SYNTHESIS OF NOVEL CHIRAL N,N-DIALKYL SUBSTITUTED 1,4-AMINO ALCOHOLS AND APPLICATIONS IN ASYMMETRIC TRANSFORMATION REACTIONS

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Approval of the Graduate School of Natural And Applied Sciences

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

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ABSTRACT

SYNTHESIS OF NOVEL CHIRAL N,N-DIALKYL SUBSTITUTED 1,4-AMINO ALCOHOLS AND APPLICATIONS IN ASYMMETRIC TRANSFORMATION REACTIONS

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Amino alcohols are valuable bioactive substances and frequently used as chiral catalyst in various asymmetric transformation reactions. In the synthetic route, the asymmetric synthesis of novel chiral N,N-dialkyl substituted chiral 1,4-amino alcohols are performed starting with *meso*-anhydride **38**. Quinine-mediated desymmetrization of the anhydride with methanol afforded *(2S,3R)-cis*-monoester **39** with a high enantiomeric excess (up to 98% ee). Chemoselective amidation of hemiester with various N,N-dialkyl substituted amines resulted in amido esters and they were subjected to LAH reduction to afford chiral 1,4-amino alcohol ligands.

The activities of the chiral ligands, *(2S,3R)*-**43**, *(2S,3R)*-**44**, *(2S,3R)*-**45**, *(2S,3R)*-**46** were tested in various asymmetric transformation reactions, i.e. asymmetric diethylzinc addition and asymmetric Diels-Alder reactions.

Keywords: 1,4-Amino alcohols, chiral ligand, asymmetric diethylzinc addition reaction, Diels-Alder reaction

ÖZ

ÖZGÜN N,N-DİALKİL SÜBSTİTÜE KİRAL 1,4-AMİNO ALKOLLERİN SENTEZİ VE ÇEŞİTLİ ASİMETRİK TRANSFORMASYON REAKSİYONLARINDA UYGULANMASI

ÇAKIR, ESEN

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Tez Yöneticisi: Prof. Dr. Cihangir Tanyeli

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Amino alkoller değerli biyoaktif maddelerdir ve çoğunlukla çeşitli asimetrik transformasyon reaksiyonlarında kiral ligand olarak kullanılırlar. Sentez aşamasında, N,N-dialkil sübstitüentli özgün kiral 1,4-amino alkollerin asimetrik olarak sentezi *mezo*-anhidrit **38**'den başlanarak tamamlanmıştır. Bu anhidritin kininli ortamda metanolle verdiği desimetrizasyon tepkimesi sonucunda yüksek enantiyomerik zenginliğe sahip *(2S,3R)-cis*-monoester **39** bileşiği elde edilmiştir. Oluşan hemiester çeşitli N,N-dialkil sübstitüe aminlerle tepkimeye sokularak kemoseçici amidasyon sağlanmış ve oluşan ürünler LAH ile muamele edilerek kiral 1,4-amino alkol ligandları elde edilmiştir.

Bu kiral ligandların, *(2S,3R)*-**43**, *(2S,3R)*-**44**, *(2S,3R)*-**45**, *(2S,3R)*-**46**, aktiviteleri çeşitli asimetrik transformasyon reaksiyonlarında, (asimetrik dietilçinko katılma reaksiyonu, asimetrik Diels-Alder reaksiyonu) test edilmiştir.

Anahtar Kelimeler: 1.4-Amino alkoller, kiral ligand, asimetrik dietilçinko katılma reaksiyonu, Diels-Alder reaksiyonu

To My Family;

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THF: Tetrahydrofurane

DCC: Dicyclohexylcarbodiimide

DMAP: 4-Dimethylaminopyridine

DCM: Dichloromethane

LAH: Lithium Aluminum Hydride

DET: Diethyl tartrate

LDA: Lithium diisopropylamine

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

ROMP : ring opening metathesis polymerization reaction

CHAPTER 1

INTRODUCTION

1.1. History of Chirality and Its Significance

In 1874, the Dutch chemist Van‘t Hoff and the French chemist Le Bel independently of each other, considered a molecule formed of a carbon atom linked by chemical bonds to four other atoms at the four corners of a tetrahedron. Thus, the molecule is said to be chiral, and the central carbon atom is known as the chiral or stereogenic center. This proposal of Van't Hoff and Le Bel was, as it turns out, completely correct; indeed, the molecule CHFClBr is today the simplest known optically active molecule (Figure 1). This breakthrough formed the basis of modern stereochemistry [1].

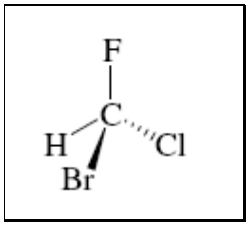


Figure 1. Optically Active Molecule

In 1894, Emil Fischer clearly outlined the concept of asymmetric synthesis based upon his experiments in the conversion of one sugar to its next higher homolog

via the cyanohydrin reaction, relating this process directly to the biochemical process for the production of optically active sugars in plants [2]. He made the assumption that carbon dioxide and water condensed to give formaldehyde under the influence of sunlight and chlorophyll. Furthermore, he assumed that the formaldehyde condensed with itself and with simple carbohydrates under the direction of the optically active substances in the chlorophyll-containing granules in the cells in such a way that the incorporation of each successive asymmetric carbon atom into the chain produced only one of the two possible stereomeric forms. As the reaction proceeded, a sugar molecule formed in close association with the chlorophyll. This formation was followed by separation of the optically active sugar and regeneration of the chlorophyll catalyst so that it was available to continue the cycle [2]. The known chemical pathway of carbon in the photosynthesis process shows little correspondence to the details of this oversimplified scheme propounded at the end of the last century. Nevertheless, the concept of asymmetric synthesis as envisaged by Emil Fischer is, in its essence, valid today [3].

The world is chiral [4-6]. All life is chiral, so all living systems have chiral environments. Nature has chosen to make all its living structures from chiral molecules (amino acids, sugars), and has selected a single enantiomeric form of each. Every amino acid in our body has the *S* and not the *R* configuration, and from this fact, along with the uniform chirality of natural sugars, derives the larger scale chirality of all living structures from the DNA [7].

Chirality (handedness; left or right) is an intrinsic universal feature of various levels of matter [8]. Hands are chiral and right and left hands cannot be superimposed on each other. Figure 2 is an example of chiral objects.

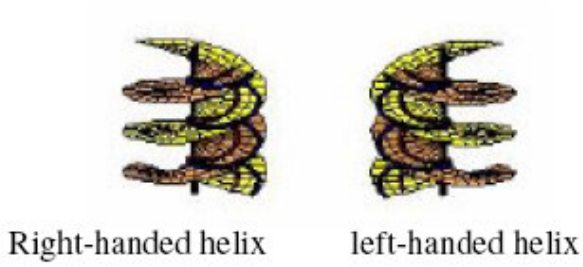


Figure 2. Chiral Objects

Carbon atoms carrying four different substituents possess a unique property [9]. If the four attached atoms are all different, then they can be arranged in two distinct ways which are mirror images known as enantiomers. However, the mirror images are twisted or turned, they never overlap exactly. This is because the three dimensional arrangements in space are different. To take a simple example, lactic acid can be obtained in two forms or enantiomers as in Figure 3, which are clearly enantiomeric in that they are related as mirror images that cannot be superimposed on each other [10].

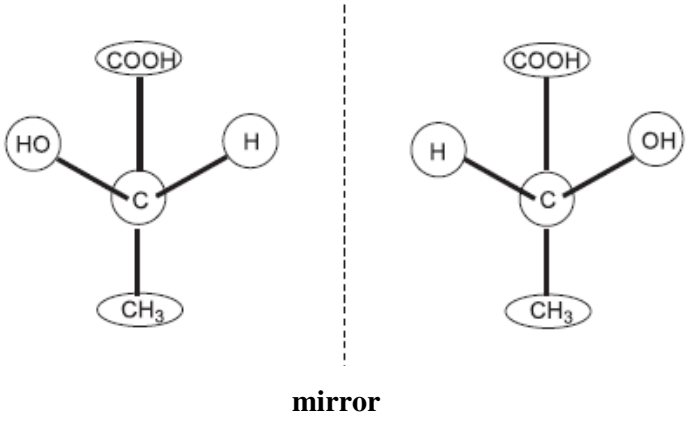


Figure 3. Mirror Images of Lactic Acid

It can be thought that both mirror images of chiral molecules (enantiomers) would be equally common in living systems. Actually, this is not the case. In humans, amino acids and the proteins and enzymes constructed from these building blocks, consist of only one of the two mirror images. *L* and *D*, or *(R)* and *(S)* are symbols used to designate the difference between enantiomers. Laboratory syntheses provide, in the absence of special chiral influences, equal quantities of *(R)* and *(S)* enantiomers. This 1:1 mixture of enantiomers is called a racemate.

1.2. Asymmetric Synthesis

Asymmetric synthesis refers to the conversion of an achiral starting material to a chiral product in a chiral environment. It is presently the most powerful and commonly used method for chiral molecule preparation. Thus far, most of the best asymmetric syntheses are catalyzed by enzymes, and the challenge before us today is to develop chemical systems as efficient as the enzymatic ones. In an asymmetric reaction, substrate and reagent combine to form diastereomeric transition states. One of the two reactants must have a chiral element to induce asymmetry at the reaction site. Most often, asymmetry is created upon conversion of trigonal carbons to tetrahedral ones at the site of the functionality. Such asymmetry at carbon is currently a major area of interest for the synthetic organic chemists [11].

Molecular chirality plays a key role in science and technology. In particular, life depends on molecular chirality, in that many biological functions are inherently dissymmetric. Most physiological phenomena arise from highly precise molecular interactions, in which chiral host molecules recognize two enantiomeric guest molecules in different ways. The structural difference between enantiomers can be serious with respect to the actions of synthetic drugs. Chiral receptor sites in the human body interact only with drug molecules having the proper absolute configuration, which results in marked differences in the pharmacological activities of enantiomers.

A compelling example of the relationship between pharmacological activity and molecular chirality was provided by the tragic administration of thalidomide to pregnant women in the 1960's. *(R)*-Thalidomide has desirable sedative properties, while its *S* enantiomer is teratogenic and induces fetal malformations [12].

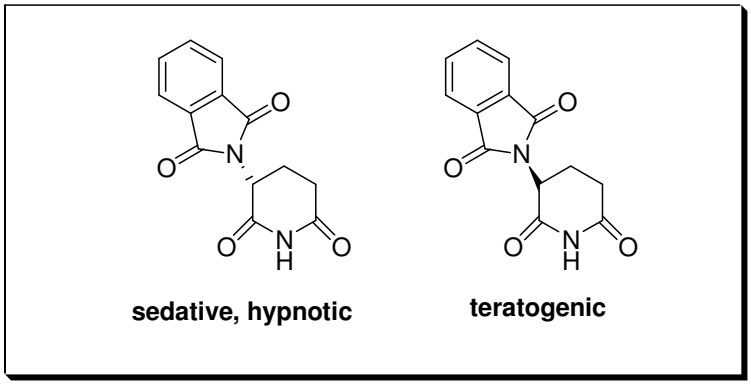


Figure 4. Enantiomers of Thalidomide

The importance of enantiomerically pure compounds comes from the central role of enantiomer recognition in biological activity [13]. There are many examples of pharmaceutical drugs, [14] agrochemicals [15] and other chemical compounds where the desired biological property is related to the absolute configuration.

A biologically active chiral compound interacts with its receptor site in a chiral manner, and enantiomers may be discriminated by the receptor in very different ways [16]. Thus, two enantiomers of a drug may interact differently with the receptor, leading to different effects [10].

In drugs tested for therapeutically use, it is often found that only one enantiomer possesses the desired biological activity, whereas the other enantiomer

is inactive or possesses a different activity and causes toxic side effects. In the case of propanolol, the *(S)* enantiomer is a β-blocker whilst the *(R)* form possesses contraceptive activity. Also, the *(S)* enantiomer of ibuprophen is active as pain reliever whereas the *(R)* enantiomer is inactive [17]. Sometimes the inactive isomer may interfere with the active isomer and significantly lower its activity. For example, when the *(R)*-derivative of the sex pheromone of a Japanese beetle is contaminated with only 2% of its enantiomer, the mixture is three times less active than the optically pure pheromone. The pheromone with as little as 0.5% of the *(S)*-enantiomer already shows a significant decrease of activity [18]. Chiral herbicides, pesticides, and plant growth regulators widely used in agriculture also show strong bio-discriminations. In fact, stereo-discrimination has been a crucial factor in designing enantiomerically pure drugs that will achieve better interaction with their receptors [19].

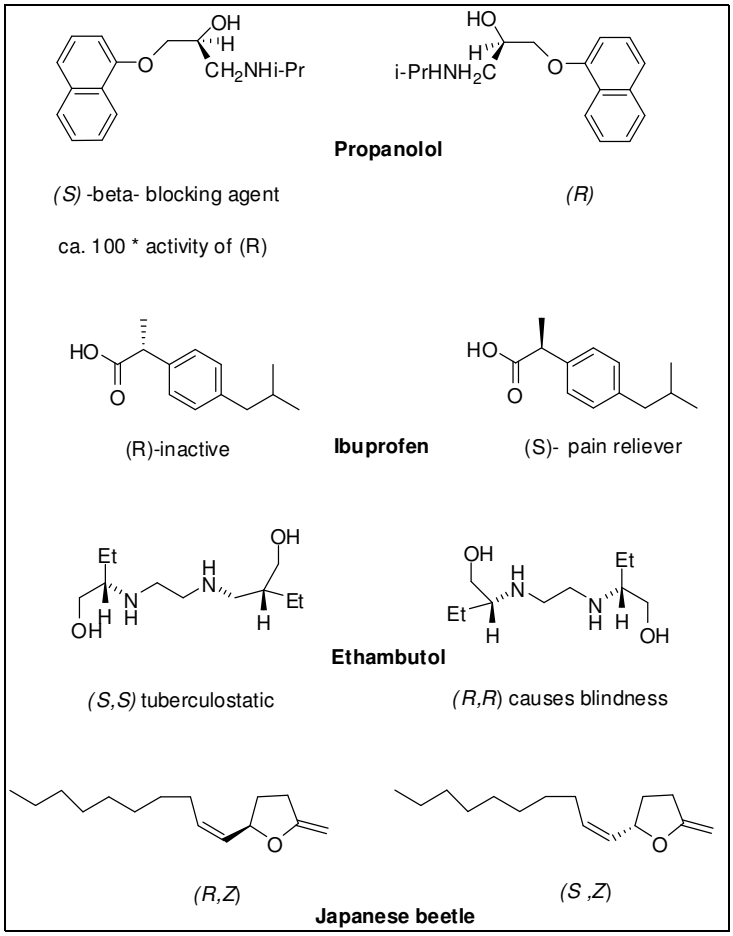


Figure 5.The Structures and Pharmacological Effects of the Enantiomers of Some Biologically Active Chiral Molecules

1.2.1. Design of Asymmetric Synthesis

Three types of reaction, or sequence of reactions, are relevant to the design of asymmetric synthesis:

1. de novo asymmetric synthesis
2. asymmetric induction
3. chirality relay

1.2.1.1. De Novo Asymmetric Synthesis

The first type of process is rare. Achiral starting material 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. The related concept of enantioselective autocatalysis is in the vanguard of new developments in asymmetric synthesis. Here, a chiral product catalyses its own enantioselective preparation.

1.2.1.2. Asymmetric Induction

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, a tiny amount of the chiral auxiliary can produce a large amount of enantiopure product, so this can be highly cost-efficient approach. Reactions of this type are enantioselective. Since the chiral auxiliary is not incorporated into the final product, the success of stereoselectivity is determined by measuring the excess of one enantiomer of the product over the other.

1.2.1.3. Chirality Relay

In some enantiomer synthesis of target molecules, optically pure starting materials are incorporated directly. These chiral centers are ‘bought-in’, and, of course, if they are simply taken through into the product, no real asymmetric synthesis has been performed. The supply of enantiopure starting materials for this purpose is sometimes referred to as ‘chiral pool’. Normally, however, the bought-in chirality must be modified, or new chiral centers introduced (substrate-controlled diastereoselectivity), a situation where diastereoselectivity is the measure of success.

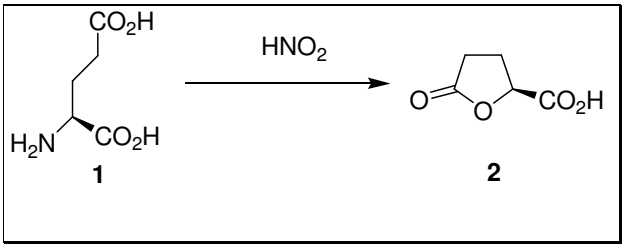
1.2.2. The Design Challenge

Approaches to asymmetric synthesis are sometimes grouped by ‘generations’, reflecting increasing sophistication of approach.

a) **First-generation asymmetric synthesis.** Diastereoselective reactions in which the formation of a new chiral centre is under the control of an existing centre in the same molecule. This is often referred to as substrate-controlled diastereoselectivity. Chirality-relay is based on first-generation asymmetric synthesis [20].

1.2.2.1. Chiral Substrates

The best scenario is to have a chiral starting material that can then control the stereoselection of the reaction itself. To achieve this, especially at the beginning of the synthetic sequence, few options are available. Nature produces chiral materials and a number of these available in quantity [21-22]. These compounds make up the ‘chiral pool’. This can be a disadvantage as there are limited amounts of natural products available. The number of steps necessary to convert natural product into a useful starting material for synthesis and the price should also be considered. If all of the parameters are favorable, this approach is the method of choice as it has the potential to eliminate resolutions or the necessity for an enantiospecific transformation in the synthetic design [23]. An example of the use of natural product for a starting material is the conversion of L-glutamic acid to the chiral butyrolactone (Scheme 1).



Scheme 1. An Example for a Chiral Substrate in an Asymmetric Synthesis [24]

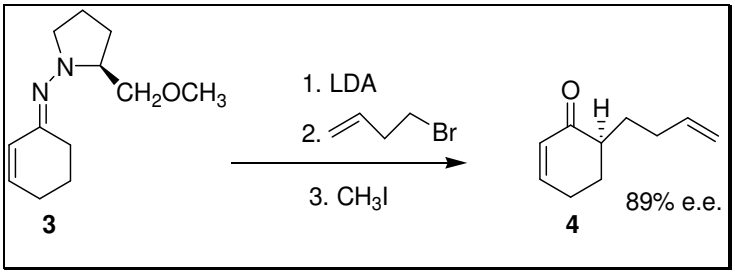
b) **Second-generation asymmetric synthesis.** A stoichiometric chiral auxiliary is covalently attached to the substrate before chirality relay is performed. Chirality in the auxiliary controls the asymmetric induction, and the auxiliary is removed for reuse once the new chiral centre is built.

1.2.2.2. Chiral Auxiliaries

Chiral auxiliaries play an important role in asymmetric syntheses of optically active compounds. A chiral auxiliary is a chiral molecule that can be covalently attached to a prochiral substrate as a 'chiral handle' so that the subsequent reaction proceeds with high diastereoselectivity. After the diastereoselective reaction, the auxiliary should be removable and recoverable in good yield and without racemization so that they can be reused. This extra two steps in the synthesis, is the major drawback of this approach. The pioneering work of Professor David A. Evans in the field of chiral auxiliaries has revolutionized the art of organic synthesis.

Evans' chiral oxazolidinones are frequently found in total syntheses and due to their widespread use and ease of preparation, have become commercially available.

An example of the use of chiral auxiliary is given as Scheme 2.



Scheme 2. An Example for a Chiral Auxiliary in an Asymmetric Synthesis [25]

c) **Third-generation asymmetric synthesis.** When a stoichiometric chiral reagent effects asymmetric induction, the inducing chirality is not part of the substrate and so is not determined directly, in the planning process, by the structure of the target molecule. The use of a chiral reagent is referred as third-generation asymmetric synthesis or reagent-controlled diastereoselectivity.

1.2.2.3. Chiral Reagents

A chiral reagent is used in order to obtain an enantiomerically enriched product. Considerable effort and expense might be required in the preparation of the reagent, and the stoichiometric amounts are needed. The need for protection should be carefully considered as this could lead to the introduction of extra steps. The reagent must be selective both in terms of induction and functional group specificity.

d) **Fourth-generation asymmetric synthesis.** Catalytic modifications of second- and third-generation methods tend to be considered together as fourth-generation approach. The chiral auxiliary (and other catalyst components, e.g. a transition metal) can become covalently to the substrate in the catalytic cycle or might act in an intermolecular fashion, inducing asymmetry in a single step.

1.2.2.4. Chiral Catalysts

Chiral catalysts cause one enantiomer to be selectively converted or only one enantiomer to be formed. Only catalytic amount of chiral catalyst is needed to produce large amount of chiral product. Transition metal catalysts are generally used and they have the advantage that the catalyst properties can be carefully tuned by changing the ligands around the metal atom.

Practical asymmetric catalysis using transition metal complexes was inspired by the work of Kagan [26] and Knowless [27]. Their important results, based on the use of chiral phosphines as ligands for asymmetric hydrogenation, have induced a tremendous amount of work dealing with synthesis and use of new chiral phosphine –containing complexes as catalysts. Numerous catalytic reactions allowing the enantioselective formation of C-H, C-C, C-O, C-N, and other bonds have been discovered over the last 30 years, often with spectacular results in terms of efficiency and selectivity.

Here are some important chiral ligands which are use both in industrial processes and laboratory experiments. These chiral ligands in Figure 6 are chosen because they can be synthesized easily, cheaply and their effectiveness in the catalytic asymmetric reactions is very high.

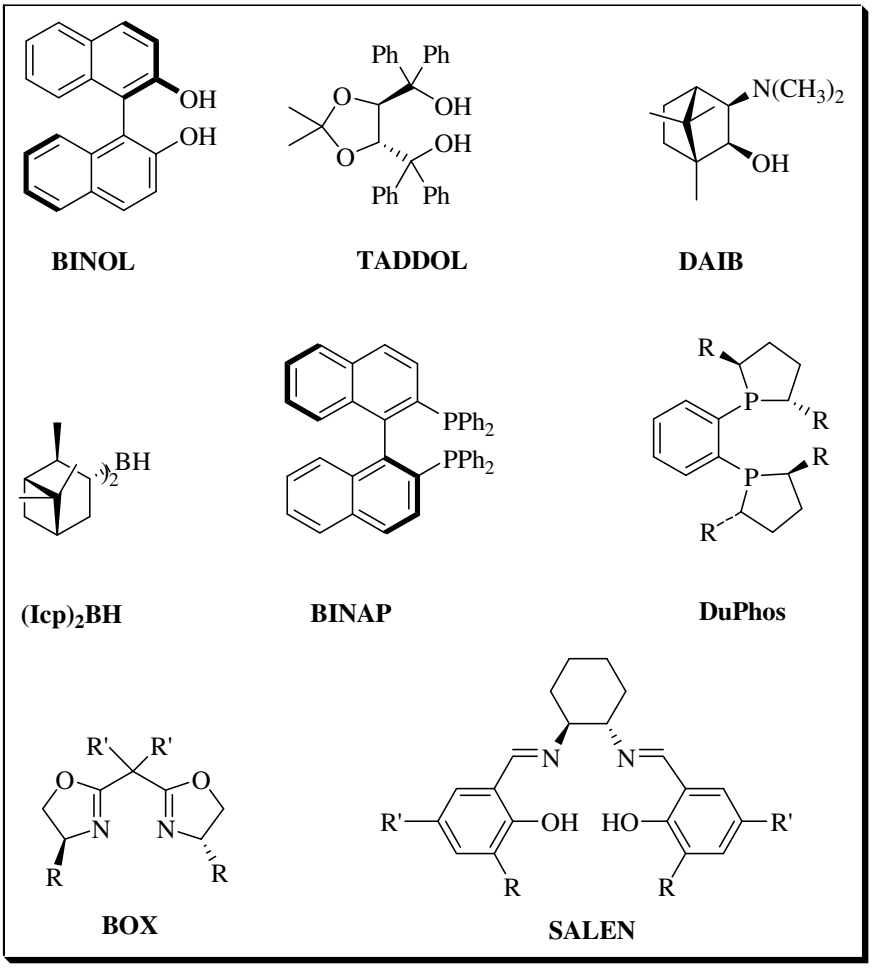


Figure 6. Some Important Chiral Ligands

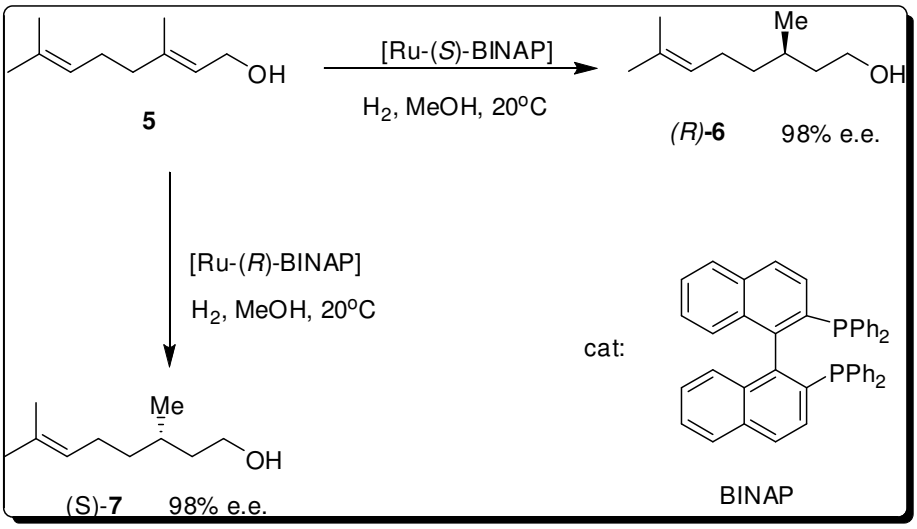
1.3. Asymmetric Transformation Reactions

1.3.1. Asymmetric Catalytic Hydrogenation

A great number of optically active compounds contain a hydrogen atom at the stereogenic centre. As this hydrogen atom can be introduced into appropriate unsaturated precursors by hydrogenation reactions, asymmetric hydrogenation is particular importance to access highly enantiomerically pure compounds [20].Enantioselective hydrogenation reactions catalyzed by optically active

transition metal catalysts appears as one of the efficient methods since a small amount of material can, in principle, produce a large amount of optically active product.

The landmark paper of Wilkinson et al. in 1966 [28] established the feasibility of homogeneous hydrogenation of alkenes with $RhCl(PPh_3)_3$ as the catalyst precursor. The mechanism for the Wilkinson catalytic systems was reasonably well-established, showing that two phosphines remain coordinated to rhodium. The most obvious approach was to introduce chiral ligands around rhodium. Horner et al. [29] and Knowles et al. [27], in 1968, independently selected monophosphine as the chiral auxiliary. One of the early and important achievements was the preparation, in 1975, of Dipamp at Monsanto by Knowles et al. [30]. This chiral diphosphine combines the good properties of a C_2-symmetric chelating system with the simultaneous presence of two asymmetric phosphorus. Asymmetric hydrogenation was boosted towards synthetic applications with the preparation of BINAP by Noyori et al. [31]. This diphosphine is a good ligand of rhodium, but it was some ruthenium/BINAP complexes which have found spectacular applications (from 1986 up to now) in asymmetric hydrogenation of many types of unsaturated substrates (C=C or C=O double bonds). Asymmetric hydrogenation has been applied since 1985 in Japan at the Takasago Company for the synthesis of (–)-menthol [32]. An example is given for asymmetric hydrogenation in Scheme 3.



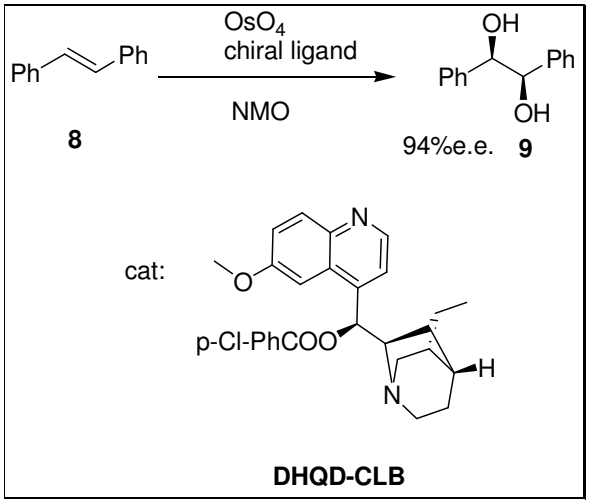
Scheme 3.Asymmetric Hydrogenation

1.3.2. Asymmetric Oxidation Reactions

Some of the most effective and commonly used techniques in asymmetric synthesis utilize oxidation reactions, especially epoxidation and (increasingly) dihydroxylation reactions. Both reactions are highly chemo-selective and can be carried out in the presence of many other functional groups [33].

As combinatorial chemistry gains momentum in the chemical community [34], osmium-catalyzed dihydroxylation of olefins retains its status as the most reliable method for the preparation of vicinal diols [35- 40].

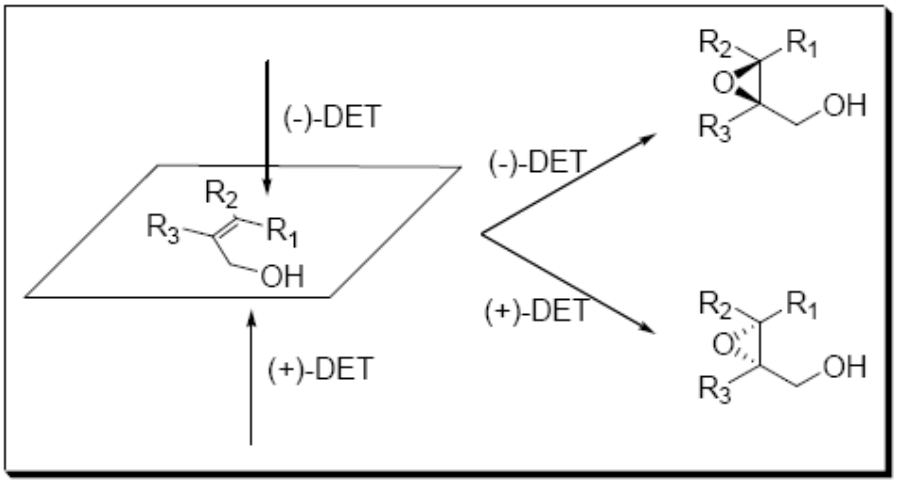
Asymmetric dihydroxylation of isolated C=C was achieved by Sharpless et al. [59] using OsO_4 in catalytic amounts in the presence of a chiral amine in an organic solvent and water, a tertiary amine *N*-oxide being the secondary oxidant. The chiral catalyst is *O*-protected dihydroquinine or dihydroquinidine, which binds to osmium by the quinuclidine nitrogen [41]. The ligands used by the Sharpless group were representatives of the cinchona alkaloid family, dihydroquinidine (DHQD) and dihydroquinine (DHQ).



Scheme 4. An Early Example of a Catalytic Dihydroxylation Reaction [41]

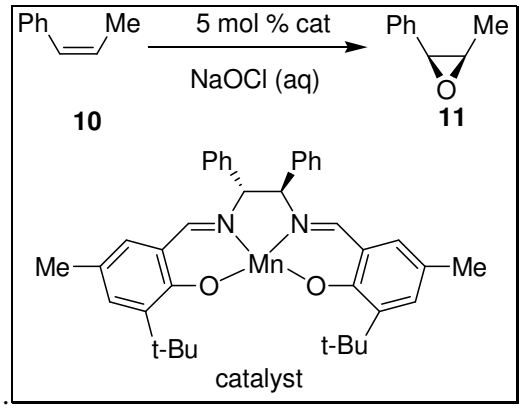
Since its introduction in 1980 [42], the Katsuki-Sharpless asymmetric epoxidation (AE) reaction of allylic alcohols has been one of the most popular methods in asymmetric synthesis [43-46].

In the 1980's, Sharpless *et al.* have discovered an enantioselective titanium-tartrate-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 [47].



Scheme 5. The Basic Mechanism for Sharpless Epoxidation

The most promising procedure so far was introduced by Jacobsen and coworkers in 1990 [48]. The method uses chiral, C_2-symmetric (salen) Mn complexes. These catalysts are related to metalloporhyrin-based epoxidation catalysts, and oxygen transfer to the alkene takes place from an oxomanganese intermediate. Most common oxidizing agents are iodosylbenzene or aqueous solutions of sodium hypochlorite, but direct utilization of molecular oxygen has also been reported [49]. Hydrogen peroxide can be used as the oxidant.



Scheme 6. An Example for the Asymmetric Epoxidation Reaction Catalysed by Jacobsen Catalyst

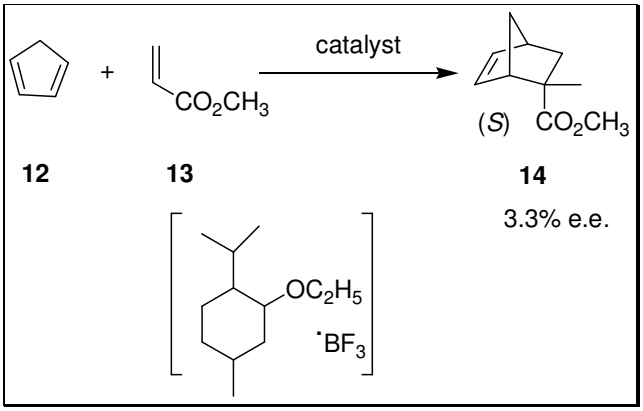
1.3.3. Asymmetric Diels-Alder Reactions

The catalytic asymmetric Diels–Alder reaction has been an area of considerable interest over the last two decades and a large number of metals, ligands and dienophiles have been studied [50-53]. The Diels-Alder reaction provides a highly efficient and rapid means of constructing functionalized six-membered ring systems often with complete control of the regio-, diastereo-, and enantioselectivity. In particular, The Diels–Alder reaction is one of the most versatile and powerful synthetic transformations in organic chemistry [54].

Diels-Alder reactions involving C=C is readily transformed into asymmetric processes generally by one of three methods: (i) attaching a chiral auxiliary to the dienophile; (ii) attaching a chiral auxiliary to the diene; (iii) using a chiral catalyst, usually a Lewis acid. Over the last few years, attachment of a chiral auxiliary remains the most common method for effecting asymmetric Diels-Alder reactions. However, the application of chiral, catalytic Lewis acids has enjoyed a surge in popularity with several excellent catalysts now readily available [20].

The asymmetric Diels- Alder reaction was first investigated more than 20 years ago by introducing a removable chiral auxiliary on the dienophile. A useful development became possible when it was found that Lewis acids (e.g. $AlCl_3$) catalyze the Diels-Alder reaction, allows to run it in very mild conditions, often below 0 ^oC [55].

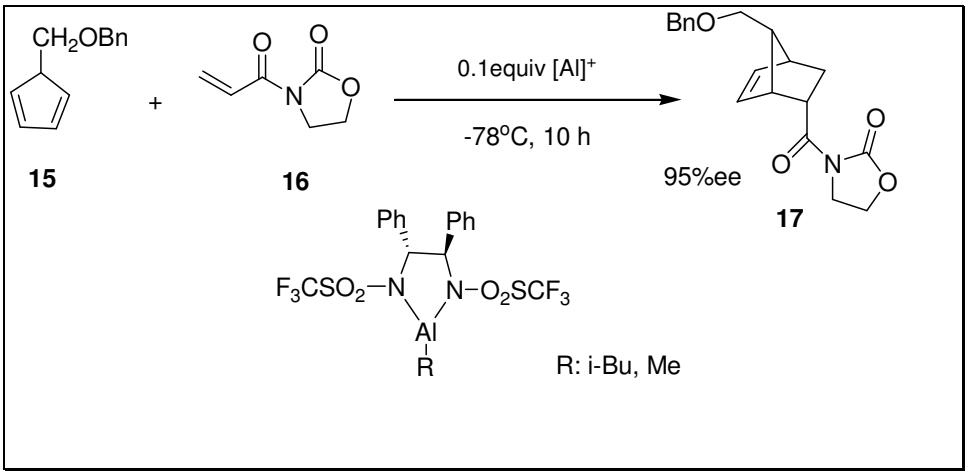
The first chiral Lewis acid was designed and applied in asymmetric Diels-Alder reaction by Idris Mecidoglu Akhmedov et.al. [56] in 1976. The enantioselectivity was poor (Scheme 7) but the seeds of success had been sown, and in the intervening years the number of examples of Diels-Alder reactions occurring with good to high levels of asymmetric induction has increased almost exponentially.



Scheme 7. An Early Example for the Asymmetric Diels-Alder Reaction

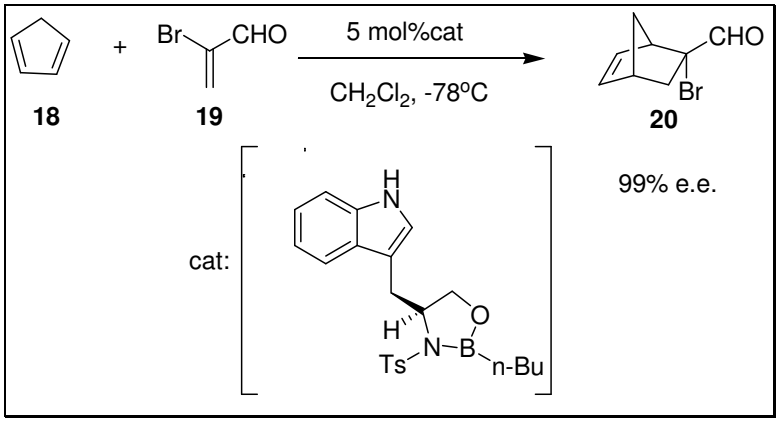
Then, Koga et a1. [57] in 1979 performed the cycloaddition of methacrolein on cyclopentadiene catalyzed by menthoxydichloroaluminum. Then, Corey et al. recently prepared chiral aluminum complexes derived from chiral bis-sulfonamides with C_2-symmetry [58]. The aluminum complex (0.1 mol equiv) acts as a catalyst for cycloaddition between 3-acryloyl-l,3-oxazolidin-2-one and cyclopentadienes.

One example is given in Scheme 8, giving an intermediate useful for production of optically active prostaglandins [59].



Scheme 8. An Example for Koga's Work

Another example of asymmetric Diels-Alder reaction is between 2-bromoacrolein and cyclopentadiene in the presence of oxazaborolidine catalyst [60] (Scheme 9).



Scheme 9. Asymmetric Diels-Alder Reaction with Bromoacrolein

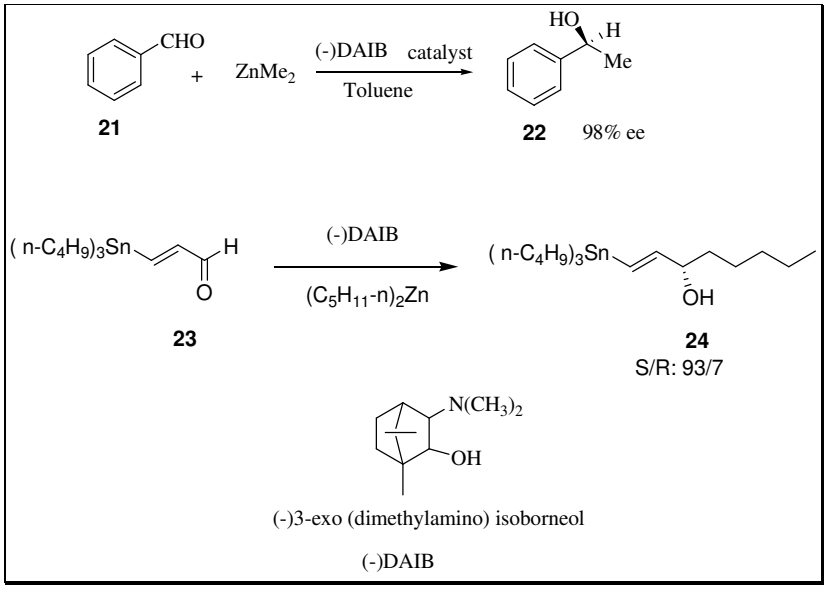
1.3.4. Asymmetric Dialkylzinc Additions to Aldehydes

Among asymmetric catalysis of C–C bond formation, the enantioselective addition of diorganozinc reagents to aldehydes in the presence of a catalytic amount of a chiral ligand is a convenient method for the preparation of optically active secondary alcohols [61]. Among the numerous chiral catalysts developed for asymmetric organozinc additions, β-amino alcohols hold a prominent position [62].

Particularly noteworthy is the finding by Oguni and Omi [63] in1984 that a small amount of *(S)*-leucinol catalyzes the reaction of diethylzinc to form *(R)*-1-phenyl-1-propanol in 49% e.e. This is a case where the ligand accelerates the catalytic reaction. Since the discovery by Oguni that various additives catalyze the addition of dialkylzinc reagents to aldehydes, there has been a rapid growth of research in this area. Most of these efforts have been directed toward the design of new chiral ligands, most of them being β-amino alcohols.

Treating benzaldehyde with diethylzinc in the presence of 2 mol % (-)–DAIB (-)-3-*exo*-dimethylaminoisobornenol) gives *(S)*-alcohol in 98% e.e.

When compound **23** is treated in the same manner, compound **24**, a chiral building block in the three component coupling prostaglandin synthesis, is also obtained with high e.e. (Scheme 10).



Scheme 10. Application of Dialkylzinc Addition Reaction

1.4. The Importance of Amino Alcohols

The development of new methods for the enantioselective synthesis of chiral amino alcohols is of great importance since these compounds have interesting biological activity and have enormous potential as chiral ligands in metal-mediated organic reactions.

In medicinal chemistry, β-amino alcohols have been shown to be effective therapeutic agents, and relationship of absolute configuration to pharmacological activity has been widely demonstrated [64].

These structures are found as components of more complex active substances or natural products [65]- for example, in the case of antibiotic chloroamphenicol (1), the coronary agent alifedrin (2), the aminopeptidase-B inhibitor bestatin, the blood pressure-reducing rennin inhibitor pepstatin(4), and its synthetic analogues, amino sugars and alkaloids (Figure 7) [66].

In addition to natural products, many amino alcohol derivatives have chemotherapeutic properties. In most cases, the stereogenic centers are derived either from a carbohydrate or an amino acid [67].

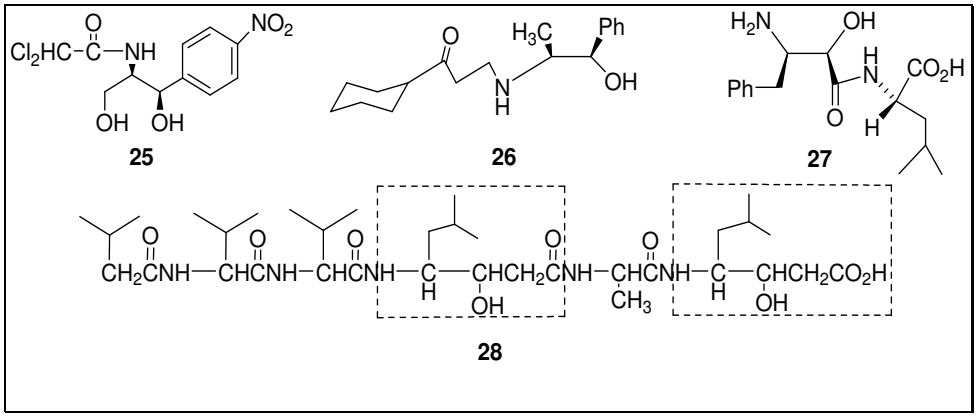


Figure 7. Pharmaceutically and Biologically Interesting Natural Compounds

In organic synthesis, many important transformations of prochiral substrates into chiral compounds can be achieved in very high enantiomeric excess by utilizing enantiomerically pure amino alcohol as chiral auxiliary. The 1,2-, 1,3-, 1,4-amino alcohols can be used as chiral ligands, both the acyclic and cyclic varieties, where the hetero atoms can be used to form a complex with a metal reaction center.

Chiral 1,2-amino alcohols are found in many biologically active compounds as important structural units. In addition they have been widely used in asymmetric reactions as chiral auxiliaries [68] and chiral sources [69-70].

1,2-Amino alcohols can either be prepared so that a chiral center is created in the reaction, or derived from a compound that already contains a stereogenic center. In the latter case, amino acids are natural compounds that are also readily available. The method of choice is often reduction of the parent amino acid [71].

While less abundant than the 1,2-amino alcohols, 1,3-amino alcohols have also contributed significantly to the advancement of asymmetric synthesis. 1,3-amino alcohols can be used as chiral ligands or auxiliaries, and there have also been applications as a resolving agent and as a phase transfer catalyst[72]. 1,3-amino alcohols derived from (+)-pulegone, [73, 74], camphor, (-)-fenchone [75] and (-)-menthone have successfully been applied as chiral catalysts, but their application is limited, as in most cases, only one of the enantiomers of the starting material is available commercially.

It is known that chiral 1,2-amino alcohols show high catalytic activity for this enantioselective alkylation; [76] however, only a few examples using chiral 1,4-amino alcohols have been reported [77]. These compounds can be more selective due to their flexibility and better complexation with metals [78].

Some examples of 1,2-, 1,3-, 1,4- amino alcohols are given in Figure 8

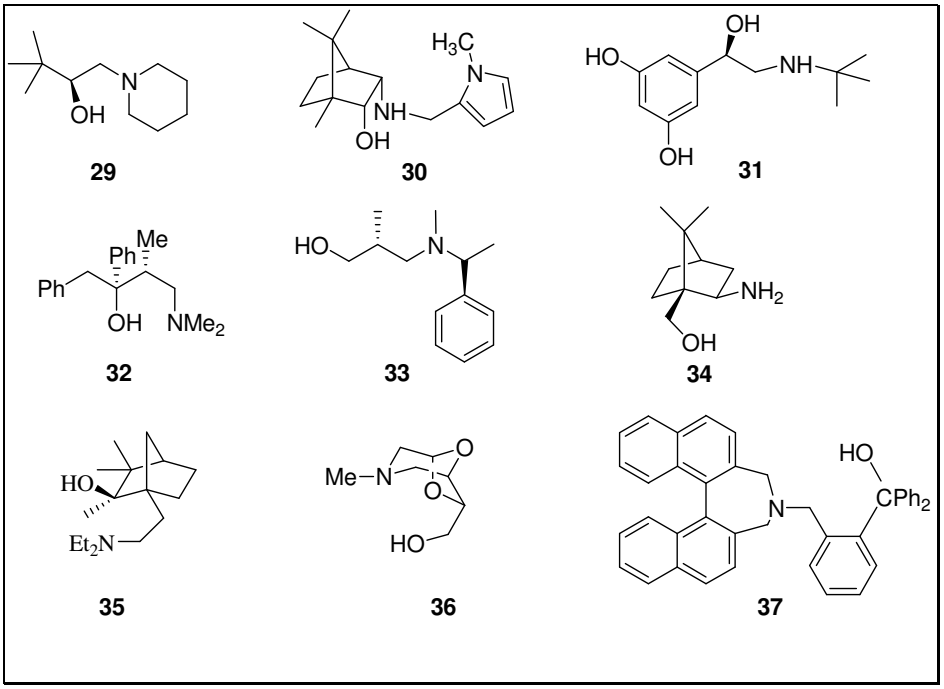
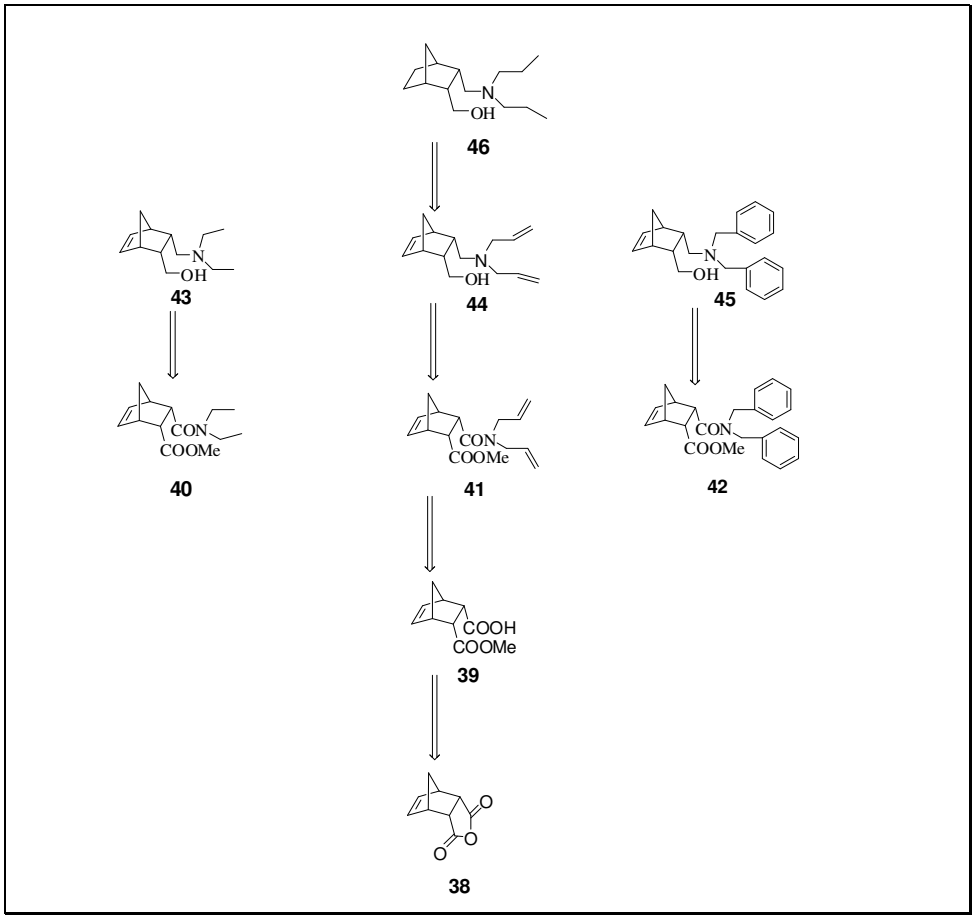


Figure 8. 1,2-, 1,3-, 1,4- Amino Alcohols

1.5. Aim of the Work

The aim of this work is to synthesize new chiral 1,4-amino alcohol ligands and test their effectiveness in various transformation reactions.

Retrosynthetic analysis of target chiral 1,4-amino alcohols are shown in Scheme 11.



Scheme 11. Retrosynthesis of the Work

CHAPTER 2

RESULTS & DISCUSSION

2.1. Perspective of the Work

During the past few decades there has been intensive research into developing methods for producing –synthesizing– one of the enantiomers rather than the other. Among the types of asymmetric reaction, the most desirable and the most challenging one is the catalytic asymmetric synthesis that only small amounts of chiral catalysts are needed to generate large quantities of chiral products just as enzymes do in biological systems. More recently, asymmetric synthesis has been developed on a practical scale, since some very efficient catalytic industrial processes are currently carried out to produce chiral building blocks. For organic synthesis, amino alcohols are versatile chiral building blocks and valuable as chiral ligands. The formation of C–C bonds has always been one of the most challenging goods in organic synthesis. Among current methods, the enantioselective addition of dialkylzinc compounds to aldehydes in the presence of chiral ligands has been widely explored since the first reports by Noyori and co-workers [61]. The chiral ligands employed for this purpose include mainly amino alcohols, with a few examples of amino thiols, amines, diols, disulfides and diselenides [80]. 1,2-Amino alcohols have mostly been used as chiral ligands in the addition of dialkylzinc to aldehydes, whereas there are only a few examples of 1,4-amino alcohols similarly employed [81-84].

The flexibility of 1,4-amino alcohols is higher than 1,2-amino alcohols, thus the complexation ability with various metals may be higher resulting more stable and more selective catalysts. In view of this, we decided to synthesize new chiral 1,4-amino alcohols including a norbornene backbone and their use in catalytic asymmetric transformation reactions.

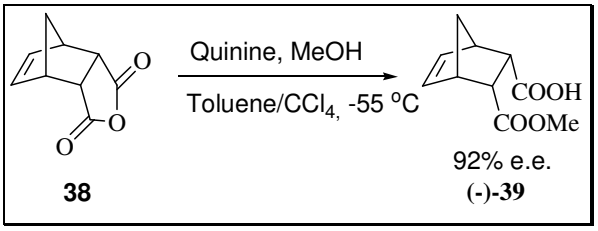
2.2. Asymmetric Synthesis of 1,4-Amino Alcohols

In order to synthesize novel 1,4-amino alcohols, norbornene *cis*-monoester *(2S,3R)*-**(-)-39** was chosen as the starting compound. This cis-monoester was synthesized by quinine-mediated desymmetrization of *meso*- anhydride **38.**

2.2.1.Desymmetrization of *Meso*-Anhydride, 38

A very efficient and practical process for desymmetrization of *meso*-anhydrides was reported by Bolm et.al. in 1999 and in subsequent publications [85]. In their approach, which is a further development and improvement in the use of alkaloids as catalysts, (-)-quinine or (+)-quinidine in this case, low reaction temperature and solvent optimization proved crucial to achieve optimum enantioselectivity. Under their conditions methanolysis of *meso*-anhydrides can be achieved in good yields and with excellent enantiomeric excesses in the presence of equimolar amounts of the inexpensive and readily available alkaloids.

In our case, quinine-mediated desymmetrization of anhydride **38** with methanol gave the *cis*-monoester **(-)-39** (Scheme 12).

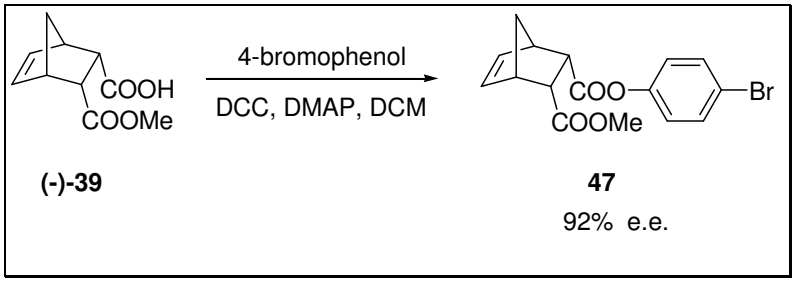


Scheme 12. Desymmetrization of compound **38**

In this desymmetrization reaction, attack of the one mole of nucleophile methanol occurs uniformly at one of the carbonyl group of the *meso*-anhydride. The reaction was carried out at -55^{o} C in a mixture of toluene and carbon tetrachloride. The product (-)-**39** was identified by using NMR spectroscopy. ^{1}H-NMR confirms the structure. According to the spectrum, the following peaks are observed: the olefinic protons gives two doublet of doublets at 6.26 (1H) and 6.16 (1H) ppm; one singlet at 3.54 (3H) ppm belonging to methoxy protons; two broad singlets appears at 3.14 (1H) and 3.11 (1H) ppm belonging to bridgehead protons; and two doublets of doublets at 3.28 (1H) and 3.22 (1H) ppm correspond to methine protons respectively; bridge protons give signals at 1.43 (1H) and 1.28 (1H) pm as two doublets (Figure 21). ^{13}C-NMR spectrum showed the following peaks; 177.8 ppm belonging to carbonyl carbon of carboxylic acid group, and 173.1 ppm belonging to carbonyl carbon of ester group; 135.6 ppm and 134.4 ppm belonged to double bond carbons; 51.6 ppm corresponds to methoxy methyl carbon; there are two methine carbons at 48.8 and 48.2 ppm for methoxycarbonyl and carboxylic acid attached ones, respectively; bridgehead carbons showed peaks at 47.9 and 46.6 ppm; and finally a peak at 46.1 ppm belonged to bridge carbon (Figure 22).

2.2.2. Enantiomeric Excess Determination of Hemiester, *(2S,3R)*-(-)-39

For determination of enantiomeric excess value of (-)-**39**, the cis-monoester was reacted with 4-bromophenol by DCC coupling method to give the corresponding diester **47** which is more UV active than hemiester. The compound was then analyzed by HPLC for enantiomeric excess determination. HPLC analysis of the methyl 4-bromophenyldiester was performed by using Chiralcel OD-H column (n-hexane / 2-propanol= 98:2, the flow rate was 0.5 mL/min, the wavelength was 254 nm,(t_1= 20.3 min (major), (t_2= 23.2 min (minor)



Scheme 13. Synthesis of compound **47**

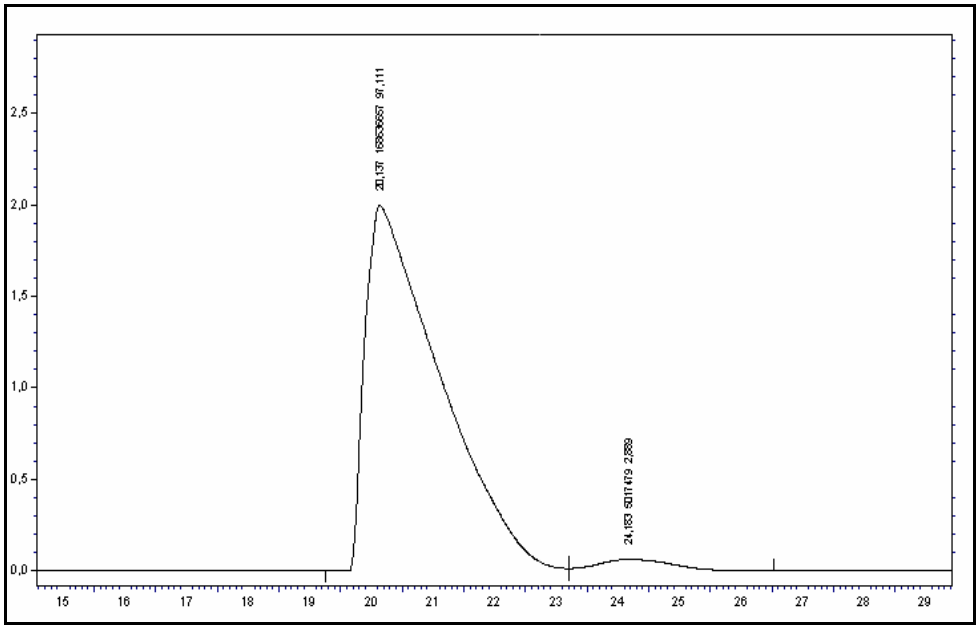


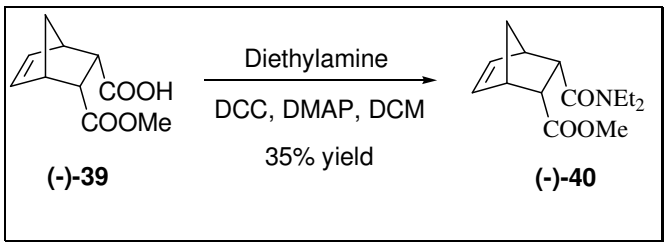
Figure 9. HPLC Chromatogram of compound **47**

The structure determination of the compound **47** was performed by NMR spectroscopy. Different from the ^{1}H-NMR and ^{13}C-NMR of the compound (-)-**39**, there are two doublets at 7.37 (2H) and 6.92 (2H) ppm belonging to aromatic hydrogens (Figure 23). In the ^{13}C-NMR spectrum, 150.3, 123.8, 119.0 and 132.7 ppm belonged to benzene ring carbons. The other characteristic signals remained almost the same like in compound **(-)-39** (Figure 24).

2.2.3. Synthesis of Amide-Ester, *(2S,3R)*-(-)-40

In the synthesis of target 1,4-amino alcohols, the first step was introduction of the amine moiety to the hemiester. In order to get the amide structure, the carboxylic acid group of the *cis*-monoester (-)-**39** was activated with DCC coupling method and then reacted by three different amines as diethylamine, diallylamine and dibenzylamine to afford corresponding *cis*-monoester amides.

The amide-ester, (-)-**40** was synthesized with 35% yield in the Scheme 13. Because of some isolation problems in flash column chromatography, the yield was low.



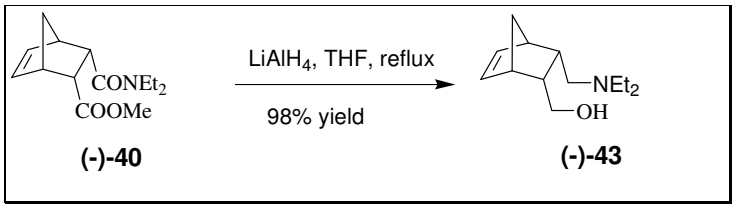
Scheme 14. Synthesis of Amide-Ester, (-)-**40**

The product was identified by using NMR spectroscopy. As the signals of the norbornene- backbone were given in details in the structure elucidation of *cis*-monoester *(2S,3R)*-(-)-**39**, there were no drastic changes in the signals in the norbornene-backbone of the compound (-)-**40**. The characteristic difference of compound (-)-**40** was arising from the amine moiety reacted with the carboxylic acid group of the *cis*-monoester (-)-**39**. There were additional signals in the ^{1}H-NMR spectroscopy and the new peaks were as follows: two methylene protons attached to the nitrogen atom gave multiplets at 3.46-3.37 (2H) and 3.23-3.19 (2H) ppm. As expected, two triplets at 1.21 (3H) and 1.06 (3H) ppm belonged to two methyl protons of the amide ester (Figure 25). In ^{13}C-NMR spectrum, carbonyl

carbon of the amide gave signal at 170.7 ppm which was shifted to the upper field comparing to carbonyl group of carboxylic acid, and carbonyl carbon of methyl ester gave signal at 173.0 ppm. Signals at 41.5 ppm and 40.1 ppm belonged to methylene groups attached to nitrogen; 14.5, 12.8 ppm for methyl groups of amide ester. The remainig carbons have similar signals like in ^{13}C-NMR spectrum of the hemiester (-)-**39** (Figure 26).

2.2.4. Reduction of Amide-Ester, *(2S,3R)*-(-)-40 with LAH

In the construction of target 1,4-amino alcohols, the reduction of amide ester function into amine moiety and methyl ester into alcohol moiety was carried out with LAH. Subsequent reduction of (-)-**40** by $LiAlH_4$ in THF afforded the N,N-diethyl substituted *cis*-1,4-amino alcohol type chiral ligand (-)-**43** with a high yield of 98% (Scheme 15).



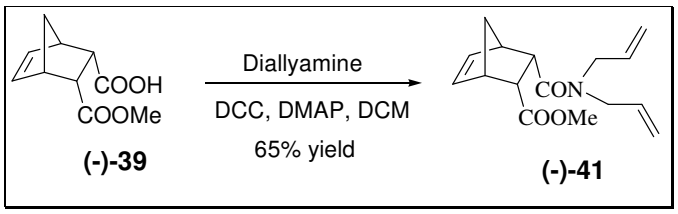
Scheme 15. Reduction of compound (-)-**40**

The structure identification of the compound **(-)-43** was done by ^{1}H-NMR and ^{13}C-NMR spectroscopy. In ^{1}H-NMR, it was seen that the characteristic signal belonging to the $-OCH_3$ protons in the amide ester disappeared and this was the key point when identifiying the proton NMR of the compound **(-)-43**. New methylene protons appeared by the reduction of carbonyl groups. Methylene protons attached to –OH group gave two different signals at 3.47 (1H) ppm as doublet and 3.19 (1H) ppm as triplet. Other methylene protons coming from the reduction of carbonyl carbon of amide and bridgehead protons overlapped and had

signals between 2.74-2.67 (4H) ppm as multiplet. In addition, different from the compound (-)-**40**, the olefinic protons gave singlet instead of doublet of doublet at 6.06 (2H) ppm. Protons belonging to methylene attached to nitrogen gave signals between 2.61-2.52 (2H) ppm and 2.44-2.35 (2H) ppm as multiplets similar to compound (-)-**40** but the difference was that protons shifted to the higher field with respect to corresponding amide ester (-)-**40**.Methine protons, H_2 and H_3 showed one doublet at 2.32 (2H) ppm which was also shifted to higher field. One triplet at 1.02 (6H) ppm belonged to methyl protons attached to methylene protons (Figure 27). From the ^{13}C-NMR spectrum, the disapperance of two carbonyl groups confirmed that the reduction was succeded. Instead of carbonyl carbons, two methylene carbons were observed in the spectrum at 39.4 and 35.0 ppm (Figure 28).

2.2.5. Synthesis of Amide-Ester, *(2S,3R)*-(-)-41

The synthesis of the compound (-)-**41** was performed by following the same route as the synthesis of amide ester (-)-**40**; first, DCC coupling method then reaction by the corresponding amine. In this case, diallyl amine was used (Scheme 16).



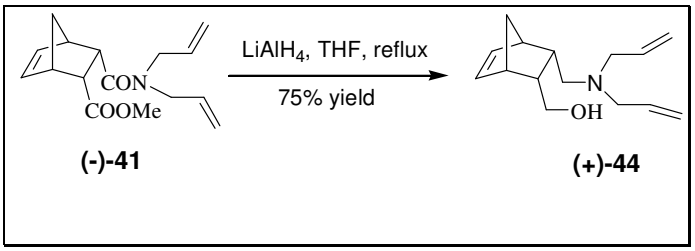
Scheme 16. Synthesis of Amide-Ester, (-)-**41**

The structure of amide-ester (-)-**41** was elucidated by ^{1}H-NMR and ^{13}C-NMR spectroscopy. Protons belonging to norbornene-backbone showed signals as given before. In ^{1}H-NMR, the new signals were as follows: methine protons gave

signals between 5.87-5.69 (2H) ppm as multiplet. New olefinic protons appeared in the olefinic region as triplet at 5.24 (2H) ppm and as doublet of doublet at 5.11 (2H) ppm. One of the signals belonging to methylene protons attached to the nitrogen appeared at 4.05 (1H) ppm as doublet of doublet and at 3.99 (1H) ppm as triplet separately. The other methylene proton gave signals at 3.88 (1H) ppm as doublet of triplet and at 3.78 (1H) ppm as doublet of doublet. As known, methoxy protons have a singlet at 3.56 (3H) ppm (Figure 29). From the ^{13}C-NMR spectroscopy, olefinic carbons rather than olefinic norbornene carbons can be seen at 133.5, 133.2, 117.0, and 116.5 ppm's. The carbonyl carbons apperaed at 172.8, and 171.9 ppm. Other carbons gave signals between 51.3-20.8 ppm (Figure 30)

2.2.6. Reduction of*(2S,3R)*-(-)-41, with LAH

The 1,4-amino alcohol (+)-**44** was obtained from amide-alcohol (-)-**41** by the reduction by LAH in THF (Scheme 17).



Scheme 17. Reduction of compound (-)-**41**

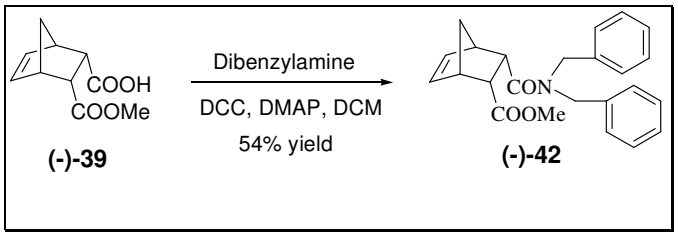
The structure elucidation of compound (+)-**44** was done by NMR spectroscopy. From the ^{1}H-NMR spectrum, it was understood that, the amide and methyl ester groups disappeared and converted to amino alcohol. Also, the reduction of the (-)-**41** can be confirmed by the disappearance of methoxy group. Methylene protons attached to nitrogen gave signals at 3.34 (1H) ppm as doublet and triplet at 3.17 (1H) ppm and other one had signals at 2.87 (2H) ppm as quartet.

As the reduction succeded, methylene groups replaced the carbonyl groups. The signals belonging to methylene protons next to –OH group observed at 3.48 (1H) ppm as doublet of doublet and doublet at 3.38 (1H) ppm. The signals between 2.63-2.56 (1H) ppm and 2.53-2.46 (1H) ppm correspond to methylene protons neighbouring to nitrogen as multiplet. While methylene protons next to oxygen appears in the lower field, other methylene protons neighboring to nitrogen gave signals in higher field. Methine protons of diallyl group gave signal between 5.89-5.79 (2H) ppm as multiplet and methylene protons showed one doublet at 5.19 (2H) ppm and one doublet at 5.16 (2H) ppm (Figure 31)

The ^{13}C-NMR spectroscopy showed that the carbonyl groups disappeared completely. Because of the symmetry, carbons belonging to diallyl group overlapped and gave three signals instead of six. 133.7 ppm corresponded to methine carbons, 118.8 ppm belonging to methylene carbons of diallyl group and 62.9 ppm for other methylene carbons. Olefinic carbons of norbornene gave signals at 135.4 and 134.4 ppm. Between 56.6 ppm and 39.3 ppm, the signals for other carbons can be seen (Figure 32).

2.2.7. Synthesis of Amide-Ester, *(2S,3R)*-(-)-**42**

The synthesis of compound (-)-**42** was achieved by activating the carboxylic acid group of the *cis*-monoester (-)-**39** by DCC coupling method and reacting with dibenzylamine as given before. The compound was obtained with a yield of 54% (Scheme 18).



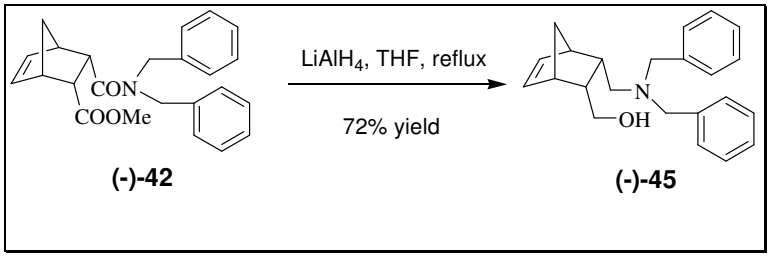
Scheme 18. Synthesis of Amide-Ester, (-)-**42**

For characterization of the compound (-)-**42**, NMR spectroscopy was used. According to the ^{1}H-NMR spectroscopy, the characteristic peaks belonging to norbornene-backbone gave similar signals as before. As new aromatic protons appeared in the spectrum these protons gave signals between 7.4-7.14 (10H) ppm as multiplet. Multiplet signals between 4.40-4.63 (4H) ppm corresponded to methylene protons attached to nitrogen. One of the bridgehead protons overlapped with the methoxy protons and gave signals at 3.54 (4H) ppm as singlet. Other bridgehead proton appeared as singlet at 3.01 (1H) ppm (Figure 33).

When the ^{13}C-NMR of the compound (-)-**42** was examined, it was seen that because of the symmetry the aromatic protons overlapped each other and gave signals between 135.3-126.4 ppm. 173.0 and 172.2 ppm belonging to two carbonyl carbons. Other carbons showed signals between 51.3 ppm and 45.9 ppm (Figure 34).

2.2.8. Reduction of *(2S,3R)*-(-)-42, with LAH

In this part, similar route was followed and 1,4-amino alcohol (-)-**45** was synthesized from (-)-**42** by $LiAlH_4$ reduction in THF with 72% yield (Scheme 19).



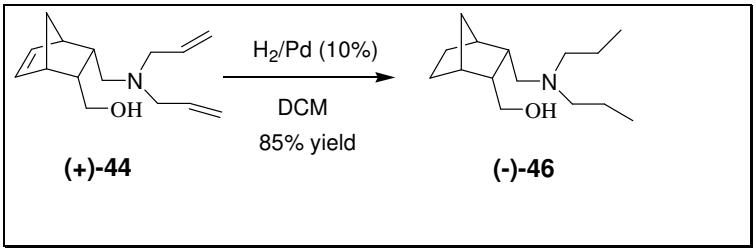
Scheme 19. Reduction of compound (-)-**42**

The identification of the reduction product was achieved by using ^{1}H-NMR and ^{13}C-NMR spectroscopy. In the ^{1}H-NMR of compound (-)-**45**, methoxy, -OCH_3, protons disappeared as expected. Aromatic protons gave signals between 7.34-7.24

(10H) ppm as multiplet. Signal at 6.52 (1H) ppm belonged to OH proton as broad singlet. One of the methylene protons attached to the nitrogen gave signals at 3.91 (1H) ppm and 3.87 (1H) ppm as singlet. 3.24 (1H) ppm and 3.21 (1H) ppm corresponding to remaining methylene protons attached to the nitrogen. Methylene protons obtained from the reduction of amide and methyl esters showed peaks different from each other. When protons attached to the –OH group gave signals as doublet at 3.39 (1H) ppm and triplet at 2.86 (1H) ppm in lower field, the methylene protons next to nitrogen had signals between 2.53-2.44 ppm as multiplet in higher field. Between these regions, one of the bridgehead protons also gave signal (Figure 35). In the ^{13}C-NMR, again the carbonyl carbons disappeared and carbons belonging to double bonds of the norbornene appeared at 136.9 and 135.4 ppm. The symmetry property arose in the aromatic carbons again and because of this, four aromatic carbons gave signals in the spectrum which were 134.3, 129.8, 128.4, and 127.4 ppm. Signal 62.7 ppm belonged to methylene carbon attached to–OH group and 58.5 ppm belonging to methylene carbon attached to nitrogen (Figure 36).

2.2.9. Hydrogenation of compound *(2S,3R)*-(+)-44

Compound (+)-**44** was hydrogenated in the presence of Pd/C. The reason for hydrogenation was that the double bonds of the diallyl substituted nitrogen may cause a problem during the asymmetric Diels-Alder reaction. Norbornane-backboned amino alcohol (-)-**46** was synthesized with a chemical yield of 85% (Scheme 20).

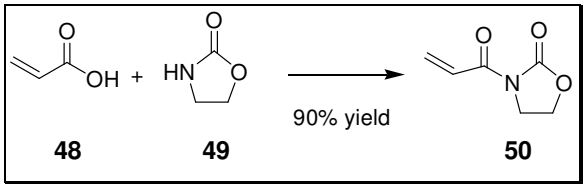


Scheme 20. Synthesis of compound (-)-**46**

The product was identified by the use of NMR spectroscopy. From the ^{1}H-NMR, following peaks were observed: one triplet at 3.76 (1H) ppm and one doublet of doublet at 3.43 (1H) belonging to methylene protons (H_8) attached to the –OH group; one triplet at 2.90 (1H) ppm and one singlet at 2.24 (1H) ppm corresponded to methylene protons neighboring to nitrogen; one multiplet at 2.60-2.52 (2H) ppm for one of the methylene protons attached to the nitrogen and one multiplet between 2.37-2.30 (2H) ppm for the other methylene proton; triplet at 0.88 (3H) ppm belonging to methyl protons. All other protons accumulated in the lower field at the range of 2.22-1.26 ppm as multiplet (Figure 37). The ^{13}C-NMR of the compound (-)-**46** showed that the double bonds in the compound (+)-**44** disappeared exactly. This confirmed that compound (+)-**44** was fully saturated. All of the carbons shifted to the higher field and gave signals between 61.5 ppm and 11.9 ppm (Figure 38).

2.3. Synthesis of 3-acryloyl-oxazolidin-2-one, 50

Compound **50** was synthesized by using acrylic acid and 2- oxazolidinone with 90% yield.This compound was used as dienophile in Diels-Alder reaction. The synthesis was shown in the Scheme 21.

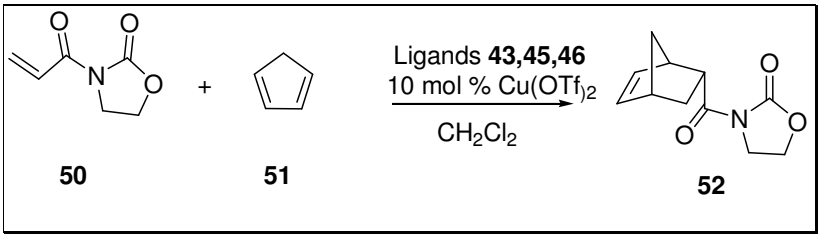


Scheme 21. Synthesis of **50**

The identification of the compound was done by ^{1}H-NMR and ^{13}C-NMR spectroscopy. The signals were identical with the literature. From ^{1}H-NMR, following peaks were obtained: one doublet of doublet at 7.43 (1H) ppm belonging to methine proton and one doublet of doublet at 6.47 (1H) ppm and one doublet of doublet at 5.82 (1H) ppm corresponding to the olefinic protons; one multiplet at 4.28-4.57 (2H) ppm for one of the methylene protons; one multiplet at 3.83-4.13 (2H) ppm for the other methylene protons (Figure 39). From the ^{13}C-NMR, 165.0 ppm and 153.4 ppm belonged to carbonyl carbon of amide; 131.7 ppm for olefinic carbon and 127.0 ppm belonging to methine carbon; 62.2 ppm and 42.6 ppm corresponded to methylene carbons (Figure 40).

2.4. Asymmetric Diels-Alder Reaction

The catalytic effectiveness of the new chiral 1,4-amino alcohols (-)-**43,** (-)-**45,** and (-)-**46** were tested first in asymmetric Diels-Alder reaction. Cyclopentadiene was reacted with 3-acryloyl-oxazolidin-2-one in the presence of chiral ligands to give optically active cycloadduct. (Scheme 22)



Scheme 22. Asymmetric Diels-Alder ReactionUsing (-)-**43,** (-)-**45,** (-)-**46**

The ligands were tested at various temperatures in DCM. The results were summarized in Table 1.

Table 1. Asymmetric Diels-Alder Reactions Using 1,4-Amino Alcohols

Entry	Ligand[a]	Temp. (°C)	Time (h)	Yield[b]	endo/exo	e.e[c] endo (%)
1	43	rt	6	100	95:5	7
2	45	rt	6	100	96:4	6
3	43	0	12	85	90:10	3
4	45	0	12	81	95:5	5
5	43	-30	24	60	95:5	12[d]
6	43	-30	24	56	93:7	6
7	45	-30	24	53	93:7	8
8	46	-30	24	52	95:5	4
9	43	-50	48	35	95:5	8
10	45	-50	48	30	95:5	4
11	46	-50	48	35	95:5	8

[a] 11% chiral ligands were used

[b]Yields were calculated after column chromatography

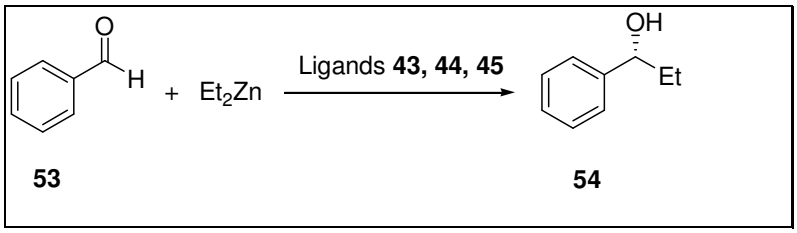
[c] Enantiomeric excess values were determined by HPLC analysis using chiral column.

[d] $In(TOf)_2$ was used.

According to the results, all the ligands exhibited low enantiomeric excess values. The reason why the e.e. values are so low is that the ligands may not form good complex with $Cu(OTf)_2$. Moreover, in one case in entry 5, $In(OTf)_2$ was used as metal complex for ligand (-)-**43** and the best enantioselectivity which was also low (12%) was obtained. The reactions were carried out at different temperatures varied between room temperature to -50˚C. However, no improvement in the enantiomeric excess values was observed. In addition, as we expected, the yields were decreased by decreasing the temperature. The reaction was selective to endo product and the endo/exo ratios were changing 90:10 to 95:5.

2.5. Enantioselective Diethylzinc Addition Reaction

The effectiveness of chiral ligands (-)-**43,** (+)-**44,** and (-)-**45** was then examined in enantioselective diethylzinc addition to benzaldehyde reaction. This addition reaction was carried out in the presence of diethylzinc, benzaldehyde and chiral ligand as given in Scheme 22.



Scheme 23. Enantioselective Diethylzinc Addition Reaction

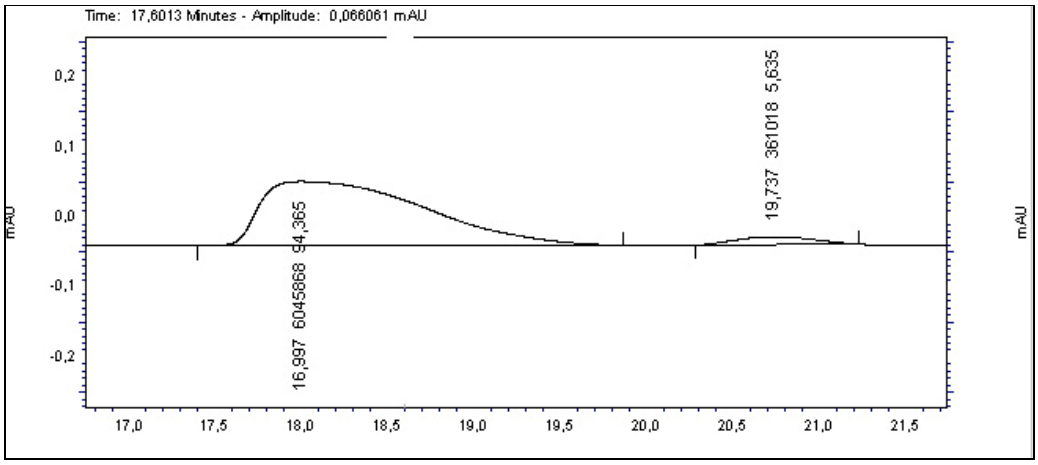


Figure.10. HPLC Chromatogram of Compound **54** Using Ligand (-)-**43**

The enantiomeric excess values of the ligands were given in Table 2.

Table 2. Applications of the Chiral Ligands in Diethylzinc Addition Reaction

Entry	Ligand (10%)	Solvent	Temp. (^{o}C)	Time(h)	e.e.	Config.
1	43	Hexane	rt	48	70	R
2	43	Toluene	0	60	**89**	R
3	43	Hexane	0	60	60	R
4	45	Toluene	0	72	58	R
5	44	Toluene	0	60	72	R

In contrast to Diels-Alder reaction, all chiral ligands gave much better enantiomeric excess values in Et_2Zn addition reaction. The best result was obtained with amino alcohol (-)-**43** which has diethyl substituents on nitrogen atom. The e.e. value was obtained as 89%. Diallyl and dibenzyl substituted chiral amino alcohols also gave acceptable enantioselectivities. When the effectiveness of ligand (-)-**43** was tested in hexane, the enantioselectivity decreased from 89 % to 60%. Since, the ligand (-)-**43** gave much homogenous mixture in toluene than hexane.

Thus, in entry 2 and 3, the effect of solvent was observed. Furthermore, ligand (-)-**43** was also examined at room temperature in hexane and when the entries 1 and 3 were compared, it was seen that the enantiomeric excess value was better at room temperature. Also, ligands (+)-**44** and (-)-**45** were tested in toluene at 0^{o}C and the best result was observed for ligand (+)-**44**. The reason for that dibenzyl substituted chiral amino alcohol may not well coordinate with diethylzinc. Additionally all chiral ligands were *(R)* configurated.

CHAPTER 3

EXPERIMENTAL

The compounds in this study were identified by the instruments mentioned below.

Proton and carbon-13 nuclear magnetic resonance spectra (^{1}H-NMR / ^{13}C-NMR) were recorded on Brucker Spectrospin Avance DPX 400 spectrometer in $CDCl_3$. Chemical shifts are given in parts per million (ppm) downfield from tetramethyl silane as the internal standard. Spin multiplicities are mentioned as: s (singlet), d (doublet), dd (doublet of doublet), t (triplet), m (multiplet).

HPLC measurements were carried out with ThermoFinnigan Spectra System instrument. Separations were performed on Chiralcel OD-H analytical column (250 x 4.60 mm) with hexane/2-propanol as eluent. The conditions are specified in each case.

Optical rotations were measured in a 1 dm cell using a Rudolph Research Analytical Autopol III automatic polarimeter at 20 ^{o}C or 25 ^{o}C.

Column chromatography was performed on silica gel (60-mesh, Merck). TLC was carried out on Merck 0.2-mm silica gel 60 F254 analytical aluminum plates. The relative proportion of solvents are in volume:volume ratio used in column chromatography as eluent.

Solvents were either in technical or high grade and when necessary they were dried with appropriate drying agents and purified by distillation. THF was distilled over benzophenone and metallic sodium, whereas DCM was distilled over phosphorus pentoxide.

3.1. Synthesis of *(2S,3R)*-2-methoxycarbonyl-bicyclo[2.2.1] hept-5-ene-3-carboxylic acid, 39

MeOH (0.63 mL, 15.6 mmol) was added dropwise to a stirred solution of the *meso*-anhydride **51** (0.85 g, 5.20 mmol) and quinine (1.85 g, 5,72 mmol) in a 1:1 mixture of toluene (60 mL) and carbon tetrachloride (60 mL) at -55 ^{o}C under argon. The reaction mixture was stirred at this temperature for 60 h. Subsequently, the resulting clear solution was concentrated in vacuo to dryness and the resulting residue was dissolved in ethyl acetate. The ethyl acetate solution was washed with 2 N HCl, and after phase separation, followed by extraction of aqueous phase with ethylacetate, the organic layer was dried over $MgSO_4$, filtered, and concentrated providing the monoester **52** (0.94 g, 92 %).

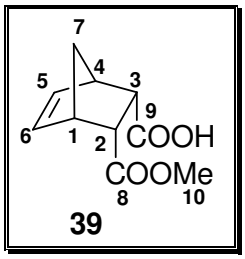


Figure 11.

$[\alpha]_D^{20}$ = -7.8 (*c* 4.0, CCl_4), [.86-87]
m.p. 75–78 °C, [.86-87] 74 °C (racemic)

^{1}H-NMR (400MHz,$CDCl_3$): δ ppm 6.26 (dd, *J*= 2.96, 5.50 Hz, 1H, H_5),
6.16 (dd, *J*= 2.94, 5.53 Hz, 1H, H_6),
3.54 (s, 3H, H_{10}),
3.28 (dd, *J*= 3.22, 10.14 Hz, 1H H_2),
3.22 (dd, *J*= 3.13, 10.15 Hz, 1H, H_3),
3.14(bs, 1H, H_1),

3.11 (bs, 1H, H_4),

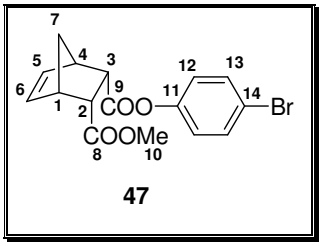
1.43 (dt, J= 1.56, 8.67Hz, 1H, H_7),

1.28 (d, J= 8.69 Hz, 1H, H_7);

^{13}C-NMR (100MHz, $CDCl_3$): δ ppm 177.8, 173.1, 135.6, 134.4, 51.6, 48.8, 48.2, 47.9, 46.6, 46.1.

3.2. Synthesis of *(2S,3R)*-3-(4-bromophenoxy)-2- methoxycarbonyl-bicyclo [2.2.1]hept-5-ene, 47

4-Bromophenol (0.088 g, 0.51 mmol) and monoester **39** (0.100 g, 0.51 mmol) were dissolved in CH_2Cl_2 (5 mL) at 0 ^oC under argon. Then, DCC (0.105 g, 0.51 mmol) and DMAP (0.016 g, 0.13 mmol) were added simultaneously at 0 ^oC. The mixture was mixed overnight at room temperature. DCC precipitated as dicyclohexylurea. The mixture was filtered and the filtrate was washed with first 5% HOAc, then 1 N NaOH and finally brine. The organic phase was dried over $MgSO_4$ and evaporation of the solvent afforded the compound **47** (0.16 g, 89%). HPLC analysis of the methyl 4-bromophenyl diester: Chiralcel OD-H at room temperature, *n*-hexane/2-propanol) = 98:2, 0.5 mL/min, 254 nm, t_1= 20.3 min (major), t_2= 23.2 min (minor)



47

Figure 12

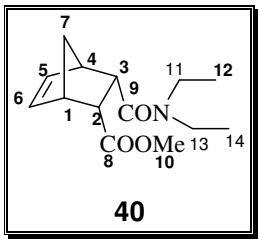
^{1}H-NMR (400MHz, $CDCl_3$): δ ppm 7.37 (d, *J*= 8.72 Hz, 2H, H_{12}),
6.92 (d, *J*= 8.71 Hz, 2H, H_{13}),
6.32 (dd, *J*= 2.91, 5.39 Hz, 1H, H_5),
6.15 (dd, *J*= 2.92, 5.41 Hz, 1H, H_6),
3.55(s, 3H, H_{10}),
3.39 (s, 2H, H_2, H_3),
3.20 (s, 1H, H_1),
3.17 (s, 1H, H_4),
1.40 (d, *J*= 8.70 Hz, 1H, H_7),
1.33 (d, *J*= 8.61, 1H, H_7);

^{13}C-NMR (100MHz, $CDCl_3$): δ ppm 173.0, 171.2, 150.3, 135.9, 135.0, 132.7, 123.8, 119.0, 52.2, 49.1, 48.7, 48.5, 47.2, 46.6.

3.3. General DCC coupling method to synthesize amide esters

Hemiester (-)-**39** (1 eq.) and amine (1 eq.) were dissolved in CH_2Cl_2 at 0 ^{o}C under argon atmosphere. Then, DCC (1,1 eq.) and DMAP (0,25 eq) were added simultaneously at this temperature. The mixture was slowly brought to room temperature and stirred overnight at room temperature. DCC precipitated as dicyclohexylurea. The mixture was filtered and filtrate was washed with first with 1 N HCl then 1 N $NaHCO_3$ and finally brine. The organic phase was dried over $MgSO_4$ and evaporation of the solvent afforded the desired amide ester product.

3.4 Synthesis of *(2S,3R)*-3-(N,N-diethylcarboxamido)-2-(methoxycarbonyl)-bicyclo[2.2.1]hept-5-ene, 40



40

Figure 13

Yield: 35%

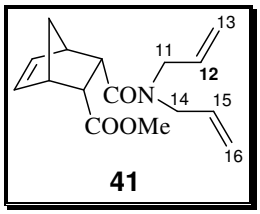
$[\alpha]_D^{20}$ = -32.4 (*c* 3.0, $CHCl_3$)

mp : 65 -68°C

^{1}H-NMR (400MHz, $CDCl_3$): δ ppm 6.30 (dd, *J*= 3.03, 5.34 Hz, 2H, H_5, H_6),
3.56 (s, 3H, H_{10}),
3.46-3.37 (m, 2H, H_{11}),
3.23-3.19 (m, 2H, H_{13}),
3.12 (d, *J*= 3.43 Hz, 1H, H_2),
3.10 (bs, 1H, H_1),
2.98 (bs, 1H, H_4),
1.45 (d, *J*= 8.43 Hz, 1H, H_7),
1.33 (d, *J*= 8.40 Hz, 1H, H_7),
1.21 (t, *J*= 7.12 Hz, 3H, H_{12})
1.06 (t, *J*= 7.07 Hz, 3H, H_{14});

^{13}C-NMR (100MHz, $CDCl_3$): δ ppm 173.0, 170.7, 135.2, 134.1, 51.2, 49.3, 48.6, 47.1, 46.3, 46.2, 41.5, 40.1, 14.5, 12.8.

3.5. Synthesis of *(2S,3R)*-3-(N,N-diallylcarboxamido)-2-(methoxycarbonyl)-bicyclo[2.2.1]hept-5-ene, 41



41

Figure 14

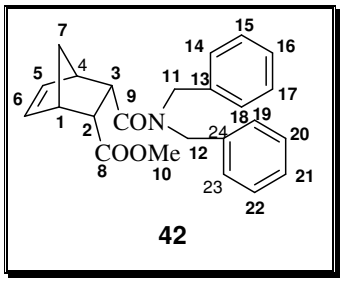
Yield: 65%

$[\alpha]_D^{20}$ = -43.9 (*c* 2.03, $CHCl_3$)

^{1}H-NMR (400MHz, $CDCl_3$): δ ppm 6.27 (dd, *J*= 3.95, 14.8 Hz, 2H, H_5, H_6),
5.87-5.69 (m, 2H, H_{12}, H_{15}),
5.24 (t, *J*= 4.45 Hz, 2H, H_{13}),
5.11 (dd, *J*= 2.98, 14.8, 2H, H_{16}),
4.05 (dd, *J*= 5.08, 15.0 Hz, 1H, H_{11}),
3.99 (t, *J*=1.85 Hz, 1H, H_{11}),
3.88 (dt, *J*= 2.14, 17.5 Hz, 1H, H_{14}),
3.78 (dd, *J*= 6.47, 15.0 Hz, 1H, H_{14}),
3.56 (s, 3H, H_{10}),
3.40 (dd, *J*= 3.18, 9.99 Hz, 1H, H_2),
3.22 (dd, *J*= 3.29, 9.97 Hz, 1H, H_3),
3.16 (s, 1H, H_1)
3.05 (s, 1H, H_4);
1.43 (d, *J*= 8.43 Hz, 1H, H_7)
1.32 (d, *J*= 8.46 Hz, 1H, H_7)

^{13}C-NMR (100MHz, $CDCl_3$): δ ppm 172.8, 171.9, 134.9, 134.3, 133.5, 133.2, 117.0, 116.5, 51.3, 49.3, 48.8, 48.6, 48.1, 47.1, 46.1, 20.8.

3.6. Synthesis of *(2S,3R)*-3-(N,N-dibenzylcarboxamido)-2-(methoxycarbonyl)-bicyclo[2.2.1]hept-5-ene, 42



42

Figure 15

Yield: 54%

$[\alpha]_D^{20}$ = -34.9 (c 2.03 $CHCl_3$)

m.p. 77-80°C

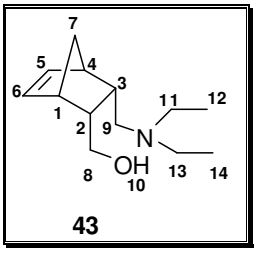
^{1}H-NMR (400MHz, $CDCl_3$): δ ppm 7.4-7.14 (m, 10H, H_{14}-H_{23}),
6.38 (dd, *J*=5.18, 3.21 Hz, 1H, H_5),
6.23 (dd, *J*=5.25,2.99 Hz, 1H, H_6),
4.40-4.63 (m, 4H, H_{11}, H_{12}),
3.54 (s, 4H, H_{10}, H_4),
3.17 (s ,2H H_2, H_3),
3.01 (s,1H, H_1),
1.43 (d,*J*=13.69 Hz, 1H, H_7),
1.25 (d, *J*=8.34 Hz, 1H, H_7);

^{13}C-NMR (100MHz, $CDCl_3$): δ ppm 173.0, 172.2, 137.6, 136.7, 135.3, 134.0, 129.0, 128.7, 128.4, 127.6, 127.3, 126.4, 51.3, 49.7, 49.4, 48.7, 48.4, 47.3, 46.2, 45.9.

3.7. General procedure for the reduction of amide ester by Lithium Aluminum Hydride (LAH).

To a suspension of $LiAlH_4$ in dry THF (5 eq), amide ester (1 eq) was added dropwise in anhydrous THF at a rate which maintained gentle reflux. The mixture was then refluxed until the starting compound is disappeared on TLC and hydrolyzed by the cautious addition of 1 mL distilled water at 0°C. The fine white precipitate which formed was washed with THF and discarded. Evaporation of solvent afforded to desired product.

3.8. Synthesis of *(2S,3R)*-3-(*N*,*N*-diethylaminomethyl)-2-(hydroxymethyl)-bicyclo[2.2.1]hept-5-ene, 43



43

Figure 16

Yield: 95%

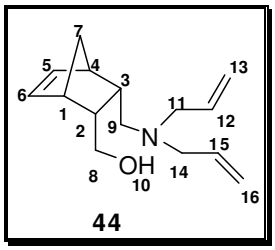
$[\alpha]_D^{20}$ = -6.4 (*c* 1.80, $CHCl_3$)

^{1}H-NMR (400MHz, $CDCl_3$):δ ppm 6.06 (s, 2H, H_5,H_6),
3.47 (d, *J*=11.30 Hz, 1H, H_8),
3.19 (t, *J*=11.25 Hz, 1H, H_8),

2.74-2.67 (m, 4H, H_9, H_9, H_1, H_4),
2.61-2.52 (m, 2H, H_{11}),
2.44-2.35 (m,2H, H_{13}),
2.32 (d, *J*=7.50 Hz, 2H, H_2, H_3),
1.40 (s, 2H, H_7),
1.02 (t, *J*=7.14Hz, 6H, H_{12}, H_{14});

^{13}C-NMR (100MHz, $CDCl_3$): δ ppm 135.1, 134.0, 62.8, 54.2, 50.0, 47.7, 47.0, 46.4, 46.3, 39.4, 35.0, 25.6, 25.0, 10.4.

3.9. Synthesis of *(2S,3R)*-3-(*N*,*N*-diallylaminomethyl)-2-(hydroxymethyl)-bicyclo[2.2.1]hept-5-ene, 44



44

Figure 17

Yield: 75%
$[\alpha]_D^{20}$ = 15.7 (*c* 1.0, $CHCl_3$)

^{1}H-NMR (400MHz, $CDCl_3$): δ ppm 6.04 (dd, *J*= 2.65, 5.52 Hz, 2H, H_5, H_6),
5.89-5.79 (m, 2H, H_{12}, H_{15}),
5.19 (d, *J*=8.18 Hz, 2H, H_{13}),
5.16 (d, *J*= 8.18 Hz, 2H, H_{16}),
3.48 (dd, *J*= 2.95, 11.65 Hz, 1H, H_8),
3.38 (d, *J*= 5.47 Hz, 1H, H_8),

3.34 (d, *J*= 5.46 Hz, 1H, H_{11}),

3.17 (t, *J*= 11.40 Hz, 1H, H_{11}),

2.87 (q, *J*= 8.03 Hz, 2H, H_{14}),

2.75 (bs, 1H, H_1),

2.69 (bs, 1H, H_4),

2.63-2.56 (m, 1H, H_9),

2.53-2.46 (m, 1H, H_9),

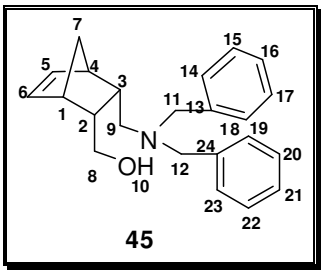
2.40 (t, *J*= 12.6 Hz, 1H, H_2),

2.29 (dd, *J*= 2.94, 12.78 Hz, 1H, H_3),

1.40 (dd, *J*= 1.58, 8.32 Hz, 2H, H_7);

^{13}C-NMR (100MHz, $CDCl_3$): δ ppm 135.4, 134.4, 133.7, 118.8, 62.9, 56.6, 54.4, 50.0, 47.7, 47.0, 46.3, 39.3.

3.10. Synthesis of *(2S,3R)*-3-(*N*,*N*-dibenzylaminomethyl)-2-(hydroxymethyl)-bicyclo[2.2.1]hept-5-ene, 45



45

Figure 18

Yield: 72%

$[\alpha]_D^{20}$ = -33.0 (c 2.00 $CHCl_3$)

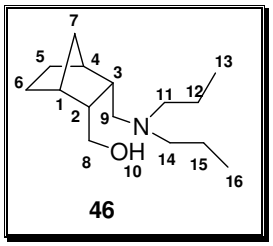
m.p. 92°C

^{1}H-NMR (400MHz, $CDCl_3$): δ ppm 7.34-7.24 (m, 10H, H_{14}-H_{23}),
6.52 (bs,1H, H_{10}),
6.02 (dd, *J*= 7.00, 9.94 Hz, 2H, H_5, H_6),
3.91 (s,1H, H_{11}),
3.87 (s, 1H, H_{11}),
3.39 (d, *J*=11.58 Hz,1H, H_8),
3.24 (s,1H, H_{12}),
3.21(s,1H, H_{12}),
2.86 (t, *J*=11.42 Hz,1H, H_8),
2.71 (s, 1H, H_1),
2.53 -2.44 (m, 3H, H_4, H_9, H_9),
2.24 (dd, *J*= 2.84, 13.1 Hz, 2H, H_2, H_3),
1.36 (s, 2H, H_7);

^{13}C-NMR(100MHz, $CDCl_3$): δ ppm 136.9, 135.4, 134.3, 129.8, 128.4, 127.4, 62.7, 58.5, 55.6, 49.9, 47.9, 46.9, 46.4, 39.3.

3.11. Synthesis of *(2S,3R)*-3-(*N*,*N*-propylaminomethyl)-2-(hydroxymethyl) bicyclo[2.2.1]heptane, 46

To a solution of **45** in CH_2Cl_2, 10% Pd/C (w/w) was added to the mixture at room temperature. The reaction mixture was stirred under H_2 atmosphere until the starting compound is disappeared on TLC. Then, the solution was filtered over celite and the solvent was evaporated to obtain the desired compound **46**.



46

Figure 19

Yield: 87%

$[\alpha]_D^{20}$ = -37.4 (*c* 2.02, $CHCl_3$)

^{1}H-NMR (400MHz, $CDCl_3$): δ ppm 3.76 (t, *J*= 11.14 Hz, 1H, H_8),
3.43 (dd, *J*= 2.77, 11.63 Hz, 1H, H_8),
2.90 (t, *J*= 12.99 Hz, 1H, H_9),
2.60-2.52 (m, 2H, H_{11}),
2.37-2.30 (m, 2H, H_{14}),
2.24 (s, 1H, H_9),
2.22-2.16 (m, 4H, H_2, H_3, H_7, H_7),
1.61-1.26 (m, 10H, H_1, H_4, H_5, H_6, H_{12}, H_{15}),
0.88 (t, *J*= 7.38 Hz, 6H, H_{13}, H_{16});

^{13}C-NMR (100MHz, $CDCl_3$): δ ppm 61.5, 56.1, 53.8, 44.1, 42.2, 41.2, 40.3, 37.5, 22.8, 22.5, 19.0, 11.9.

3.12. Synthesis of 3-acryloyl-oxazolidin-2-one, 50

To a solution of freshly distilled acrylic acid (1.03 gr, 14.4 mmol) in EtOAc at 0˚C was added first triethylamine (2.1 mL, 14.4 mmol), followed by acroyl chloride (1.29 g, 14.4 mmol) via syringe over a period of about 2 min. An immediate white precipitate formed. The reaction was stirred at 0˚C for 40 min, then at room temperature for 30 min. The reaction was then filtered through paper, and the filter cake was washed with EtOAc. The resultant cloudy solution was concentrated in vacuo. The residue was taken up in hexane and swirled, then filtered and concentrated in vacuo again. The anhydride was dissolved in THF andimmediately used in the following step.

To a suspension of 2-oxazolidinone (1 g, 11.5 mmol) and LiCl (0.608 g, 14.4 mmol) in THF was added triethylamine (2.1 mL, 14.4 mmol) via syringe, followed by the anhydride solution, followed by a 20 mL wash. The resulting slurry was

stirred at room temperature for 4 h. The solvent was removed in vacuo. 1N HCl solution was added and extracted 3x with CH_2Cl_2. The combined CH_2Cl_2 layers were washed with 1:1 sat.aq. $NaHCO_3/H_2O$ then brine, then dried over $MgSO_4$, filtered and concentrated in vacuo. The resulting compound was purified with flash column chromatography.(30%EtOAc/ hexane)

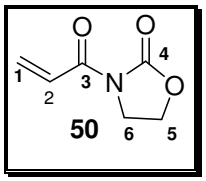


Figure 20

^{1}H-NMR (400MHz, $CDCl_3$): δ ppm 7.43 (dd, *J*=10, 16.8 Hz, 1H, H_2),
6.47 (dd, *J*=2, 16.8 Hz, 1H, H_1),
5.82(dd, *J*=2.10 Hz, 1H, H_1),
4.28-4.57 (m,2H, H_5),
3.83-4.13 (m, 2H, H_6);

^{13}C-NMR (100MHz, $CDCl_3$): δ ppm 165.0, 153.4, 131.7, 127.0, 62.2, 42.6.

3.13 General Procedure for Catalytic asymmetric Diels-Alder Reaction;

A mixture of $Cu(OTf)_2$ (0.025 mmol, 10mol %) and the ligand (0.0275 mmol, 11 mol %) in dry CH_2Cl_2 was stirred for 2 h at room temperature under argon atmosphere. Stirring was continued for 30 min.Then, the reaction was cooled to desired temperature and the catalysis was started by adding the dienophile, 3-acryloyl-oxazolidin-2-one, (0.035 g, 0.25 mmol) as a solution in CH_2Cl_2 (650µL) via syringe.

The resulting solution was stirred at the desired temperature for the specified amount of time, followed by adding freshly distilled cyclopentadiene. The reaction was monitored by TLC, then, the mixture was washed with saturated NH_4Cl and extracted with CH_2Cl_2 (2x10 mL). The combine organic phases were dried over $MgSO_4$ and the solvent was removed under reduced temperature. The enantiomeric excess value was obtained by HPLC analysis employing a Daicel Chiracel OD-H column (98% hexane: 2% i-propanol, flow rate:0.8 mL/min, which resolves the four diastereomers (exo_1 t_r= 49.1 min, exo_2 t_r= 51.2 min, $endo_1$ t_r= 56.3 min, $endo_2$ t_r= 59.9 min)

3.14. General Procedure for Enantioselective Diethylzinc Addition to Benzaldehyde Reaction

Diethylzinc (1.0 mmol, 1 M in hexane) was added to a solution of ligand (0.05 mmol) dissolved in toluene (or hexane) (5 mL) at room temperature under argon atmosphere. The mixture was stirred for 30 minutes. Then, the reaction was cooled to desired temperature and distilled benzaldehyde (0.5 mmol) was added to the reaction mixture. The reaction was continued under TLC control. Then, 1 M HCl (10 mL) was used to quench the reaction followed by extracting with ethyl acetate (25 mL). The organic phase was dried over $MgSO_4$ and the solvent was evaporated to give the corresponding alcohol. HPLC-analysis of 1-phenyl-1-propanol: Chiralcel OD-H at room temperature, *n*-hexane/2-propanol = 98:2, 1.0 mL/min, 254 nm, t_1= 14.3 min (*R*), t_2= 16.7 min (*S*).

CHAPTER 4

CONCLUSION

In this study, four novel chiral N,N-dialkyl substituted 1,4-amino alcohols *(2S,3R)-(-)-***43**, *(2S,3R)-*(+)**-44**, *(2S,3R)-*(-)**-45**, *(2S,3R)-*(-)**-46** were synthesized. The catalytic properties of these chiral ligands were examined in asymmetric Diels-Alder reaction and enantioselective diethylzinc addition to benzaldehyde reaction.

Firstly, the compounds (-)-**43, (+)-44, (-)-46** were used as ligands in asymmetric Diels-Alder reaction. All the ligands showed low enantiomeric excesses. Changing the temperatures did not provide any improvement in enantiomeric excess values. $Cu(OTf)_2$ was used as metal complex, but the complexation of the ligands with this metal .was not achieved. In addition, $In(OTf)_2$ was used once but there was no drastic change in e.e. value.

The chiral amino alcohol ligands (-)-**43, (+)-44, (-)-45** gave better results in enantioselective diethylzinc addition reaction. Ligand (-)-**43** showed higher enantiomeric excess value which was 89% in toluene at 0 ^{o}C. Among the results, the activities of the ligands were better in toluene than in hexane.

For future work, different temperatures and ligand ratios will be tested in Et_2Zn addition reaction. In addition, for Diels-Alder reaction, different metal complexes will be used. These types of chiral ligands may be used in the synthesis of reusable macro molecules by the ring opening metathesis polymerization reaction with the usage of Grubbs catalyst

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APPENDIX

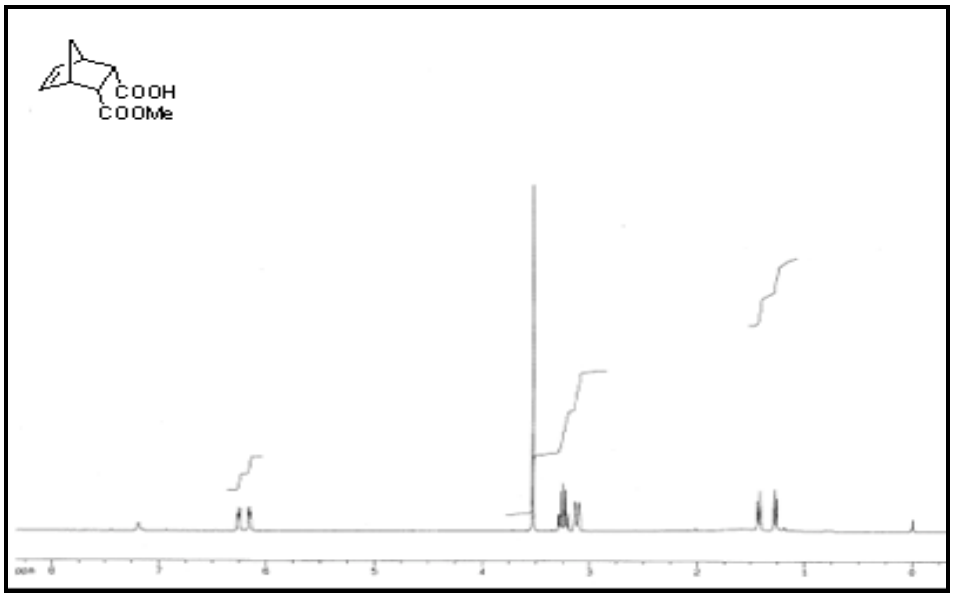

Figure 21. ^{1}H-NMR Spectrum of Compound (-)-**39**

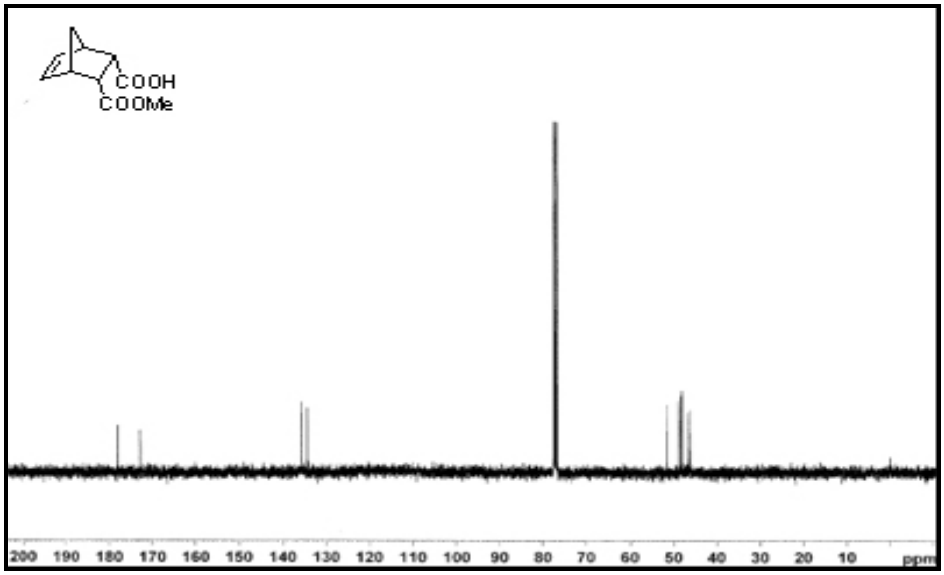

Figure 22. ^{13}C-NMR Spectrum of Compound (-)-**39**

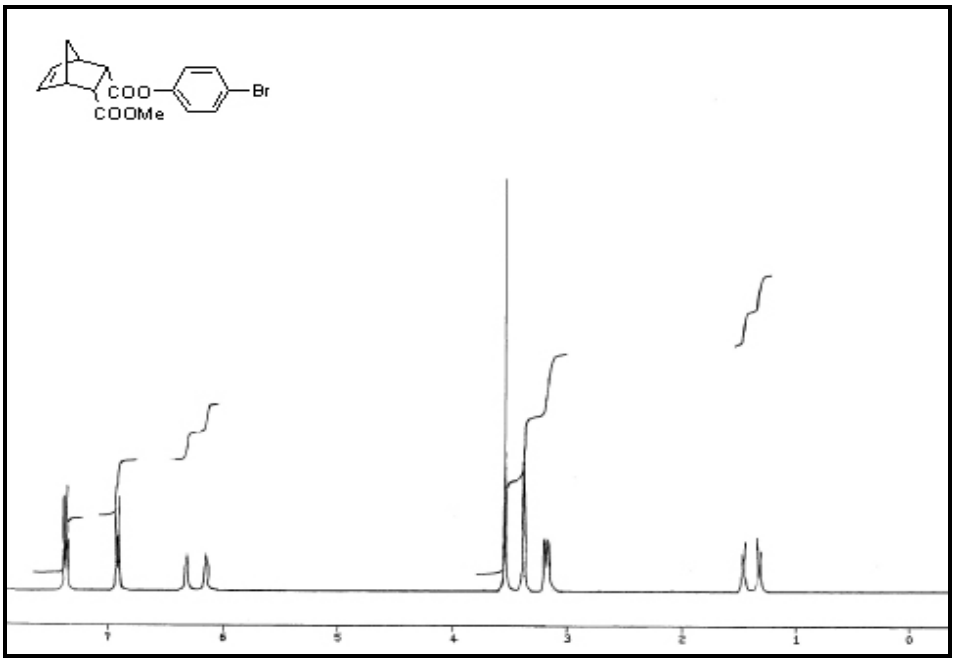

Figure 23. ^{1}H-NMR Spectrum of Compound **47**

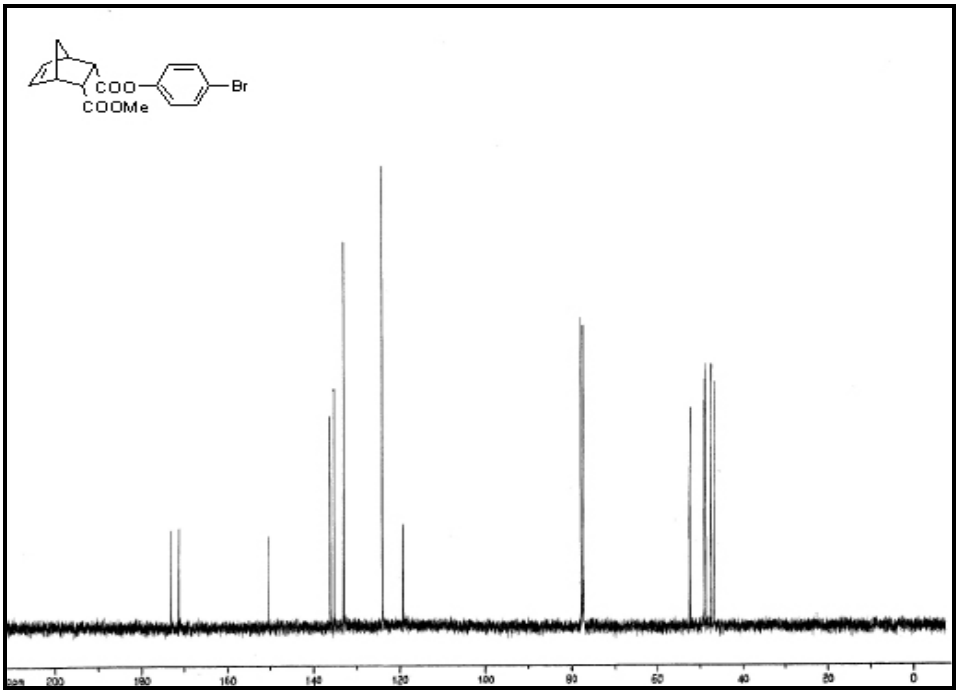

Figure 24.^{13}C-NMR Spectrum of Compound **47**

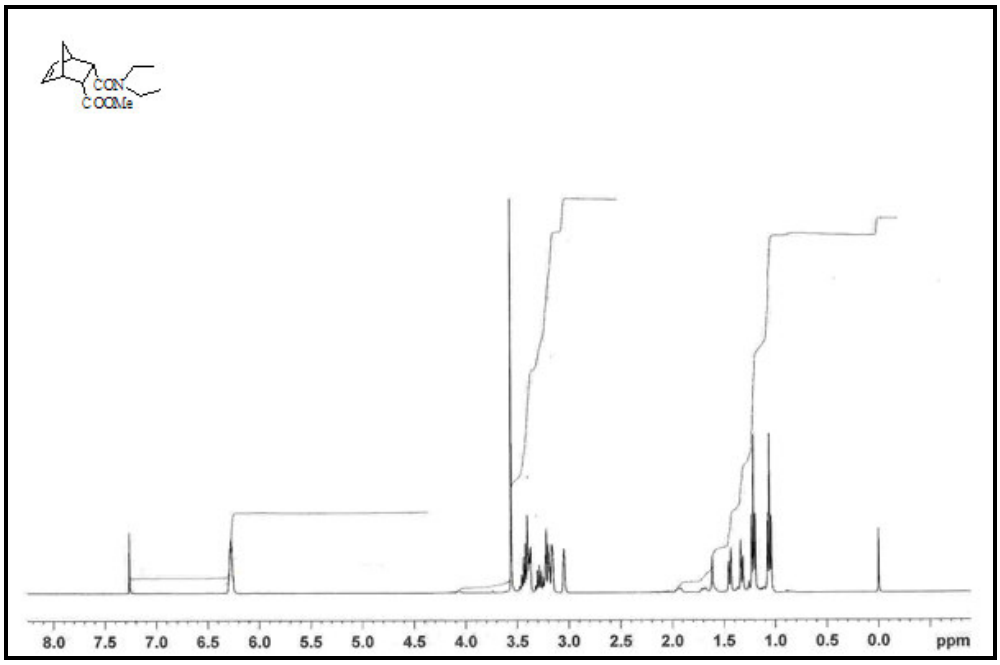

Figure 25. ^{1}H-NMR Spectrum of Compound (-)-**40**

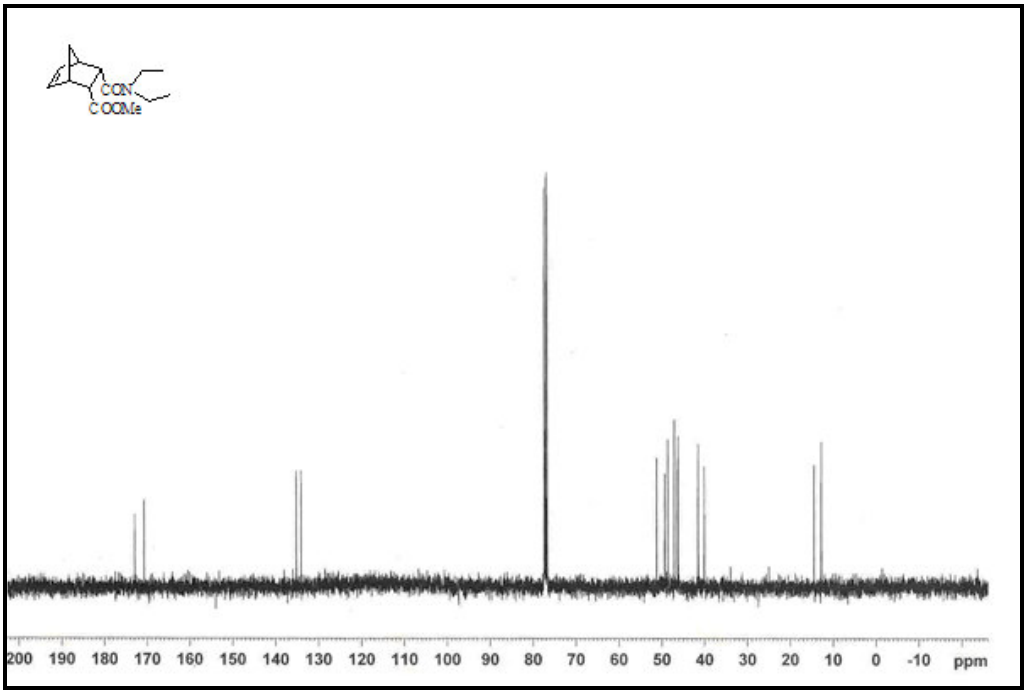

Figure 26. ^{13}C-NMR Spectrum of Compound (-)-**40**

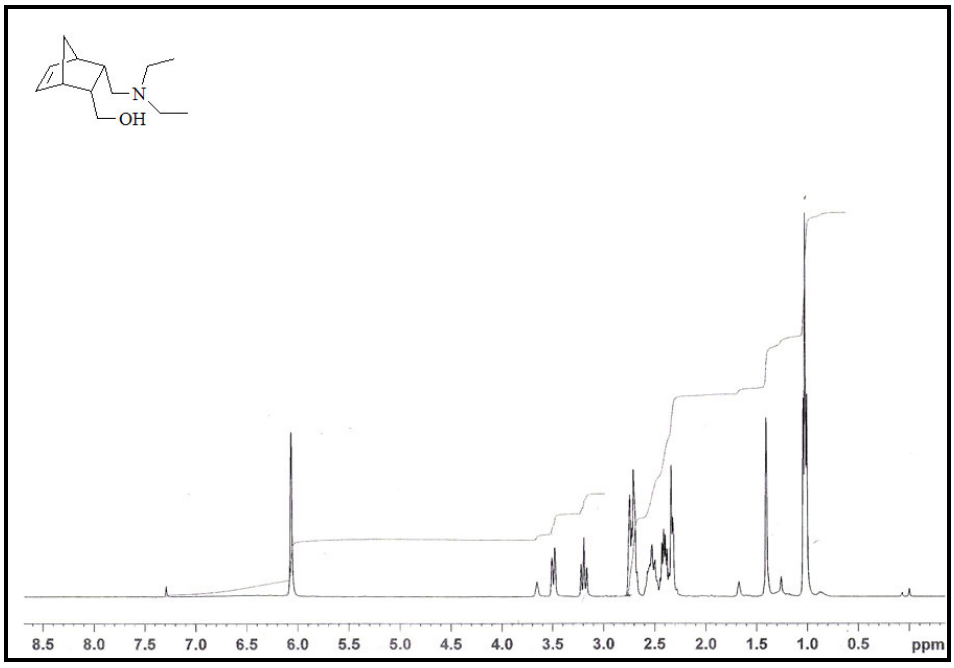

Figure 27. ^{1}H-NMR Spectrum of Compound (-)-**43**

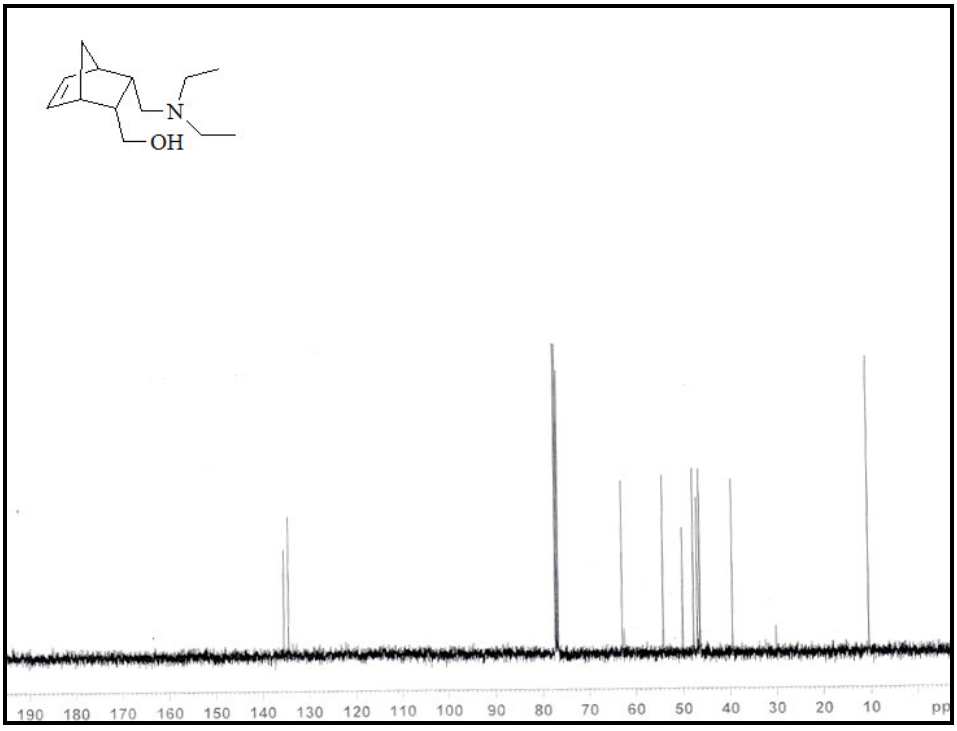

Figure 28. ^{13}C-NMR Spectrum of Compound (-)-**43**

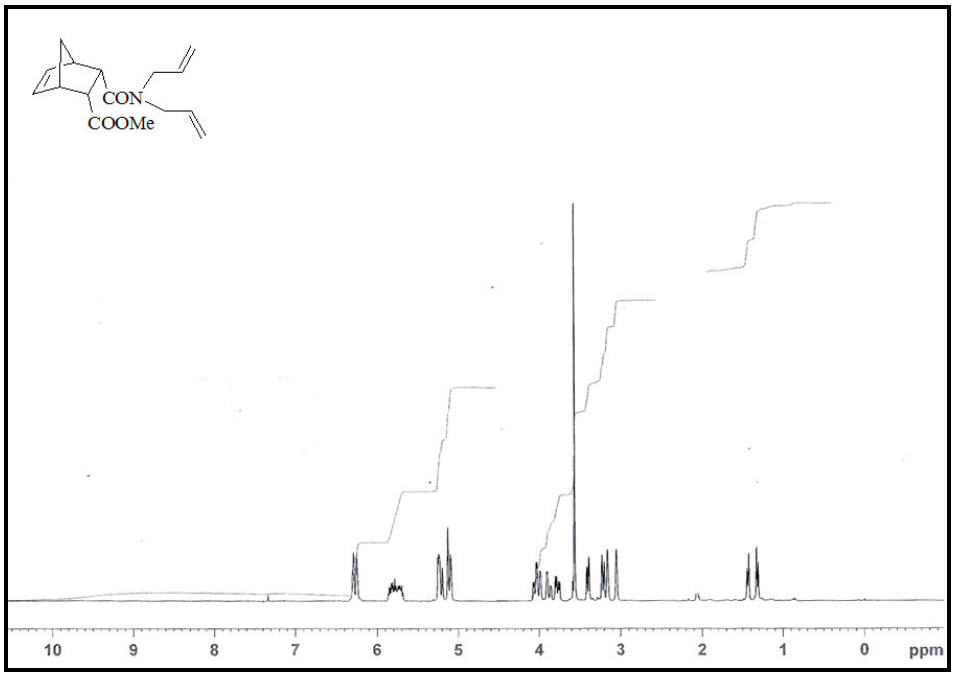

Figure 29. ^{1}H-NMR Spectrum of Compound (-)-**41**

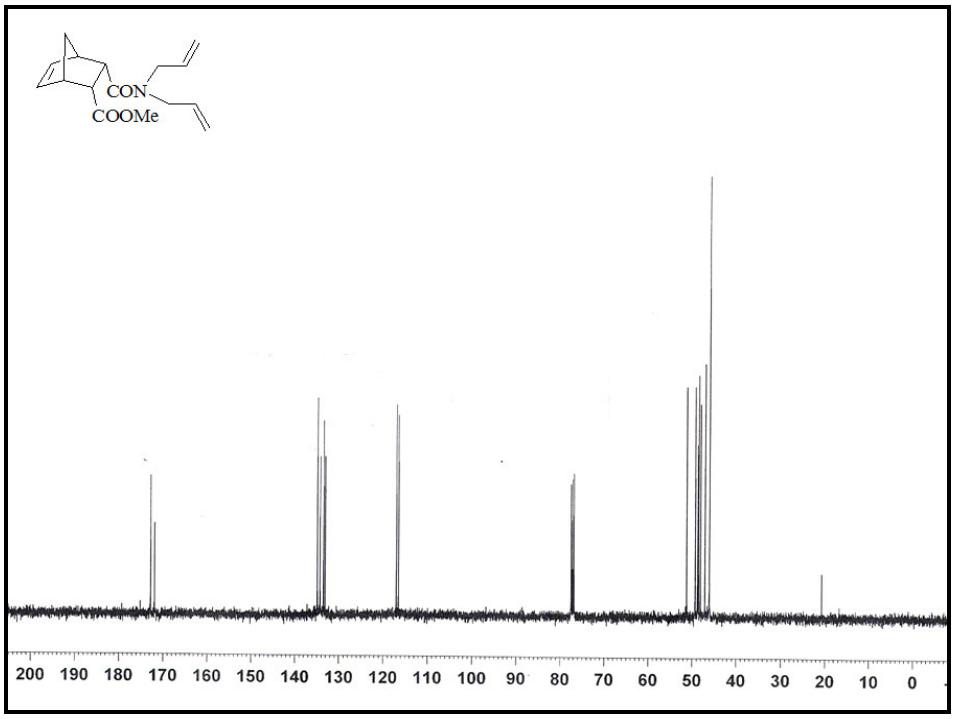

Figure 30. ^{13}C-NMR Spectrum of Compound (-)-**41**

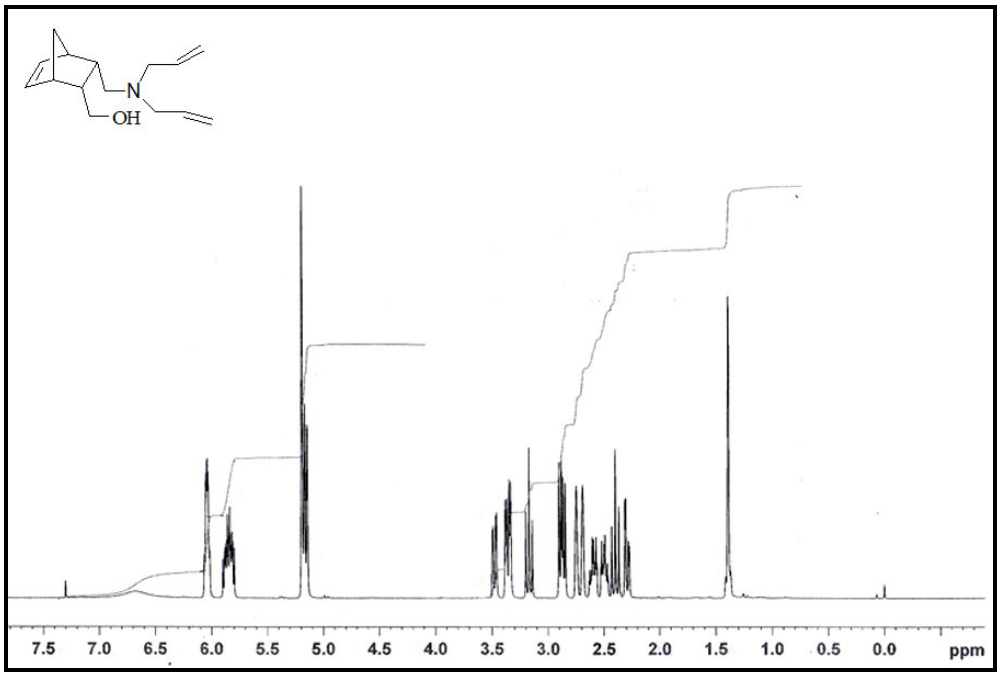

Figure 31. ^{1}H-NMR Spectrum of Compound (+)-**44**

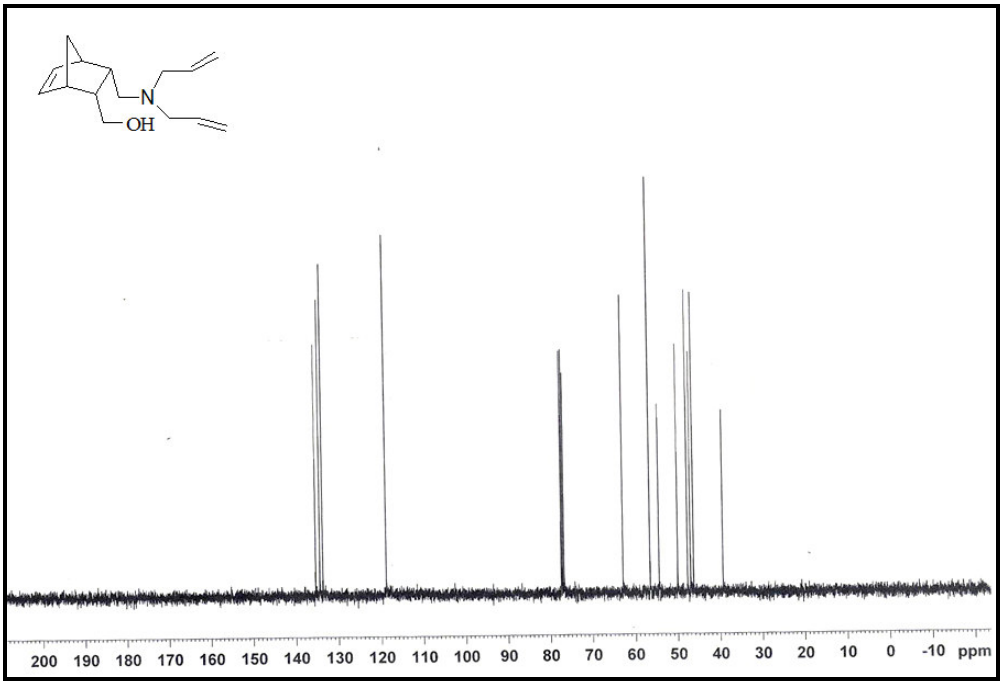

Figure 32. ^{13}C-NMR Spectrum of Compound (+)-**44**

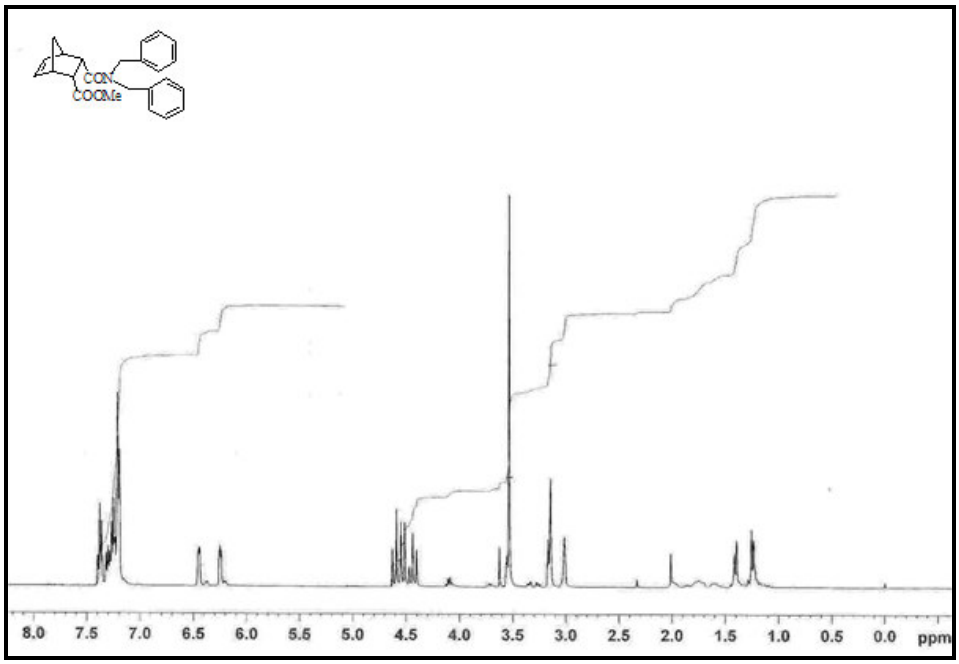

Figure 33. ^{1}H-NMR Spectrum of Compound (-)-**42**

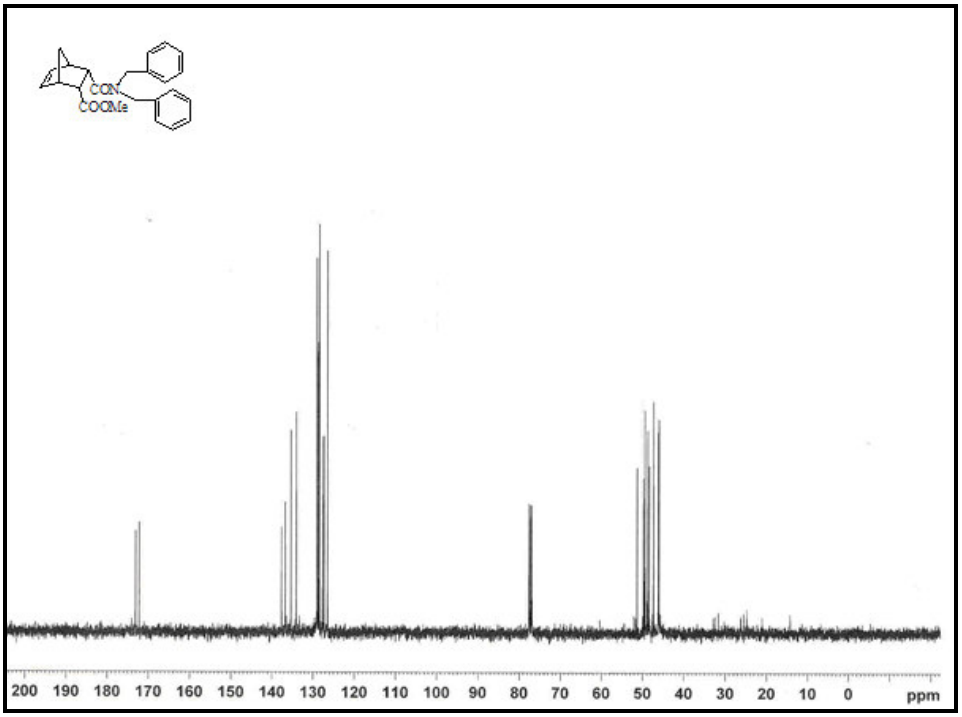

Figure 34. ^{13}C-NMR Spectrum of Compound (-)-**42**

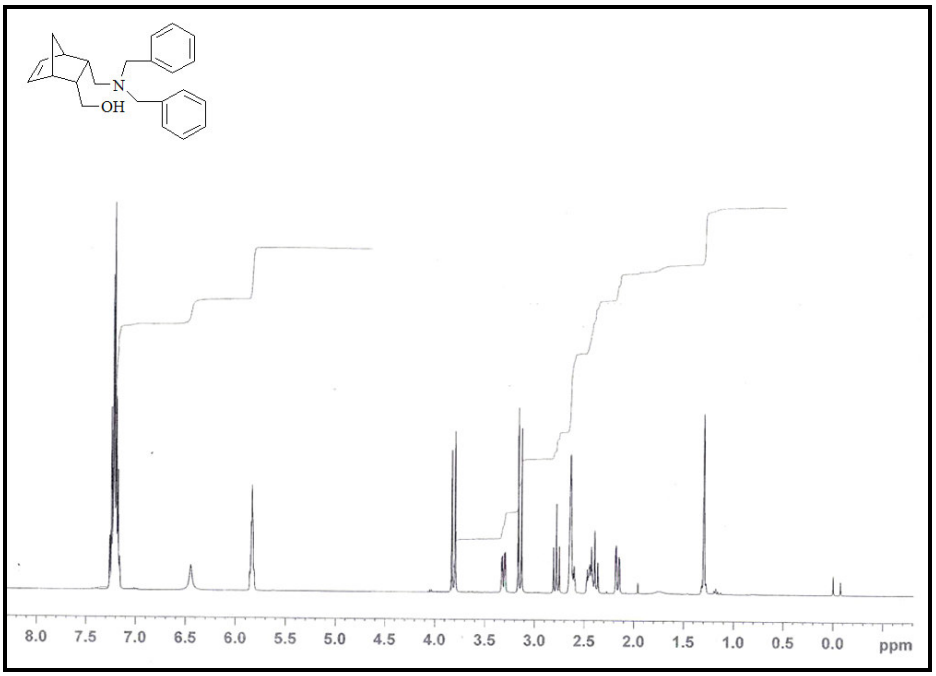

Figure 35. ^{1}H-NMR Spectrum of Compound (-)-**45**

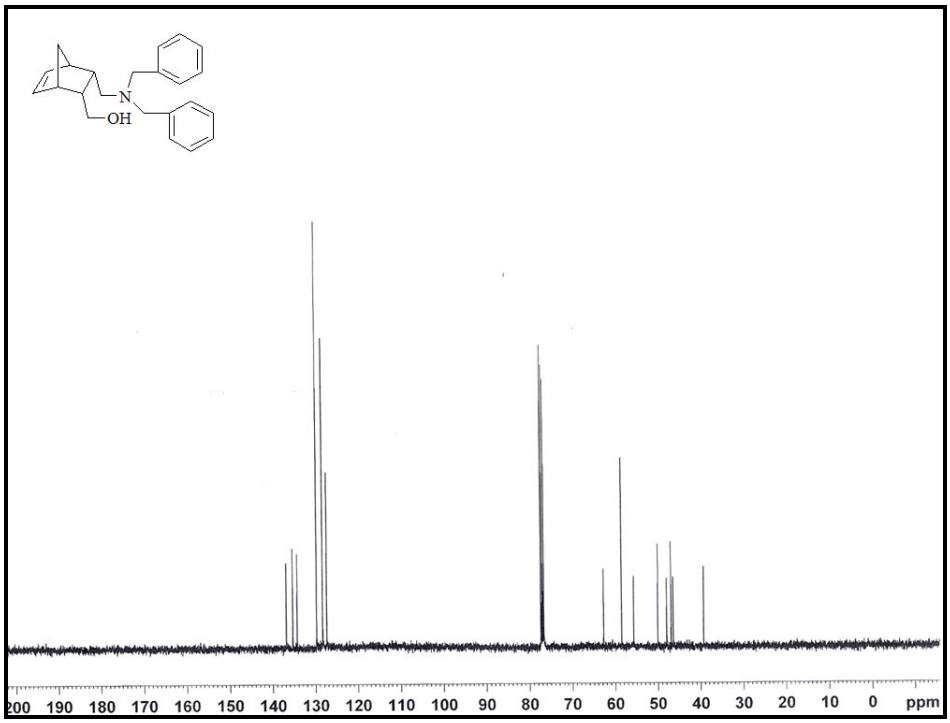

Figure 36. ^{13}C-NMR Spectrum of Compound (-)-**45**

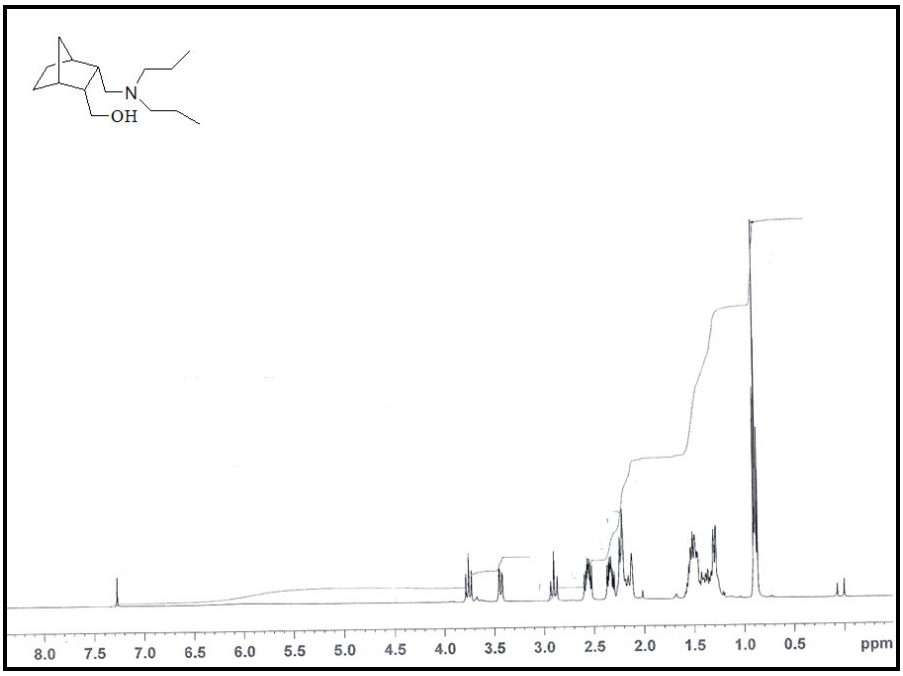

Figure 37. ^{1}H-NMR Spectrum of Compound (-)-**46**

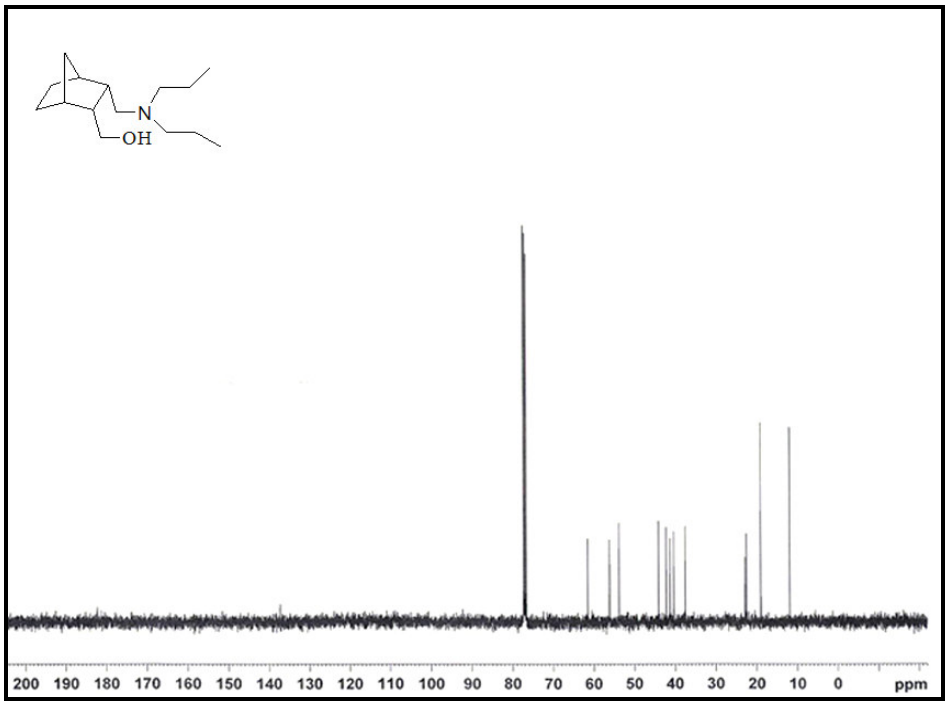

Figure 38. ^{13}C-NMR Spectrum of Compound (-)-**46**

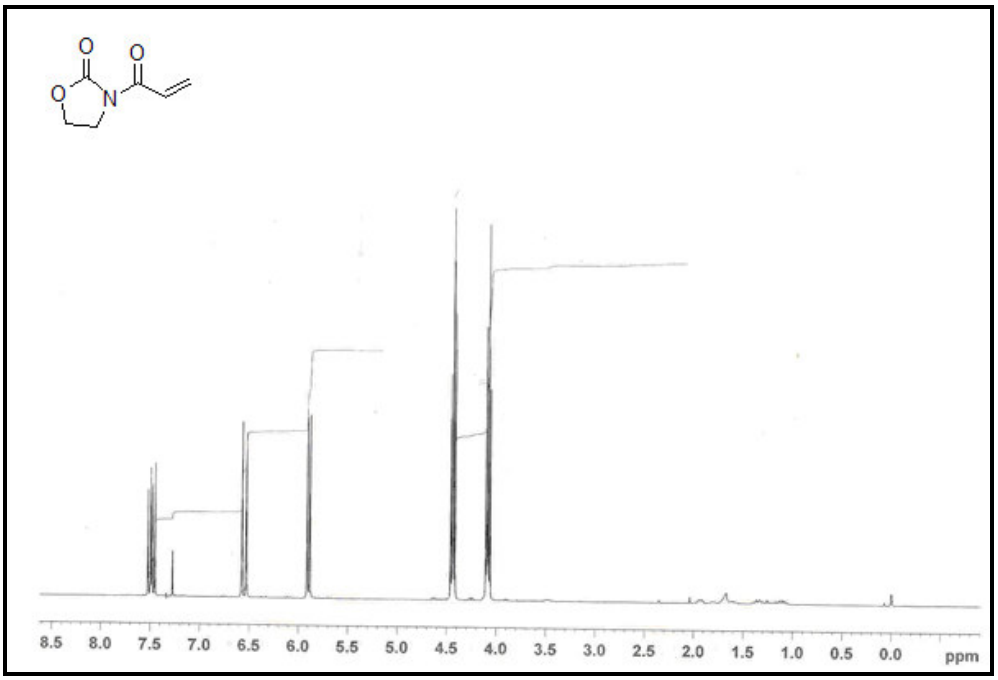

Figure 39. ^{1}H-NMR Spectrum of Compound **50**

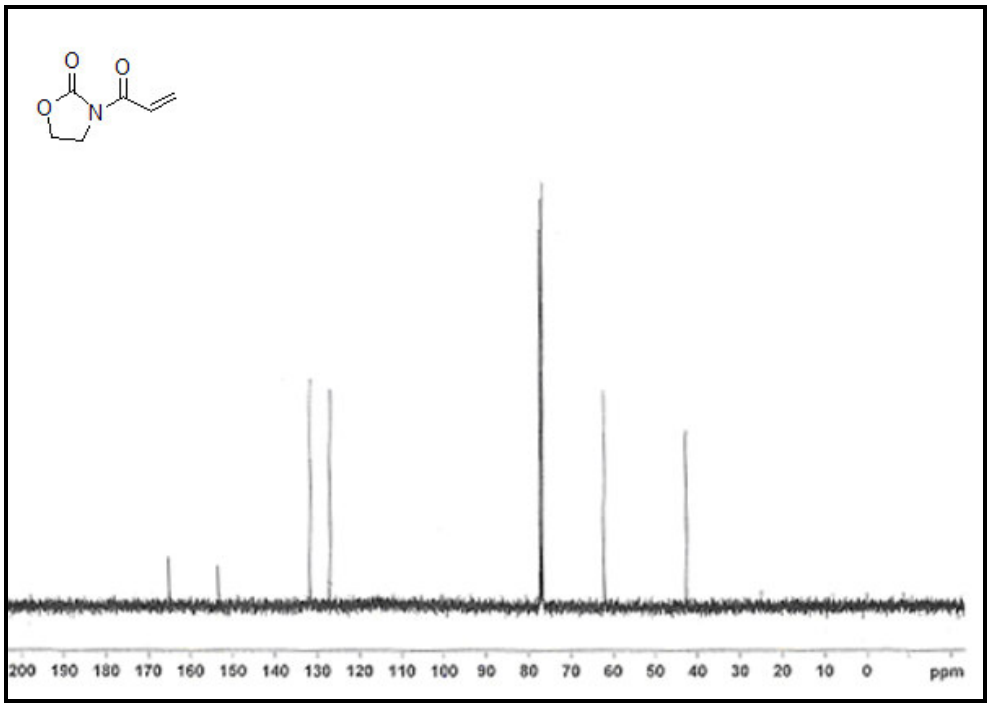

Figure 40. ^{13}C-NMR Spectrum of Compound **50**