E U GRADUATE SCHOOL OF NATURAL AND APPLIED SCIENCES

EGE UNIVERSITY

DOCTORATE THESIS

AN INVESTIGATION INTO STRUCTURAL EFFECTS ON THE CATALYTIC ACTIVITY OF CHIRAL METAL-LIGAND COMPLEXES

Pakize Arzu AKINCI

Supervisor: Prof. Dr. Stephen T. ASTLEY

Department of Chemistry

Department Code: 405.02.01
Presentation Date: 25.10.2017

Bornova-İZMİR

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Pakize Arzu AKINCI tarafından doktora tezi olarak sunulan "**An investigation into structural effects on the catalytic activity of chiral metal-ligand complexes**" başlıklı bu çalışma EÜ Lisansüstü Eğitim ve Öğretim Yönetmeliği ile EÜ Fen Bilimleri Enstitüsü Eğitim ve Öğretim Yönergesi'nin ilgili hükümleri uyarınca tarafımızdan değerlendirilerek savunmaya değer bulunmuş ve 25.10.2017 tarihinde yapılan tez savunma sınavında aday oybirliği/~~oyçokluğu~~ ile başarılı bulunmuştur.

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Raportör Üye:	**Prof. Dr. Hayati TÜRKMEN**	.....
Üye	**: Doç. Dr. Kadir AY**	.....
Üye	**: Doç. Dr. Süleyman GÜLCEMAL**	.....
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EGE ÜNİVERSİTESİ FEN BİLİMLERİ ENSTİTÜSÜ

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EÜ Lisansüstü Eğitim ve Öğretim Yönetmeliğinin ilgili hükümleri uyarınca Doktora Tezi olarak sunduğum "**An investigation into structural effects on the catalytic activity of chiral metal-ligand complexes**" başlıklı bu tezin kendi çalışmam olduğunu, sunduğum tüm sonuç, doküman, bilgi ve belgeleri bizzat ve bu tez çalışması kapsamında elde ettiğimi, bu tez çalışmasıyla elde edilmeyen bütün bilgi ve yorumlara atıf yaptığımı ve bunları kaynaklar listesinde usulüne uygun olarak verdiğimi, tez çalışması ve yazımı sırasında patent ve telif haklarını ihlal edici bir davranışımın olmadığını, bu tezin herhangi bir bölümünü bu üniversite veya diğer bir üniversitede başka bir tez çalışması içinde sunmadığımı, bu tezin planlanmasından yazımına kadar bütün safhalarda bilimsel etik kurallarına uygun olarak davrandığımı ve aksinin ortaya çıkması durumunda her türlü yasal sonucu kabul edeceğimi beyan ederim.

25 / 10 / 2017

Pakize Arzu AKINCI

This thesis has been dedicated to my perfect family that have always given me love, confidence and support to come to this stage of my life

Gülay and Ilgaz AKINCI

Mert AKGÜN

without whom none of my success would be possible...

ÖZET

KİRAL METAL-LİGANDLARIN KATALİTİK AKTİVİTESİ ÜZERİNDEN YAPISAL ETKİLERİNİN İNCELENMESİ

AKINCI, Pakize Arzu

Doktora Tezi, Kimya Anabilim Dalı
Tez Danışmanı: Prof. Dr. Stephen T. ASTLEY
2017, 252 sayfa

Bu tez, kiral bileşiklerin katalitik aktivitesi üzerinden yapısal etkilerinin incelenmesini açıklamaktadır. Yeni kiral moleküllerin sentezi, karakterizasyonları ve asimetrik reaksiyonlarda katalitik etkilerinin incelenmesi ana hedef olarak belirlenmiştir. Bu tez, yedi bölümden oluşmaktadır.

Birinci bölümde, kiralite ve enantiyomer kavramları açıklanmış ve asimetrik sentez hakkında genel bilgiler verilmiştir.

İkinci bölümde, üç dişli kiral ligandların asimetrik Henry reaksiyonunda katalizör olarak kullanımı anlatılmıştır. Amino asitlerden başlayarak, amino alkol türevleri elde edilmiş ve bunlardan türeyen kiral Schiff bazı ve indirgenmiş amino alkol bileşikleri sentezlenerek, yapıları aydınlatılmıştır ve sübstitüent etkileri $Cu(OAc)_2.nH_2O$ varlığında Henry reaksiyonu üzerinden araştırılmıştır.

Üçüncü bölümde ise kiral amino alkoller ve aromatik aldehitlerden hazırlanan bakır kompleksleri ve Henry reaksiyonundaki katalitik etkileri anlatılmıştır.

Dördüncü bölümde, bakır asetat yerine Cu(II) tuzu olarak, farklı karboksilat tuzlarının enantiyoseçicilikteki etkileri açıklanmaktadır. İkinci bölümde sentezlenen ve yüksek verimle en iyi enantiyomerik seçiciliği sağlayan ligand seçilerek, farklı bakır tuzları ile etkileştirilmiştir.

Beşinci bölümde kiral amino alkoller ve bunlardan türetilen kiral ligandların kullanımı açıklanmıştır. Sentezlenen iki dişli kiral ligandlar $Cu(OAc)_2.nH_2O$ ile etkileştirilerek asimetrik Henry reaksiyonunları gerçekleştirilmiştir.

Altıncı bölümde, β-amino alkoller ve bunların metillenmesi ile oluşturulan üçüncül amino alkol türevlerinin, asimetrik reaksiyonlardaki etkileri anlatılmıştır. Epoksitlerin halka açılması yoluyla, yeni iki dişli kiral ligandlar sentezlenmiştir. Katalitik etkileri asimetrik Henry ve transfer hidrojenasyon reaksiyonlarında araştırılmıştır.

Yedinci bölümde, önceki bölümlerde Cu (II) katalizli asimetrik Henry reaksiyonunda gözlemlenen yapısal etkiler, genel özet olarak sunulmuştur.

Anahtar Kelimeler: Kiral bileşikler, Schiff bazı, amino alkol, asimetrik sentez, Henry reaksiyonu, kiral bakır (II) katalizörü

ABSTRACT

AN INVESTIGATION INTO STRUCTURAL EFFECTS ON THE CATALYTIC ACTIVITY OF CHIRAL METAL-LIGAND COMPLEXES

AKINCI, Pakize Arzu

Ph.D. in Chemistry
Supervisor: Prof. Dr. Stephen T. ASTLEY
2017, 252 Pages

This thesis describes investigations into the structural effects of chiral compounds on catalytic activity. The synthesis of new chiral molecules, their characterization, and their catalytic effects on asymmetric reactions have been identified as the main targets. This thesis consists of seven chapters.

In the first chapter, the concept of chirality and enantiomerism are explained and general information about asymmetric synthesis is given.

In the second chapter, the use of tridentate chiral ligands as catalysts in the asymmetric Henry reaction is described. Starting from amino acids, amino alcohol derivatives were obtained, from which chiral Schiff base and reduced amino alcohol compounds were synthesized and characterized and the substituent effects were investigated on the Henry reaction in the presence of $Cu(OAc)_2.nH_2O$.

In the third chapter the catalytic effect of copper complexes prepared from chiral amino alcohols and aromatic aldehydes in the Henry reaction are described.

In the fourth chapter, the enantioselective effects of different carboxylate salts as Cu (II) salt instead of copper acetate are described. The ligand, synthesized in the second chapter and providing the best enantiomeric selectivity with high yield, was selected and interacted with different copper salts.

In the fifth chapter, the use of chiral amino alcohols and chiral ligands derived therefrom are described. The synthesized bidentate chiral ligands were reacted with $Cu(OAc)_2.nH_2O$ for carrying out the asymmetric Henry reaction.

In the sixth chapter, the effects of *β*-amino alcohols and tertiary amino alcohol derivatives formed by their methylation on asymmetric reactions are described. Through the ring opening of epoxides, new bidentate chiral ligands were synthesized. The catalytic effects were investigated in the asymmetric Henry and transfer hydrogenation reactions.

In the seventh chapter, structural effects observed in Cu (II) catalyzed asymmetric Henry reaction in previous chapters are presented in general summary.

Key words: Chiral compounds, Schiff base, amino alcohol, asymmetric synthesis, Henry reaction, Chiral copper (II) catalyst.

ACKNOWLEDGEMENT

I thank to my supervisor, Prof. Dr. Stephen T. Astley, whose encouraging guidance and considerable contributions from the initial to the final level of the study inspired me. This thesis would not have been possible without his precious suggestions and supports.

I would like to thank Prof. Dr. Hayati Türkmen and Doc. Dr. Kadir Ay, and I also thank them participated in the thesis follow-up committee during my thesis work, for their thoughtful comments and guidance in committee meetings. I am also grateful to Prof. Dr. Hayati Türkmen and Doc. Dr. Süleyman Gülcemal for their permission in using the GC device. I also have to thank to them and Doc. Dr. Mustafa Emrullahoğlu for their corrective comments on final presentation of my thesis.

Special thanks go to my colleagues and friends for their supportive behaviours, collaborations and assistance. Dr. Lütfiye Gök Pezuk, a gifted chemist and my dear friend, whom I have shared many things with and she was always with me since my post graduate. Dr. Rabia Nur Ün, a good teacher and perfect friend who is more than a nice person sharing everything. We shared the same fume cupboard with Dr. Seda Yüksekdanacı and she never deprived me of her practical intelligence. Dr. Leman Alkan, a highly talented researcher and a great teacher, my groupmate, whom I have seen her close interest and support throughout my studies. Doç. Dr. Gökhan Kök is a great role model and a perfect person for encouraging me in every aspect. Uzm. Dr. Salih Günnaz did not only optimize the NMR spectroscopy data, at the same time, he always was there with his help. A very hardworking person MSc. Batıkan Kavukcu, who helped me in GC analyzes even if he was very busy, besides, he answered all my questions. Dr. Behnaz Aslanipour a good-hearted person, who always wanted to help. I would like to thank Asuman Ökten and Murat Günal for their exemplary work ethics and to give examples to everyone. Working with such talented and hardworking people was a source of inspiration for me and I enjoyed chatting with everyone. I thank them so much for everything we shared. During my studies, we shared the same laboratory with many teachers and graduate students. I am very happy to have talented and enthusiastic colleagues. I am so glad to meet such beautiful people.

I thank Ege University research fund (Project Number : 15-FEN-035) for supporting this work.

Finally, I wish to express my warmest and deepest thanks to my family, especially my dear friend Mert Akgün for his love, encouragement, understanding and support. My mom and dad, Gülay Akıncı and Ilgaz Akıncı, were always with me with their love and support while I was walking on this hard way to be a researcher. If I did not get their support, words of encouragement and continuous love, I would not have made it.

P. Arzu Akıncı, 2017

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SYMBOLS AND ABBREVIATIONS

Abbreviation		Explanations
Ar	:	Aryl
ATH	:	Asymmetric Transfer Hydrogenation
Bn	:	Benzyl
Bu_3N	:	Tributlyamine
cat.	:	Catalyst
$CDCl_3$	:	Deuteriochloroform
DCM	:	Dichloromethane
DET	:	Diethyl tartarate
ee	:	Enantiomeric excess
Et_2O	:	Diethylether
EtOH	:	Ethanol
EtOAc	:	Ethyl acetate
FT-IR	:	Fourier Transformation Infrared
GC	:	Gas Chromatography
HPLC	:	High Performance Liquid Chromatography
HCl	:	Hydrochloric acid
HCN	:	Hydrogen cynanide
HF	:	Hydrofluoric acid
HBr	:	Hydrobromic acid
HNO_2	:	Nitrous acid
H_2SO_4	:	Sulfuric acid
H_3PO_4	:	Phosphoric acid
Hz	:	Hertz
H_2O	:	Water
IPA	:	Isopropyl alcohol
IR	:	Infrared Spectroscopy
^{i}Pr	:	Isopropyl
KBr	:	Potassium hydroxide
$KO^{t}Bu$	:	Potassium *tert*-butoxide
m.p.	:	Melting point
Me	:	Methyl
MeOH	:	Methanol
Na_2SO_4	:	Sodium sulphate
$NaBH_4$	:	Sodium borohydride

SYMBOLS AND ABBREVIATIONS (Continue)

NH_4Cl	:	Ammonium chloride
NMR	:	Nuclear Magnetic Resonance
R	:	Alkyl
RT	:	Room temperature
$SnCl_4$	:	Tin(IV)chloride
$SOCl_2$	:	Thionyl chloride
^{t}Bu	:	*tert*-Butyl
TBME	:	*tert*-Butyl methyl ether
THF	:	Tetrahydrofuran
TLC	:	Thin layer chromatography
X	:	Halogen
[α]	:	Specific optical rotation
s	:	Singlet
d	:	Doublet
t	:	Triplet
dd	:	Double doublet
m	:	Multiplet
br	:	Broad
δ	:	Chemical shift
J	:	Coupling constant
β	:	Beta

1. INTRODUCTION

1.1 The Origin of Chirality

The term of chirality, one of the most common examples in general; the palm of the right hand and the palm of the left hand can cover each other but they are mirror reflection of each other (Figure 1.1). Chiral molecules are literally molecules that are not superimposable on their mirror image, and has a "handedness". It is called chiral because the word “chiral” comes from the Greek word for “hand”.

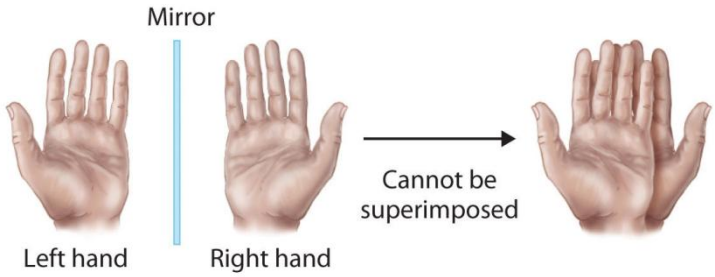


Figure 1.1 Chiral objects

Enantiomers are stereoisomers that are non-superimposable mirror images, which is called chirality, meaning that one enantiomer will be the mirror image of the other enantiomer. In order to draw an enantiomer, it can be determined the stereocenter, then swap the two groups attached to the stereocenter. It can be used for naming chiral center or a stereogenic center instead of stereocenter, which has a tetrahedral carbon, it is sp^3 hybridized. It has four different groups attached to the central carbon. The physical properties of enantiomers, such as melting point, boiling point, density, solubility and refractive index are identical. They differ in only one physical property, the direction in which they rotate plane-polarized light. Hence, enantiomers are optically active molecules. Optical activity is the aptitude of a chiral molecules, in other words enantiomers, to rotate the light, measured using a polarimeter. The amount of rotation is determined as the number of degrees that the analyzing lens of the polarimeter in exactly equal amounts and same magnitude but in opposite directions. Rotating to the right designated as (+) is called the *dextro* isomer, rotating to the left designated as (-) is called the *levo* isomer (Figure 1.2).

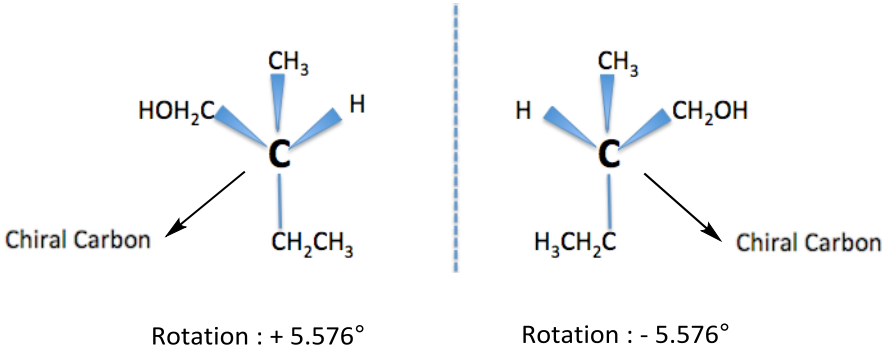


Figure 1.2 Enantiomers optical rotation

In order to calculate specific rotation and % enantiomeric excess on a standard by the equation as shown in figure 1.3. The specific rotation of an enantiomer is a characteristic property of the compound which depends on the temperature, the wave length of the light and the solution concentration or density for liquids.

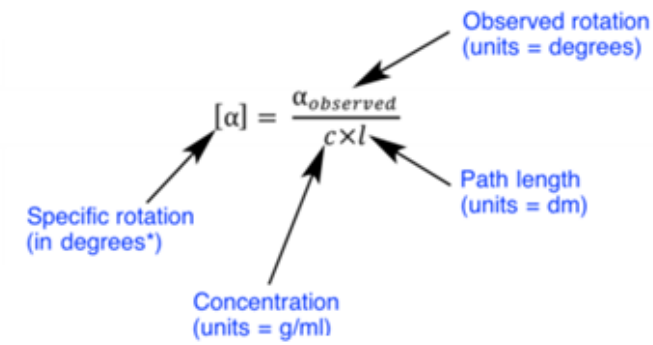


Figure 1.3 Formula for specific rotation of an enantiomer

The Chan-Ingold-Prelog (CIP) rules are used to name for enantiomers. It was recommended by Robert Cahn, Chris Ingold, and Vladimir Prelog in 1966 for denominating stereochemistry, that deal with looking at the groups attached to a chirality center and giving priority based on atomic number. If the chiral center is directed in order that the lowest-priority of the four atoms is pointed away from a center, and so it will be two possibilities: If the priority of other substituents decreases in clockwise direction, it is *R* stereoisomer (Rectus; it is Latin and means right), if it decreases in counterclockwise direction, it is *S* stereoisomer (Sinister; it is Latin and means left) (Figure 1.4).

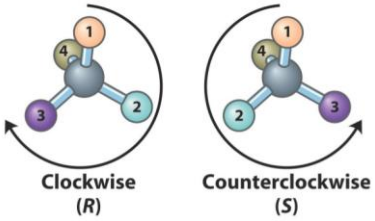


Figure 1.4 Illustration of CIP rules

An achiral molecule is superimposable with its mirror image and do not have "handedness". On the contrary of chiral molecules, achirals have contain a plane of symmetry (Figure 1.5).

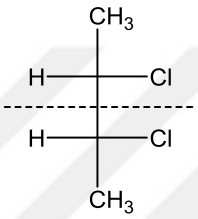


Figure 1.5 Example for a molecule which contains plane of symmetry

Diastereomers are stereoisomers like enantiomers, but that are non-superimposable non-mirror images and also opposite configurations at some chirality centers (Figure 1.6). They can vary greatly properties of physically and chemically, while enantiomers are similar. They have different melting points, boiling points, solubility, adsorbtion and physical constants; hence, during the reaction, the speeds can be different and can be given different products. By utilizing these differences, sometimes enantiomers are separated from each other.

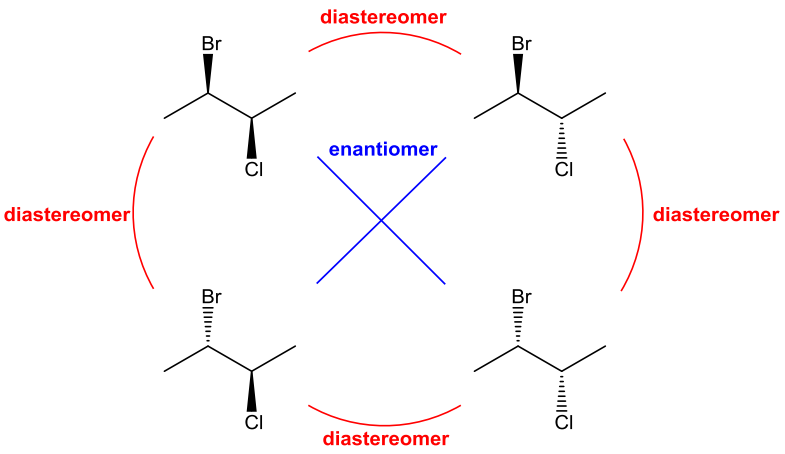


Figure 1.6 Demonstration of enantiomers and diastereomers

A mixture containing two enantiomers in the same proportion is ineffective on polarized light that is called racemic mixture or racemates. Because of enantiomers have identical physical properties resolution or separation is extremely difficult but not impossible. It have to be determined how much more of one enantiomer there is than the other. In order to measured enantiomeric excess in other words optical purity by the following equations (Solomons, 2000):

$$\text{Enantiomeric excess (\%)} = \frac{(\text{Enantiomer 1}) - (\text{Enantiomer 2})}{(\text{Enantiomer 1}) + (\text{Enantiomer 2})} \times 100$$

$$\text{Optical purity (\%)} = \frac{\text{Optical rotation of mixture}}{\text{Optical rotation of single enantiomer}} \times 100$$

1.2 The Importance of Chiral Compounds

Chirality has an extremely significant role for the nature and also human life. A lot of biologically active molecules are chiral for examle, amino acids, sugars, vitamins and enzymes. Many metabolic reactions that take place in the living structure occur through enzymes known as biological catalysts. In other words, we have the synthesis of asymmetric molecules through enzymes in our body. During the recent years, obtaining the enantiomerically pure compounds is very important for pharmaceutical industry, agricultural chemicals (*e.g.* insecticide, herbicide, fungicide), food and perfume industry. The main cause of interest in optically active products is that the enantiomers are different biological activities.

In medicines, while one of the enantiomers has the desired activity, the other enantiomer has different and often harmful pharmacological properties (Ong et al., 2006). Enantiomers almost have very different effects in racemic mixtures as forementioned. Although the inactivated enantiomer exhibits severe side effects in the presence of the desired activity, the two coexisting enantiomers may have different therapeutic effects independently of each other or the combination of both enantiomers may provide an advantage for treatment (Sheldon, 1993). Pharmaceutical effect of thalidomide that was called disaster in history has shown how important it is to separate enantiomers. It was synthesized for treating morning sickness, nausea and vomiting in pregnancy. It was not realized that enantiomers of thalidomide molecules could show different effects until it was too late. *R*-enantiomer has right influence, even as *S*-enantiomer has teratogenic effect

that caused death to babies, born with missing limb, deafness or blindness. Figure 1.7 show several examples of opposite effects of enantiomers (Enantiopure drugs, 2017).

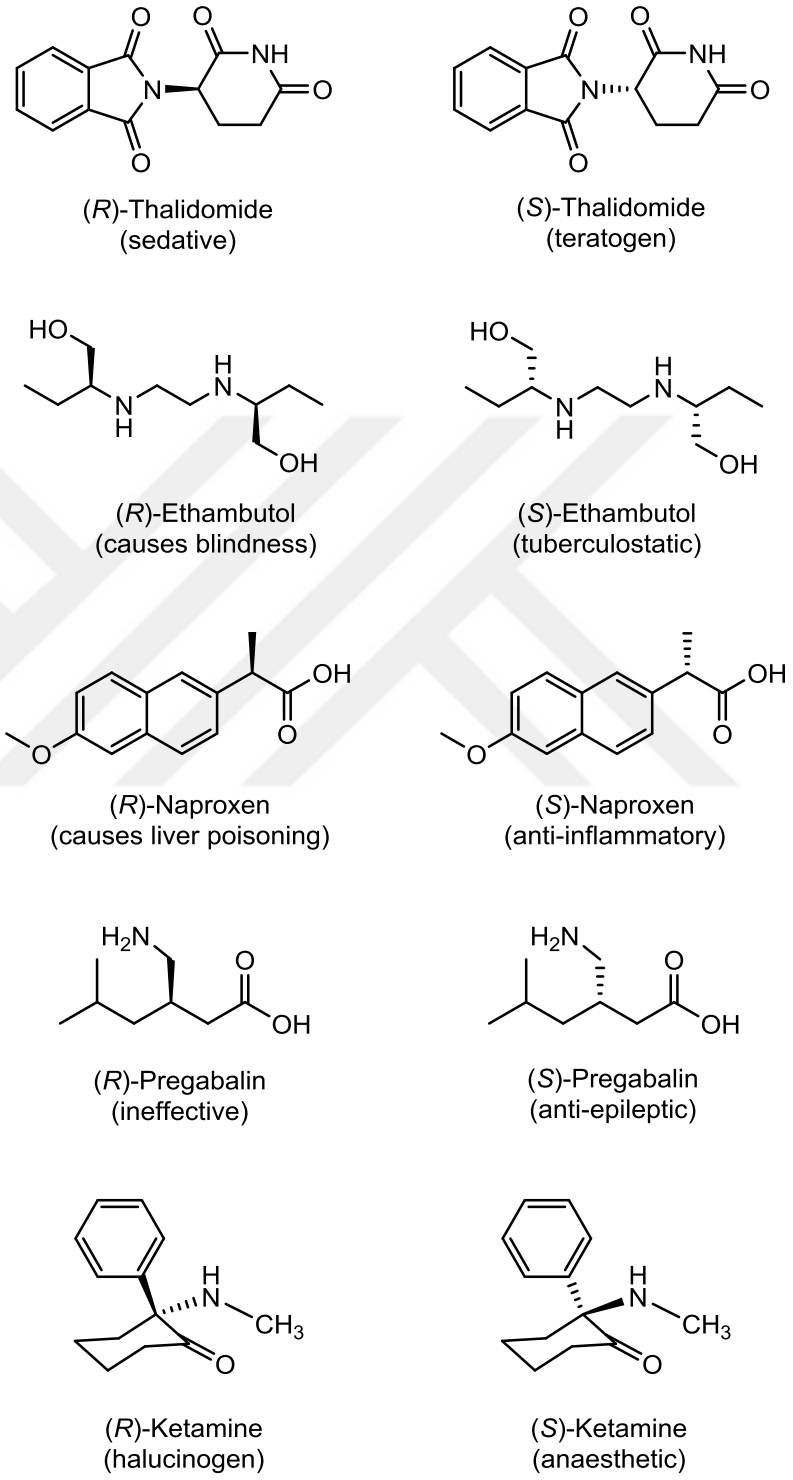


Figure 1.7 Examples of different effects of enantiomers

1.3 The Methods for Enantiopure Compounds

Isolation of enantiopure compounds is very important as it is mentioned before. There are three general strategies to obtain enantiomerically pure compounds as shown in figure 1.8.

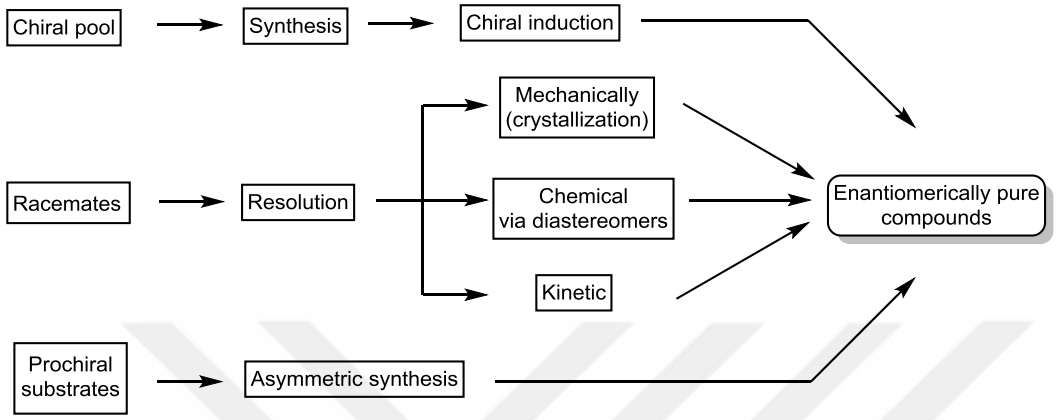


Figure 1.8 Methods to achieve enantiopure compounds

1.3.1 Chiral pool

Chiral pool synthesis using for obtaining chiral compound that accomplish the efficiency of chiral synthesis from an enantiomerically pure starting compound. If the desired final product and chiral compound, which is natural and cheap for instance; α-amino acids, hydroxyacids, carbohydrates and terpenes, used are structurally similar, this method is very purposive. Although this method has some advantages, it is not preferable methodology, not only a long and many steps may be required, but also one enantiomer is available (Levillain et al., 2003) (Figure 1.9).

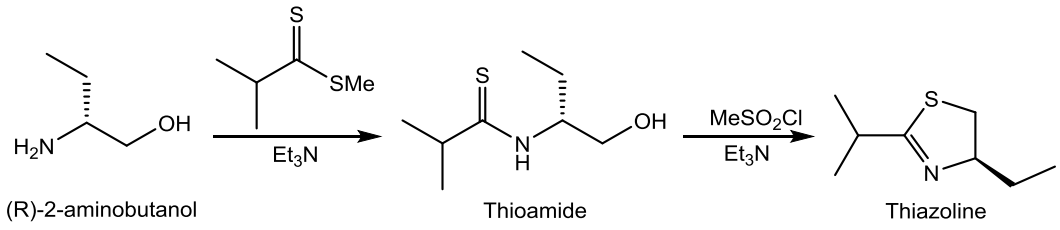
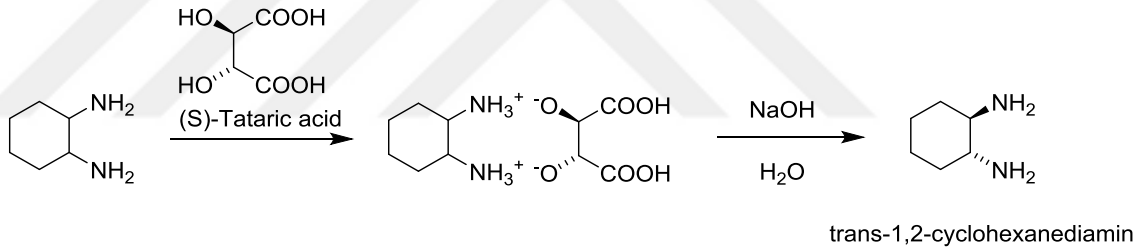


Figure 1.9 Example of chiral pool synthesis

1.3.2 Resolution of racemates

Chiral resolution is the another methodology to seperation of enantiomers. There are several ways for separation or resolution into their pure molecules. The first way is separating mechanically the crystals based on differences in their shapes. It was known as the oldest method of separating pairs of enantiomers first used by Louis Pasteur.

The second way is diastereomer crystallization. In this method, the enantiomers of the racemic mixture are converted to diastereomeric derivatives using resolving reagent with a pure, chiral auxiliary. After formation of diastereomers, thay can be separated by general separation techniques like recrystallization or chromatography, because of having different physical properties. So, the pure enantiomers and chiral auxiliary which is added at first, are acquired. In a standard and the most common method of the separation of racemates has presented by Jacopsen in 1998 (Larrow and Jacopsen, 1998) (Scheme 1.1).



Scheme 1.1 Example of diastereomer crystallization

The third resolution way is kinetic resolution employs enzymes. They are protein molecules which has stereogenic center play a role as catalysts react with only one enantiomer in the mixture. In this procedure two enantiomers have different reaction rates which means one is faster than the other till last molecule of more reactive is used (Figure 1.10). Even though this method has some advantages like do not need auxiliary cleavage and selectivity of cheap enzymes, still it is limited in scope.

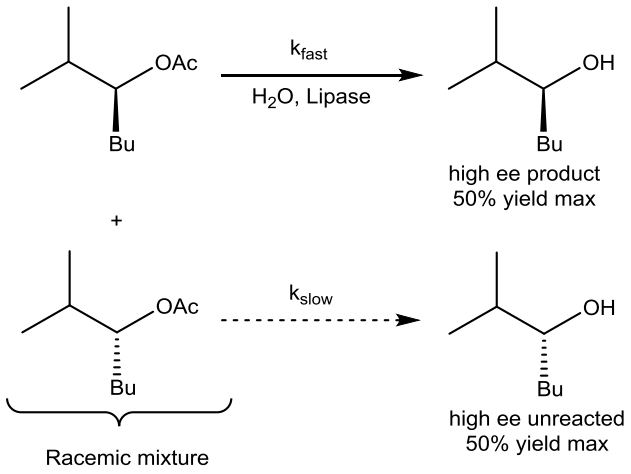


Figure 1.10 Illustration of kinetic resolution

The another way which is a general technique of the separation of enantiomers is the chromatography on chiral stationary phases. Mobile phase can be choosen a gas or liquid. The two enantiomers have different interactions with chiral material, so one enantiomer will separation from the column before the other one; therefore, the two enantiomers have different retention times (Figure 1.11).

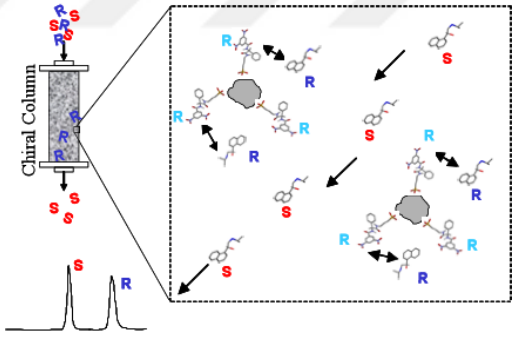
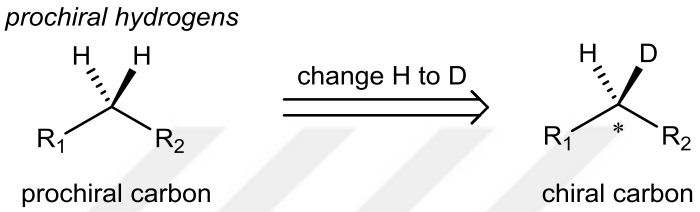


Figure 1.11 Illustration of chiral column separation

1.3.3 Asymmetric synthesis

Asymmetric synthesis is not just the area of research of scientists, also it is a fertile ground for the production of high value medicines and chemical pesticides, stains, polymers and industrial applications of synthetic chemistry with advanced technologies. Today, while increasing the number of chiral drugs, asymmetric synthesis and effective chiral separation technologies acquire more importance; as a result of this, it has become one of the most interesting topics for industry and research in recent years (Hordern, 2010).

Prochiral substrates are used in asymmetric synthesis the most important goal of enantioselectivity. Molecules that allow an achiral molecule to transform into a chiral molecule in a single step are called prochiral molecules. If it is meant by carbon, carbonyl carbon having the sp^2 hybrid may be converted into chiral sp^3 hybrid carbon by incorporating nucleophiles, leading to the chiral center. Another explanation is that, if a sp^3 hybrid tetrahedral carbon is replaced by one of the groups to which it is attached, chiral carbon can be obtained, it is defined as prochiral carbon, and as we have seen in scheme 1.2, a chiral center occurs when we turn off one of the molecules, also defined as proline hydrogen.

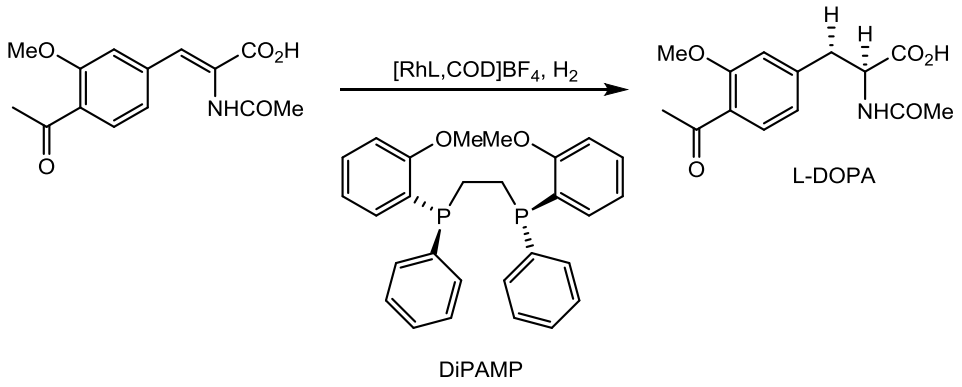


Scheme 1.2 Synthesis of chiral molecules from prochiral substrates

The basis of asymmetric synthesis that creates one configuration of new stereogenic elements or other words desired chiral centers by this reaction of a chiral reagent, auxillary or solvent acting on heterotopic groups of a substrate. Metal ligand complexes with chiral ligands, chiral organocatalysts (Sohtome et al.,2007), biocatalysis, chiral lewis acids are can be used for the reaction (Lin et al., 2001).

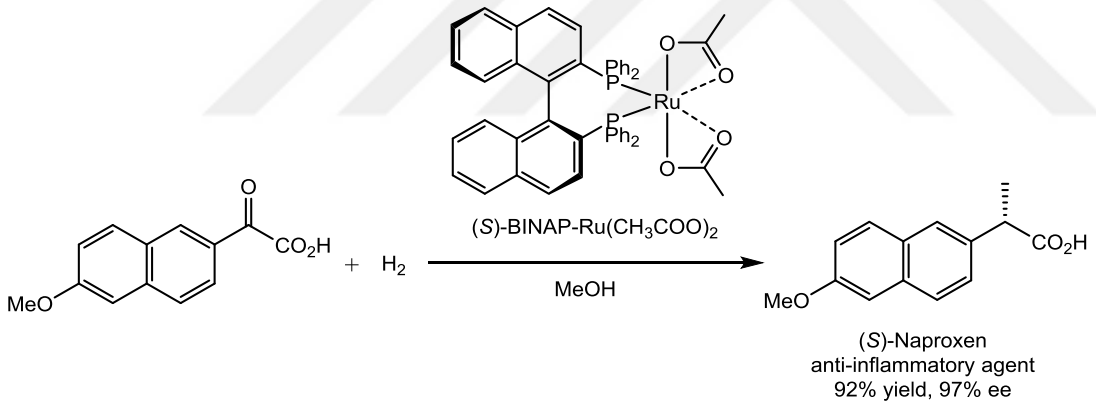
In the literature, there are a large variety of typical reaction demonstrations, for example, Asymmetric Aldol, Diels-Alder, reduction, epoxydation, transfer hydrogenation or hydrosilation reactions. In 2001, the Nobel Prize for Chemistry was shared to William S. Knowless, Noyori Ryoji and K.Barry Sharpless for work chiral chemistry and also developing the first chiral catalysts.

The drug DOPA is chiral molecule which has two enantiomers used in treating Parkinson's disease. One form reduces symptoms of Parkinson's, while another form is toxic. In the 1968, William S. Knowless accomplished a way process to produce high yield of the most suitable form of the drug. His process is called asymmetric hydrogenation which is used a chiral catalyst is still important to manufacture anti-Parkinson drugs (Knowles et al., 1968; 2002) (Scheme 1.3).



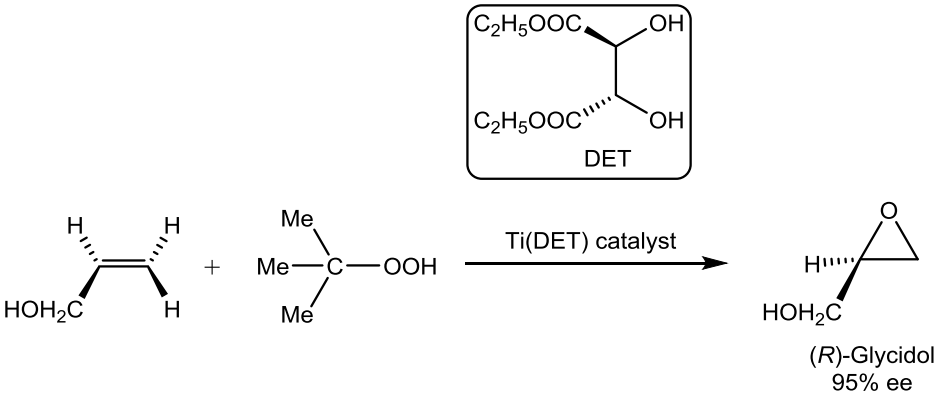
Scheme 1.3 Synthesis of L-Enantiomer of DOPA

Another work about chiral catalyst which was synthesized in asymmetric hydrogenation by Ryoji Noyori based on BINAP phosphine ligand (Scheme 1.4). The chiral phosphine ligand of the rhodium complexes were used as a catalyst in asymmetric hydrogenation with high enantioselectivity (85-97% ee), while being a structure not used until that time in asymmetric synthesis (Noyori et al., 1987; Ohta et al., 1987).



Scheme 1.4 Using of BINAP ligand

Another owner of the prize Barry Sharpless who is improving methods for using chiral catalysts during oxidation reactions in the later 1970s. In metal catalyzed epoxidation of allylic alcohol containing structures with titanium tetraisopropoxide and *tert*-butyl hydroperoxide, higher enantiomeric excess values were obtained (up to 90%) as a more selective catalytic reaction than other asymmetric syntheses. Along with the mechanism of the reaction, different modifications of the chiral ligands were also investigated (Sharpless, 1980) (Scheme 1.5).

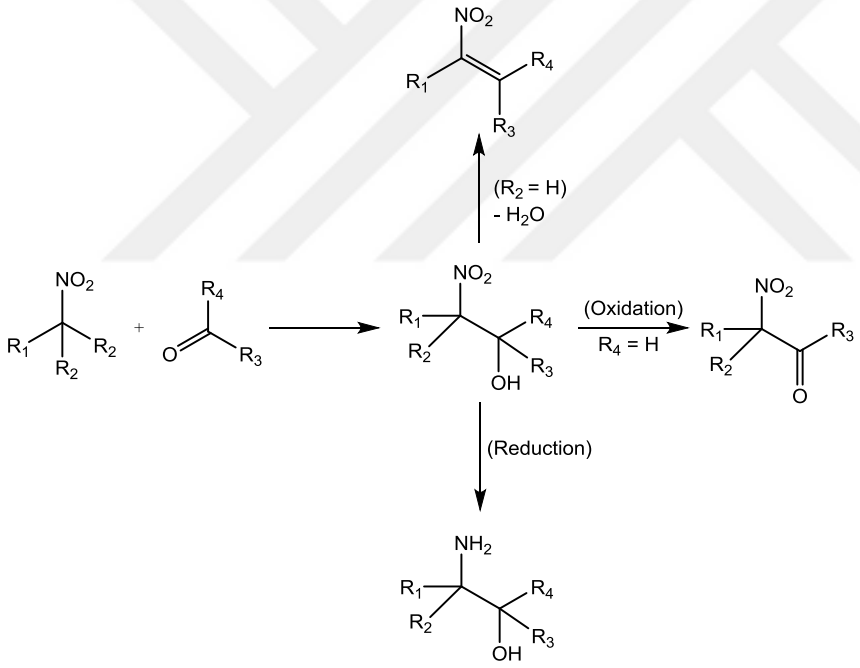


Scheme 1.5 Metal complex enantioselective oxidation

2. LIGAND SUBSTITUENT EFFECTS WHEN USING ONO SCHIFF BASES AND THEIR CORRESPONDING REDUCED AMINO ALCOHOLS IN THE COPPER (II) CATALYSED ASYMMETRIC HENRY REACTION

2.1 General Information

The Henry Reaction that is also known as the nitroaldol reaction is a classic carbon-carbon bond formation reaction in organic chemistry. Since it was discovered in 1895 by Louis Henry (Henry, 1895), it has been the combination of a nitroalkane and an aldehyde or ketone in the presence of a base to form *β*-nitroalcohols which can be modified to a variety of functional organic compounds because of their chirality, for instance *β*-amino alcohol, amino acids, alkene or carboxylic acids (Luzzio, 2001) (Scheme 2.1).



Scheme 2.1 Synthetic steps of the nitro group for *β*-nitroalcohol

The first catalytic asymmetric Henry reaction was performed and published by Shibasaki and coworkers in 1992 (Sasai et al., 1992) with a lanthanide based catalyst as shown in figure 2.1.

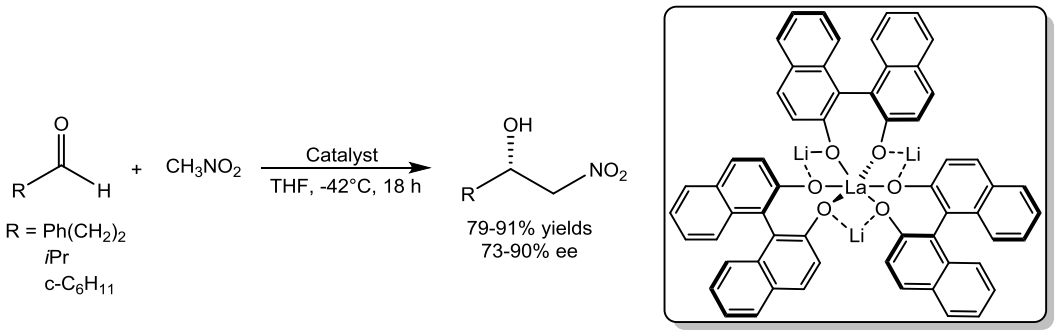
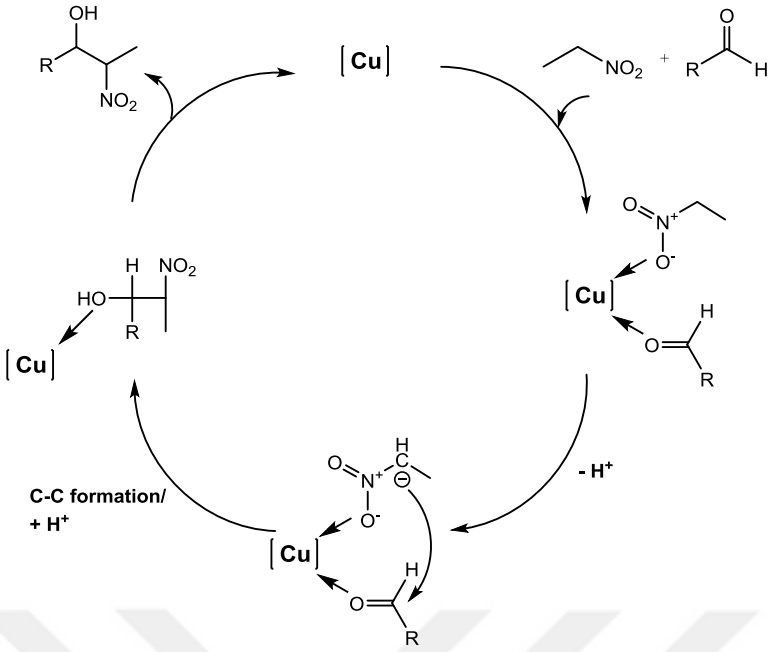


Figure 2.1 Henry reaction is catalyzed by BINOL-La complex

2.1.2 Metal based catalysts applied in the asymmetric Henry reaction

Since the first asymmetric type of the Henry reaction was published by Shibasaki (Sasai, 1992), several versions of metal-catalyzed asymmetric Henry reactions have been reported, because of its cost-effective, non toxicity and suitable chelating properties with ligands (Palomo et al., 2004; Boruwa et al., 2006). It is known from the literature many complexes of metals, e.g., Zn, Co, Ni and Cu have been used as catalysts for the Henry reaction (Trost and Yeh, 2002; Ananthi and Velmathi, 2013; Chelucci, 2013) The most distinguished results have been achieved with complexes of copper. Copper has been considerably used in organometallic synthesis, because can be coordinated with a variety of ligands, for example, bisoxazolines, trisoxazolines, bisoxazolidine, amino alcohol, imino alcohols, aminopyridine, iminopyridine, thiaoline, bipiperidine, imidazole derivatives, diamine, Schiff-base; thus, these consisted copper based complexes catalyze the asymmetric Henry reaction with high yields and enantiomeric excess values (Bartok, 2010; Liu and Du, 2009).

Based on consideration of the mechanism of the Henry reaction, both the nitroalkane and aldehyde can coordinate to the metal center. In this way, the aldehyde is activated and brought into close proximity with the nitroalkane. Proposed catalytic cycle for the formation of the β-nitroalkanol in the Henry reaction is seen in scheme 2.2 (Karmakar et al., 2014).

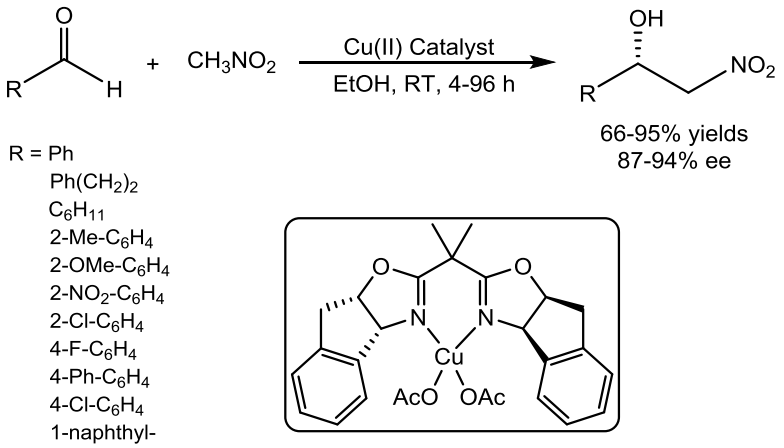


Scheme 2.2 Formation of C-C bond from Henry reaction

There are two ways to use metal complexes as catalyst for performing the asymmetric Henry reaction. The first one involves formation of a metal complex, which is synthesized and isolated before; the second one involves *in situ* formation from a chiral ligand and a transition metal complex. There are a number of different catalytic systems generated from Schiff base ligands have been used in the literature.

2.1.3 NN type ligands

Evans and co-workers described NN type chiral catalyst system in which bis(oxazoline) (BOX) ligand combined with copper(II)acetate salt (Scheme 2.3). The aldehyde was used as the electophile and Cu(II)-BOX complex coordinated both to nitroalkane and to carbonyl which comes from aldehyde, the complex was catalyzed the reaction in good yields (66-95 %) and high enantiomeric excess (94 %) under mild reaction conditions (Evans, 2003).



Scheme 2.3 Evans' BOX catalyst for asymmetric Henry reactions

As far as we can see from published works (Zhou et al., 2011; Liu et al., 2014; Ni and He, 2013; Zhang et al., 2008), the diamine ligands containing chiral centers have been synthesized to be applied in the Henry reaction such as catalyst loading, solvent, temperature, especially with different substrate effects to achieve high yields and enantioselectivities. In addition, the resulting copper (II) complexes of diamine bidentate and tridentate ligands can be given as an example of a NN type (Figure 2.2).

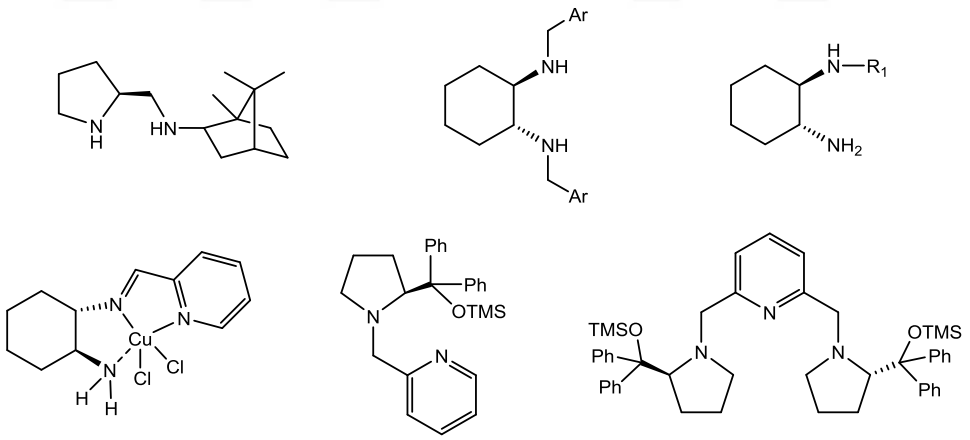


Figure 2.2 Different chiral diamines

Another example for this type is dinitrogen ligands derived from Schiff bases. The bidentate ligands were synthesized from substituted imidazole derivatives by Zhou and Gong, and examined the substituent effects in the Henry reaction according to different enantiomeric excesses (Figure 2.3). Although the variable yields and ee values were obtained, the L1 ligand which was bearing one methyl group gave the best results (95% yield, 92% ee).

The most important comparison was observed between the ligands L6 and L7, since L7, which was reduced form of L6, gave high values when the L6 was not working in the reaction (Zhou and Gong, 2011).

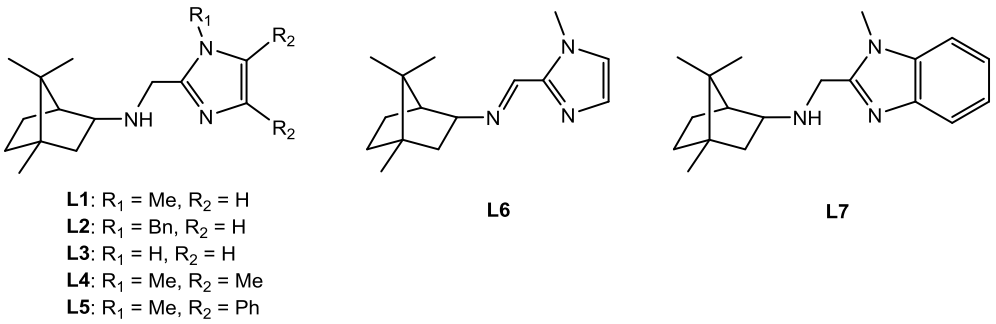


Figure 2.3 Ligands developed from diamines

2.1.4 NO type ligands

Efficient and selective catalytic systems have been designed for metal-catalyzed asymmetric Henry reaction. One of them is the NO type ligands. 1,2- and 1,4-amino alcohols are useful compounds in the asymmetric Henry reaction which are NO type ligands. Chen and co-workers prepared chiral 1,2-amino alcohol ligands and used them as catalyst in Henry reaction with various aromatic aldehydes. They obtained the resulting product in moderate yields (up to 89%) and high enantiomeric excess (up to 95%) (Chen et al., 2017) (Figure 2.4).

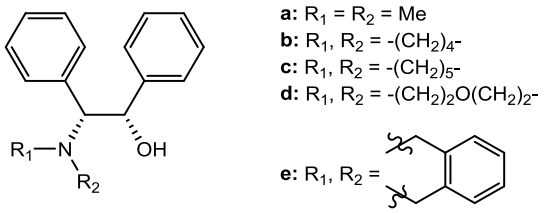


Figure 2.4 Structures of chiral ligands synthesized by Chen and co-workers

Wang and co-workers synthesized 1,2-aminophenol ligands derived from the aziridine backbones. Using these ligands in a $Cu(OAc)_2$.nH2O catalyzed asymmetric Henry reaction, they achieved high yields (up to 93%) and enantioselectivity (up to 82%) (Wang et al., 2014) (Figure 2.5).

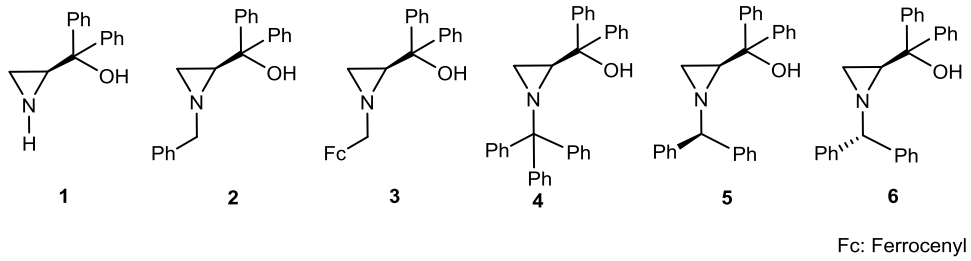


Figure 2.5 Samples of chiral aziridinyl 1,2-amino alcohols

2.1.5 ONO type ligands

The scope of ONO type ligands are one of the most important ligands in asymmetric Henry reaction, which are synthesized from amino alcohol and aldehyde derivatives, also is called as tridentate Schiff base ligands. As we can see from the previously works, this type of ligands have been greatly investigated via copper complexes in catalytic reacitons as catalyst (Figure 2.6).

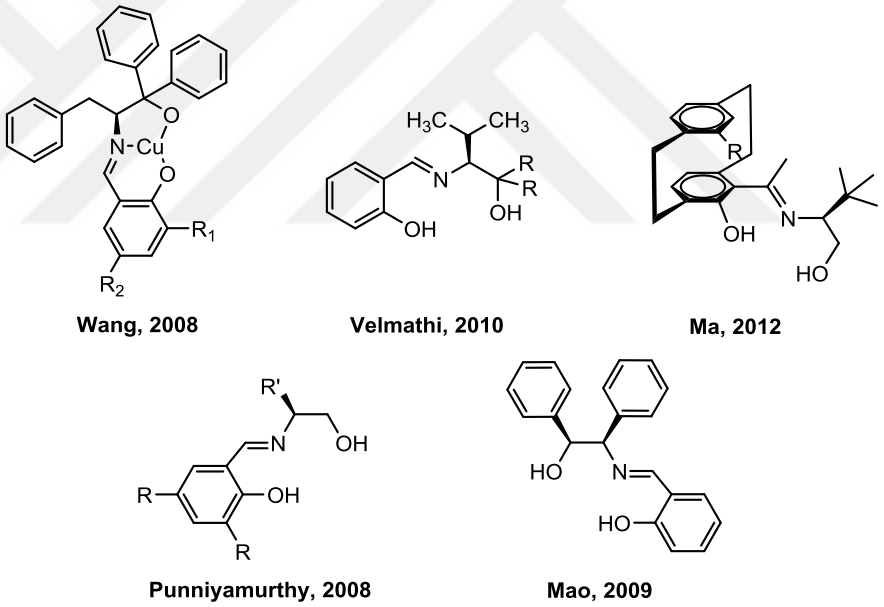


Figure 2.6 Tridentate Schiff base ligands and complexes derived from amino alcohols

Song and co-workers investigated substituent effects in chiral ONO Schiff bases which was beared different halogen atoms. Their purpose was to investigate the halogen effect of a series of ligands and their catalytic application in Henry reaction (Song et al., 2014). After the ligands were tried in the Henry reaction, as shown in figure 2.7, they have been shown to act as useful, because of their high yield (20-98%) and ee values (29-97%), especially 1e which had two bromine atoms and Bn group with 98% yield and 97% ee values.

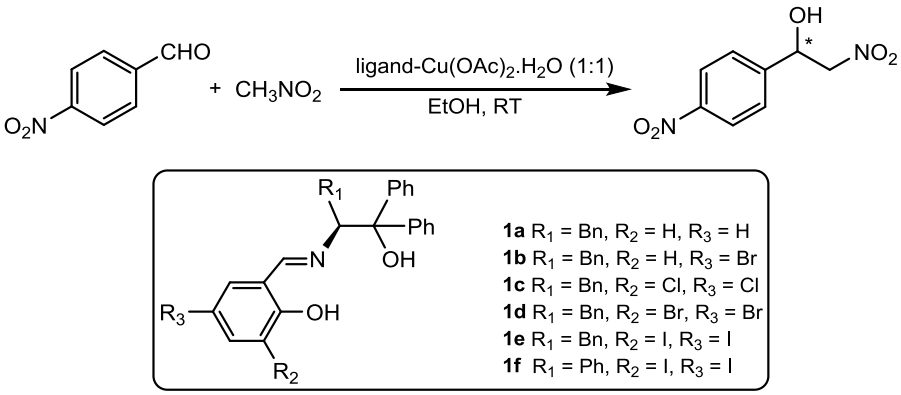


Figure 2.7 Asymmetric Henry reaction with Songs' tridentate ONO ligands

Here various examples of ONO type Schiff bases are derived from amino alcohols. As seen in figure 2.6, L-(+)-aspartic acid was used for creating a new ligand (Figure 2.8). The synthesized ligand used with copper salt in the Henry reaction carried out under various conditions with various aldehydes and nitromethane gave high yields (up to 96%) and ee value (up to 92%) (Koz et al., 2011).

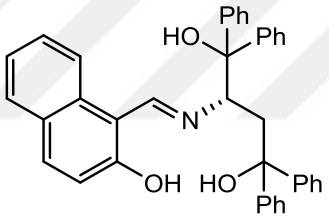
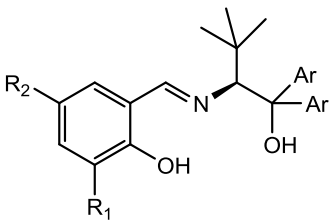


Figure 2.8 Schiff base ligands derived from L-(+)-Aspartic acid

In another study, substituent effects of ligands derived from L-*tert*-Leucine skeleton have been examined for the Henry reaction (Korkmaz et al., 2011). Solvent and catalyst loading studies were carried out based on the obtained yield (25-72%) and ee values (2-47%) from the ligand optimization (Figure 2.9).



R_1 = H, R_2 = H, Ar = Ph
R_1 = H, R_2 = *t*Bu, Ar = Ph
R_1 = H, R_2 = *Br*, Ar = Ph
R_1 = -OH, R_2 = H, Ar = Ph
R_1 = -OBn, R_2 = H, Ar = Ph
R_1 = -OMe, R_2 = H, Ar = Ph
R_1 = H, R_2 = -OH, Ar = Ph
R_1 = *t*Bu, R_2 = *t*Bu, Ar = Ph
R_1 = H, R_2 = H, Ar = 3-Me-Ph
R_1 = H, R_2 = H, Ar = 4-Me-Ph
2-naphtol Ar = Ph

Figure 2.9 Schiff base ligands derived from L-*tert*-Leucine

Very closely and a good example for this type chiral catalyst was published by White and Shaw (2012). It was shown that the synthesis of a new salen ligand and its copper complex. The important part is that, contrary to what is expected, the reduced product gave the best results in the Henry reaction compared to the others (89% yield, 94% ee) (Figure 2.10).

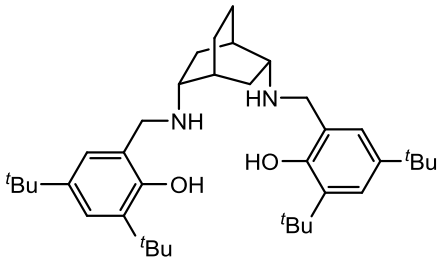


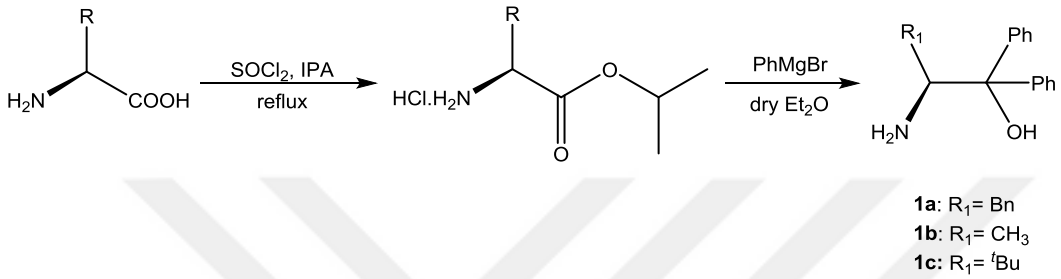
Figure 2.10 Salen ligand synthesized by White and Shaw

2.2 Results and Discussion

Asymmetric applications of Schiff bases derived from amino alcohols have previously been reported, it was shown that these ligands were used with copper salts as catalysts for Henry reaction with good yields and high enantioselectivity (Punniyamurthy, 2008; Wang, 2008; Mao, 2009). Although Schiff bases have been previously used as ligands, we felt that a better understanding of the substituent effects in this type of ligand might lead to greater enantioselectivities. In addition, despite promising results from amine containing NN, NO and ONNO ligands, there have been no reported asymmetric Henry reactions in which ONO ligands containing secondary amines have been used. Therefore, we present here the preparation of amino acid derived tridentate Schiff base and related amino alcohol ligands and their application in the Henry reaction.

2.2.1 Synthesis of ONO type Schiff base ligands derived from amino acids

Amino alcohols (**1a-c**) were synthesized from commercially available amino acids which were L-Alanine, L-Phenylalanine and L-*tert*-Leucine in two steps. Firstly, isopropyl ester salts were prepared by the classical esterification reaction of amino acids, after that, the desired amino alcohols were synthesized from these ester salts by Grignard reaction (Scheme 2.4).



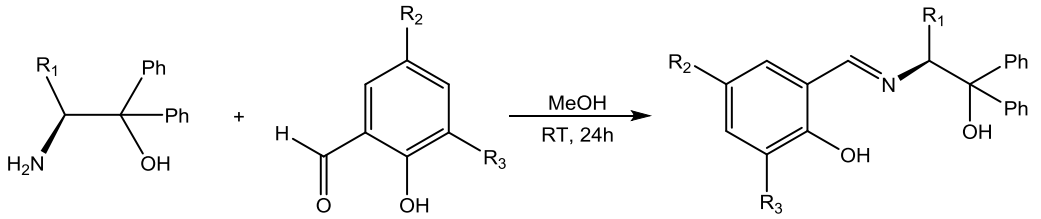
Scheme 2.4 Synthesis of amino alcohols from amino acids

Selected physical properties and characteristic chemical shifts of amino alcohols were given in table 2.1. In the material and method part, the characterizations of amino alcohols are given fully. **1c** was used from previously synthesized compound (Korkmaz et al., 2011).

Table 2.1 Melting points, yields, IR vibrations and selected ^{1}H NMR data of the compounds **1a,1b**

Compound	Yield (%)	mp (°C)	υ (O-H, N-H) cm^{-1}	Selected ^{1}H NMR data
1a	71	141-142	3450, 3389	4.20 (dd, *J* = 2.2, 10.8 Hz, 1H, C***H***) 2.67 (dd, *J* = 2.2, 14.0 Hz, 1H, C***H*$_2$**-Ph) 2.47 (dd, *J* = 10.8, 14.0 Hz, 1H, C***H*$_2$**-Ph)
1b	63	143-146	3433, 3390	4.38 (q, *J* = 6.4 Hz, 1H, C***H***) 1.24 (d, *J* = 6.4 Hz, 3H, C***H*$_3$**)

The resulting chiral amino alcohols (**1a-c**) were reacted with different aldehydes to synthesize Schiff base ligands by condensation reaction. The nine Schiff base ligands used for this part contained either tertiary butyl or benzyl groups as shown in scheme 2.5.



1a: R_1= Bn
1b: R_1= CH_3
1c: R_1= ^{t}Bu

2a : R_2 = H, R_3 = H
2b : R_2 = H, R_3 = Bn
2c : R_2 = ^{t}Bu, R_3 = ^{t}Bu

3a : R_1 = Bn, R_2 = H, R_3 = H
3b : R_1 = CH_3, R_2 = H, R_3 = H
3c : R_1 = ^{t}Bu, R_2 = H, R_3 = H
3d : R_1 = Bn, R_2 = H, R_3 = Bn
3e : R_1 = CH_3, R_2 = H, R_3 = Bn
3f : R_1 = ^{t}Bu, R_2 = H, R_3 = Bn
3g : R_1 = Bn, R_2 = ^{t}Bu, R_3 = ^{t}Bu
3h : R_1 = CH_3, R_2 = ^{t}Bu, R_3 = ^{t}Bu
3i : R_1 = ^{t}Bu, R_2 = ^{t}Bu, R_3 = ^{t}Bu

Scheme 2.5 Synthesis of the chiral Schiff bases

Selected physical properties, being melting points, yields and characteristic IR vibrations of the ligands **3a-i** are given in table 2.2. They were obtained as yellow air stable compounds. They were soluble in polar solvents. The infrared spectra of **3a-i** showed several vibrations bands of different intensities in the 4000–400 cm^{-1} region. The presence of the –C=N– group in the Schiff base ligands **3a-i** was confirmed with υ(C=N) vibrations between 1629 and 1622 cm^{-1}.

Table 2.2 Melting points, yields, C=N vibrations of the compounds **3a-j**

Compound	Yield (%)	mp (°C)	υ (C=N) cm^{-1}
3a	64	153	1627
3b	62	109	1629
3c	75	174	1628
3d	80	140.3	1622
3e	72	-	1626
3f	77	141-142	1625
3g	69	151-152	1626
3h	55	-	1628
3i	69	156	1627

The characterization of the ligands were further verified with NMR spectroscopy. C-***H*** resonances of the imine bond were observed as singlet between (δ 8.43-7.62 ppm) for **3a-i**. As an example of the ^{1}H NMR of the Schiff base ligands **3a-I**, the spectrum of **3f** is shown below in figure 2.11. In the material and method part, their characterizations are given fully.

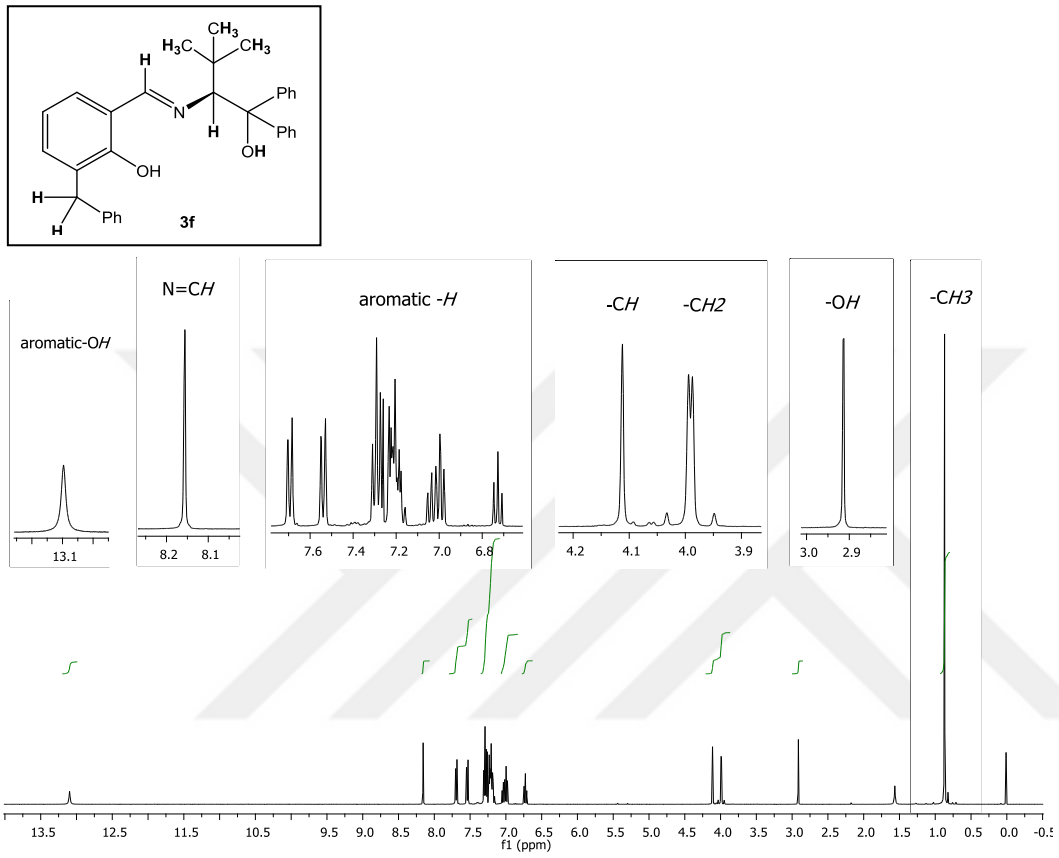
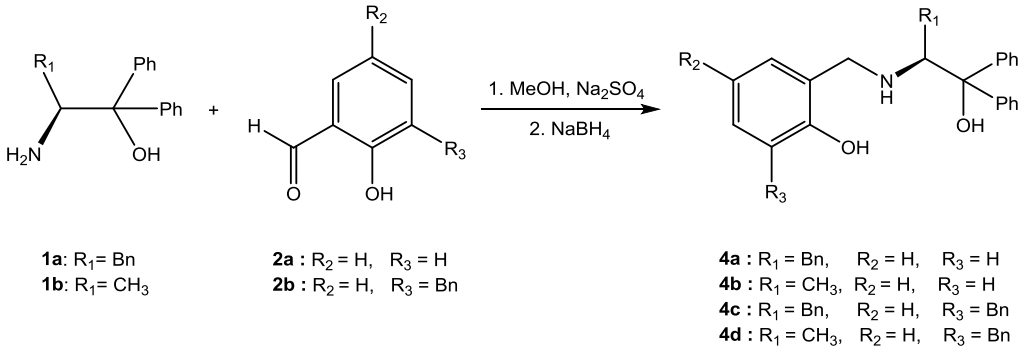


Figure 2. 11 Example ^{1}H NMR for Schiff base ligands (**3f**)

2.2.2 Synthesis of secondary amino alcohols

Secondary amino alcohols (**4a-d**), could be obtained by reduction of isolated Schiff base ligands, as well as synthesized in a single step without isolation. As shown in scheme 2.6, amino alcohols (**1a-b**) were used in a condensation reaction with salicylaldehyde and 3-benzyl-2-hydroxy-benzaldehyde (**2a-b**) to give Schiff bases, which were reduced in the reaction medium without isolation of the Schiff bases.



Scheme 2.6 Synthesis of the chiral secondary amino alcohols

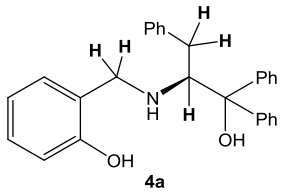
Selected physical properties, being melting points, yields and characteristic IR vibrations of the ligands **4a-d** are given in table 2.3. They were obtained as white-colorless air stable compounds. They were soluble in polar solvents. Infrared spectra of **4a-d** showed several vibrations bands of different intensities in the 4000–400 cm^{-1} region. The presence of the O-H and N-H groups in secondary amino alcohols **4a-d** were confirmed with υ (O-H, N-H) stretching vibrations between 3558 and 3305 cm^{-1}.

Table 2.3 Melting points, yields, specific bond vibrations of the compounds **4a-d**

Compound	Yield (%)	mp (°C)	υ (O-H, N-H) cm^{-1}
4a	67	125.3	3548, 3309
4b	71	103-104	3449, 3305
4c	76	63-64	3548, 3309
4d	65	-	3558, 3307

The characterization of the secondary alcohols were further verified with NMR spectroscopy. C-$\boldsymbol{H_2}$ resonances of the reduced double bond were observed as doublets, approximitely at 3.4 and 3.2 ppm (J = 12 Hz). As an example of the ^{1}H NMR spectra of the ligands **4a-d**, the spectrum of **4a** is shown below in figure 2.12. Selected peaks and coupling constants of ligand **4a** are given in table 2.4. In the material and method part, their characterizations are given fully.

Table 2.4 Selected ^{1}H NMR data of the compound **4a**

Compound	Selected ^{1}H NMR data	
	Aromatics	**Others**
 **4a**	7.66 (d, *J* = 7.2 Hz, 2H) 7.63 (d, *J* = 7.2 Hz, 2H) 7.40-7.06 (m, 12H) 6.70 (d, *J* = 8.4 Hz, 1H) 6.66 (t, *J* = 7.2 Hz, 1H) 6.52 (d, *J* = 7.2 Hz, 1H)	3.97 (dd, *J* = 2, 9 Hz, 1H, -C***H***-) 3.40 (d, *J* = 12 Hz, 1H, -C***H***$_2$-NH) 3.17 (d, *J* = 12 Hz, 1H, -C***H***$_2$-NH) 3.07 (dd, *J* = 2, 14 Hz, 1H, Ph-C***H***$_2$-CH-) 2.60 (dd, *J* = 9, 14 Hz, 1H, Ph-C***H***$_2$-CH-)

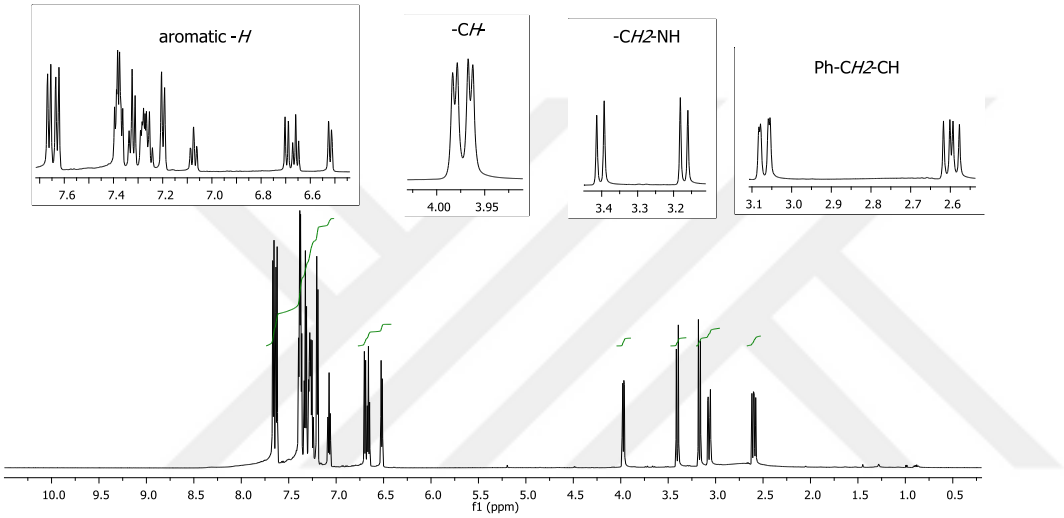


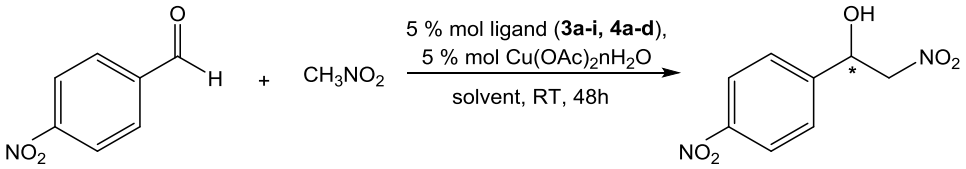
Figure 2.12 Example ^{1}H NMR for secondary amino alcohol ligands (**4a**)

2.2.3 Asymmetric Henry reaction catalyzed by chiral ONO amino alcohols

The synthesized chiral Schiff base and aminoalcohol ligands were used in the asymmetric Henry (nitroaldol) reaction between 4-nitrobenzaldehyde and nitromethane in the presence of $Cu(OAc)_2.nH_2O$. Essentially, the Henry reaction of nitromethane with 4-nitrobenzaldehyde was explored in order to search for the substituents effect in the optimal conditions (Table 2.5).

All reactions were performed with 1 mmol 4-nitrobenzaldehyde, 5% mmol ligand and $Cu(OAc)_2.nH_2O$ and 10 mmol nitromethane in 2 mL solvent at ambient temperature in 48 h. The resulting *β*-nitroalcohols were isolated by column chromatography using 1:3 EtOAc:hexane system.

Table 2.5 Optimization of the ligand effect in the asymmetric Henry reaction



Entry	Ligand	Solvent	Yield[a](%)	ee[b](%)	Config.[c]
1	**3a**	EtOH	44	45	*S*
2	**3a**	MeOH	64	57	*S*
3	**3b**	EtOH	64	59	*S*
4	**3c**	MeOH	28	3	*R*
5	**3d**	EtOH	45	47	*S*
6	**3d**	MeOH	57	44	*S*
7	**3e**	EtOH	80	64	*S*
8	**3f**	MeOH	75	59	*S*
9	**3g**	MeOH	45	62	*S*
10	**3h**	EtOH	71	49	*S*
11	**3i**	MeOH	24	4	*S*
12	**4a**	EtOH	38	21	*S*
13	**4b**	EtOH	40	8	*S*
14	**4c**	EtOH	40	7	*S*
15	**4d**	EtOH	30	5	*S*

[a]Isolated yields after column chromatography.

[b]Determined by HPLC analysis using a Chiracel OD-H column.

[c]The absolute configuration of the major product was assigned by comparison with the literature values (Evans et al., 2003).

In each instance, the reaction was carried out at the same stoichiometric ratios and under the same conditions except solvent as described above. The desired Henry reaction product was obtained in the reactions performed. Alcoholic solvents such as methanol and ethanol were preferred; however, only small differences were observed between the two solvents in the reactions (Table 2.5, Entries 1-2, 5-6).

For the ligands **3a**, **3d**, **3g** that were derived from L-Phenylalanine the different groups on the aromatic ring were found to have no important effect on the ee values. Enantiomeric excess values for these three ligands varied between 44-62% in EtOH and MeOH (Table 2.5, Entries 1,2,5,6,9). Disappointing ee values (3-4%) and yields (24-28%) were observed for ligands **3c** and **3i** which were derived from L-*tert*-Leucine in MeOH (Table 2.5, Entries 4, 11). In general, slightly better enantiomeric excesses were observed for **3d**, **3e** and **3f** which contained a benzyl group on the aromatic ring (Table 2.5, Entries 5-8). To our surprise, the compound **3g** which contained both benzyl and *tert*-butyl groups, the product was obtained with low yield, although the value of ee was increased (45% yield, 62% ee). On the other hand, when ligands **3b**, **3e** and **3h** which were derived from L-Alanine were evaluated, the best result was seen with ligand **3e** that bears a methyl group and a benzyl group (80% yield and 64% ee) (Table 2.5, Entry 7). The ee values (up to 21%) and yields (up to 40%) of ligands **4a-d** are seen in table 2.4, entries 12-15. The experimental results (Table 2.5) showed that Schiff base ligands (**3a-i**) gave higher ee values than secondary amino alcohol ligands (**4a-d**). This could be ascribed to the lesser planarity of the reduced Schiff base adopting a different configuration when bonding to the copper ion.

In summary, the enantiomeric excess showed an unpredictable dependence on the alkyl groups on the amino alcohol and the alkyl groups on the aromatic ring. The ligands which were derived from L-*tert*-Leucine showed low yields and ee values. The reaction enantioselectivity increased in the presence of the benzyl group which was bonded to the 2-position of the aromatic ring. The ligands, which were derived from L-Phenylalanine, which contained a benzyl group at the 2-position of the aromatic ring did not show any further increase in the enantioselectivity. The best enantioselectivities (62, 64%) were obtained with the ligands **3e** and **3g**. Ligand **3e** was derived from L-Alanine, bearing a methyl group on amino alcohol part and benzyl group on the aromatic ring. Ligand **3g** was derived from L-Phenylalanine, bearing a benzyl group on amino alcohol part and the *tert*-butyl groups at 3- and 5- positions of the aromatic ring (Figure 2.13). Ligand **3e** gave higher reaction yield than ligand **3g**.

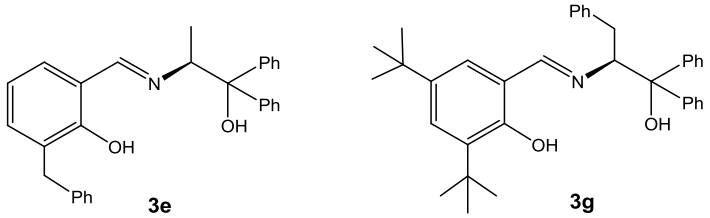


Figure 2.13 Structures and the Henry reaction results of ligands **3e** and **3g**

The generally observed positive effect of a CH_2PH group on the aromatic ring could be ascribed to π-π interaction between the CH_2PH group and the substrate aldehyde in the transition state.

2.3 Conclusion

In this study, novel chiral Schiff bases and secondary amino alcohols which were derived from amino acids were synthesized and characterized by spectroscopic methods. The Henry reaction was performed with these ligands in the presence of $Cu(OAc)_2.nH_2O$ to obtain *β*-nitro alcohols with moderately good enantiomeric excess values (up to 64%) and yields (up to 80%). Thus, the effects of ligand substituents when using ONO type tridentate ligands in the asymmetric Henry reaction was observed. In general, the results showed that the presence of the benzyl group in the aromatic ring increased the enantioselectivity. It was also found that the synthesized ONO type Schiff bases had higher activity than their corresponding reduced amino alcohol derivatives.

2.4 Material and Method

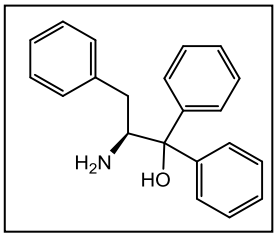
Unless otherwise noted all reactions were performed in air, except involving air-sensitive components were performed under argon atmosphere. The solvents were analytical grade and obtained from commercial suppliers. All chemicals were commercially available and purchased from Merck, Sigma-Aldrich, Alfa Aesar, Fluka, Acros or BDH and used without any purification. The amino acid isopropyl ester hydrochloride salts derived from L-Alanine and L-Phenylalanine were prepared by standard esterification procedures, and also (*S*)-2-amino-3,3-dimethyl-1,1-diphenylbutan-1-ol (**1c**) was synthesized by Grignard addition process (Kyba et al., 1978; Korkmaz et al., 2011). (*S*)-2,4-di-*tert*-butyl-6-[(1-hydroxy-3,3-dimethyl-1,1-diphenyl butan-2-ylimino)methyl]phenol (**3i**) was characterized by comparison with the literature, in order to compare the substituent effect in the Henry reaction. By the way ligands **3b, 3h** were synthesized before (Itagaki et al., 2004; Koho, 2002) however, there is no information about using as ligands in the asymmetric Henry reaction. 3-benzyl-2-hydroxy-benzaldehyde (**2b**) was prepared according to previously published procedure (Streit et al., 2013). Representative protocol was given for the same class of compounds bearing different substituents and data were presented in schemes.

FTIR Spectra were recorded on a Perkin Elmer Spectrum 100 series. ^{1}H NMR and ^{13}C NMR spectra were recorded on using 400 MHz Varian NMR spectrometer and 600 MHz Agilent Premium Compact NMR spectrometer at ambient temperature. As solvent $CDCl_3$ was employed, *J* values were in Hz. Melting points were recorded with Gallenkamp electrothermal melting point apparatus. Silica gel F_{254} (Merck 5554) precoated plates were used for the monitoring of all reactions by thin-layer chromatography and visualized by ultra-violet light or by staining with ninhydrin dissolved in alcohol. For column chromatography silica gel 60 (Merck 7743) was used. Chiralcel OD-H column was used for HPLC analyses. The enantiomeric excess of the products were determined by HPLC using a 10:90 IPA:hexane system, flow rate 1 mL/min, 267 nm. Elemental analysis was performed by CHNS-932 (LECO) elemental analyzer.

2.4.1 Preparation of amino alcohols derived from amino acids

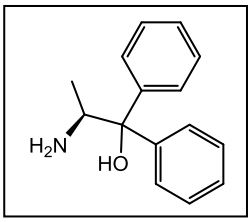
Under argon atmosphere, a reflux condenser was fitted with a two-necked round-bottomed flask. Mg (20 mmol) was added in the flask and furbished in anhydrous diethyl ether (20 mL). The mixture was stirred and bromobenzene (10 mmol) were added dropwise, then refluxed for 30 minutes. After cooling, it was added as soon as possible to a mixture of an amino acid isopropyl ester hydrochloride (2 mmol) in 5 mL of diethyl ether. After the mixture was stirred for 24 h at RT quenched with saturated NH_4Cl in ice water bath. The solution was filtered and extracted with diethyl ether. The organic phase was dried using Na_2SO_4 and evaporated under reduced pressure.

2.4.2 (*S*)-2-amino-3-phenyl-1,1-diphenylpropan-1-ol (1a)



The yellow solid was purified with column chromatography ethyl acetate:hexane system (1:5) to give the crude product, white solid, 71 % yield, mp: 141-142 ˚C. IR (CH_2Cl_2): 3450, 3389, 3084, 3059, 3025, 1596, 1493, 1447, 1362, 1171, 1054, 955, 750, 701 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 7.68-7.61 (m, 4H), 7.36-7.19 (m, 11H), 4.20 (dd, *J* = 2.2, 10.8 Hz, 1H), 2.67 (dd, *J* = 2.2, 14.0 Hz, 1H), 2.47 (dd, *J* = 10.8, 14.0 Hz, 1H). ^{13}C-NMR (400 MHz, $CDCl_3$, δ ppm): 146.9, 144.4, 139.7, 129.1, 128.7, 128.5, 128.3, 126.8, 26.6, 126.5, 125.8, 125.4, 78.6, 58.2, 36.8. Elemental analysis, calculated for $C_{21}H_{21}NO$: C, 83.13; H, 6.98; N, 4.62. Found: C, 83.54; H, 7.13; N, 4.96 %.

2.4.3 (*S*)-2-amino-1,1-diphenylpropan-1-ol (1b)

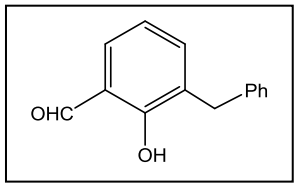


The yellow solid was purified with column chromatography ethyl acetate:hexane system (1:1) to give the crude product, white solid, 63 % yield, mp: 143-146 °C. IR (CH_2Cl_2): 3433, 3390, 3058, 2988, 2903, 2594, 1578, 1490, 1448, 1316, 1177, 970, 839, 707 cm^{-1}. ^{1}H-NMR (400 MHz, CD_3OD, δ ppm) 7.60-7.21 (m, 10H), 4.38 (q, *J* = 6.4 Hz, 1H), 1.89 (s, 2H), 1.24 (d, *J* = 6.4 Hz, 3H). Elemental analysis, calculated for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16. Found: C, 78.63; H, 7.47; N, 6.06 %.

2.4.4 Preparation of 3-benzyl-2-hydroxy-benzaldehyde (2b)

To the mixture of 2-benzyl phenol (1 mol) dissolved in 130 mL of dry toluene was added $SnCl_4$ (0.1 mol) under argon atmosphere. Bu_3N (0.4 mol) was then added and the mixture was stirred at room temperature for 15 minutes. By adding paraformaldehyde (2.2 mol), the reaction was refluxed for 4 h. After being controlled by TLC, the reaction mixture was poured into water and acidified to pH 1 with 2N HCl. The organic phases were separated by extraction with Et_2O, dried with Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography using hexane:ethylacetate (10:1) system and crude product as a yellow oil.

2.4.5 3-Benzyl-2-hydroxy-benzaldehyde (2b)

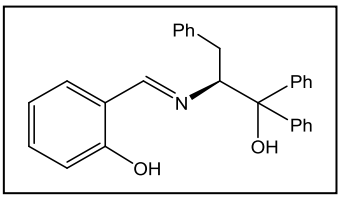


Yellow oil, 56 %. IR (CH_2Cl_2): 3409, 3026, 2926, 1726, 1651, 1602, 1494, 1452, 1262, 1206, 1078, 998, 751, 698 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 11.36 (s, 1H), 9.89 (s, 1H), 7.43 (dd, *J* = 1.6, 7.6 Hz, 1H), 7.36-7.22 (m, 6H), 6.95 (t, *J* = 7.6 Hz, 1H), 4.02 (d, *J* = 14.0 Hz, 2H).

2.4.6 General procedure for synthesis of the chiral Schiff bases

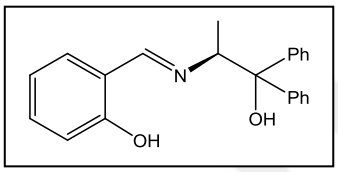
The solution of aldehyde (1 mmol) in 5 mL MeOH was added dropwise into the solution of amino alcohol (1 mmol) in 5 mL of MeOH. The reaction mixture was stirred for 24 h at room temperature. After the reaction was controlled by TLC plate, the solvent was evaporated under reduced pressure. The residue was crystallized from CH_2Cl_2:hexane or pentane to give yellow crystals.

2.4.7 (*S*)-2-[(1-hydroxy-1,1,3-triphenylpropan-2-ylimino)methyl] phenol (3a)



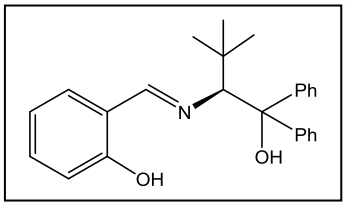
This compound was prepared according to general Schiff base procedure and characterised by comparison with literature data (Çolak and Demirel, 2008). Yellow crystals, 64 % yield, mp: 153 °C. IR (CH_2Cl_2): 3494, 3060, 3026, 2934, 2884, 1627, 1581, 1494, 1449, 1278, 1152, 1032, 960, 754, 700 cm^{-1}. $[\alpha]_D^{29}$ = - 160 (*c* 0.25, CH_2Cl_2).

2.4.8 (*S*)-2-[(1-hydroxy-1,1-diphenylpropan-2-ylimino)methyl] phenol (3b)



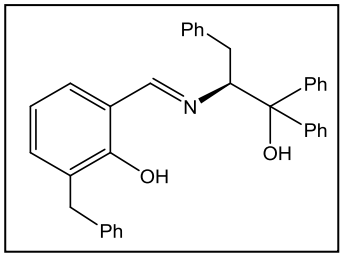
This compound was prepared according to general Schiff base procedure and characterised by comparison with literature data (Itagaki et al., 2004). Yellow solid, 62 % yield, mp: 109 °C. IR (CH_2Cl_2): 3488, 3058, 3025, 2935, 2876, 1629, 1581, 1493, 1449, 1278, 1152, 1033, 1001, 754, 702 cm^{-1}. $[\alpha]_D^{29}$ = + 72 (*c* 0.25, CH_2Cl_2).

2.4.9 (*S*)-2-[(1-hydroxy-3,3-dimethyl-1,1-diphenylbutan-2-ylimino) methyl]phenol (3c)



This compound was prepared according to general Schiff base procedure and characterised by comparison with literature data (Korkmaz et al., 2011). Yellow crystals, 75 % yield, mp: 174 °C. IR (CH_2Cl_2): 3556, 3060, 2957, 2866, 1628, 1583, 1493, 1449, 1275, 1152, 1062, 754, 704 cm^{-1}. $[\alpha]_D^{29}$ = + 104 (*c* 0.25, CH_2Cl_2).

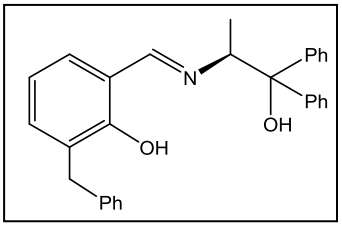
2.4.10 (*S*)-2-benzyl-6-[(1-hydroxy-1,1,3-triphenylpropan-2-ylimino)methyl]phenol (3d)



Yellow crystals, 80 % yield, mp: 140.3 ˚C. IR (CH_2Cl_2): 3583, 3571, 3060, 3026, 2927, 2886, 1622, 1494, 1449, 1275, 1163, 1087, 1003, 893, 746, 700 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 12.99 (br s, 1H), 7.68 (d, *J* = 7.2 Hz, 2H), 7.62 (s, 1H), 7.51 (d, *J* = 7.2 Hz, 2H), 7.14 (t, *J* = 8.0 Hz, 2H), 7.33-6.98 (m, 12H), 6.76 (dd, *J* = 8.0 Hz, 1.6 Hz, 1H), 6.68 (t, *J* = 7.6 Hz, 1H), 4.38 (dd, *J* = 2.0, 10.4 Hz, 1H), 4.01 (d, *J* = 1.6 Hz, 2H), 3.05 (dd, *J* = 1.6, 13.6 Hz, 1H), 2.99 (br s, 1H), 2.90 (dd, *J* = 10.4, 13.6 Hz, 1H). Elemental analysis, calculated for

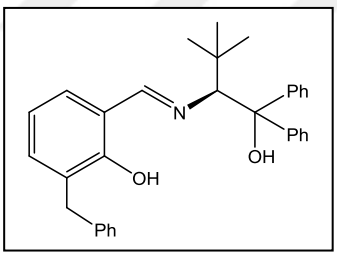
$C_{35}H_{31}NO_2$: C, 84.48; H, 6.28; N, 2.81. Found: C, 83.69; H, 6.68; N, 2.69 %. $[\alpha]_D^{18}$ = - 144 (*c* 0.5, CH_2Cl_2).

2.4.11 (*S*)-2-benzyl-6-[(1-hydroxy-1,1-diphenylpropan-2-ylimino) methyl]phenol (3e)



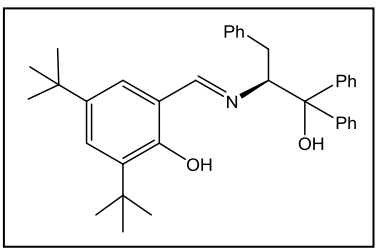
Yellow oil, 72 % yield. IR (CH_2Cl_2): 3569, 3058, 3025, 2923, 2852, 1626, 1495, 1449, 1275, 1164, 1031, 1005, 886, 749, 700 cm^{-1}. ^{1}H-NMR (600 MHz, $CDCl_3$, δ ppm) 12.87 (br s, 1H), 8.36 (s, 1H), 7.54 (d, *J* = 7.8 Hz, 2H), 7.50 (d, *J* = 7.8 Hz, 2H), 7.32 (t, *J* = 7.8 Hz, 2H), 7.28-7.14 (m, 9H), 7.06 (d, *J* = 7.8 Hz, 2H), 6.76 (t, *J* = 7.8 Hz, 1H), 4.54 (q, *J* = 6.6 Hz, 1H), 4.02-3.90 (m, 2H), 2.72 (s, 1H), 1.25 (d, *J* = 6.6 Hz, 3H). ^{13}C-NMR (600 MHz, $CDCl_3$, δ ppm): 165.7, 158.5, 145.6, 144.2, 140.5, 133.1, 129.8, 129.0, 128.3, 128.2, 128.2, 126.8, 126.8, 126.2, 125.9, 125.9, 118.3, 118.3, 79.6, 70.3, 35.0, 17.4. Elemental analysis, calculated for $C_{29}H_{27}NO_2$: C, 82.63; H, 6.46; N, 3.32. Found: C, 82.55; H, 6.54; N, 2.69 %. $[\alpha]_D^{29}$ = + 32 (*c* 0.25, CH_2Cl_2).

2.4.12 (*S*)-2-benzyl-6-[(1-hydroxy-3,3-dimethyl-1,1-diphenylbutan-2-ylimino)methyl]phenol (3f)



Yellow crystals, 77 % yield, mp: 141-142 °C. IR (CH_2Cl_2): 3585, 3059, 3026, 2958, 2870, 1625, 1494, 1450, 1266, 1164, 1086, 1014, 744, 698 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 13.10 (br s, 1H), 8.16 (s, 1H), 7.69 (d, *J* = 7.6 Hz, 2H), 7.54 (d, *J* = 8.4 Hz, 2H), 7.31-6.73 (m, 14H), 4.11 (s, 1H), 3.99 (s, 2H), 2.91 (s, 1H), 0.87 (s, 9H). Elemental analysis, calculated for $C_{32}H_{33}NO_2$: C, 82.90; H, 7.17; N, 3.02. Found: C, 82.72; H, 7.11; N, 3.01 %. $[\alpha]_D^{18}$ = + 88 (*c* 0.5, CH_2Cl_2).

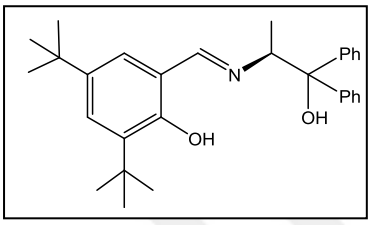
2.4.13 (*S*)-2,4-di-*tert*-butyl-6-[(1-hydroxy-1,1,3-triphenylpropan-2-ylimino)methyl]phenol (3g)



Yellow crystals, 69 % yield, mp: 151-152 °C. IR (CH_2Cl_2): 3464, 3061, 3027, 2958, 2866, 1626, 1449, 1362, 1273, 1251, 1173, 1030, 894, 748, 701 cm^{-1}. ^{1}H-NMR (600 MHz, $CDCl_3$, δ ppm) 12.82 (br s, 1H), 7.67 (d, *J* = 7.2 Hz, 2H), 7.63 (s, 1H), 7.51 (d, *J* = 7.8 Hz, 2H), 7.40 (t, *J* = 7.2 Hz, 2H), 7.32-7.12 (m, 8H), 6.98 (d, *J* = 6.6 Hz, 2H), 6.67 (d, *J* = 2.4 Hz, 1H), 4.36 (d, *J* = 10.2 Hz, 1H), 3.02 (d, *J* = 18.6 Hz, 2H), 2.87 (dd, *J* = 10.2, 13.8 Hz, 1H), 1.41 (s, 9H),

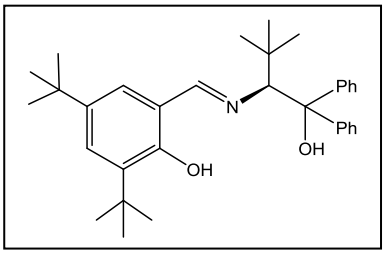
1.23 (s, 9H). ^{13}C-NMR (600 MHz, $CDCl_3$, δ ppm): 167.7, 157.5, 145.6, 144.2, 139.9, 139.2, 136.3, 129.7, 128.4, 128.3, 128.2, 127.1, 127.0, 126.8, 126.2, 126.1, 126.0, 125.9, 117.6, 79.8, 78.4, 37.5, 34.9, 34.0, 31.4, 29.4. Elemental analysis, calculated for $C_{36}H_{41}NO_2$: C, 83.20; H, 7.95; N, 2.70. Found: C, 83.20; H, 8.18; N, 2.72 %. $[\alpha]_D^{29}$ = - 72 (*c* 0.25, CH_2Cl_2).

2.4.14 (*S*)-2,4-di-*tert*-butyl-6-[(1-hydroxy-1,1-diphenylpropan-2-ylimino)methyl]phenol (3h)



This compound was prepared according to general Schiff base procedure and characterised by comparison with literature data (Koho, 2002). Yellow oil, 55 % yield. IR (CH_2Cl_2): 3578, 3059, 2959, 2870, 1628, 1598, 1468, 1448, 1272, 1173, 1001, 739, 702 cm^{-1}. ^{1}H-NMR (600 MHz, $CDCl_3$, δ ppm) 12.86 (br s, 1H), 8.43 (s, 1H), 7.57 (d, *J* = 7.2 Hz, 2H), 7.54 (d, *J* = 7.8 Hz, 2H), 7.37-7.05 (m, 8H), 4.56 (q, *J* = 6.6 Hz, 1H), 2.81 (br s, 1H), 1.41 (s, 9H), 1.31 (s, 9H), 1.25 (d, *J* = 6.6 Hz, 3H). $[\alpha]_D^{29}$ = + 33 (*c* 0.25, CH_2Cl_2).

2.4.15 (*S*)-2,4-di-*tert*-butyl-6-[(1-hydroxy-3,3-dimethyl-1,1-diphenylbutan-2-ylimino)methyl]phenol (3i)



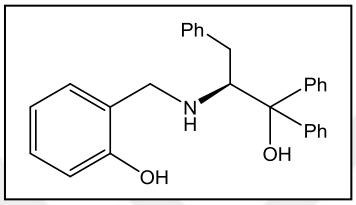
This compound was prepared according to general Schiff base procedure and characterised by comparison with literature data (Korkmaz et al., 2011). Yellow crystals, 69 % yield, mp: 156 °C. IR (CH_2Cl_2): 3583, 3058, 2927, 2907, 2869, 1627, 1598, 1468, 1449, 1249, 1172, 1062, 747, 705 cm^{-1}. $[\alpha]_D^{29}$ = + 24 (*c* 0.25, CH_2Cl_2).

2.4.16 General procedure for synthesis of the secondary amino alcohols

This reaction can be accomplished by the reduction of isolated Schiff bases or it can be completed one pot, without isolation. Amino alcohols (1 mmol) and aldehydes (1 mmol) were dissolved in 20 mL MeOH under argon atmosphere and was added Na_2SO_4 (0.5 g). The mixture was stirred for 4 h at room temperature for the formation of Schiff base.

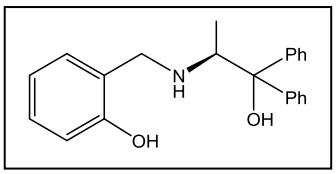
The mixture was filtered and then, the residue was reduced with $NaBH_4$ (1.5 mmol, 57.0 mg) was stirred for 24 h and checked by TLC. The solvent was evaporated. After addition of 20 mL of water, it was neutralized with acetic acid and extracted 3 times with DCM. The organic phases were collected and dried with Na_2SO_4 before evaporation. The residue was purified by column chromatography using hexane:ethyl acetate (3:1) system and crude product was crystallized from CH_2Cl_2:hexane to give the compound.

2.4.17 (*S*)-2-[(1-hydroxy-1,1,3-triphenylpropan-2-ylamino)methyl] phenol (4a)



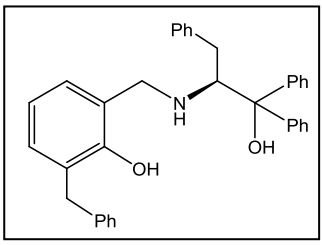
White solid, 67 % yield, mp: 125.3 °C. IR (CH_2Cl_2): 3548, 3309, 3059, 3026, 2933, 2859, 1588, 1491, 1449, 1264, 1180, 1100, 1031, 752, 700 cm^{-1}. ^{1}H-NMR (600 MHz, $CDCl_3$, δ ppm) 7.66 (d, *J* = 7.2 Hz, 2H), 7.63 (d, *J* = 7.2 Hz, 2H), 7.40-7.06 (m, 12H), 6.70 (d, *J* = 8.4 Hz, 1H), 6.66 (t, *J* = 7.2 Hz, 1H), 6.52 (d, *J* = 7.2 Hz, 1H), 3.97 (dd, *J* = 2.4, 9.6 Hz, 1H), 3.40 (d, *J* = 12.6 Hz, 1H), 3.17 (d, *J* = 12.6 Hz, 1H), 3.07 (dd, *J* = 2.4, 13.8 Hz, 1H), 2.60 (dd, *J* = 9.6, 14.4 Hz, 1H). Elemental analysis, calculated for $C_{28}H_{27}NO_2$: C, 82.12; H, 6.65; N, 3.42. Found: C, 81.62; H, 6.57; N, 3.54 %. $[\alpha]_D^{29}$ = - 56 (*c* 0.25, CH_2Cl_2).

2.4.18 (*S*)-2-[(1-hydroxy-1,1-diphenylpropan-2-ylamino)methyl] phenol (4b)



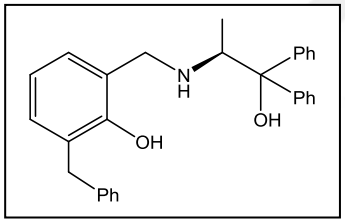
White crystals, 71 % yield, mp: 103-104 °C. IR (CH_2Cl_2): 3449, 3305, 3057, 3033, 2936, 2856, 1589, 1491, 1449, 1252, 1152, 1104, 1034, 755, 704 cm^{-1}. ^{1}H-NMR (600 MHz, $CDCl_3$, δ ppm) 7.53 (d, *J* = 8.34 Hz, 2H), 7.46 (d, *J* = 8.34 Hz, 2H), 7.35 (t, *J* = 7.5 Hz, 2H), 7.31 (t, *J* = 7.5 Hz, 2H), 7.27 (t, *J* = 7.2 Hz, 1H), 7.21 (t, *J* = 7.2 Hz, 1H), 7.13 (t, *J* = 7.8 Hz, 1H), 6.95 (d, *J* = 7.2 Hz, 1H), 6.77-6.74 (m, 2H), 3.98 (d, *J* = 13.2 Hz, 1H), 3.82 (m, 2H), 1.16 (d, *J* = 6.6 Hz, 3H). ^{13}C-NMR (600 MHz, $CDCl_3$, δ ppm): 157.7, 144.9, 144.7, 128.8, 128.6, 128.3, 128.2, 127.3, 126.9, 125.6, 123.1, 119.1, 116.5, 80.6, 58.8, 50.8, 14.3. Elemental analysis, calculated for $C_{22}H_{23}NO_2$: C, 79.25; H, 6.95; N, 4.20. Found: C, 78.13; H, 6.38; N, 4.05 %. $[\alpha]_D^{29}$ = - 25 (*c* 0.25, CH_2Cl_2).

2.4.19 (*S*)-2-benzyl-6-[(1-hydroxy-1,1,3-triphenylpropan-2-yl-amino)methyl]phenol (4c)



White solid, 76 % yield, mp: 63-64 °C. IR (CH_2Cl_2): 3548, 3309, 3059, 3026, 2926, 2857, 1595, 1494, 1451, 1262, 1160, 1080, 1030, 748, 700 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 7.65 (t, *J* = 8.0 Hz, 4H), 7.40-7.19 (m, 16H), 6.89 (d, *J* = 7.2 Hz, 1H), 6.60 (t, *J* = 7.2 Hz, 1H), 6.44 (d, *J* = 7.2 Hz, 1H), 3.99 (dd, *J* = 2.4, 9.2 Hz, 1H), 3.87 (s, 2H), 3.43 (d, *J* = 12.8 Hz, 1H), 3.29 (d, *J* = 12.4 Hz, 1H), 3.11 (dd, *J* = 2.4, 14.4 Hz, 1H), 2.64 (dd, *J* = 9.6, 14.4 Hz, 1H). ^{13}C-NMR (400 MHz, $CDCl_3$, δ ppm): 155.0, 145.4, 144.6, 141.1, 139.4, 129.5, 129.2, 129.1, 128.8, 128.7, 128.6, 128.5, 128.3, 128.2, 127.3, 127.1, 126.6, 126.5, 125.8, 125.7, 125.6, 122.9, 118.8, 81.0, 66.1, 52.6, 37.7, 35.4. Elemental analysis, calculated for $C_{35}H_{33}NO_2$: C, 84.14; H, 6.66; N, 2.80. Found: C, 83.52; H, 6.54; N, 2.63 %. $[\alpha]_D^{29}$ = - 40 (*c* 0.25, CH_2Cl_2).

2.4.20 (*S*)-2-benzyl-6-[(1-hydroxy-1,1-diphenylpropan-2-ylamino) methyl]phenol (4d)



White oil, 65 % yield. IR (CH_2Cl_2): 3558, 3307, 3060, 3026, 2923, 2855, 1594, 1493, 1451, 1264, 1157, 1081, 1030, 745, 700 cm^{-1}. ^{1}H-NMR (600 MHz, $CDCl_3$, δ ppm) 7.50 (d, *J* = 7.8 Hz, 2H), 7.45 (d, *J* = 7.8 Hz, 2H), 7.33-6.80 (m, 13H), 6.67 (t, *J* = 7.2 Hz, 1H), 4.86 (s, 1H), 4.01 (s, 2H), 3.92 (d, *J* = 15.0 Hz, 1H), 3.87 (d, *J* = 15.0 Hz, 1H), 3.81-3.76 (m, 1H), 1.15 (d, *J* = 4.2 Hz, 3H). ^{13}C-NMR (600 MHz, $CDCl_3$, δ ppm): 155.5, 144.8, 144.6, 141.1, 130.6, 129.6, 129.0, 128.8, 128.6, 128.4, 128.3, 128.2, 127.2, 126.9, 126.4, 125.9, 125.7, 119.7, 118.8, 80.5, 65.0, 58.7, 35.4, 14.4. Elemental analysis, calculated for $C_{29}H_{29}NO_2$: C, 82.24; H, 6.90; N, 3.31. Found: C, 81.92; H, 6.33; N, 2.98 %. $[\alpha]_D^{29}$ = - 32 (*c* 0.25, CH_2Cl_2).

2.4.21 General procedure for the asymmetric Henry reaction

The dark green solution of $Cu(OAc)_2.nH_2O$ (0.01 mmol) and ligand (0.01mmol) in 2 mL solvent at RT for 2 h. 4-Nitrobenzaldehyde (0.2mmol) and nitromethane (2.0 mmol) were added to the appropriate solution. The reaction mixture was stirred at which point TLC analysis confirmed most of the aldehyde had been consumed. After the solvent was evaporated, the crude product was purified with column chromatography using 3:1 hexane:ethylacetate system.

APPENDIX A: Spectra and Chromatograms

A.1 IR Spectrums

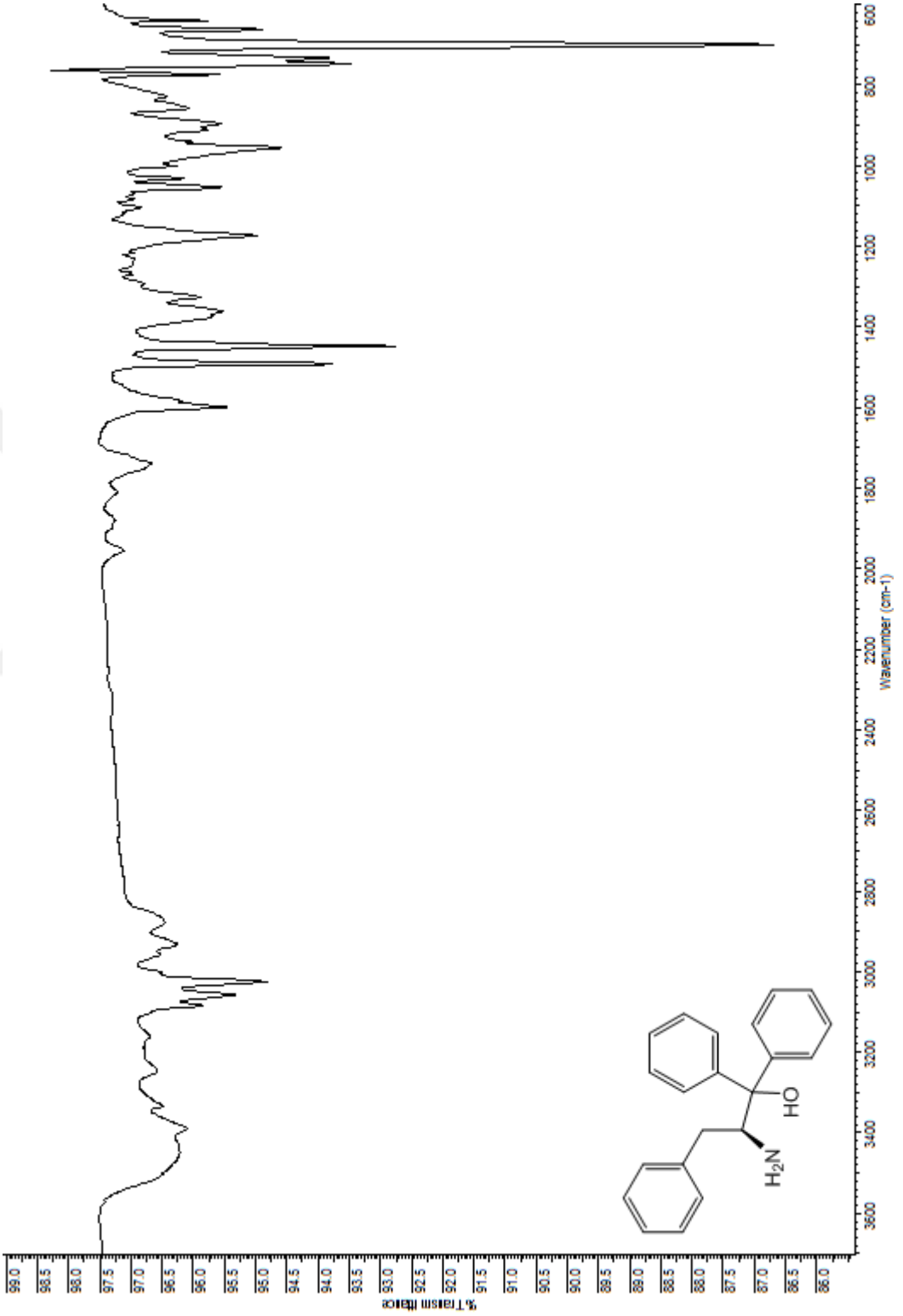


Figure A.1.1 IR spectrum of (*S*)-2-amino-3-phenyl-1,1-diphenylpropan-1-ol (**1a**)

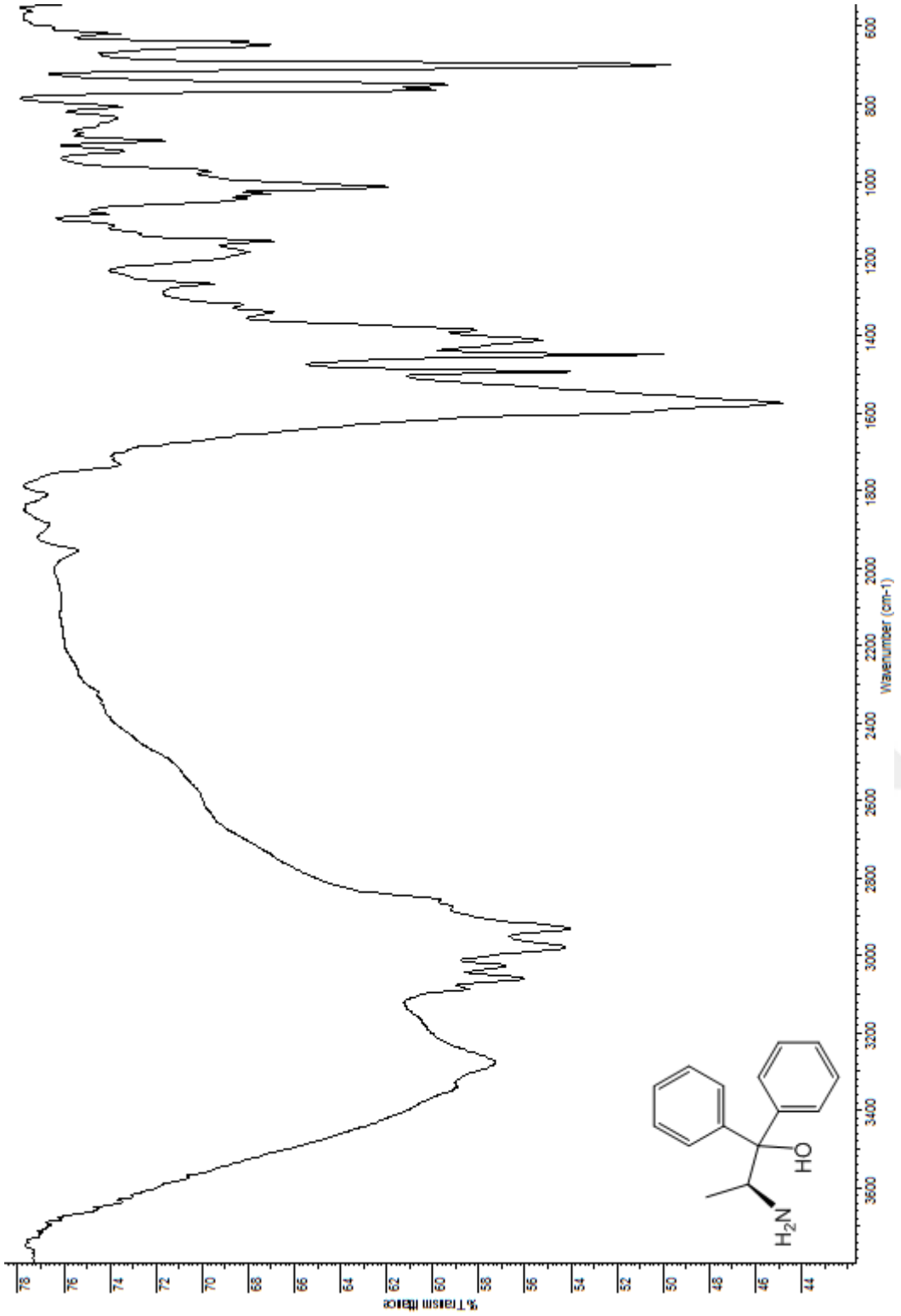


Figure A.1.2 IR spectrum of (*S*)-2-amino-1,1-diphenylpropan-1-ol (**1b**)

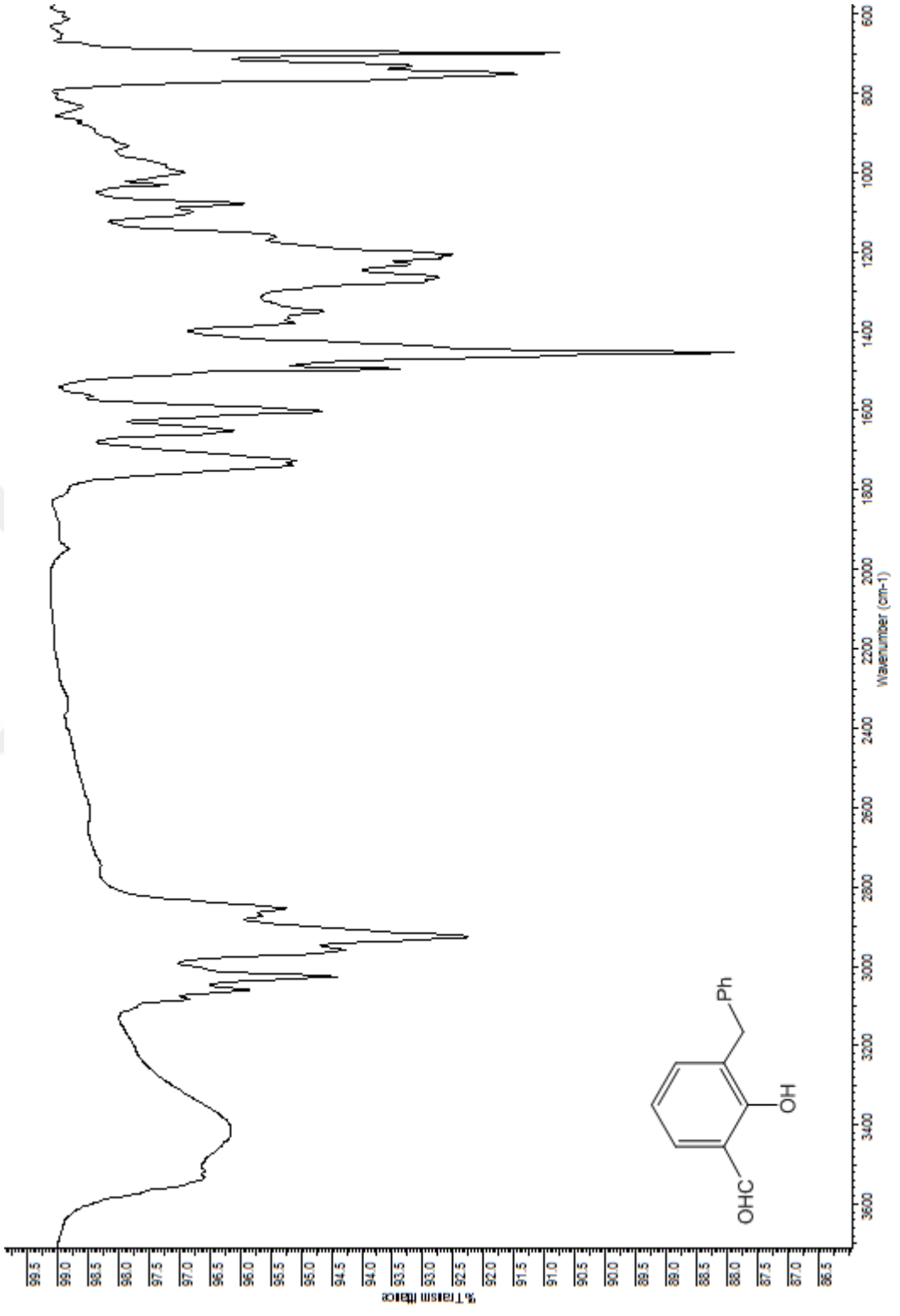


Figure A.1.3 IR spectrum of 3-benzyl-2-hydroxy-benzaldehyde (**2b**)

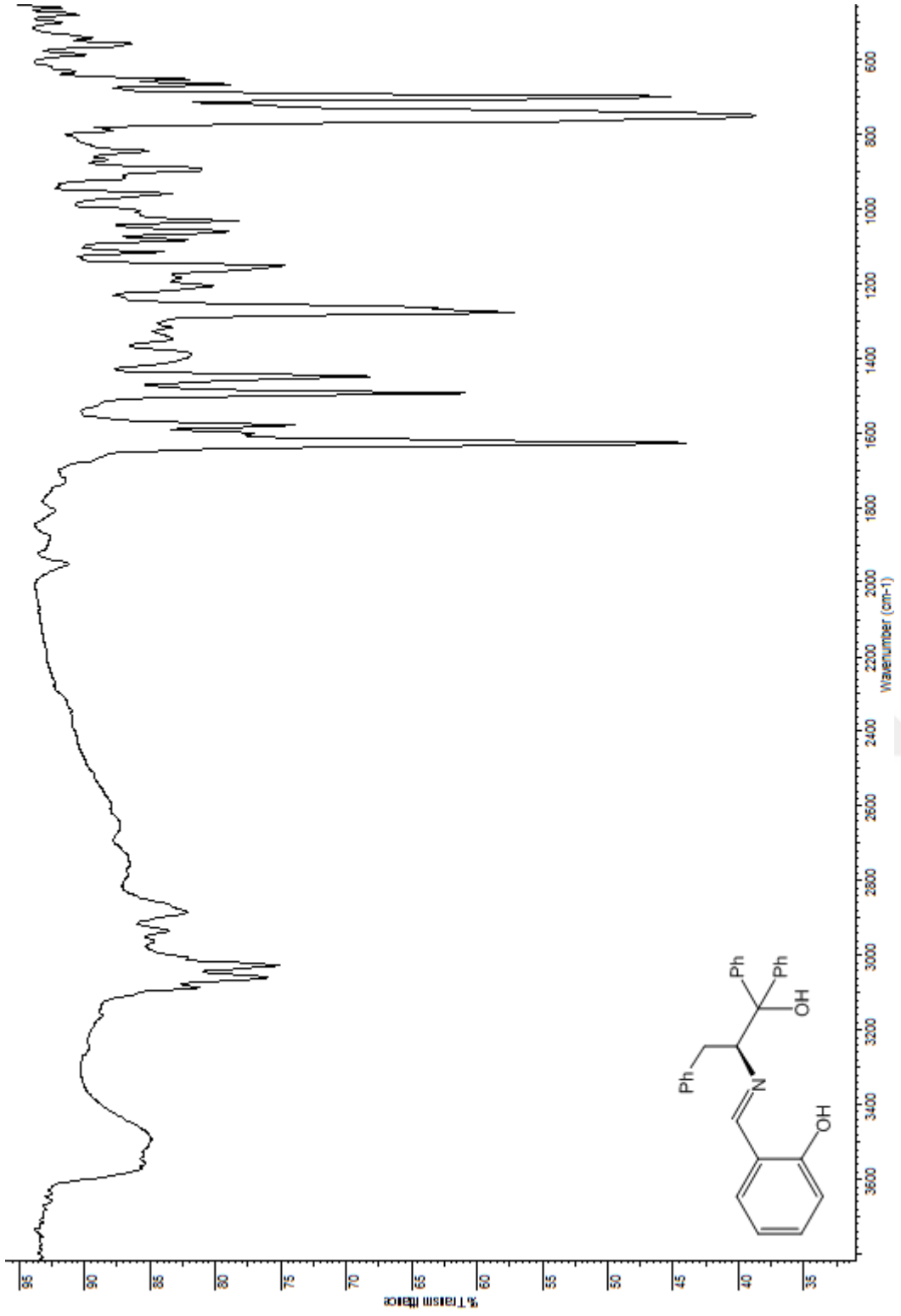


Figure A.1.4 IR spectrum of (*S*)-2-[(1-hydroxy-1,1,3-triphenylpropan-2-ylimino)methyl]phenol (**3a**)

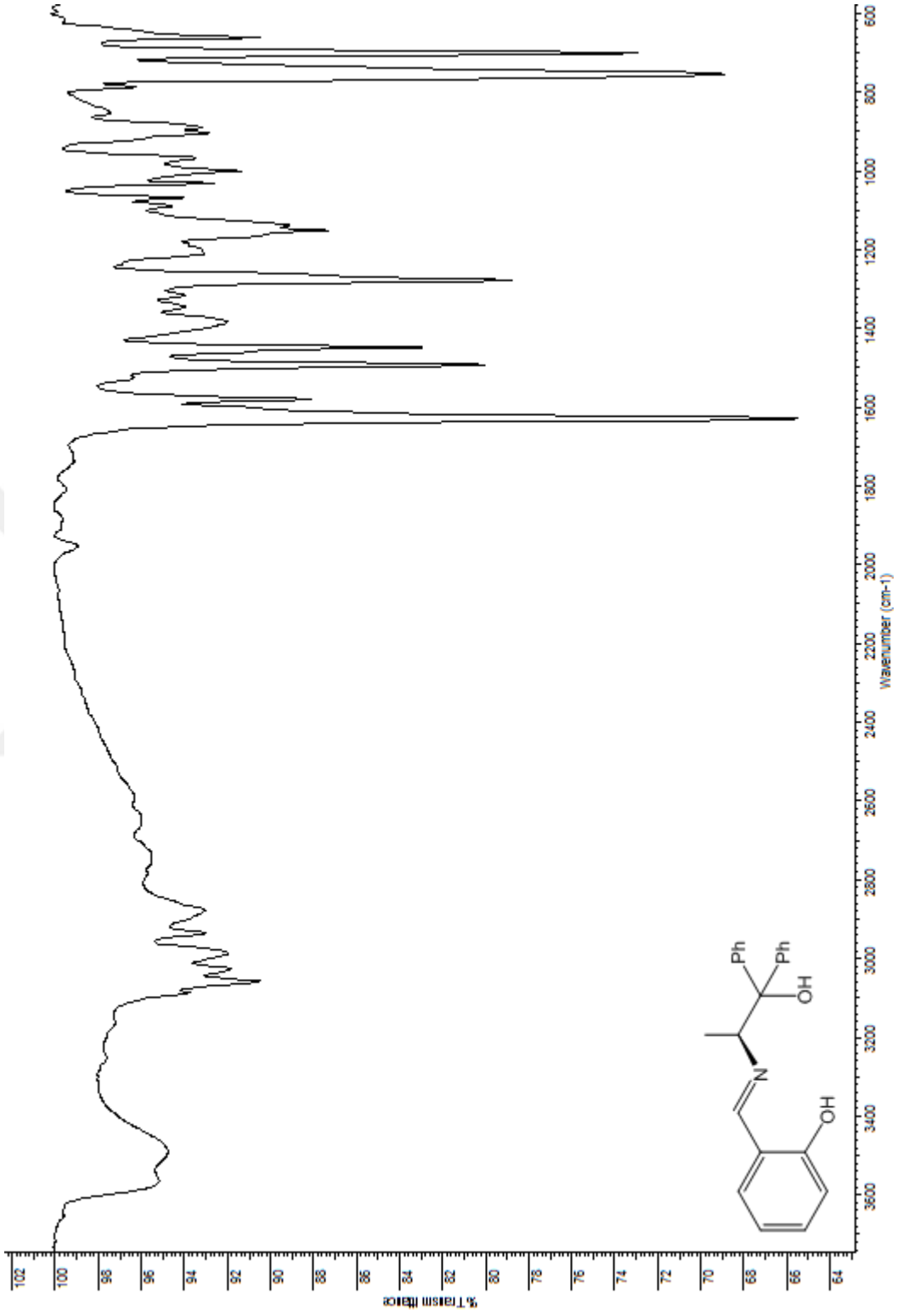


Figure A.1.5 IR spectrum of (*S*)-2-[(1-hydroxy-1,1-diphenylpropan-2-ylimino)methyl]phenol (**3b**)

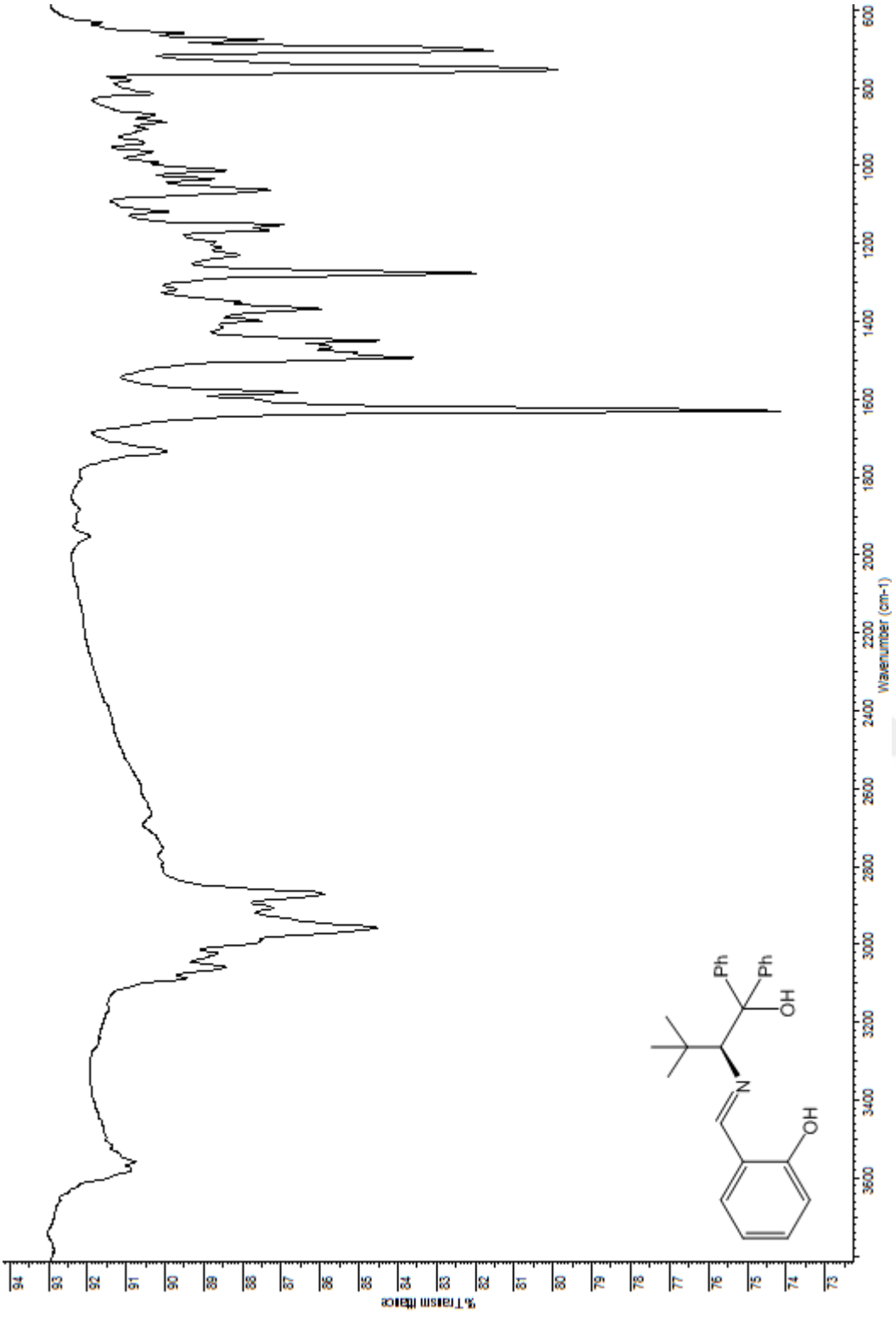


Figure A.1.6 IR spectrum of (*S*)-2-[(1-hydroxy-3,3-dimethyl-1,1-diphenylbutan-2-ylimino)methyl]phenol (**3c**)

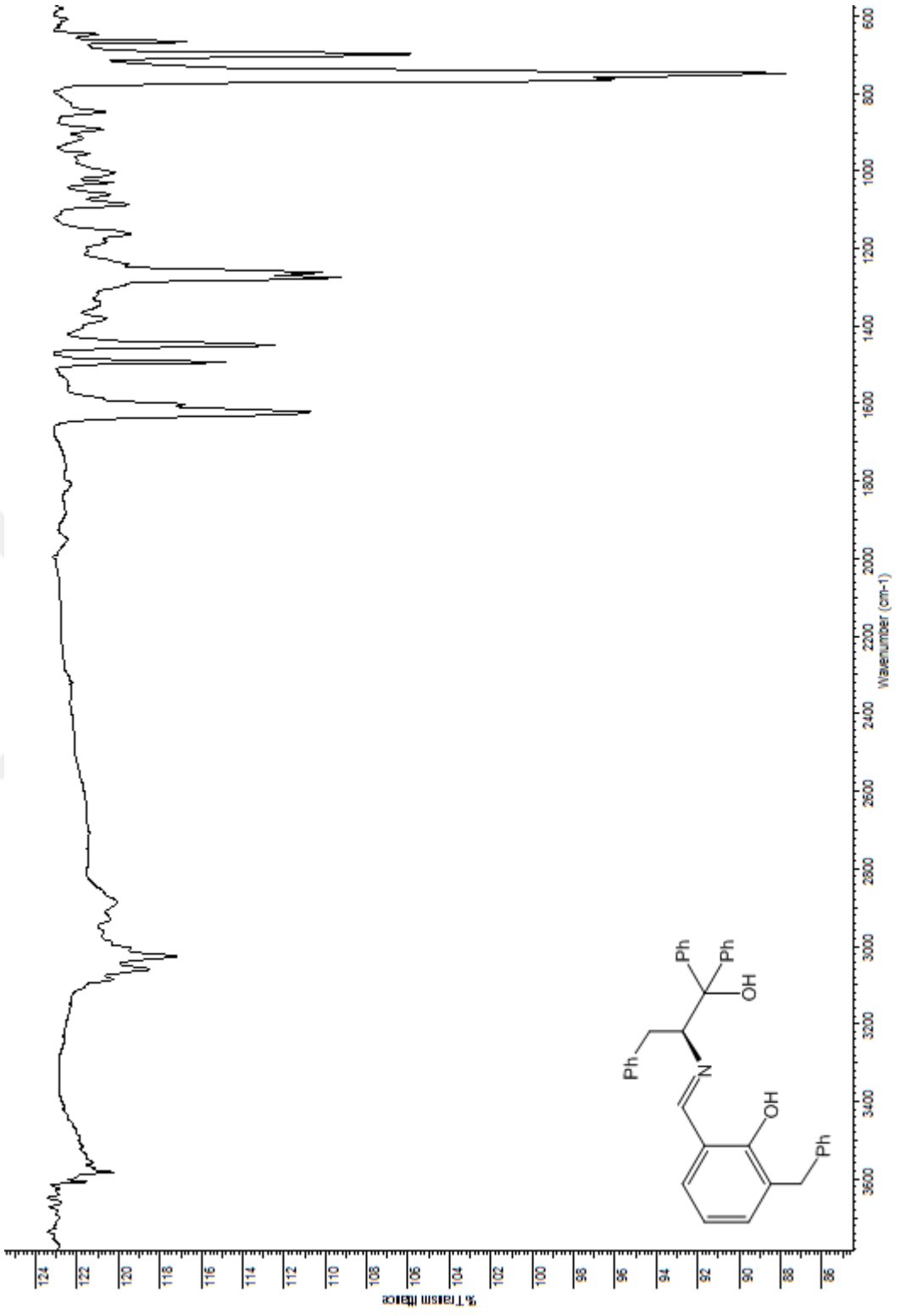


Figure A.1.7 IR spectrum of (*S*)-2-benzyl-6-[(1-hydroxy-1,1,3-triphenylpropan-2-ylimino)methyl]phenol (**3d**)

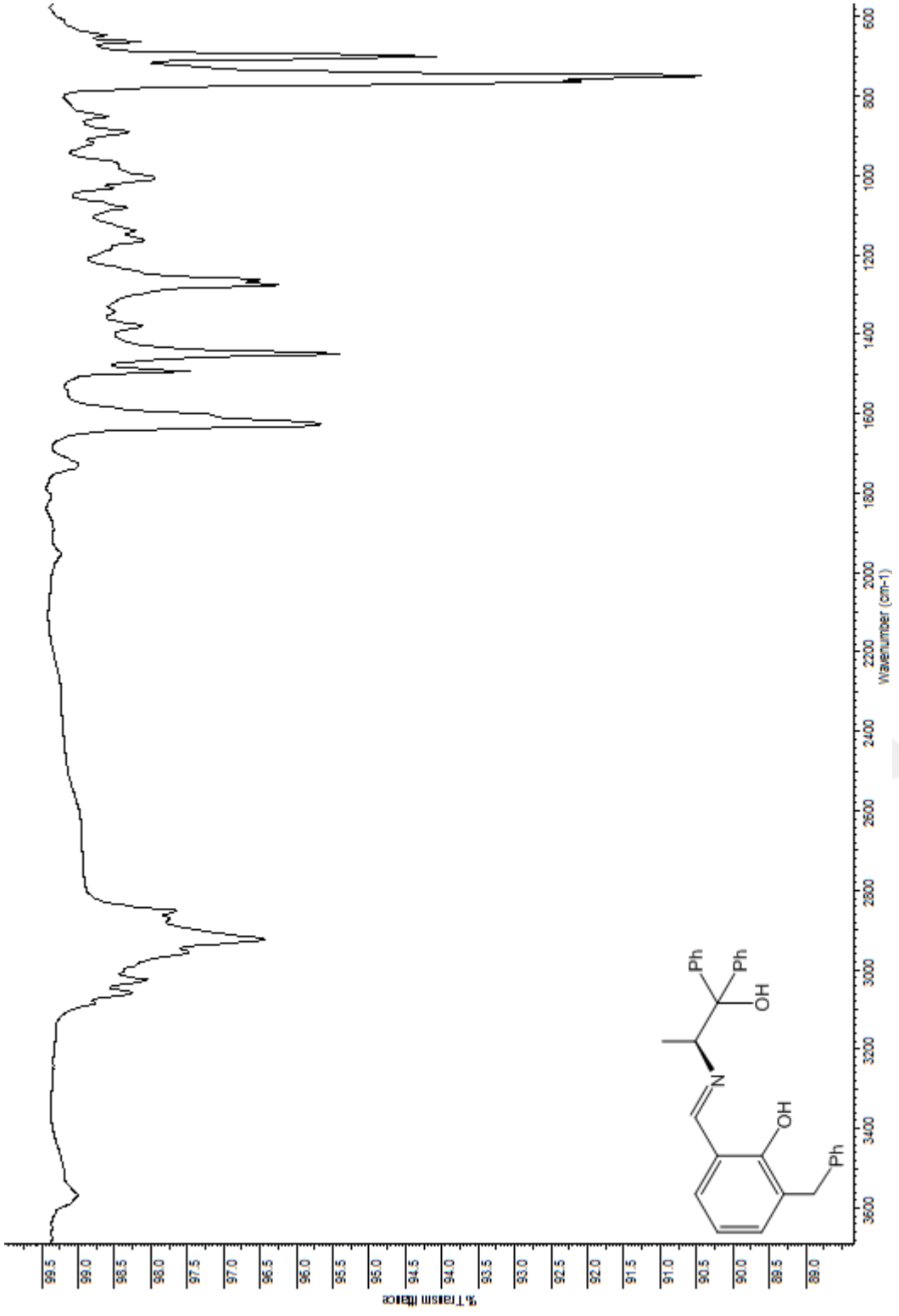


Figure A.1.8 IR spectrum of (*S*)-2-benzyl-6-[(1-hydroxy-1,1-diphenylpropan-2-ylimino)methyl]phenol (**3e**)

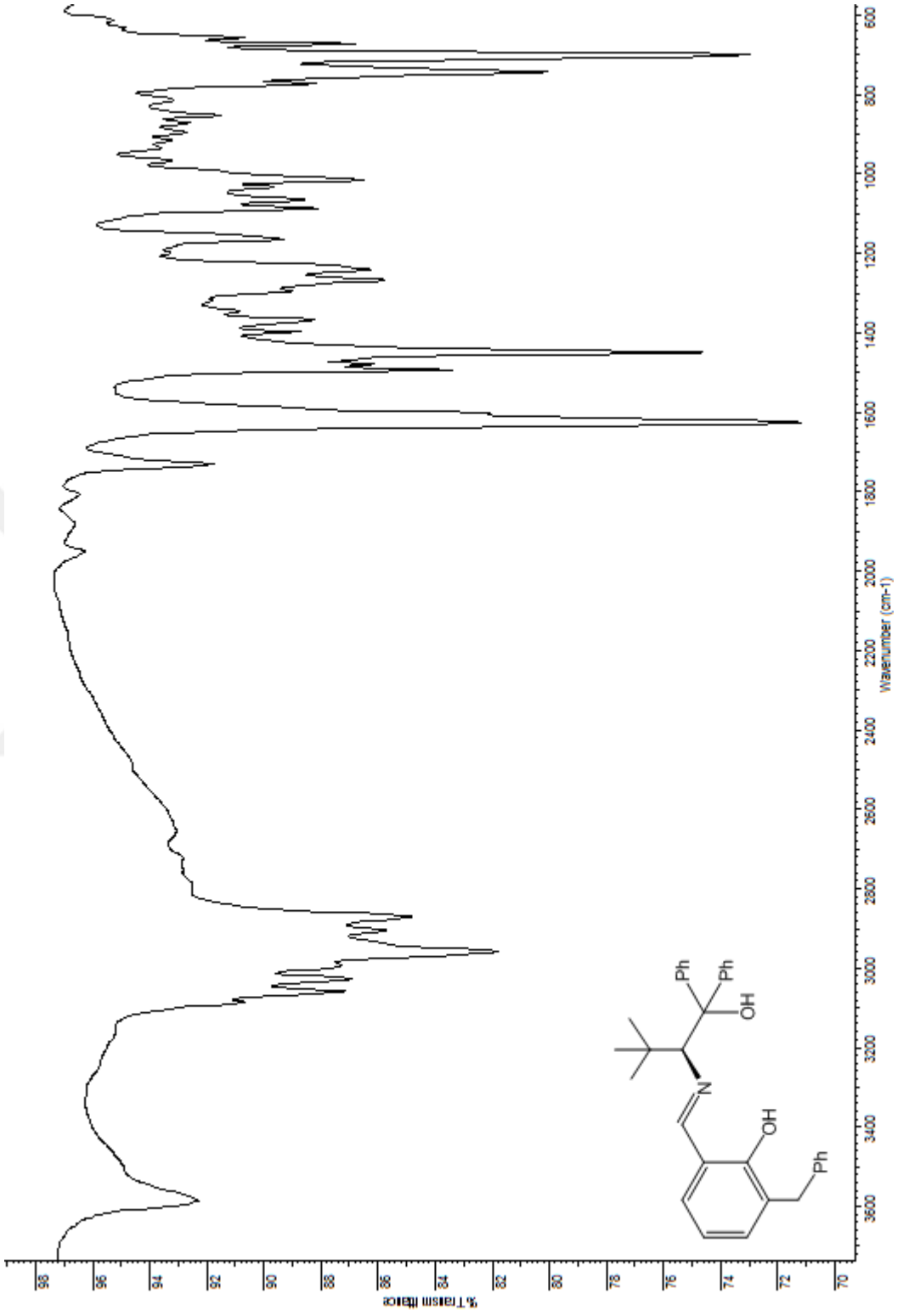


Figure A.1.9 IR spectrum of (*S*)-2-benzyl-6-[(1-hydroxy-3,3-dimethyl-1,1-diphenylbutan-2-ylimino)methyl] phenol (**3f**)

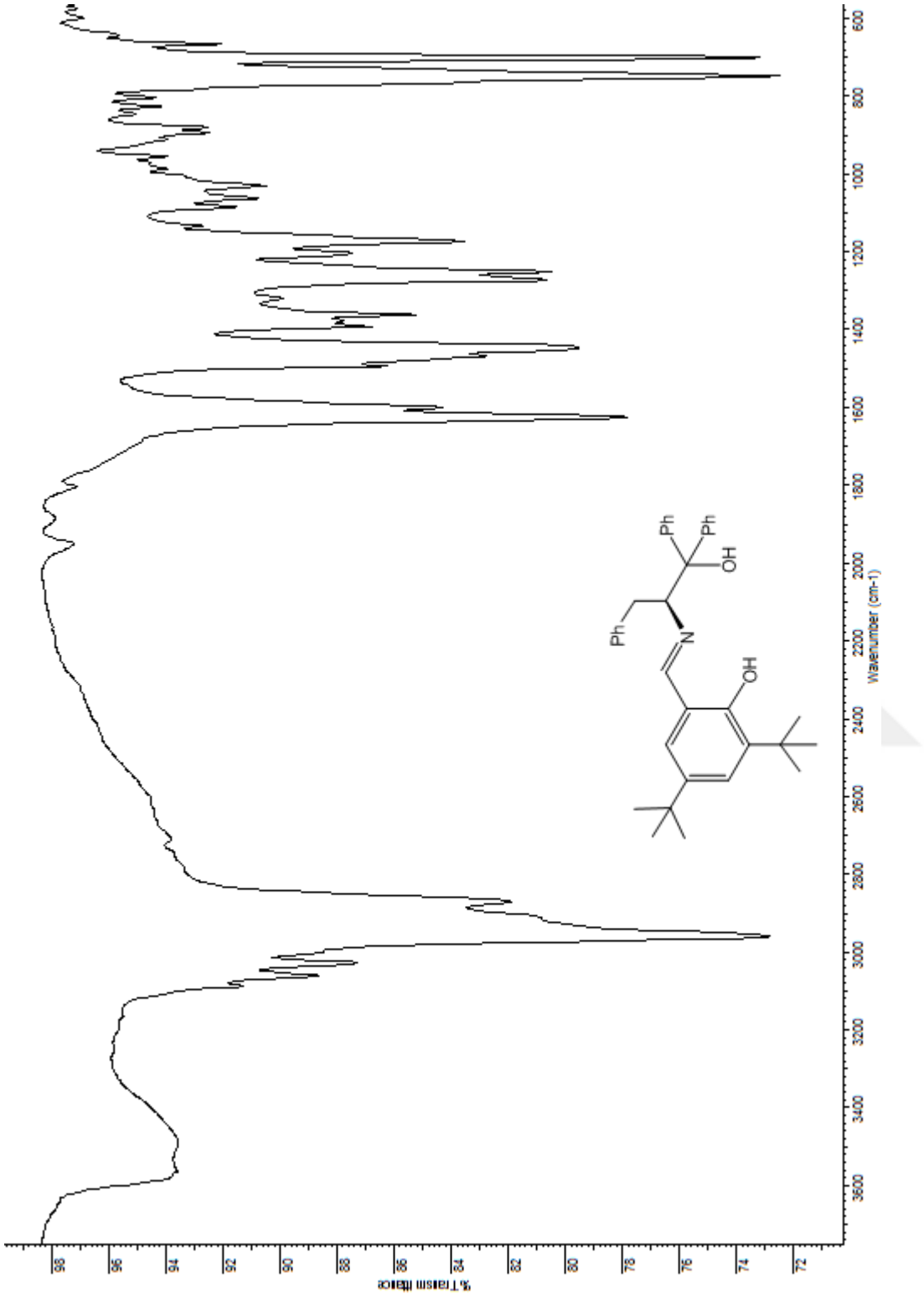


Figure A.1.10 IR spectrum of (*S*)-2,4-di-*tert*-butyl-6-[(1-hydroxy-1,1,3-triphenylpropan-2-ylimino)methyl]phenol (**3g**)

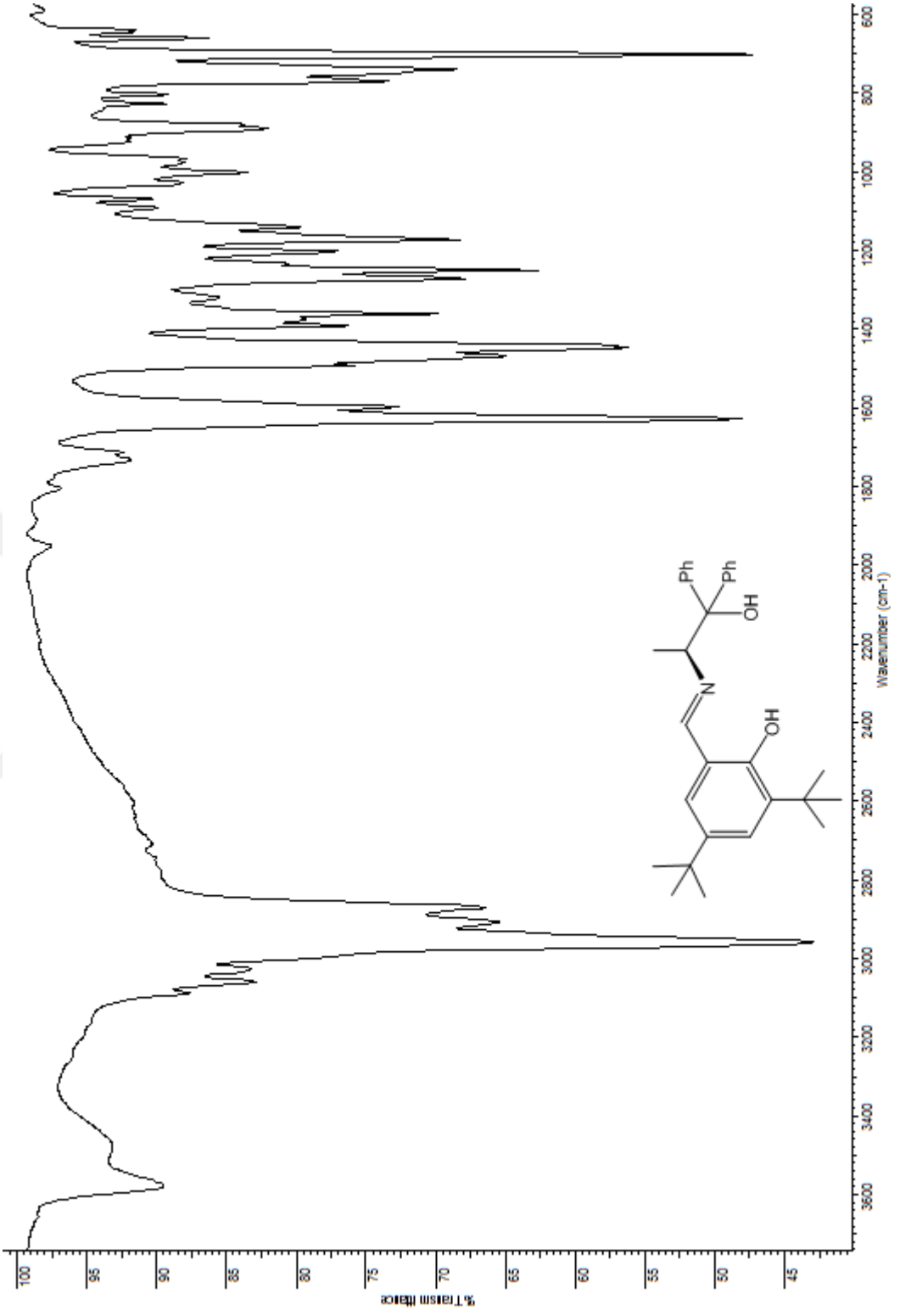


Figure A.1.11 IR spectrum of (*S*)-2,4-di-*tert*-butyl-6-[(1-hydroxy-1,1-diphenylpropan-2-ylimino)methyl]phenol (**3h**)

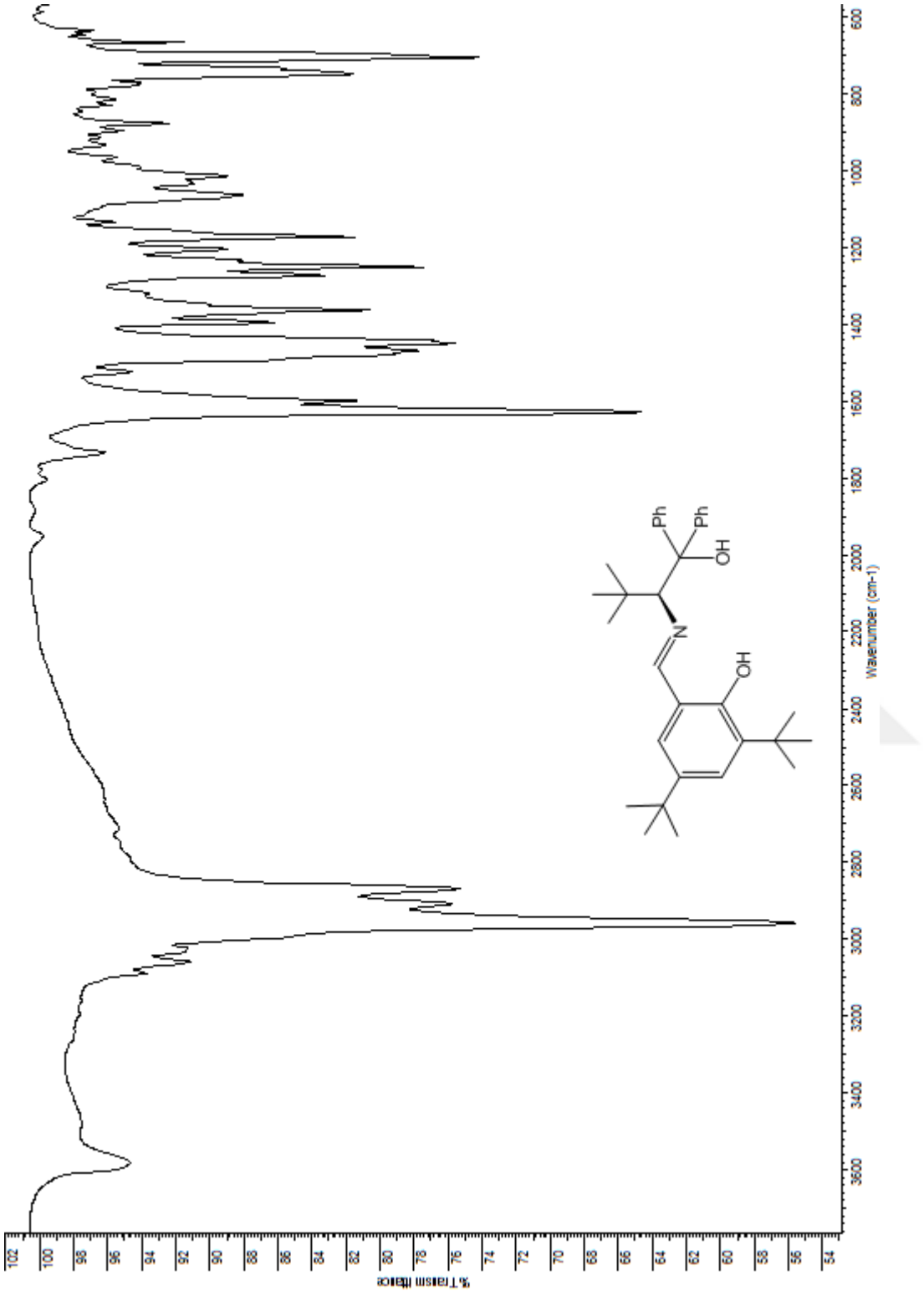


Figure A.1.12 IR spectrum of (*S*)-2,4-di-*tert*-butyl-6-[(1-hydroxy-3,3-dimethyl-1,1-diphenyl butan-2-ylimino)methyl]phenol (**3i**)

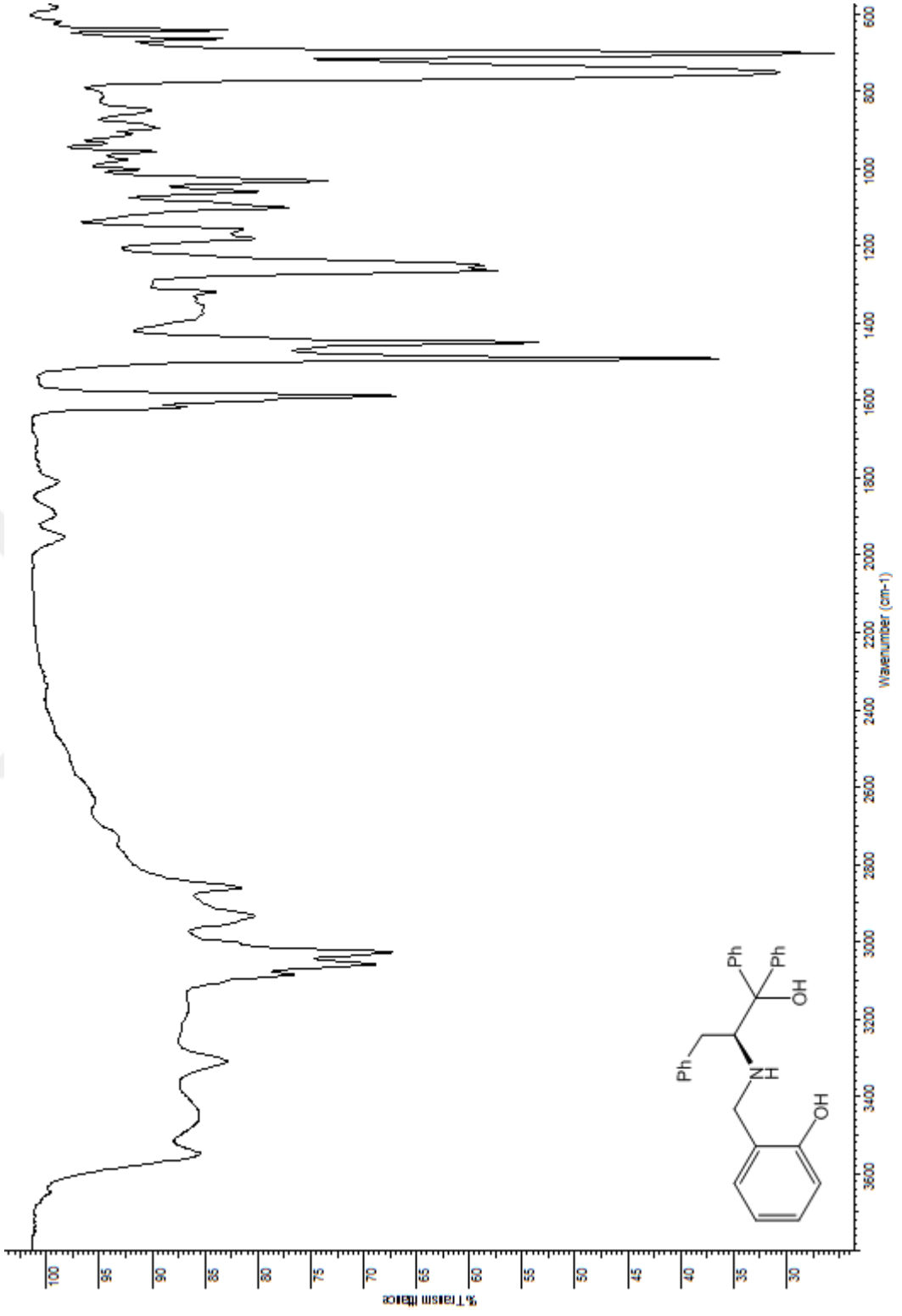


Figure A.1.13 IR spectrum of (*S*)-2-[(1-hydroxy-1,1,3-triphenylpropan-2-ylamino)methyl]phenol (**4a**)

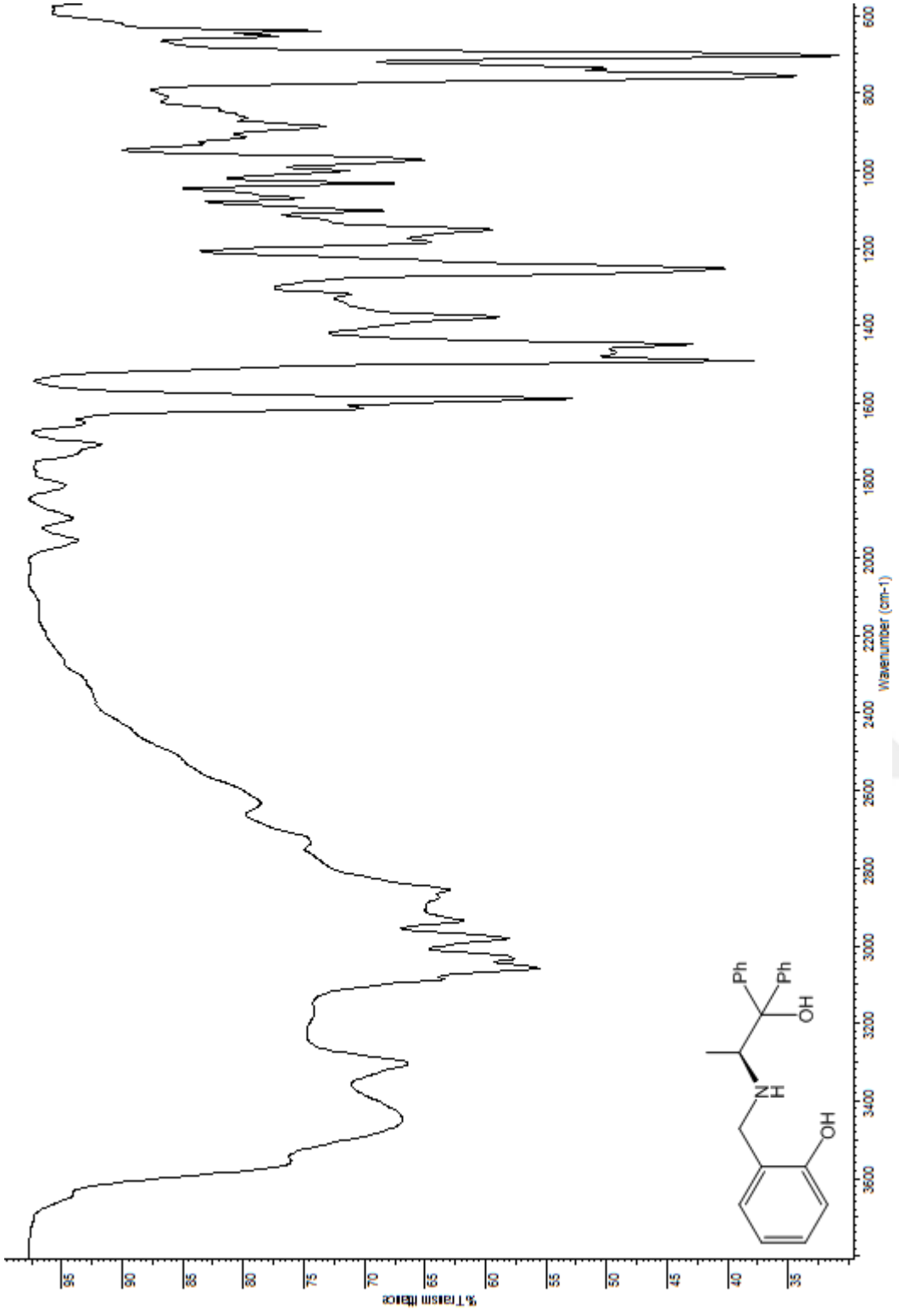


Figure A.1.14 IR spectrum of (*S*)-2-[(1-hydroxy-1,1-diphenylpropan-2-ylamino)methyl]phenol (**4b**)

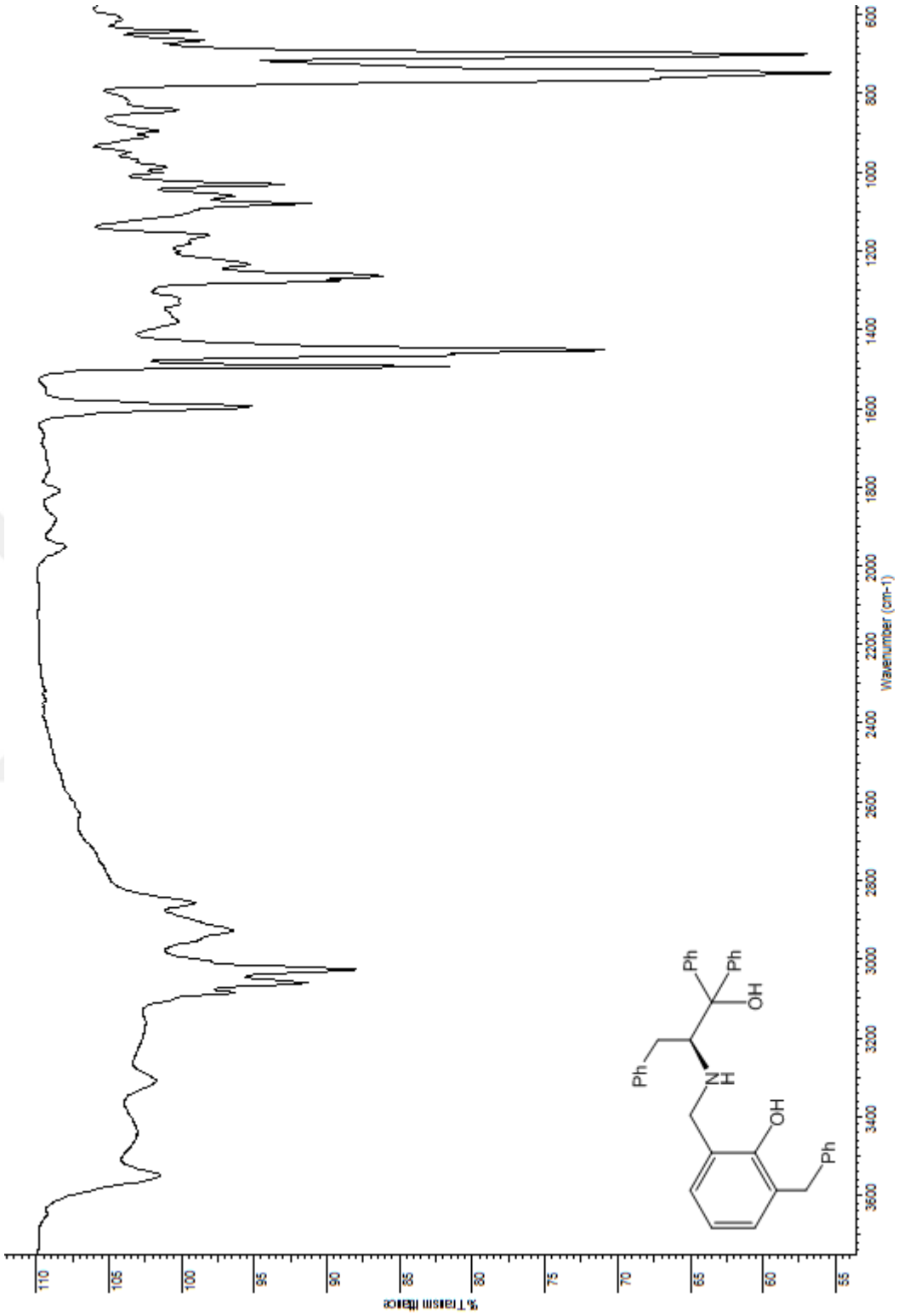


Figure A.1.15 IR spectrum of (*S*)-2-benzyl-6-[(1-hydroxy-1,1,3-triphenylpropan-2-yl-amino)methyl]phenol (**4c**)

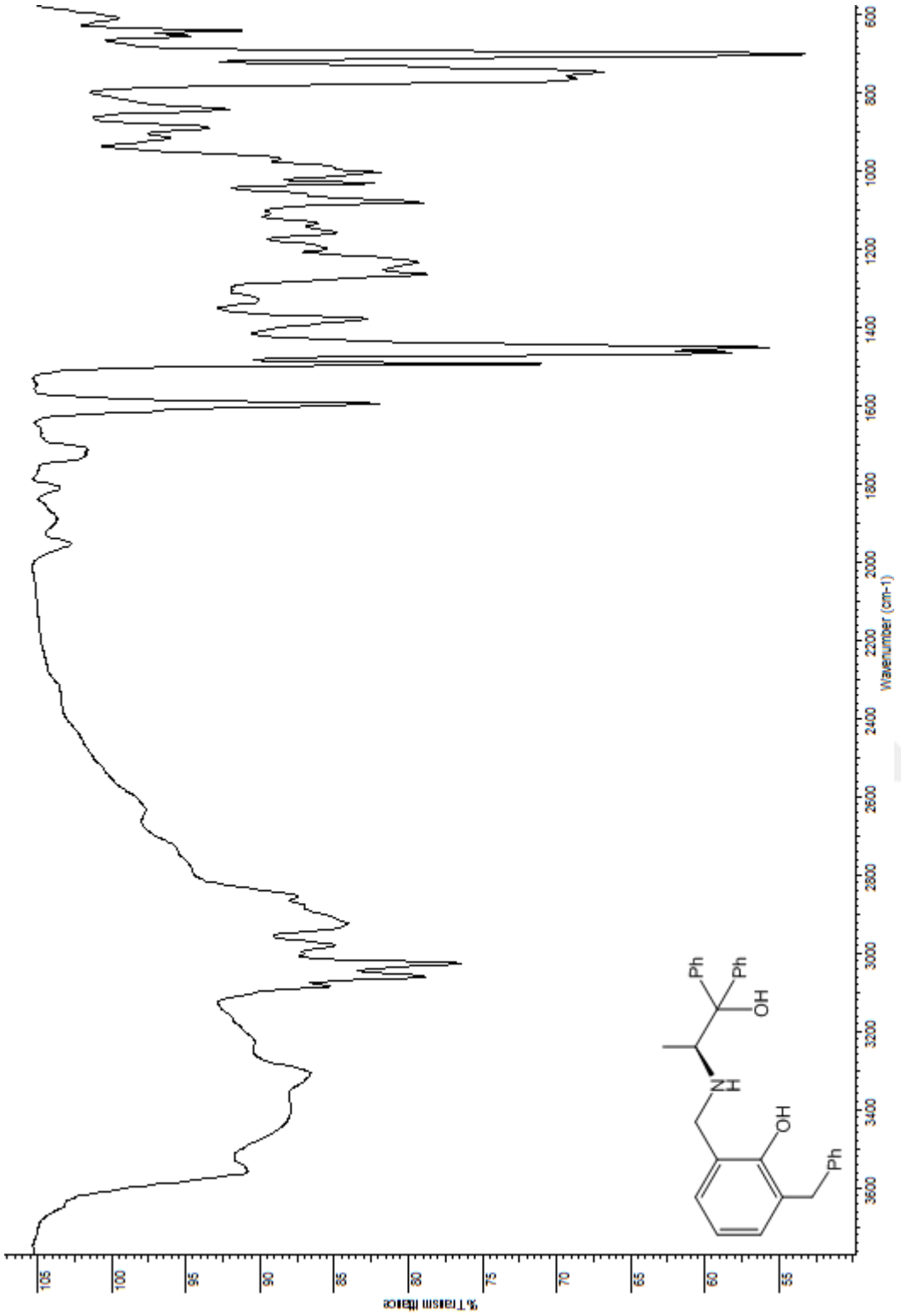


Figure A.1.16 IR spectrum of (*S*)-2-benzyl-6-[(1-hydroxy-1,1-diphenylpropan-2-ylamino)methyl]phenol (**4d**)

A. 2 ^{1}H NMR Spectrums

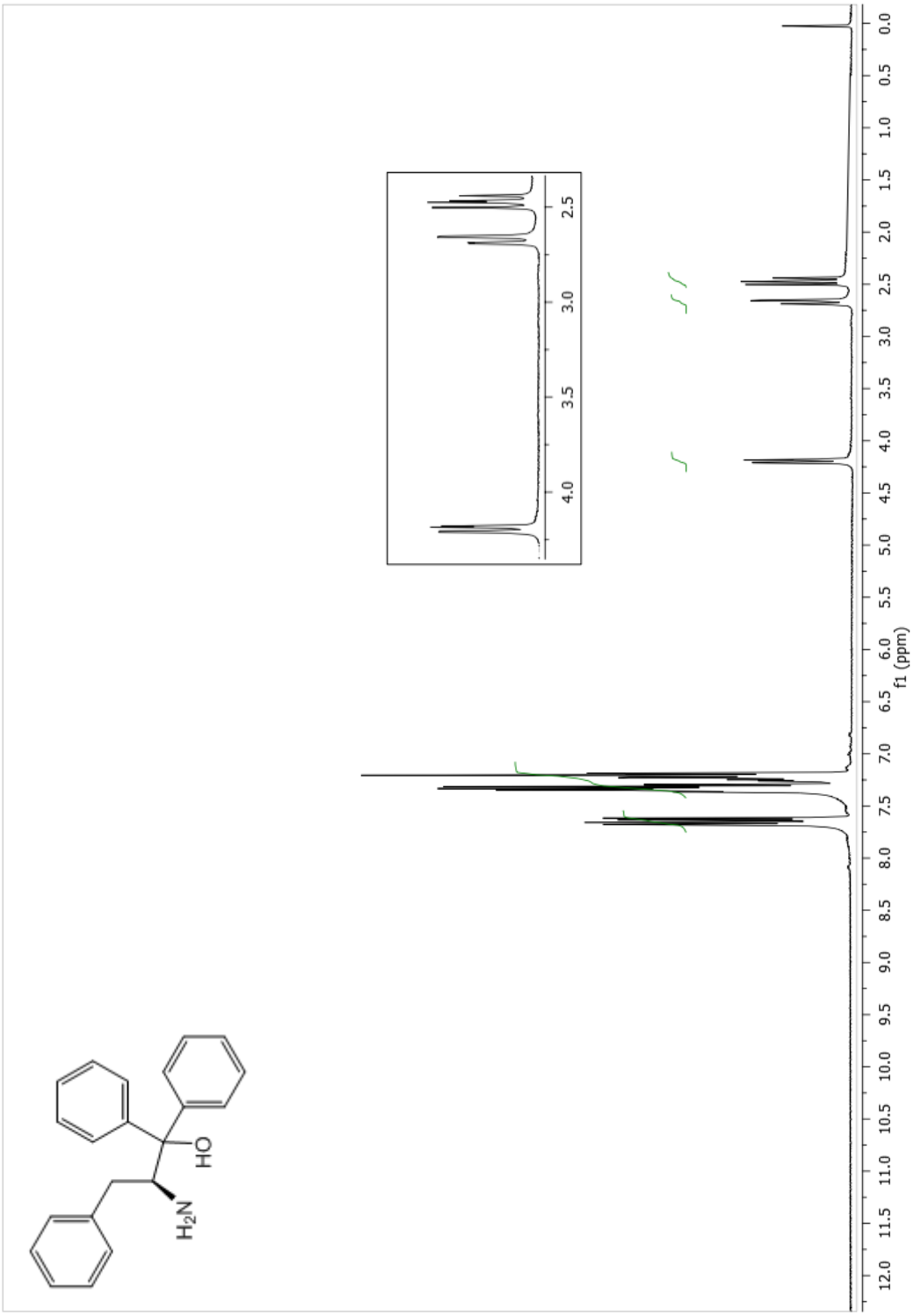


Figure A.2.1 ^{1}H NMR spectrum of (*S*)-2-amino-3-phenyl-1,1-diphenylpropan-1-ol (**1a**)

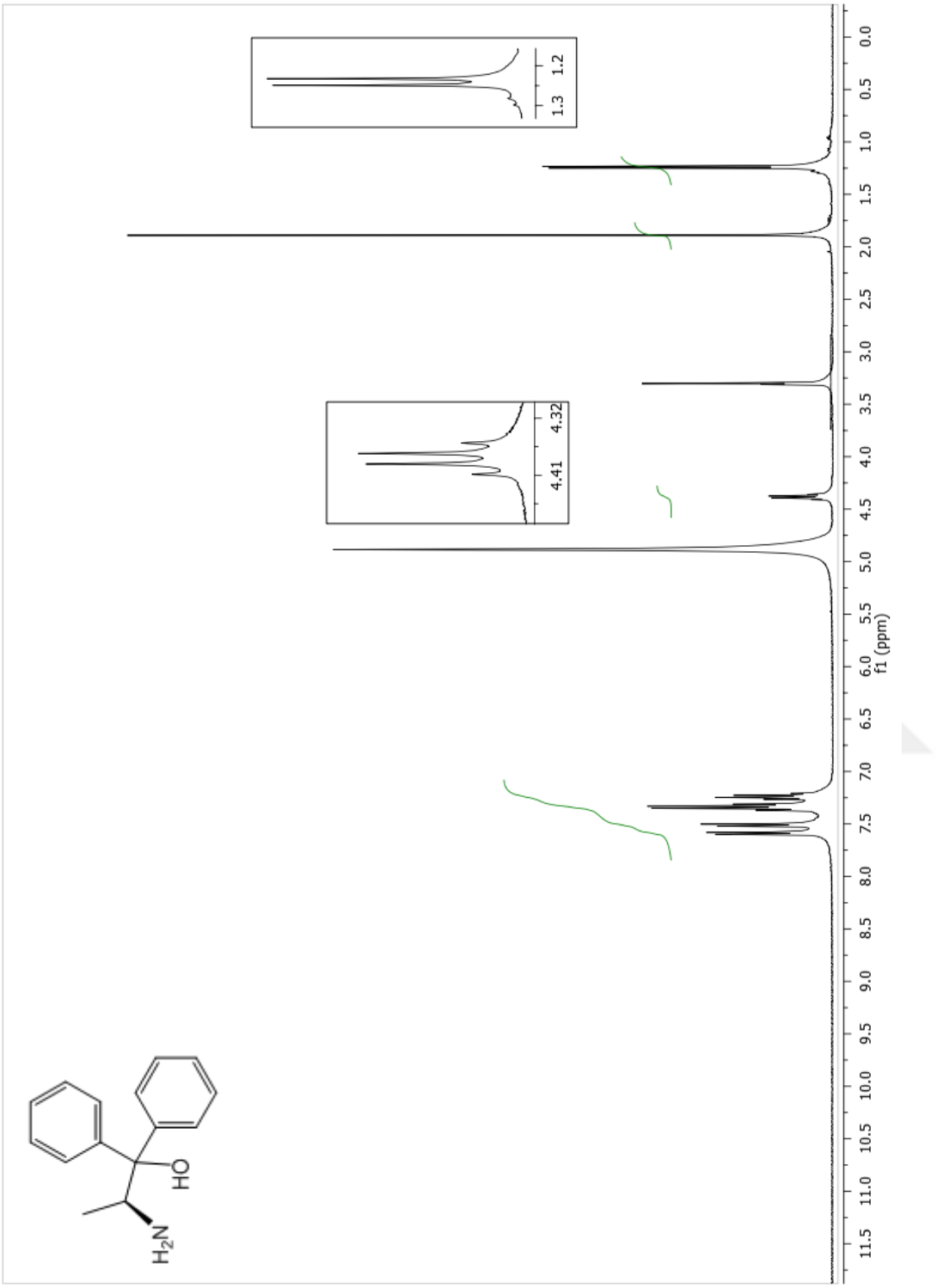


Figure A.2.2 ^{1}H NMR spectrum of (*S*)-2-amino-1,1-diphenylpropan-1-ol (**1b**)

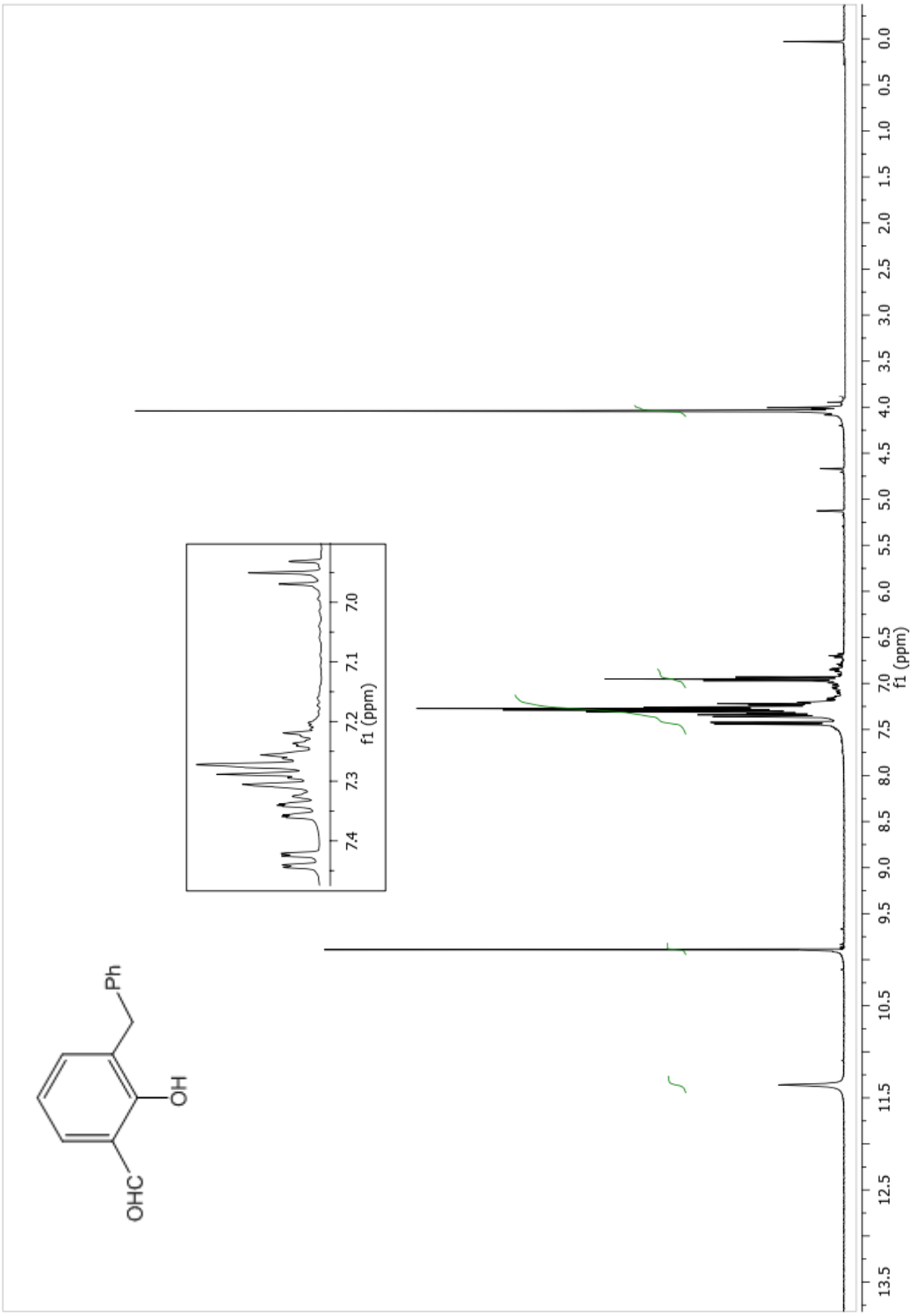


Figure A.2.3 ^{1}H NMR spectrum of 3-benzyl-2-hydroxy-benzaldehyde (**2b**)

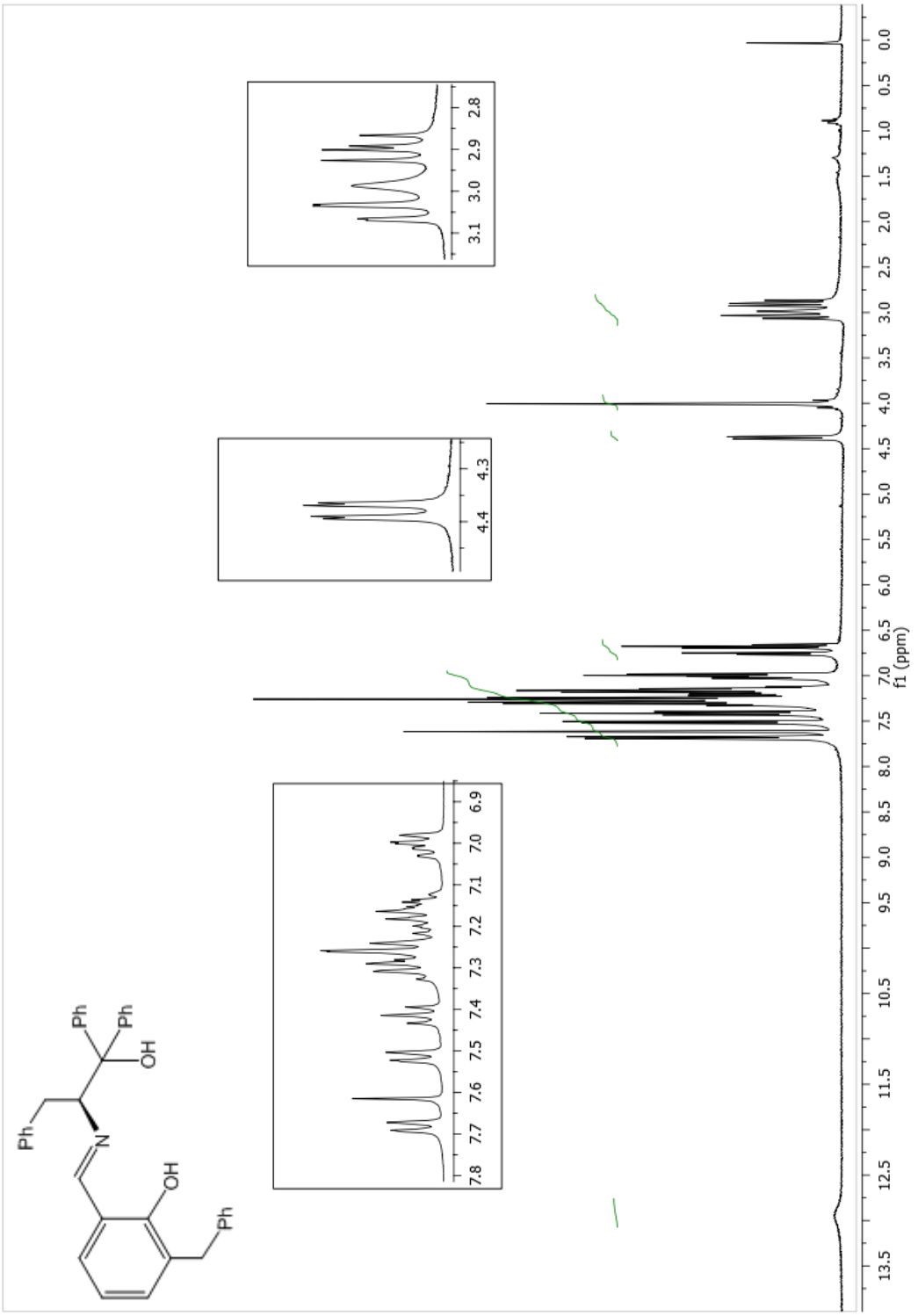


Figure A.2.4 ^{1}H NMR spectrum of (*S*)-2-benzyl-6-[(1-hydroxy-1,1,3-triphenylpropan-2-ylimino) methyl]phenol (**3d**)

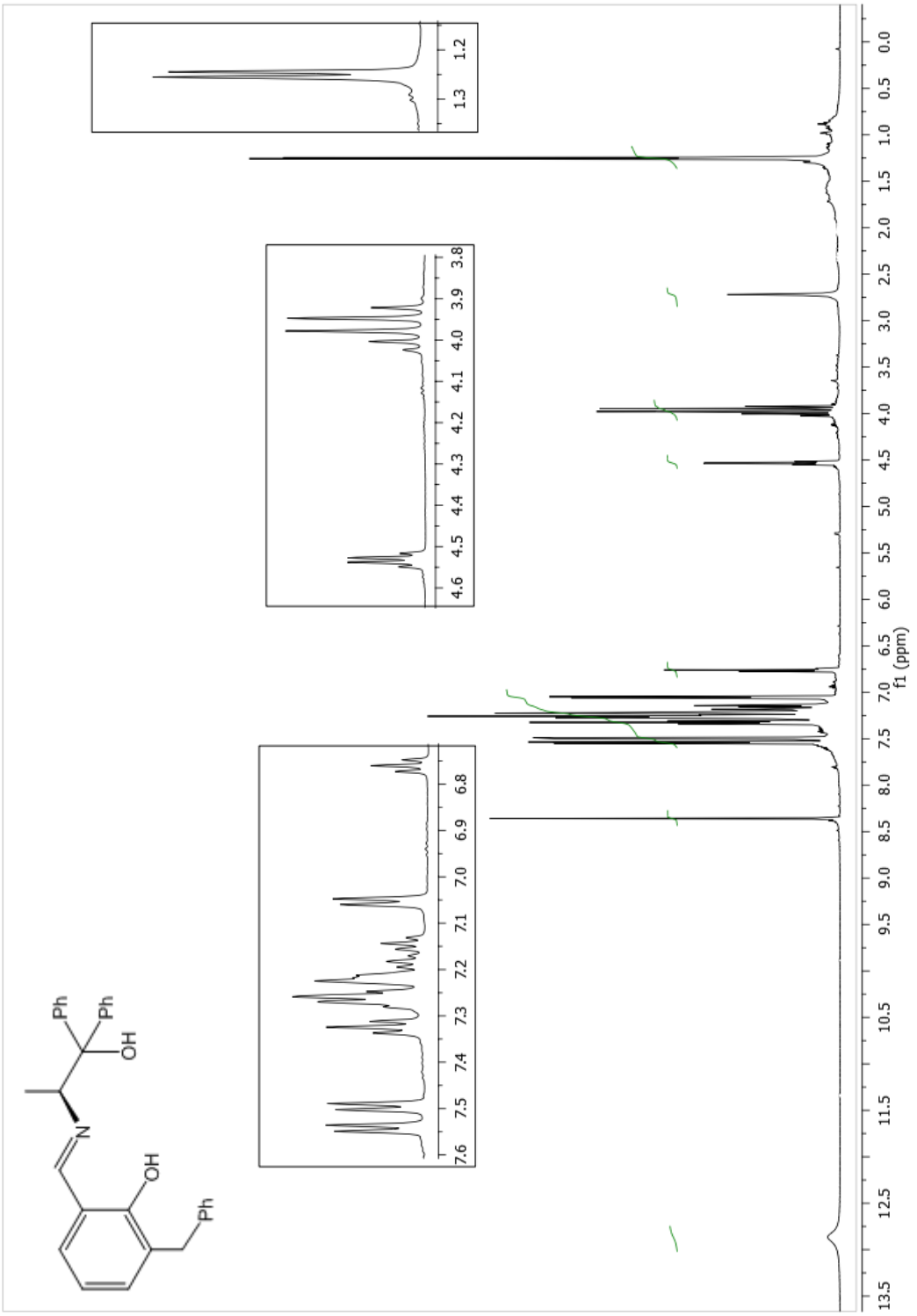


Figure A.2.5 ^{1}H NMR spectrum of (*S*)-2-benzyl-6-[(1-hydroxy-1,1-diphenylpropan-2-ylimino) methyl]phenol (**3e**)

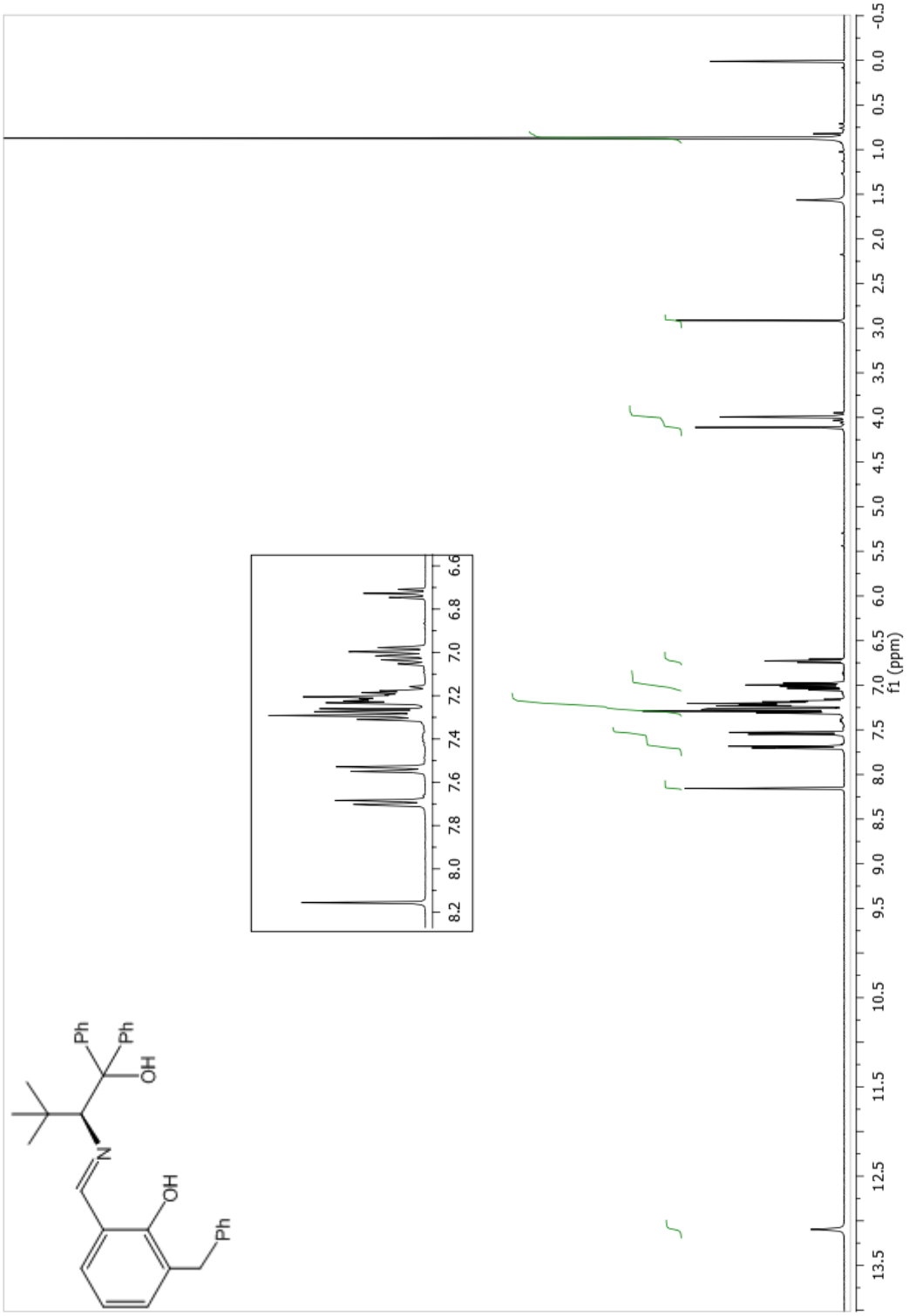


Figure A.2.6 ^{1}H NMR spectrum of (*S*)-2-benzyl-6-[(1-hydroxy-3,3-dimethyl-1,1-diphenylbutan-2-ylimino)methyl]phenol (**3f**)

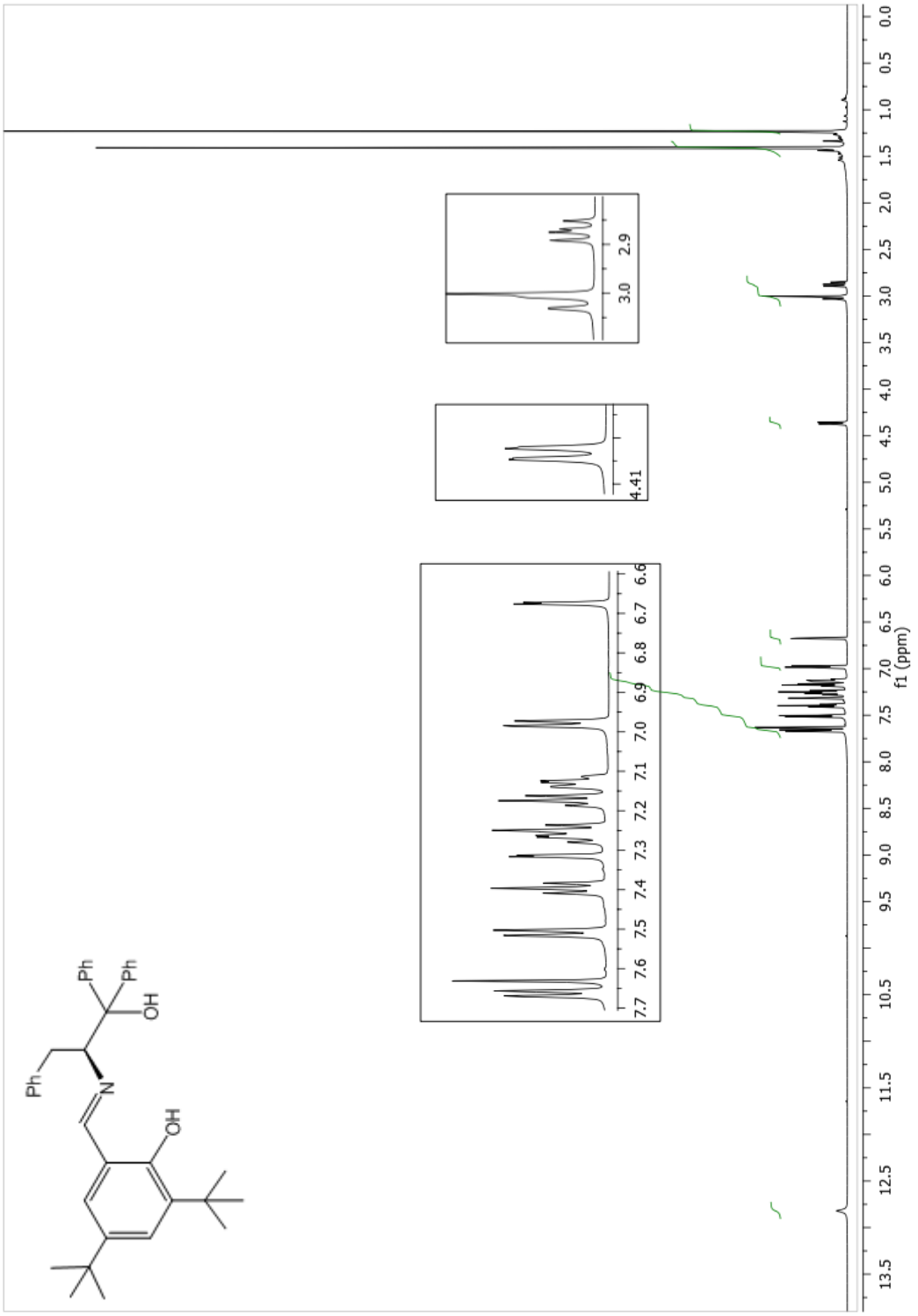


Figure A.2.7 ^{1}H NMR spectrum of (*S*)-2,4-di-*tert*-butyl-6-[(1-hydroxy-1,1,3-triphenylpropan-2-ylimino)methyl]phenol (**3g**)

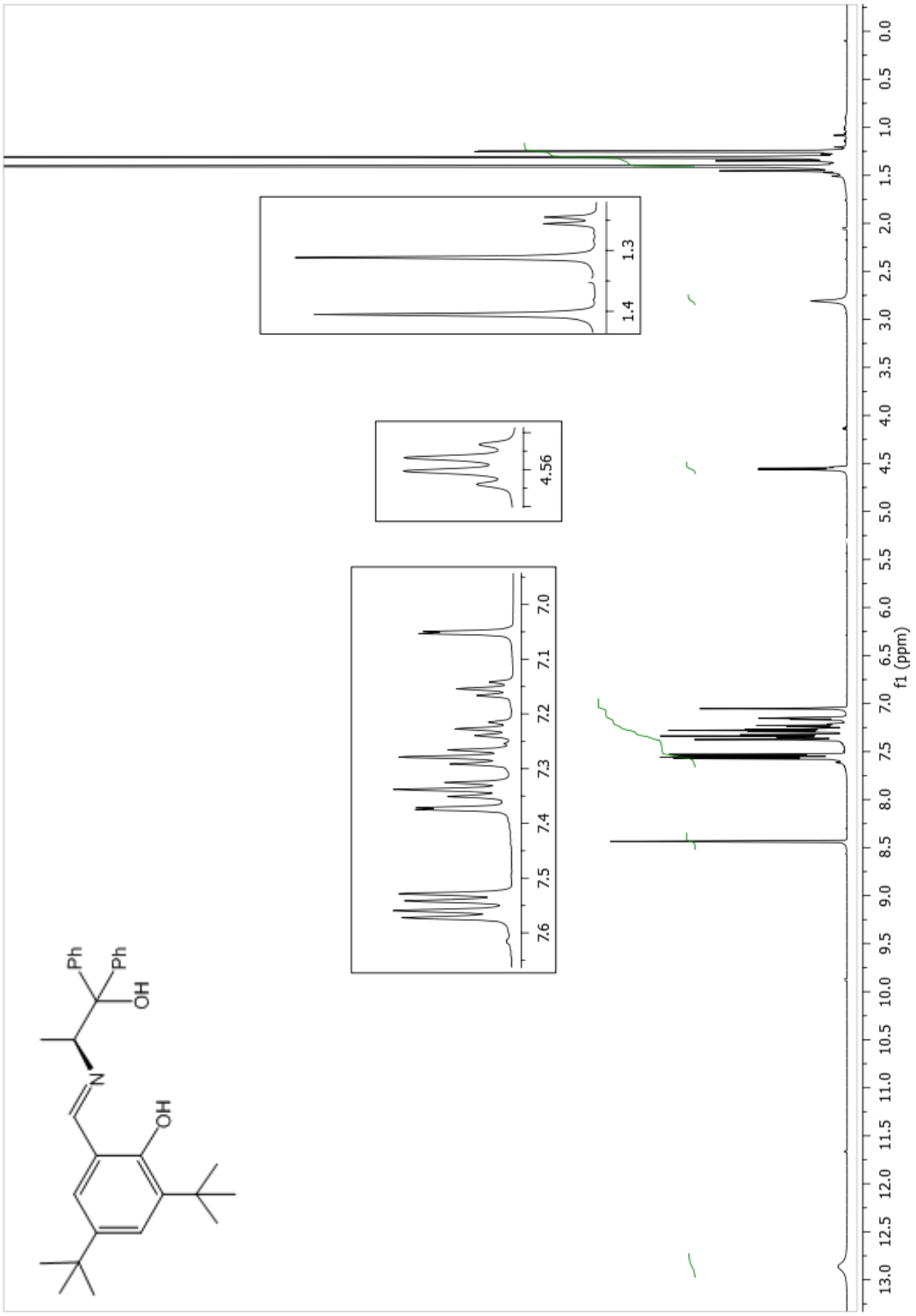


Figure A.2.8 ^{1}H NMR spectrum of (*S*)-2,4-di-*tert*-butyl-6-[(1-hydroxy-1,1-diphenylpropan-2-ylimino)methyl]phenol (**3h**)

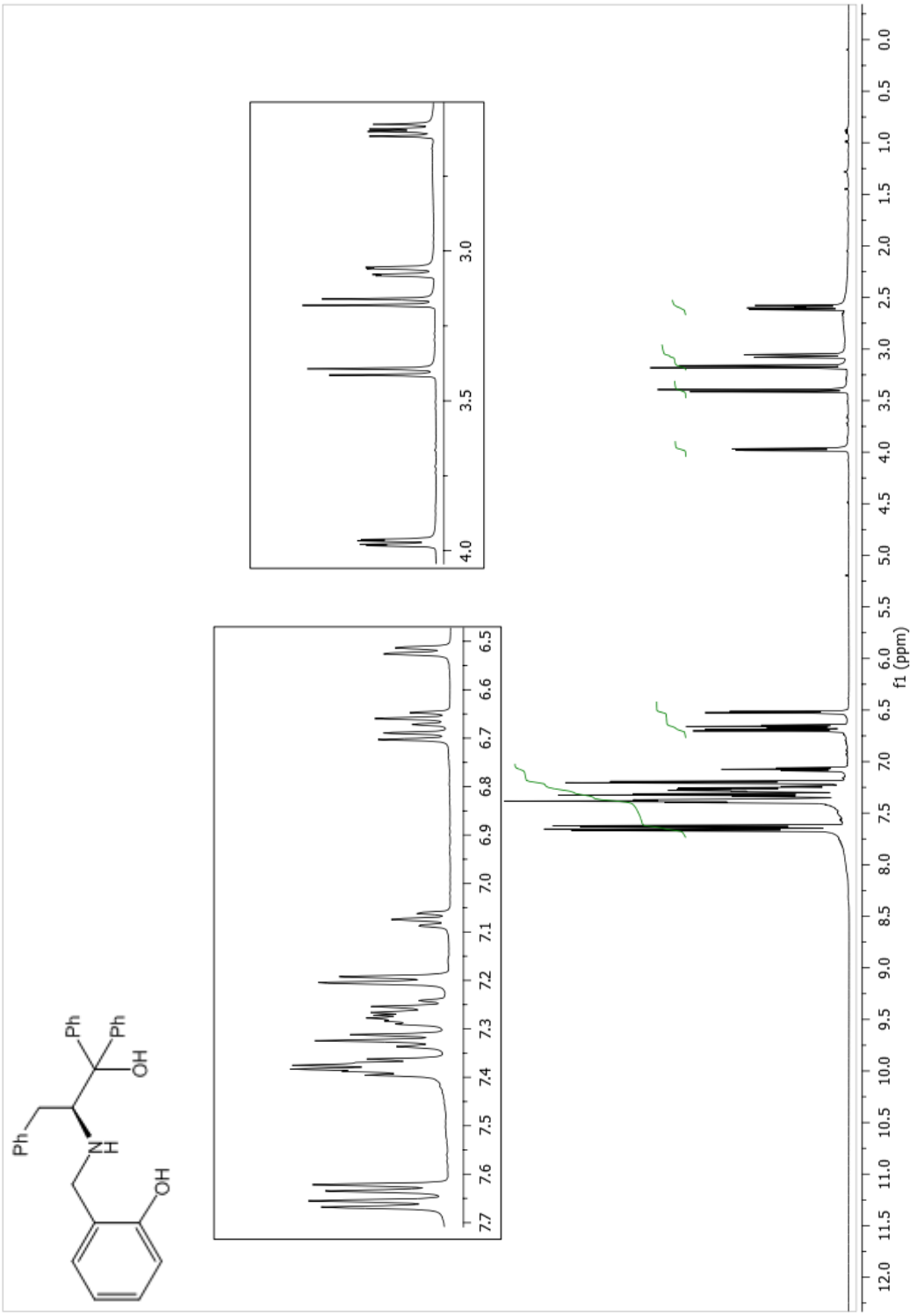


Figure A.2.9 ^{1}H NMR spectrum of (*S*)-2-[(1-hydroxy-1,1,3-triphenylpropan-2-ylamino)methyl] phenol (**4a**)

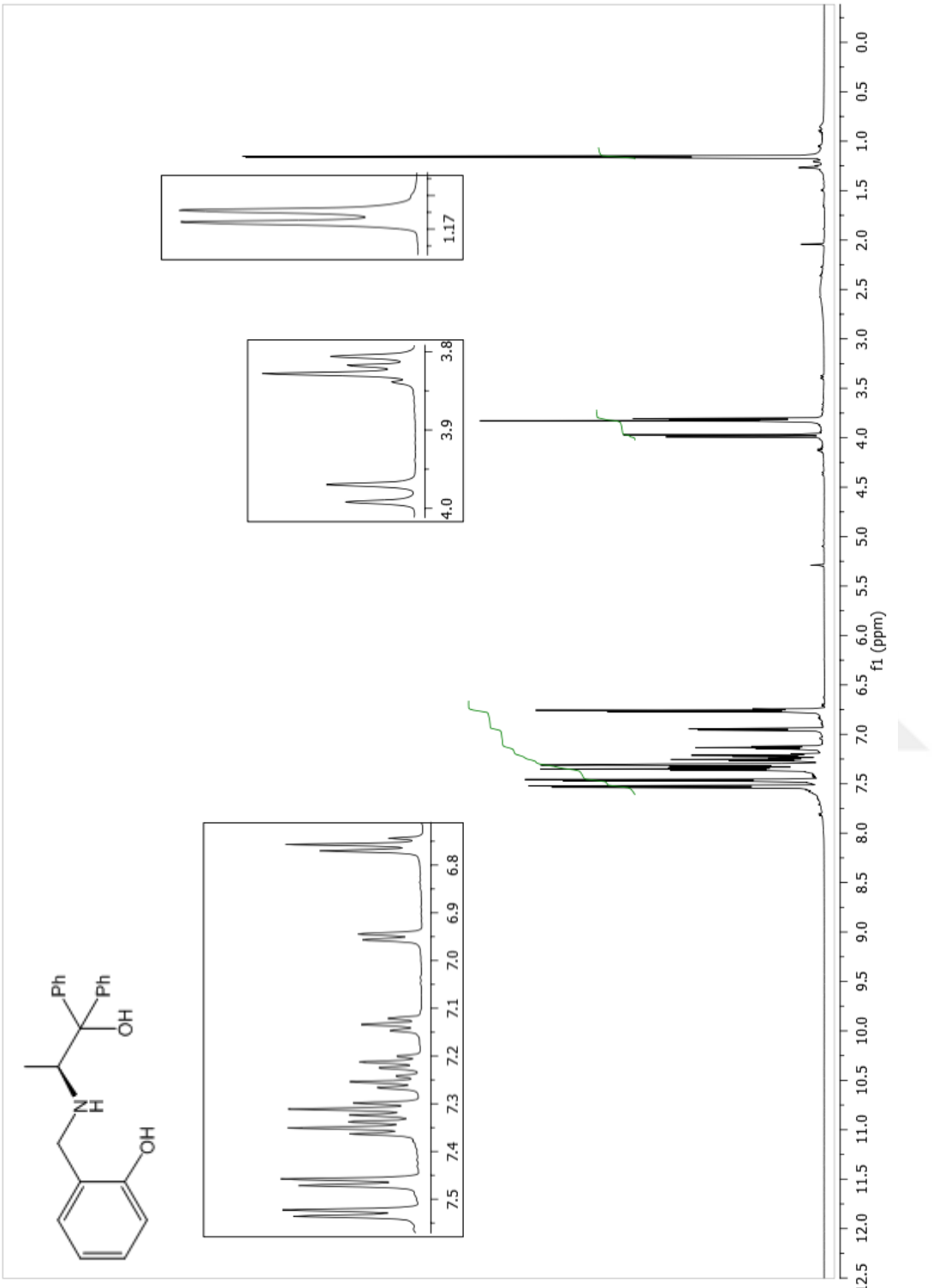


Figure A.2.10 ^{1}H NMR spectrum of (*S*)-2-[(1-hydroxy-1,1-diphenylpropan-2-ylamino)methyl] phenol (**4b**)

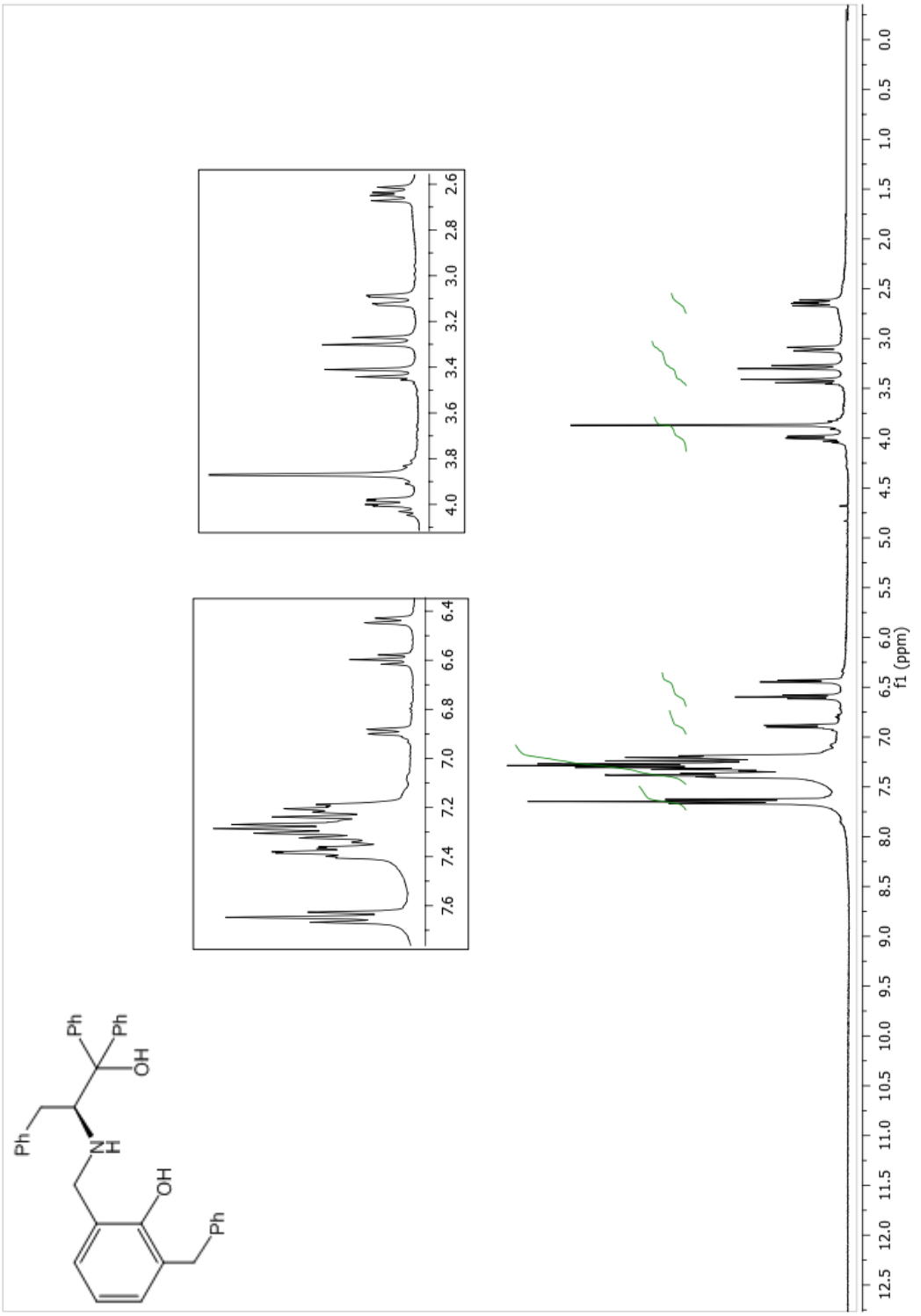


Figure A.2.11 ^{1}H NMR spectrum of (*S*)-2-benzyl-6-[(1-hydroxy-1,1,3-triphenylpropan-2-yl-amino)methyl]phenol (**4c**)

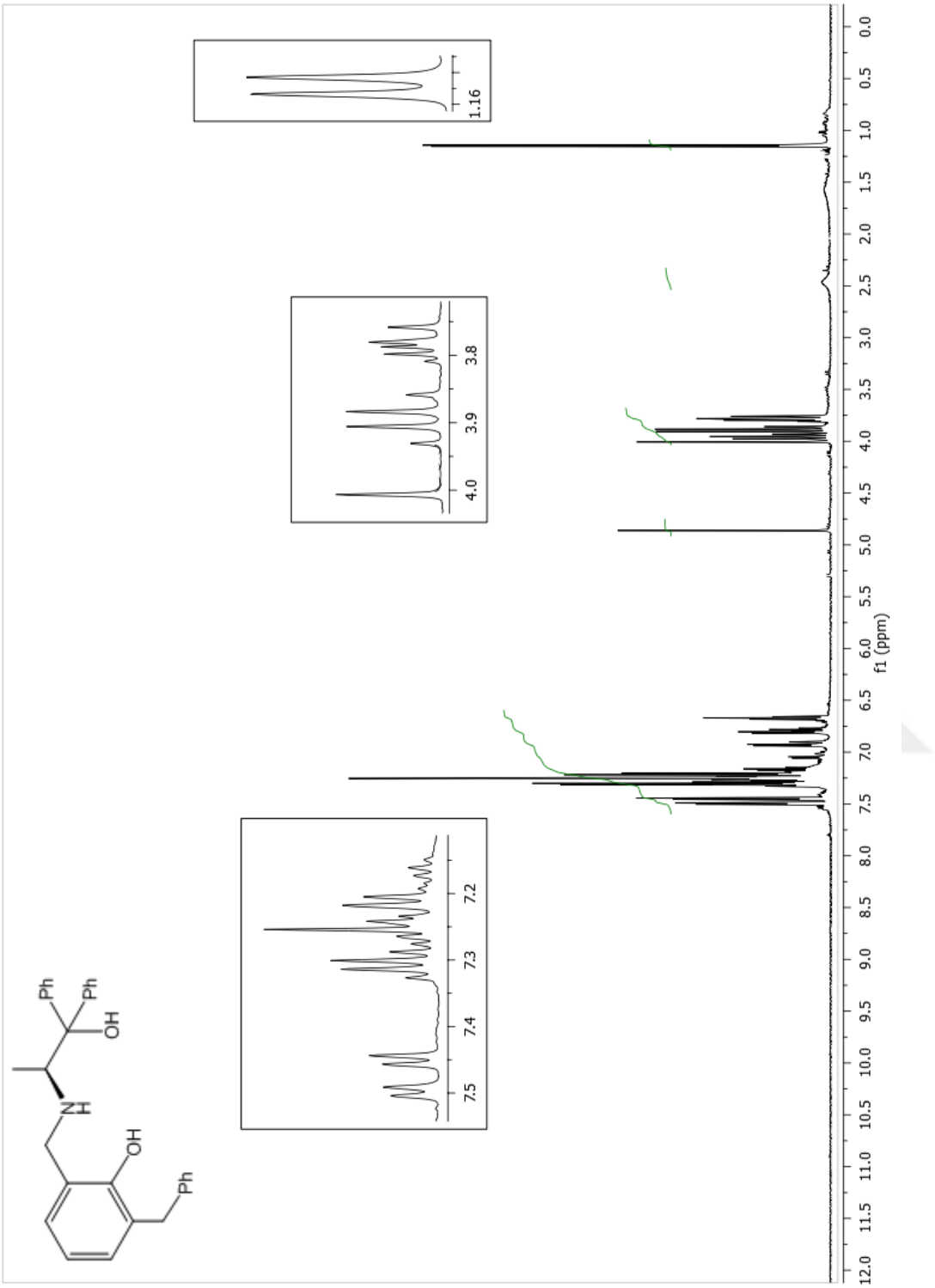


Figure A.2.12 ^{1}H NMR spectrum of (*S*)-2-benzyl-6-[(1-hydroxy-1,1-diphenylpropan-2-ylamino) methyl]phenol (**4d**)

A. 3 ^{13}C NMR Spectrums

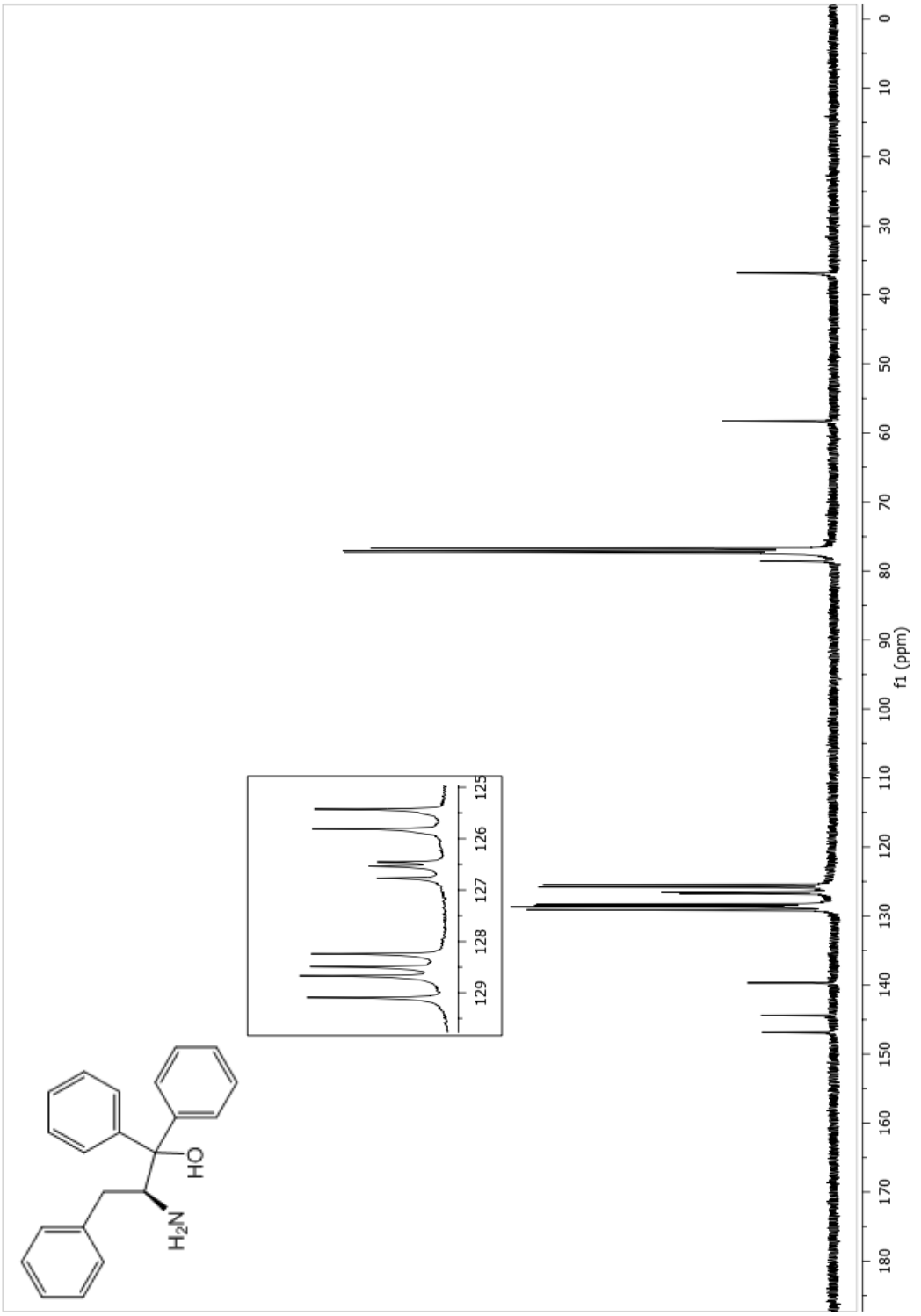


Figure A.3.1 ^{13}C NMR spectrum of (*S*)-2-amino-3-phenyl-1,1-diphenylpropan-1-ol (**1a**)

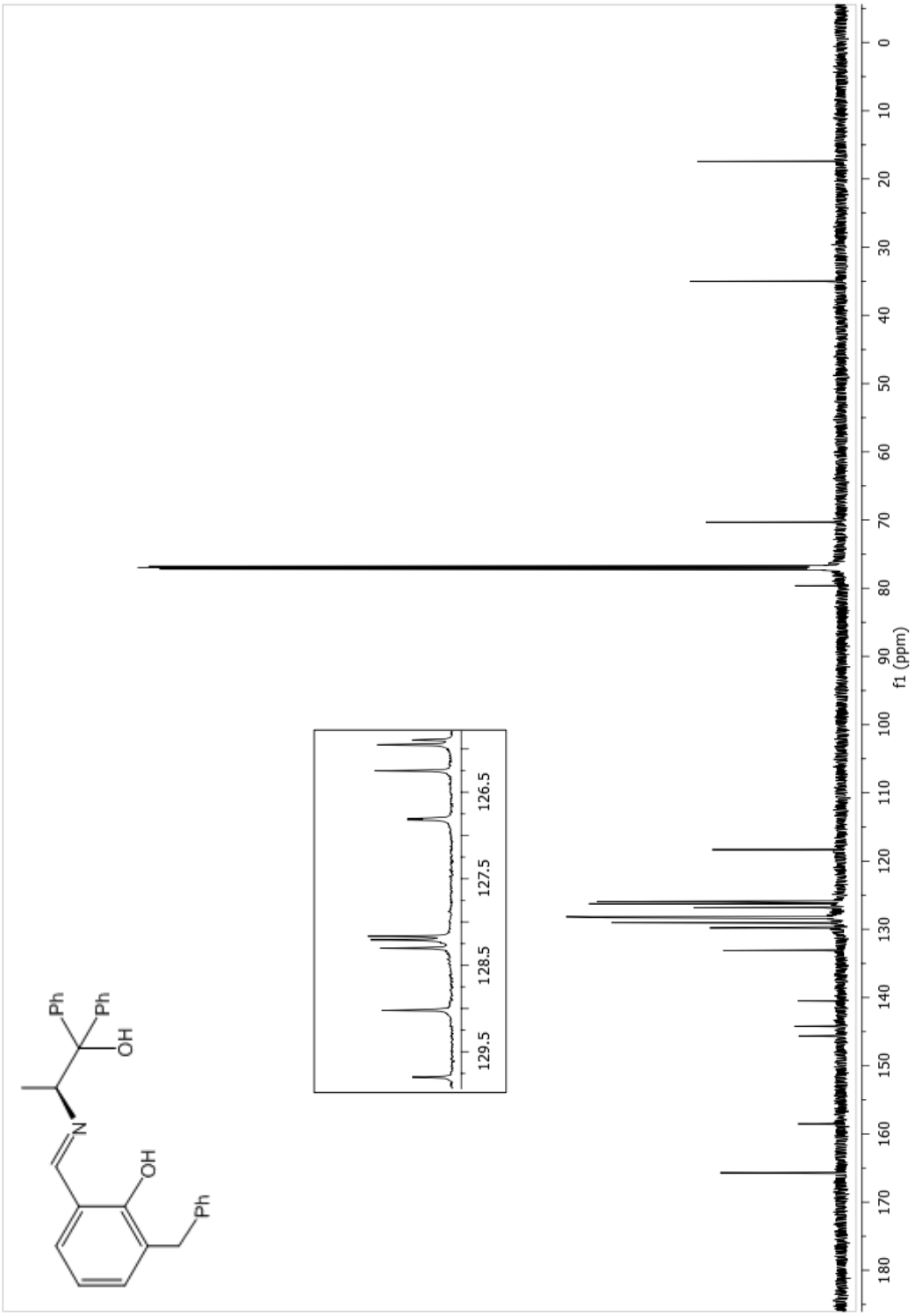


Figure A.3.2 ^{13}C NMR spectrum of (*S*)-2-benzyl-6-[(1-hydroxy-1,1-diphenylpropan-2-ylimino) methyl]phenol (**3e**)

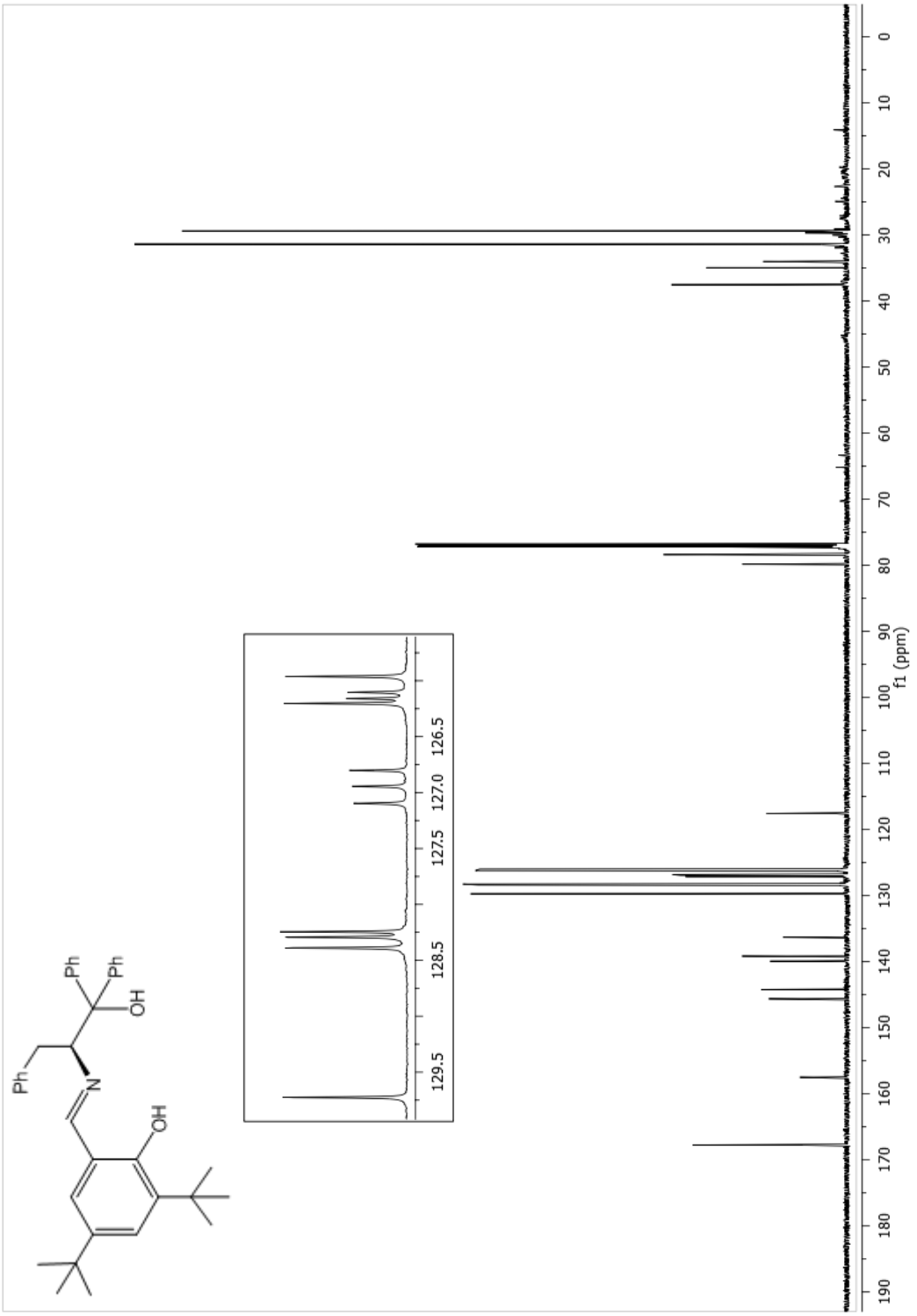


Figure A.3.3 ^{13}C NMR spectrum of (*S*)-2,4-di-*tert*-butyl-6-[(1-hydroxy-1,1,3-triphenylpropan-2-ylimino)methyl]phenol (**3g**)

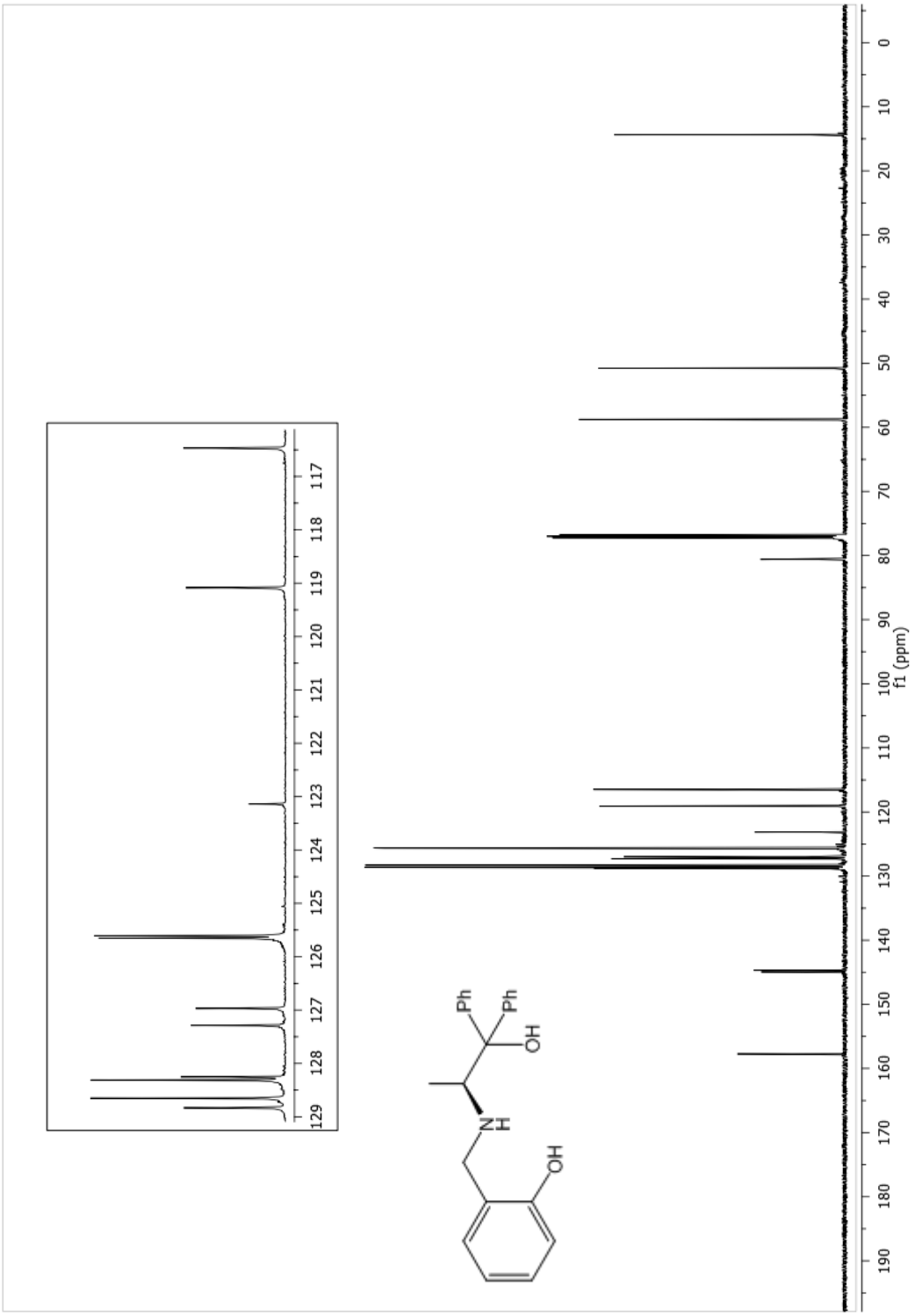


Figure A.3.4 ^{13}C NMR spectrum of (*S*)-2-[(1-hydroxy-1,1-diphenylpropan-2-ylamino)methyl] phenol (**4b**)

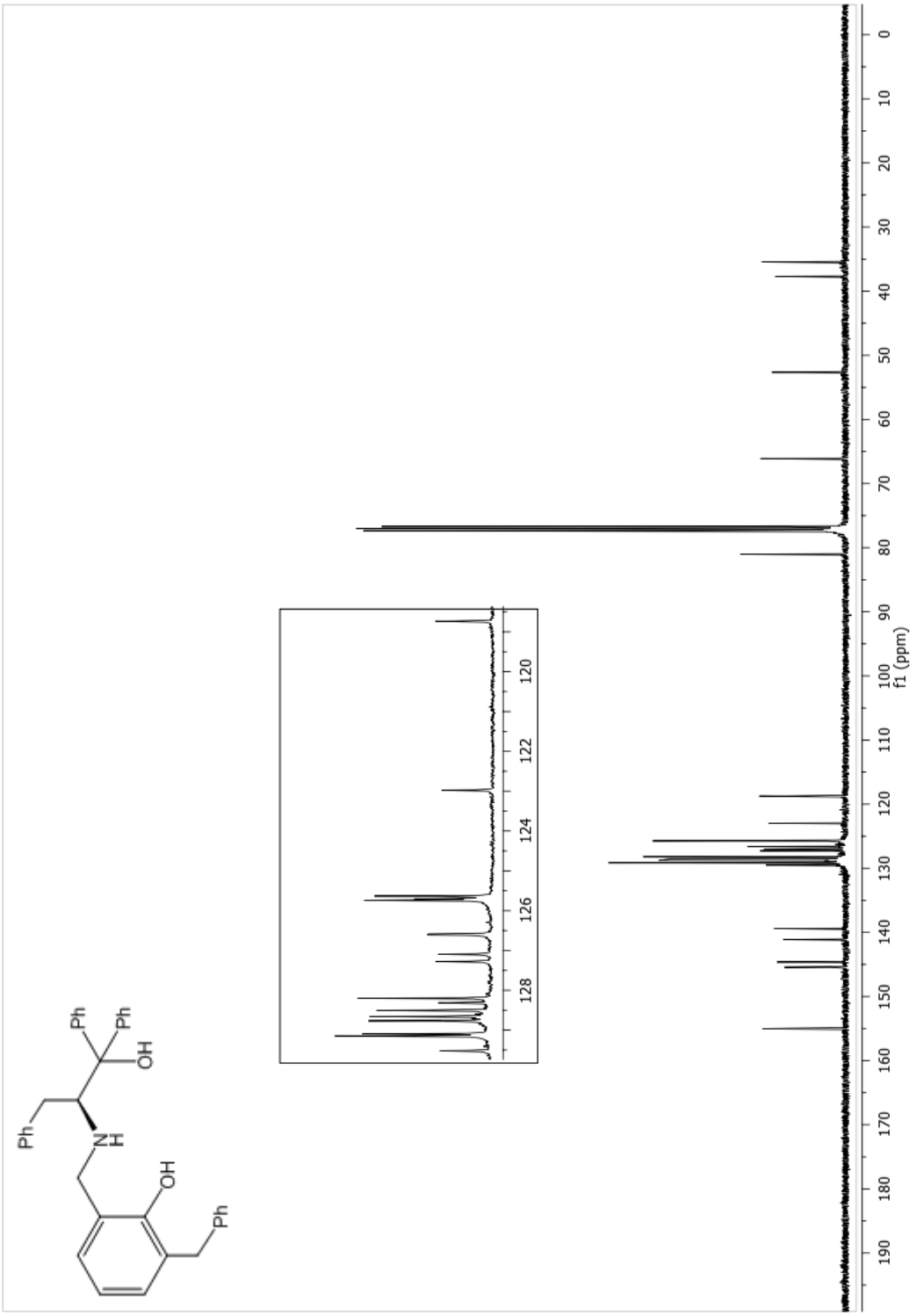


Figure A.3.5 ^{13}C NMR spectrum of (*S*)-2-benzyl-6-[(1-hydroxy-1,1,3-triphenylpropan-2-yl-amino)methyl]phenol (**4c**)

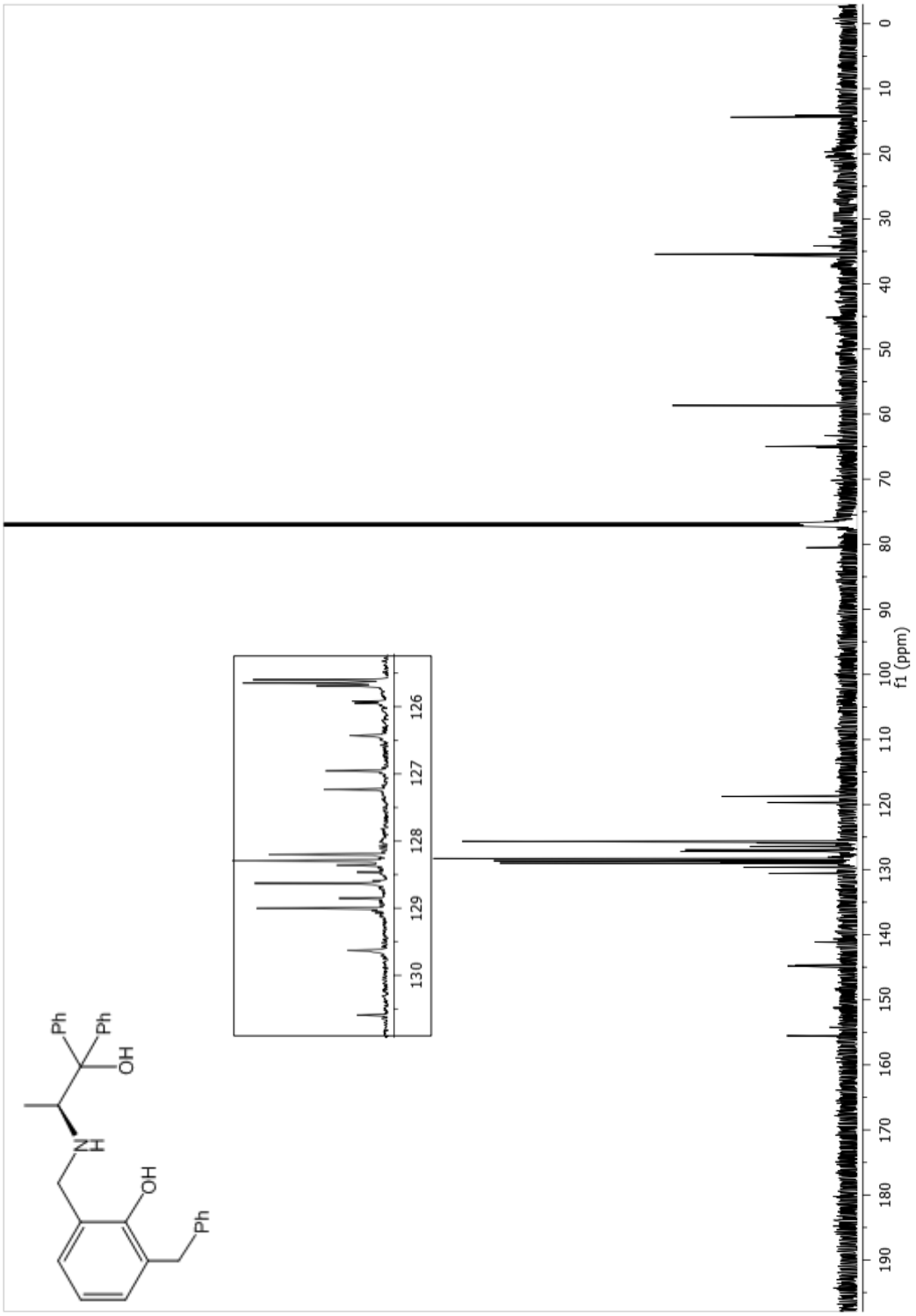


Figure A.3.6 ^{13}C NMR spectrum of (*S*)-2-benzyl-6-[(1-hydroxy-1,1-diphenylpropan-2-ylamino) methyl]phenol (**4d**)

A.4 Chromatogram

```
Data File C:\CHEM32\1\DATA\DECEMBER16\AA-K-169000002.D
Sample Name: AA-k-169

==========================================================================
Acq. Operator    : Arzu
Acq. Instrument : Instrument 1                    Location : Vial 1
Injection Date   : 12/29/2016 2:14:51 PM
Method           : C:\CHEM32\1\METHODS\GAMZE.M
Last changed     : 7/14/2015 2:59:52 PM by Arzu
Sample Info      : 90:10 Hex/IPA, 267nm, 1 ml/min
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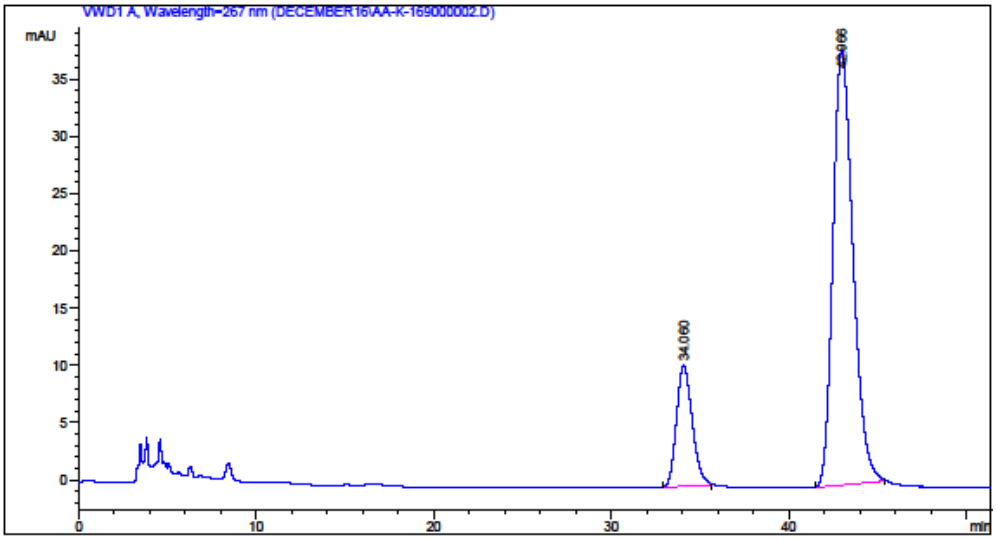


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==========================================================================
                        Area Percent Report
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Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=267 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s    [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  34.060 BB    0.9366  653.21100   10.56743  17.9718
   2  42.966 BB    1.2110 2981.43481   37.93696  82.0282

Totals :                  3634.64581   48.50439


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                        *** End of Report ***

Instrument 1 6/17/2017 4:42:04 PM Arzu                        Page   1 of 1
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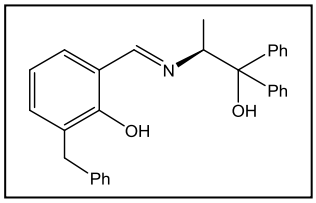
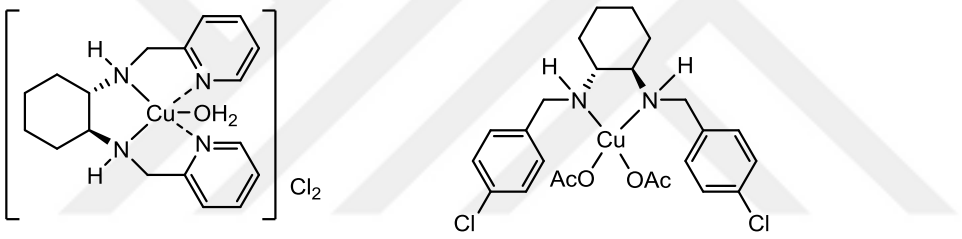


Figure A.4.1 HPLC chromatogram of the nitroaldol reaction of 4-NO_2-benzaldehyde in EtOH at RT with **3e**

3. THE ASYMETRIC HENRY REACTION USING PREPARED COMPLEXES

3.1. General Information of Copper Complexes

The asymmetric Henry reaction is used to obtain chiral nitroaldols under mild reaction conditions with high yield and enantiomeric purity, using transition metal complexes as catalysts. Several studies have been carried out on Cu (II) complexes used in the Henry reaction, using ligands, such as dipyridyl, diamine, Schiff base, salen, oxazoline, pyridine. For example, a copper-diamine complex was used as a catalyst in the Henry reaction at room temperature between aromatic aldehydes and nitromethane to give good yields, but low ee values were obtained (up to 94% yield, up to 7% ee) (Zhang et al., 2008). Another example of a Cu(II) diamine complex catalysed the reaction with high yields and selectivity (up to 97% yield, up to 99% ee) (Kowalczyk and Skarzewski, 2009) (Figure 3.1).



Zhang, 2008 **Kowalczyk, 2009**

Figure 3.1 Copper(II) complexes derived from diamines

Chiral Cu(II)-salan complexes have been used as effective catalysts in the Henry reaction. Hydrogenated chiral salan complexes were synthesized as mononuclear and binuclear, and the structures were characterized (Figure 3.2). At the same time, these five coordinated complexes were used as catalysts and reported to form chiral nitroalkanes; highest enantiomeric excess value was 83% using a naphthyl substituted aldehyde with nitromethane in EtOH at room temperature (Shi et al., 2012).

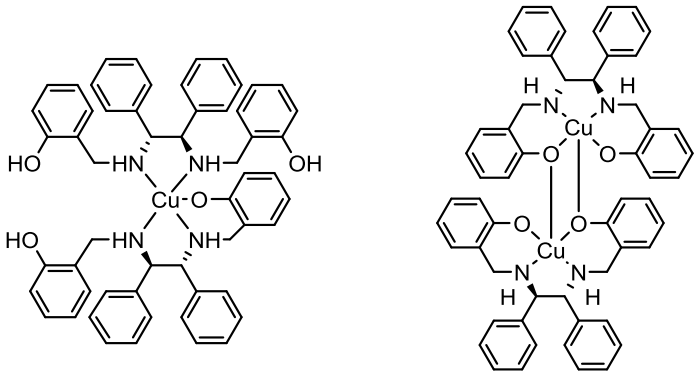
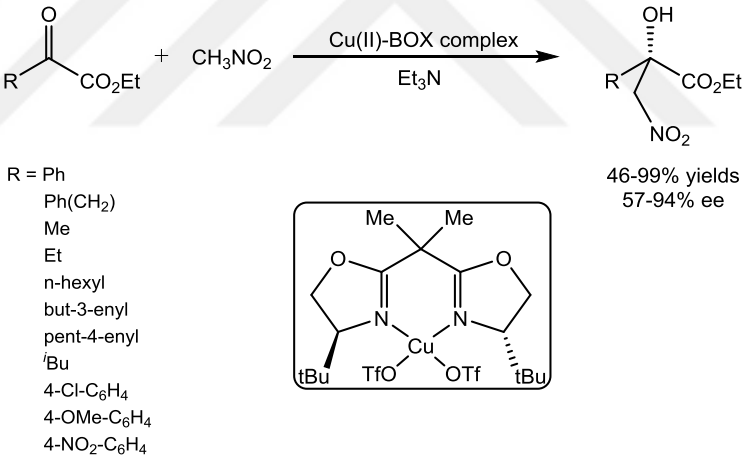


Figure 3.2 The salan-copper(II) complexes

Particularly the first application of Cu (II) complexes with bidentate bis(oxazoline) ligands to the asymmetric Henry reaction was reported by Jorgensen (1999). The reaction of keto esters with nitromethane in the presence of chiral Cu(II)BOX complexes were investigated with different substrates at room temperature (Scheme 3.1). It was found that the enantioselectivity was above 90% with aliphatic and electron-poor aromatic aldehydes.



Scheme 3.1 Henry reactions between α-keto esters catalysed by Cu(II)-BOX complex

Another example of bis(oxazoline)-copper(II) complexes derived from bidentate NN type chiral ligands is given by Evans et al. (2003) for the Henry reaction between nitromethane and aldehydes which were carried out at room temperature with polar protic solvents. The best results were obtained with the Indabox ligand. The solvent effect on the enantiomeric excess of the product was also investigated. The reaction was observed using the same catalyst and ee values were found to be 74% in methanol and 81% in ethanol. At the same time, this study was important, because the bidentate copper complex in the square planar

structure also revealed a transition state model in the Henry reaction. The transition model suggested that this reactions of copper (II) complexes derived from bidentate ligands could advance through a square pyramidal intermediate where the aldehyde had an equatorial position and the nitronate anion was in an apical position (Figure 3.3).

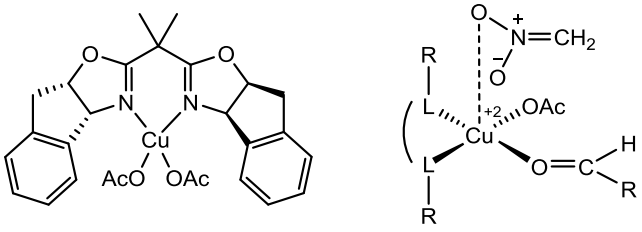
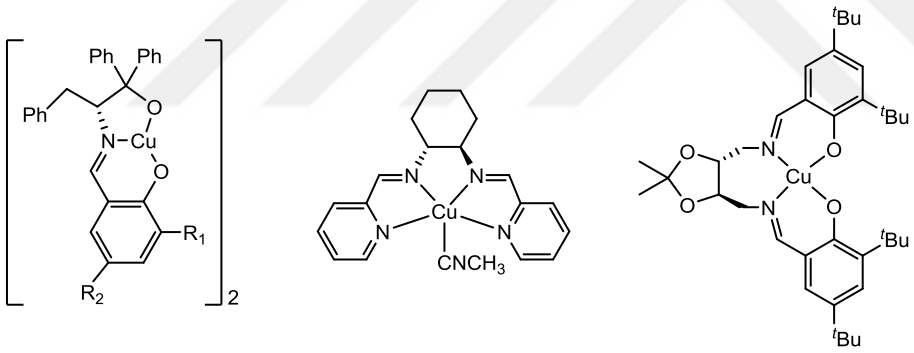


Figure 3.3 Evans' Indabox catalyst with proposed Cu(II) intermediate for enantioselective Henry reaction

Chiral Schiff base complexes are widely used in catalytic asymmetric syntheses. These complexes were reported to catalyze the nitroaldol reaction with high yields and variable enantioselectivities in mild conditions (Figure 3.4).



Lai, 2006, 2008
67-90% yield
84-86% ee

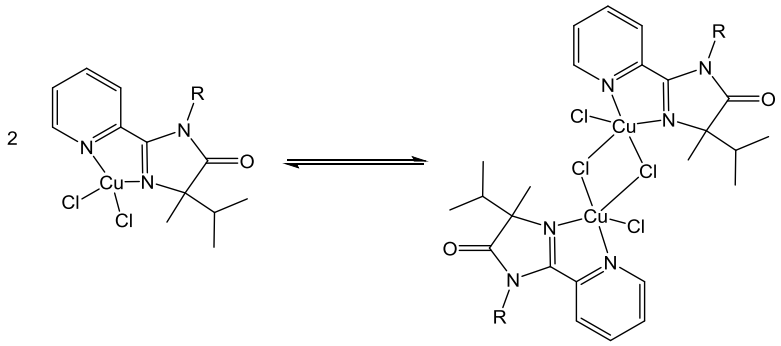
Nguyen and Jeong, 2006
up to 97% yield
up to 29 % ee

Gan, 2008
up to 79% yield
up to 80 % ee

Figure 3.4 The chiral Schiff base-copper (II) complexes

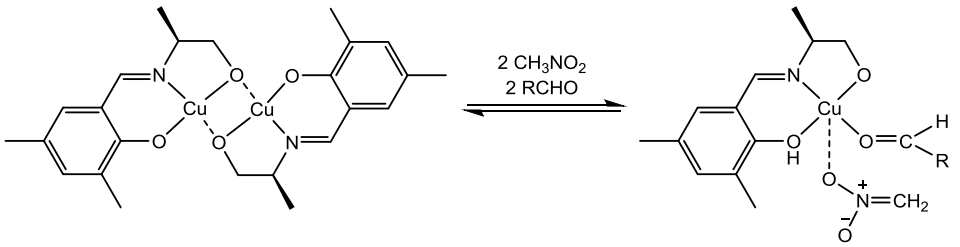
Another important study was published by Sedlak (Sedlak et al., 2006). Complexes of chiral substituted bidentate pyridine ligands with copper chloride were synthesized and used as catalysts. An important part of the work was the determination of these synthesized complexes by mass spectrometry in two forms, monomer and dimer in the solvent medium. From these two forms, the dimer form was isolated by the selected ethanol-hexane solvent system and it was found to crystallize in dimeric form in two square pyramidal structure.

But on the other hand, it was stated that the complexes catalyze the Henry reaction in coordination with the triethylamine in monomeric form (ee values up to 19%, yields up to 97%) (Scheme 3.2).



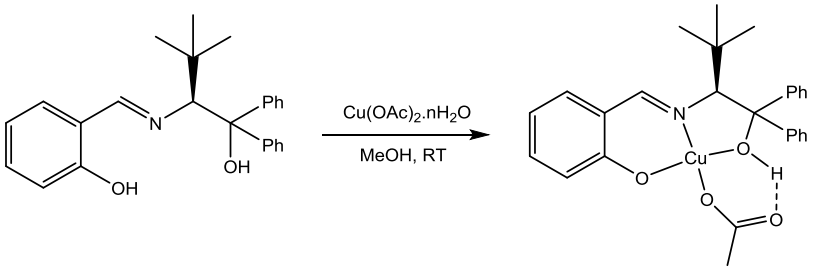
Scheme 3.2 The two forms of copper complexes

The use of amino alcohol derived tridentate ligands in the asymmetric Henry reaction of complexes synthesized with copper(II)acetate was given as an example to explain the behavior of copper(II)complexes (Punniyamurthy et al., 2008). X-ray analysis showed that the complexes were in dimer form. At the same time, an active intermediate could be formed by titration of the catalyst prepared with HCl of *tert*-Leucinol and salicylaldehyde derivative to elucidate the catalytic cycle, by initial dimerization and proton exchange with complex phenolic oxygen (Scheme 3.3).



Scheme 3.3 Suggested copper (II) intermediate for Henry reaction by Punniyamurthy

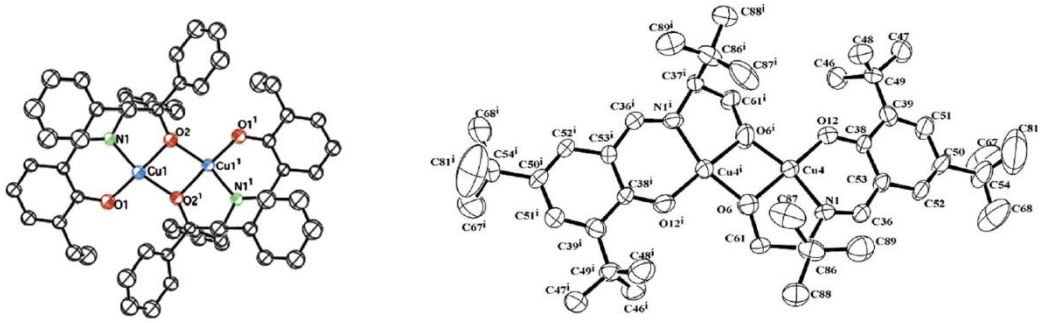
Astley et al. found that the carboxylate anion in the copper (II) complexes had significant catalytic activity for the asymmetric Henry reaction. The center atom of the complex which was derived from L-*tert*-Leucine was bounded to ONO type tridentate ligand and the acetate anion. There was a hydrogen bond between proton of the alcoholic oxygen on the ligand and the carbonyl oxygen of the acetate anion (Astley et al., 2017) (Scheme 3.4).



Scheme 3.4 Synthesis of monomeric complex from Astley

3.2 Results and Discussion

It is known from the literature that, there are important works using copper (II) complexes of asymmetric reactions (Palomo et al., 2004; Boruwa et al., 2006). One of these reactions is asymmetric Henry reaction. Copper (II) complexes which are derived from bidentate or tridentate ligands have been synthesized for being used as catalyst in the Henry reaction. The solid form of the complexes has been determined by X-ray diffraction method. In previous studies, chiral copper (II) complexes of tridentate ligands were prepared from chiral amino alcohols and aromatic aldehydes (Gan et al., 2006; Lai et al., 2008; Punniyamurthy et al., 2008). The structures of these complexes were characterised by X-ray and also were found to be in dimeric forms (Figure 3.5).



Lai, 2008 **Punniyamurthy, 2008**

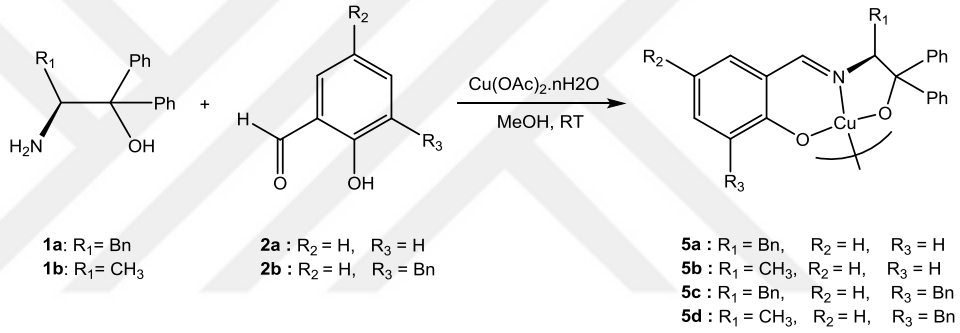
Figure 3.5 The crystal structures of synthesized tridentate dimer copper complexes

There was another study showing that the complexes could not be crystallized in solid form, but the composition and structure of them were determined using spectroscopic methods such as elemental analysis and IR spectroscopy (Dontsova et al., 2003).

In chapter 2, the effects of ONO type tridentate ligands in the asymmetric Henry reaction were investigated *in situ* using $Cu(OAc)_2.nH_2O$. In this section, copper (II) complexes were synthesized from amino alcohols and aromatic aldehydes. The synthesized complexes were isolated and used in the Henry reaction as a catalyst. The activity of the isolated complexes were compared with in situ generated catalysts.

3.2.1 Synthesis of copper (II) complexes

Copper (II) complexes were synthesized in one-pot without isolation by the addition of copper acetate followed by the interaction of amino alcohols derived from amino acids (**1a-b**) with different aldehydes (**2a-b**).



Scheme 3.5 Preparation of the copper complexes derived from amino alcohols

Selected physical properties including melting points and yielding of the complex **5a-d** which are all given in table 3.1. The complexes were obtained as dark green solid-crystals and air stable compounds. They were soluble in polar solvents.

Table 3.1 Melting points and yielding of the complexes **5a-d**

Compound	Yield (%)	mp (°C)
5a	61	242-246
5b	58	175-182
5c	78	231-234
5d	69	234-237

Although the complexes were synthesized in solid forms, unfortunately the crystals of them could not be prepared for X-ray analysis. Therefore, structures of the complexes were tried to be determined by elemental analysis and IR spectroscopy. The infrared spectra of **5a-d** showed several vibrations bands of different intensities in the 4000-400 cm^{-1} region. The presence of the O-H group in Schiff base ligands were determined with υ(O-H) stretching vibrations between 3583-3464 cm^{-1} as described in chapter 2. However, it was not observed any vibration at 3500-3400 cm^{-1} in the IR spectra of the complexes **5a-d**. A υ(C=N) imino stretching vibration was observed at 1623 cm^{-1} for **5a**. It was shifted to lower value than the free ligand by 4 cm^{-1}. The IR spectrum comparisons of Schiff base and the complex are visually shown below in figures 3.6 and 3.7.

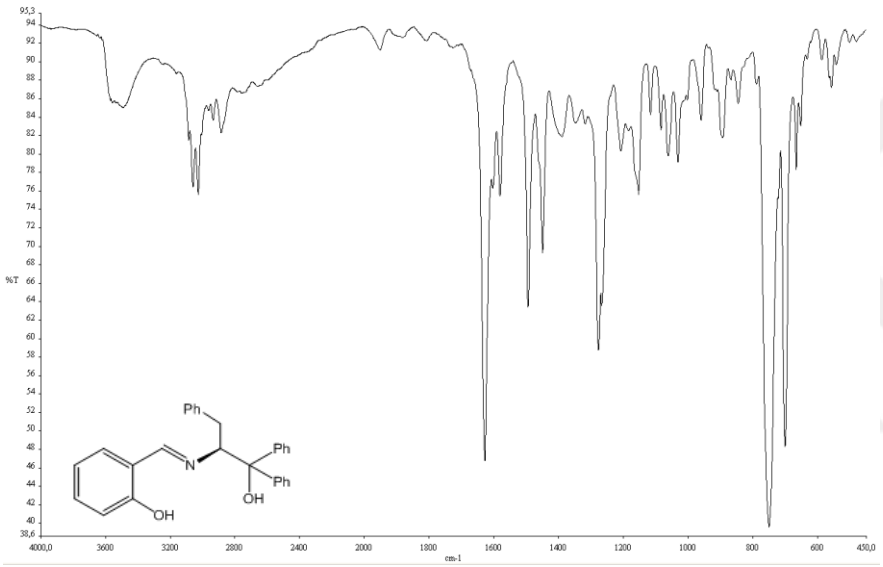


Figure 3.6 Example IR spectra for Schiff base ligands (**3a**)

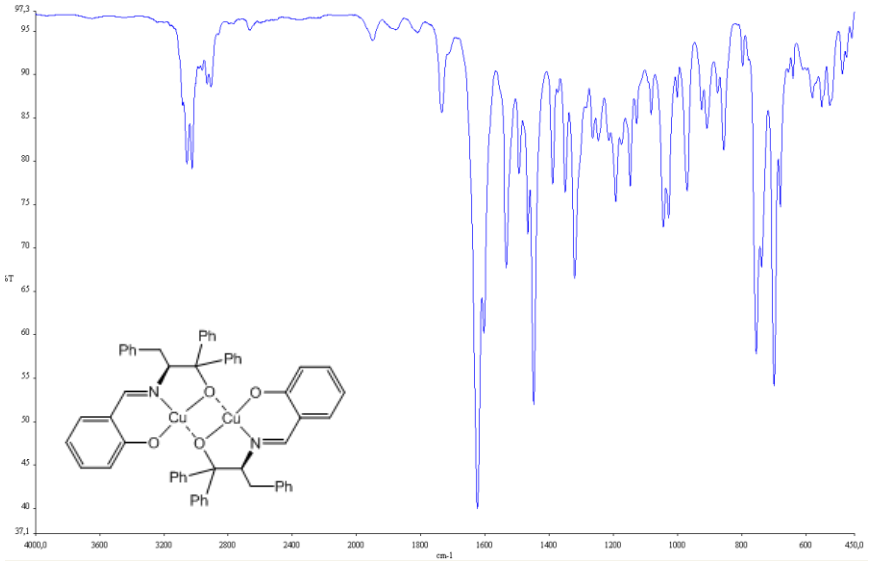


Figure 3.7 Example IR spectra for the Copper complex (**5a**)

At the same time, elemental analysis results of the synthesized complexes showed that the structures were close to binuclear dimer form (Table 3.2). The ligands were calculated in the doubly deprotonated form in the metal-ligand complex system as in the literature (Lai et al, 2008; Dontsova et al., 2003).

Table 3.2 Elemental analysis results of complexes **5a-d**

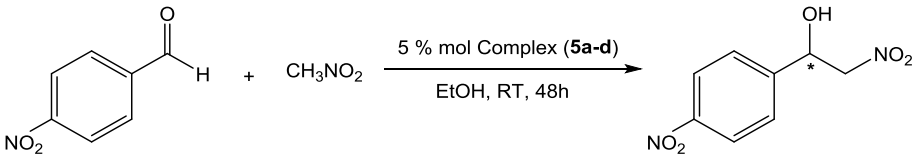
Compound	Empirical formula	Composition (calculated/found), %		
		C	H	N
5a	$C_{56}H_{46}Cu_2N_2O_4$	71.7 / 71.6	4.9 / 4.6	2.9 / 2.8
5b	$C_{44}H_{38}Cu_2N_2O_4$	67.3 / 63.1	4.8 / 5.5	3.5 / 3.0
5c	$C_{70}H_{88}Cu_2N_2O_4$	75.2 / 72.2	5.2 / 5.5	2.5 / 2.3
5d	$C_{58}H_{50}Cu_2N_2O_4$	72.1 / 71.7	5.2 / 5.0	2.9 / 2.7

3.2.2 Asymmetric Henry reaction of copper (II) complexes

In chapter 2, complexes were formed in the medium of catalytic reaction with Schiff bases (**3a**, **3b**, **3d** and **3e**). In this chapter, after the copper (II) complexes were synthesized and isolated, they were used in the Henry reaction as catalyst.

The reactions were seen in table 3.3 were carried out at the same stoichiometric ratios, 1 mmol 4-nitrobenzaldehyde, 5% mmol Cu (II) complex and 10 mmol nitromethane in 2 mL EtOH, at ambient temperature in 48 h. The desired products were obtained in the reactions performed isolated by column chromatography using 1:3 EtOAc:hexane system. The enantiomeric excess of the products were determined by HPLC.

Table 3.3 The Henry reaction using prepared complexes



Entry	Complex	Yield[a](%)	ee[b](%)	Config.[c]
1	**5a**	80	40	*S*
2	**5b**	79	55	*S*
3	**5c**	71	49	*S*
4	**5d**	87	62	*S*

[a]Isolated yields after column chromatography.

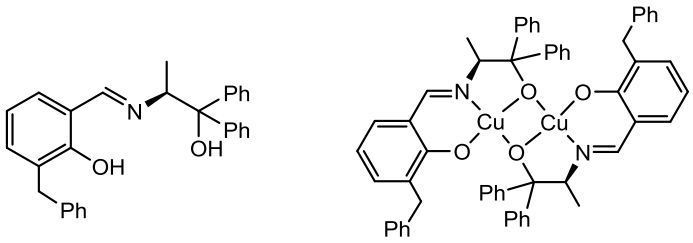
[b]Determined by HPLC analysis using a Chiracel OD-H column.

[c]The absolute configuration of the major product was assigned by comparison with the literature values (Evans et al., 2003).

As shown in table 3.3, the best result was obtained with complex **5d** which was derived from L-Alanine, bears a methyl group on amino alcohol (87% yield, 62% ee). The reactions gave almost the same results as *in situ* studies with Schiff bases as described in chapter 2 (Figure 3.8). The enantiomeric excess values and yields of Henry reactions of the ligands and complexes were shown comparatively in table 3.4. According to these results, it could be said that the ee values were similar but the yields were slightly higher. Although the synthesis conditions were not different for the isolated complexes and *in situ* generated complexes, the yield values of the Henry reaction were different. Perhaps, the isolated complexes had been isolated and purified, the catalysts possessed a greater structural integrity than *in situ* generated complexes. The catalytic reaction also seemed to proceed faster.

Table 3.4 Henry reaction data of ligands and complexes

In-situ	Yield(%)	ee(%)	Complex	Yield(%)	ee(%)
3a	44	45	**5a**	80	40
3b	64	59	**5b**	79	55
3d	45	47	**5c**	71	49
3e	80	64	**5d**	87	62



3e
80 % yield, 64 % ee

5d
87 % yield, 62 % ee

Figure 3.8 The comparison of the Henry reaction values **3e** and **5d**

3.3 Conclusion

Novel chiral copper (II) complexes were synthesized from amino alcohol derivatives (**1a-b**) and Schiff bases with aromatic aldehydes (**2a-b**). These complexes were used as catalyst in the asymmetric Henry reaction to determine the enantiomeric excess and yield values. These results were evaluated and compared with *in situ* results in chapter 2. The enantiomeric excess values were similar (up to 62% ee), but the yields were slightly higher (up to 87% yields). It was observed that using obtained complexes for the asymmetric Henry reaction could have a beneficial effect on the yield, but not on enantiomeric excess.

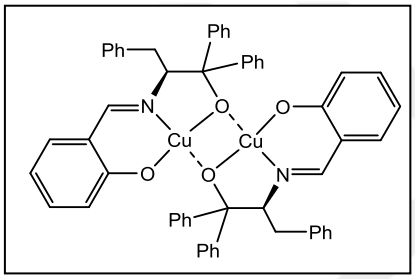
3.4 Material and Method

All reactions were performed in air. The solvents were analytical grade and obtained from commercial suppliers. All chemicals were commercially available and purchased from Merck, Sigma-Aldrich, Alfa Aesar, Fluka, Acros or BDH and used without any purification. FTIR Spectra were recorded on a Perkin Elmer Spectrum 100 series. Melting points were recorded with Gallenkamp electrothermal melting point apparatus. Silica gel F_{254} (Merck 5554) precoated plates were used for the monitoring of all reactions by thin-layer chromatography and visualized by ultra-violet light or by staining with ninhydrin dissolved in alcohol. For column chromatography silica gel 60 (Merck 7743) was used. Chiralcel OD-H column was used for HPLC analyses. The enantiomeric excess of the products were determined by HPLC using a 10:90 IPA:hexane system, flow rate 1 mL/min, 267 nm. Elemental analysis was performed by CHNS-932 (LECO) elemental analyzer.

3.4.1 General procedure for synthesis of copper(II) complexes

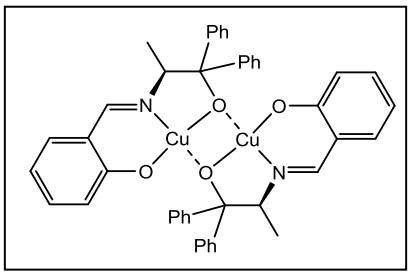
The solution of amino alcohol (1 mmol) in MeOH was added dropwise into the solution of aldehyde (1 mmol) with $Cu(OAc)_{2.}\ nH_2O$ (1 mmol) in 5 mL of MeOH. The reaction mixture was stirred for 24 h at room temperature up to amino alcohol consuming. After the reaction was controlled by TLC plate, the solvent was removed by rotary evaporation. The product was crystallized from DCM:hexane or DCM:MeOH to give green solids or crystals.

3.4.2 Copper complex from amino alcohol derivative L-Phenylalanine and salicylaldehyde (5a)



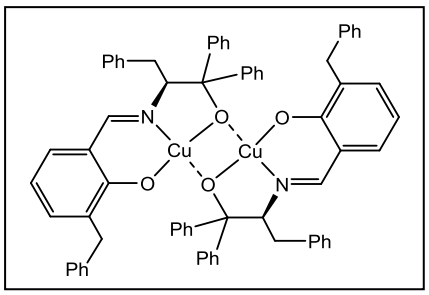
Green crystals, 61% yield, mp: 242-246 °C. Elemental analysis, calculated for $C_{56}H_{46}Cu_2N_2O_4$: C, 71.70; H, 4.94; N, 2.99. Found: C, 71.61; H, 4.579; N, 2.835 %. IR (CH_2Cl_2): 3056, 3024, 2906, 1623, 1603, 1533, 1466, 1448, 1389, 1320, 1192, 1147, 1045, 970, 756, 700cm^{-1}. $[\alpha]_D^{29}$ = - 336 (*c* 0.125, CH_2Cl_2).

3.4.3 Copper complex from amino alcohol derivative L-Alanine and salicylaldehyde (5b)



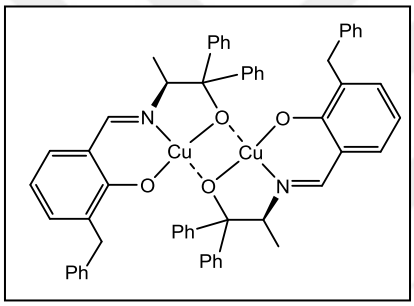
Green solid, 58% yield, mp: 175-182 °C. Elemental analysis, calculated for $C_{44}H_{38}Cu_2N_2O_4$: C, 67.25; H, 4.87; N, 3.56. Found: C, 63.14; H, 5.481; N, 3.013 %. IR (CH_2Cl_2): 3056, 3022, 2930, 1627, 1603, 1533, 1447, 1389, 1319, 1194, 1148,1131, 996, 757, 700 cm^{-1}. $[\alpha]_D^{29}$ = -288 (*c* 0.125, CH_2Cl_2).

3.4.4 Copper complex from amino alcohol derivative L-Phenylalanine and 3-benzyl-2-hydroxy-benzaldehyde (5c)



Green crystals, 78 % yield, mp: 231-234 °C. Elemental analysis, calculated for $C_{70}H_{88}Cu_2N_2O_4$: C, 75.18; H, 5.23; N, 2.50. Found: C, 72.24; H, 5.524; N, 2.257 %. IR (CH_2Cl_2): 3060, 3025, 2905, 1625, 1598, 1545, 1421, 1318, 1276, 1164, 1046, 858, 750, 699 cm^{-1}. $[\alpha]_D^{29}$ = - 352 (*c* 0.125, CH_2Cl_2).

3.4.5 Copper complex from amino alcohol derivative L-Alanine and 3-benzyl-2-hydroxy-benzaldehyde (5d)



Green solid, 69 % yield, mp: 234-237 °C. Elemental analysis, calculated for $C_{58}H_{50}Cu_2N_2O_4$: C 72.11, H 5.22, N 2.90. Found: C 71.72, H 5.000, N 2.680 %. IR (CH_2Cl_2): 3056, 3024, 2928, 1628, 1599, 1525, 1493, 1423, 1391, 1321, 1223, 1120, 1008, 753, 699 cm^{-1}. $[\alpha]_D^{29}$ = - 144 (*c* 0.125, CH_2Cl_2).

3.4.6 General procedure for the Henry reaction

The appropriate aldehyde (0.2 mmol), nitromethane (2.0 mmol) and copper complex (5 % mmol) were added. The reaction mixture was stirred at room temperature until most of the aldehyde had been consumed. The solvent was evaporated under reduced pressure and the crude product was purified with column chromatography (1:3 ethyl acetate:hexane).

APPENDIX B: Spectra and Chromatograms

B.1 IR Spectrums

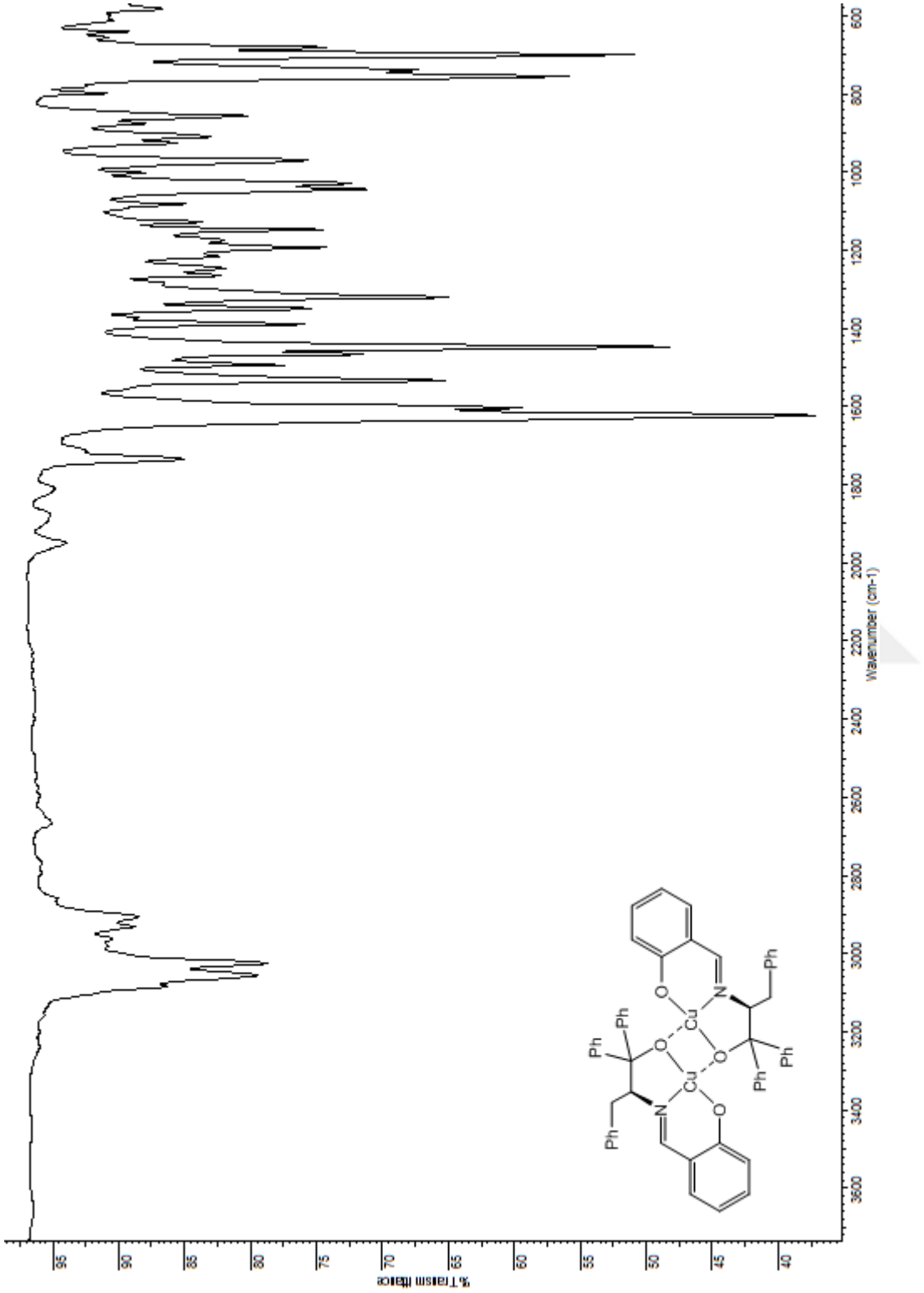


Figure B.1.1 IR spectrum of complex **5a**

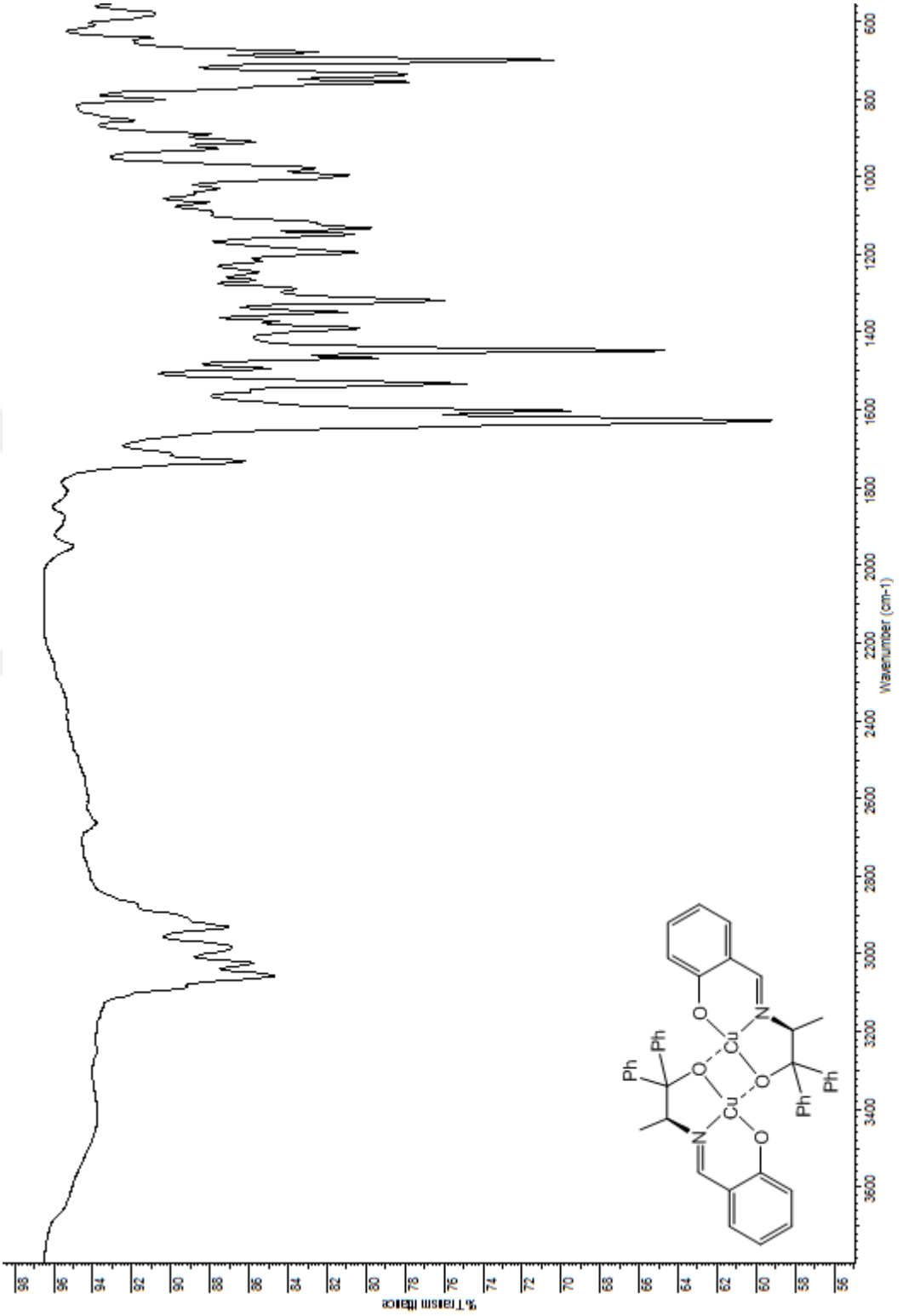


Figure B.1.2 IR spectrum of complex **5b**

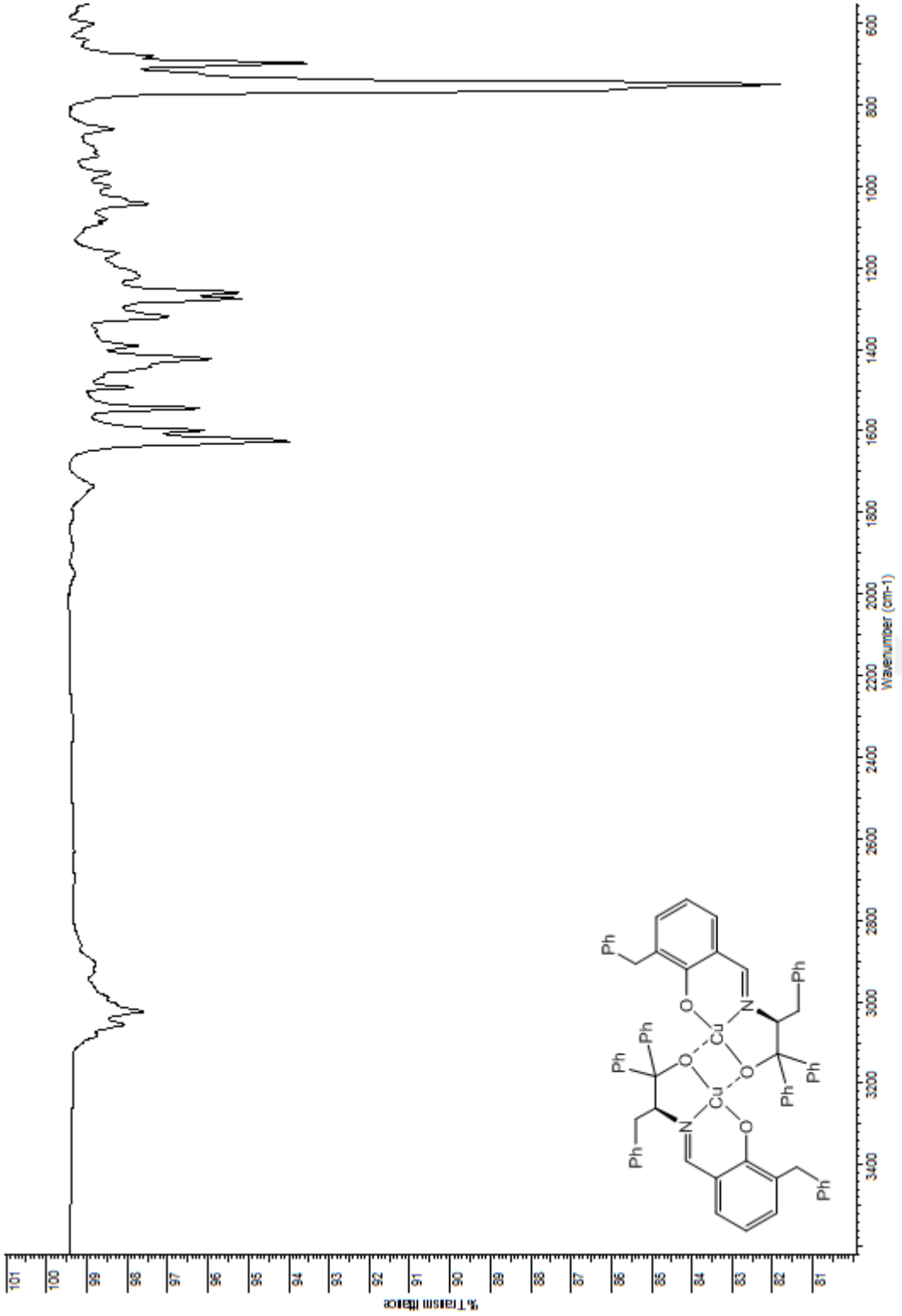


Figure B.1.3 IR spectrum of complex **5c**

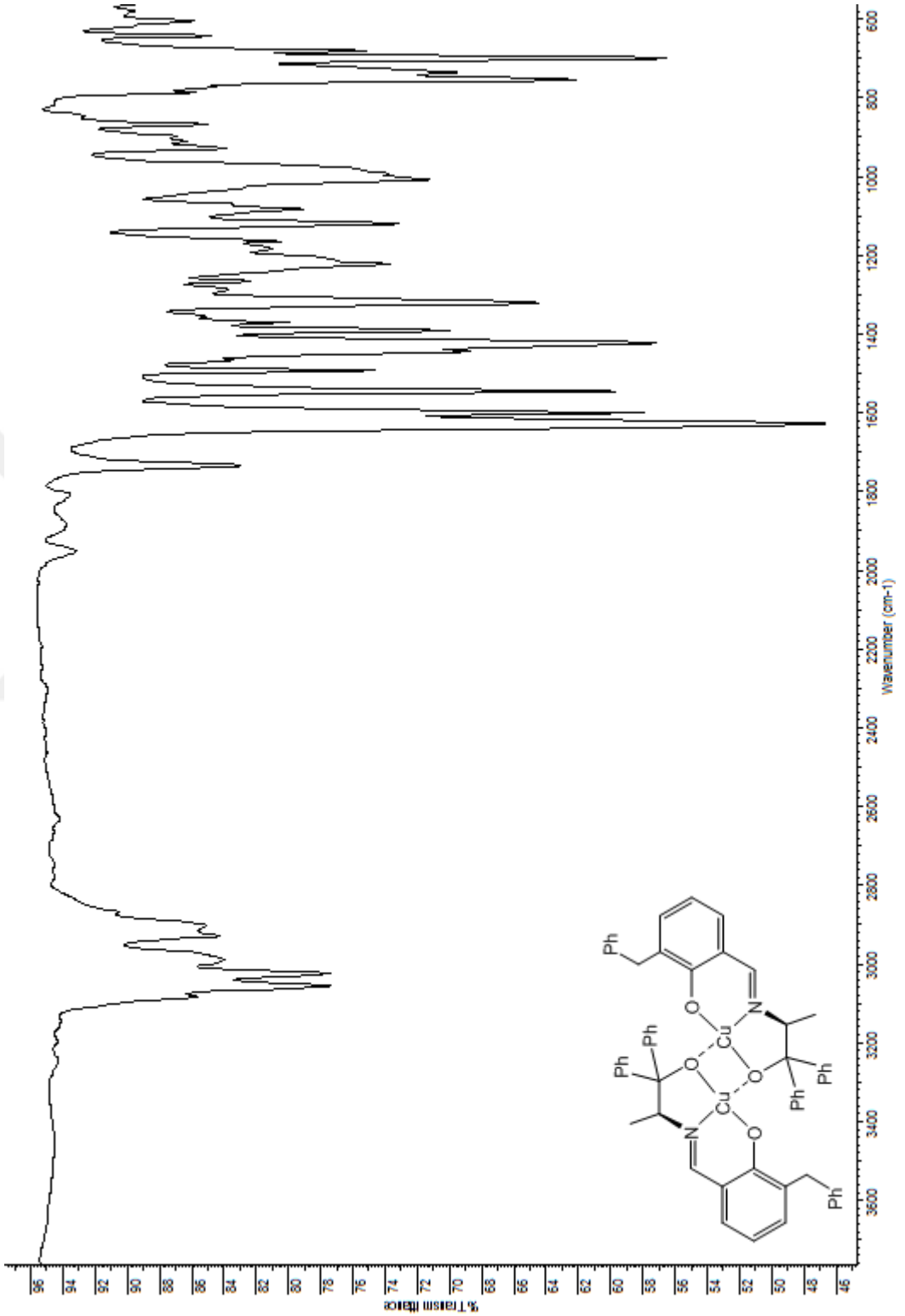
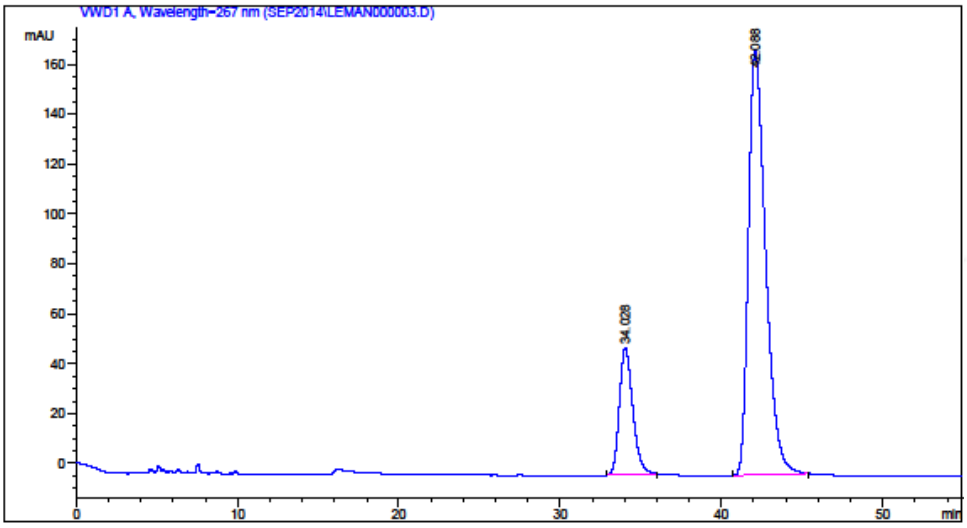


Figure B.1.4 IR spectrum of complex **5d**

B.2 Chromatogram

```
Data File C:\CHEM32\1\DATA\SEP2014\LEMAN000003.D
Sample Name: LC-2

======================================================================
Acq. Operator   : SA
                                                  Location : Vial 1
Injection Date  : 25-Sep-14, 14:14:13
Acq. Method     : GAMZE.M
Analysis Method : C:\CHEM32\1\METHODS\GAMZE.M
Last changed    : 7/14/2015 2:59:52 PM by Arzu
Sample Info     : 90:10 Hex/IPA, 267nm, 1 ml/min, RT,
```




```
======================================================================
                        Area Percent Report
======================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=267 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s    [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  34.028 BB    0.8839 2948.78638   50.91269  18.9081
   2  42.088 BB    1.1559 1.26466e4   170.63600  81.0919

Totals :                  1.55954e4   221.54869

======================================================================
                        *** End of Report ***

Instrument 1 6/19/2017 12:50:24 PM Arzu                    Page   1 of 1
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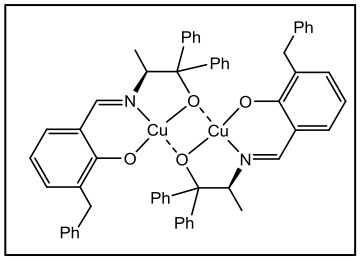


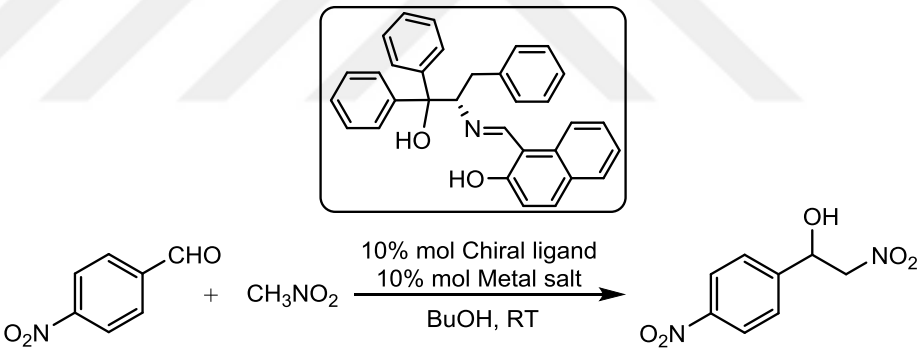
Figure B.2.1 HPLC chromatogram of the nitroaldol reaction of 4-NO_2-benzaldehyde in EtOH at RT with **5d**

4. THE EFFECTS OF DIFFERENT COUNTER IONS IN THE COPPER (II) CATALYSED ASYMMETRIC HENRY REACTION USING ONO SCHIFF BASE LIGANDS

4.1 General Information

The synthesis of tridentate ONO ligands and the results of using them as ligands in the Cu-catalyzed asymmetric Henry reaction were presented in chapter 2 and chapter 3. As is known from previous studies, different copper salts have been prefered as catalysts for the asymmetric Henry reaction, such as acetate, triflate, chloride, bromide, nitrate or sulfate (Zhou et al., 2012; Li et al., 2014).

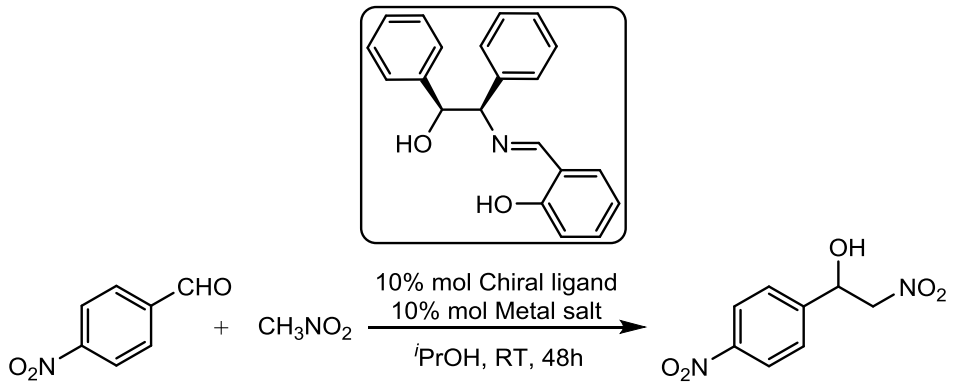
The effect of the copper salts in the Henry reaction was studied by Ran and co-workers (Ran et al., 2013). The results showed that copper acetate was preferred over other copper salts with serious differences when the enantiomeric excess values of 4-nitrobenzaldehyde on the Henry reaction with nitromethane were taken into account (Scheme 4.1).



Entry	Copper salt	Yield (%)	ee (%)
1	$Cu(OAc)_2.H_2O$	69	81
2	$CuSO_4.5H_2O$	23	31
3	$CuCl_2.2H_2O$	30	59
4	$Cu(OTf)_2$	15	31

Scheme 4.1 Effect of copper salts according to Rans' work

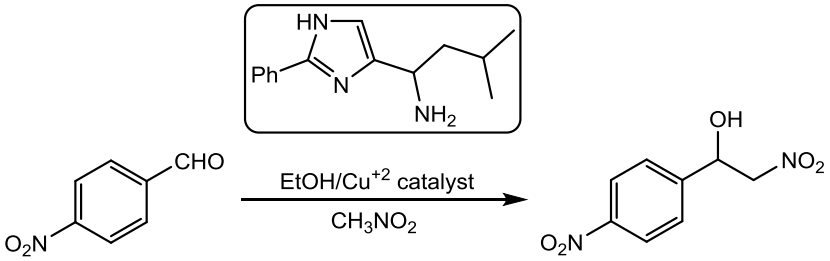
Different metal salts have also been screened to observe the enantiomeric excess values in the Henry reaction by Guo and Mao (Guo and Mao, 2009). As can be seen from scheme 4.2, the results were best with $Cu(OAc)_2$.



Entry	Catalyst	Yield (%)	ee (%)	Config.
1	$Cu(OAc)_2.H_2O$	36	77	*S*
2	-	ND	-	-
3	$Ni(OAc)_2.H_2O$	ND	-	-
4	$Zn(OAc)_2$	ND	-	-
5	$Co(OAc)_2.4H_2O$	63	15	*R*
6	AgOAc	27	0	-
7	CuCl	ND	-	-
8	CuBr	11	66	*S*
9	$CuSO_4$	ND	-	-

Scheme 4.2 Catalyst system of Guo and Mao in the Henry reaction

Bures and co-workers synthesized bidentate ligands with imidazole rings using chiral amines. The ligands synthesized were used as catalysts in the Henry reaction at different reaction conditions, such as different temperature, catalyst loading, solvent or copper salt precursors (Bures et al., 2006). Although the ee values were low, high yields were obtained as seen from scheme 4.3. The low ee values were explained by the different acidities and structures of the salt anions.



Entry (at room temperature)	Time (h)	yield (%)	ee (%)
without the presence of catalyst	-	-	-
in the presence of $Cu(OAc)_2$ without ligand	144	52	0.0
in the presence of $Cu(OAc)_2$	13	97	12.1
half concentration of catalyst	48	91	9.4
in the presence of Cu(II) trifluoroacetate	120	32	2.7
in the presence of Cu(II) benzoate	48	88	16.1
in the presence of Cu(II) 4-nitrobenzoate	240	48	3.5
in the presence of Cu(II) 4-methoxybenzoate	2.5	97	13.6
in the presence of Cu(II) chloride	24	94	12.5

Scheme 4.3 Comparison of different copper salts in Henry reaction where the chiral amine was used as ligand

4.2 Results and Discussion

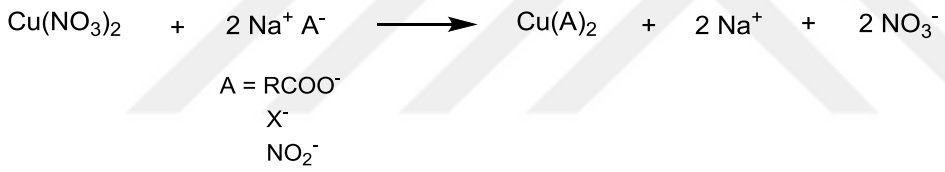
Different copper salts have been used for metal-catalyzed asymmetric Henry reactions. There are numerous examples of the catalytic use of copper salts in the Henry reaction due to their chelating properties, non-toxic, low cost and significant enantioselectivity in good yields (Evans, 2003; Guo and Mao, 2009).

In chapter 2, the tridentate ONO type chiral ligands which were derived from amino acids were synthesized. Their substituent effects were investigated in the Henry reaction in the presence of $Cu(OAc)_2.nH_2O$. The ligand **3e** bearing a methyl group and a benzyl group gave the best results (80 % yield and 64 % ee). In chapter 3, chiral copper (II) complexes were synthesized and used as catalyst in the asymmetric Henry reaction.

Herein it was exhibited how replacing an acetate counter anion with different anions of the Cu (II) salts had important effects on enantioselectivity of the asymmetric Henry reaction. To the best of our knowledge, there have not been any studies examining the effects of different anionic groups such as halides, carboxylates, nitrates...*e.g.*, on the catalytic activities. Therefore, we were strongly interested to investigate the effects of the copper (II) precursors derived from acid salts and copper nitrate in the asymmetric Henry reaction. Thus, optimization studies were carried out with different copper (II) salts and ligand **3e**.

4.2.1 The asymmetric Henry reaction with different copper salts

L-(+)-Alanine derivative Schiff base ligand (**3e**) which contained a benzyl group on the aromatic ring was used in the Henry reaction between 4-nitrobenzaldehyde and nitromethane in the presence of different copper (II) salts. Copper nitrate and different sodium salts were used to synthesize copper (II) salts as shown in scheme 4.4. Initially, different copper ions effects on the catalyst were investigated (Table 4.1 and 4.2).



Scheme 4.4 Synthesis of copper (II) salts

If copper nitrate was used instead of copper (II) acetate, the reaction product was not formed, because of the acidic value of copper (II) nitrate. Nitroalkene was formed instead of *β*-nitroalcohol (Table 4.1, Entry 1). The Henry reaction was performed with $Cu(OAc)_2.nH_2O$ to obtain the reaction product which was *β*-nitroalcohol with 64 % ee and 80 % yield as explained in chapter 2 (Table 4.1, Entry 2). It was observed that the reaction proceeded when sodium acetate was added to the reaction medium in the presence of copper (II) nitrate, in a similar way to using $Cu(OAc)_2.nH_2O$ (Table 4.1, Entry 3). As illustrated in scheme 4.5, it is expected that, copper (II) acetate will be formed from sodium acetate salt and copper (II) nitrate.

Scheme 4.5 Synthesis of copper (II) acetate from sodium acetate

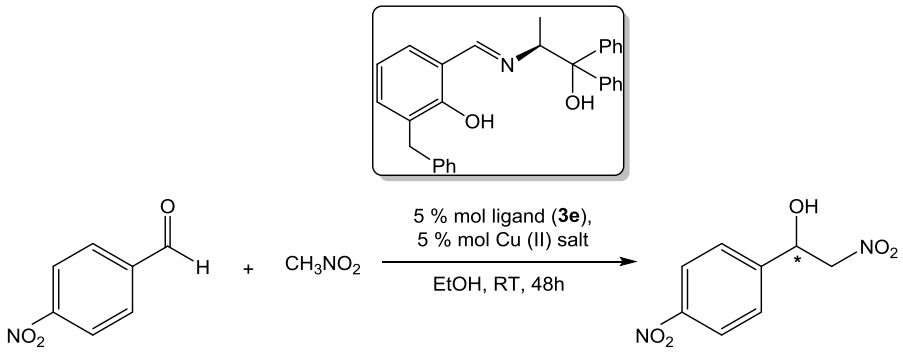


Table 4.1 The Henry reaction using ligand **3e** in the presence of either $Cu(NO_3)_2$ or $Cu(OAc)_2$

Entry	Additive	Cu salt	Yield[a](%)	ee[b](%)	Conf.[c]
1	-	$Cu(NO_3)_2$	-	-	-
2	-	$Cu(OAc)_2\,nH_2O$	80	64	*S*
3[d]	$2Na^+CH_3COO^-$	$Cu(NO_3)_2$	91	56	*S*

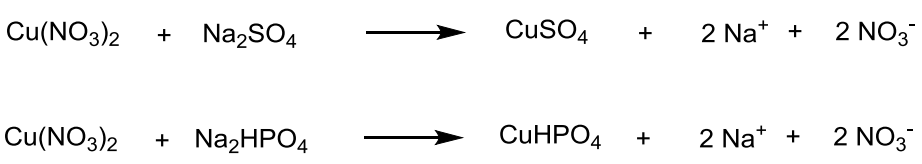
[a]Isolated yields after column chromatography.

[b]Determined by HPLC analysis using a Chiracel OD-H column.

[c]The absolute configuration of the major product was assigned by comparison with the literature values (Evans et al., 2003).

[d] 10 % mol Sodium salt were added to the reaction.

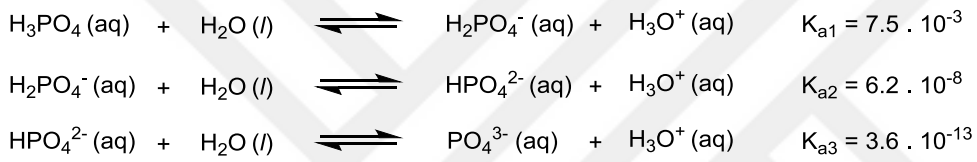
The reactions, in which the salt effect was examined, can be seen in tables 4.1 and 4.2. All reactions were performed with 1 mmol 4-nitrobenzaldehyde, 10 mmol nitromethane 5 % mmol ligand (**3e**) and $Cu(NO_3)_2$ with 10 % sodium salt in 2 mL EtOH at ambient temperature in 48 h. Regarding to the sulphate and hydrogen phosphate groups carrying two negative charges, Na_2SO_4 and Na_2HPO_4 5 % mmol sodium salt were used in entries 4 and 22 (Scheme 4.6). The resulting *β*-nitroalcohols were isolated by column chromatography using 1:3 EtOAc:hexane system.



Scheme 4.6 Synthesis of copper (II) salts from Na_2SO_4 and Na_2HPO_4

When sodium salts of carboxylate ion were used, the enantiomeric excess values could be improved to 86% or 88% respectively (Table 4.2, Entries 7-11, 15-20). If glycine or *β*-Alanine were chosen to form the carboxylate source, the reaction yields were decreased to 35% or 59% (Table 4.2, Entries 6, 14).

When sodium salts were prepared from strong acids which had high pKa values, a nitroalkene product was formed instead of the desired *β*-nitro alcohol (Table 4.2, Entries 1-4). In entry 5, the anion of the sodium salt was $H_2PO_4^-$. It is the conjugate base of H_3PO_4 in water. In entry 22, the anion of the sodium salt was HPO_4^{2-}. As shown in scheme 4.7, these are ambiphilic species interestingly. It was seen from table 4.2, entries 5 and 22, when these salts were used in the Henry reaction, the product was obtained with the same enantioselectivity but low yields (27-29% yields, 88% ee).



Scheme 4.7 Phosphoric acid behaviors as a triprotic acid in water

The nitrite anion and acetate anion are used in entry 13 and 20, the products were obtained with moderate ee results in high yields (92, 91% yields, 74, 56% ee). The best result for a carboxylate counter ion was obtained with the sodium crotonate salt, 74 % yield and 86 % ee (Table 4.2, Entry 19).

Table 4.2 The Henry reaction using ligand **3e**, $Cu(NO_3)_2$ and different sodium salts

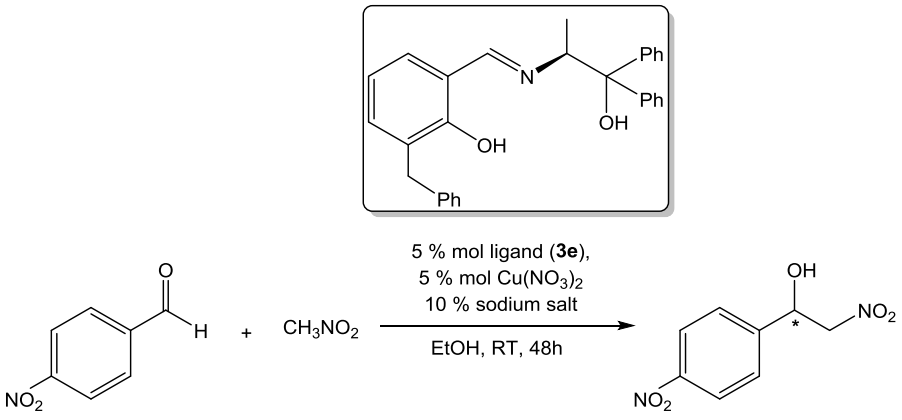


Table 4.2 The Henry reaction using ligand **3e**, $Cu(NO_3)_2$ and different sodium salts (continue)

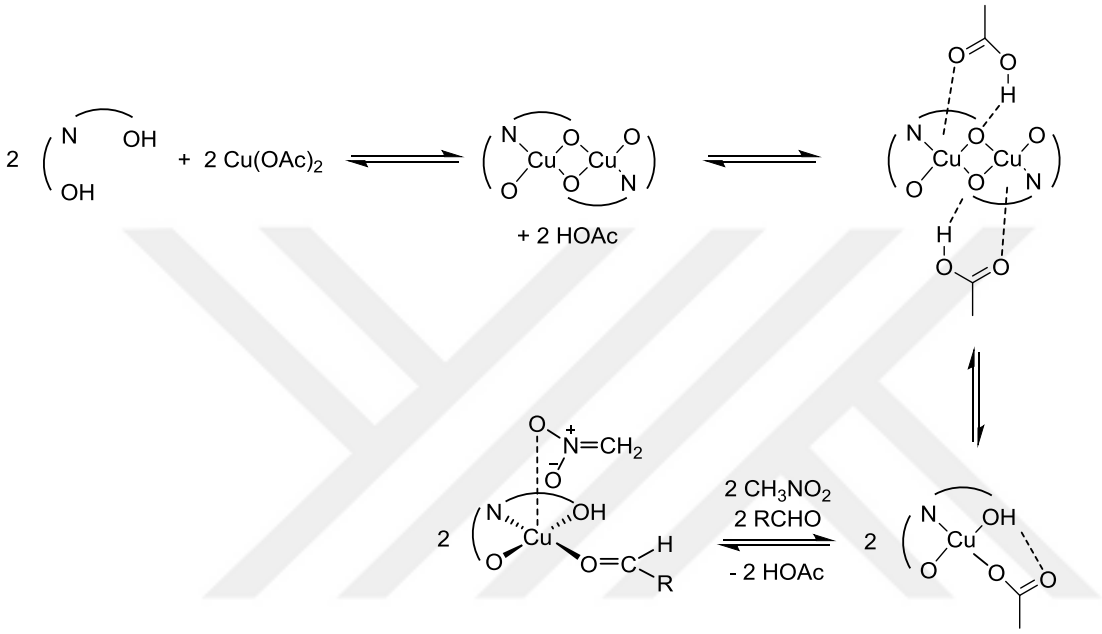
Entry	Acid	Additive a sodium salt	pKa of acid	Yield[a](%)	ee[b](%)	Conf.[c]
1	HBr	Br^-	< 1	-	-	-
2	HCl	Cl^-	< 1	-	-	-
3	H_2SO_4 (1)	HSO_4^-	< 1	-	-	-
4	H_2SO_4 (2)	SO_4^{2-}	1.92	-	-	-
5	H_3PO_4 (1)	$H_2PO_4^-$	2.12	27	88	*S*
6	Glycine	$C_2H_4NO_2^-$	2.34	35	79	*S*
7	Malonic	$C_3H_3O_4^-$	2.83	34	87	*S*
8	Chloroacetic	$C_2H_2ClO_2^-$	2.85	40	86	*S*
9	2-Iodobenz.	$C_7H_4IO_2^-$	2.86	41	87	*S*
10	Salicylic	$C_7H_5O_3^-$	2.97	57	86	*S*
11	Citric (1)	$H_2C_6H_5O_7^-$	3.08	24	87	*S*
12	HF	F^-	3.14	57	56	*S*
13	HNO_2	NO_2^-	3.39	92	74	*S*
14	*β*-Alanine	$C_3H_6NO_2^-$	3.63	59	85	*S*
15	HCOOH	$HCOO^-$	3.75	62	63	*S*
16	Benzoic	$C_6H_5COO^-$	4.19	40	67	*S*
17	Succinic (1)	$C_4H_5O_4^-$	4.20	51	88	*S*
18	Acrylic	$C_3H_3O_2^-$	4.25	16	86	*S*
19	Crotonic	$C_4H_5O_2^-$	4.69	74	86	*S*
20	Acetic	CH_3COO^-	4.75	91	56	*S*
21	Carbonic (1)	HCO_3^-	6.37	90	65	*S*
22	H_3PO_4 (2)	HPO_4^{2-}	7.21	29	88	*S*
23	HCN	CN^-	9.21	69	83	*S*

[a]Isolated yields after column chromatography.

[b]Determined by HPLC analysis using a Chiracel OD-H column.

[c]The absolute configuration of the major product was assigned by comparison with the literature values (Evans et al., 2003).

In this asymmetric reaction, the tridentate ligands and the copper (II) carboxylate forms a copper complex in the reaction medium. But it may be formed as a dimeric or a monomeric form as shown below in scheme 4.8. There is an equilibrium between these two structures. In the bridging structure with the acetate anion, a hydrogen bond is formed between the alcoholic oxygen proton on the ligand and the carbonyl oxygen of the acetate anion. Proton transfer can cause the dimeric structure to shift to the square planar monomer form.



Scheme 4.8 Suggested mechanism Cu(II) intermediate and dimer dissociation

Evidence for such an equilibrium is found in crystal structure of the dimeric and the monomeric forms (Figure 4.1).

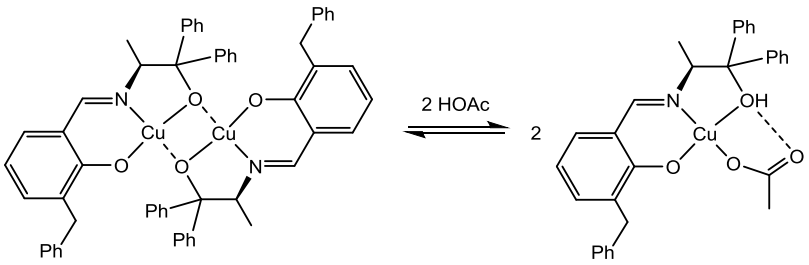
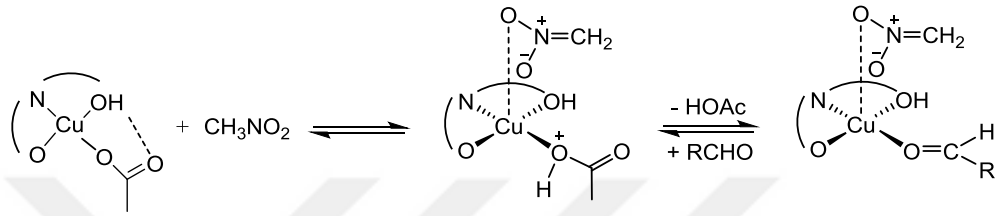


Figure 4.1 The equilibrium with the dimeric and the monomeric forms

In the reaction cycle, dissociation of the acetate ion an association of the aldehyde and nitromethane can occur as shown in scheme 4.9. Thus, as in the bidentate structure of Evans, it is possible to construct a five coordinate square pyramidal intermediate. It is also possible that after dissociation, the carboxylic acid may remain weakly bound to the complex, either by hydrogen bonding or possibly via coordination to the sixth coordination site of the copper center. Such a sequence of events would adequately explain the observed dependence of the enantioselectivity on the nature of the carboxylate anion (Astley et al., 2017).



Scheme 4.9 The dissociation of the acetate ion

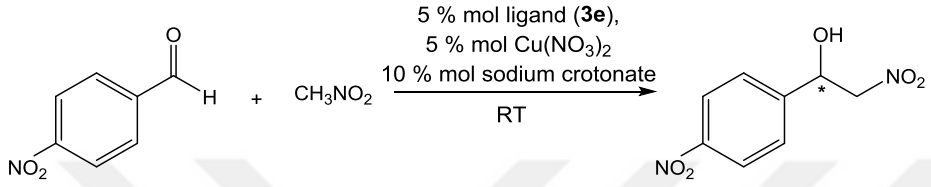
Here, we observed that the basicity and the substituents present of the anion in the Henry reaction medium can change the efficiency and enantioselectivity of the reaction. Thus, according to the reaction results (Tables 4.1 and 4.2), the anion of the copper salt plays a very notable role in the catalytic cycle.

In view of these results, the effect of the solvent was investigated using sodium crotonate with copper (II) nitrate. When methanol was used as solvent, the reaction resulted in moderate; 58% yield and 76% ee. (Table 4.3, Entry 1). Using a polar protic solvent such as IPA, the reaction gave the desired product with low ee (37%) in good yield (95%) (Table 4.3, Entry 2). When DCM, TBME or hexane were used as solvent, the reaction proceeded in low yields (12-25%) and preferable ee (up to 69%) (Table 4.3, Entries 3,4,5). As can be seen, EtOH, which is polar protic solvent, was superior to others.

Next, the duration of reactions at ambient temperature was determined by the amount of 4-nitrobenzaldehyde consumption controlled by TLC plates; however, it was need to determine the change in ee valuees and yields of the reaction over different time periods at ambient temperature. In table 4.3, entries 6, 7 and 8 showed that the reaction reached high ee values at 24 hours and there was no significant change in enantioselectivity by over time, only the yield value increased slightly from 64% to 83%.

After that, the effect of the amount of chiral ligand **3e** and sodium crotonate were examined in the presence of $Cu(NO_3)_2$ as metal source. When the amount of chiral ligand **3e** and Cu (II) salt were decreased from 5% to 2.5%, the corresponding product was obtained in 71% yield and 83% ee (Table 4.3, Entry 9). Increasing the amount of catalyst system from 5% to 10% led to increased yield (91%) and high ee (87%) (Table 4.3, Entry 10).

Table 4.3 Solvent, temperature and catalyst loading effects in the Henry reaction of 4- nitrobenzaldehyde and nitromethane

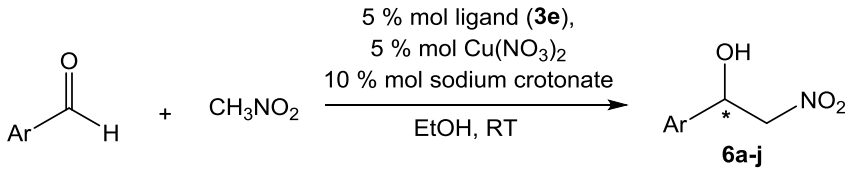


Entry	Solvent	Time(h)	Yield[a](%)	ee[b](%)	Config.[c]
1	MeOH	48	58	76	*S*
2	IPA	48	95	37	*S*
3	DCM	48	12	50	*S*
4	TBME	48	15	62	*S*
5	Hexane	48	25	69	*S*
6	EtOH	24	64	89	*S*
7	EtOH	48	78	87	*S*
8	EtOH	72	83	85	*S*
9[d]	EtOH	48	71	83	*S*
10[e]	EtOH	48	91	87	*S*

[a]Isolated yields after column chromatography. [b]Determined by HPLC analysis using a Chiracel OD-H column. [c]The absolute configuration of the major product was assigned by comparison with the literature values (Evans et al., 2003). [d] 2.5 % mol ligand and $Cu(NO_3)_2$ were used. [e] 10 % mol ligand and $Cu(NO_3)_2$ were used.

Finally, according to the determined optimization conditions, the Henry reaction was carried out with chiral ligand **3e** using various aromatic aldehydes as substrates. The results are summarized in table 4.4. A range aromatic aldehydes which were bearing electron donating or electron withdrawing groups on the aromatic ring were used in the reaction. The corresponding Henry products **6a-j** were obtained in good enantiomeric excess values (70-86%) with moderate yields (42-74%).

Table 4.4 Henry reaction of nitromethane with range of aromatic aldehydes



Entry	Aldehyde	Time (d)	Yield[a](%)	ee[b](%)	Config.[c]
1	4-Nitrobenzaldehyde	2	74	86	*S*
2	3-Nitrobenzaldehyde	2	68	79	*S*
3	2-Nitrobenzaldehyde	2	70	78	*S*
4	2-Chlorobenzaldehyde	3	62	83	*S*
5	4-Chlorobenzaldehyde	3	57	84	*S*
6	4-Methylbenzaldehyde	5	42	81	*S*
7	4-Ethylbenzaldehyde	4	45	82	*S*
8	4-Methoxybenzaldehyde	4	44	79	*S*
9	2-Methoxybenzaldehyde	5	47	81	*S*
10	Benzaldehyde	4	59	70	*S*

[a]Isolated yields after column chromatography. [b]Determined by HPLC analysis using a Chiracel OD-H column. [c]The absolute configuration of the major product was assigned by comparison with the literature values (Evans et al., 2003; Boruwa et al.,2006; Xu and Wolf, 2010).

A different steric effect was identified by comparing the enantioselectivities of the same substituent group at various positions on benzaldehyde, for example -NO_2 group. It was found that, when the -NO_2 substituent was on the para-position, it gave higher ee values than the ortho- and meta- subtituted forms (Table 4.4, Entries 1, 2, 3). If other ortho- and para-substituted substrates were compared, they demonstrated almost the same effect. Similar results were observed between 2-chloro, 4-chloro and 2-methoxy, 4-methoxy (Table 4.4, Entries 4, 5 and 8, 9). Benzaldehyde showed a value of ee in modarete yield when it was compared to other subtituted aromatic aldehydes (Table 4.4, Entry 10). All the aromatic aldehydes were also suitable substrates, but it was seen that the steric hindrance had not much influence on the reactions (Table 4.4, Entries 1-10). It appears that best result was seen with 4-nitrobenzaldehyde both yield (74%) and enantiomeric excess (86%) values at room temperature in two days.

4.3 Conclusion

In this chapter, sodium salts were prepared from carboxylic acids, amino acids and inorganic acids with different acidity values. An ONO type Schiff base ligand (**3e**) bearing a methyl group on the amino alcohol and a benzyl group on the aromatic ring was used as catalyst precursor. It has been found that a complex was formed in the reaction medium by the use of sodium salts with $Cu(NO_3)_2$. This *in situ* prepared complex was used instead of $Cu(OAc)_2.nH_2O$ in the asymmetric Henry reaction. There was a significant effect on the observed ee values (up to 88%) and yield (up to 92%). Various optimizations such as solvent, catalyst loading and time consuming were put into practice. The effects of the carboxylate counter ion in the Henry reaction were also investigated with a variety of aromatic aldehydes. The aldehydes were used as substrates to react with nitromethane, giving the expected products with moderate yields (up to 74%) and high enantiomeric excess values (up to 86%). It was suggested that the counter ion may play an important in the formation of the active intermediate, and possibly via a weak coordination to the active intermediate.

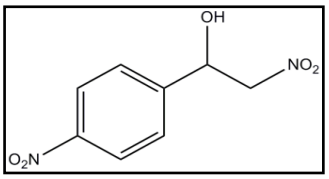
4.4 Material and Method

All reactions were performed in air. The solvents were analytical grade and obtained from commercial suppliers. All chemicals were commercially available and purchased from Merck, Sigma-Aldrich, Alfa Aesar, Fluka, Acros or BDH and used without any purification. Silica gel F_{254} (Merck 5554) precoated plates were used for the monitoring of all reactions by thin-layer chromatography and visualized by ultra-violet light or by staining with ninhydrin dissolved in alcohol. For column chromatography silica gel 60 (Merck 7743) was used. The enantiomeric ratios of the products were determined by HPLC using hexane:IPA system, flow rate 1 mL/min, 267 nm with Chiralcel OD-H column.

4.4.1 General procedure for the Henry reaction

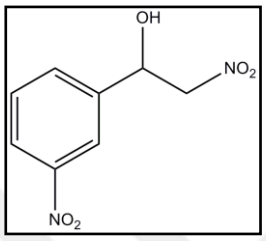
Ligand **3e** (0.01 mmmol) was added to the solution of copper nitrate (0.01 mmol) and sodium salt (0.02 mmol) combination in 2 mL solvent at room temperature for 2 hours. The aldehydes (0.2mmol) and nitromethane (2.0 mmol) were added to the appropriate solution. The reaction mixture was stirred for several hours while the aldehyde consumption was controlled by TLC. After the solvent was evaporated under reduced pressure, the crude product was purified with column chromatography using 1:3 EtOAc:hexane system.

4.4.2 (*S*)-1-(4-nitrophenyl)-2-nitroethanol (6a)



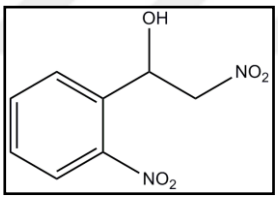
White crystals, 74 % yield, ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 3.17 (bs, 1H), 4.58 (d, *J* = 2 Hz, 1H), 4.60 (d, *J* = 6 Hz, 1H), 5.61 (m, 1H), 7.63 (m, 2H), 8.26 (m, 2H). HPLC: Chiracel OD-H colomn, hexane:IPA (90:10) mL/min, 267 nm, t_{minor}= 32.5 min (*R*), t_{major}= 40.9 min (*S*), % 86 ee, $[\alpha]_D^{29}$ = + 28.9 (*c* 1.00, CH_2Cl_2).

4.4.3 (*S*)-1-(3-nitrophenyl)-2-nitroethanol (6b)



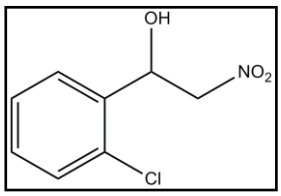
Yellow oil, 68 % yield, ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 3.51 (bs, 1H), 4.63 (m, 2H), 5.61 (dd, *J* = 4.4, 7.6 Hz, 1H), 7.61 (t, *J* = 7.6Hz, 1H), 7.78 (m, 1H), 8.19 (m, 1H), 8.30 (m, 1H). HPLC: Chiracel OD-H colomn, hexane:IPA (90:10) mL/min, 267 nm, t_{minor}= 29.0 min (*R*), t_{major}= 32.6 min (*S*), % 79 ee, $[\alpha]_D^{29}$ = + 29.3 (*c* 1.00, CH_2Cl_2).

4.4.4 (*S*)-1-(2-nitrophenyl)-2-nitroethanol (6c)



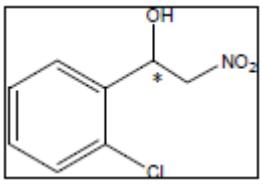
Brown crystals, 70 % yield, ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 3.35 (bs, 1H), 4.56 (dd, *J* = 9.2, 13.6 Hz, 1H), 4.85 (dd, *J* = 2.4, 14 Hz, 1H), 6.03 (d, *J* = 8Hz, 1H), 7.55 (td, *J* = 1.6, 8.4 Hz, 1H), 7.75 (td, *J* = 0.8, 7.6 Hz, 1H), 7.95 (d, *J* = 8Hz, 1H), 8.06 (dd, *J* = 1.2, 8Hz, 1H). HPLC: Chiracel OD-H colomn, hexane:IPA (90:10) mL/min, 267 nm, t_{minor}= 16.7 min (*R*), t_{major}= 19.3 min (*S*), % 78 ee, $[\alpha]_D^{29}$ = - 25.6 (*c* 1.00, CH_2Cl_2).

4.4.5 (*S*)-1-(2-chlorophenyl)-2-nitroethanol (6d)



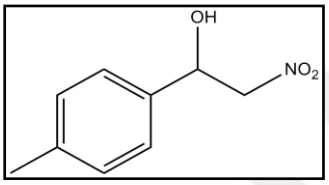
Colorless oil, 62 % yield, ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 4.36 (dd, *J* = 9.6, 13.6 Hz, 1H), 4.57 (dd, *J* = 2.4, 13.6 Hz, 1H), 5.75 (m, 1H), 7.24 (m, 3H), 7.56 (dd, *J* = 2, 7.6 Hz, 1H). HPLC: Chiracel OD-H colomn, hexane:IPA (95:5) mL/min, 267 nm, t_{minor}= 14.7 min (*R*), t_{major}= 15.5 min (*S*), % 83 ee, $[\alpha]_D^{29}$ = + 44.0 (*c* 1.00, CH_2Cl_2).

4.4.6 (*S*)-1-(4- chlorophenyl)-2-nitroethanol (6e)



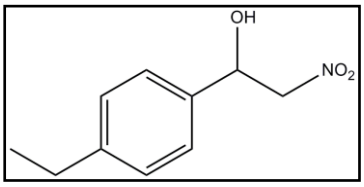
Colorless oil, 57 % yield, ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 2.96 (br, 1H), 4.49 (dd, *J* = 9.2, 13.2 Hz, 1H), 4.57 (dd, *J* = 9.2, 13.6 Hz, 1H), 5.44 (dd, *J* = 2.8, 9.6 Hz, 1H), 7.33 (m, 4H). HPLC: Chiracel OD-H colomn, hexane:IPA (90:10) mL/min, 267 nm, t_{minor}= 13.9 min (*R*), t_{major}= 17.2 min (*S*), % 84 ee, $[\alpha]_D^{29}$ = + 22.7 (*c* 1.00, CH_2Cl_2).

4.4.7 (*S*)-1-(4-methylphenyl)-2-nitroethanol (6f)



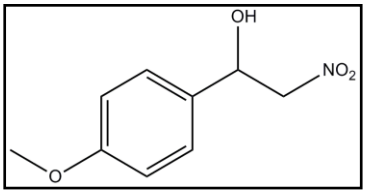
Yellow crystals, 42 % yield, ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 2.36 (s, 3H), 2.74 (bs, 1H), 4.48 (dd, *J* = 2.8, 13.2 Hz, 1H), 4.60 (dd, *J* = 10.4, 13.6 Hz, 1H), 5.42 (d, *J* = 9.2 Hz, 1H), 7.26 (m, 4H), 13.6 Hz, 1H), 5.44 (dd, *J* = 2.8, 9.6 Hz, 1H), 7.33 (m, 4H). HPLC: Chiracel OD-H colomn, hexane:IPA (90:10) mL/min, 267 nm, t_{minor}= 13.4 min (*R*), t_{major}= 16.3 min (*S*), % 81 ee, $[\alpha]_D^{29}$ = + 18.3 (*c* 0.5, CH_2Cl_2).

4.4.8 (*S*)-1-(4-ethylphenyl)-2-nitroethanol (6g)



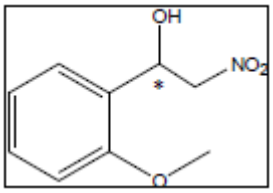
Yellow oil, 45 % yields, ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 1.23 (t, *J* = 7.6 Hz, 3H), 2.65 (q, *J* = 7.6 Hz, 2H), 2.86 (d, *J* = 3.6 Hz, 1H), 4.48 (dd, *J* = 3.2, 13.2 Hz, 1H), 4.50 (dd, *J* = 9.6, 13.2 Hz, 1H), 5.42 (m, 1H), 7.22 (m, 2H), 7.29 (m, 2H). HPLC: Chiracel OD-H colomn, hexane:IPA (90:10) mL/min, 267 nm, t_{minor}= 12.4 min (*R*), t_{major}= 15.4 min (*S*), % 82 ee, $[\alpha]_D^{29}$ = + 32.3 (*c* 0.75, CH_2Cl_2).

4.4.9 (*S*)-1-(4-methoxyphenyl)-2-nitroethanol (6h)



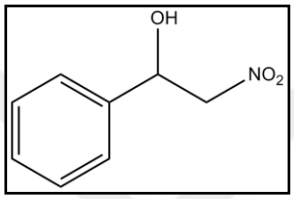
Yellow oil, 44 % yield, ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 2.84 (bs, 1H), 3.81 (s, 3H), 4.46 (dd, *J* = 2.8, 12.8 Hz, 1H), 4.59 (dd, *J* = 9.6, 13.2 Hz, 1H), 5.39 (m, 1H), 6.91 (d, *J* = 8.8 Hz, 2H), 7.30 (d, *J* = 8.8 Hz, 2H). HPLC: Chiracel OD-H colomn, hexane:IPA (90:10) mL/min, 267 nm, t_{minor}= 20.6 min (*R*), t_{major}= 25.5 min (*S*), % 79 ee, $[\alpha]_D^{29}$ = + 26.0 (*c* 0.5, CH_2Cl_2).

4.4.10 (*S*)-1-(2-methoxyphenyl)-2-nitroethanol (6i)



Yellow oil, 47 % yield, ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 3.15 (d, *J* = 6 Hz, 1H), 3.88 (s, 3H), 4.57 (dd, *J* = 9.2, 13.2, 1H), 4.64 (dd, *J* = 3.2, 13.2 Hz, 1H), 5.65-5.61 (m, 1H), 6.91 (d, *J* =8.8 Hz, 1H), 7.01 (td, *J* = 0.8, 7.6 Hz, 1H), 7.33 (td, *J* = 0.8, 1.6 Hz, 1H), 7.44 (dd, *J* = 0.8, 7.2 Hz, 1H). HPLC: Chiracel OD-H colomn, hexane:IPA (90:10) mL/min, 267 nm, t_{minor}= 12.2 min (*R*), t_{major}= 13.5 min (*S*), % 81 ee, $[\alpha]_D^{29}$ = + 25.4 (*c* 1.00, CH_2Cl_2).

4.4.11 (*S*)-1-(1-phenyl)-2-nitroethanol (6j)



Yellow oil, 59 % yield, ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 3.08 (bs, 1H), 4.49 (dd, *J* = 2.8, 13.2 Hz, 1H), 4.59 (dd, *J* = 9.6, 13.6 Hz, 1H), 5.43 (dd, *J* = 2.8, 9.6 Hz, 1H), 7.38 (m, 5H). HPLC: Chiracel OD-H colomn, hexane:IPA (90:10) mL/min, 267 nm, t_{minor}= 13.3 min (*R*), t_{major}= 17.0 min (*S*), % 70 ee, $[\alpha]_D^{29}$ = + 32.3 (*c* 1.00, CH_2Cl_2).

APPENDIX C: Spectra and Chromatograms

C.1 ^{1}H NMR Spectrums

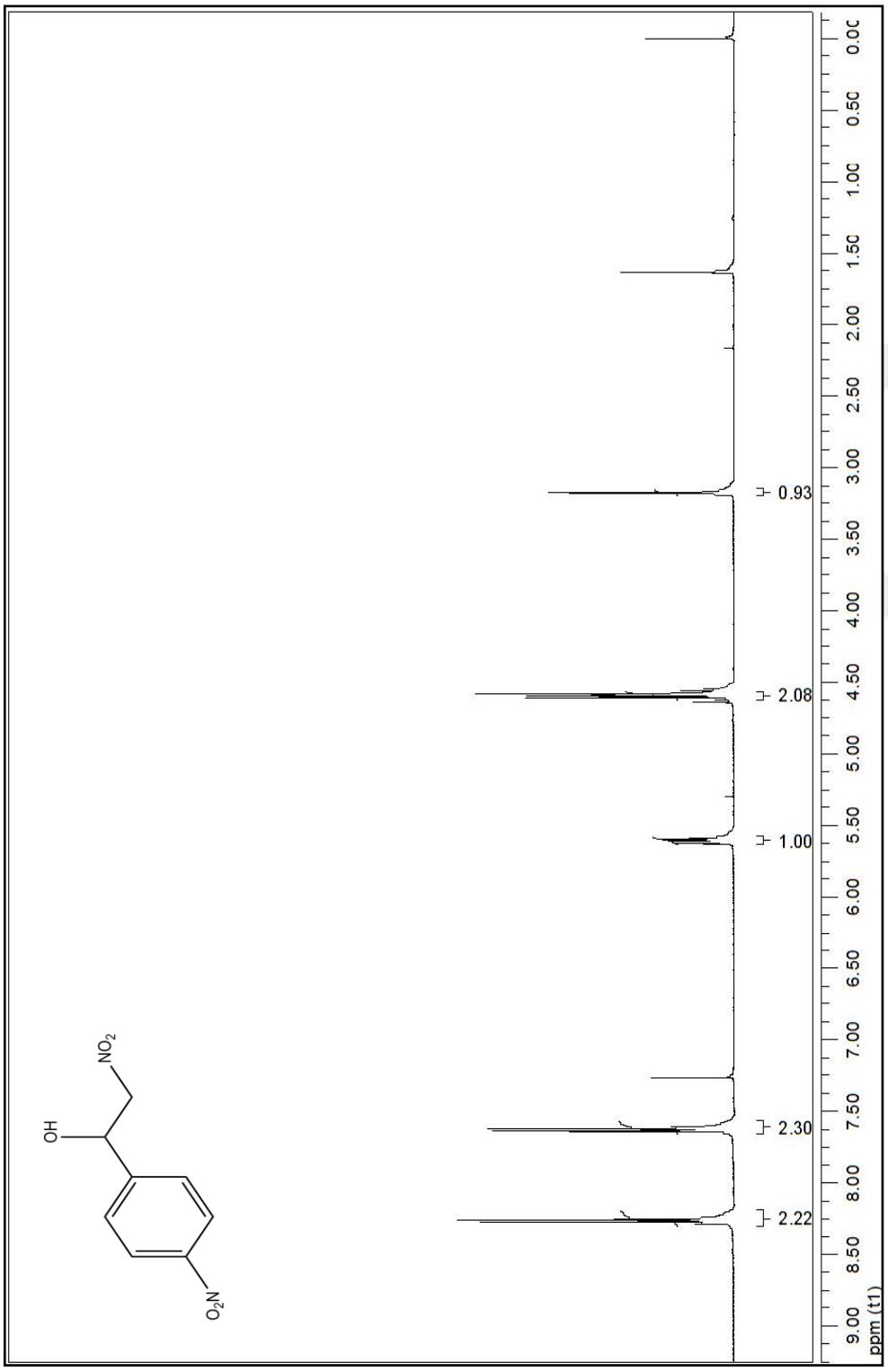


Figure C.1.1 ^{1}HNMR spectrum of (*S*)-1-(4-nitrophenyl)-2-nitroethanol (**6a**)

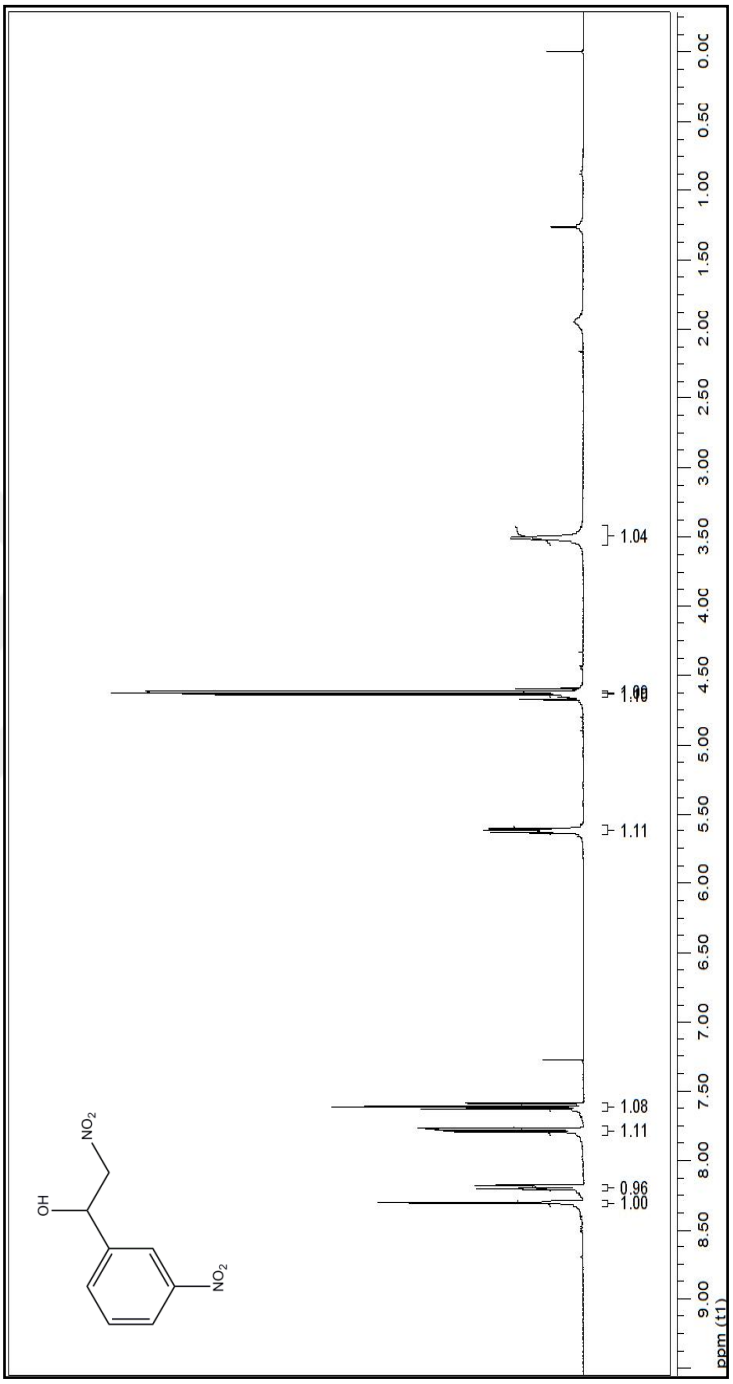


Figure C.1.2 [1]HNMR spectrum of (*S*)-1-(3-nitrophenyl)-2-nitroethanol (**6b**)

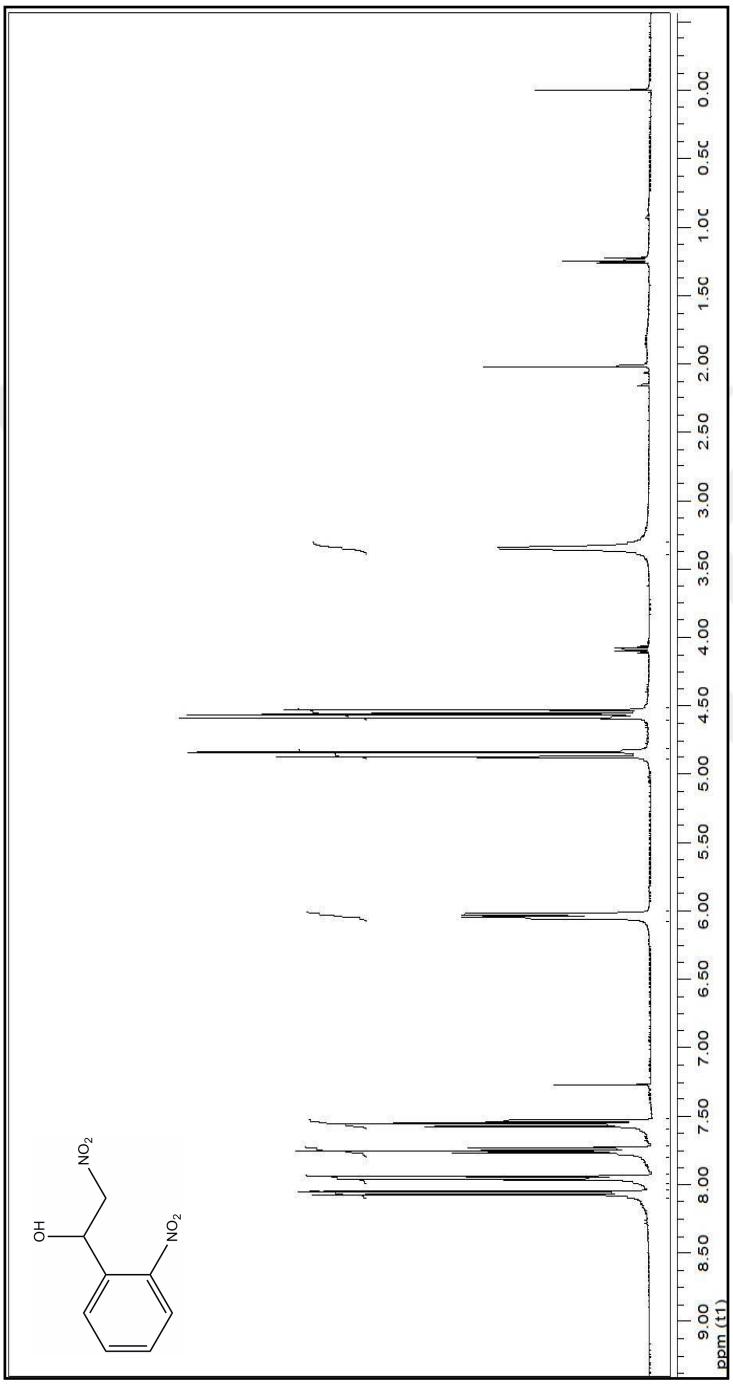


Figure C.1.3 ^{1}HNMR spectrum of (*S*)-1-(2-nitrophenyl)-2-nitroethanol (**6c**)

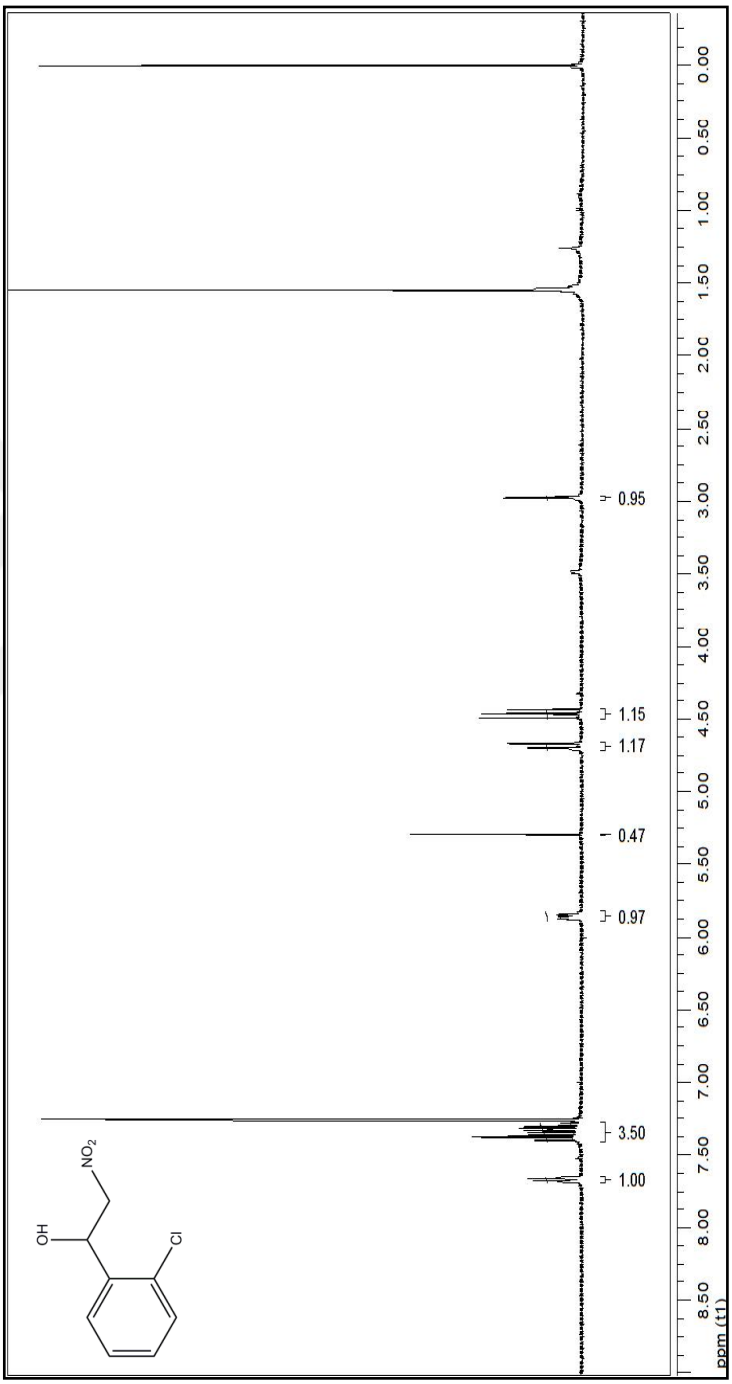


Figure C.1.4 ^{1}HNMR spectrum of (*S*)-1-(2-chlorophenyl)-2-nitroethanol (**6d**)

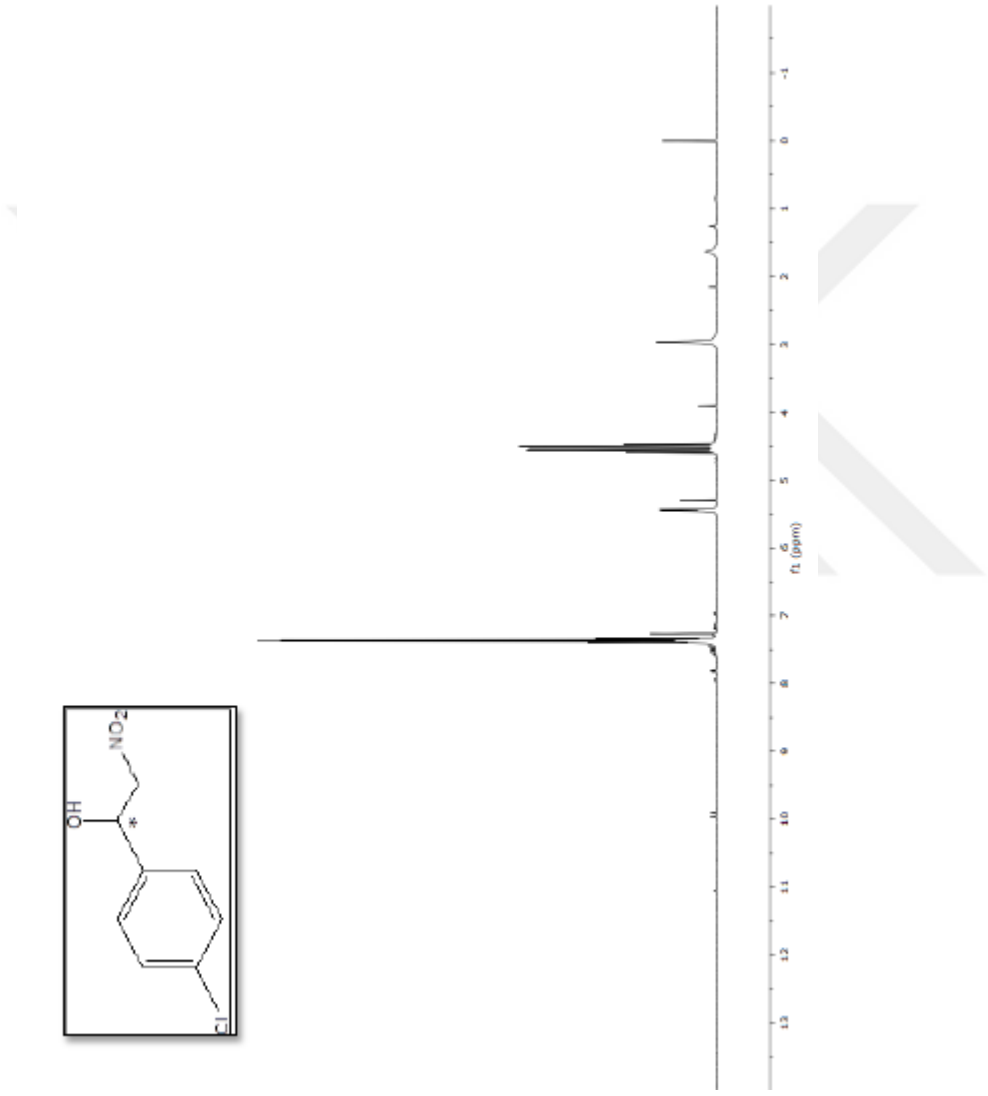


Figure C.1.5 ^{1}HNMR spectrum of (*S*)-1-(4-chlorophenyl)-2-nitroethanol (**6e**)

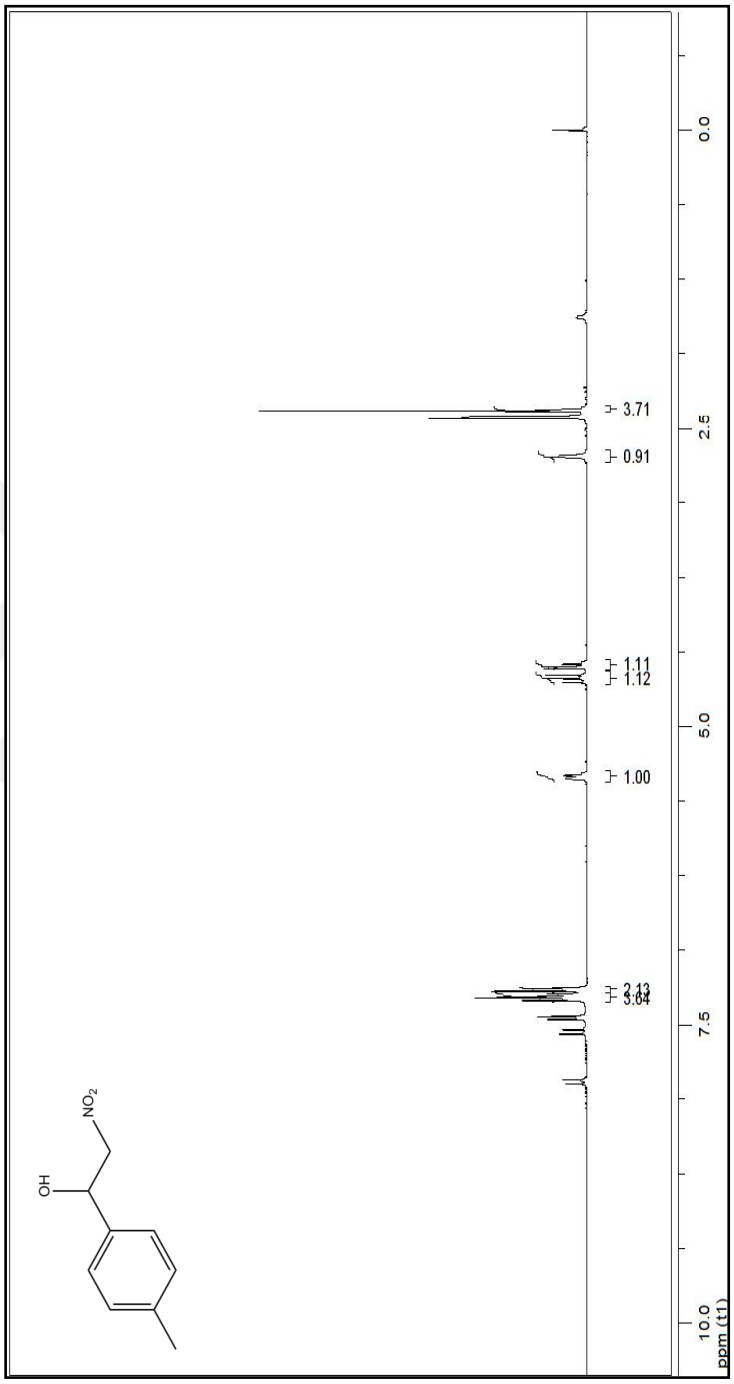


Figure C.1.6 ^{1}HNMR spectrum of (*S*)-1-(4-methylphenyl)-2-nitroethanol (**6f**)

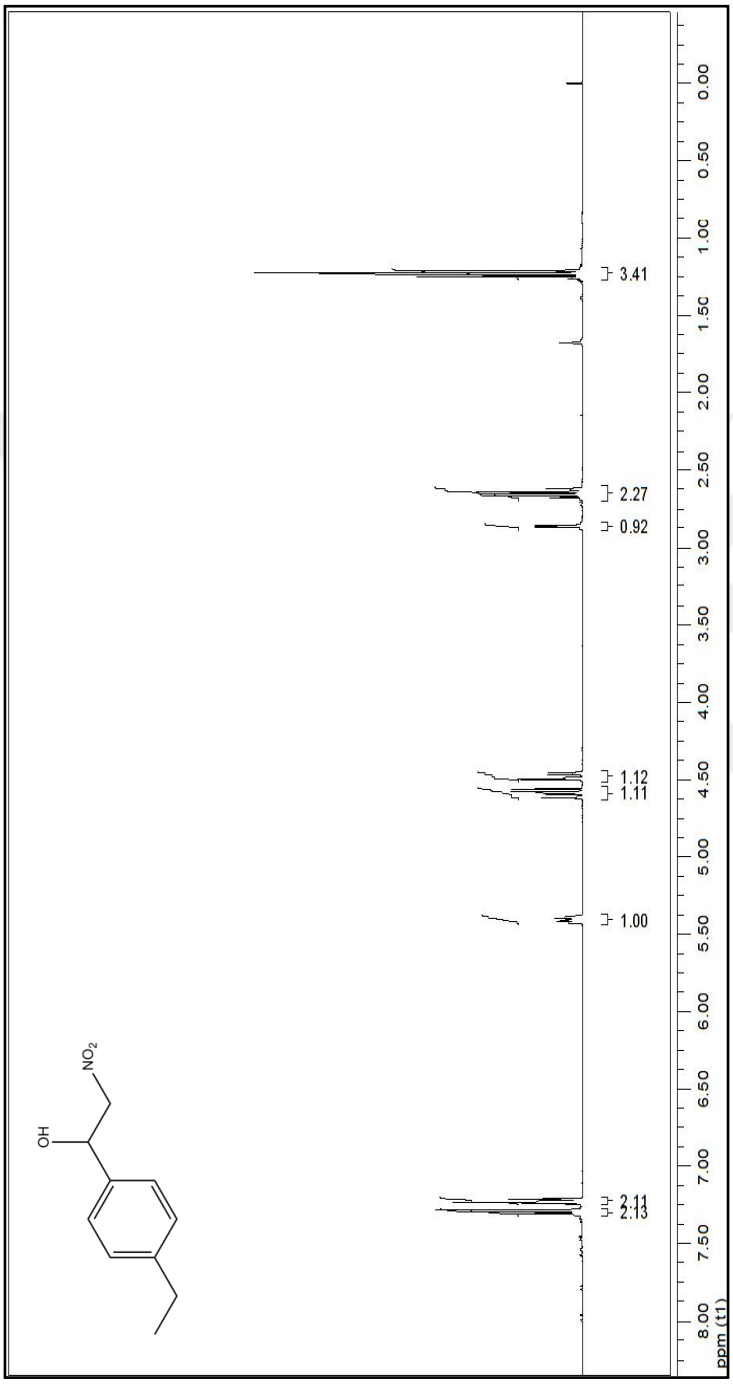


Figure C.1.7 ^{1}HNMR spectrum of (*S*)-1-(4-ethylphenyl)-2-nitroethanol (**6g**)

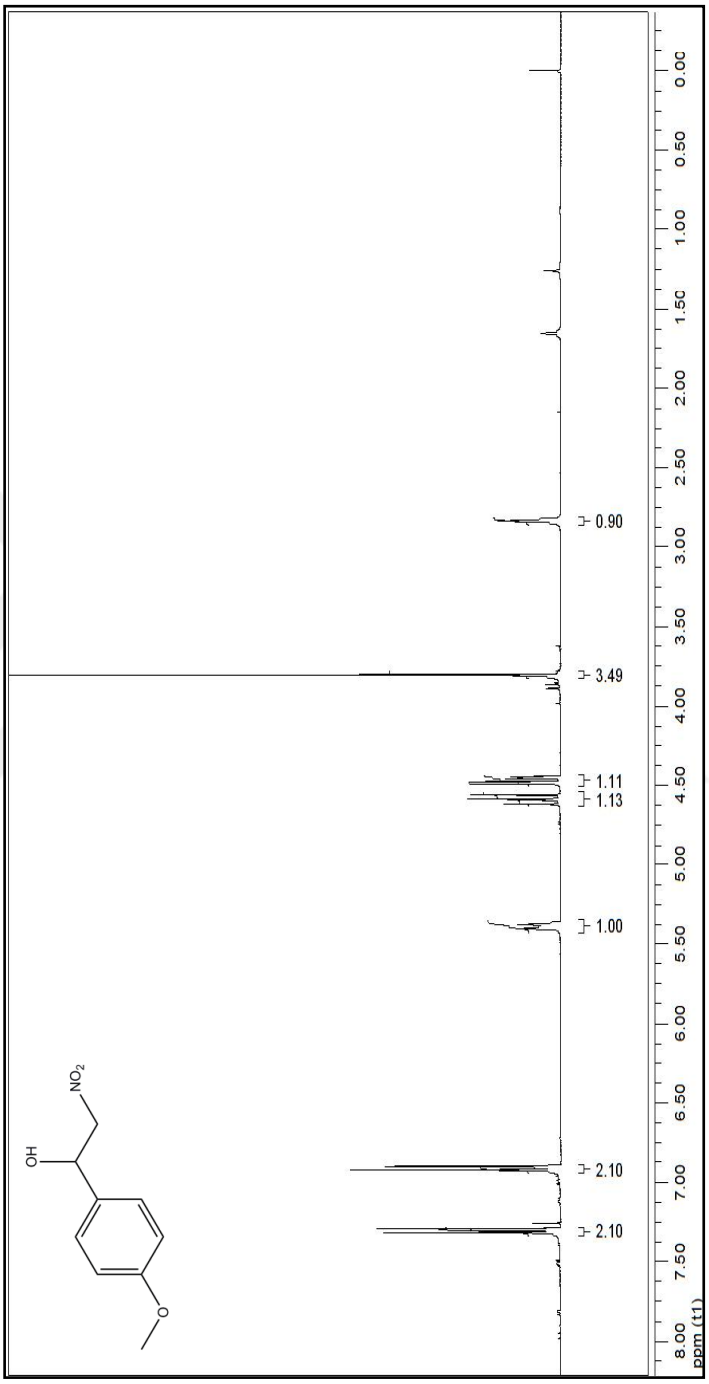


Figure C.1.8 [1]HNMR spectrum of (*S*)-1-(4-methoxyphenyl)-2-nitroethanol (**6h**)

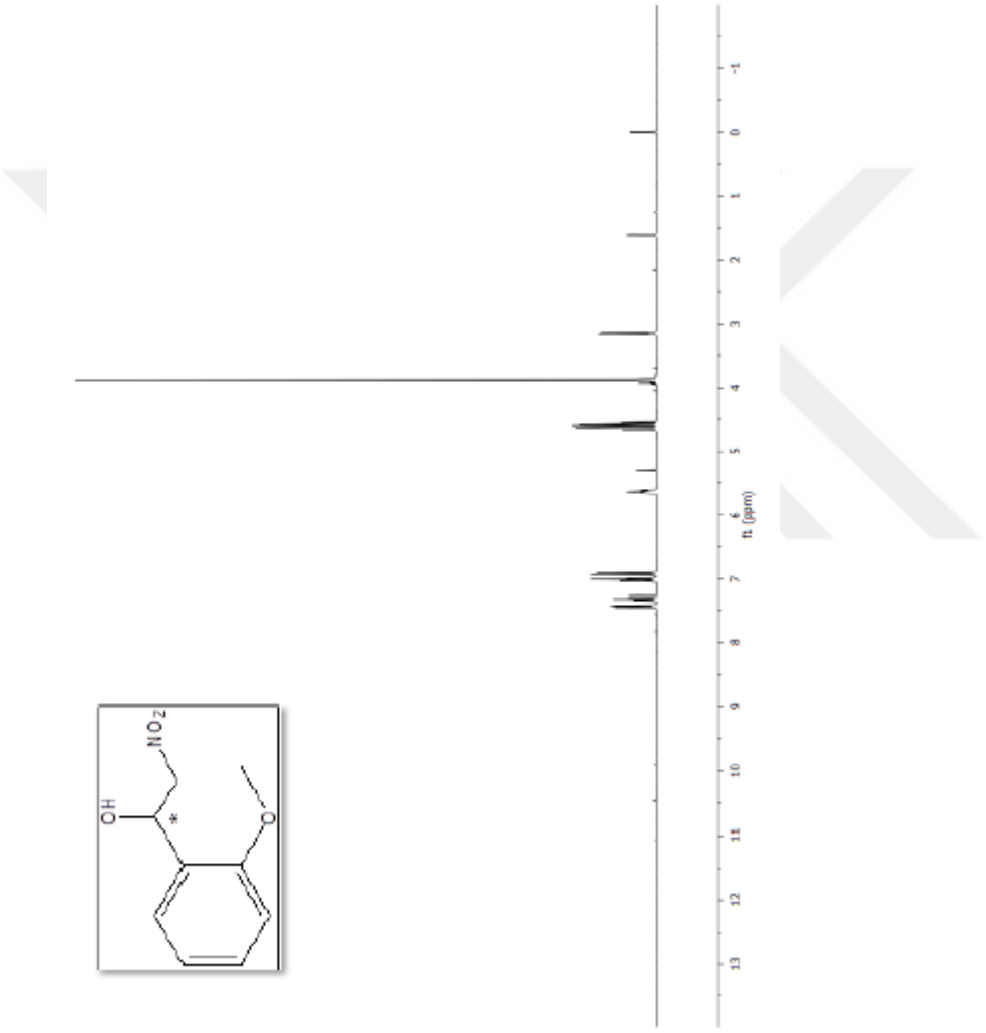


Figure C.1.9 ^{1}HNMR spectrum of (*S*)-1-(2-methoxyphenyl)-2-nitroethanol (**6i**)

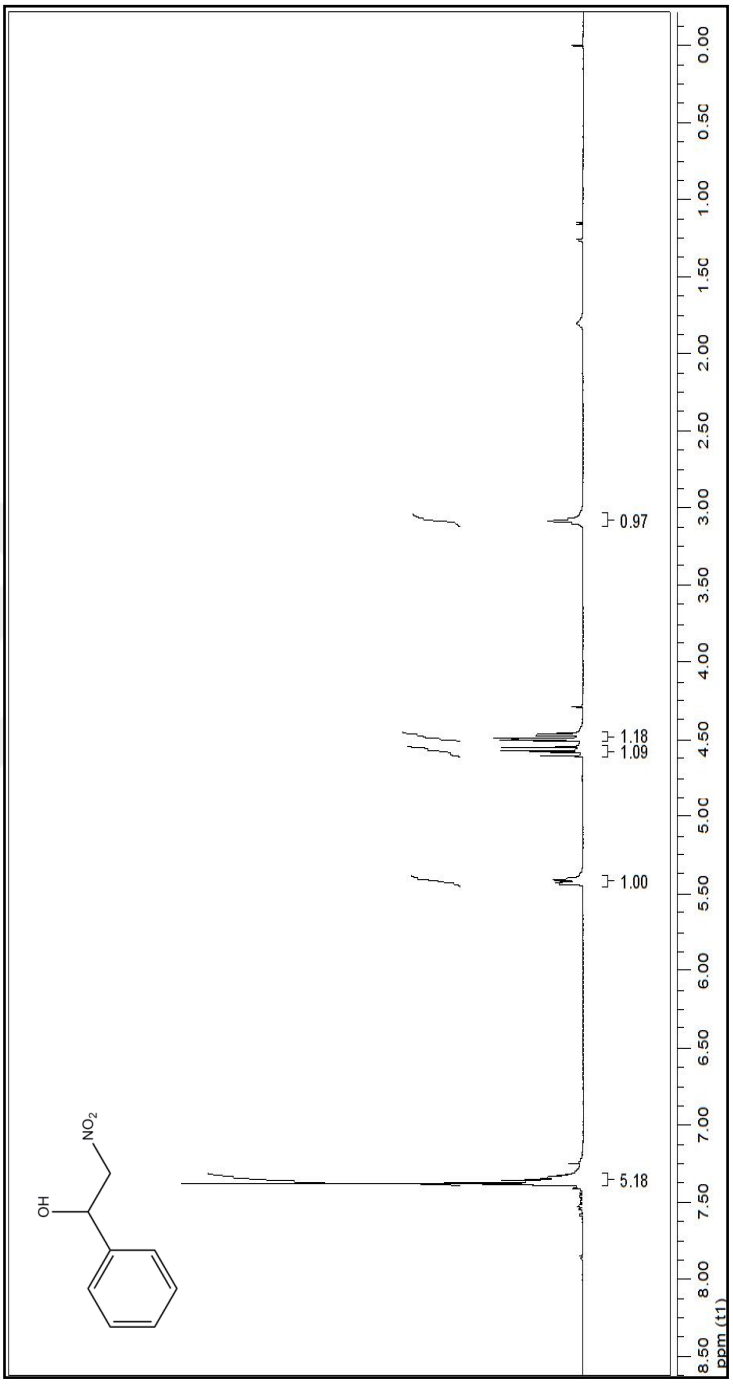


Figure C.1.10 [1]HNMR spectrum of (*S*)-1-(1-phenyl)-2-nitroethanol (**6j**)

C.2 Chromatograms

```
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Sample Name: AA-k-217

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    Acq. Instrument : Instrument 1                    Location : Vial 1
    Injection Date  : 3/26/2017 2:58:08 PM
    Method          : C:\CHEM32\1\METHODS\GAMZE.M
    Last changed    : 7/14/2015 2:59:52 PM by Arzu
    Sample Info     : 90:10 Hex/IPA, 267nm, 1.0 ml/min
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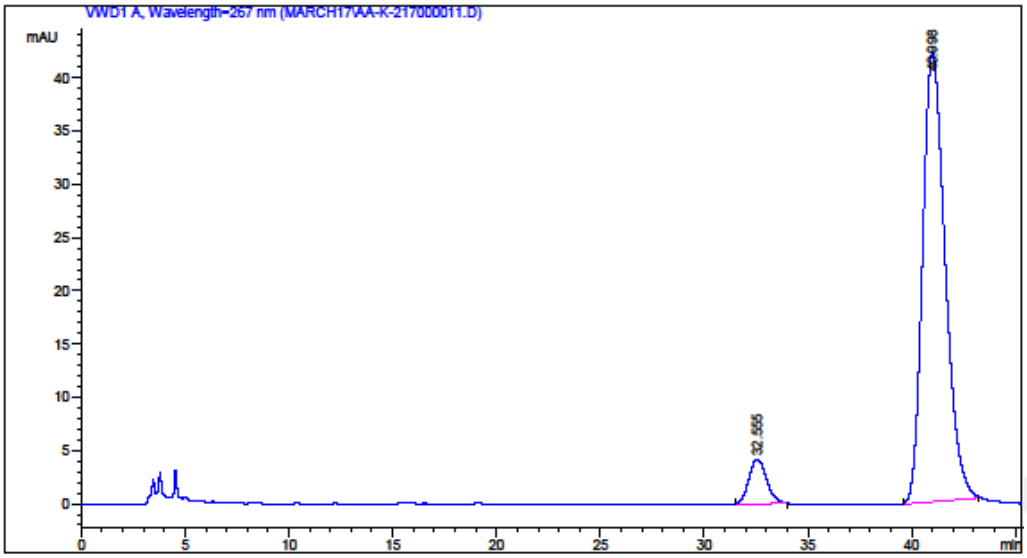


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    ========================================================================
                           Area Percent Report
    ========================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: VWD1 A, Wavelength=267 nm

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]  mAU   *s    [mAU   ]      %
    ----|-------|----|-------|----------|----------|--------|
       1  32.555 BB    0.8475  249.28172    4.20433   7.2637
       2  40.998 BB    1.1686 3182.59448   42.24642  92.7363

    Totals :                  3431.87621   46.45075


    ========================================================================
                           *** End of Report ***

Instrument 1 6/17/2017 5:43:22 PM Arzu                          Page   1 of 1
```

Figure C.2.1 HPLC chromatogram of the nitroaldol reaction of 4-NO_2-benzaldehyde using **$Cu(NO_3)_2$ 2($C_4H_5O_2$)** in EtOH (**6a**)

```
Data File C:\CHEM32\1\DATA\APRIL17\AA-K-235000001.D
Sample Name: AA-k-235

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Acq. Instrument : Instrument 1                    Location : Vial 1
Injection Date  : 4/9/2017 5:25:09 PM
Method          : C:\CHEM32\1\METHODS\GAMZE.M
Last changed    : 7/14/2015 2:59:52 PM by Arsu
Sample Info     : 90:10 Hex/IPA, 267nm, 1.0 ml/min
```
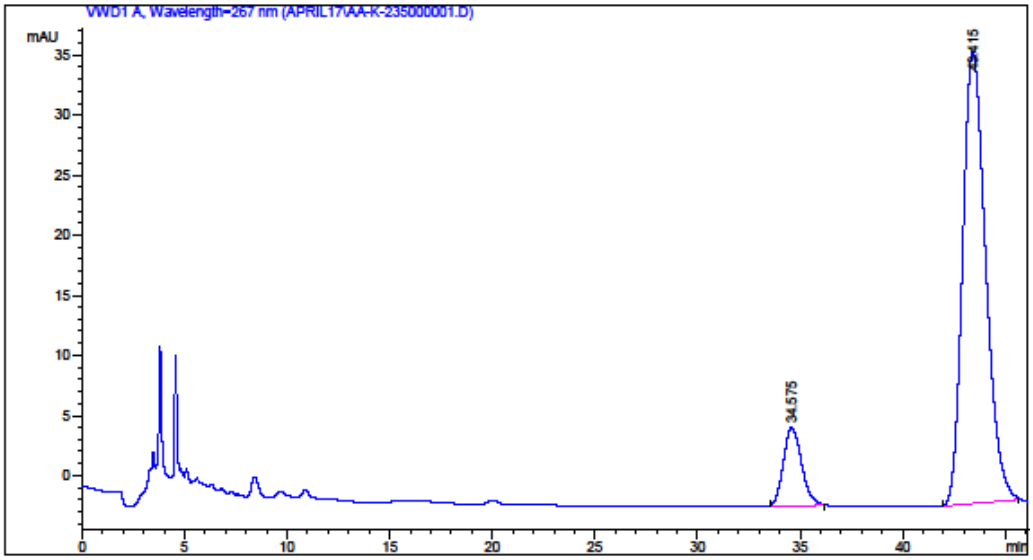
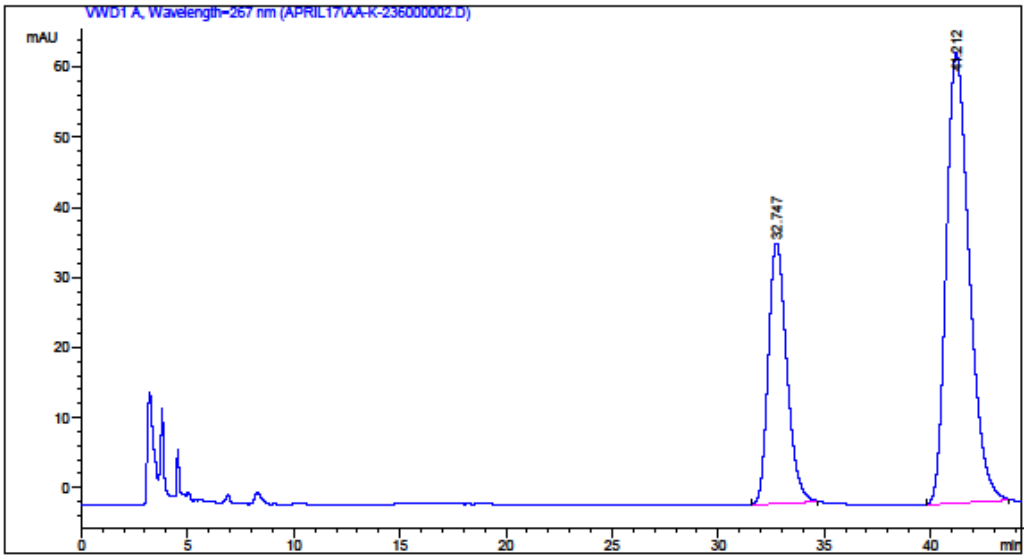




```
==================================================================
                        Area Percent Report
==================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=267 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s   [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  34.575 BB    0.9060  403.78485    6.54573  12.1138
   2  43.415 BB    1.1882 2929.46655   37.61501  87.8862

Totals :                  3333.25140   44.16074


==================================================================
                        *** End of Report ***

Instrument 1 6/17/2017 5:57:40 PM Arsu                    Page   1 of 1
```

Figure C.2.2 HPLC chromatogram of the nitroaldol reaction of 4-NO_2-benzaldehyde using **$Cu(NO_3)_2$ $2(C_4H_5O_2)$ in MeOH** (**6a**)

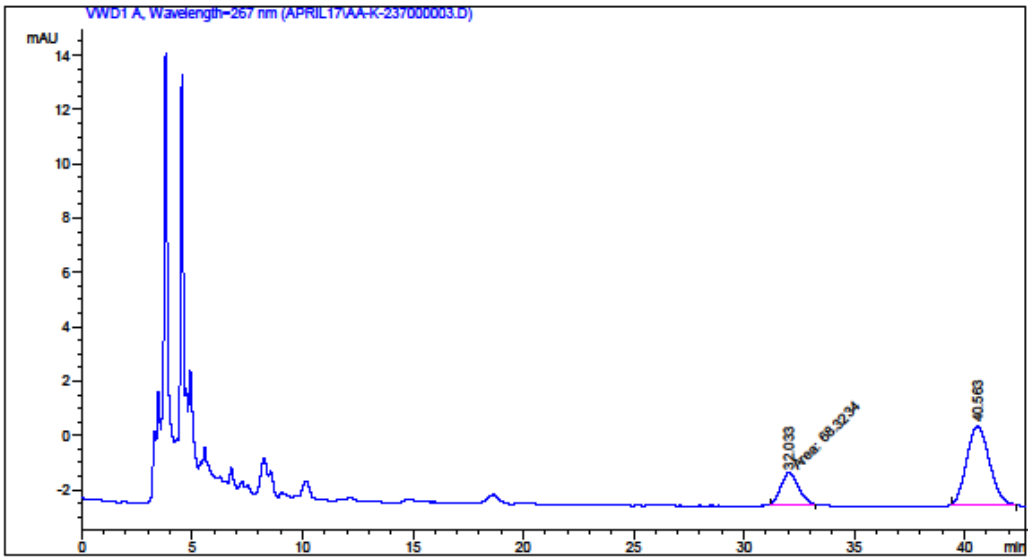
```
Data File C:\CHEM32\1\DATA\APRIL17\AA-K-236000002.D
Sample Name: AA-k-236

==========================================================================
Acq. Operator    : Arsu
Acq. Instrument : Instrument 1                    Location : Vial 1
Injection Date  : 4/9/2017 6:12:26 PM
Method          : C:\CHEM32\1\METHODS\GAMZE.M
Last changed    : 7/14/2015 2:59:52 PM by Arsu
Sample Info     : 90:10 Hex/IPA, 267nm, 1.0 ml/min
```




```
==========================================================================
                        Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=267 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s    [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  32.747 BB    0.9293 2252.94629   37.20438  31.7599
   2  41.212 BB    1.1489 4840.73779   64.31342  68.2401

Totals :                  7093.68408  101.51780

==========================================================================
                        *** End of Report ***

Instrument 1 6/17/2017 5:58:16 PM Arsu                        Page   1 of 1
```

Figure C.2.3 HPLC chromatogram of the nitroaldol reaction of 4-NO_2-benzaldehyde using **$Cu(NO_3)_2$ 2($C_4H_5O_2$) in IPA** (**6a**)

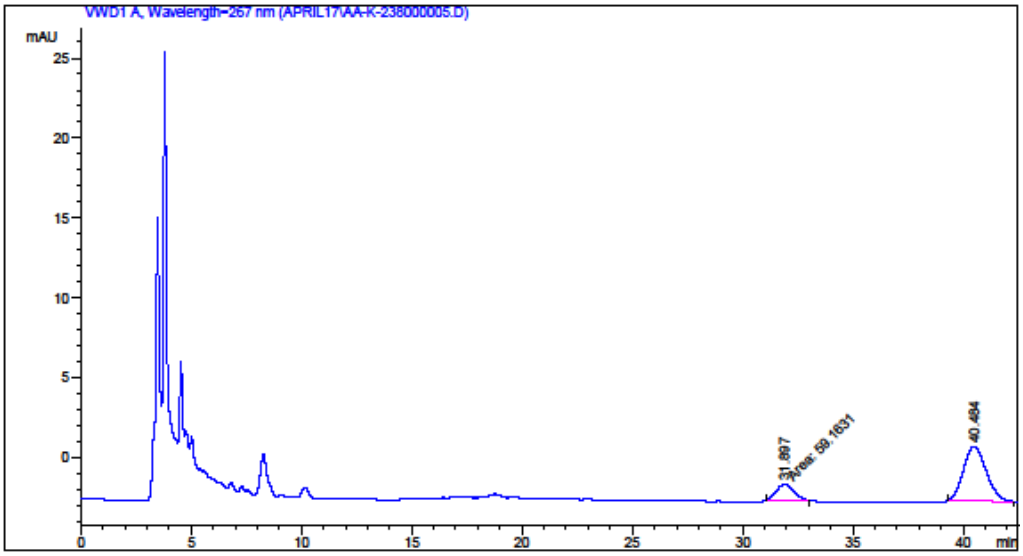
```
Data File C:\CHEM32\1\DATA\APRIL17\AA-K-237000003.D
Sample Name: AA-k-237

==================================================================
Acq. Operator    : Arzu
Acq. Instrument : Instrument 1                    Location : Vial 1
Injection Date  : 4/9/2017 6:58:00 PM
Method          : C:\CHEM32\1\METHODS\GAMZE.M
Last changed    : 7/14/2015 2:59:52 PM by Arzu
Sample Info     : 90:10 Hex/IPA, 267nm, 1.0 ml/min
```




```
==================================================================
                        Area Percent Report
==================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=267 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s   [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  32.033 MM    0.9589   68.32341    1.18749  24.6228
   2  40.563 BB    0.9247  209.15735    2.89913  75.3772

Totals :                   277.48076    4.08661

==================================================================
                        *** End of Report ***

Instrument 1 6/17/2017 6:01:15 PM Arzu                  Page   1 of 1
```

Figure C.2.4 HPLC chromatogram of the nitroaldol reaction of 4-NO_2-benzaldehyde using **$Cu(NO_3)_2$ $2(C_4H_5O_2)$ in DCM** (**6a**)

```
Data File C:\CHEM32\1\DATA\APRIL17\AA-K-238000005.D
Sample Name: AA-k-238

    ======================================================================
    Acq. Operator    : Arsu
    Acq. Instrument : Instrument 1                    Location : Vial 1
    Injection Date  : 4/9/2017 8:27:13 PM
    Method          : C:\CHEM32\1\METHODS\GAMZE.M
    Last changed    : 7/14/2015 2:59:52 PM by Arsu
    Sample Info     : 90:10 Hex/IPA, 267nm, 1.0 ml/min
```

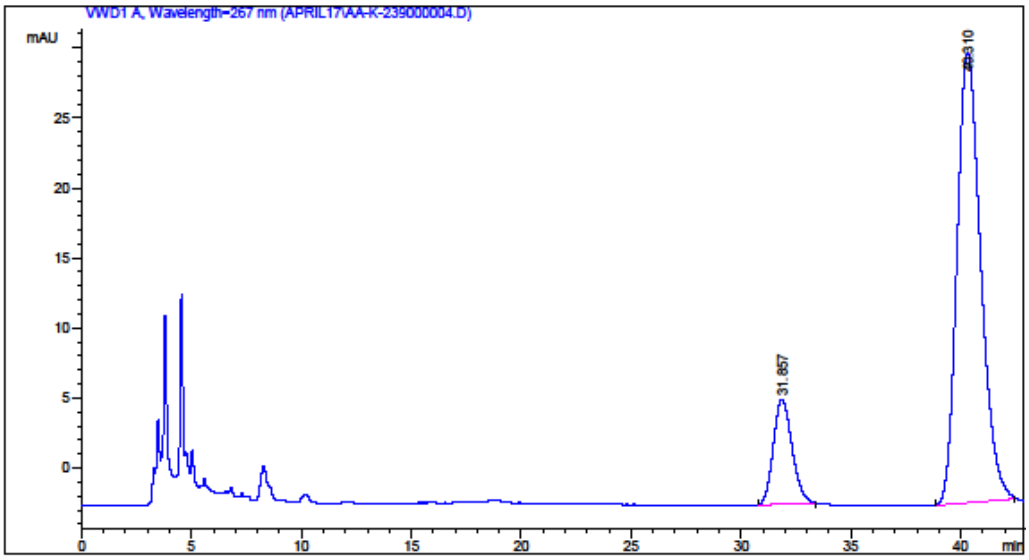



```
    ======================================================================
                            Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: VWD1 A, Wavelength=267 nm

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]  mAU   *s    [mAU   ]      %
    ----|-------|----|-------|----------|----------|--------|
       1  31.897 MM    0.9365   59.16309    1.05288  19.1598
       2  40.484 BB    1.0594  249.62488    3.42739  80.8402

    Totals :                  308.78797    4.48028

    ======================================================================
                            *** End of Report ***

Instrument 1 6/17/2017 6:02:14 PM Arsu                          Page   1 of 1
```

Figure C.2.5 HPLC chromatogram of the nitroaldol reaction of 4-NO_2-benzaldehyde using **$Cu(NO_3)_2$ 2($C_4H_5O_2$) in TBME (6a)**

Data File C:\CHEM32\1\DATA\APRIL17\AA-K-239000004.D
Sample Name: AA-k-239

```
Acq. Operator    : Arzu
Acq. Instrument  : Instrument 1                    Location : Vial 1
Injection Date   : 4/9/2017 7:43:20 PM
Method           : C:\CHEM32\1\METHODS\GAMZE.M
Last changed     : 7/14/2015 2:59:52 PM by Arzu
Sample Info      : 90:10 Hex/IPA, 267nm, 1.0 ml/min
```



Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=267 nm

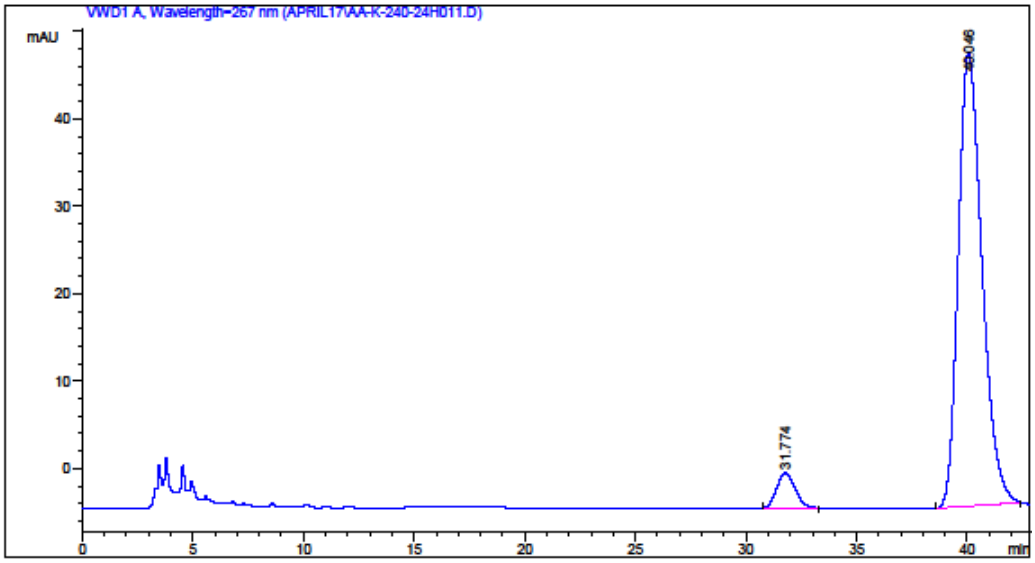
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	31.857	BB	0.9133	447.39334	7.47974	15.6571
2	40.310	BB	1.1708	2410.04614	32.12366	84.3429
Totals :				2857.43948	39.60340	

*** End of Report ***

Instrument 1 6/17/2017 6:02:41 PM Arzu Page 1 of 1

Figure C.2.6 HPLC chromatogram of the nitroaldol reaction of 4-NO_2-benzaldehyde using **$Cu(NO_3)_2$ 2($C_4H_5O_2$) in hexane** (**6a**)

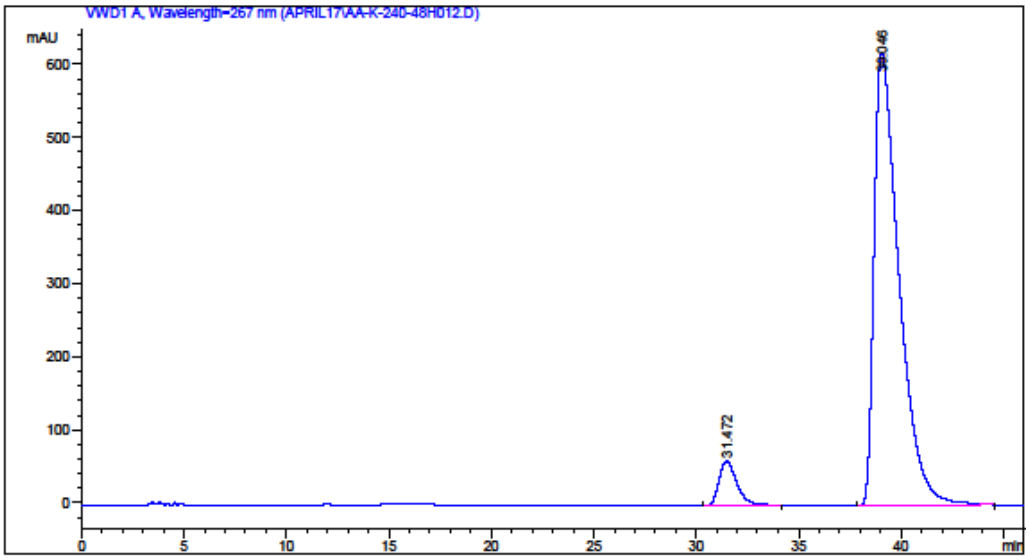
```
Data File C:\CHEM32\1\DATA\APRIL17\AA-K-240-24H011.D
Sample Name: AA-k-240-24h

    ======================================================================
    Acq. Operator    : Arzu
    Acq. Instrument : Instrument 1                    Location : Vial 1
    Injection Date  : 4/13/2017 7:20:15 PM
    Method          : C:\CHEM32\1\METHODS\GAMZE.M
    Last changed    : 7/14/2015 2:59:52 PM by Arzu
    Sample Info     : 90:10 Hex/IPA, 267nm, 1.0 ml/min
```




```
    ======================================================================
                           Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: VWD1 A, Wavelength=267 nm

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]  mAU   *s   [mAU   ]      %
    ----|-------|----|-------|----------|----------|--------|
       1  31.774 BB    0.8520  234.70467    4.01727   5.7077
       2  40.046 BB    1.1556 3877.35693   51.98341  94.2923

    Totals :                  4112.06160   56.00068


    ======================================================================
                              *** End of Report ***

Instrument 1 6/17/2017 6:03:08 PM Arzu                          Page   1 of 1
```

Figure C.2.7 HPLC chromatogram of the nitroaldol reaction of 4-NO_2-benzaldehyde using **$Cu(NO_3)_2$ $2(C_4H_5O_2)$ in EtOH 24 h (6a)**

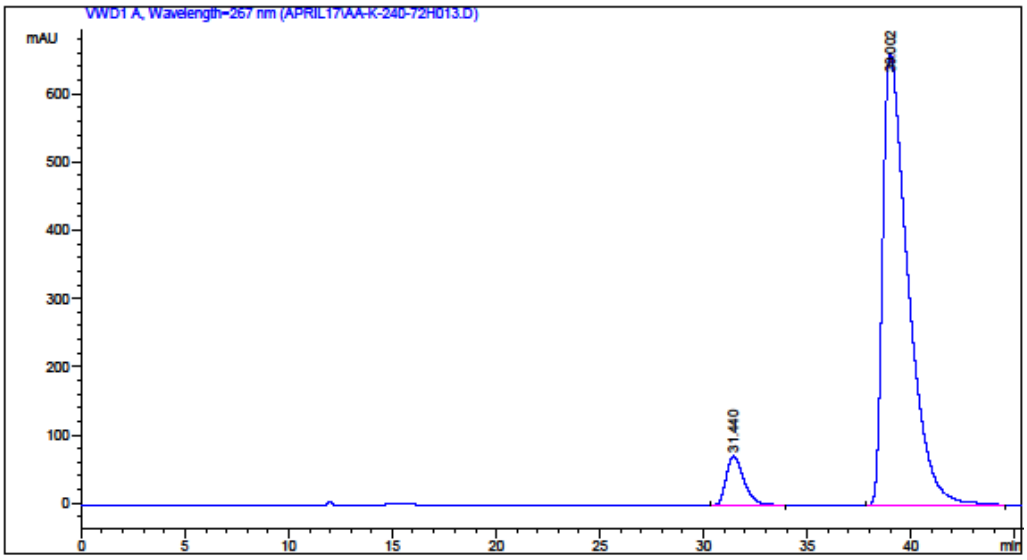
```
Data File C:\CHEM32\1\DATA\APRIL17\AA-K-240-48H012.D
Sample Name: AA-k-240-48H

==========================================================================
Acq. Operator   : Arzu
Acq. Instrument : Instrument 1                    Location : Vial 1
Injection Date  : 4/13/2017 8:09:39 PM
Method          : C:\CHEM32\1\METHODS\GAMZE.M
Last changed    : 7/14/2015 2:59:52 PM by Arzu
Sample Info     : 90:10 Hex/IPA, 267nm, 1.0 ml/min
```




```
==========================================================================
                        Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=267 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s   [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  31.472 BB    0.9340 3720.12842   60.89703   6.6203
   2  39.046 BB    1.2258 5.24723e4   620.24609  93.3797

Totals :                  5.61924e4   681.14312

==========================================================================
                        *** End of Report ***

Instrument 1 6/17/2017 6:03:40 PM Arzu                    Page   1 of 1
```

Figure C.2.8 HPLC chromatogram of the nitroaldol reaction of 4-NO_2-benzaldehyde using **$Cu(NO_3)_2$ 2($C_4H_5O_2$) in EtOH 48 h** (**6a**)

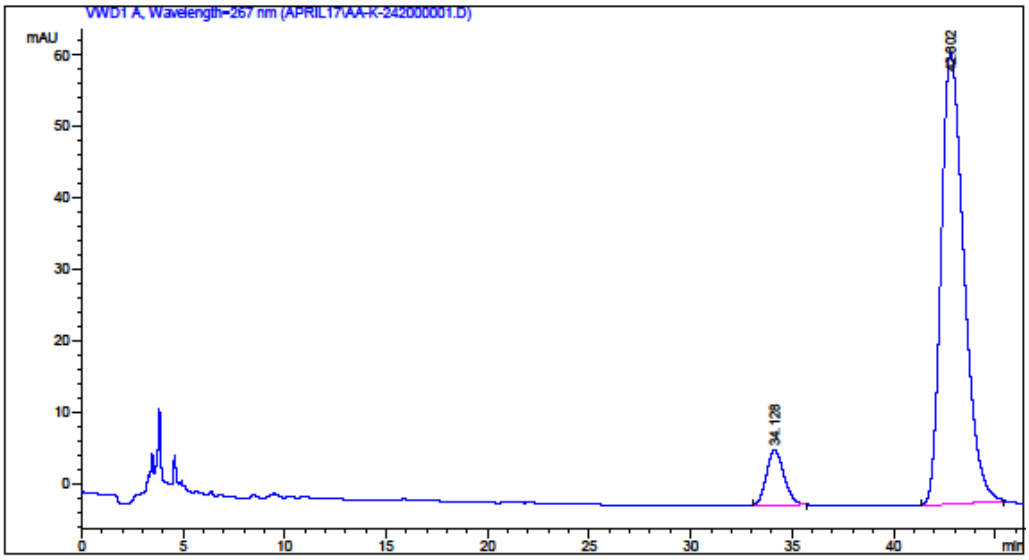
```
Data File C:\CHEM32\1\DATA\APRIL17\AA-K-240-72H013.D
Sample Name: AA-k-240-72H

==========================================================================
Acq. Operator   : Arzu
Acq. Instrument : Instrument 1                    Location : Vial 1
Injection Date  : 4/13/2017 8:57:34 PM
Method          : C:\CHEM32\1\METHODS\GAMZE.M
Last changed    : 7/14/2015 2:59:52 PM by Arzu
Sample Info     : 90:10 Hex/IPA, 267nm, 1.0 ml/min
```




```
==========================================================================
                        Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=267 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s    [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  31.440 BB    0.9274 4419.79590   72.73190   7.3071
   2  39.002 BB    1.2594 5.60664e4   663.63580  92.6929

Totals :                  6.04862e4   736.36771

==========================================================================
                        *** End of Report ***

Instrument 1 6/17/2017 6:04:02 PM Arzu                        Page   1 of 1
```

Figure C.2.9 HPLC chromatogram of the nitroaldol reaction of 4-NO_2-benzaldehyde using **$Cu(NO_3)_2$ 2($C_4H_5O_2$) in EtOH 72 h** (**6a**)

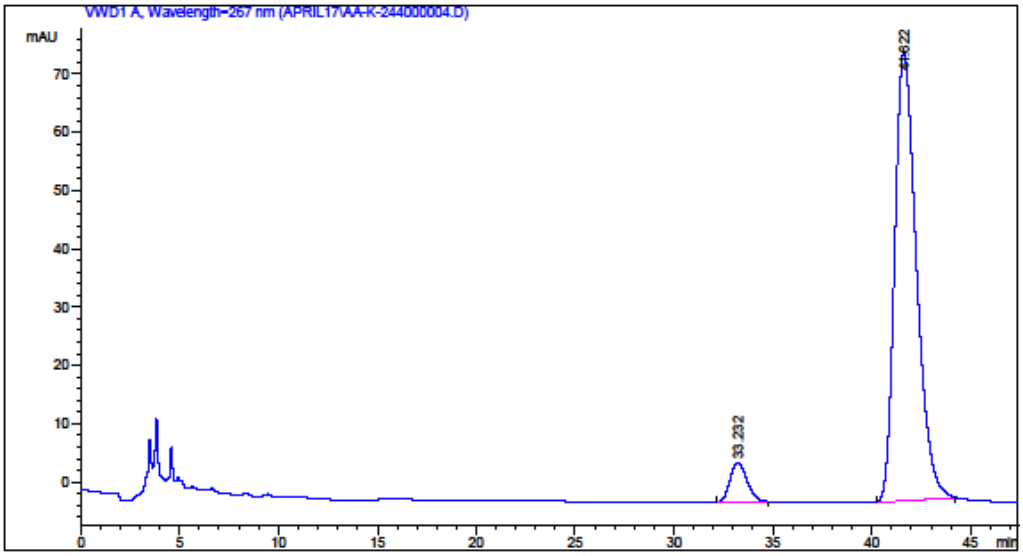
```
Data File C:\CHEM32\1\DATA\APRIL17\AA-K-242000001.D
Sample Name: AA-k-242

==========================================================================
Acq. Operator    : Arzu
Acq. Instrument : Instrument 1                    Location : Vial 1
Injection Date  : 4/16/2017 2:49:23 PM
Method          : C:\CHEM32\1\METHODS\GAMZE.M
Last changed    : 7/14/2015 2:59:52 PM by Arzu
Sample Info     : 90:10 Hex/IPA, 267nm, 1.0 ml/min
```




```
==========================================================================
                        Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=267 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s   [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  34.128 BB    0.9176  470.37173    7.72017   8.6975
   2  42.802 BB    1.1946 4937.77539   63.15529  91.3025

Totals :                  5408.14713   70.87546

==========================================================================
                        *** End of Report ***

Instrument 1 6/17/2017 6:05:05 PM Arzu                    Page   1 of 1
```

Figure C.2.10 HPLC chromatogram of the nitroaldol reaction of 4-NO_2-benzaldehyde **in EtOH** with **2.5 % mol** catalyst loading (**6a**)

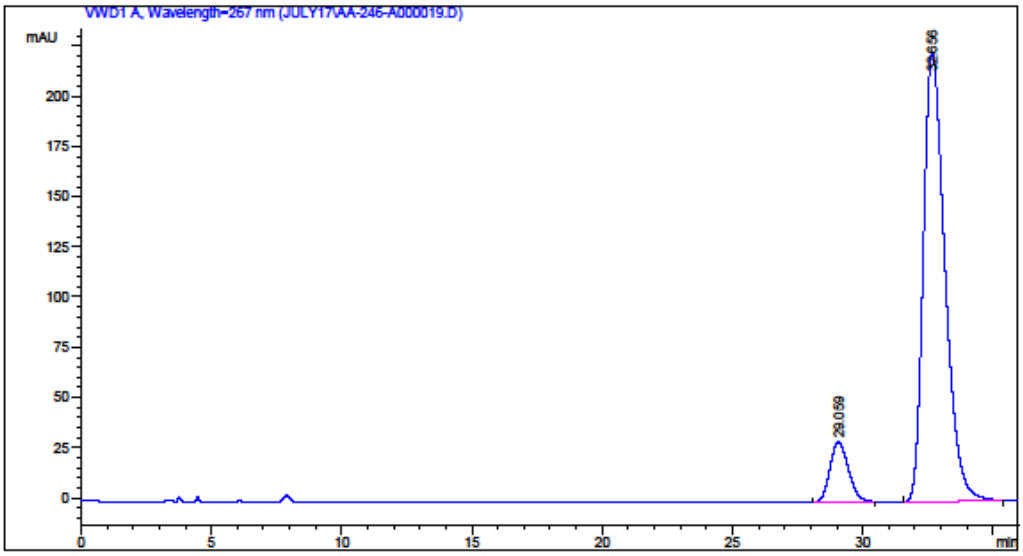
```
Data File C:\CHEM32\1\DATA\APRIL17\AA-K-244000004.D
Sample Name: AA-k-244

==========================================================================
Acq. Operator    : Arsu
Acq. Instrument : Instrument 1                    Location : Vial 1
Injection Date  : 4/18/2017 12:13:16 PM
Method          : C:\CHEM32\1\METHODS\GAMZE.M
Last changed    : 7/14/2015 2:59:52 PM by Arsu
Sample Info     : 90:10 Hex/IPA, 267nm, 1.0 ml/min
```




```
==========================================================================
                        Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=267 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s    [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  33.232 BB    0.9073  407.10675    6.82256   6.4779
   2  41.622 BB    1.1663 5877.41504   77.07104  93.5221

Totals :                  6284.52179   83.89361

==========================================================================
                        *** End of Report ***

Instrument 1 6/17/2017 6:05:57 PM Arsu                        Page   1 of 1
```

Figure C.2.11 HPLC chromatogram of the nitroaldol reaction of 4-NO_2-benzaldehyde **in EtOH with 10 % mol** catalyst loading (**6a**)

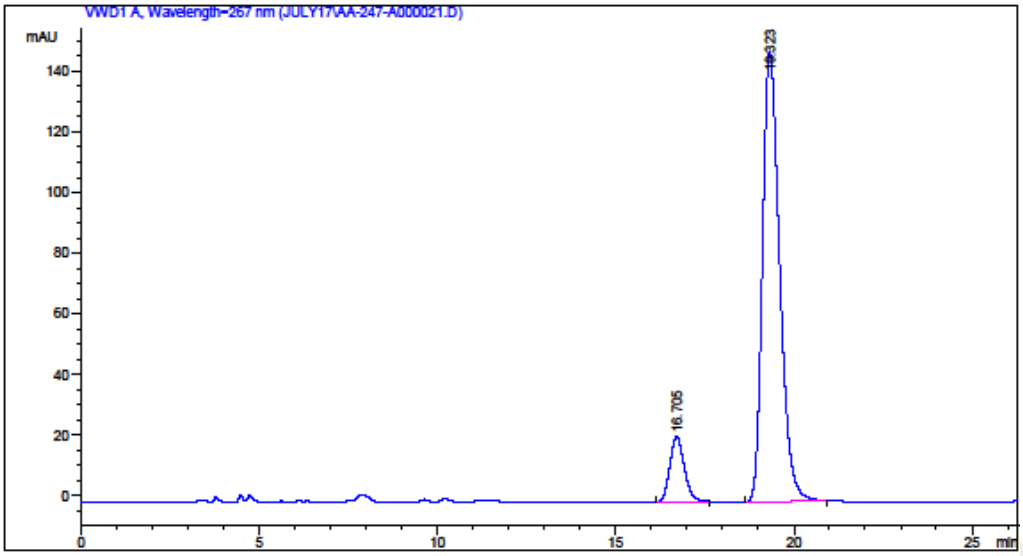
```
Data File C:\CHEM32\1\DATA\JULY17\AA-246-A000019.D
Sample Name: aa-246-a

==========================================================================
Acq. Operator   : Arzu
Acq. Instrument : Instrument 1                    Location : Vial 1
Injection Date  : 7/28/2017 1:22:41 PM
Method          : C:\CHEM32\1\METHODS\GAMZE.M
Last changed    : 7/14/2015 2:59:52 PM by Arzu
Sample Info     : 90:10 Hex/IPA, 267nm, 1.0 ml/min
```




```
==========================================================================
                        Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=267 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s   [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  29.059 BB    0.7687 1491.86084   30.11474  10.3898
   2  32.656 BB    0.8876 1.28670e4   223.83784  89.6102

Totals :                  1.43589e4   253.95258


==========================================================================
                          *** End of Report ***

Instrument 1 8/3/2017 2:13:03 PM Arzu                        Page   1 of 1
```

Figure C.2.12 HPLC chromatogram of the nitroaldol reaction of 3-NO_2-benzaldehyde using $Cu(NO_3)_2$ $2(C_4H_5O_2)$ in EtOH with 5 % mol catalyst loading (**6b**)

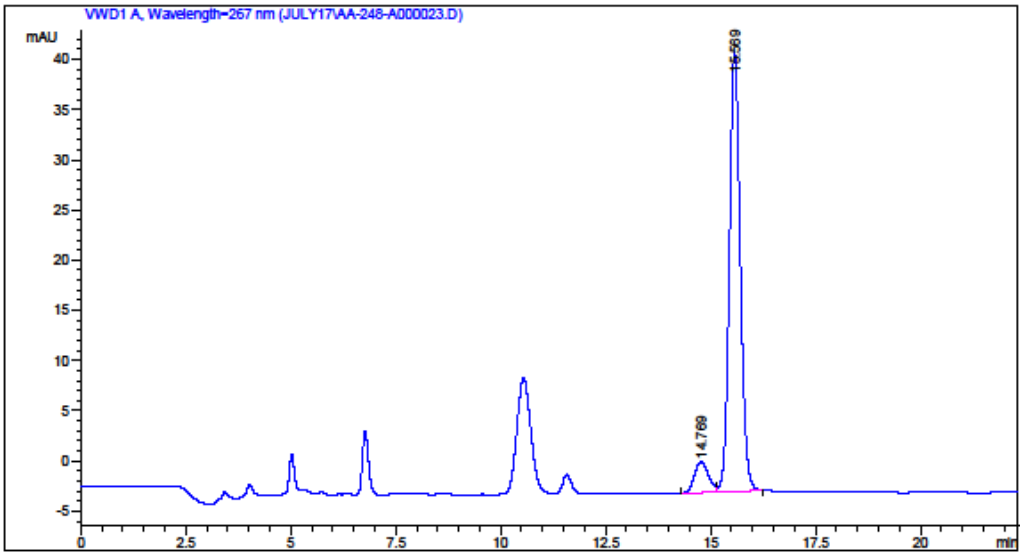
```
Data File C:\CHEM32\1\DATA\JULY17\AA-247-A000021.D
Sample Name: aa-247-a

==================================================================
Acq. Operator    : Arzu
Acq. Instrument : Instrument 1                    Location : Vial 1
Injection Date  : 7/28/2017 2:22:57 PM
Method          : C:\CHEM32\1\METHODS\GAMZE.M
Last changed    : 7/14/2015 2:59:52 PM by Arzu
Sample Info     : 90:10 Hex/IPA, 267nm, 1.0 ml/min
```




```
==================================================================
                      Area Percent Report
==================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=267 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s    [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  16.705 BB    0.4374  610.96344   21.52797  10.9803
   2  19.323 BB    0.5145 4953.22900  148.46349  89.0197

Totals :                  5564.19244  169.99145

==================================================================
                      *** End of Report ***

Instrument 1 8/3/2017 2:15:05 PM Arzu                    Page   1 of 1
```

Figure C.2.13 HPLC chromatogram of the nitroaldol reaction of 2-NO_2-benzaldehyde using $Cu(NO_3)_2$ $2(C_4H_5O_2)$ in EtOH with 5 % mol catalyst loading (**6c**)

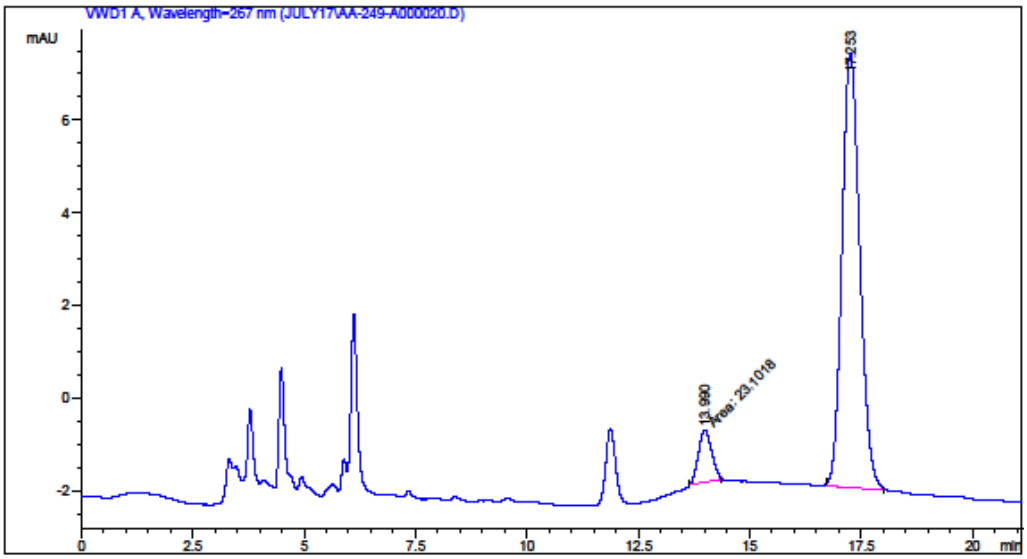
```
Data File C:\CHEM32\1\DATA\JULY17\AA-248-A000023.D
Sample Name: aa-248-a

==========================================================================
Acq. Operator    : Arzu
Acq. Instrument : Instrument 1                    Location : Vial 1
Injection Date  : 7/28/2017 3:21:13 PM
Acq. Method     : C:\CHEM32\1\METHODS\GAMZE.M
Last changed    : 7/28/2017 3:19:24 PM by Arzu
                  (modified after loading)
Analysis Method : C:\CHEM32\1\METHODS\GAMZE.M
Last changed    : 7/14/2015 2:59:52 PM by Arzu
Sample Info     : 95:5 Hex/IPA, 267nm, 1.0 ml/min
```




```
==========================================================================
                        Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=267 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s   [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  14.769 BV    0.3717   73.06513    3.06061   8.4738
   2  15.569 VB    0.2775  789.18494   43.73854  91.5262

Totals :                  862.25007   46.79916

Instrument 1 8/3/2017 2:20:57 PM Arzu                    Page   1 of 2
```

Figure C.2.14 HPLC chromatogram of the nitroaldol reaction of 2-Cl-benzaldehyde using $Cu(NO_3)_2$ $2(C_4H_5O_2)$ in EtOH with 5 % mol catalyst loading (**6d**)

```
Data File C:\CHEM32\1\DATA\JULY17\AA-249-A000020.D
Sample Name: aa-249-a

================================================================================
Acq. Operator    : Arzu
Acq. Instrument : Instrument 1                    Location : Vial 1
Injection Date  : 7/28/2017 2:00:09 PM
Method          : C:\CHEM32\1\METHODS\GAMZE.M
Last changed    : 7/14/2015 2:59:52 PM by Arzu
Sample Info     : 90:10 Hex/IPA, 267nm, 1.0 ml/min
```




```
================================================================================
                          Area Percent Report
================================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=267 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s    [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  13.990 MM    0.3445   23.10181    1.11755   8.1256
   2  17.253 BB    0.4323  261.20679    9.38900  91.8744

Totals :                  284.30860   10.50655

================================================================================
                          *** End of Report ***

Instrument 1 8/3/2017 2:24:49 PM Arzu                          Page   1 of 1
```

Figure C.2.15 HPLC chromatogram of the nitroaldol reaction of 4-Cl-benzaldehyde using $Cu(NO_3)_2$ $2(C_4H_5O_2)$ in EtOH with 5 % mol catalyst loading (**6e**)

```
Data File C:\CHEM32\1\DATA\JULY17\AA-250-A000027.D
Sample Name: aa-250-a

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Acq. Instrument : Instrument 1                    Location : Vial 1
Injection Date  : 8/1/2017 1:07:47 PM
Method          : C:\CHEM32\1\METHODS\GAMZE.M
Last changed    : 7/14/2015 2:59:52 PM by Arzu
Sample Info     : 95:5 Hex/IPA, 267nm, 1.0 ml/min
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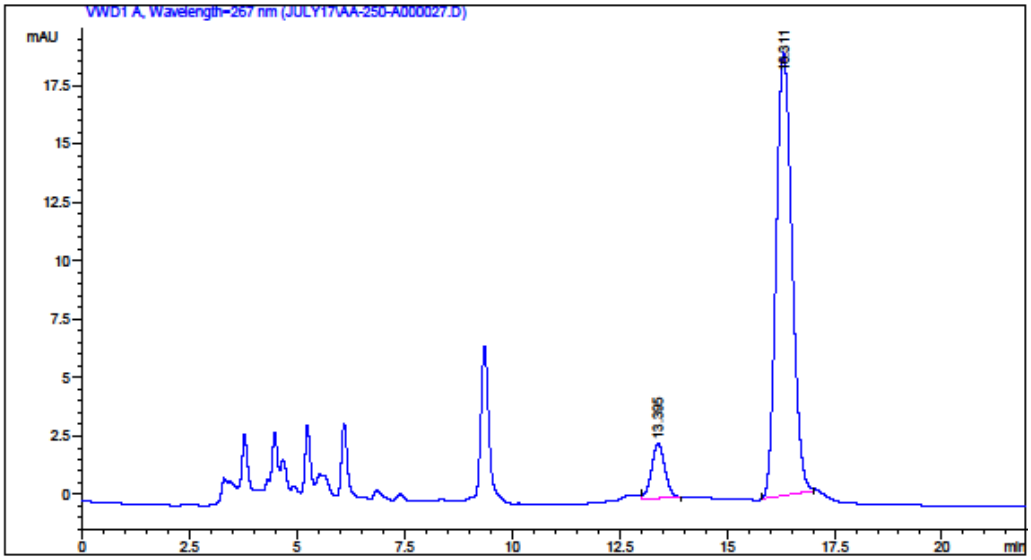


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                        Area Percent Report
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Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=267 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s   [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  13.395 BB    0.3289   51.14091    2.37006   9.5363
   2  16.311 BB    0.3985  485.13556   18.98863  90.4637

Totals :                   536.27647   21.35869


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                        *** End of Report ***

Instrument 1 8/3/2017 2:28:25 PM Arzu                        Page   1 of 1
```

Figure C.2.16 HPLC chromatogram of the nitroaldol reaction of 4-Me-benzaldehyde using $Cu(NO_3)_2$ $2(C_4H_5O_2)$ in EtOH with 5 % mol catalyst loading (**6f**)

```
Data File C:\CHEM32\1\DATA\JULY17\AA-251-A000026.D
Sample Name: aa-251-a

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Method          : C:\CHEM32\1\METHODS\GAMZE.M
Last changed    : 7/14/2015 2:59:52 PM by Arsu
Sample Info     : 95:5 Hex/IPA, 267nm, 1.0 ml/min
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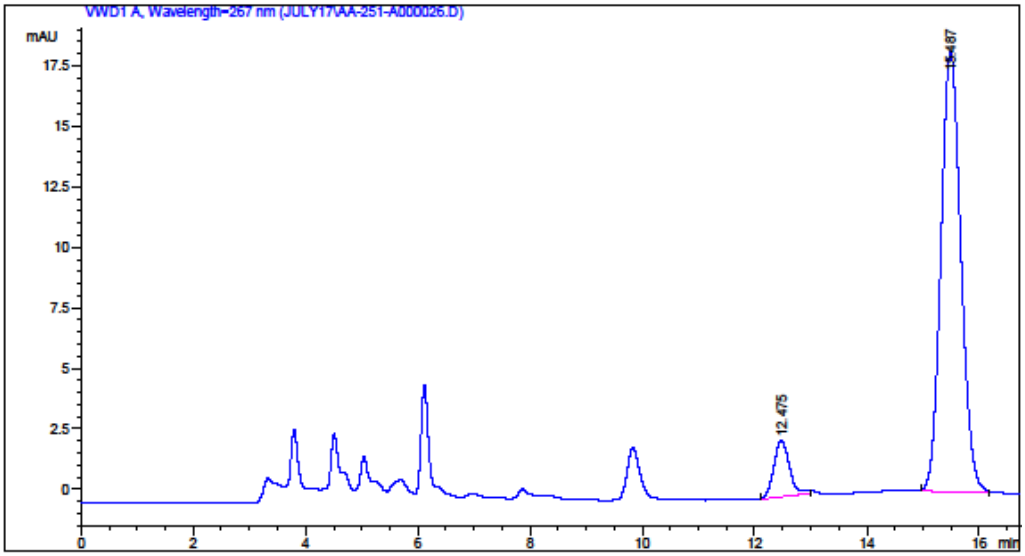


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Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=267 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s    [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  12.475 BB    0.3011   45.62451    2.33125   9.2321
   2  15.487 BB    0.3850  448.56876   18.20385  90.7679

Totals :                  494.19326   20.53511

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                        *** End of Report ***

Instrument 1 8/3/2017 2:33:05 PM Arsu                    Page   1 of 1
```

Figure C. 2. 17 HPLC chromatogram of the nitroaldol reaction of 4-Et-benzaldehyde using $Cu(NO_3)_2\,2(C_4H_5O_2)$ in EtOH with 5 % mol catalyst loading (**6g**)

```
Data File C:\CHEM32\1\DATA\JULY17\AA-252-A000022.D
Sample Name: aa-252-a

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Acq. Instrument : Instrument 1                    Location : Vial 1
Injection Date  : 7/28/2017 2:51:02 PM
Method          : C:\CHEM32\1\METHODS\GAMZE.M
Last changed    : 7/14/2015 2:59:52 PM by Arzu
Sample Info     : 90:10 Hex/IPA, 267nm, 1.0 ml/min
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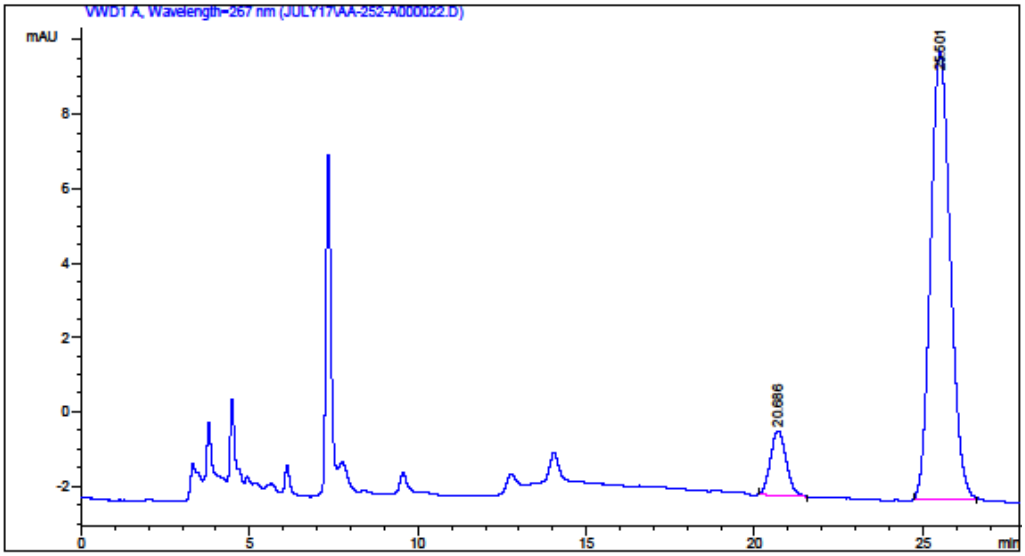


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==========================================================================
                        Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=267 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s    [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  20.686 BB    0.5089   56.65972    1.74285  10.3699
   2  25.501 BB    0.6326  489.72665   12.05607  89.6301

Totals :                   546.38637   13.79891

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                        *** End of Report ***

Instrument 1 8/3/2017 2:38:37 PM Arzu                    Page   1 of 1
```

Figure C.2.18 HPLC chromatogram of the nitroaldol reaction of 4-OMe-benzaldehyde using $Cu(NO_3)_2$ $2(C_4H_5O_2)$ in EtOH with 5 % mol catalyst loading (**6h**)

```
Data File C:\CHEM32\1\DATA\JULY17\AA-254-A000024.D
Sample Name: aa-254-a

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Injection Date  : 8/1/2017 12:11:09 PM
Method          : C:\CHEM32\1\METHODS\GAMZE.M
Last changed    : 7/14/2015 2:59:52 PM by Arsu
Sample Info     : 95:5 Hex/IPA, 267nm, 1.0 ml/min
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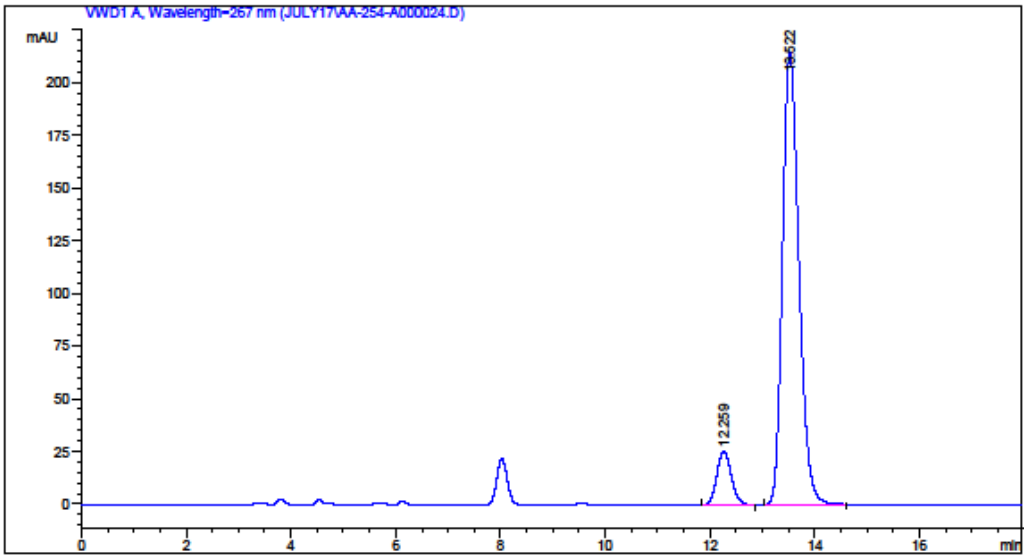


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                        Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=267 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s   [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  12.259 BB    0.2964  496.29047   25.90009   9.6124
   2  13.522 BB    0.3351 4666.73779  214.73337  90.3876

Totals :                  5163.02826  240.63346

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                        *** End of Report ***

Instrument 1 8/3/2017 2:49:10 PM Arsu                        Page   1 of 1
```
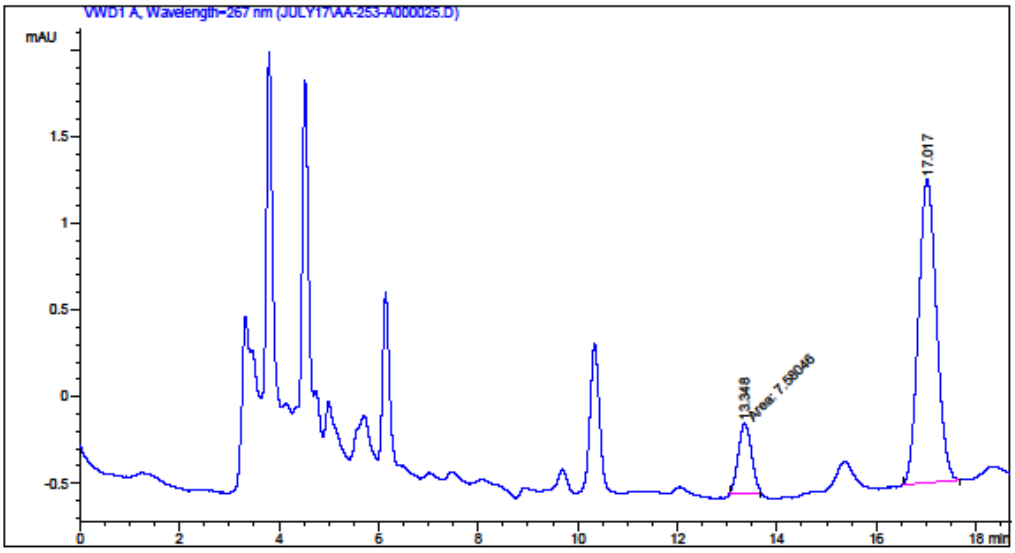

Figure C.2.19 HPLC chromatogram of the nitroaldol reaction of 2-OMe-benzaldehyde using $Cu(NO_3)_2$ $2(C_4H_5O_2)$ in EtOH with 5 % mol catalyst loading (**6i**)

```
Data File C:\CHEM32\1\DATA\JULY17\AA-253-A000025.D
Sample Name: aa-253-a

=====================================================================
Acq. Operator   : Arsu
Acq. Instrument : Instrument 1                    Location : Vial 1
Injection Date  : 8/1/2017 12:30:16 PM
Method          : C:\CHEM32\1\METHODS\GAMZE.M
Last changed    : 7/14/2015 2:59:52 PM by Arsu
Sample Info     : 95:5 Hex/IPA, 267nm, 1.0 ml/min
```




```
=====================================================================
                        Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=267 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s    [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  13.348 MM    0.3111    7.58046 4.06124e-1  14.7653
   2  17.017 BB    0.3825   43.75909    1.74677  85.2347

Totals :                   51.33955    2.15289

=====================================================================
                          *** End of Report ***

Instrument 1 8/3/2017 2:46:28 PM Arsu                    Page   1 of 1
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Figure C.2.20 HPLC chromatogram of the nitroaldol reaction of benzaldehyde using $Cu(NO_3)_2$ $2(C_4H_5O_2)$ in EtOH with 5 % mol catalyst loading (**6j**)

5. SUBSTITUENT EFFECTS IN BIDENTATE "NO" LIGANDS DERIVED FROM CHIRAL AMINES

5.1 General Information of Chiral Building Blocks

As demand for enantiomerically pure compounds continues to increase, work in the field of asymmetric synthesis is increasing day by day. Research scientists who use building blocks to develop new and different chiral auxiliaries, ligands, or to obtain advanced and enantiomerically enriched molecules need to faithfully access new chiral building blocks and architectures to obtain success.

Chiral building blocks such as alcohols, diols, amines, pyrrolidines, epoxides are commercially available (Chiral building blocks, 2017) for use as starting materials or as ligands in synthesizing both pure stereoisomers and in the synthesis of intermediates (Figure 5.1).

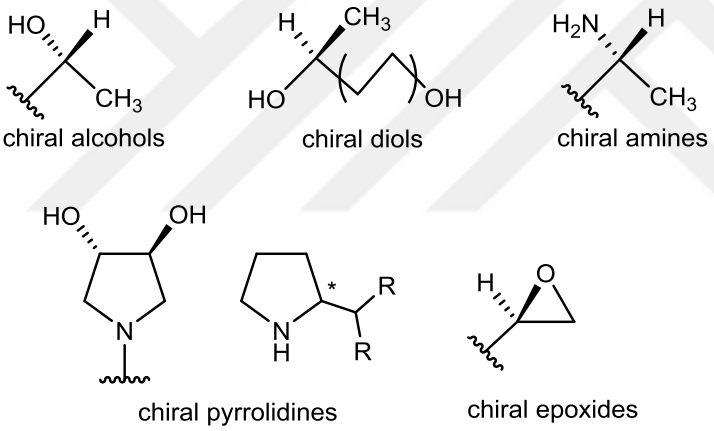
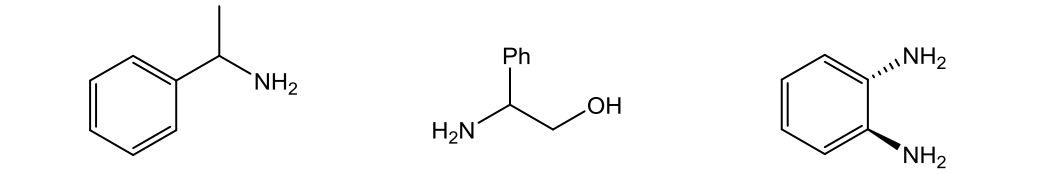


Figure 5.1 Some of chiral building blocks

5.1.1 Synthesis methodologies of chiral amines

Chiral amines are used in many areas, such as pharmaceutical drugs, natural products, agrochemicals and building blocks used in the chemical industry (Jacques et al., 1981; Whitesell, 1989; Vogl et al., 1999; Nogradi, 1995). For this reason, a lot of methodologies have been developed for the synthesis of chiral amines. Obtaining enantiomerically pure products with high yields is important for both academic and industrial production (Figure 5.2).



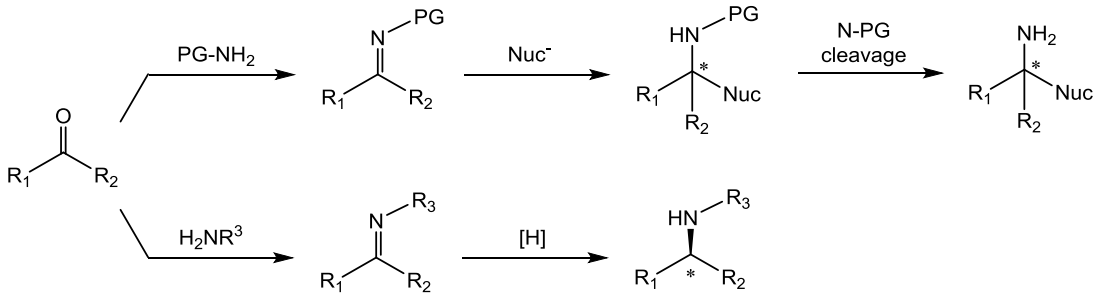
(*R*)- or (*S*)-a-methylbenzylamine (*R*)-or (*S*)-phenylglycinol (1*S*,2*S*)-cyclohexane 1,2-diamine

Figure 5.2 Some of the commercially available chiral amines

Many methods of synthesis have been applied to chiral amines. Conventional synthesis methods known to date include carbonyl addition, enantioselective reduction, hydroamination, hydrogenation and organocatalytic reactions. Biocatalytic-enzymatic reactions are a method that facilitates synthesis from simple and inexpensive ways that continue to gain importance in recent years (Nugent, 2010).

5.1.1.1. From carbonyl compounds

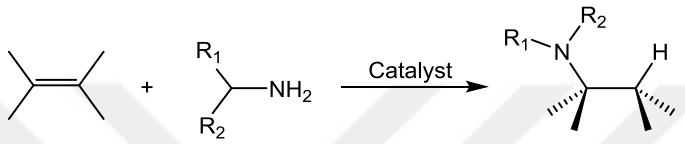
The preparation of α-chiral amines from carbonyl compounds such as ketones and aldehydes, requires three steps. The first is the formation of imine; the second is nucleophilic addition; the third is protecting or activating group decomposition. Chiral amines can be obtained by reduction of the imine intermediates obtained on prochiral ketones. Synthesis methods that are frequently used today; hydrogenation (Morrison, 1983), hydrosilylation (Reding and Buchwald, 1998), organocatalytic reduction (Hoffman et al., 2005), asymmetric transfer hydrogenation (Samec et al., 2006). All of the reactions can be illustrated below in scheme 5.1.



Scheme 5.1 Chiral amine synthesis from carbonyl derivative compounds

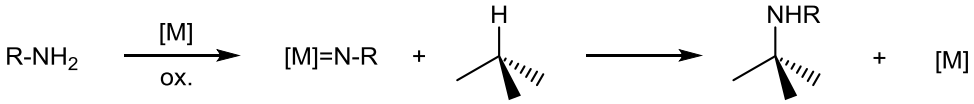
5.1.1.2. From hydroamination reactions

Chiral amines can be obtained from simple and economical routes, with an alkene and amine in the hydroamination reaction. Not only alkenes, but also those containing multiple carbon double bonds, such as 1,3-dienes, have been obtained with suitable catalyst systems and bioactive substances (Roesky and Muller, 2003; Aillaud et al., 2007). The hydroamination reactions shown in scheme 5.2 have also led to the introduction of important catalyst systems. Catalytic systems using the main group metals and transition group metals and bronsted acids were used (Hultzsch, 2005).



Scheme 5.2 Illustration of the general hydroamination reactions

The conversion of the carbon-hydrogen bond to the carbon-nitrogen bond with the use of metal catalysts is an important method of amination. In these reactions, the transition metal and the substrate do not react directly, but interact with the metal-nitrile product. Studies using ruthenium and rhodium metal complexes are quite striking because they have selectivity-providing amination reactions. (Che et al., 2004; Du Bois et al., 2001). The overall reaction is shown in scheme 5.3.

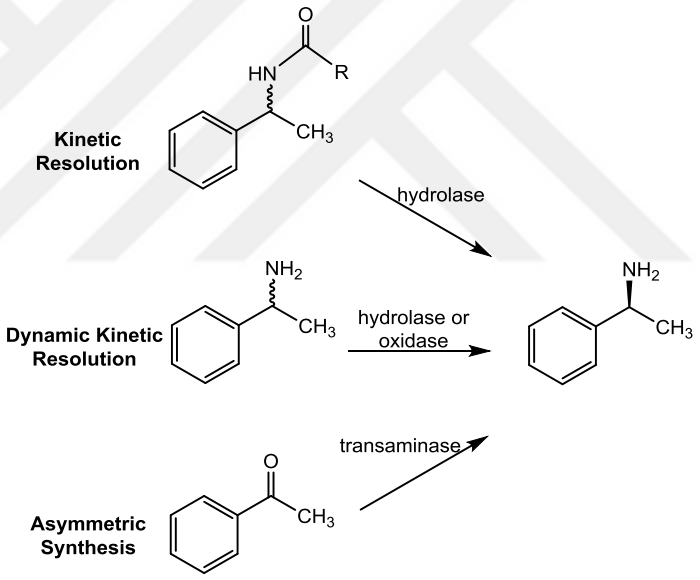


Scheme 5.3 Metal-catalyzed C-H amination reaction

5.1.1.3. From biocatalytic routes

The advantages of biocatalytic methods over traditional synthesis methods have been increasing in recent years. Biochemical catalysts are non-toxic, cheap, selective, easy to recycle, and complement the reaction with high efficiency. These structures are used in many areas such as biofuels, food, and health. When chiral amines are obtained by biocatalytic methods, enantioselectivity can be achieved by enzyme catalysis and high catalytic activity is observed.

Kinetic resolution, dynamic kinetic resolution, and asymmetric synthesis are used in the synthesis of chiral molecules, while microbial cells and enzyme classes derived from these cells can be used as biocatalysts. In order to be able to give information about these methods, studies carried out for synthesizing α-methylbenzylamine can be examined (Scheme 5.4). The resolution of racemic amines with the presence of hyrolytic enzymes such as lipases and proteases was first performed by Kitaguchi et al. (Kitaguchi et al., 1989). Another study carried out the oxidation of amines with the amine oxidase copper-containing enzyme derived from Escherichia coli and Klebsiella oxytoca bacteria (Hacisalihoglu et al., 2000). The transaminase enzyme catalyzes the ketoacid reaction with an amino acid in the liver in the human body and leads to damage. Another research group have developed (*R*)- and (*S*)- selective transaminases in asymmetric synthesis, which are active with different aromatic and aliphatic amines (Matcham, G.W. and Bowen, 1996).

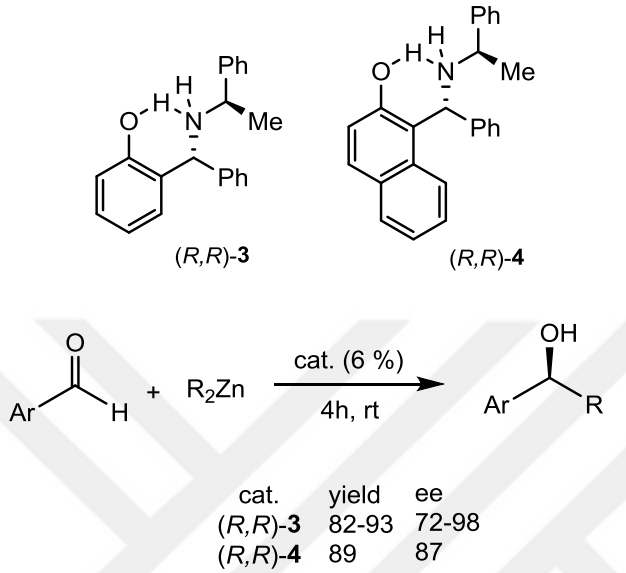


Scheme 5.4 Biocatalytic methods and biocatalysts used for synthesis of chiral amines

5.1.2 Catalytic reactions of ligands derived from chiral amines

The use of ligands derived from chiral amines for the asymmetric nucleophilic addition to carbonyl group-containing compounds of the organometallics is a great potential area in synthesis. Dialkylzinc derivatives (Arnott and Hunter, 2006), lithium compounds (Cimarelli et al., 2003) or Grignard reagents (Cimarelli, 2002) are used for organometal compounds.

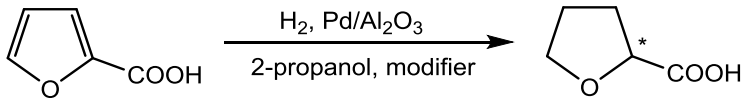
Palmieri used chiral ligands derived from secondary and tertiary amines to determine enantioselectivity towards carbonyl in the asymmetric diethylzinc addition reaction (Palmieri, 2000) As seen from scheme 5.5, in the reaction, which takes place in short time and under mild conditions, high enantiomeric excess values and yields were obtained.



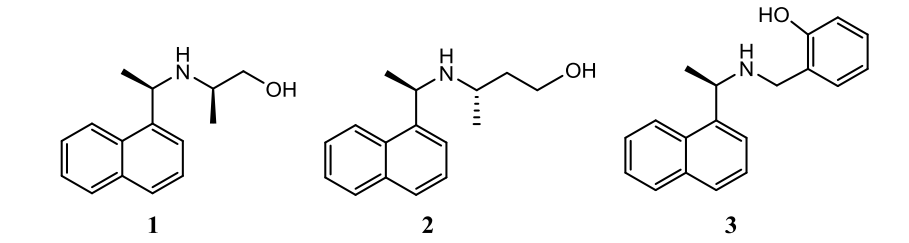
Scheme 5.5 Enantioselective catalyzed of aldehydes using organozinc reagents

Asymmetric hydrogenation of organic structures containing carbonyl groups is presently very large. As noted in the introduction, Knowles and Noyori were awarded the Nobel Prize in 2001 for their work in this area. Ru or Rh salts (Brunner et al., 2003) can be used for these transformations as well as modified systems of Pt or Pd with H_2 (Diezi et al., 2005; Orglmeister et al., 2005).

The application of range enantioselective hydrogenation by a platinum catalyst system modified with bidentate NO type ligands containing oxygen and nitrogen atoms was investigated by Maris and co-workers (Maris et al., 2004). Furan-2-carboxylic acid was investigated for transformations under mild conditions with chiral amines having a naphthyl ring and a Pd/Al_2O_3 system (Scheme 5.6). It was observed that the ligands used gave very low conversions and ee values (Figure 5.3).



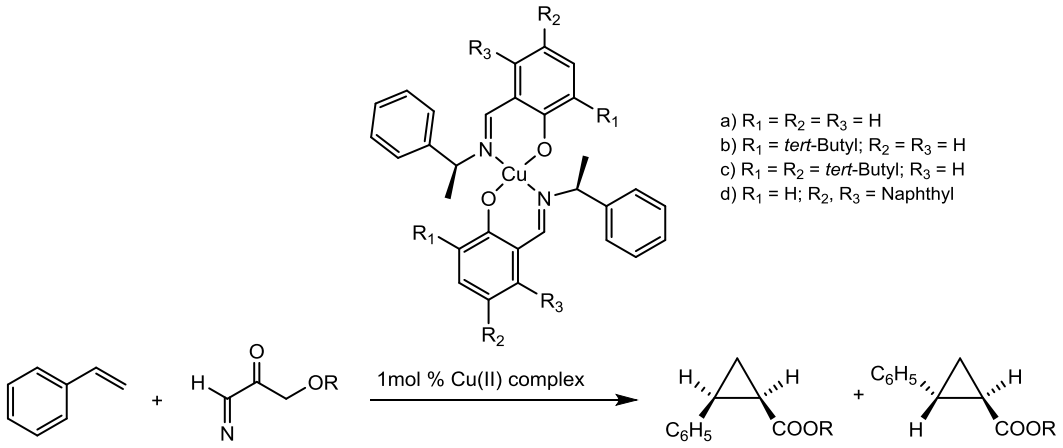
Scheme 5.6 Enantioselective hydrogenation of furan-2-carboxylic acid



Modifier	Conversion (%)	ee (%)
1	23	32
2	21	27
3	19	26
4	15	0
5	19	0
6	13	6
7	37	0

Figure 5.3 Conversion and ee values of enantioselective hydrogenation with H_2/ Pd/Al_2O_3

In addition to the different studies on the catalytic reactions of bidentate and tridentate ligands, another important asymmetric synthesis is the cyclopropanation of alkenes in which the catalytic activities of chiral ligands or metal complexes are measured. Schiff bases derived from chiral amines and substituted salicyl aldehydes and their copper (II) complexes were synthesized (Iglesias et al., 2004). The stereoselectivity and yields of the different chiral copper complexes is illustrated in scheme 5.7, for the asymmetric cyclopropanation of the styrene. The cyclopropanation reaction was carried out using diisooacetate of the styrenes and yields ranged from 59 to 89, while ee values were much less than expected.



Scheme 5.7 Structure of Cu complexes were synthesized by Iglesias et al.

5.1.3 NO Ligands in the Henry reaction

Chiral amines have found widespread application in asymmetric synthesis, for example in enantioselective deprotonation or hydrogenation, alkylation, enantioselective addition, cyclopropanation, isomerization reactions (Nugent, 2010). While the observation of enantioselectivity with high yield is expected in asymmetric synthesis (Title 5.1.2), the studies according to this issue have given variable results. These different results may be due to different substituents on the ligand, as well as natural mechanisms of preferred asymmetric reactions.

Bidentate ligands have been previously used in asymmetric Henry reactions, giving variable enantioselectivity and yield (Bez et al., 2013; Pedro et al., 2007). NO type bidentate ligands have been generally derived from 1,2- and 1,4- amino alcohol (Chen et al., 2017; Wang et al., 2014) (Figure 5.4).

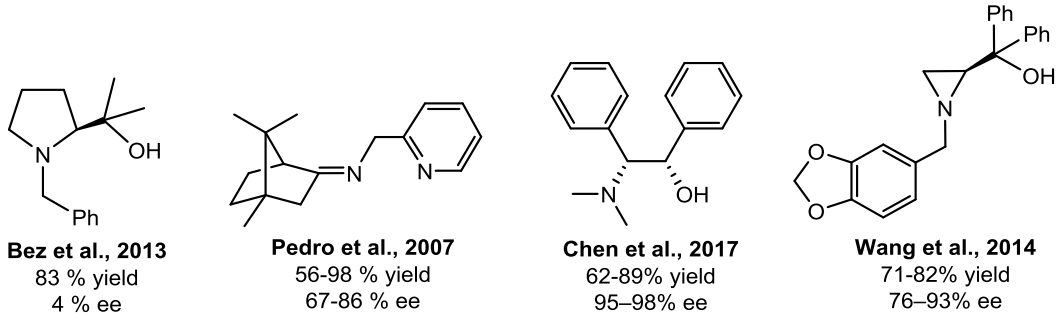


Figure 5.4 Bidentate ligands have been previously synthesized

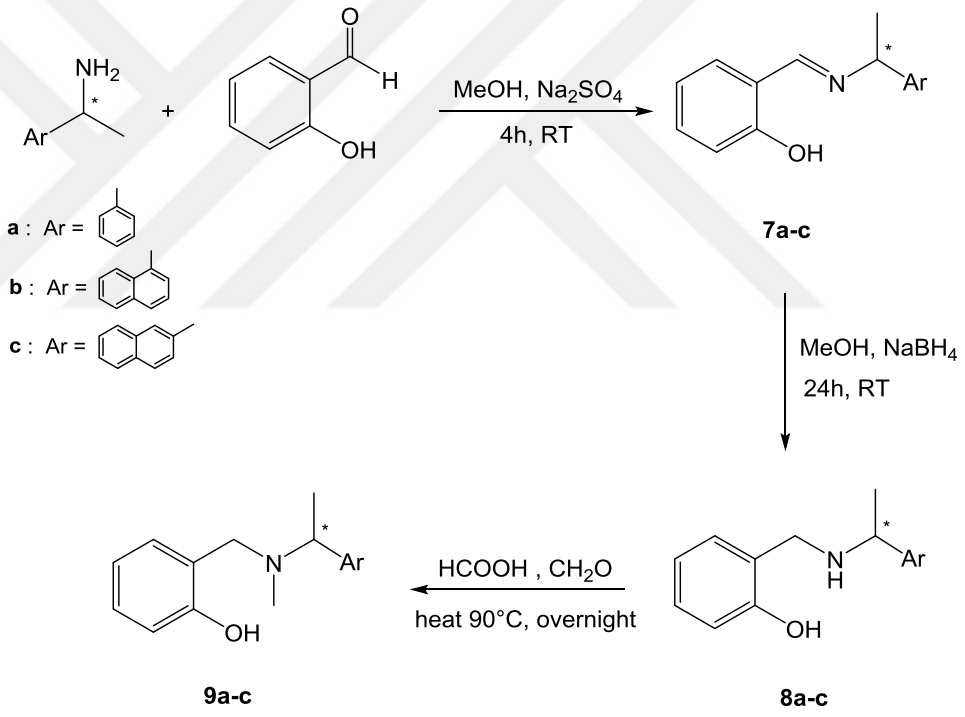
Therefore, we decided to prepare some bidentate NO type ligands to investigate in the Henry reaction.

5.2 Results and Discussion

The series of Schiff bases and aminophenol derivatives were prepared using chiral amine derivatives and salicyl aldehyde. The synthesized compounds were used as ligands in the presence of $Cu(OAc)_2.nH_2O$ in the Henry reaction.

5.2.1 Synthesis of bidentate ligands derived from chiral amines

Schiff bases (**7a-c**) derived from chiral amines and secondary aminophenol derivatives (**8a-c**), which could be obtained by the reduction of **7a-c**, were synthesized. Finally, the Eschweiler-Clarke reaction in the presence of formic acid and formaldehyde was carried out to prepare tertiary methylamines (**9a-c**) from the secondary amines (**8a-c**) obtained.



Scheme 5.8 General procedure of Schiff bases and aminophenol derivatives

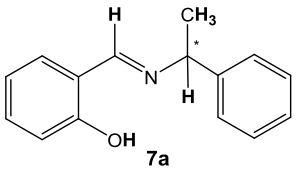
Selected physical properties, being melting points, yields and characteristic IR vibrations of the ligands **7a-c, 8a-c, 9a-c** are given in table 5.1. The Schiff base ligands **7a-c** were obtained as yellow crystals. Other ligands **8a-c, 9a-c** were obtained as yellow or colorless oil. All of the ligands were air stable compounds. They were soluble in polar solvents. The infrared spectra of the ligands showed several vibrations bands of different intensities in the 4000–400 cm^{-1} region.

The presence of the –C=N– groups in Schiff base ligands **7a-c** were confirmed with υ (C=N) vibrations between 1629 and 1627 cm^{-1}. The presence of the N-H groups in secondary aminophenols **8a-d** were confirmed with υ (N-H) stretching vibrations between 3384 and 3293 cm^{-1}. Tertiary aminophenols (**9a-c**) showed characteristic υ (C-N) vibrations between 1174-1150 cm^{-1}.

Table 5.1 Melting points, yields, IR vibrations of the compounds

Compound	Yield (%)	mp (°C)	IR (υ cm^{-1})
7a	86	75-76	1629 (C=N)
7b	93	89-90	1627 (C=N)
7c	89	126-127	1628 (C=N)
8a	80	-	3293 (N-H)
8b	88	-	3353 (N-H)
8c	93	117	3384 (N-H)
9a	50	-	1150 (C-N)
9b	57	-	1174 (C-N)
9c	51	-	1150 (C-N)

The characterization of the synthesized bidentate ligands were further verified with NMR spectroscopy. C-***H*** resonances of the imine bond were observed as singlet between 8.46-8.42 ppm for **7a-c**. C-$\boldsymbol{H_2}$ resonances of the secondary phenols **8a-c** were observed two doublets between 3.98-3.76 ppm. C-$\boldsymbol{H_3}$ resonances of tertiary methylamines **9a-c** were obtained singlet at 2.3-2.21 ppm. As examples, ^{1}H NMR spectra of the ligands **7a**, **8a**, **9a** are given below in figures 5.5, 5.6, 5.7. In the material and method part, their characterizations are given fully.



7a

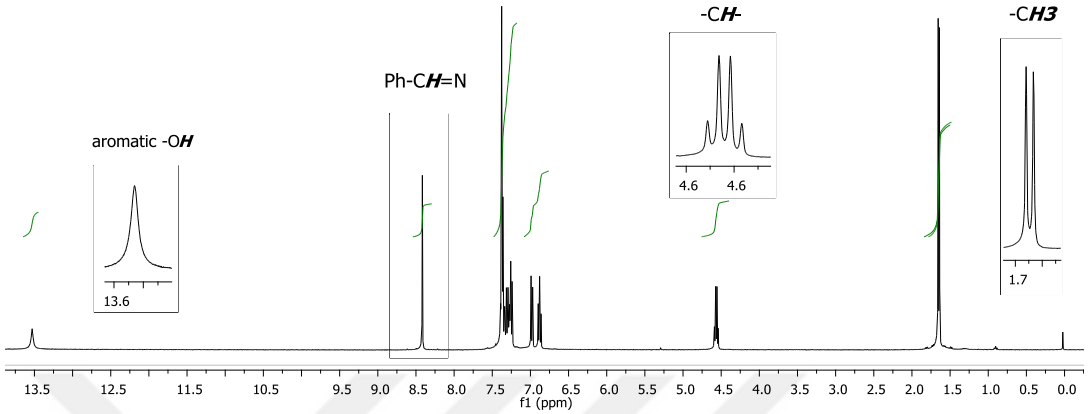
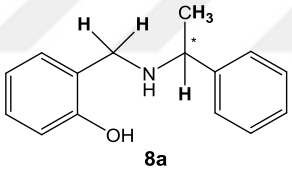


Figure 5.5 ^{1}H NMR of the ligand **7a**



8a

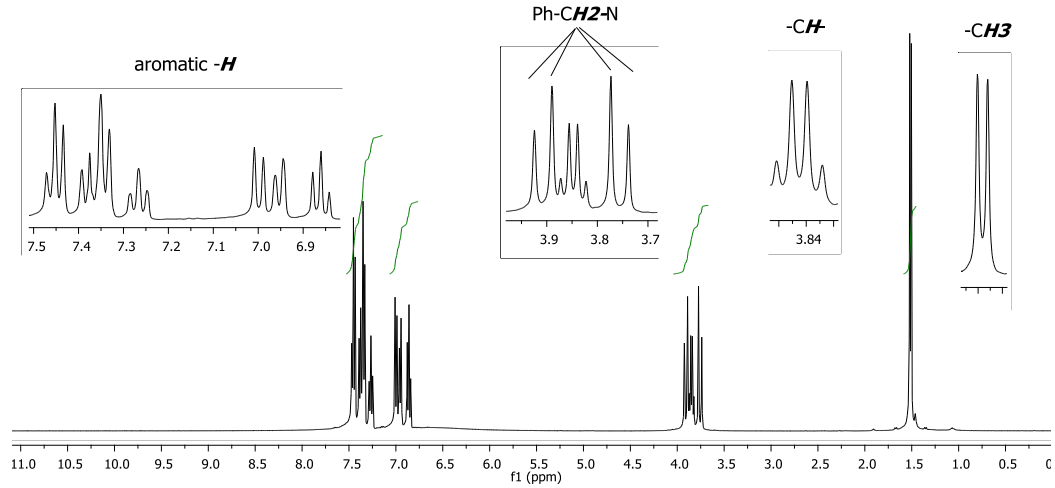
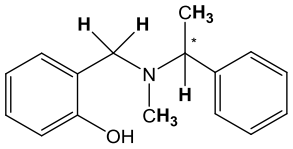


Figure 5.6 ^{1}H NMR of the ligand **8a**



9a

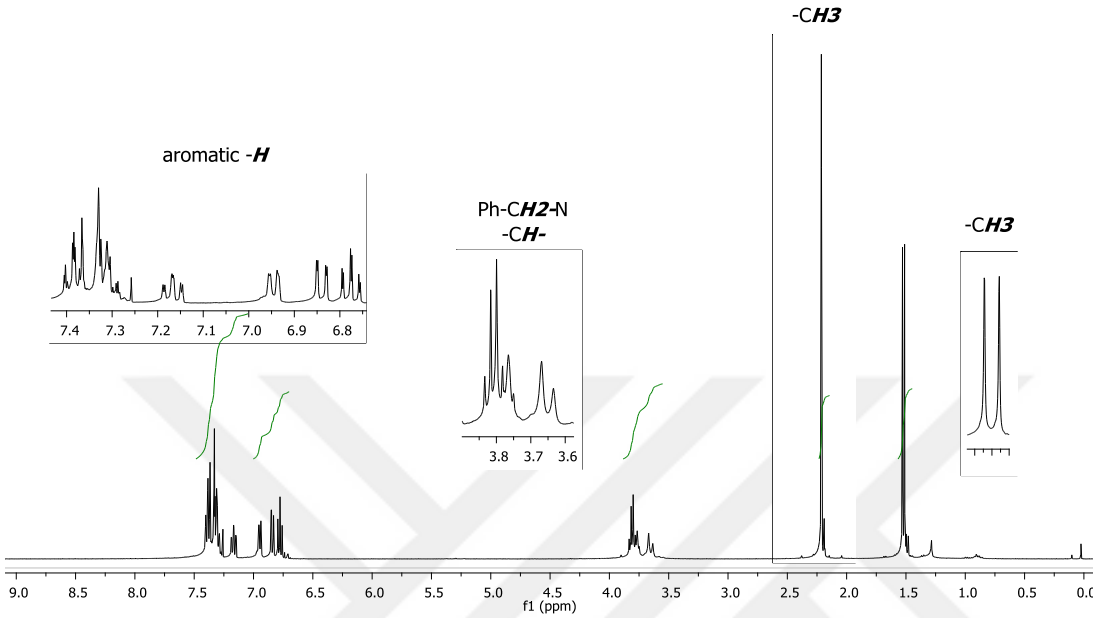


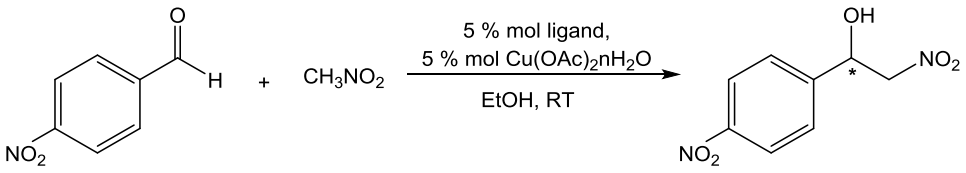
Figure 5.7 ^{1}H NMR of the ligand **9a**

5.2.2 Asymmetric Henry reaction catalyzed by bidentate ligands derived from chiral amines

The ligands **7a-c, 8a-c, 9a-c** were used as catalysts in the asymmetric Henry reaction by carriying out reactions with 4-nitrobenzaldehyde and nitromethane in EtOH in the presence of $Cu(OAc)_2.nH_2O$ at RT (Table 5.2).

In each instance, the reaction was performed with 1 mmol 4-nitrobenzaldehyde, 5% mmol ligand and $Cu(OAc)_2.nH_2O$ and 10 mmol nitromethane in 2 mL of EtOH at ambient temperature within the given reaction time. The resulting products were isolated by column chromatography using 3:1 hexane: EtOAc system.

Table 5.2 Optimization of the ligand effect in the asymmetric Henry reaction



Entry	Ligand	Time (h)	Yield[a](%)	enantiomeric ratio[b]
1	**7a**	72	59	49.9 : 50.1
2	**7b**	48	57	48.4 : 51.6
3	**7c**	48	54	50.2 : 49.8
4	**8a**	72	75	49.4 : 50.5
5	**8b**	48	85	51.6 : 48.4
6	**8c**	48	81	52.8 : 47.2
7	**9a**	48	55	43.2 : 56.8
8	**9b**	48	57	50.8 : 49.2
9	**9c**	48	62	50.3 : 49.7

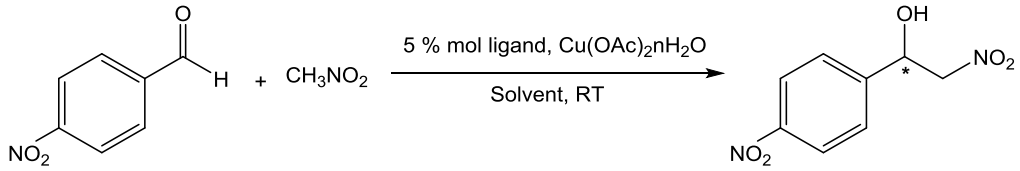
[a]Isolated yields after column chromatography. [b]Determined by HPLC analysis using a Chiracel OD-H column.

The desired Henry reaction products were obtained in the reactions performed. The enantiomeric ratio of the products were very poor with all the catalysts systems (Table 5.2). Therefore, it was not necessary to determine the absolute configuration of the products. The reaction took a much longer time than others for completion with ligands **7a** and **8a** (Table 5.2, Entries 1, 4). When using naphthyl substituted aminophenol ligands **8b**, **8c**, the yield of the reactions were higher than the others (81, 85% yields) (Table 5.2, Entries 5 and 6).

The effect of solvent on the enantioselectivity was also investigated (Table 5.3). Ethereal solvents such as THF, Et_2O, EtOAc, TBME or apolar solvents such as hexane have been previously used and affected the reaction mechanism in different ways (Tanaka et al., 2015; Korkmaz et al., 2011; Heshmat et al., 2014). When hexane was used as a solvent, the reaction yield was decreased with ligands **7c** and **8c** (Table 5.3, Entries 3 and 6). Higher results were obtained when water was used with ligands **7c**, **8c**, **9a** (Table 5.3, Entries 2, 5 and 9). It was seen that, when alcoholic solvents such as IPA were used, no significant change in

enantiomeric excess values occurred, but high yields were obtained. (Table 5.3, Entries 1, 4, 8, 10 and 11).

Table 5.3 Solvent effect of the selected ligands in the asymmetric Henry reaction



Entry	Ligand	Solvent	Time (h)	Yield[a](%)	enantiomeric ratio[b]
1	**7b**	IPA	48	87	50.2 : 49.8
2	**7c**	H_2O	48	80	49.7 : 50.3
3	**7c**	Hexane	48	21	51.0 : 49.0
4	**8c**	IPA	48	90	48.0 : 52.0
5	**8c**	H_2O	48	78	52.4 : 47.6
6	**8c**	Hexane	48	33	54.5 : 45.5
7	**9a**	THF	48	30	52.1 : 47.9
8	**9a**	IPA	48	84	51.2 : 48.8
9	**9a**	H_2O	48	77	53.7 : 46.3
10	**9b**	IPA	48	82	49.9 : 50.1
11	**9c**	IPA	48	89	47.5 : 52.5

[a]Isolated yields after column chromatography; [b]Determined by HPLC analysis using a Chiracel OD-H column.

In summary, chiral amine based ligands which were Schiff base, secondary and tertiary aminophenols were designed (Figure 5.8). These synthesized ligands were used as a catalyst with $Cu(OAc)_2.nH_2O$ in the Henry reaction affording enantioselectivity in good yields. The observed enantiomeric excess values were not as high as it was expected. Whereas, it was found that naphthyl substituted secondary aminophenol **8c** were formed the product with high yields in polar solvents (81%, 90%) (Table 5.2, Entry 6; Table 5.3, Entry 4). The best observed enantiomeric ratio was 43.2:56.8 with ligand **9a** (Table 5.2, Entry 7).

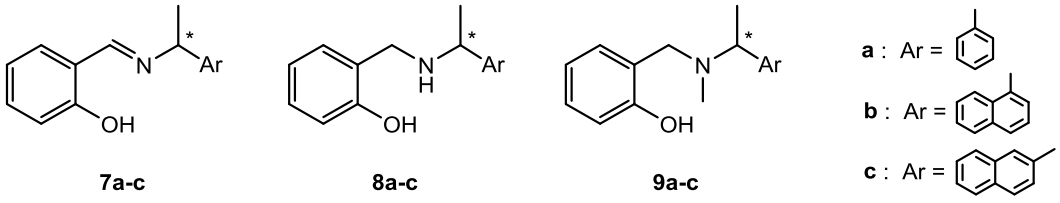


Figure 5.8 Synthesized chiral amine based ligands

5.3 Conclusion

In this chapter, NO type bidentate ligands which were Schiff bases and aminophenol derivatives were synthesized from chiral amines with salicylaldehyde. The synthesized ligands were characterized by spectroscopic techniques. The catalytic activities of these ligands were studied in the presence of $Cu(OAc)_2.nH_2O$ for asymmetric Henry reaction. The reaction products were obtained without enantioselectivity in good yields.

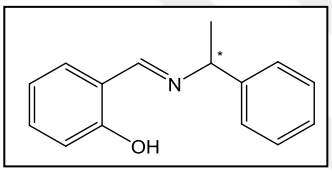
5.4 Material and Method

Unless otherwise noted all reactions were performed in air, except involving air-sensitive components were performed under argon atmosphere. The solvents were analytical grade and obtained from commercial suppliers. All chemicals were commercially available and purchased from Merck, Sigma-Aldrich, Alfa Aesar, Fluka, Acros or BDH and used without any purification. Representative protocol was given for the same class of compounds bearing different substituents and data were presented in Schemes. FTIR Spectra were recorded on a Perkin Elmer Spectrum 100 series. ^1H NMR and ^{13}C NMR spectra were recorded on using 400 MHz Varian NMR spectrometer and 600 MHz Agilent Premium Compact NMR spectrometer at ambient temperature. As solvent $CDCl_3$ was employed, *J* values were in Hz. Melting points were recorded with Gallenkamp electrothermal melting point apparatus. Silica gel F_{254} (Merck 5554) precoated plates were used for the monitoring of all reactions by thin-layer chromatography and visualized by ultra-violet light or by staining with ninhydrin dissolved in alcohol. For column chromatography silica gel 60 (Merck 7743) was used. The enantiomeric ratios of the products were determined by HPLC using a 90:10 hexane:IPA system, flow rate 1 mL/min, 267 nm with Chiralcel OD-H column. Elemental analysis was performed by CHNS-932 (LECO) elemental analyzer.

5.4.1. Preparation of Schiff bases (7a-c)

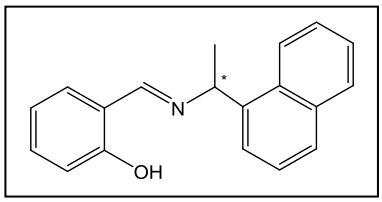
(*R*)-(+)-α-methylbenzylamine (1 mmol, 121.2 mg) and salicylaldehyde (1 mmol, 122.1 mg) were dissolved in 20 mL MeOH. After addition of Na_2SO_4 (0.5 g), the mixture was stirred for 4 h at room temperature. The reaction was controlled by TLC plate. The solvent was removed under reduced pressure after filtration. The residue was crystallized from CH_2Cl_2:pentane to give light yellow crystals. The rest of Schiff bases were synthesized with the same method as the mentioned above using (*R*)-(+)-1-(1-naphthyl)ethylamine and (*R*)-(+)-1-(2-naphthyl)-ethylamine, respectively.

5.4.2 (*R*)-2-[(1-phenyl-ethyl)iminomethyl]phenol (7a)



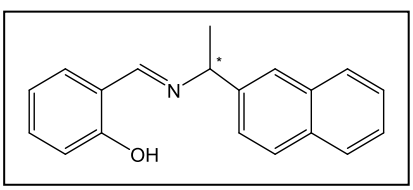
Yellow crystals, 86 % yield, mp: 75-76 °C, IR (CH_2Cl_2): 3061, 2974, 2928, 2867, 1629, 1581, 1494, 1454, 1279, 759, 699 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 13.53 (br, 1H), 8.42 (s, 1H), 7.39-7.24 (m, 6H), 6.98 (d, *J* = 8.4 Hz, 1H), 6.88 (t, *J* = 7.2 Hz, 1H), 4.56 (q, *J* = 6.8 Hz, 1H), 1.65 (d, *J* = 6.4 Hz, 3H). $[\alpha]_D^{29}$ = -152 (*c* 0.25, CH_2Cl_2).

5.4.3 (*R*)-2-[(8-naphthalenyl-ethyl)iminomethyl]phenol (7b)



Yellow crystals, 93 % yield, mp: 89-90 °C, IR (CH_2Cl_2): 3050, 2972, 2927, 2868, 1627, 1579, 1497, 1459, 1278, 776, 756 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 13.69 (br, 1H), 8.44 (s, 1H), 8.15 (d, *J* = 8.4, 1H), 7.90 (d, *J* = 8.4 Hz, 1H), 7.80 (d, *J* = 8.4 Hz, 1H), 7.66 (d, *J* = 7.2 Hz, 1H), 7.58-7.48 (m, 4H), 7.34-7.30 (m, 1H), 7.20 (dd, *J* = 2.0 Hz, 8.0 Hz, 1H), 7.00 (d, *J* = 8.4 Hz, 1H), 6.86 (td, *J* = 1.2 Hz, 8.0 Hz, 1H), 5.42 (q, *J* = 6.8 Hz, 1H), 1.81 (d, *J* = 6.4 Hz, 3H). $[\alpha]_D^{29}$ = - 344 (*c* 0.25, CH_2Cl_2).

5.4.4 (*R*)-2-[(7-naphthalenyl-ethylimino)methyl]phenol (7c)



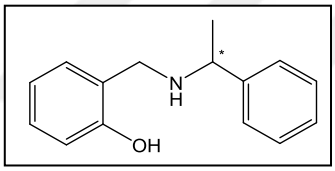
Yellow crystals, 89 % yield, mp: 126-127 °C, IR (CH_2Cl_2): 3049, 2978, 2931, 2884, 1628, 1577, 1494, 1457, 1278, 756, 749 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 13.57 (s, 1H), 8.46 (s, 1H), 7.86-7.79 (m, 4H), 7.54-7.45 (m, 3H), 7.34-7.24 (m, 2H), 7.00 (d, *J* = 8.0 Hz, 1H),

6.88 (t, *J* = 7.6 Hz, 1H), 4.73 (q, *J* = 6.8 Hz, 1H), 1.73 (d, *J* = 6.4 Hz, 3H). $[\alpha]_D^{29}$ = -216 (*c* 0.25, CH_2Cl_2).

5.4.5 Preparation of aminophenols (8a-c)

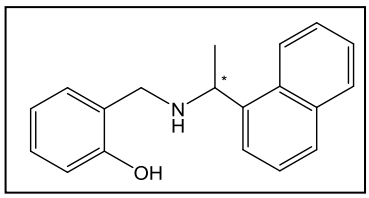
This reaction can be accomplished by the reduction of isolated Schiff bases or it can be completed one pot, without isolation. (*R*)-(+)-α-methylbenzyl-amine (1 mmol, 121.2 mg) and salicylaldehyde (1 mmol, 122.1 mg) were dissolved in 20 mL MeOH under argon atmosphere and was added Na_2SO_4 (0.5 g). The mixture was stirred for 4 h at room temperature for the formation of Schiff base. The mixture was filtered and then, the residue was reduced with $NaBH_4$ (1.5 mmol, 57.0 mg) was stirred for 24 h. After the product was checked by TLC, the solvent was evaporated. After addition of 20 mL of water, it was neutralized with acetic acid and extracted 3 times with DCM. The organic phases were collected and dried with Na_2SO_4 before evaporation.

5.4.6 N-(2-hydroxybenzyl)-(*R*)-methylbenzylamine (8a)



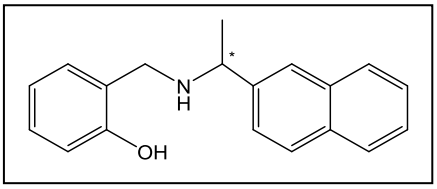
Light yellow oil, 80 % yield, IR (CH_2Cl_2): 3293, 3028, 2967, 2925, 2855, 1589, 1472, 1256, 1102, 1033, 755, 701 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 7.47-7.33 (m, 5H), 7.27 (t, *J* = 6.8 Hz, 1H), 7.01-6.94 (m, 2H), 6.86 (t, *J* = 7.2 Hz, 1H), 3.91 (d, *J* = 14 Hz, 1H), 3.85 (q, *J* = 6.8 Hz, 1H), 3.76 (d, *J* = 14 Hz, 1H), 1.51 (d, *J* = 6.8 Hz, 3H). $[\alpha]_D^{29}$ = + 48 (*c* 0.5, CH_2Cl_2).

5.4.7 N-(2-hydroxybenzyl)-(*R*)-(8-naphthyl)ethylamine (8b)



Oil, 88 % yield, IR (CH_2Cl_2): 3353, 3049, 2970, 2927, 2788, 1734, 1458, 1377, 1258, 753, 699 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 8.06-8.03 (m, 1H), 7.92-7.89 (m, 1H), 7.82-7.80 (m, 1H), 7.56-7.49 (m, 4H), 7.17 (t, *J* = 8.0 Hz, 1H), 6.88-6.84 (m, 2H), 6.74 (td, *J* = 0.8 Hz, 7.6 Hz, 1H), 4.76 (q, *J* = 6.8 Hz, 1H), 3.98 (d, *J* = 14 Hz, 1H), 3.84 (d, *J* = 13.6 Hz, 1H), 1.62 (d, *J* = 6.8 Hz, 3H).). $[\alpha]_D^{29}$ = - 56 (*c* 0.25, CH_2Cl_2).

5.4.8 N-(2-hydroxybenzyl)-(*R*)-(7-naphthyl)ethylamine (8c)

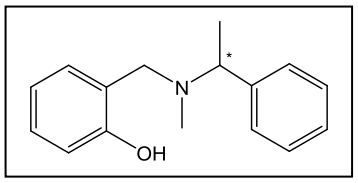


White powder, 93 % yield, mp: 117 °C, IR (CH_2Cl_2): 3384, 3169, 2996, 2901, 2787, 1726, 1595, 1490, 1458, 1376, 1244, 994, 751, 702 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 7.89-7.82 (m, 3H), 7.68 (s, 1H), 7.52-7.42 (m, 3H), 7.17 (t, *J* = 7.6 Hz, 1H), 6.86 (d, *J* = 8.4 Hz, 2H), 6.75 (t, *J* = 7.6 Hz, 1H), 3.99 (q, *J* = 6.8 Hz, 1H), 3.90 (d, *J* = 13.6 Hz, 1H), 3.76 (d, *J* = 14 Hz, 1H), 1.55 (d, *J* = 6.8 Hz, 3H). $[\alpha]_D^{29}$ = + 48 (*c* 0.25, CH_2Cl_2).

5.4.9 Methylation of aminophenols (9a-c)

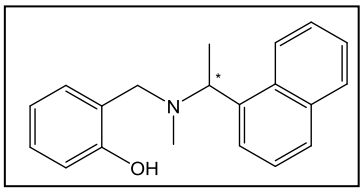
Aminophenol derivative (1 mmol) was added to the mixture of formaldehyde (37 %, 0.3 mL, 10 mmol) and formic acid (98 %, 0.42 mL, 11 mmol) and the mixture was warmed at 90°C for overnight. After the mixture being cooled to room temperature, made basic with aqueous sodium hydroxide (pH = 10). The suspended reaction mixture was extracted with dichloromethane three times. The combined organic phases were washed with brine and dried with Na_2SO_4, then filtered to remove the solvent under reduced pressure. The crude product was purified by column chromatography (3:1, hexane:EtOAc) which afforded the desired product as coloursless oil.

5.4.10 N-(2-hydroxybenzyl)-N-methyl-(*R*)-methylbenzylamine (9a)



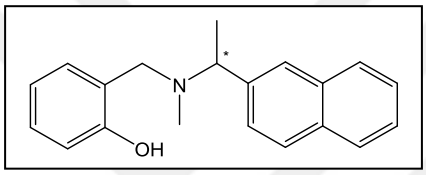
Colorless oil, 50 % yield, IR (CH_2Cl_2): 3029, 2975, 2851, 1590, 1492, 1475, 1453, 1421, 1376, 1257, 1150, 994, 755, 702 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 7.40-7.26 (m, 5H), 7.19-7.14 (m, 1H), 6.94 (d, *J* = 4 Hz, 1H), 6.84 (dd, *J* = 8.4, 1.2 Hz, 1H), 6.80-6.76 (m, 1H), 3.81 (q, *J* = 7.2 Hz, 1H), 3.77 (d, *J* = 4.4 Hz, 1H), 3.65 (d, *J* = 14 Hz, 1H), 2.21 (s, 3H), 1.52 (d, *J* = 6.8 Hz, 3H). $[\alpha]_D^{29}$ = + 16 (*c* 0.25, CH_2Cl_2).

5.4.11 N-(2-hydroxybenzyl)-N-methyl-(*R*)-(8-naphthyl)ethyl-amine (9b)



Colorless oil, 57 % yield, IR (CH_2Cl_2): 3048, 2977, 2851, 1590, 1490, 1420, 1318, 1376, 1255, 1174, 940, 779, 755 cm^{-1}. ^{1}H-NMR (600 MHz, $CDCl_3$, δ ppm) 8.19 (d, *J* = 12 Hz, 1H), 7.90 (d, *J* = 6 Hz, 1H), 7.81 (d, *J* = 12 Hz, 1H), 7.60-7.48 (m, 4H), 7.12 (t, *J* = 6 Hz, 1H), 6.92 (d, *J* = 6 Hz, 1H), 6.76-6.73 (m, 2H), 4.66 (q, *J* = 6 Hz, 1H), 3.83 (d, *J* = 12 Hz, 2H), 2.3 (s, 3H), 1.64 (d, *J* = 7.2 Hz, 3H). $[\alpha]_D^{29}$ = - 8 (*c* 0.25, CH_2Cl_2).

5.4.12 N-(2-hydroxybenzyl)-N-methyl-(*R*)-(7-naphthyl)ethyl-amine (9c)

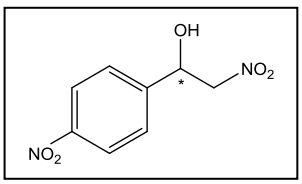


Colorless oil, 51 % yield, IR (CH_2Cl_2): 3053, 2975, 2851, 1590, 1476, 1421, 1379, 1257, 1150, 1075, 859, 820, 753, 628 cm^{-1}. ^{1}H-NMR (600 MHz, $CDCl_3$, δ ppm) 7.89-7.85 (m, 3H), 7.74 (s, 1H), 7.51 (d, *J* = 12 Hz, 3H), 7.18 (t, *J* = 6 Hz, 1H), 6.96 (d, *J* = 12 Hz, 1H), 6.88 (d, *J* = 6 Hz, 1H), 6.79 (t, *J* = 6 Hz, 1H), 3.97 (q, *J* = 6 Hz, 1H), 3.82 (d, *J* = 18 Hz, 1H), 3.72 (d, *J* = 18 Hz, 1H), 2.3 (s, 3H), 1.62 (d, *J* = 6.6 Hz, 3H). $[\alpha]_D^{29}$ = + 36 (*c* 0.5, CH_2Cl_2).

5.4.13 General procedure for the asymmetric Henry reaction

The dark green solution of $Cu(OAc)_2.nH_2O$ (0.01 mmol) and ligand (0.01mmol) in 2 mL solvent at room temperature for 2 h. 4-Nitrobenzaldehyde (0.2mmol) and nitromethane (2.0 mmol) were added to the appropriate solution. The reaction mixture was stirred at which point TLC analysis confirmed most of the aldehyde had been consumed. After the solvent was evaporated, the crude product was purified with column chromatography using 1:3 EtOAc:hexane system.

5.4.14 (*S*)-1-(4-nitrophenyl)-2-nitroethanol (6a)



White crystals, % 71 yields, ^{1}HNMR (400 MHz, $CDCl_3$) δ (ppm) 3.17 (bs, 1H), 4.58 (d, *J* = 2 Hz, 1H), 4.60 (d, *J* = 6 Hz, 1H), 5.61 (m, 1H), 7.63 (m, 2H), 8.26 (m, 2H). $[\alpha]_D^{25}$ = - 21 (*c* 1.25, CH_2Cl_2).

APPENDIX D: Spectra and Chromatograms

D.1 IR Spectrums

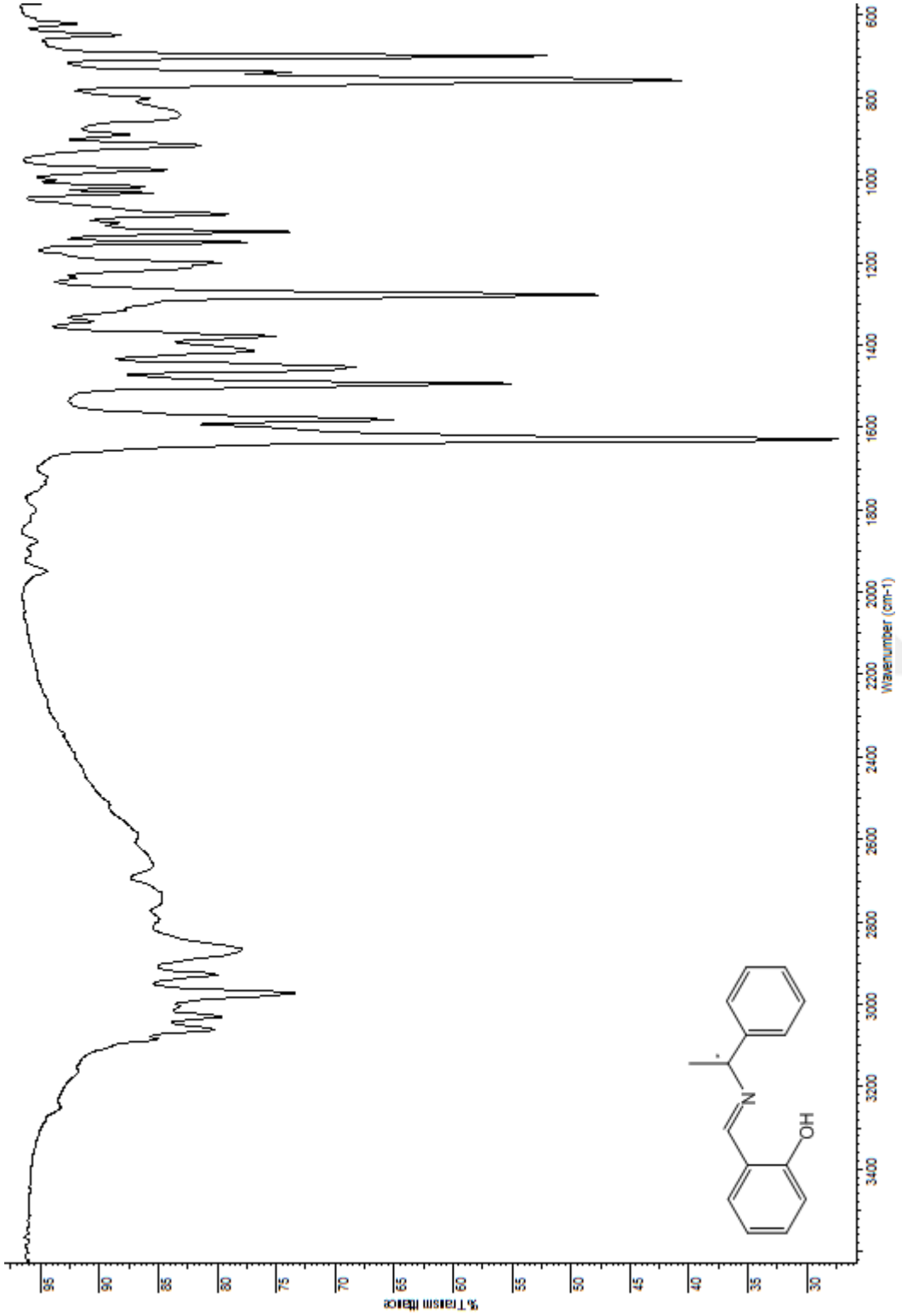


Figure D.1.1 IR spectrum of (*R*)-2-[(1-phenyl-ethyl)iminomethyl]phenol **(7a)**

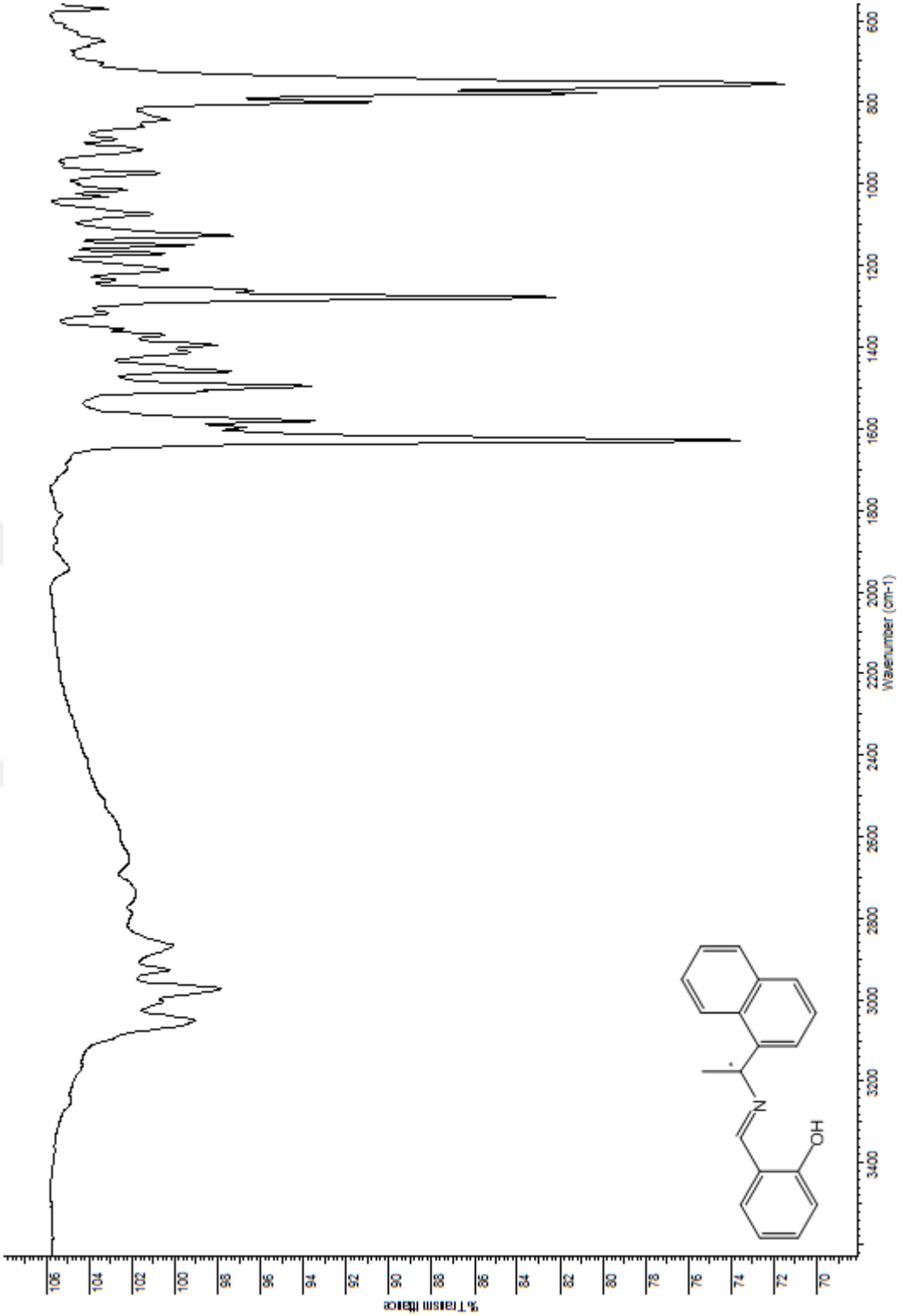


Figure D.1.2 IR spectrum of (*R*)-2-[(8-naphthalenyl-ethyl)iminomethyl]phenol (**7b**)

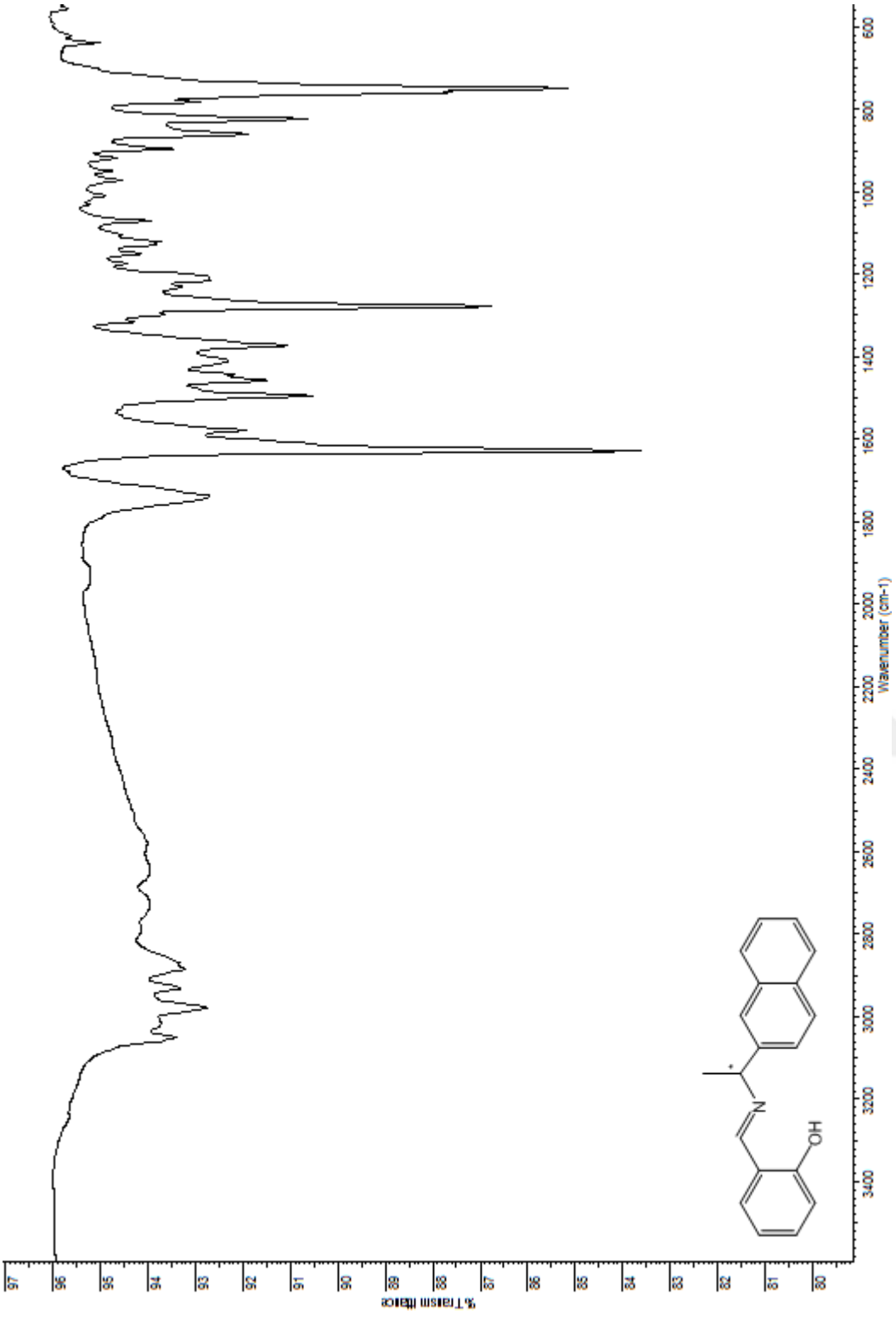


Figure D.1.3 IR spectrum of (*R*)-2-[(7-naphthalenyl-ethylimino)methyl]phenol (**7c**)

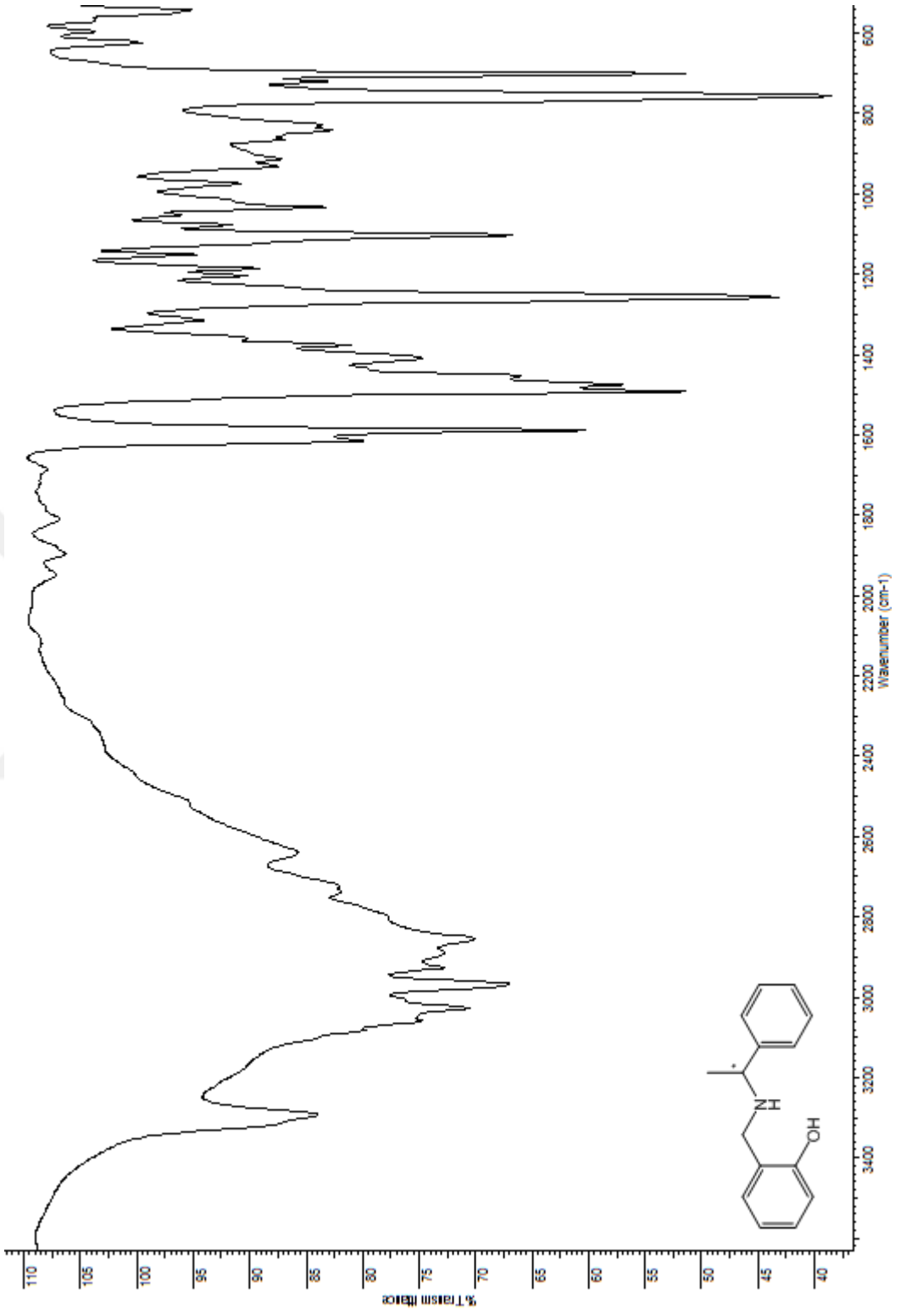


Figure D.1.4 IR spectrum of N-(2-hydroxybenzyl)-(*R*)-methylbenzylamine (**8a**)

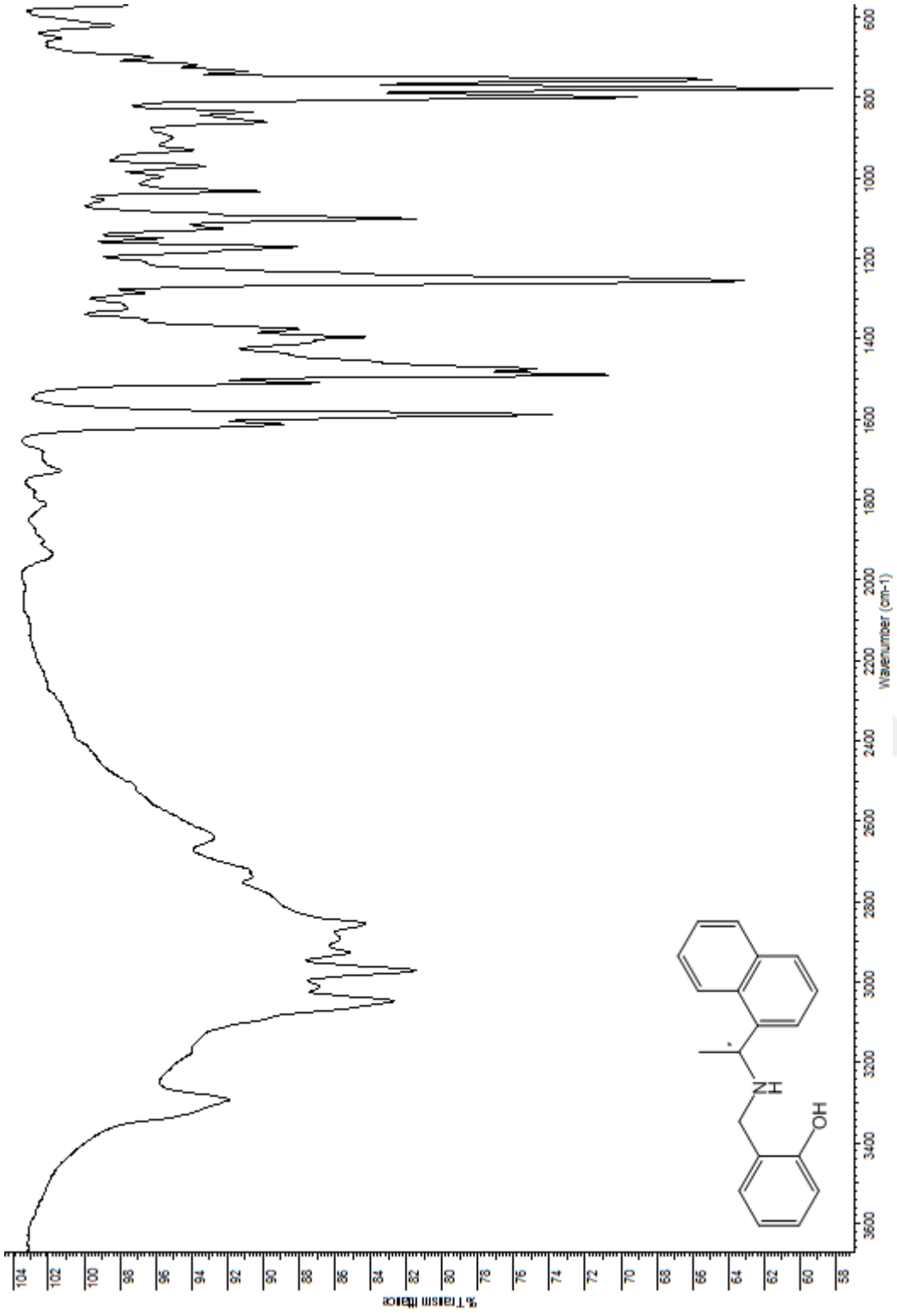


Figure D.1.5 IR spectrum of N-(2-hydroxybenzyl)-(*R*)-(8-naphthyl)ethylamine (**8b**)

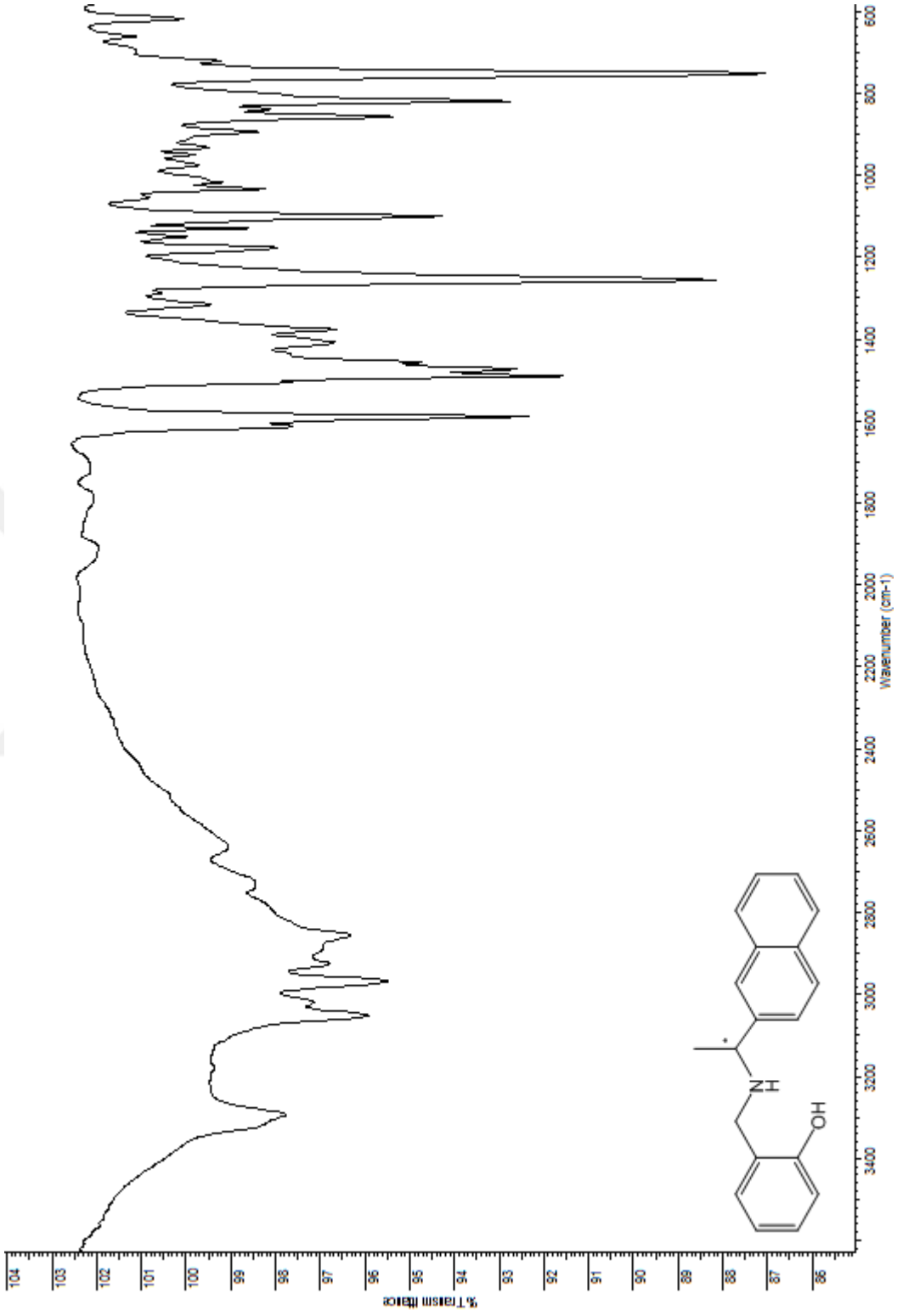


Figure D.1.6 IR spectrum of N-(2-hydroxybenzyl)-(*R*)-(7-naphthyl)ethylamine (**8c**)

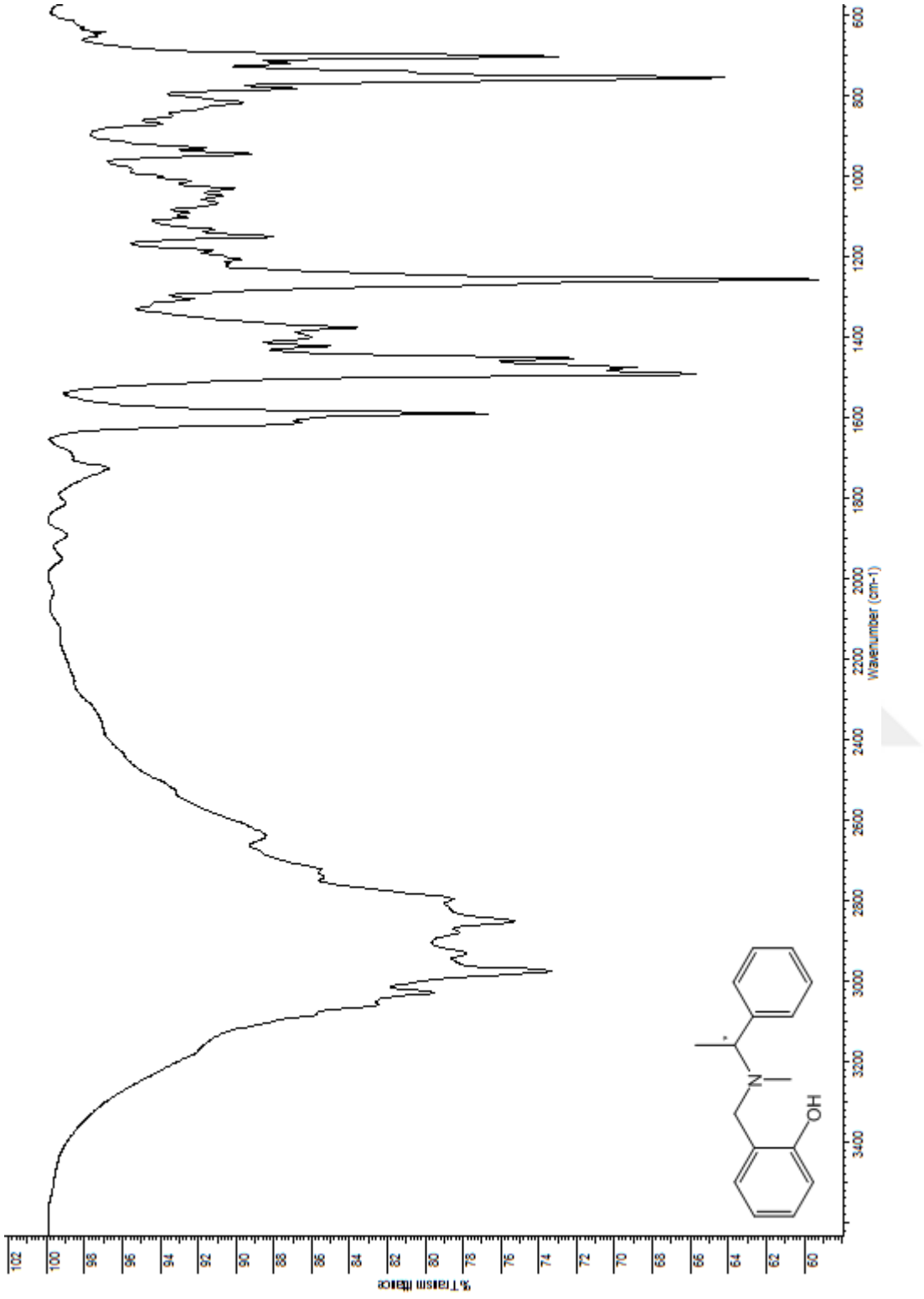


Figure D.1.7 IR spectrum of N-(2-hydroxybenzyl)-N-methyl-(*R*)-methylbenzylamine (**9a**)

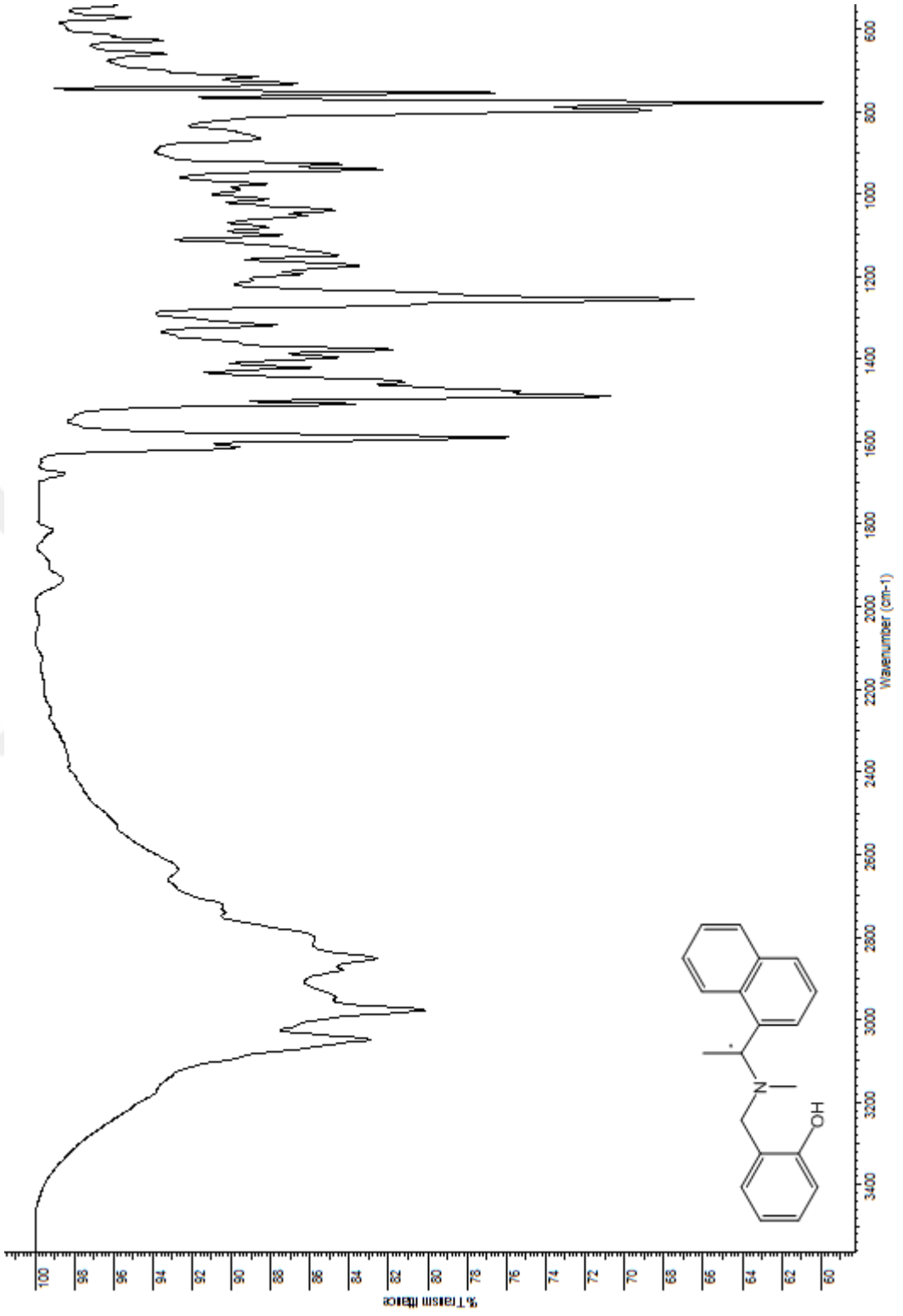


Figure D.1.8 IR spectrum of N-(2-hydroxybenzyl)-N-methyl-(*R*)-(8-naphthyl)ethyl-amine (**9b**)

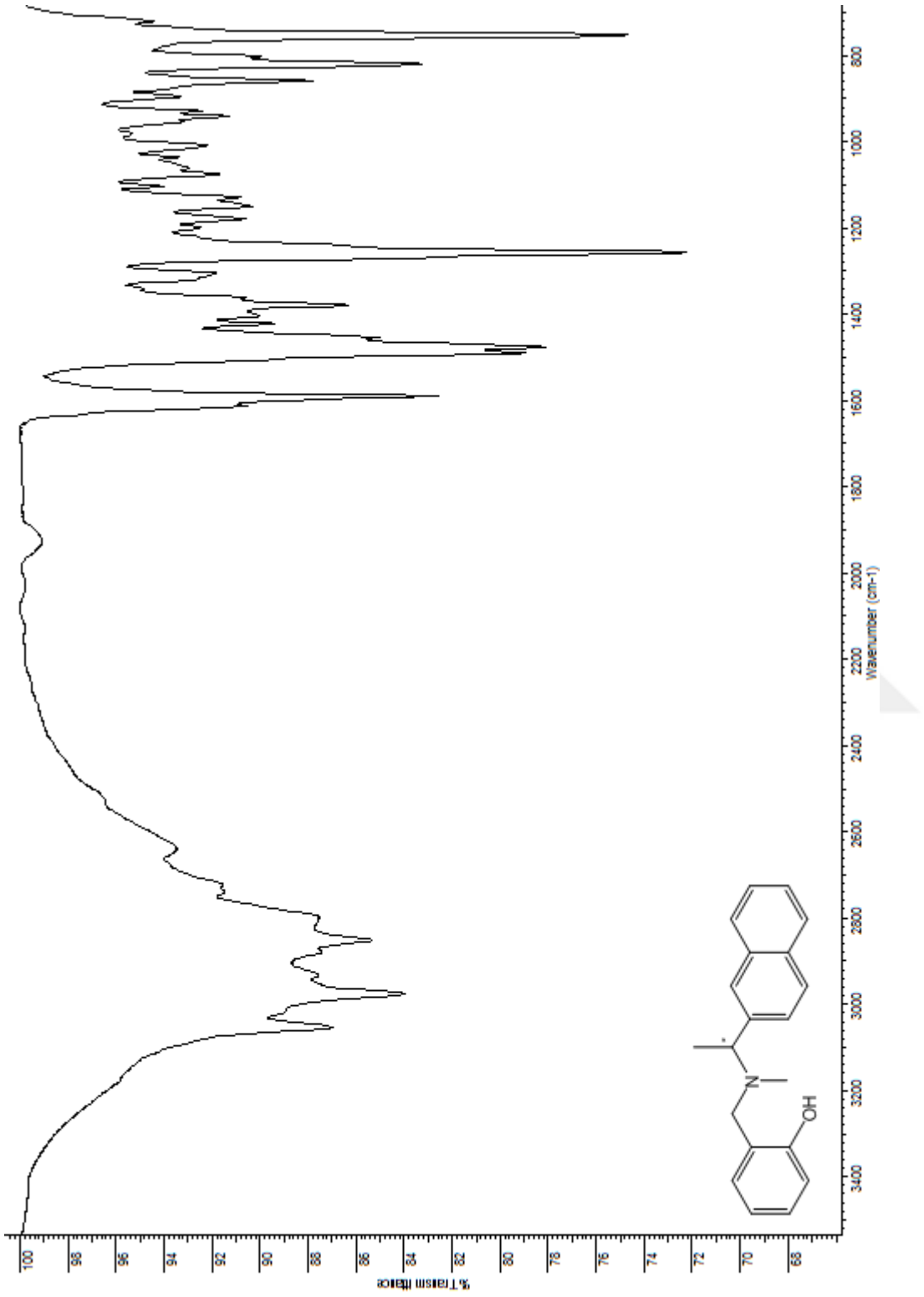


Figure D.1.9 IR spectrum of N-(2-hydroxybenzyl)-N-methyl-(*R*)-(7-naphthyl)ethyl-amine (**9c**)

D.2 ^{1}H NMR Spectrums

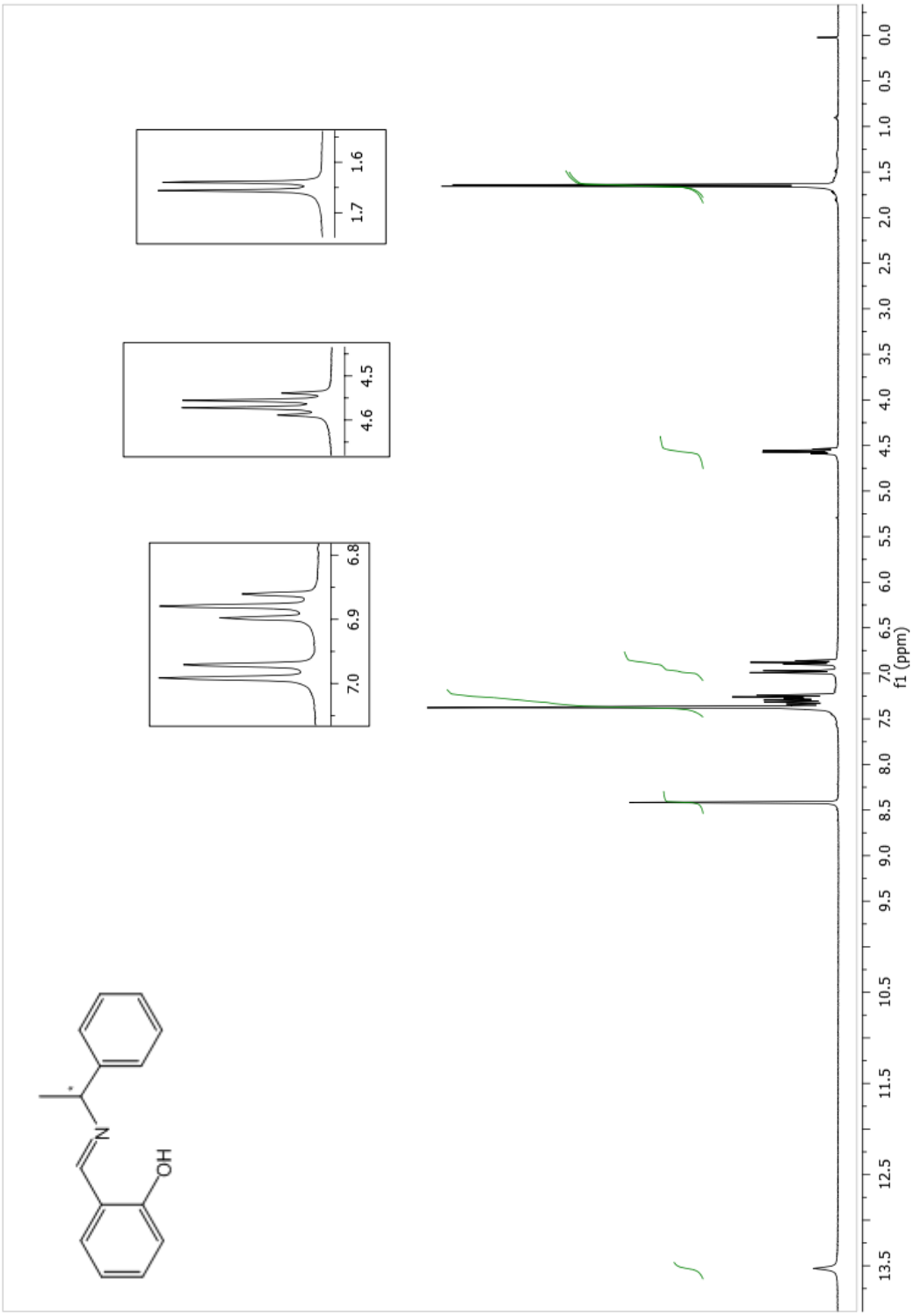


Figure D.2.1 ^{1}H NMR spectrum of (*R*)-2-[(1-phenyl-ethyl)iminomethyl]phenol (**7a**)

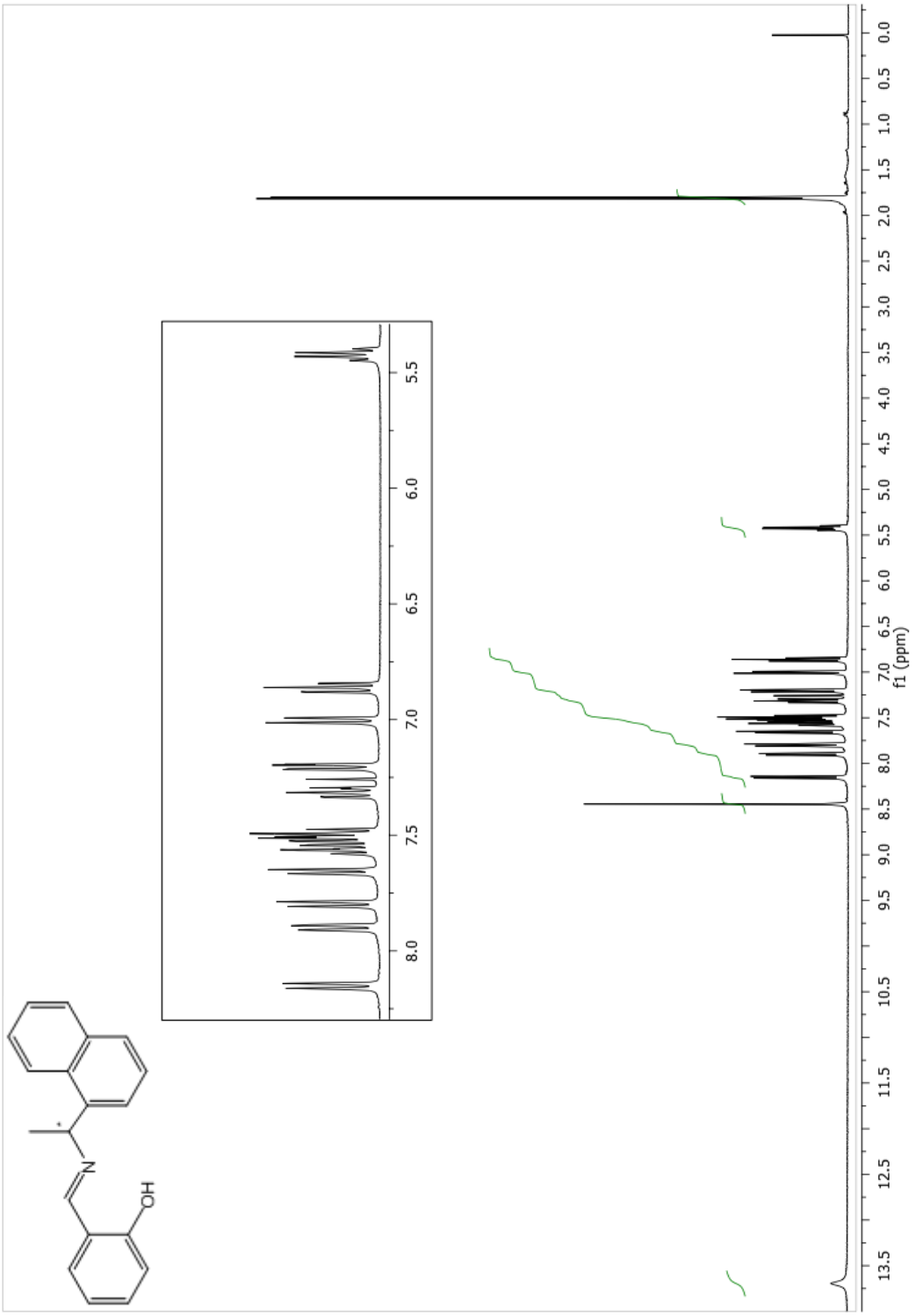


Figure D.2.2 ^{1}H NMR spectrum of (*R*)-2-[(8-naphthalenyl-ethyl)iminomethyl]phenol (**7b**)

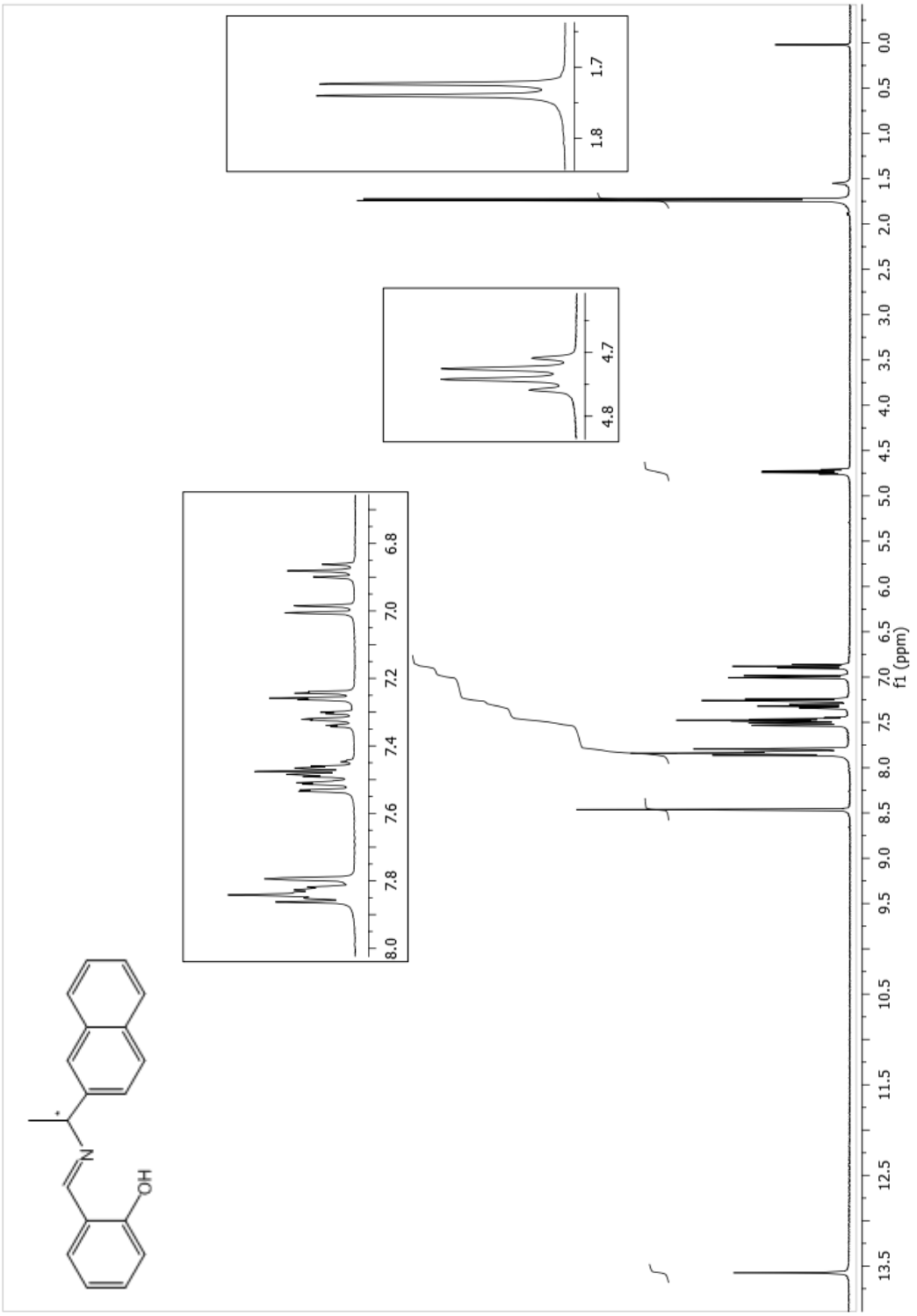


Figure D.2.3 ^{1}H NMR spectrum of (*R*)-2-[(7-naphthalenyl-ethylimino)methyl]phenol (**7c**)

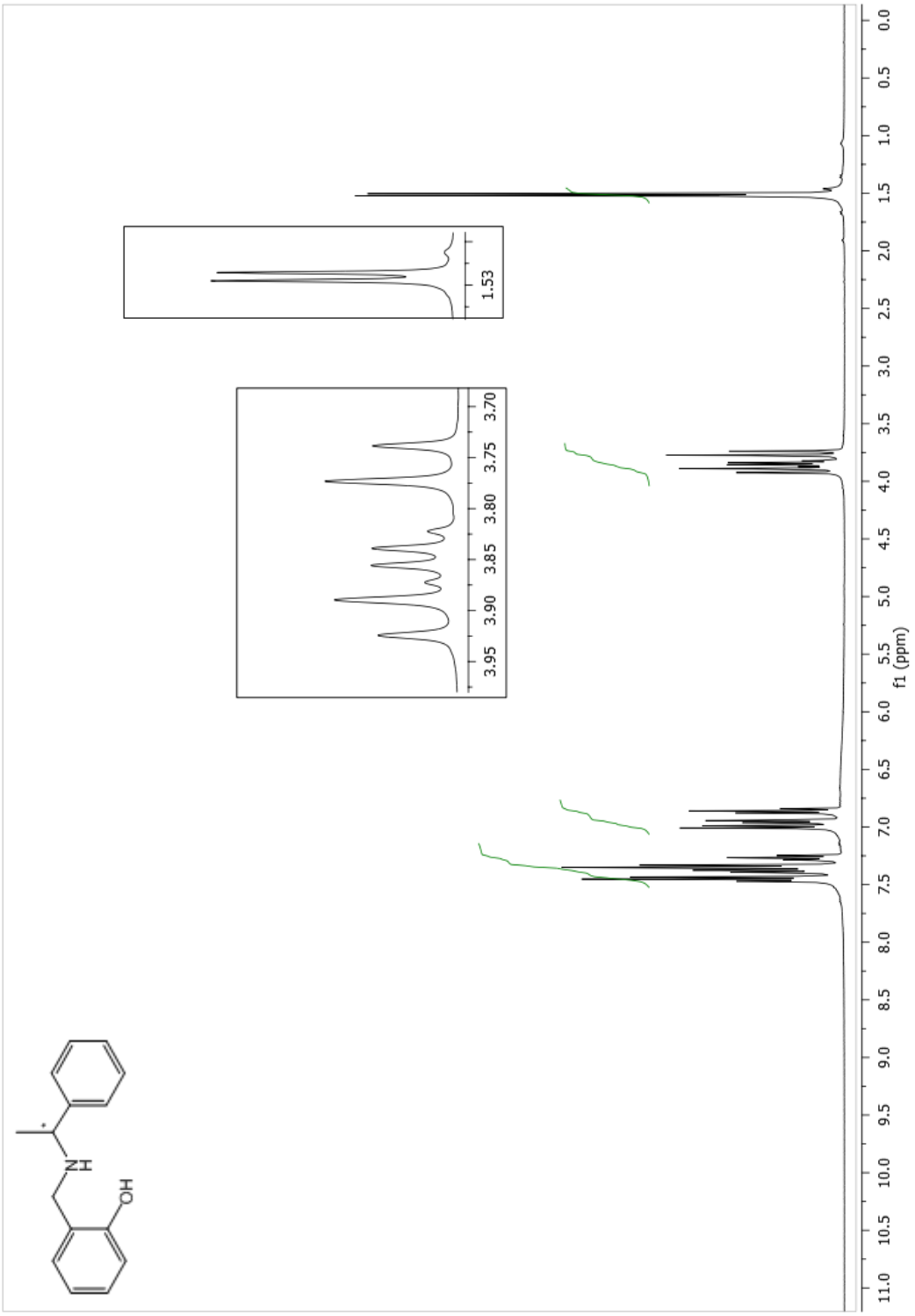


Figure D.2.4 ^{1}H NMR spectrum of N-(2-hydroxybenzyl)-(*R*)-methylbenzylamine (**8a**)

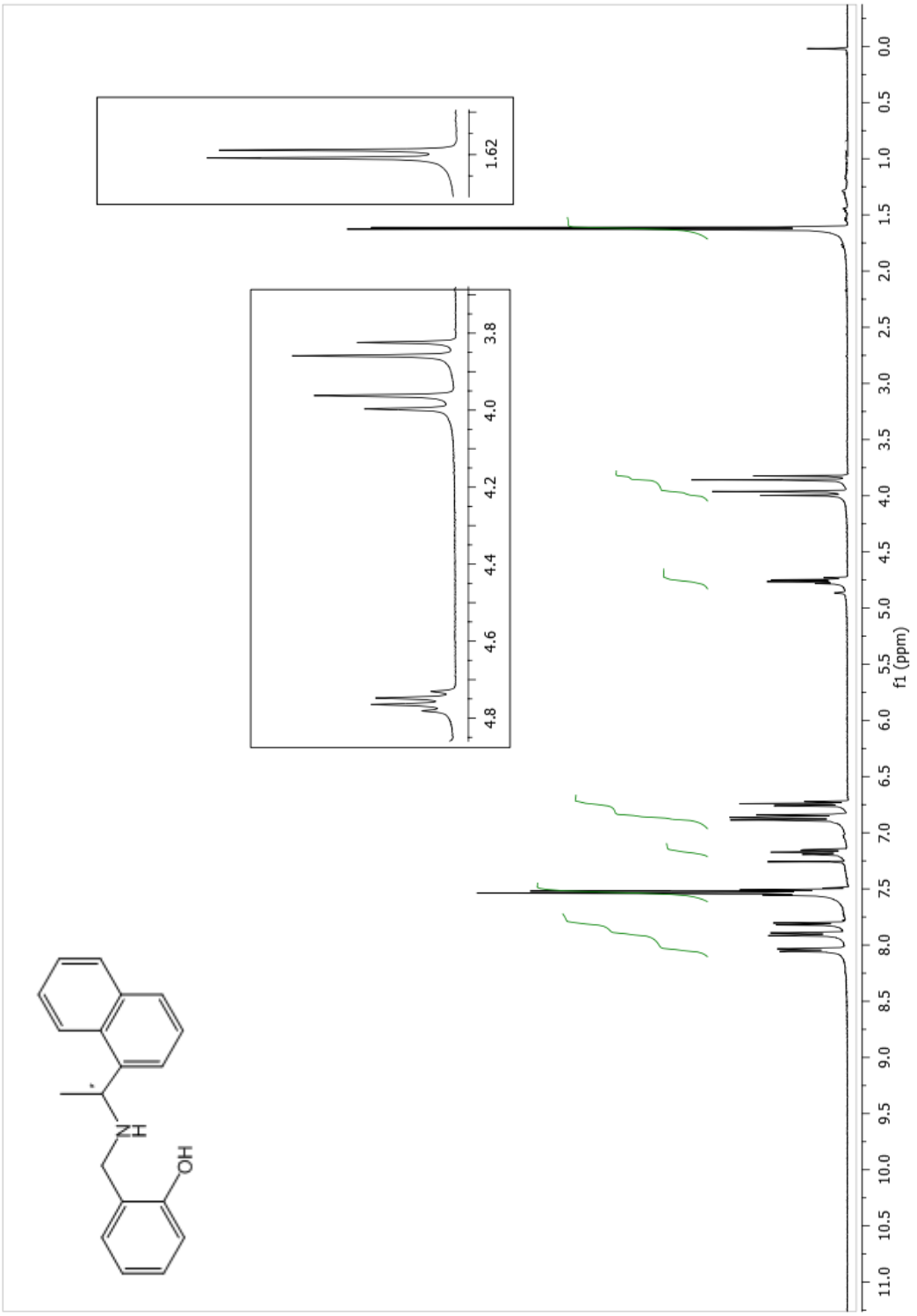


Figure D.2.5 ^{1}H NMR spectrum of N-(2-hydroxybenzyl)-(*R*)-(8-naphthyl)ethylamine (**8b**)

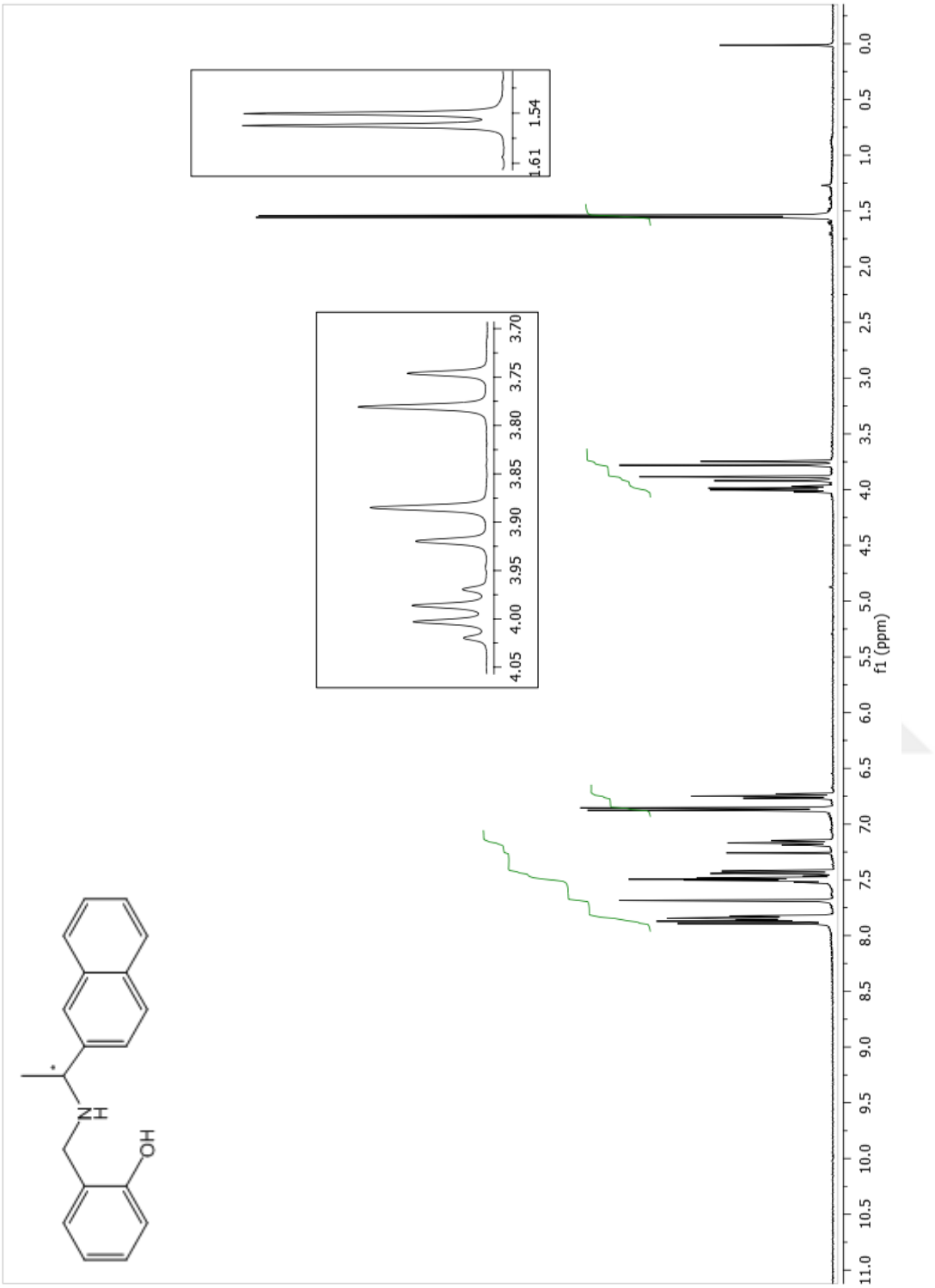


Figure D.2.6 ^{1}H NMR spectrum of N-(2-hydroxybenzyl)-(*R*)-(7-naphthyl)ethylamine **(8c)**

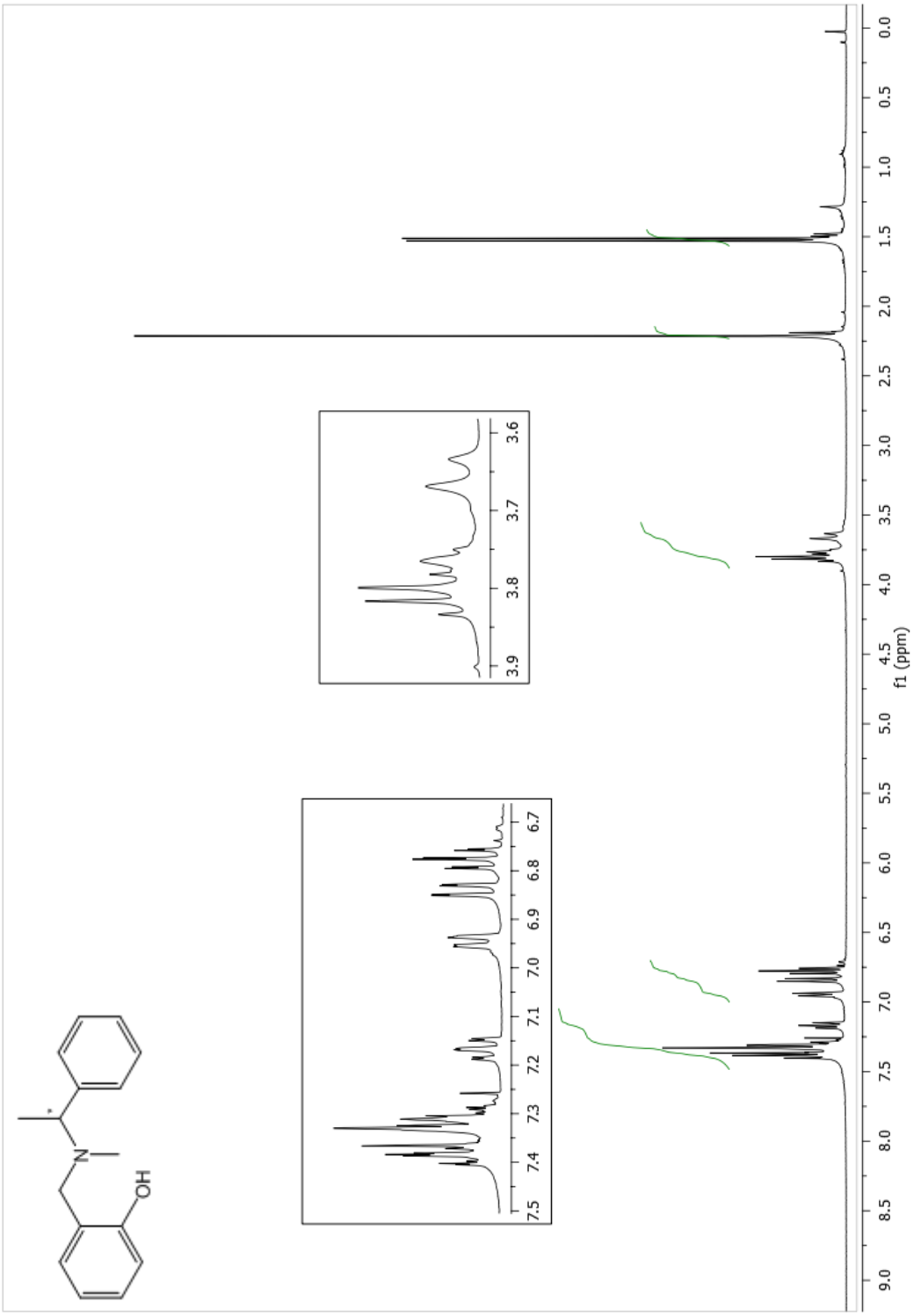


Figure D.2.7 ^{1}H NMR spectrum of N-(2-hydroxybenzyl)-N-methyl-(*R*)-methylbenzylamine (**9a**)

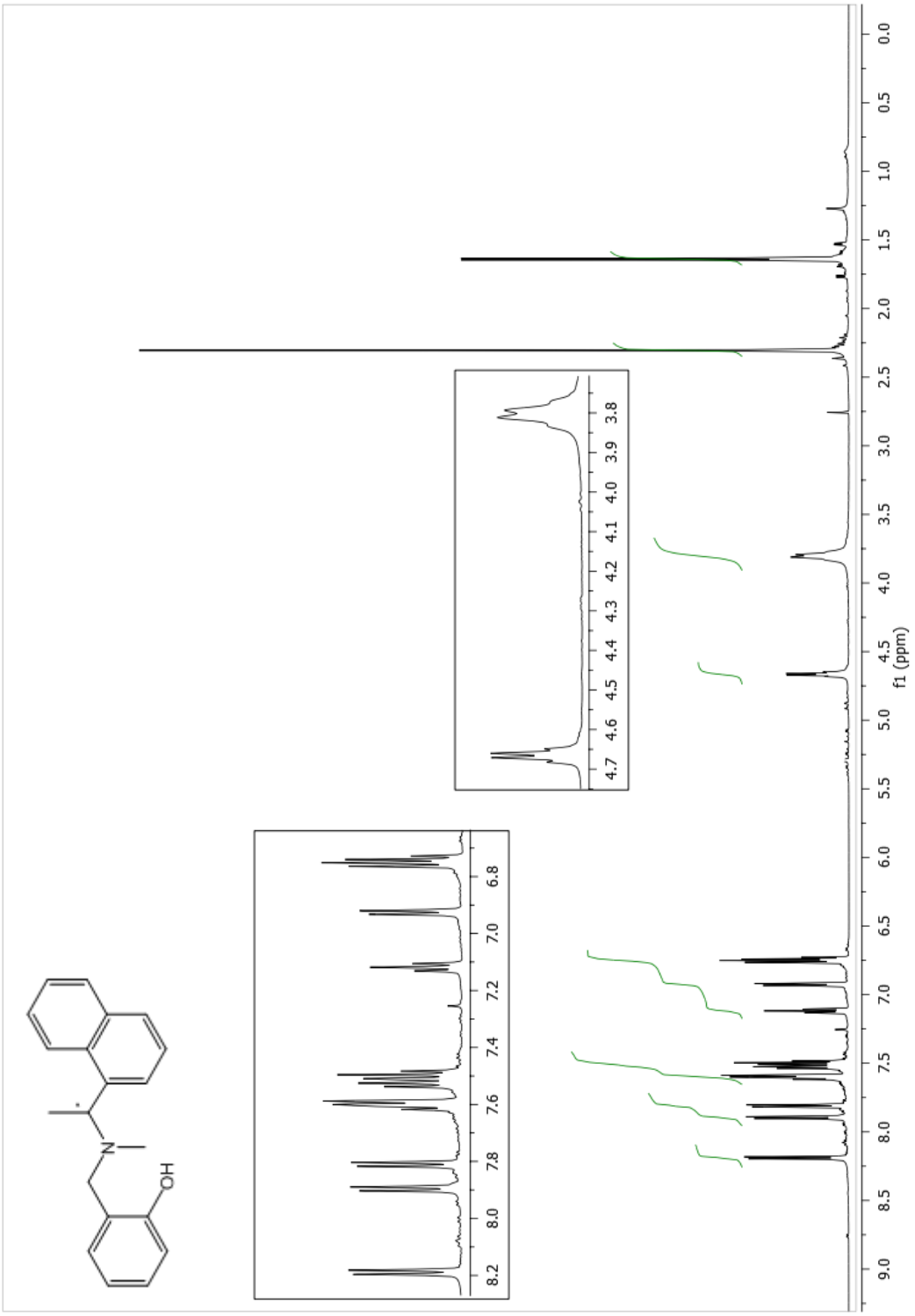


Figure D.2.8 ^{1}H NMR spectrum of N-(2-hydroxybenzyl)-N-methyl-(*R*)-(8-naphthyl)ethyl-amine (**9b**)

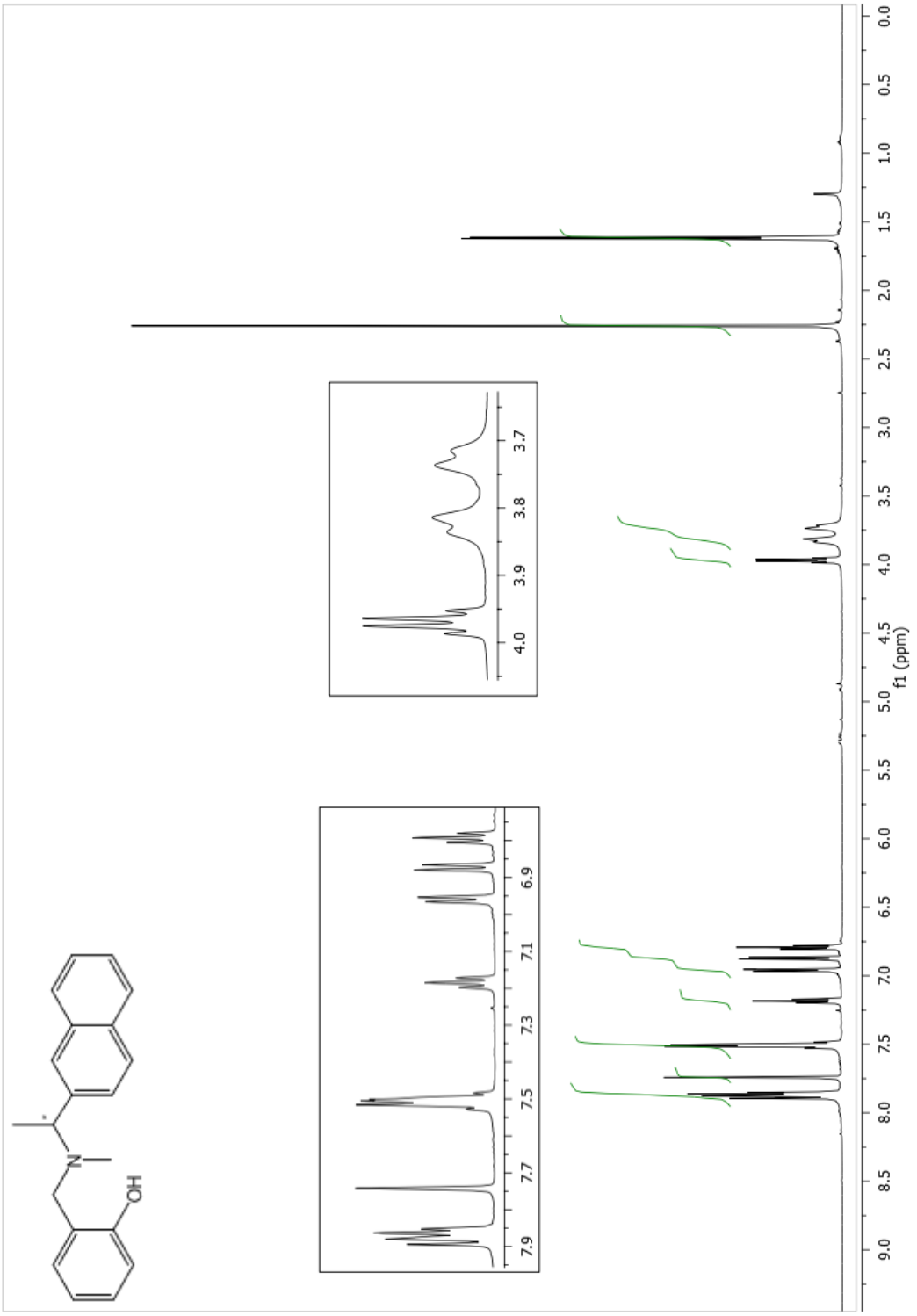


Figure D.2.9 ^{1}H NMR spectrum of N-(2-hydroxybenzyl)-N-methyl-(*R*)-(7-naphthyl)ethyl-amine (**9c**)

D.3 Chromatograms

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Analysis Method : C:\CHEM32\1\METHODS\GAMZE.M
Last changed    : 7/14/2015 2:59:52 PM by Arzu
Sample Info     : 90:10 Hex/IPA, 267nm, 1.0 ml/min, RT
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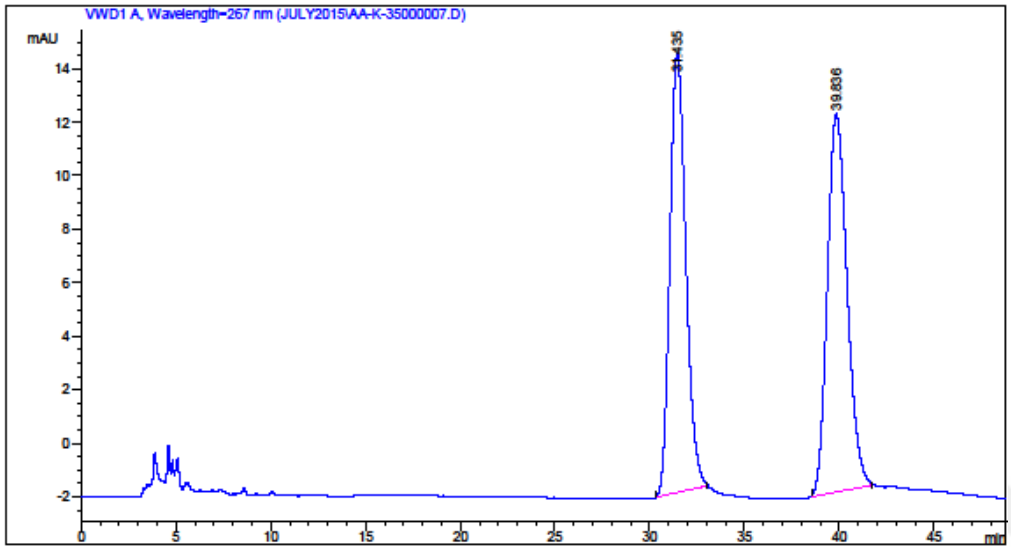


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Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


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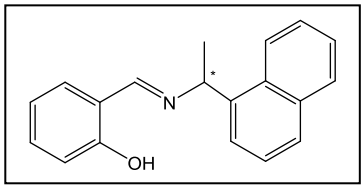

Figure D.3.1 HPLC chromatogram of the nitroaldol reaction of 4-NO_2-benzaldehyde in EtOH at RT with **7b**

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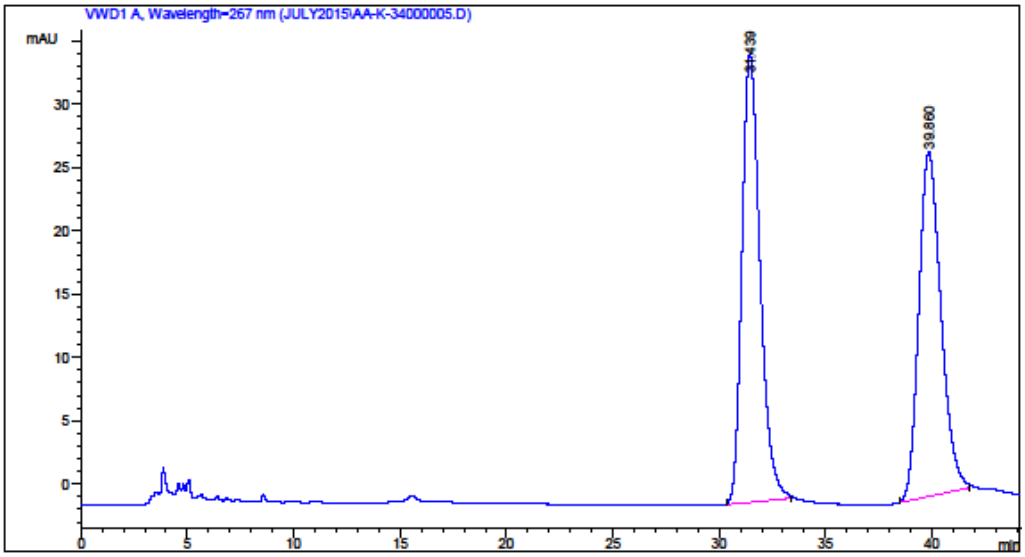


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Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=267 nm

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Instrument 1 5/21/2017 4:46:02 PM Arzu                    Page   1 of 2
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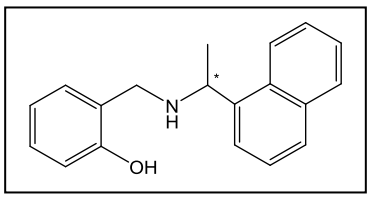

Figure D.3.2 HPLC chromatogram of the nitroaldol reaction of 4-NO_2-benzaldehyde in EtOH at RT with **8b**

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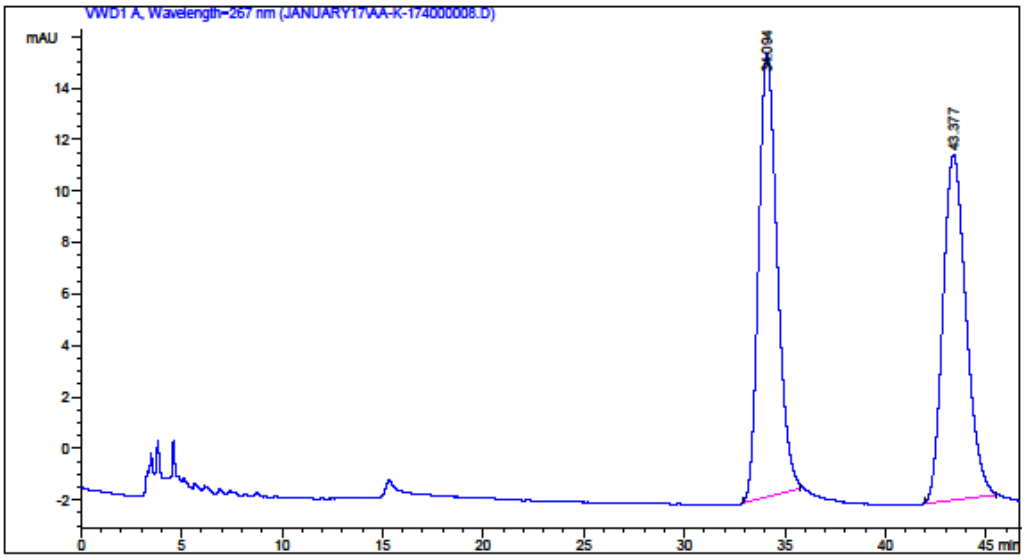


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                              Area Percent Report
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    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: VWD1 A, Wavelength=267 nm

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]  mAU   *s    [mAU   ]      %
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       2  43.377 BB    1.1960 1074.50049   13.44394  49.2278

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Instrument 1 5/21/2017 5:18:02 PM Arzu                          Page   1 of 1
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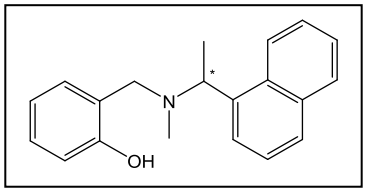


Figure D.3.3 HPLC chromatogram of the nitroaldol reaction of 4-NO_2-benzaldehyde in EtOH at RT with **9b**

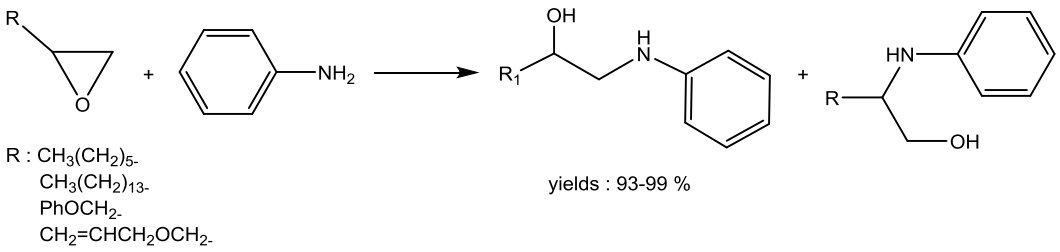
6. SUBSTITUENT EFFECTS IN PHENYL SUBSTITUTED AMINO ALCOHOLS DERIVED FROM EPOXIDES

6.1 General Information

β-amino alcohols, which contain both an amine and an alcohol group, play an important role in optically active and asymmetric synthesis (Martin and Sharpless, 1988). In addition to being used as chiral auxiliaries, enantiomerically pure *β*-amino alcohols are also pharmacologically important and form the building blocks of biologically active compounds (Rogers et la., 1989; Bergmeimer, 2000).

6.1.1 Synthesis of *β*-amino alcohols

Many methods have been proposed for the synthesis of these compounds, including aminohydroxylation of olefins (Li et al., 1996), addition of ketones to imines (List, 2000) or reduction of amino acids with $NaBH_4$ (Rodriguez et al., 1991). However, the most commonly used method is the aminolysis of an epoxide with an amine (Deyrup and Moyer, 1969). Bonollo and co-workers synthesized a series of *β*-amino alcohol compounds with high yields by reacting various meso and end epoxides with aromatic amines in a catalystless and solvent free environment (Bonollo et al., 2006) (Scheme 6.1).

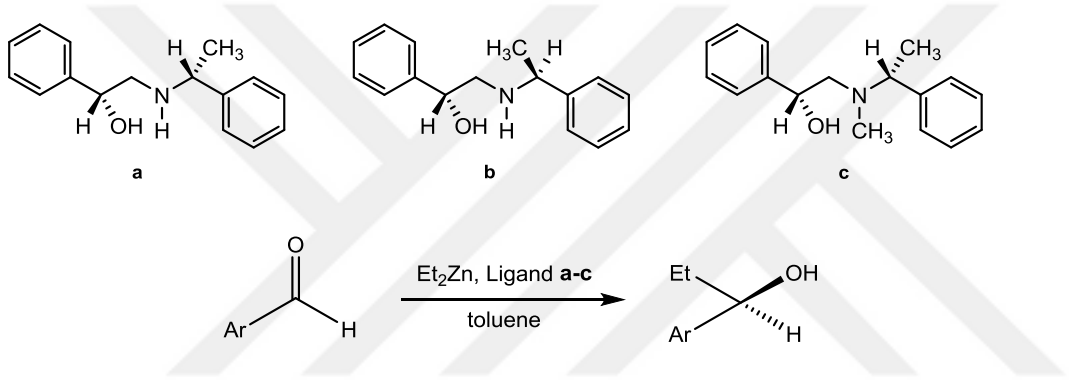


Scheme 6.1 Aminolysis of alkyl epoxides by aniline in water at 60 °C

The reaction can be carried out with a wide variety of catalysts, such as Lewis acids, metal salts, triphthalates and boron, as well as being able to be carried out in a catalyzed environment and at a selectable temperature with high yields, making this method attractive. There were also studies in the literature in which *β*-amino alcohol compounds were obtained using primary or secondary amines and various metal catalysts such as SiO_2, $AlCl_3$, $ZnCl_2$, $LiClO_4$, $CoCl_2$ (Boukhari et al., 2010; Reyes and Juaristi, 1998; Sundararajan et al., 2004).

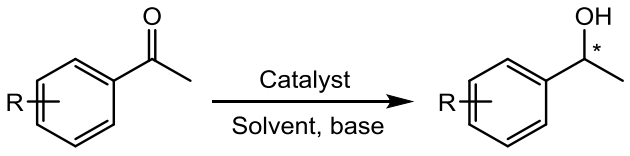
6.1.2 Applied catalysts in the asymmetric reactions

The main goal of asymmetric synthesis in modern organic chemistry is to develop catalysts with high enantioselectivity that are readily obtainable by simple methods. *β*-Amino alcohols play an important role in many asymmetric synthesis (epoxidation, Diels-Alder, enantioselective addition to carbonyl groups and hydrogenation, etc.) as chiral ligands and auxiliary intermediate ligands and are widely used. Iuliano et al. reported that amino alcohols derived from *R*-mandelic acid were used as chiral catalysts in the enantioselective diethyl zinc addition to aldehydes and that the ligand a exhibitted the best enantioselectivity when high ratios of ee (up to 88%) and yields (50 to 80%) were observed as shown in scheme 6.2 (Iuliano et al., 1995).



Scheme 6.2 The addition of Et_2Zn of arylaldehydes and the ligands synthesized by Iuliano et al.

One of the first described enantioselective reactions was asymmetric hydrogenation (AH). In this reaction, where chiral ligands and complexes were used as homogeneous catalysts, gaseous hydrogen was used as the hydrogen source. Asymmetric transfer hydrogenation (ATH) is focused on using the hydrogen source in the reaction mixture. In this reaction, chiral catalysts comprising a transition metal ion in combination with chiral ligands are used. The most active and selective catalysts published up to now include catalysts containing ligands such as pyridine derivative, diphosphonite, amino alcohol, aza-norbornyl alcohol, amide amines (Scheme 6.3).



Scheme 6.3 Asymmetric transfer hydrogenation of ketones

Mao and Guo successfully developed chiral amino amides as ligands and used them in the Ru(II) catalyzed asymmetric transfer hydrogenation of ketones in water at 24 h. The conversion of prochiral ketones were completed with good yields (up to 95%) and high enantioselectivities (up to 90%) using this catalyst system (Mao and Guo, 2010). Baratta et al. published that acetophenone Ru (II) triphenylphosphine catalyzed asymmetric transfer hydrogenation using pyridine-derivatized secondary amino alcohols as the ligand, providing 92% ee to 98% acetophenone conversion in 30 minutes in alcoholic media at 60 °C (Baratta et al., 2010). Petra et al. investigated various substituted amino ethanol based bidentate and tetradentate ligands for the transfer hydrogenation of the prochiral ketones with $RuCl_2$(*p*-cymene)]$_2$. The best results were obtained using the benzyl substituted amino alcohol skeleton as the ligand (acetophenone conversion was 91% with 95% ee). Furthermore, it was indicated that the bidentate coordination was desirable even for the tetradentate ligand and that the catalytic activity was significantly reduced by the tetradentate ligands (Petra et al., 1999) (Figure 6.1).

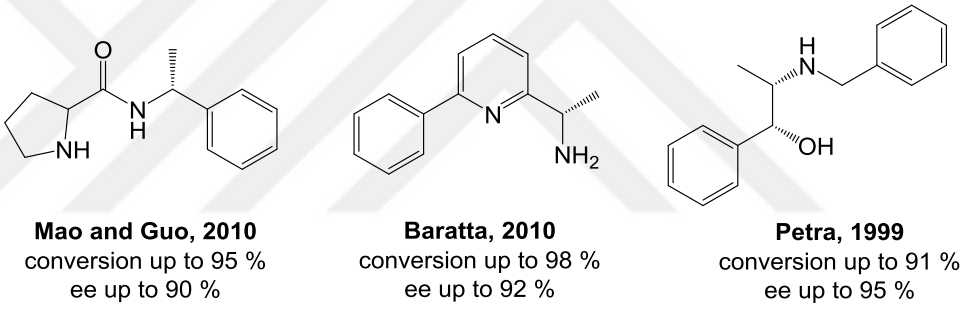
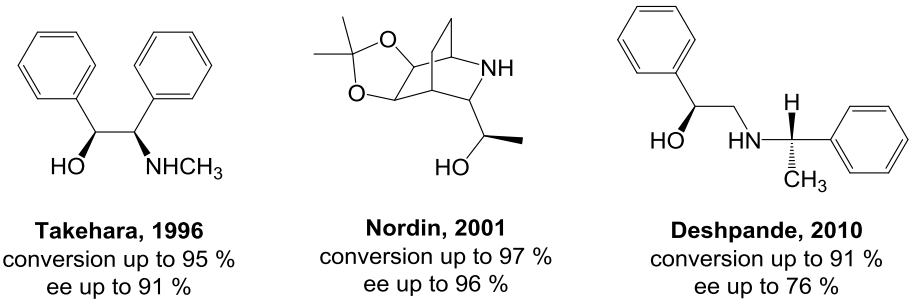


Figure 6.1 Transfer Hydrogenation of ketones using amino alcohol ligands

Takehara et al. prepared ephedrine molecules containing an amino alcohol backbone and used them as chiral auxiliaries for transfer hydrogenation of aromatic ketones with Ru (II). The best results were optained with acetophenone in one hour at mild conditions; ee 91%, conversions 95% (Takehara et al., 1996). Another important study was carried out by Nordin et al. They reported on the use of dioxolane based amino alcohols derivatives in the Ru-catalyzed transfer hydrogenation of aromatic ketones with azanorboronyl alcohol as a ligand, obtained high ee values (85-99%) were obtained. The best conversion of acetophenone achieved was 97% with 96% ee (Nordin et al., 2001). Deshpande et al. synthesized amino alcohol ligands starting from cheaper and easily accessible amino acids such as lactic acid and mandelic acid, and used synthesized ligands in ATH as catalysts with different Ru (II) salts. The best results were achieved with

$[RuCl_2(p\text{-cymene})]_2$ high conversion values (up to 91%) and enantioselectivity (up to 76%) (Deshpande et al., 2010) (Figure 6.2).



Takehara, 1996
conversion up to 95 %
ee up to 91 %

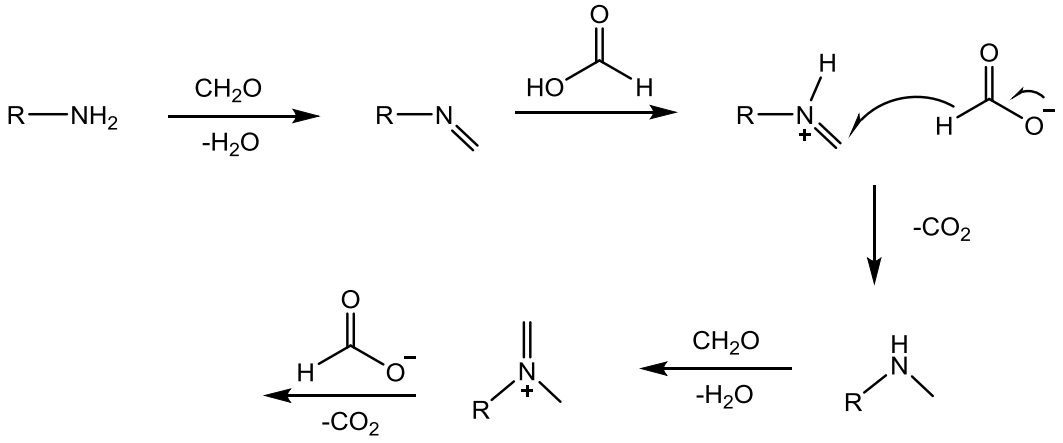
Nordin, 2001
conversion up to 97 %
ee up to 96 %

Deshpande, 2010
conversion up to 91 %
ee up to 76 %

Figure 6.2 Transfer Hydrogenation of acetophenone using amino alcohol ligands

6.1.3 Eischweiler Clarke reaction

This reaction allows the formation of tertiary amines from primary or secondary amines using formaldehyde and formic acid. Protonated formaldehyde forms the iminium ion. The resulting iminium ion interacts with the formic acid and the carbon dioxide is released to form the methylated ammonium ion. After deprotonation, the final product, methylated amine, is obtained. The reaction mechanism is shown in scheme 6.4. The methylated chiral amino alcohol-derived ligands can be readily prepared with this reaction.



Scheme 6.4 The general mechanism of methylation

6.1.4 Asymmetric Henry reaction using *β*-amino alcohols

There are a number of important studies on the use of *β*-amino alcohols as ligands in the Henry reaction (Mansawat et al., 2007; Guo et al.,2011)(Figure 6.3).

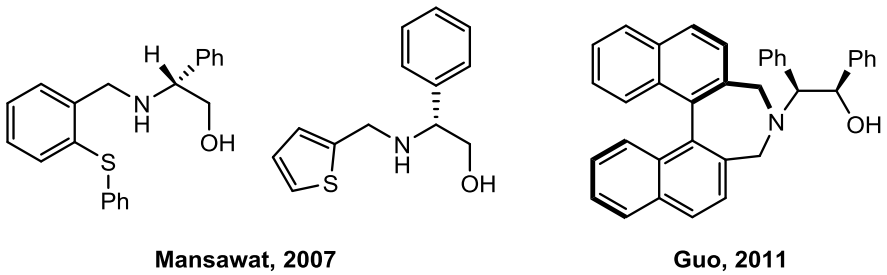
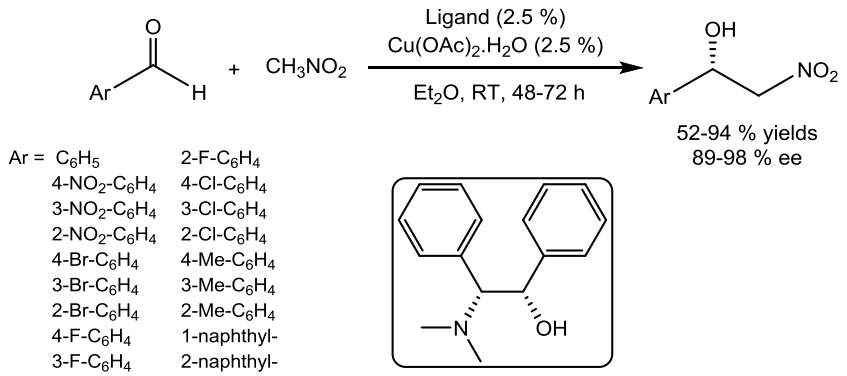


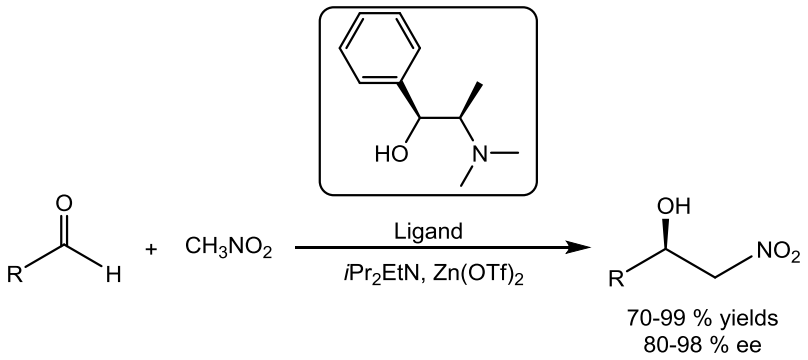
Figure 6.3 Examples of *β*-amino alcohols used in the Henry reaction

Qin and co-workers prepared amino alcohol derivatives and obtained simple and enantioselective catalysts over Cu(II) salt. They synthesized tertiary amine derivatives using commercially available chiral amino ethanol and amino indanol derivatives and investigated their catalytic effects with different optimization studies. Different metal salts, different solvents, different catalyst ratios and substrates were investigated on a wide scale and the effects on the enantioselectivity in the reaction (Qin et al., 2012) (Scheme 6.5).



Scheme 6.5 Henry reactions of aromatic aldehydes with Qins' ligand

In one of the earliest applications of the Henry reaction, Palomo and colleagues reported a simple and good enantioselective catalytic by using *β*-chiral amino alcohol-zinc(II) complex using *N*-methylephedrine and $Zn(OTf)_2$ with *i*PrNEt$_2$. With the catalyst system used, enantiomeric excess values of 80-98% were generally achieved with yields of 70-99% (Palomo et al., 2005) (Scheme 6.6).



Scheme 6.6 Henry reaction of an aldehyde promoted by a chiral *β*-amino alcohol ligand over zinc triflate in the presence of nitrometane and *i*Pr_2EtN.

6.1.5 Configurations of *β*-amino alcohols

Enantiomers have identical physical and chemical properties except for their interactions with anything chiral. Diastereomers have different melting points, boiling points, physical constants and chemical reactivity. Their rates of reaction are different.

In *β*-amino alcohols obtained by epoxide opening, more than one stereogenic center may be present, depending on the configuration of the epoxide and the substrate used. While purifying the resulting structures, more than one stereoisomer may be obtained. This is an open situation for selection, in other words diastereoselectivity, in which one or more occurrences of a diastereomer are preferred in an organic reaction using different catalysts. On the other hand, these diastereomers can be obtained in pure form by chromatographic methods and purification methods such as crystallization. It can also be identified by various instrumental methods. The most commonly used method is NMR. The ^{1}H NMR chemical shifts and signals of the protons are extremely characteristic. The position of the tertiary carbon and the signals of the adjacent carbons in ^{13}C NMR give an idea of the characterization of the diastereomers.

6.2 Results and Discussion

It is clear from the literature that substituents connected to an amino alcohol structure significantly affect the selectivity and conversion of catalytic reactions. As explained in general information, the use of synthesized ligands as catalysts by combining different commercially available epoxides with different chiral amine building blocks can bring many advantages.

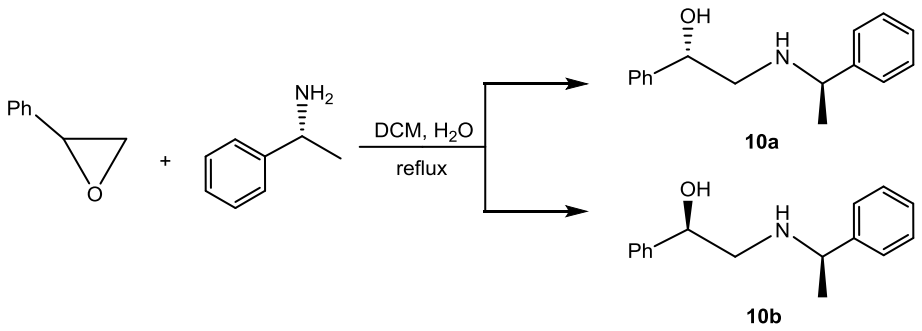
Although chiral *β*-amino alcohols are widely used in catalytic asymmetric syntheses, asymmetric Henry reactions using such amino alcohols as ligands have not been well studied and only a few examples have been published.

In the light of this information, our aim describes the synthesis and characterizations of a series of *β*-amino alcohols using amine derivatives and different epoxides (Figure 6.4). Another aim of the work is to test the ability of the NO type bidentate ligands to catalyze the asymmetric Henry and transfer hydrogenation reactions.

Figure 6.4 Chiral *β*-amino alcohols ligands

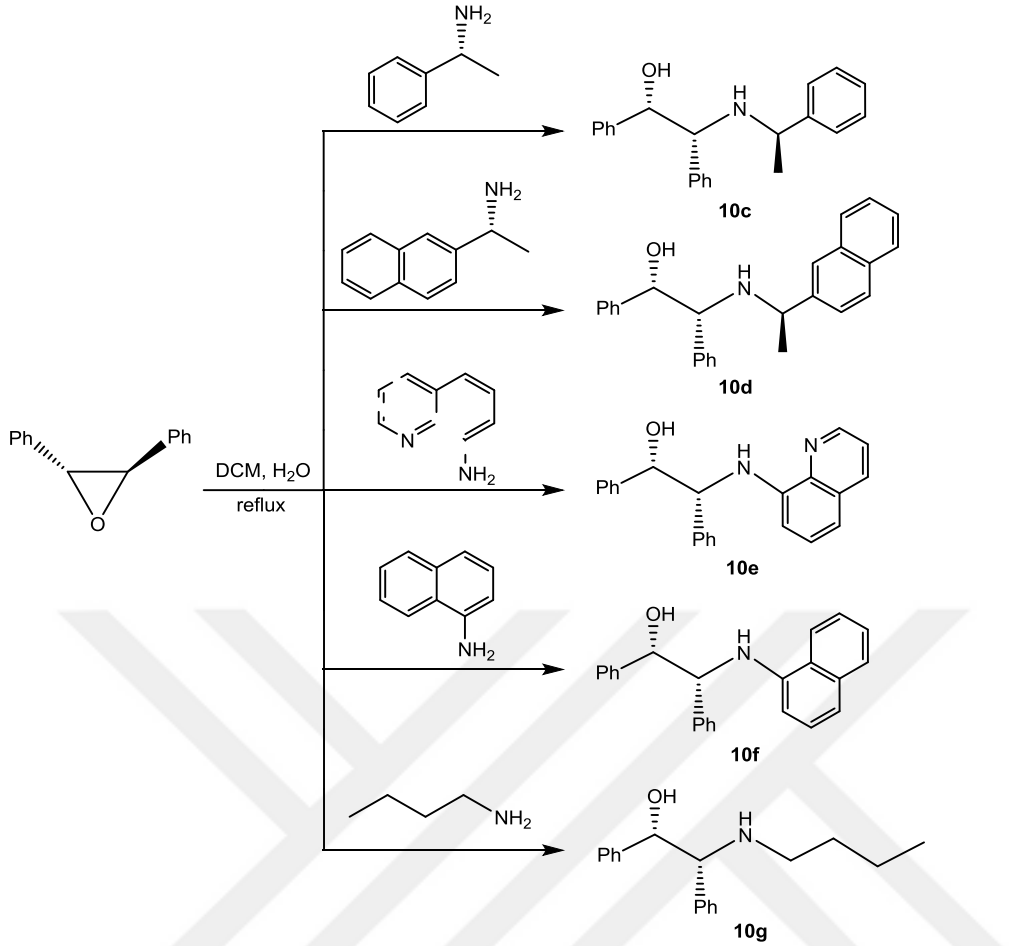
6.2.1 Preparation of *β*-amino alcohols

The chiral *β*-amino alcohol ligands **10a** and **10b** were synthesized with (*R*)-(+)-methylbenzylamine starting from the racemic styrene oxide (Scheme 6.7). A chiral center was found on the carbon attached to the -OH group, while the other chiral center was on the carbon linked to -N of the amino alcohol.



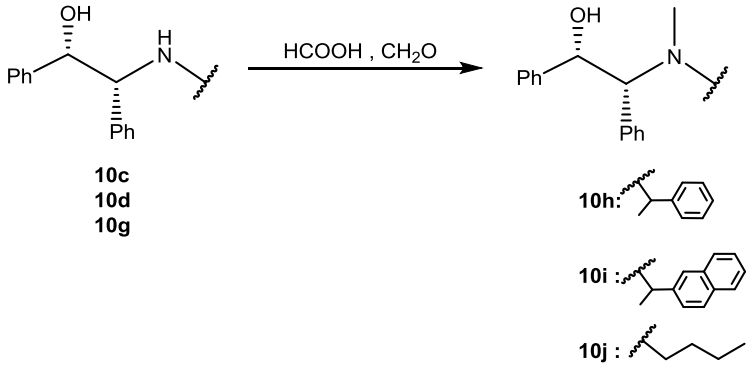
Scheme 6.7 Amino alcohols derived from (±) styrene oxide

The ligands **10c-g** were obtained as a result of opening the *trans*-stilbene oxide ring with aromatic amines ((*R*)-(+)-methylbenzylamine, (*R*)-(+)-1-(2-naphthyl)ethylamine, 8-aminoquinoline and 1-naphthylamine) and aliphatic *n*-butylamine, as shown in scheme 6.8. In the ligands **10c** and **10d** which were derived from ((*R*)-(+)-methylbenzylamine and (*R*)-(+)-1-(2-naphthyl)ethylamine three chiral centers were formed, while the ligands **10e**, **10f**, **10g** had two chiral centers.



Scheme 6.8 Different substituents of amino alcohols derived from *trans*-stilbene oxide

The tertiary methylamine derivatives ligands **10h**, **10i**, **10j** were synthesized from ligands **10c**, **10d**, **10g**, which were secondary amines, by the classical methylation reaction known as Eischweiler Clarke in the literature (Scheme 6.9).



Scheme 6.9 Methylation of *β*-amino alcohols

Selected physical properties, being melting points, yields and characteristic IR vibrations of the ligands **10a-j** are given in table 6.1. Ligands **10a-g** were obtained as white or colored solid. Ligands **10h-j** were obtained as colorless oil. All of the ligands were air stable compounds. They were soluble in polar solvents. The infrared spectra of **10a-j** showed several vibrations bands of different intensities in the 4000-400 cm^{-1} region. The presence of the N-H groups in secondary amino alcohols **10a-g** were confirmed with υ(N-H) stretching vibrations between 3544 and 3285 cm^{-1}. Tertiary methylamines (**10h-j**) showed characteristic υ(C-N) vibrations between 1175-1140 cm^{-1}.

Table 6.1 Melting points, yields, selected IR vibrations of the compounds **10 a-j**

Compound	Yield (%)	mp (°C)	IR (υ cm^{-1})
10a	22	90-91	3285 (N-H)
10b	64	144-145	3289 (N-H)
10c	90	133-134	3295 (N-H)
10d	84	156-157	3296 (N-H)
10e	67	148-150	3395 (N-H)
10f	71	149-150	3544 (N-H)
10g	79	128-130	3303 (N-H)
10h	65	-	1141 (C-N)
10i	70	-	1140 (C-N)
10j	68	-	1175 (C-N)

The characterization of the ligands were further verified with NMR spectroscopy. Ph-C***H***-OH resonances were observed as dublet between 5.39-2.66 ppm. In some of the spectra, O-***H*** and N-***H*** peaks were clearly observed as broad singlet. C$\boldsymbol{H_2}$-NH resonances of ligands **10a** and **10b** were obtained as double doublet at 2,80-2,60 ppm. Ph-C***H***-NH resonances of amino alcohols **10c-j** were obtained doublet between 4.85-3.81 ppm. The tertiary methylamine derivatives ligands **10h-j** were given C$\boldsymbol{H}_3$ resonances as singlet at 2.32-2.30 ppm. As examples, ^{1}H NMR spectra of the amino alcohol ligands **10c** and **10h** are given below in figures 6.5 and 6.6. In the material and method part, their characterizations are given fully.

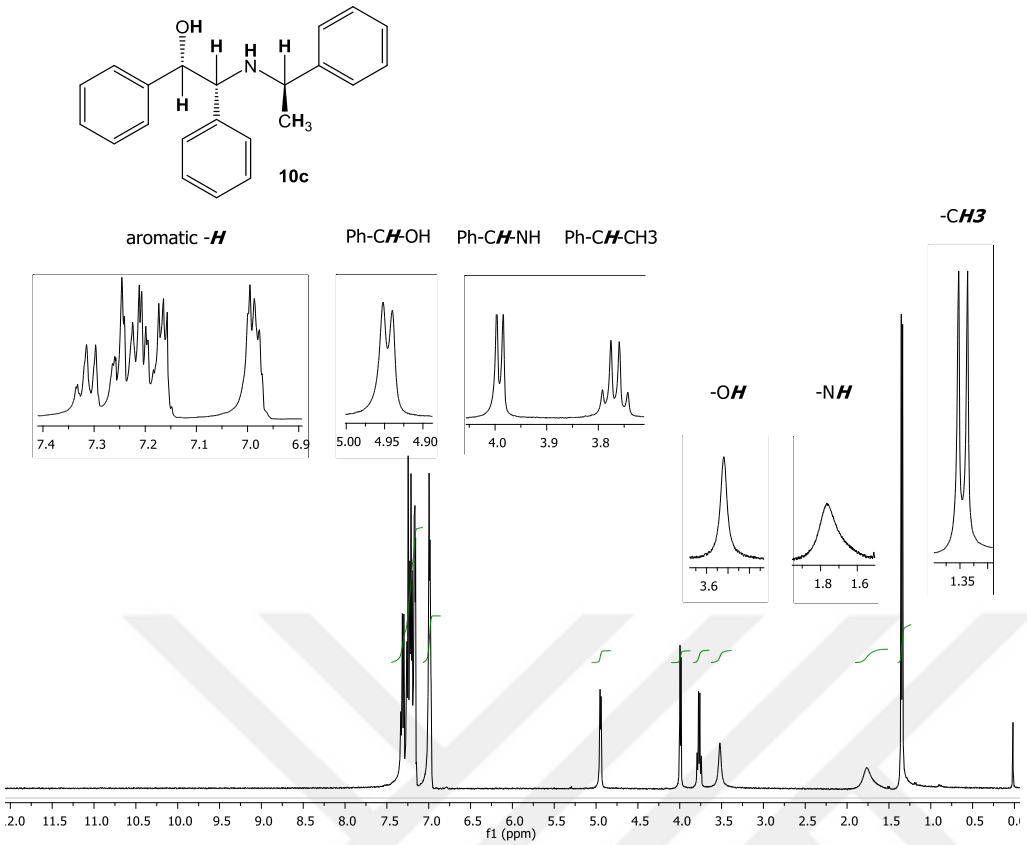


Figure 6.5 [1]H NMR of the ligand **10c**

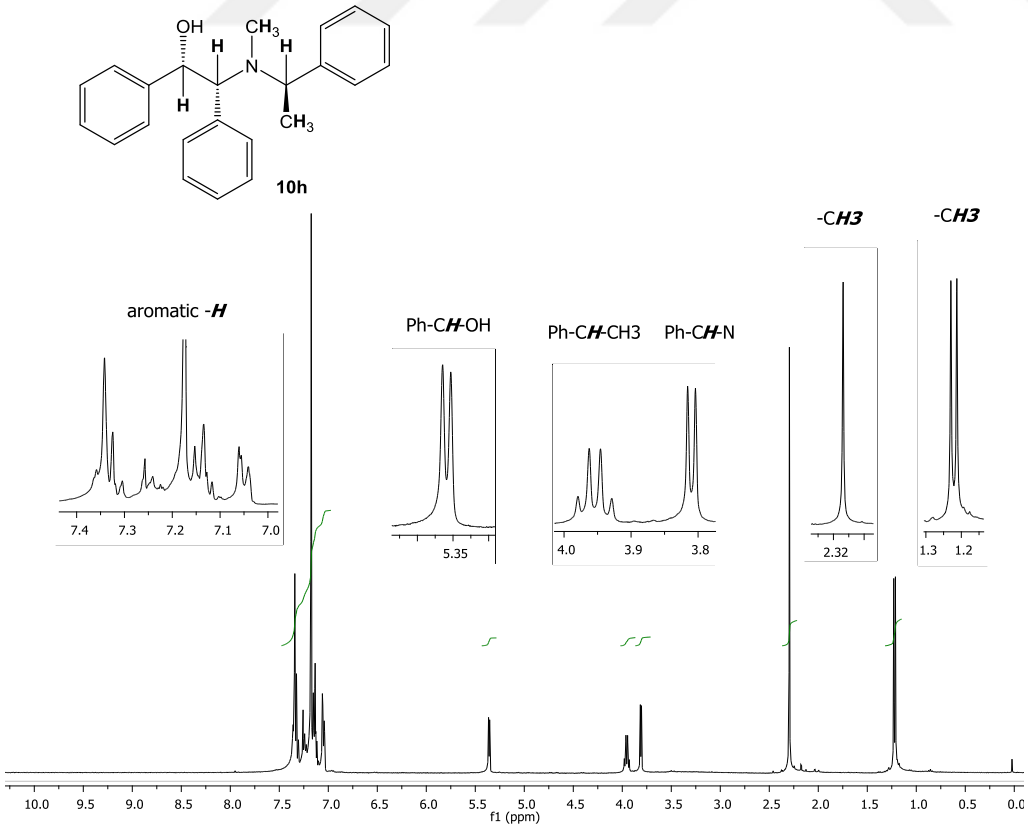


Figure 6.6 [1]H NMR of the ligand **10h**

6.2.2 Determination of configuration of the synthesized *β*-amino alcohols

Characterization of the chiral *β*-amino alcohol ligands (**10a-j**) was carried out using ^{1}H NMR. Previously, ligands having the same scaffold as **10a** and **10b** synthesized using racemic epoxide and (*S*)-(-)-methylbenzylamine have been reported (Boukhari et al., 2010). They obtained different products A and B from (*S*)-(-)-methylbenzylamine, but did not determine the exact configurations. ^{1}H NMR makes use of the difference in the chemical shift of the proton carried by the tertiary carbon. The chemical shift values of this proton shielded by oxygen position were interpreted (Figure 6.7).

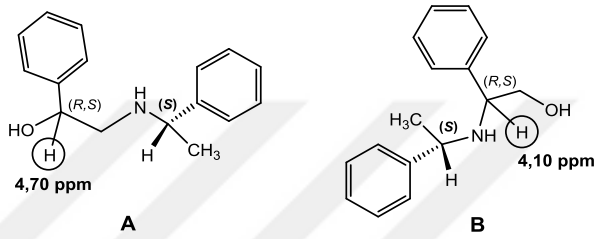
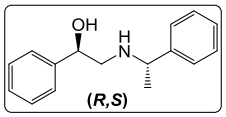
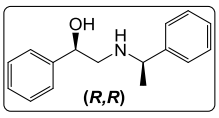


Figure 6.7 The identidication of isomers A and B by Boukhari

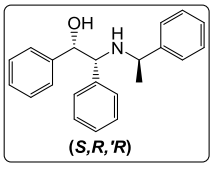
The configuration of ligands **10a** (*S,R*), **10b** (*R,R*) and **10c** (*S,R,'R*) were determined by comparison with the literature data given below. Iuliano and co-workers reported the structure of the *R, R* product, **10b** (Iuliano et al., 1995). This showed significant differences from the ^{1}H NMR of structure **A** reported by Boukhari. This means the Boukhari structure **A** must have the *R, S* configuration and therefore be the enantiomer of **10a**. Likewise, ligand **10c** was synthesized for use in the asymmetric hydrogenation reaction and showed the same confuguration as our target structure (Gamsey et al., 2005). The configuration of the ligands we synthesize, their physical properties and the comparison of ^{1}H NMR data were shown below in figure 6.8.



Author	CH-OH	CH_2-NH	CH-NH	mp (°C)
Boukharis'	4,70 dd	2,80; 2,60 dd	3,80 q	86



Iulianos'	4,55 dd	2,8-2,6 m	3,75 q	145



Gamseys'	4,96 t	-	3,78 q	132

Figure 6.8 ^{1}H NMR chemical shifts, signals and melting points of the comparative compounds

At the same time NMR data give a clear idea of whether the synthesized diastereomers are pure or not. The excess of the peaks, which are characteristically distinguishable, can be used to understand the diastereomers in the mixture. As seen in the figure 6.9, there are double doublet and quartet peaks of two different compounds. In the mixture, it can be said that one diastereomer is the major and the other is the minor. In the material and method part, the characterizations of ligands were extensively explained.

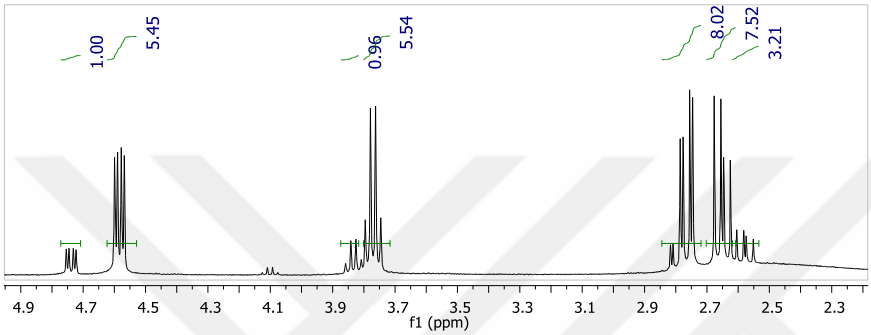


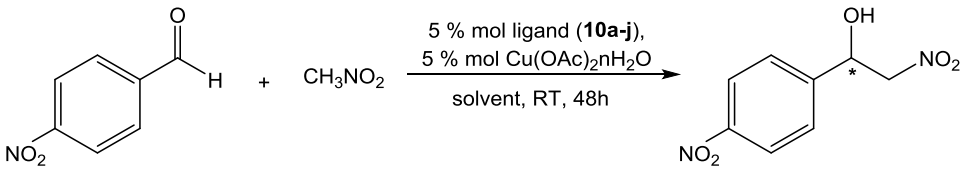
Figure 6.9 ^{1}H NMR of the mixture of diastereomers **10a** and **10b** initially obtained

6.2.3 Asymmetric Henry reaction catalyzed by *β*-amino alcohols derived from epoxides

The NO type bidentate ligands **10a-j** were used as catalysts in the asymmetric Henry reaction by going through reactions with 4-nitrobenzaldehyde and nitromethane in the presence of $Cu(OAc)_2.nH_2O$. The experimental results are summarized in Table 6.2.

The reactions were carried out with different solvents taking into account that the solvent effect may lead to different results. When Et_2O and THF were used as solvent with ligand **10c**, the yield of the reactions was decreased from 66 % to 35-59 % compared with EtOH (Table 6.2, Entries 3, 4, 5). When the solvent of the reaction with ligand **10d** was changed from EtOH to THF, the reaction yield decreased from 73 to 30 with almost the same ee (15%, 12%) (Table 6.2, Entries 6, 7). The decrease in the yield of the reaction was observed in the same manner as the ligand **10e** from 76% to 57% (Table 6.2, Entries 8, 9). The decrease in the reaction yield due to solvent effect was also observed with ligand **10g** (Table 6.2, Entries 11, 12). Without the solvent in the reaction medium, the obtained ee values were not increased (Table 6.2, Entry 16).

Table 6.2 Optimization of the ligand and solvent effect in the Henry reaction[a]



Entry	Ligand	Solvent	Yield[b](%)	ee[c](%)	Config.[d]
1	**10a**	EtOH	78	15	*S*
2	**10b**	EtOH	62	0.5	*R*
3	**10c**	EtOH	66	13	*S*
4	**10c**	Et_2O	35	7	*S*
5	**10c**	THF	59	20	*R*
6	**10d**	EtOH	73	15	*R*
7	**10d**	THF	30	12	*R*
8	**10e**	EtOH	76	3	*S*
9	**10e**	THF	57	0.7	*S*
10	**10f**	EtOH	62	1	*S*
11	**10g**	EtOH	80	3	*R*
12	**10g**	THF	59	3	*R*
13	**10h**	EtOH	35	1	*R*
14	**10h**	THF	48	2	*R*
15	**10h**	H_2O	87	2	*R*
16	**10h**	-	68	0.3	*R*
17	**10i**	EtOH	40	9	*R*
18	**10i**	THF	52	10	*R*
19	**10j**	EtOH	47	0.1	*R*

[a]All reactions were performed with 1 mmol 4-nitrobenzaldehyde, 5% mmol ligand and $Cu(OAc)_2.nH_2O$ and 10 mmol nitromethane in 2 mL EtOH at ambient temperature in 48 h.

[b]Isolated yields after column chromatography using 3:1 hexane:EtOAc solvent system.

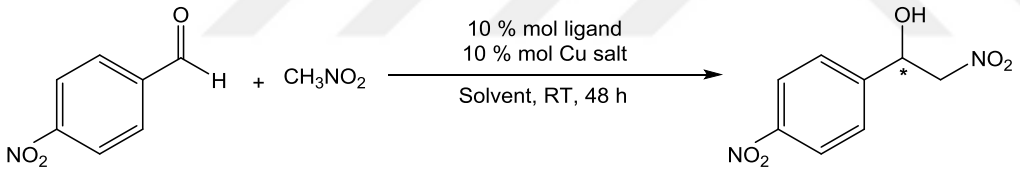
[c]Determined by HPLC analysis using a Chiracel OD-H column 90:10 hexane:IPA system, flow rate 1 mL/min, 267 nm.

[d]The absolute configuration of the major product was assigned by comparison with the literature values.

Slightly better reaction yield was observed in EtOH with ligand **10g** which contained a butyl group (80%) (Table 6.2, Entry 11). Although, the highest yield (87%) was obtained when H_2O was selected as the solvent with ligand **10h** which was tertiary methylamine derivative, the ee value was very low (2%) (Table 6.2, Entry 15). Desired Henry reaction product was obtained in the reactions performed in moderate yields (30 to 87%), but the observed enantiomeric excess values were not as high as it was expected. The highest ee was 20% with ligand **10c** in THF. The enantioselectivities were very poor and almost close to the racemate with all the catalysts systems (Table 6.2).

The acidity of the complex in the Henry reaction medium can change the efficiency and enantioselectivity of the reaction. The Lewis acidity of copper salt can facilitate deprotonation in the reaction. In the literature, it was shown that copper (I) halide salts catalyze the reaction with *β*-amino alcohols, resulting in high enantioselectivity (Constable et al., 2009; Xu et al., 2015). Thus, the effect of copper (I) halide salts on enantiomeric excess was investigated (Table 6.3).

Table 6.3 Results of catalytic screening using selected ligands with copper(I) salts in the asymmetric Henry reaction[a]



Entry	Ligand	Cu Salt	Solvent	Yield[b](%)	ee[c](%)	Config.[d]
1	**10a**	Cu(I)Cl	IPA	64	10	*R*
2	**10b**	Cu(I)Cl	IPA	78	2	*R*
3	**10c**	Cu(I)Cl	IPA	64	2	*R*
4	**10e**	Cu(I)Cl	IPA	52	6	*S*
5	**10e**	Cu(I)CN	EtOH	24	8	*R*
6	**10e**	Cu(I)Br	EtOH	26	6	*R*
7	**10g**	Cu(I)Cl	IPA	62	4	*S*

[a] All reactions were performed with 1 mmol 4-nitrobenzaldehyde, 10 % mmol ligand and Cu(I) salt and 10 mmol nitromethane in 2 mL solvent at ambient temperature in 48 h. [b]Isolated yields after column chromatography using 3:1 hexane:EtOAc solvent system. [c]Determined by HPLC analysis using a Chiracel OD-H column 90:10 hexane:IPA system, flow rate 1 mL/min, 267 nm. [d]The absolute configuration of the major product was assigned by comparison with the literature values.

The catalyst ratio and solvent selection were selected parallel to the previous work of Xu et al. (Table 6.3, Entries 1-4 and 7). All observed ee values of the synthesized ligands with Cu (I) salts were disappointing. The ee values (up to 10%) and yields (up to 78%) of *β*-amino alcohol ligands are shown in table 6.3. However, Cu (I) chloride could be said to give the reaction product with higher yield in polar protic solvent as IPA (Table 6.3, Entries 1-4).

NO type bidentate *β*-amino alcohol ligands (**10a-j**) derived from styrene oxide and *trans*-stilbene oxide were carried out for the Henry reaction. Unfortunately, the reaction products were achieved in moderate yields without high enantioselectivity. So, further optimizations such as catalyst loading, temperature and substrate selection were not be performed.

6.2.4 Transfer hydrogenation reaction catalyzed by *β*-amino alcohols derived from epoxides

Chiral ligands (**10a-g)** were used in the transfer hydrogenation reaction of acetophenone using $[RuCl_2(p\text{-cymene})]_2$ complex as a catalyst precursor and IPA as a hydrogen donor. The results are presented in figure 6.10. Reactions were monitored at reflux temperature for 2 hours with 5 mL IPA in 10% mol KO^{t}Bu. The results showed that *β*-amino alcohol ligands **10a-g** could catalyze the reaction with ruthenium salt (up to yield 100 %).

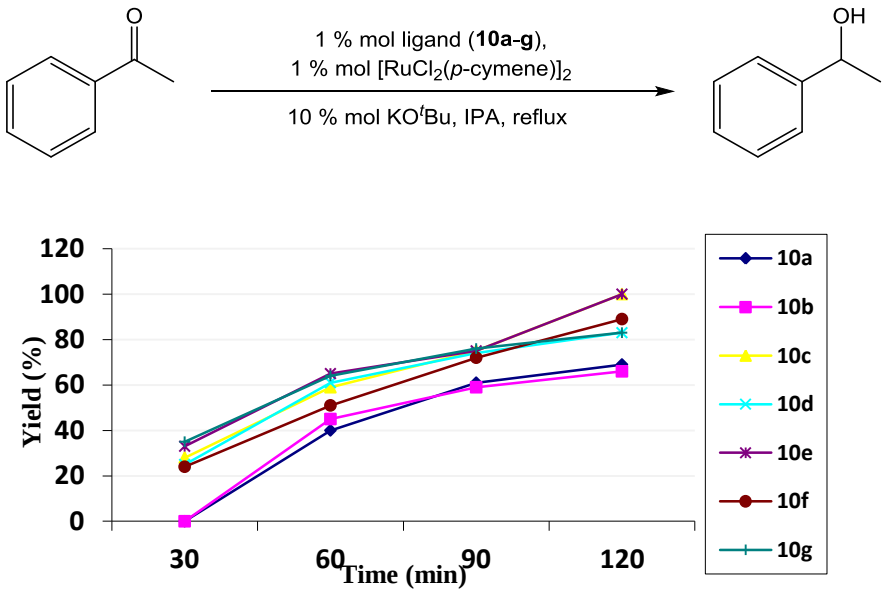


Figure 6.10 Time dependency of the catalytic TH of acetophenone using chiral *β*-amino alcohol ligands

Ligand **10e** gave higher conversion due to the effect of a bulky substituent on the nitrogen atom. Using the same stoichiometric ratios with the amount of 2 mL IPA, the ligand **10e** showed complete conversion in a shorter time (90 min), while there was no significant change in ee value (Table 6.4, Entry 6). Thus, based on 90 minutes, the enantioselectivity of the reactions was studied as shown in table 6.4. However, although the conversion of the reactions was high, the enantiomeric excess values were low. Therefore, in order to enhance enantioselectivity, the ligand **10e** was selected and tested at the same stoichiometric ratio at lower temperature. At 40 °C and 25 °C, the formation of the transfer hydrogenation product of acetophenone which is 1-phenylethanol, was not observed (Table 6.4, Entries 7 and 8).

Table 6.4 Transfer hydrogenation of acetophenone using chiral *β*-amino alcohol ligands[a]

Entry	Ligand	IPA (mL)	T (°C)	Conv. %[b] (90 min)	ee (%)[c]
1	**10a**	5	82	61	1
2	**10b**	5	82	59	1
3	**10c**	5	82	75	3
4	**10d**	5	82	74	3
5	**10e**	5	82	75	2
6	**10e**	2	82	100	7
7	**10e**	2	40	-	-
8	**10e**	2	25	-	-
9	**10f**	5	82	72	5
10	**10g**	5	82	76	10

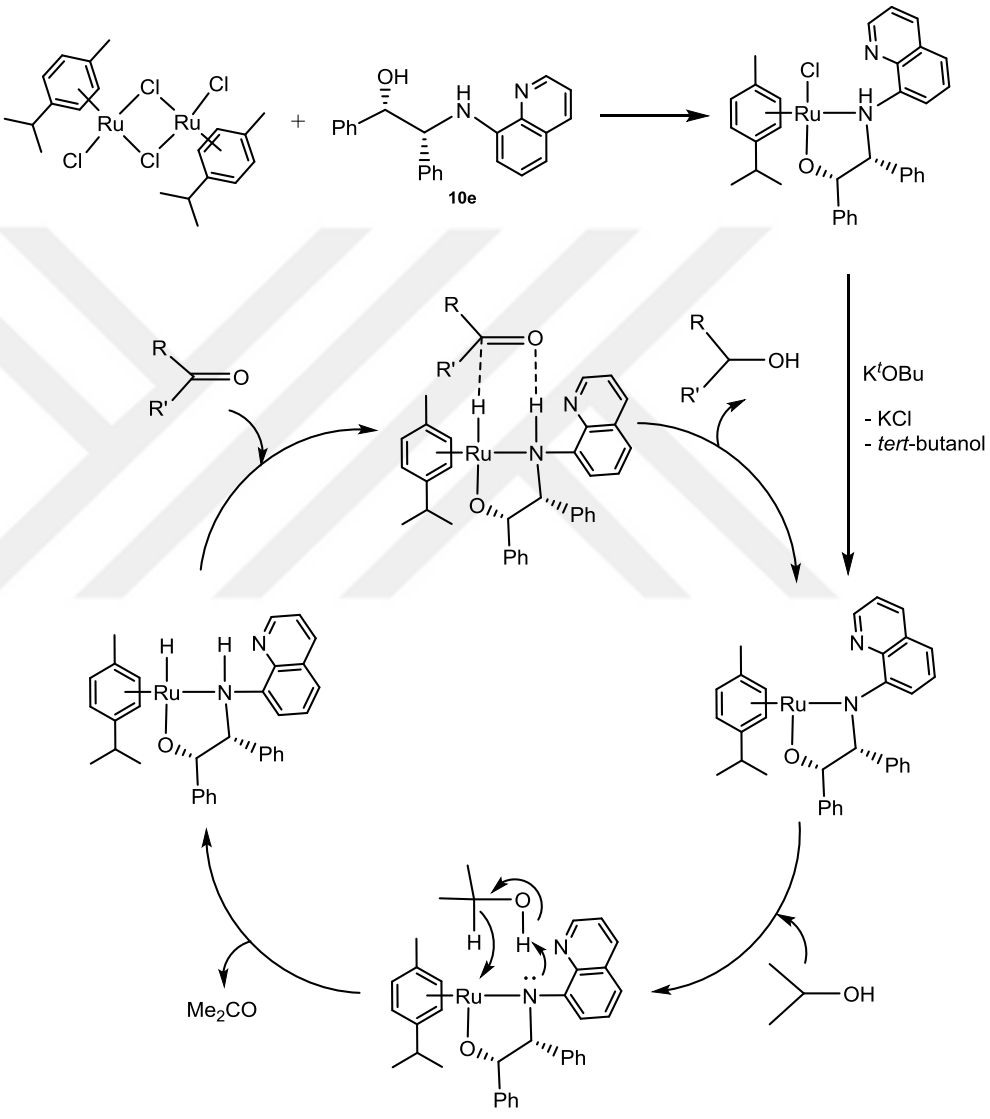
[a]All the reactions were performed 1 mmol acetophenon, 10 % mmol KO^{t}Bu in IPA for 90 minutes. Substrate/Ru/ligand/Base: 100:1:2:10

[b]Determined by gas chromatography for an average of 2 runs.

[c]Determined by HPLC analysis using a Chiracel OD-H column.

The observed yield-conversion values gave similar results when compared with the literature (Deshpande et al., 2010; Petra et al., 1999; Agac et al., 2016). However, the expected high enantioselectivity was not achieved possibly because of the decomposition of the complex in the reaction medium or instability of the catalyst at low temperature (Arena et al., 2012).

The catalytic activity was higher when electron donating, bulky groups, such as quinolinyl, butyl and naphthyl were present. According to the results, ligand **10e** which was derived from 8-aminoquinoline and *trans*-stilbene oxide showed better catalytic activity than the other bidentate NO type *β*-amino alcohol ligands. The reaction mechanism suggested for the transfer hydrogenation of acetophenone in IPA with $[RuCl_2(p\text{-cymene})]_2$ of the ligand **10e** was shown below (Scheme 6.10).



Scheme 6.10 Suggusted mechanism for transfer hydrogenation reaction

6.3 Conclusion

NO type bidentate chiral *β*-amino alcohol ligands (**10a-j**) were prepared in the presence of different amine derivatives by ring opening of epoxides and characterized by spectroscopic methods. The synthesized *β*-amino alcohol ligands were used as catalysts in the presence of $Cu(OAc)_2.nH_2O$ in the asymmetric Henry reaction of 4-nitrobenzaldehyde. The reaction products, *β*-nitro alcohols, were obtained in the absence of enantioselectivity. Catalytic asymmetric transfer hydrogenation of acetophenone was perfomed with synthesized *β*-amino alcohol ligands **10a-g** in the presence of $[RuCl_2(p\text{-cymene})]_2$. These ligands, especially **10e**, showed good catalytic activity, but showed poor enantioselectivity.

6.4 Material and Method

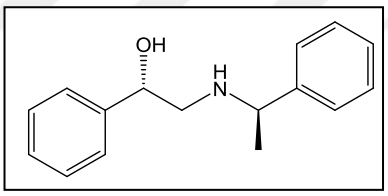
Unless otherwise noted all reactions were performed in air, except involving air-sensitive components were performed under argon atmosphere. The solvents were analytical grade and obtained from commercial suppliers. All chemicals were commercially available and purchased from Merck, Sigma-Aldrich, Alfa Aesar, Fluka, Acros or BDH and used without any purification. Although ligands **10a**, **10b, 10c** and **10f** were previously synthesized compounds as the main skeleton there were different isomers and diastereomers; they were used in catalytic reactions such as imino ketone reduction, enantioselective addition, ring opening and cyclopropanation, and Henry and ATH studies were not performed. (Alcaide et al., 1981; Iuliano et al., 1995; Gamsey et al., 2005; More and Bhanage, 2013; Schön and Naef, 1999). Representative protocol was given for the same class of compounds bearing different substituents and data were presented in Schemes. FTIR Spectra were recorded on a Perkin Elmer Spectrum 100 series. ^1H NMR and ^{13}C NMR spectra were recorded on using 400 MHz Varian NMR spectrometer and 600 MHz Agilent Premium Compact NMR spectrometer at ambient temperature. As solvent $CDCl_3$ was employed, *J* values were in Hz. Melting points were recorded with Gallenkamp electrothermal melting point apparatus. Optical rotations were calculated by Rudolph Research Analytical Autopol I automatic polarimeter with wavelength of 589 nm. Silica gel F_{254} (Merck 5554) precoated plates were used for the monitoring of all reactions by thin-layer chromatography and visualized by ultra-violet light or by staining with ninhydrin dissolved in alcohol. For column chromatography silica gel 60 (Merck 7743) was used. The enantiomeric ratios of the products were determined by HPLC using a 90:10 hexane:IPA system, flow rate 1 mL/min, 267 nm with

Chiralcel OD-H column. Elemental analysis was performed by CHNS-932 (LECO) elemental analyzer. Analysis of catalytic experiments perfomed by GC using a Hewlett-Packard 6890 GC.

6.4.1 Preparation of *β*-amino alcohols derived from epoxides (10a-g)

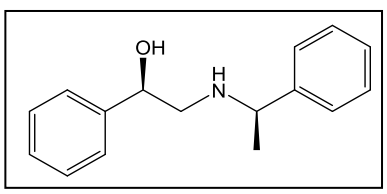
A mixture of 3 mol amine derivative (dissolved in 5 mL of dichloromethane) and 10 mL water were added at 1 mol of racemic epoxide derivative (dissolved in 5 mL of dichloromethane). The mixture was heated to reflux and stirred. The evalution of the reaction was followed by TLC until the epoxide was disappeared. After completion of the reaction, was extractated of aqueous phase with DCM (3 × 10 mL), the organic phase was dried by addition of Na_2SO_4. After evaporating solvent under reduced pressure, the product was purified with column chromatography (1:6 ethyl acetate:hexane) to give the title compound as diastereomers. The crude product was crystallized hexane to give the title compound as white powder.

6.4.2 (1*S*, 2*R*)-2-(1-phenylethyl)amino-1-phenylethanol (10a)



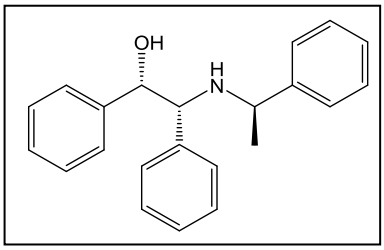
White crystals, 22 % yield, mp: 90-91 °C, IR (CH_2Cl_2): 3285, 3083, 3025, 2965, 2904, 2848, 1956, 1881, 1810, 1671, 1602, 1584, 1548, 1492, 1450, 1421, 1346, 1087, 945, 753 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 7.35-7.23 (m, 10H), 4,72 (dd, *J* = 3.2 Hz, 8.8 Hz, 1H), 3.84 (q, *J* = 6,4 Hz, 1H), 2,80 (dd, *J* = 3.2 Hz, 12 Hz, 1H), 2.57 (dd, *J* = 9.2 Hz, 12.4 Hz, 1H), 1,39 (d, *J* = 6.4 Hz, 3H). $[\alpha]_D^{29}$ = + 136 (*c* 0.5, CH_2Cl_2).

6.4.3 (1*R*, 2*R*)-2-(1-phenylethyl)amino-1-phenylethanol (10b)



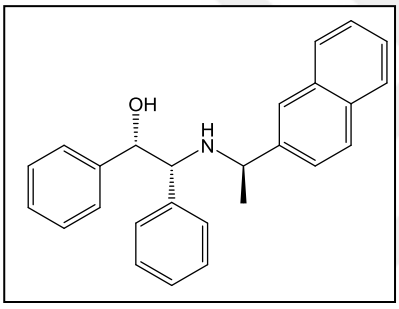
White powder, 64 % yield, mp: 144-145 °C, IR (CH_2Cl_2): 3289, 3082, 3022, 2972, 2941, 2898, 2847, 1949, 1878, 1809, 1756, 1675, 1601, 1492, 1449, 1219, 1123, 1082, 1063, 1028, 982, 759, 700 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 7.34-7.22 (m, 10H), 4.57 (dd, *J* = 3.6 Hz, 8.4 Hz, 1H), 3.77 (q, *J* = 6,8 Hz, 1H), 2.77 (dd, *J* = 4.0 Hz, 12.0 Hz, 1H), 2.64 (dd, *J* = 8.4 Hz, 12.0 Hz, 1H), 1.38 (d, *J* = 6.8 Hz, 3H). $[\alpha]_D^{29}$ = + 36 (*c* 0.5, CH_2Cl_2).

6.4.4 (1*S*,2*R*,1′*R*)-2-(1′-phenylethyl)amino-1,2-diphenylethanol (10c)



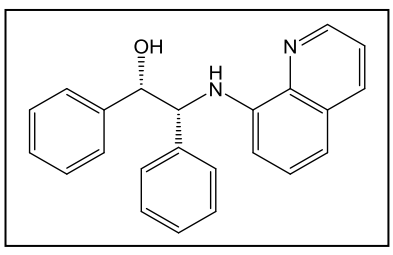
White powder, 90 % yield, mp: 133-134 °C, IR (CH_2Cl_2): 3295, 3087, 3062, 3025, 2913, 2874, 1953, 1877, 1755, 1602, 1493, 1455, 1435, 1377, 1336, 1263, 1194, 1115, 1090, 1054, 926, 882, 832, 754, 710 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 7.33-6.97 (m, 15H), 4.95 (d, *J* = 4.8 Hz, 1H), 3.99 (d, *J* = 5.2 Hz, 1H), 3.77 (q, *J* = 6.8 Hz, 1H), 3.52 (br, s, OH), 1.77 (br, s, NH), 1.35 (d, *J* = 6.4 Hz, 3H). $[\alpha]_D^{29}$ = + 40 (*c* 0.25, CH_2Cl_2).

6.4.5 (1*S*,2*R*,1′*R*)-2-(1′-(2-naphthyl)ethylamino-1,2-diphenylethanol (10d)



White powder, 84 % yield, mp: 156-157 °C, IR (CH_2Cl_2): 3296, 3083, 3060, 3051, 3022, 2970, 2868, 2323, 1951, 1737, 1489, 1453, 1382, 1275, 1267, 1053, 820, 750, 702 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 7.84-7.00 (m, 17H), 5.00 (d, *J* = 5.2 Hz, 1H), 4.02 (d, *J* = 4.8 Hz, 1H), 3.95 (q, *J* = 6.4 Hz, 1H), 3.52 (br, s, OH), 1.84 (br, s, NH), 1.43 (d, *J* = 6.8 Hz, 3H). ^{13}C-NMR (400 MHz, $CDCl_3$, δ ppm): 142.8, 140.5, 139.2, 133.4, 132.8, 128.4, 128.2, 128.0, 127.8, 127.6, 127.4, 127.3, 126.6, 126.1, 125.6, 124.9, 124.7, 75.4, 65.7, 54.7, 22.9. Elemental analysis, calculated for $C_{26}H_{25}NO$: C, 84.98; H, 6.86; N, 3.81. Found: C, 83.87; H, 6.76; N, 3.83 %. $[\alpha]_D^{29}$ = + 24 (*c* 0.25, CH_2Cl_2).

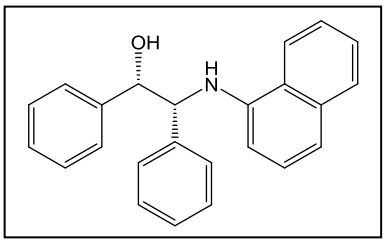
6.4.6 (1*S*,2*R*)-2-(quinolin-8-ylamino)-1,2-diphenylethanol (10e)



Light yellow powder, 67 % yield, mp: 148-150 °C, IR (CH_2Cl_2): 3395, 3060, 3030, 2879, 1575, 1518, 1479, 1453, 1379, 1339, 1128, 1060, 818, 790, 745, 701 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 8.71 (dd, *J* = 4.4 Hz, 1.6 Hz,, 1H), 8.01 (dd, *J* = 8.4 Hz, 1.6 Hz,, 1H), 7.36-7.11 (m, 12H), 7.00 (d, *J* = 8.0 Hz, 1H), 6.45 (d, *J* = 7.6 Hz, 1H), 5.27 (t, *J* = 5.2 Hz, 1H), 4.85 (dd, *J* = 7.2 Hz, 5.2 Hz, 1H), 2.66 (br, s, OH), 1.72 (br, s, NH). ^{13}C-NMR (600 MHz, $CDCl_3$, δ ppm): 147.1, 143.3, 140.4, 138.5, 138.3, 135.9, 128.5, 128.2, 128.1, 128.0, 127.8, 127.6, 127.5,

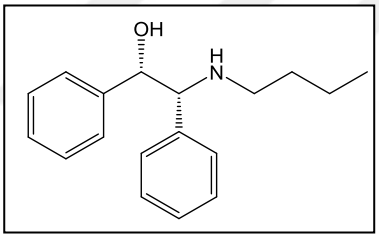
126.6, 121.3, 114.5, 106.4, 63.6. Elemental analysis, calculated for $C_{23}H_{20}N_2O$: C, 81.15; H, 5.92; N, 8.23. Found: C, 79.99; H, 5.62; N, 8.20 %. $[\alpha]_D^{29}$ = - 8 (*c* 0.25, CH_2Cl_2).

6.4.7 (1*S*,2*R*)-2-(naphthalen-1-ylamino)-1,2-diphenylethanol (10f)



Light pink powder, 71 % yield, mp: 149-150 °C, IR (CH_2Cl_2): 3544, 3424, 3061, 3031, 2889, 1950, 1709, 1580, 1525, 1479, 1453, 1408,1346, 1285, 1265, 1125, 1054, 850, 770, 736, 701 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 7.87-7.82 (m, 1H), 7.79-7.75 (m, 1H), 7.49-7.12 (m, 12H), 6.37 (dd, *J* = 7.6 Hz, 1.2 Hz, 1H), 5.20 (t, *J* = 5.2 Hz, 1H), 5.16 (br, s, OH), 4.85 (d, *J* = 4.4 Hz, 1H), 2.42 (d, *J* = 5.2 Hz, 1H), 1.55 (s, 1H). $[\alpha]_D^{29}$ = + 62 (*c* 0.25, CH_2Cl_2).

6.4.8 (1*S*,2*R*)-2-(buta-1-ylamino)-1,2-diphenylethanol (10g)

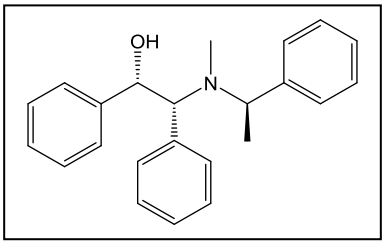


white powder, 79 % yield, mp: 128-130 °C, IR (CH_2Cl_2): 3029, 2952, 2922, 2854, 1930, 1610, 1449, 1428, 1351, 1284, 1198, 1160, 1088, 1056, 964, 919, 887, 837, 766, 701 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 7.26-7.07 (m, 10H), 4.94 (d, *J* = 5.2 Hz, 1H), 3.92 (d, *J* = 5.2 Hz, 1H), 2.58-2.45 (m, 2H), 1.45 (p, *J* = 7.2 Hz, 2H), 1.29-1.21 (m, 2H), 0.84 (t, *J* = 8.0 Hz, 3H). $[\alpha]_D^{29}$ = + 77 (*c* 0.25, CH_2Cl_2).

6.4.9 Preparation of amino alcohols (10h-j)

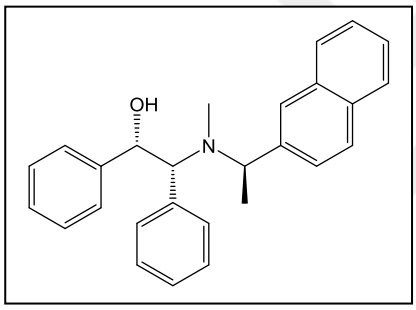
β-Amino alcohol derivative (**10c**, **10d** or **10g**) (1 mmol) was added to the mixture of formaldehyde (37 %, 0.3 mL, 10 mmol) and formic acid (98 %, 0.42 mL, 11 mmol) and the mixture was warmed at 90°C for overnight. After the mixture being cooled to room temperature, made basic with aqueous sodium hydroxide (pH = 10). The suspended reaction mixture was extracted with dichloromethane three times. The combined organic phases were washed with brine and dried with Na_2SO_4, then filtered to remove the solvent under reduced pressure. The crude product was purified by column chromatography (3:1, hexane:EtOAc) which afforded the desired product as coloursless oil.

6.4.10 (1*S*,2*R*,1′*R*)-2-N-methyl-N-[(1′-phenylethyl)]amino-1,2-diphenylethanol (10h)



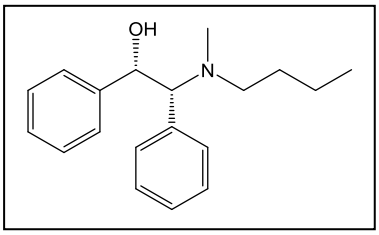
White oil, 65 % yield, IR (CH_2Cl_2): 3453, 3085, 3060, 3028, 2917, 2856, 2797, 1948, 1878, 1807, 1726, 1602, 1493, 1452, 1371, 1203, 1141, 1050, 1028, 776, 738, 700 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 7.36-7.04 (m, 15H), 5.36 (d, *J* = 4.4 Hz, 1H), 3.95 (q, *J* = 6.8 Hz, 1H), 3.81 (d, *J* = 4.0 Hz, 1H), 2.30 (s, 3H), 1.22 (d, *J* = 6.8 Hz, 3H). ^{13}C-NMR (400 MHz, $CDCl_3$, δ ppm):143.9, 141.4, 136.7, 129.5, 128.1, 127.7, 127.6, 127.5, 127.3, 126.8, 126.6, 126.2, 73.0, 72.6, 57.1, 33.5, 11.4. $[\alpha]_D^{29}$ = + 70 (*c* 0.5, CH_2Cl_2).

6.4.11 (1*S*,2*R*,1′*R*)-2-N-methyl-N-[(1′-(2-naphthyl)ethyl]amino-1,2-diphenylethanol (10i)



Oil, 70 % yield, IR (CH_2Cl_2): 3445, 3058, 3028, 2972, 2796, 1734, 1601, 1494, 1453, 1374, 1274, 1193, 1140, 1049, 942, 915, 858, 820, 749, 702 cm^{-1}. ^{1}H-NMR ($CDCl_3$, δ ppm) 7.85-7.20 (m, 17H), 5.39 (d, *J* = 4.4 Hz, 1H), 4.08 (q, *J* = 6.8 Hz, 1H), 3.90 (d, *J* = 4.4 Hz, 1H), 2.32 (s, 3H), 1.33 (d, *J* = 6.8 Hz, 3H). ^{13}C-NMR (400 MHz, $CDCl_3$, δ ppm): 141.7, 136.6, 133.2, 132.5, 129.5, 127.8, 127.7, 127.6, 127.5, 127.4, 126.8, 126.5, 126.3, 125.9, 125.6, 72.9, 72.6, 57.4, 33.6, 11.7. $[\alpha]_D^{29}$ = + 224 (*c* 0.5, CH_2Cl_2).

6.4.12 (1*S*,2*R*)-2-N-methyl-N-(buthyl)amino-1,2-diphenylethanol (10j)



This compound was prepared according to general methylation procedure and characterised by comparison with literature data (Schön and Naef, 1999). Oil, 68 % yield, IR (CH_2Cl_2): 3332, 3060, 3030, 2957, 2928, 2858, 1724, 1682, 1597, 1496, 1450, 1271, 1212, 1175, 1073, 1027, 756, 725, 710 cm^{-1}. $[\alpha]_D^{29}$ = + 60 (*c* 0.25, CH_2Cl_2).

6.4.13 General procedure of Henry reaction

The dark green solution of $Cu(OAc)_2.nH_2O$ (0.01 mmol) and ligand (**10a-j**) (0.01mmol) in 2 mL solvent at room temperature for 2 h. 4-Nitrobenzaldehyde (0.2mmol) and nitromethane (2.0 mmol) were added to the appropriate solution. The reaction mixture was stirred at which point TLC analysis confirmed most of the aldehyde had been consumed. After the solvent was evaporated, the crude product was purified with column chromatography using 1:3 EtOAc:hexane.

6.4.14 General procedure of transfer hydrogenation

All the reactions were carried out with carousel under argon. A mixture of ligand (0.02 mmol) and $[Ru(p\text{-cymene})Cl_2]_2$ (0.01 mmol) were strirred in IPA at 82 °C for a while to form complex. After additon of acetophenone (1 mmol) and 1 mL of 0.1 M KO^tBu (0.1 mmol) solution in IPA was added to the reaction mixture and it was stirred at the refluxing temperature. At the desired reaction times, aliquots were withdrawn from reaction vessel and purified. The reaction progress was monitored by GC.

APPENDIX E: Spectra and Chromatograms

E.1 IR Spectrums

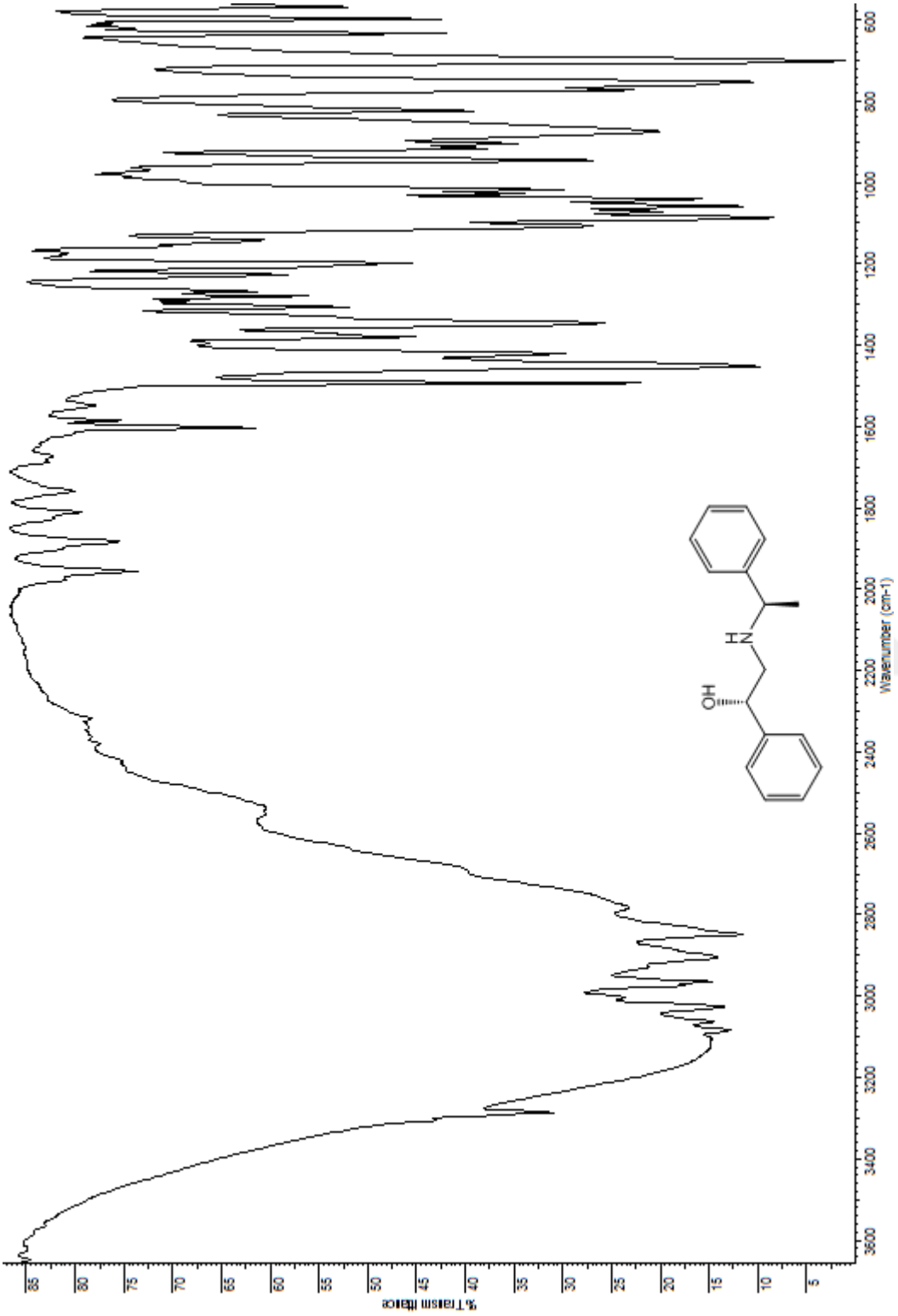


Figure E.1.1 IR spectrum of (1*S*, 2*R*)-2-N[(1-phenylethyl)]amino-1-phenylethanol (**10a**)

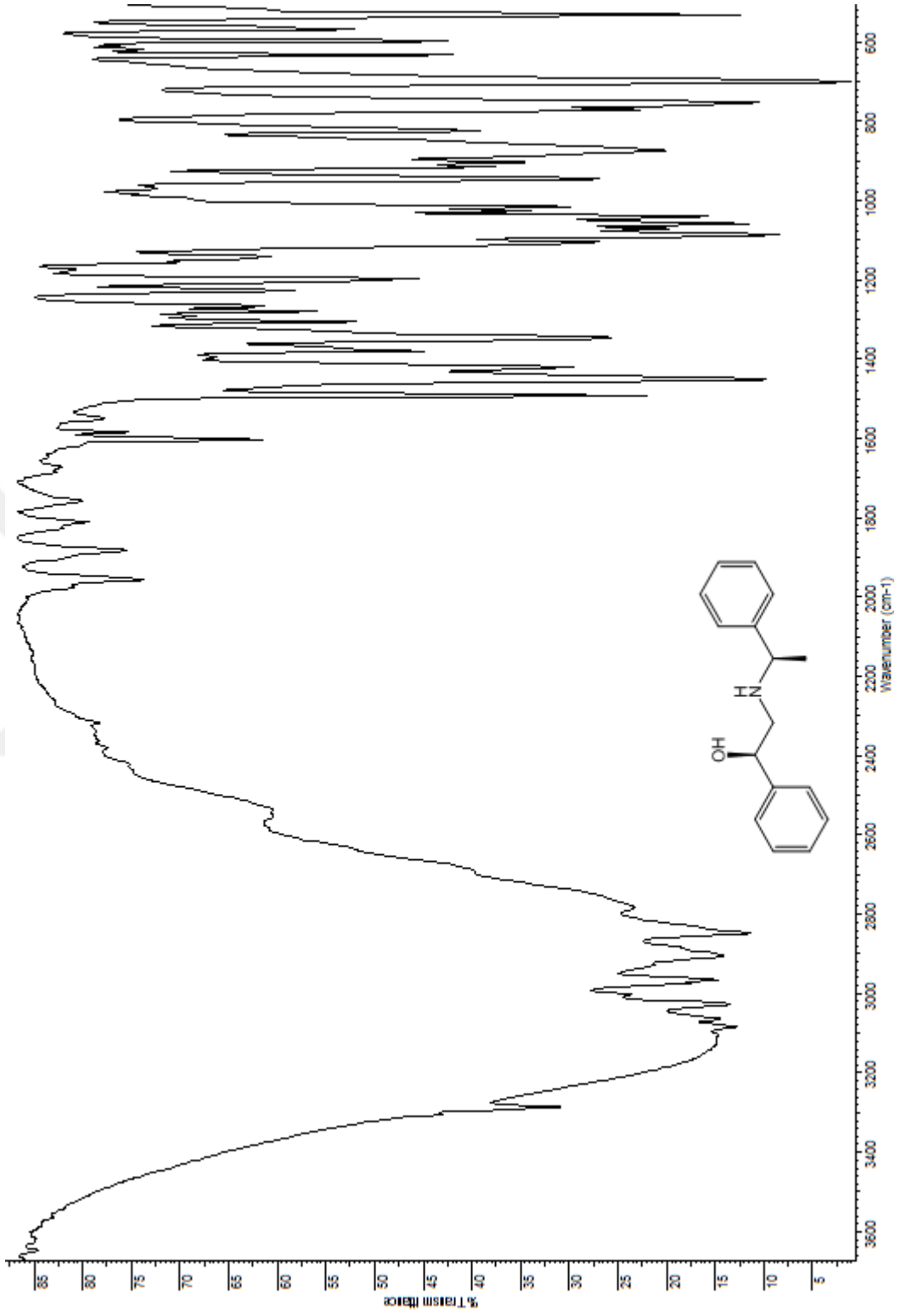


Figure E.1.2 IR spectrum of (1*R*, 2*R*)-2-N[(1-phenylethyl)]amino-1-phenylethanol (**10b**)

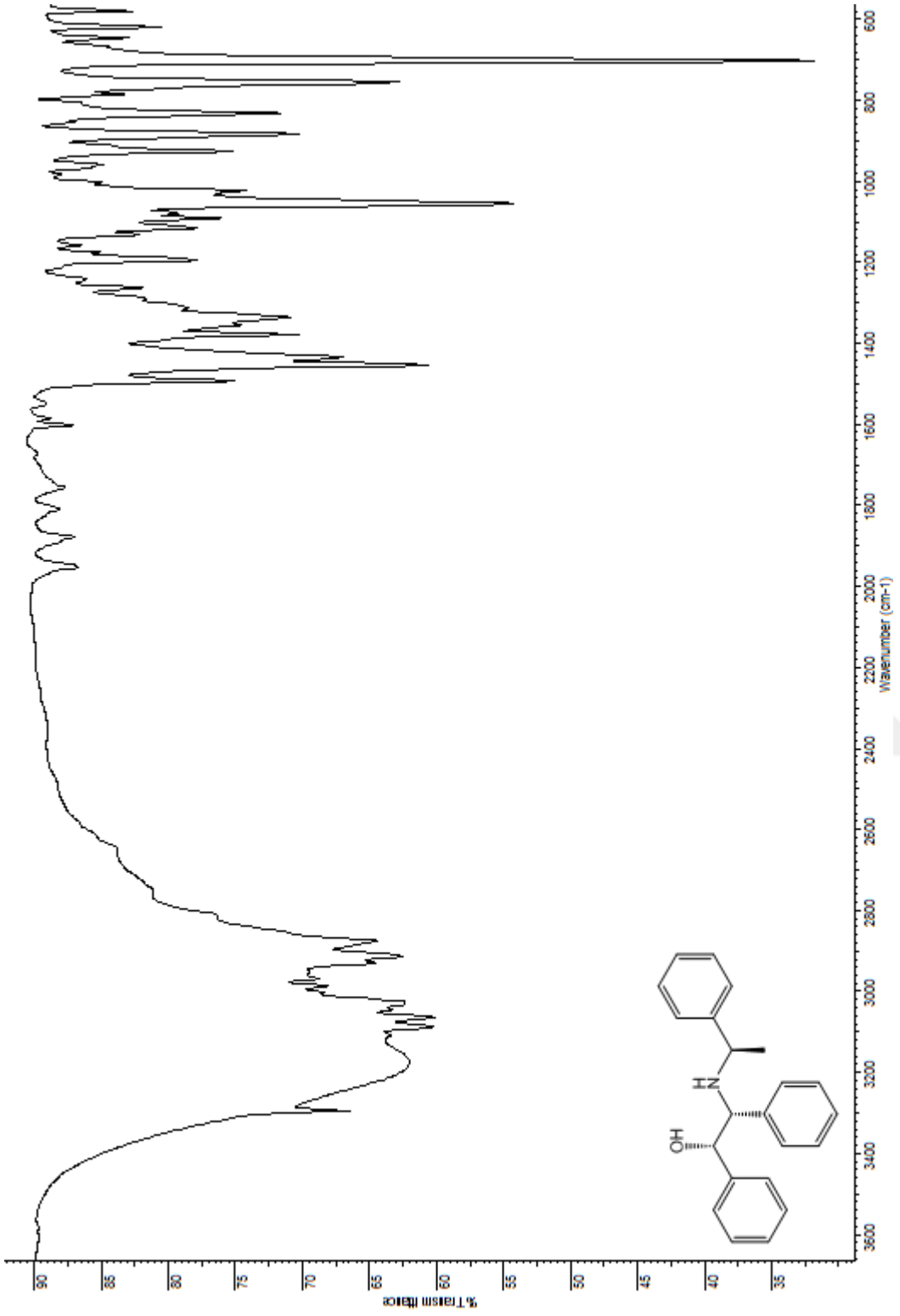


Figure E.1.3 IR spectrum of (1*S*,2*R*,1′*R*)-2-N[(1′-phenylethyl)]amino-1,2-diphenylethanol (**10c**)

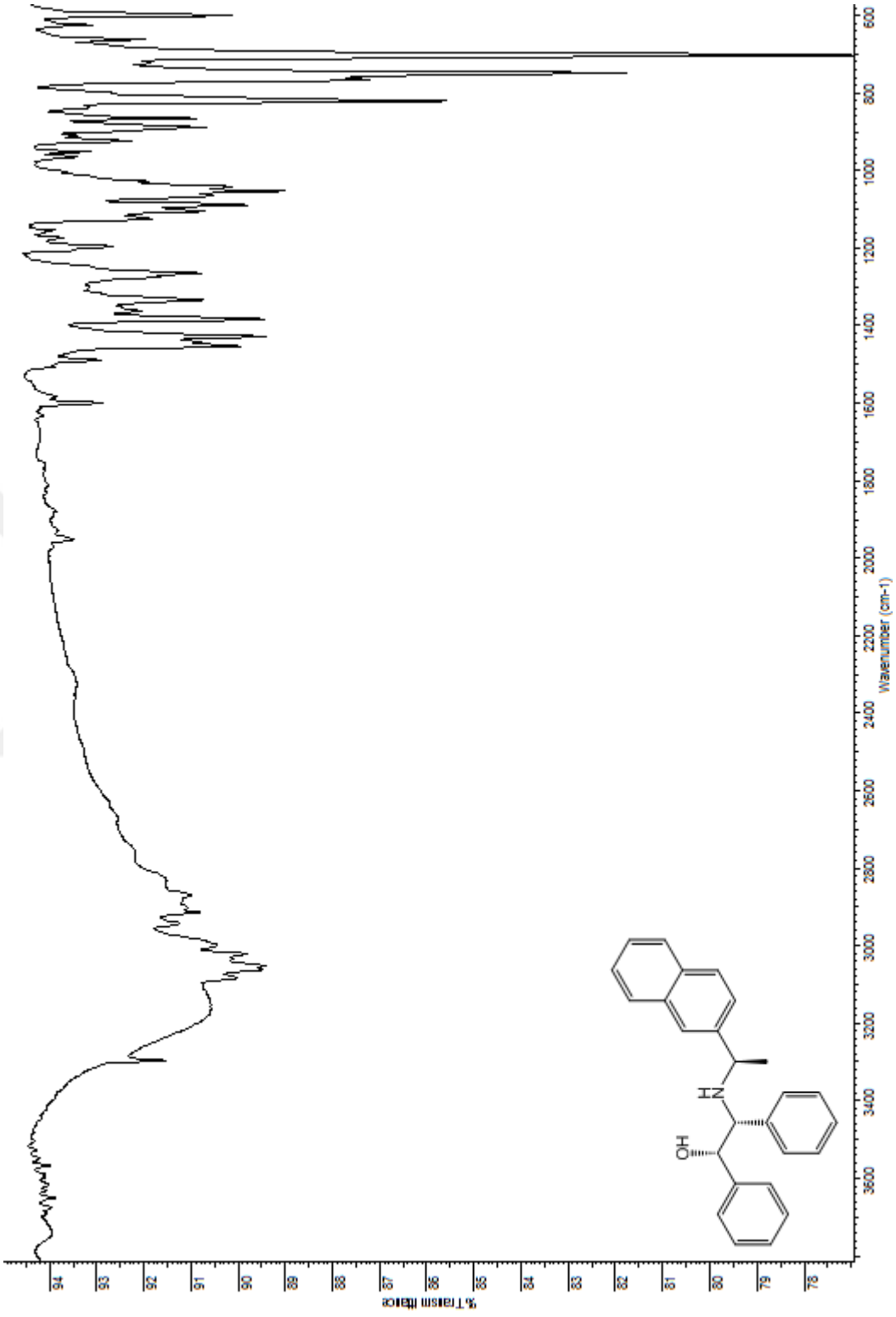


Figure E.1.4 IR spectrum of (1*S*,2*R*,1′*R*)-2-N[(1′-(2-naphthyl)ethyl]amino-1,2-diphenyl-ethanol (**10d**)

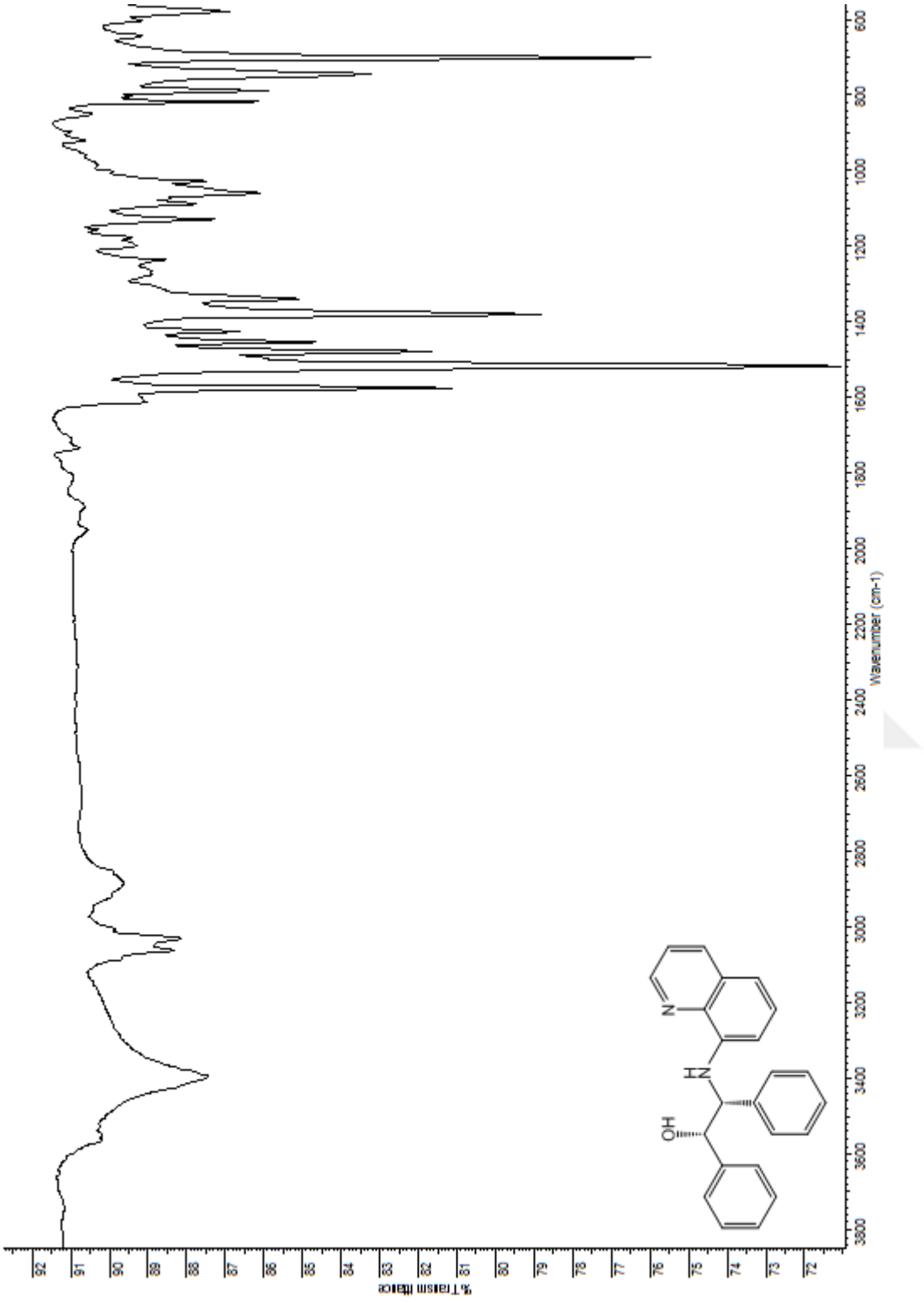


Figure E.1.5 IR spectrum of (1*S*,2*R*)-2-(quinolin-8-ylamino)-1,2-diphenylethanol (**10e**)

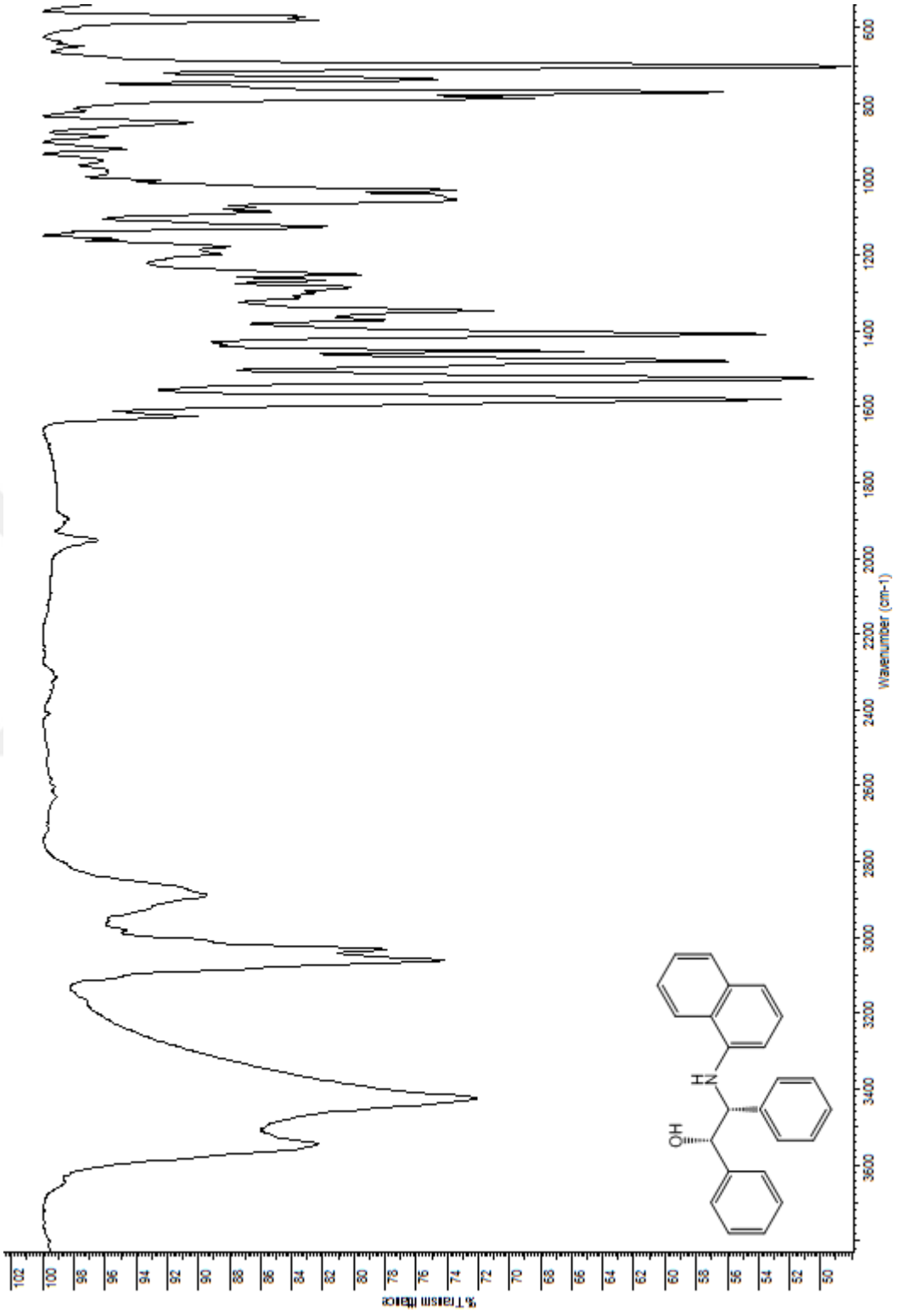


Figure E.1.6 IR spectrum of (1*S*,2*R*)-2-(naphthalen-1-ylamino)-1,2-diphenylethanol (**10f**)

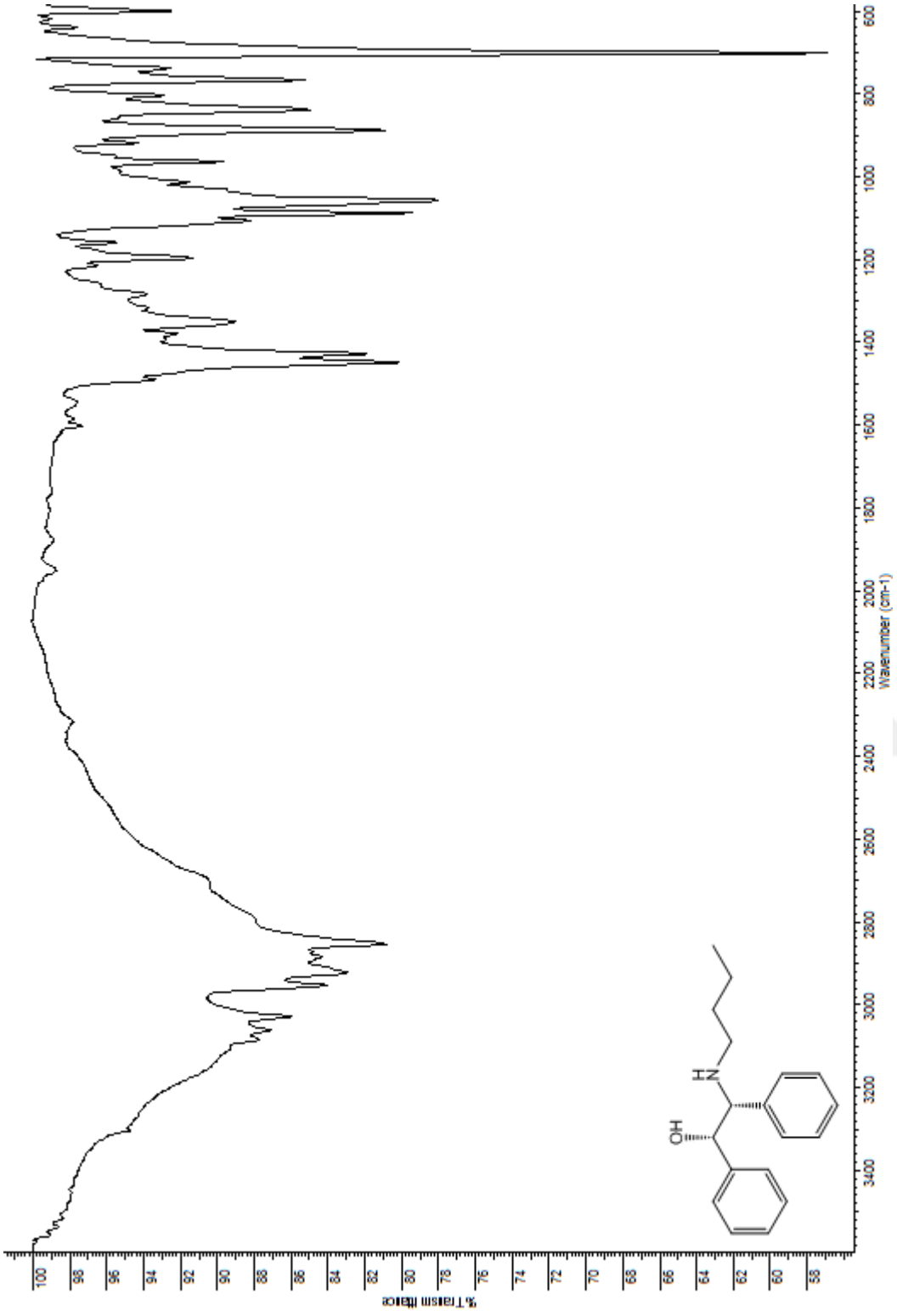


Figure E.1.7 IR spectrum of (1*S*,2*R*)-2-(buta-1-ylamino)-1,2-diphenylethanol (**10g**)

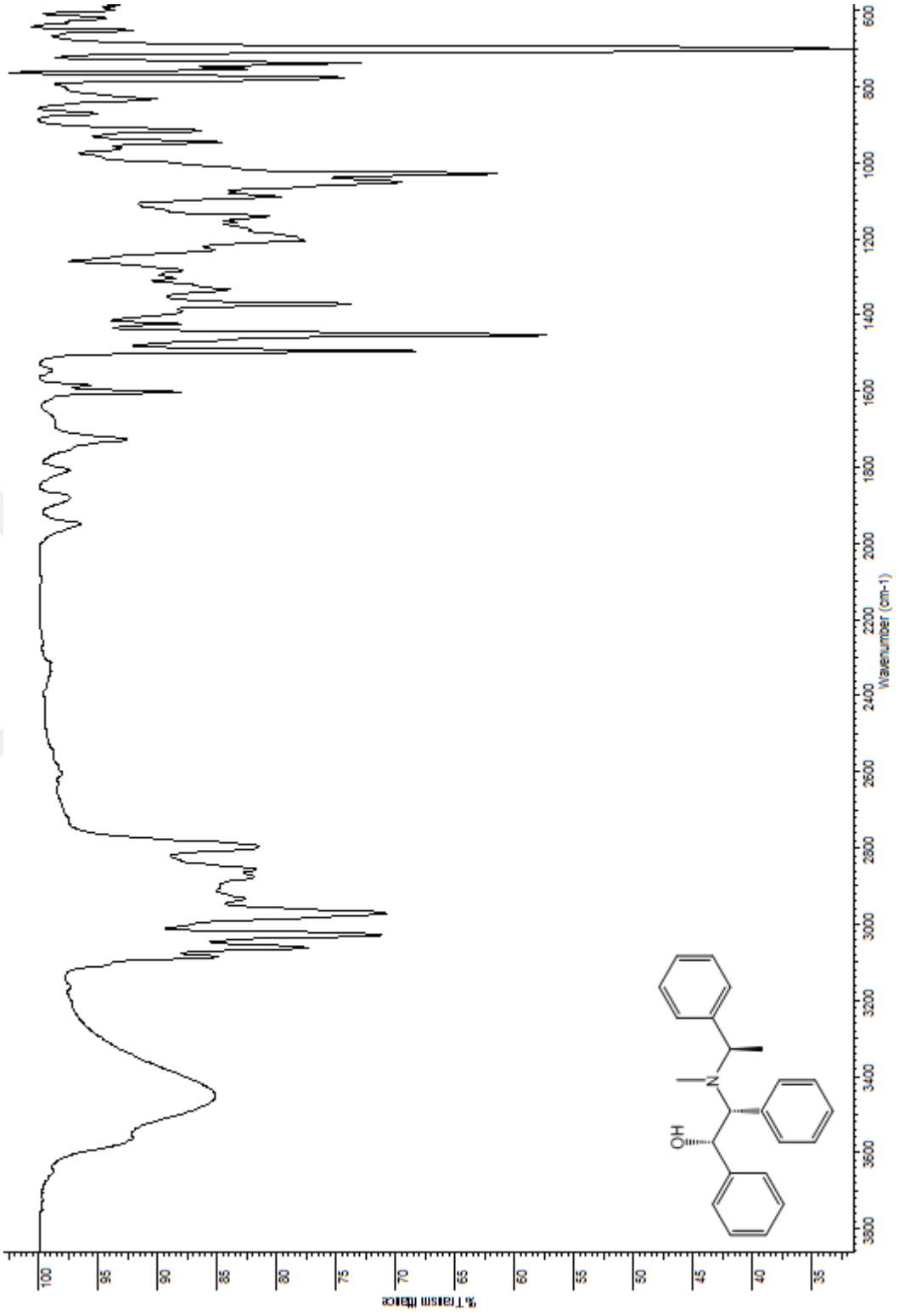


Figure E.1.8 IR spectrum of (1*S*,2*R*,1′*R*)-2-N-methyl-N[(1′-phenylethyl)]amino-1,2-diphenylethanol (**10h**)

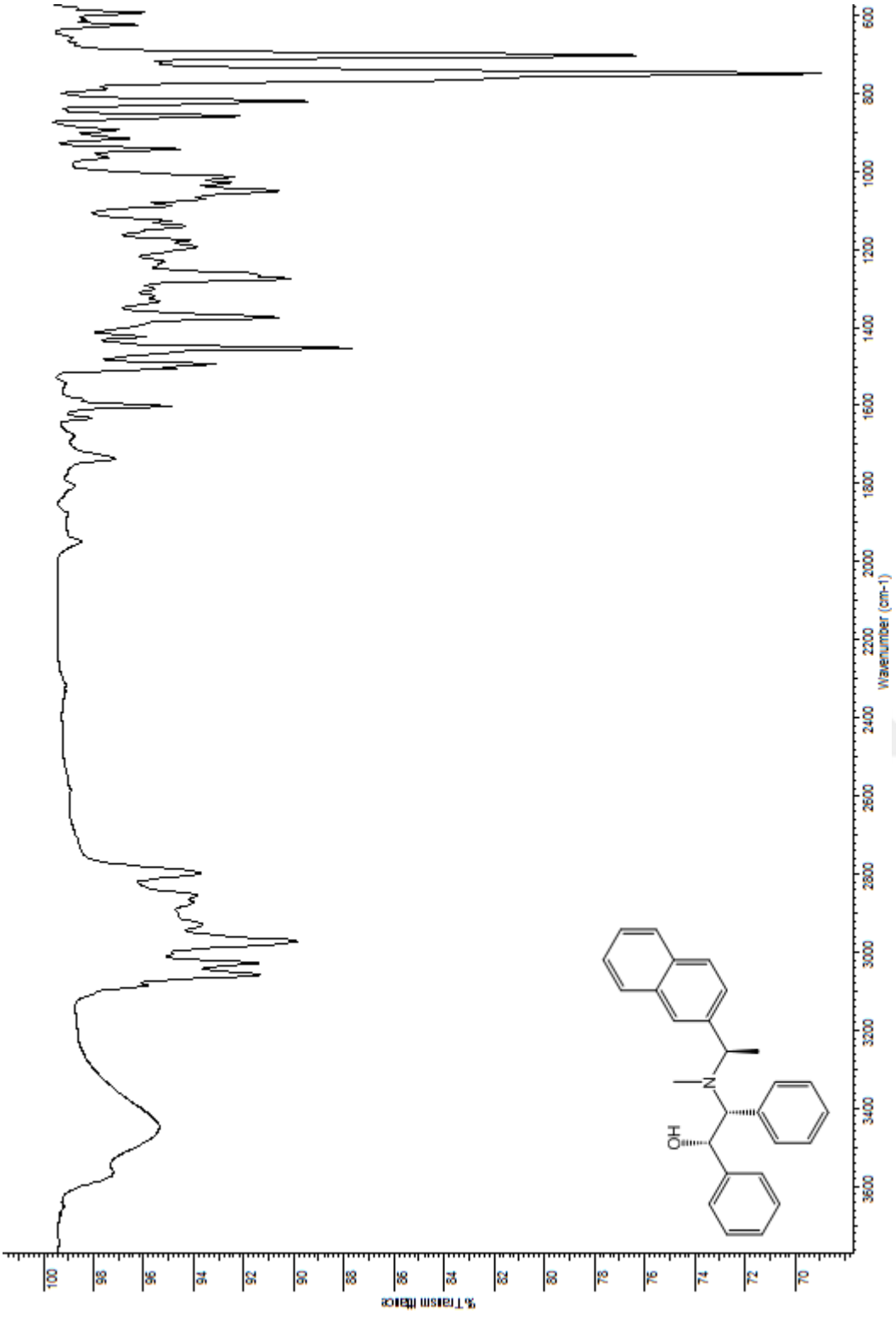


Figure E.1.9 IR spectrum of (1*S*,2*R*,1′*R*)-2-N-methyl-N[(1′-(2-naphthyl)ethyl]amino-1,2-diphenylethanol (**10i**)

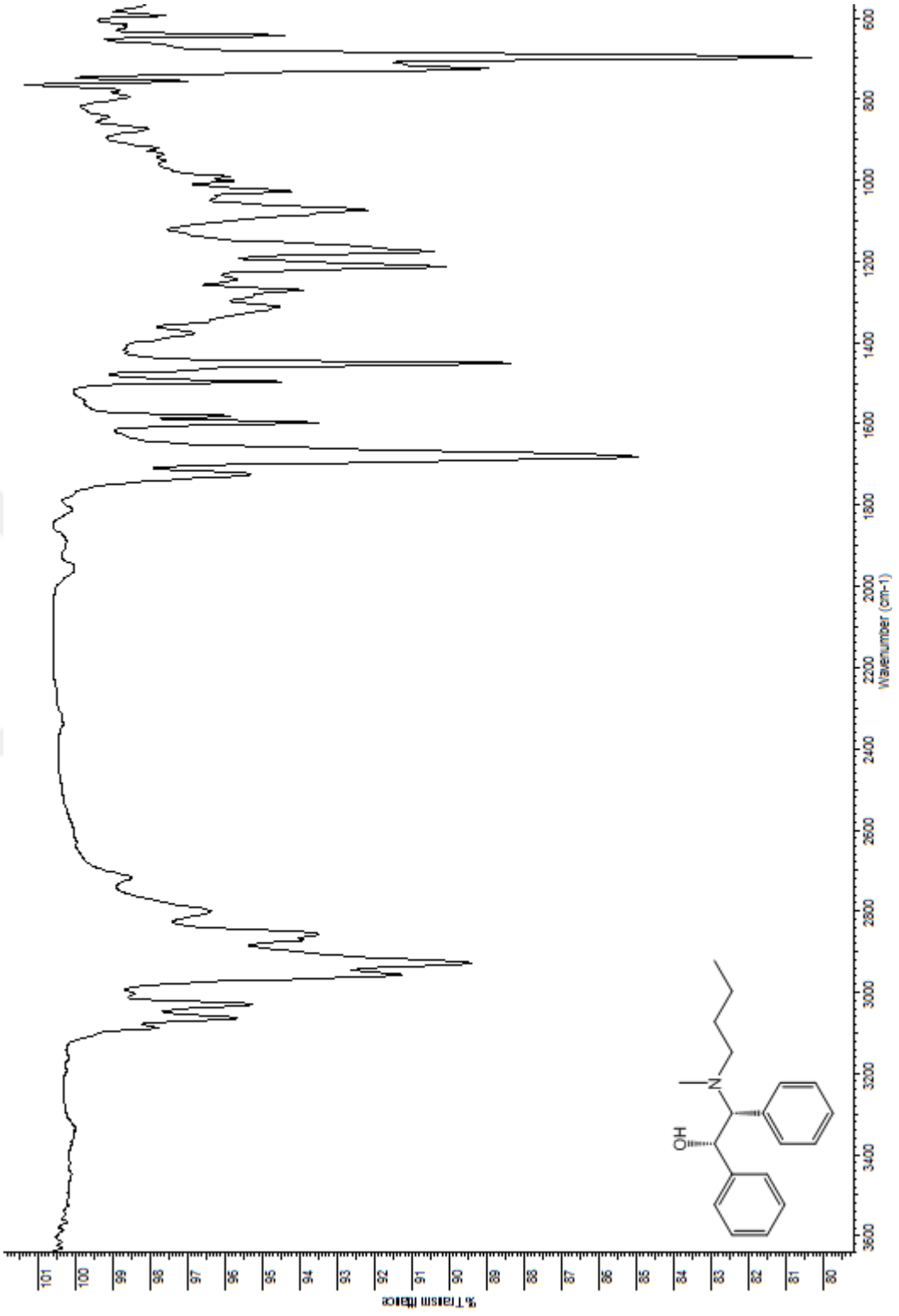


Figure E.1.10 IR spectrum of (1*S*,2*R*,1′*R*)-2-N-methyl-N[(1′-(2-naphthyl)ethyl]amino-1,2-diphenylethanol (**10j**)

E.2 ^{1}H NMR Spectrums

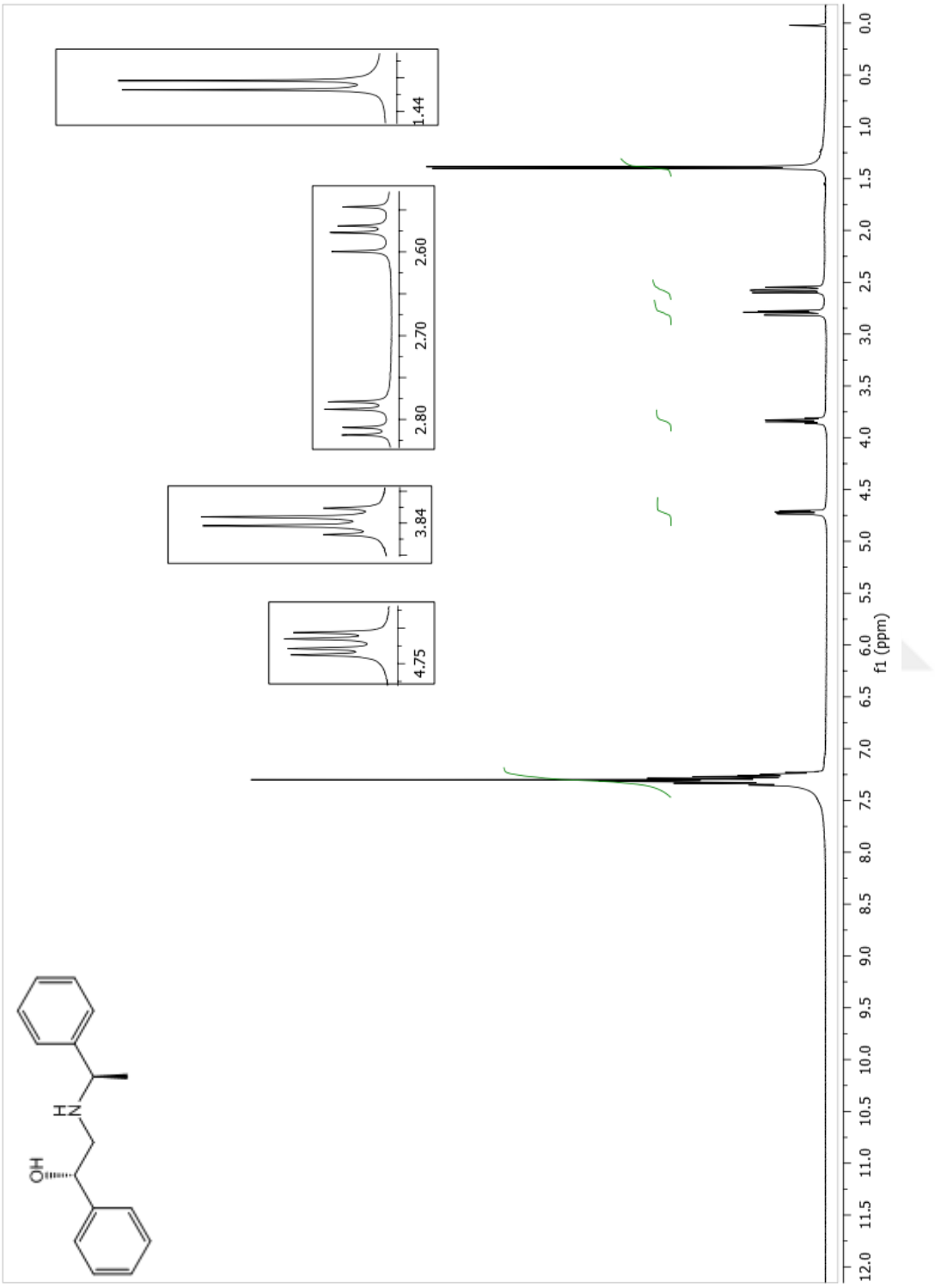


Figure E.2.1 ^{1}H NMR spectrum of (1*S*, 2*R*)-2-N[(1-phenylethyl)]amino-1-phenylethanol (**10a**)

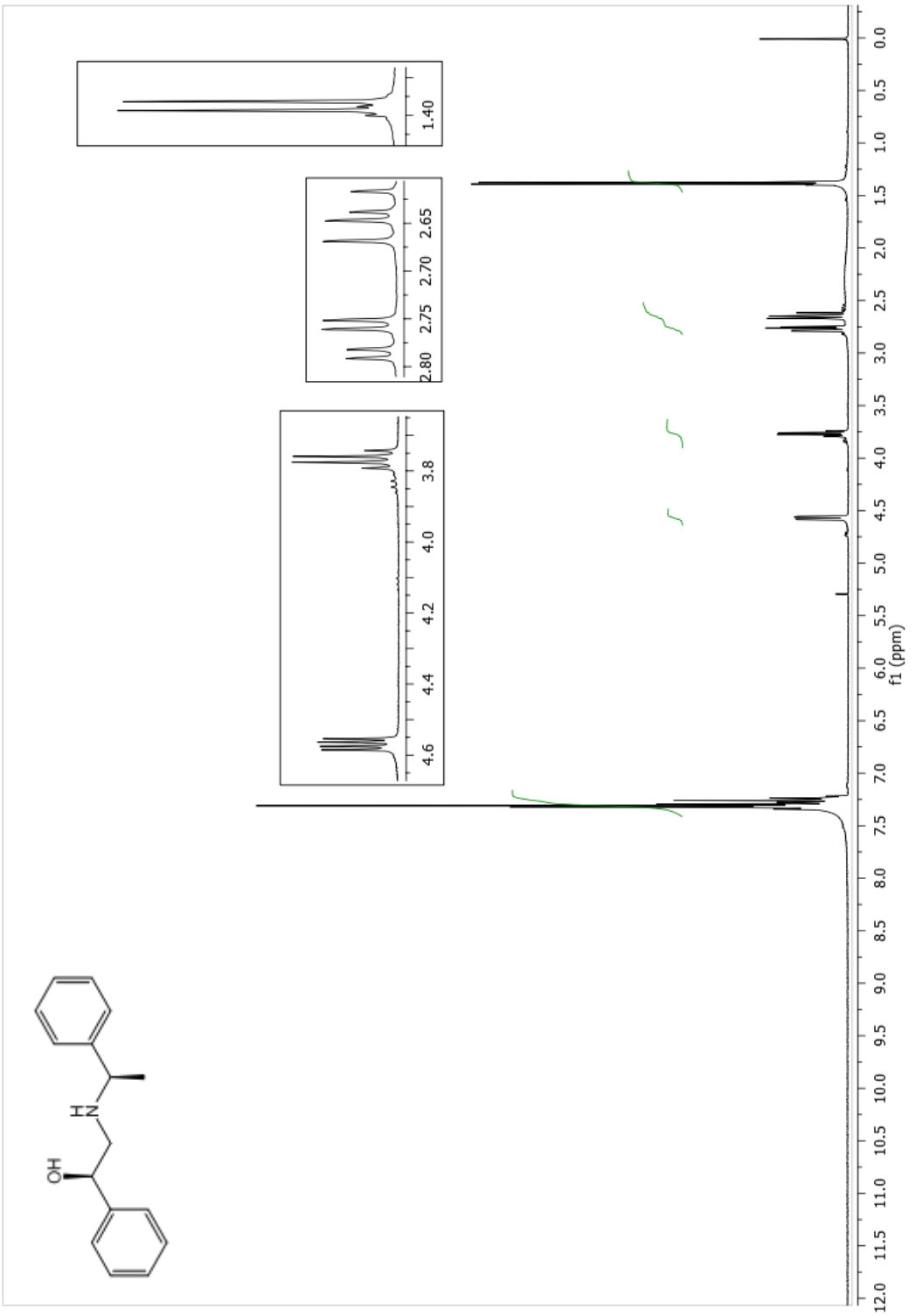


Figure E.2.2 ^{1}H NMR spectrum of (1*R*, 2*R*)-2-N[(1-phenylethyl)]amino-1-phenylethanol (**10b**)

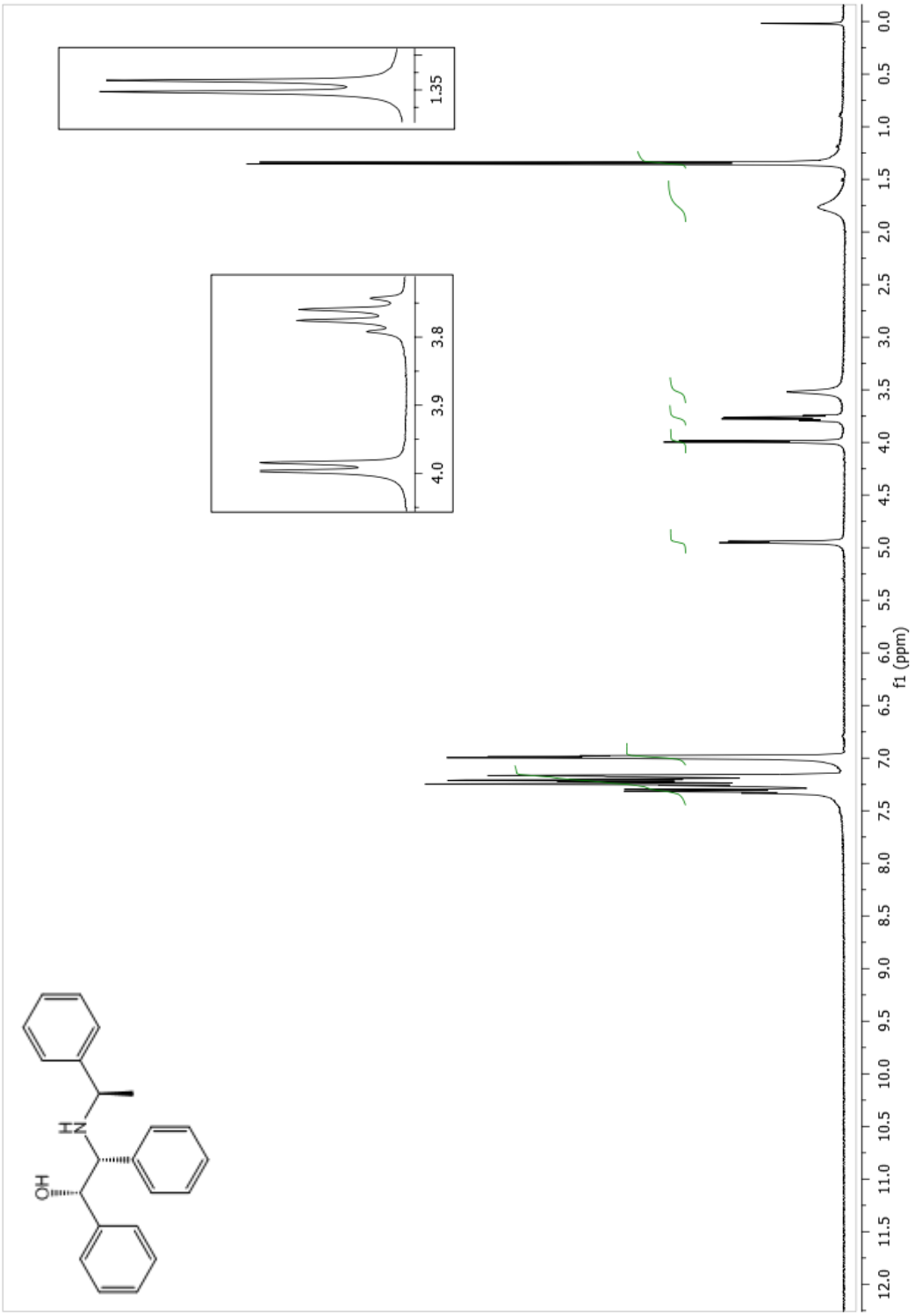


Figure E.2.3 ^{1}H NMR spectrum of (1*S*,2*R*,1′*R*)-2-N[(1′-phenylethyl)]amino-1,2-diphenylethanol (**10c**)

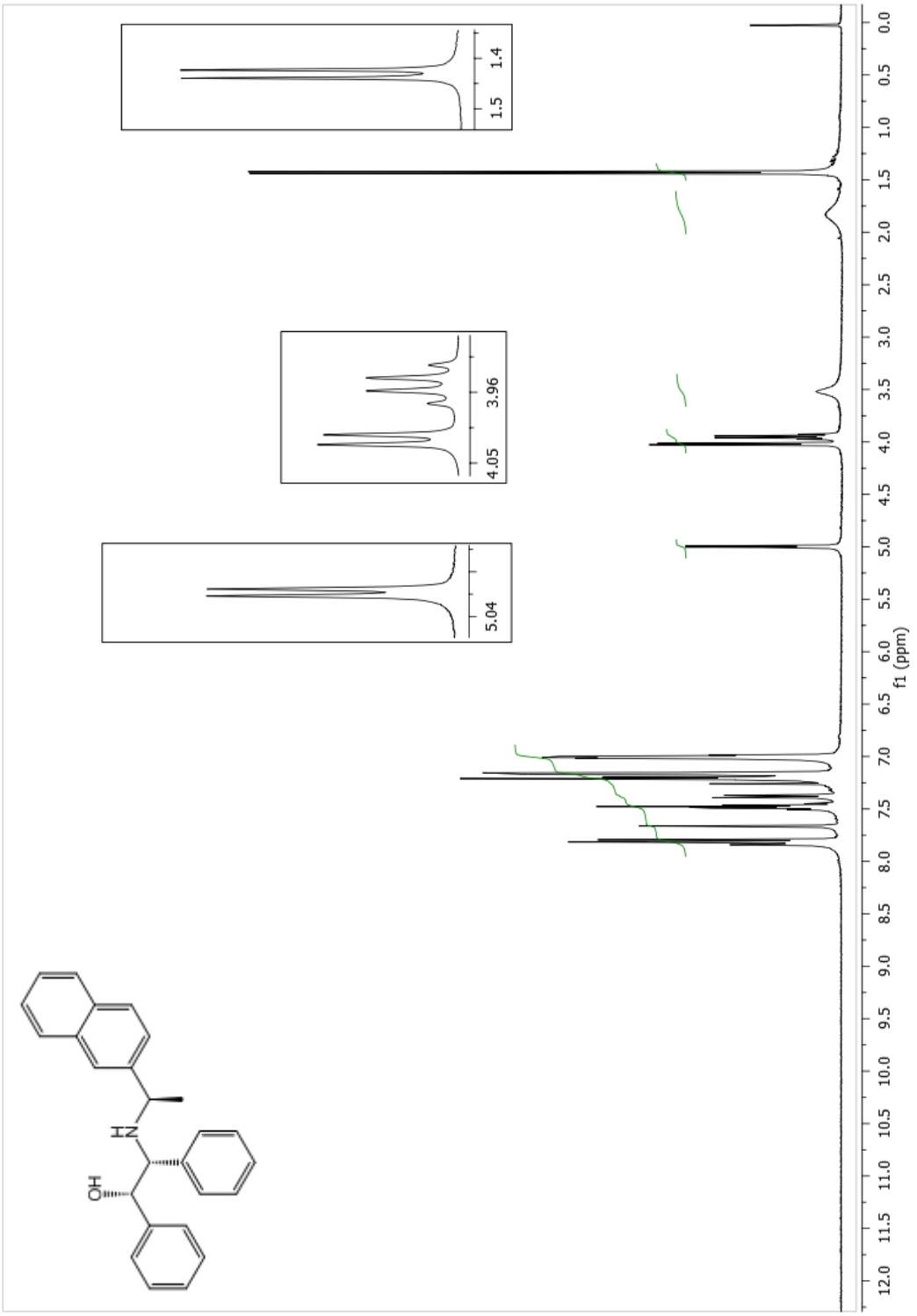


Figure E.2.4 ^{1}H NMR spectrum of (1*S*,2*R*,1′*R*)-2-N[(1′-(2-naphthyl)ethyl]amino-1,2-diphenyl-ethanol (**10d**)

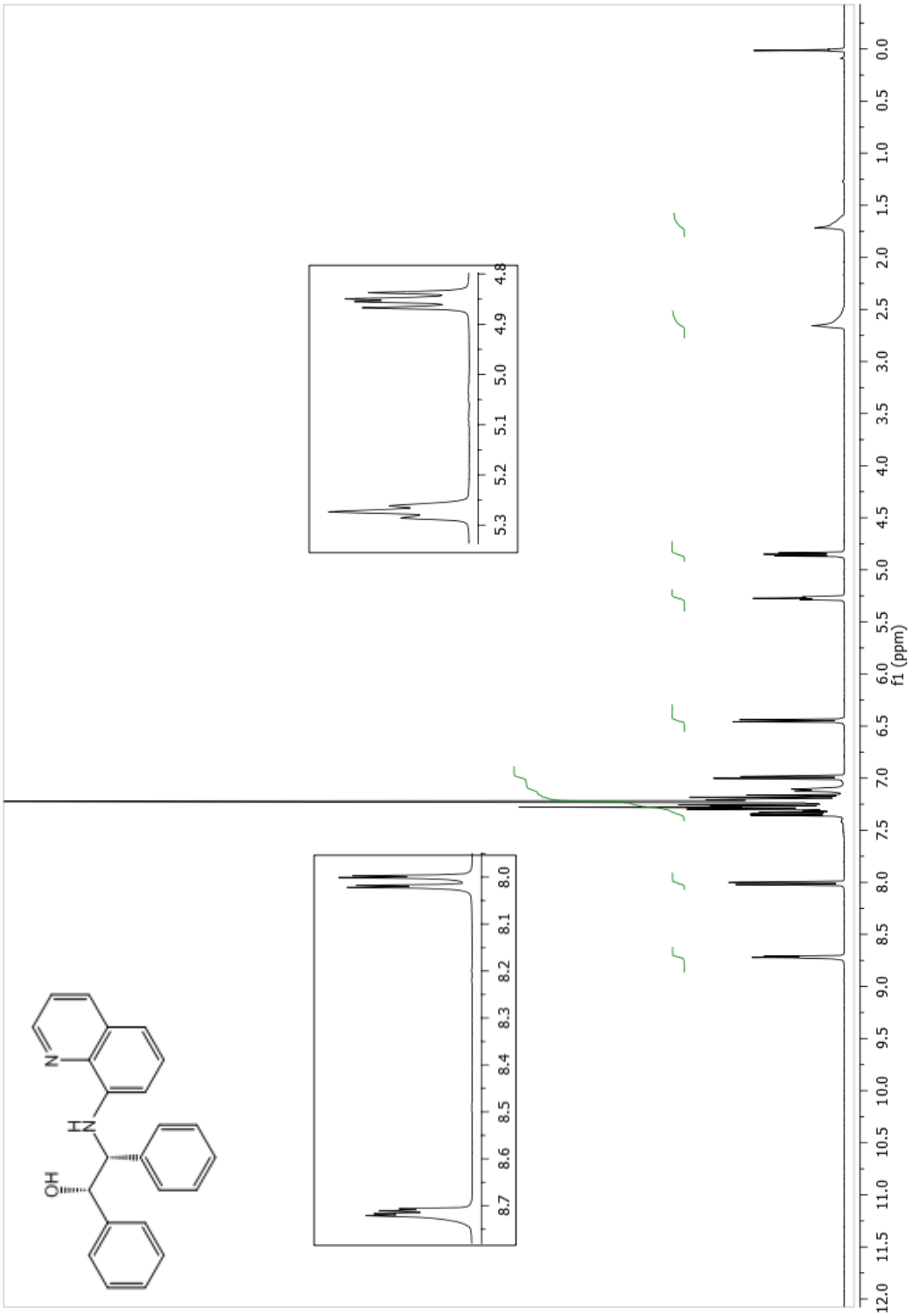


Figure E.2.5 ^{1}H NMR spectrum of (1*S*,2*R*)-2-(quinolin-8-ylamino)-1,2-diphenylethanol **(10e**)

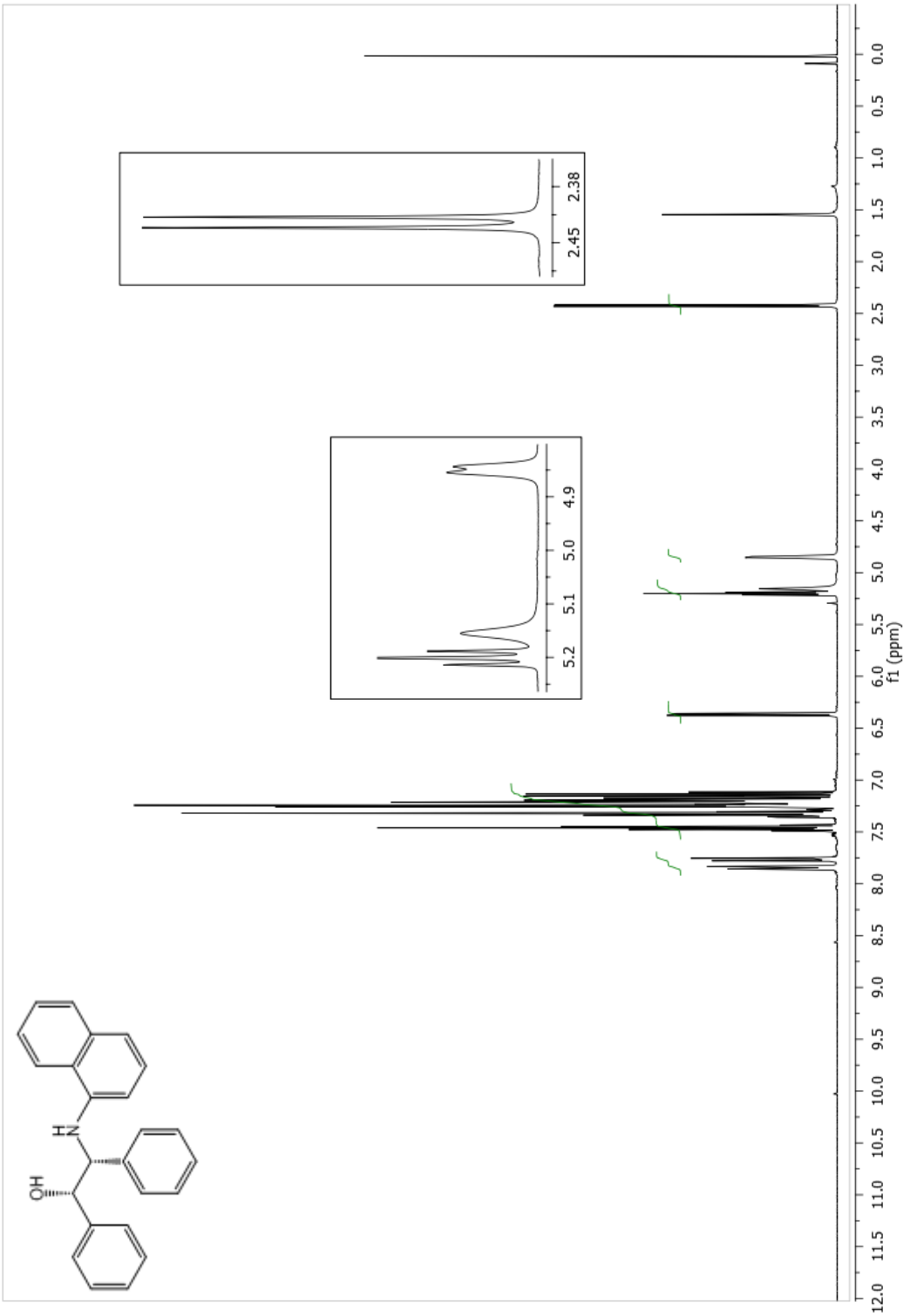


Figure E.2.6 ^{1}H NMR spectrum of (1*S*,2*R*)-2-(naphthalen-1-ylamino)-1,2-diphenylethanol (**10f**)

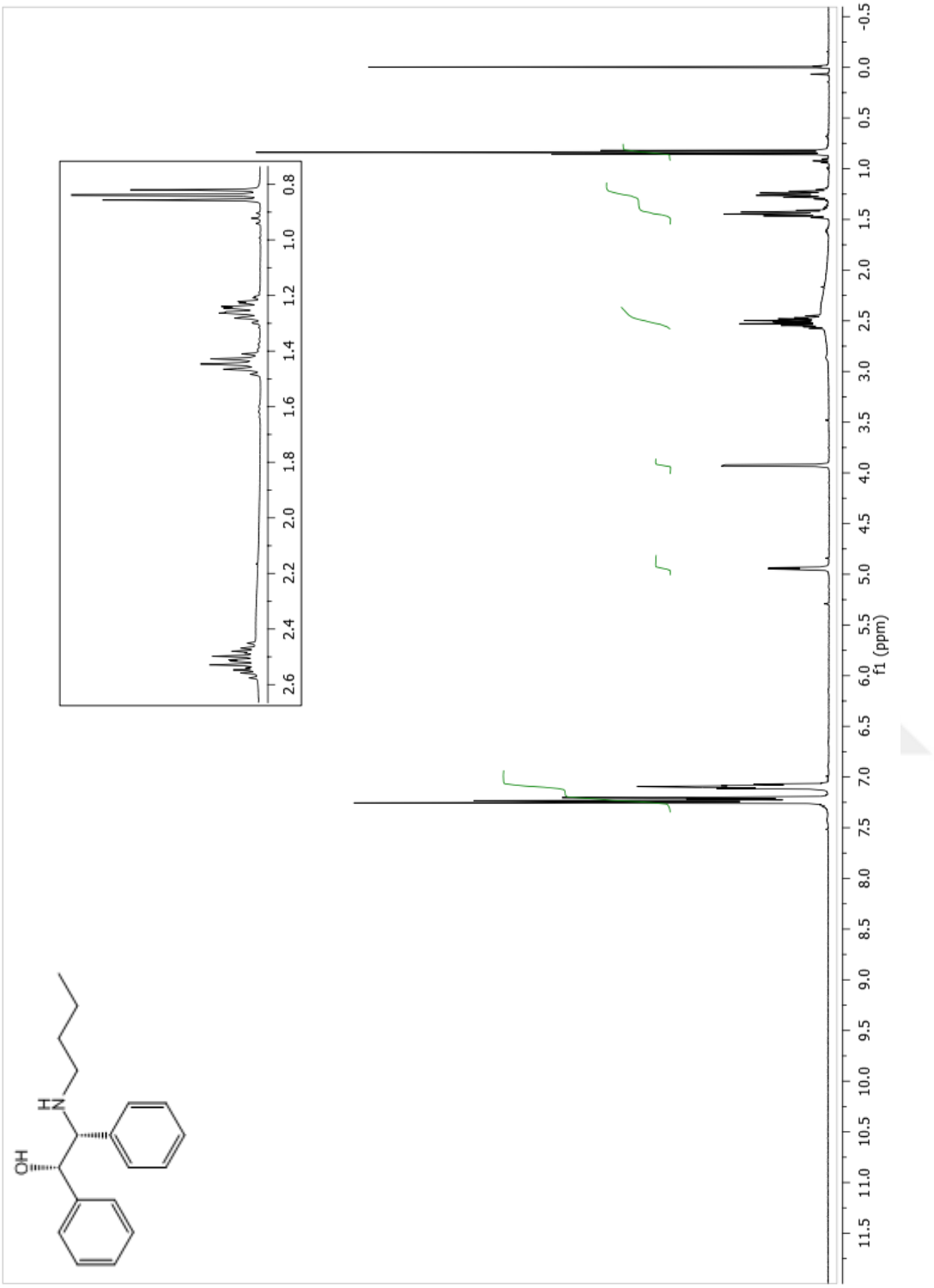


Figure E.2.7 ^{1}H NMR spectrum of (1*S*,2*R*)-2-(buta-1-ylamino)-1,2-diphenylethanol (**10g**)

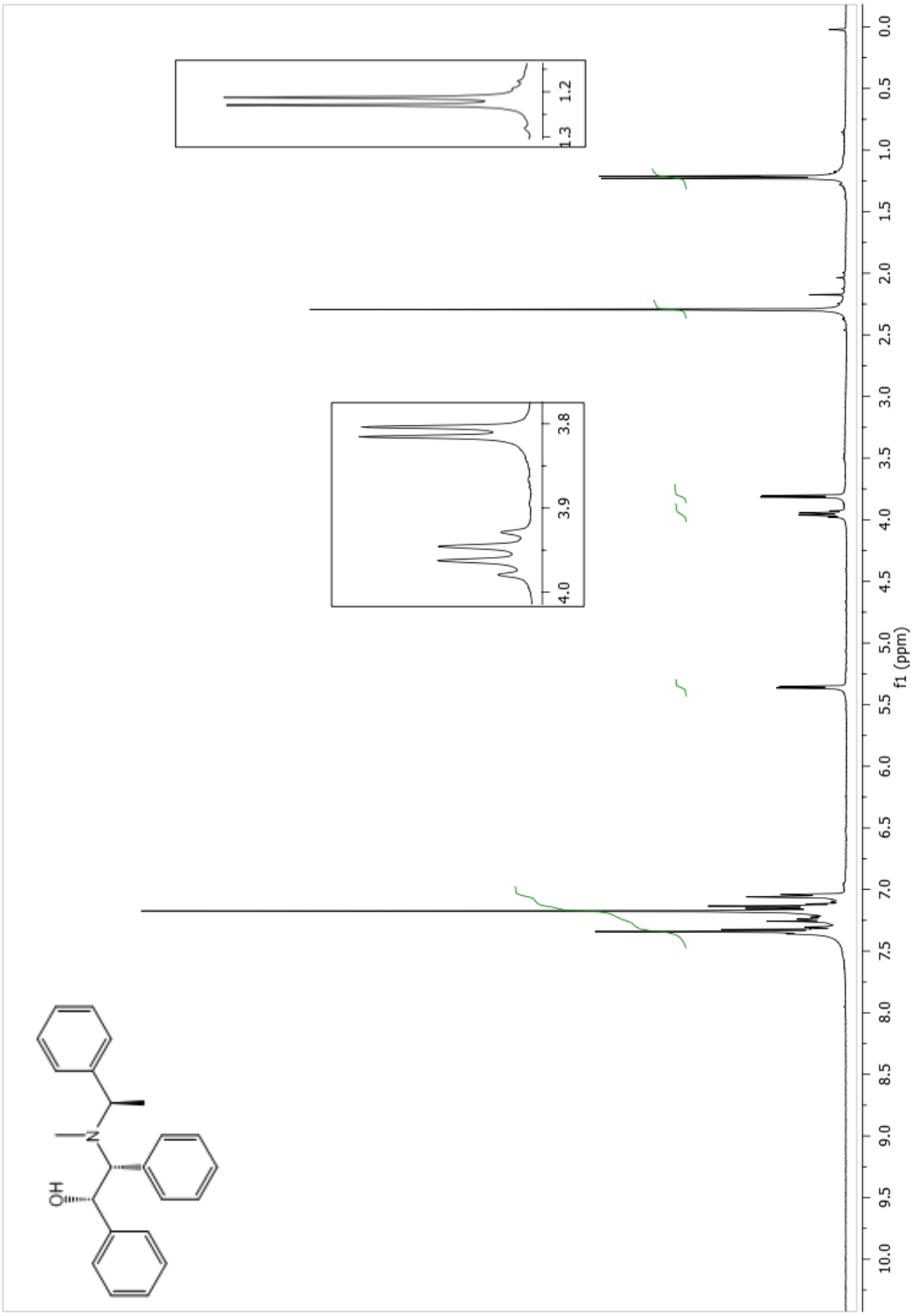


Figure E.2.8 ^{1}H NMR spectrum of (1*S*,2*R*,1′*R*)-2-N-methyl-N[(1′-phenylethyl)]amino-1,2-diphenylethanol (**10h**)

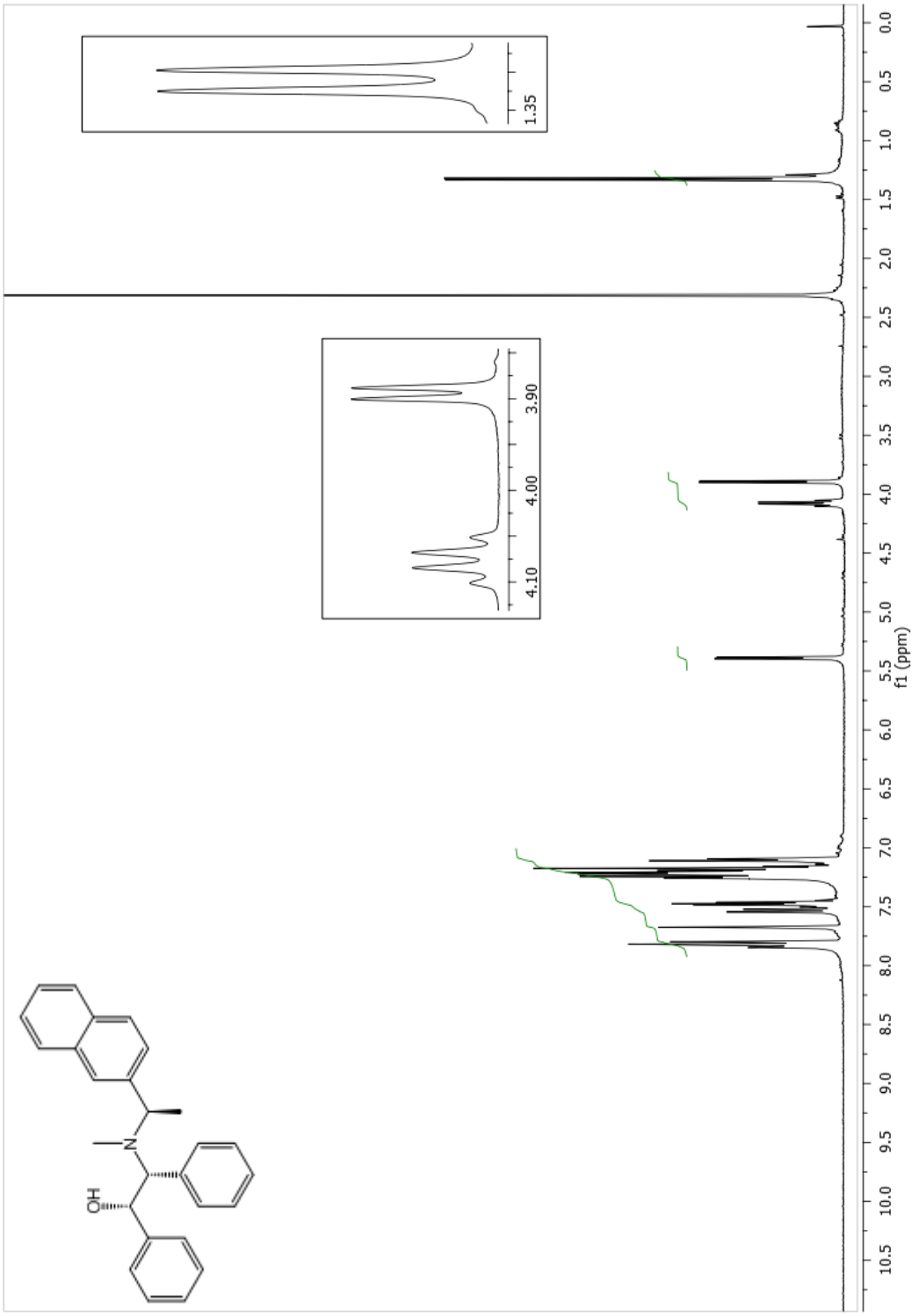


Figure E.2.9 ^{1}H NMR spectrum of (1*S*,2*R*,1′*R*)-2-N-methyl-N[(1′-(2-naphthyl)ethyl]amino-1,2-diphenylethanol (**10i**)

E.3 ^{13}C NMR Spectrums

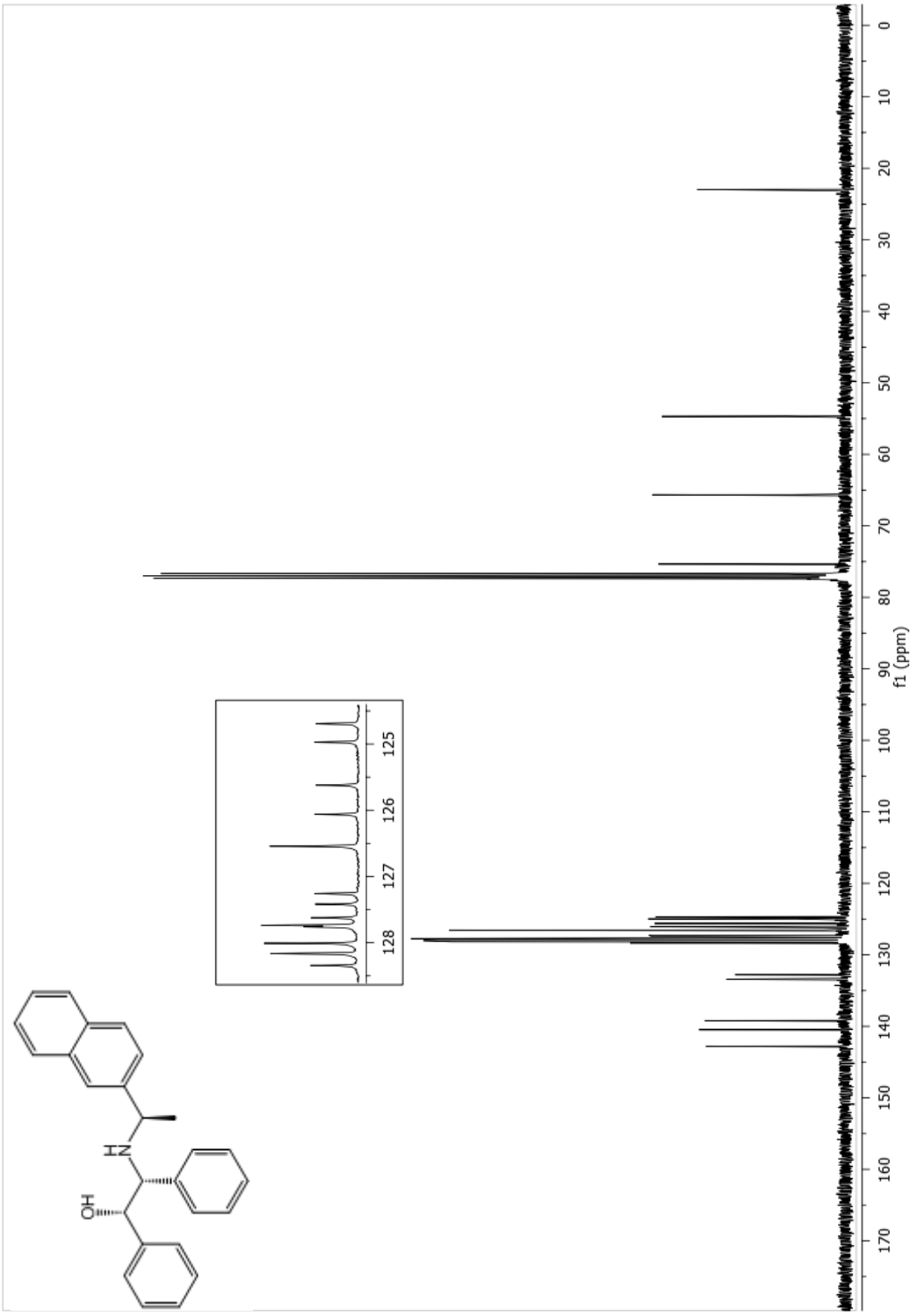


Figure E.3.1 ^{13}C NMR spectrum of (1*S*,2*R*,1′*R*)-2-N[(1′-(2-naphthyl)ethyl]amino-1,2-diphenyl-ethanol (**10d**)

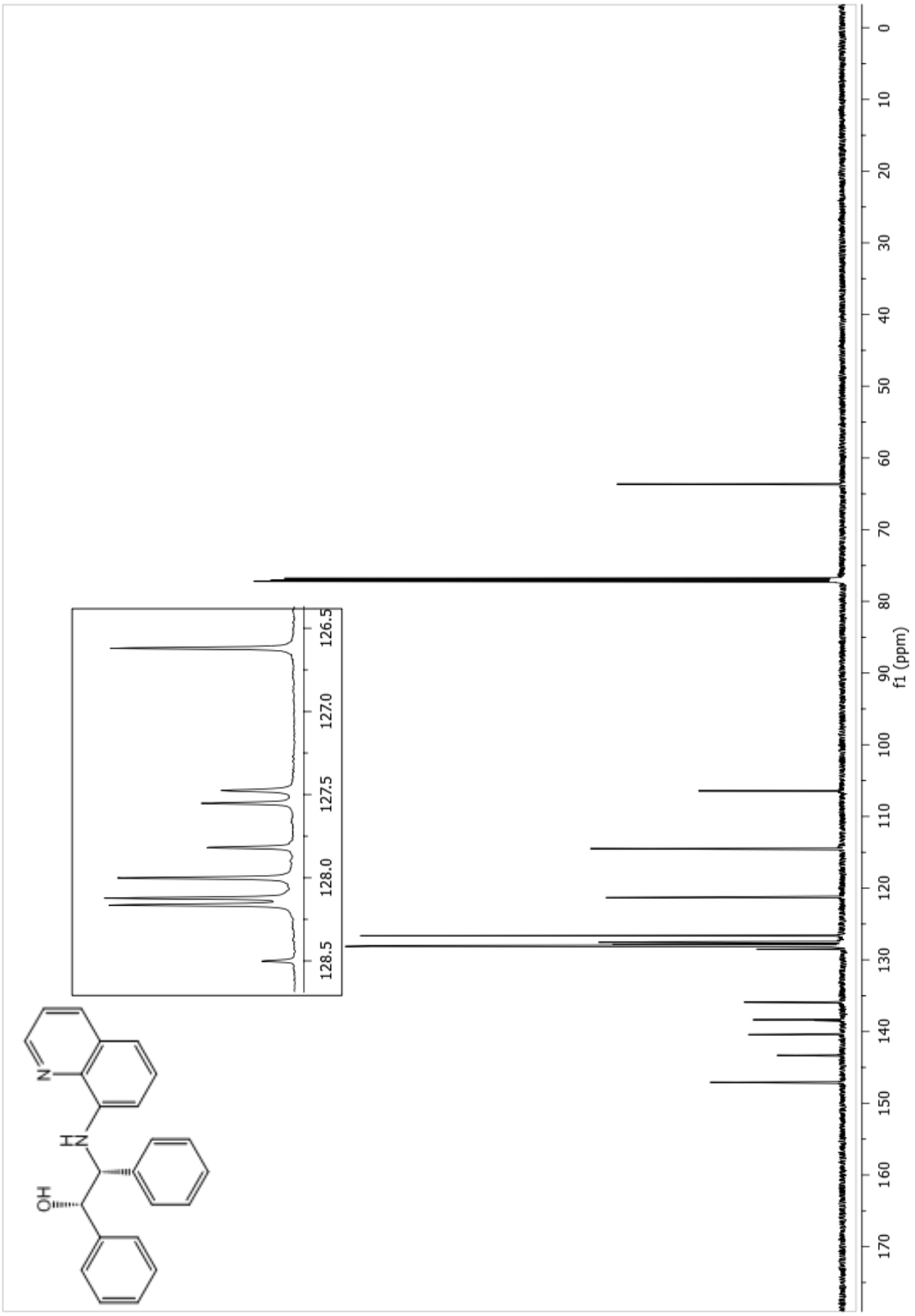


Figure E.3.2 ^{13}C NMR spectrum of (1*S*,2*R*)-2-(quinolin-8-ylamino)-1,2-diphenylethanol (**10e**)

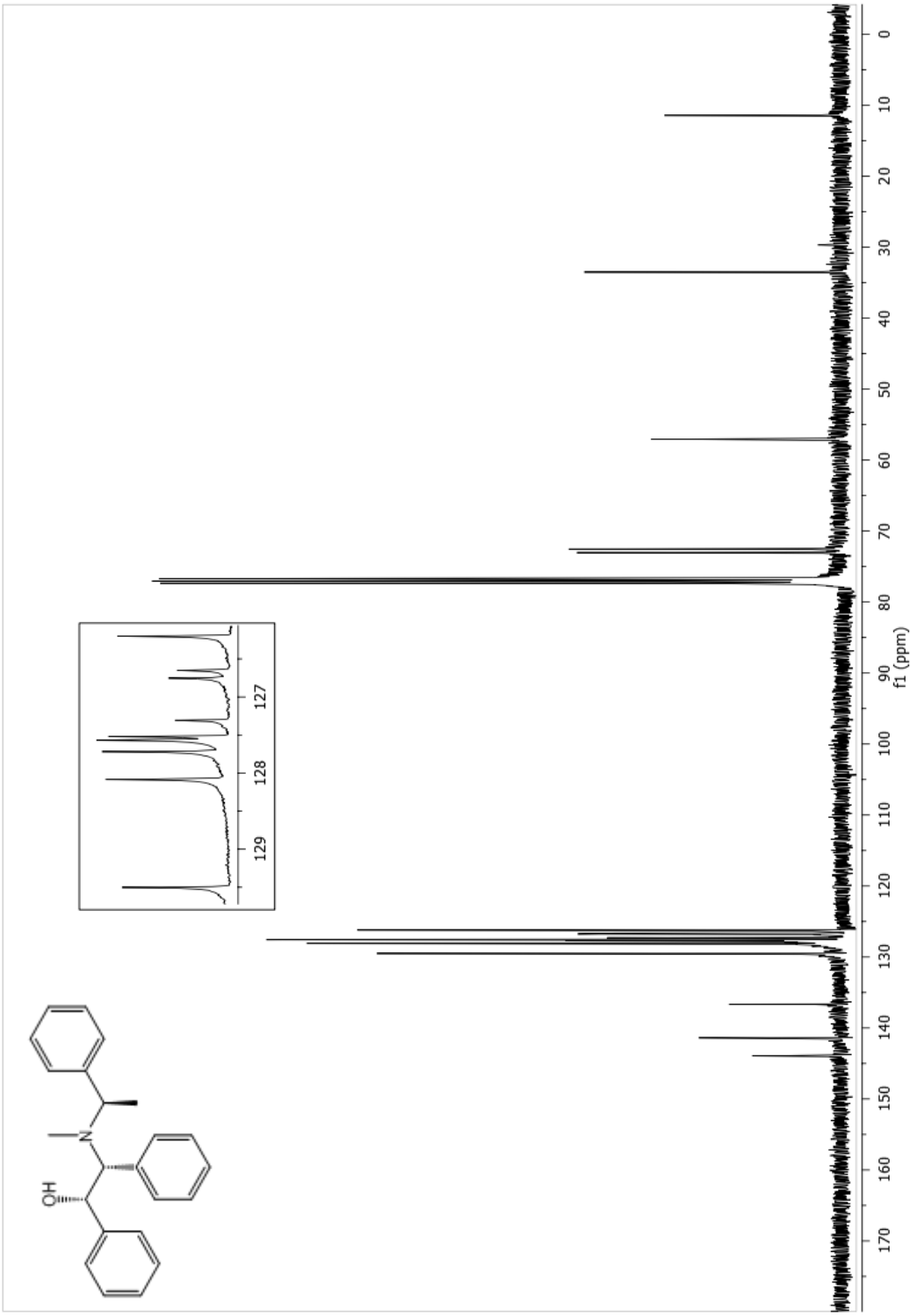


Figure E.3.3 ^{13}C NMR spectrum of (1*S*,2*R*,1′*R*)-2-N-methyl-N[(1′-phenylethyl)]amino-1,2-diphenylethanol (**10h**)

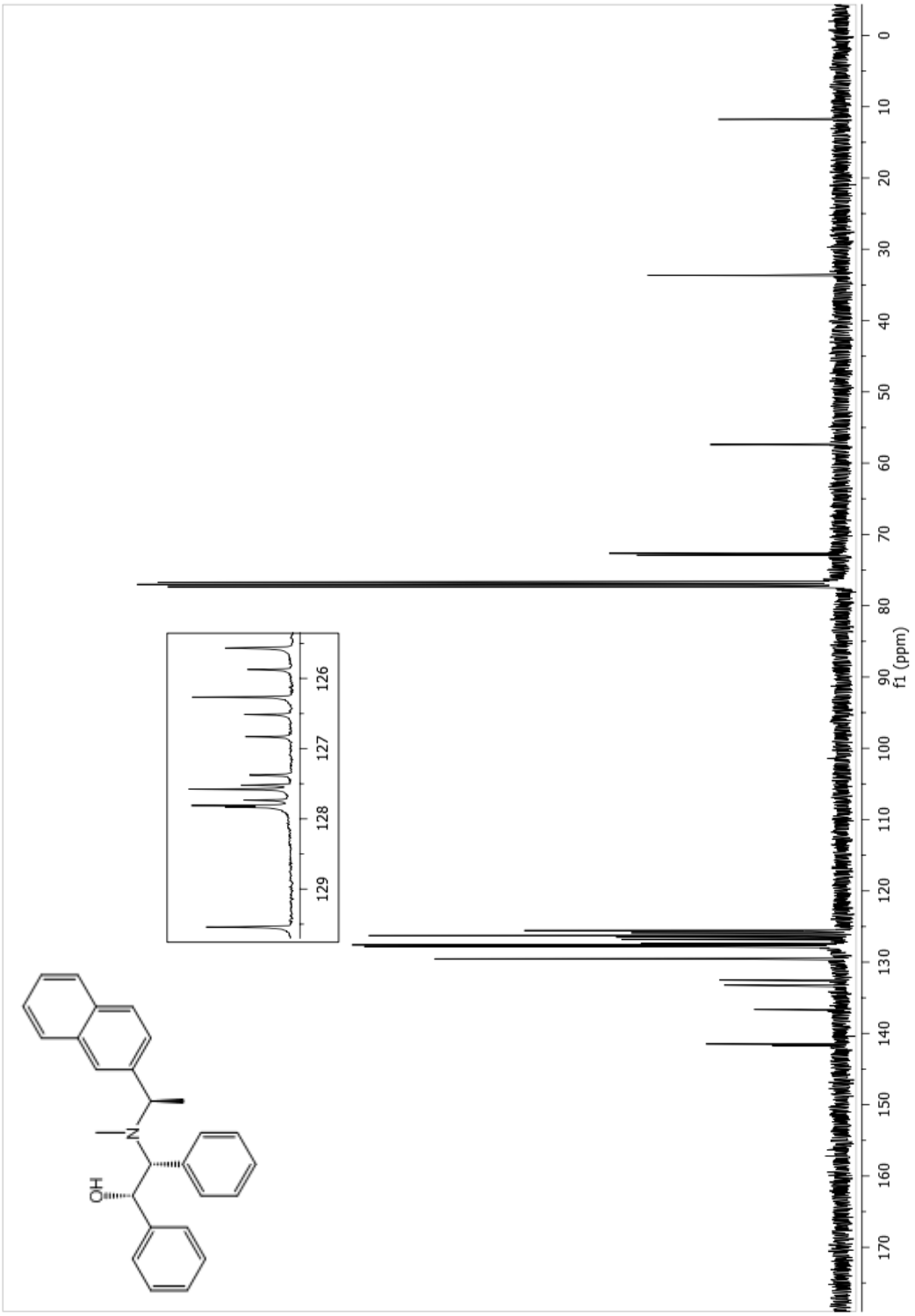


Figure E.3.4 ^{13}C NMR spectrum of (1*S*,2*R*,1′*R*)-2-N-methyl-N[(1′-(2-naphthyl)ethyl]amino-1,2-diphenylethanol (**10i**)

E.4 Chromatograms

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Acq. Instrument : Instrument 1                    Location : Vial 1
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Method          : C:\CHEM32\1\METHODS\GAMZE.M
Last changed    : 7/14/2015 2:59:52 PM by Arzu
Sample Info     : 90:10 Hex/IPA, 267nm, 1 ml/min, RT, 4-NO2
```

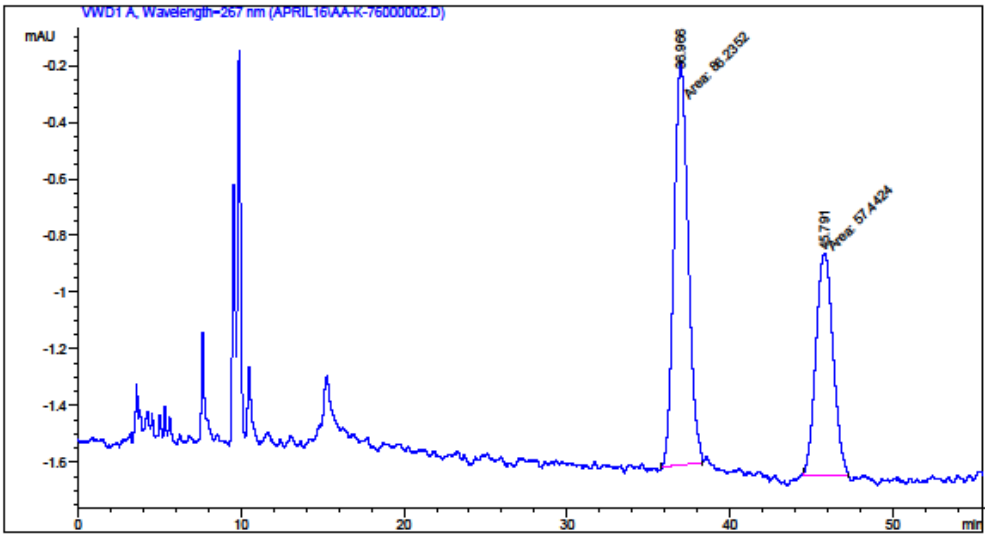


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==========================================================================
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Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=267 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s    [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  36.966 MM    1.0122   86.23521    1.41989  60.0199
   2  45.791 MM    1.2264   57.44241 7.80641e-1  39.9801

Totals :                   143.67762    2.20053

==========================================================================
                        *** End of Report ***

Instrument 1 6/17/2017 6:16:38 PM Arzu                    Page   1 of 1
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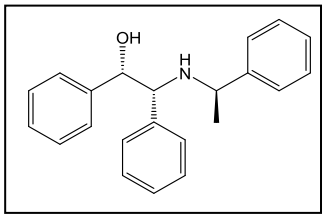

Figure E.4.1 HPLC chromatogram of the nitroaldol reaction of 4-NO_2-benzaldehyde in THF at RT, Cu(II) salt with **10c**

```
Data File C:\CHEM32\1\DATA\SEPTEMBER16\AA-K119-T000006.D
Sample Name: AA-k119-t

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    Method          : C:\CHEM32\1\METHODS\GAMZE.M
    Last changed    : 7/14/2015 2:59:52 PM by Arsu
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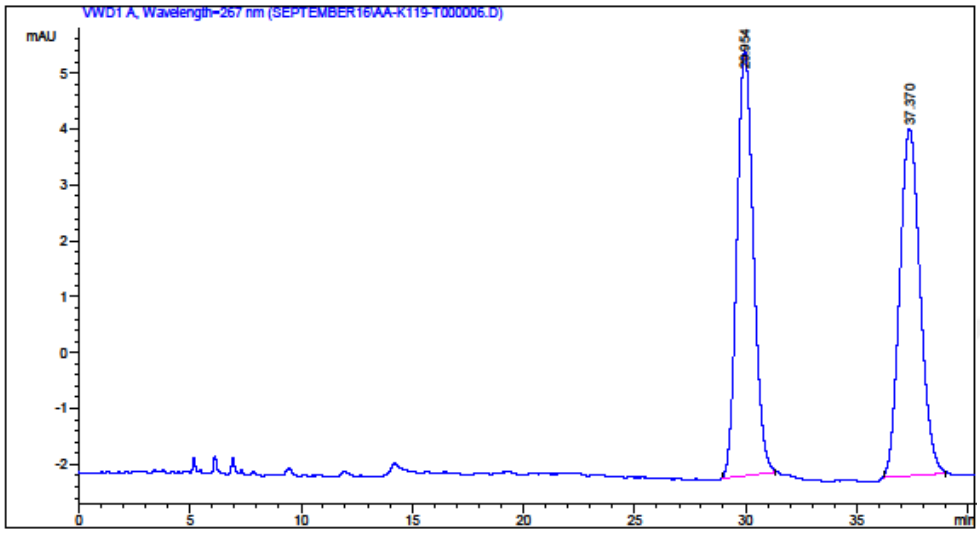


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    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: VWD1 A, Wavelength=267 nm

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    ----|-------|----|-------|----------|----------|--------|
       1  29.954 BB    0.7822  393.45898    7.61096  49.6687
       2  37.370 BB    0.9516  398.70862    6.22108  50.3313

    Totals :                   792.16760   13.83204


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Instrument 1 6/17/2017 7:10:12 PM Arsu                        Page   1 of 1
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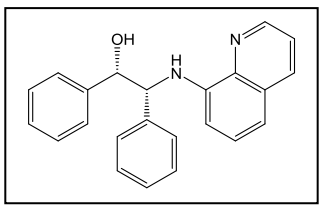

Figure E.4.2 HPLC chromatogram of the nitroaldol reaction of 4-NO_2-benzaldehyde in THF at RT, Cu(II) salt with **10e**

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Data File C:\CHEM32\1\DATA\MAY16\AA-K-82000003.D
Sample Name: AA-k-82

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Acq. Instrument : Instrument 1                    Location : Vial 1
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Method          : C:\CHEM32\1\METHODS\GAMZE.M
Last changed    : 7/14/2015 2:59:52 PM by Arsu
Sample Info     : 90:10 Hex/IPA, 267nm, 1 ml/min, RT, 4-NO2
```

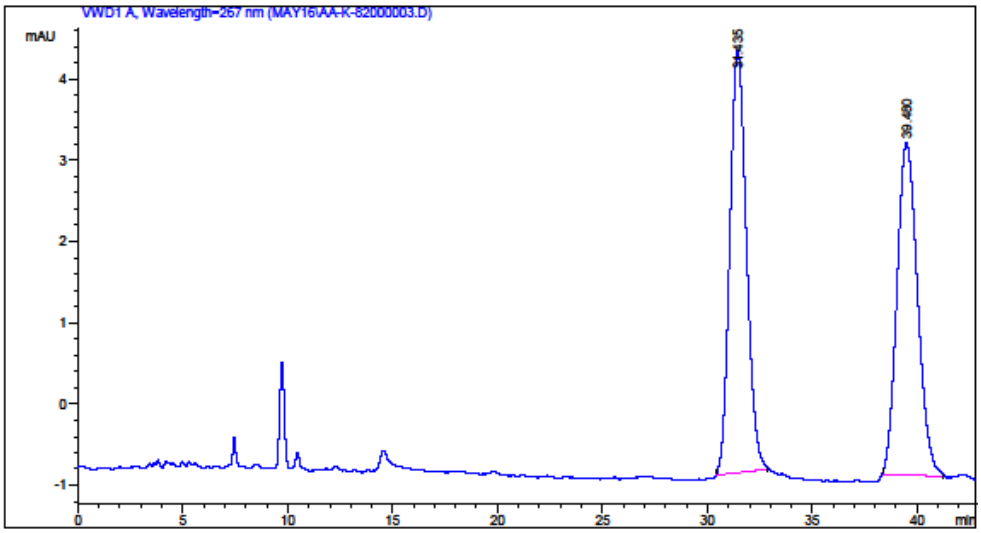


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Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=267 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s    [mAU   ]      %
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   1  31.435 BB    0.8347  284.77054    5.19480  50.5207
   2  39.480 BB    0.9245  278.90042    4.10084  49.4793

Totals :                   563.67096    9.29564

======================================================================
                        *** End of Report ***

Instrument 1 6/17/2017 6:20:22 PM Arsu                    Page   1 of 1
```

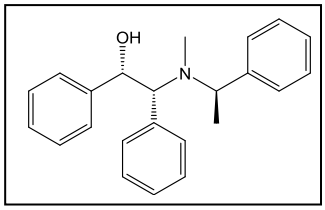
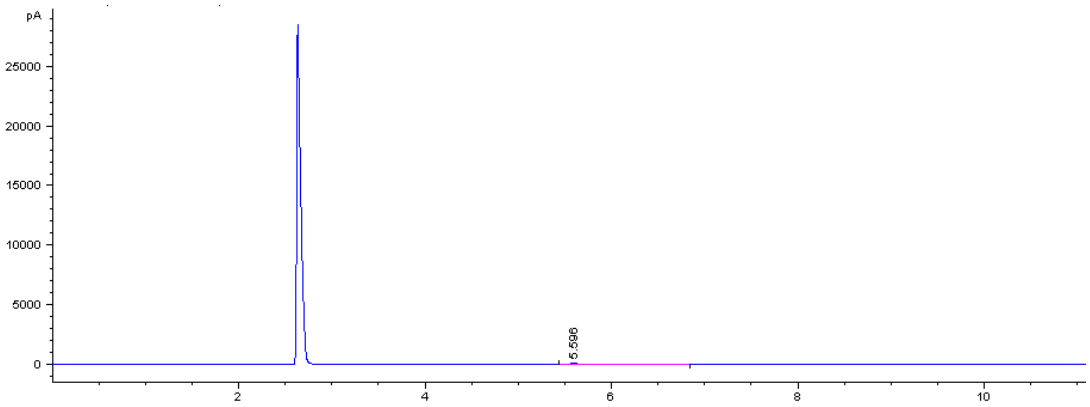
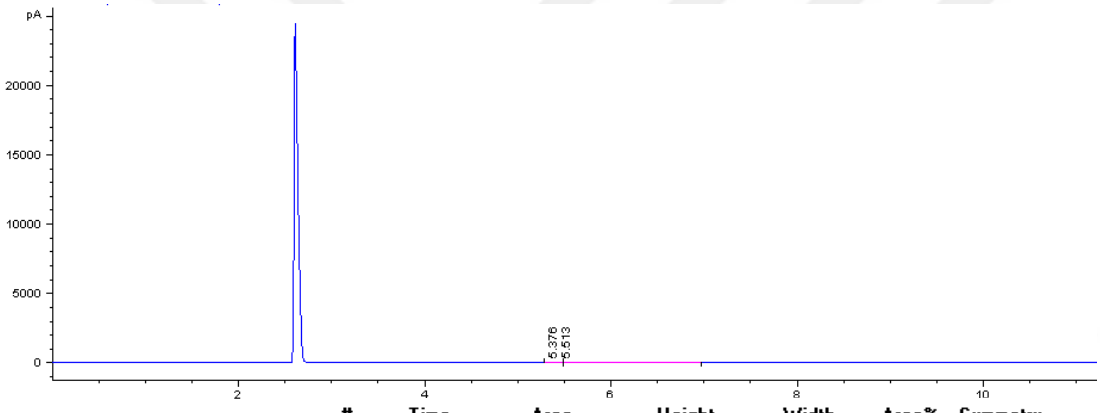


Figure E.4.3 HPLC chromatogram of the nitroaldol reaction of 4-NO_2-benzaldehyde in H_2O at RT, Cu(II) salt with **10h**



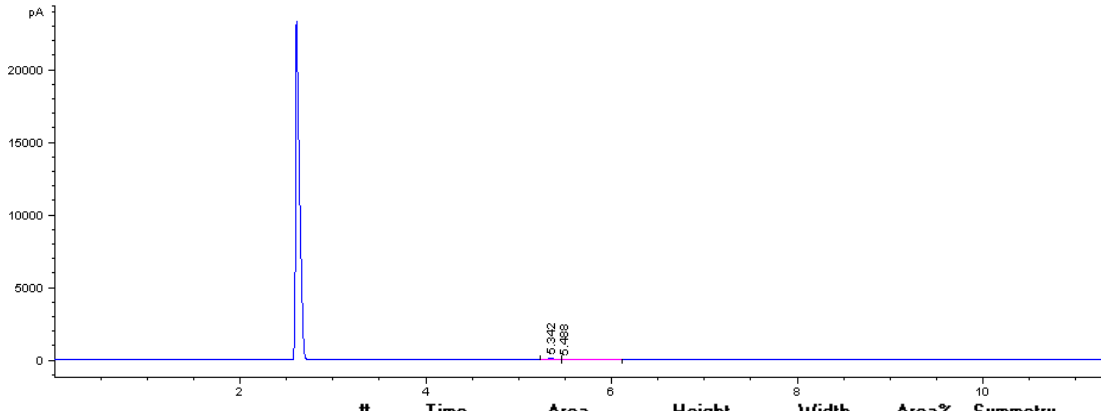
#	Time	Area	Height	Width	Area%	Symmetry
1	5.596	1632.7	91.8	0.2123	100.000	0.312

Figure E.4.4 GC chromatogram of acetophenone



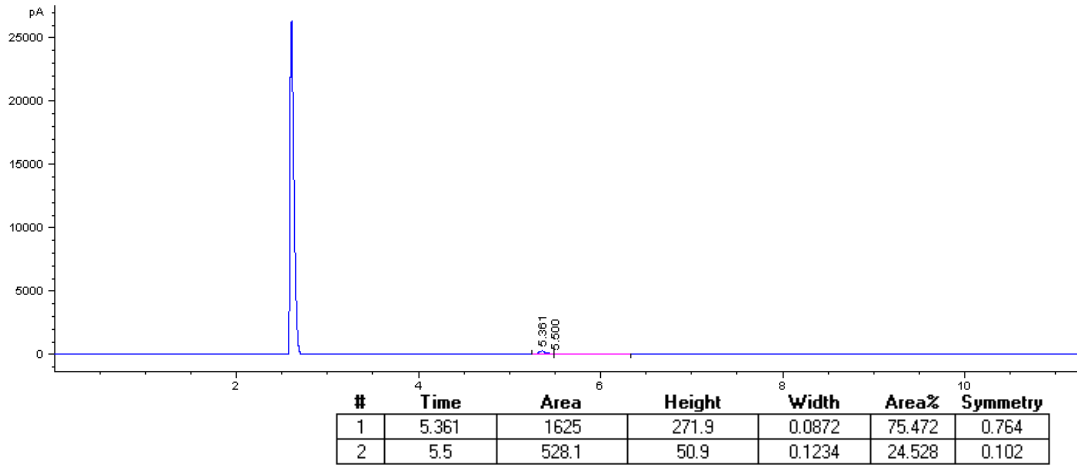
#	Time	Area	Height	Width	Area%	Symmetry
1	5.376	445.4	62.4	0.0977	32.969	0.411
2	5.513	905.7	33.9	0.3153	67.031	4.51E-2

Figure E.4.5 GC chromatogram of the TH reaction of acetophenone in 30 minutes with **10e**



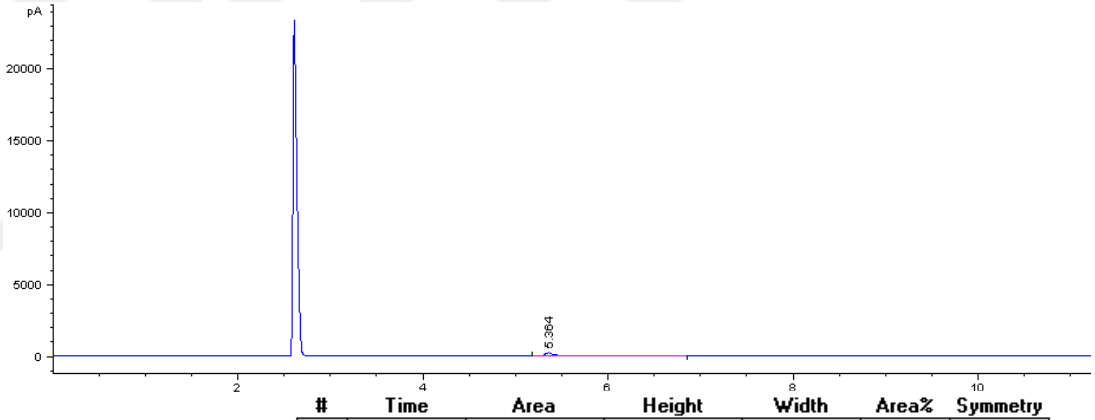
#	Time	Area	Height	Width	Area%	Symmetry
1	5.342	542.5	83.7	0.0964	65.370	0.5
2	5.488	287.4	24.4	0.1414	34.630	0.113

Figure E.4.6 GC chromatogram of the TH reaction of acetophenone in 60 minutes with **10e**



#	Time	Area	Height	Width	Area%	Symmetry
1	5.361	1625	271.9	0.0872	75.472	0.764
2	5.5	528.1	50.9	0.1234	24.528	0.102

Figure E.4.7 GC chromatogram of the TH reaction of acetophenone in 90 minutes with **10e**



#	Time	Area	Height	Width	Area%	Symmetry
1	5.364	2503.3	229.3	0.1459	100.000	0.257

Figure E.4.8 GC chromatogram of the TH reaction of acetophenone in 120 minutes with **10e**

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    ======================================================================
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                      (modified after loading)
    Analysis Method : C:\CHEM32\1\METHODS\GAMZE.M
    Last changed    : 7/14/2015 2:59:52 PM by Arsu
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```

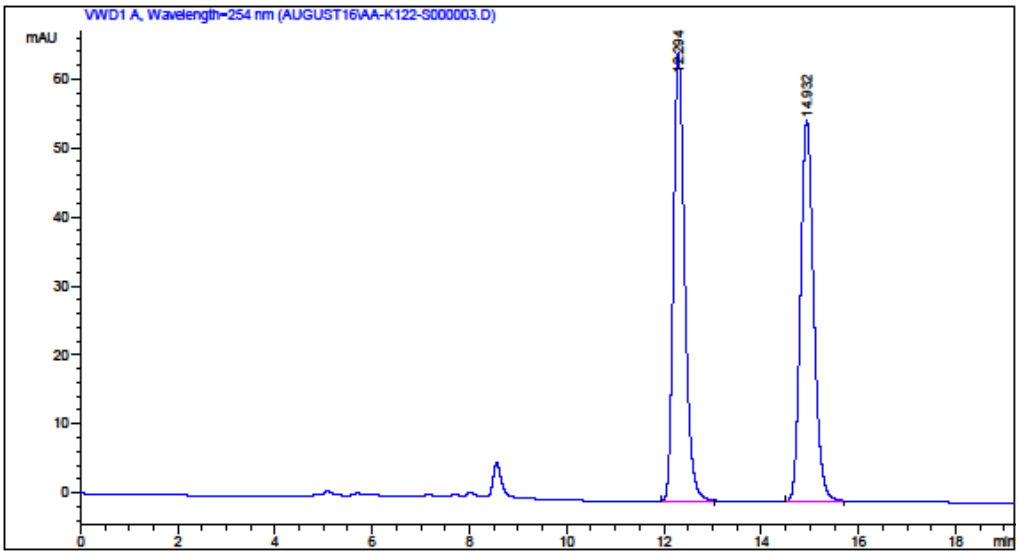


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    ======================================================================
                           Area Percent Report
    ======================================================================

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    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: VWD1 A, Wavelength=254 nm

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]  mAU   *s    [mAU   ]      %
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       1  12.294 BB    0.2476 1046.28101   64.97321  50.0008
       2  14.932 BB    0.2923 1046.24719   55.25169  49.9992

    Totals :                  2092.52820  120.22491

Instrument 1 6/17/2017 6:54:18 PM Arsu                          Page   1 of 2
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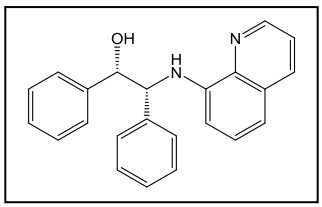
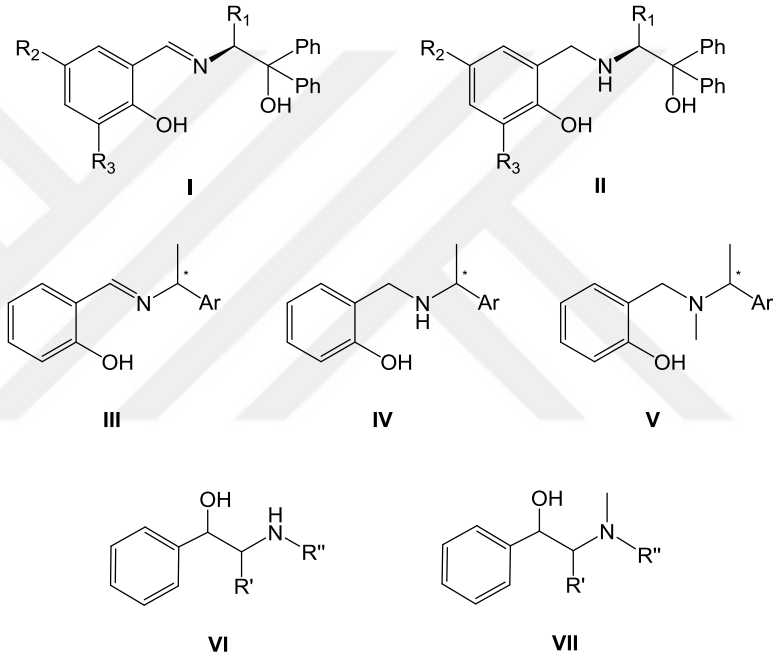


Figure E.4.9 Sample HPLC chromatogram of the TH reaction of acetophenone in IPA with **10e**

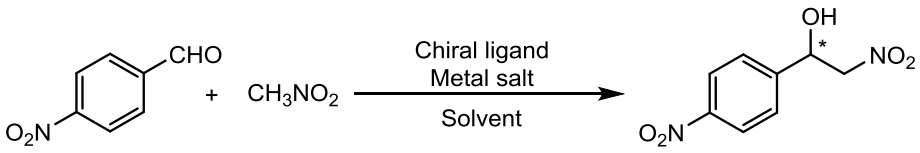
7. OBSERVED STRUCTURAL EFFECTS IN THE CU(II) CATALYSED ASYMMETRIC HENRY REACTION A SUMMARY

7.1 Results and Discussion

Our goal in this thesis was to examine the structural effects of chiral ligands on their catalytic activity. Schiff bases (**I**, **III**), aminophenols (**II**, **IV**, **V**) and *β*-amino alcohols (**VI**, **VII**) were synthesized. The characterization of the ligands synthesized was carried out by suitable methods such as IR, elemental analysis, ^{1}H-NMR, ^{13}C-NMR and by comparing with the literature.

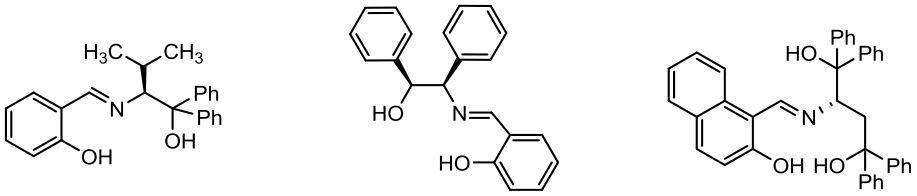


The synthesis of new chiral molecules, their characterization, and their catalytic effects in the asymmetric Henry reactions have been described in five chapters. The catalytic activities of all the ligands in the presence of Cu (II) salts were examined in the asymmetric Henry reaction employing nitromethane and 4-nitrobenzaldehyde as a model reaction (Scheme 7.1).



Scheme 7.1 The Henry reaction of 4-nitrobenzaldehyde and nitromethane

Our first interest examined the structural effects of ONO type tridentate Schiff base ligands (**3a-i**) with the Henry reaction, as examined in the chapter 2. Asymmetric applications of Schiff bases derived from amino alcohols have previously been reported. These ONO type tridentate ligands were used with Cu(II) salts as catalysts for Henry reaction *in situ*. It is shown in figure 7.1, that such ligands have shown high reaction yields and enantioselectivity.



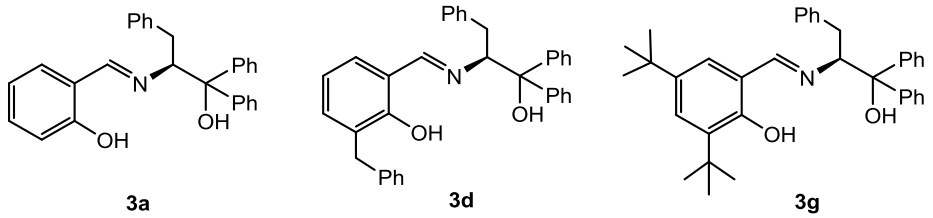
Velmathi, 2010
up to 99 % yield
70-95 % ee

Mao, 2009
36-92 % yield
34-81 % ee

Koz, 2011
up to 96 % yield
up to 92 % ee

Figure 7.1 Schiff base ligands derived from amino alcohol

The effects of compounds wherein different groups at the aromatic ring were present was studied. For the ligands **3a**, **3d**, **3g** that were derived from L-Phenylalanine the different groups on the aromatic ring were found to have no important effect on the ee values. Enantiomeric excess values for these three ligands varied between 44-62% in polar protic solvents. The compound **3g** which contained both benzyl and *tert*-butyl groups, the product was obtained with moderate yield, although the value of ee was increased (Figure 7.2).



3a
44, 64% yield
45, 57% ee

3d
45, 57% yield
44, 47% ee

3g
45% yield
62% ee

Figure 7.2 Synthesized Schiff base ligands **3a, 3d, 3g**

Disappointing ee values and yields were observed for ligands **3c** and **3i** which were derived from L-*tert*-Leucine in MeOH. When the results were compared to the previous results (Korkmaz et al., 2011). By using these ligands **3c** and **3i**, better results were obtained with etheric solvents.

In the same study, slightly better ee values were observed when the electron donor groups on the aromatic ring changed. When a methoxy group was present in the 2-position of the aromatic ring, enantiomeric excess was increased (Figure 7.3).

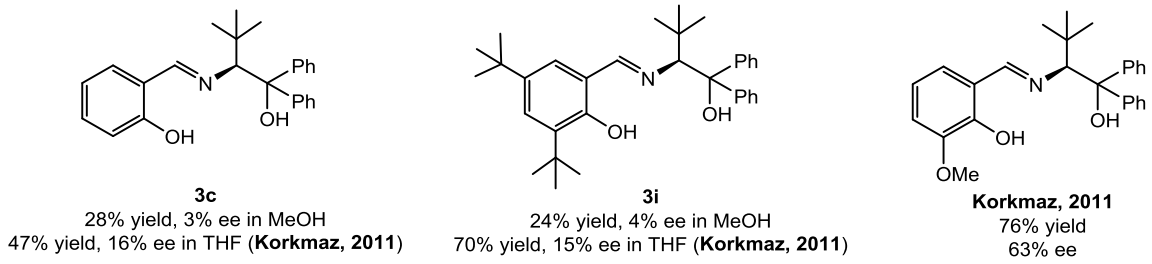


Figure 7.3 The Schiff base ligand derived from L-*tert*-Leucine

That was comparable to other works; when there were different halogen atoms attached to the aromatic ring, superior results were observed (Song et al., 2014). As seen from the figure 7.4, the Schiff base ligand which was bearing hologen atoms on aromatic ring, gave high yield with ee values. The benzyl group on the amino alcohol also appeared to increase reaction results.

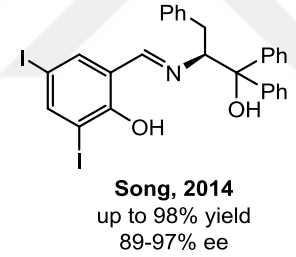


Figure 7.4 The Schiff base ligand derived from L-Phenylalanine

The presence of the benzyl group in the aromatic ring enhanced the yield and ee values. The ligands **3d**, **3e**, **3f** which had benzyl group, or bulky electron donating groups on the ligand were seen to give better results where enantiomerically enriched product was obtained (Figure 7.5).

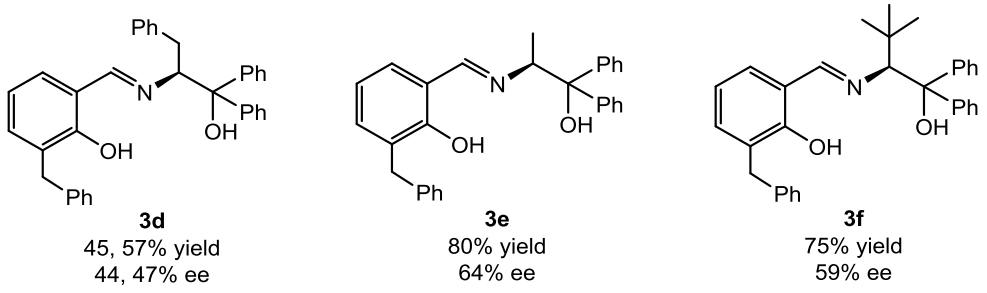


Figure 7.5 The ligands which were beared benzyl groups

Ligands **3b**, **3e** and **3h** which were derived from L-Alanine were evaluated, the best result was seen with ligand **3e** that bears a methyl group and a benzyl group as seen in figure 7.6.

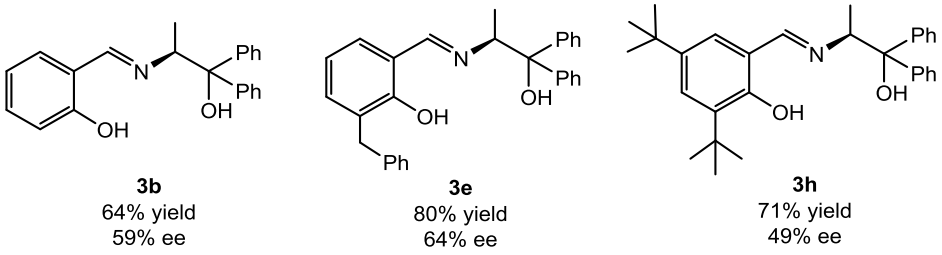


Figure 7.6 The Schiff base ligands derived from L-Alanine

There have been variety of studies in the literature from amine containing ligands. NN type bidentate Schiff base and secondary amine ligands were used for Henry reaction comparatively (Zhou and Gong, 2011). When Schiff base ligand was used as a catalyst, the product of the reaction was not observed. The reaction was catalyzed by the secondary amine derivative with high yield and ee as seen in figure 7.7.

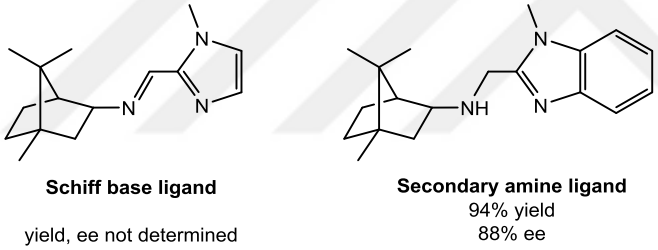


Figure 7.7 Chiral dinitrogen ligands

Despite, there have been no reported asymmetric Henry reaction in which ONO type tridentate ligands containing secondary amines have been used. So, the reduced form of the Schiff base ligands were prepared for evaluating in the Henry reaction. Secondary amino alcohol ligands (**4a-d**) catalyzed the reaction but did not show high enantioselectivity. up to 21% ee, up to 40% yields. The results showed that the presence of the electron donor benzyl group increased the catalytic activity (**4a**) (Figure 7.8).

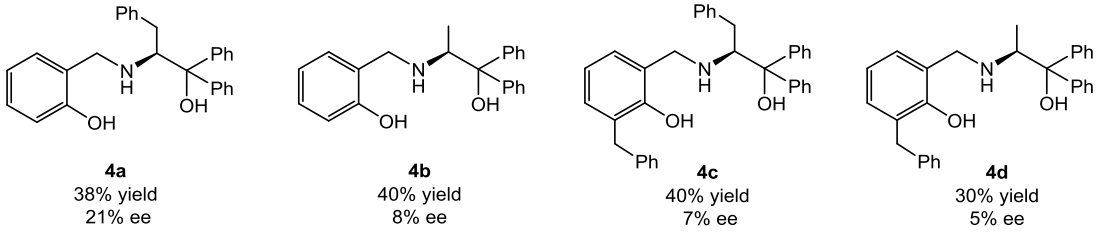
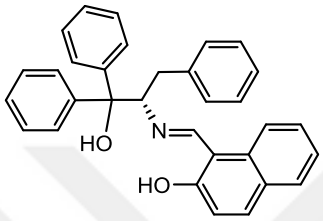


Figure 7.8 Synthesized ONO type tridentate secondary amino alcohol ligands

The experimental results showed that Schiff base ligands (**3a-i**) gave higher ee values than secondary amino alcohol ligands (**4a-d**). This could be ascribed to the lesser planarity of the reduced Schiff base adopting a different configuration when bonding to the copper ion.

In chapter 4, the effect of copper salt on Henry reaction was investigated. It was known from literature, $Cu(OAc)_2.nH_2O$ has superior effect over other copper salts (Ran et al., 2013) (Figure 7.9).

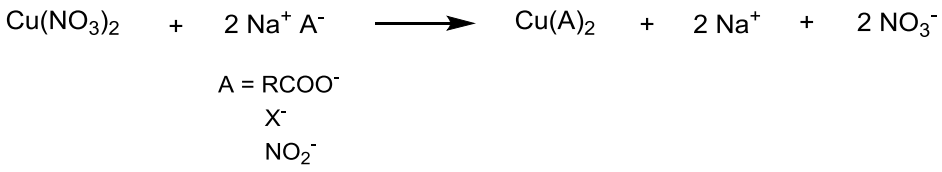


Ran, 2013

Entry	Copper salt	Yield (%)	ee (%)
1	$Cu(OAc)_2.H_2O$	69	81
2	$CuSO_4.5H_2O$	23	31
3	$CuCl_2.2H_2O$	30	59
4	$Cu(OTf)_2$	15	31

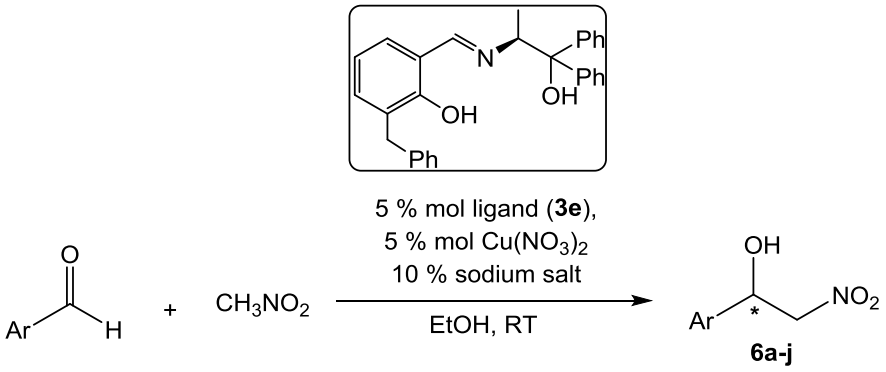
Figure 7.9 Effect of the copper salts according to Rans' work

Sodium salts were synthesized using carboxylic acids, amino acids and inorganic acids with different acidity values (Scheme 7.2).



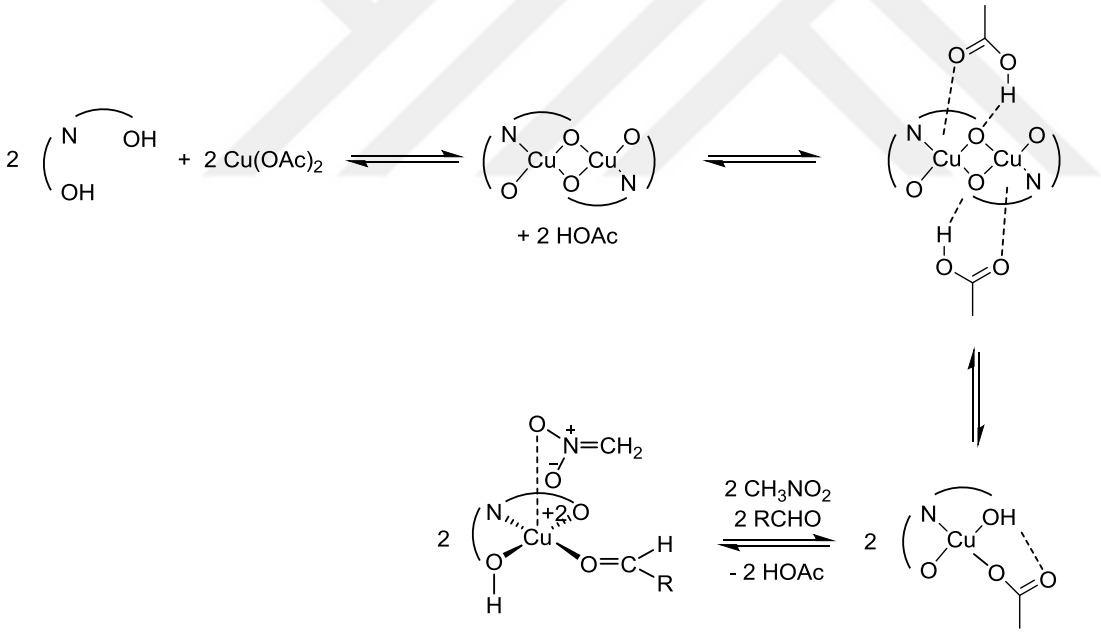
Scheme 7.2 Synthesis of copper salts from copper nitrate and different sodium salts

ONO type Schiff base ligand (**3e**) bearing a methyl group on the amino alcohol and a benzyl group on the aromatic ring was used as catalyst precursor. It has been found that a complex was formed in the reaction medium by the use of sodium salts with $Cu(NO_3)_2$. This *in situ* prepared complex was used instead of $Cu(OAc)_2.nH_2O$ in the asymmetric Henry reaction (Scheme 7.3).



Scheme 7.3 The Henry reaction using ligand **3e**, $Cu(NO_3)_2$ and sodium salt

The copper salts in the Henry reaction exhibited the counter anion plays a significant role in replacing an carboxylate counter anion with different anions of the Cu (II) salts with enantioselectivity of the asymmetric Henry reaction. At the same time, the effect of the anion on copper (II) intermediate and dimer dissociation was investigated (Scheme 7.4) (Astley et al., 2017).



Scheme 7.4 Suggested mechanism Cu(II) intermediate of ONO type tridentate ligand-metal complexes

When the reaction was carried out over the sodium crotonate salt, the enantiomeric excess was obtained with 86% ee and 74% yield. The effect of the solvent, catalyst loadings and the amount of aldehyde consumption were investigated using sodium crotonate with copper(II)nitrate and ligand **3e**. Thus, it was found that the 5% mol catalyst ratio in EtOH gave the best results and did not show any significant change with time.

Ligand **3e** was used in the Henry reaction between various aromatic aldehydes. The enantiomeric excess values of the products with para-substituted aldehydes gave higher then ortho- and meta- subtituted aldehydes. In aromatic aldehydes, the substrates bearing electron-withdrawing groups exhibited reactivity compared to that having electron-donating groups.

The best result was seen using 5% mol ratio of catalyst system (sodium crotonate and copper(II)nitrate with ligand **3e** in EtOH with 4-nitrobenzaldehyde both yield (74%) and enantiomeric excess (86%) values at room temperature in two days. When these studies are compared with the literature (Figure 7.10), it can be concluded that the effect of the bidentate and tridentate ligands on the catalytic activity can be considered. Our results are comparable and higher than, Guo and Mao's work in the presence of $Cu(OAc)_2.nH_2O$ using a tridentate ligand and the bidentate dimer copper-complex of Punniyamurthy (Punniyamurthy et al., 2008; Guo and Mao, 2009). In Gao's study, the presence of bulky groups at 3- and 5-positions of the aromatic ring on the amino alcohol did not affect the enantiomeric excess values, but on the contrary, low ee values were obtained with average yield (Gao et al., 2007).

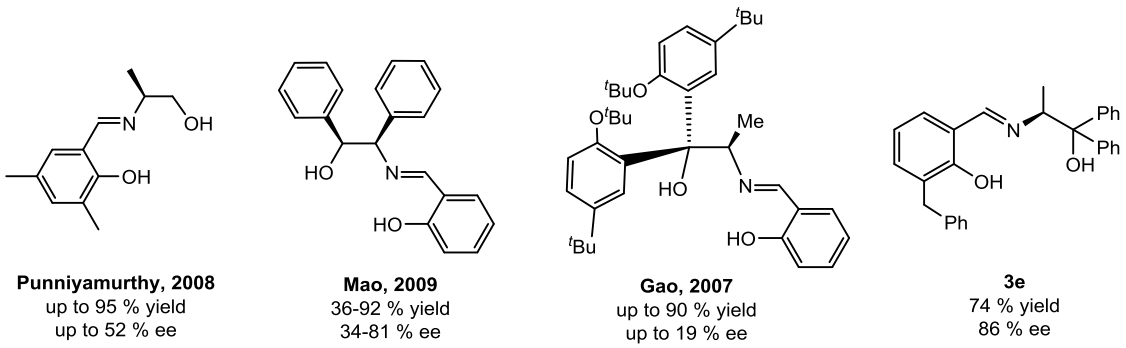


Figure 7.10 Comparing the ONO type tridentate Schiff base ligands

NN and NO type bidentate ligands have been previously used in asymmetric Henry reactions, giving variable enantioselectivity and yield (Figure 7.11). NO type bidentate ligands have been generally derived from 1,2- and 1,4- amino alcohol.

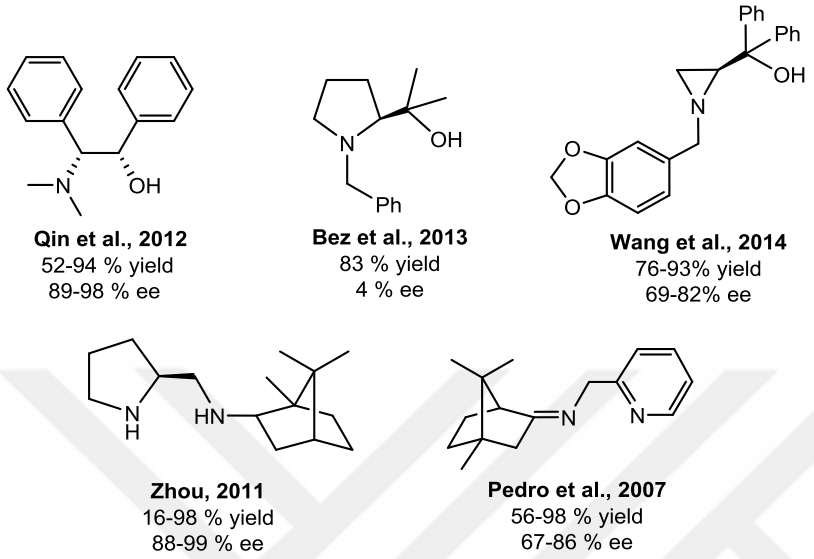


Figure 7.11 NO type bidentate ligands

Asymmetric Henry reaction applications of NO type bidentate ligands which were Schiff bases and amino alcohol derivatives have not been found in the previous works. In the same way, *β*-amino alcohol ligands are widely used in different asymmetric catalytic synthesis (Figure 7.11) (Qin et al., 2012; Wang et al., 2014). Thus, in chapters 5 and 6, we wanted to study the structural effects of the NO type bidentate ligands which were derived different structures in the asymmetric Henry reaction.

In chapter 5, synthesized in the presence of salicyl aldehyde and chiral primer amines, Schiff bases (**7a-c**), secondary (**8a-c**) and tertiary amine (**9a-c**) ligands were evaluated for the Henry reaction (Figure 7.12). This ligands were active as a catalyst with copper (II) acetate in the Henry reaction. It was found that the ligands which were substituted naphthyl groups (**8c** and **9c**) formed the Henry reaction product with high yields (81-90%), but unfortunately no enantioselectivity was observed. The best observed enantiomeric ratio was 43.2 : 56.8 with 55% yield using ligand **9a**.

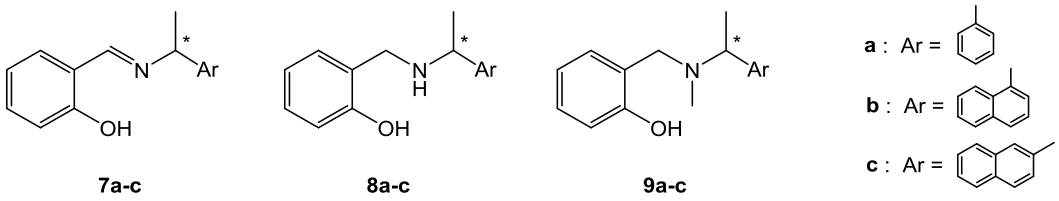


Figure 7.12 Schiff base and aminophenol ligands derived from chiral amines

In chapter 6, structural effects of NO type bidentate *β*-amino alcohol ligands (**10a-j**) derived from chiral amines obtained by epoxide ring opening were investigated in the Henry reaction (Figure 7.13).

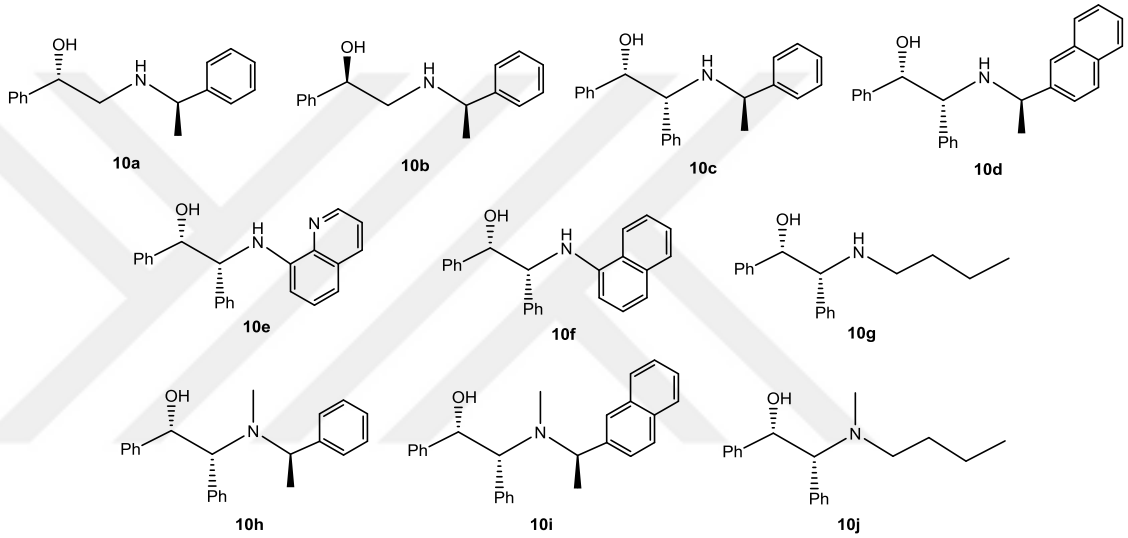
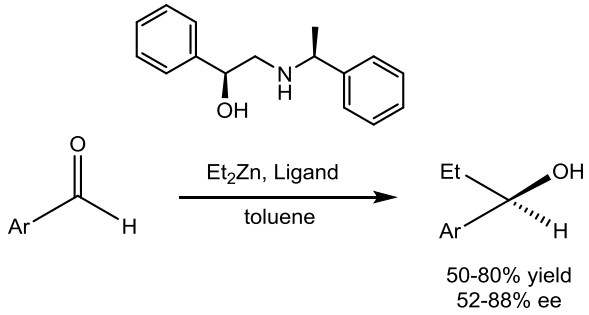


Figure 7.13 *β*-amino alcohols ligands derived from epoxides

Henry reaction applications of ligands **10a-j** were observed in moderate yields (35-87%), unfortunately, the enantiomeric excess values were unsatisfactory. The best observed enantiomeric excess was 20% with 59% yield using ligand **10c**.

Ligand **10b** was previously used as a catalyst in the enantioselective addition of $ZnEt_2$. It is seen in scheme 7.5 that high yield products were obtained with better enantioselectivity (Iuliano et al., 1995).



Scheme 7.5 Use of ligand **10b** as catalyst in the addition of $ZnEt_2$ to aldehydes

The asymmetric Henry reaction was accomplished with high yields and enantioselectivities by using NO type bidentate tertiary amine ligands in the presence of $Cu(OAc)_2.nH_2O$ as catalyst (Qin et al., 2012). For this reason, tertiary amine ligands (**10h, 10i, 10j**) were synthesized and used in the Henry reaction. The results of Qin have been much better than our results (Figure 7.14). The presence of methyl groups which are small and less steric hindrance on the nitrogen may have affected the reaction mechanism.

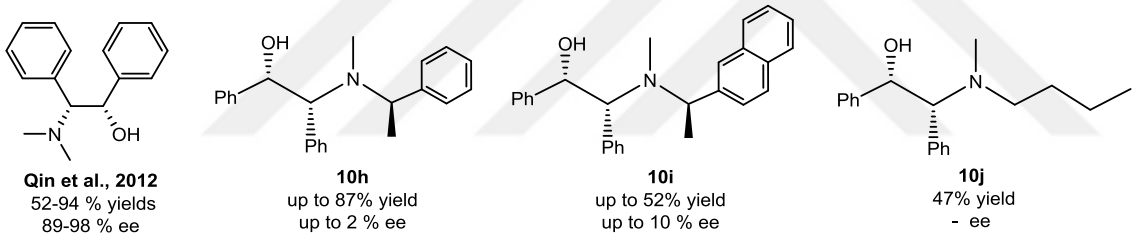


Figure 7.14 NO type bidentate tertiary amine ligands and their Henry reaction values

7.2 Conclusions

According to the results obtained, it was found that the ONO type tridentate ligands (**I, II**) exhibited higher enantioselectivity and yields than NO type bidentate ligands (**IV**, **V**, **VII**). Similar observations have been obtain from other studies. Bez and co-workers prepared NNO type tridentate, NN and NO type bidentate ligands which were derived from L-Piroline (Bez et al., 2014). Compared with each other, it was determined that tridentate ligands exhibited higher enantioselectivity (Figure 7.15).

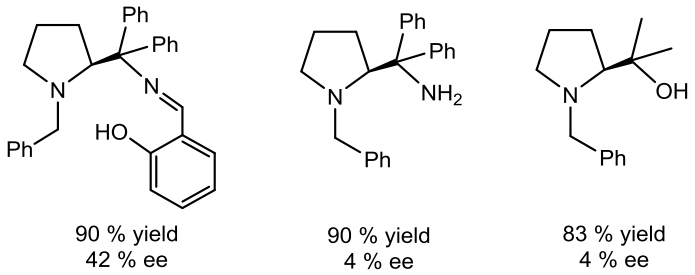


Figure 7.15 L-piroline base ligands

Similarly, Bures and co-workers synthesized bidentate ligands which were derived from imidazole. The ligands were used as catalysts in the Henry reaction at different reaction conditions. The ee values were low, high yields were obtained as seen below. (Bures et al., 2006). Sedlak et al. prepared bidentate ligands which were derived from pyridine and used as catalysts (Sedlak et al., 2006). The observed ee values were not too high as expected (Figure 7.16).

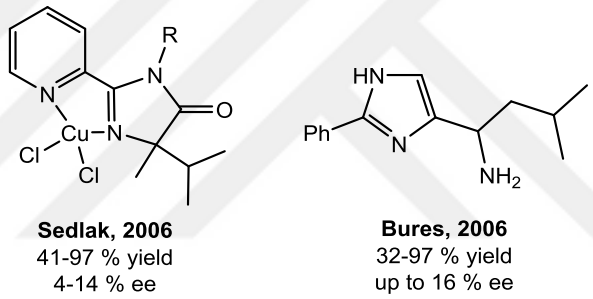


Figure 7.16 NN type bidentate ligands

Structural effects of chiral ligands were investigated on the catalytic activities in the Henry reaction. It has been found that the substituents in the aromatic ring and the side chain of the Schiff base change the catalytic activity in the ONO type tridentate ligands. The effects of the alkyl groups on the amino alcohol and the electron donating groups on the aromatic ring affected the enantiomeric excess. The reaction results increased in the presence of the benzyl group bonded from the 2-position of the aromatic ring (Figure 7.17).

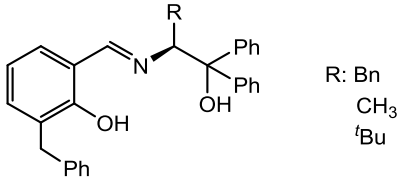


Figure 7.17 Benzyl substituted Schiff base ligands at the 2-position of the aromatic ring

The effects of substituents were noticed by using different optimization studies, such as copper salt, solvent and substrate.

The copper (II) complexes were extensively examined in the Henry reaction. The anion of the copper salt played an important role in the catalytic cycle, depending on the substituents, and had a direct effect on enantioselectivity.

It is known that different copper (II) complexes can be formed according to the reaction medium (Astley et al., 2017). So, the effects of substituents on the solvent were investigated. The Henry reaction was carried out with polar solvents such as IPA, EtOH, MeOH. It was determined that the enantioselectivity was achieved by EtOH.

The effects of the substituent groups on the substrate were studied according to their different steric effects. The electron donor -NO_2 group at the 4-position showed high yield and enantioselectivity. For the first time, it has been noted that substituents on the carboxylate counter ion have an important effect on the observed enantioselectivity of the reactions.

Structural effects of NO type bidentate and β-amino alcohols ligands were used as catalysts in the presence of $Cu(OAc)_2.nH_2O$ in the asymmetric Henry reaction of 4-nitrobenzaldehyde. It was found that bulky groups substituted on the NO type bidentate ligands formed the Henry reaction product with good yields, but low enantioselectivity.

Briefly, as part of an existing research program for examining the structural effects of chiral ligands, it was proposed that the metal complexes of the ligands synthesized here could be evaluated in asymmetric reactions, particularly in the Henry reaction. It is thought that the completed researches in this thesis study will draw attention to the chemistry of chiral ligands, together with the studies of other chiral structures in the literature. Thanks to the experience gained in this work, further developments in the asymmetric Henry reactions may occur.

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CURRICULUM VITAE

PERSONEL INFORMATION

Name-Surname : Pakize Arzu AKINCI
Profession : Chemist
Date/Place of Birth : 06.05.1987 / UŞAK, TURKEY
Nationality : T.C
Gender : Female
Marital Statue : Single

PERSONEL INFORMATION

Address : Kazımdirik M. 153 S. Anıl Apt. No:67/2 Bornova-İzmir
Phone Number : +90 505 874 10 82
E-mail : p.arzu.akinci@gmail.com.tr
arzuakinci03@hotmail.com

EDUCATION BACKROUND

2012-2017 : Ege University, Institute of Natural and Applied Science, Chemistry, Izmir, TURKEY **Ph.D. in Organic Chemistry,** The subject of doctor of philosophy thesis "An investigation into structural effects on the catalytic activity of chiral metal-ligand complexes"

2010-2015 : Ege University, Institute of Natural and Applied Science, Chemistry, Izmir, TURKEY **MSc. in Organic Chemistry,** The subject of master of science thesis "Synthesis and Properties of Perimidine Derivatives"

2005-2009 : Selçuk University, Faculty of Science, Chemistry Dept. Konya, TURKEY

2001-2005 : Orhan Dengiz Anatolian High School, Natural Science and Maths Uşak, TURKEY

WORK EXPERIENCE

2015-2016 : MEDBAR TIBBİ MALZEMELER LTD. ŞTİ.,İZMİR, Research and Development Department, Final product development

2014 : YILPAR AMBALAJ SANAYİ VE TİCARET A.Ş., İZMİR, Quality Control Department, Process and total quality control, preparation of analysis certificates

2012 : KARBEM (Karabağlar Belediyesi Eğitim Merkezi), 4 months through Chemistry teacher

2009 : B.K. HOLZEM RETAIL INC. (U.S.A.), 4 months through Work and travel program - Cashier

2009 : AMERICAN WORLD INC. (U.S.A.), 4 months through Work and travel program – Hotel/Housekeeping

INTERNSHIPS

2009 : B.K. HOLZEM RETAIL INC. (U.S.A.), 4 months through Work and travel program - Cashier

2008 : PETKİM PETROKİMYA HOLDİNG A.Ş, 45 civil days, Research and Development Department : Polymer, catalyst, process modelling and projection; Instrumental analysis with GC-MS, AAS, HPLC, UV, IR, DCM, Polarimeter; Quality Control Department : Incoming, process and total quality control.

2007 : MURATBEY GIDA VE SÜT ÜRÜNLERİ PAZARLAMA SAN. Ve TİC. LTD. ŞTİ. (UŞAK), 2 weeks - Quality Control Department and Manufacture process, Quality Control Department : Incoming, process and total quality control, oil, analysis, determination of acid-base number, determination of shelf life.

PUBLICATIONS

2017 : Carboxylate ion dependency in the Cu (II) catalysed asymmetric Henry reaction: Structural characterisation of a tridentate Schiff base complex containing a coordinated carboxylic acid,, Applied Organometallic Chemistry, 2017, in press.

2014 : Perimidin-2-ylidene rhodium (I) complexes; unexpected halogen exchange and catalytic activities in transfer hydrogenation reaction, Journal of Organometallic Chemistry, 765, 23-30.

CONGRESSES

2016 : CPhI (Convention on Pharmaceutical Ingredients), İstanbul, 1-3 June, pharmaceutic-medicine congress

2013 : Tokat IV. Convention of National Inorganic Chemistry 30 May-2 June, Poster, "Perimidinium Salts and Their Rhodium Complexes"

PROJECTS

2011 : Ege University, Research Fund Accountancy, 11-FEN-048

2015-2017 : Ege University, Research Fund Accountancy, 15-FEN-035