ASYMMETRIC SYNTHESIS OF NORBORNENE BASED 1,4-AMINO ALCOHOL DERIVATIVES AND APPLICATIONS IN ASYMMETRIC TRANSFORMATIONS

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Approval of the Graduate School of Natural and Applied Science

_____

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I certify that this thesis satisfies all the requirements as a thesis for the degree of Master of Science.

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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 Master of Science.

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ABSTRACT

ASYMMETRIC SYNTHESIS OF NORBORNENE BASED 1,4-AMINO ALCOHOL DERIVATIVES AND APPLICATIONS IN ASYMMETRIC TRANSFORMATIONS

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The asymmetric synthesis of cis-1,4-aminoalcohols with norbornene backbone was performed starting with simple and cheap anhydride **30**. Quinine-mediated desymmetrization of anhydride **30** with methanol resulted in (2*S*,3*R*)-(-)-cis-hemiester **31** (98% e.e.). Chemoselective amination with HMPTA and NH_4OH followed by LAH reduction afforded (2*S*,3*R*)-(+)-**36** and (2*S*,3*R*)-(-)-**37**, respectively. The amidoester (2*S*,3*R*)-(-)-**32** was transformed into chiral ligand (2*S*,3*R*)-(-)-**35** with Grignard reaction followed by LAH reduction.

The chiral ligands (2*S*,3*R*)-(-)-**35**, (2*S*,3*R*)-(+)-**36** and (2*S*,3*R*)-(-)-**37** were subjected to asymmetric diethylzinc addition reaction to examine their effectiveness as chiral catalyst. Among these, chiral ligand **36** exhibited the highest enantioselectivity (88% e.e.)

Key words: Amino alcohol, diethyl zinc, chiral ligand, asymmetric reaction

ÖZ

NORBORNEN TEMELLİ 1,4-AMİNO ALKOL TÜREVLERİNİN
ASİMETRİK OLARAK SENTEZİ VE ASİMETRİK
TRANSFORMASYONLARDA KULLANIMI

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Norbornen temelli cis-1,4-amino alkollerin asimetrik olarak sentezi, basit ve ucuz bir madde olan anhidrit **30**'dan başlanarak tamamlanmıştır. Anhidrit **30**'un quinine'li ortamda metanolle verdiği tepkime sonucu (2*S*,3*R*)-(-)-cis-hemiester **31** (98% e.e.) maddesi oluşmuştur. Bu maddenin HMPTA ve NH_4OH ile kemoseçici olarak amidasyonu ve arkasından LAH ile indirgenmesi sonucu sırasıyla (2*S*,3*R*)-(+)-aminoalkol **36** ve (2*S*,3*R*)-(-)-aminoalkol **37** ligandları oluşmuştur. (2*S*,3*R*)-(-)-aminoalkol **35** ligandı**,** (2*S*,3*R*)-(-)-amitester **32**'nin önce Grignard tepkimesi, arkasından LAH ile indirgenmesi sonucu oluşmuştur.

(2*S*,3*R*)-(-)-**35**, (2*S*,3*R*)-(+)-**36** and (2*S*,3*R*)-(-)-**37** ligandları, kiral katalizör olarak verimliliklerini ölçmek için, asimetrik dietilçinko tepkimesinde kullanılmıştır ve bu aminoalkoller içinde en yüksek enantioseçiciliği kiral ligand **36** göstermiştir. (88% e.e.)

Anahtar Kelimeler: Amino alkol, dietil çinko, kiral ligand, asimetrik tepkime

To My Family

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TEA: Triethylamine

THF: Tetrahydrofurane

DCC: Dicyclohexylcarboxydiimide

DMAP: Dimethylaminopyridine

HMPTA: Hexamethylenephosphoroustriamide

DCM: Dichloromethane

LAH: Lithium aluminum hydride

LDA: Lithium diisopropylamide

CHAPTER 1

INTRODUCTION

1.1. History and Significance of Chirality

"The universe is dissymmetrical; for if the whole of the bodies which compose the solar system were placed before a glass moving with their individual movements, the image in the glass could not be superimposed on reality.... Life is dominated by dissymmetrical actions. I can foresee that all living species are primordially, in their structure, in their external forms, functions of cosmic dissymmetry."

–Louis Pasteur

These visionary words of Pasteur, written 100 years ago, have profoundly influenced the development of stereochemistry. It has increasingly become clear that many fundamental phenomena and laws of nature result from dissymmetry. In modern chemistry, an important term to describe dissymmetry is chirality or handedness. Like a pair of hands, the two enantiomers of a chiral compound are mirror images of each other that cannot be superimposed.

In 1846, Pasteur observed that all the crystals of dextrorotatory tartaric acid had hemihedral facets with the same orientation and thus assumed that the hemihedral structure of a tartaric acid salt was related to its optical rotatory power. In 1848, Pasteur separated enantiomorphous crystals of sodium ammonium salts of tartaric acid from solution. He observed that large crystals were formed by slowly evaporating the aqueous solution of racemic tartaric acid salt. Pasteur was able to separate the different crystals using a pair of tweezers with the help of a lens. He then

found that a solution of enantiomorphous crystals could rotate the plane of polarized light. One solution rotated the polarized light to the right, while the other one rotated the polarized light to the left. Pasteur thus made the important deduction that the rotation of polarized light caused by different tartaric acid salt crystals was the property of chiral molecules. The (+) and (-) tartaric acids were thought to be related as an object to its mirror image in three dimensions. These tartaric acid salts were dissymmetric and enantiomorphous at the molecular level. It was this dissymmetry that provided the power to rotate the polarized light.

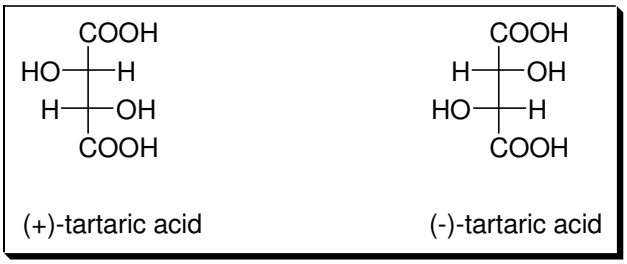


Figure 1. Enantiomers of Optically Active Tartaric Acid

Chirality is a fundamental property of many three-dimensional objects. An object is chiral if it cannot be superimposed on its mirror image. In such a case, there are two possible forms of the same object, which are called enantiomers, and thus these two forms are said to be enantiomeric with each other. To take a simple example, tartaric acid can be obtained in two forms or enantiomers, (+)-tartaric acid and (-)-tartaric acid in Figure 1, which are clearly enantiomeric in that they are related as mirror images that cannot be superimposed on each other.

Enantiomers have identical chemical and physical properties in the absence of an external chiral influence. This means that (+)-tartaric acid and (-)-tartaric acid have the same melting point, solubility, chromatographic retention time, infrared spectroscopy (IR), and nuclear magnetic resonance (NMR) spectra.

Chirality is of prime significance, as most of the biological macromolecules of living systems occur in nature in one enantiomeric form only. 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.[1] Thus it is

not surprising that the two enantiomers of a drug may interact differently with the receptor, leading to different effects. Indeed, it is very important to keep the idea of chiral discrimination or stereoisomeric discrimination in mind when designing biologically active molecules. As human enzymes and cell surface receptors are chiral, the two enantiomers of a racemic drug may be absorbed, activated, or degraded in very different ways. The two enantiomers may have unequal degrees or different kinds of activity. For example, one may be therapeutically effective, while the other may be ineffective or even toxic. An interesting example of the above difference is L-DOPA, which is used in the treatment of Parkinson's disease. The active drug is the achiral compound dopamine formed from L-DOPA via in vivo decarboxylation. As dopamine cannot cross the blood-brain barrier to reach the required site of action, the "prodrug" L-DOPA is administered. Enzyme-catalyzed in vivo decarboxylation releases the drug in its active form (dopamine). The enzyme L-DOPA decarboxylase, however, discriminates the stereoisomers of DOPA specifically and only decarboxylates the L-enantiomer. It is therefore essential to administer DOPA in its pure L-form. Otherwise, the accumulation of D-DOPA, which cannot be metabolized by enzymes in the human body, may be dangerous. Currently L-DOPA is prepared on an industrial scale via asymmetric catalytic hydrogenation.

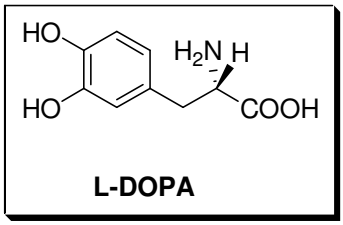


Figure 2. Structure of L-Dopamine

From the above example one can see that stereoisomeric discrimination is very striking in biological systems, and for this reason chirality is recognized as a central concept. If we consider the biological activities of chiral compounds in general, there are four different behaviors: (1) only one enantiomer has the desired biological activity, and the other one does not show significant bioactivity; (2) both enantiomers have identical or nearly identical bioactivity; (3) the enantiomers have quantitatively different activity; and (4) the two enantiomers have different kinds of

biological activity. Figure 3 presents a number of examples of differences in the behavior of enantiomers.

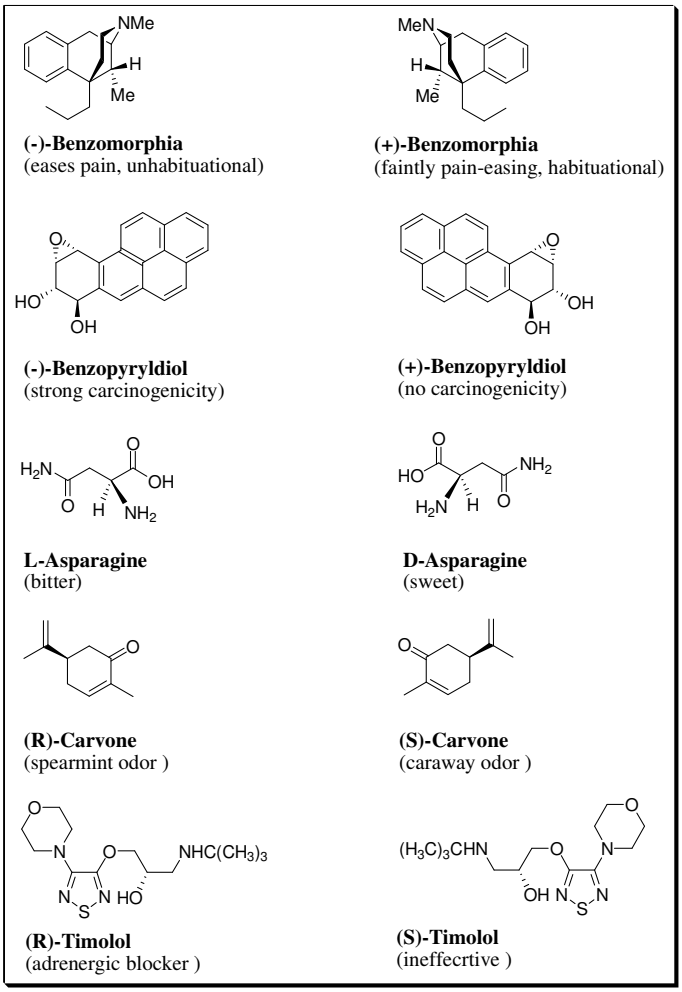


Figure 3. Examples of the Different Behaviours of Enantiomers

The listed enantiomers may have different taste or odor and, more importantly, they may exhibit very different pharmacological properties. For example, a tragedy occurred in Europe during the 1950s involving the drug thalidomide. This is a powerful sedative and antinausea agent that was considered especially appropriate for use during early pregnancy. Unfortunately, it was soon found that this drug was a very potent teratogen and thus had serious harmful effects on the fetus. Further study showed that this teratogenicity was caused by the (S)-isomer (which had little sedative effect), but the drug was sold in racemic form. The (R)-isomer (the active sedative) was found not to cause deformities in animals even in high doses.[2] The administration of enantiomerically pure drugs can have the

following advantages: (1) decreased dosage, lowering the load on metabolism; (2) increased latitude in dosage; (3) increased confidence in dose selection; (4) fewer interactions with other drugs; and (5) enhanced activity, increased specificity, and less risk of possible side effects caused by the enantiomer. Now it is quite clear that asymmetry (or chirality) plays an important role in life sciences.

1.2. Methods of Producing Optically Active Compounds

Optically active substances in solution can be obtained only through the intervention of some chiral reagents to give diastreomeric transition states, products or complexes (including solvates). The general processes whereby optically active substances are obtained from opticaly inactive materials can be grouped into four broad categories: physical separations via enantiomeric crystalline forms, resolutions based upon separations of diastereomeric forms, thermodynamically controlled asymmetric transformations of stereochemically labile diastereomers, kinetically controlled asymmetric transformations.[3]

1.2.1. Physical Separations via Enantiomeric Crystalline Forms

a) Physical sorting of enantiomeric crystals: One need not have a chiral molecule in order to have a chiral crystal (e.g. SiO_2 and quartz)[4]. Pasteur is the first people to use this method to separate the enantiomeric crystals of racemic sodium ammonium tartrate. However the cases in which this can be done are rare and unpredictable unless the phase diagram has been determined.

b) Selective seeding of a solution of racemate with crystals of one enantiomer (or isomorphous crystals): The seeding of a solution of a racemate by the crystals of one pure enantiomer (or an isomorphic crystal) can, under the proper circumstances, lead to the separation of one form and the retention of the other in solution. Separation can then be achieved by filtration or centrifugation. Additional racemate may then be dissolved in the mother liquor which is then seeded with the other enantiomer and this alternating process repeated indefinitely.[4]

c) Preferential incorporation of one enantiomer in an inclusion compound[5]: repetition of such spontaneous crystallizations under conditions which rigorously exclude accidental seeding must give, on the average, one chiral form as often as other. This doesn't mean that in one crystallization container there will be as many (+) crystals as (-) crystals, since self seeding may take place. Soret[6] carried out the spontaneous crystallization of sodium chlorate 938 times in sealed ampoules. Dextrorotatory crystals formed 433 times, levorotatory crystals, 411 times; and a mixture of both, 94 times.

1.2.2. Resolutions Based upon Separations of Diastereomeric Forms

Resolution of a racemic pair is most generally carried out by formation of a diastereomeric derivative, which can then be separated by virtue of some differences in physical properties. Most generally this is a difference in solubility of a crystalline derivative such as an alkaloid salt, but differences in boiling point, in chromatographic adsorption, as well as in gas chromatographic retention times[7] can be employed.

Resolutions can also be achieved by formation of an unstable combination of a stable racemate and stable optically active resolving agent.[4b] The following are some representative examples: the resolution of Troeger's base by chromatography on lactose column,[8] metallocenes on acetyl cellulose columns,[9] amino acids by chromatography on chiral ion exchange resins,[10] of trifluoroacetyl amino acids by gas chromatography using a chiral stationary phase.[11]

1.2.3. Thermodynamically Controlled Asymmetric Transformations of Stereochemically Labile Diastereomers

If the isomers being subjected to resolution are stereochemically labile under the conditions of the separation, there is no sharp division between the physical separation associated with resolution and that which has been termed an asymmetric transformation. Both processes, physical separation and asymmetric transformation, can occur at the same time and a clear distinction may be difficult to establish. Such a case involving a stereochemically labile racemate does not constitute a true

resolution, nor can it be classified as an asymmetric synthesis since the starting point is a racemic mixture, albeit one in which the enantiomers are equilibrated via a symmetrical intermediate.

A variety of structural and mechanistic processes exist which permit thermodynamic equilibratin of optically active compounds.

a) Unimolecular inversion without bond breaking of an unsymmetrically distributed tetrahedral atom (such as nitrogen, sulfur, phosphorous or antimony)

b) Unimolecular rotation around a conformationally mobile bond so that one chiral form is converted to another (as in the atropisomerism of ortho-substituted biphenyls)

c) Interconversion of chiral centers via an achiral intermediate (for example, enol-keto isomerism, ring-chain tautomerism, formation of carbanions, etc.)

d) Reversible isomerism about a double bond, C=N, N=N, C=C, in such a way that chiral forms are interconverted.

1.2.4. Kinetically Controlled Asymmetric Transformations

The fourth general method for obtaining chiral compounds is also the most interesting from a mechanistic viewpoint since diastreomeric transition states or intermediates (including complexes and solvates) are the controlling factors in the stereochemical course of the reaction. In these processes the ground state free energies of the reactants for the competing pathways must be identical ($\Delta G^{o} = 0$). Only the free energies of activation ($\Delta G^{\ddagger}$) of the two pathways differ; the extent of asymmetric transformation depends only upon the differences in the free energies ($\Delta\Delta G^{\ddagger}$) of the competing pathways.

Kinetically controlled asymmetric transformations include the use of enzymes, chiral auxiliaries, chiral ligands and chiral environment. Enzymes are chiral molecules and their active sites include chiral molecules. Lock and key model is the main principle of enzymes and according to this rule only right handed or left handed product is formed. Chiral auxiliaries and chiral ligands can be used too. Both of them are chiral molecules and they carry chiral information to the product. Chiral ligands have the advantage that they are used in catalytic amount whereas chiral

auxiliaries have to be used in stochiometric amount. Another method is using chiral environment. Chiral environment can be chiral solvent, chiral glass or chiral light!

1.3. Determining Enantiomeric Composition

The presence of an asymmetric carbon is neither a necessary nor a sufficient condition for optical activity. Each enantiomer of a chiral molecule rotates the plane of polarized light to an equal degree but in opposite directions. A chiral compound is optically active only if the amount of one enantiomer is in excess of the other. Measuring the enantiomer composition is very important in asymmetric synthesis, as chemists working in this area need the information to evaluate the asymmetric induction efficiency of asymmetric reactions. The enantiomer composition of a sample may be described by the enantiomer excess (ee), which describes the excess of one enantiomer over the other:

$$ee = \left| \frac{[S] - [R]}{[S] + [R]} \right| x100\%$$

where [R] and [S] are the composition of R and S enantiomers, respectively. Correspondingly, the diastereomer composition of a sample can be described by the diastereomer excess (de), which refers to the excess of one diastereomer over the other:

$$de = \left| \frac{[S*S] - [S*R]}{[S*S] + [S*R]} \right| x100\%$$

where S*S and S*R are the composition of the diastereomers, respectively.

Different methods have been developed for determining the enantiomer compositions of a pair of enantiomers. Some apply measurements of the original molecules, while others use derivatives of the orresponding compounds. To determine how much one isomer is in excess over the other, analytical methods based on high-performance liquid chromatography (HPLC) or gas chromatography (GC) on a chiral column have proved to be most reliable. Chiral chemical shift

reagents for NMR analysis are also useful, and so are optical methods. A variety of methods are also available when the compound under investigation can be converted with a chiral reagent to diastereomeric products, which have readily detectable differences in physical properties. If a derivatizing agent is employed, it must be ensured that the reaction with the subject molecule is quantitative and that the derivatization reaction is carried out to completion. This will ensure that unintentional kinetic resolution does not occur before the analysis. The derivatizing agent itself must be enantiomerically pure, and epimerization should not occur during the entire process of analysis.

1.3.1. Measuring Specific Rotation

One of the terms for describing enantiomer composition is optical purity. It refers to the ratio of observed specific rotation to the maximum or absolute specific rotation of a pure enantiomer sample. For any compound for which the optical rotation of its pure enantiomer is known, the ee value may be determined directly from the observed optical rotation.

$$[\alpha]_D^{20} = \frac{[\alpha]}{L \times c} \times 100$$

where [α] is the measured rotation; L is the path length of cell (dm); c is concentration (g/100 ml); D is the D line of sodium, the wave length of light used for measurement (5983A); and 20 is the temperature in degrees (Celsius).

$$\text{Optical purity (\%)} = [\alpha]_{obs} / [\alpha]_{max} \times 100\%$$

The classic method of determining the optical purity of a sample is to use a polarimeter. However, this method can be used to determine enantiomeric purity only when the readings are taken carefully with a homogenous sample under specific conditions. The method provides comparatively fast but, in many cases, not very precise results. There are several drawbacks to this method: (1) One must have knowledge of the specific rotation of the pure enantiomer under the experimental conditions in order to compare it with the measured result from the sample. (2) The measurement of optical rotation may be affected by numerous factors, such as the

wavelength of the polarized light, the presence or absence of solvent, the solvent used for the measurement, the concentration of the solution, the temperature of measurement, and so forth. Most importantly, the measurement may be affected significantly by the presence of impurities that have large specific rotations. (3) Usually a large quantity of sample is needed, and the optical rotation of the product must be large enough for accurate measurement. (This problem, however, has somewhat been alleviated by advances in instrumentation, such as the availability of the capillary cell.) (4) In the process of obtaining a chemically pure sample for measurement, an enrichment of the major enantiomer may occur and cause substantial errors.[12-14]

1.3.2. The Nuclear Magnetic Resonance Method

NMR spectroscopy cannot normally be used directly for discriminating enantiomers in solution. The NMR signals for most enantiomers are isochronic under achiral conditions. However, NMR techniques can be used for the determination of enantiomer compositions when diastereomeric interactions are introduced to the system.[15-17]

We can use chiral chemical shift reagents in NMR. Lanthanide complexes can serve as weak Lewis acids. In nonpolar solvents (e.g., $CDCl_3$, CCl_4, or CS_2) these paramagnetic salts are able to bind Lewis bases, such as amides, amines, esters, ketones, and sulfoxides. As a result, protons, carbons, and other nuclei are usually deshielded relative to their positions in the uncomplexed substrates, and the chemical shifts of those nuclei are altered. The extent of this alteration depends on the strength of the complex and the distance of the nuclei from the paramagnetic metal ion. Therefore, the NMR signals of different types of nuclei are shifted to different extents, and this leads to spectral simplification. The spectral nonequivalence observed in the presence of chiral chemical shift reagents (CSR) can be explained by the difference in geometry of the diastereomeric CSR-chiral substrate complexes, as well as the different magnetic environment of the coordinated enantiomers that causes the anisochrony.[18] Achiral lanthanide shifting reagents may be used to enhance the anisochrony of diastereomeric mixtures to facilitate their quantitative analysis. Chiral lanthanide shift reagents are much more commonly used to

quantitatively analyze enantiomer compositions. Sometimes it may be necessary to chemically convert the enantiomer mixtures to their derivatives in order to get reasonable peak separation with chiral chemical shift reagents.

1.3.3. Chromatographic Methods Using Chiral Columns

One of the most powerful methods for determining enantiomer composition is gas or liquid chromatography, as it allows direct separation of the enantiomers of a chiral substance. Early chromatographic methods required the conversion of an enantiomeric mixture to a diastereomeric mixture, followed by analysis of the mixture by either GC or HPLC. A more convenient chromatographic approach for determining enantiomer compositions involves the application of a chiral environment without derivatization of the enantiomer mixture. Such a separation may be achieved using a chiral solvent as the mobile phase, but applications are limited because the method consumes large quantities of costly chiral solvents. The direct separation of enantiomers on a chiral stationary phase has been used extensively for the determination of enantiomer composition.

Gas chromatography is commonly used method for the analysis of mixtures of enantiomers is chiral GC.[19-21] In addition to being quick and simple, this sensitive method is normally unaffected by trace impurities. The method is based on the principle that molecular association between the chiral stationary phase and the sample may lead to some chiral recognition and sufficient resolution of the enantiomers. The chiral stationary phase contains an auxiliary resolving agent of high enantiomeric purity. The enantiomers to be analyzed undergo rapid and reversible diastereomeric interactions with the stationary phase and hence may be eluted at different rates (indicated as t_R, the retention time).

Liquid Chromatography is another rapid, simple liquid chromatographic method for determining the enantiomeric purity of chiral compounds. It is probably one of the most important developments in the study of asymmetric synthesis in the last 10 years. Several books have been published providing thorough evaluations of various enantiomeric separation techniques and their practical applications.[22] Initially, chiral stationary phases for chiral liquid chromatography were designed for

preparative purposes, mostly based on the concept of "three-point recognition".[23] Pirkle and other scientists[24] developed a series of chiral stationary phases that usually contain an aryl-substituted chiral compound connected to silica gel through a spacer.

1.3.4. Capillary Electrophoresis with Enantioselective Supporting Electrolytes

Electrophoresis is based on the transport of electrically charged compounds in a gel or a buffer solution under the influence of an electric field. The instrumentation involves a capillary tube filled with buffer solution and placed between two buffer reservoirs. The electric field is applied by means of a high-voltage power supply. This is similar to a chromatographic method in which the enantiomer mixture forms diastereomer complexes with a chiral mobile phase to accomplish the separation. In chromatographic separation, the driving force comes from the mobile phase, whereas in electrophoresis the driving force is the electroosmotic and electrophoretic action. Differences in complexation constants cause these transient charged species to acquire different mobilities under the influence of the applied electric field. It should be noted that in electrophoresis no mobile phase is used. The method depends on the different migration rates of charged enantiomers in a chiral supporting electrolyte. The method is fast and highly sensitive, which permits the rapid (about 10 minutes) and accurate analysis of samples in femtomolar concentration.[25] Capillary electrophoresis (CE) was originally developed as a microanalytical technique for analysis and purification of biopolymers. The separation of bio-polymers can be achieved according to their different electrophoretic mobilities. Capillary gel electrophoresis is based on the distribution of analytes in a carrier electrolyte, and this method has been extensively used in analysis and separation of proteins and nucleic acids.

Compared with GC and HPLC, the most important advantage of CE is its high peak efficiency. It can give a baseline resolution of peaks even when the separation factor is low. Volatile chiral samples are best analyzed by GC, whereas HPLC and CE are more suitable for nonvolatile samples. CE is the best choice for a charged compound or for a high-molecular-weight sample. The different separation mechanisms make it possible to separate a wide variety of substances depending on their mass, charge, and chemical nature.[26]

1.4. Determining Absolute Configuration

The most commonly used nomenclature for chiral systems follows the CIP rules or sequence rules, although Fischer's convention is still applied for carbohydrates and amino acids. In the area of asymmetric synthesis, one of the most important parameters one has to know in order to evaluate the efficiency of asymmetric induction is the enantiomer composition. Another important parameter is the configuration of the major product of an asymmetric reaction. Thus, in an asymmetric reaction, there are two important elements. One is to know the predominant configuration, and the other is to determine the extent to which this configuration is in excess of the other.

It is very important to define the absolute configuration of a chiral molecule in order to understand its function in a biosystem. First, definite chirality is involved in most biological processes; second, only one of the enantiomeric forms is involved in most of the building blocks for proteins, nucleotides, and carbohydrates, as well as terpenes and other natural products. Many biological activities are exclusive to one specific absolute configuration. Without a good understanding of the absolute configuration of a molecule, we often cannot understand its chemical and biological behavior.

1.4.1. X-Ray Diffraction Methods

Normal X-ray diffraction cannot distinguish between enantiomers. The amplitude of a given reflection depends on the scattering power of the atoms and phase differences in the wavelets scattered by them. When the diffraction involves light nuclei (e.g., C, H, N, O, F), the interference pattern is determined only by the internuclear separations, and the phase coincidence is independent of the spatial orientation of these nuclei. Thus, from the diffraction pattern it is possible to calculate various internuclear distances and constitutions in the molecule and to deduce the relative positions of these nuclei in space. One can build the relative configuration of a compound, but it is normally difficult to distinguish enantiomers or to get the absolute configurations for chiral compounds containing only light atoms. When molecules containing only light nuclei are subjected to X-ray analysis, only diffraction occurs and no significant absorption can be observed. During the

experiment, the phase change in the radiation is almost the same for both enantiomers. Nuclei of heavy atoms absorb X-rays over a particular range of the absorption curve. If the wavelength of the radiation coincides with the absorption edge of the heavy atom, there will be absorption, and both diffraction and phase lag can be observed. Because of this phase lag or anomalous scattering, the interference pattern will depend not only on the distance between atoms but also on their relative positions in space, thus making it possible to determine the absolute configuration of molecules containing heavy atoms.

This principle was first applied[27] to determine the absolute configuration of a sodium rubidium salt of natural tartaric acid by using Zr-K_a X-rays in an X-ray crystallographic study. This method is now referred to as the *Bijvoet* method. With the absolute configuration of sodium rubidium tartrate as a starting point, the absolute configuration of other compounds has been determined in a step by step fashion through correlation based on either physical-chemical comparison or transformation by chemical reactions.

For a molecule without a heavy atom, the absolute configuration can also be determined by attaching another chiral moiety of known configuration to the sample. The absolute configuration can then be determined by comparison with this known configuration.

1.4.2. Chiroptical methods

The electric vectors of a beam of normal light are oriented in all planes, whereas in polarized light the electric vectors lie in the same plane perpendicular to the direction of propagation. Materials capable of rotating the plane of polarized light are termed optically active. Optical activity comes from the different refractions of right and left circularly polarized light by chiral molecules. The difference in refractive indices in a dissymmetric medium corresponds to the slowing down of one beam in relation to the other. This can cause a rotation of the plane of polarization or optical rotation. The value of specific rotation varies with wavelength of the incident polarized light. This is called optical rotatory dispersion (ORD).

Optical activity also manifests itself in small differences in the molar extinction coeffcients ε_L and ε_R of an enantiomer toward the right and left circularly polarized light. The small differences in ε are expressed by the term *molecular ellipticity*:

$$[\theta]_{\lambda}^{T} = 3300(\varepsilon_L - \varepsilon_R)$$

As a result of the difference in molar extinction coefficients, a circularly polarized beam in one direction is absorbed more than the other. Molecular ellipticity is dependent on temperature, solvent, and wavelength. The wavelength dependence of ellipticity is called circular dichroism (CD). CD spectroscopy is a powerful method for studying the three-dimensional structures of optically active chiral compounds, for example, for studying their absolute configurations or preferred conformations.[28] CD spectra are usually measured in solution, and these spectra result from the interaction of the individual chromophores of a single molecule with the electromagnetic field of light. The interaction with neighboring molecules is often negligible. Moreover, because molecules in solution are tumbling and randomly oriented, the mutual interaction between two molecules, which is approximated by a dipole-dipole interaction, is negligible.

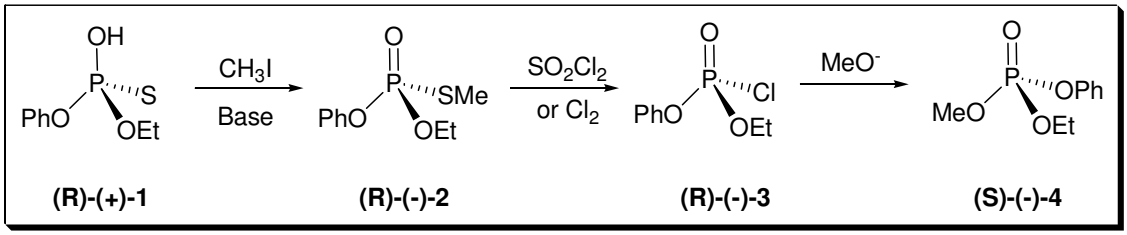
Organic molecules with π-electron systems interact with the electromagnetic field of ultraviolet or visible light to absorb resonance energy. The ultraviolet and visible absorption spectra of a variety of p-electron systems have been applied extensively in structural studies. Measuring the CD of optically active compounds is a powerful method for studying the three-dimensional structure of organic molecules, and, most importantly, this method is being used for the structural study of biopolymers.

The wavelength dependence of specific rotation and/or molecular ellipticity is called the *Cotton effect*. The Cotton effect can provide a wealth of information on relative or absolute configurations. The sign of the Cotton effect reflects the stereochemistry of the environment of the chromophore. By comparing the Cotton effect of a compound of known absolute configuration with that of a structurally similar compound, it is possible to deduce the absolute configuration or conformation of the latter. In a plot of molecular specific rotation or molecular ellipticity versus wavelength,

the extremum on the side of the longer wavelength is called the first extremum, and the extremum on the side of the shorter wavelength is called the second extremum. If the first extremum is positive and the second one is negative, this is called a positive Cotton effect; the first extremum is called a peak, and the second extremum is called a trough. Conversely, in a negative Cotton effect curve, the first extremum is a trough and the second one is a peak. Comparing the signs of the Cotton effect is applicable to substances with suitable chromophores connected to a rigid cyclic substructure. With the aid of an empirical rule, or "octant rule", it is possible using this comparison to predict the absolute configurations of certain five-, six-, and seven-membered cyclic
ketones.[29]

1.4.3. The Chemical Interrelation Method

The chemical interrelation method for determining the absolute configuration of a compound involves the conversion of this compound to a compound with a known configuration, and then the absolute configuration is deduced from the resulting physical properties, such as optical rotation or GC behavior. An example is shown in Scheme 1.



Scheme 1. Chemical Interrelation Method

Alkylation of the configurationally unknown compound (+)-1 followed by chlorination in Scheme 1 afforded product (R)-(-)-**3** with retained configurations. This was then converted to (S)-(-)-**4** with an inversion of configuration.[30] In this manner, the correlation between compounds (+)-**1** and (S)-(-)-**4** in the sense of absolute configuration has been established, and the starting (+)-**1** is determined to have an absolute configuration of (R) (Scheme 1).

This method of determining the absolute configuration is commonly used, as it is convenient, economical, and does not need expensive instruments.

1.5. Asymmetric Synthesis

In its broadest interpretation, an asymmetric synthesis is a reaction in which achiral unit in an ensemble of substrate molecules is converted by a reactant into a chiral unit in such a manner that the stereoisomeric products are produced in unequal amounts. For the purpose of this definition, reactant includes not only the usual chemical reagents but also solvents, catalysts and physical forces such as a circularly polarized light.

Asymmetric organic reactions have proved to be very valuable in the study of reaction mechanisms, in the determination of relative and absolute configurations, and in the practical synthesis of optically active compounds. The pharmaceutical industry, in particular, has shown markedly increased interest in asymmetric organic reactions. Currently, an expanding number of drugs, food additives, and flavoring agents are being prepared by synthetic methods. Most often, the desired compound is obtained through resolution of the corresponding racemic species performed at the end of the synthetic sequence. Because only one optical antipode is useful, half of the synthetic product is often discarded. Obviously, this is a wasteful procedure from the preparative point of view. Even if the wrong isomer can be converted to the active form via racemization and resolution, extensive work is required. Also, resolution is usually a tedious, repetitious, and laborious process. It is economically appealing to exclude the unwanted optical isomers at the earliest possible stage through the asymmetric creation of chiral centers. In the interest of effective use of raw material, it is wise to choose an early step in the synthetic sequence for the asymmetric operation and to consider carefully the principles of convergent synthesis.

The resolution of racemates has been an important technique for obtaining enantiomerically pure compounds. Other methods involve the conversion or derivatization of readily available natural chiral compounds (chiral pools) such as amino acids, tartaric and lactic acids, terpenes, carbohydrates, and alkaloids. Biological transformations using enzymes, cell cultures, or whole microorganisms

are also practical and powerful means of access to enantiomerically pure compounds from prochiral precursors, even though the scope of such reactions is limited due to the highly specific action of enzymes. Organic synthesis is characterized by generality and flexibility. During the last three decades, chemists have made tremendous progress in discovering a variety of versatile stereoselective reactions that complement biological processes.

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.

1.5.1. "Chiron" Approaches

Naturally occurring chiral compounds provide an enormous range and diversity of possible starting materials. To be useful in asymmetric synthesis, they should be readily available in high enantiomeric purity. For many applications, the availability of both enantiomers is desirable. Many chiral molecules can be synthesized from natural carbohydrates or amino acids.

1.5.2. Acyclic Diastereoselective Approaches

In principle, asymmetric synthesis involves the formation of a new stereogenic unit in the substrate under the influence of a chiral group ultimately derived from a naturally occurring chiral compound. These methods can be divided into four major classes, depending on how this influence is exerted: (1) substratecontrolled methods; (2) auxiliary-controlled methods; (3) reagent-controlled methods, and (4) catalyst-controlled methods.

1.5.3. Double Asymmetric Synthesis

Double asymmetric synthesis was pioneered by Horeau et al.,[31] and the subject was reviewed by Masamune et al.[32] in 1985. The idea involves the asymmetric reaction of an enantiomerically pure substrate and an enantiomerically pure reagent. There are also reagent-controlled reactions and substrate-controlled reactions in this category. Double asymmetric reaction is of practical significance in the synthesis of acyclic compounds.

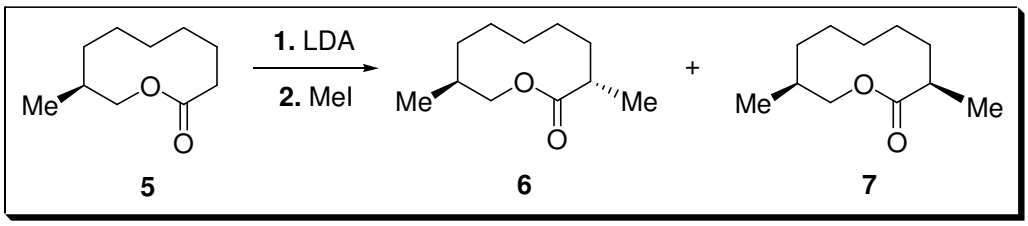
1.6. Illustrative Examples of Asymmetric Synthesis

Previous sections introduced the history of chirality, the determination of enantiomer composition, and the determination of absolute configuration. This section discusses different types of asymmetric reactions with a focus on asymmetric carbon-carbon bond formation. The asymmetric α-alkylation, aldol reactions, oxidations, Diels-Alder reactions and catalytic hydrogenation reactions constitute important methods for asymmetric synthesis.

1.6.1. Alkylation and Catalytic Alkylation of Carbonyl Compounds

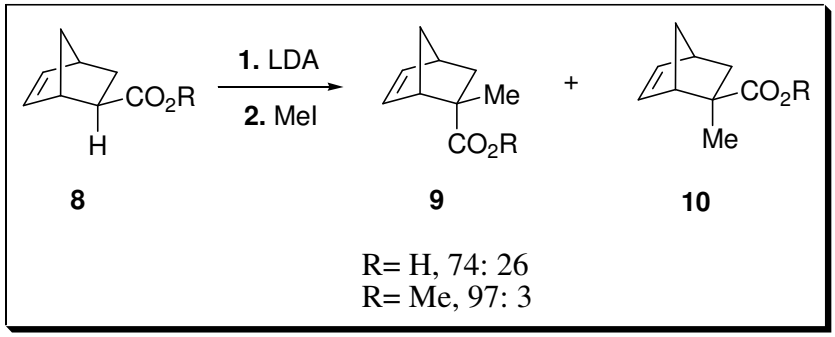
The carbonyl group in a ketone or aldehyde is an extremely versatile vehicle for the introduction of functionality. Reaction can occur at the carbonyl carbon atom using the carbonyl group as an electrophile or through enolate formation upon removal of an acidic proton at the adjacent carbon atom.

The objective of this section is to survey the issue of asymmetric inductions involving the reaction between enolates derived from carbonyl compounds and alkyl halide electrophiles. The addition of a nucleophile toward a carbonyl group, especially in the catalytic manner, is presented as well. To generate an enolate from a carbonyl substrate, a suitable base should be chosen to meet two criteria: adequate basicity to ensure the selective deprotonation process for enolate generation and a sterically hindered structure so that nucleophilic attack of this base on the carbonyl centers can be prevented.

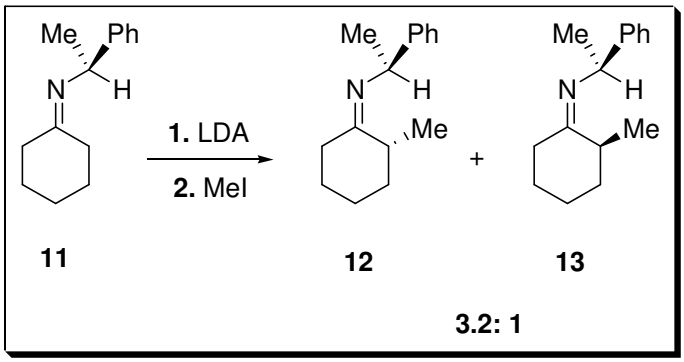


Scheme 2. Intra-annular Chirality Transfer

The metal amide bases had enjoyed much popularity since the introduction of sterically more hindered bases. The introduction of sterically hindered bases has been a particularly important innovation in this field, and these reagents have now been accepted as the most suitable and commonly used bases for carbonyl deprotonation. Lithium diisopropylamide (LDA)[33] has been recognized as the most important strong base in organic chemistry. Both LDA and lithium isopropylcyclohexyl amide (LICA)[34] exhibit similarly high kinetic deprotonation selectivity.



Scheme 3. Diastreoselective Alkylation Reaction in the Norbornene Ring System

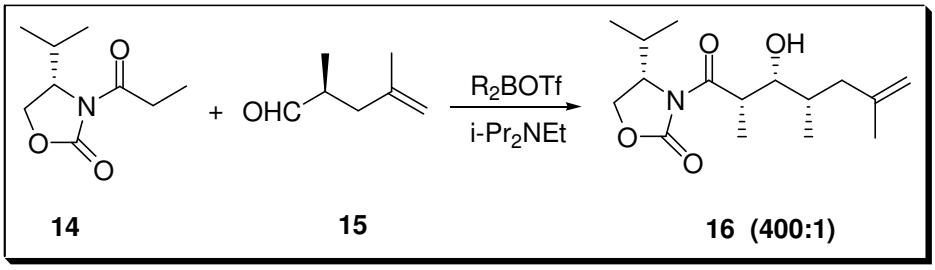


Scheme 4. Extra-annular Chirality Transfer

1.6.2. Asymmetric Aldol Reactions

Aldol reactions refer to the condensation of a nucleophilic enolate species with an electrophilic carbonyl moiety along with its analogs. These reactions are among those transformations that have greatly simplified the construction of asymmetric C-C bonds and, thus, satisfied the most stringent requirements for asymmetric organic synthesis methodology. Numerous examples of asymmetric aldol reactions can be found for syntheses of both complex molecules and small optically active building blocks. Acyclic stereocontrol has been a striking concern in modern organic chemistry, and a number of useful methods have been developed for stereoregulated synthesis of conformationally nonrigid complex molecules such as macrolide and polyether antibiotics. Special attention has therefore been paid to the aldol reaction because it constitutes one of the fundamental bond constructions in biosynthesis.[35]

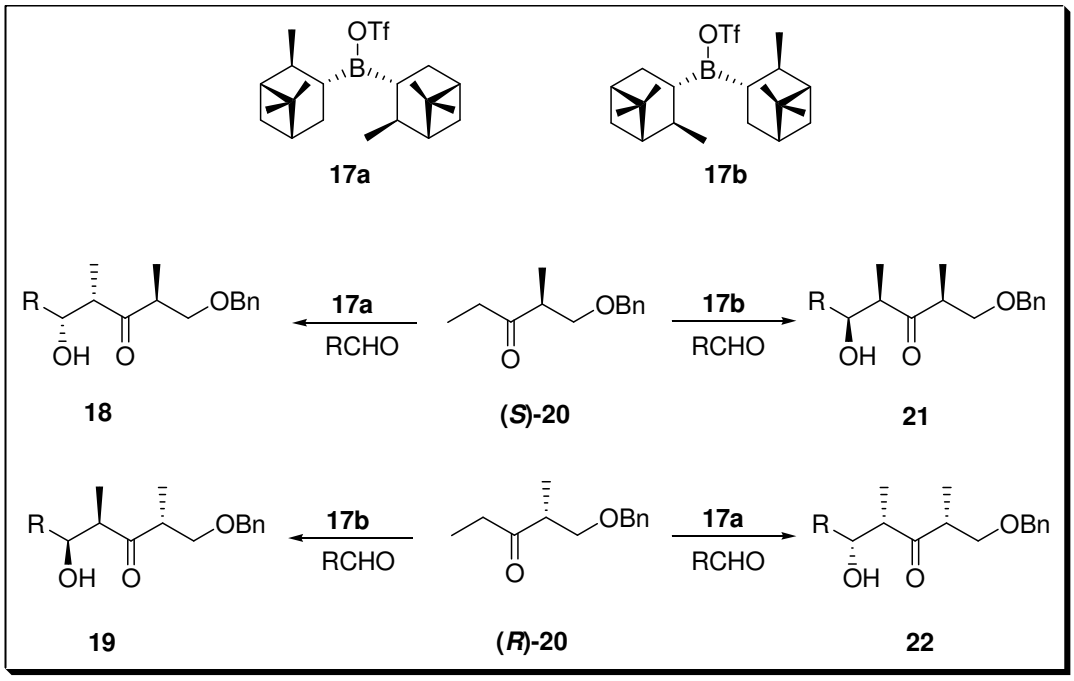
Many studies have focused on the diastereoselective (enantioselective) aldol reactions. The major control variables in these asymmetric aldol reactions are the metal counterions, the ligands binding to these metals, and the reaction conditions. Several approaches are available for imposing asymmetric control in aldol reactions:
1. Substrate control: This refers to the addition of an achiral enolate (or allyl metal reagent) to a chiral aldehyde (generally bearing a chiral center at the a-position). In this case, diastereoselectivity is determined by transition state preference according to Cram-Felkin-Ahn considerations.[36]



Scheme 5. Substrate Controlled Asymmetric Aldol Reaction

2. Reagent control: This involves the addition of a chiral enolate or allyl metal reagent to an achiral aldehyde. Chiral enolates are most commonly formed through

the incorporation of chiral auxiliaries in the form of esters, acyl amides (oxazolines), imides (oxazolidinones) or boron enolates. Chiral allyl metal reagents are also typically joined with chiral ligands.



Scheme 6. Reagent Controlled Asymmetric Aldol Reactions

3. Double stereodifferentiation: This refers to the addition of a chiral enolate or allyl metal reagent to a chiral aldehyde. Enhanced stereoselectivity can be obtained when the aldehyde and reagent exhibit complementary facile preference (matched case). Conversely, diminished results might be observed when their facial preference is opposed (mismatched pair).

1.6.3. Asymmetric Oxidation Reactions

The asymmetric oxidation of organic compounds, especially the epoxidation, dihydroxylation, aminohydroxylation, aziridination, and related reactions have been extensively studied and found widespread applications in the asymmetric synthesis of many important compounds.

Asymmetric epoxidation of allylic alcohols (Sharpless epoxidation)[37] was once one of the leading areas of investigation in synthetic organic chemistry, mainly due to the fact that very high enantioselective induction for a wide range of substrates is possible using several classes of reagents. In terms of both chemical and optical yields, this procedure allows a chemical reaction to compete with an enzymatic process.

The Sharpless epoxidation is a popular laboratory process that is both enantioselective and catalytic in nature. Not only does it employ inexpensive reagents and involve various important substrates (allylic alcohols) and products (epoxides) in organic synthesis, but it also demonstrates unusually wide applicability because of its insensitivity to many aspects of substrate structure. Selection of the proper chirality in the starting tartrate esters and proper geometry of the allylic alcohols allows one to establish both the chirality and relative configuration of the product.

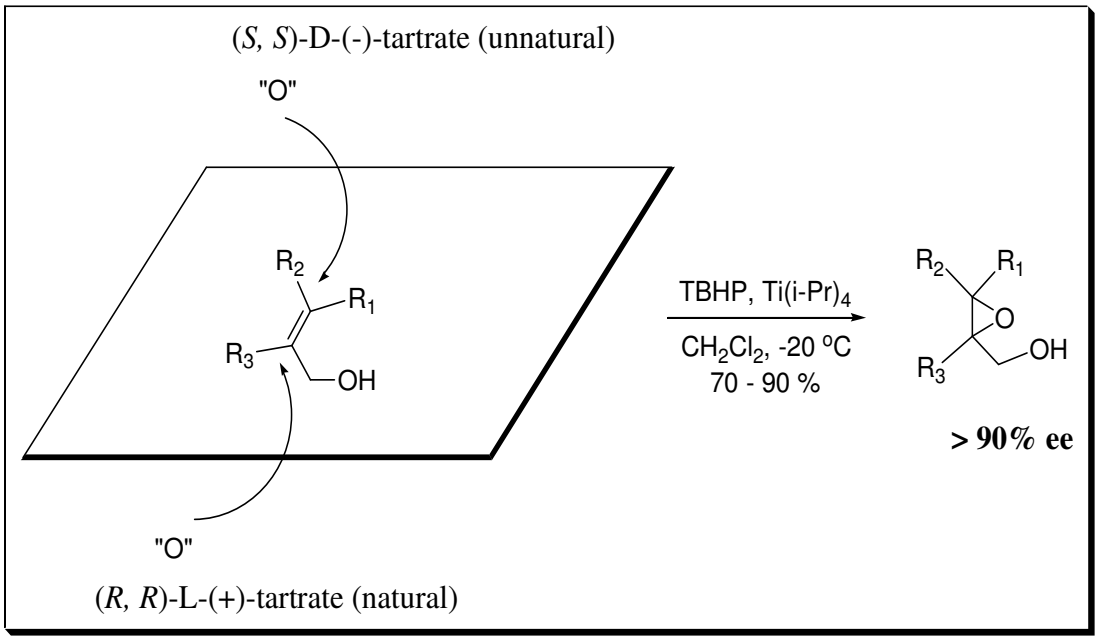
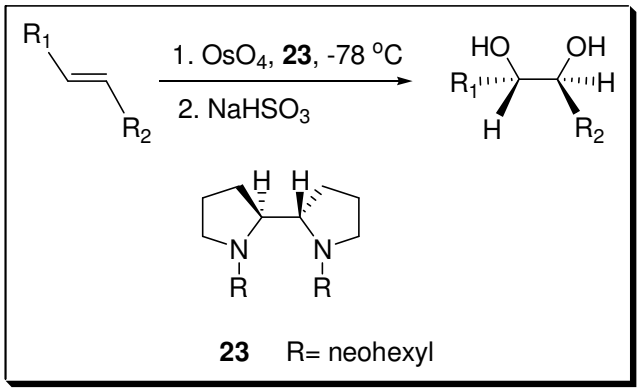


Figure 4. The Shrapless Epoxidation Reaction

The reaction of osmium tetroxide with alkenes is a reliable and selective transformation. Chiral diamines and cinchona alkakoid are most frequently used as chiral auxiliaries. Complexes derived from osmium tetroxide with diamines do not

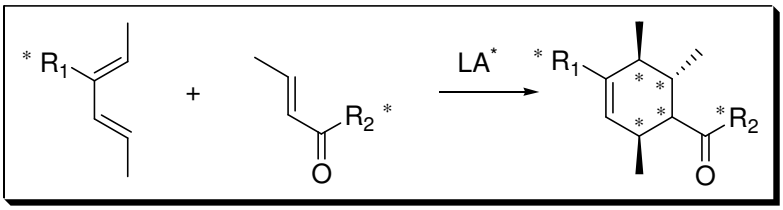
undergo catalytic turnover, whereas dihydroquinidine and dihydroquinine derivatives have been found to be very effective catalysts[38] for the oxidation of a variety of alkenes. OsO_4 can be used catalytically in the presence of a secondary oxygen donor (e.g., H_2O_2, TBHP, N-methylmorpholine-N-oxide, sodium periodate, O_2, sodium hypochlorite, potassium ferricyanide). Furthermore, a remarkable rate enhancement occurs with the addition of a nucleophilic ligand such as pyridine or a tertiary amine.



Scheme 7. Enantioselective Dihydroxylation of Olefins Using OsO_4 .**23**

1.6.4. Asymmetric Diels-Alder Reactions

The Diels-Alder reaction is a powerful synthetic process for constructing complex molecules. The reaction has been extensively studied and refined since its discovery in 1928.[39] The most attractive feature of the Diels-Alder reaction is its simultaneous, regioselective construction of two bonds, resulting in the creation of up to four chiral centers with largely predictable relative stereochemistry at the bond formation sites. Theoretically, there are a total of $2^4 = 16$ stereoisomers when atoms marked with an asterisk are all chiral centers (Scheme 8), therefore the complete control of the reaction process to obtain enantiomerically pure products has been the object of active research in many laboratories. In addition to the syn-facial addition of the reaction, considerable advances have been made in achieving asymmetric induction through the following three methods: (1) attaching chiral auxiliaries to dienophiles (2) attaching a chiral auxiliary to the diene, and (3) employing a chiral catalyst, usually a Lewis acid, such as LA*.



Scheme 8. Designation of Asymmetric Diels-Alder Reaction

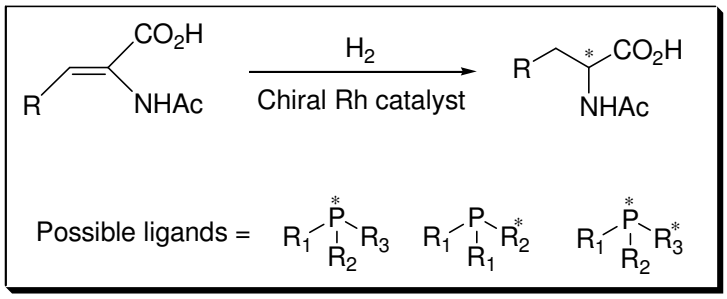
The first and the second approaches have been the most commonly employed method for achieving asymmetric induction in the Diels-Alder reaction during the past decade. However, applying chiral catalytic Lewis acids has shown widespread utility, with several excellent catalysts readily available. Indeed, the search for efficient chiral Lewis acids has been the prevailing issue in the study of asymmetric Diels-Alder reactions.

1.6.5. Asymmetric Catalytic Hydrogenation Reactions

Asymmetric addition of hydrogen to sp^2 carbon is the main theme of this chapter. Unsaturated bonds like C=C, C=O, or C=N are converted to the corresponding saturated CH-CH, CH-OH, and CH-NH bonds. Chiral metal-hydride reduction and the catalytic transfer hydrogenation of ketones are also discussed. These reactions are of great interest industrially. Indeed, many of them have been used for the production of highly enantiomerically pure amino acids, flavor and fragrance materials, and important pharmaceuticals and agrochemicals, which are all highly valued.

Before the 1960s, heterogeneous catalysis was a topic of indisputable importance in chemical research. The first asymmetric reaction was the application of chiral supports in the catalytic dehydrogenation of racemic 2-butanol by Schwab in 1932. Attempts to hydrogenate olefins with the aid of heterogeneous catalysts produced chiral products with only 10-15% ee in the 1950s. By the mid-1960s, it was becoming apparent that heterogeneous catalysts in general were not capable of providing satisfactory results in the hydrogenation of prochiral olefins. A new approach to asymmetric hydrogenation emerged in the late 1960s. In 1965, Wilkinson discovered a practical homogenous catalyst, $Rh(PPh_3)_3Cl$, which showed

very high activity in the hydrogenation of alkenes under mild conditions, and more attention has since been focused on modifying this catalyst by replacing the common triphenyl phosphine with chiral phosphine ligands.



Scheme 9. Possible Chiral Phosphine Ligands and Asymmetric Hydrogenation Reaction

1.7. Asymmetric Catalysis

The substrate-controlled reaction is often called the first generation of asymmetric synthesis. It is based on intramolecular contact with a stereogenic unit that already exists in the chiral substrate. Formation of the new stereogenic unit most often occurs by reaction of the substrate with an achiral reagent at a diastereotopic site controlled by a nearby stereogenic unit.

The auxiliary-controlled reaction is referred to as the second generation of asymmetric synthesis. This approach is similar to the first generation method in which the asymmetric control is achieved intramolecularly by a chiral group in the substrate. The difference is that the directing group, the 'chiral auxiliary', is deliberately attached to the original achiral substrate in order to direct the enantioselective reaction. The chiral auxiliary will be removed once the enantioselective transformation is completed.

Although second-generation methods have proved useful, the requirement for two extra steps, namely, the attachment and the removal of the chiral auxiliary, is a cumbersome feature. This is avoided in the third-generation method in which an achiral substrate is directly converted to the chiral product using a chiral reagent. In

contrast to the first- and second-generation methods, the stereocontrol is now achieved intermolecularly.

In all three of the above-mentioned chiral transformations, stoichiometric amounts of enantiomerically pure compounds are required. An important development in recent years has been the introduction of more sophisticated methods that combine the elements of the first-, second-, and third-generation methods and involve the reaction of a chiral substrate with a chiral reagent. The method is particularly valuable in reactions in which two new stereogenic units are formed stereoselectively in one step.

The most significant advance in asymmetric synthesis in the past three decades has been the application of chiral catalysts to induce the conversion of achiral substrates to chiral products. In ligand-accelerated catalysis, the addition of a ligand increases the reaction rate of an already existing catalytic transformation. Both the ligand-accelerated and the basic catalytic process operate simultaneously and complement each other. The nature of the ligand and its interaction with other components in the metal complex always affect the selectivity and rate of the organic transformation catalyzed by such a species. The obvious benefit of catalytic asymmetric synthesis is that only small amounts of chiral catalysts are needed to generate large quantities of chiral products. The enormous economic potential of asymmetric catalysis has made it one of the most extensively explored areas of research in recent years.

1.8. Some Important Chiral Catalysts

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

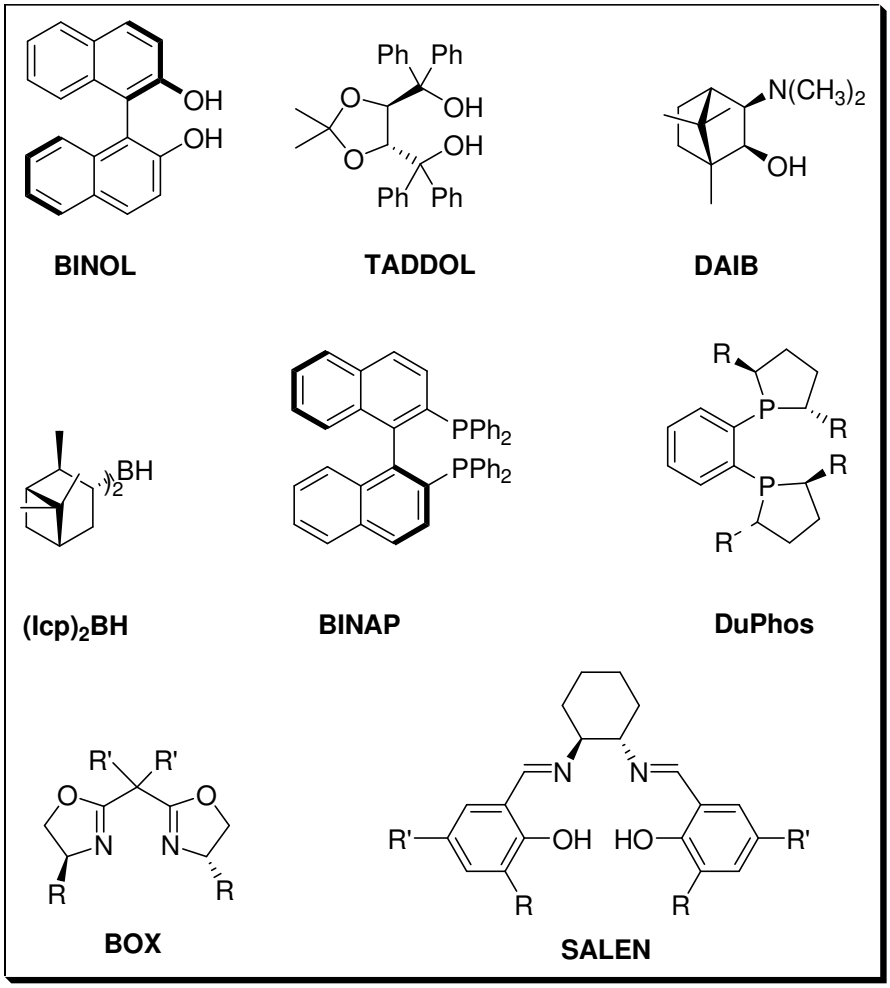


Figure 5. Some Important Chiral Catalysts

1.9. Dialkylzinc Addition to Aldehydes: Use of Aminoalcohols as Catalysts

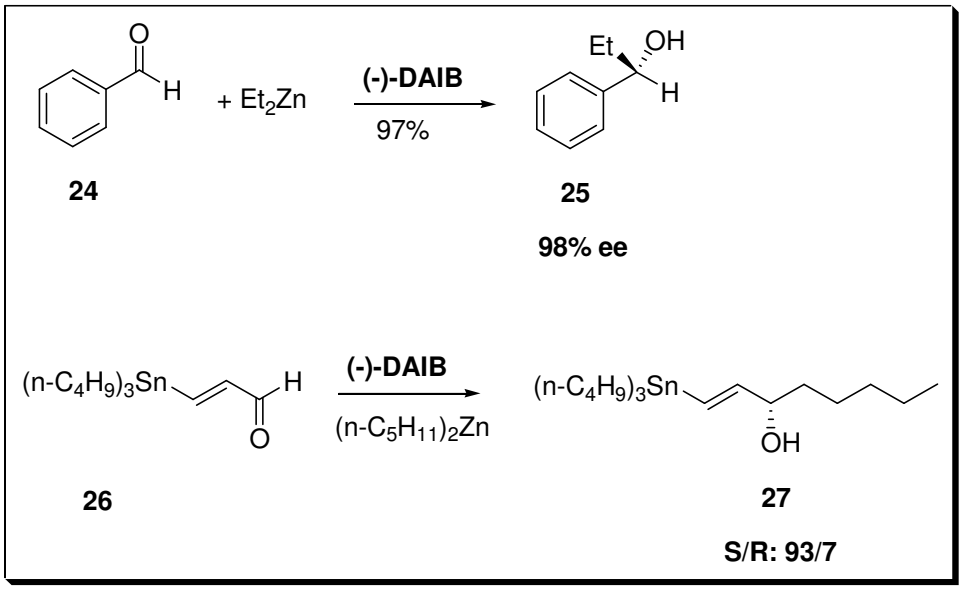
Nucleophilic addition of metal alkyls to carbonyl compounds in the presence of a chiral catalyst has been one of the most extensively explored reactions in asymmetric synthesis. Various chiral amino alcohols as well as diamines with C_2 symmetry have been developed as excellent chiral ligands in the enantioselective catalytic alkylation of aldehydes with organozincs. Although dialkylzinc compounds are inert to ordinary carbonyl substrates, certain additives can be used to enhance their reactivity.

The metallic compounds are not simple monomers, but usually exist as aggregates. To obtain high enantioselectivity, the ligand X* must possess a suitable three-dimensional structure that is able to differentiate the diastereomeric transition

states during the alkyl delivery step. The key issue is that at first the rate of alkylation by RMX* should substantially exceed that of the original achiral nucleophile R_2M; then, chiral ligand X* must be quickly detached from the initially formed metal alkoxide by the action of the alkyl donor or carbonyl substrate to complete the catalytic cycle.

The reaction between dialkylzinc and several chiral amino alcohol ligands satisfies these two key factors. 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.

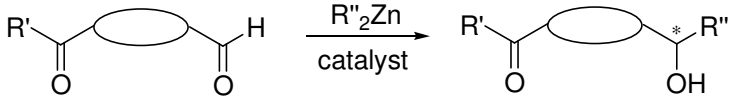
Treating benzaldehyde with diethylzinc in the presence of 2 mol % (-) -DAIB gives (S)-alcohol in 98% ee (Scheme 10). When compound **26** is treated in the same manner, compound **27**, a chiral building block in the three component coupling prostaglandin synthesis, is also obtained with high ee (Scheme 10).

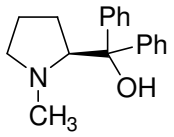


Scheme 10. Application of Dialkyl Zinc Addition Reaction

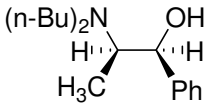
Most organometallic reagents, such as alkyllithium and Grignard reagents, are such strong nucleophiles that they usually fail to react chemoselectively with only aldehydes in the presence of ketones. Table 1 depicts the advantage of catalytic

asymmetric synthesis of hydroxyketone by the chemo- and enantioselective alkylation of ketoaldehydes with dialkylzinc reagents using chiral catalysts. In these reactions, optically active hydroxyketones can be obtained with high chemo- and enantioselectivity (up to 93% ee).



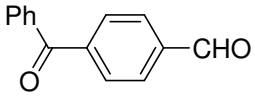
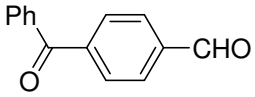
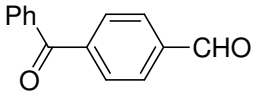
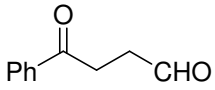
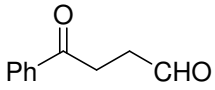
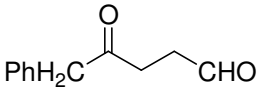
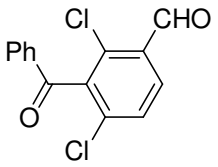


(S)-(+)-28



(1S, 2R)-(-)-29

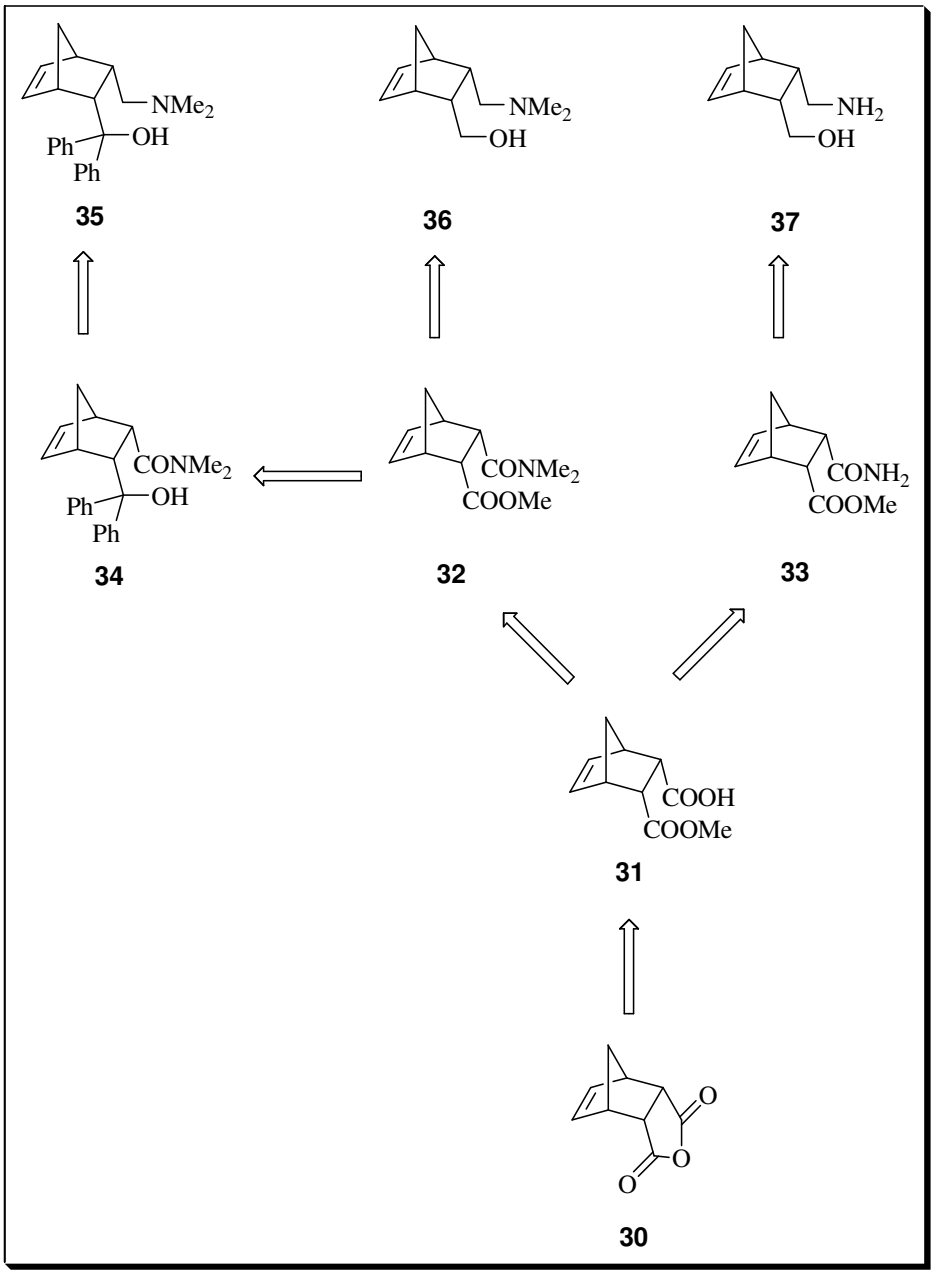
Table 1. Chemo and Enantioselective Alkylation of Ketoaldehydes

Entry	R_2Zn	Substrate	Catalyst	ee (%)
1	Et_2Zn		(S)-28	93
2	Et_2Zn		(1S, 2R)-29	91
3	$(n\text{-}Bu)_2Zn$		(S)-28	92
4	Et_2Zn		(1S, 2R)-29	87
5	Et_2Zn		(1R, 2S)-29	85
6	Et_2Zn		(1S, 2R)-29	81
7	Et_2Zn		(S)-28	88

1.10. Aim of the Work

The aim of this work is to synthesize chiral 1,4-aminoalcohol ligands and test their effectiveness in diethyl zinc addition reactions. It was deliberately decided to synthesize 1,4-aminoalcohols, because they may form more flexible and more stable complexes, when they coordinate to any metal atom.

The aim of the work is shown retrosynthetically in scheme 11.



Scheme 11. Retrosynthesis of the Work

CHAPTER 2

RESULTS AND DISCUSSION

2.1. Perspective of the Work

Aminoalcohols are versatile chiral building blocks for organic synthesis[40] and have also been used extensively as chiral auxiliaries[41] or ligands in asymmetric synthesis.[42] In particular, the formation of C-C bonds has always been one of the most challenging area in organic synthesis. Among these, the enantioselective addition of diethylzinc to aldehydes in the presence of chiral ligands has been first reported by Noyori et.al.[43] Although different types of chiral ligands such as diamines,[44] diols,[45] aminothiols,[46] and aminosulfides[46] were used in this reaction, aminoalcohols are the most common type of ligands among them. Chiral 1,2-aminoalcohols are widely used in diethylzinc addition reactions, however, there are just a few examples of chiral 1,4-amino alcohols used in this reaction.[40, 47-51] 1,4-Aminoalcohols have more flexible structures with respect to 1,2-aminoalcohols for complexation with various types of metals, thus they may form more stable and more selective catalysts in the reaction. This prompted us to develop new chiral 1,4-aminoalcohols including a norbornene backbone and their use in the alkylation of benzaldehyde by diethylzinc.

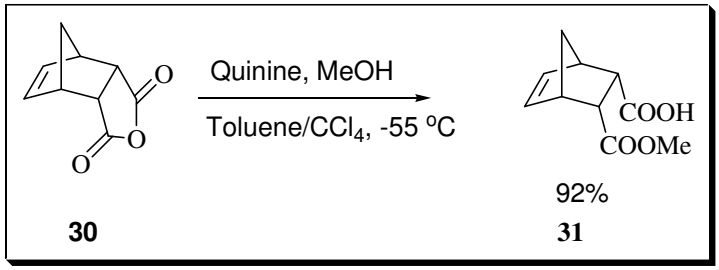
2.2. Asymmetric Synthesis of Aminoalcohol Ligands

In our synthetic strategy, cis-monoester **(-)-31** was chosen as the starting compound for the construction of norbornene backbone and this compound was converted to various types of amino alcohols.

2.2.1. Desymmetrization of Meso-Anhydride

Bolm et al.[52] have recently reported a highly efficient method for enantioselective desymmetrizaton of meso-anhydrides via alkaloid-mediated opening with methanol. Quinine or quinidine are used as chiral directing agents and both enantiomers of the corresponding cis-monoester can be obtained with very high enantiomeric excess values (up to 99% e.e.) and chemical yield.

Quinine-mediated desymmetrization of anhydride **30** with methanol resulted in cis-monoester **(-)-31**. (Scheme 12).



Scheme 12. Synthesis of **(-)-31**

In this reaction one mole of MeOH reacted enantioselectively with the one carbonyl group of the anhydride. The product was identified by using NMR spectroscopy. From the ^{1}H-NMR, it can easily be understood that the starting material completely lost its symmetry and the following peaks are observed: one singlet at 3.54 (3H) ppm belonging to -OC**H**$_3$; two doublet of doublets at 6.26 (1H) and 6.16 (1H) ppm belonging to the double bond hydrogens; two doublets at 1.43 (1H) and 1.28 (1H) ppm belonging to the H_7 hyrdrogens; two broad singlets at 3.14 (1H) and 3.11 (1H) ppm belonging to H_1 and H_4 protons, and two doublet of doublets at 3.28 (1H) and 3.22 (1H) ppm belonging to H_2 and H_3 protons (Figure 6). From the ^{13}C-NMR spectroscopy, following peaks are observed: 177.8 (C_9); 173.1 (C_8); 135.6 and 134.4 corresponding to C_5 and C_6; 51.6 (C_{10}); 48.8 and 48.2 corresponding to C_2 and C_3; 47.9 and 46.6 corresponding to C_1 and C_4, and 46.1(C_7) ppm (Figure 7). The melting point of the compound **31** is 75-78 ^{o}C and has $[\alpha]_D^{20}$ = -7.8 (c 4.0, CCl_4).

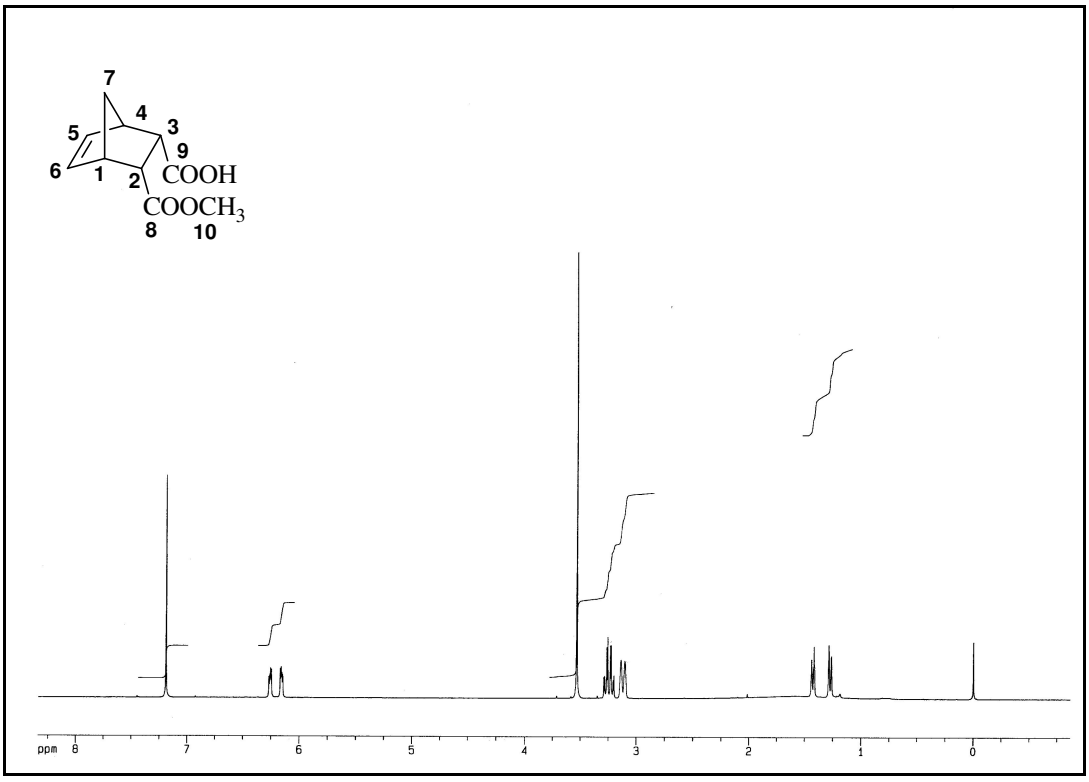


Figure 6. ^{1}H-NMR Spectrum of **31**

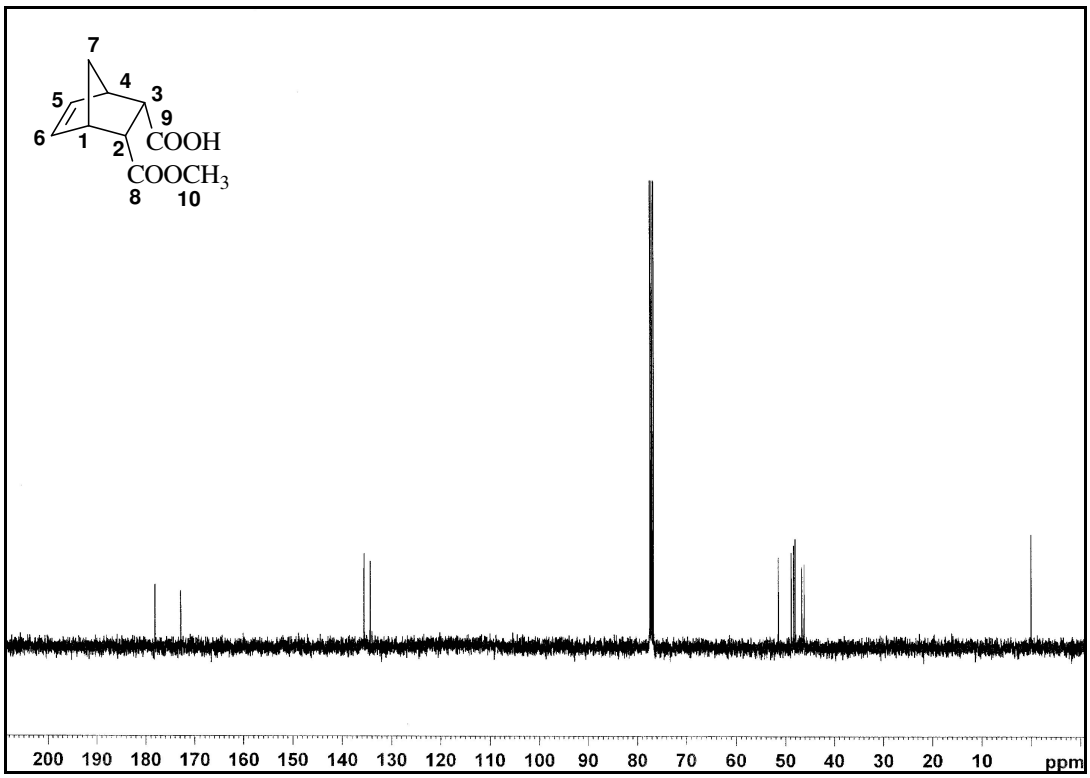
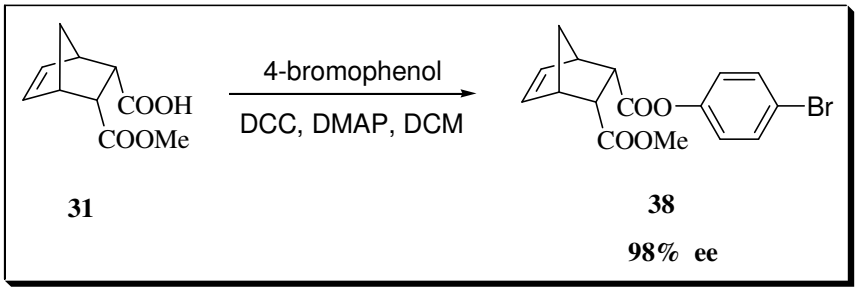


Figure 7. ^{13}C-NMR Spectrum of **31**

2.2.2. Enantiomeric Excess Determination of the Hemiester, 31

Monoester (-)-**31** was reacted with p-bromophenol via DCC coupling method to produce corresponding diester **38** (Scheme 13), which was then analyzed by HPLC for enantiomeric excess determination (Figure 8). HPLC analysis of the methyl 4-bromophenyldiester was carried out by using Chiralcel OD-H column and the process was done at room temperature by using n-hexane/2-propanol = 98:2 system, the flow rate was 0.5 mL/min and the wavelength of the detector was 254 nm. [t_1=20.3 min (major), t_2= 23.2 min (minor)]



Scheme 13. Synthesis of **38**

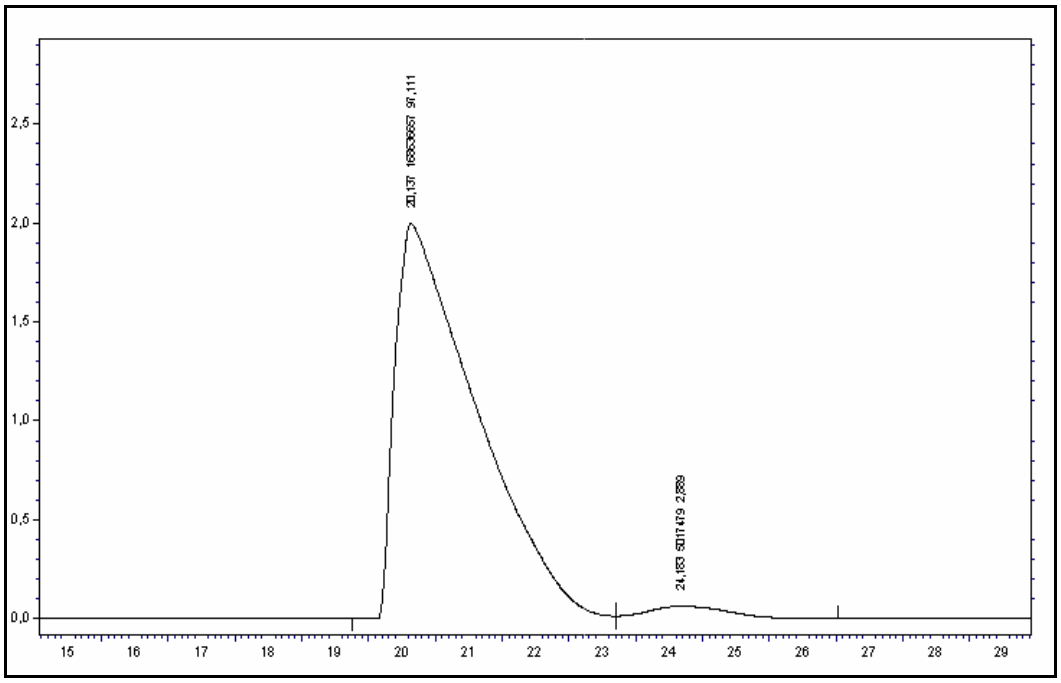


Figure 8. HPLC Chromotagram of Compound **38**

In this reaction, carboxylic acid group of the compound **31** was activated with DCC and then reacted with 4-bromophenol to afford the product **38**. The product was identified by using NMR spectroscopy.

From the ^{1}H-NMR, the following peaks are observed: singlet at 3.55 (3H) ppm belonging to -OC**H**$_3$; two doublet of doublets at 6.32 (1H) and 6.15 (1H) ppm belonging to the double bond hydrogens; two doublets at 7.37 (2H) and 6.92 (2H) ppm belonging to aromatic protons H_{12} and H_{13} respectively; two doublets at 1.40 (1H) and 1.33 (1H) ppm belonging to the H_7 hyrdrogens; one broad singlets at 3.39 (2H) belonging to H_2 and H_3 protons; two broad singlets at 3.20 (1H) and 3.17 (1H) ppm belonging to H_1 and H_4 protons (Figure 9). From the ^{13}C-NMR spectroscopy, following peaks are observed: 173.0 (C_8); 171.2 (C_9); 150.3 (C_{11}); 135.9 and 135.0 corresponding to C_5 and C_6; 132.7 (C_{14}), 123.8 (C_{12}); 119.0 (C_{13}); 52.2 (C_{10}); 49.1 and 48.7 corresponding to C_2 and C_3; 48.5 and 47.2 corresponding to C_1 and C_4; 46.6 (C_7) ppm (Figure 10). HPLC analysis of the methyl 4-bromophenyldiester: 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).

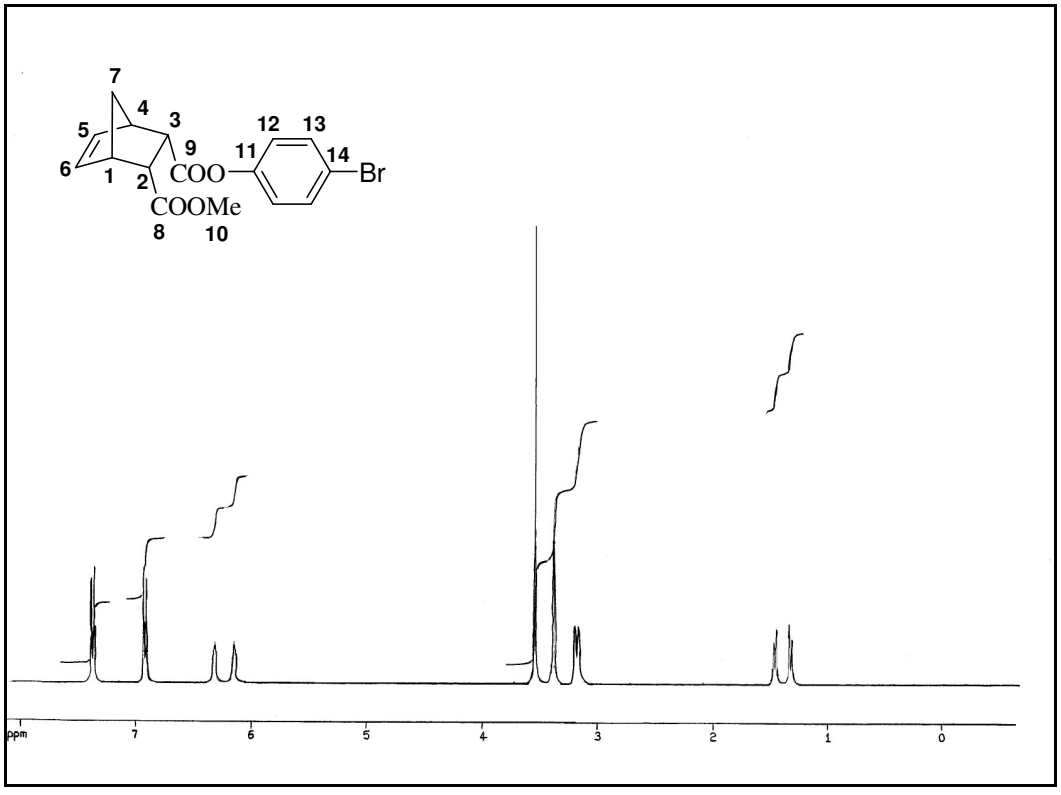


Figure 9. ^{1}H-NMR Spectrum of **38**

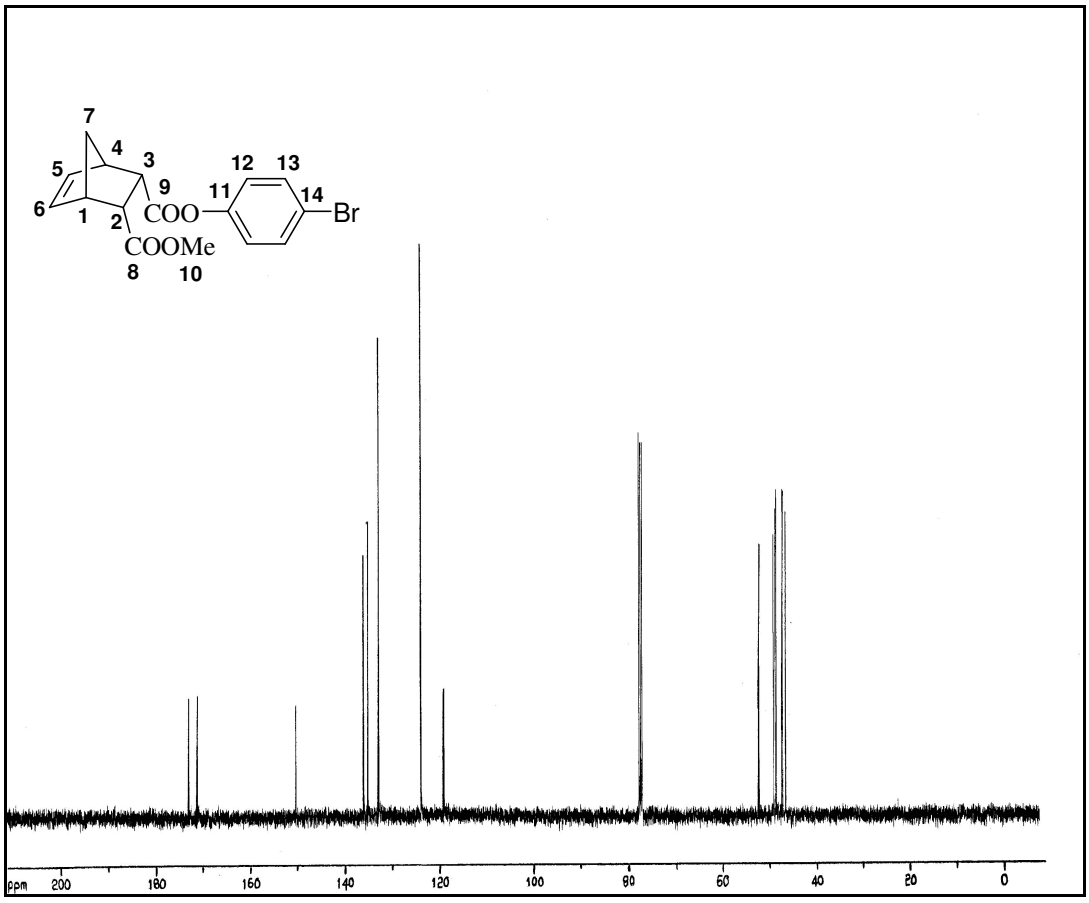
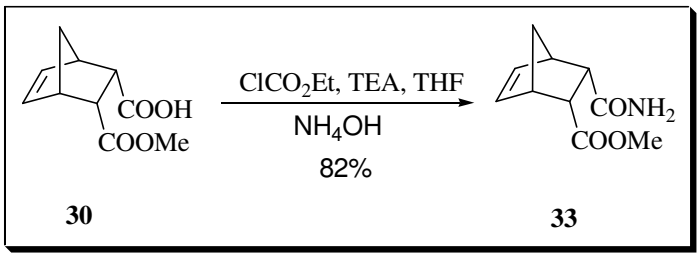


Figure 10. ^{13}C-NMR Spectrum of **38**

2.2.3. Chemoselective Synthesis of Amide-Ester, 33

In our synthetic route, carboxylic acid group of monoester **(-)-30** was chemoselectively activated with ethylchloroformate and then reacted with NH_4OH to afford corresponding cis-monoester amide **33** with 82% yield.



Scheme 14. Synthesis of **33**

The product was identified by using NMR spectroscopy. From the ^{1}H-NMR, following peaks are observed: singlet at 3.54 (3H) ppm belonging to -OC**H**$_3$; two doublet of doublets at 6.45 (1H) and 6.11 (1H) ppm belonging to the double bond hydrogens; one broad singlet at 5.54 (2H) ppm belonging to N**H**$_2$ protons, two doublets at 1.44 and 1.28 ppm belonging to the H_7 hyrdrogens; one multiplet at 3.07 (2H) ppm belonging to H_1 and H_4 protons and two doublet of doublets at 3.18 (1H) and 3.23 (1H) ppm belonging to H_2 and H_3 protons (Figure 11).

From the ^{13}C-NMR spectroscopy, following peaks are observed: 174.3 (C8); 173.6 (C9); 137.0 and 133.3 corresponding to C_5 and C_6; 51.5 (C_{10}), 49.8 and 49.3 corresponding to C_2 and C_3; 49.0 and 47.2 corresponding to C_1 and C_4; 45.7 (C_7) ppm (Figure 12).

The melting point of the compound **33** is 130-131 ^{o}C and has $[\alpha]_D^{20}$ = -2.5 (*c* 2.77, MeOH).

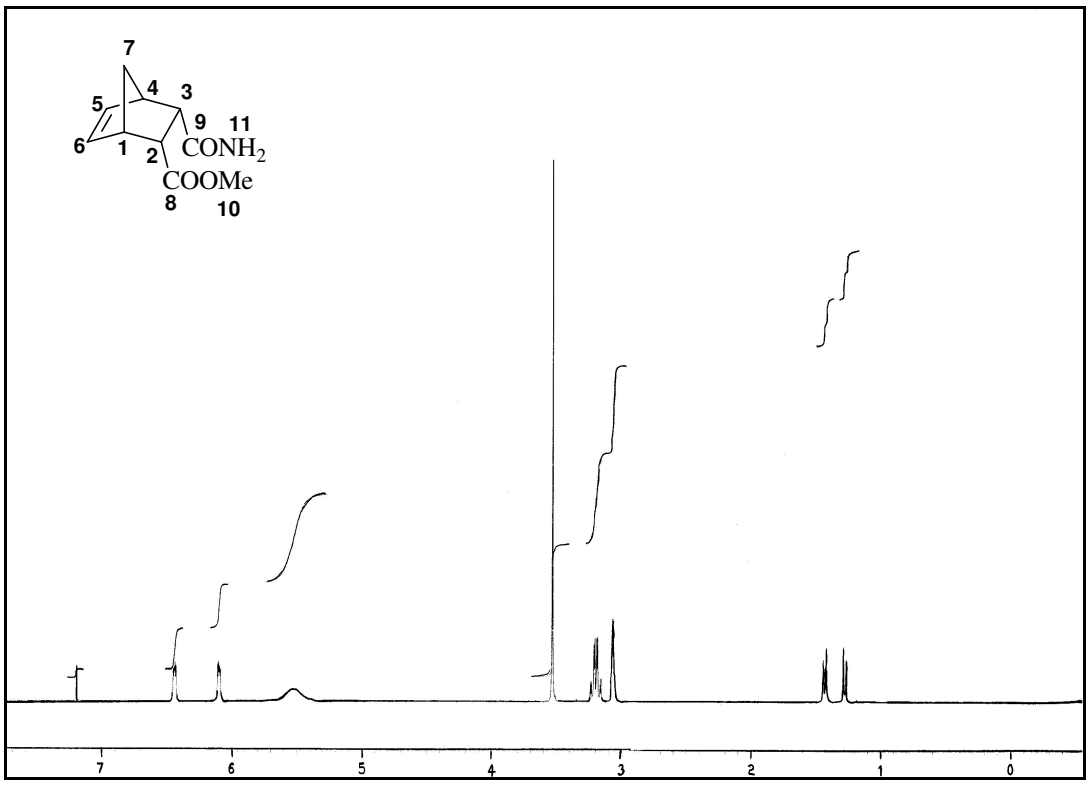


Figure 11. ^{1}H-NMR Spectrum of **33**

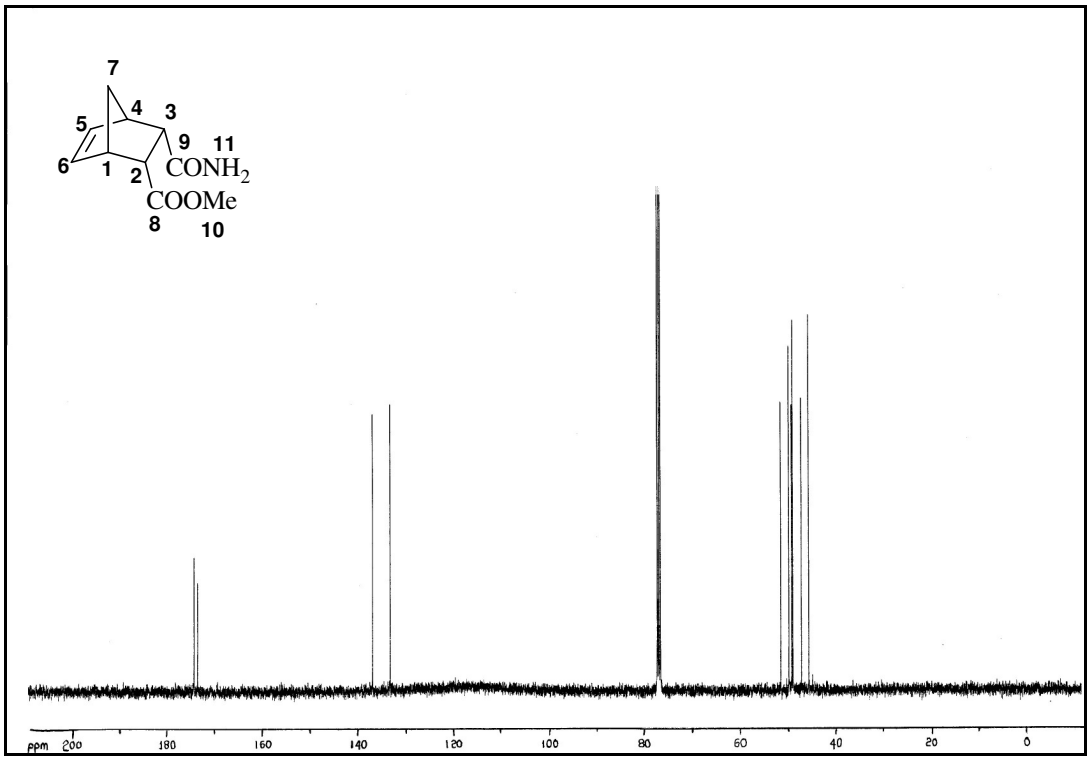
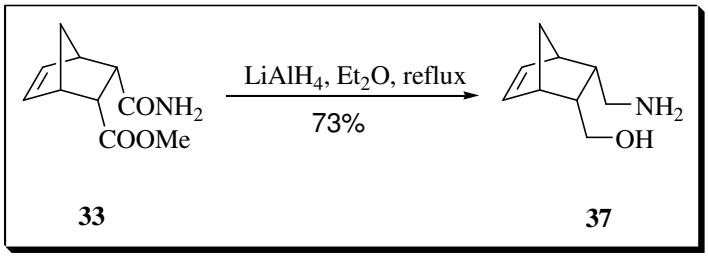


Figure 12. ^{13}C-NMR Spectrum of **33**

2.2.4. Reduction of Amide-Ester, 33, with LAH

One of the target cis-1,4-unsubstituted amino alcohol derivative **37** was obtained by subsequent $LiAlH_4$ reduction of **33** in ether with 73 % yield.



Scheme 15. Synthesis of **37**

The product was identified by using NMR and HRMS spectroscopy. From the ^{1}H-NMR, following peaks are observed:

Two doublet of doublets at 6.06 (1H) and 6.02 (1H) ppm belonging to the double bond hydrogens; one broad singlet at 3.74 (2H) ppm belonging to N**H**$_2$ protons, two doublets at 1.40 and 1.39 ppm belonging to the H_7 hyrdrogens; two multiplets between 2.28-2.35 (1H) and 2.56-2.60 (1H) ppm belonging to H_4 and H_1 protons respectively; one doublet of doublet at 3.55 (1H) and one triplet at 3.32 (1H) belonging to H_8 and $H_{8'}$, one doublet of doublet at 2.98 (1H) and one triplet at 2.44 ppm belonging to H_2 and H_3 protons, and one triplet at 2.77 (2H) ppm belonging to H_9 and $H_{9'}$ protons (Figure 13). From the ^{13}C-NMR spectroscopy, following peaks are observed: 135.5 and 134.4 ppm corresponding to C_5 and C_6; 63.2 (C_8); 49.8 (C_9); 47.6 and 46.9 corresponding to C_1 and C_4; 46.2 and 44.4 corresponding to C_2 and C_3; 44.2 (C_7) ppm (Figure 14). The melting point of the compound **37** is 102-104 ^{o}C and has $[\alpha]_D^{20}$ = -8.9 (*c* 0.56, MeOH). According to HRMS calculations, $(M+H)^+$ was found to be $C_9H_{16}NO$.

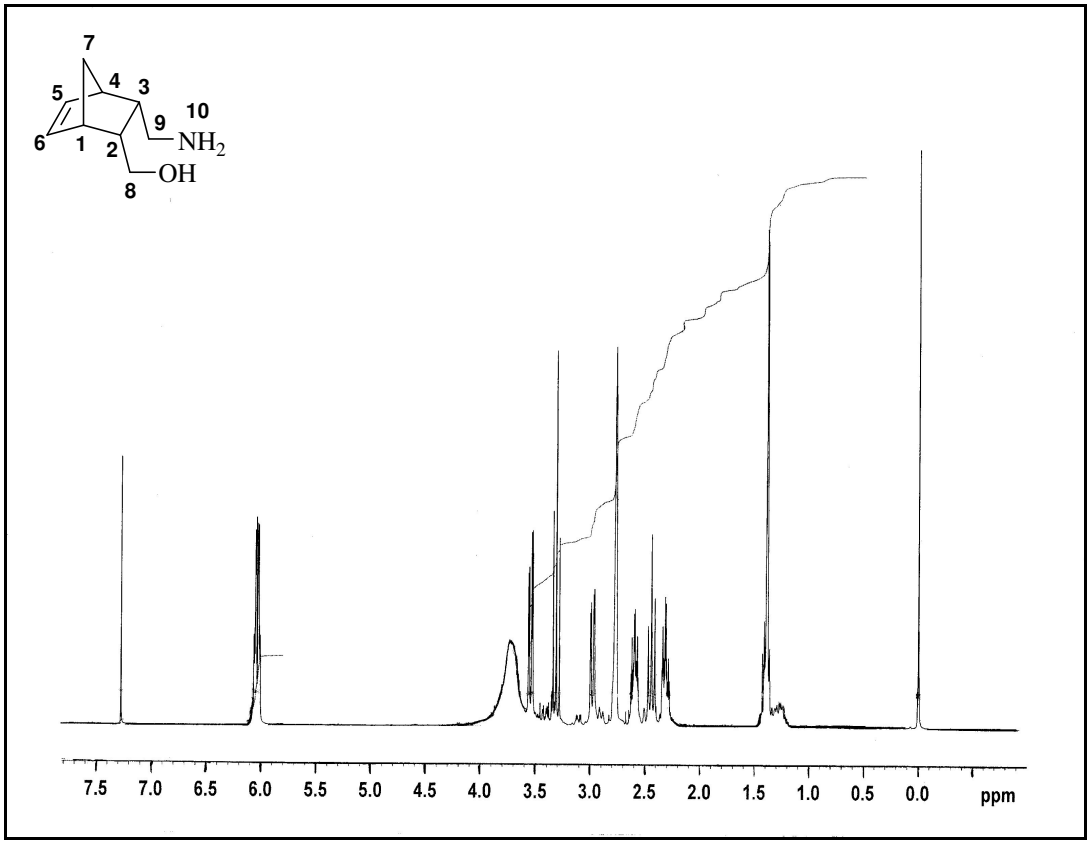


Figure 13. ^{1}H-NMR Spectrum of **37**

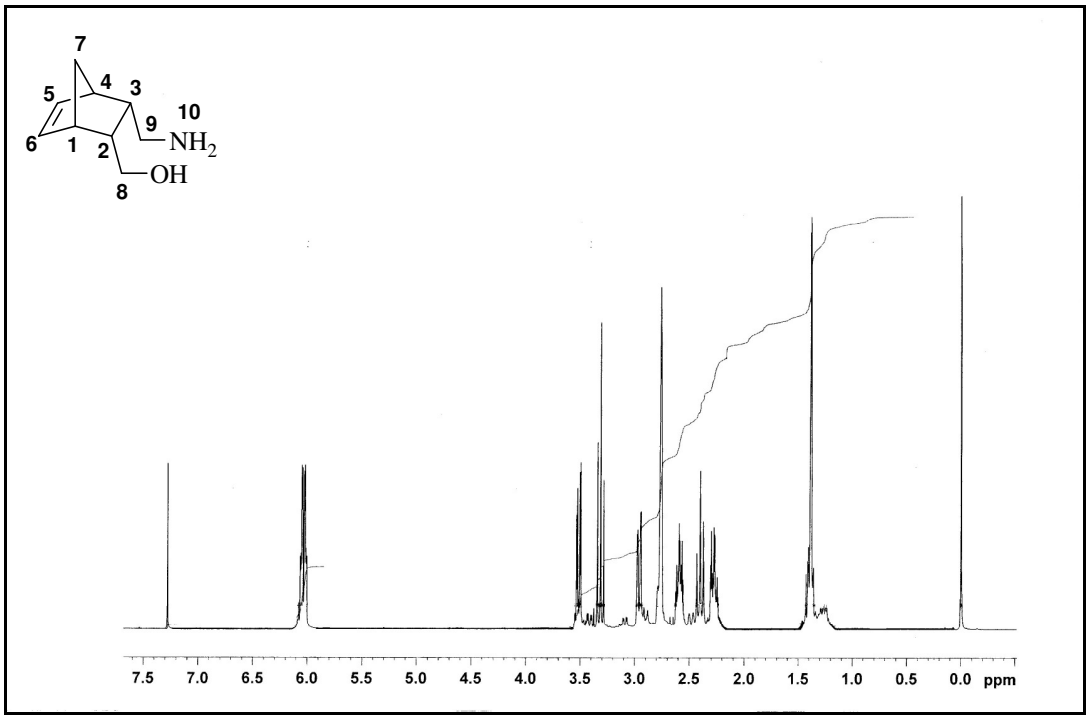


Figure 14. ^{1}H-NMR Spectrum of **37** in the presence of 1 drop D_2O

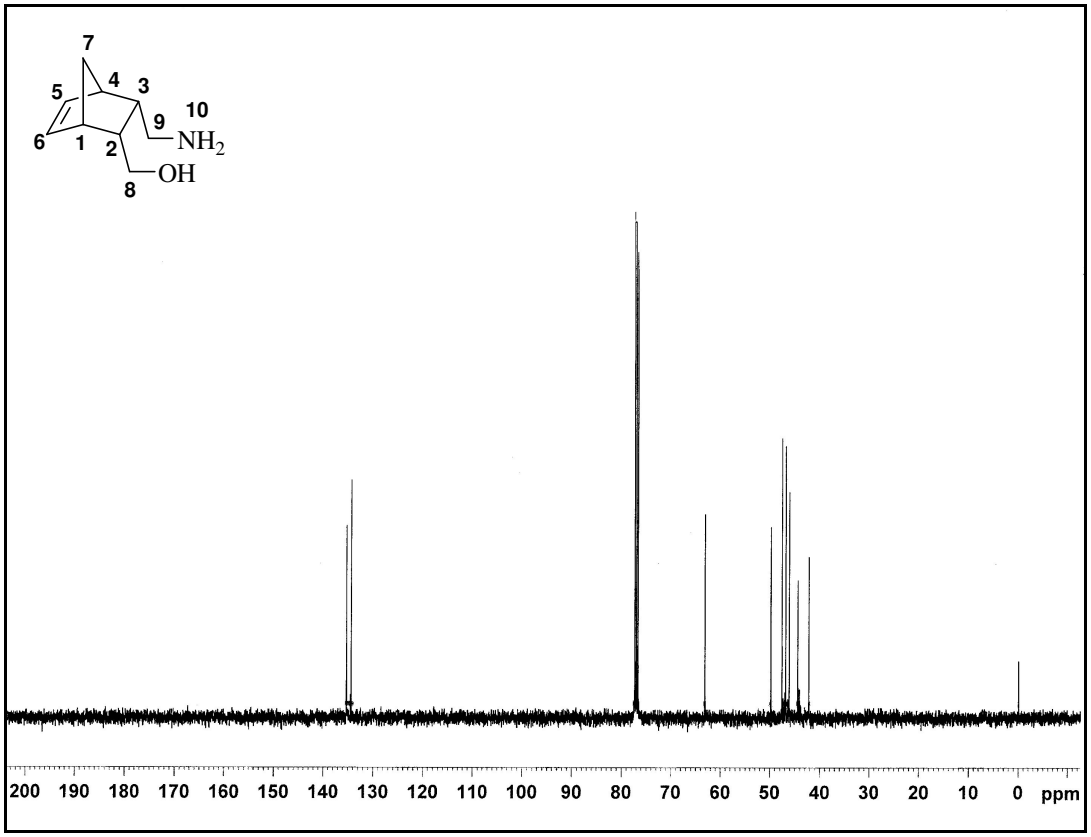
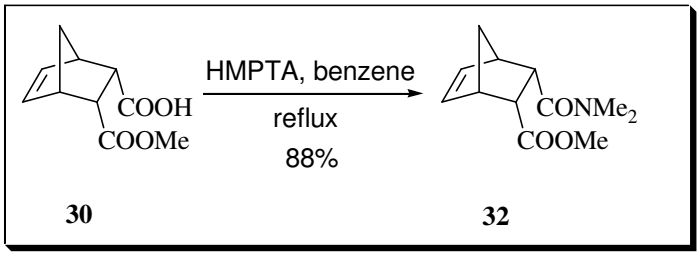


Figure 15. ^{13}C-NMR Spectrum of **37**

2.2.5. Chemoselective Synthesis of Amide-Ester, 32

Substitution on norbornene based cis-1,4-amino alcohol nitrogen and methylene bearing hydroxy group would presumably cause an impact on the catalytic activity of the resulting chiral ligands used in the asymmetric addition of diethylzinc to benzaldehyde. In the synthesis of sterically and electronically modified chiral ligands, monoester **(-)-30** was reacted with hexamethylphosphorous triamide which transformed the carboxylic acid group into corresponding N,N-dimethyl amide derivative **32** with 88 % yield.[53]



Scheme 16. Synthesis of **32**

The product was identified by using NMR spectroscopy. From the ^{1}H-NMR, following peaks are observed: singlet at 3.52 (3H) ppm belonging to -OC**H**$_3$; two singlets at 2.81 (3H) and 2.95 (3H) ppm belonging to methylene groups attached to the nitrogen atom; two doublet of doublets at 6.30 (1H) and 6.12 (1H) ppm belonging to the double bond hydrogens; two doublets at 1.38 (1H) and 1.27 (1H) ppm belonging to the H_7 hyrdrogens; two broad singlets at 3.12 (1H) and 3.04 (1H) ppm belonging to the H_1 and H_4 protons and two doublet of doublets at 3.19 (1H) and 3.35 (1H) ppm belonging to H_2 and H_3 protons (Figure 16). From the ^{13}C-NMR spectroscopy, following peaks are observed: 173.3 (C_8); 172.4 (C_9), 136.6 and 133.9 corresponding to C_5 and C_6; 51.9 (C_{10}); 49.2 and 48.9 corresponding to C_{11} and C_{12}; 47.3 and 47.0 corresponding to C_2 and C_3; 46.9 and 37.3 corresponding to C_1 and C_4 and 36.0 (C_7) ppm (Figure 17). The melting point of the compound **32** is 78-79 ^{o}C and has $[\alpha]_D^{20}$ = -35.7 (*c* 1.16, $CHCl_3$). According to HRMS calculations, $(M+H)^+$ was found to be $C_{12}H_{18}NO_3$.

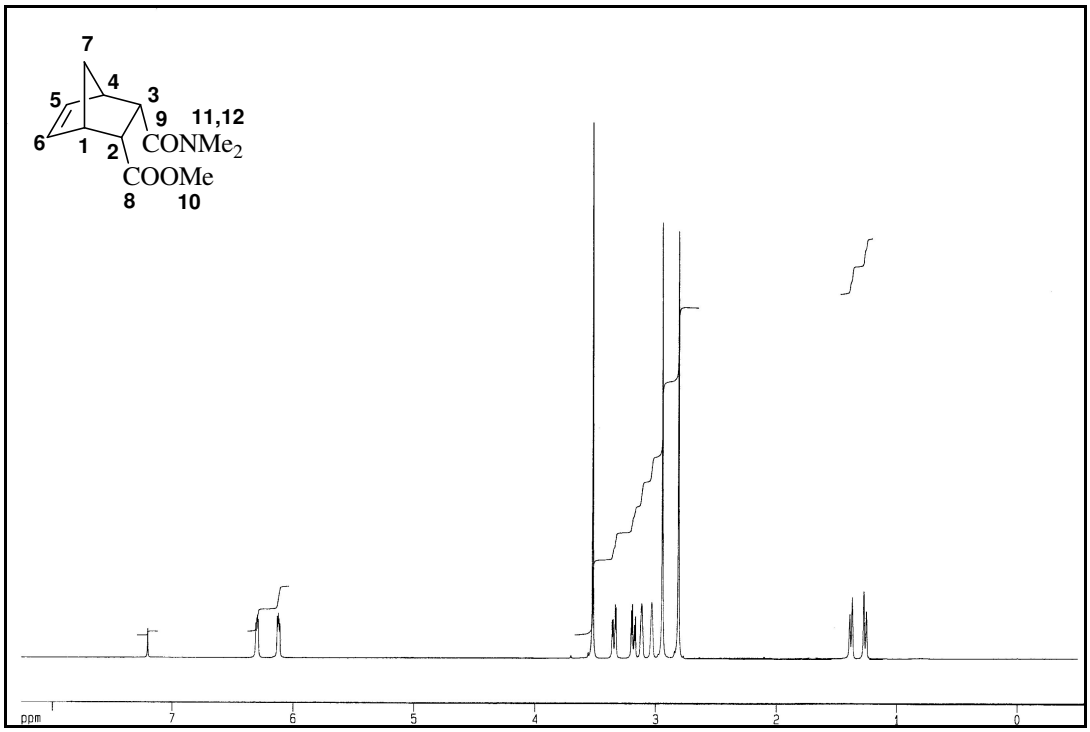


Figure 16. ^{1}H-NMR Spectrum of **32**

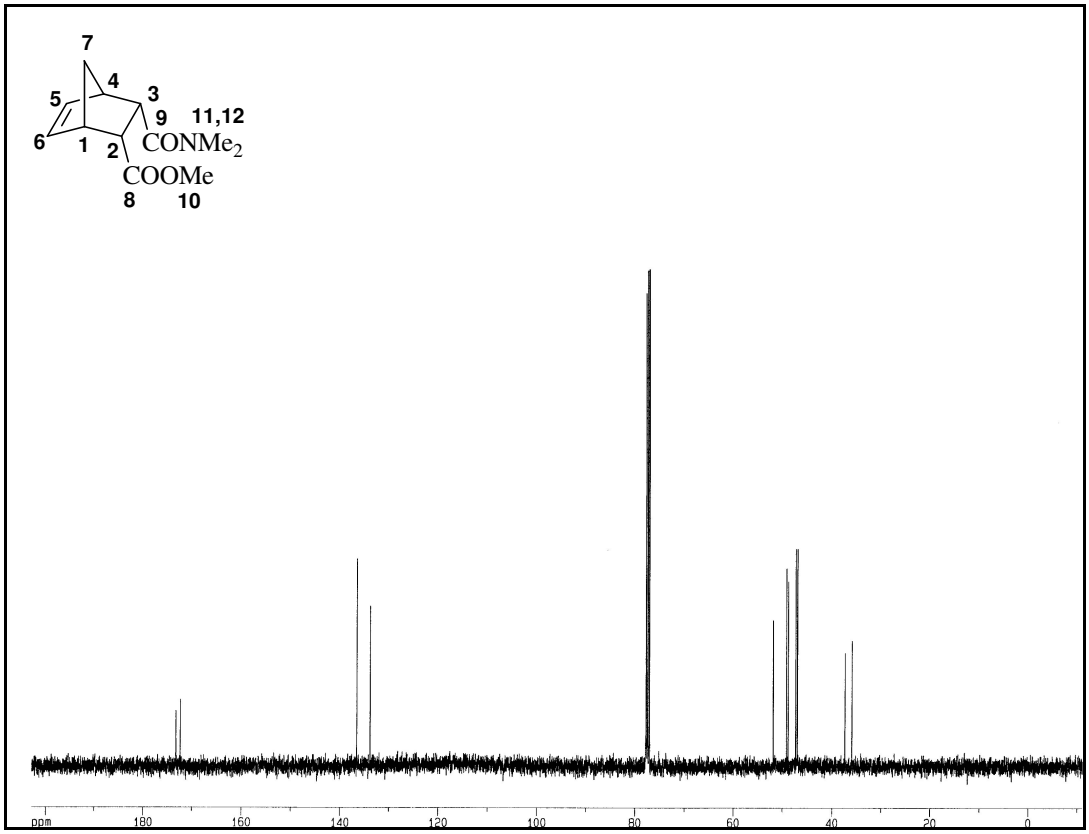
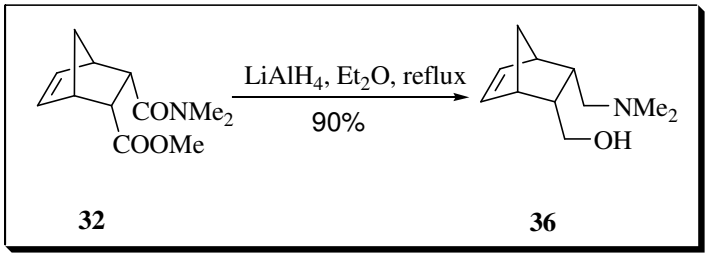


Figure 17. ^{13}C-NMR Spectrum of **32**

2.2.6. Reduction of Amide-Ester, 32, with LAH

Subsequent reduction of **32** by $LiAlH_4$ in ether afforded the N,N-dimethyl substituted cis-1,4-amino alcohol type chiral ligand **36** with 90 % yield.



Scheme 17. Synthesis of **36**

The product was identified by using NMR and HRMS spectroscopy. From the ^{1}H-NMR, following peaks are observed: one multiplet at 5.98 (2H) ppm belonging to the double bond hydrogens; one multiplet at 1.33 (2H) ppm belonging to the H_7 hydrogens; one singlet at 2.16 (6H) ppm belonging to two methyl groups attached to the nitrogen atom; one doublet of doublet at 3.43 (1H) and one triplet at 3.13 (1H) ppm belonging to H_8 and $H_{8'}$, one doublet of doublet at 2.03 (1H) ppm and one triplet at 2.24 (1H) ppm belonging to H_2 and H_3 protons; one multiplet at 2.42 (2H) belonging to H_9 and $H_{9'}$ protons; two singlets at 2.64 (1H) and 2.61 (1H) ppm belonging to H_1 and H_4 protons (Figure 18).

From the ^{13}C-NMR spectroscopy, following peaks are observed: 135.8 and 134.8 corresponding to C_5 and C_6; 63.5 (C_8); 61.0 (C_9); 50.4 (C_{10}); 48.0 and 47.3 corresponding to C_2 and C_3; 46.5 and 45.6 corresponding to C_1 and C_4 and 40.2 (C_7) ppm (Figure 19).

The melting point of the compound **36** is 90-92 ^{o}C and has $[\alpha]_D^{20}$ = +15.1 (*c* 1.16, MeOH). According to HRMS calculations, $(M+H)^+$ was found to be $C_{11}H_{20}NO$.

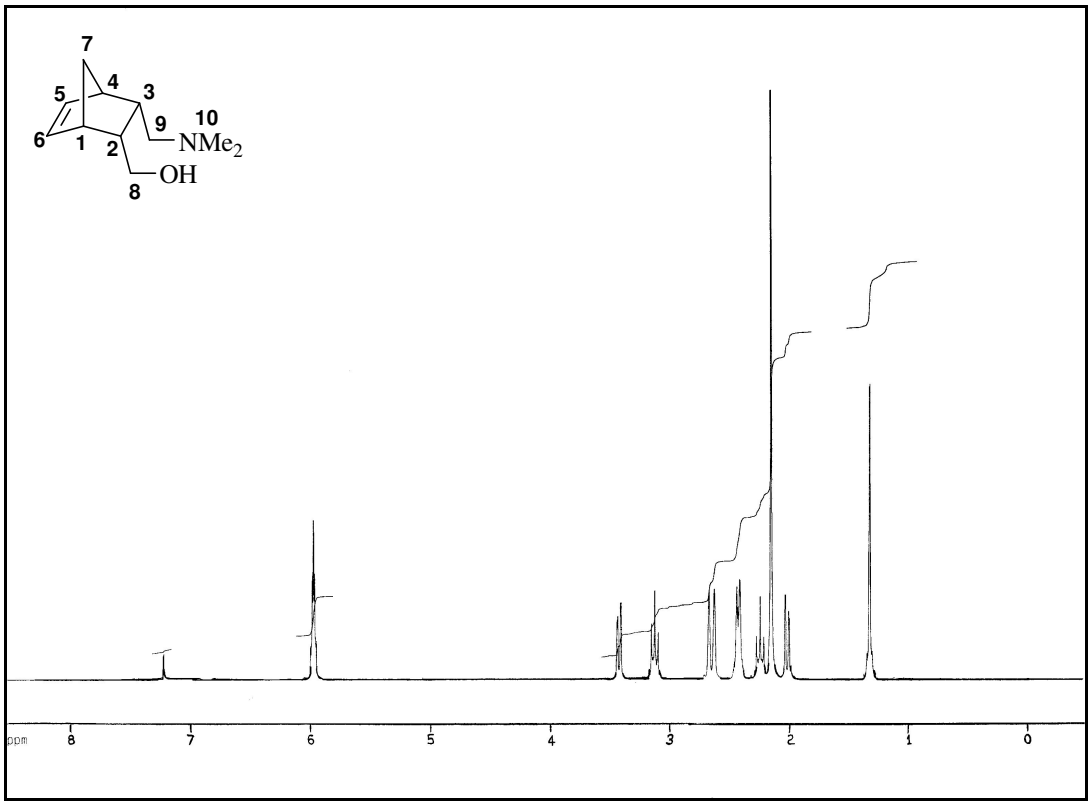


Figure 18. ^{1}H-NMR Spectrum of **36**

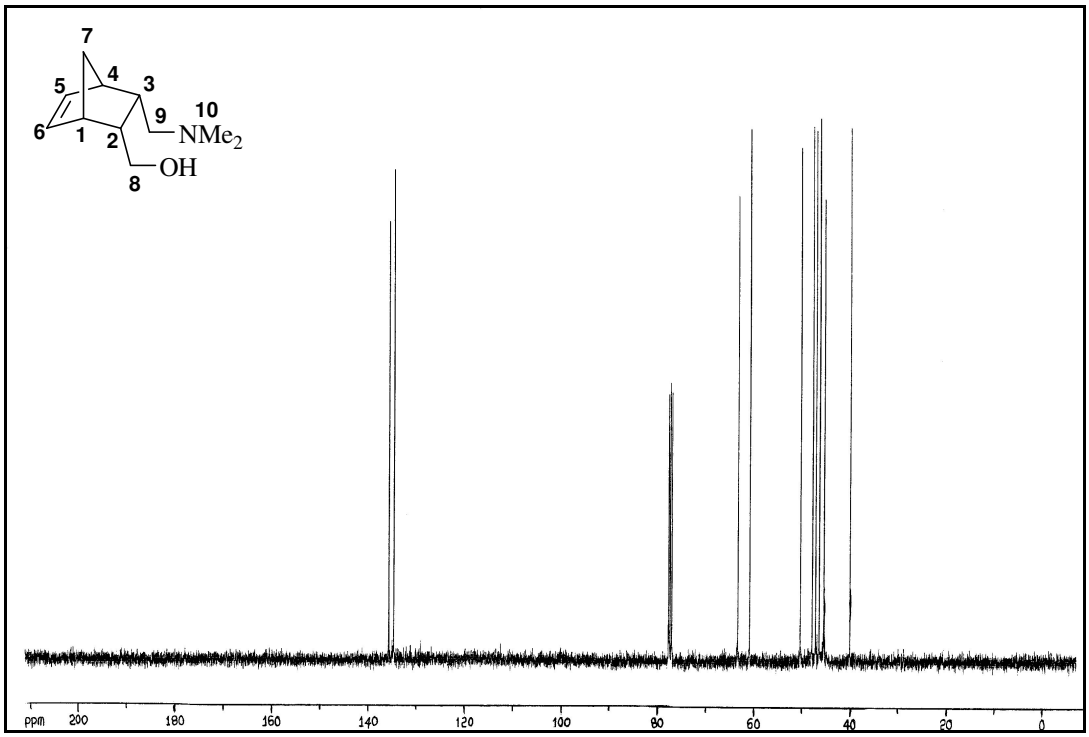
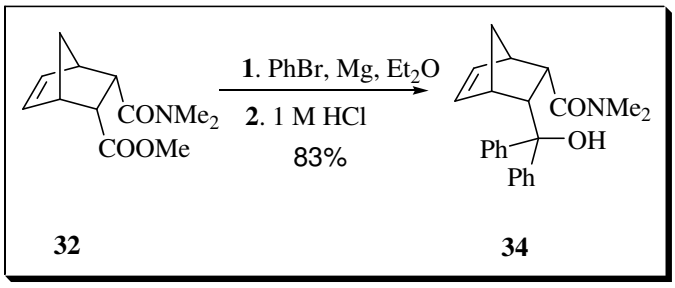


Figure 19. ^{13}C-NMR Spectrum of **36**

2.2.7. Grignard Reaction of Amide-Ester, 32, with Phenylbromide

Using Grignard method, the ester group of **32** was functionalized with phenylmagnesium bromide giving diphenyl substituted derivative **34**.



Scheme 18. Synthesis of **34**

The product was identified by using NMR and HRMS spectroscopy. From the ^{1}H-NMR, following peaks are observed: three multiplets between 7.45-7.50 (4H), 7.16-7.21 (4H) and 7.02-7.08 (2H) ppm belonging to the aromatic protons; two doublet of doublets at 6.53 (1H) and 5.87 (1H) ppm belonging to double bond hydrogens; two doublet of doublets at 3.56 (1H) and 3.46 (1H) ppm belonging to H_2 and H_3 protons; two singlets 2.86 (1H) and 2.56 (1H) ppm belonging to H_1 and H_4 protons; two singlets 2.84 (3H) and 2.30 (3H) ppm belonging to methyl groups attached to amide nitrogen and one singlet at 1.29 (2H) ppm belonging to H_7 hydrogens. (Figure 20).

From the ^{13}C-NMR spectroscopy, following peaks are observed: 175.3 (C_9); 150.8 and 148.5 corresponding to C_{11} and $C_{11'}$; 138.8 and 131.0 corresponding to C_5 and C_6; 128.2, 128.1, 128.0, 126.4, 126.3 and 126.2 corresponding to C_{12}, C_{13}, C_{14}, $C_{12'}$, $C_{13'}$ and $C_{14'}$; 78.1 (C_8); 58.7 and 50.5 corresponding to C_{10a} and C_{10b}; 47.8 and 46.4 corresponding to C_2 and C_3; 45.1 and 38.5 corresponding to C_1 and C_4 and 36.4 (C_7) ppm (Figure 21).

The melting point of the compound **34** is 90-92 ^{o}C and has $[\alpha]_D^{20}$ = +8.3 (*c* 0.7, $CHCl_3$). According to HRMS calculations, $(M+H)^+$ was found to be $C_{23}H_{26}NO_2$.

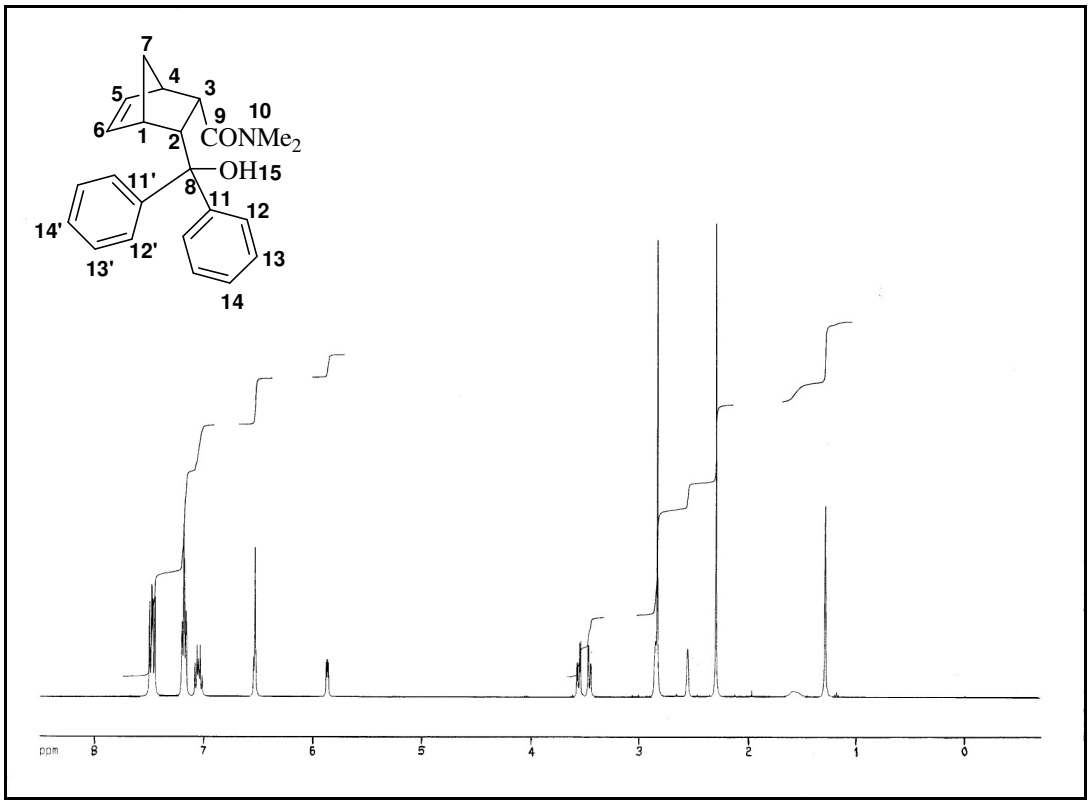


Figure 20. ^{1}H-NMR Spectrum of **34**

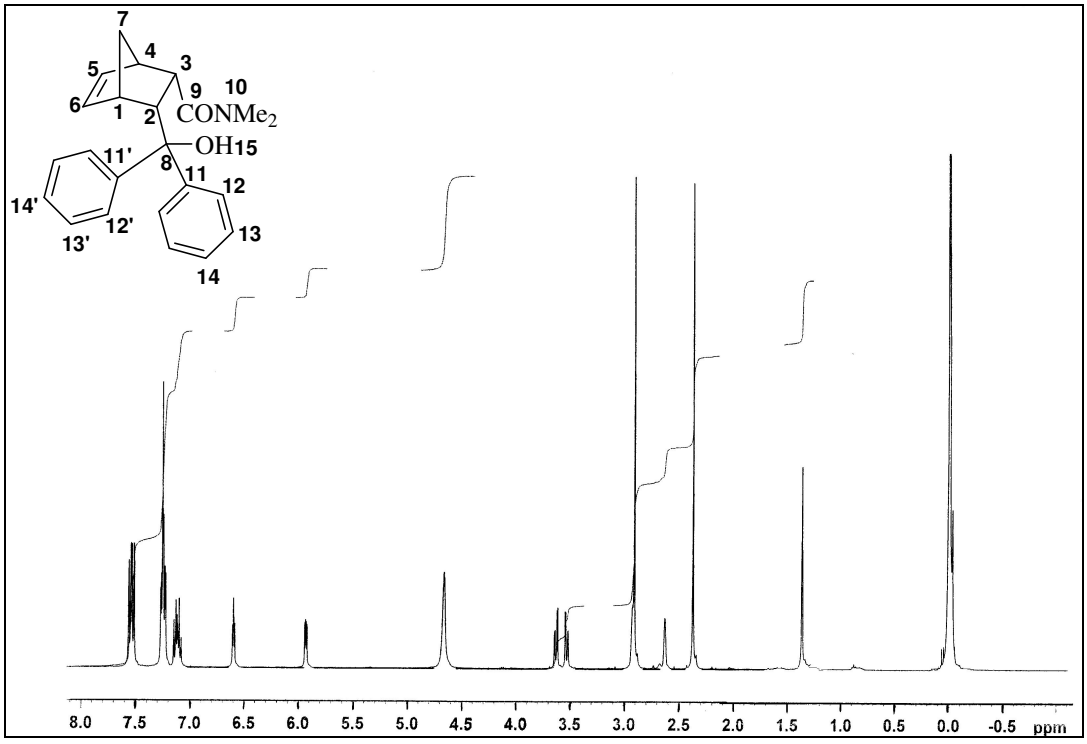


Figure 21. ^{1}H-NMR Spectrum of **34** in the presence of 1 drop D_2O

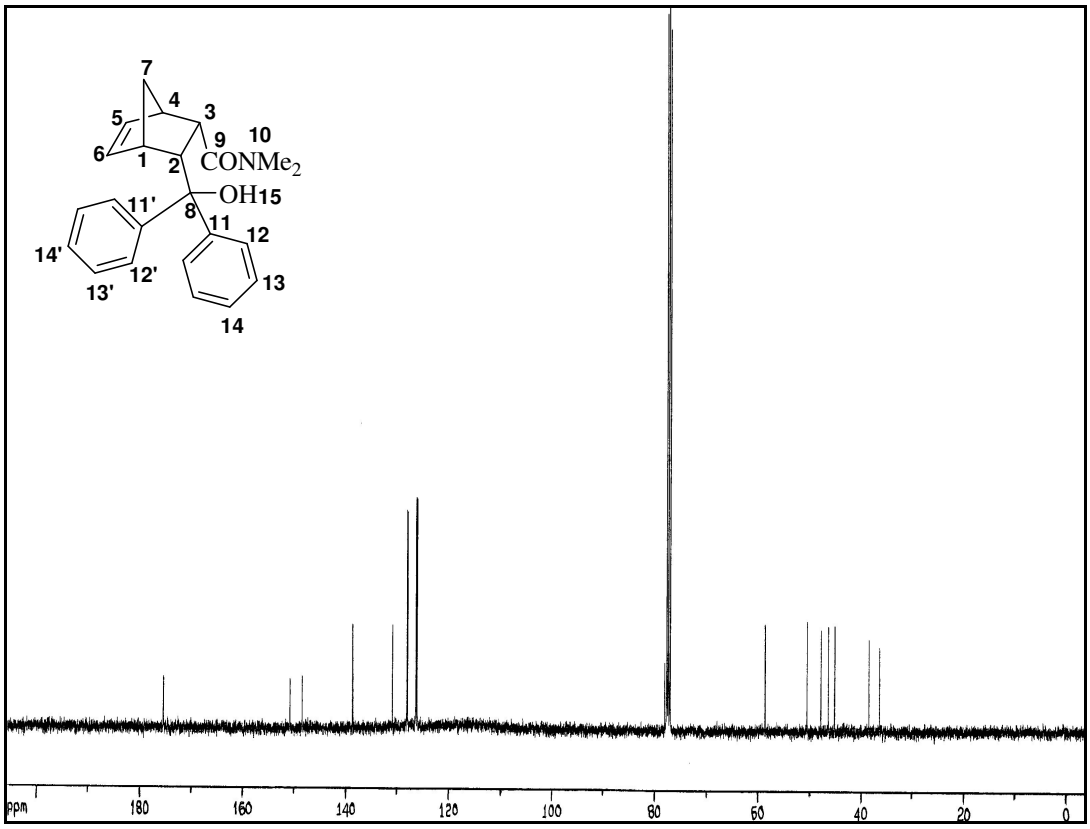
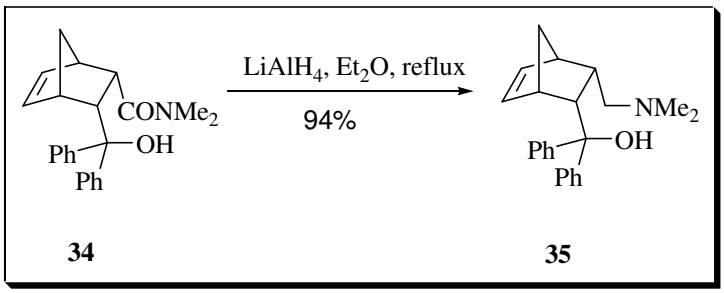


Figure 22. ^{13}C-NMR Spectrum of **34**

2.2.8. Reduction of Amide-Alcohol, 34, with LAH

The reduction of N,N-dimethyl amide function was accomplished by $LiAlH_4$ in ether to afford the chiral ligand **35** with 94 % yield (Scheme 19).



Scheme 19. Synthesis of **35**

The product was identified by using NMR and HRMS spectroscopy. From the ^{1}H-NMR, following peaks are observed:

Two multiplets at 7.27 (4H) and 7.15 (2H) and two doublets at 7.55 (2H) and 7.39 (2H) ppm belonging to the aromatic protons; one multiplet at 6.33 (2H) ppm belonging to the double bond hydrogens; one singlet at 1.98 (6H) ppm belonging to methyl groups attached to amine nitrogen; one singlet at 1.39 (2H) ppm belonging to the H_7 hydrogens; one doublet of doublet at 3.53 (1H) and one multiplet at 2.75 (1H) ppm belonging to H_9 and $H_{9'}$; two singlets at 3.06 (1H) and 2.35 (1H) ppm belonging to H_1 and H_4; one doublet of doublet 1.89 (1H) ppm and one triplet at 2.13 (1H) ppm blonging to H_2 and H_3 protons. (Figure 23).

From the ^{13}C-NMR spectroscopy, following peaks are observed: 149.3 and 148.7 corresponding to C_{11} and $C_{11'}$; 137.4 and 135.7 corresponding to C_5 and C_6; 128.1, 127.9, 126.4, 125.9, 125.3 and 125.1 corresponding to C_{12}, C_{13}, C_{14}, $C_{12'}$, $C_{13'}$ and $C_{14'}$; 79.6 (C_8); 60.6 (C_9); 52.2 (C_{10}); 50.6 and 47.3 corresponding to C_2 and C_3; 46.6 and 45.8 corresponding to C_1 and C_4 and 42.8 (C_7) ppm (Figure 24).

The melting point of the compound **35** is 130-131 ^{o}C and has $[\alpha]_D^{20}$ = -17.8 (*c* 2.77, MeOH). According to HRMS calculations, $(M+H)^+$ was found to be $C_{23}H_{28}NO$.

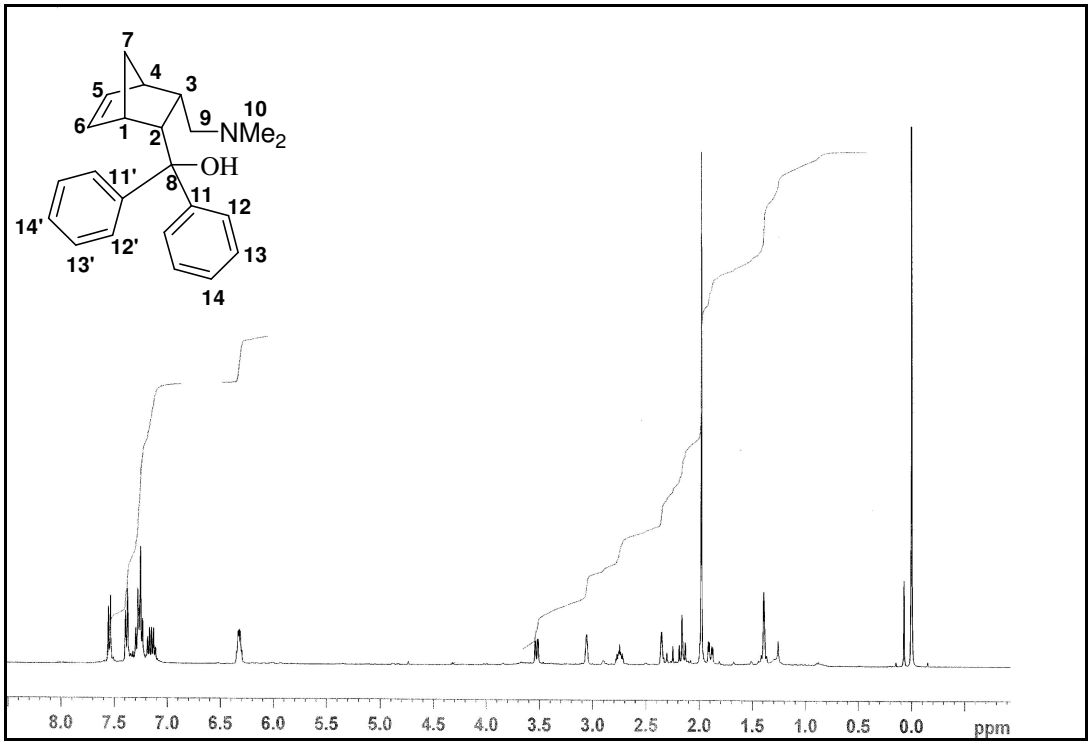


Figure 23. ^{1}H-NMR Spectrum of **35**

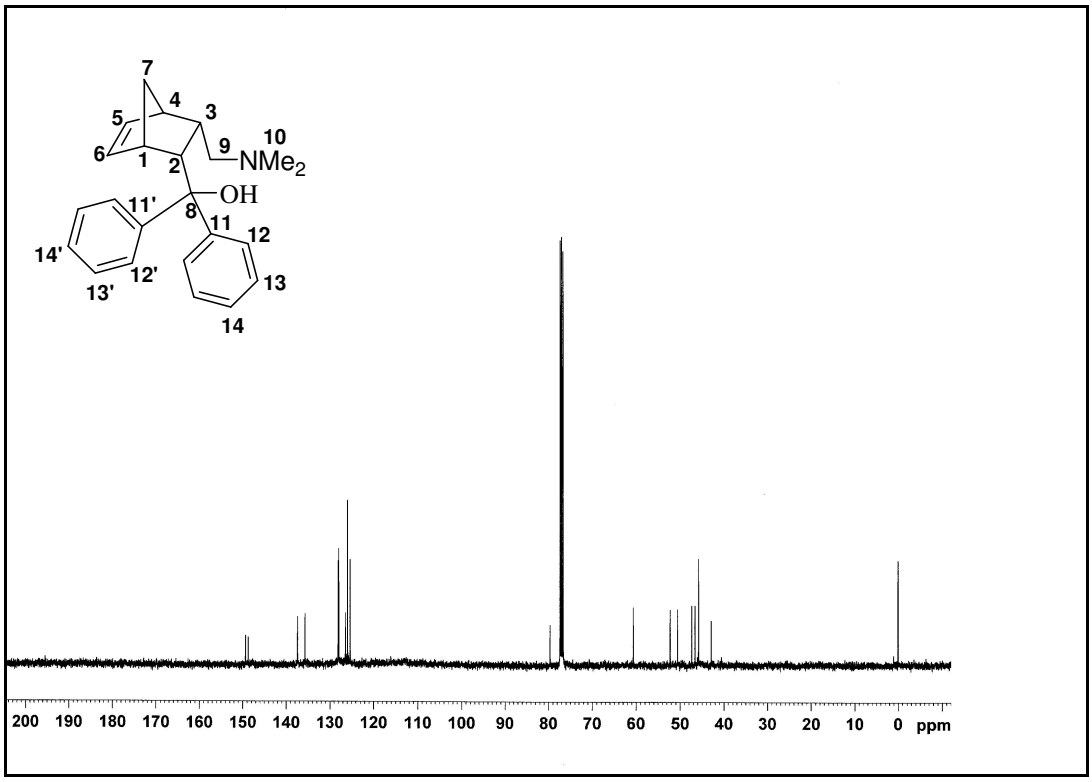


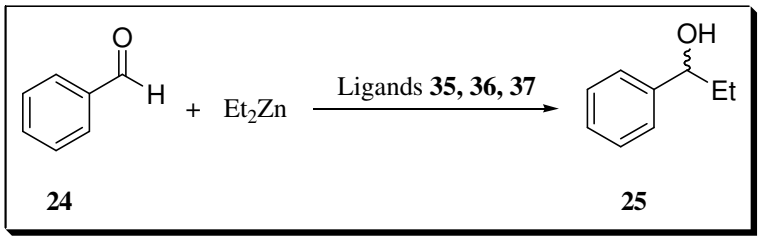
Figure 24. ^{13}C-NMR Spectrum of **35**

2.2.9. Absolute Configuration Determination

The absolute configurations of **(-)-37**, **(+)-36** and **(-)-35** were determined as (2S,3R) by comparing specific rotation signs determined at equal concentration in the same solvent with cis-monoester **(+)-31** that has been reported in the literature.[52,54] Since transformation of cis-monoester **(-)-31** to chiral ligands 35, 36 and 37 has no effect on the stereocenters of the norbornene backbone, the absolute configuration of each ligand was not changed during transformation reactions.

2.3. Diethyl Zinc Experiments

The catalytic properties of the three new chiral 1,4-amino alcohols **35**, **36** and **37** were explored in asymmetric diethylzinc addition to benzaldehyde. The results are summarized in the following sections.



Scheme 20. Asymmetric Diethylzinc Addition to Benzaldehyde Using **35, 36, 37**

2.3.1. Effect of Different Ligands

All the ligands exhibited acceptable enantioselectivities (up to 82% e.e.) and afforded 1-phenylpropanol in good yields (up to 98%). The best result was obtained with aminoalcohol **36**, which has dimethyl substituents on nitrogen atom. Catalysts without any substituent on nitrogen and hydroymethylene carbon **37** and with dimethyl and diphenyl substituents on nitrogen and hydroxymethylene carbon **35**, respectively gave the products with lower e.e. values (Table 2). These results promted us towards the investigation of the conditions to improve the enantioselectivity of the chiral catalyst **36**. For this purpose, the temperature and solvent dependence enantioselectivity of chiral ligand **36** was explored.

Table 2. Asymmetric Diethylzinc Addition to Benzaldehyde Using Norbornene Based 1,4-Aminoalcohol Catalysts

Entry	Ligand[a]	Yield (%)[b]	Ee (%)[c]
1	**35**	97	49
2	**36**	98	82
3	**37**	15	53

[a] 10 mol % of chiral catalysts were used. Toluene was used as solvent. All reactions were done at 0 ^{o}C.

[b] Yields were calculated after column chromatography.

[c] Enantiomeric ratios were determined by HPLC analysis using a chiral column. The major product has S configuration.

2.3.2. Effect of Temperature

The asymmetric diethylzinc addition reaction was carried out in toluene with 10 mol % of chiral catalyst **36** at –10 ^{o}C and at 20 ^{o}C and compared with the result given in Table 2 (entry 2). At –10 ^{o}C, the catalyst **36** revealed 76 % e.e. and afforded 1-phenylpropanol with a yield of 67 %. Both the enantioselectivity and the chemical yield were lower than entry 2. When the temperature raised up to 20 ^{o}C, no chemical yield change was observed. The enantioselectivity decreased as the former case (75% e.e.). The results are summarized in Table 3.

Table 3. Effect of Temperature on the Diethylzinc Experiment

Entry[a]	Temperature, ^{o}C	Yield (%)[b]	Ee (%)[c]
1	**-10**	67	76
2	**0**	98	82
3	**20**	98	75

[a] 10 mol % of chiral catalyst **36** was used. Toluene was used as solvent.

[b] Yields were calculated after column chromatography.

[c] Enantiomeric ratios were determined by HPLC analysis using a chiral column. The major product has S configuration.

2.3.3. Effect of Solvent

We also examined the effect of solvent using hexane, DCM and THF. All the results are given in Table 4. The reactions were carried out at the optimized temperature 0 ^{o}C and among the solvents, the best result was obtained in hexane (88% e.e.) (Table 4, entry 2). We obtained very low e.e. with DCM and THF, 30% and 59% e.e., respectively (entries 3 and 4).

Table 4. Effect of Solvent on the Diethylzinc Experiment

Entry[a]	Solvent	Yield (%)[b]	Ee (%)[c]
1	Toluene	98	82
2	Hexane	98	88
3	DCM	5	30
4	THF	15	59

[a] 10 mol % of chiral catalyst was used. All reactions were done at 0 ^{o}C.

[b] Yields were calculated after column chromatography.

[c] Enantiomeric ratios were determined by HPLC analysis using a chiral column. The major product has S configuration.

CHAPTER 3

EXPERIMENTAL

In this study, the structure elucidation of the compounds was done with the instruments as written.

The ^{1}H and ^{13}C-NMR spectra were recorded in $CDCl_3$ on a Brucker Spectrospin Avance DPX 400 spectrometer. Chemical shifts are given in ppm downfield from tetramethylsilane. Apparent splittings are given in all cases.

Infrared spectra were obtained from KBr pellets on a Mattson 1000 FT-IR spectrophotometer.

Mass spectra were recorded on a Varian MAT 212. Melting points are uncorrected.

Optical rotations were measured in a 1 dm cell using a Bellingham and Stanley P20 polarimeter at 20 ^{o}C.

HPLC measurements were performed with ThermoFinnigan Spectra System instrument. Separations were carried out on Chiralcel OD-H analytical column (250 x 4.60 mm) with hexane/2-propyl alcohol as eluent.

Column chromatography was performed on silica gel (60-mesh, Merck). TLC was carried out on Merck 0.2-mm silica gel 60 F_{254} analytical aluminum plates.

3.1. Synthesis of (2*S*,3*R*)-3-methoxycarbonylbicyclo[2.2.1]hept-5-ene-2-carboxylic acid, 31

MeOH (1.48 mL, 36 mmol) was added dropwise to a stirred solution of the *meso*-anhydride **30** (2.00 g, 12 mmol) and quinine (4.35 g, 13 mmol) in a 1:1 mixture of toluene (120 mL) and carbontetrachloride (120 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 ethylacetate 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 **31** (2.17 g, 92 %). $[\alpha]_D^{20}$= -7.8 (*c* 4.0, CCl_4), lit.[54,55] $[\alpha]_D^{20}$= -7.9 (*c* 4.8, CCl_4); mp 75–78 °C, lit.[54, 55] 74 °C (racemic); ^{1}H NMR: δ 6.26 (dd, J= 2.96, 5.50 Hz, 1H), 6.16 (dd, J= 2.94, 5.53 Hz, 1H), 3.54 (s, 3H), 3.28 (dd, J= 3.22, 10.14 Hz, 1H), 3.22 (dd, J= 3.13, 10.15 Hz, 1H), 3.14(bs, 1H), 3.11 (bs, 1H), 1.43 (dt, J= 1.56, 8.67 Hz, 1H), 1.28 (d, J= 8.69 Hz, 1H); ^{13}C NMR: δ 177.8, 173.1, 135.6, 134.4, 51.6, 48.8, 48.2, 47.9, 46.6, 46.1.

To recover the quinine, the acidic aqueous phase was neutralized with Na_2CO_3 and extracted with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$ and filtered. Evaporation of the solvent yielded the quinine almost quantitatively.

3.2. Synthesis of (2*S*,3*R*)-2-(4-bromophenoxy)-3-methoxycarbonylbicyclo[2.2.1]hept-5-ene, 38

4-Bromophenol (0.088 g, 0.51 mmol) and monoester **31** (0.100 g, 0.51 mmol) were dissolved in CH_2Cl_2 (5 mL) at 0 ^{o}C under argon. Then, DCC (0.105 g, 0.51 mmol) and DMAP (0.016 g, 0.13 mmol) were added simultaneously at 0 ^{o}C. The mixture was mixed overnight at room temperature. DCC precipitated as dicyclohexylurea. The mixture was filtered and 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 **38** (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); ^{1}H NMR: δ 7.37 (d, *J*= 8.72 Hz, 2H), 6.92 (d, *J*= 8.71 Hz, 2H), 6.32 (dd, *J*= 2.91, 5.39 Hz, 1H), 6.15 (dd, *J*= 2.92, 5.41 Hz, 1H), 3.55(s, 3H), 3.39 (s, 2H), 3.20 (s, 1H), 3.17 (s, 1H), 1.40 (d, *J*= 8.70 Hz, 1H), 1.33 (d, *J*= 8.61, 1H); ^{13}C NMR: δ 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. Synthesis of (2*S*,3*R*)- 2-carboxamido-3-methoxycarbonylbicyclo[2.2.1]hept-5-ene, 33

Ethylchloroformate (0.97 mL, 10.2 mmol) was added to a mixture of monoester **31** (2.00 g, 10.2 mmol) dissolved in dry THF (15 mL) and triethylamine (1.42 mL, 10.2 mmol) over a period of 5 min at -7 ^{o}C. The resultant mixture was stirred for an additional 30 min. at -7 ^{o}C and then, the mixture was filtered, and the cake was washed with THF (3x5 mL). NH_4OH (3 mL) was added to filtrate in one portion and the mixture was stirred for 1 h at 10 ^{o}C, then the mixture was concentrated. The solid residue was dissolved in CH_2Cl_2 and washed with 1 N HCl. The organic phase was dried over $MgSO_4$ and the solvent was evaporated. The crude product was purified by column chromatography (5% MeOH: 95% $CHCl_3$) to give compound **33** (1.63 g, % 82). $[\alpha]_D^{20}$= -2.50 (*c* 2.77, MeOH); mp 130-131 °C; IR (KBr): 3325, 3198, 1738, 1671 cm^{-1}; ^{1}H-NMR: δ 6.45 (dd, *J*= 3.04, 5.44 Hz, 1H), 6.11 (dd, *J*= 2.97, 5.48 Hz, 1H), 5.54 (s, 2H), 3.54 (s, 3H), 3.23 (dd, *J*= 3.04, 10.45 Hz, 1H), 3.18 (dd, *J*= 2.83, 10.49 Hz, 1H), 3.07 (m, 2H), 1.44 (d, *J*= 8.61 Hz, 1H), 1.28 (d, *J*= 8.59, 1H); ^{13}C-NMR: δ 174.3, 173.6, 137.0, 133.3, 51.5, 49.8, 49.3, 49.0, 47.2, 45.7.

3.4. Synthesis of (2*S*,3*R*)-2-aminomethyl-3-hydroxymethylbicyclo[2.2.1]hept-5-ene, 37

To a suspension of $LiAlH_4$ (0.11 g, 3.0 mmol) in dry THF (10 mL) was added a solution of amideester **33** (0.20 g, 1.0 mmol) in THF (5 mL) at a rate which maintained gentle reflux. The mixture was then refluxed for 1 day and hydrolized by the cautious addition of water and 15% NaOH solution. The fine white precipitate which formed was washed with ether and discarded. The filtrate was concentrated

and purified by column chromatography (8% MeOH: 2% NH_4OH: 90% $CHCl_3$) to afford compound **37** (1.11 g, 73%). $[\alpha]_D^{20}$= -8.89 (*c* 0.56, MeOH); mp 102-104 °C; IR (KBr): 3378, 3077, 2665, 1608 cm^{-1}; ^{1}H-NMR: δ 6.06 (dd, *J*= 3.00, 5.39 Hz, 1H), 6.02 (dd, *J*= 2.39, 5.80 Hz, 1H), 3.74 (bs, 2H), 3.55 (dd, *J*= 3.23, 11.61 Hz, 1H), 3.32 (t, *J*= 11.42 Hz, 1H), 2.98 (dd, *J*= 2.57, 11.76 Hz, 2H), 2.77 (t, *J*= 1.42 Hz, 2H), 2.56-2.60 (m, 1H), 2.44 (t, *J*= 11.95 Hz, 1H), 2.28-2.35 (m, 1H), 1.40 (d, *J*= 1.83 Hz, 1H), 1.39 (d, *J*= 1.87 Hz, 1H); ^{13}C-NMR: δ 135.3, 134.4, 63.2, 49.8, 47.6, 46.9, 46.2, 44.5, 42.2; HRMS calcd for $C_9H_{16}NO$ $(M+H)^+$, 154.1232. Found 154.1240.

3.5. Synthesis of (2*S*,3*R*)-2-(*N*,*N*-dimethylcarboxamido)-3-methoxycarbonylbicyclo[2.2.1]hept-5-ene, 32

To the solution of monoester **31** (2.00 g, 10.2 mmol) in benzene (5 mL) was added hexamethylphosphorous triamide (1.85 mL, 5.1 mmol) at a rate that maintained reflux of the reaction. After 2 h, the resulting cloudy solution was allowed to cool to room temperature and a saturated $NaHCO_3$ solution was added. The aqueous layer was extracted with DCM. The organic solutions were combined, dried over $MgSO_4$ and concentrated to give compound **32** (2.01 g, 88%). $[\alpha]_D^{20}$= -35.7 (*c* 1.16, $CHCl_3$); mp 78-79 °C; IR (KBr): 2998, 1742, 1637 cm^{-1}; ^{1}H-NMR: δ 6.30 (dd, *J*= 3.03, 5.34 Hz, 1H), 6.12 (dd, *J*= 2.93, 5.39 Hz, 1H), 3.52 (s, 3H), 3.35 (dd, *J*= 3.16, 9.91 Hz, 1H), 3.19 (dd, *J*= 3.48, 9.92 Hz, 1H), 3.12 (s, 1H), 3.04 (s, 1H), 2.95 (s, 3H), 2.81 (s, 3H), 1.38 (d, *J*=8.5 Hz, 1H), 1.27 (d, *J*= 8.5 Hz, 1H); ^{13}C-NMR: 173.3, 172.4, 136.6, 133.9, 51.9, 49.2, 48.9, 47.3, 47.0, 46.9, 37.3, 36.0; HRMS calcd for $C_{12}H_{18}NO_3$ $(M+H)^+$, 224.1287. Found 224.1277.

3.6. Synthesis of (2*S*,3*R*)-2-dimethylaminomethyl-3-hydroxymethylbicyclo[2.2.1]hept-5-ene, 36

To a suspension of $LiAlH_4$ (0.26 g, 6.72 mmol) in anhydrous ether (1 mL) was added a solution of amideester **32** (0.50 g, 2.24 mmol) in dry THF (5 mL) at a rate which maintained gentle reflux. The mixture was then refluxed for 3 h and hydrolized by the cautious addition of water and 15% NaOH solution. The fine white precipitate which formed was washed with ether and discarded. The filtrate was concentrated to give amino alcohol **36** (0.37 g, 90%). $[\alpha]_D^{20}$= +15.1 (*c* 1.16, MeOH); mp 90-92 °C; IR (KBr): 3131, 2959, 2361, 1507 cm^{-1}; ^{1}H-NMR: δ 5.98 (m, 2H),

3.43 (dd, *J*= 2.12, 11.61 Hz, 1H), 3.13 (t, *J*= 11.32 Hz, 1H), 2.64 (s, 1H), 2.61 (s, 1H), 2.42 (m, 2H), 2.24 (t, *J*= 12.49 Hz, 1H), 2.16 (s, 6H), 2.03 (dd, *J*= 1.79, 12.42 Hz, 1H), 1.33 (m, 2H); ^{13}C-NMR: δ 135.8, 134.8, 63.5, 61.0, 50.4, 48.0, 47.3, 46.5, 45.6, 40.2; HRMS calcd for $C_{11}H_{20}NO$ $(M+H)^+$, 182.1546. Found 182.1550.

3.7. Synthesis of (2*S*,3*R*)-2-(*N*,*N*-dimethylcarboxamido)-3-(diphenylhydroxy-thyl)-bicyclo[2.2.1]hept-5-ene, 34

Bromobenzene (3.2 g, 20.4 mmol) was dissolved in 10 mL of anhydrous diethyl ether and put into the addition funnel. This solution was added to magnesium (0.6 g, 25,0 mmol) turnings. Once the reaction has begun, rest of the bromobenzene solution was added dropwise at a rate that maintains gentle reflux. When the addition of the bromobenzene solution was complete, the mixture was refluxed for 20 min. Compound **32** (1.51 g, 6.78 mmol) was dissolved in 15 mL of anhydrous diethyl ether and added to the prepared Grignard mixture. After all of the compound **32** solution has been added, the reaction mixture was refluxed for 2 h. The resultant mixture was poured into the mixture of ice (25 g) and 3 M H_2SO_4 (30 mL). Organic phase was washed with 5% $NaHCO_3$ and then brine. It was dried over $MgSO_4$ and the solvent was evaporated and the crude product was purified by column chromatography (5% MeOH, 95% $CHCl_3$) to give compound **34** (1.96 g, 83%). $[\alpha]_D^{20}$= +8.28 (*c* 0.7, $CHCl_3$); mp 203-204 °C; IR (KBr): 3479, 3217, 1605 cm^{-1}; ^{1}H-NMR: 7.45-7.50 (m, 4H), 7.16-7.21 (m, 4H), 7.02-7.08 (m, 2H), 6.53 (dd, *J*= 3.40, 5.20 Hz, 1H), 5.87 (dd, *J*= 3.00, 5.42 Hz, 1H), 3.56 (dd, *J*= 3.22, 9.58 Hz, 1H), 3.46 (dd, *J*=2.56, 9.57 Hz, 1H), 2.86 (s, 1H), 2.84 (s, 3H), 2.56 (s, 1H), 2.30 (s, 3H), 1.29 (s, 2H); ^{13}C-NMR: 175.3, 150.8, 148.5, 138.8, 131.0, 128.2, 128.1, 128.0, 126.4, 126.3, 126.2, 78.1, 58.7, 50.5, 47.8, 46.4, 45.1, 38.5, 36.4; HRMS calcd for $C_{23}H_{26}NO_2$ $(M+H)^+$, 348.1964. Found 348.1977.

3.8. Synthesis of (2*S*,3*R*)-2-(dimethylaminomethyl)-3-(diphenylhydroxymethyl) bicyclo[2.2.1]hept-5-ene, 35

To a suspension of $LiAlH_4$ (0.033 g, 0.86 mmol) in anhydrous ether (10 mL) was added a solution of amide alcohol **34** (0.15 g, 0.43 mmol) in dry THF (5 mL) at a rate which maintained gentle reflux. The mixture was then refluxed for 3 h and hydrolized by the cautious addition of water and 15% NaOH solution. The fine white

precipitate which formed was washed with ether and discarded. The filtrate was concentrated to give amino alcohol **35** (0.135 g, 94%). $[\alpha]_D^{20}$= -17.78 (*c* 0.56, MeOH); mp 133-136 °C; IR (KBr): 3528, 1976, 1653 cm^{-1}; ^{1}H-NMR: 7.55 (d, *J*= 7.72 Hz, 2H), 7.39 (d, *J*= 7.73 Hz, 2H), 7.27 (m, 4H), 7.15 (m, 2H), 6.33 (m, 2H), 3.53 (dd, *J*= 2.67, 9.85 Hz, 1H), 3.06 (bs, 1H), 2.75 (m, 1H), 2.35 (bs, 1H), 2.13 (t, *J*= 10.65 Hz, 1H), 1.98 (s, 6H), 1.89 (dd, J= 4.14, 12.78 Hz, 1H), 1.39 (bs, 2H); ^{13}C-NMR: 149.3, 148.7, 137.4, 135.7, 128.1, 127.9, 126.4, 125.9, 125.3, 79.6, 60.6, 52.2, 50.6, 47.3, 46.6, 45.8, 42.8; HRMS calcd for $C_{23}H_{28}NO$ $(M+H)^+$, 334.2172. Found 334.2161.

3.9. General procedure for diethylzinc addition reactions

Ligand (0.05 mmol) was dissolved in hexane (or toluene) (3 mL) at room temperature under argon atmposphere and diethyl zinc (1.0 mmol, 1 M in hexane) was added to this solution. The mixture was stirred for 30 minutes , then cooled to 0 ^oC. Benzaldehyde (0.5 mmol) was added to the mixture and the reaction mixture was stirred for 48 h at 0 ^oC . After adding 1 M HCl (10 mL), it was extracted with ethyl acetate (25 mL). Then 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= 26.3 min (*R*), t_2= 31.5 min (*S*).

CHAPTER 4

CONCLUSION

We have synthesized a series of chiral norbornene-based 1,4-aminoalcohols (2S,3R)-**35**, (2S,3R)-**36** and (2S,3R)-**37** by using chemoselective methods. These compounds were used as ligands in the asymmetric diethylzinc addition to benzaldehyde. All the ligands showed selectivity toward benzaldehyde. The ligand (2S,3R)-**36** showed the best enantioselectivity over the others. We optimized the asymmetric diethylzinc addition condition for the ligand **36** found that the solvent should be hexane, the temperature should be 0 ^{o}C . All the ligands directed the catalytic process toward the formation of (1*S*)-1-phenylpropanol.[56]

These amino alchol ligands were only used in asymmetric diethylzinc addition to benzaldeyde. Their effectiveness as ligands toward aldehydes other than benzaldehyde would be discovered in the future.

These aminoalcohols are also potential chiral ligands in the various asymmetric reactions. For example, they can be used in asymmetric Aldol, Diels-Alder and hydroboration reactions.

CHAPTER 5

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