98 mmol) was added and the resulting mixture was stirred for the additional 4 h while exposed to air. The mixture was filtered off and the solvent was removed from the filtrate. The residue thus obtained was extracted with dichloromethane (3x10 ml) followed by washing with water (2x10 ml), brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the crude product was recrystallized with petroleum ether to get the desired complex **5**. (**Scheme 4.1**) M. P. = >280°C. Yield 90%. $[\alpha]_D^{27}$ = + 793 (c = 0.06, CH_2Cl_2). Configuration (*R*). IR (KBr): 3440, 2956, 1604, 1531, 1457, 1426, 1308, 1178, 1026, 817, 779, 698, 572. cm^{-1}. Anal. Calcd. for $C_{37}H_{38}ClN_2O_2Mn$: C, 70.19, H, 6.05, N, 4.42, Found: C, 70.08, H, 5.98, N, 4.48. UV-Vis. (CH_2Cl_2) $\lambda_{max}(\varepsilon)$: 206(3658), 220(4851), 238(16342), 242(16881), 264(179755), 266(17674), 280(17485), 296(17168), 316(15602), 328(15602), 412(47416), 416(4695), 448(5011), 490(2248) nm.



Scheme 4.1 Synthesis of Polymeric Mn(III) salen complex **(5)**

4.3.4 Synthesis of 3,5-di-*tert*-butyl salicylaldehyde (3,5-DTBS)

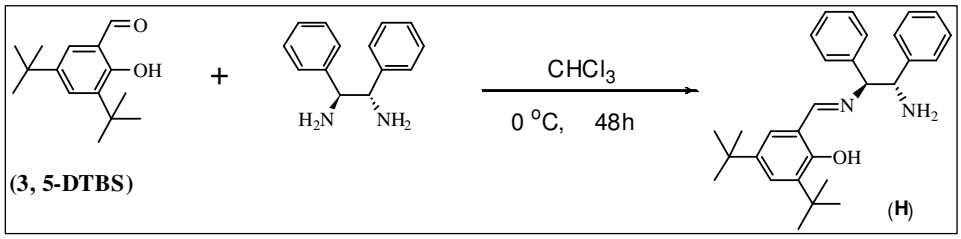
The compound 3,5-di-*tert*-Butyl salicylaldehyde (3,5-DTBS) was synthesized according to the procedure described in the experimental part of chapter 2.

4.3.5 Synthesis of *N*-(2-Hydroxy-3,5-di-*tert*-butyl benzaldehyde)-1-amino-1,2-diphenyl ethaneimine (H)

3,5-di-*tert*-butyl salicylaldehyde **(3,5-DTBS)** (0.001mol) was dissolved in 10 ml chloroform and the resulting solution was allowed to react with 0.001mol of *1S,2S*-(-)-1,2-diphenylethylenediamine in 50 ml of cold chloroform under stirring for 48 h at 0^0C. The progress of the reaction was checked on TLC using a hexane:ethyl acetate (9:1) mixture. The reaction was concentrated under cold condition in vacuum. A low melting viscous liquid (**Scheme 4.2**) thus obtained was characterized as follows.

Yield 89%. ^{1}H NMR. ($CDCl_3$, 200 MHz) δ: 13.60 (s, 1H, OH exchangeable with D_2O), 8.46 (s, 1H, H-C=N), 6.87-7.30 (bs, 12H, aromatic), 4.72 (d, 1H), 4.29-4.44, (q, 1H), 1.66 (2H, s,

br), NH_2 proton D_2O exchangeable), 1.47 (9H, s), 1.29 (9H, s) ppm. IR (KBr): 3448, 2958, 2868, 1626, 1598, 1453, 1414, 1391, 1249, 1173, 1047, 879 cm^{-1}. Anal. Calcd. for $C_{29}H_{36}N_2O$: C, 81.32; H, 8.40; N, 6.53, Found: C, 81.25; H, 8.36; N, 6.48%. LCMS 429.30 $[M+H]^+$.



Scheme 4.2 Synthesis of compound **H**

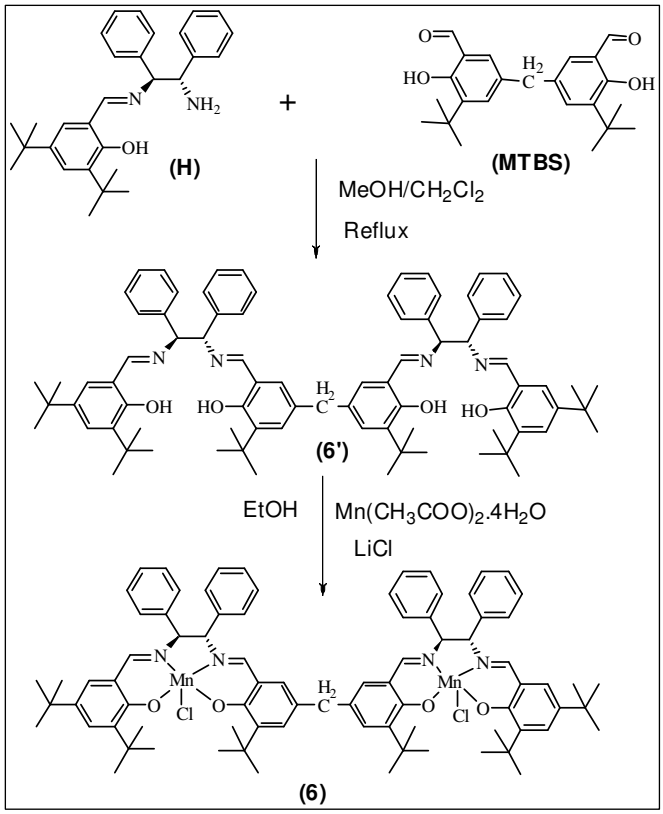
4.3.6 Synthesis 5,5-methylene di-[(*R,R*)-{*N*-(3-*tert*-butyl salicylidine)-*N′*-(3',5'-di-*tert*-butyl salicylidene)]- 1, 2-diphenylethylene diamin] (6')

Compound **H** (0.002 mol) in CH_2Cl_2 and 5,5-methylene-di-3-*tert*-butyl salicylaldehyde (**MTBS**) (0.001 mol) in ethanol were refluxed for 6-8 h. The resulting solution on concentration precipitated out the desired chiral ligand (**6'**) (**Scheme 4.3**).Yield 85%. IR (KBr): 1620 ν(H-C=N) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.23 (s, 18H), 1.40 (s, 36H), 1.54-2.0 (m, 16 H), 3.22 (s, 4H), 3.68 (s, 2H), 6.74 (s, 4H), 7.05 (s, 4H), 8.21 (s, 4H), 13.69 (bs, 4H exchangeable with D_2O) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ 23.3, 24.8, 28.3, 29.4, 31.6, 34.9, 35.4, 40.2, 42.2, 65.1, 69.4, 121.3, 125.0, 127.1, 128.4, 128.8, 137.1, 138.2, 139.2, 139.5, 157.3, 161.4 ppm; Anal. Calcd for ($C_{65}H_{92}O_4N_4$): C, 78.58; H, 9.34; N, 5.64, Found: C, 78.26; H, 9.30; N, 5.47%.

4.3.7 Synthesis of 5,5-methylene di-[(*R,R*)-{N-(3-tert-butyl salicylidine)-N'-(3',5'-di-tert-butyl salicylidene)}-1, 2-diphenylethylene diaminato(2-) manganese(III) chloride] 6

5,5-methylene di-[(*R,R*)-{*N*-(3-*tert*-butyl salicylidine)-*N′*-(3',5'-di-*tert*-butyl salicylidene)}-1, 2-diphenylethylenediamine ligand (**6'**) (1.2 gm, 0.001 mol) in CH_2Cl_2 (15 ml) was stirred under reflux with manganese acetate (0.48 gm, 0.002 mol) in CH_3OH (5 ml)

under an inert atmosphere for 8–10 h. The reaction mixture was cooled to room temperature. Lithium chloride (0.25 gm, 0.006 mol) was added and the mixture was stirred for a further 4 h while exposed to air. The mixture was filtered and the solvent was removed from the filtrate. The evaporation residue was extracted with dichloromethane (3x10 ml) and washed with water (2x10 ml), brine and dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure and the crude product thus obtained was re-crystallized with petroleum ether to get the desired complex **6** (**Scheme 4.3**) (1.0 gm, yield 90%) as solid brown powder. IR (KBr): 3437, 2954, 2868, 1607, 1535, 1456, 1428, 1388, 1311, 1250, 1172, 1024, 850, 698 cm^{-1}; UV–vis: (CH_2Cl_2): λ_{max} (ε) 323 (73078), 440 (23548), 507 (8265), 538 (6608) nm. Anal. calcd. for $C_{81}H_{92}Cl_2Mn_2N_4O_4$ (1364): C, 71.44; H, 6.95; N 4.01. Found: C, 71.39; H, 6.92; N, 3.98%; $[\alpha]_D^{25}$ = +142 (c= 0.14, CH_2Cl_2). MS (ESI): *m/z* =1382 $[M + H_2O]^+$



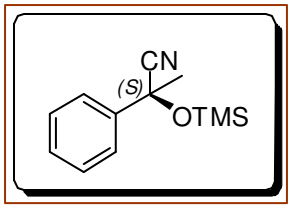
Scheme 4.3 Synthesis of dimeric Mn(III) salen complex **6**

4.4 Typical experimental procedure for addition of TMSCN to ketones

Polymeric\Dimeric Mn(III) salen complexes **5\6** (0.02mmol) were dissolved in dry CH_2Cl_2 (0.5ml) and the solution was stirred at room temperature under nitrogen atmosphere. To this solution acetophenone (0.046 ml, 0.4mmol) was added, and the resulting mixture was stirred for 30 minutes at the same temperature after that triphenylphosphine oxide (44 mg, 0.16mmol) was added followed by drop wise addition of TMSCN (106µl, 0.8mmol) over a period of 20 minutes. The reaction was monitored on GC using a capillary column SPB-5 (60 meter) at 150 °C isotherm and the product quantification was done by comparison of peak area with respect to dodacane used as an internal standard. The product was purified by flash column chromatography on silica gel (eluted with hexane/ethyl acetate = 95:5). The purified products were characterized by ^1H and ^{13}C NMR and were in agreement with the reported values.[15,16]

4.5 Characterization data of the products

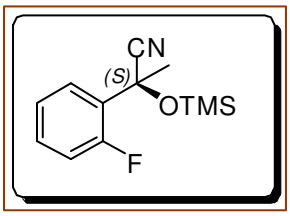
4.5.1 2-phenyl-2-(trimethylsilyloxy)propanenitrile (Table 4.3, entry 1)



^1H NMR (200 MHz, $CDCl_3$): δ = 0.17 (s, 9H), 1.85 (s, 3H), 7.37–7.57 (m, 5H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 1.8, 34.2, 71.8, 115.0, 125.3, 129.3, 144.2ppm; $[\alpha]_D^{27}$ = -18.1 (c =1, CH_2Cl_2); GC analysis: CHIRASIL CYDEX -B (0.22mm x 50 m), column temperature: 120 ^oC (isothermal), injection temperature: 200 ^oC, detector temperature: 250 ^oC, t_{r1}(major) = 35.88 min, t_{r2}(minor) = 36.10 min.

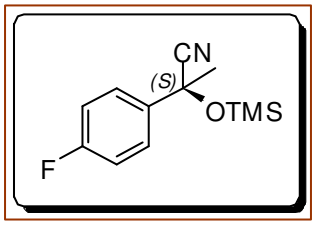
4.5.2 2-(2-Fluorophenyl)-2-(trimethylsiloxy)propanenitrile

(Table 4.3, entry 2) ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.19 (s, 9H), 1.94 (s, 3H), 7.09-7.58(m, 4H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 1.7, 31.5, 70.8, 115.0, 117.4, 124.9, 127.4, 131.2, 162.5 ppm; $[\alpha]_D^{27}$ = -16.2(c =1, CH_2Cl_2); HPLC analysis: CHIRALCEL OJ–H column, hexane/isopropanol = 99.75: 0.25, flow rate 0.5 ml/min, t_{r1}(major) = 18.75 min, t_{r2}(minor) = 19.52min.



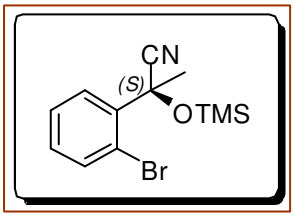
4.5.3 2-(4-Fluorophenyl)-2-(trimethylsiloxy)propanenitrile (Table 4.3 entry 3)

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.18 (s, 9H), 1.84(s, 3H), 7.03-7.55(m, 4H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 1.7, 34.2, 71.3, 116.0, 121.6, 127.1, 161.8 ppm; $[\alpha]_D^{27}$ = -15.0 (c =1, CH_2Cl_2); HPLC analysis: CHIRALCEL OJ–H column, hexane/isopropanol = 99.75: 0.25, flow rate 0.5 ml/min, t_{r1}(major) = 20.53 min, t_{r2}(minor) = 21.78min.

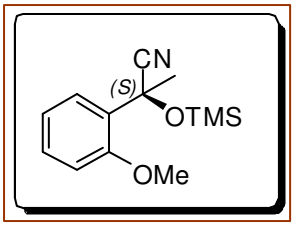


4.5.4 2-(2-Bromophenyl)-2-(trimethylsiloxy)propanenitrile (Table 4.3, entry 4)

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.18 (s, 9H), 2.02 (s, 3H), 7.16-7.75(m, 4H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ =1.9, 31.6, 70.5, 115.0, 127.9, 128.3, 129.2, 130.7, 135.9 ppm; $[\alpha]_D^{27}$ = -17.5 (c =1, CH_2Cl_2); HPLC analysis: CHIRALCEL OJ–H column, hexane/isopropanol = 99.95: 0.05, flow rate 0.5 ml/min, t_{r1}(major) = 19.52 min, t_{r2}(minor) = 20.22min.

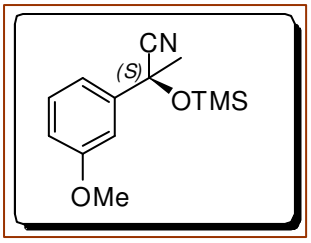


4.5.5 2-(2-Methoxyphenyl)-2-(trimethylsiloxy)propanenitrile (Table 4.3, entry 5)



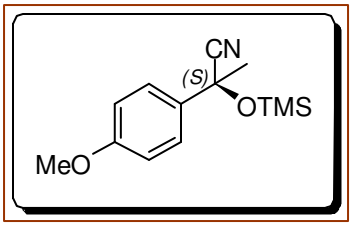
^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.19 (s, 9H), 1.88 (s, 3H), 3.91(s, 3H), 6.91-7.50(m, 4H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 1.9, 30.7, 56.1, 70.9, 112.3, 116.2, 121.2, 126.3, 130.4, 160.5 ppm. $[\alpha]_D^{27}$ = -16.4 (c =1, CH_2Cl_2); HPLC analysis: CHIRALCEL OD–H column, hexane/isopropanol = 99.95: 0.05, flow rate 0.3 ml/min, t_{r1}(minor) = 44.06 min, t_{r2}(major) = 45.79min.

4.5.6 2-(3-Methoxyphenyl)-2-(trimethylsiloxy)propanenitrile (Table 4.3, entry 6)



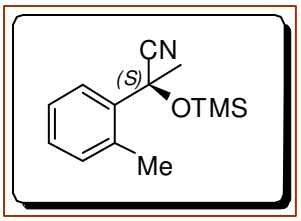
^{1}H NMR (200 MHz, $CDCl_3$): 0.19 (s, 9H), 1.86(s, 3H), 3.83(s, 3H), 6.96-7.39(m, 4H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 1.9, 31.2, 56.1, 71.0, 113.9, 116.6, 120.5, 130.9, 133.7, 160.8 ppm. $[\alpha]_D^{27}$ = -15.9 (c =1, CH_2Cl_2); HPLC analysis: CHIRALCEL OJ–H column, hexane/isopropanol = 99.75: 0.25, flow rate 0.5 ml/min, t_{r1}(major) = 24.25 min, t_{r2}(minor) = 32.83min.

4.5.7 2-(4-Methoxyphenyl)-2-(trimethylsiloxy)propanenitrile (Table 4.3, entry 7)



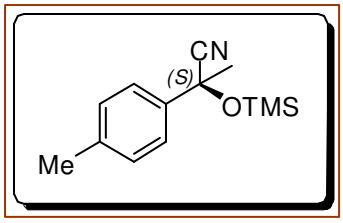
^{1}H NMR (200 MHz, $CDCl_3$): 0.19(s, 9H), 1.88(s, 3H), 3.85(s, 3H), 6.94-7.44(m, 4H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ 1.9, 30.7, 56.0, 70.9, 113.9, 115.3, 130.3, 132.6, 161.9 ppm. $[\alpha]_D^{27}$ = -17.3 (c =1, CH_2Cl_2); HPLC analysis: CHIRALCEL OJ–H column, hexane/isopropanol = 99.75: 0.25, flow rate 0.5 ml/min, t_{r1}(minor) = 29.08 min, t_{r2}(major) = 30.01min.

4.5.8 2-(2-Methylphenyl)-2-(trimethylsiloxy)propanenitrile



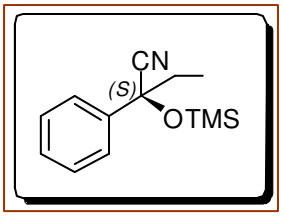
(Table 4.3, entry 9) ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.19 (s, 9H), 1.94 (s, 3H), 2.43(s, 3H), 7.29-7.41 (m, 4H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 1.8, 20.6, 34.4, 71.6, 115.2, 122.3, 126.4, 129.8, 137.2 ppm; $[\alpha]_D^{27}$ = -21.9 (c =1, CH_2Cl_2); HPLC analysis: CHIRALCEL OD–H column, hexane/isopropanol = 99.75: 0.25, flow rate 0.5 ml/min, t_{r1}(major) = 24.21 min, t_{r2}(minor) = 26.21min.

4.5.9 2-(4-Methylphenyl)-(trimethylsiloxy)propanenitrile(Table 4.3, entry 10)



^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.18 (s, 9H), 1.88(s, 3H), 2.38(s, 3H), 7.19-7.42(m, 4H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 1.8, 21.5, 34.4, 70.6, 115.2, 126.4, 129.8, 135.7 ppm. $[\alpha]_D^{27}$ = -19.8 (c =1, CH_2Cl_2); GC analysis: CHIRASIL CYDEX- B (0.22mm x 50 m), column temperature: 105 ^{o}C (isothermal), injection temperature: 200 ^{o}C, detector temperature: 200 ^{o}C, t_{r1}(major) = 115.81 min, t_{r2}(minor) = 116.41 min.

4.5.10 2-phenyl-2-(trimethylsiloxy)butanenitrile (Table 4.3, entry 12)



^{1}H NMR (200 MHz, $CDCl_3$): 0.13 (s, 9H), 0.97 (t, J = 8.0, 3H), 2.0 (q, J = 6, 2H), 7.35-7.53 (m, 5H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 1.5, 9.3, 39.9, 69.8, 115.0, 125.8, 129.1, 129.2, 141.6 ppm; $[\alpha]_D^{27}$ = -18.8 (c =1, CH_2Cl_2); GC analysis: CHIRASIL CYDEX -B (0.22mm x 50 m), column temperature: 105 ^{o}C (isothermal), injection temperature: 200 ^{o}C, detector temperature: 200 ^{o}C, t_{r1}(major) = 85.52min, t_{r2}(minor) = 87.89min.

4.6 Recycling of the chiral polymeric/dimeric Mn(III) salen complexes

After one catalytic cycle (checked on GC) the solvent was removed completely by rota evaporator. The catalysts were precipitated out with hexane followed by thorough washing with hexane (10 ml). They were dried under reduced pressure at 50 $^{\circ}$C for 1–2h and were used as recovered catalysts for successive catalytic runs using acetophenone as representative substrate for cyanosilylation reaction.

4.7 Results and discussion

Polymeric Mn(III) salen complex *viz.* poly [(*R,R*)-*N,N'*-bis{3-(1,1-dimethyl ethyl)-5-methylene- salicylidine}1,2-diphenyl-1,2 ethane diaminato manganese(III) chloride] **5** was prepared by the condensation of 1*R*,2*R*-(+)-1,2-diphenyl ethylenediamine with 5,5'-methylene-di-3-*tert*-butylsalicylaldehyde in 1:1 molar ratio in methanol followed by its complexation with manganese ion. The average molecular weight of the polymeric ligand was found to be ~5200 (*Mn*= ~5200, *n* = ~10) as measured by vapour pressure osmometry (VPO). While chiral dimeric Mn(III) salen complex, viz. 5,5-methylene di-[(*R,R*)-{*N*-(3-*tert*butyl salicylidine)-*N*'-(3',5'-di-*tert*-butylsalicylidene)}-1,2-diphenylethylene diaminato (2-)- manganese(III) chloride] **6** which carries two catalytically active metal centers was synthesized according **Scheme 4.3.** Both the complexes **5** and **6** were used to catalyze the cyanosilylation of acetophenone as a representative substrate at room temperature using TMSCN as a source of cyanide with triphenylphosphine oxide (TPPO) as an additive. The amount of the catalysts was varied over 2.5 mol% to 10 mol% and it was found that a catalyst loading of 5 mol% (Entries 3,4) is optimum for both the catalysts to achieve best conversions and enantio-induction at room temperature (conversion 89-93%, ee 75-80%) (Table 4.1). On conducting the reaction at 0 ^{0}C with optimized catalyst loading (5 mol%)

there was a marginal increase in the ee of the product with considerable decrease in the yield of cyanohydrintrimethylsilyl ether (Entries 7, 8). A further decrease in the reaction temperature (-20 ^{0}C) no further improvement in the ee of the product but caused poor conversion (Entries 9, 10). On increasing the reaction temperature above room temperature there was an improvement in the conversion but at the cost of enantioselectivity (Entries 11, 12).

Solvent plays a crucial role for cyanosilylation of ketones. In view of this, the effect of solvents viz. dichloromethane, dichloroethane, chloroform, tetrahydrofuran, toluene and acetonitrile in cyanosilylation of acetophenone as a representative substrate was carried out using the polymeric and dimeric Mn(III) salen complexes as a catalysts under identical reaction conditions (Table 4.2). Out of all the solvents used, CH_2Cl_2 (Table 4.2, Entries 1, 2) was found to be the best solvent for this system in the case of both the catalysts **5** and **6**.

Table 4.1 Data for the effect of catalysts loading and temperature on conversion and Ee of enantioselective addition of TMSCN to acetophenone using polymeric **5** and dimeric **6** Mn(III) salen complexes[a]

Entry	Catalyst loading [mol%]	Temp. [ºC]	Conversion [%][b]	Ee [%][c]
1(2)	2.5	RT	66(59)	60(58)
3(4)	5	RT	93(89)	80(75)
5(6)	10	RT	92(85)	80(65)
7(8)	5	0	32(35)	83(80)
9(10)	5	-20	25(20)	83(82)
11(12)	5	40	95(92)	61(61)

[a]All the reactions were conducted at a given temperature with catalyst **5** and **6** with TPPO (0.16mmol), acetophenone (0.4mmol) and TMSCN (0.8mmol) in dry CH_2Cl_2 (0.5ml) for 24h.[b]The conversion of the cyanosilylether was determined based on the GC analysis. Results in the parenthesis belong to catalyst **6.** [c]The Ee was determined by GC CHIRASIL CYDEX -B column (0.22mm x 50 m).

The optimized reaction conditions (as per Entries 1, 2 in Table 4.3) was used to explore the scope of polymeric and dimeric Mn(III) salen complexes in the cyanosilylation of a range of aromatic ketones viz. acetophenone, 4-methyl-, 2-methyl-, 4-fluoro-, 2-fluoro-, 2-methoxy-, 3-methoxy-, 4-methoxy-, 2-bromo- and 4-nitroacetophenone in the presence of triphenylphosphine oxide as an additive. give corresponding cyanohydrintrimethylsilyl ethers.

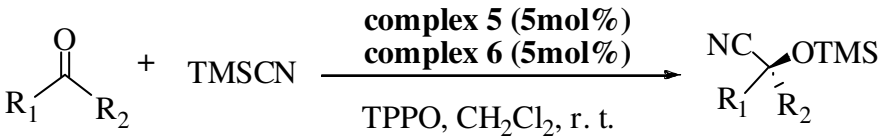
Table 4.2 Cyanosilylation of acetophenone using polymeric and dimeric Mn(III) salen complexes with different solvents under optimized reaction condition.[a]

Entry	Solvent	Conversion [%][b]	Ee [%][c]
1(2)	Dichloromethane	93(89)	80(75)
3(4)	Chloroform	70(83)	57(60)
5(6)	1,2-Dichloroethane	73(60)	60(59)
7(8)	Toluene	75(79)	63(62)
9(10)	Acetonitrile	60(58)	50(46)
11(12)	THF	59(30)	52(53)

[a]All the reactions were conducted for 24h at room temperature using catalysts **5** and **6** (0.02mmol), acetophenone (0.4mmol), TPPO (0.16mmol) and TMSCN (0.8mmol) in dry solvents (0.5ml).[b]The conversion of the cyanohydrin trimethylsilylether was determined based on the GC peak area. Results in parenthesis belong to catalyst **6.**[c]The Ee was determined by GC CHIRASIL CYDEX –B column (0.22mm X 50m).

The results shown in Table 4.3 indicates that in general both polymeric and dimeric Mn(III) salen complexes are fairly active (conversion, 78-98%) for all the substrates used in the present study except for 4-MeO, 2-MeO, 2-Me and 4-Me- acetophenones where the conversions were moderate (Entries 9, 10, 13, 14, 17-20). While the enantiomeric excess was relatively better in case of polymeric Mn(III) salen complex **5** (ee, 80-85%) than dimeric complex **6** for most of the substrates used in the present study except for 2-Me and 4-Me acetophenones where dimmer showed better enantioselectivity (ee, 80-83). However, the ee obtained for the respective products of 4-nitro and 2-,3-, 4-methoxy acetophenones were at par (Entries 9-16) with both the catalysts.

Table 4.3 Enantioselective cyanosilylation of various ketones catalyzed by polymeric and dimeric Mn(III) salen complexes under optimized reaction condition.[a]



Entry	Substrate	Time [h]	Conversion [%][b]	Ee [%][c]	TOF [h^{-1}][d]
1(2)	Acetophenone	24	93(89)	80(75)	0.77(0.74)
3(4)	2-Fluoro acetophenone	24	98(87)	86(77)	0.81(0.72)
5(6)	4- Fluoro acetophenone	24	79(80)	81(73)	0.65(0.66)
7(8)	2-Bromo acetophenone	24	80(78)	79(74)	0.66(0.65)
9(10)	2-Methoxy acetophenone	24	61(67)	75(76)	0.50(0.55)
11(12)	3-Methoxy acetophenone	24	92(89)	70(68)	0.76(0.74)
13(14)	4-Methoxy acetophenone	24	72(46)	72(70)	0.60(0.76)
15(16)	4-Nitro acetophenone	24	98(98)	65(65)	0.81((0.81)
17(18)	2-Methyl	24	73(58)	70(83)	0.61(0.48)

	acetophenone				
19(20)	4-Methyl acetophenone	24	72(73)	75(80)	0.60(0.61)
21(22)	*Trans*-4-phenyl-3-butene-2-one	24	84(98)	59(51)	0.70(0.81)
23(24)	Propiophenone	24	84(70)	67(60)	0.70(0.58)
25(26)	2-Acetonaphthone	24	93(90)	76(74)	0.77(0.75)

[a]All the reactions were conducted for 24h at room temperature using catalyst **5** and **6** (0.02mmol), ketone (0.4mmol), TPPO (0.16mmol) and TMSCN (0.8mmol) in dry CH_2Cl_2 (0.5ml).[b]The conversion of the cyanohydrin trimethylsilylether was determined based on the GC peak area. Results in parenthesis belong to catalyst **6**.[c]The ee was determined by using a GC, CHIRASIL CYDEX -B column (0.22mm x 50 m), Chiralpak HPLC OD-H and OJ-H column.[d]TOF = [Product]/[Catalyst] x time (h).

When cyanosilylation of propiophenone, 2-acetonaphthone and *trans*-4-phenyl-3-butene-2-one was carried out, 83-93% conversion with 59-76% ee of cyanohydrin trimethylsilyl ethers was obtained under identical conditions. These observations are in consonance with the earlier reports for cyanosilylation reaction.[26]

To compare the efficiency of dimeric and polymeric Mn(III) salen complexes **5** and **6** with monomeric Mn(III) salen complex[26] we carried out cyanosilylation of acetophenone in the presence of triphenylphosphine oxide as an additive under identical reaction conditions. The cyanosilylation of acetophenone with monomeric Mn(III) salen complex (5mol%) gave 62% conversion with 45% ee for cyanohydrintrimethylsilyl ether of acetophenone in 24h, while dimeric and polymeric Mn(III) salen complexes **5** and **6** gave 89-93% conversion with 75-80% ee with similar catalyst loading under identical reaction condition. The remarkable improvement in the performance of dimeric and polymeric complexes over monomeric Mn(III) salen complex can be attributed to the increase in the number of active catalytic sites in complexes **5** and **6** which might be working in cooperation rather than in isolation (**Figure 4.1**).

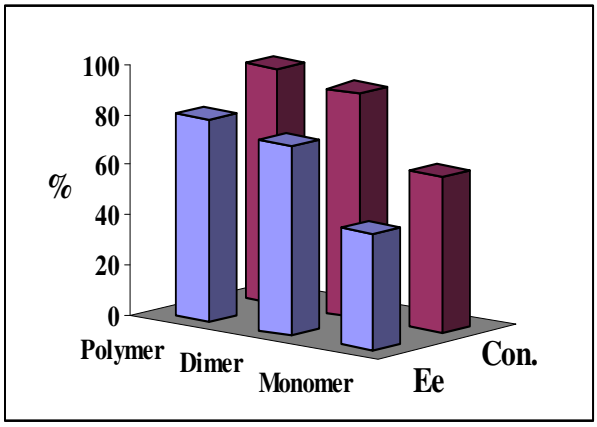


Figure 4.1 3D view representation of % Conversion and % Ee of Cyanosilylether of Acetophenone using monomer, dimer and polymer Mn(III) salen complexes.

For reusability experiments, cyanosilylation of acetophenone was carried out with polymeric and dimeric Mn(III) salen complexes under optimized reaction conditions. After first catalytic run was over, the dimeric and polymeric complexes were retrieved from the reaction mixture by the addition of excess of n-hexane. The precipitated complexes thus obtained was washed thoroughly with hexane, dried in vacuum and used for the subsequent run without further purification. Data in Table 4.4 has shown that the enantioselectivity of the recovered complexes did not change during four reuse experiments.

Table 4.4 Enantioselective cyanosilylation of acetophenone using recovered polymeric and dimeric Mn(III) salen complexes for recycling under optimized reaction condition[a]

Run	**1**	**2**	**3**	**4**
Time [h]	24	24	24	24
Conversion [%][b]	93(89)	92(84)	92(80)	91(78)
Ee [%][c]	80(75)	79(75)	80(75)	80(75)

[a]All the reactions were conducted for 24h at room temperature using catalysts **5** and **6** (0.02mmol), acetophenone (0.4mmol), TPPO (0.16mmol) and TMSCN (0.8mmol) in dry CH_2Cl_2 (0.5ml).[b]The conversion of the cyanohydrintrimethylsilyl ether was determined based on the GC peak area. Results in parenthesis belong to catalyst **6.** [c]The ee was determined by GC CHIRASIL CYDEX –B column (0.22mm X 50 m).

4.8 Mechanism

To understand the possible mechanism, control experiments for cyanosilylation of acetophenone in the presence of TPPO were conducted and the data are summarized in Table 4.5 Neither catalyst **5** nor TPPO on its own was efficient enough to expedite the addition of TMSCN to acetophenone (Table 4.5, Entry 1, 2) suggesting that both catalyst and TPPO together are essential for high activity and enantioselectivity. Subsequent experiments with the conditions mentioned in entries 3-6 of Table 4.5, suggest that in our case TPPO has dual role to play.

i) It acts as an axial ligand and activates the catalyst,

ii) It activates TMSCN,

Accordingly, an equimolar quantity of TPPO with respect to the catalyst **5** has substantially improved conversion however ee of the product remained unchanged (Entry 3). The interaction of TPPO with catalyst can be seen in the shift of IR asymmetric stretching band of azomethine to 1611 cm^{-1} (in complex **5** this band is at 1607 cm^{-1}). In a separate experiment when 5mol% TPPO was mixed with TMSCN instead of adding it to the catalyst and substrate mixture there was a considerable drop in conversion and enantioselectivity (Entry 4). This particular result suggests that there is some change to TPPO occurred that prevents it to work as axial ligand. This seems logical considering the observations made by Corey and co-workers[28] based on NMR experiments where they suggested the formation of an isocyanide (**ISOCN)** by the interaction of TPPO and TMSCN as per the following reaction.

$$Ph_3PO + TMSCN \rightleftharpoons \underset{\textbf{ISOCN}}{Ph_3P(OTMS)(N{=}C{:})}$$

Corey proposed that **ISOCN** is a reactive cyanide source responsible for high efficiency for the cyanosilylation reaction. In our case too the ^{1}HNMR spectra of 1:1 mixture of TMSCN

and Ph_3PO in $CDCl_3$ at 25 ^oC witnessed the development of a new TMS peak at 0.05 (TMSCN peak at 0.36) (**Figure 4.2**). Similarly in ^{13}CNMR (in $CDCl_3$) new peaks appeared at δ 2.03 and 110.13 ppm (TMSCN peaks at δ -1.99 (CH_3) and 127.21 (CN)) (**Figure 4.3**). Therefore, next we interacted catalyst **5** (5mo%), 10 mol% TPPO and acetophenone for 30 minutes to which a premixed solution of 30mol% TPPO and TMSCN in CH_2Cl_2 was added (Entry 5). The results obtained were found to be at par with the optimized condition used for cyanosilylation of acetophenone as per entry 6, thus supporting our hypothesis that TPPO is working both as promoter to the catalyst and activating the TMSCN. Based on the above observations a probable transition state for the formation of cyanohydrin trimethylsilyl ether is shown in **Scheme 4.4**. Since the product distribution for monomeric, dimeric or polymeric catalyst remain similar, except for reactivity and enantioselectivity, it is logical to conclude that the transition state for all these catalysts would be nearly identical, hence only one Mn(III) salen unit is shown in **Scheme 4.4**.

To provide additional evidence for the above proposition stepwise infrared spectra of TPPO and TMSCN were recorded (spectra **A** and **B** respectively, **Figure 4.4A**). The IR absorption bands at 2189 and 2089 cm^{-1} were observed which are assigned to C≡N; then infrared spectrum after thorough mixing of TMSCN and TPPO was recorded where IR band at 2089 was shifted to 2079 cm^{-1} suggesting the interaction between oxygen atoms of P-O moiety of TPPO and Si atom of TMSCN to enhance the nucleophilicity[28]. The same observations were also seen during the process of cyanosilylation of acetophenone catalyzed by the polymeric Mn(III) salen complex **5** (Spectrum **Z**, **Figure 4.4B**).

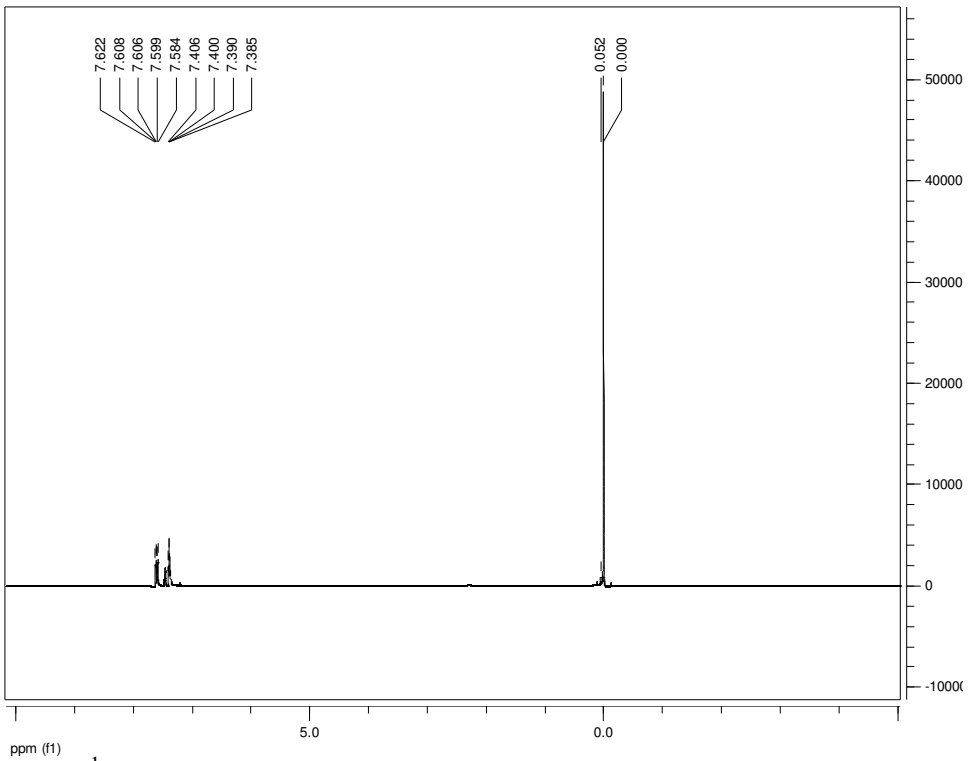


Figure 4.2 ^{1}H NMR spectrum a mixture of Triphenyl phosphine oxide and TMSCN

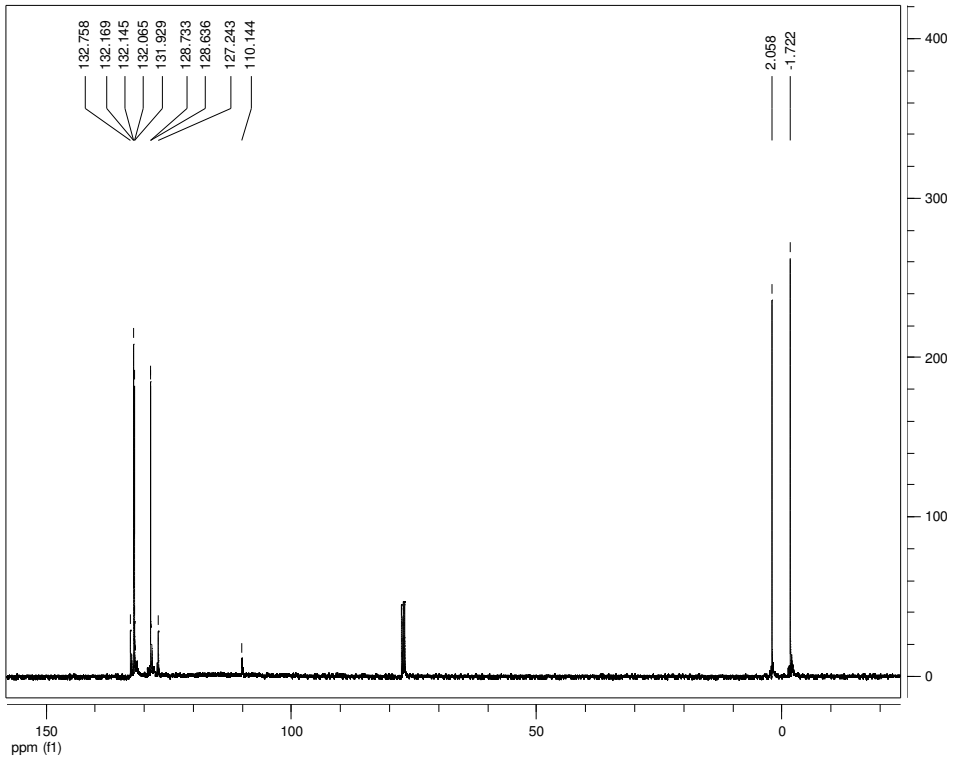
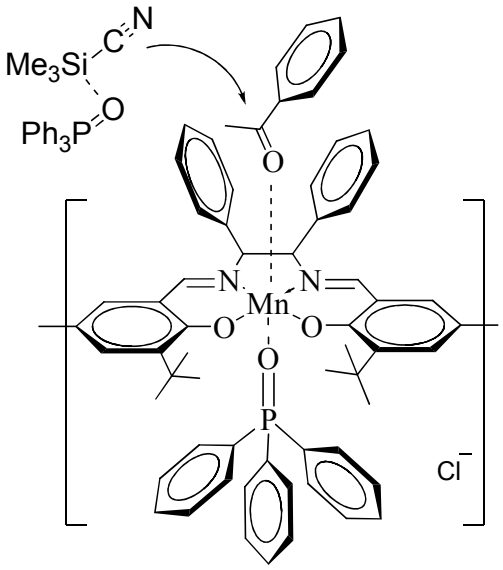


Figure 4.3 ^{13}C NMR spectrum a mixture of triphenylphosphine oxide and TMSCN



Scheme 2 Possible transition state involved in the enantioselective cyanosilylation of ketone

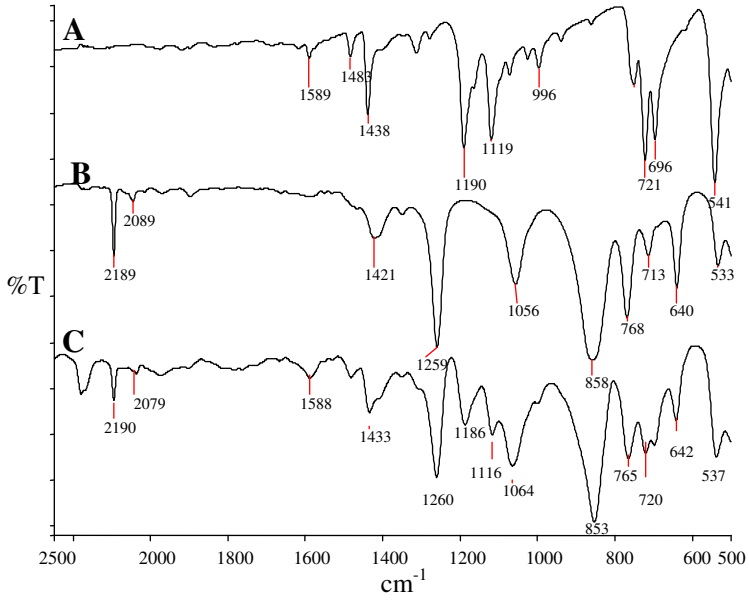


Figure 4.4A Infrared spectra of A) TPPO, B) TMSCN and C) mixture of TPPO and TMSCN in 1:5 mol ratio

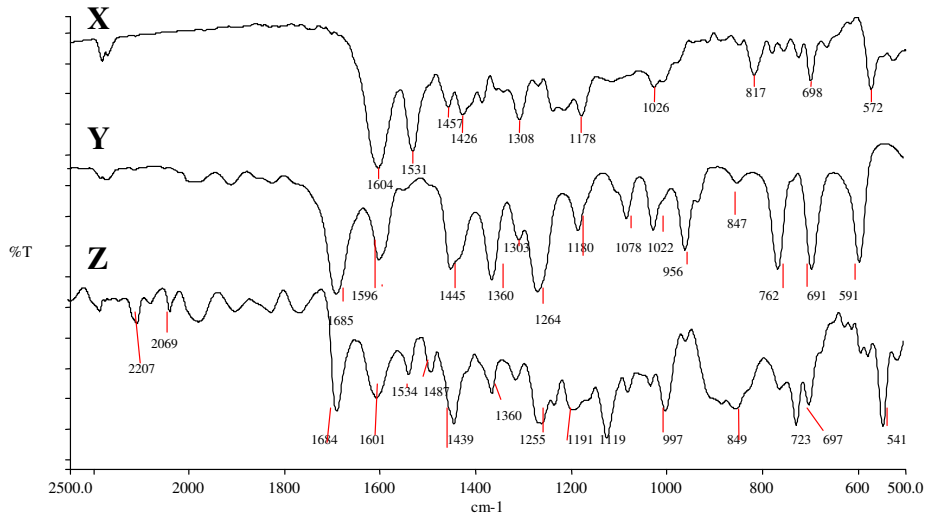


Figure 4.4B Infrared spectra of X) catalyst **5**, Y) actophenone and Z) catalytic mixture

Table 4.5 Data for control experiments for cyanosilylation of acetophenone at RT in CH_2Cl_2.

Entry	Catalyst 5 [mol%]	TPPO [mol%]	[%] Conversion	Ee [%]
1	-	40	15	3
2	5	-	32	48
3[a]	5	5	53	48
4[b]	5	5	18	32
5[c]	5	40	92	80
6[d]	5	40	93	80

[a]Catalyst+TPPO+acetophenone were stirred for 30 min in CH_2Cl_2 and TMSCN was added to the reaction mixture. [b]Catalyst+acetophenone were stirred for 30 min, to which the mixture of 5mol% TPPO+TMSCN in CH_2Cl_2 was added. [c]Catalyst+10 mol% TPPO+acetophenone were stirred for 30 min to which a mixture of 30 mol% TPPO+TMSCN in CH_2Cl_2 was added. [d]Reaction condition similar to the Entry 3 of Table 4.1

4.9 Conclusion

This chapter described the use of recyclable chiral polymeric and dimeric Mn(III) salen complexes as an efficient catalysts for the enantioselective cyanosilylation of a series of ketones in the presence of triphenylphosphine oxide as an additive at room temperature. Excellent yield (up to 98%) with 86% ee of chiral cyanohydrintrimethylsilyl ether was achieved in 24h in the case of 2-fluoroacetophenone under optimized reaction condition with the catalyst **5.** For most of the substrates the catalysts **5** showed slightly better reactivity and enantioselecitivity than the catalyst **6**. The chiral polymeric and dimeric Mn(III) salen complexes were recovered easily and reused four times with retention of performance.

4.10 References

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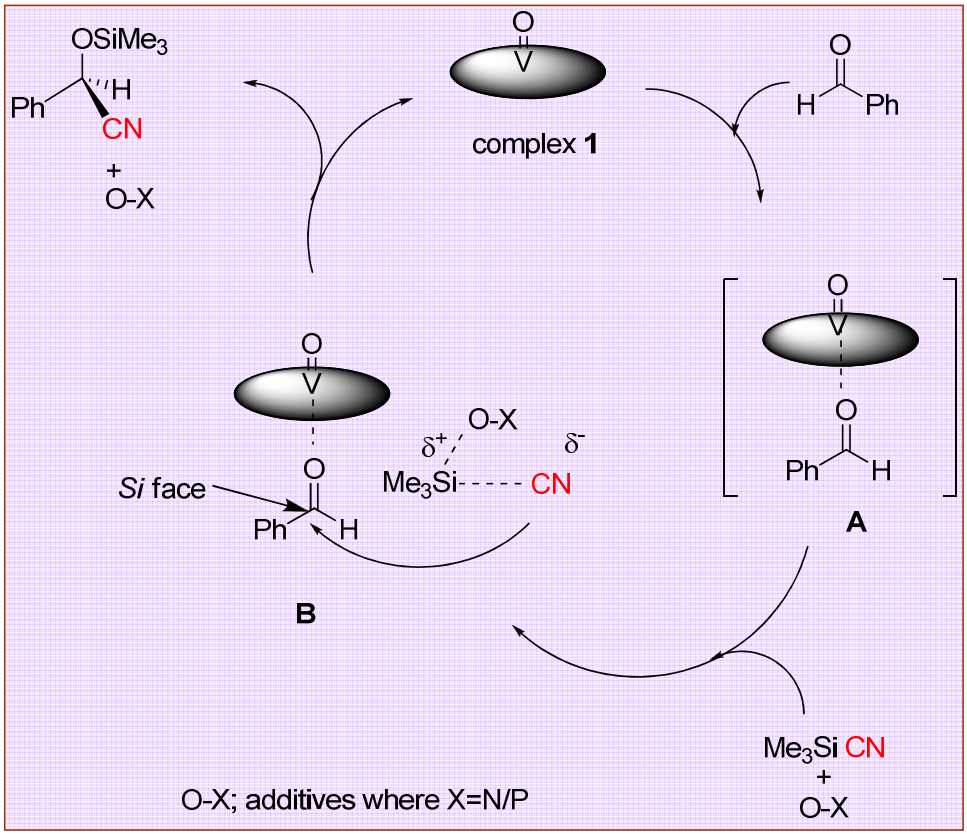
Chapter-3



Polymer V(V) salen complex as a Recyclable Catalyst for the cyanation of aldehyde

5.1 Introduction

To achieve high chiral induction in cyanohydrins, various catalytic systems for the enantioselective cyanation of aldehydes and ketones were explored with different sources of cyanide like KCN, NaCN, trimethylsilyl cyanide (TMSCN) and HCN,[1-19] where both HCN and TMSCN are volatile and hence hazardous. Recently, attempts were made to utilize various other sources of cyanide *e.g.*, cyanoformate esters (ROCOCN), acetyl cyanide, diethyl cyanophosphonate and benzoyl cyanide to synthesize optically pure cyanohydrins with different catalytic systems.[20-42] Excellent results in term of reactivity and enantioselectivity were achieved by Belokon[25] and Moberg[33] in Ti(IV) salen system at low reaction temperatures (-73 to -40 ^{0}C) in the presence of ethylcyanoformate as a source of cyanide in the absence[25] or presence of triethylamine[33] as a co-catalyst. This chapter describes for the first time the use of V(V) salen complex **7** [derived from the reaction of 3,5-di-*tert*-butyl-salicylaldehyde with mono-tartrate salt of (1*R*,2*R*)**-**diaminocyclohexane) with vanadyl sulphate followed by auto-oxidation] as an efficient catalyst for the enantioselective cyanation of aldehydes using ethylcyanoformate as a source of cyanide in combination with various co-catalyst. Notably, the product cyanohydrin carbonates are more stable towards unwanted hydrolysis that takes place in the case of cyanohydrin trimethylsilyl ethers. Excellent yield (92%) and ee for ethylcyanocarbonate of hydrocinnamaldehyde (97% ee) was achieved in the presence of imidazole as co-catalyst (ee was improved to >99% on re-crystallization).

5.2 Experimental

5.2.1 Materials & methods

Vanadyl sulphate hydrate (Loba Chemie, India), imidazole, LiOH, Triethylamine (s. d. Fine-Chem. India), KCN (Merck), 2,6 Lutidine, 2-methylimidazole, ethylcyanoformate, benzaldehyde (**2a**), 2-naphthaldehyde (**2b**), 2-methoxybenzaldehyde (**2f**), 3-methoxybenzaldehyde (**2g**), 4-methoxybenzaldehyde (**2h**), 2-ethoxybenzaldehyde (**2i**), 2-benzyloxybenzaldehyde (**2j**), 4-fluorobenzaldehyde (**2k**), 4-chlorobenzaldehyde (**2l**), 4-bromobenzaldehyde (**2m**), *E*-cinnamaldehyde (**2n**), crotonaldehyde (**2o**), hydrocinnamaldehyde (**2p**), isovaraldehyde (**2q**), hexanal (**2r**) were purchased from Aldrich Chemicals and 2-methylbenzaldehyde (**2c**), 3-methylbenzaldehyde (**2d**), 4-methylbenzaldehyde (**2e**) were purchased from Merck chemicals and were used as received. All the solvents were dried by standard procedures,[43] distilled and stored under nitrogen. Chiral salen ligand *viz.*, (*1R, 2R*)-*N,N'*-bis[3, 5-di(*tert*-butyl)salicylidene] cyclohexane-1, 2-diamine was synthesized by the reported method.[44] NMR spectra were obtained with a Bruker F113V spectrometer (500 MHz and 125 MHz for ^{1}H and ^{13}C respectively) and are referenced internally with TMS. FTIR spectra were recorded on Perkin Elmer Spectrum GX spectrophotometer in KBr window. High-resolution mass spectra were obtained with a LC-MS (Q-TOFF) LC (Waters), MS (Micromass) instruments. For the product purification flash chromatography was performed using silica gel 60-200 mesh purchased from s. d. Fine-Chem. Limited Mumbai (India). Enantiomeric excesses (ee) of the products were determined by HPLC (Shimadzu SCL-10AVP) using Daicel Chiralpak AD and OD chiral columns with 2-propanol/hexane as eluent. Optical rotations were measured with a Digipol 781 Automatic Polarimeter Rudolph Instruments.

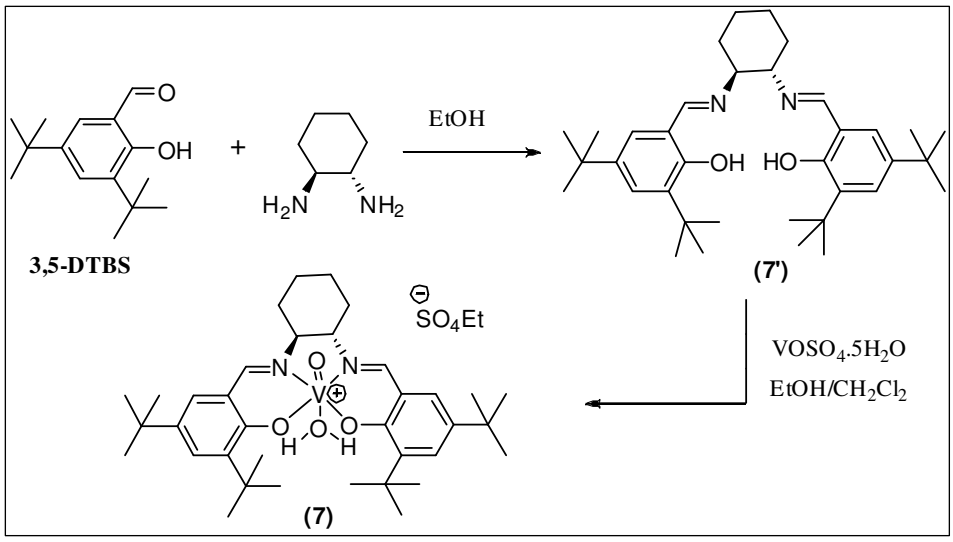
5.3 Synthesis of V(V) salen complex 7 and its precursor are described as fellows

5.3.1 3,5-di-*tert*-butyl salicylaldehyde (3,5- DTBS)

Synthesis of 3,5-di-*tert*-Butyl salicylaldehyde (3,5-DTBS) is described in chapter 2.

5.3.2 Synthesis of complex 7

The complex **7** was synthesized by the reported procedure.[6] The solution of (*1R, 2R*)-*N,N'*-bis[3, 5-di(*tert*-butyl)salicylidene] cyclohexane-1, 2-diamine (1.5ml, 2.7mmol,) in THF (20 mL) and vanadyl sulfate hydrate (0.69gm, 2.7mmol) in hot ethanol (30 ml) were mixed. The resulting solution was refluxed for 2 h under inert atmosphere and then cooled to room temperature. The reaction mass was further allowed to stir for additional 12 h while opening the side arm of the reaction flask for auto-oxidation. Solvent was completely evaporated and the residue was dissolved in DCM (15 ml), washed with water (3 x 5ml) and finally with brine. The organic layer was dried over anhydrous Na_2SO_4, the complex was purified by column chromatography as a dark green solid (**Scheme 5.1**). ^{1}H NMR: 0.83 (t, *J* = 7.2, 3H), 1.34 (s, 18H), 1.49 (s, 18H), 1.7 -2.3 (m, 8H), 3.42 (q, *J* = 7.2, 2H), 3.82 (m, 1H), 4.25 (m, 1H), 7.48 (s, 1H), 7.51 (s, 1H), 7.69 (s, 1H), 7.74 (s, 1H), 8.52(s,1H), 8.73 (s, 1H); $[\alpha]_D^{25}$ = -913 (c=0.01, $CHCl_3$); Anal. Calc. for $C_{38}H_{59}N_2O_7SV.H_2O$:0.30, H 8.12, N 3.70, found: C 60.42, H 8.13, N 3.65.

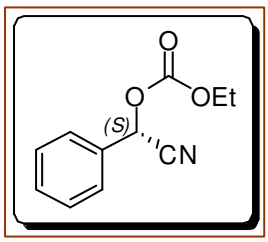


Scheme 5.1 Synthesis of chiral V(V) salen complex **7**

5.4 Typical experimental procedure for the enantioselective ethylcyanoformylation of aldehydes

A solution of V(V) salen complexes **7** (0.015mmol) and appropriate aldehyde (0.62mmol,) in dry CH_2Cl_2 (0.8ml) was stirred for 10 minutes at room temperature under N_2 atmosphere. To this solution imidazole (4 mg, 0.062mmol) was added and the solution was cooled to -20 ^oC. To this cooled solution ethylcyanoformate (0.077 ml, 0.78 mmol) was added drop-wise over a period of 5 minutes. The reaction was monitored on TLC. After completion of the reaction the product was purified by flash column chromatography on a silica gel column (eluted with hexane/ethyl acetate = 90/10). The purified products were characterized by ^1H and ^{13}C NMR which were in agreement with the reported values.[26,41]

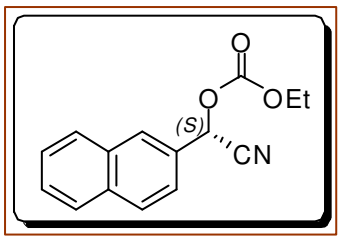
5.5 Characterization data of the products



5.5.1 2-Ethoxycarbonyl (*S*)-2-hydroxy-2-phenyl-acetonitrile (3a) ^1HNMR δ = 1.32 (t, *J* = 7.5, 3H), 4.25-4.30 (m, 2H), 6.26 (s, 1H), 7.43-7.54 (m, 5H)ppm. $^{13}CNMR$ 14.21, 65.73, 66.48,

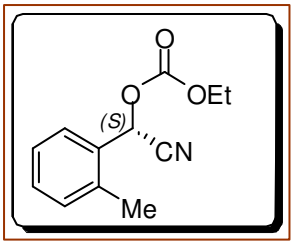
115.93, 127.99, 129.38, 130.74, 131.37, 153.53; $[\alpha]_D^{25}$ = - 17.6 (c = 2.0, $CHCl_3$) (93 % ee){ lit. $[\alpha]_D^{21.7}$ +16.2 (c = 2.8, $CHCl_3$) for *R* enantiomer in 94% ee} HPLC analysis: CHIRALCEL OD column, hexane/isopropanol 99:1, flow rate 1 ml/ min, wavelength 220 nm.

5.5.2 2-Ethoxycarbonyl (*S*)-2-hydroxy-2-(2-naphthyl)-acetonitrile (3b) ^{1}H NMR δ = 1.34 (t, *J* = 7.5, 3H), 4.28-4.33(m, 2H), 6.43 (s, 1H), 7.25 (s, 1H), 7.54-7.59 (m, 3H), 7.86-8.04 (m, 3H) ppm. ^{13}C NMR **δ** = 14.32, 65.87, 66.77, 116.00, 124.37, 127.29, 127.86, 128.03, 128.29, 128.63, 129.69, 133.01, 134.18, 153.68ppm. $[\alpha]_D^{25}$ = + 19.32 (c = 1.0, $CHCl_3$) 95% ee HPLC analysis: CHIRALCEL OD-H column, hexane/isopropanol 99:1, flow rate 1 ml/ min, wavelength 260 nm.

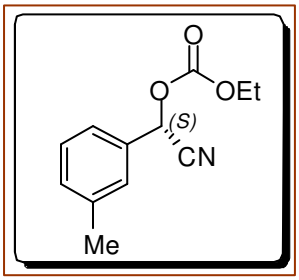


5.5.3 2-Ethoxycarbonyl (*S*)-2-hydroxy-2-(2-methylphenyl)-acetonitrile (3c)

^{1}H NMR δ = 1.33 (t, *J* = 7.5, 3H), 2.44 (s, 3H), 4.25-4.31 (m, 2H), 6.38(s, 1H), 7.23-7.37(m, 3H), 7.55(d, J =8, 1H)ppm. ^{13}C NMR δ = 14.27, 19.06, 64.72, 65.75, 115.83, 126.93, 128.75, 129.55, 130.83, 131.48, 136.90, 153.61ppm. $[\alpha]_D^{25}$ = - 20.2 (c = 1.0, $CHCl_3$) 91% ee { lit. $[\alpha]_D^{20}$ -21.5 (c = 1.0, $CHCl_3$) for *S* enantiomer in 97% ee} HPLC analysis: CHIRALCEL OD column, hexane/isopropanol 99:1, flow rate 1 ml/ min, wavelength 220 nm.

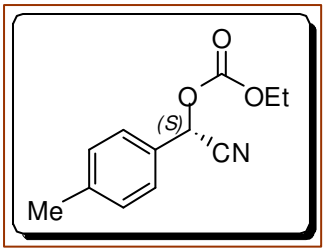


5.5.4 2-Ethoxycarbonyl (*S*)-2-hydroxy-2-(3-methylphenyl)-acetonitrile (3d) ^{1}H NMR δ = 1.33 (t, *J* = 7, 3H), 2.38 (s, 3H), 4.24-4.30 (m, 2H), 6.22(s, 1H), 7.26-7.34(m, 4H)ppm. ^{13}C NMR δ = 14.24, 21.24, 65.70, 66.53, 116.02, 125.09, 128.57, 129.26, 131.26, 131.51, 139.40, 153.57ppm. $[\alpha]_D^{25}$ = - 10.4 (c = 1.0, $CHCl_3$) 94% ee HPLC analysis: CHIRALCEL OD column, hexane/isopropanol 99:1, flow rate 1 ml/ min, wavelength 220 nm.



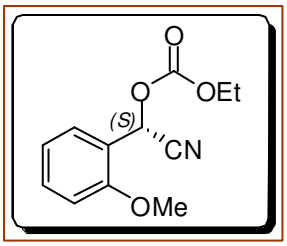
5.5.5 2-Ethoxycarbonyl(*S*)-2-hydroxy-2-(4-methylphenyl)-acetonitrile (3e)

^{1}H NMR δ = 1.33 (t, *J* = 7, 3H), 2.38 (s, 3H), 4.28 (q, *J* = 6.5, 2H), 6.22 (s, 1H), 7.24-7.26 (m, 2H), 7.42-7.43 (m, 2H) ppm. ^{13}C NMR δ = 14.32, 21.53, 66.48, 65.73, 116.10, 128.12, 130.10, 141.14, 153.65ppm. $[\alpha]_D^{25}$ -2.1 (c = 1.0, $CHCl_3$) 90 % ee { lit. $[\alpha]_D^{20}$ -1.9 (c = 1.55), $CHCl_3$) for *S* enantiomer in 99% ee}HPLC analysis: CHIRALCEL OD-H column, hexane/isopropanol 99:1, flow rate 1 ml/ min, wavelength 220 nm.



5.5.6 2-Ethoxycarbonyl (*S*)-2-hydroxy-2-(2-ethoxylphenyl)-acetonitrile (3f)

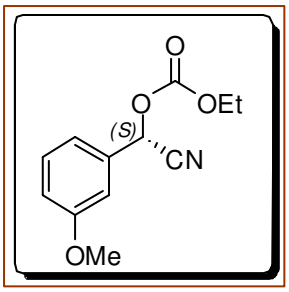
^{1}H NMR δ = 1.32 (t, *J* = 7, 3H), 3.86 (s, 3H), 4.26-4.29 (m, 2H), 6.58 (s, 1H), 6.94(d, *J* = 8, 1H), 7.00-7.03 (m, 1H), 7.40-7.4(m, 1H), 7.55(dd, *J* = 2, 6, 1H)ppm. ^{13}C NMR δ =14.28, 55.90, 61.85, 65.57, 111.25, 116.10, 119.60, 121.09,



128.09, 132.21, 153.66, 156.89ppm. $[\alpha]_D^{25}$ +2.1 (c = 1.0, $CHCl_3$) 96% ee { lit. $[\alpha]_D^{20}$ = +2.8(c = 1.0, $CHCl_3$) for *S* enantiomer in 100% ee}HPLC analysis: CHIRALCEL OD-H column, hexane/isopropanol 99:1, flow rate 1 ml/ min, wavelength 220 nm.

5.5.7 2-Ethoxycarbonyl (*S*)-2-hydroxy-2-(3-methoxylphenyl)-acetonitrile (3g)

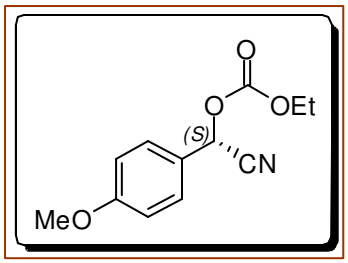
^{1}H NMR δ = 1.33 (t, *J* = 7, 3H), 3.82 (s, 3H), 4.26-4.29 (m, 2H), 6.23 (s, 1H), 6.97-7.11(m, 3H), 7.33-7.36(m, 1H)ppm. ^{13}C NMR δ =14.12, 55.44, 65.65, 66.24, 113.12, 115.80, 116.38, 119.97, 130.39, 132.55, 153.41, 160.13ppm. $[\alpha]_D^{25}$ -9.7 (c = 2.0, $CHCl_3$) 89% ee { lit. $[\alpha]_D^{25.4}$ = -9.4(c = 2.0, $CHCl_3$) for *S* enantiomer in 83 % ee}



HPLC analysis: CHIRALCEL OD-H column, hexane/isopropanol 99:1, flow rate 1 ml/ min, wavelength 225 nm.

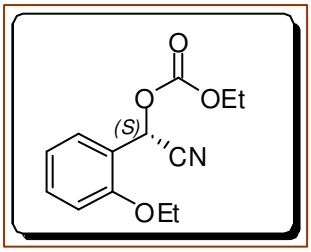
5.5.8 2-Ethoxycarbonyl (*S*)-2-hydroxy-2-(4-methoxylphenyl)-acetonitrile (3h)

^{1}H NMR δ = 1.25 (t, *J* = 7, 3H), 3.75 (s, 3H), 4.18-4.21 (m, 2H), 6.13 (s, 1H), 6.88 (d, *J* =8.5, 2H), 7.40 (d, *J* = 8.5, 2H)ppm. ^{13}C NMR δ = 14.23, 55.54, 65.60, 66.26, 114.69, 116.13, 123.44, 129.85, 153.58, 161.44ppm. $[\alpha]_D^{25}$ + 2.1 (c = 1, $CHCl_3$) 93%ee { lit. $[\alpha]_D^{20}$ =+1.8 (c = 1.35, $CHCl_3$) for *S* enantiomer in 90% ee}



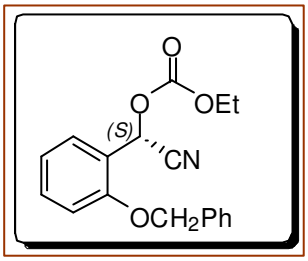
HPLC analysis: CHIRALCEL OD-H column, hexane/isopropanol 99:1, flow rate 1 ml/ min, wavelength 234 nm.

5.5.9 2-Ethoxycarbonyl (*S*)-2-hydroxy-2-(2-ethoxylphenyl)-acetonitrile (3i)



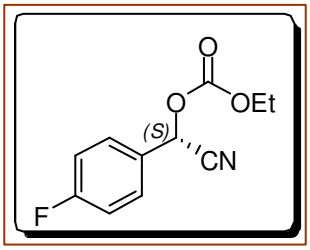
^{1}H NMR δ = 1.33(t, *J* = 6.5, 3H), 1.42 (t, *J* = 6.5, 3H), 4.10 (brd, 2H), 4.28 (brs, 2H), 6.62 (s, 1H), 6.92(d, *J* = 8, 1H), 7.00 (t, *J* = 7, 1H), 7.39 (t, *J* = 7.5, 1H), 7.57 (d, *J* = 7, 1H)ppm. ^{13}C NMR 14.70, 14.26, 61.98, 64.29, 65.48, 111.94, 116.08, 119.60, 120.83, 128.77, 132.07, 153.65, 156.27ppm. $[\alpha]_D^{25}$ = - 14.9 (c = 1.0, $CHCl_3$) 93% ee HPLC analysis: CHIRALCEL OD column, hexane/isopropanol 99:1, flow rate 1 ml/ min, wavelength 220 nm.

5.5.10 2-Ethoxycarbonyl (*S*)-2-hydroxy-2-(2-benzyloxyphenyl)-acetonitrile (3j)



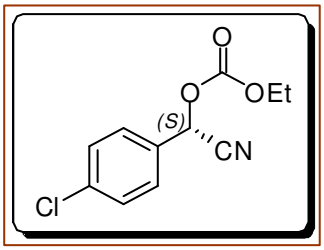
^{1}H NMR δ = 1.27 (t, *J* = 7, 3H), 4.18-4.22 (m, 2H), 5.11 (s, 2H), 6.64 (s, 1H), 6.95 (d, *J* = 8.5, 1H), 7.01 (t, *J* = 7.5, 1H), 7.29-7.41 (m, 6H), 7.60 (d, *J* = 7.5, 1H)ppm. ^{13}C NMR δ = 14.18, 62.00, 65.45, 70.46, 112.43, 115.98, 119.86, 121.26, 127.31, 128.23, 128.71, 128.85, 132.06, 136.09, 153.53, 155.89ppm. $[\alpha]_D^{25}$ = - 15.1 (c = 1.0, $CHCl_3$) 96% ee. HPLC analysis: CHIRALCEL OD column, hexane/isopropanol 99:1, flow rate 1 ml/ min, wavelength 220 nm.

5.5.11 2-Ethoxycarbonyl (*S*)-2-hydroxy-2-(4-fluorophenyl)-acetonitrile (3k)



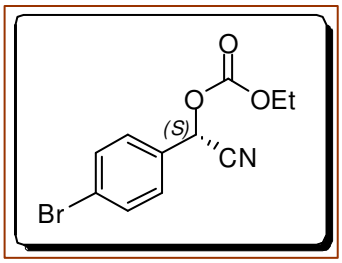
^{1}H NMR δ = 1.33 (t, *J* = 7, 3H), 4.28 (q, *J* = 7.5, 2H), 6.25 (s, 1H), 7.13-7.16(m, 2H), 7.53-7.55 (m, 2H)ppm. ^{13}C NMR δ =14.23, 65.72, 66.12, 115.43, 129.66, 130.10, 137.97, 153.39ppm. $[\alpha]_D^{25}$ - 20.2 (c = 2, $CHCl_3$) 93% ee{ lit. $[\alpha]_D^{23.1}$ = - 18.7 (c = 2, $CHCl_3$) for *S* enantiomer in 84% ee} HPLC analysis: CHIRALCEL OD column, hexane/isopropanol 99:1, flow rate 1 ml/ min, wavelength 220 nm.

5.5.12 2-Ethoxycarbonyl (*S*)-2-hydroxy-2-(4-chlorophenyl)-acetonitrile (3l)



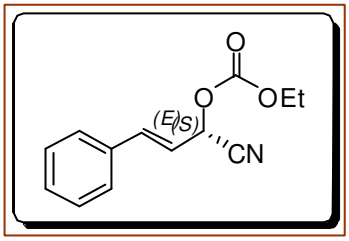
^{1}H NMR δ = 1.31 (t, *J* = 7, 3H), 4.25-4.29 (m, 2H), 6.22 (s, 1H), 7.41-7.47 (m, 4H)ppm. ^{13}C NMR δ =14.23, 65.91, 65.72, 115.57, 129.66, 129.89, 136.97, 153.39ppm. $[\alpha]_D^{25}$ -4.8 (c = 2.0, $CHCl_3$) 85%ee { lit. $[\alpha]_D^{25}$ = - 4.6 (c = 2, $CHCl_3$) for *S* enantiomer in 81% ee} HPLC analysis: CHIRALCEL OD column, hexane/isopropanol 99:1, flow rate 1 ml/ min, wavelength 220 nm.

5.5.13 2-Ethoxycarbonyl (*S*)-2-hydroxy-2-(4-bromophenyl)-acetonitrile (3m)



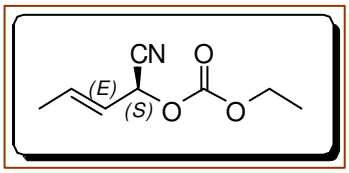
^{1}H NMR δ = 1.31 (t, *J* = 7, 3H), 4.22-4.30 (m, 2H), 6.20 (s, 1H), 7.40 (d, J = 8.5, 2H), 7.57 (d, J = 8.5, 2H)ppm. ^{13}C NMR δ =14.24, 65.78, 65.92, 115.52, 125.21, 129.60, 130.40, 132.63, 153.38ppm. $[\alpha]_D^{25}$ = + 9.3 (c = 1.35, $CHCl_3$) 91% ee. HPLC analysis: CHIRALCEL OD column, hexane/isopropanol 99:1, flow rate 1 ml/ min, wavelength 220 nm.

5.5.14 2-Ethoxycarbonyl (*S*)-2-hydroxy-4-phenyl-but-3-enonitrile (3n)



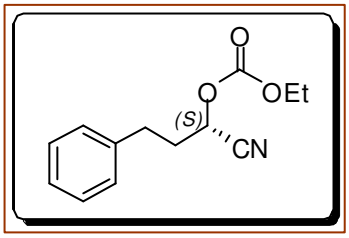
^{1}H NMR δ = 1.35(t, *J* = 7, 3H), 4.32 (q, *J* = 2H), 5.89 (d, *J* = 6.5, 1H), 6.24 (m, 1H), 6.96 (d, J = 15.5, 1H), 7.14-7.42 (m, 5H)ppm. ^{13}C NMR δ = 14.27, 65.69, 66.35, 115.30, 117.98, 127.38, 128.59, 128.98, 129.06, 129.64, 134.40, 138.44, 153.48ppm. $[\alpha]_D^{25}$ = + 15.3 (c = 2, $CHCl_3$) 92%ee { lit. $[\alpha]_D^{25.3}$ = +11.3(c = 2, $CHCl_3$) for *S* enantiomer in 80% ee}HPLC analysis: CHIRALCEL OD-H column, hexane/isopropanol 99:1, flow rate 1 ml/ min, wavelength 240 nm.

5.5.15 2-Ethoxycarbonyl (*S*)-2-hydroxy- pent-3-enonitrile (3o)



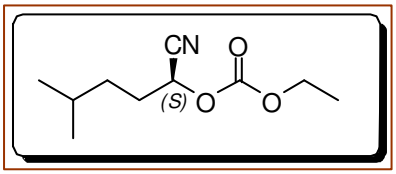
$[\alpha]_D^{25}$ = + 6.0 (c = 1, $CHCl_3$) 90% ee { lit. $[\alpha]_D^{20}$ = +6.6 (c = 1, $CHCl_3$) for *S* enantiomer in 93% ee} HPLC analysis CHIRALCEL AD column, hexane/isopropanol 99:1, flow rate 1 ml/ min, wavelength 210 nm.

5.5.16 2-Ethoxycarbonyl (*S*)-2-hydroxy-4-phenyl-butanonitrile (3p)



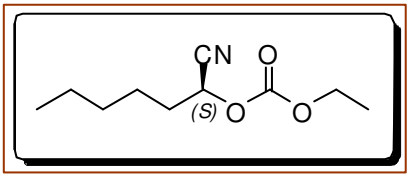
^{1}H NMR δ = 1.34 (t, *J* = 7, 3H), 2.23-2.29(m, 2H), 2.85 (t, *J* = 7, 2H), 4.26-4.28 (m, 2H), 5.12 (t, *J* = 6, 1H), 7.18-7.32 (m, 5H)ppm. $[\alpha]_D^{25}$ = - 23.4 (c = 1.0, $CHCl_3$) 97% ee. HPLC analysis: CHIRALCEL OD-H column, hexane/isopropanol 99:1, flow rate 1 ml/ min, wavelength 260 nm

5.5.17 2-Ethoxycarbonyl (*S*)-2-hydroxy-5-hexanenitrile (3q)



^{1}H NMR δ = 1.0 (d, *J* = s, 6H), 1.25 (br, 1H), 1.35 (t, *J* = 7, 3H), 1.66 (br, 1H), 1.80-1.09 (m, 3H), 4.28 (q, *J* = 5, 2H), 5.23 (t, *J* = 7, 1H)ppm. ^{13}C NMR δ = 14.30, 22.22, 22.35, 24.53, 41.02, 63.64, 65.97, 116.95, 153.81ppm. $[\alpha]_D^{25}$ = - 18.14 (c = 1.0, $CHCl_3$) 76% ee.GC analysis CHIRALDEX G-TA (30m, 0.25mm) column, column temp. 70 ^{o}C -140 ^{o}C, programming rate 2, Injector temp. 200 ^{o}C, Detector temp. 200 ^{o}C

5.5.18 2-Ethoxycarbonyl (*S*)-2-hydroxy heptanenitrile (3r)



^{1}HNMR($CDCl_3$) δ = 0.87-0.90 (m, 3H), 1.31-1.32 (m, 7H), 1.46-1.54 (m, 2H), 1.89-1.94 (m, 2H), 4.23-4.37(m, 2H), 5.18 (t *J* = 6.7 Hz, 1H). $[\alpha]_D^{25}$ -54.1(C = 2.0, $CHCl_3$) 83%

ee{ lit. $[\alpha]_D^{23}$ = +61.7(c = 2.02 $CHCl_3$) for *R* enantiomer in 94% ee} GC analysis CHIRALDEX G-TA (30m, 0.25mm) column, column temp. 70 ^oC -140 ^oC, programming rate 2, Injector temp. 200 ^oC, Detector temp. 200 ^oC

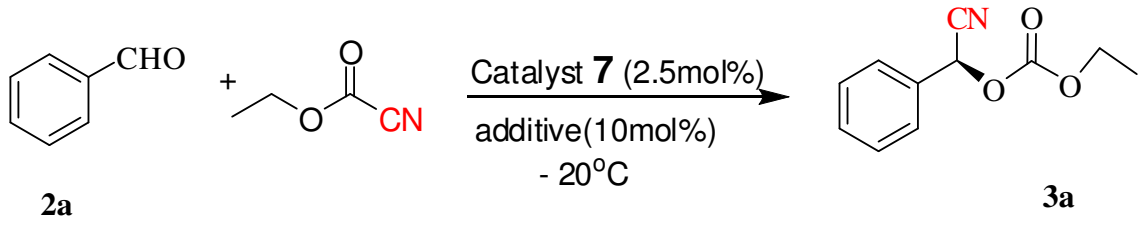
5.6 Results and discussion

The systematic study started with asymmetric ethylcyanoformylation of benzaldehyde (**2a**) using chiral V(V) salen complex **7** as catalyst at -20 ^0C in dichloromethane. However, even after 48 h there was no product formation (Table 5.1, Entry 1). When the same reaction was conducted in the presence of imidazole as co-catalyst (Table 5.1, Entry 2), excellent conversion (96%) of ethylcyanocarbonate with 93% ee was achieved with catalyst **7.** We further explored the other co-catalysts viz., KCN, LiOH, 2,6-lutidine, pyridine, 2-methyl imidazole and triethylamine using the catalyst **7** (Table 5.1, entries 3-8), very good to excellent yield of ethylcyanocarbonate was achieved except for pyridine where there was no product formation in 24 h (Entry 6). The use of triethylamine as co-catalyst accelerated the ethylcyanoformylation reaction tremendously however, the reaction took non-enantioselective route (Entry 8). Among all the co-catalysts used in the present study, imidazole was found to be the most efficient in terms of high chiral induction and product yield (Entry 2). Therefore, our subsequent studies for asymmetric ethylcyanoformylation were carried out with chiral V(V) salen complex **7** as catalyst and imidazole as co-catalyst.

In order to get the optimal reaction conditions asymmetric ethylcyanoformylation of benzaldehyde (**2a**) was carried out for 18 h at varied temperature, catalyst loading, co-catalyst loading and ethylcyanoformate loading and the results are summarized in Table 5.2. At first the catalyst loading was varied over a range of 1 to 7.5 mol% keeping the co-catalyst loading at 10 mol% at – 20 ^oC (Table 5.2, Entries 1-4). It is evident from the results that 2.5

mol% catalyst-loading is optimum (Entry 2) at -20 °C. Further, it is observed that for most enantioselective reactions, decreasing the reaction temperature improves the enantioselectivity.

Table 5.1. Effect of Co-catalyst on the Asymmetric Addition of Ethylcyanoformate to Benzaldehyde at -20°C[a]



2a **3a**

Entry	complex	Additives	Time[h]	Yield[%][b]	*ee*[%][c]
1	V(V) $EtSO_4$	-------	48	-----	-----
2	V(V) $EtSO_4$	Imidazole	18	96	93
3	V(V) $EtSO_4$	KCN	18	91	92
4	V(V) $EtSO_4$	LiOH	18	93	03
5	V(V) $EtSO_4$	2,6-Lutidine	36	89	93
6	V(V) $EtSO_4$	Pyridine	24	----	-----
7	V(V) $EtSO_4$	2-Methylimidazole	12	95	90
8	V(V) $EtSO_4$	Triethylamine	08	95	09

[a]All the reactions were carried out at -20 °C using catalyst (0.031 mmol), benzaldehyde (0.62 mmol), ethylcyanoformate (1.24 mmol), additive (0.062 mmol), dry DCM (0.8ml). [b]Isolated yield. [c]*ee* was determined using chiracel OD column.

Therefore, cyanoformylation reaction was also examined at -40 °C. Expectedly there was an improvement in the enantioselectivity though marginal but there was a concomitant decrease in the yield of the product (Entry 5). Whereas, raising the temperature from -20 °C to 0 °C and rt, the yield of ethylcyanohydrincarbonate was increased but at the expense of the enantioselectivity (Entries 6, 7). Therefore, for the rest of the catalytic experiments -20 °C was taken as optimum temperature (Entry 2). Next optimization of loadings of co-catalyst and ethyl cyanoformate was carried out by keeping the other parameters constant (Entries 8-

12). It was emerged that 10 mol% co-catalyst loading with 200 mol% ethylcyanoformate is optimum (Entry 2).

Table 5.2 Effect of Catalyst Loading, Co-catalyst Loading, Temperature and Solvent Variation on Synthesis of Ethylcyanocarbonate of Benzaldehyde[a]

Entry	Solvent	Catalyst [mol%]	Co-Catalyst loading [mol%]	Temp. [°C]	Yield[b]	*ee* [%][c]
1	CH_2Cl_2	1	10	-20	92	86
2	CH_2Cl_2	2.5	10	-20	96	93
3	CH_2Cl_2	5	10	-20	96	93
4	CH_2Cl_2	7.5	10	-20	96	95
5	CH_2Cl_2	2.5	10	-40	85	96
6	CH_2Cl_2	2.5	10	0	91	84
7	CH_2Cl_2	2.5	10	RT	93	80
8	CH_2Cl_2	2.5	5	-20	86	88
9	CH_2Cl_2	2.5	15	-20	96	93
10[d]	CH_2Cl_2	2.5	10	-20	89	90
11[e]	CH_2Cl_2	2.5	10	-20	96	93
12[f]	CH_2Cl_2	2.5	10	-20	96	93
13	$CHCl_3$	2.5	10	-20	90	89
14	1, 2-DCE	2.5	10	-20	87	82
15	THF	2.5	10	-20	68	70
16	CH_3CN	2.5	10	-20	79	72
17	Toluene	2.5	10	-20	70	73

[a]all the reactions were carried out using Catalyst **1** , 0.62 mmol aldehydes, 1.24 mmol ethylcyanoformate, 10mol % imidazole as co-catalyst. [b]Isolated yield. [c]*ee* was determined using chiracel OD column. [d]Using 160 mol% of ethylcyanoformate. [e]Using 240 mol% of ethylcyanoformate. [f]Using 320 mol% of ethylcyanoformate.

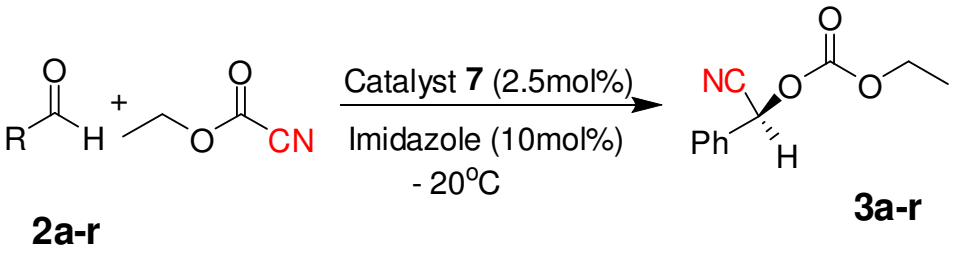
Catalytic ethylcyanoformylation of benzaldehyde (**2a**) using the V(V) salen complex **7** as a catalyst was also carried out under the above optimized reaction conditions in various solvents *e.g.*, 1,2-dichloroethane (1,2-DCE), dichloromethane (DCM), chloroform ($CHCl_3$), tetrahydrofuran (THF), toluene and acetonitrile (CH_3CN) (Table 5.2, Entries 2, 13-17). Out of all the solvents used, DCM was found to be the best solvent for this system (Table 5.2, Entry 2).

Under the optimized reaction conditions the scope of this protocol for the ethylcyanoformylation reaction was further extended to a variety of aromatic and aliphatic aldehydes using chiral V(V) salen complex **7** as catalyst in the presence of imidazole as co-catalyst. Overall good to excellent isolated yields (80-97%) and enantiomeric excess (76-97%) was obtained (Table 5.3). Benzaldehyde and aromatic aldehydes with smaller substituents at 2 and 3 positions reacts faster (Entries 1-4) as compared to the aromatic aldehydes having relatively bulkier groups on the same positions (24-48 h; Entries 6, 7, 9, 10). In general 4-substituted aromatic aldehydes reacted slowly (24-60 h; Entries 5, 8, 11-13). In the case of α, β-unsaturated aldehydes high yield and ee was achieved in 24-48h (Entries 14, 15). Aliphatic aldehyde bearing aromatic ring in alkyl chain such as hydrocinamaldehyde gave the highest ee 97% with 92% isolated yield within 24h (entry 16) while aliphatic aldehydes with no such functionality gave moderate yield and ee (entries 17,18). In all catalytic runs, with the (*R*)-form of V(V) salen complex as catalyst resulted in to (*S*)-form of the product ethylcyanohydrincarbonates. Further, ethylcyanohydrincarbonate of 2-naphthaldehyde was obtained as a white solid which on re-crystallization (Hexane: DCM, 60:40) gave 99% ee of the product .This can be explained by taking into account of the phenomenon of homochiral aggregation having preference over heterochiral aggregation (resulting racemic product) in the solvent system used for the crystallization[45].

5.7 Mechanism

To understand the probable mechanism of the catalytic reaction (**Scheme 5.1, X**) we carried out a series of experiments with catalyst **7** with benzaldehyde as the substrate (**S**) and imidazole (**E**) as a co-catalyst by using ethyl cyanoformate (**D**) as a cyanide source. The reaction was monitored by UV/Vis spectrophotometry and ^{1}H and ^{13}C NMR spectroscopy.

Table 5.3 Synthesis of Ethylcyanocarbonate of Various Aldehydes using V(V) Salen Complex at Optimum Reaction conditions[a]



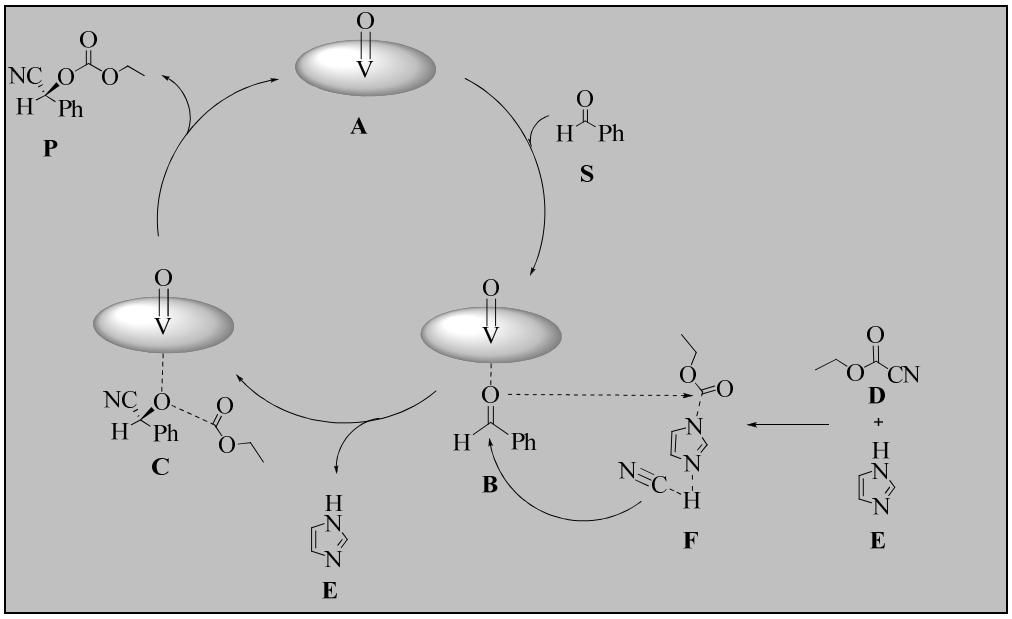
2a-r **3a-r**

Entry	Substrate	Time [h]	Yield[b]	*ee* [%][c]
1	Benzaldehyde (**2a**)	18	95	93
2	2-Naphthaldehyde (**2b**)	18	93	95
3	2-Me-benzaldehyde(**2c**)	18	96	91
4	3-Me-benzaldehyde(**2d**)	18	97	94
5	4-Me-benzaldehyde(**2e**)	24	91	90
6	2-MeO-benzaldehyde(**2f**)	24	90	96
7	3-MeO-benzaldehyde(**2g**)	48	89	89
8	4-MeO-benzaldehyde(**2h**)	60	90	93
9	2-EtO-benzaldehyde(**2i**)	48	92	93
10	2-$PhCH_2O$-benzaldehyde(**2j**)	48	93	96
11	4-F-Benzaldehyde(**2k**)	48	95	93
12	4-Cl-Benzaldehyde(**2l**)	48	80	85
13	4-Br-Benzaldehyde(**2m**)	48	90	91
14	*E*-cinnamaldehyde(**2n**)	24	91	92
15	Crotonaldehyde(**2o**)	48	91	90[d]
16	Hydrocinnamaldehyde(**2p**)	24	92	97
17	Isovarladehyde(**2q**)	24	89	76[e]
18	Hexanal(**2r**)	24	82	83[e]

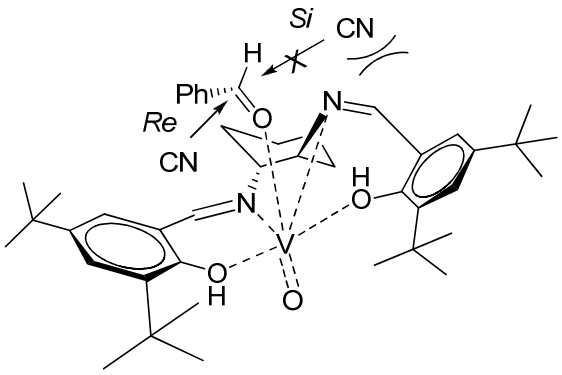
[a]All the reactions were carried out using 2.5 mol % Catalyst, 0.62 mmol of aldehydes, 1.24 mmol of ethylcanoformate, 10mol % imidazole as an additive at -20°C. [b]Isolated Yield. [c]*ee* is determined by using OD, OD-H chiral column. [d]*ee* is determined by using AD Chiral column. [e]*ee* is determined by using GC chiral G-TA column.

During the catalytic run **D** first reacts with imidazole to form an intermediate species with a probable structure **F** (**Scheme 5.1 X**), as evidenced by the emergence of new sets of peaks at δ = 8.125, 7.438, 7.038 ppm in the ^{1}HNMR spectrum (**Figure 5.2**). Similar changes were also observed in the ^{13}C NMR (**Figure 5.3**) spectrum. Species **F** is likely to react with intermediate **B** [formed by the interaction of **S** with **1**(**A**)] to form species **C**, which

eventually gives product **P**. On the basis of the X-ray structure of the vanadium salen complex reported by Belokon et al.,[6] the potential transition state was generated where the attack of cyanide through the less hindered *Re* face is favored to form the (*S*) enantiomer in excess (**Scheme 5.1 Y**).



Scheme 5.1 X Probable mechanism for the cyanoethylation of aldehydes



Scheme 5.1 Y Probable favorable transition state

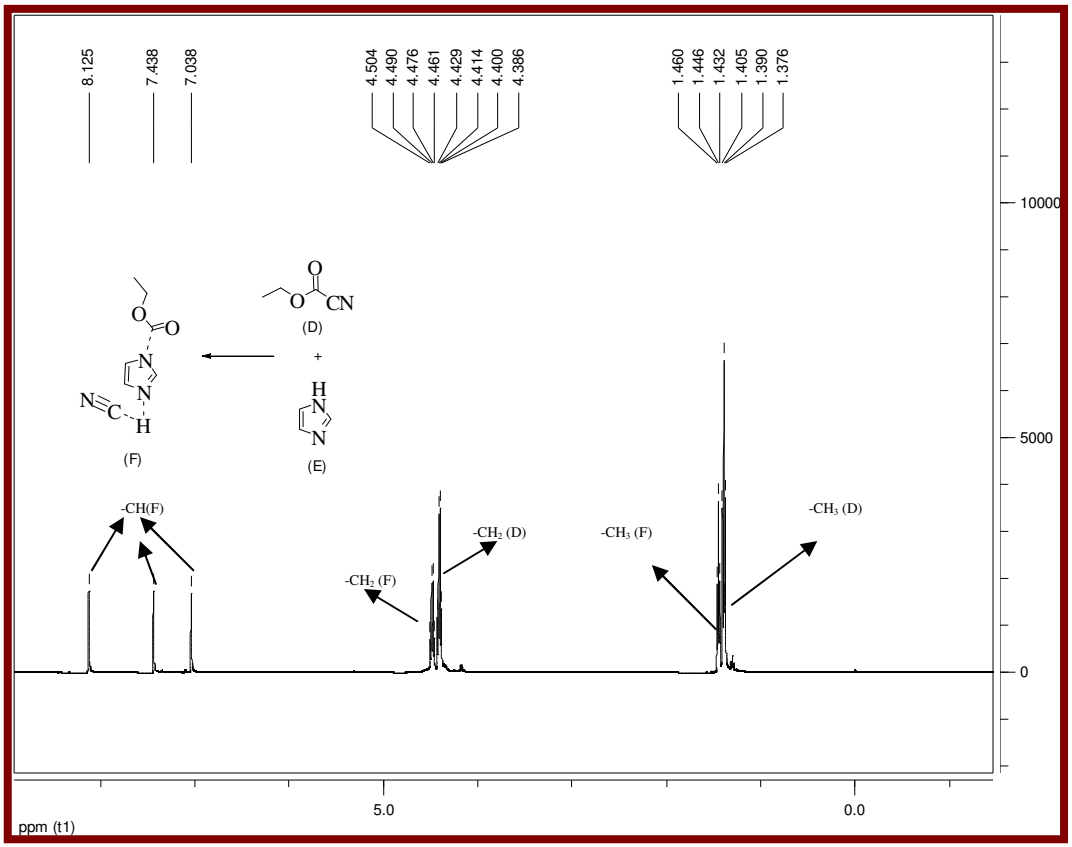


Figure 5.2 ^{1}H NMR Spectrum of mixture of ethylcyanoformate and imidazole

5.8 Conclusion

enantioselective ethylcyanoformylation of various aromatic and aliphatic aldehydes were carried out using V^{V} chiral salen complex **7** as catalyst with ethylcyanoformate as a source of cyanide in the presence of imidazole as co-catalysts. Excellent yield up to 97% with enantioselectivity (97%) for the product ethylcyanocarbonate was achieved at -20 ^{0}C and the ee of the product was further improved to >99% by re-crystallization step.

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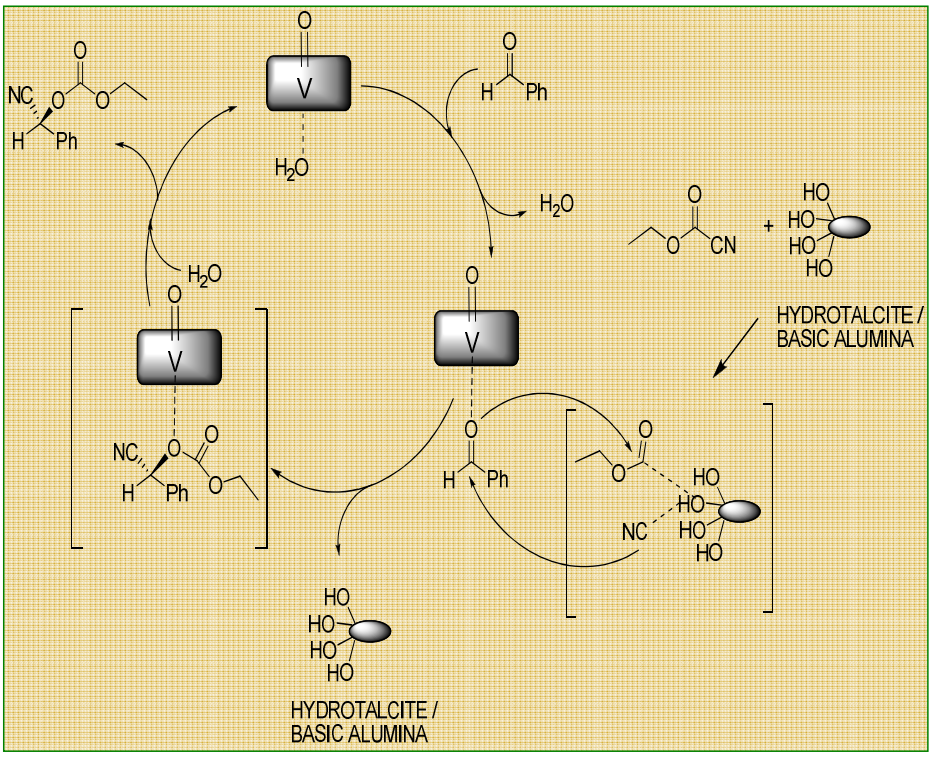
Chapter-6



Polymer V(V) salen complex as a Recyclable Catalyst for the cyanoformylation of aldehyde using solid base as co-catalyst.

6.1 Introduction

In the preceding chapter, we presented the results based on the studies on cyanoformylation of various aldehydes using V(V) salen complex with the imidazole as a co-catalyst however the system was not recyclable. This chapter deals with the use of monomeric and recyclable polymeric version of the monomeric V(V) salen complexes used in the chapter 5. The polymeric complex was used with the recyclable solid base as a co-catalyst for the cyanoethylation of aldehydes. The polymeric V(V) salen complex **3 (Figure 6.1)** and monomeric V(V) salen complex **7** (**Figure 6.2**) were synthesized as describe in chapter 3 and 5 respectively. High chiral purity (93%) and yield (95%) was achieved for the ethylcyanohydrincarbonate of 2-benzyloxybenzaldehyde when complex **3** was used as a catalyst with hydrotalcite/basic alumina as a co-catalyst. The complex **3** and hydrotalcite were easily recycled several times without any noticeable loss in its catalytic activity.

6.2 Experimental section

6.2.1 Materials and methods.

Vanadyl sulphate hydrate (Loba Chemie, India), hydrotalcite $\{Mg_6Al_2(CO_3)(OH)_{16}.4H_2O\}$, benzaldehyde, 4-methoxybenzaldehyde, 3-methoxybenzaldehyde, 2-methoxybenzaldehyde, 4-chlorobenzaldehyde, 4-bromobenzaldehyde, 4-fluorobenzaldehyde, crotonaldehyde, isovaraldehyde, hexanal, 3-methyle-2-butenal, 2-ethoxybenzaldehyde, 2-benzyloxybenzaldehyde, ethylcyanoformate were purchased from Aldrich Chemicals and were used as received. 2-Methylbenzaldehyde, 3-methylbenzaldehyde, 4-methylbenzaldehyde were from Merck chemicals where as basic Al_2O_3, NaOH, KOH were from s. d. Fine-Chemicals Limited, Mumbai (India). All the solvents were distilled and dried by standard procedure[1] and stored under nitrogen. The

synthesis and characterization of poly [(*R,R*)-*N,N'*-bis-{3-(1,1-dimethylethyl)-5-methylene salicylidene} cyclohexane-1,2 -diamine] and its precursors was carried out as described in reference.[2]

Microanalysis of the complex was done on CHNS analyzer, Perkin Elmer model 2400. NMR spectra were obtained with a Bruker F113V spectrometer (500 MHz and 125 MHz for ^{1}H and ^{13}C respectively) and are referenced internally with TMS. FTIR spectra were recorded on Perkin Elmer Spectrum GX spectrophotometer in KBr window. High-resolution mass spectra were obtained with a LC-MS (Q-TOF) LC (Waters), MS (Micromass) instruments. For the product purification, flash chromatography was performed using silica gel 60-200 mesh purchased from s. d. Fine-Chemicals Limited, Mumbai (India). The product formation and quantification was determined on capillary GC column SPB-5 (60 meter) using Shimadzu 2010 with respect to internal standard (n-*tri*decane). Enantiomeric excess (ee) were determined by HPLC (Shimadzu SCL-10AVP) using Daicel Chiralpak OD and OD-H chiral columns with 2-propanol/hexane as eluent. HPLC traces were compared to racemic samples and GC analysis CHIRALDEX G-TA (30m, 0.25mm) column. Optical rotations were measured with a Digipol 781 Automatic Polarimeter, Rudolph Instrument.

6.3 Synthesis of complex 3

The synthetic procedure of complex **3** is describe in chapter 3 (**Figure 6.1**)

6.3.1 Synthesis of complex 7

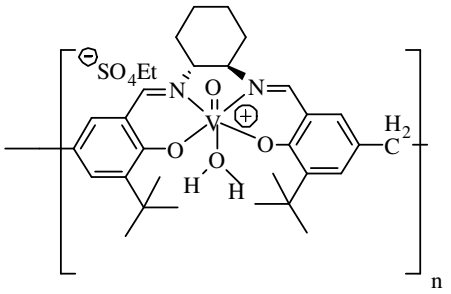
The synthetic procedure of complex **7** is describe in chapter 5 (**Figure 6.1**)

6.4 Typical experimental procedure for the enantioselective cyanoformylation of aldehydes.

A solution of V(V) salen complexes **3/7** (0.015mmol) and an appropriate aldehyde (0.62mmol) in dry CH_2Cl_2 (0.8ml) was stirred for 10 minutes at room temperature under N_2 atmosphere. To this solution hydrotalcite/basic alumina (25 mg,) was added and the solution was cooled to 15 ^oC. To this cooled solution ethyl cyanoformate (0.08 ml, 0.78mmol) was added drop-wise over a period of 5 minutes. The reaction was monitored on TLC. After completion of the reaction the product was purified by flash column chromatography on a silica gel column (eluent, hexane/ethyl acetate = 90:10). The purified products were characterized by ^1H and ^{13}C NMR which were in agreement with the reported values.[3-18]

6.5 Results and discussion

Chiral vanadium salen complexes **3** and **7** were synthesized by the reaction of poly[(*R,R*)-*N,N'*-bis-{3-(1,1-dimethylethyl)-5-methylene salicylidene} cyclohexane 1,2-diamine] / (*1R, 2R*)-*N,N'-bis*[3, 5-di(*tert*-butyl)salicylidene] cyclohexane-1, 2-diamine with vanadyl sulfate hydrate followed by auto-oxidation by the reported method (Figure 1).[19-21] Earlier we[22] and others [7,9,10] have reported that the presence of a co-catalyst greatly influence the chiral metal complexes catalyzed enantioselective addition of ethylcyanoformate to aldehydes. The co-catalysts used so far to this reaction are essentially organic bases and are non-recoverable after the catalytic run is over. Here the use of solid bases like hydrotalcite and basic alumina as recoverable co-catalysts is explored with polymeric V (V) salen complex as an active and recoverable catalyst for the ethylcyanoformylation of aldehydes.



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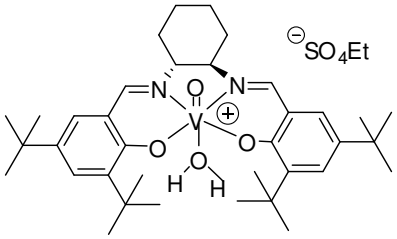

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Figure 6.1 Structure of complexes **3** and **7**

Feasibility of the enantioselective cyanoformylation reaction using benzaldehyde as a model substrate with poly V(V) salen complex **3** (2.5 mol%) as catalyst and various inorganic bases as co-catalyst at 0-25 ^{o}C was systematically studied and the data are presented in **Figure 6.2** and **Table 6.1.** Both hydrotalcite and basic alumina were effective co-catalysts however; former was better (**Table 6.1**, Entries 1, 2). The use of NaOH and KOH (**Table 6.1**, Entries 3, 4) as co-catalyst hasten the reaction (8-9h) but the reaction took racemic pathway (ee, 3-20%), due to the fact that alkali alone (Entry 5) is an active achiral catalyst for this reaction. In the absence of any co-catalyst the catalyst **3** failed to catalyze this reaction (Entry 8). Investigation of reaction parameters viz., catalyst and hydrotalcite loading, and temperature suggest that catalyst **3** loading 2.5 mol% and 25 mg of hydrotalcite at 15 ^{o}C is optimum for this reaction at 0.62 mol of aldehyde scale.

Table 6.1 Optimization of reaction condition for the enantioselective addition of ethyl cyanoformate to benzaldehyde in presence of Polymeric V(V) salen complex **3**[a]

Entry	Catalyst [mol%]	Co-catalyst	Time[h]	Temp[^{o}C]	Yield[%][b]	Ee[%][c]
1	2.5	HT (25 mg)	24	15	94	88
2	2.5	Al_2O_3 (25mg)	24	15	93	75
3	2.5	NaOH (5 mg)	8	15	96	03
4	2.5	KOH (7 mg)	9	15	97	20
5	----	KOH (7 mg)	9	15	98	racemic
6	-----	Al_2O_3 50mg)	30	25	20	---
7	----	HT (50 mg)	30	15	Trace	---
8	2.5	---------	48	25	-----	-------
9	5	HT (25 mg)	30	15	90	87
10	1	HT (25 mg)	30	15	75	72
11	2.5	HT (50 mg)	24	15	94	87
12	2.5	HT (75 mg)	24	15	94	86
13	2.5	HT (15 mg)	36	15	75	82
14	2.5	HT (10 mg)	48	15	68	79
15	2.5	Al_2O_3 (50 mg)	18	15	97	50
16	2.5	Al_2O_3 (15 mg)	36	15	92	83
17	2.5	Al_2O_3 (10 mg)	48	15	82	81
18	2.5	HT (25 mg)	24	25	89	75
19	2.5	HT (25 mg)	48	0	Trac	-----

[a]All the reactions were carried out at 0-25 ^{o}C using catalyst **3** (indicated amount), benzaldehyde (0.62 mmol), ethyl cyanoformate (1.24 mmol), co-catalyst (indicted amount) in dry DCM (0.8ml). [b]Isolated yield.[c]ee was determined using chiracel OD column.

Under the optimized reaction conditions as given above (**Table 6.1**, Entry 1) we extended this protocol of ethyl cyanoformylation reaction to a variety of aromatic and aliphatic aldehydes using the complex **3** as catalyst. Data in **Table 6.2** is an indicative of applicability of this protocol over a range of substrates where good to excellent isolated yield (88-95%) and ee (75-94%) for the products were achieved in 21-30h (Entries 1-24).

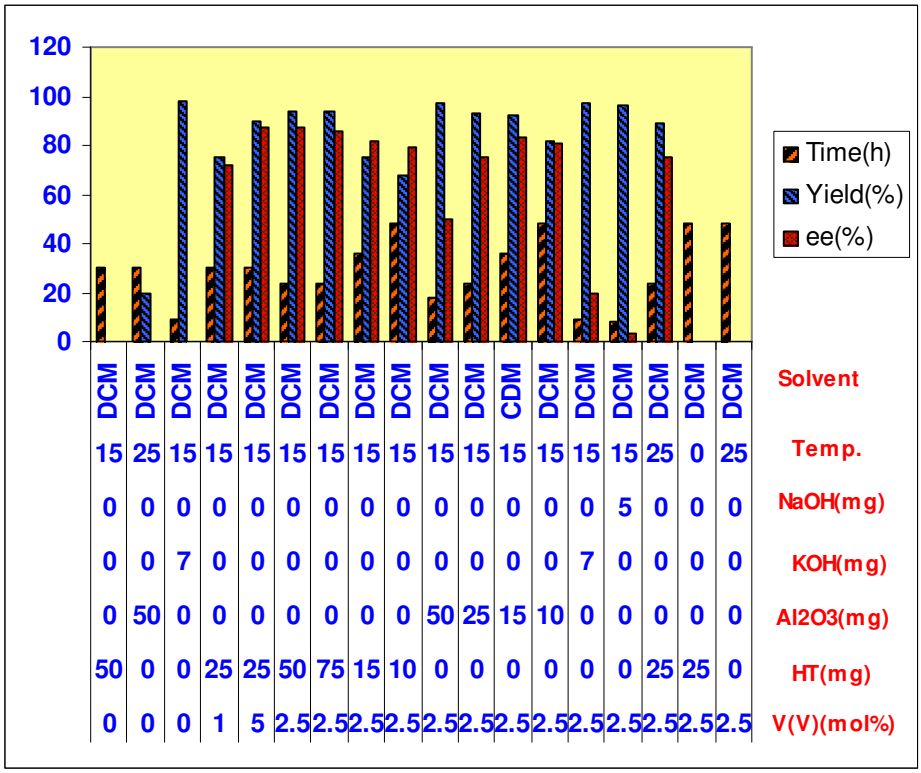
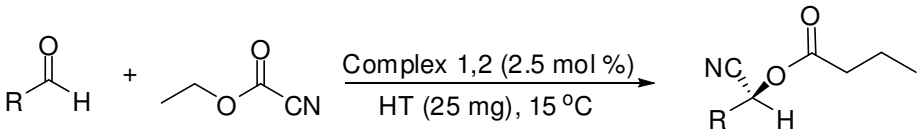


Figure 6.2 Optimization of reaction conditions for asymmetric cyanoformylation of benzaldehyde with ethyl cyanoformate as cyanide source

Surprisingly, electronic and steric factors for different substituents on the aromatic substrate did not have any noticeable effect on the yield and selectivity of the products. Similarly aliphatic substrates were also used for ethyl cyanoformylation with similar yield and enantioselectivity (**Table 6.2**, Entries 25-31). Monomeric V(V) salen complex **7** as catalyst also showed comparable yields and enantioselectivities for the cyanoformylation of these substrates using this protocol. However, the reaction took longer time as compared to the use of polymeric V(V) salen complex **3** as catalyst (**Table 6.2**, Entries 2,4,6,810,12,14,16,18,22,24,26,28,30,32). Moreover, in the case of monomeric complex **7** the catalyst was not recoverable though the hydrotalcite was recovered and recycled at the end of the catalytic run. While in the case of polymeric catalyst both catalyst and hydrotalcite

were recoverable and recyclable. The enhanced reactivity in the case of polymeric complex as against monomeric complex may be attributed to the increase reactive sites which may be working in co-operation.[20,21,23] In all the catalytic runs, the *(R)*- form of V(V) salen complexes **3** and **7** as catalysts resulted in to *(S)* enantiomer of the product ethyl cyanohydrincarbonates.

Table 6. 2 Enantioselective addition of ethyl cyanoformate to various aldehydes using V(V) salen complexes **3** & 7 with HT as a co-catalyst[a].



Entry	Substrate	Time[h]	Yield [%][b]	ee [%][c]
1(2)[d]	Benzaldehyde	24(30)	94 (93)	88 (87)
3 (4)	2-methylbenzaldehyde	30 (36)	91 (90)	81 (80)
5 (6)	3-methylbenzaldehyde	24 (36)	93 (91)	83(81)
7 (8)	4- methylbenzaldehyde	24 (28)	91 (89)	80 (78)
9 (10)	2-methoxybenzaldehyde	24 (36)	92 (89)	91 (90)
11 (12)	3-Methoxybenzaldehyde	24 (36)	89 (87)	84 (82)
13 (14)	4- Methoxybenzaldehyde	24(36)	90 (89)	83 (79)
15 (16)	2-ethoxy benzaldehyde	24 (36)	90 (87)	84 (81)
17 (18)	2-benzyloxybenzaldehyde	24 (30)	92 (91)	94 (92)
19 (20)	4-fluorobenzaldehyde	24(24)	95 (93)	90 (88)
21 (22)	4-chlorobenzaldehyde	24 (30)	88 (89)	75 (71)
23 (24)	4-Bromobenzaldehyde	24 (30)	89 (90)	85 (86)
25 (26)	Hexanal	21 (30)	93 (91)	81 (80)
27 (28)	3-methyl-2-butene	24 (36)	91 (89)	83 (82)
29 (30)	Crotonaldehyde	24 (36)	88 (87)	77 (75)
31 (32)	Isovaraldehyde	21 (30)	90 (92)	86 (85)

[a]All reaction carried out at 15 °C using catalyst **3** and **7** (2.5 mol%), aldehyde (0.62 mmol), ethyl cyanoformate (1.24 mmol), HT(25 mg) in dry DCM (0.8ml).
[b] Isolated yield.[c] ee determined by chiral HPLC and GC.[d]Data in parentheses given for complex **7**

In order to assess the recyclability of the polymeric complex **3,** the catalytic run for the ethyl cyanoformylation of benzaldehyde was taken as representative test run under the reaction condition mentioned in Entry 1, **Table 6.1.** Consequently, after the first catalytic run excess amount of hexane was added to the reaction mixture and the resulting solid was collected by filtration. The recovered solid was thoroughly washed with hexane and vacuum dried before reuse. The recovered solid containing both the catalyst **1** and the co-catalyst hydrotalcite was used as such in the manner same as fresh catalyst in the ethyl cyanoformylation of benzaldehyde which showed similar activity and enantioselectivity in the recycle experiments (**Table 6.3**, runs 2-4) though there was some increase in reaction time. The recyclability of this catalytic system has clear edge over previously reported polymeric V(V) salen complexes.[20,21,24]

Table 6.3 Data for the enantioselective addition of ethyl cyanoformate to benzaldehyde using recycle polymeric V (V) salen complex **3** with recycle HT as a co-catalyst[a]

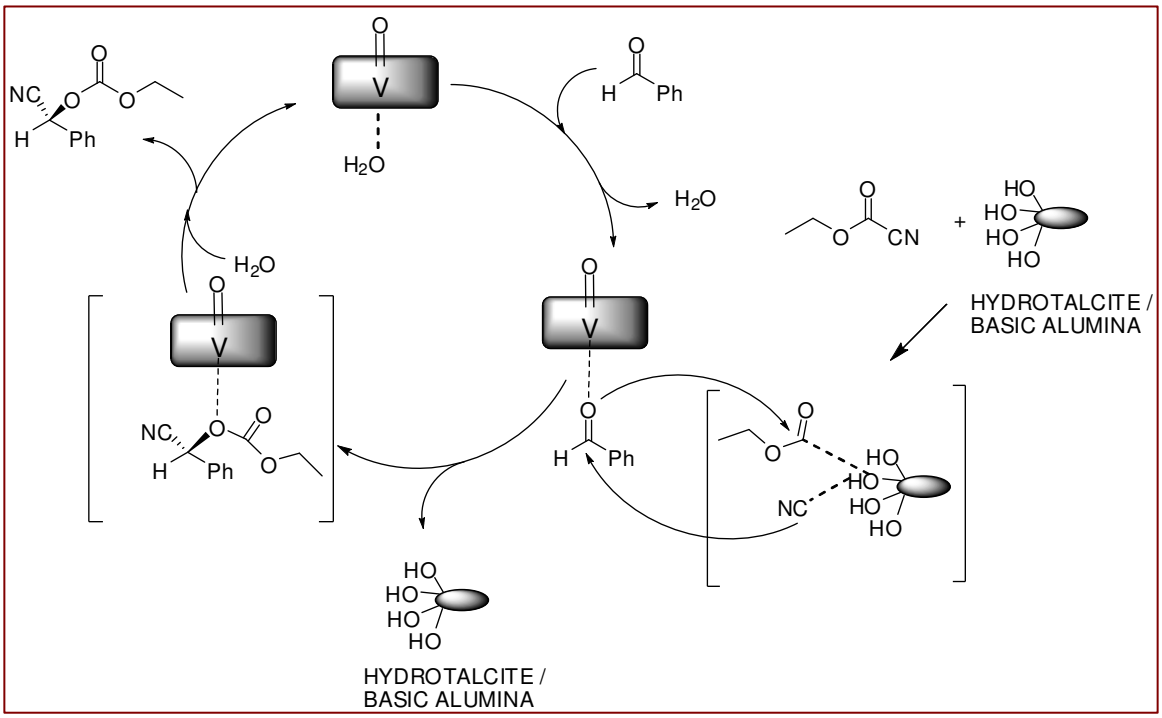
Run	**1**	**2**	**3**	**4**
Time [h]	24	28	30	30
Yield [%][a]	93	92	92	89
ee [%][b]	87	87	86	87

[a] Isolated yield.[b]The ee was determined by using chiralpak HPLC OD column.

6.6 Mechanism

On the basis of the product distribution a probable mechanism of cyanoformylation of aldehydes is proposed (**Scheme 6.1**). In view of high chiral induction in the product it would be appropriate to consider that the substrate is activated by way of its interaction with the acidic metal site of the chiral complex. Concomitantly the solid base activates the source of cyanide. In a concerted manner then nucleophilic attack of CN took

place while the ethylformyl group moves to the aldehydic oxygen to produce the desired product in high chiral purity.[22]



Scheme 6.1 Probable mechanism for cyanoformylation of benzaldehyde using hydrotalcite/basic alumina using chiral V(V) salen complex

6.7 Conclusion

In conclusion, a highly efficient enantioselective ethyl cyanoformylation of various aromatic and aliphatic aldehydes was carried out by using VV chiral polymeric and monomeric salen complexes **3** and **7** respectively as catalysts with ethyl cyanoformate as a source of cyanide in the presence of several co-catalysts. Excellent yield (95%) and enantioselectivity up to 93% for the product ethyl cyanohydrincarbonate was achieved when hydrotalcite was used as co-catalyst. The chiral polymeric catalyst **3** and hydrotalcite as solid base used as co-catalysts were recyclable several times with retention of their performances.

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List of Publications:

[1] Asymmetric synthesis of *O*-Acetylcyanohydrins by reaction of aldehydes with NaCN/KCN catalyzed by recyclable chiral dimeric Titanium (IV)/ Vanadium (V) salen complexes. N. H. Khan, **Santosh Agrawal**, R. I. Kureshy, S. H. R. Abdi, V. J. Mayani, R. V. Jasra, ***Eur. J. Org. Chem.*** **2006**, 3175-3180.

[2] Asymmetric addition of trimethylsilyl cyanide to aldehydes promoted by chiral polymeric vanadium (V) salen complex as an efficient and recyclable catalyst. N. H. Khan, **Santosh Agrawal**, R. I. Kureshy, S. H. R. Abdi, V. J. Mayani, R. V. Jasra, ***Tetrahedron: Asymmetry*** **2006**, 17, 2659-2666.

[3] Enantioselective aminolytic kinetic resolution (AKR) of epoxides catalyzed by recyclable polymeric Cr(III) salen complexes. R. I. Kureshy, S. singh, N. H. Khan, S. H. R. Abdi, **S. Agrawal**, R. V. Jasra, ***Tetrahedron: Asymmetry*** **2006**, 17, 1638-1643.

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[10] Synthesis and characterization of mesoporous silica modified with chiral auxiliaries for their potential application as chiral stationary phase. V. J. Mayani, S. H. R. Abdi, R. I. Kureshy, N. H. Khan, **S. Agrawal**, R. V. Jasra, ***J. Chromatogr. A*** **2008**, 1191, 223-230.

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[14] Enantioselective cyanosilylation of ketones catalyzed by recyclable polymeric and dimeric Mn(III) salen complexes at room temperature. N. H. Khan, **Santosh**

Agrawal, R. I. Kureshy, S. H. R. Abdi, K. J. Prathap, R. V. Jasra, **Chirality 2009**, 262-270,

[15] Highly efficient recyclable Co(III) salen complexes-catalyzed asymmetric synthesis of *N*-protected 1, 2-aminoalcohols. R. I. Kureshy, K. J. Prathap, **S. Agrawal**, N. H. Khan, S. H. R. Abdi, H. C. Bajaj, *Eur. J. Org. Chem.* (Accepted **2009**)

[16] Enantioselective cyanoformylation of aldehydes: A cooperative catalysis through chiral V(V) salen complex with solid base. N. H. Khan, **S. Agrawal**, R. I. Kureshy, S. H. R. Abdi, K. Pathak, H. C. Bajaj, ***Chirality*** (Accepted **2009**)

Review Article

[1] Metal catalyzed asymmetric cyanation reactions. N. H. Khan, R. I. Kureshy, S. H. R. Abdi, **Santosh Agrawal**. R. V. Jasra, ***Coordination Chemistry Review*** **2008**, 252, 593-623,

Monograph (Book Chapter)

[1] New approaches for reusable chiral heterogeneous catalysts for epoxide ring opening reaction" R. I. Kureshy, N. H. Khan, S. H. R. Abdi, **Santosh Agrawal**, K. Jeya Prathap, R. V. Jasra, ***Nova Science Publication*** (Accepted **2009**).

Patent filed

[1] Preparation of organic-inorganic hybrid chiral Sorbent. S. H. R. Abdi, R. I. Kureshy, N. H. Khan, R. V. Jasra, V. J. Mayani, **S. Agrawal**, submitted for US patent of Patent Division New Dehli (**2006**)

Highlighted Articles

[1] Enantioselective aminolytic kinetic resolution (AKR) of epoxides catalyzed by recyclable polymeric Cr(III) salen complexes. R. I. Kureshy, S. singh, N. H. Khan, S.

H. R. Abdi, **S. Agrawal**, R. V. Jasra. ***Tetrahedron: Asymmetry*** **2006**, 17, 2659-2666, (**Appeared among 25 HOT Article**)

[2] Vanadium(V) salen complex catalyzed highly enantioselective cyanoformylation of aldehydes in the presence of imidazole as a co-catalyst. N. H. Khan, **Santosh Agrawal**, R. I. Kureshy, S. H. R. Abdi, K. J. Prathap, R. V. Jasra. ***Eur. J. Org. Chem.*** **2008**, 4511-4515. (**Selected in Synfact for highlighted organic work**)

Conferences and Symposia

[1] A Poster entitled, Recyclable dimeric Ti (IV) salen complex-catalyzed asymmetric synthesis of *O*-Acetylcyanohydrin using NaCN is presented in **11th Symposium on Modern Trends in Inorganic Chemistry (MTIC-XI)** held at IIT Dehli during **15-17 Dec**. **2005**.
S. Agrawal, N. H. Khan, R. I. Kureshy, S. H. R. Abdi, V. J. Mayani, R. V. Jasra**.**

[2] A Poster entitled, Asymmetric synthesis of *O*-Acetylcyanohydrin from NaCN/KCN, Ac2O and aldehydes catalyzed by recyclable dimeric salen V(V) complex is presented in **All Gujarat Research Scholar meet (AGRSM-06)** held at M. S. University, Vadodara on **22nd Jan. 2006**.
S. Agrawal, N. H. Khan, R. I. Kureshy, S. H. R. Abdi, V. J. Mayani, R. V. Jasra**.**

[3] A Oral presentation entitled Chiral polymeric V(V) salen complex as efficient and recyclable catalyst for the asymmetric addition of trimithylsilysl cyanide to aldehydes. In **18th National Symposium on Catalysis** held at IIP Dehradun during **16-18 April** 2007**.**
S. Agrawal, N. H. Khan, R. I. Kureshy, S. H. R. Abdi, V. J. Mayani, R. V. Jasra.

[4] A Oral presentation entitled Catalytic cyanosilylation of carbonyl compounds using Fe(Cp)2PF6 as an efficient catalyst under solvent free conditions. In **12th Symposium on Modern Trends in Inorganic Chemistry (MTIC-XII)** held at Department of Chemistry, IIT Madras, Chennai, during **6-8 Dec. 2007**.
S. Agrawal, N. H. Khan, R. I. Kureshy, S. H. R. Abdi, V. J. Mayani, R. V. Jasra.

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K. Pathak, **S. Agrawal**, S. H. R. Abdi, R. I. Kureshy, N. H. Khan, R. V. Jasra.

[6] A Oral presentation entitled Highly Enantioselective Cyanoethylation of Aldehydes Catalyzed by V(V) salen Complex. In **XXII Gujarat Science Congress 2008** held at Bhavnagar University, Bhavnagar on **9th march 2008**,
S. Agrawal, N. H. Khan, R. I. Kureshy, S. H. R. Abdi, K. J. Prathap, R. V. Jasra.

[7] A Oral presentation entitled Highly Enantioselective Cyanoformylation of Aldehydesusing Chiral V(V) Salen Complex with Imidazole as a Co-Catalyst. In **19th National Symposium on Catalysis (CATSYMP-19)** held at National Chemical Laboratory (NCL)Pune, India during 18-21 Jan. 2009.
S. Agrawal, A. Sadhukhan, N. H. Khan, R. I. Kureshy, S. H. R. Abdi, and H. C. Bajaj.

Awards

[1] **Best Poster presentation Award** during **All Gujarat Research Scholar meet (AGRSM-06)** held at M. S. University, Vadodara on **22nd Jan. 2006**.

[2] **Best Oral Presentation Award** in Organic Division during **XXII Gujarat Science Congress 2008 held** at Bhavnagar University, Bhavnagar on **9th March 2008**.

[3] **CSIR –Senior Research Fellowship** Award from **1st April 2008** to till now.

[4] **Hindustan Platinum Award for Best Oral Presentation during 19th National Symposium on Catalysis (CATSYMP-19)** held at National Chemical Laboratory (NCL) Pune, India during **18-21 Jan. 2009.**