ASYMMETRIC SYNTHESES OF VARIOUS NOVEL CHIRAL LIGANDS WITH NORBORNENE BACKBONE: THE USE OF CHIRAL CATALYST IN ASYMMETRIC REACTIONS

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IN
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Approval of the Graduate School of Natural and Applied Sciences.

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I certify that this thesis satisfies all the requirements as a thesis for the degree of Doctor of Philosophy.

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This is to certify that we have read this thesis and that in our opinion it is fully adequate, in scope and quality, as a thesis for the degree of Doctor of Philosophy.

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ABSTRACT

ASYMMETRIC SYNTHESES OF VARIOUS NOVEL CHIRAL LIGANDS WITH NORBORNENE BACKBONE: THE USE OF CHIRAL CATALYST IN ASYMMETRIC REACTIONS

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The synthetic strategy of this study mainly depends upon the asymmetric desymmetrization of meso norbornene type an anhydride. Asymmetric desymmetrization was achieved by using chinchona alkaloids under kinetically controlled conditions. The resultant mono ester carboxylic acid was epimerized to *trans* configuration. Subsequent esterification followed by lithium aluminum hydride reduction afforded the first chiral diol ligand with 98 % ee. Transformation of diol to corresponding *trans* diamine was achieved via Mitsunobu-Gabriel combination. The resultant diamine was first transformed into salen type ligand with 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde. Throughout this process, no racemization was observed and all the ligands tested in asymmetric reactions have 98 % ee value.

The second part of the thesis involves the asymmetric test reactions of the chiral ligands to check the effectiveness of them. The first testing method was diethylzinc

addition to benzaldehyde. The ligands showed moderate effectiveness. The salen type ligand was tested in asymmetric epoxidation and aziridination reactions and it showed good effectiveness. Another applied method was desymmetrization of *meso* 2-cyclohexene-3,4-diol in which 2-(diphenylphosphino)benzoic acid attached *trans*-diol and *trans*-diamine type ligands were tested. Since norbornene type strained bicyclic systems are available in ring opening methathesis polymerization (ROMP) reactions, *trans*-diamine was subjected to ROMP to get an enlarged macromolecular system

Key words : salen ligands, asymmetric epoxidation, asymmetric aziridination, diethylzinc addition, desymmetrization

ÖZ

TEMELDE NORBORNEN TİPİ YAPI TAŞIYAN YENİ KİRAL LİGANDLARIN ASİMETRİK SENTEZİ: KİRAL KATALİZÖRLERİN ASİMETRİK REAKSİYONLARDA KULLANIMI

ELMALI, OLCAY

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Tez Yöneticisi : Prof. Dr. Cihangir Tanyeli

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Bu çalışmada takip edilen yol ana hatlarıyla meso norbornen tipi bir anhidritin asimetrik desimetrizasyonuna bağlıdır. Asimetrik desimetrizasyon ise kinkona alkaloitler yardımıyla kinetik olarak kontrollü bir ortamda yapılmıştır. Sonuçta elde edilen *cis* mono ester karboksilik asit, *trans* konfigurasyona epimerleştirilmiş, takiben yapılan lityumalüminyum hidrür indirgenmesi ilk ligantımız olan kiral *trans*-diolün % 98 ee ile eldesini sağlamıştır. Mitsunobu ve Gabriel reaksiyonlarının ortak kullanımıyla *trans* diol *trans* diamin'e dönüştürülmüş, elde edilen diamin ise öncelikle 3,5-di-*tert*-butil-2-hidroksibenzaldehit ile salen tipi bir liganta dönüştürülmüştür. Bu işlemlerin tümünde rasemizasyon olmadığı için asimetrik reaksiyonlarda denenecek ligantların ee değerleri % 98'dir.

Çalışmanın ikinci bölümünde elde edilen kiral ligantların asimetrik reaksiyonlardaki etkinliklerini ölçmek için deneme reaksiyonları yapılmıştır. İlk metot

benzaldehite dietilçinko katılım reaksiyonudur. Bu reaksiyonda ligantlar ortalama etkinlik göstermişlerdir. Salen tipi ligand ise asimetrik epoksitleme ve asimetrik aziridinlemes reaksiyonlarında denenmiş ve olumlu bir etkinlik göstermiştir. Denenen diğer bir metot ise meso 2-siklohekzen-3,4-diol'ün desimetrizasyon reaksiyonudur, bu reaksiyonda 2-(difenilfosfino)benzoik asit takılı *trans*-diamin ve *trans*-diol ligant olarak denenmişlerdir. Norbornen tipi gerilimli bisiklik sistemler halka açılımlı metastas polimerizasyon reaksiyonlarına (ROMP) uygun yapılar oldukları için trans-diamin yapı daha geniş makromoleküler bir sistem oluşturmak üzere ROMP reaksiyonunda da denenmiştir.

Anahtar Kelimeler : salen ligantları, asimetrik epoksidasyon, asimetrik aziridinasyon, dietilçinko katılımı, desimetrizasyon

Ailem’e

To My Family

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LIST OF ABBREVIATIONS

DAIB : dimethylaminoisoborneol

acac : acetic acid

2-DPPBA : 2-(diphenylphosphino)benzoic acid

TMSCN : trimethylsilyl cyanide

4-PPNO : 4-phenylpyridine N-oxide

DET : diethyl tartrate

TBME : tert-butylmethylether

DCC : dicyclohexylcarbodiimide

DMAP : dimethylamino pyridine

DEAD : diethylazodicarboxylate

NMO : *N*-methylmorpholine-*N*-oxide

***m*-CPBA :** *meta*-chloroperbenzoic acid

LDA : lithium diisopropylamine

THF : tetrahydrofurane

ROMP : ring opening metathesis polymerization reaction

TLC : thin layer chromatography

HPLC : high performance liquid chromatography

ee : enantiomeric excess

NMR : nuclear magnetic resonance

App. No : appendix number

CHAPTER I

INTRODUCTION

1.1. Importance of Asymmetric Synthesis

The importance of enantiomerically pure compounds comes from the central role of enantiomer recognition in biological activity. When one chiral molecular species and another interact, diverse properties of substances can be obtained, such as smell of a fruit, the antibacterial activity of a drug [1]. There are many examples of pharmaceutical drugs, agrochemicals and other chemical compounds where the desired biological property is related to the absolute configuration. Moreover, the three main classes of biopolymers are all chiral, nucleic acids and polysaccharides contain sugar subunits, also proteins contain chiral aminoacids.

The recognition events in biology and the action of drugs that intervene in these events will always involve the molecular recognition of a biologically active molecule by a chiral nonracemic receptor structure. It is well known, that the interactions between chiral molecules change dramatically when one molecule is replaced by its mirror image. This chiral specificity is the basis of a major industry producing chiral drugs. The two enantiomers of a drug molecule cannot bind equally well to the receptor and therefore cause different biological responses [2]. Therefore understanding chirality is extremely important in the preparation of therapeutic drugs. For example, one enantiomer of penicillamine is a potent anti-arthritic agent whereas the other enantiomer is highly toxic. Perhaps the most startling example of the difference in activity between enantiomers is Thalidomide. This drug was seen as

a panacea for the treatment of morning sickness in pregnant women, and indeed one enantiomer reliably has this effect. The other enantiomer, unfortunately, has been associated with the well-characterized birth defects that arose from use of Thalidomide.

Enantioselective synthesis is of growing importance, particularly in the pharmoceutical industry, and is currently the subject of intense research in academic and industrial laboratories around the world [2].

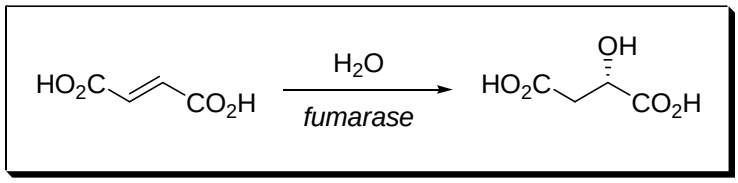
In principle, a general solution to the problem of obtaining enantiomerically pure organic compounds would be to have available an array of synthetic methods which result in the desired transformation and control the absolute stereochemistry of chiral centers which are created as a result of the synthetic operation. This is the realm of asymmetric synthesis.

Selectivity can be defined as discrimination observed in a reaction involving competitive attack on two or more substrates or at two or more positions, groups or faces in the same substrate [3].

One can identify three types of selectivity which may be required in the reactions of organic molecules.

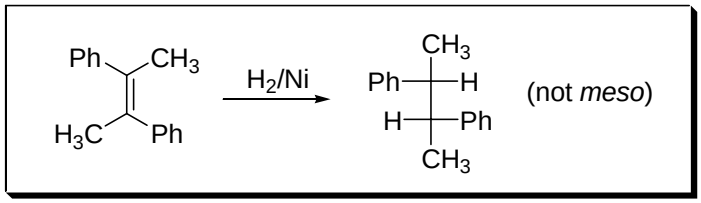
- *chemoselectivity*
- *regioselectivity*
- *stereoselectivity*
    - *enantioselectivity*
    - *diastereoselectivity*

Enantioselectivity in a reaction is either the preferential formation of one enantiomer of the product over the other or the preferential reaction of one enantiomer of the (usually racemic) starting material over the other. The latter is also known as an asymmetric transformation or de-racemization.



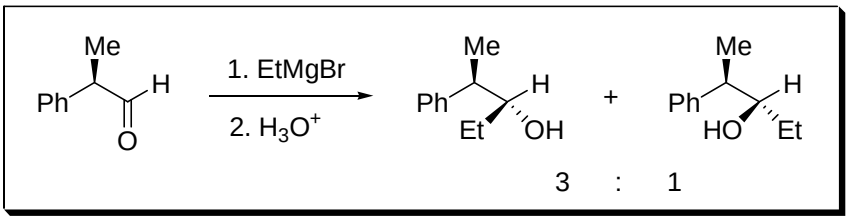
Scheme 1. Example for enantioselectivity

Diastereoselectivity occurs when the products which can be formed are diastereomers. Diastereoselectivity can be subdivided into two types; simple and absolute diastereoselectivity. Simple diastereoselectivity can occur in a reaction in which two or more new stereogenic centers are created, even when the reaction involves an achiral substrate and an achiral reagent [3].



Scheme 2. Example for simple diastereoselectivity

Absolute diastereoselectivity is seen in the reaction of a chiral substrate with an achiral reagent.



Scheme 3. Example for absolute diastereoselectivity

1.2. Asymmetric Synthesis

An asymmetric synthesis is one which creates new stereogenic units in a controlled way. Such processes may be enantioselective or diastereoselective (or both), and so they may give rise to enantiopure products or racemic products, with control of relative stereochemistry [1].

Nowadays asymmetric synthesis is used for reactions capable of giving rise to enantiopure products, which is certainly the most important and possess the greatest challenge. In principle this can be achieved by using a chiral, non-racemic substrate, reagent, solvent or catalyst.

1.2.1. Design of asymmetric synthesis

Achiral starting materials can in certain circumstances become converted into chiral non-racemic products, and some process of this type must have been responsible for the original biasing of natural products to favor one enantiomeric series. Here, chiral product catalyses its own enantioselective preparation, this method is known as De novo asymmetric synthesis [1].

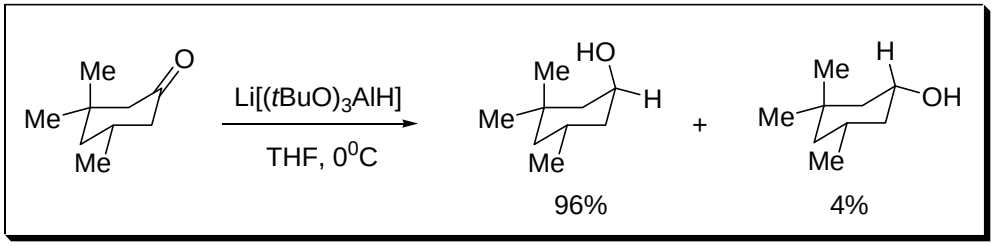
A prochiral substrate or functional group is converted into an enantiopure product in a reaction mediated by a chiral auxiliary, either in a stoichiometric or catalytic fashion. When a chiral catalyst is involved, tiny amount can produce a large amount of enantiopure product.

In some enantiomer syntheses of target molecules, optically pure starting materials are incorporated directly. The supply of enantiopure starting materials for this purpose is sometimes referred to as the *chiral pool*. The efficiency of stereocontrol is determined by measuring the excess of the desired diastereoisomer over the others [4].

The above mentioned selectivities can be characterized as follows:

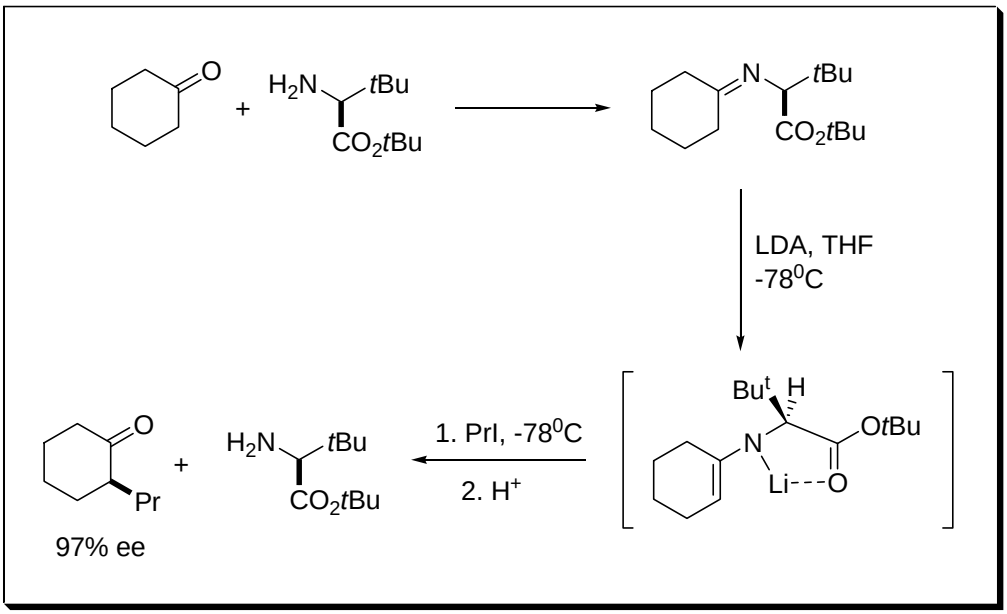
- Photochemical transformations induced by "chiral", i.e. circulary polarized light. This is an impractical method giving only a few percent ee or less.

- *Diastereoselective reactions*, in which the formation of a new chiral center is under the control of an existing center in the same molecule.



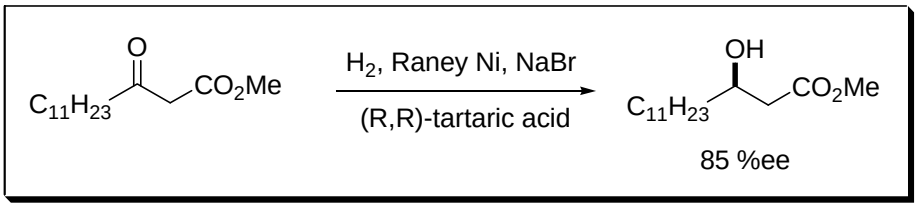
Scheme 4. Example for diastereoselective reactions [5]

- A stoichiometric chiral auxiliary is covalently attached to the substrate before chirality relay is performed. Chirality in the auxiliary controls the asymmetric induction, and the auxiliary is removed for reuse once the new chiral center is built [1].



Scheme 5. Example for the chiral auxiliary in asymmetric synthesis [5]

- When a stoichiometric chiral reagent effects asymmetric induction, the inducing chirality is not part of the substrate and is not determined directly, in the planning process, by the structure of the target molecule.



Scheme 6. Example for the use of chiral reagent in asymmetric synthesis [5]

- Reactions conducted in a chiral solvent which is likely to be involved in transition states [2]. Chiral solvents are generally low efficient, very expensive and thus do not qualify for practical stereoselective synthesis [5].

- Catalytic modifications of the above mentioned processes, is another approach for asymmetric synthesis. The chiral auxiliary and other catalyst components e.g. a transition metal can become covalently attached to the substrate in an intermediate in the catalytic cycle or might act in an intermolecular fashion, inducing asymmetry in a single step [1].

- An alternative approach to asymmetric synthesis is that of kinetic resolution, in which a resolution of a racemic substrate is achieved at the same time as an asymmetric reaction. This approach relies on the difference in the rate of reaction of the individual enantiomers of the racemate with an enantiomerically pure reactant, reagent or catalyst.

Among the types of asymmetric reaction, the most desirable and the most challenging catalytic asymmetric synthesis, since one chiral catalyst molecule can create millions of chiral product molecules, just as enzymes do in biological systems. Catalytic asymmetric synthesis often has significant economic advantages over stoichiometric asymmetric synthesis [6].

1.3. Catalysts Used in Asymmetric Synthesis

A catalyst can affect both reactivity and selectivity of organic transformations, and affords the possibility of conducting organic synthesis in a highly controlled manner. There are two types of catalysts which have been widely applied for this purpose, namely enzymes and homogeneous transition-metal complex catalysts [7].

1.3.1. Enzyme Catalysis:

Enzymes are proteins with catalytic activity evolved in nature to speed up and coordinate the multitude of chemical reactions necessary to develop and maintain life [8].

There is a high degree of evolutionary fine tuning in enzyme structure, with two particular consequences- the substrate is matched to the enzyme active site by both steric (repulsive) and electrostatic (attractive) forces and its recognition by the enzyme is a global effect in that groups remote from the active site can effect specificity and reactivity [9].

Enzyme catalysis is sensitive to the overall shape and molecular structure of the reactant. Besides, transition state is often of different geometry to the bound reactant resting site.

There is a requirement for many special enzymes to cover the diversity of chemical reactions desired in organic chemistry. The enzyme needed in a specific case may not be available.

1.3.2. Transition Metal Complex Catalysts:

Metal complexes of oxene, nitrene, and carbene react with C=C and C-H bonds, forming C-O, C-N, and C-C bonds, respectively. These bond formations are in most cases accompanied with generation of asymmetric center(s) at the reaction site. Much effort has been directed toward stereocontrol of the reactions of these active species, and considerable advancement has already been made. Carbenoid chemistry, especially, has been studied for more than four decades, and high enantioselectivity has been achieved generally in intra- and inter-molecular C-H insertion reactions. Oxene and nitrene transfer reactions have also been extensively studied in the last two decades and highly enantioselective methodologies have been developed by introducing new types of catalysts. Among these catalysts, metal complexes of optically active N,N'-ethylenebis(salicyldeneaminato) ligands are

versatile catalyst for these asymmetric atom transfer and their related reactions [6- 10].

These types of ligands are generally called as Schiff base ligands which are named by Hugo Schiff in 1864. Schiff base ligands are obtained by condensation of an aldehyde and an amine. Those ligands are able to coordinate metals through imine nitrogen and another group, usually linked to the aldehyde. In fact, Schiff bases are able to stabilize many different metals in various oxidation states, controlling the performance of metals in a large variety of useful catalytic transformations. Schiff bases are also able to transmit chiral information to produce nonracemic products through a catalytic process; chiral aldehydes or chiral amines can be used.

When two equivalents of chiral or achiral salicylaldehyde derivative are combined with a diamine, a particular chelating Schiff base is produced. This particular class of Schiff bases the so-called Salen ligands, with four coordinating sites and two axial sites open to ancillary ligands. Although the term Salen was used originally only to describe the tetradentate Schiff bases derived from ethylenediamine, the more general term Salen-type is used in the literature to describe the class of [O,N,N,O] tetradentate bis-Schiff base ligands (Figure 1) [11, 12].

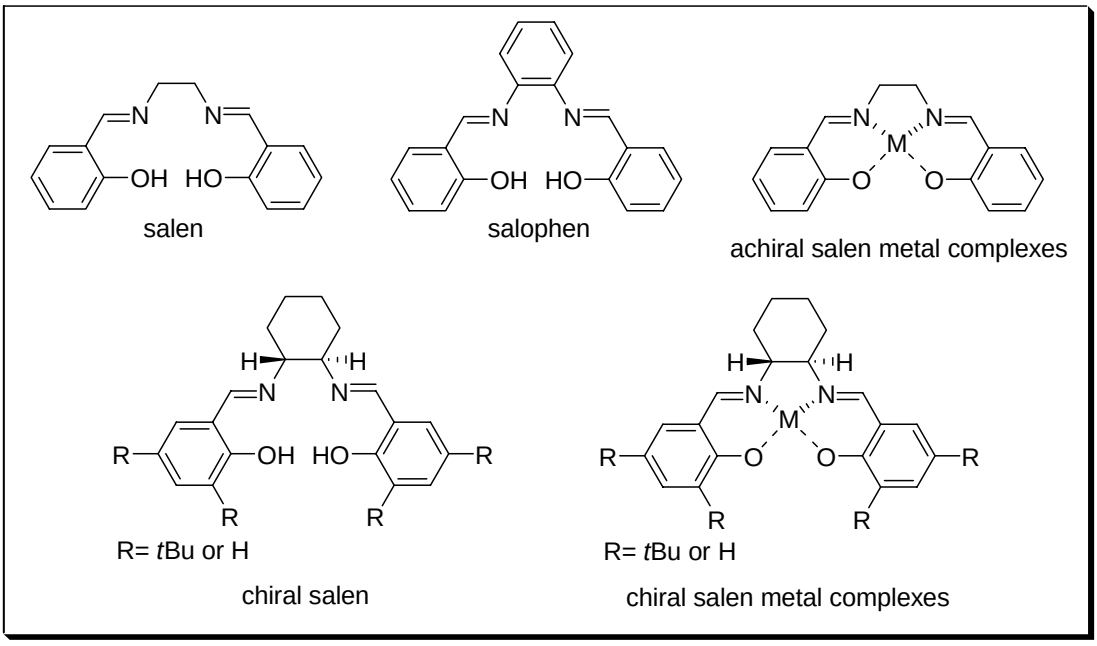


Figure 1. Different salen ligands and M-salen complexes

Since the development of efficient catalytic asymmetric reactions is the most challenging task in current synthetic chemistry, much effort has been devoted to create the chiral metal complexes of advanced asymmetric synthesis [11]. Therefore many brand-new ligands have been introduced in the last two decades and their combination with various metal ions has realized the syntheses of highly efficient asymmetric catalysts.

The practical utility of a chiral ligand is closely associated with its availability in large amounts from inexpensive precursors, its good activity, and optical purity and possible recycling.

The first salen ligand and its Cu complex (Figure 2; **1)** was prepared by Combes in 1889, then in 1934 Pfeiffer *et al.* reported the formation of achiral Schiff bases (Figure 2; **2a**, **2b**) and their complexation with various metals. Three decades later, Uhlemann developed the synthesis of a new chiral Schiff base (Figure 2; **3a)**, derived from o-nitrobenzaldehyde and 1*R*, 2*R*-*trans*-diaminocyclohexane [13].

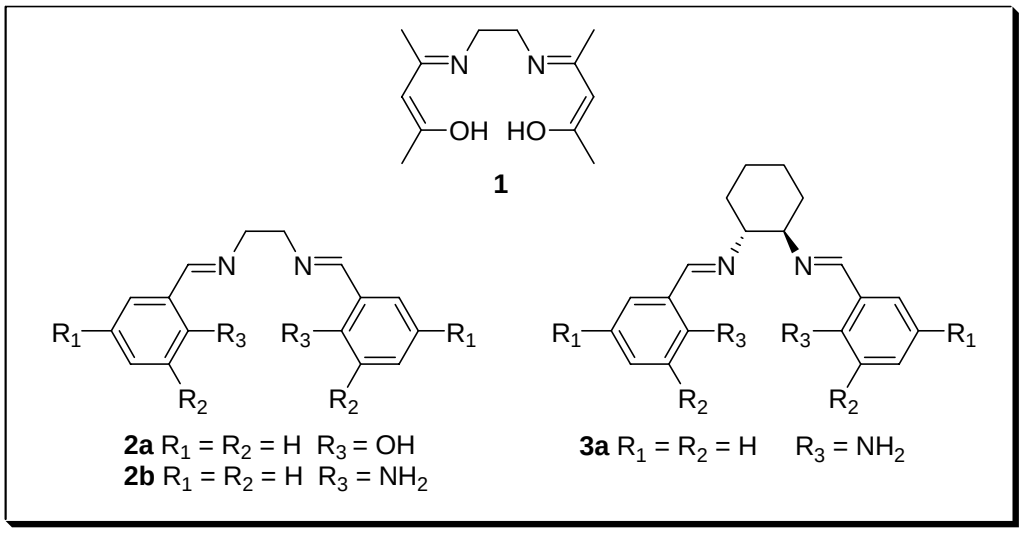


Figure 2. Schiff bases of 1,2-diamines with substituted benzaldehydes

These nitrogen containing ligands have been widely used as chelating ligands for metal cations such as Ni(II), Cu(II), Co(II), Fe(III) and many others, but examples for asymmetric transformations catalyzed by such complexes are still rare [14]. However, in the last years, the use of nitrogen containing ligands in catalysis has received increasing attention. Their high complex stability and good availability in enantiomerically pure form are advantageous for practical applications.

The above mentioned complexes are now used as the catalysts for a variety of enantioselective reactions such as oxidations, aziridination, cyclopropanation, Diels-Alder reaction, addition of TMSCN to aldehydes, and Strecker reaction and for kinetic resolution of racemic epoxides [15-20].

A prominent example is Jacobsen's Mn(III)-salen complex, which is currently the most efficient catalyst available for enantioselective epoxidation of unfuctionalized alkenes [21].

1.4. The Jacobsen Catalyst - N,N'-Bis(3,5-di-*t*-butylsalicylidene)-1,2-cyclohexanediamino-manganese(III) chloride

In the early nineties, Jacobsen and his colleagues designed the chiral Mn(III)-Schiff base complex **4** (Figure 3). The catalyst was the result of a logical sequence of ligand modifications involving more than fifty complexes [22].

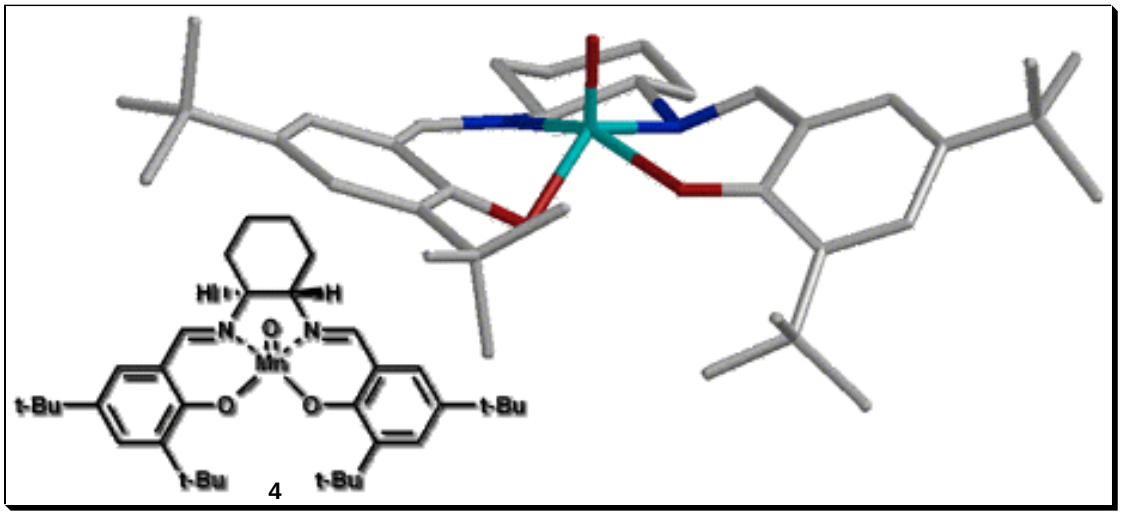
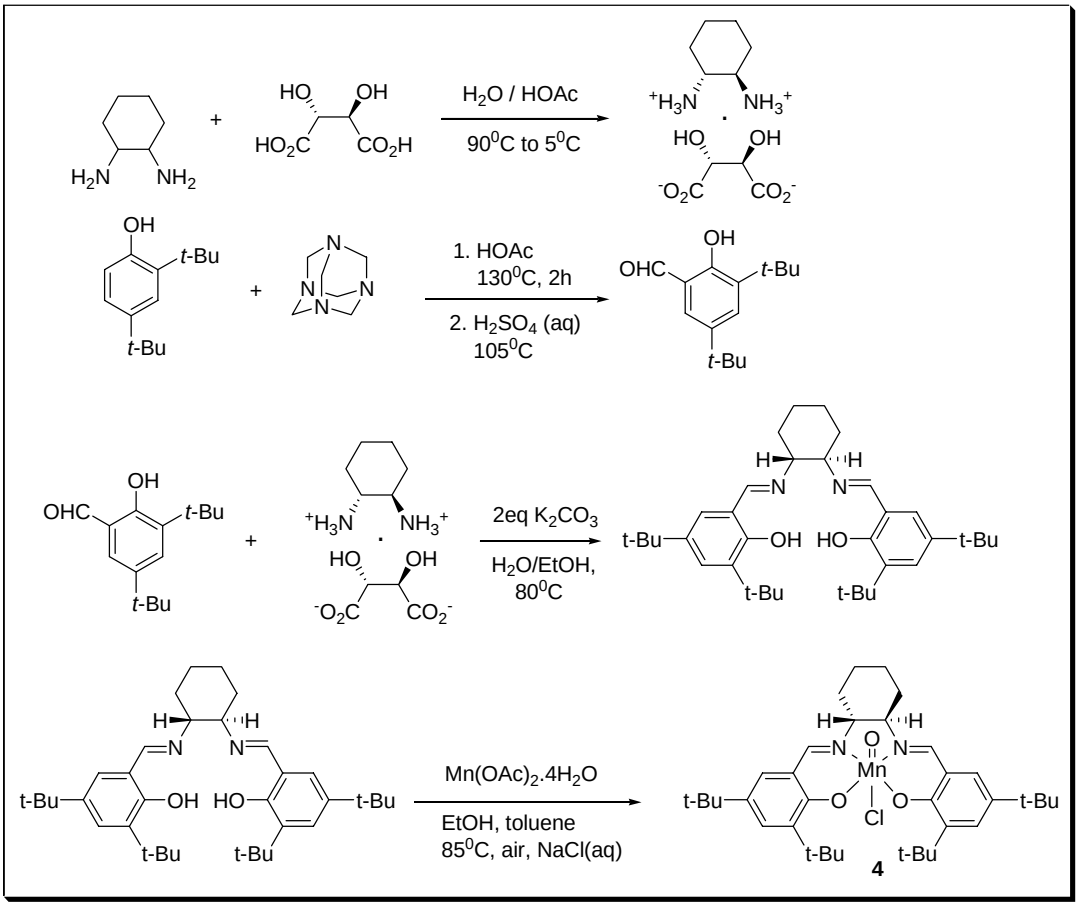


Figure 3. Jacobsen catalyst

The synthesis of Jacobsen catalyst is outlined in Scheme 7 [23]. The effectiveness of this catalyst especially in asymmetric epoxidation reactions will be explained later.



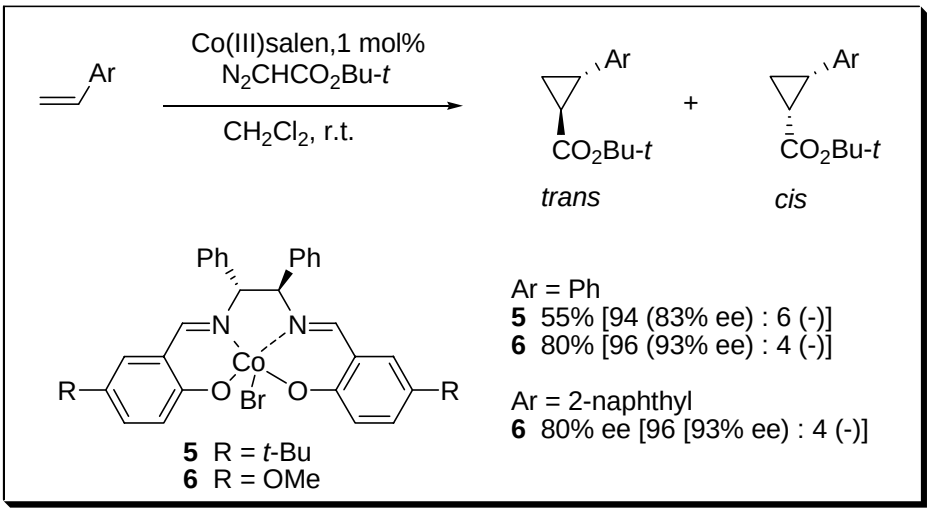
Scheme 7. The synthesis of Jacobsen catalyst

1.5. Various asymmetric reactions using metal(salen) complexes:

1.5.1. Asymmetric cyclopropanation:

Cyclopropanation, which is a type of carben transfer reactions, can also be performed in highly enantioselective manner by using metallosalen complex as a catalyst. In 1978, Nakamura and Otsuka reported cyclopropanation using chiral (salen)cobalt(II) complex as a catalyst, though enantioselectivity was low [24].

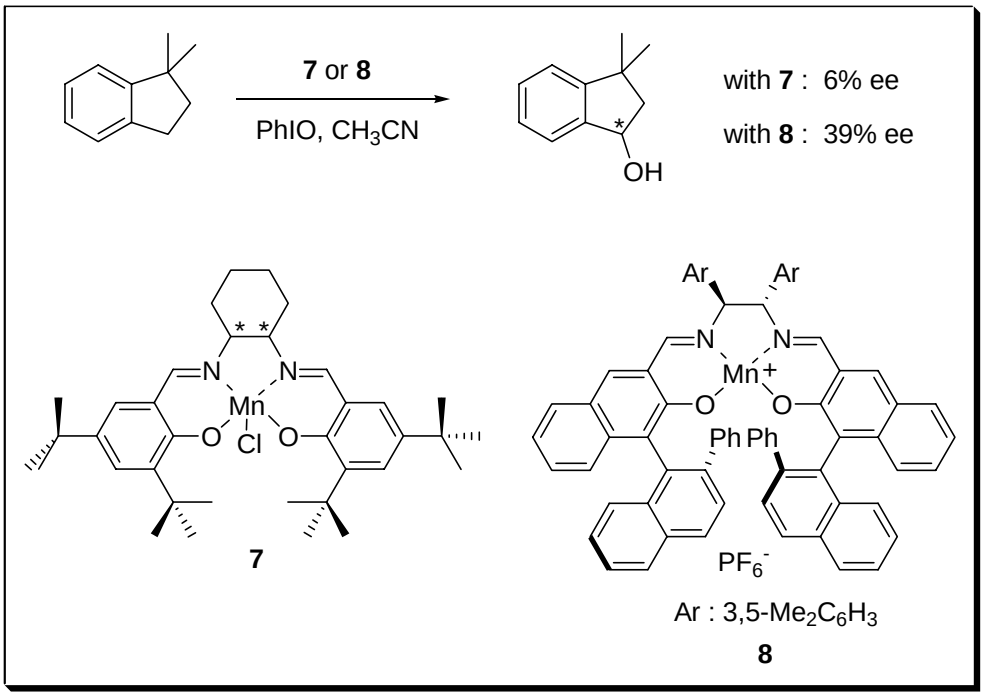
Katsuki *et al.* also showed that Co(salen) complex **5**, **6** catalysed the asymmetric cyclopropanation of styrene with *tert*-butyl diazoacetate (Scheme 8) [25].



Scheme 8. Example for asymmetric cyclopropanation

1.5.2. Asymmetric hydroxylation of C-H bonds:

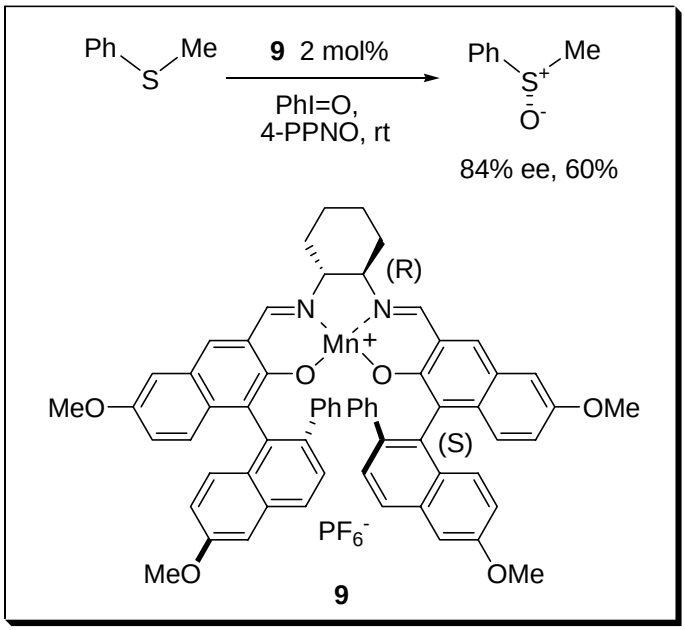
Katsuki *et al.* examined enantioselective benzylic oxidation with Mn(salen)s **7** and **8** as the catalyst [26] (Scheme 9).



Scheme 9. Example for asymmetric hydroxylation of C-H bonds

1.5.3. Asymmetric oxidation of alkyl aryl sulfides:

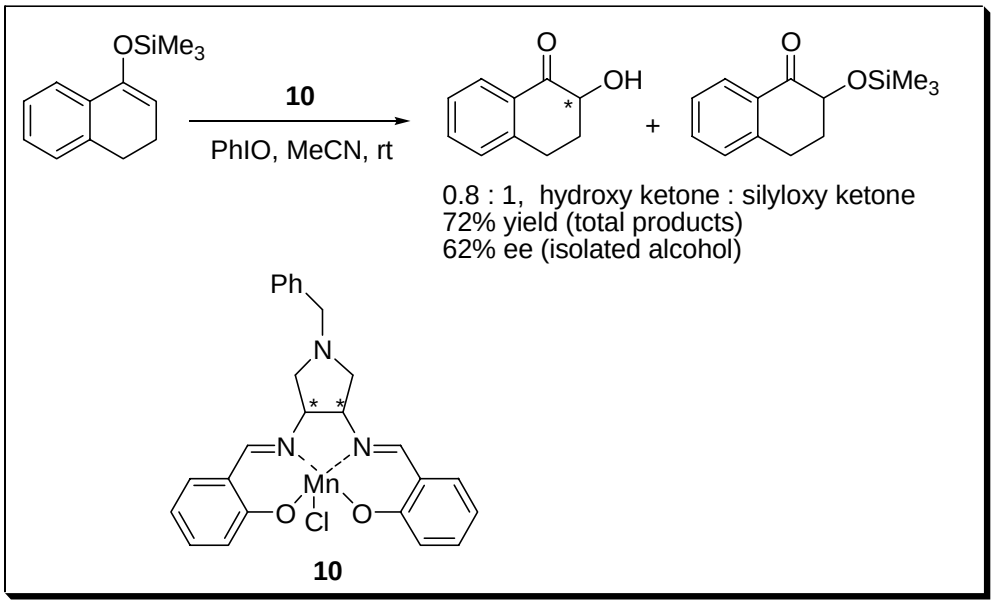
Optically active sulfoxides are useful auxiliaries for asymmetric synthesis and many excellent methodologies have been developed for asymmetric oxidation of sulfides. Various metal(salen) complexes have been used as catalyst for this reaction (Scheme 10), Fujita *et al.* studied with V-salen complexes [27]; and also with Ti(salen) complexes, they obtained high chemical yield, however low enantiomeric excess values [28]. Katsuki *et al.* had reported high enantiomeric excess with Mn(salen) complex bearing methoxy groups [29].



Scheme 10. Example for asymmetric oxidation of sulfides

1.5.4. Asymmetric oxidation of silylenol ethers:

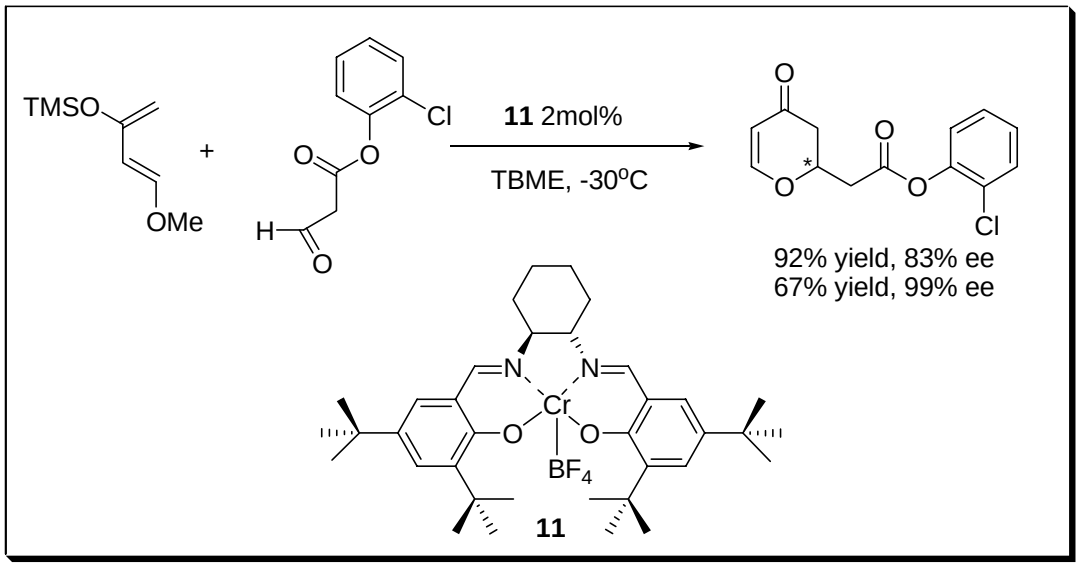
Thornon *et al.* reported that **10** catalyzed the oxidation of a range of ketone silyl enol ethers to give α-hydroxyketones [30] (Scheme 11).



Scheme 11. Example for asymmetric oxidation of silylenol ethers

1.5.5. Asymmetric Diels-Alder reactions:

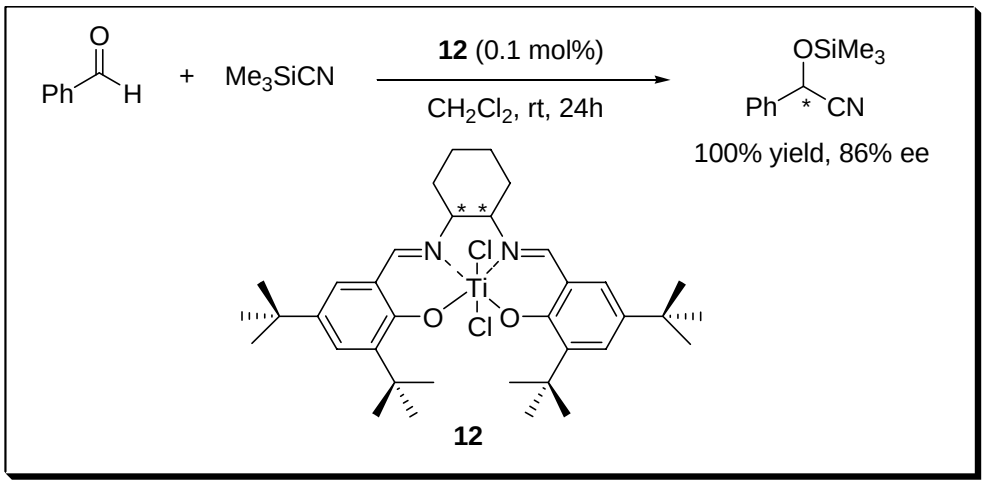
Jacobsen *et al.* tried asymmetric hetero Diels-Alder reaction [31] between [(2-chlorobenzoyl)oxy]-acetaldehyde and 1-methoxy-3-[(trimethylsilyl)oxy]buta-1,3-diene in the presence of 2 mol% Cr(salen) (Scheme 12).



Scheme 12. Example for asymmetric Diels-Alder reaction

1.5.6. Asymmetric trimethylsilycyanation reactions:

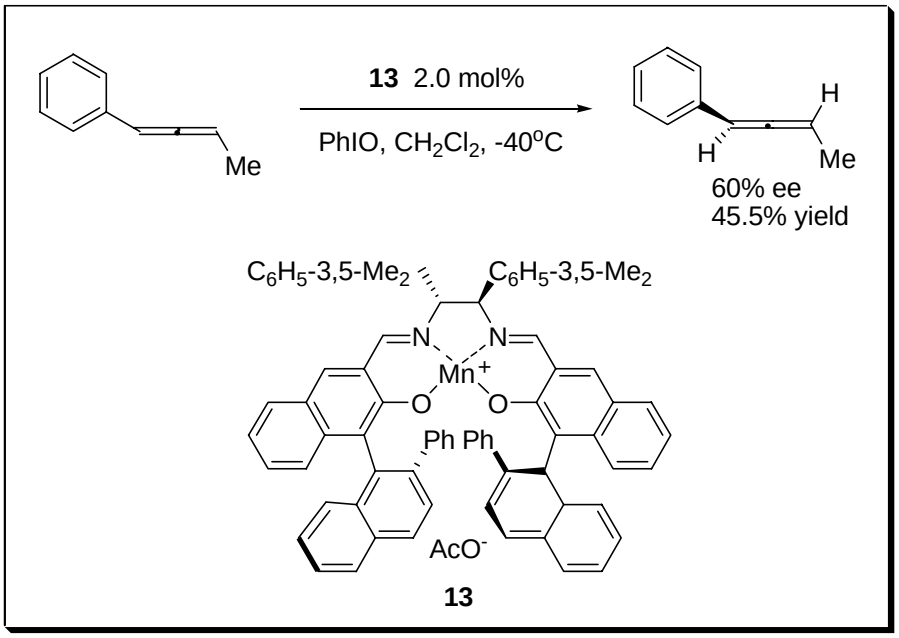
North *et al.* used the optically active Ti(salen) catalyst **12** in the enantioselective trimethylsilylcyanation of benzaldehyde (Scheme 13) [32].



Scheme 13. Example for asymmetric trimethylsilyl cyanation reaction

1.5.7. Kinetic resolution of racemic allenes:

Katsuki and his colleagues investigated kinetic resolution of racemic allenes [33] with Mn (salen) complex **13** (Scheme 14).



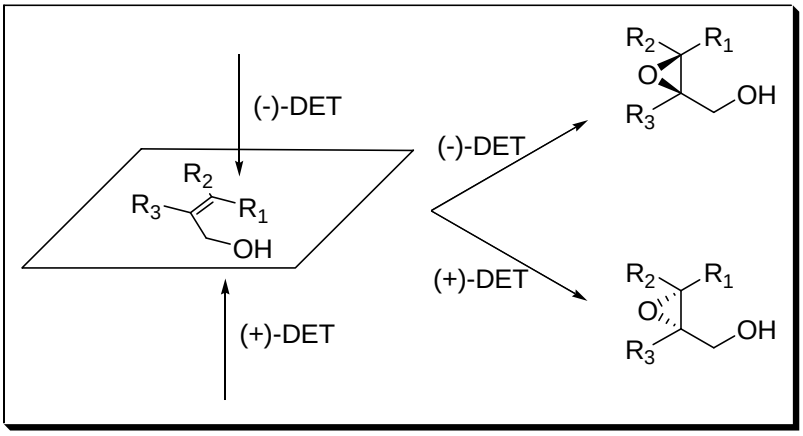
Scheme 14. Example for kinetic resolution of racemic allenes

1.5.8. Asymmetric Epoxidation:

Epoxidation of olefins is one of the most important processes for functional group manipulation in organic synthesis and the preparation of biologically active compounds; therefore many efforts have been directed toward the exploitation of highly enantioselective epoxidation reactions of olefins [34].

In the 1980's Sharpless *et al.* have discovered an enantioselective titanium-tartarate-catalyzed epoxidation of a wide variety of allylic alcohols, which is the only

restriction of this method. The basic mechanism of the reaction is shown in Scheme 15 [35].



Scheme 15. Basic mechanism for Sharpless epoxidation

After the first application of porphyrine systems [36] and other more or less effective catalysts or steochiometrically used systems [37] as epoxidation agents for the formation of epoxides from *unfunctionalized*, prochiral olefins in the 1980's, Jacobsen and Katsuki have suggested a new methodology in the 1990's.

They have used catalytic amounts of chiral, C_2-symmetric Mn(III)- salen complexes of general structure of **14** (Figure 4) in the presence of a stoichiometric oxidation agent, meanwhile over 100 complexes of this kind have been reported [6]. The most efficient and the most widely used one as mentioned before is *N,N'*-bis(3,5-di-*t*-butylsalycilydene)-1,2-cyclohexanediamino-manganese(III) chloride, the so called Jacobsen catalyst. This complex stable under air and can be stored for long period of time without decomposition [38].

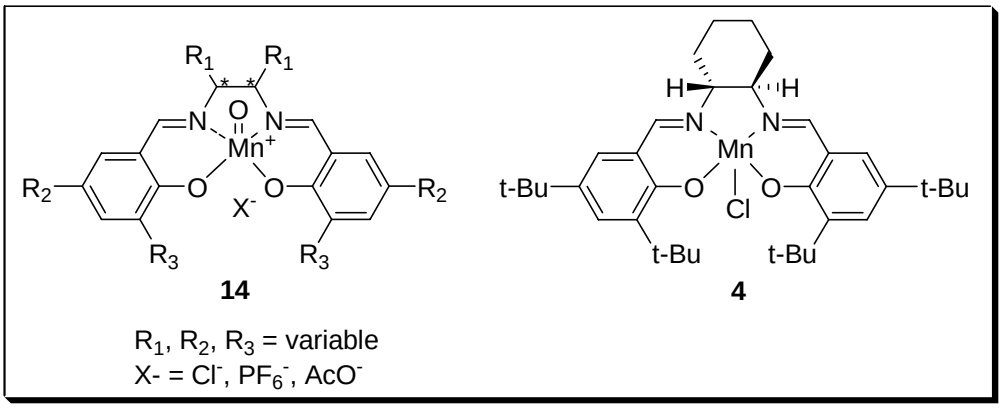
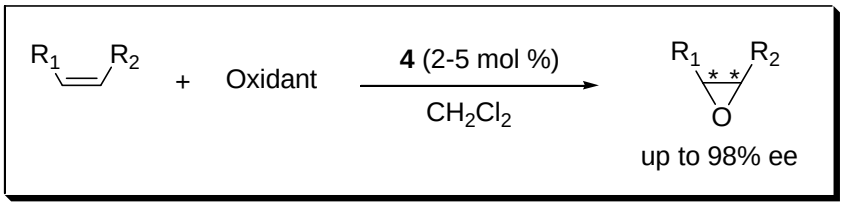


Figure 4. General structure of Jacobsen catalyst

This complex is currently the most efficient catalyst available for the enantioselective epoxidation of unfunctionalized olefins as well as of conjugated olefins (Scheme 16).

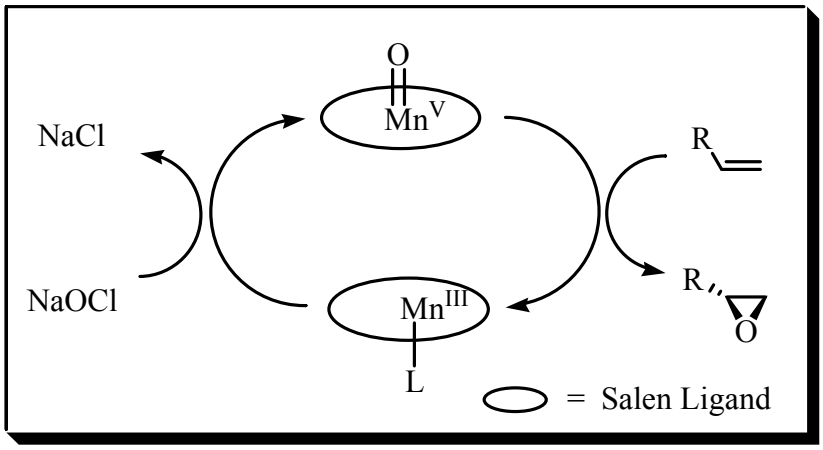


Scheme 16. General example for epoxidation reactions

The method involves 2 to 5 mol % of catalyst in an organic solvent such as CH_2Cl_2. The source of oxygen used can be either aqueous oxidant such as sodium hypochlorite or an organic peracid, for example *m*-chloroperbenzoic acid [39].

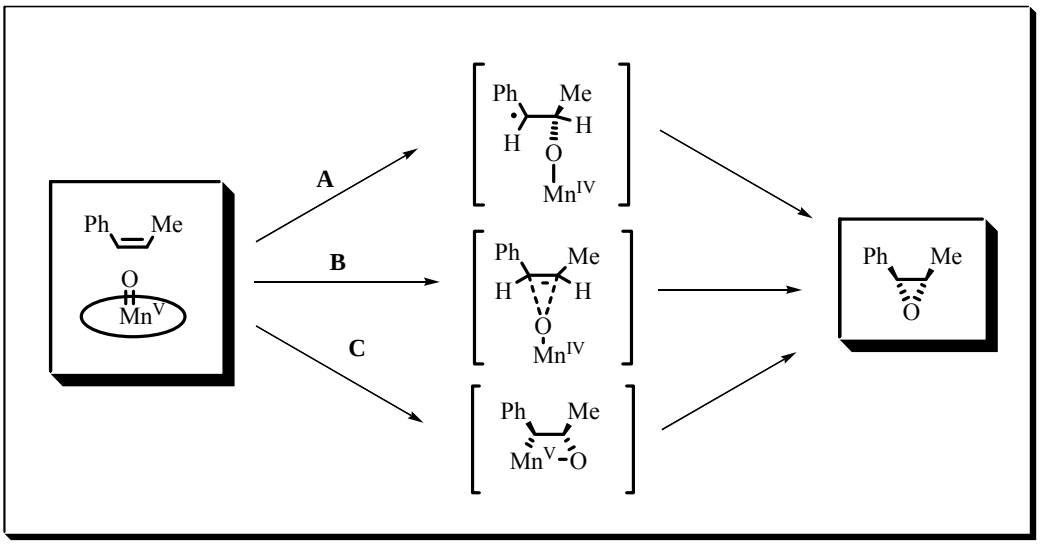
A lot of attention has been put on the evaluation of the mechanism of the Jacobsen epoxidation [40]. Some of the examined salen complexes could be recrystallized, and the X-ray-structures attempts to explain the dependence of the degree of enantioselectivity on the steric and electronic situation of the complexes have been made [41].

Catalytically active species is represented by the oxygenated form, the Mn(V)-oxo-intermediate which is easily formed from the Mn(III) complex in the presence of an oxidant Scheme 17. This Mn(V)-oxo-intermediate could be detected for the first time via electronspray-tandem-mass spectroscopy by Plattner et al [42].



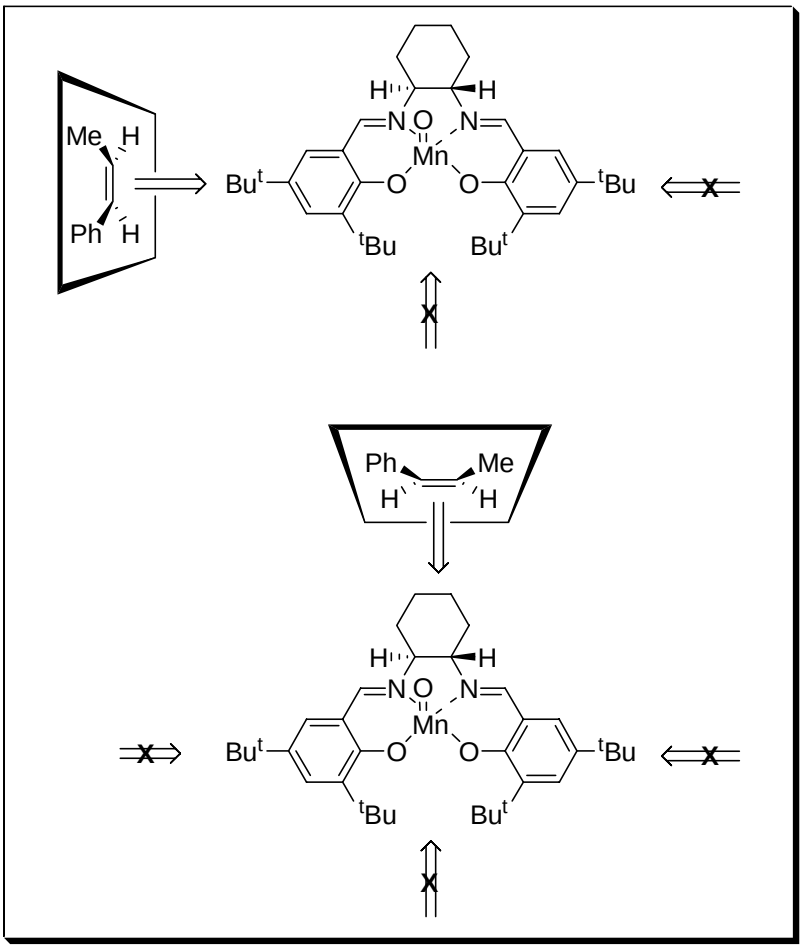
Scheme 17. Oxidation of Mn-salen complex

The question of oxygen transfer from the complex to alkene is still not known in detail. At least three possible ways have bee discussed mainly by Jacobsen and Katsuki and Åkermark (Scheme 18)[43-45].



Scheme 18. Oxygen transfer mechanism

Concerning the attack of the alkene to the chiral complex both Jacobsen and Katsuki propose a side on mechanism. The key feature of the Jacobsen catalyst especially **4**, is that the catalyst was designed to disfavour all side-on olefin approaches except the ones shown in Scheme 19 [46].



Scheme 19. Side-on attack on the Jacobsen catayst

In a series of papers it is proven that the catalytic epoxidations with these types of catalysts the highest level of asymmetric induction achieved in *cis*-olefins over *trans* ones [47-49] (Figure 5).

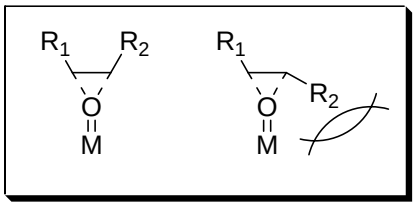
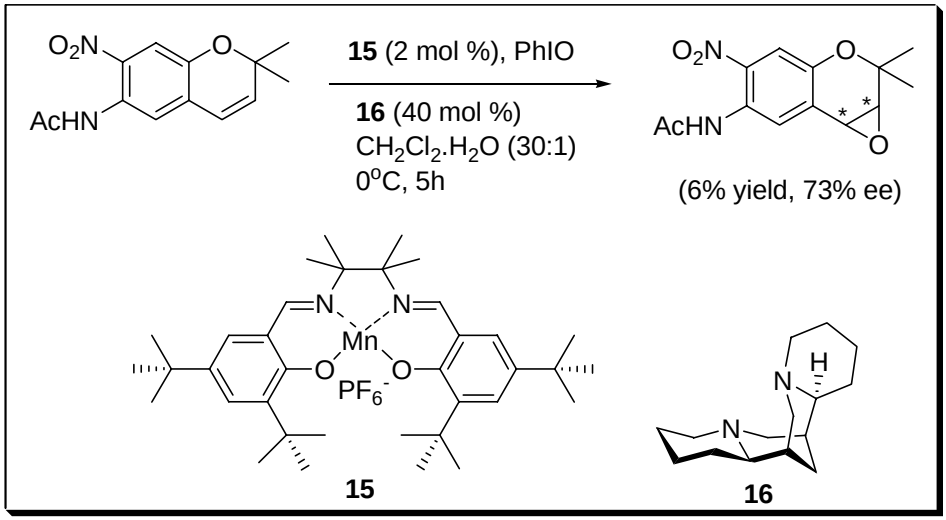


Figure 5. Comparison for *cis* and *trans* approach

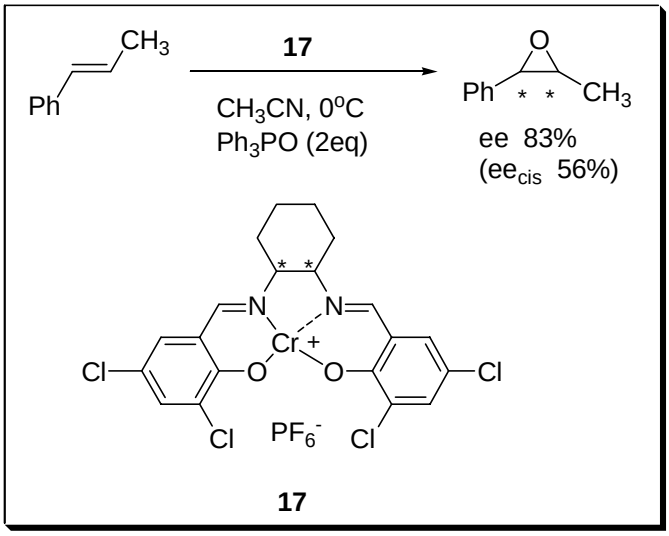
Several kinds of M-(salen) complexes were prepared and used for catalytic asymmetric epoxidation of unfunctionalized olefins, some of them can be summarized:

Katsuki and his colleagues [25] examined epoxidation of 2,2-dimethylchromene derivatives using achiral Mn (salen) complexes **15** in the presence of chiral additives **16** (Scheme 20).



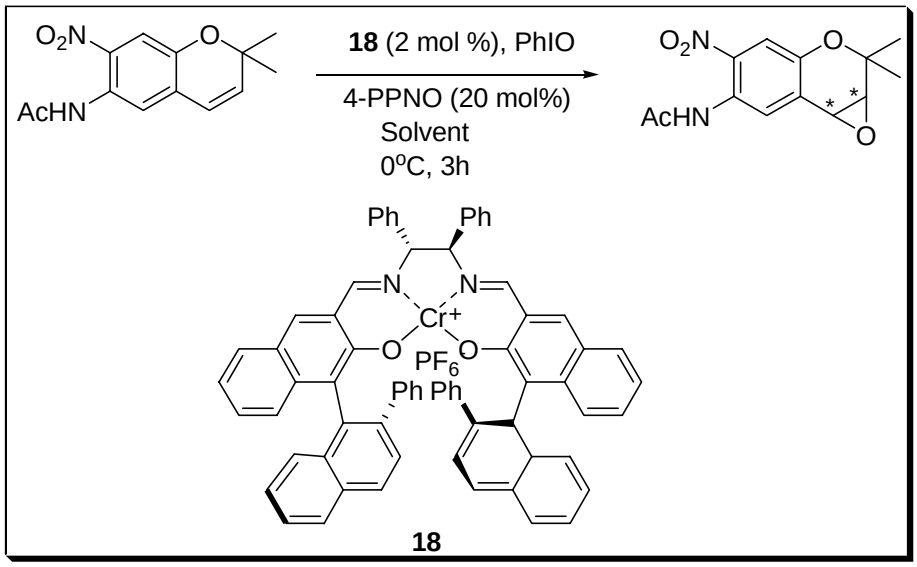
Scheme 20. Epoxidation of 2,2-dimethylchromene by Katsuki *et al.*

Gilheany reported that the Cr(salen)complex **17** catalysed asymmetric epoxidation of unfunctionalised *trans* olefins in higher enantiomeric excess than the corresponding *cis* isomer [50] (Scheme 21).



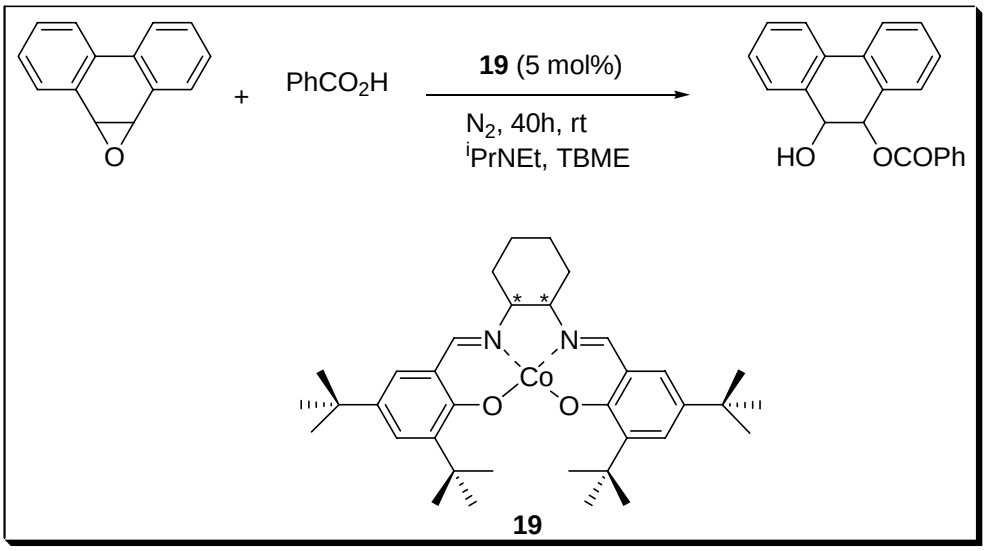
Scheme 21. Epoxidation of (E)-β-methylstyrene by Gilheany *et al.*

Katsuki [51] examined the epoxidation of conjugated alkenes using Cr(salen) complexes **18** (Scheme 22).



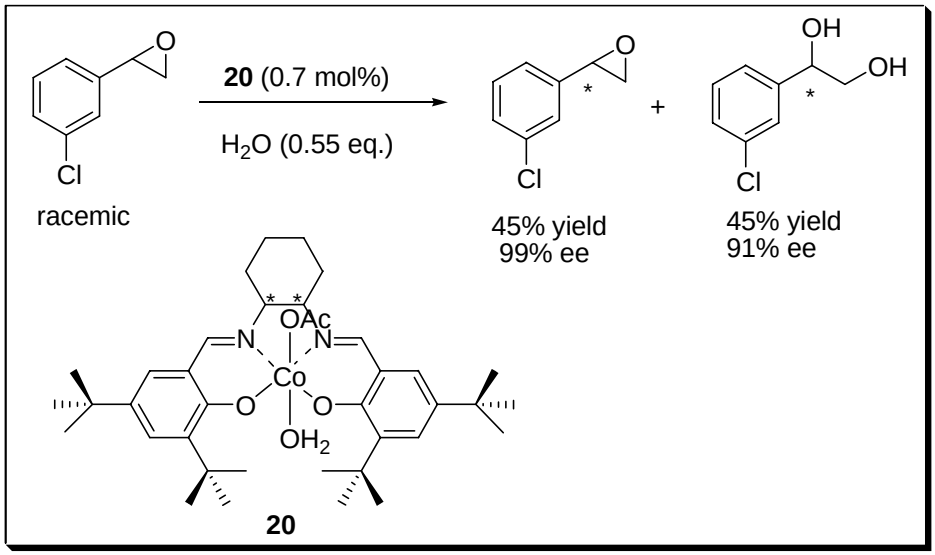
Scheme 22. Example for epoxidation of conjugated alkenes by Katsuki *et al.*

Jacobsen *et al.* described asymmetric ring opening of meso epoxides [52] with Co(salen) complex **19** (Scheme 23).



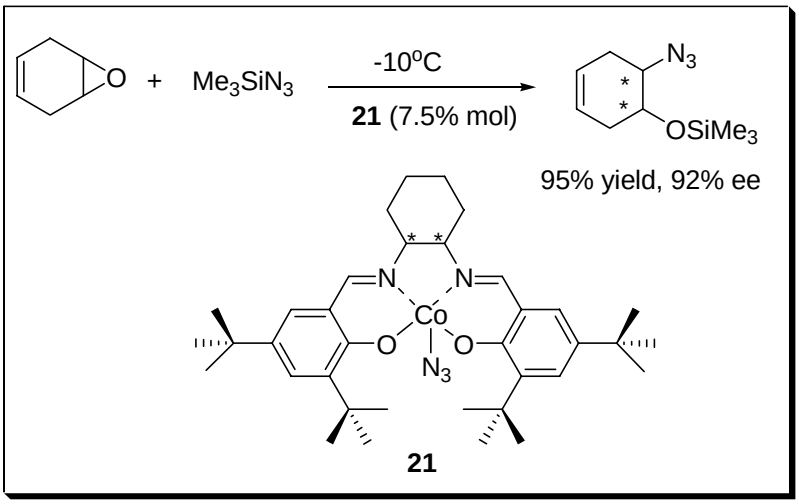
Scheme 23. Example for asymmetric ring opening of meso epoxides

Jacobsen also discovered that Co(salen) complex **20** was active in the hydrolytic kinetic resolution of racemic epoxides [53] (Scheme 24).



Scheme 24. Example for hydrolytic kinetic resolution of racemic epoxides

Jacobsen group also tried asymmetric ring opening of cyclohexa-1,4-diene monoepoxide with catalyst **21** (Scheme 25) [54].

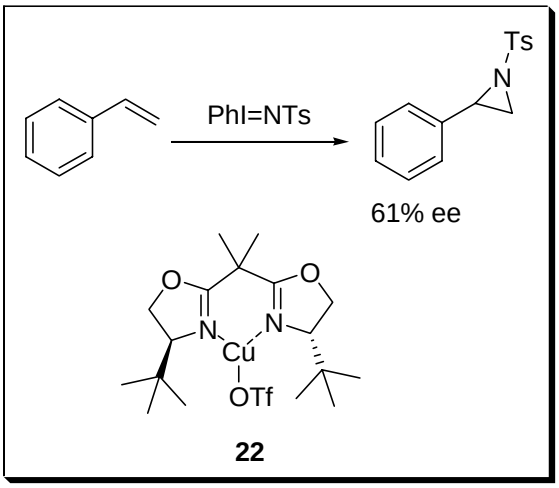


Scheme 25. Example for asymmetric ring opening by Jacobsen *et al.*

1.5.9. Asymmetric Aziridination

Aziridines are nitrogen equivalents of epoxides and are useful intermediates for the synthesis of compounds containing nitrogen functionalities; alkaoloids, aminoacids, amino sugars and β-lactams [55]. In addition, aziridines have also found applications as chiral auxiliaries and lately also as chiral ligands in asymmetric catalysis [56, 57]. Therefore many methodologies have been developed for asymmetric aziridination, but there is no general methodology. Very promising reactions for the direct conversion of olefins into aziridines have recently been reported by several research groups [58, 59].

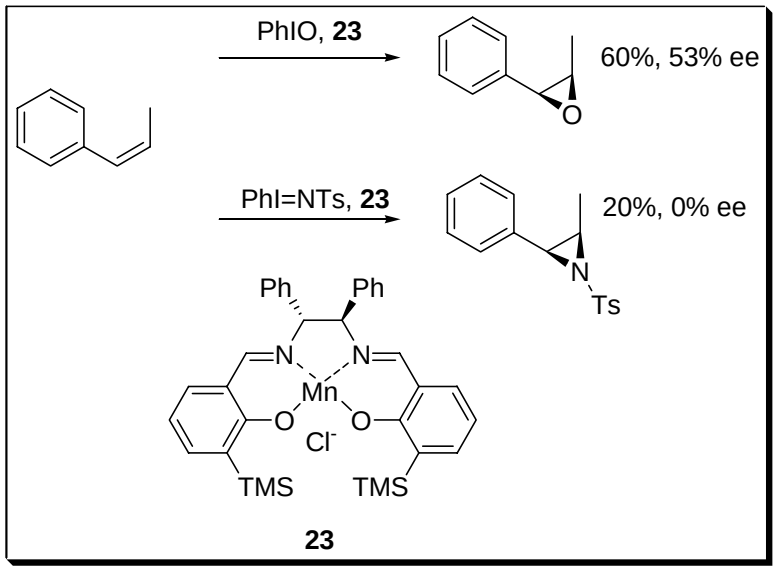
A few catalytic asymmetric aziridinations were performed by using chiral copper bis(oxazolines) complexes **22** as catalysts (Scheme 26) [60].



Scheme 26. Example for the usage of copper bis(oxazolines) complexes

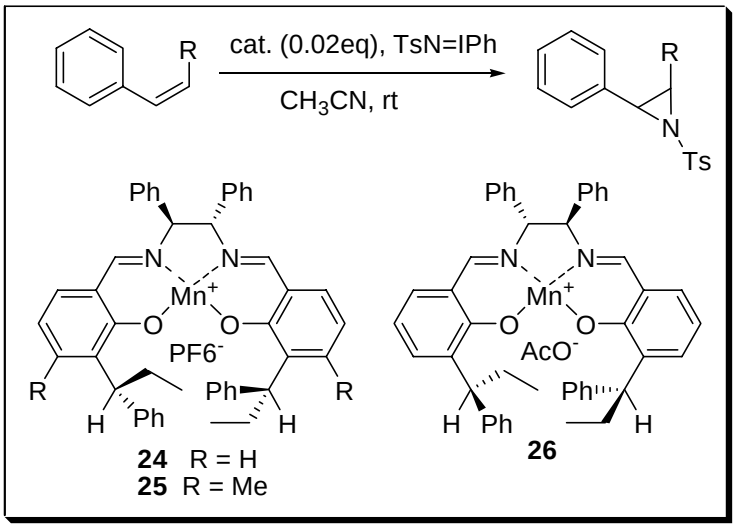
In fact, porphyrin and salen complexes show very similar catalytic activity for epoxidation of olefins and optically active salen complexes have been proven to be good catalysts for enantioselective epoxidation, therefore, it was expected that those salen complexes could also be used as catalysts for asymmetric aziridination of olefins. As a result systems used for asymmetric epoxidations also were tried for asymmetric aziridinations [61, 62].

However, Burrows *et al.* reported that chiral (salen)manganese(III) complex **23** did not show any asymmetric induction in the aziridination of *cis*-β-methylstyrene, while it exhibited moderate level of asymmetric induction in the corresponding epoxidation. (Scheme 27) [63].



Scheme 27. Example of a Burrows study

Katsuki *et al.* had also examined the aziridination of styrene derivatives by using their salen complexes **24-26**. They obtained poor results but they found that their catalysts did induce asymmetric induction Scheme 28 [64].



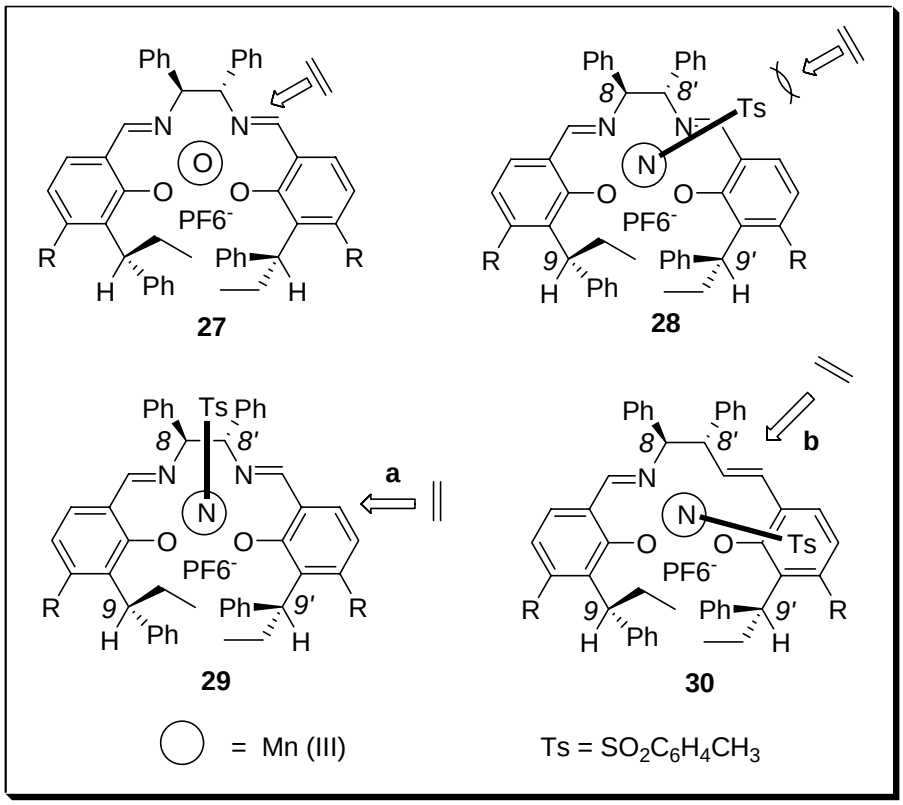
Scheme 28. Example for one of Katsuki's study

The results of this study can be shown in Table 1.

Table 1. Results of Katsuki's study

Entry	Substrate	Catalyst	% Yield	% ee	Abs. conf.
1	R = H	24	18	8	*S*
2	R = H	25	11	4	*R*
3	R = H	26	15	20	*R*
4	R = Me	26	*cis*1.6/*trans*2.4	*cis*26/*trans*6	1*R*,2*S*

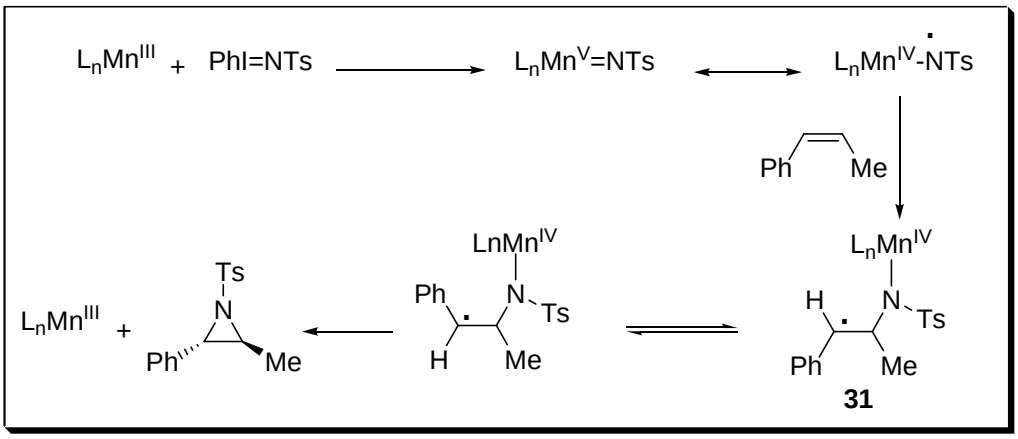
The difference in asymmetric induction between aziridination and epoxidation can be attributed to the structural difference in active species in those reactions catalyzed by porphyrin and salen complexes. For the salen-catalyzed epoxidation, as shown before, olefin approaches to the oxo-metal bond from the open space **27**, but in the case of aziridination, N-sulfonyl group is considered to occupy that open space blocking the excess of olefin from that direction to retard aziridination **28** (Scheme 29).



Scheme 29. Schematic representation of olefin epoxidation and aziridination

Only when-sulfonyl group leans toward C8, **29** or C9, **30** substituent, olefin can approach nitrene-metal bond following path **a** or path **b** respectively [64].

As in Burrows' study the mechanism of metal catalyzed aziridination was believed through radical intermediates (Scheme 30) [63].



Scheme 30. Mechanism of metal catalyzed aziridination

Nitrene-metal species (Mn^{V}=NTs) has been suggested to be in equilibrium with radical species (Mn^{IV}-N˙-Ts) which leads to the formation of radical intermediate **31** (Scheme 30). If the reaction proceeds via intermediate **31,** such a radical most likely has a sufficiently long lifetime to allow for C-C bond rotation to compete effectively with ring closure. One way of obtaining higher ee's is to form a metal-imino species which transfers its nitrogen atom in a concerted fashion to the olefin.

It has been known also that addition of donor ligand often improved the enantioselectivity in the epoxidation catalyzed by chiral (salen)manganese complexes [65]. When this property tested in aziridination reactions by adding pyridine N-oxide for example, increase in selectivity has been observed.

On the other hand, Evans *et al.* had proven that low valent copper complexes catalyze the aziridination of various types of olefins [66, 67]. They have made series of experiments to decide an optimal Cu salt for aziridination reactions. Among Cu(I) salts $CuClO_4$ is the favored one since it is easily prepared and air sensitive, however, Cu(I)OTf gives the most promising results. Moreover Cu(II) catalysts have been found to be competent in aziridination reactions e. g. $Cu(acac)_2$, $Cu(OTf)_2$ they are commercially available and air sensitive.

In order to decide the most effective nitrogen atom transfer reagent Holm *et al.* [68] have performed a study the best yield of aziridine was obtained by (N-(*p*-toluenesulfonyl)imino)pheyliodinane) PhI=NTs.

Evans *et al.* also had studies to obtain standard solvent for the reaction, for styrene aziridination they have found that benzene (99%), CH_2Cl_2 (92%), $MeNO_2$ (90%), and MeCN (92%). However with less reactive substrates more polar solvents need to be used, $MeNO_2$ and MeCN for example.

Keeping that in mind, Jacobsen *et al.* had tried enantioselective alkene aziridination with simple benzylidene derivatives of 1,2-diaminocyclohexane as ligands for the Cu(I)-catalyzed asymmetric aziridination of olefins by PhI=NTs [69]. They have used the salen ligands shown in Figure 6 in asymmetric aziridination reactions with Cu(I)OTf.

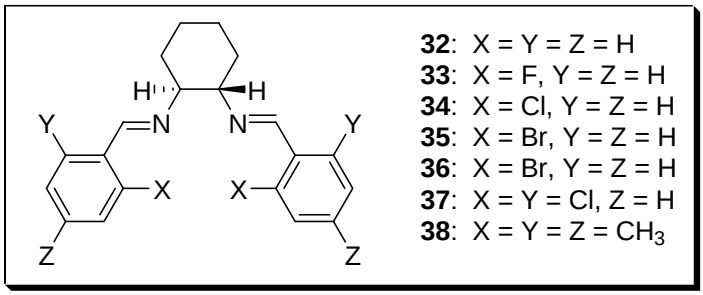
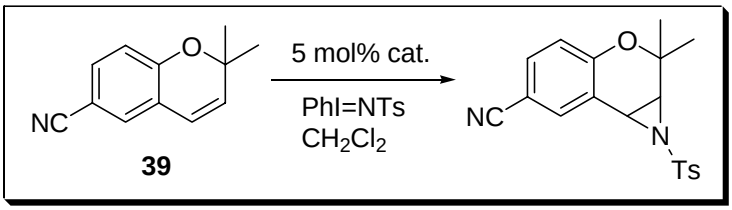


Figure 6. Ligands synthesized by Jacobsen *et al.* for aziridination reactions

In order to understand the effectiveness of these ligand as catalysts together with Cu(I)OTf in aymmetric aziridination reactions, they chose 6-cyano-2,2-dimethyl chromene **39**, as a reference substrate (Scheme 31).



Scheme 31. Aziridination reaction of 6-cyano-2,2-dimethyl chromene

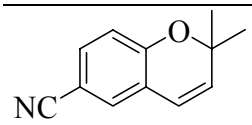
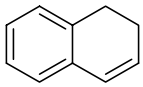
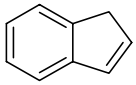
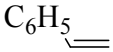
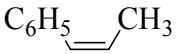
Results of this study can be examined in Table 2.

Table 2. Results of Jacobsen's study

	Ligand						
	32	**33**	**34**	**35**	**36**	**37**	**38**
ee %	50	64	72	81	42	>98	92

The most promising results were obtained with ligand **37** as shown in Table 2. Therefore Jacobsen *et al.* had performed series of aziridination reactions with ligand **37** and results can be seen in Table 3.

Table 3. Results of aziridination of various olefins

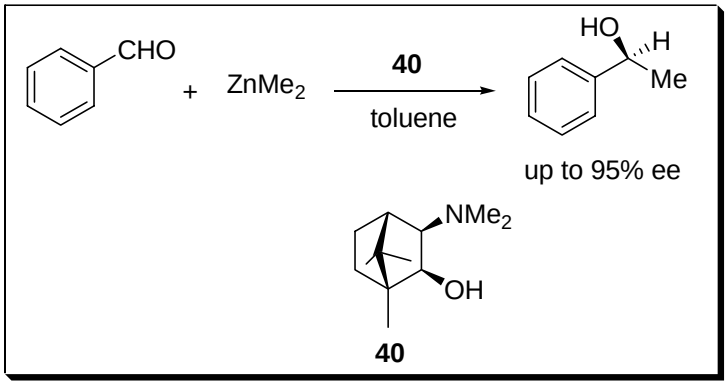
Substrate	aziridine yield %	ee %	aziridine conf.
	75	> 98	(3*R*-4*R*)-(+)
	70	87	(1*R*,2*S*)-(+)
	50	58	(1*R*,2*S*)-(-)
	79	66	(*R*)-(-)
	79 (*cis*/*trans*:3/1)	67 / 81 (*cis*/*trans*)	(1*R*,2*S*)-(-) (1*S*,2*S*)-(-)

As a result of Jacobsen's study it was claimed that the failure of (salen)Cu complexes and the preclusion of catalysis with tetradentate neutral ligands indicated that existence of multiple open coordination sites on the copper may be crucial to catalysis of aziridination.

1.6. Asymmetric Diethylzinc additions to aldehydes:

Enantioselective addition of organometallic reagents to aldehydes affords optically active secondary alcohols. The reaction is one of the most important and fundamental asymmetric reactions. The optically active secondary alcohols are components of many naturally occurring compounds, biologically active compounds that are ubiquitous in the structures of natural products and drug compounds. They are also important as synthetic intermediates of various functionalities such as halide, amine, ester, ether, etc [70].

Since the initial report of Oguni and Omi on the reaction of diethylzinc with benzaldehyde in the presence of a catalytic amount of (*S*)-leucinol with moderate enantioselectivity (49 % ee) in 1984, research on asymmetric organozinc additions to carbonyl compounds has grown dramatically. In 1986, (-)-3-*exo*-dimethylaminoisobornenol [(-)-DAIB, **40**] was discovered by Noyori and co-workers to be the first highly enantioselective ligand for the dialkylzinc addition to aldehydes (Scheme 32).



Scheme 32. Example for dialkylzinc addition by Noyori

In the presence of 2 mol % of **40**, reaction of dimethylzinc with benzaldehyde at 25-40°C in toluene gave (*S*)-1-phenylethanol with up to 95 % ee [71].

Over the past decades, a large number of chiral catalysts have been developed and high enantioselectivities have been achieved. In addition, the reaction of diethylzinc with aldehydes has also become a classical test in the design of new ligands for catalytic enantioselective syntheses [72, 73].

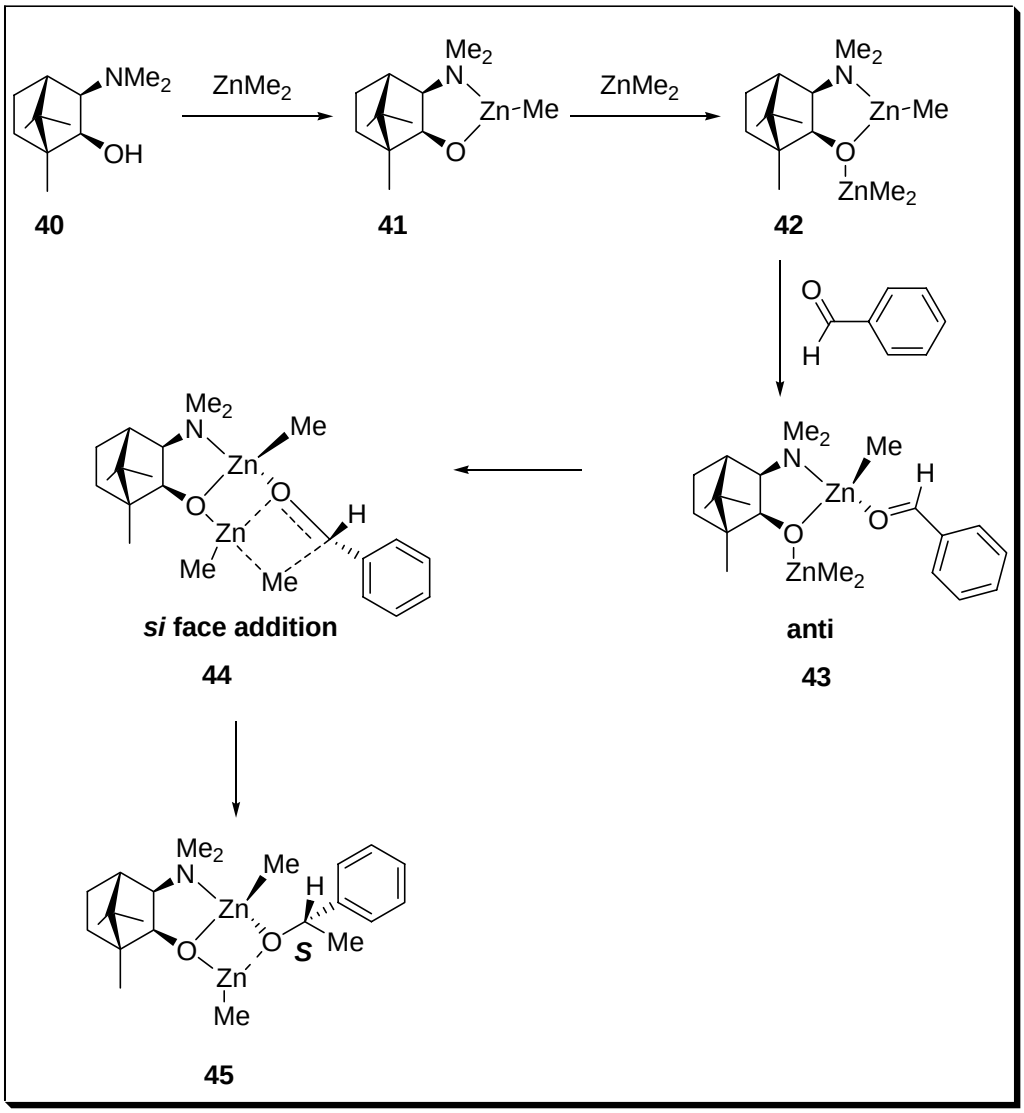
Previous studies have shown that coordination of ligands to dimethylzinc converts its linear structure into an approximate tetrahedral structure. This reduces the bond order of the Zn-C bond and increases the nucleophilicity of the zinc alkyl

groups. Thus, chiral ligands not only control the stereochemistry of the organozinc addition, but also activate the zinc reagents [74].

A number of chiral ligands developed for the asymmetric organozinc additions are derived from amino alcohols. These compounds react with dialkylzincs to generate a zinc-based chiral Lewis acid complex which can further coordinate with both the aldehyde substrates and the dialkylzinc reagents to conduct the catalytic addition. Thus, the *in situ* generated zinc complex is a multifunctional catalyst. It acts as a Lewis acid to activate the carbonyl substrates and also as a Lewis base to activate the organozinc reagents. The chiral environment of the ligand controls the stereoselectivity [75].

Amino alcohols constitute an important part of the chiral ligands developed for dialkylzinc additions to aldehydes. Noyori and co-workers conducted extensive experimental and theoretical studies on the mechanism of the dialkylzinc addition to aldehydes catalyzed by **40** [76]. Houk and co-workers also carried out a theoretical analysis of dialkyzinc addition [77].

The mechanism of diethylzinc addition with (-)-3-*exo*-dimethylaminoisobornenol [(-)-DAIB, **40**] can be explain as in Scheme 33 [78].



Scheme 33. The mechanism of dimethylzinc addition with **40**

In the first step, compound **40** reacts with dimethylzinc to generate the zinc complex **41**. It was found that 1 equiv of **41** cannot react with benzaldehyde. That is, the Zn-Me group of **41** cannot add to an aldehyde and a second equivalent of dimethylzinc is needed. The alkoxy oxygen atom in **41** coordinates with dimethylzinc to give **42**. Coordination of benzaldehyde with **42** generates **43**. Molecular orbital and density functional calculations indicate that the anti coordination of benzaldehyde (with respect to the chiral ligand) in **43** and a tricyclic transition state **44** are most favorable. In transition state **44**, methyl migrates to the *si*

face of the aldehyde to form **45**, which can react with dimethylzinc to dissociate (*S*)-(1-phenyl)ethoxy-ZnMe and regenerate **42**. Aqueous workup gives (*S*)-1-phenylethanol.

There are lots of studies which have been made by different researches in order to find effective catalysts in the catalytic asymmetric dialkylzinc addition reactions to aldehydes [75]. Some of the catalysts shown in Figure 7 performed high enantioselectivities.

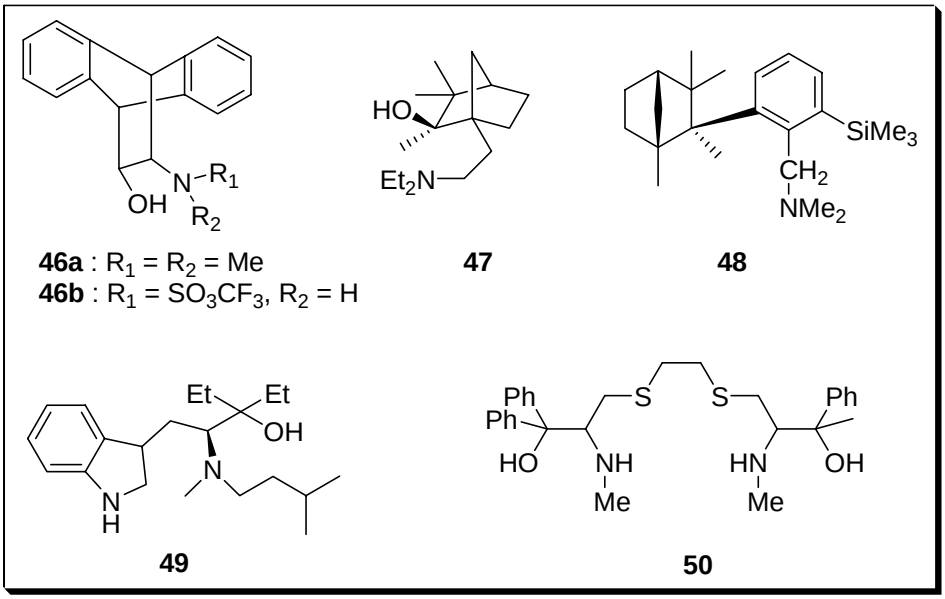


Figure 7. Examples for aminoalcohols as catalysts

46a,b prepared by Kunieda *et al.*, are sterically very similar to each other but electronically quite different due to the substituents on the nitrogen [79]. Both showed high enantioselectivity (96 % (*S*) and 98 % (*R*) ee, respectively) for the diethylzinc addition to benzaldehyde but gave the opposite enantiomeric product. Ligand **47** was prepared by Fujita *et al.* [80], showed good enantioselectivity for the reaction of benzaldehyde as well as a couple of *para*-substituted benzaldehydes

(88 %-95 % ee). Ligand **48** was used by Goldfuss *et al.*[81], showed 93 % ee for diethylzinc addition to banzaldehyde reaction, such high enantioselectivity was attributed to the presence of the bulky trimethylsilyl group. Dai *et al.* found that ligand **49** had very good enantioselectivity for diethylzinc additions to certain aromatic and aliphatic aldehydes up to 97 % ee [82]. As an example for C_2-symmetric aminoalcohols ligand **50** can be given, which was synthesized by Kossenjans and Martens *et al.* [83] showing up to 94 % ee for diethylzinc addition to benzaldehyde at room temperature.

There are also studies with cyclic and multicyclic amino alcohols as an example **51a-c** (Figure 8) can be given for the promising ligand. These ligands were synthesized by Pericàs *et al.* [84]. These ligands gives (*S*)-1-phenylpropanol with 94-97 % ee.

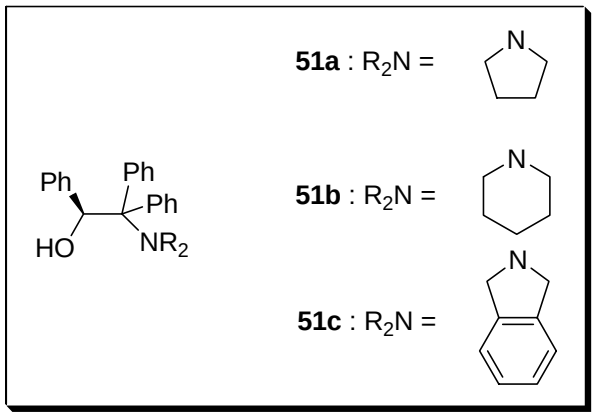


Figure 8. Examples from Pericàs' study

Pyridyl and iminyl alcohols can also be used as ligands in asymmetric dialkylzinc addition reactions. Pyridyl alcohol ligands for example, were studied by Bolm *et al.* The C_2-symmetric bipyridine ligand **53** was synthesized via dimerization of **52** in the presence of a nickel (0) complex (Figure 9) [85].

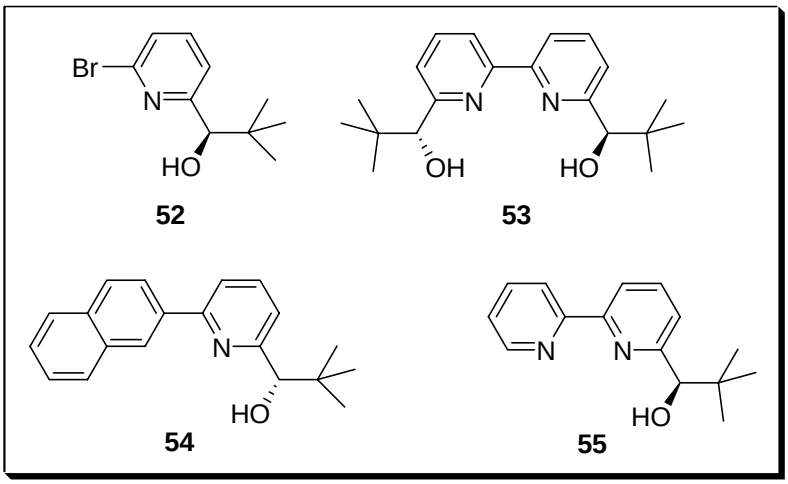


Figure 9. Examples for Bolm's study

A 5 mol % amount of **53** was used to catalyze diethylzinc additions in toluene solution at 0°C and found to show good enantioselectivity for aromatic aldehydes (90-97 % ee). Compouds **54** and **55** containing various substituents at the pyridine ring were also prepared by the cross-coupling reactions of **52**. Compound **54** gave 95 % ee for the reaction of diethylzinc with benzaldehyde. Compound **55** which contain additional coordinative heteroatoms had lower enantioselectivity, 86 % ee.

In 1996, Cozzi and U.-Ronchi *et al.* had tried to use salen based ligands in asymmetric diethylzinc addition reactions [86]. They have used commercially available (R,R)-(-)-N,N'-bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediamine **56** as catalyst. The zinc complex of **56** was generated in situ by the addition of one equivalent of Et_2Zn to the chiral Schiff base at room temperature (Figure 10).

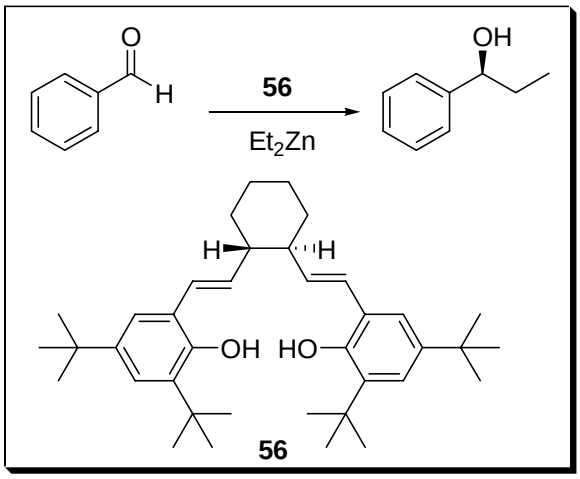


Figure 10. Study of Cozzi and U-Ronchi *et al.*

They have tried this experiment by varying temperature and solvent, and they have obtained up to 70 % ee value with toluene at lower temperatures (-40-0°C). After optimizing the conditions they tried to use different aldehydes, and found that higher ee values were obtained with aromatic aldehydes then with aliphatic ones.

They have also suggested the model shown in Figure 11, to illustrate a plausible interaction between the metallo-Schiff base complex, Et_2Zn, and a representative aldehyde.

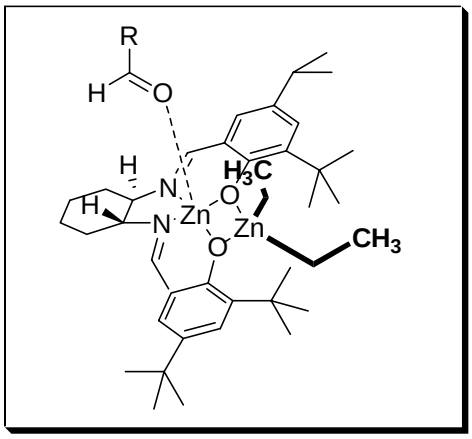


Figure 11. Suggested model by Cozzi and U.-Ronchi *et al.*

In 2001 Kozlowski *et al.* has prepared a set of salen derived catalysts and tried them in diethylzinc addition reactions [87]. They prepared the zinc complexes of the ligands **57-61** shown in Figure 12, and used them as catalysts in asymmetric diethylzinc addition reactions to benzaldehyde.

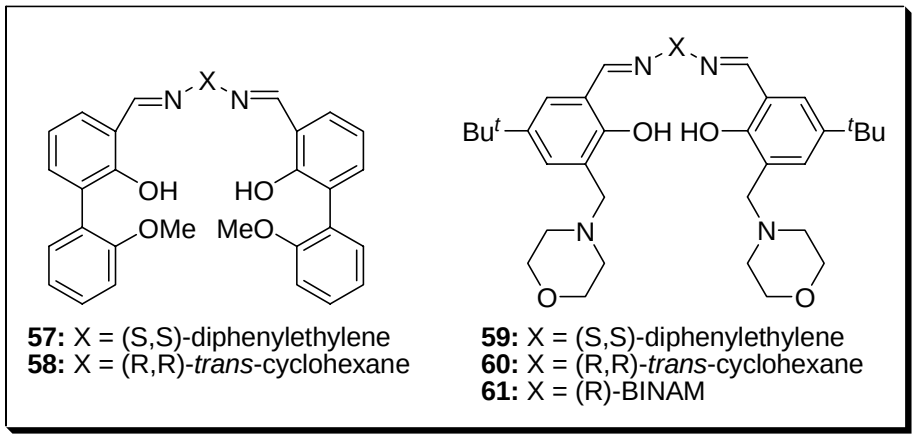


Figure 12. Ligands used in Kozlowski's study

They have found that ligands containing amine Lewis bases (**59**, **60** and **61**; 23 % ee-*S*; 54 % ee-*S*; 19 % ee-*S*, respectively) were much more efficient catalysts than the salens containing ethereal Lewis bases (**57** and **58**; 28 % ee-*S*; 2 % ee-*R*; respectively) (Figure 13).

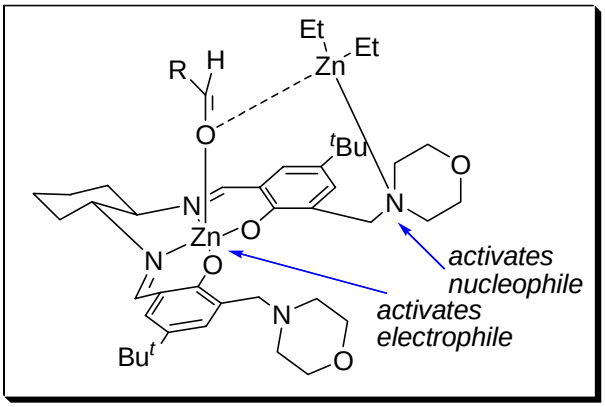
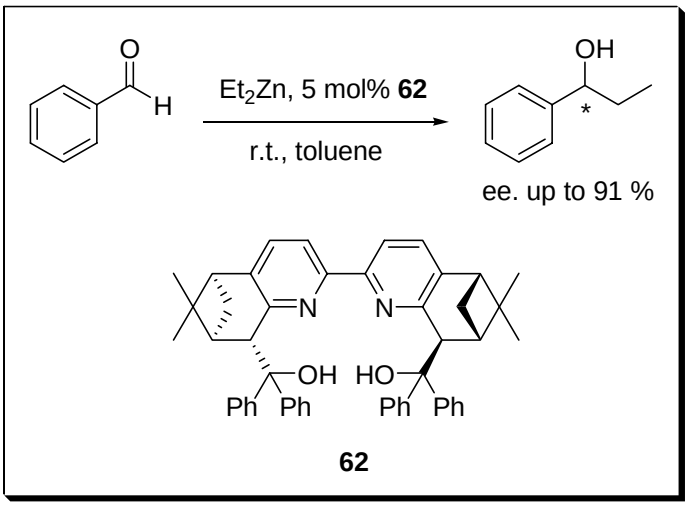


Figure 13. Model for Kozlowski's study

This result is consistent with the supposition that superior activation of the nucleophilic Et_2Zn would be achieved with more Lewis basic group.

In 2004, Chen *et al.* have also worked with salen based ligands. They have synthesized C_2-symmetric, salen-like, bipyridine type ligand, **62,** as shown in Scheme 34, and used this in diethylzinc addition reaction to benzaldehyde in the presence of $Ti(O\text{-}^iPr)_4$ [88].



Scheme 34. Study of Chen *et al.*

Chiral amines containing no hydroxyl group but having multiple nitrogen atoms capable of chelate coordination were also found to be effective in the dialkylzinc additions to aldehydes. For example, (*S*)-2-(2'-pyrrolidinyl)pyridine **63** was shown by Falorni *et al.* to catalyze the diethylzinc addition with up to 100 % ee for aromatic aldehydes (Figure 14) [89].

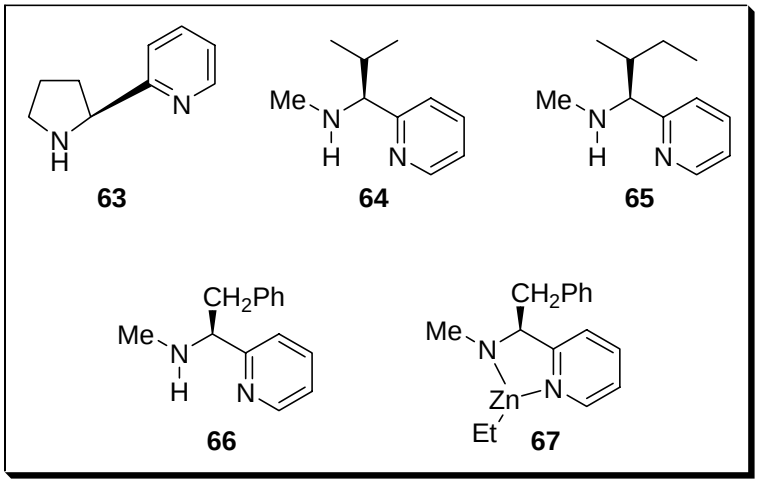


Figure 14. Ligands catalyzed by Falorni *et al.*

Other ligands, **64-66** gave 90-98 % ee for the same reaction with bezaldehyde. When **64** was treated with 1 eq. of diethyzinc, its ^{1}H-NMR spectrum showed the disappearance of the N-H signal, indicating the formation of **67**. Addition of 1 eq. of benzaldehyde to **67** did not lead to an ethyl migration product. The ^{1}H-NMR study revealed that there was a tight coordination of the aldehyde to the zinc center. Therefore as in the aminoalcohol case, another equivalent of diethylzinc was needed for the alkyl addition to aldehyde to occur.

Compounds containing optically active *trans*-cyclohexane-1,2-diamine moiety have also proven to be useful in asymmetric synthesis [90]. König *et al.* have synthesized two new chiral cyclic tetraaza ligands (Figure 15) and tested their catalytic activity in asymmetric addition of diethylzinc to benzaldehyde [91].

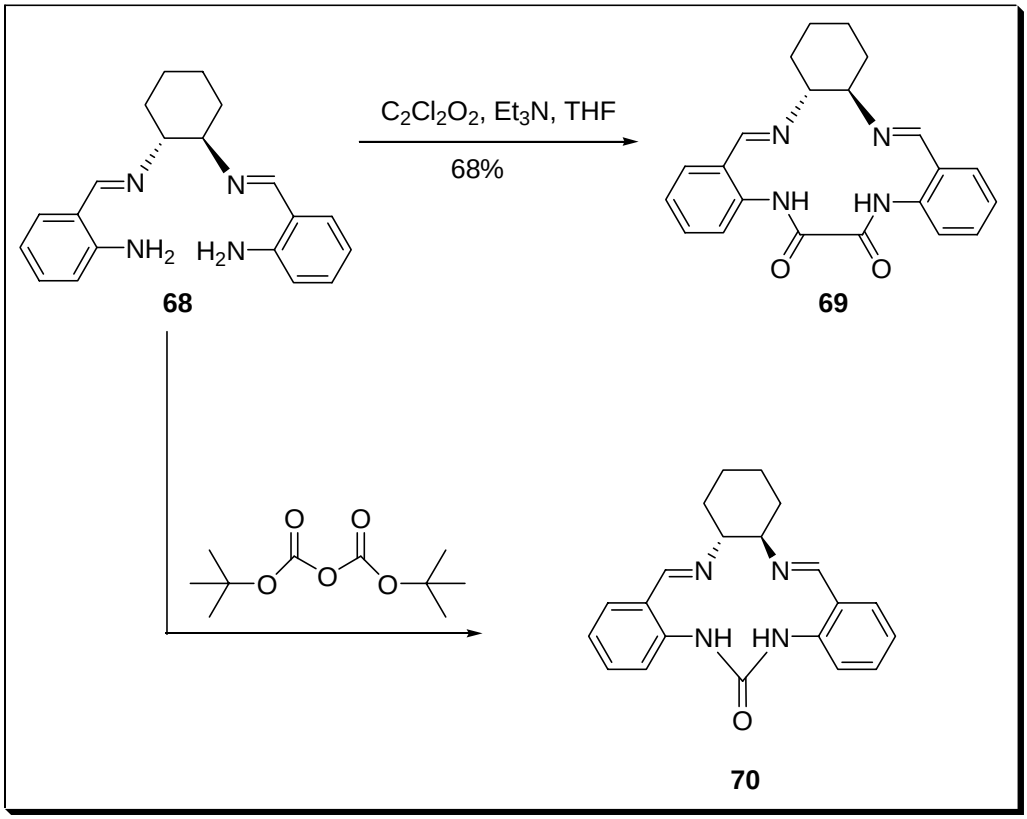


Figure 15. Study of König *et al.*

The ligands **69** and **70** were synthesized from compound **68**, and they were examined as catalysts for the asymmetric addition of dietylzinc to benzaldehyde. However, moderate yields (51 and 88 %, respectively) of 1-phenylpropanol were obtained with no or very low enantioselectivities.

Extensive studies on the use of the C_2-symmetric bistriflamide **71** (Figure 16) in the catalytic asymmetric organozinc addition have been conducted since the original work of Ohno *et al.* [92]. In the presence of titanium complexes such as $Ti(O^iPr)_4$, **71** can catalyze the reaction of a variety of alkylzincs with many aldehydes with excellent enantioselectivities.

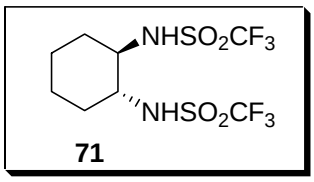


Figure 16. C_2-symmetric bistriflamide

Walsh *et al.* [93] prepared the titanium complexes of ligands **72**, and found that two sulfonyl groups of the ligands also coordinated to the titanium center through the oxygen atoms to form a hexacoordinated complex **73** (Figure 17).

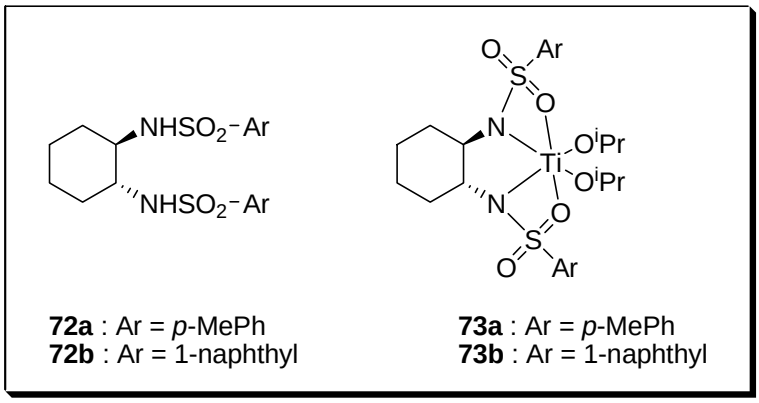
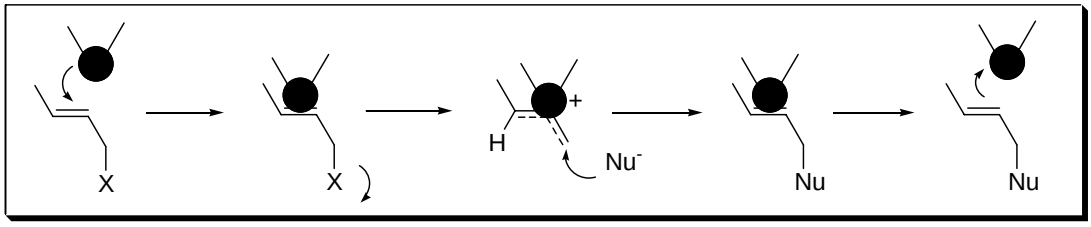


Figure 17. Ligands from Walsh's study

The mixture of **72** (Figure 17) and $Ti(O^iPr)_4$ catalyzed the diethylzinc addition to benzaldehydes with enantioselectivities up to 97 %.

1.7. Asymmetric palladium catalyzed desymmetrization reaction:

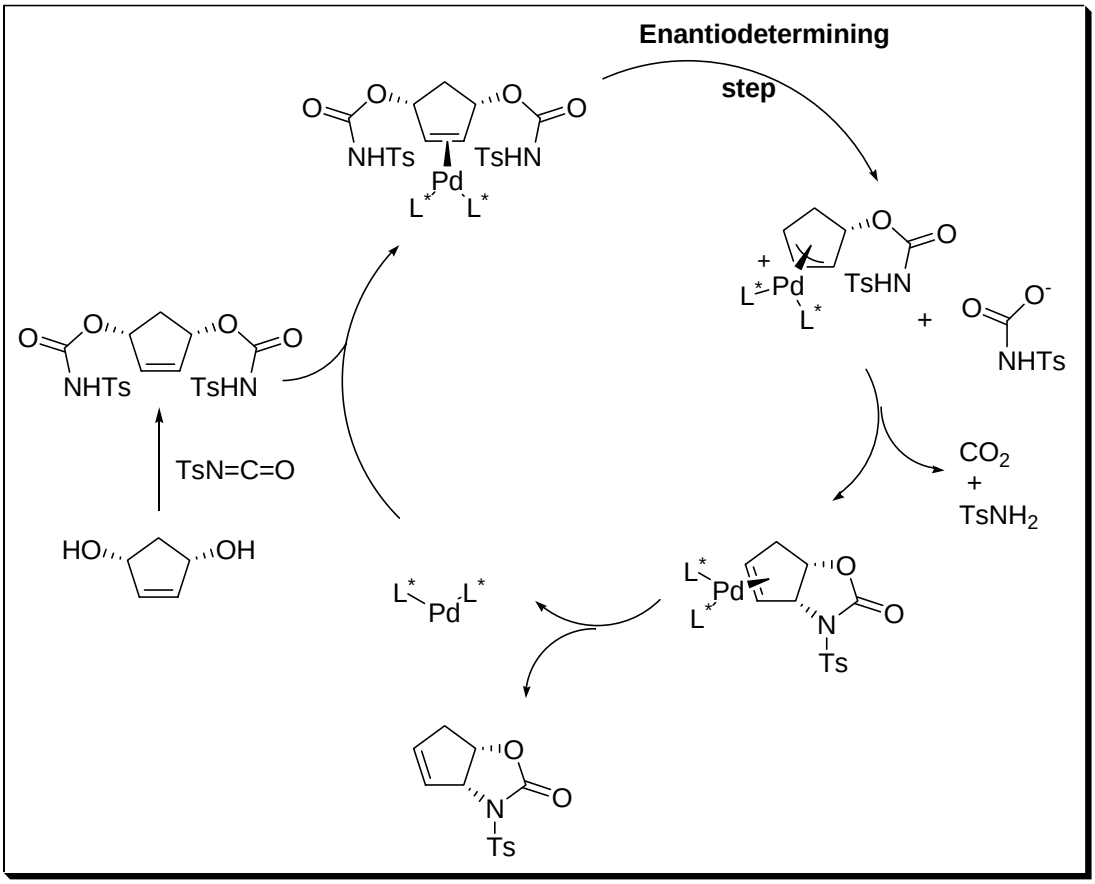
Transition metal-catalyzed allylations have emerged as extremely versatile and powerful reactions; however they are not broadly applicable in enantioselective processes [94]. The general mechanism for a palladium-catalyzed allylation reaction with a nucleophile can be shown in Scheme 35.



Scheme 35. Palladium catalyzed allylic alkylation

The basic catalytic cycle consists of metal-olefin complexation, ionization, alkylation, and decomposition. With the exception of decomplexation, each step in the catalytic cycle of allylic alkylation provides the opportunity for enantiodiscrimination [95].

As a model reaction for asymmetric palladium catalysis Trost *et al.* have chosen oxazolidinone formation reaction (Scheme 36).



Scheme 36. Asymmetric induction in a Pd-catalyzed oxazolidin-2-one synthesis

The oxazolidinone forming reaction was easily carried out by preparing the bis-carbamate substrate in situ. *Cis*-cyclopent-2-ene-1,4-diol in THF was treated with 2.05 eq. of *p*-tolunesulfonyl isocyanate to give the bis-carbamate in an exothermic reaction [96]. The palladium catalyzed desymmetrization of meso-2-ene-1,4-diol diesters has proven to give the monosubstitution products enantioselectively [97, 98].

Only moderate ee values were obtained with commonly used asymmetric ligands. Part of the difficulty encountered in achieving asymmetric induction using chiral ligands in Pd-catalyzed ionizations or alkylations results from the fact that bond breaking/bond forming occurs on the face of the allylic moiety which is opposite that of the chiral metallophosphine moiety (Figure 18) [99].

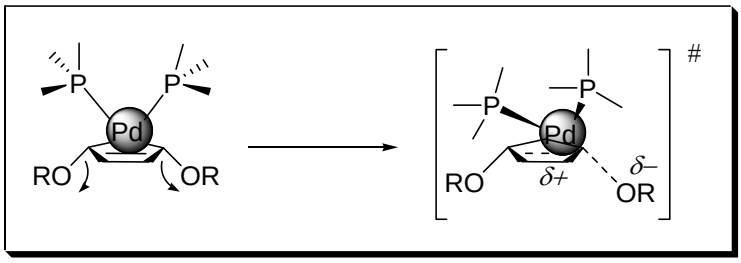
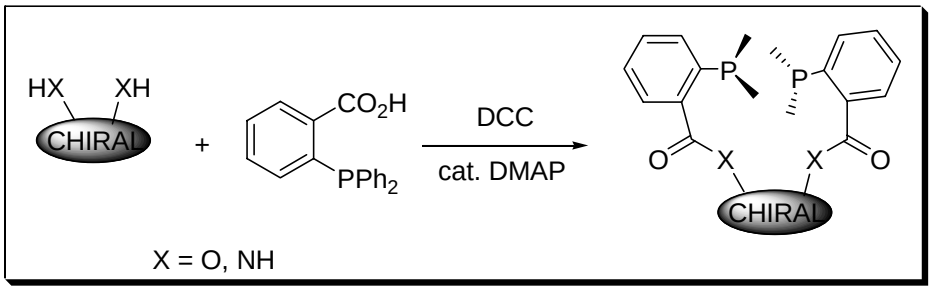


Figure 18. Bond forming/Bond breaking modeling

Trost *et al.* have tried different types of phosphine ligands based on 2-(diphenylphosphino)benzoic acid (2-DPPBA) from chiral alcohols and amines (Scheme 37) [100].



Scheme 37. Strategy for preparing phosphine ligands

They claimed that in order to obtain only one enantiomer at the end of the reaction, the system should be restricted to only one transition state. This was achieved by restricting the number of degrees of freedom in the phosphine-metal substrate complex.

It can be understood from the model shown in Figure 19 that the chiral environment created by the conformation of the phenyl rings dictates the chiral regognition in the ionization step.

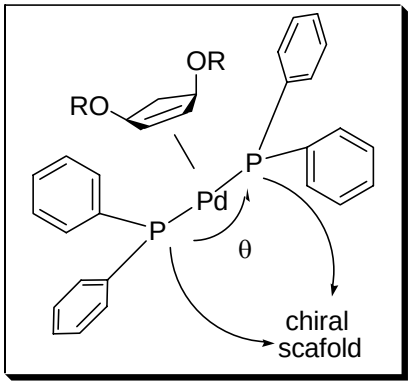


Figure 19. Model for ligand effect

Since bond breaking and bond making occur distal to palladium and thus the chiral ligands, forcing the chiral environment to embrace the substrate by opening the "bite angle", θ, is necessary for high chiral recognition.

They have prepared the ligands, **74-78**, shown in Figure 20, and tried to examine the improvements in enantiomeric excess values.

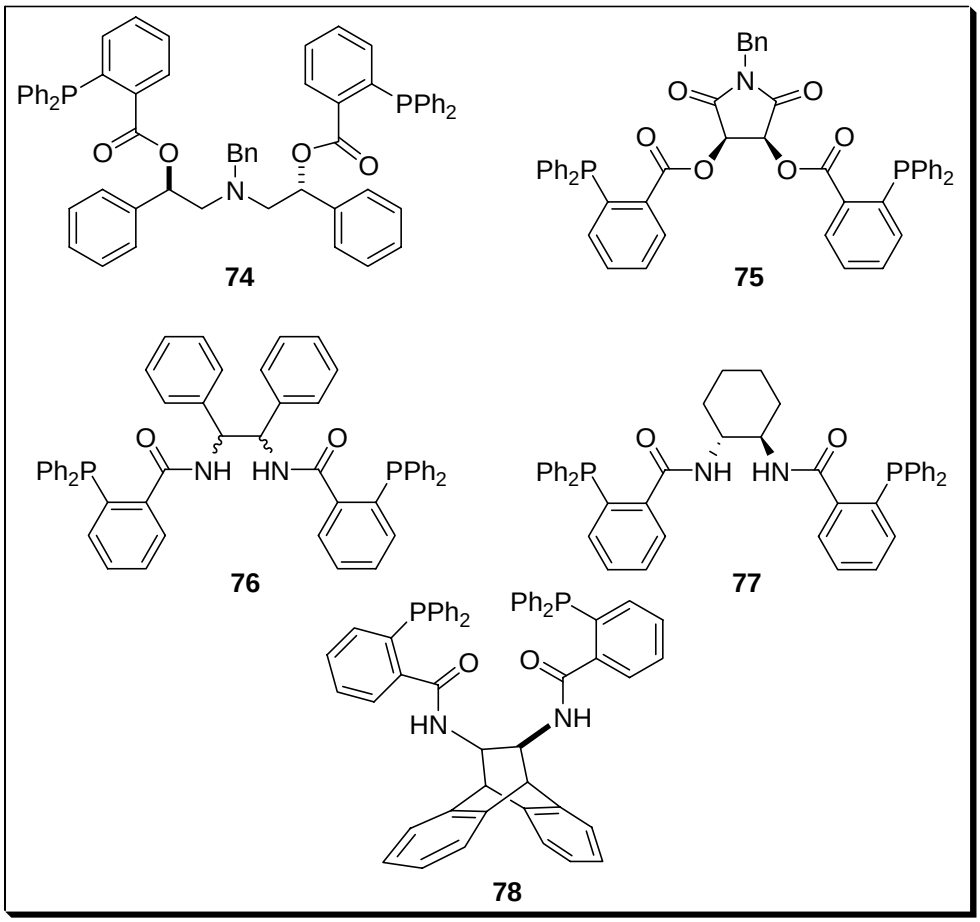


Figure 20. Ligands synthesized by Trost *et al.*

The diester ligand **74** gave oxazolidinone with an ee of 60 %. When they synthesized ligand **75** they have obtained a system more rigid than **74**, and their

results would be changed in a better way to 75 % ee. Then they tried to improve rigidity by synthesizing amide linkage containing ligands as in **76** and **77**, the combination of C_2-symmetry and restricted rotation have resulted in enantiomeric excesses over 80 %. Finally, Trost *et al.* have synthesized ligand **78**, in which the dihedral angle of the N-C-C-N linkage has increased. This ligand gave oxazolidinone with 88.1 % ee, which was attributed to the restriction of the degree of freedom.

Therefore, they have concluded that the large chelating C_2-symmetric bis-phosphine and increased the dihedral angle of the vicinal diols and diamines constituting the chiral scaffold and increased the bite angle increase the chiral recognition.

CHAPTER II

RESULTS & DISCUSSION

2.1. Aim of the work:

During the development of asymmetric synthesis the design of new chiral ligands has become an important issue to improve enantioselectivity of organic reactions. There are a lot of researchers who work for the synthesis of novel chiral ligands.

Among various types of chiral ligands, the ones having nitrogen atoms as donors are attracting much attention. For instance, 1,2-diamines; especially chiral *trans*-1,2-diamines, are the most commonly used ones as efficient chiral inductors; they have found applications in many asymmetric transformation reactions [101].

In this study, we aimed to synthesize an alternative 1,4-diamine type chiral ligand with norbornene backbone (Figure 21).

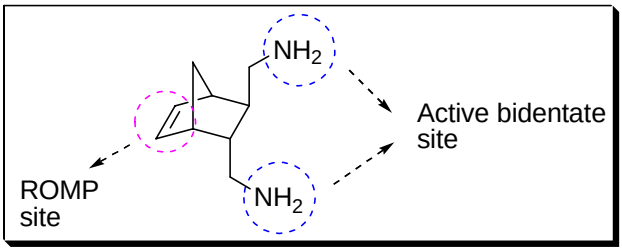


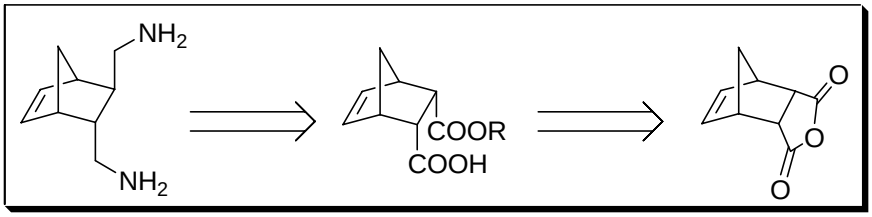
Figure 21. The target 1,4-diamine

Even in literature there are so many studies were done with 1,2-diamine as mentioned above, whereas only few can be found for 1,4-diamine. Why was 1,4-diamine moiety chosen? It was thought that they are more flexible than 1,2-diamines to form metal complexes in some asymmetric reactions. In addition to this expected advantage, especially in the last years, strained cyclic norbornene structures can undergo ring opening metathesis polymerization (ROMP) reactions to synthesize homogenous macromolecular chiral ligands [102]. As can be seen in Figure 21 our target chiral ligand possesses strained norbornene backbone which can be susceptible to ROMP, and enlarge this unit to macromolecular ligand systems.

Starting with commercially available and cheap compounds, the target 1,4-diamine moiety is planned to be synthesized, which was previously designed in our group and preliminary results were published [108]. Also the chiral compounds which will be synthesized throughout the synthesis is planned to be used in some asymmetric reactions i.e. asymmetric diethyl zinc addition, epoxidation, aziridination and desymmetrization reactions. Besides, the target 1,4-diamine moiety was planned to be tested in ROMP reactions.

2.2. The synthesis of [2*R*,3*R*]-2,3-bis(diaminomethyl)bicyclo[2.2.1]heptane:

In our asymmetric synthetic strategy, it was thought that the most suitable starting compound for 1,4-diamine moiety, as shown in a rough retrosynthetic strategy (Scheme 38), was a mesoanhydride which can easily be synthesized via Diels-Alder reaction of cyclopentadiene with maleic anhydride in quantitative yield.



Scheme 38. Retrosynthetic strategy

2.2.1. Desymmetrization of mesoanhydride:

Bolm *et al.* studied the desymmetrization of a variety of prochiral cyclic-anhydrides by cinchona alkaloid-mediated methanolysis and obtained corresponding optically active hemiesters with high enantioselectivities, up to 99 % ee [103]. The used cinchona alkaloids, quinine and quinidine, are shown in Figure 22.

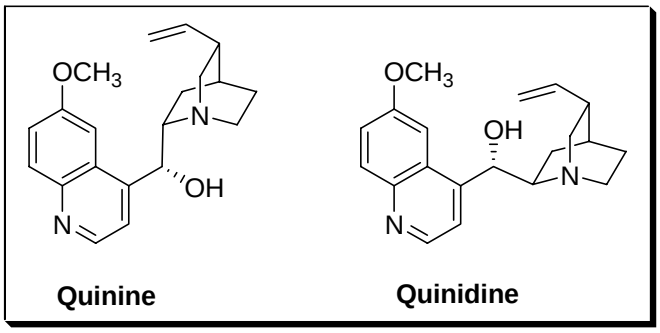
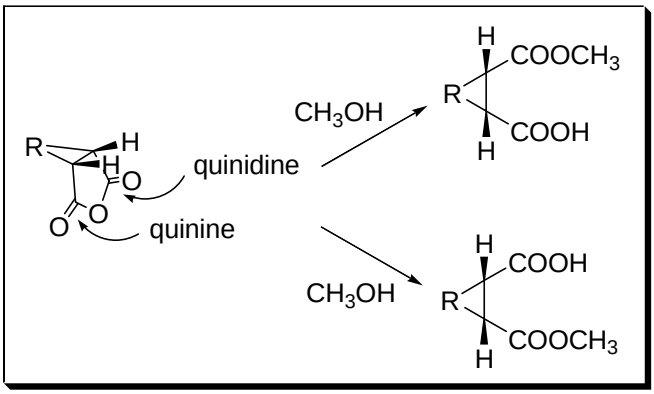


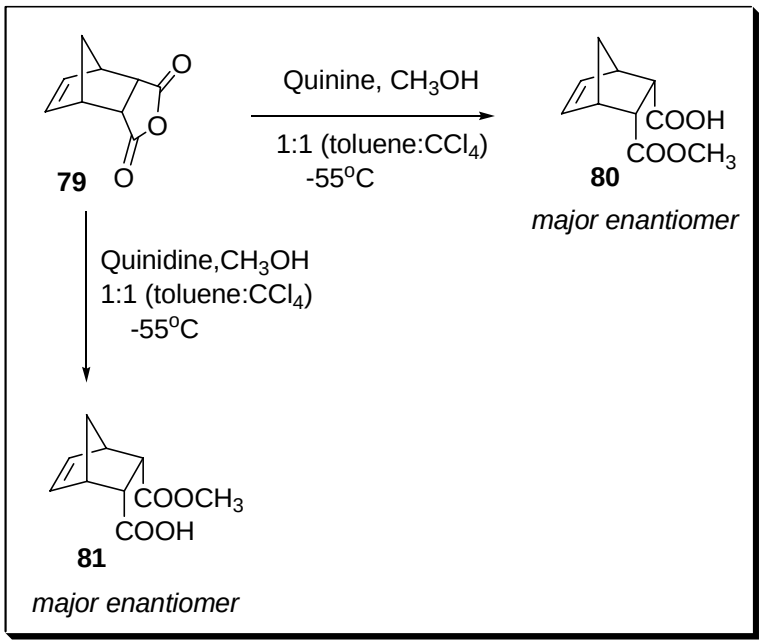
Figure 22. The used alkaloids in Bolm's study

The mentioned diastereomeric alkaloids can be considered as pseudo-enantiomer of each other. Therefore, in the reaction, they generated opposite enantiomers of the products, as can be seen in Scheme 39.



Scheme 39. The effect of quinine/quinidine

A well-known meso-anhydride with norbornene backbone was chosen as a starting compound which was subjected to desymmetrization via quinine / quinidine method (Scheme 40). This step is actually the most important part of the project since the chirality source of all target ligands depends upon it. The stereoselectivity of cinchona alkaloid mediated desymmetrization directly influences the optical purity of the related chiral ligands.



Scheme 40. Desymmetrization via ring opening of a tricyclic anhydride

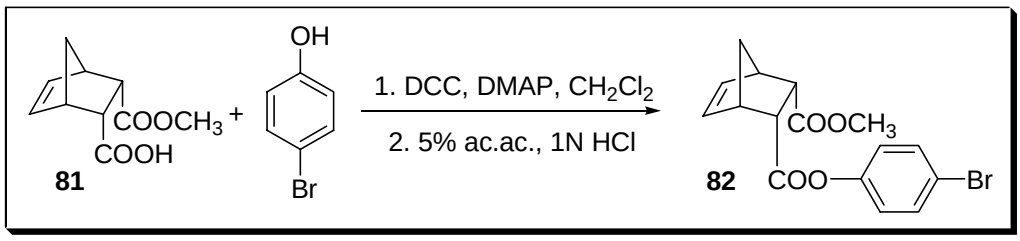
Desymmetrization process was carried out at -55°C with stoichiometric amount of methanol as nucleophile in 1:1 / toluene : CCl_4 solvent system for 60 hours. Under this condition the alkaloids were used in 1.1 eq. of anhydride. In the case of quinidine, toluene : CCl_4 system was arranged in such a way that the concentration of anhydride should be 0.2 M. However, in the case of quinine the reaction mixture had to be more dilute due to solubility reasons, in this case the concentration of anhydride should be 0.05 M.

Both of the alkaloids were used separately to synthesize methyl monoesters, **80** and **81**, the methods shown in Scheme 40 yielded very high enantiomeric excess values.

The resulting mono methyl ester, **81**, for example, was characterized with ^{1}H- and ^{13}C-NMR spectroscopies, the spectra can be seen in appendix part, **A 1**. In ^{1}H-NMR spectrum, one of the bridge protons gives doublet at 1.34 ppm and the other gives doublet of doublet at 1.49 ppm the coupling constant of these geminal protons

is 8.6 Hz. The *exo* protons resonate as doublet of doublets at 3.28 and 3.34 ppm with a vicinal coupling as 10.2 Hz. The bridge head protons give broad singlets at 3.17 and 3.20 ppm. Methyl protons of ester group give a singlet resonance at 3.60 ppm and the olefinic protons give doublet of doublet at 6.22 ppm (J = 2.9 Hz; 5.4 Hz) and 6.32 ppm (J = 3.1 Hz; 5.4 Hz). In ^{13}C-NMR spectrum, carboxylic acid and ester carbonyl groups give signals at 178.1 and 172.9 ppm respectively and olefinic carbons at 135.6 and 134.4 ppm. Methyl carbon of ester group gives a signal at 51.5 ppm and carbons of norbornene ring give signals between 46.1 and 48.8 ppm.

The absolute configuration of starting compound **81**, was determined as (2*R*,3*S*) by comparing specific rotation sign determined at equal concentration in the same solvent given in the literature for cis-monoester (+)-**81** [103]. (2*R*,3*S*)-3-*endo*-methoxycarbonyl-bicyclo[2.2.1]hept-5-ene-2-*endo*-carboxylic acid, is a very polar substance and additionally has very low UV activity. Thus it was converted to its *p*-bromo phenyl ester derivative with bromophenol in the presence of DCC and DMAP, as shown in Scheme 41, to control its polarity and increase its UV activity to be detected with UV detector.



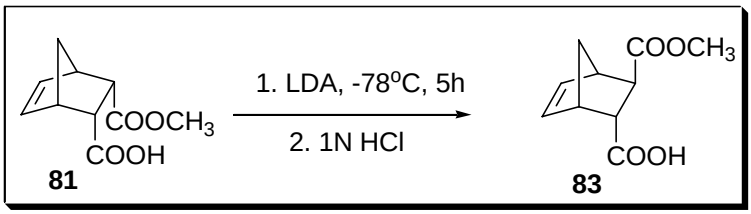
Scheme 41. The reaction between hemiester and bromophenol

HPLC study of compound **82**, was performed with Chiralcel OD-H column, 98 : 2 (Hexane : Isopropanol) as eluent with 1 ml/min flow rate and at the end enantiomeric excess was measured as 98 %.

The ^{1}H- and ^{13}C-NMR data of compound **82** can be seen in appendix part, **A 2** and the explanation of the spectra in experimental part.

2.2.2. Regioselective epimerization of hemiester:

The next step was the conversion of *cis*-monoester into *trans* form. This was done by applying Seebach epimerization method [104]. In this method ester substituted center was regioselectively epimerized to corresponding *trans*-2,3-disubstituted hemiester, **83**. It was also controlled by HPLC and no racemization was observed. This method involves the reaction of *cis*-monoester with LDA at -78°C for 5 hours. Then the reaction was quenched with 1 N HCl then the desired *trans*-monoester was separated by column chromatography with 85 % chemical yield (Scheme 42).



81 **83**

Scheme 42. Regioselective epimerization

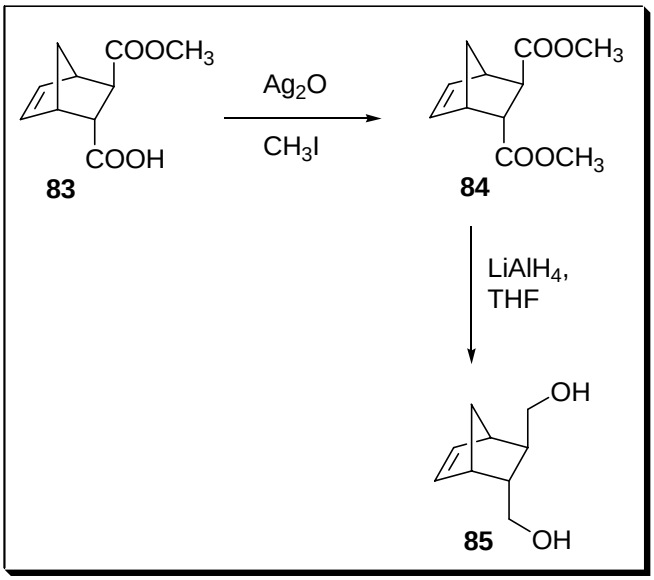
Characterization of **83**, (2*R*,3*R*)-3-*exo*-methoxycarbonyl-bicyclo[2.2.1]hept-5-ene-2-*endo*-carboxylic acid, was done by ^{1}H- and ^{13}C-NMR methods, the spectra can be seen in appendix part, **A 3**. The change in the configuration of the compound from *cis* to *trans* can be identified from ^{1}H-NMR spectrum. In the spectrum one of the signals of *exo* protons in compound **81** shifted to higher field from 3.28 ppm to 2.59 ppm this difference show that the proton changed its configuration to *endo* form, the other one which is an α-proton to carboxylic acid group, also shifted from 3.34 ppm to 3.36 ppm. The coupling constants of the two protons also decreased

from 10.2 Hz to 4.5 Hz, this is also due to the configuration change. The bridge head protons also are affected, that is; the proton near to configuration changed center is shifted from 3.17 ppm to 3.07 ppm and the other proton gives signal at 3.23 ppm. The bridge protons give doublet of doublets in the nearly same region as 1.41 and 1.56 ppm with geminal coupling constant as 8.9 Hz. The olefinic protons give doublet of doublet at 6.07 ppm (J = 2.8 Hz; 5.6 Hz) and 6.22 ppm (J = 3.1 Hz; 5.6 Hz), and carboxylic acid proton gives a broad singlet at 11.0 ppm. Methyl protons of ester group give a singlet resonance at 3.65 ppm. In ^{13}C-NMR spectrum carbonyl groups of acid and ester functionalities give signals at 179.1 and 174.7 ppm, respectively, and the olefinic carbons give resonances at 135.2 and 137.7 ppm which are all in the lower field than *cis* one. Methyl carbon of ester group gives signal at 52.2 ppm, and the norbornene carbons give signals between 45.6 and 47.9 ppm.

2.2.3. *trans* 1,4-diol formation reaction:

The next step in our synthetic strategy was transferring *trans*-1,4-monoester, **83**, into the corresponding diol, **85** that was the first chiral ligand used in this study. Since it has two heteroatoms, it can easily form the complex with metal systems and can catalyze some asymmetric transformation reactions.

The synthesis of diol **85** can be done in two different ways, either direct reduction of hemiester with $LiAlH_4$, or converting the hemiester into diester with Ag_2O in iodomethane, then reduction of diester with $LiAlH_4$. Both methods were performed and the second method was preferred since in this case quantitative conversion to diol was observed. The synthetic strategy can be seen in Scheme 43.



Scheme 43. The synthesis of diol

As mentioned before, hemiester, **83**, was firstly reacted with iodomethane in the presence of Ag_2O, this step afforded total conversion of monoester to diester, **84**. After esterification the obtained diester was reduced to give diol, **85** in the presence of $LiAlH_4$. Again in that step, complete reduction was obtained.

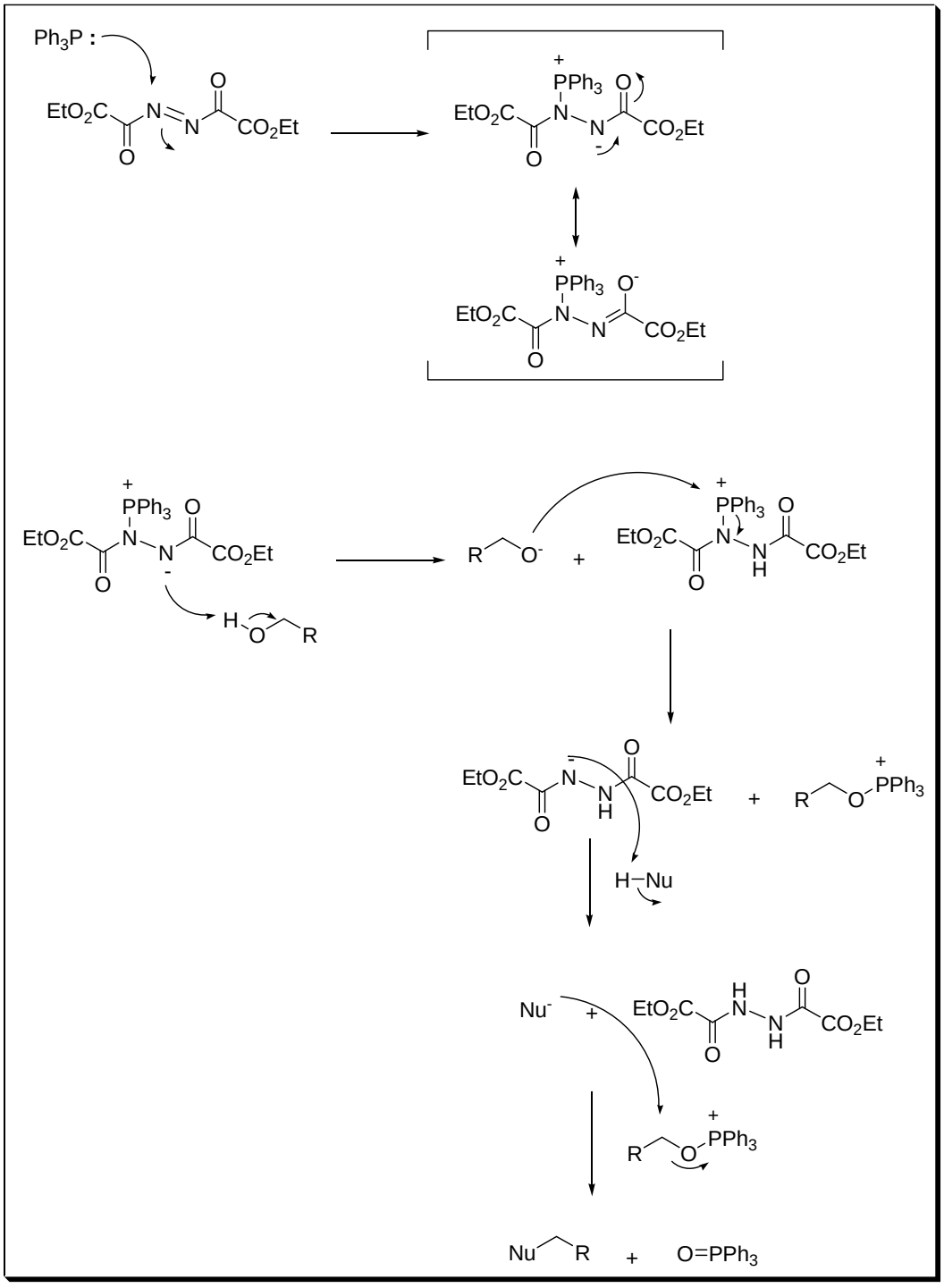
All products were analyzed with ^{1}H- and ^{13}C-NMR spectroscopies, the spectra can be seen in appendix part, **A 4**. In the ^{1}H-NMR spectrum of diester, **84**, when compared to hemiester, **83**, the bridge and bridge head protons, the protons at second and third carbon centers give signals at approximately the same regions. Differently, in the spectrum of diester, two singlets of methyl groups can be examined at 3.58 and 3.65 ppm and also disappearance of the carboxylic acid proton peak can be observed. In the ^{13}C-NMR spectrum of diester, olefinic carbons give resonances at 137.7 and 135.2 ppm, and the norbornene backbone carbons give resonances between 45.6 and 47.9 ppm which are similar to that of compound **83**. However, there are two methyl carbons of ester groups at 52.1 and 51.8 ppm in the spectrum of diester, **84**, and the two carbonyl carbons give signals at 174.9 and 173.7 ppm which are in the region of ester carbonyls.

The ^{1}H and ^{13}C-NMR spectra of compound **85**, diol, (App. no: **A 5**) can be explained by comparing with the spectra of diester. In the ^{1}H-NMR spectrum the most striking changes are the disappearance of methoxy methyl signals, the appearance of two diastereotopic proton groups and the hydroxyl proton signals. In the spectrum, one of the diastereotopic proton groups, –C$\underline{H}_2$OH, give AB splitting as doublet of doublets at 3.46 ppm (J =5.8 Hz; 9.6 Hz) and 3.59 ppm (J =5.8 Hz; 9.6 Hz); the other –C$\underline{H}_2$OH, group give two triplet signals at 2.91 and 3.29 ppm with 9.8 Hz coupling constants. The alcohol protons give a signal at 3.92 ppm as a broad singlet. The olefinic protons give doublet of doublets at 5.86 ppm (J = 2.6 Hz; 5.2 Hz) and 6.10 ppm (J = 3.2 Hz; 5.2 Hz). The other norbornene protons give signals at higher field in the spectrum when compared to diester, because of the disappearance of ester functionalities, bridge protons at 1.06 and 1.78 ppm; bridge head protons at 2.55 and 2.78 ppm and the protons at second and third carbon centers a broad singlet at 1.32 ppm. In the ^{13}C-NMR spectrum, olefinic carbons give signals at 138.0 and 133.4 ppm and the norbornene carbons between 44.5 and 47.9 ppm similar to diester. Besides, in the diol spectrum carbons of –$\underline{C}H_2$OH groups give signals at 66.1 and 66.6 ppm. Also when compared to diester spectrum the disappearance of carbonyl carbons can be observed.

2.2.4. The synthesis of diamine:

2.2.4.1. The synthesis of diphthalimide norbornene from diol by applying Mitsunobu reaction

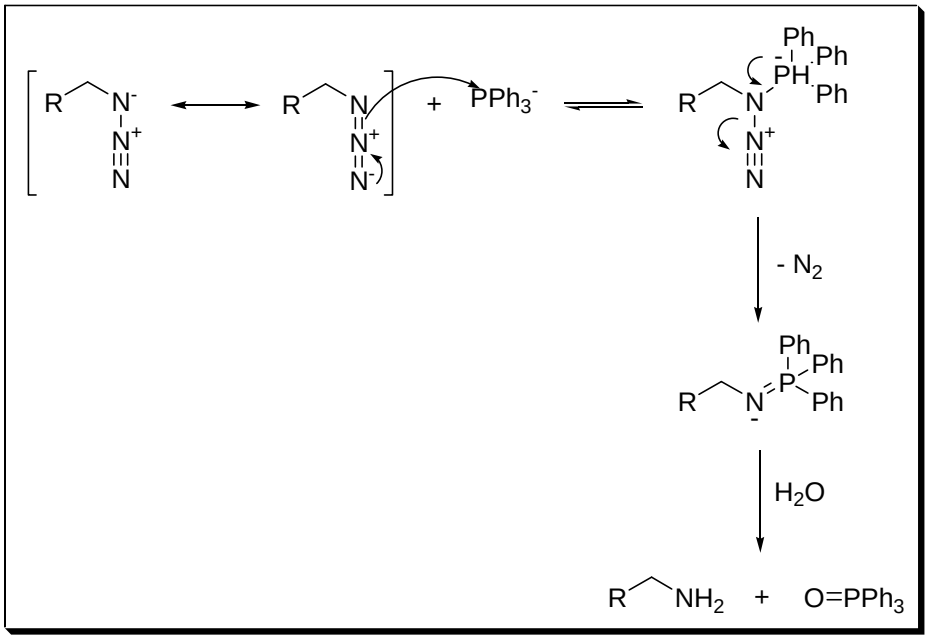
The next step was the synthesis of diamine from the synthesized diol, in this case the mostly applied reaction, called Mitsunobu reaction, was performed. The Mitsunobu reaction is a widely excepted method in organic synthesis due to its effectiveness and versatility [105]. It performs a stereospecific conversion of an alcohol to a primary amine with inversion of configuration. The alcohol is treated with triphenylphosphine, diethyl azodicarboxylate (DEAD) and, usually with suitable nitrogen nucleophiles including phthalimide or hydrogen azide (Scheme 45); subsequent hydrolysis (in the case of using phthalimide, Gabriel Synthesis) or selective reduction (in the case of azide formation, Staudinger Reaction) makes the corresponding amines accessible [106].



Scheme 44. General mechanism for Mitsunobu reaction

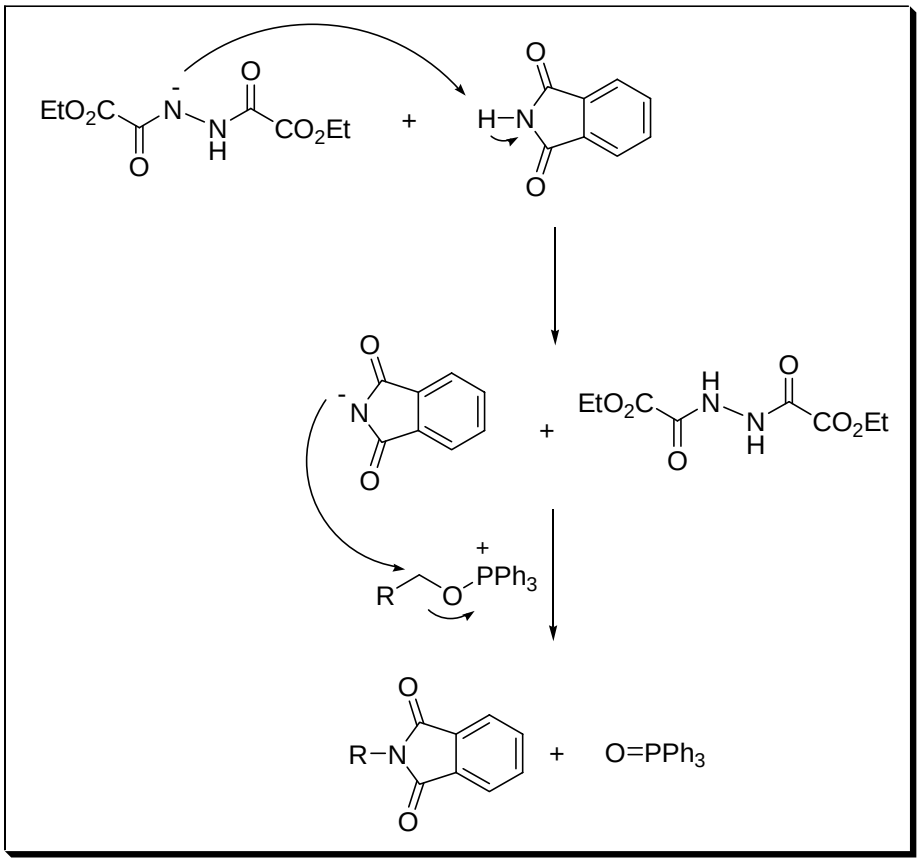
In the mechanism shown in Scheme 44, triphenylphosphine combines with DEAD to generate a phosphonium intermediate that binds to the alcohol oxygen, activating it as a leaving group. The remaining unprotonated DEAD must be protonated to prevent from side reactions. This protonation is done with reacting carboxylate or nucleophiles as mentioned before hydrogen azide or phthalimide.

In the study firstly hydrogen azide was studied as a nucleophile and diamine was obtained by Staudinger method, but in this case the desired diamine could not be recovered from the medium. In this method at the last step, as seen in Scheme 45, triphenylphosphine oxide was removed with water treatment and the removal of diamine from the aqueous medium was not easy.



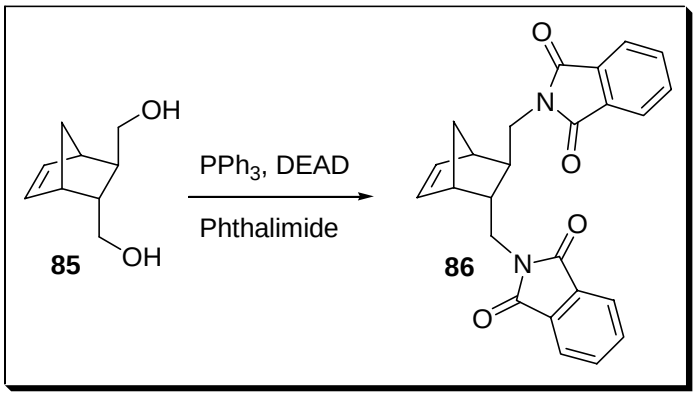
Scheme 45. The general mechanism of Mitsunobu with HN_3 as nucleophile

Therefore, phthalimide was tried as nucleophile as seen in Scheme 46.



Scheme 46. The general mechanism of Mitsunobu-Gabriel combination

In the study, as in the mechanism shown in Scheme 46, diol moiety was subjected to Mitsunobu reaction with phthalimide as nucleophile. Firstly diol was treated with triphenylphosphine, diethyl azodicarboxylate (DEAD) and, phthalimide for two days at room temperature. After purification the product was obtained in 65 % chemical yield (Scheme 47).



Scheme 47. Mitsunobu application

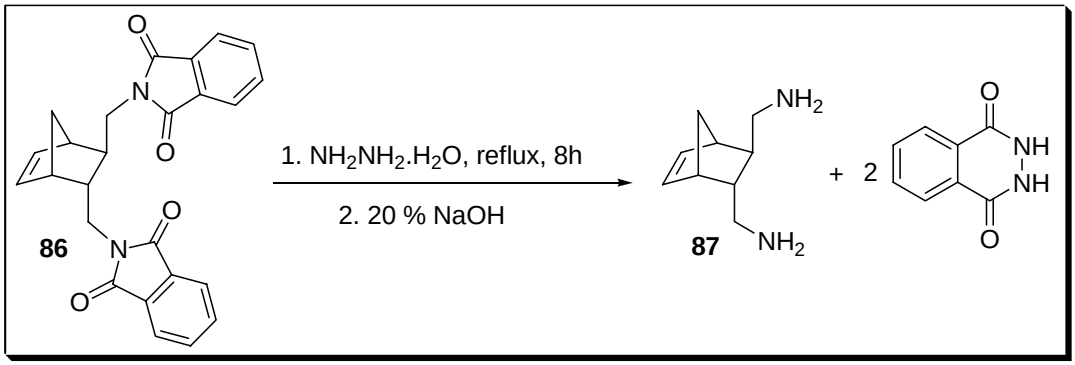
The resulting diimide product was characterized with NMR spectroscopies, the spectra can be seen in appendix part, **A 6**. In ^{1}H-NMR spectrum, bridge protons give signals at 1.46 ppm as doublet of doublet (J = 1.4 Hz; 8.8 Hz) and 1.58 ppm as doublet (J = 9.3 Hz), one of the protons at chiral centers gives a broad singlet at 1.52 ppm and the other proton gives a multiplet at 2.18 ppm. Bridge head protons give singlets at 2.56 and 2.71 ppm. One of the methylene group gives a doublet at 3.32 ppm (J = 7.6 Hz) and the other methylene group gives a multiplet at 3.63 ppm. The olefinic protons give a multiplet at 6.20 ppm and the phenyl protons give two multiplets at 7.58 and 7.67 ppm.

In ^{13}C-NMR spectrum, carbonyl groups give resonances at 168.2 and 168.4 ppm, olefinic and aromatic carbons between 120.0 – 140.0 ppm and the norbornene and methylene carbons between 41.7 and 46.3 ppm.

2.2.4.2. The synthesis of diamine by applying Gabriel synthesis:

After the application of Mitsunobu reaction the resulting diimide, **86**, structure was subjected to hydrazinolysis reaction as in Gabriel synthesis [107]. Therefore the desired primary diamine, **87**, was obtained.

Hydrazinolysis of product **86** was done by refluxing with hydrazine hydrate for eight hours, by this way the desired unsaturated diamine was obtained in 52 % chemical yield (Scheme 48). However, in the previous studies done in our group, using excess amount of hydrazine caused the saturation of the double bond [108].



Scheme 48. Hydarzinolysis reaction

The resulting desired diamine compound, **87**, was characterized with ^{1}H- and ^{13}C-NMR spectroscopies, the spectra can be seen in appendix part, **A 7**. In the ^{1}H-NMR spectrum of the ligand the bridge protons can be examined as two multiplets at 0.87 and 1.52 ppm; and the protons at second and third carbon centers give a singlet at 1.37 ppm which are in higher field region compared to diimide, **86**, case. The $-NH_2$ protons give a broad singlet at 1.25 ppm. The diastereotopic protons of two $-C\underline{H_2}NH_2$ groups give doublet of doublet as AB splittings, one group at 2.36 ppm (J = 8.4 Hz; 12.3 Hz) and 2.43 ppm (J = 6.8 Hz; 12.3 Hz) and the other at 2.62 ppm (J = 8.2 Hz; 12.4 Hz) and 2.74 ppm (6.7 Hz; 12.4 Hz). The bridge head protons give broad singlets at 2.55 and 2.77 ppm. The olefinic protons give doublet of doublet at 5.95 ppm (J = 2.8 Hz; 5.6 Hz) and 6.13 ppm (J = 3.2 Hz; 5.6 Hz).

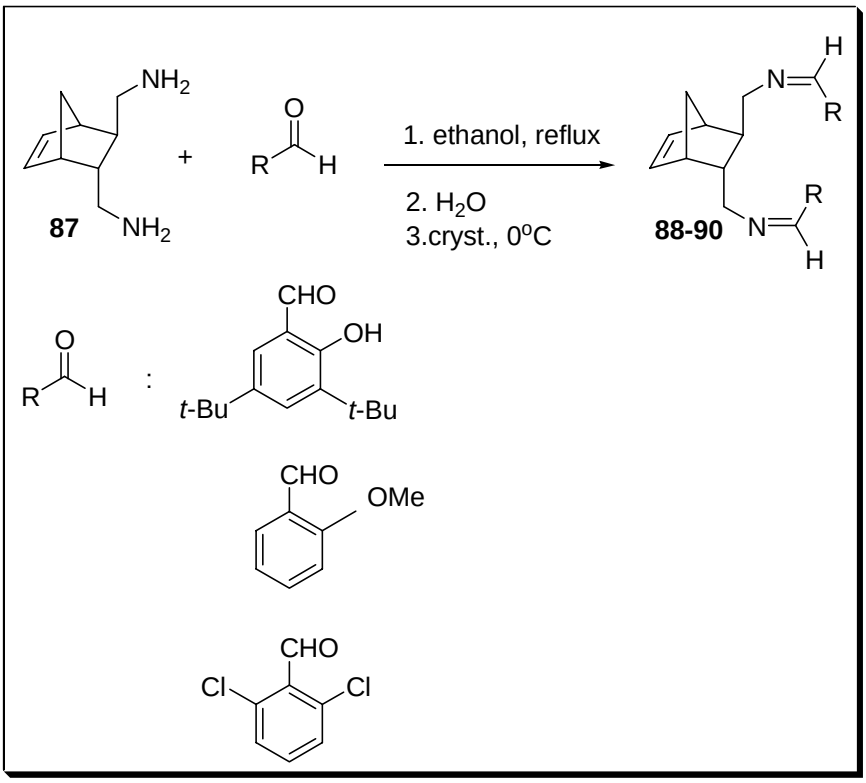
In the ^{13}C-NMR spectrum, the olefinic carbons give signals at 133.9 and 138.2 ppm. The carbons of –$\underline{C}H_2NH_2$ groups and the norbornene carbons give signals between 44.5 and 49.3 ppm.

2.3. Synthesis of salen ligands:

The salen ligand is a versatile dianionic, tetradendate ligand that has been exploited by Eric Jacobsen and many others. Jacobsen *et al.* has used 1,2-diamines especially cyclohexane-1,2-diamine in the formation of salen ligands. Those salen ligands are used in asymmetric reactions some of which are asymmetric epoxidation, aziridination, cyclopropanation.

In this study, the synthesized 1,4-diamine moiety was used in the formation of salen type ligands. Besides, the effectiveness of the synthesized ligands were tested in some asymmetric reactions as catalysts.

Those ligands were synthesized by simple refluxing of one equivalent of diamine and two equivalents of benzaldehyde derivatives in absolute ethanol (Scheme 49).



Scheme 49. The synthesis of salen ligands

Therefore the synthesized diimine ligands can be shown in Figure 23.

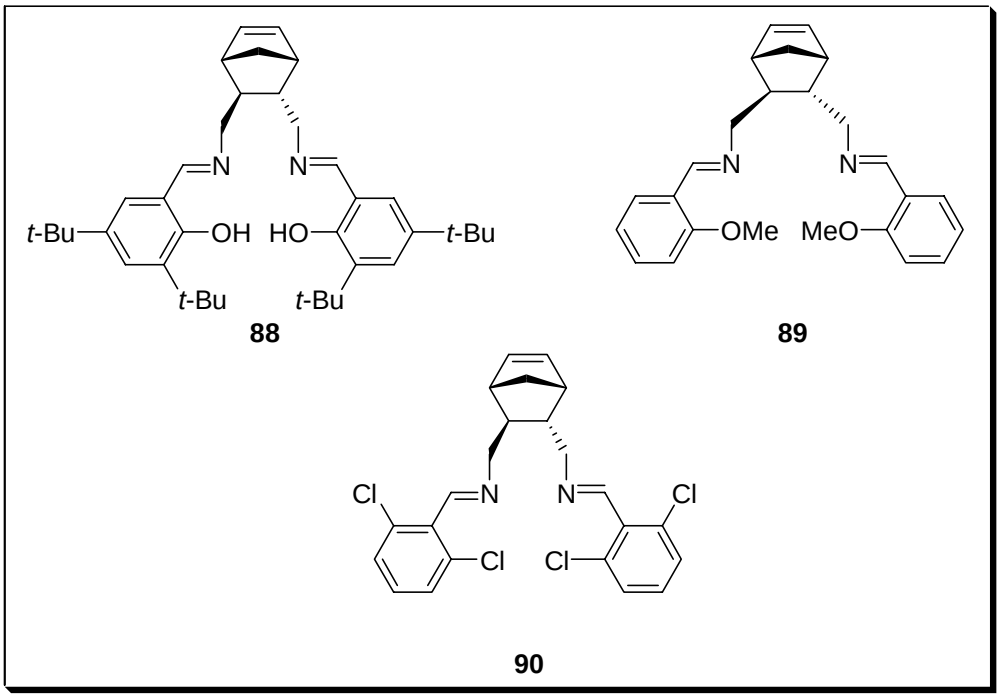


Figure 23. The ligands synthesized by condensation of diamine and benzaldehyde derivatives

Those ligands were characterized with ^{1}H- and ^{13}C-NMR spectroscopies, spectra can be seen in appendix part, **A 8**, **A 9**, **A 10**, respectively.

In the ^{1}H-NMR spectrum of compound **88**, there are two singlets, each is a result of resonances of eighteen tertiary butyl protons at 1.38 and 1.47 ppm. The bridge protons can be observed as a multiplet at 1.53 ppm; the *endo*, *exo* protons, as broad singlets at 1.43 and 2.00 ppm. The bridge head protons on the other hand give singlets at 2.79 and 2.95 ppm. The diastereotopic protons of –C$\underline{H}_2$N= groups give again AB splittings. One of the groups gives doublet of doublets at 3.34 ppm (J = 8.6 Hz; 11.6 Hz) and 3.42 ppm (J = 6.9 Hz; 11.6 Hz). The other group gives again doublet of doublets at 3.61 ppm (J = 8.2 Hz; 11.7 Hz) and 3.72 ppm (J = 6.7 Hz; 11.7 Hz). The olefinic protons give doublet of doublets at 6.14 ppm (J = 2.6 Hz; 5.4 Hz) and 6.28 ppm (J = 3.2 Hz; 5.4 Hz). The aromatic protons give

signals at 7.06 and 7.38 ppm, the imine protons give singlets at 8.33 and 8.38 ppm and the hydroxyl protons gives signals at 14.00 and 14.02 ppm.

In the ^{13}C-NMR spectrum of ligand **88**, the carbons of tertiary butyl groups give signals between 29.5 and 35.6 ppm and the norbornene carbons give signals between 44.8 and 46.8 ppm. The signals at 63.8 and 64.7 ppm belong to the carbon of –$\underline{C}H_2N$= groups. The aromatic carbons can be observed between 117.1 and 158.2 ppm and the imine carbons at 165.8 and 166.1 ppm.

In the ^{1}H-NMR spectrum of ligand **89**, the bridge protons give signals at 1.34 ppm, as broad doublet. and 1.41 ppm as doublet (J = 10.2 Hz), the protons at second and third carbon centers give broad multiplets; one of them coincides with one bridge protons at 1.34 ppm and the other at 2.02 ppm, and the bridge head protons give signals as broad singlets at 2.58 and 2.73 ppm. There are three multiplets for four diastereotopic protons at 3.16, 3.49, and 3.77 ppm. The methoxy methyl groups give singlets at 3.72 and 3.73 ppm. The olefinic protons give doublet of doublets at 5.98 ppm (J = 2.7 Hz; 5.6 Hz) and 6.13 ppm (J = 3.1 Hz; 5.6 Hz). The phenyl protons give signals between 6.78 and 7.85 ppm, the imine protons also give resonances at 8.52 and 8.59 ppm as singlets.

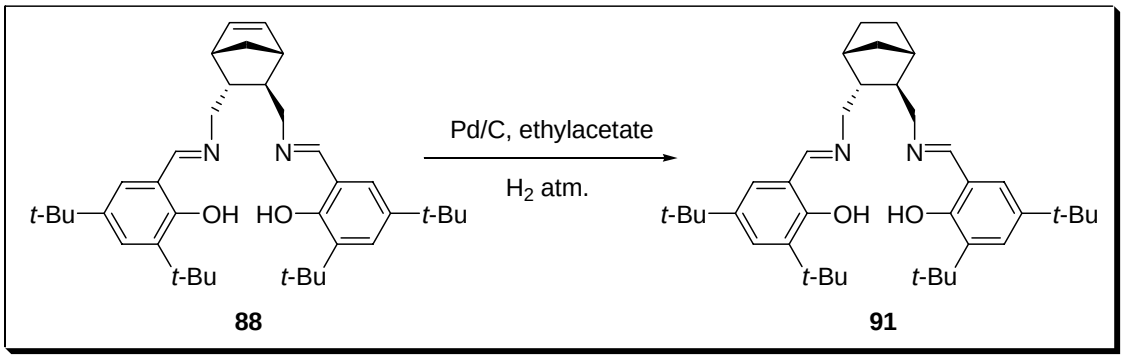
In the ^{13}C-NMR spectrum of ligand **89**, aliphatic norbornene carbons can be observed between 44.7 and 46.3 ppm. –O$\underline{C}H_3$ carbons give signals at 55.5 ppm and –$\underline{C}H_2$-N carbons at 66.1 and 66.9 ppm. Other aromatic and olefinic carbons can be observed between 111.0 and 158.7 ppm.

In the ^{1}H-NMR spectrum of compound **90**, the norbornene protons give resonances at nearly the same region of the spectrum as in the case of ligands **88** and **89**. The geminal bridge protons give doublets at 1.44 (J = 8.4 Hz) and 1.54 ppm (J = 8.4 Hz); the protons at second and third carbon centers give two multiplets at 1.48 and 2.15 ppm; the bridge head protons at 2.72 and 2.89 ppm. One of the diastereotopic protons groups give triplets at 3.26 ppm (J = 11.0 Hz) and 3.60 ppm (J = 9.5 Hz), and the other group gives doublet of doublets at 3.73 ppm (J = 5.5 Hz; 11.3 Hz) and 3.98 ppm (5.4 Hz; 11.3 Hz). The olefinic protons can be observed as

doublet of doublets at 6.07 ppm (J = 2.8 Hz; 5.6 Hz) and 6.20 ppm (J = 3.2 Hz; 5.6 Hz), and the aromatic protons at 7.16 and 7.26 ppm, the imine protons at 8.30 and 8.36 ppm.

In the ^{13}C-NMR spectrum of compound **90**, the norbornene carbons give signals between 45.1 and 46.4 ppm, the methylene carbons at 66.8 and 67.6 ppm, the aromatic carbons between 129.0 and 138.4 ppm, the olefinic carbons at 157.0 and 157.3 ppm, and finally the imine carbons at 189.1 ppm.

Between those ligands the easiest prepared one was ligand **88**, because it was obtained in 95 % chemical yield. Therefore for the applications; ligand **88** was chosen as chiral ligand. The chiral diimine ligand, **88**, was obtained by condensing chiral diamine and 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde, for some applications such as asymmetric epoxidation and asymmetric aziridination reactions, the ligand **88** was needed to be reduced. It was done by hydrogenation in the presence of Pd / C as catalyst this procedure was yielded total conversion (Scheme 50).



Scheme 50. The reduction of diimine

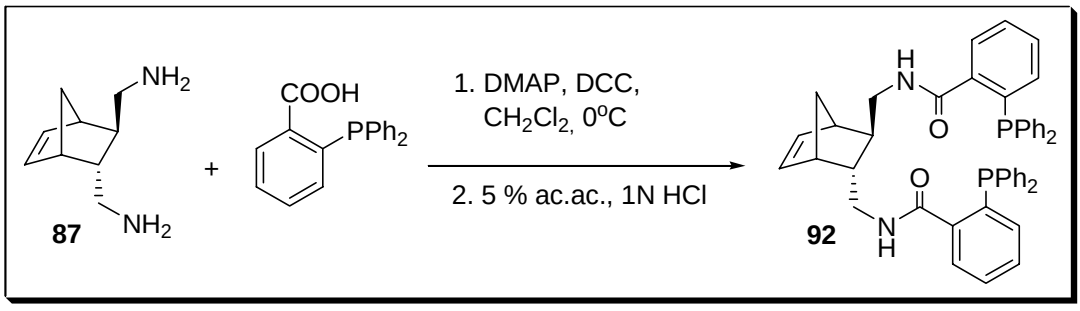
The resulting reduced diimine ligand, **91**, was characterized with ^{1}H- and ^{13}C-NMR spectroscopies, the spectra can be seen in appendix part, **A 11**. The spectrums can be explained by comparing with compound **88**. In ^{1}H-NMR spectrum

the disappearance of olefinic carbons around 6.0 ppm is the most striking difference. Besides when the double bond was reduced, the norbornene protons shifted to higher field in the spectrum, between 1.10 and 2.25 ppm with increased number of signals. In the ^{13}C-NMR spectrum the disappearance of two olefinic carbons can be observed.

2.4. The synthesis of other chiral bidentate norbornane type ligands:

2.4.1. The synthesis of diphenylphosphine containing ligands:

The first ligand was synthesized by reacting chiral diamine, **87**, with two equivalents of 2-(diphenylphosphino)benzoic acid. The reaction was carried out in the presence of DCC and DMAP in dichloromethane at 0°C then with continuous stirring overnight at room temperature (Scheme 51).

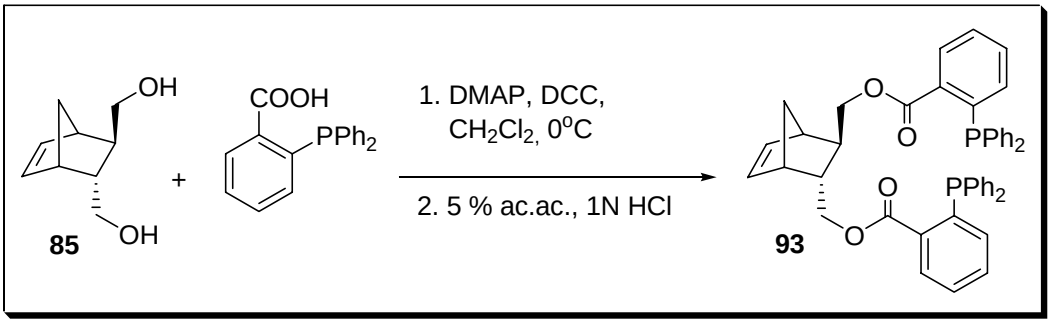


Scheme 51. The synthesis of chiral diphenylphosphine containing ligand

The synthesized ligand, **92** was characterized by ^{1}H- and ^{13}C-NMR methods (App. No: **A 12**). In the ^{1}H-NMR spectrum, the bridge protons of norbornene backbone can be observed at 1.03 and 1.65 ppm as multiplets, the methine protons attached to second and third carbon centers give a singlet at 1.35 ppm. The bridge head protons give singlets at 2.43 and 2.60 ppm, one of the diastereotopic protons group gives triplet at 3.00 ppm (J = 6.6 Hz) and the other gives doublet of doublet at

3.28 ppm (J = 6.0 Hz; 12.5 Hz). The olefinic protons can be observed as doublet of doublets at 5.92 ppm (2.7 Hz; 5.6 Hz) and 6.09 ppm (3.1 Hz; 5.6 Hz), and the –NH- protons as broad singlets at 6.35 and 6.49 ppm. Aromatic protons can be observed between 6.93 and 7.60 ppm. In the ^{13}C-NMR spectrum, the norbornene carbons give signals between 43.9 and 46.5 ppm, the aromatic and olefinic carbons between 128.0 and 141.4 ppm and finally the carbonyl carbons at 169.0 and 169.1 ppm.

The other ligand, **93**, was synthesized by reacting chiral diol which was synthesized during the total synthesis of diamine ligand, with two equivalents of 2-(diphenylphosphino)benzoic acid. The reaction conditions were the same as in the previous case, in the presence of DCC and DMAP in dichloromethane at 0°C then continuous stirring overnight at room temperature (Scheme 52).



Scheme 52. The synthesis of chiral diphenylphosphine containing ligand

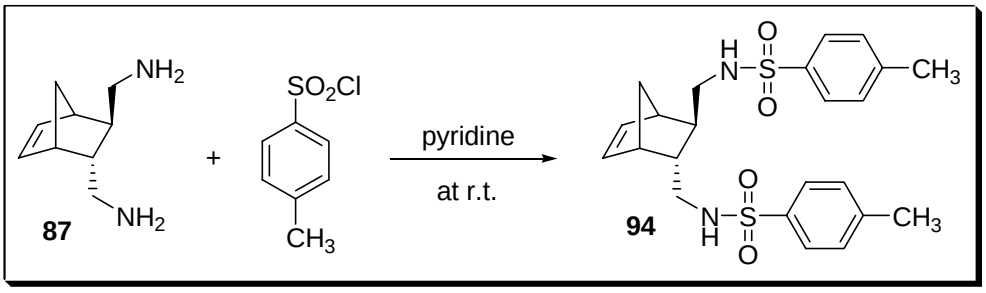
The synthesized ligand **93** was again characterized by ^{1}H- and ^{13}C-NMR spectroscopies, the spectra can be seen in appendix part, **A 13**. In the ^{1}H-NMR spectrum geminal protons give multiplets at 1.21 and 1.84 ppm, the protons at second and third carbon centers give multiplets at 1.36 ppm, the bridge head protons give singlets at 2.57 and 2.69 ppm. The diastereotopic protons give AB splittings as doublet of doublets at 3.82 ppm (J = 6.4 Hz; 10.8 Hz) and 3.92 ppm (J = 6.4 Hz; 10.8 Hz) and at 4.07 ppm (J = 6.3 Hz; 11.0 Hz) and 4.22 ppm (J = 6.3 Hz; 11.0 Hz).

The olefinic protons can be observed as doublet of doublets at 5.93 ppm (J = 2.8 Hz; 5.6 Hz) and 6.11 ppm (J = 3.1 Hz; 5.6 Hz). There are twenty eight aromatic protons in the spectrum and the signals can be observed between 6.93 and 8.05 ppm.

In the ^{13}C-NMR spectrum the norbornene carbons give signals between 42.2 and 46.1 ppm and the methylene carbons at 68.0 and 68.3 ppm. The aromatic carbons give signals between 125.8 and 140.5, and the carbonyl groups at 166.72 ppm.

2.4.2. The synthesis of tosyl group containing ligands:

The synthesized chiral diamine ligand was reacted with 2.2 equivalents of toslychloride in the presence of pyridine at room temperature for two days as seen in Scheme 53.



Scheme 53. The synthesis of ligand containing tosyl group

The synthesized ligand **94** was again characterized by ^{1}H- and ^{13}C-NMR spectroscopies (App. No: **A 14**). In the ^{1}H-NMR spectrum, bridge protons give multiplets at 1.13 and 1.81 ppm, the protons at second and third carbon centers give signals at 1.40 ppm, bridge head protons give singlets at 2.54 and 2.77 ppm and the diastereotopic protons give multiplets at 2.74 and 2.96 ppm. Methyl groups give a singlet at 2.43 ppm and =N<u>H</u>- protons give triplets at 4.65 ppm (J = 6.7 Hz) and

4.74 ppm (J = 6.5 Hz), the olefinic protons give doublet of doublets at 5.92 ppm (J = 2.9 Hz; 5.6 Hz) and 6.16 ppm (J = 3.1 Hz; 5.6 Hz) and finally the aromatic protons give multiplets at 7.32 and 7.75 ppm. In the ^{13}C-NMR spectrum of compound **94**, methyl carbons give signals at 21.5 and 29.7 ppm, the norbornene carbons between 44.8 and 48.6 ppm, aromatic and olefinic carbons between 127.1 and 144.2 ppm.

2.5. Asymmetric diethylzinc addition reactions:

The formation of optically active secondary alcohols by the enantioselective addition of organometallic reagents to carbonyl compounds is an important method in organic chemistry. Due to excellent chemoselectivity, the mostly used organometallic reagent is diethylzinc. There are lots of studies on the preparation of suitable catalysts for this addition reaction. The first highly enantioselective catalyst was reported by Noyori *et al.* in 1986, as mentioned before they used aminoalcohols as catalysts, after that so many researchers studied for the synthesis of new types of aminoalcohols as well as other type of catalysts such as; amino thiols, amines, diols and phosphoramide complexes [109].

In this study we have used some of the synthesized ligands to serve as chiral catalysts in asymmetric diethylzinc addition reactions to benzaldehyde. Those ligands can be shown in Figure 24.

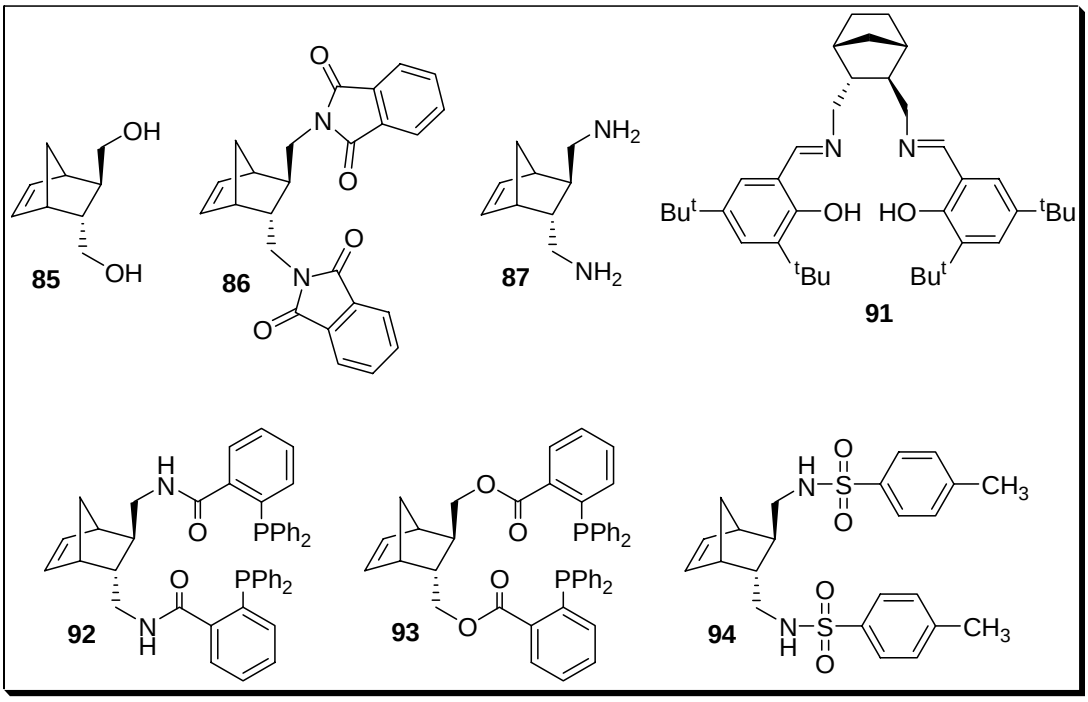
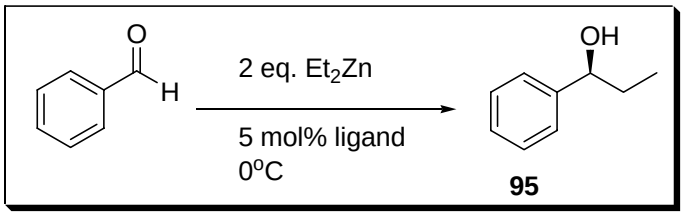


Figure 24. Ligands used in asymmetric diethylzinc addition reactions

The ligands shown in Figure 24 were used as catalysts in the asymmetric diethylzinc addition to benzaldehyde as shown in Scheme 54.



Scheme 54. Asymmetric diethylzinc addition reaction to benzaldehyde

The general method of the reaction can be summarized as follows; 5 mol % of the ligands shown in Figure 24, was dissolved in 5 ml of toluene under an argon

atmosphere at room temperature and 2 mol equivalent of diethyl zinc was added, then benzaldehyde was added at 0°C and the mixture was stirred at this temperature and followed by thin layer chromatography. The resulting 1-phenylpropan-1-ol, **95**, was characterized by ^{1}H- and ^{13}C-NMR spectroscopies, the spectra can be seen in appendix part, **A 15**.

The enantiomeric excess values were determined by applying HPLC studies with Chiralcel OD-H column, 98 : 2 (hexane : isopropanol) as eluent at 1 ml/min flow rate.

The ligands **92** and **93** have shown the highest enantioselectivities as 79 % and 81 % respectively. In this chiral ligand system the following mechanism can be proposed (Figure 25).

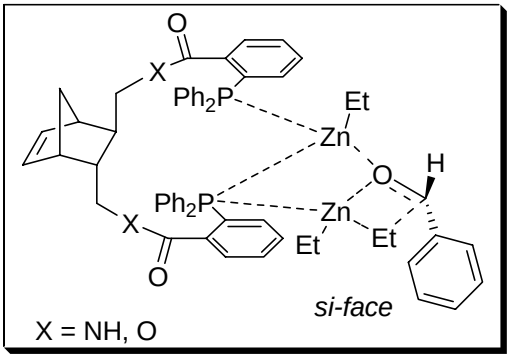


Figure 25. Plausible mechanism for ligands **92** & **93** in diethylzinc addition reactions

The high enantioselectivities of these ligands can be attributed to the great binding ability of phosphorus metal.

Unsubstituted diol, **85** and diamine **87**, ligands have shown moderate enantioselectivities as 68 % and 71 % respectively. In this type of ligand system,

because of unsubstitution, the ligands are open to free rotation around $–CH_2-$ linkage. This may lead heteroatoms of the ligands to find stable binding sites with metal.

In the case of ligands **86** and **94**, the free rotation was prevented by substituted large groups. In the synthesis of these ligands, the aim was to investigate the steric and electronic effects of electron withdrawing groups substituted to heteroatoms on the selectivity of diethylzinc addition reactions. In the reaction the eanantioselectivities were found as 30 % for ligand **86** and 33 % for ligand **94**. These low results may show the negative effects of electronwithdrawing groups near heteroatoms; in other words, they may decrease the binding abilities of heteroatoms to metal. A plausible mechanism for the ligands **85-87** and **94**, can be proposed as in Figure 26.

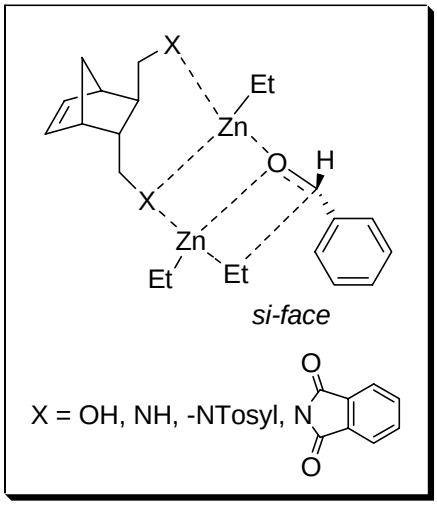


Figure 26. Plausible mechanism for ligands **85-87** & **94** in diethylzinc addition reactions

Salen ligand **91**, gave very low enantioselectivity as 28 %. For this ligand system, a plausible interaction between the metallo-schiff base complex, diethylzinc and benzaldehyde can be seen in Figure 27.

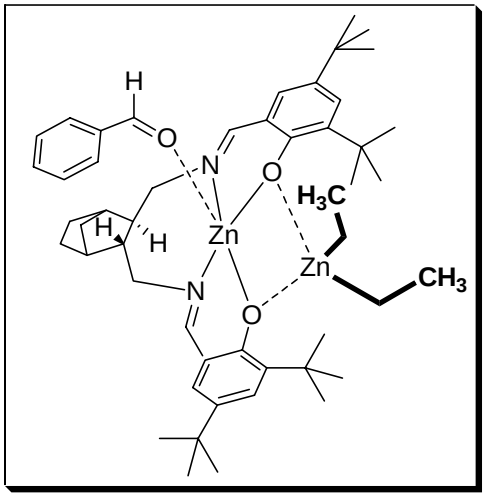


Figure 27. Plausible mechanism for salen ligand in diethylzinc addition reactions

In this ligand system, there are four coordination sites on salen ligand and diethylzinc forms complex with oxygens as well as nitrogens. That means because of the crowdening of complexation sites, benzaldehyde was forced to approach from the cyclohexene ring site. However in this case the presence of $–CH_2-$ linkage and the bridge on cyclohexene ring may also affect aldehyde to find proper reacting site. Therefore, the designed salen type ligand was not suitable for diethlznic addition reaction mechanism.

All of the ligands used in diethylzinc addition reactions in this study, have lead to the formation of *S* configurated 1-phenylpropan-1-ol. That may be caused by the norbornene geometry.

2.6. Applications of salen ligand 91, in asymmetric reactions:

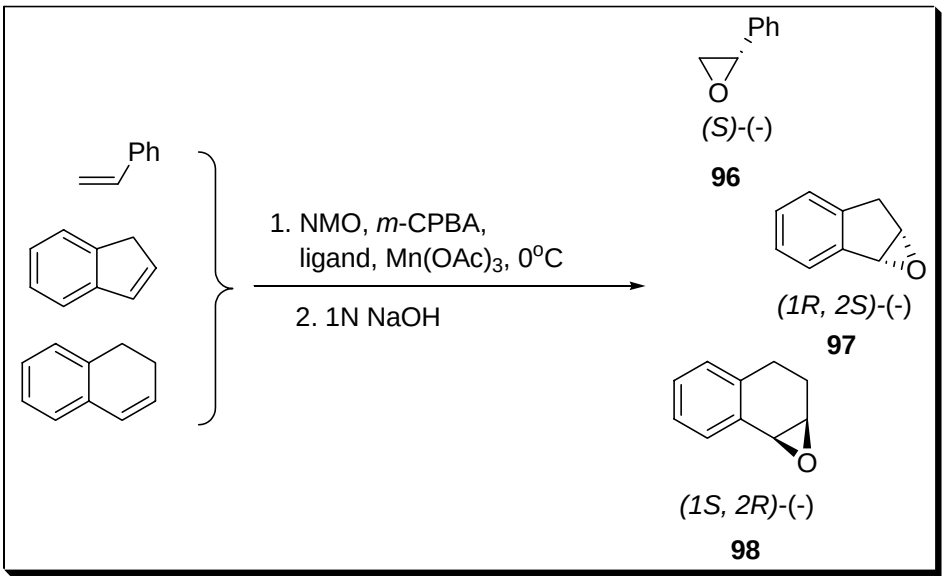
As mentioned earlier salen ligands are used in several asymmetric reactions and in this study, we used the synthesized salen ligand, **91**, in asymmetric epoxidation and aziridination reactions of several olefins as catalyst.

The diimine ligand having four coordination centers can serve as a catalyst by complexing with some metals through coordination sites in reaction media, *in situ*.

In our ligand system, the norbornene ring causes rigidity in the system, however, there is an extra flexibility coming from the $-CH_2$ linkage between nitrogen and the chiral centers which is different from other synthesized salen complexes. This flexibility may help the coordination of metal easier through rotation around that sigma bond.

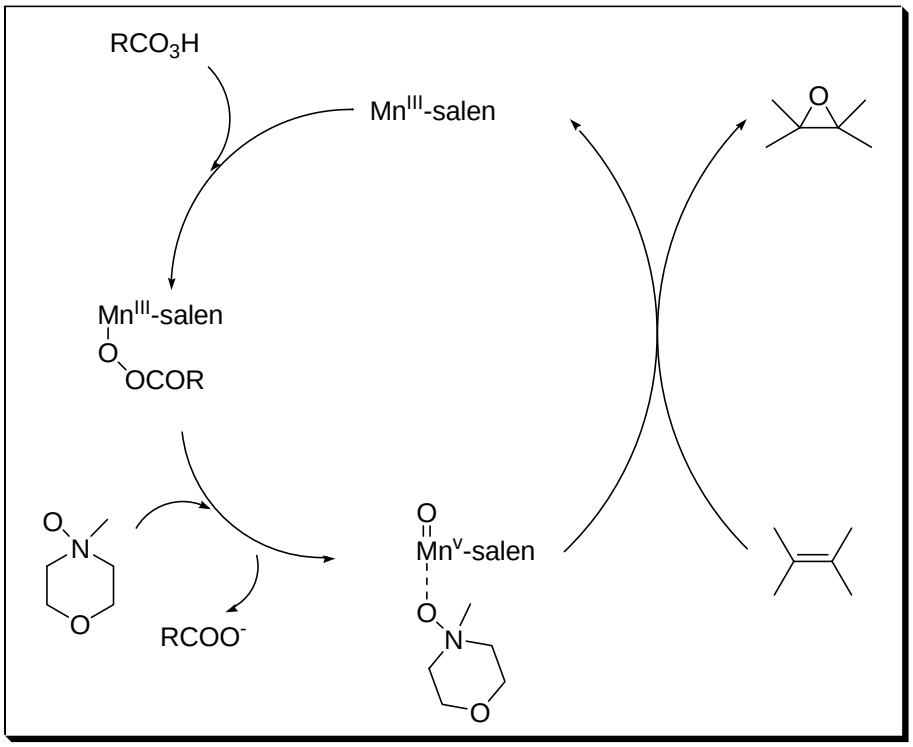
2.6.1. Asymmetric epoxidation reactions:

In this part of the study, epoxidation reactions have been applied to several olefins, such as; styrene, indene, and 1,2-dihydronaphthalene. The reactions were performed in the presence of 5 mol % of the synthesized ligand **91** as catalyst and *N*-methyl morpholine-*N*-oxide (NMO), *m*-chloro perbenzoic acid (*m*-CPBA) and $Mn(OAC)_3$ as oxidizing agents shown in Scheme 55. The absolute configurations were determined by comparing the measured optical rotations with the literature values [110].



Scheme 55. Epoxidation reactions

In these reactions NMO was used as an additive. Generally, NMO and other nitrogen heterocycles are considered to act as axial ligands to the salen metal catalysts (Scheme 56) and as bases [111]. In the case of Jacobsen's epoxidation system NMO has some additional roles. Jacobsen *et al.* observed that NMO and *m*-CPBA generate a 1:1 salt which is unreactive towards alkenes but oxidizes the (salen)Mn(III) catalyst. Also, excess NMO was critical in preventing the uncatalyzed epoxidation pathways that take place in the absence of the additive [112].



Scheme 56. Possible catalytic route for the asymmetric epoxidation with peroxyacids

As shown in Scheme 55, when styrene was undergone epoxidation reaction, 2-phenyloxirane was obtained in 45 % chemical yield. The characterization of 2-phenyloxirane, **96**, was performed with ^{1}H- and ^{13}C-NMR spectroscopies (App. No: **A 16**). In ^{1}H-NMR spectrum, diastereotopic protons give AB type splitting as doublet of doublets at 3.59 ppm (J = 3.6 Hz; 11.2 Hz) and 3.69 ppm (J = 3.4 Hz; 11.2 Hz). The proton at chiral center gives a multiplet at 4.84 ppm, and the aromatic protons can be seen as a multiplet between 7.26 and 7.33 ppm. In ^{13}C-NMR spectrum, carbons carrying epoxide function give signals at 51.4 and 58.3 ppm, and the aromatic carbons between 125.1 and 137.5 ppm.

HPLC study of 2-phenyloxirane was performed with commercial Whelk-O1 column, 99 : 1 (hexane : isopropanol) as eluent at 1 ml/min flow rate and the enantiomeric excess was determined as 33 %, (*S*)-(+).

1,2-Epoxyindane, **97**, was obtained in 52 % chemical yield when the procedure shown in Scheme 55 was applied. The characterization of the compound was done with NMR spectroscopies (App. No: **A 17**). In the ^{1}H-NMR spectrum, one of the diastereotopic protons gives doublet of doublet at 2.90 ppm (J = 2.5 Hz; 18.0 Hz) and the other gives doublet at 3.14 ppm (J = 18.0 Hz). Between the protons at chiral centers, the one near to diastereotopic protons gives a multiplet at 4.05 ppm and the other one gives a broad singlet at 4.19 ppm. The aromatic protons can be seen between 7.11 and 7.42 ppm.

In the ^{13}C-NMR spectrum, the aromatic carbons give signals between 125.5 and 128.9 ppm. The carbons at the junction of two rings can be seen at 142.2 and 143.9 ppm, and the other carbons between 35.0 and 59.5 ppm.

In the HPLC study of 1,2-epoxyindane Whelk-O1 column was used with 99 : 1 (hexane : isopropanol) as eluent at 1 ml/min flow rate. The enantiomeric excess value was measured as 41 % and the configuration was determined as 1*R*,2*S*-(-) when compared to absolute configuration value in the literature [110].

1,2-Epoxy-1,2,3,4-tetrahydronaphthalene, **98**, was obtained in 47 % chemical yield and characterized with ^{1}H- and ^{13}C-NMR spectroscopies (App. No: **A 18**). In the ^{1}H-NMR spectrum, diastereotopic protons give doublet of triplet at 1.70 ppm (J = 5.6 Hz; 13.9 Hz) and doublet of doublet of triplet at 2.33 ppm (J = 2.2 Hz; 6.3 Hz; 14.2 Hz). The neighboring -CH_2- protons give doublet of doublet at 2.48 ppm (J = 5.5 Hz; 15.5 Hz) and doublet of triplet at 2.72 ppm (J = 6.5 Hz; 14.4 Hz). The protons carrying epoxy function give a triplet at 3.66 ppm (J = 3.3 Hz) and a doublet at 3.77 ppm (J = 4.2 Hz). The aromatic protons give signals between 7.02 and 7.32 ppm. In ^{13}C-NMR spectrum, the aromatic carbons can be observed between 125.1 and 135.7 ppm, the epoxy carbons at 51.8 and 54.1 ppm and the others at 20.8 and 23.4 ppm.

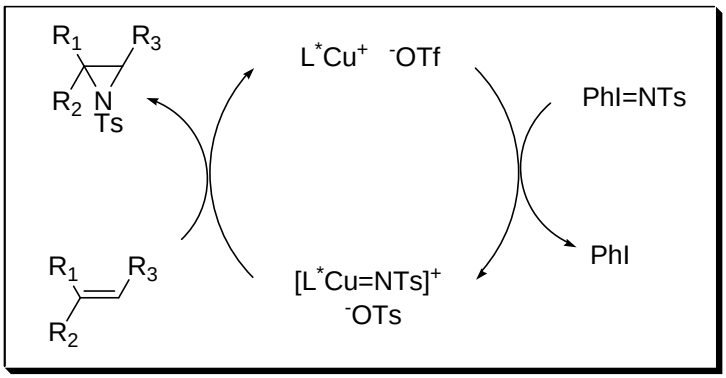
The HPLC study of compound **98** was performed with chiral Whelk-O1 column, with 99 : 1 (hexane : isopropanol) as eluent at flow rate 0.5 ml/min. The enantiomeric excess value was determined as 43 % and the configuration was measured as 1*S*,2*R*-(-).

2.6.2. Asymmetric aziridination reactions:

Aziridines are important building blocks for the preparation of compounds containing nitrogen functionality, and also occur as subunits in many natural products. Furthermore, chiral aziridines have been employed as efficient chiral auxiliaries and ligands for asymmetric catalysis [113]. Due to the versatile utilities of chiral aziridines in organic synthesis, the development of efficient enantioselective synthetic methods for chiral aziridines has received considerable interest. Among all the reported methods, transition metal-catalyzed asymmetric alkene aziridination has drawn a lot of attention [114].

In the last decade, Evans and Jacobsen have reported promising results in the asymmetric aziridination of olefins using copper catalysts with chiral dinitrogen ligands [115]. In 1993, they have independently reported Cu(I)-catalyzed asymmetric alkene aziridination using [*N*-(*p*-tolylsulfonyl)imino]phenyliodane (PhI=NTs) as the nitrene source [116]. Since then, many studies on asymmetric aziridination have been carried out with chiral copper(I) complexes as catalysts.

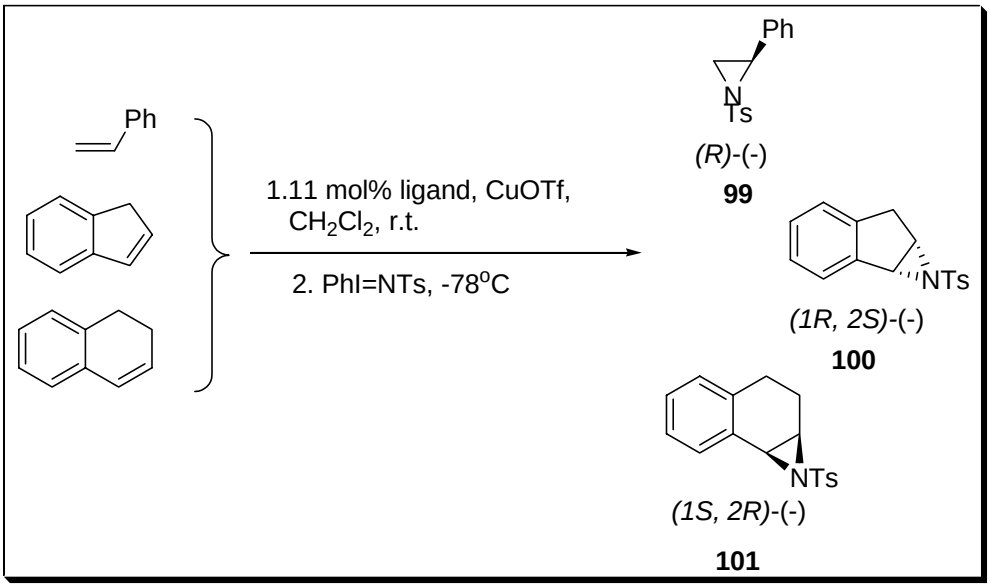
In 1995, Jacobsen *et al.* have proposed plausible mechanism for asymmetric aziridination with diimine-Cu(I) catalyzed syatems in the presence of PhI=NTs (Scheme 57) [117].



Scheme 57. Suggested mechanism for asymmetric aziridinations

The mechanism in Scheme 57, is a redox mechanism in which PhI is fully dissociated from the aziridinating species and leading the formation of Cu-nitroid complex. Besides, in 1997, Andersson *et al.* have proven that the nature of the nitrene precursor has a strong influence on the yield as well as on the enantioselectivity of the reaction [118]. This study can also prove the formation of Cu-nitroid complex in the suggested mechanism.

Since chiral diimine ligands in Cu-catalyzed asymmetric aziridinations show high catalytic activities, new types of diimine ligands are trying to be synthesized. In our study the synthesized chiral salen ligand, **91**, was subjected to asymmetric aziridination reaction as catalyst with the conditions applied by Jacobsen *et al.* in the presence of PhI=NTs (Scheme 58).



Scheme 58. Aziridination reactions

The reactions were performed under an argon atmosphere, firstly the chiral ligand and CuTf were mixed then olefin was added and the solution was cooled to

-78°C. Then PhI=NTs was added at that temperature and the reactions were followed by TLC. The absolute configurations were determined by comparing the measured optical rotations with the reported ones [69].

When styrene underwent aziridination reaction, the product, **99**, was obtained in 40 % chemical yield. The product was characterized with NMR spectroscopies (App. No: **A 19**). In the ^{1}H-NMR spectrum, the diastereotopic protons can be seen as doublets at 2.31 ppm (J = 4.4 Hz) and 2.95 ppm (J = 4.2 Hz). Methyl group gives a singlet at 2.36 ppm and the proton at chiral center gives a multiplet at 3.70 ppm. The aromatic protons can be observed between 7.18 and 7.80 ppm. In the ^{13}C-NMR spectrum, the aromatic carbons give signals between 127.0 and 145.0 ppm, and methyl carbon at 22.0 ppm and the other two carbons at 36.3 and 41.4 ppm.

The HPLC study of styrene aziridine was performed with chiral Whelk-O1 column with 98 : 2 (hexane : isopropanol) as eluent at 2 ml/min flow rate. The enantiomeric excess value was determined as 72 % and the configuration was measured as *R*-(-) when compared to literature value [69].

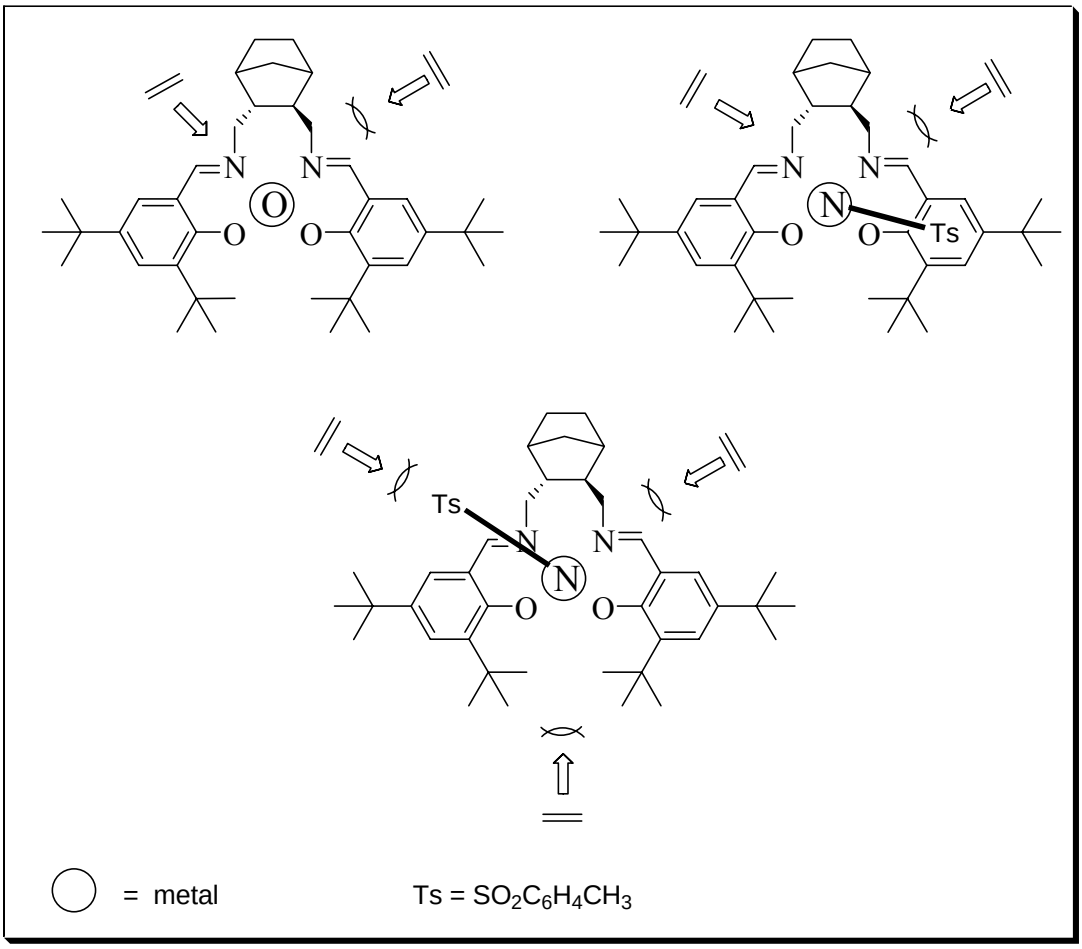
When indene was used as olefin in the aziridination reaction the product, **100**, was obtained in 47 % chemical yield, and characterized with NMR spectroscopies (App. No: **A 20**). In ^{1}H-NMR spectrum, methyl protons were observed as a singlet at 2.35 ppm, the diastereotopic protons give a broad singlet at 3.05 ppm. Between the chiral protons, the one which is near to diastereotopic protons gives a multiplet at 3.82 ppm, the other one gives a doublet at 4.22 ppm (J = 5.3 Hz). The aromatic protons can also be observed between 7.18 and 7.75 ppm. In the ^{13}C-NMR spectrum, the aromatic carbons give signals between 125.0 and 144.3 ppm and the methyl group at 21.5 and the other carbons between 34.6 and 50.1 ppm.

HPLC study of compound **100** was performed with chiral Whelk-O1 column with 95 :5 (hexane : isopropanol) as eluent at 2 ml/min flow rate. Enantiomeric excess value was determined as 78 % and the configuration was measured as 1*R*, 2*S*-(-).

When 1,2-dihydronaphthalene was used as olefin in aziridination reaction the product, **101**, was obtained in 35 % chemical yield, and characterized with NMR spectroscopy (App. No: **A 21**). In ^{1}H-NMR spectrum, diastereotopic groups give doublet of doublet of triplet at 1.60 ppm (J = 1.4 Hz; 5.4 Hz; 13.7 Hz) and doublet of doublet of triplet at 2.19 ppm (J = 2.0 Hz; 5.3 Hz; 13.3 Hz), neighboring –C$\underline{H}_2$- protons give doublet of doublet at 2.47 ppm (5.3 Hz; 15.6 Hz) and doublet of triplet at 2.69 ppm (J = 6.4 Hz; 14.4 Hz). Methyl group can be seen as a singlet at 2.35 ppm and the protons carrying aziridine function give doublets at 3.49 ppm (J = 6.9 Hz) and 3.74 ppm (J = 7.0 Hz). Aromatic protons can be observed between 6.98 and 7.75 ppm. In ^{13}C-NMR spectrum, aziridine carbons give signals at 42.1 and 42.5 ppm, aromatic carbons between 126.7 and 144.6 ppm and the others between 20.4 and 25.1 ppm.

In the HPLC study of compound **101** chiral Whelk-O1 column was used with 90 : 10 (hexane : isopropanol) as eluent at 2 ml/min flow rate. Enantiomeric excess was measured as 52 % and the configuration was determined as 1*R*, 2*S*-(+) when compared to literature value [69].

At the end of the studies on asymmetric epoxidation and aziridination reactions, the chiral salen ligand was found to catalyze asymmetric aziridination reaction more selectively than that of epoxidation reactions. In literature aziridination reactions were less selectively catalyzed by salen type chiral ligands, this may due to the number of open sites available for olefin approach (Scheme 29) [64, 69]. However, in the case of ligand **91** because of the structure and the presence of bulky tosyl group, as shown in Scheme 59, there is only one possible way for olefin approach as in the case of epoxidation.



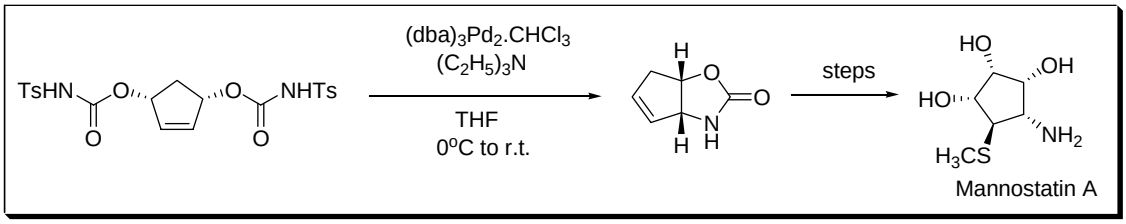
Scheme 59. Possible reaction mechanism for asymmetric epoxidation and aziridination reactions

2.7. Palladium catalyzed desymmetrization reactions of *meso*-diols:

The asymmetric desymmetrization of *meso*-diols is an important and powerful methodology for obtaining optically active substances. Numerous methods for the asymmetric desymmetrization of *meso*-diols have been developed [119].

The mostly applied method generated by Trost *et al.* was the desymmetrization of *cis*-cyclopentene-1,4-diol as can be seen in Scheme 60. In this method the cyclization of dicarbamate, generated *in situ* from the diol and p-toluenesulfonyl isocyanate, gave the oxazolidin-2-one in excellent yield and

enantioselectivity. The resulting compound has proven to be useful for the synthesis of glycosidase inhibitor mannostatin A [120].



Scheme 60. The study of B.M.Trost

The studies made on the mechanism of this type of asymmetric allylic alkylation reactions have shown that the chiral information must be transmitted from one face of the substrates to that on the side opposite to the metal. As shown in Figure 28, the metal induced ionization of the leaving group represents the enantiodiscriminating step.

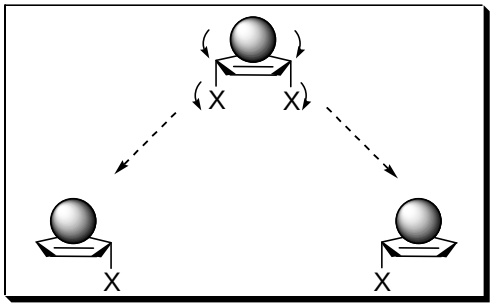


Figure 28. Model for catalyst mechanism

With the help of this model the researchers have tried to generate suitable chiral ligands to make complexes with palladium metal. Trost *et al.* have studied on the ligand shown in Figure 29a, and tried to examine how the chiral scaffold transmits stereochemical information to the reacting substrate when this ligand coordinates to palladium via the phosphines [121].

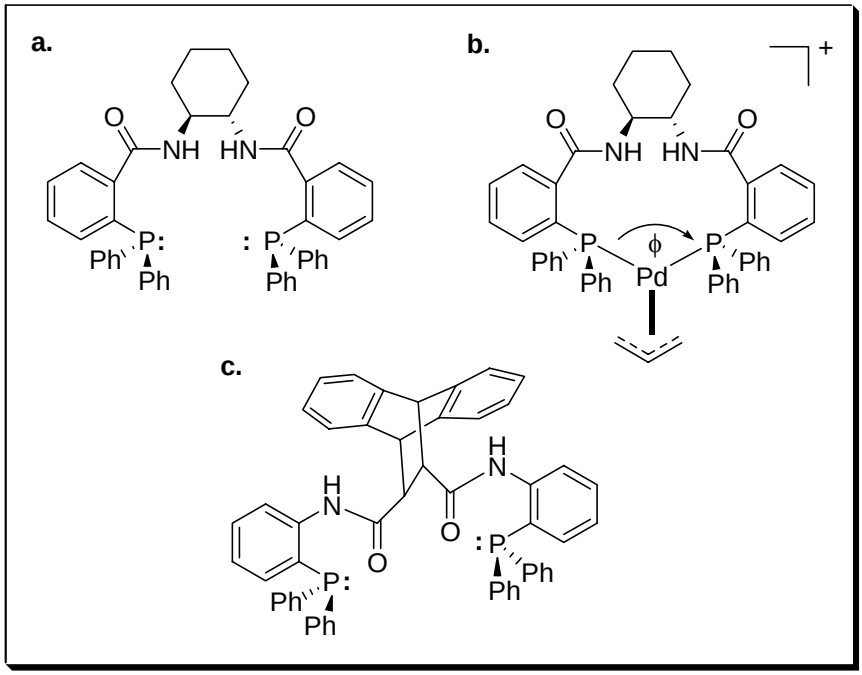


Figure 29. The ligand studied by Trost *et al.*

They have found that enantioselectivity is greatly affected by influence of the dihedral angle on the bite angle Φ in the ligand (Figure 29b). Therefore they claimed that opening the dihedral angle should lead to increasing the bite angle with a corresponding increase of interactions with the triarylphosphino moieties and the allyl fragments coordinated to palladium. When they used the ligand shown in Figure 29c, in this type of desymmetrization reactions they observed excellent enantioselectivities compared to ligand shown in Figure 29a [122].

In our study in the synthesized ligands, shown in Figure 30, **92** and **93,** methylene groups carrying diamine functionalities cause an increase in bite angle Φ. Therefore they can be used as chiral ligands to catalyze desymmetrization reaction of cyclohex-2-ene-1,4-diol by complexing with palladium metal.

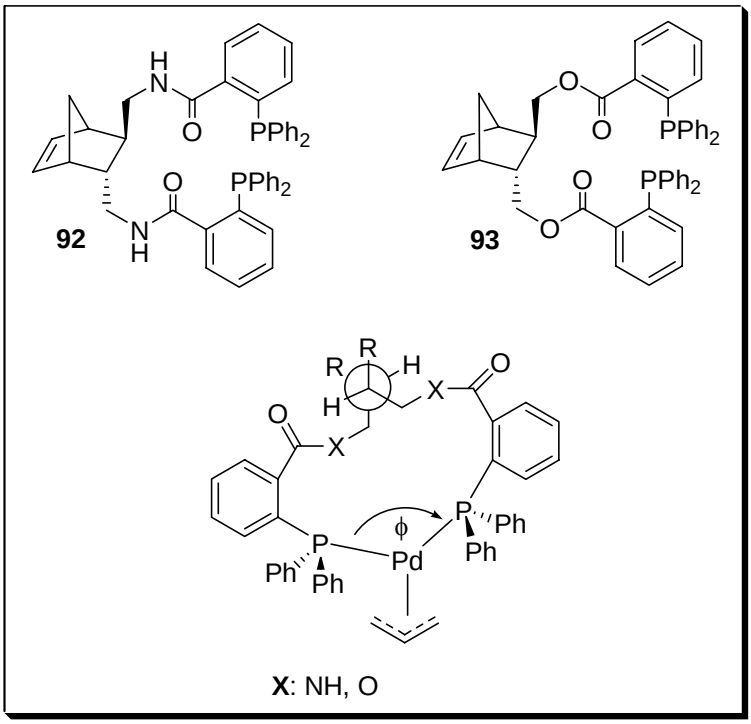
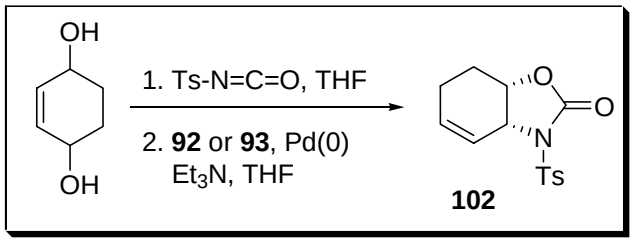


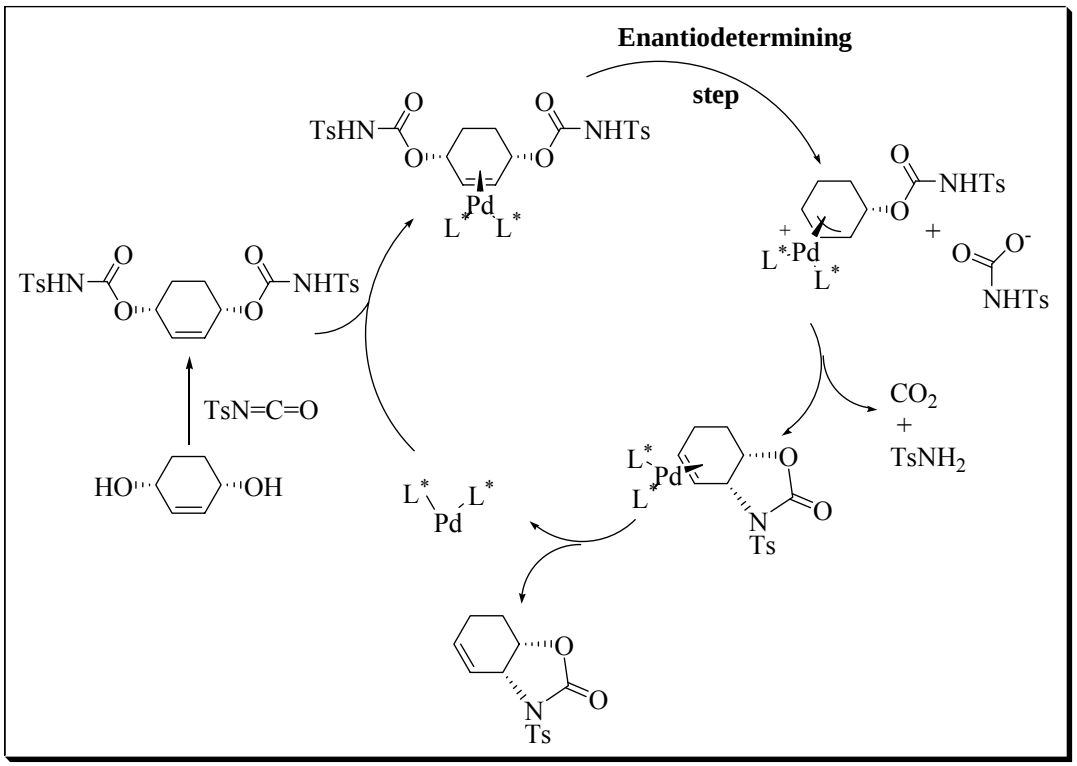
Figure 30. Ligands used in desymmetrization reactions

Meso-diol, cyclohex-2-ene-1,4-diol, was mixed with 2.2 eq. of tosyl isocyanate and refluxed then 1 eq. of triethylamine was added at room temperature. Then tris(dibenzylidineacetone)dipalladium(0) chloroform complex and 0.075 eq. of ligand, **92** or **93** were added at 0°C, then the resulting oxazolidine-2-one, **102,** was purified with column chromatography (Scheme 61).



Scheme 61. Desymmetrization reaction of meso diol

The plausible mechanism of the reaction can be seen in Scheme 62.



Scheme 62. The mechanism of desymmetrization of cyclohex-2-ene-1,4-diol

The characterization of the resulting oxazolidinone was done by ^{1}H- and ^{13}C-NMR spectroscopies (App. No: **A 22**). In ^{1}H-NMR spectrum, methyl group gives a singlet at 4.30 ppm, the two diastereotopic protons gives two multiplets at 1.77 and 2.02 ppm and the neighboring two geminal protons give a multiplet at 2.16 ppm. The protons at chiral centers give singlets at 4.83 and 4.86 ppm, and the olefinic protons give signals at 5.97 and 6.09 ppm. Finally, the aromatic protons give two doublets at 7.34 and 7.96 ppm. In ^{13}C-NMR spectrum, the chiral centered carbons give signals at 54.8 and 73.9 ppm, the other aliphatic carbons can be observed between 18.6 and 24.3 ppm. The carbonyl carbon gives a signal at 151.8 ppm, olefinic and aromatic carbons give signals between 122.2 and 145.4 ppm.

When ligand **92** was used as catalyst in desymmetrization reaction enantiomeric excess value was determined by applying HPLC study with Chiralcel OD-H column with 80 : 20 (hexane : isopropanol) as eluent at 0.5 ml/min flow rate. At the end 24 % enantiomeric excess was measured and the configuration was determined as 4*R*,5*S*.

When ligand **93** was used in the reaction enantiomeric excess value was determined by applying HPLC under the same conditions and measured as 12 %, the configuration was found as 4*R*,5*S*.

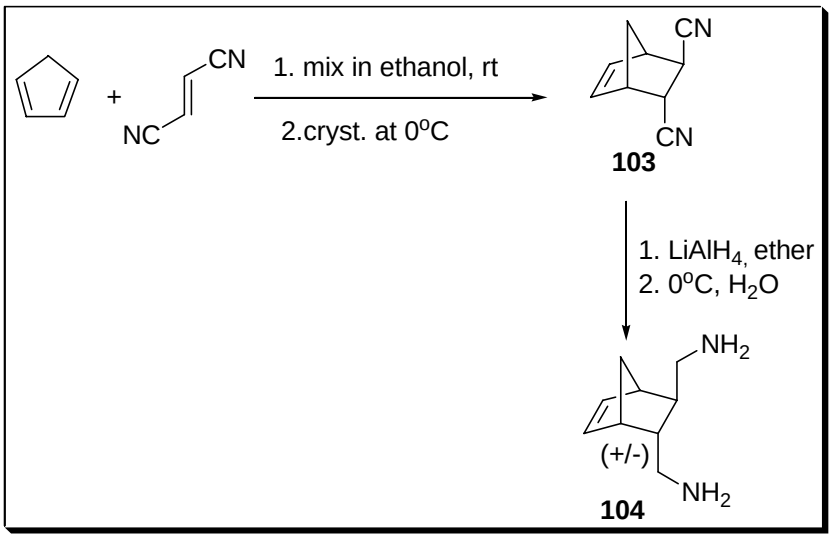
In the desymmetrizations reactions of cis-2-cyclohexene-1,4-diol the compexations of the synthesized ligands, **92** and **93**, formed complexes with palladium metal easily. When the designed complexes were used as catalysts in the reaction low enantioselectivities were obtained.

2.8. Ring Opening Methathesis Polymerization (ROMP) studies:

2.8.1. The synthesis of racemic diamine:

In order to synthesize the racemic diamine the used synthetic strategy was involved simple Diels-Alder reaction. It was performed between cyclopentadiene and fumaronitrile in ethanol. Then the resulting adduct, **103**, was reduced in the presence

of $LiAlH_4$ to give racemic *trans*-5,6-bis(diaminomethyl)bicyclo-[2,2,1]hept-2-ene, **104**, (Scheme 63).



Scheme 63. Synthesis of racemic diamine moiety

The synthesized adduct, **103**, was characterized with ^{1}H- and ^{13}C-NMR spectroscopies (App. No: **A 23**). In ^{1}H-NMR spectrum of the compound, one of the bridge protons gives doublet at 1.61 ppm (J = 9.9 Hz) and the other gives doublet of doublet at 1.71 ppm (J = 1.7 Hz; 9.9 Hz), *trans* protons at second and third carbon centers give doublet of doublet at 2.44 ppm (J = 2.0 Hz; 4.19 Hz) and a triplet at 3.10 ppm (J = 3.9 Hz), bridge head protons give singlets at 3.34 and 3.37 ppm and the olefinic protons at 6.31 ppm as a broad singlet. In ^{13}C-NMR spectrum, norbornene carbons can be observed between 35.1 and 48.7 ppm, nitrile carbons at 119.8 and 120.3 ppm and olefinic carbons at 136.1 and 137.6 ppm. The spectra of diamine can be seen in appendix part, **A 7**.

2.8.2 ROMP studies with 1,4-diamine ligand:

The olefinic metathesis reaction, in which simultaneous cleavage and reformation of carbon-carbon double bond occur, has led to widespread use in the design of useful organic molecules and polymers. This is generally called as ring opening metathesis polymerization (ROMP) reactions; the application of this type of reactions to norbornene and norbornadiene derivatives using Grubbs well-defined ruthenium initiator has widely used [123].

The general mechanism of ring opening metathesis polymerization can be shown in Figure 31.

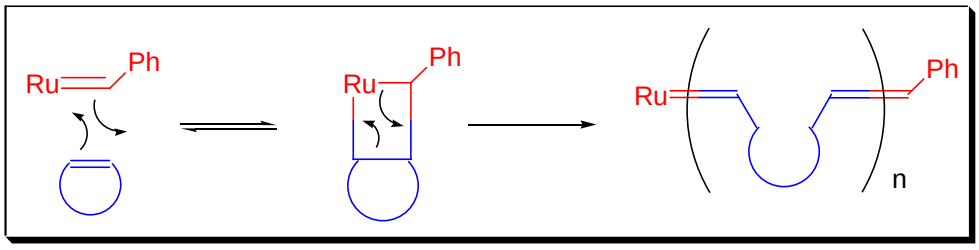
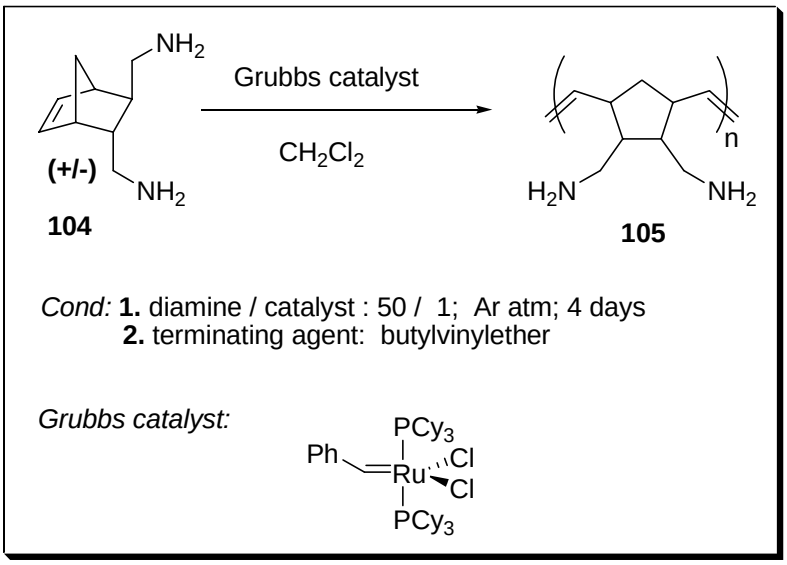


Figure 31. General ROMP mechanism

In our study the synthesized racemic diamine, **104**, was subjected to ring opening methathesis polymerization reactions by using Grubbs catalyst as shown in Scheme 64 [124, 125].



Scheme 64. Polymerization reaction of racemic diamine

This reaction was performed under an argon atmosphere; diamine and Grubbs catalyst were mixed in CH_2Cl_2 in 50 / 1 molar ratio at room temperature. The terminating agent used in this polymerization reaction was butylvinyl ether. After the polymerization was stopped the polymers were settled down and washed with ether.

The resulting polymerized diamine **105**, moiety was characterized by NMR spectroscopy, the ^{1}H-NMR spectrum can be seen in appendix part, **A 24**. In the ^{1}H-NMR spectrum of the polymer, the olefinic protons give broad signals between 5.86 and 6.18 ppm and -N$\underline{H}_2$ protons between 4.10 and 4.51 ppm. -C$\underline{H}_2$- and –C$\underline{H}$-CH_2NH_2 protons of cyclopentane ring give broad signals between 1.00 and 1.60 ppm, –C$\underline{H}_2NH_2$ protons and the other two protons of cyclopentane ring can be observed between 2.29 and 2.56 ppm.

The resulting macromolecule does not contain any chiral induction. However, this reaction was a preliminary study which shows the polymerization ability of the norbornene backbone. When chirality is induced in norbarnene backbone, as in this study, and by changing the substituted moieties on amine groups, new types of monomers will be synthesized, having various coordination sites. After

macromization of these monomers, new types of macromolecular chiral systems will be synthesized. Nowadays this type of macromolecular systems and the polymer bound types of these macromolecules are used as new type of catalytic systems.

CHAPTER III

CONCLUSION

Asymmetric synthesis of organic compounds with high enanitoselectivities is extremely important in modern synthetic and pharmaceutical chemistry. Consequently, the development of chiral catalysts is one of the most important challenges in modern organic chemistry. Nowadays, the most promising enantioselective catalysts in this area are metal complexes carrying chiral organic ligands.

The aim of this study was the synthesis of novel chiral ligands, suitable for several asymmetric reactions. Chiral 1,2-diamines in particular, cyclohexane *trans* 1,2-diamines constitutes the backbone of some important catalyst systems; the ligands that Trost has used in desymmetrization of meso-diols and the ligands that Jacobsen has designed for asymmetric epoxidation and aziridination reactions, are some of the examples. The backbone of the ligands synthesized in this study was chosen as a new diamine system; 1,4-diamine in which a strained bicyclic ring system was replaced with cyclohexane ring. By this way, the rotation on cyclohexane ring was restricted, however, by inserting an additional $–CH_2-$ linkage between the chiral centers and the coordination sites to metal system the flexibility was imparted. The synthesis of target diamine was started with asymmetric desymmetrization of *meso* norbornene anhydride by chinchona alkaloids in a kinetically controlled way. The enantioselectivity of the product was measured by applying HPLC, and the enantiomeric excess was found as 98 %. Then the obtained *cis*-mono ester carboxylic acid was epimerized in *trans* configuration. In this synthetic strategy since there was

no racemization through the synthesis of the chiral ligands, the obtained enantiomeric excess value was preserved. After that *trans*-monoester carboxylic acid was converted to *trans* diester then subsequently reduced to corresponding *trans*-diol by lithium aluminum hydride reduction. The resulting trans-diol was then subjected to Mitsunobu reaction with phthalimide then Gabriel type reaction to give *trans*-diamine in 52 % chemical yield.

In the second part of the study, the target chiral ligands were synthesized from the *trans*-diamine and *trans*-diol. One of the target chiral ligand was salen type, tetradentate ligand system. This ligand was obtained by reacting trans-1,4-diamine with 3,5-di-tert-butyl-2-hydroxybenzaldehyde. That ligand was especially used as chiral catalyst in asymmetric epoxidation and asymmetric aziridination reactions. In asymmetric epoxidation reactions manganese complex of the ligand was prepared in situ and the reaction was performed in the presence of *m*-chloroperbenzoic acid and *N*-methyl morpholine-*N*-oxide. The epoxidations of the olefins; styrene, indene and 1,2-dihydronaphthalene were studied and when enantiomeric excess of the products were measured it was found that the designed catalyst system had shown low selectivities between 33 to 43 %. These low results may be explained with the structure proposed by Jacobsen, that is; the presence of a bridge carbon on cyclohexene ring may prevent the complexation of the ligand with manganese and the approach of olefins. This may also be the reason for low chemical yields.

In asymmetric aziridination reactions, firstly PhI=NTs complex was synthesized to serve as nitrogen source. In this case copper complex of the synthesized salen ligand was formed in reaction medium and aziridination of the same olefins were studied. Fortunately, higher selectivities were observed with the same ligand used in asymmetric epoxidation case, as between 52 to 78 %.

Other type of ligands were synthesized by reacting trans-diamine and trans-diol with 2-(diphenylphosphino)benzoic acid. The resulting ligand system was appropriate for the palladium catalyzed asymmetric desymmetrization of *meso* 2-cyclohexene-1,4-diol. In this type of reaction *meso* diol was first converted to isotosylated derivative then by intramolecular cyclization with the help of palladium

ligand complex, the desired oxazolidinone was obtained. The ligands had shown low enantioselectivities in this type of reaction as 24 % and 12 %, respectively. The ligand that was designed by Trost, was obtained by reacting cyclohexene trans-1,2-diamine with 2-(diphenylphosphino)benzoic acid. When this ligand was applied on the same reactions higher selectivities were achieved. The difference of the results may be caused by the distance between the reacting phosphorus site and the chiral centers.

The ligands, including *trans*-diol, *trans*-diamine and also *trans*-diphthalimide which was synthesized in Mitsunobu application, were subjected to addition of diethylzinc to benzaldehyde reactions as catalysts. The ligands have shown varying enantioselectivities depending on their structures. Ligands having binding site on phosphorus, **92** and **93**, have shown highest enantioselectivities as 79 % and 81 %, because of the higher binding ability of phosphorous to metal. Ligands having free rotation through sigma bond, **85** and **87**, have shown moderate selectivities. Ligands having electronwithdrawing groups on heteroatoms have shown low selectivities, **86** and **94**, due to the reduction of binding ability of the heteoratoms with those groups. Finally, salen ligand **91**, have shown the lowest selectivity as 28 %.

Besides, in this study the effect of ring opening metathesis polymerization (ROMP) reactions on norbornene backbone was performed by polymerizing diamine moiety in the presence of Grubbs catalyst. At the end the system was found suitable for ROMP reaction. When chirality is induced into such systems, they may be useful as chiral macromolecular ligands in asymmetric reactions. Considering the results in this study the ligands, which show high selectivities on specific reactions, may be enlarged in a controlled way to give homogeneous chiral macromolecular system.

CHAPTER IV

EXPERIMENTAL

In this study, the structural determinations of the compounds were done by the instruments mentioned below.

Nuclear Magnetic Resonance (^{1}H-NMR and ^{13}C-NMR) spectra were recorded with a Bruker GmbH DWP-400, 400 MHz High Performance Digital FT-NMR Spectrometer by using $CDCl_3$ (otherwise mentioned) as a solvent and trimethylsilane (TMS) as an internal standard. Chemical shifts for ^{1}H-NMR spectra are as in parts per million (δ) downfield from an internal standard TMS. Spin multiplicities are mentioned as s (singlet), d (doublet), dd (doublet of doublet), t (triplet), q (quartet) and m (multiplet).

Flash column choromatography was employed using thick-walled glass columns with a flash grade silica-gel (Merck Silica Gel 60, particle size: 0.040-0.063 mm, 230-400 mesh ASTM). Reactions were monitored by thin layer chromatography using precoated silica gel plates (Merck Silica Gel PF-254), visualized with UV-light and polymolybden phosphoric acid in methanol as appropriate. The relative portion of solvents are in volume : volume ratio used in column chromatography as eluent.

Enantiomeric excess values were determined by applying High Performance Liquid Chromatography (HPLC) with chiral columns: Chiralcel OD-H column and Whelk-O1 column with a 254 nm UV-VIS detector and 20 μL injection volume, and the solvents; hexane and isopropanol, were used in relative portions.

Optical rotation values were determined by Krüss type polarimetry (A. Krü. P3002 RS MOD) at room temperature and the melting points were measured in open glass capillaries with Gallenkamp apparatus.

Solvents were either in technical or high grade, when necessary they were purified and dried with drying agents and by distillation.

4.1. The synthesis of (2*R*,3*R*)-2,3-bis(diaminomethyl)bicyclo[2.2.1]heptane

4.1.1. The synthesis of (2*R*,3*S*)-3-*endo*-methoxycarbonyl-bicyclo[2.2.1]hept-5-ene-2-*endo*-carboxylic acid, 81:

Methanol (5.21 ml, 0.128 mol) was added to a stirred suspension of the anhydride, **79** (7.0 g, 0.043 mol) and quinidine / quinine (15.24 g, 0.047 mol) in a 1:1 mixture of toluene and CCl_4 (210 ml in the case of quinidine, 850 ml in the case of quinine) at -55°C under an argon atmosphere. The reaction mixture was stirred at this temperature for 60 h during which the material gradually dissolved. Then the resulting clear solution was concentrated under vacuum to dryness, and the resulting residue was then dissolved in ethyl acetate. The solution was washed with 2N HCl, and after the phase separation, the aqueous phase was washed with ethyl acetate, the combined organic phase dried over Mg_2SO_4, filtered and concentrated to give cis-monoester, **81** (7.66 g, 92 % chemical yield).

m.p.: 75-78°C

Rf: 0.45 (Silica gel, 1:1:1% ethyl acetate/hexane/acetic acid)

^{1}H-NMR ($CDCl_3$): δ ppm

1.34 (d, J = 8.6 Hz, 1H)
1.49 (dd, J =1.6 Hz, 7.7 Hz, 1H)
3.17 (br s, 1H)
3.20 (br s, 1H)

3.28 (dd, J = 3.0 Hz, 10.2 Hz, 1H)

3.34 (dd, J = 3.2 Hz, 1H)

3.60 (s, 3H, methyl ester)

6.22 (dd, J = 2.9 Hz, 5.4 Hz, 1H,)

6.32 (dd, J = 3.1 Hz, 5.4 Hz, 1H)

^{13}C-NMR ($CDCl_3$): δ ppm

46.1, 46.6, 48.0, 48.3, 48.8, 51.5, 134.4, 135.6, 172.9, 178.1

4.1.1.1. The synthesis of *p*-bromo phenyl ester derivative of compound 81:

4-Bromophenol (0.0882 g, 0.510 mol) and hemiester (0.1 g 0.510 mol) were dissolved in 5 ml CH_2Cl_2 at 0°C under an argon atmosphere. Then DCC (0.105, 0.510 mol) and DMAP (0.0156 g, 0.127 mol) were added simultaneously at 0°C, then mixed overnight and reaction was controlled with TLC. The solution was filtered and washed with 5 % acetic acid then 1N HCl and extracted with CH_2Cl_2 and dried over Mg_2SO_4, filtered and concentrated, after column chromatography compound **82** was obtained.

Rf: 0.61 (Silica gel, 1:1:1% ethyl acetate/hexane/acetic acid)

^{1}H-NMR ($CDCl_3$): δ ppm

1.33 (d, J = 8.6 Hz, 1H)

1.40 (d, J = 8.7 Hz, 1H)

3.17 (s, 1H)

3.18 (s, 1H)

3.39 (br s, 2H)

3.54 (s, 3H)

6.15 (dd, J = 2.9 Hz, 5.4 Hz, 1H)

6.32 (dd, J = 2.9 Hz, 5.4 Hz, 1H)

6.92 (d, J = 8.7 Hz, 2H)

7.37 (d, J = 8.7 Hz, 2H)

^{13}C-NMR ($CDCl_3$): δ ppm

46.6, 47.2, 48.5, 48.7, 49.1, 52.2, 119.0, 123.8, 132.7, 135.0, 135.9, 150.3, 171.2, 173.0

4.1.2. (2*R*,3*R*)-3-Methoxycarbonyl-bicyclo[2.2.1]-5-heptene-2-carboxylic acid, 83:

Diisopropylamine (4.29 ml, 30.6 mmol) was diluted with 25 ml THF at 0°C, under an argon atmosphere, then buthyl lithium (32.75 mmol, 2.5 M in hexane, 13.10 ml) was added in portions. Then the reaction mixture was cooled to -78°C and mixed for 30 min at that temperature. Hemiester, **81**, (2.0 g, 10.2 mmol) was dissolved in 20 ml THF then added to prepared LDA solution and mixed for 5 h at -78°C. 1N HCl was added in portions to the solution until acidic pH was obtained. Then the phases were separated and aqueous phase was washed with CH_2Cl_2, then dried over Mg_2SO_4, filtered and evaporated. The oily product was purified with column chromatography in 85 % chemical yield.

m.p.: 73°C

Rf: 0.56 (Silica gel, 1:1:1% ethyl acetate/hexane/acetic acid)

^{1}H-NMR ($CDCl_3$): δ ppm

1.41 (dd, J = 1.6 Hz, 8.9 Hz, 1H)
1.56 (d, J = 8.9 Hz, 1H)
2.59 (dd J = 1.5 Hz, 4.5 Hz, 1H)
3.07 (br s, 1H)
3.23 (br s, 1H)
3.36 (dd, J = 3.9 Hz, 4.3 Hz, 1H)
3.65 (s, 3H)
6.07 (dd, J = 2.8 Hz, 5.6 Hz, 1H)
6.22 (dd, J = 3.1 Hz, 5.6 Hz, 1H)
11.0 (br s, 1H)

^{13}C-NMR ($CDCl_3$): δ ppm

45.6, 47.0, 47.4, 47.6, 47.9, 52.2, 135.2, 137.7, 174.7, 179.1

4.1.3. The synthesis of (2*R*,3*R*)-2,3-dimethoxycarbonyl-bicyclo[2.2.1]hept-5-ene, 84:

Trans hemiester, **83** (3.38 g, 0.0173 mol), Ag_2O (5.00 g, 0.0256 mol), methyl iodide (49 ml, 0.345 mol), calcium sulphate (3.53 g, 0.0259 mol) and a piece of crushed glass were placed in a flask and mixed. The reaction was monitored with TLC and at the end filtered and washed with CH_2Cl_2 then dried over Mg_2SO_4, filtered and evaporated giving the desired product, **84**, in 100 % chemical yield.

Rf: 0.77 (Silica gel, 1:1:1 % ethyl acetate/hexane/acetic acid)

^{1}H-NMR ($CDCl_3$): δ ppm

1.40 (dd, J = 1.5 Hz, 8.8 Hz, 1H)
1.55 (dd, J = 1.7 Hz, 7.5 Hz, 1H)
2.62 (dd, J = 1.3 Hz, 4.4 Hz, 1H)
3.06 (br s, 1H)
3.20 (br s, 1H)
3.31 (t, J = 4.1 Hz, 1H)
3.58 (s, 3H)
3.65 (s, 3H)
6.01 (dd, J = 2.8 Hz, 5.6 Hz, 1H)
6.21 (dd, J = 3.2 Hz, 5.5 Hz, 1H)

^{13}C-NMR ($CDCl_3$): δ ppm

45.6, 47.1, 47.3, 47.6, 47.9, 51.8, 52.1, 135.2, 137.6, 173.7, 174.9

4.1.4. The synthesis of (2*R*,3*R*)-bicyclo[2.2.1]hept-5-ene-2,3-dimethylenediol, 85:

Lithiumaluminium hydride (1.50 g, 40.0 mmol) was added in 20 ml THF. Then, trans diester, **82** (3.33 g, 15.8 mmol), was diluted with 15 ml THF and added to the lithiumaluminium hydride solution drop wise in 20 min and mixed overnight at room temperature. The reaction was followed by TLC when it was over; 2-3 ml water was added drop wise at 0°C. The slurry white solution was filtered and the residue was washed with $CHCl_3$, and the organic phase was dried over Mg_2SO_4, filtered and evaporated giving the desired product, **85**, in 100 % chemical yield.

Rf: 0.21 (Silica gel, 1:1:1% ethyl acetate/hexane/acetic acid)

^{1}H-NMR ($CDCl_3$): δ ppm

1.06 (m, 1H)
1.32 (br s, 2H)
1.78 (m, 1H)
2.55 (br s, 1H)
2.78 (br s, 1H)
2.91 (t, J = 9.8 Hz, 1H)
3.29 (t, J = 9.8 Hz, 1H)
3.46 (dd, J = 5.8 Hz, 9.6 Hz, 1H)
3.59 (dd, J = 5.8 Hz, 9.6 Hz, 1H)
3.92 (br s, 2H)
5.86 (dd, J = 2.6 Hz, 5.2 Hz, 1H)
6.10 (dd, J = 3.2 Hz, 5.2 Hz, 1H)

^{13}C-NMR ($CDCl_3$): δ ppm

44.5, 44.6, 46.9, 47.1, 47.9, 66.1, 66.6, 133.4, 138.0

4.1.5. The synthesis of diphthalimide, 86:

Diethyl diazodicarboxylate (4.46 g, 25.6 mmol) was added at 0°C to a solution of diol, **84** (1.66 g, 10.8 mmol), phthalimide (3.77 g, 25.6 mmol) and triphenylphosphine (6.71 g, 25.6 mmol) in 70 ml THF. The mixture was stirred at room temperature for 48 h. Then filtered and the white residue was washed with cold THF. The filtrate was evaporated and additional product was recrystallized with CH_3OH. The combined crystals were filtered through silica gel with ethyl acetate as eluent. The desired product was obtained as a white solid in 65 % chemical yield.

Rf: 0.81 (Silica gel; ethyl acetate)

^{1}H-NMR ($CDCl_3$): δ ppm

1.46 (dd, J = 1.4 Hz, 8.8 Hz, 1H)
1.52 (s, 1H)
1.58 (d, J = 9.3 Hz, 1H)
2.18 (m, 1H)
2.56 (s, 1H)
2.71 (s, 1H)
3.32 (d, J = 7.6 Hz, 2H)
3.63 (m, 2H)
6.20 (m, 2H)
7.58 (m, 4H)
7.67 (m, 4H)

^{13}C-NMR ($CDCl_3$): δ ppm

41.7, 42.5, 43.3, 44.0, 45.0, 45.6, 46.3, 122.3, 123.1, 123.2, 132.0, 133.7, 133.8, 134.7, 137.7, 168.2, 168.4

4.1.6. The synthesis of (2*R*,3*R*)bicyclo[2.2.1]hept-5-ene-2,3-dimethylene diamine, 87:

Hydrazine hydrate (2.05 g, 64 mmol) was added to a stirred solution of diphthalimide, **86** (1.65 g, 4.01 mmol) in isopropanol, and the solution was heated to reflux for 8 h. Then it was cooled to room temperature and 20 % NaOH solution was added. The resulting two layers were then extracted with CH_2Cl_2. The combined organic phase was then dried over Mg_2SO_4, filtered, and then evaporated. The desired diamine product was obtained in 52 % chemical yield.

^{1}H-NMR ($CDCl_3$): δ ppm

0.87 (m, 1H)
1.25 (br s, 2H)
1.37 (s, 2H)
1.52 (m, 1H)
2.36 (dd, J = 8.4 Hz, 12.3 Hz, 1H)
2.43 (dd, J = 6.8 Hz, 12.3 Hz, 1H)
2.55 (br s, 1H)
2.62 (dd, J = 8.2 Hz, 12.4 Hz, 1H)
2.74 (dd, J = 6.7 Hz, 12.4 Hz, 1H)
2.77 (br s, 1H)
5.95 (dd, J = 2.8 Hz, 5.6Hz, 1H)
6.13 (dd, J = 3.2 Hz, 5.6 Hz, 1H)

^{13}C-NMR ($CDCl_3$): δ ppm

44.4, 45.2, 46.7, 46.8, 47.8, 48.6, 49.3, 133.9, 138.2

4.2. The synthesis of salen type ligands:

4.2.1. The general procedure for imine formation:

Diamine (1 eq.), **87**, was diluted with absolute ethanol and placed in a two necked flask, heated to reflux. Dialdehyde (2 eq.) was dissolved in minimum amount of ethanol and added drop wise to diamine solution. The mixture was refluxed for 2 h then small amount of water was added and the heating was discontinued. The mixture was cooled to ≤ 5°C over 2 h and maintained at that temperature for an additional 1 h. The product was collected by vacuum filtration and washed with ethanol. The crude solid was redissolved in CH_2Cl_2 and washed with water and brine. After drying over Mg_2SO_4, the solvent was removed under vacuum.

Dialdehyde: 3,5-di-*tert*-butyl-hydroxybenzaldehyde, **88**

m.p.: 208°C

$[\alpha]^{rt}_D$: -0.577 (c: 0.00281, CH_3Cl)

^{1}H-NMR ($CDCl_3$): δ ppm

1.38 (s, 18H)
1.43 (br s, 1H)
1.47 (s, 18H)
1.53 (m, 2H)
2.00 (br s, 1H)
2.79 (s, 1H)
2.95 (s, 1H)
3.34 (dd, J = 8.6 Hz, 11.6 Hz, 1H)
3.42 (dd, J = 6.9 Hz, 11.6 Hz, 1H)
3.61 (dd, J = 8.2 Hz, 11.7 Hz, 1H)
3.72 (dd, J = 6.7 Hz, 11.7 Hz, 1H)
6.14 (dd, J = 2.6 Hz, 5.4 Hz, 1H)

6.28 (dd, J = 3.2 Hz, 5.4 Hz, 1H)
7.06 (m, 2H)
7.38 (s, 2H)
8.33 (s, 1H)
8.38 (s, 1H)
14.00 (s, 1H)
14.02 (s, 1H)

^{13}C-NMR ($CDCl_3$): δ ppm

29.5, 31.5, 34.1, 35.1, 44.8, 45.0, 46.0, 46.3, 46.8, 63.8, 64.7, 117.9, 125.8, 125.9, 126.7, 126.8, 133.9, 136.6, 138.1, 139.9, 134.0, 158.2, 165.8, 166.1

Dialdehyde: 2-methoxybenzaldehyde, **89**

^{1}H-NMR ($CDCl_3$): δ ppm

1.32 (m, 1H)
1.34 (br d, 8.3 Hz, 1H)
1.41 (d, J = 10.2 Hz, 1H)
2.02 (m, 1H)
2.58 (s, 1H)
2.73 (s, 1H)
3.16 (br t, 1H)
3.49 (m, 2H)
3.72 (s, 3H)
3.73 (s, 3H)
3.77 (m, 1H)
5.98 (dd, J = 2.7 Hz, 5.6 Hz, 1H)
6.13 (dd, J = 3.1 Hz, 5.6 Hz, 1H)
6.78 (d, J = 8.3 Hz, 2H)
6.86 (t, J = 7.2 Hz, 7.4 Hz, 2H)
7.24 (t, J = 7.6 Hz, 8.0 Hz, 2H)

7.85 (m, 2H)
8.52 (s, 1H)
8.59 (s, 1H)

^{13}C-NMR ($CDCl_3$): δ ppm

44.7, 44.9, 45.4, 46.1, 46.3, 55.5, 66.1, 66.9, 111.0, 111.6, 120.8, 124.9, 125.0, 127.3, 127.4, 131.5, 131.6, 133.9, 135.9, 137.9, 156.7, 156.8, 158.7

Dialdehyde: 2,6-dichlorobenzaldehyde, **90**

^{1}H-NMR ($CDCl_3$): δ ppm

1.44 (d, J = 8.4 Hz, 1H)
1.48 (m, 1H)
1.54 (d, J = 8.4 Hz, 1H)
2.15 (m, 1H)
2.72 (s, 1H)
2.89 (s, 1H)
3.26 (t, J = 11.0 Hz, 1H)
3.60 (t, J = 9.5 Hz, 1H)
3.73 (dd, J = 5.5 Hz, 11.3 Hz, 1H)
3.98 (dd, J = 5.4 Hz, 11.3 Hz, 1H)
6.07 (dd, J = 2.8 Hz, 5.6 Hz, 1H)
6.20 (dd, J = 3.2 Hz, 5.6 Hz, 1H)
7.16 (m, 2H)
7.26 (d, J = 8.0 Hz, 4H)
8.30 (s, 1H)
8.36 (s, 1H)

^{13}C-NMR ($CDCl_3$): δ ppm

45.1, 45.2, 45.4, 46.2, 46.4, 66.8, 67.6, 129.0, 130.1, 130.49, 130.53, 130.8, 133.70, 133.74, 134.0, 134.3, 135.0, 137.2, 138.4, 157.0, 157.3, 189.1

4.2.2. The reduction of diimine ligand, 88:

Diimine, **88** (0.2 g) was dissolved in 30 ml ethyl acetate and placed in one-necked flask and Pd / C was added under an argon atmosphere. The mixture was stirred at room temperature overnight carrying a H_2 balloon. Then the mixture was filtered and concentrated under vacuum to give reduced diimine, **91**.

m.p.:192°C

$[\alpha]^{rt}_D$: -0.519 (c: 0.0024, CH_3Cl)

^{1}H-NMR ($CDCl_3$): δ ppm

1.10 (m, 2H)
1.23 (s, 18H)
1.31 (m, 1H)
1.39 (s, 18H)
1.47 (m, 2H)
1.70 (s, 1H)
2.12 (s, 1H)
2.25 (s, 1H)
3.32-3.42 (m, 2H)
3.45-3.55 (m, 2H)
6.96 (m, 2H)
7.27 (s, 2H)
8.25 (d, 2H)
13.88 (br s, 2H)

^{13}C-NMR ($CDCl_3$): δ ppm

22.3, 29.5, 30.0, 31.5, 34.1, 35.0, 36.9, 39.2, 40.0, 47.8, 49.1, 61.4, 64.6, 117.9, 125.8, 125.9, 126.7, 131.9, 136.6, 139.9, 158.2, 165.8, 166.1

4.3. The synthesis of ligands used in Et_2Zn addition reactions to benzaldehyde:

4.3.1. The synthesis of ligand 92:

2-(Diphenylphosphino)benzoic acid (2 eq.) was dissolved in minimum amount of CH_2Cl_2 at room temperature. Then the mixture was cooled to 0°C and DMAP (0.8 eq.) and DCC (2.4 eq.) were added. Lastly diamine, **87** (1 eq.) was added in minimum amount of CH_2Cl_2 at 0°C through syringe. Then, the mixture was stirred overnight at room temperature. When the reaction was completed, it was filtered and the filtrate was washed with 5 % acetic acid solution, then 1 N HCl solution. Then the organic phase was dried over Mg_2SO_4, filtered and evaporated in vacuum. The product was purified with column chromatography. The product, **92**, was purified with column chromatography.

m.p.: 123.2°C

$[\alpha]_D^{rt}$: -0.118 (c = 4.8, $CHCl_3$)

Rf: 0.10 (Silica gel; 1 : 3 ethylacetate/hexane)

^{1}H-NMR ($CDCl_3$): δ ppm

1.03 (m, 1H)
1.35 (s, 2H)
1.65 (m, 1H)
2.43 (br s, 1H)
2.60 (br s, 1H)
3.00 (t, J = 6.6 Hz, 2H)

3.28 (dd, J = 6.0 Hz; 12.5 Hz, 2H)
5.92 (dd, J = 2.7 Hz; 5.6 Hz, 1H)
6.09 (dd, J = 3.1 Hz; 5.6 Hz, 1H)
6.35 (br s, 1H)
6.49 (br s, 1H)
6.93 (m, 2H)
7.23-7.31 (m, 24H)
7.60 (m, 2H)

^{13}C-NMR ($CDCl_3$): δ ppm

43.9, 44.3, 44.7, 44.8, 44.9, 45.6, 46.5, 128.0, 128.56, 128.63, 128.8, 128.8, 130.1, 133.8, 134.0, 134.1, 134.2, 135.8, 137.3, 138.0, 141.2, 141.4, 169.0, 169.1

4.3.2. The synthesis of ligand 93:

2-(Diphenylphosphino)benzoic acid (2 eq.) was dissolved in minimum amount of CH_2Cl_2 at room temperature. Then the mixture was cooled to 0°C and DMAP (0.8 eq.) and DCC (2.4 eq.) were added. Lastly diol, **85** (1 eq.) was added in minimum amount of CH_2Cl_2 at 0°C through syringe. Then, the mixture was stirred overnight at room temperature. When the reaction was completed, the mixture was filtered and the filtrate was washed with 5 % acetic acid solution, then 1 N HCl solution. Then the organic phase was dried over Mg_2SO_4, filtered and evaporated in vacuum. The product was purified with column chromatography.

Rf: 0.5 (Silica gel; 1:7 ethylacetate/hexane)

$[\alpha]_D^{rt}$: -0.161 (c = 10.7, $CHCl_3$)

^{1}H-NMR ($CDCl_3$): δ ppm

1.21 (m, 1H)
1.36 (m, 2H)

1.84 (m, 1H)
2.57 (br s, 1H)
2.69 (br s, 1H)
3.82 (dd, J = 6.4 Hz, 10.8 Hz, 1H)
3.92 (dd, J = 6.4 Hz, 10.8 Hz, 1H)
4.07 (dd, J = 6.3 Hz, 11.0 Hz, 1H)
4.22 (dd, J = 6.3 Hz, 11.0 Hz, 1H)
5.93 (dd, J = 2.8 Hz, 5.6 Hz, 1H)
6.11 (dd, J = 3.1 Hz, 5.6 Hz, 1H)
6.93 (m, 2H)
7.28 (br s, 20H)
7.34 (m, 4H)
8.05 (m, 2H)

^{13}C-NMR ($CDCl_3$): δ ppm

42.2, 42.7, 44.5, 44.7, 46.1, 68.0, 68.3, 125.8, 126.0, 128.1, 128.3, 128.4, 128.5, 128.6, 128.6, 128.9, 129.6, 130.7, 131.8, 131.9, 133.4, 133.8, 133.98, 134.00, 134.02, 134.1, 134.3, 134.5, 134.7, 134.8, 137.69, 137.74, 137.95, 137.97, 138.01, 138.03, 138.06, 138.08, 138.12, 138.14, 140.1, 140.2, 140.39, 140.5, 166.7

4.3.3. The synthesis of ligand 94:

Diamine, **87** (1 eq.), tosylchloride (2.2 eq.) and pyridine as a solvent were mixed at room temperature; the reaction was monitored by TLC. After the reaction has completed, the mixture was concentrated in vacuum and the product was purified with column chromatography.

Rf: 0.60 (Silica gel; 1:1 ethyl acetate/hexane)

^{1}H-NMR ($CDCl_3$): δ ppm

1.13 (m, 1H)
1.40 (m, 2H)
1.81 (m, 1H)
2.43 (s, 6H)
2.54 (br s, 1H)
2.74 (m, 2H)
2.77 (br s, 1H)
2.96 (m, 2H)
4.65 (t, J = 6.7 Hz, 1H)
4.74 (t, J = 6.5 Hz, 1H)
5.92 (dd, J = 2.9 Hz, 5.6 Hz, 1H)
6.16 (dd, J = 3.1 Hz, 5.6 Hz, 1H)
7.32 (m, 4H)
7.75 (m, 4H)

^{13}C-NMR ($CDCl_3$): δ ppm

21.5, 29.7, 44.8, 45.6, 47.0, 47.1, 48.6, 127.1, 129.8, 133.6, 137.5, 144.2

4.4. Diethyl zinc addition reactions:

4.4.1. The general procedure for Et_2Zn addition reactions to benzaldehyde:

Ligand, **85-87, 91-94** (5 mol %) was dissolved in 5 ml of toluene under an argon atmosphere at room temperature and diethylzinc (2 eq.) was added then the mixture stirred at room temperature for 30 min. Then the reaction was cooled to 0°C and benzaldehyde (1 eq.) was added. The reaction mixture was stirred at that temperature and monitored by TLC, when it was over, 10 ml of 1 N HCl was added and extracted with CH_2Cl_2 and the organic phase was dried over Mg_2SO_4, filtered and evaporated in vacuum. The desired product, 1-phenylpropan-1-ol was purified with column chromatography.

Rf: 0.24 (Silica gel; 1:6 ethyl acetate/hexane)

^{1}H-NMR ($CDCl_3$): δ ppm

0.87 (t, J = 7.5 Hz, 3H)
1.73 (m, 2H)
2.30 (br s, 1H)
4.51 (t, J = 6.6 Hz, 1H)
7.23 (m, 2H)
7.29 (m, 3H)

^{13}C-NMR ($CDCl_3$): δ ppm

10.12, 31.87, 75.96, 126.03, 127.44, 128.37, 144.68

4.5. The general procedure for epoxidation reactions:

A solution of olefin (1 eq.), NMO (5 eq.), chiral ligand (10 mol %) and $Mn(OAc)_3$ (5 mol %) in CH_2Cl_2 was cooled to 0°C. Solid *m*-CPBA (2 eq.) was added in four portions. The reaction mixture was stirred for at least 24 h at this temperature, monitored by TLC. Then 1 NaOH was added and the organic phase was separated and washed with brine. The combined aqueous phase was extracted with CH_2Cl_2, and the combined organic phases were dried over Mg_2SO_4 and solvent was removed under vacuum. The desired product was purified with column chromatography.

2-phenyloxirane, 97:

Rf: 0.35 (Silica gel; 1:6 Ethyl acetate/hexane)

$[\alpha]_D^{rt}$: +0.045 (c = 17.7, $CHCl_3$)

^{1}H-NMR ($CDCl_3$): δ ppm

3.59 (dd, J = 3.6 Hz, 11.2 Hz, 1H)
3.69 (dd, J = 3.4 Hz, 11.2 Hz, 1H)
4.84 (m, 1H)
7.26-7.33 (m, 4H)

^{13}C-NMR ($CDCl_3$): δ ppm

51.4, 58.3, 125.1, 128.4, 128.7, 137.5

1,2-Epoxyindane, 97:

Rf: 0.47 (Silica gel; 1:6 Ethyl acetate/hexane)

$[\alpha]_D^{rt}$: -0.056 (c = 25.0, $CHCl_3$)

^{1}H-NMR ($CDCl_3$): δ ppm

2.90 (dd, J = 2.5 Hz, 18.0 Hz, 1H)
3.14 (d, J = 18.0 Hz, 1H)
4.05 (m, 1H)
4.19 (br s, 1H)
7.11 (m, 1H)
7.15-7.23 (m, 2H)
7.42 (m, 1H)

^{13}C-NMR ($CDCl_3$): δ ppm

35.0, 58.1, 59.5, 125.5, 126.5, 127.8, 128.9, 141.2, 143.9

1,2-Epoxy-1,2,3,4-tetrahydronaphthalene, 98:

Rf: 0.42 (Silica gel; 1:6 Ethyl acetate/hexane)

$[\alpha]_D^{rt}$: -0.051 (c = 16.2, $CHCl_3$)

^{1}H-NMR ($CDCl_3$): δ ppm

1.70 (dt, J = 5.6 Hz, 13.9 Hz, 1H)
2.33 (ddt, J = 2.2 Hz, 6.3 Hz, 14.2 Hz, 1H)
2.48 (dd, J = 5.5 Hz, 15.5 Hz, 1H)
2.72 (dt, J = 6.5 Hz, 14.4 Hz, 1H)
3.66 (t, J = 3.3 Hz, 1H)
3.77 (d, J = 4.2 Hz, 1H)
7.02 (d, J = 7.3 Hz, 1H)
7.15 (m, 2H)
7.32 (dd, J = 1.1 Hz, 7.6 Hz, 1H)

^{13}C-NMR ($CDCl_3$): δ ppm

20.8, 23.4, 51.8, 54.1, 113.2, 125.1, 127.39, 127.42, 128.5, 131.5, 135.7

4.6. The formation of aziridine products:

4.6.1. The formation of PhI=NTs:

(Diacetoxyiodo)benzene (3.20 g, 10 mmol) was added to a stirred mixture of p-toluenesulfonamide (1.71 g, 10 mmol), potassium hydroxide (1.40 g, 25 mmol) and 40 ml methanol below 10°C. The resulting yellow colour homogenous solution was stirred for 3 h at room temperature. Then, the reaction mixture was poured into water to precipitate a yellow colour solid on standing overnight, which was recrystallized from methanol to give N-tosyliminophenyliodinane in 70 % yield.

m.p. 101°C

^{1}H-NMR (DMSO-d_6): δ ppm

2.30 (s, 3H, CH_3)
7.00-7.80 (m, 9H, aromatic protons)

4.6.2. The general procedure for aziridine formation reactions:

Under an argon atmosphere chiral ligand (0.054 mmol, 11 mol %) was added as a solid to a stirred suspension of CuOTf (0.05 mmol, 10 mol %) in CH_2Cl_2 (3 ml) at room temperature. After 1 h, the nearly homogeneous solution was filtered, and the filtrate was transferred to a round-bottomed flask and diluted with additional CH_2Cl_2 back to a total volume of 3 ml. Olefin (0.5 mmol) was added, and the solution was cooled to -78°C. Solid PhI=NTs (0.75 mmol, 1.5 eq.) was added under an argon atmosphere, and the heterogeneous mixture was stirred at that temperature as the reaction progress was monitored by TLC. After the reaction process has ceased, the mixture was filtered through a 2 cm pad of silica with ethyl acetate, the filtrate was concentrated in vacuum, and the desired product was purified by column chromatography.

Olefin: Styrene, compound **99**

Rf: 0.25 (Silica gel; 1:6 ethyl acetate/hexane)

$[\alpha]_D^{rt}$: -0.040 (c = 37.6, $CHCl_3$)

^{1}H-NMR ($CDCl_3$): δ ppm

2.31 (d, J = 4.4, 1H)
2.36 (s, 3H)
2.95 (d, J = 4.2 Hz, 1H)
3.70 (m, 1H)

7.18-7.24 (m, 5H)
7.26 (d, J = 8.1 Hz, 2H)
7.80 (d, J = 8.2 Hz, 2H)

^{13}C-NMR ($CDCl_3$): δ ppm

22.0, 36.3, 41.5, 127.0, 128.4, 128.7, 129.0, 130.2, 135.4, 135.5, 145.0

Olefin: Indene, compound **100**

Rf: 0.24 (Silica gel; 1:6 Ethyl acetate/hexane)

$[\alpha]_D^{rt}$: -0.031 (c = 30.1, $CHCl_3$)

^{1}H-NMR ($CDCl_3$): δ ppm

2.35 (s, 3H)
3.05 (br s, 2H)
3.82 (m, 1H)
4.22 (d, J = 5.3 Hz, 1H)
7.07-7.18 (m, 3H)
7.24 (d, J = 8.1 Hz, 2H)
7.34 (d, J = 7.3 Hz, 1H)
7.75 (d, J = 8.2 Hz, 2H)

^{13}C-NMR ($CDCl_3$): δ ppm

21.5, 34.6, 44.8, 50.1, 125.0, 125.5, 126.6, 127.6, 128.6, 129.6, 135.4, 138.2, 143.5, 144.3

Olefin: 1,2-dihydronaphthalene, compound **101**

Rf: 0.21 (Silica gel; 1:6 Ethyl acetate/hexane)

$[\alpha]_D^{rt}$: +0.076 (c = 67.6, $CHCl_3$)

^{1}H-NMR ($CDCl_3$): δ ppm

1.60 (ddt, J = 1.4 Hz, 5.4 Hz, 13.7 Hz, 1H)
2.19 (ddt, J = 2.0 Hz, 5.3 Hz, 13.3 Hz, 1H)
2.35 (s, 3H)
2.47 (dd, J = 5.3 Hz, 15.6 Hz, 1H)
2.69 (dt, J = 6.4 Hz, 14.4 Hz, 1H)
3.49 (d, J = 6.9 Hz, 1H)
3.74 (d, J = 7.0 Hz, 1H)
6.98 (d, J 7.3 Hz, 2H)
7.09 - 7.19 (m, 4H)
7.23 (d, J = 8.0 Hz, 2H)
7.75 (d, J = 8.2 Hz, 2H)

^{13}C-NMR ($CDCl_3$): δ ppm

20.4, 22.0, 25.1, 42.1, 42.5, 126.7, 128.0, 128.8, 129.0, 129.8, 130.1, 130.4, 136.1, 137.0, 144.6

4.7. Pd-catalyzed oxazolidin-2-one synthesis:

To a solution of the meso diol, cyclohex-2-ene-1,4-diol (1 eq.) in 1.5 ml THF was added tosyl isocyanate (2.2 eq.). This colourless solution was stirred at room temperature for 15 min. and at 60°C for 30 min. the reaction was allowed to cool to room temperature and triethylamine (1 eq.) was added. The resulting solution was cooled to 0°C, and the solution of tris(dibenzylidineacetone)dipalladium(0) chloroform complex and ligand, **92** or **93** (0.075 eq.), in 2.5 ml THF was added. The reaction mixture was stirred at 0°C for 2 h and at room temperature overnight. The solvent was removed under vacuum, and the desired product, **102**, was purified with column chromatography.

m.p.:128°C

Rf: 0.79 (Silica gel; 1:1 ethyl acetate/hexane)

^{1}H-NMR ($CDCl_3$): δ ppm

1.77 (m, 1H)
2.02 (m, 1H)
2.16 (m, 2H)
4.30 (s, 3H)
4.83 (s, 1H)
4.86 (s, 1H)
5.97 (d, J = 10.3 Hz, 1H)
6.09 (m, 1H)
7.34 (d, J = 8.2 Hz, 2H)
7.96 (d, J = 8.2 Hz, 1H)
^{13}C-NMR ($CDCl_3$): δ ppm

18.6, 21.7, 24.3, 54.830, 73.9, 122.2, 128.5, 129.7, 133.2, 135.4, 145.4, 151.8

4.8. The synthesis of racemic bicyclo[2.2.1]heptane-2,3-dimethylene, 104:

4.8.1. The synthesis of trans bicyclo[2.2.1]heptane-2,3-dicarbonitrile, 103:

Freshly distilled cyclopentadiene (2.31 g, 35 mmol) was added drop wise to a cooled solution of fumaronitrile (2.5 g, 32 mmol) in dry ethanol (18 ml) in 15 min. The solution was concentrated in vacuum to half its original volume. Then it was cooled to 0°C in an ice-bath. After crystallization was completed, solvent was removed by decantation and the product was recrsytallized in ethanol. The product, **103**, was isolated in 94 % chemical yield.

m.p: 92-96°C

^{1}H-NMR ($CDCl_3$): δ ppm

1.61 (d, J = 9.9 Hz, 1H)
1.71 (dd, J = 1.7 Hz, 9.9 Hz, 1H)
2.44 (dd, J = 2.0 Hz, 4.19 Hz, 1H)
3.10 (t, J = 3.9 Hz, 1H)
3.34 (s, 1H)
3.37 (s, 1H)
6.31 (s, 2H)

^{13}C-NMR ($CDCl_3$): δ ppm

35.1, 35.2, 46.7, 47.7, 48.7, 119.8, 120.3, 136.1, 137.6

4.8.2. Reduction of *trans*-bicyclo[2.2.1]heptane-2,3-dicarbonitrile:

Lithiumaluminium hydride (0.85 g, 22.4 mmol) and 10 ml dry ether were placed in a flask under an argon atmosphere. Then the solution of carbodinitrile, **103**, (0.80 g, 5.57 mmol in 15 ml dry ether) was added drop wise over 20 min. The resulting solution was stirred overnight at room temperature. Then the flask was placed in ice-bath and 2-3 ml of water was added. The resulting white cloudy solution was filtered and dried over Mg_2SO_4, filtered, then evaporated. The product, **104**, was isolated in 81 % chemical yield.

4.9. The polymerization reaction of diamine:

Racemic diamine (0.5 eq.) was diluted with minimum amount of CH_2Cl_2 under an argon atmosphere. Then 0.01 eq. of Grubbs catalyst was added and the mixture was stirred at room temperature under an argon atmosphere for four days. In order to terminate the reaction butylvinyl ether was added and waited overnight to complete precipitation of the entire polymer, **105**.

^{1}H-NMR ($CDCl_3$): δ ppm

1.00 - 1.60 (multiplets, 4H)

2.29 - 2.56 (multiplets, 6H)

4.10 - 4.51 (br s, 4H)

5.86 - 6.18 (multiplets, 2H)

APPENDIX A

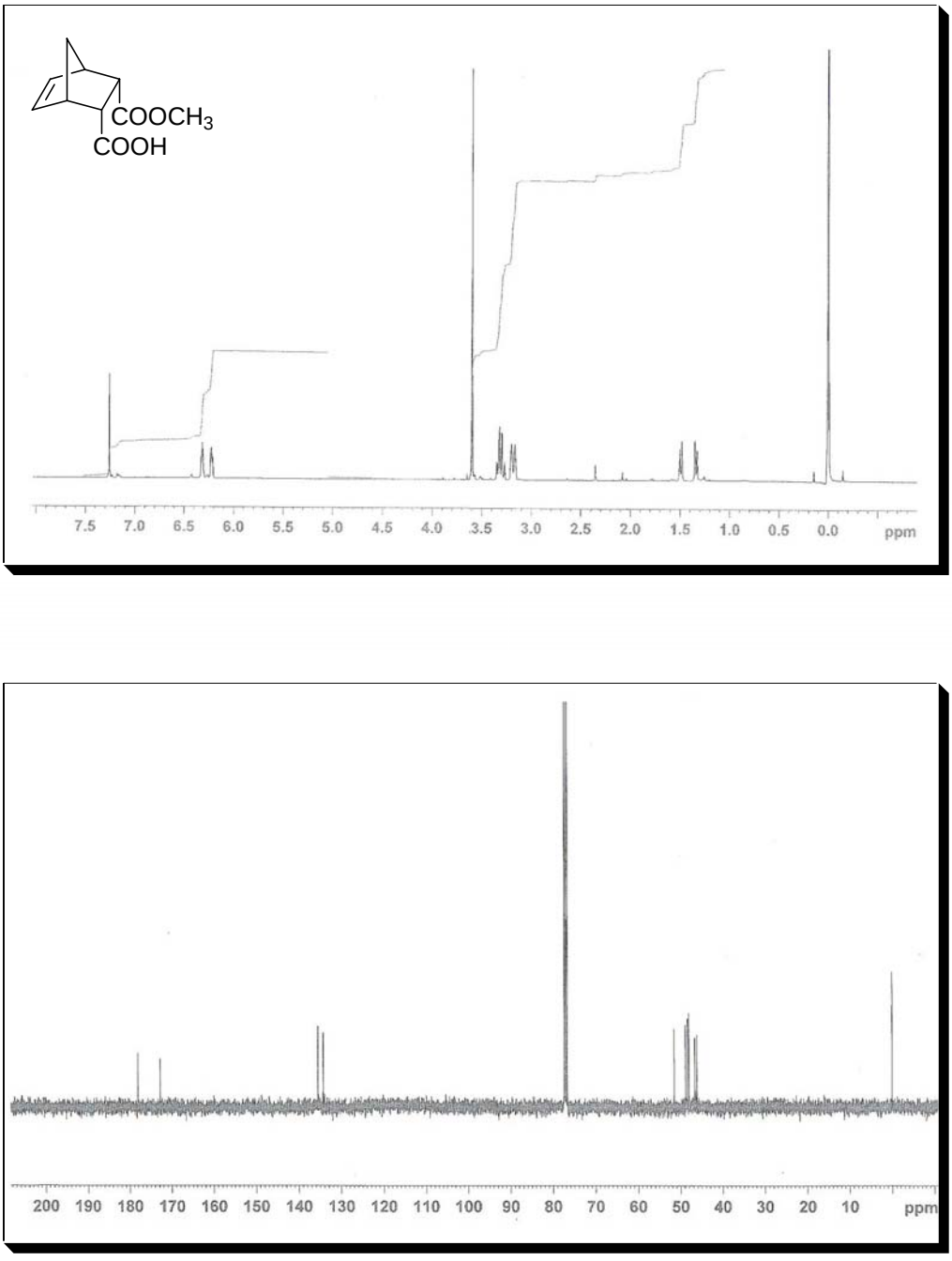
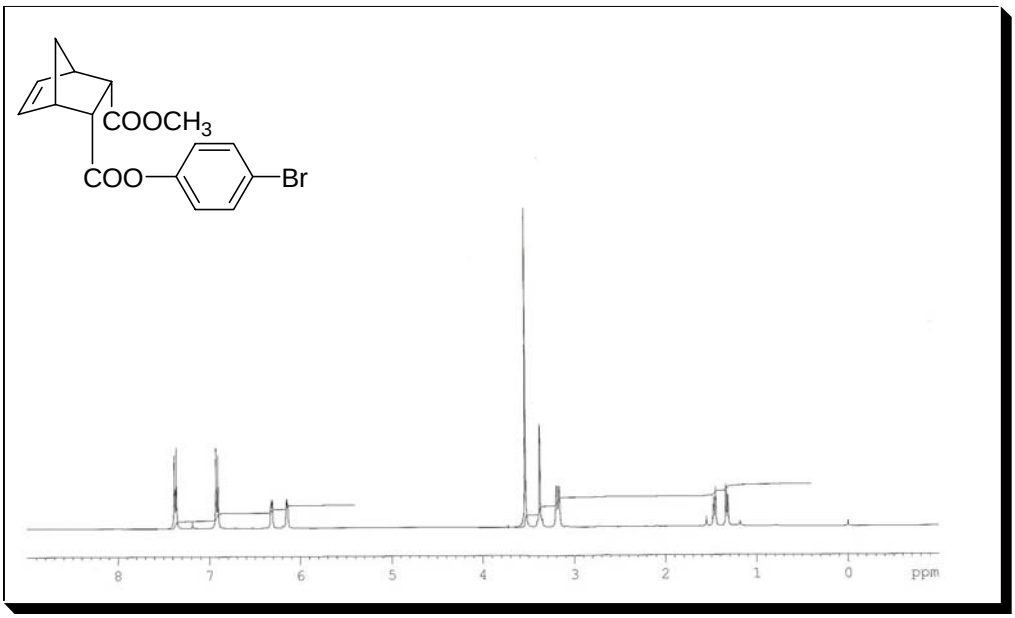


Fig. A 1. ^{1}H- and ^{13}C-NMR spectra of compound **81**



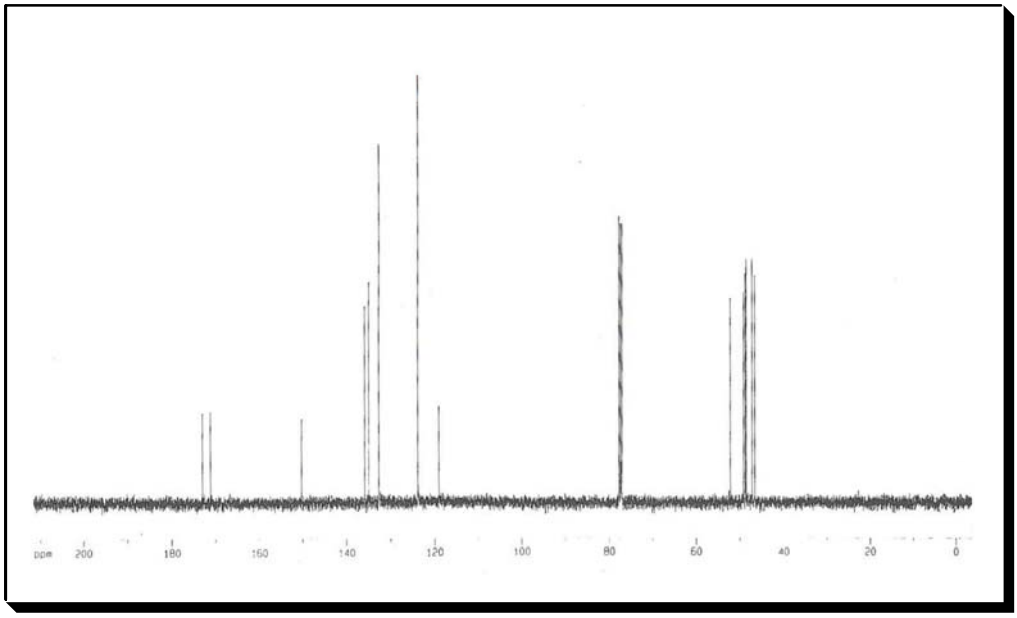
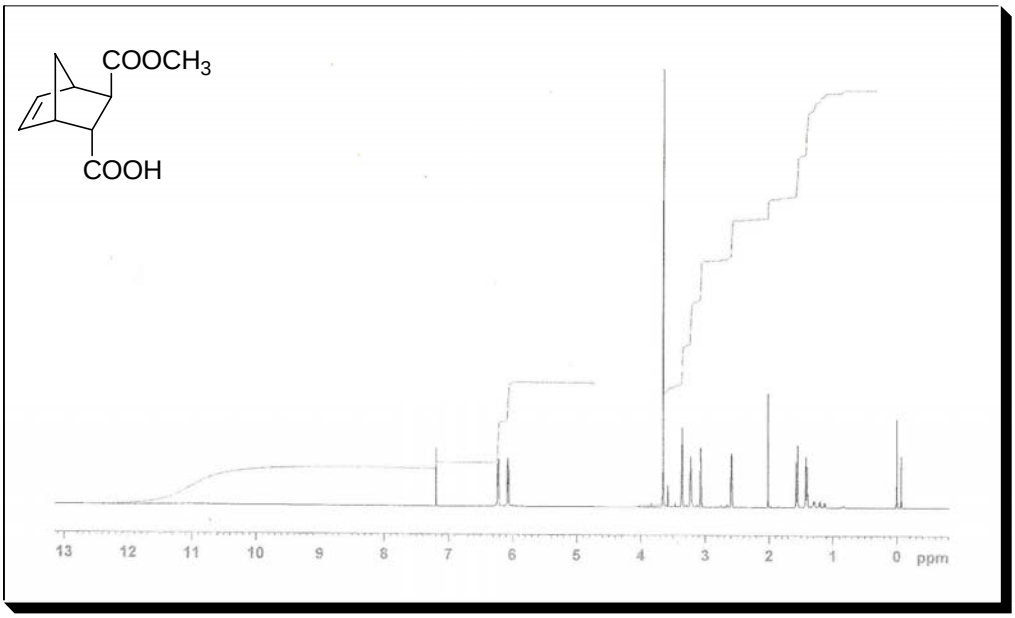


Fig. A 2. ^{1}H and ^{13}C-NMR of compound **82**.



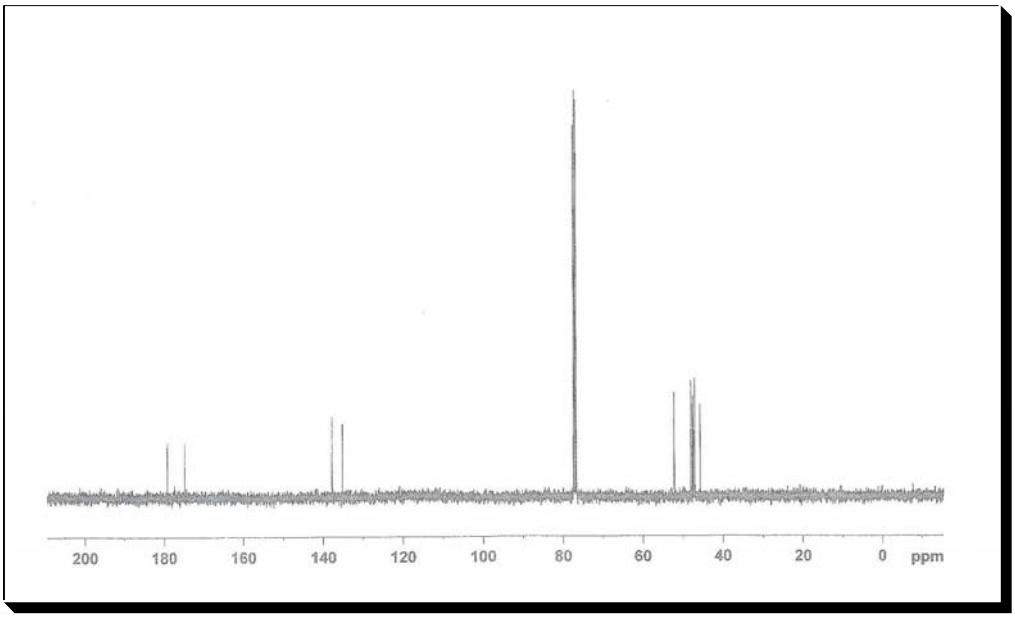
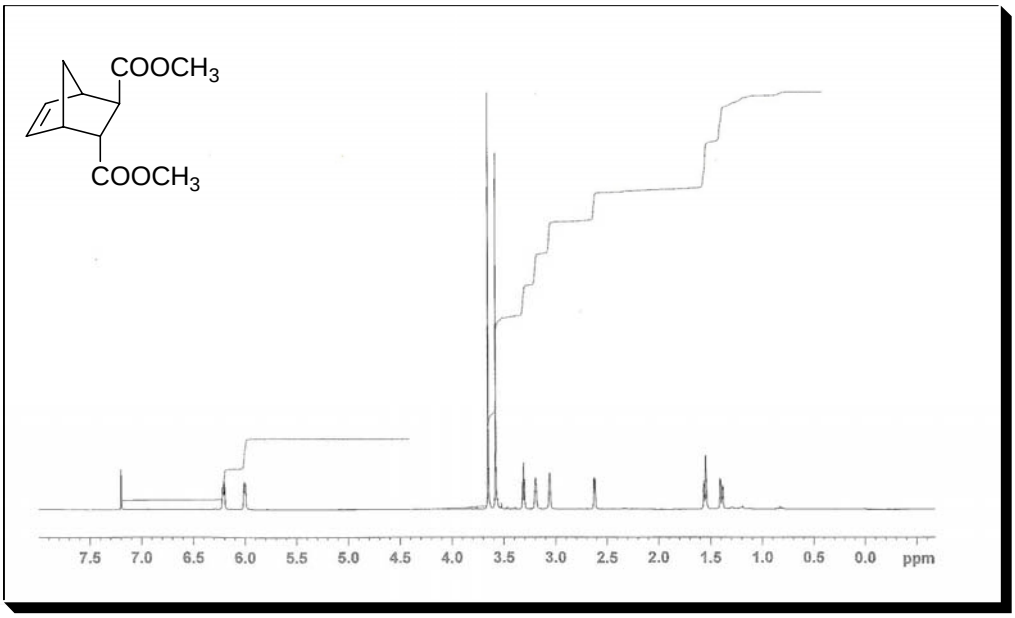


Fig. A 3. ^{1}H and ^{13}C-NMR spectra of compound **83**



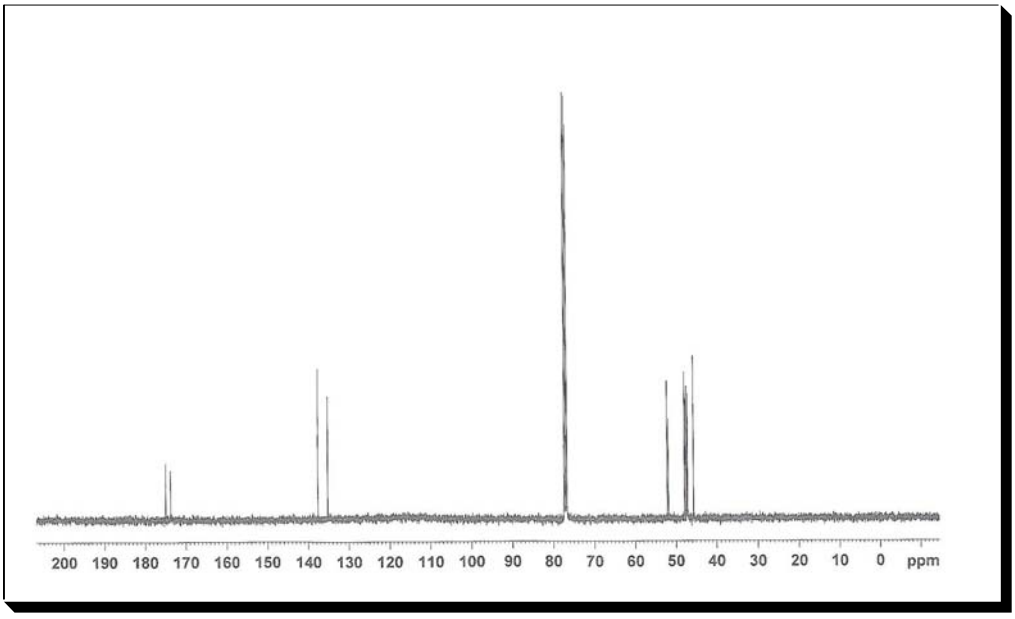
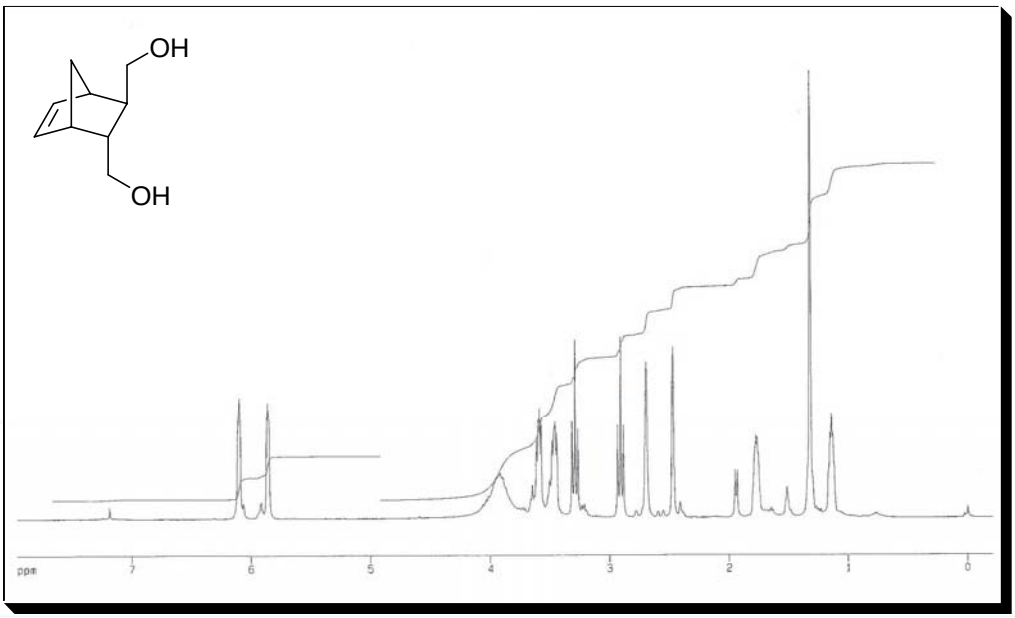


Fig. A 4. ^{1}H and ^{13}C-NMR spectra of compound **84**



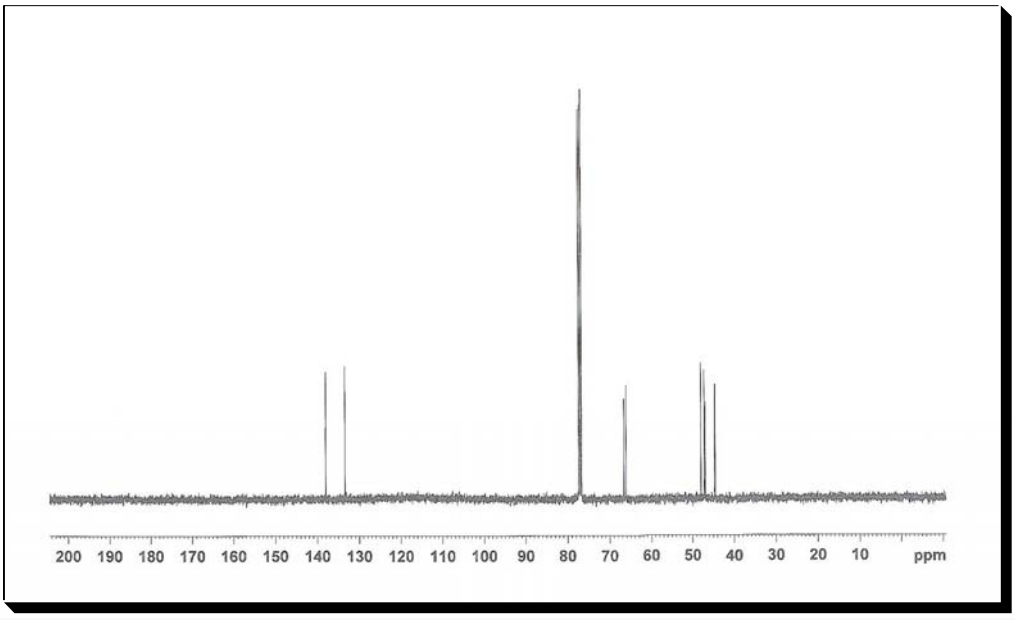
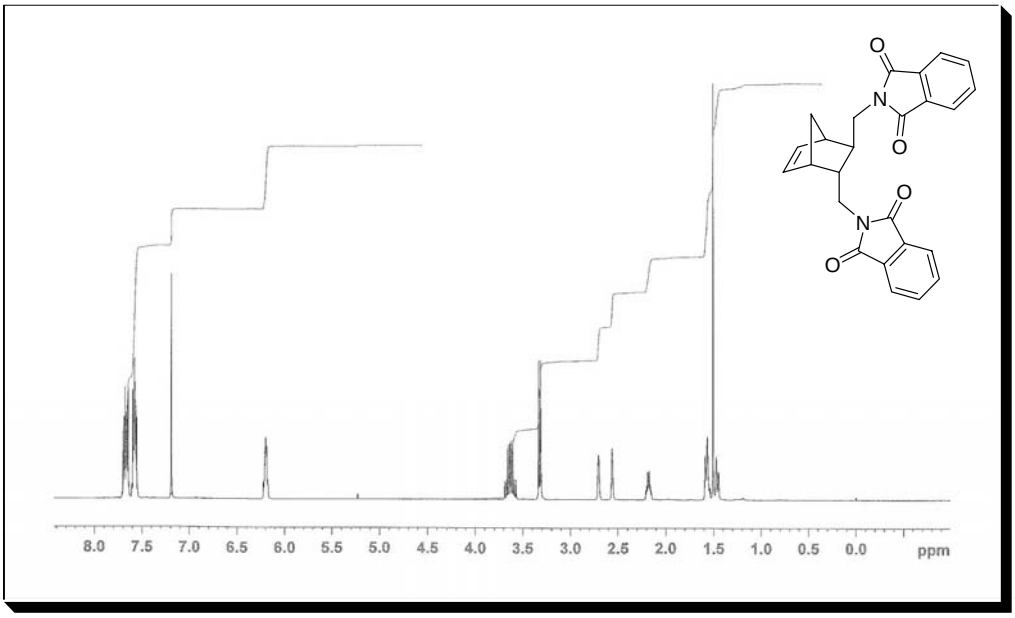


Fig. A 5. ^{1}H and ^{13}C-NMR spectra of compound **85**



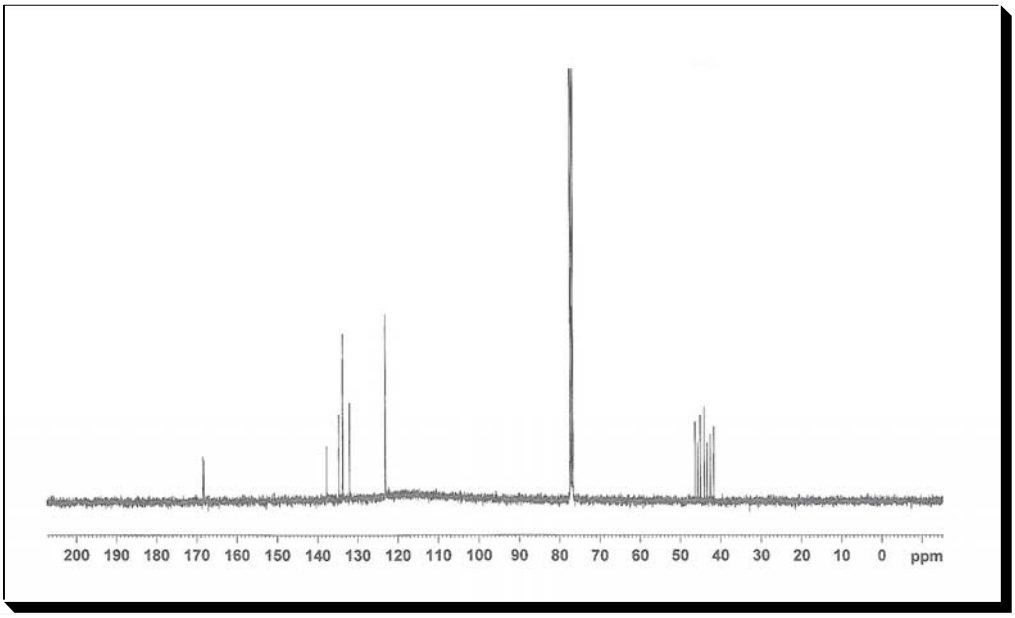
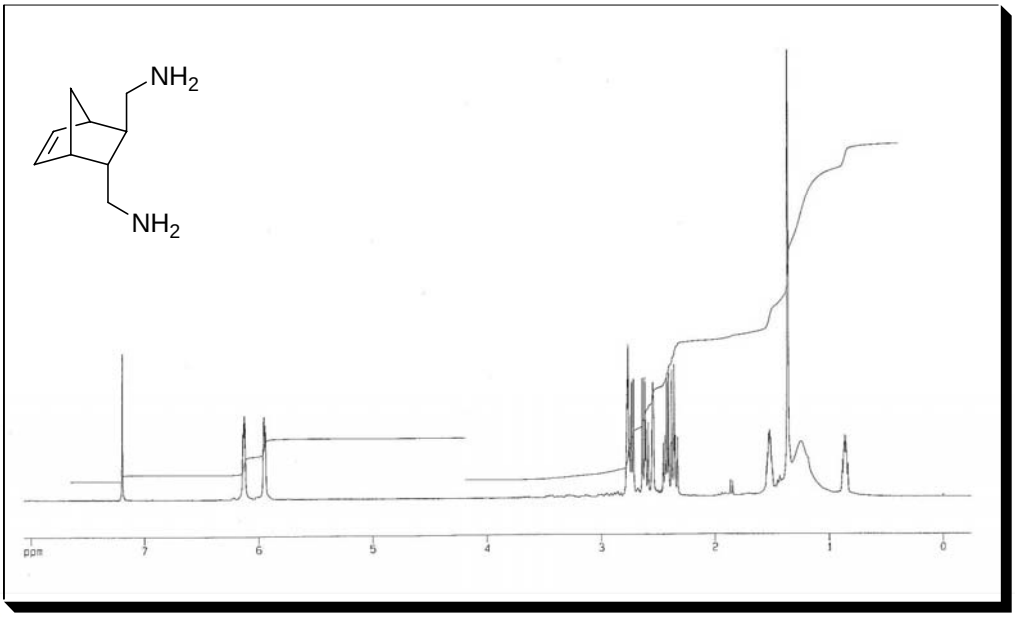


Fig. A 6. ^{1}H and ^{13}C-NMR spectra of compound **86**



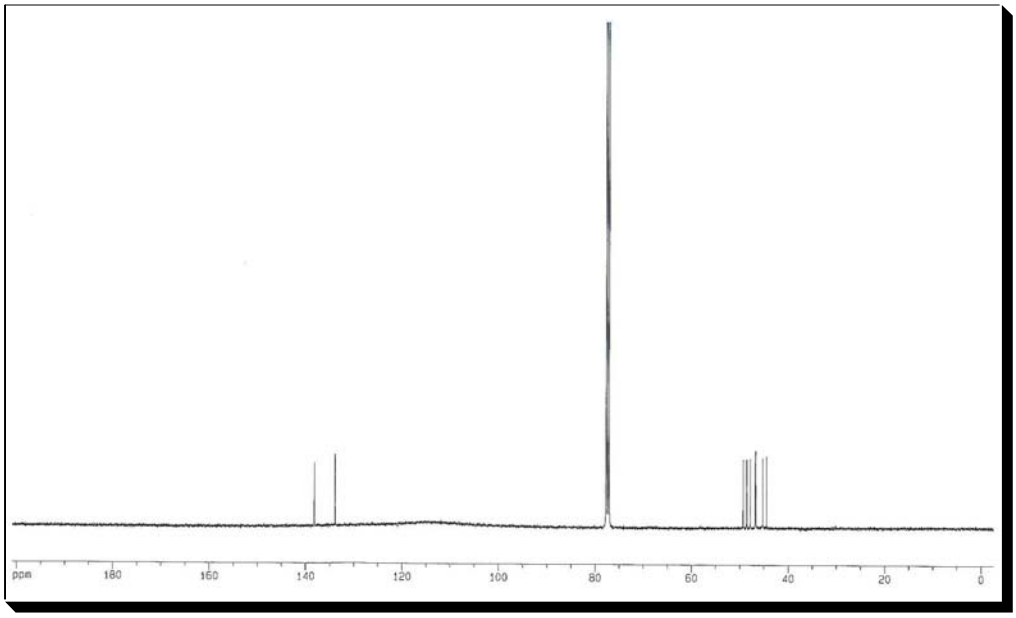


Fig. A 7. ^{1}H and ^{13}C-NMR spectra of compound **87**

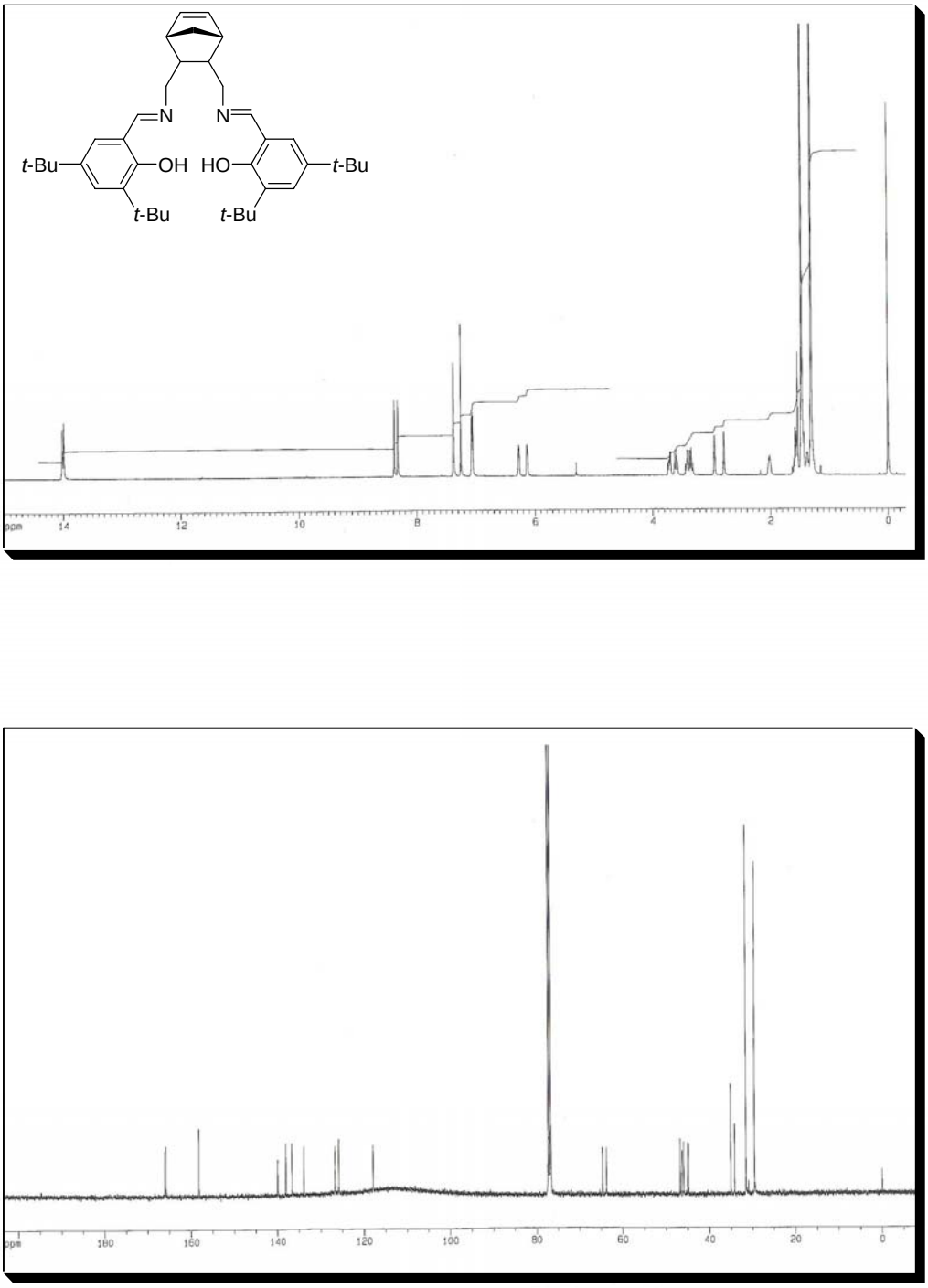
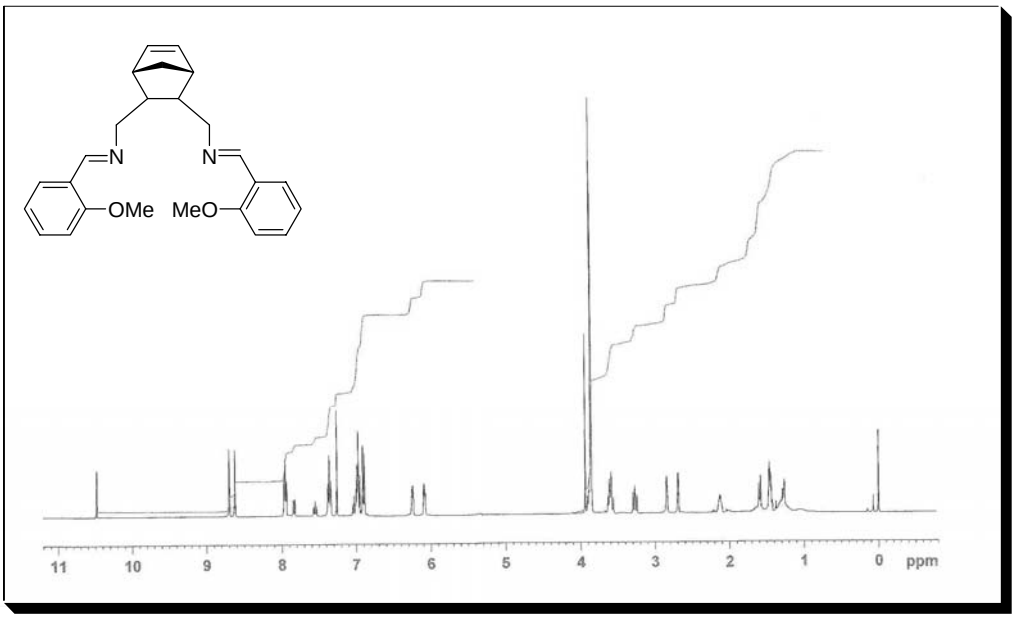


Fig. A 8. ^{1}H and ^{13}C-NMR spectra of compound **88**



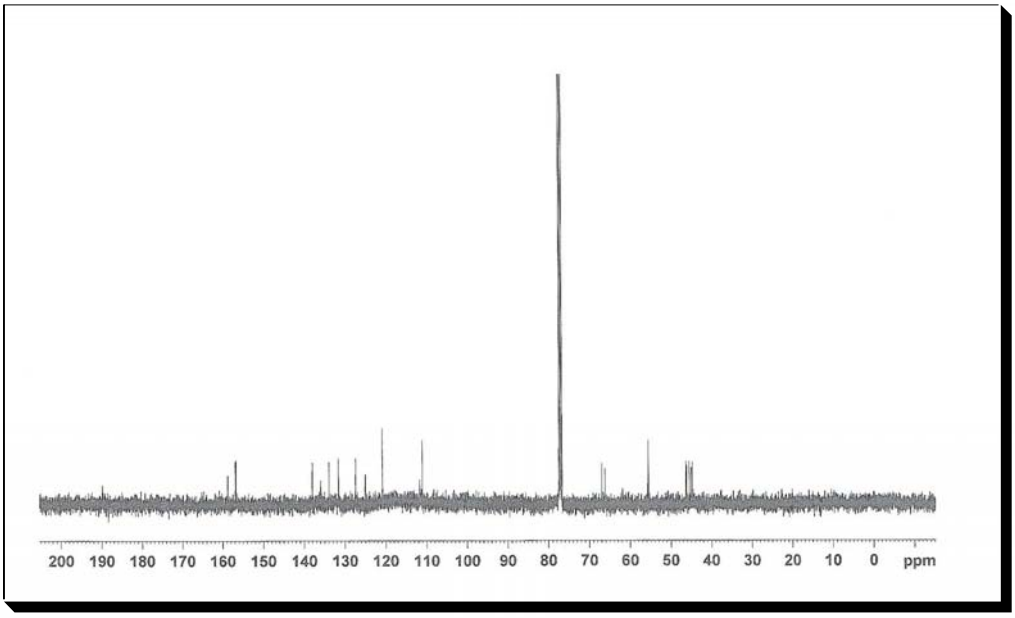
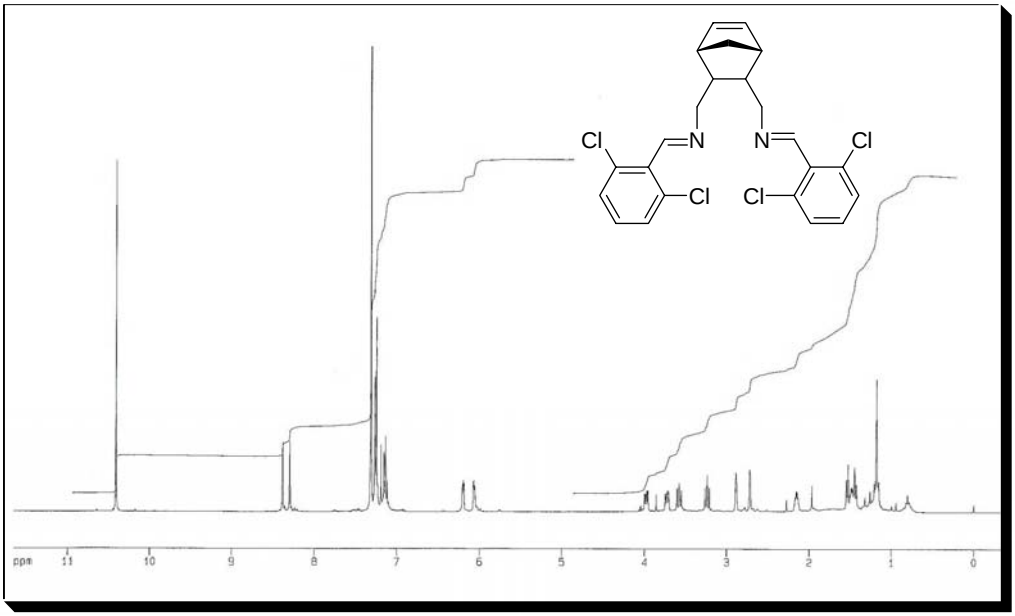


Fig. A 9. ^{1}H and ^{13}C-NMR spectra of compound **89**



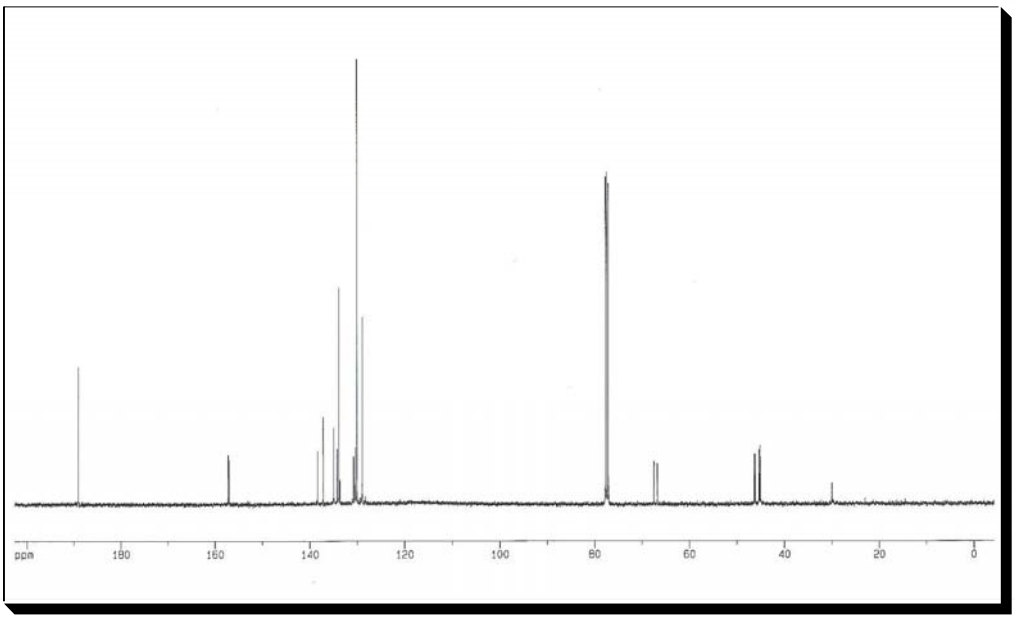


Fig. A 10. ^{1}H and ^{13}C-NMR spectra of compound **90**

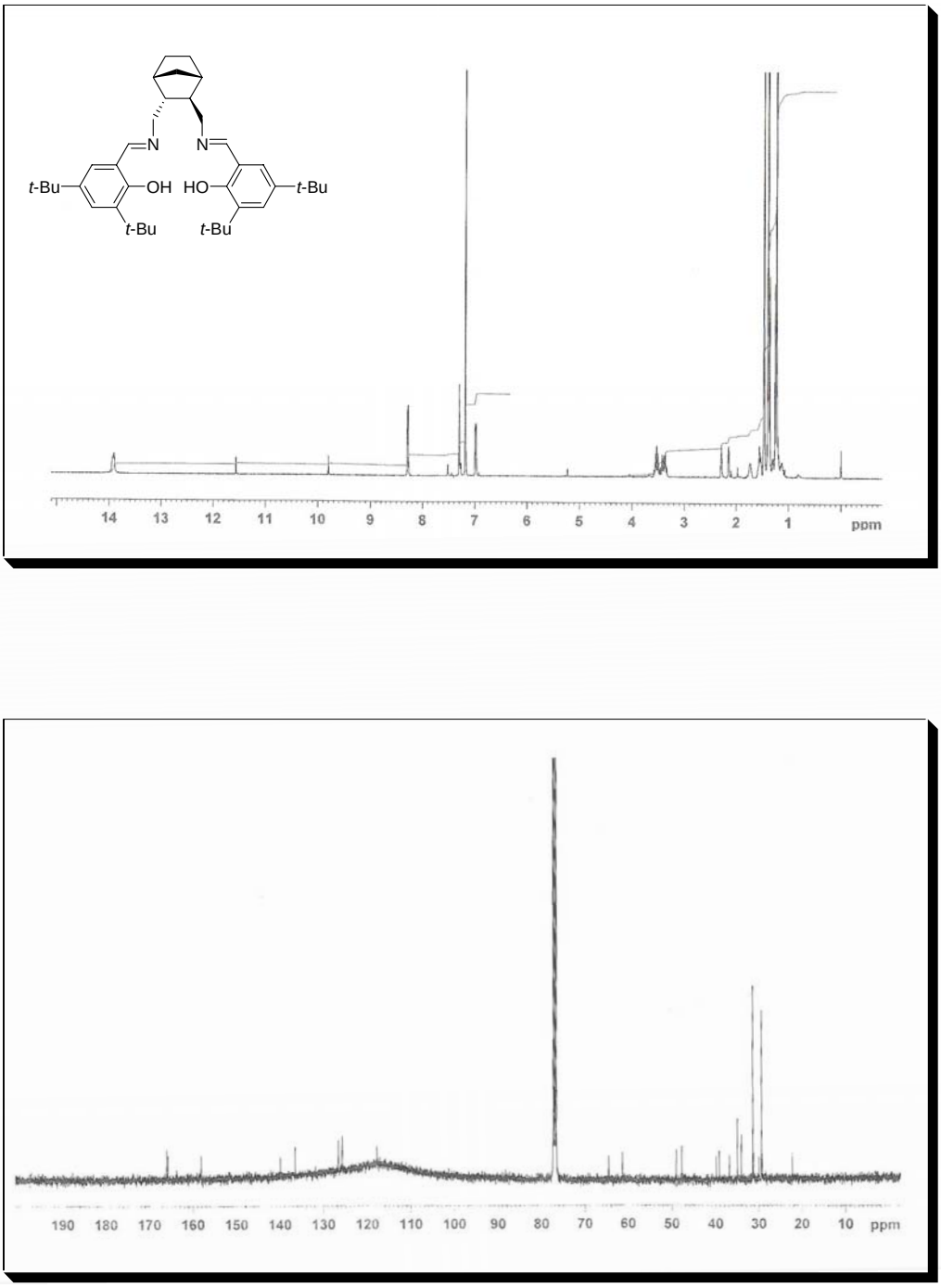
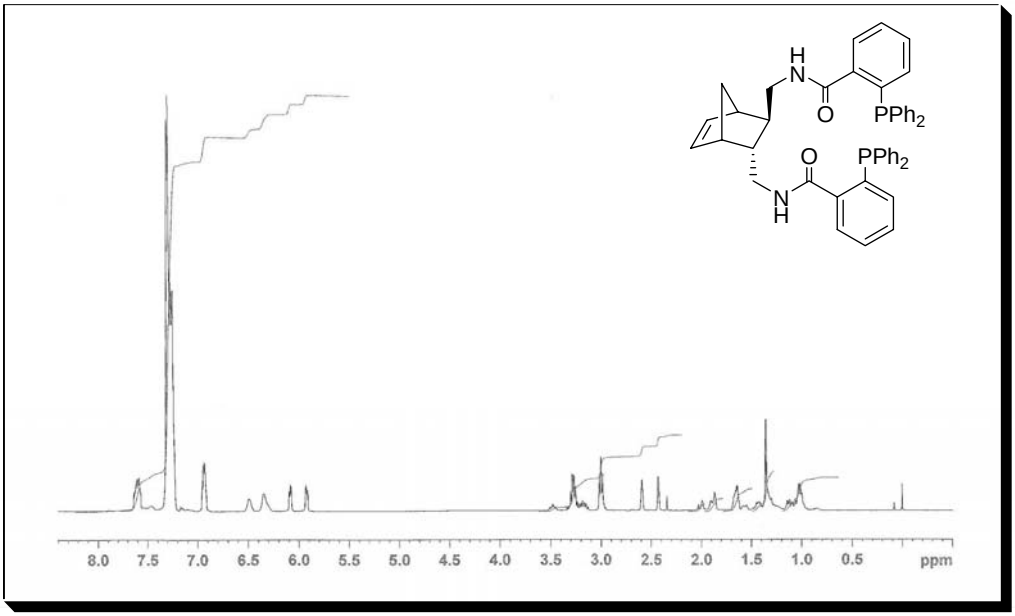


Fig. A 11. ^{1}H and ^{13}C-NMR spectra of compound **91**



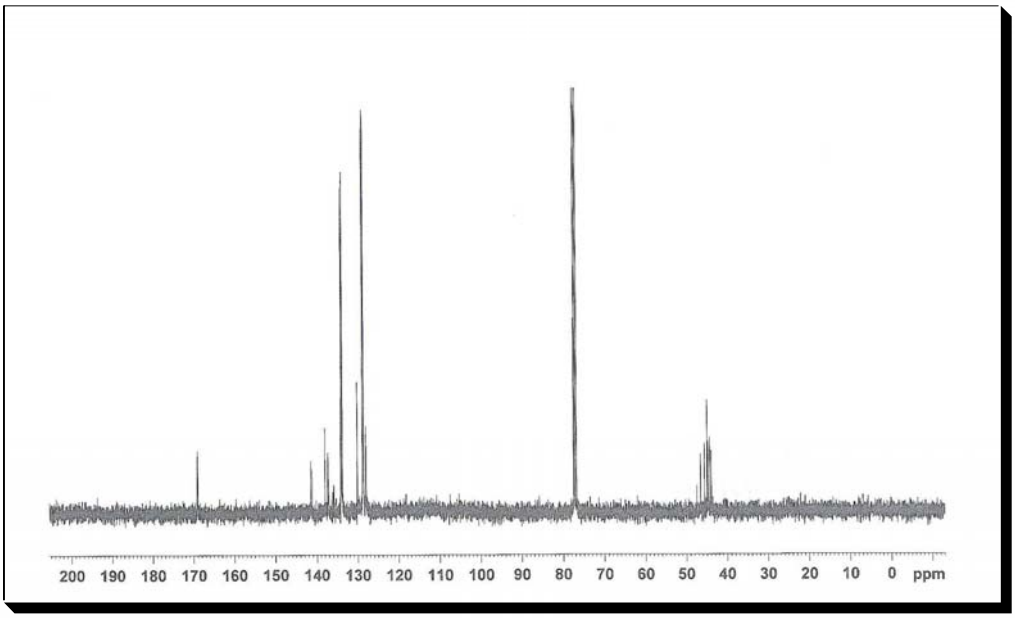


Fig. A 12. ^{1}H and ^{13}C-NMR spectra of compound **92**

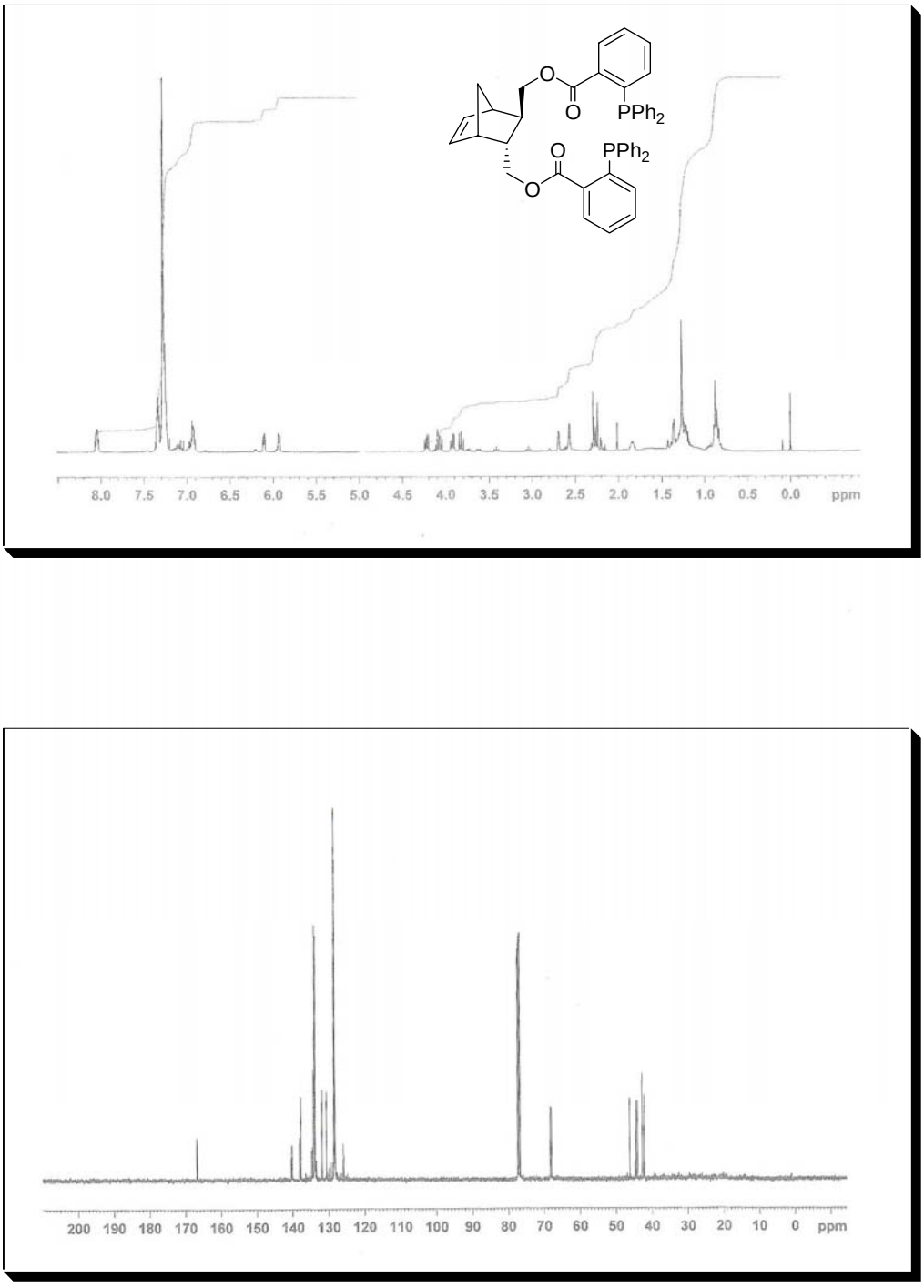
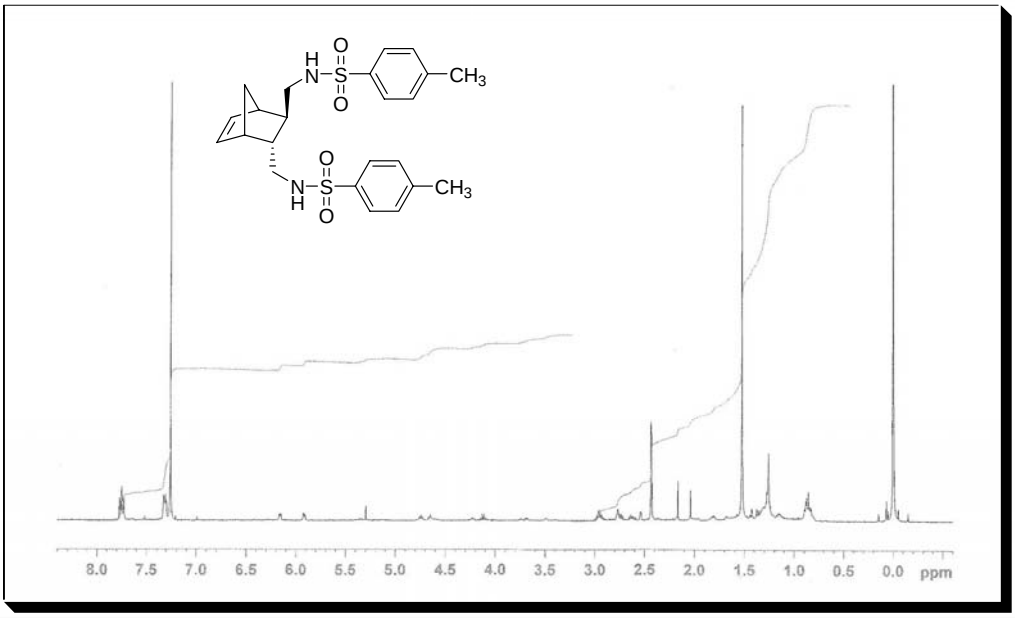


Fig. A 13. ^{1}H and ^{13}C-NMR spectra of compound **93**



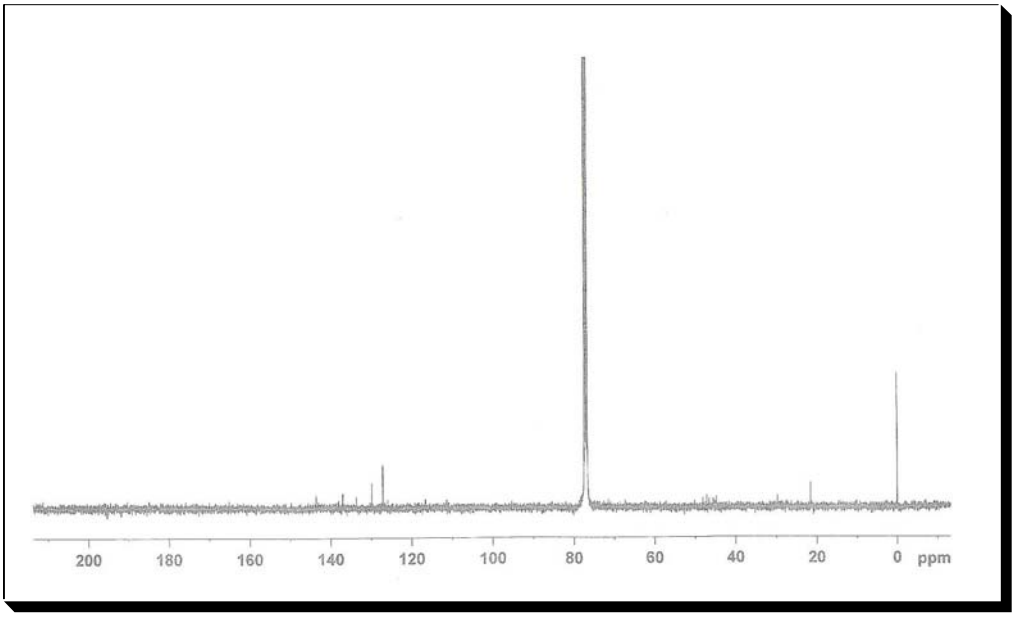
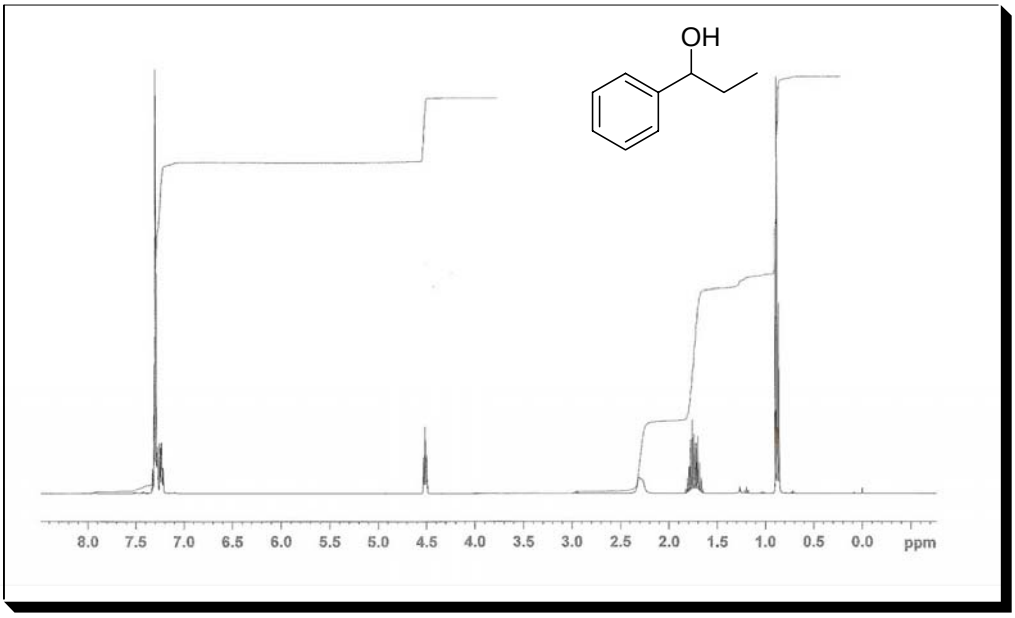


Fig. A 14. ^{1}H and ^{13}C-NMR spectra of compound **94**



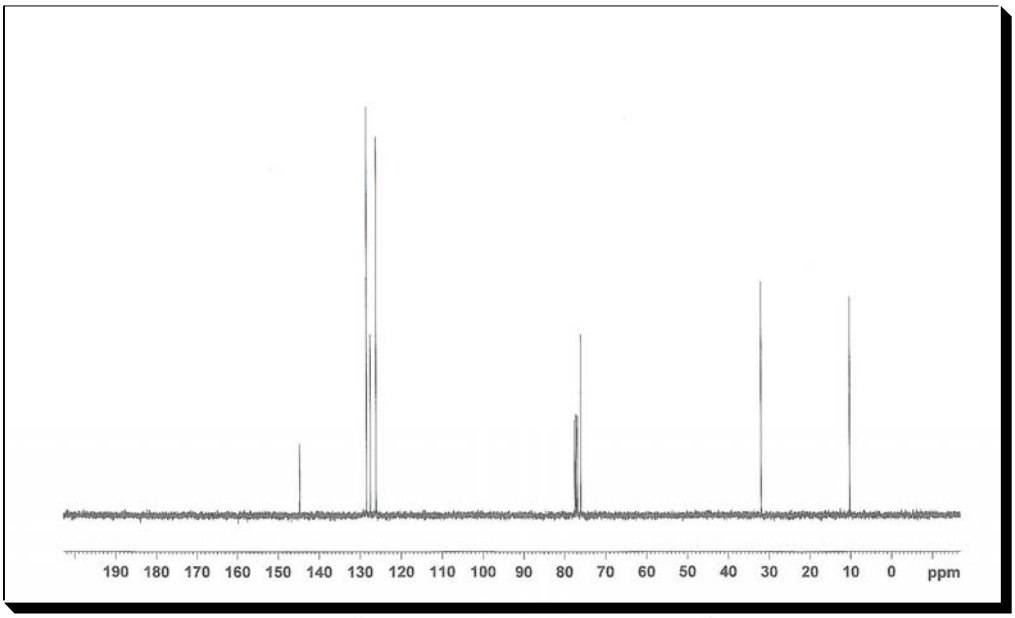
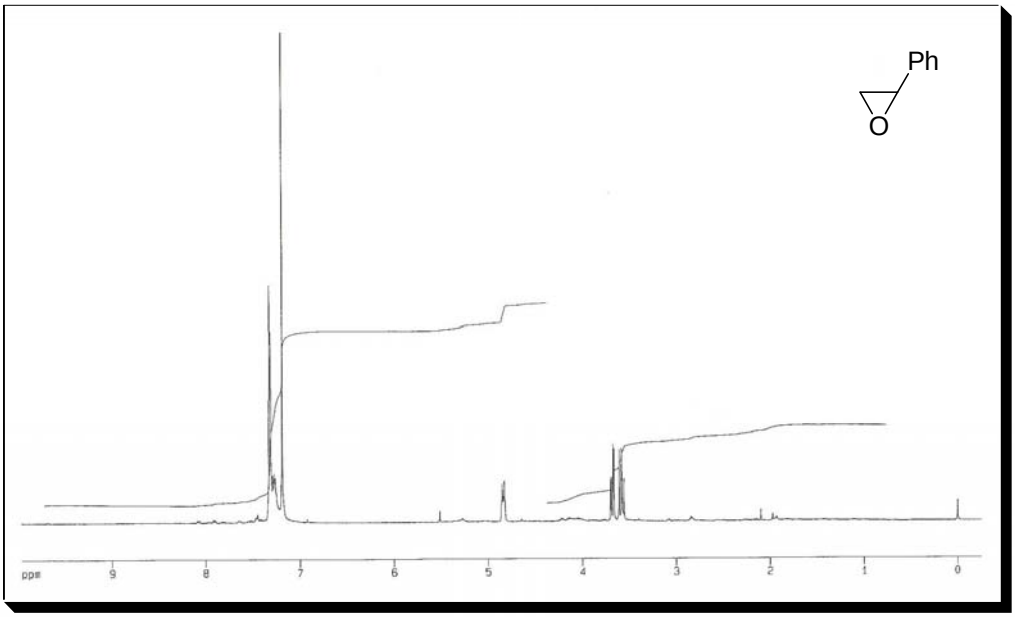


Fig. A 15. ^{1}H and ^{13}C-NMR spectra of compound **95**



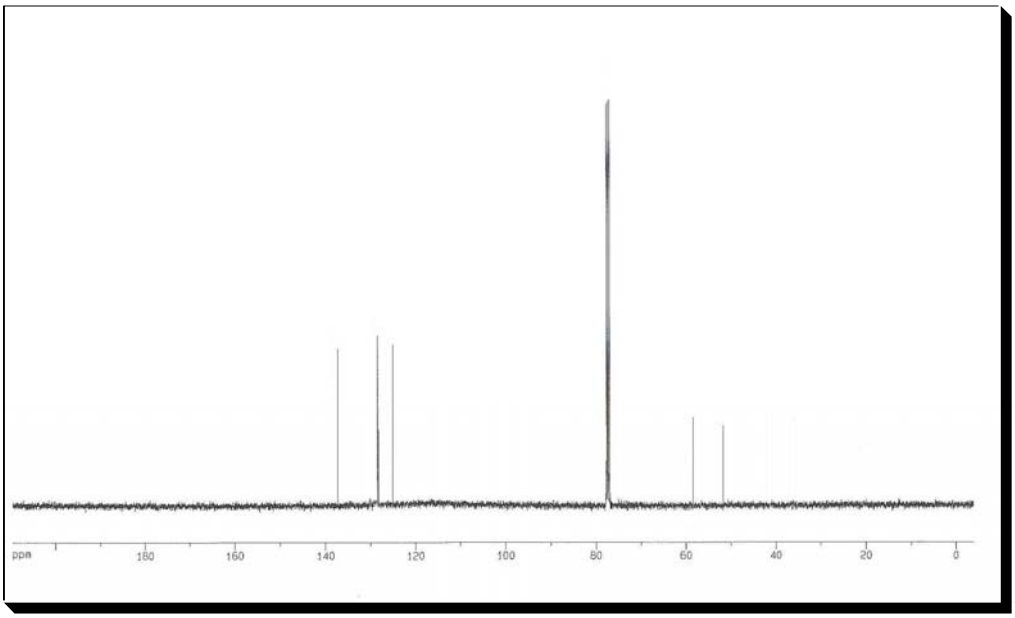
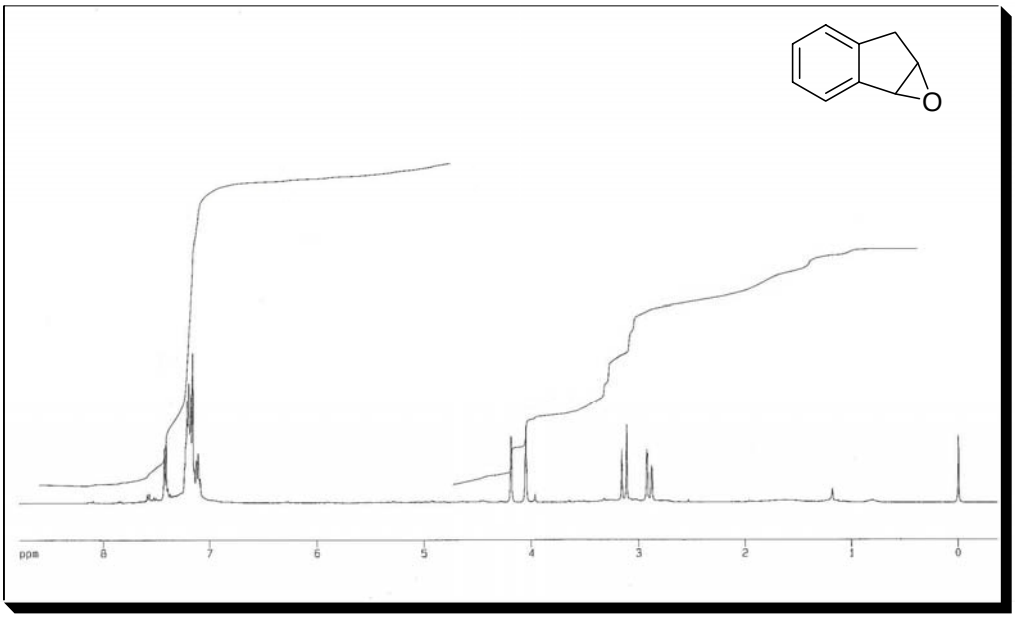


Fig. A 16. ^{1}H and ^{13}C-NMR spectra of compound **96**



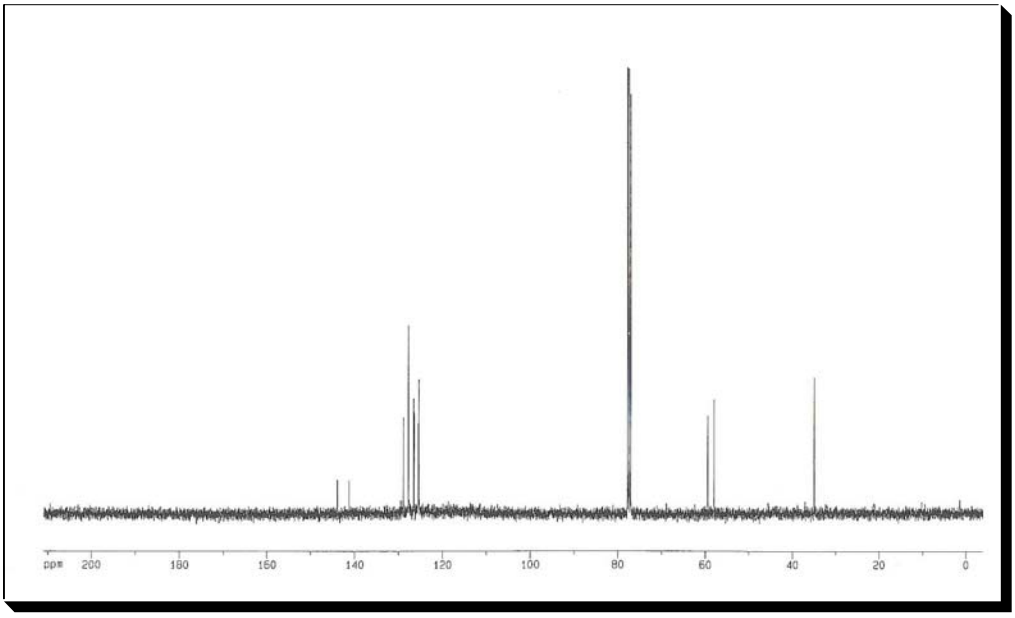
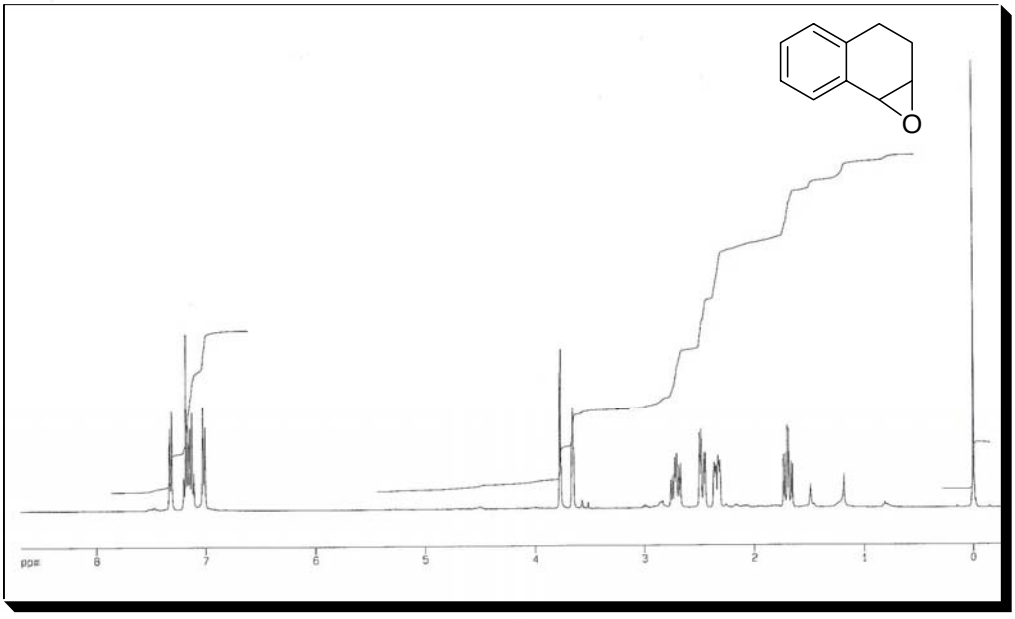


Fig. A 17. ^{1}H and ^{13}C-NMR spectra of compound **97**



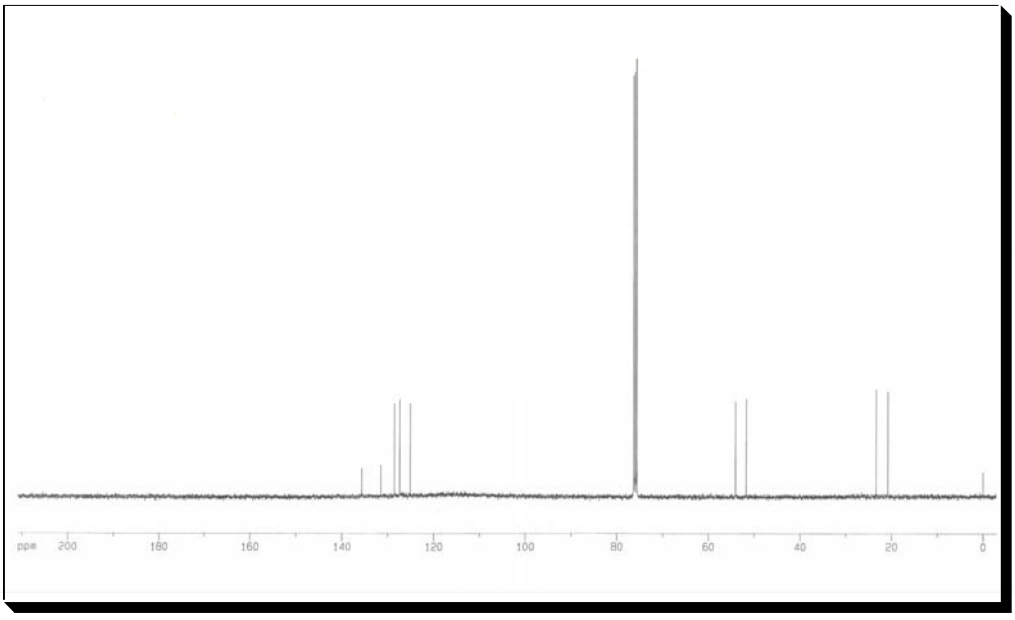
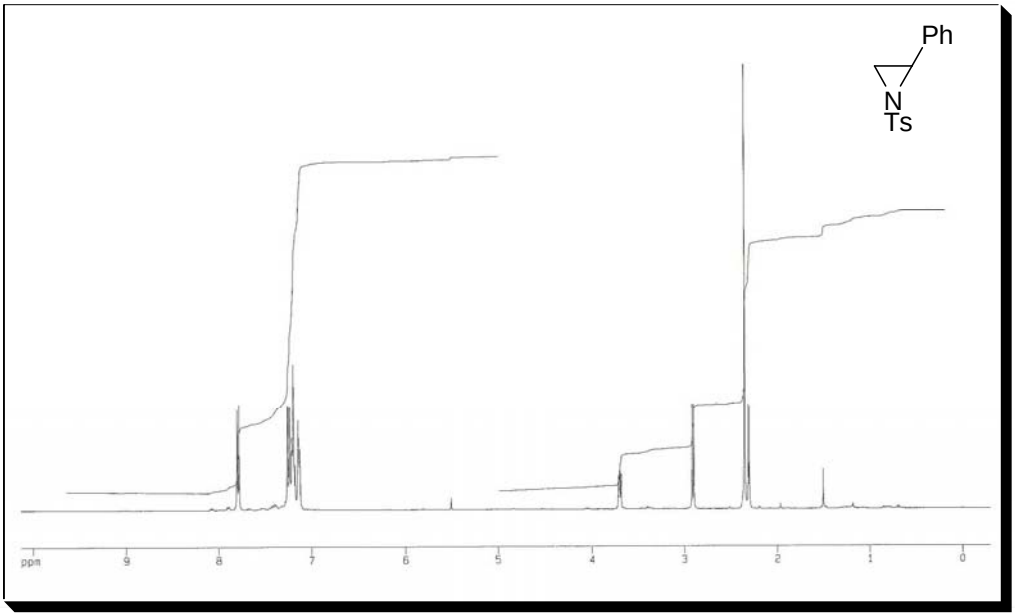


Fig. A 18. ^{1}H and ^{13}C-NMR spectra of compound **98**



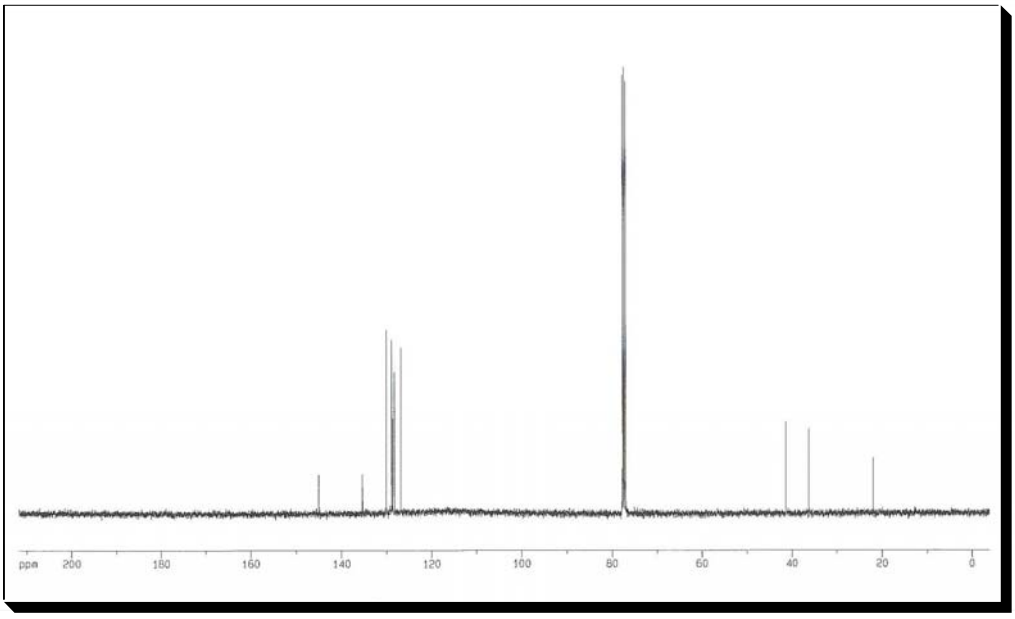
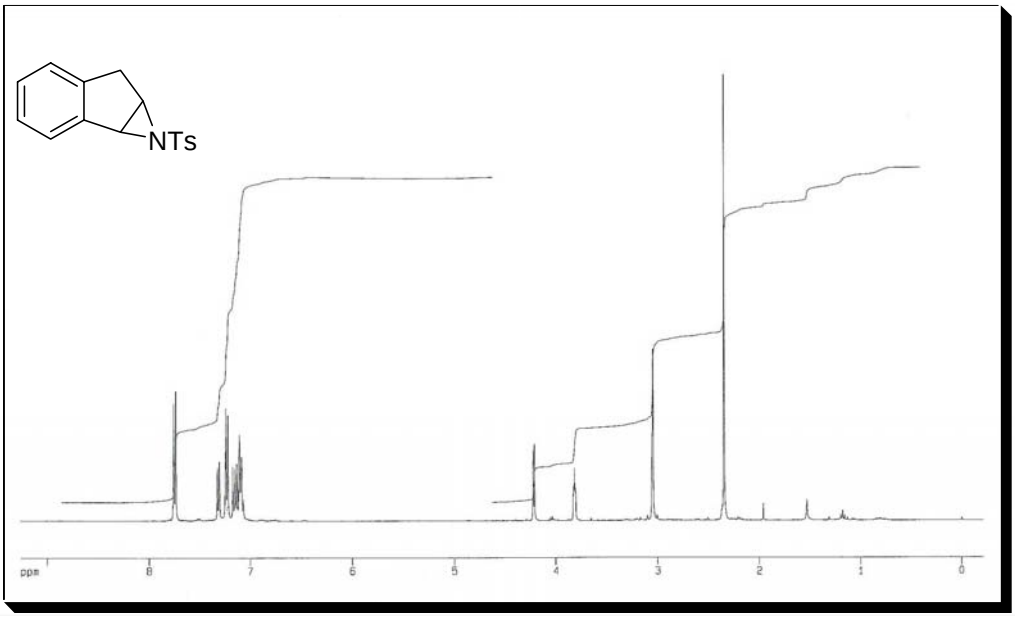


Fig. A 19. ^{1}H and ^{13}C-NMR spectra of compound **99**



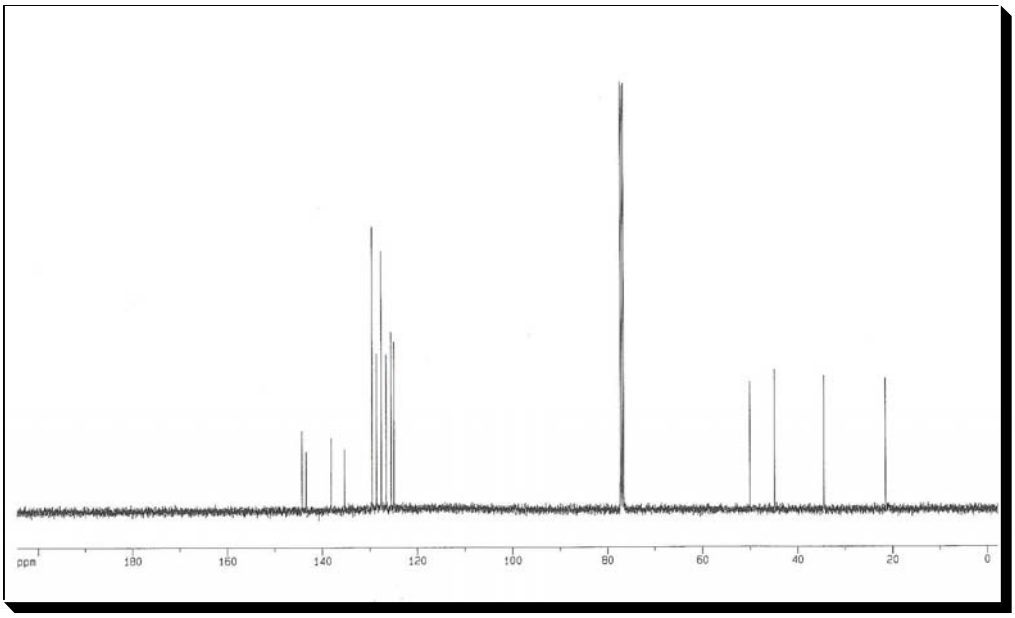


Fig. A 20. ^{1}H and ^{13}C-NMR spectra of compound **100**

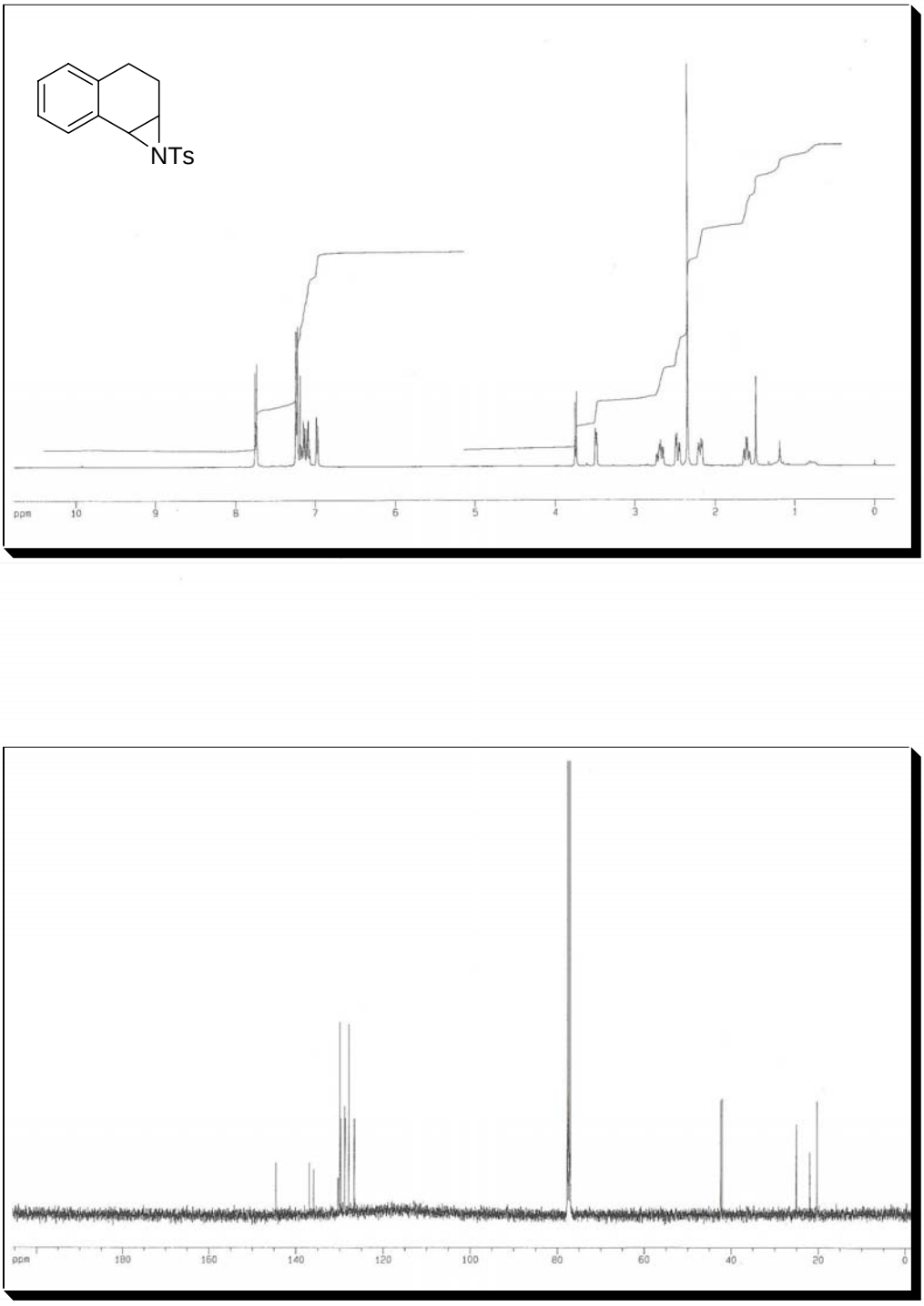
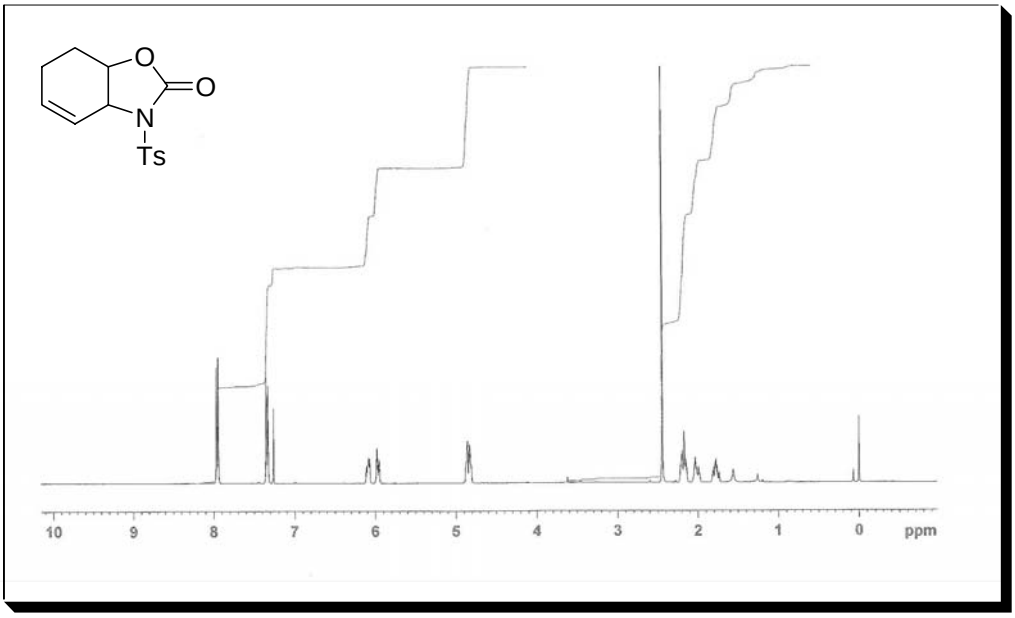


Fig. A 21. ^{1}H and ^{13}C-NMR spectra of compound **101**



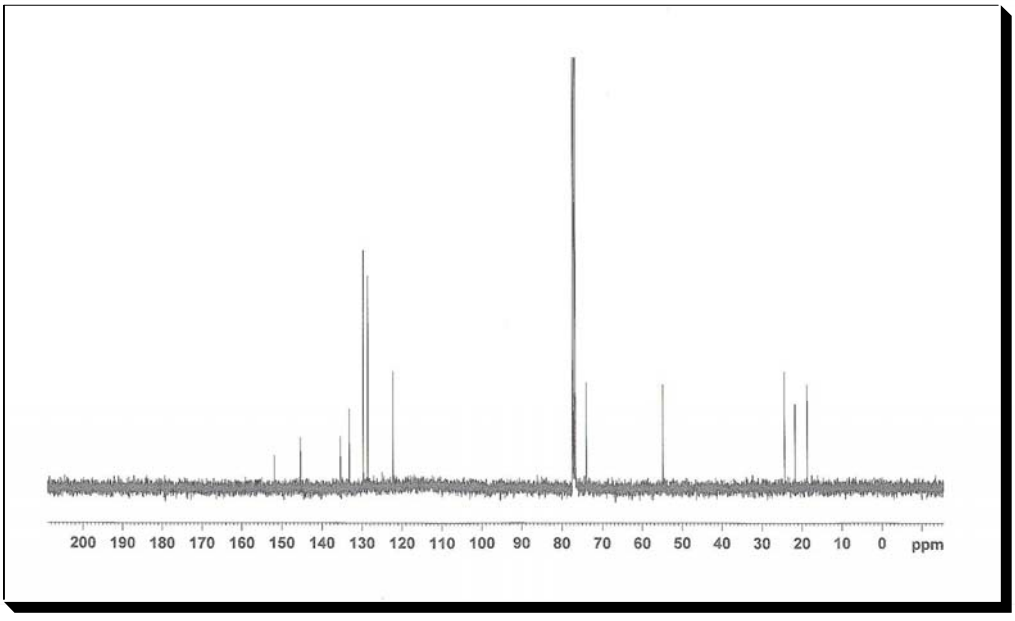
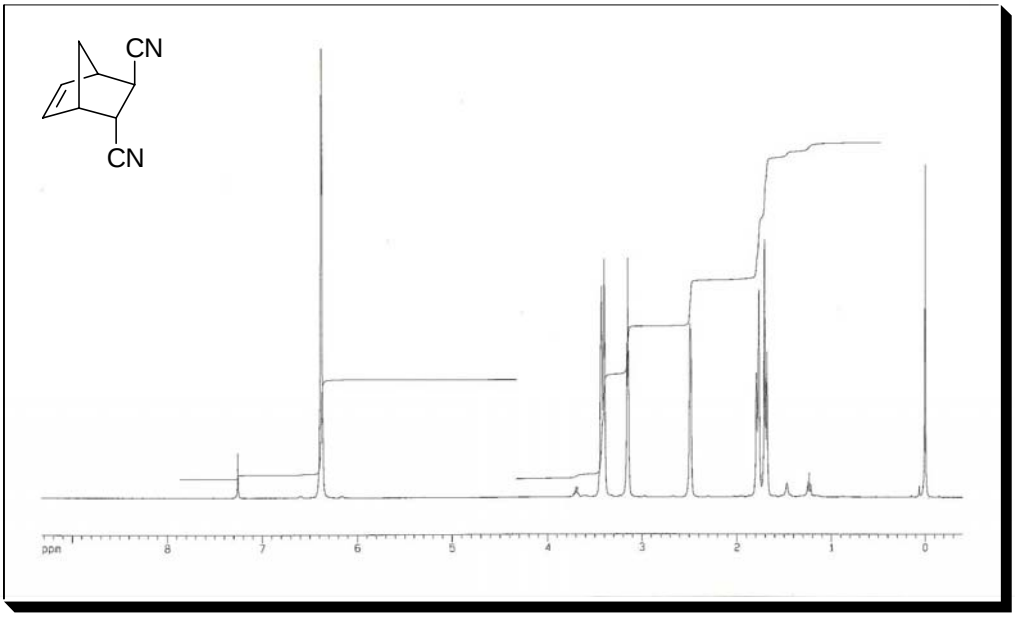


Fig. A 22. ^{1}H and ^{13}C-NMR spectra of compound **102**



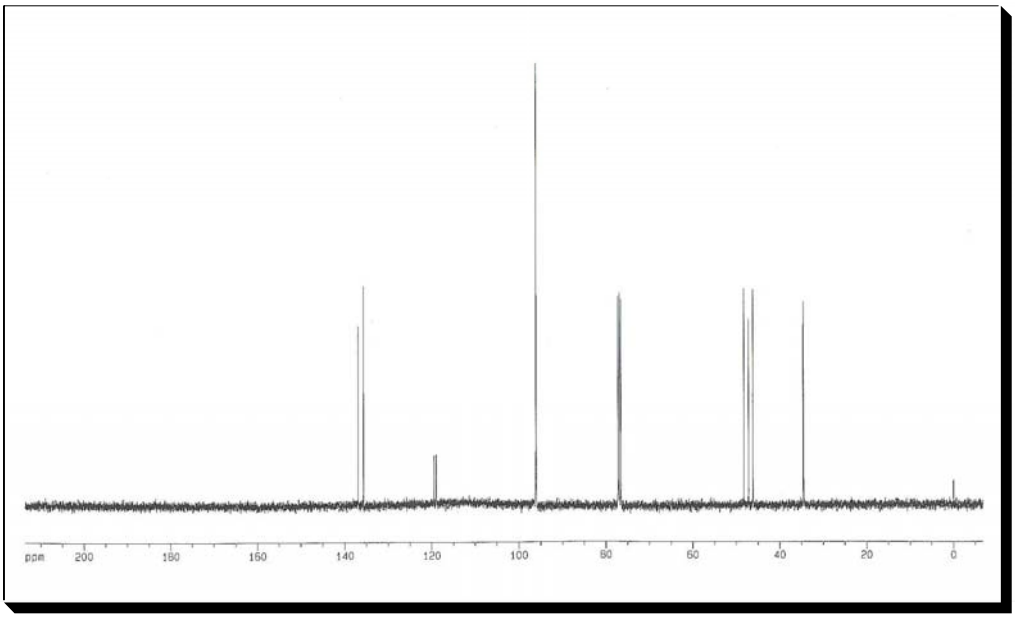


Fig. A 23. ^{1}H and ^{13}C-NMR spectra of compound **103**

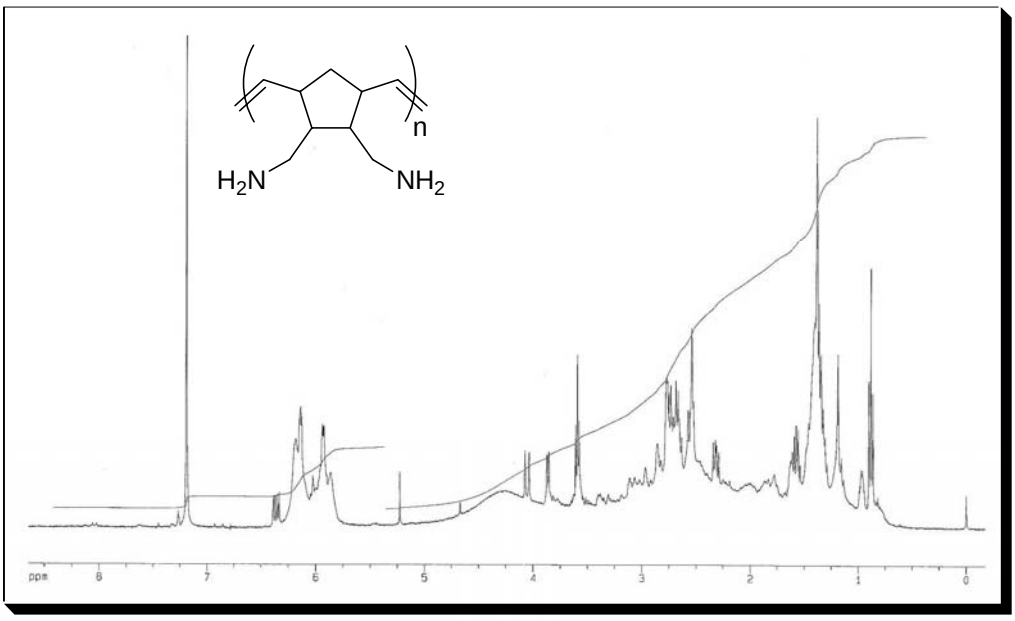


Fig. A 24. ^{1}H-NMR spectra of compound **105**

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