SYNTHESIS OF *N*-(2-PROPYLPHENYL) SUBSTITUTED CHIRAL AMINO ALCOHOLS AND THEIR USAGE IN ENANTIOSELECTIVE DIETHYLZINC ADDITION REACTIONS

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SYNTHESIS OF *N*-(2-PROPYLPHENYL) SUBSTITUTED CHIRAL AMINO ALCOHOLS AND THEIR USAGE IN ENANTIOSELECTIVE DIETHYLZINC ADDITION REACTIONS

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ABSTRACT

SYNTHESIS OF *N*-(2-PROPYLPHENYL) SUBSTITUTED CHIRAL AMINO ALCOHOLS AND THEIR USAGE IN ENANTIOSELECTIVE DIETHYLZINC ADDITION REACTIONS

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Chiral 1,2-amino alcohols were synthesized *via* newly developed "*intramolecular unsaturation transfer*" using cyclohexanone, propargyl bromide, and various chiral amino alcohols as starting components. These amino alcohols can be potential chiral ligands for many asymmetric transformation reactions. Therefore, their effectiveness as chiral ligands in diethylzinc addition to benzaldehyde and *N*-diphenylphosphinoyl imines were tested. Various parameters including temperature, solvent, ligand amount etc. were screened for the synthesized chiral ligands. In diethylzinc addition to benzaldehyde high enantioselectivity could not be obtained. When *N*-diphenylphosphinoyl imines were used as substrate good ee values up to 80% were achieved.

Key words: 1,2-amino alcohols, chiral ligand, diethylzinc, *N*-diphenylphosphinoyl imine

ÖZ

N-(2-PROPİLFENİL) SÜBSTİTÜE KİRAL AMİNO ALKOLLERİN SENTEZİ VE ÇEŞİTLİ ENANTİYOSEÇİCİ DİETİLÇİNKO KATILMA REAKSİYONLARINDA KULLANIMI

Günler, Zeynep İnci

Yüksek Lisans, Kimya Bölümü

Tez Yöneticisi: Prof. Dr. Cihangir Tanyeli

Şubat 2011, 77 sayfa

Kiral 1,2-aminoalkoller yeni geliştirilmiş bir method ile siklohekzanon, proparjil bromür ve çeşitli kiral amino alkollerden başlanarak sentezlenmiştir. Sentezlenen amino alkoller çeşitli asimetrik transformasyon reaksiyonlarında potansiyel kiral ligandlardır. Bu sebeple, bu amino alkollerin benzaldehite ve çeşitli *N*-difenilfosfinoyil iminlere dietilçinko katılma reaksiyonlarındaki etkinlikleri test edilmiştir. Sentezlenen ligandlar için sıcaklık, çözücü, ligand miktarı gibi parametreler taranmıştır. Benzaldehite dietilçinko katılması reaksiyonunda yüksek enantiyoseçicilik elde edilememiştir. Substrat olarak *N*-difenilfosfinoyil iminler kullanıldığında oldukça iyi ee değerlerine ulaşılmıştır (80%).

Anahtar Kelimeler: 1,2-amino alkol, kiral ligand, dietilçinko, *N*-difenilfosfinoyil imin

Dedicated to my precious mother...

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LIST OF ABBREVIATIONS

THF: Tetrohydrofuran

DMSO: Dimethyl sulfoxide

BTF: Benzenyl trifloride

DAIB: Dimethylaminoisobornenol

DBNE: *N,N*-Dibutylnorephedrine

PTSA: *p*-Toluenesulfonic acid

TADDOL: *α,α,α',α'*-Tetraaryl-1,3-dioxalane-4,5-dimethanol

CHAPTER 1

INTRODUCTION

1.1. What is asymmetric synthesis ?

In 1904 the original definition was formed by Marckwald as "*asymmetric synthesis are those reactions which produce optically active substances from symmetrically constituted compounds with the intermediate use of optically active materials but with the exclusion of all analytical processes*" [1]. This definition ignores chiron approach in which one of the starting materials have chiral unit. According to Marckwald, an asymmetric reaction must be performed using an achiral substance, therefore it is assumed to be a narrow definition. The broadest definition was made by James D.Morrison and Harry S. Mosher in 1971 "a*n asymmetric reaction is a reaction in which an achiral unit in an ensemble of substrate molecules is converted by a reactant into a chiral unit in such a manner that the stereoisomeric products are produced in unequal amounts".* This expanded definiton involves a wider range of reactions and specifies that a prochiral center which is converted to a chiral center, may belong to either a chiral or an achiral substance [2]. In order to success asymmetric synthesis at least one of the reaction components such as reagents, catalyst or solvent must be chiral. If none of these has an asymmetry component, the transition state will be enantiomeric which are equal in energy, consequently reaction rates for the two enantiomers will be the same and a racemate will be formed. If we consider an unsymmetric carbonyl compound as in Figure 1, the heterotopic faces of the molecule could be enantiotopic if there is no stereocenter or diastereotopic if there is a chiral unit in the molecule. Nucleophilic attack from the heterotopic *Re* or *Si*

faces in presence of an achiral reagent will cause enantiotopic transition states. If there is a chiral component in the reaction medium or the products are diastereomers themselves, then diastereomeric transition states having unequal energy barriers occur, the enantiomer with the lower energy will be produced in excess over the other enantiomer and the stereoselectivity is achieved [3].

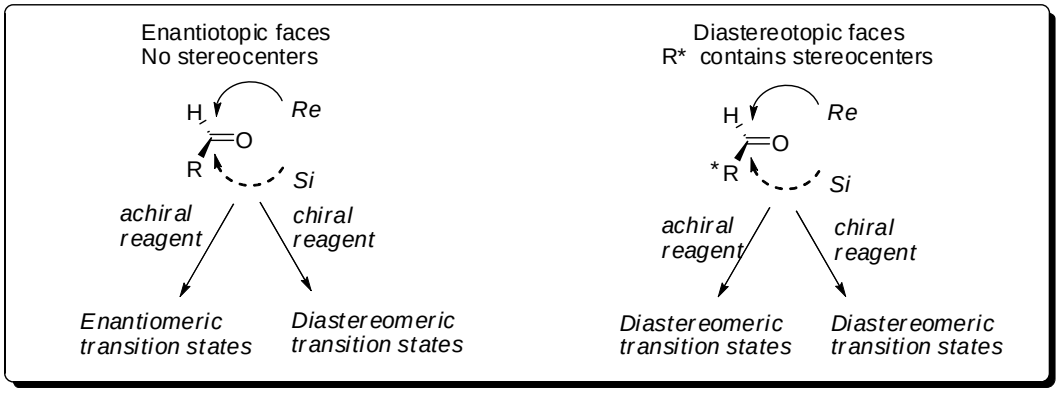


Figure 1. Nucleophilic attack to heterotopic faces of an aldehyde

1.2. Methods to produce optically active compounds

1.2.1. De novo asymmetric synthesis

This type of reactions are rare and generally not in use in asymmetric synthesis but in growing interest of search. In this method achiral starting compounds are converted into chiral products under certain conditions without using any chiral reagent and this chiral product autocatalyses its own formation.

1.2.2. Chirality relay

This method is also referred to as *chiral pool.* In this method, chiral centers are directly incorporated by using optically pure reagents as starting materials. This is a bought-in chirality and not a real asymmetric synthesis. Some modifications are

done on chiral compounds to obtain the target molecule. Enantiopure starting materials must be supplied and used in stoichiometric ratios which can be expensive if they are not present in nature.

1.2.3. Chiral auxiliary

Chiral auxiliaries are used to convert a prochiral compound to an optically active product. A prochiral molecule is an achiral molecule which can be converted to a chiral molecule in one step. The chiral species are covalently bonded to the substrate to transport chiral information. The chiral auxiliary is not incorporated in the product so that after removal of the auxiliary, the product is enriched in one enantiomer and the stereoselectivity can be designated by measuring the enantiomeric excess. As most of the chiral auxiliaries are expensive they should be recovered after the reaction and reused. This provides an economical synthesis but also brings the disadvantage of adding on two extra steps; binding the auxiliary on the target molecule and then removal [4]. The strategy for this method is shown in Figure 2.

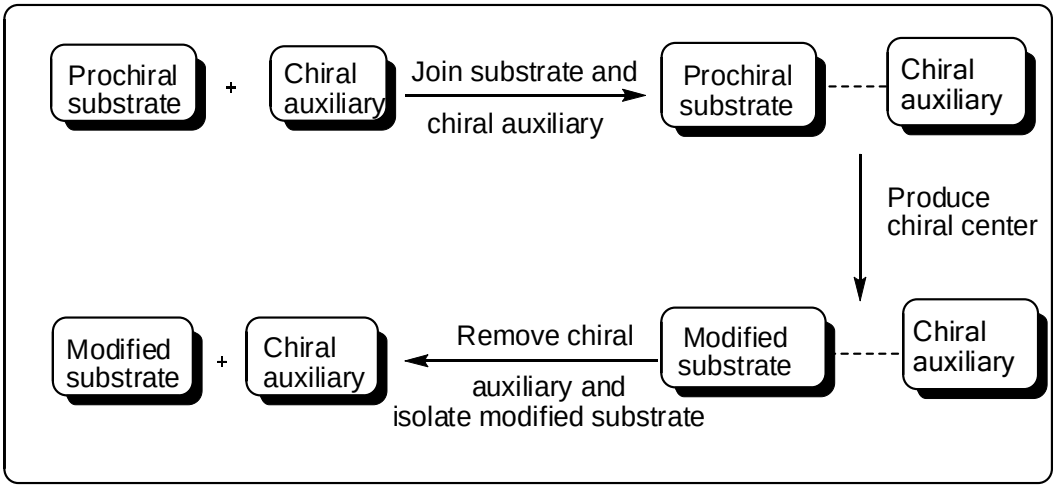


Figure 2. Strategy for chiral auxiliary approach

1.2.4. Asymmetric catalysis

This method has significant advantages over the other methods. Using small amount of a chiral catalyst which are regenerated, a large amount of chiral product molecules can be produced. The working principle of asymmetric catalysis is represented in Figure 3. Catalyst is involved in the transition state which leads to a diastereomeric transition states and consequent asymmetric synthesis. Chiral catalysts can be classified as;

- metal-ligand complexes involving chiral ligands
- biocatalysts
- organocatalysts.

In nature many compounds are produced by enzymatic catalysis. Alternatively, the same compounds can be synthesized by using synthetic asymmetric catalysis with ee values up to 100%. The pioneering work in this field was done by William S. Knowles and Ryoji Noyori in 1968 (Nobel Prize in Chemistry 2001). They synthesized the first asymmetric catalyst by replacing the achiral triphenylphosphine units in Wilkinson's catalyst [$RhCl(PPh_3)_3$] with chiral ones P(Ph)(Me)(Propyl). This catalyst was used in asymmetric hydrogenation reaction [5, 6].

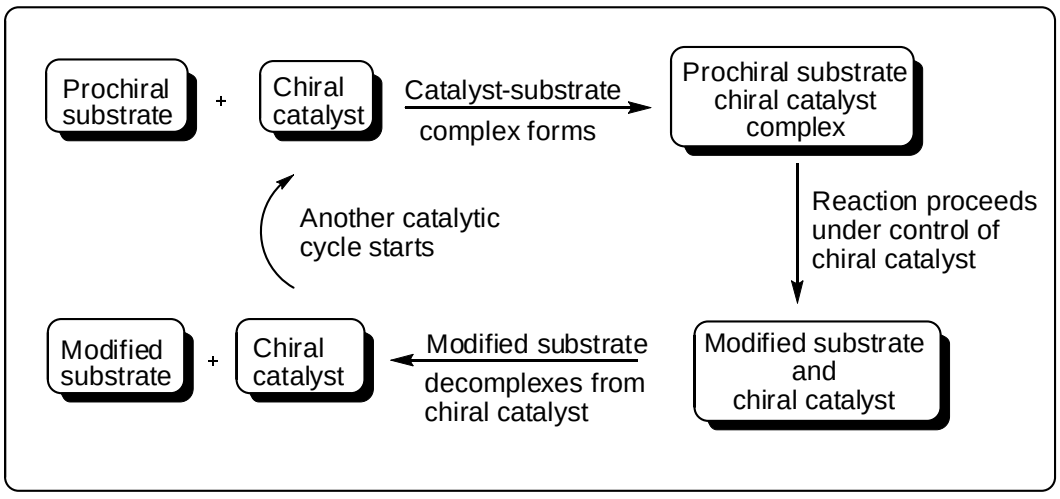


Figure 3. Schematic representation for asymmetric catalysis

1.3. Why we do asymmetric synthesis

The importance of asymmetric synthesis comes from the fact that nature is made up of mostly chiral compounds. Biologically important polymers which consist of amino acids, nucleotides, carbohydrates all have asymmetric carbon atoms. The value of enantiomerically pure compounds grows out of the recognition of chiral molecules in human body. All biological receptors have a chiral, non-racemic structure. Therefore to provide physiological response (e.g., catalysis, neural impulse, *etc*.), the binding site and the chiral molecule must have the correct handedness. In Figure 4, two enantiomers of an amino acid and the binding site are illustrated. Only one of the enantiomers can provide matching with the binding site.

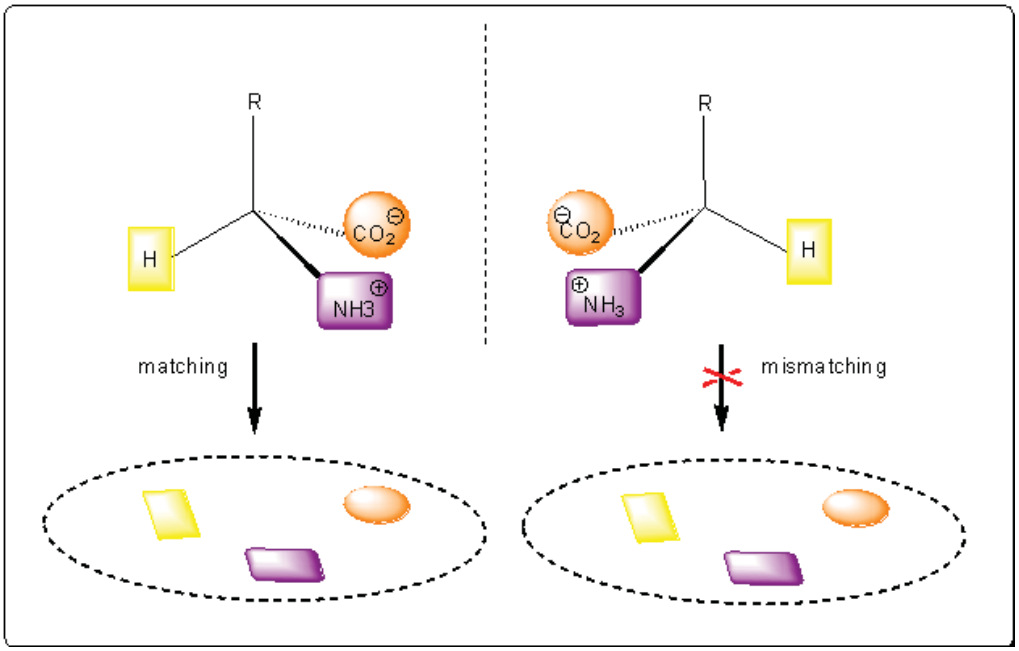


Figure 4. Two enantiomers of an amino acid molecule

As a consequence of enantiomer recognition in our body, these two enantiomers causes different responses and accordingly different physiological effects. For

instance enantiomers generally have different odors and tastes, like in the case of limonene. One enantiomer of limonene accounts for the odor of lemon and the other one for the odor of orange. In pharmacology, the two enantiomers should be considered as two different compounds because they have totally different effects on human body. One enantiomer can bring about harmful side-effects while the other one brings the aimed biological activity. The most well-known case is the one with thalidomide. It was used as a drug to reduce the morning sickness symptoms in pregnant women. Then, it was found that thalidomide caused horrible birth defects as a result of the drug consumption. The *(S)* enantiomer of thalidomide shows teratogenic activity while the *(R)* enantiomer acts as a sedative. Similarly, the *(R)* enantiomer of ibuprofen is inactive but the *(S)* enantiomer is an active pain reliever. This causes the drug potential of an active enantiomer doubles comparing to the racemic mixture so that the dose can be reduced to half. This is also another reason for synthesizing optically pure compounds which is economical as the inactive enantiomer brings out the waste consumption of starting materials. There are also many examples in food industry, agrochemicals, cosmetics where the desired property depends on the absolute configuration [4,7]. Aspartame is a chemical used in food industry. *(S,S)* Aspartame isomer is used as a commercial sweetener but the *(S,R)* isomer has a bitter taste and should not be used. In Figure 5, some examples for the structures and different activities of these biologically important enantiomers are shown.

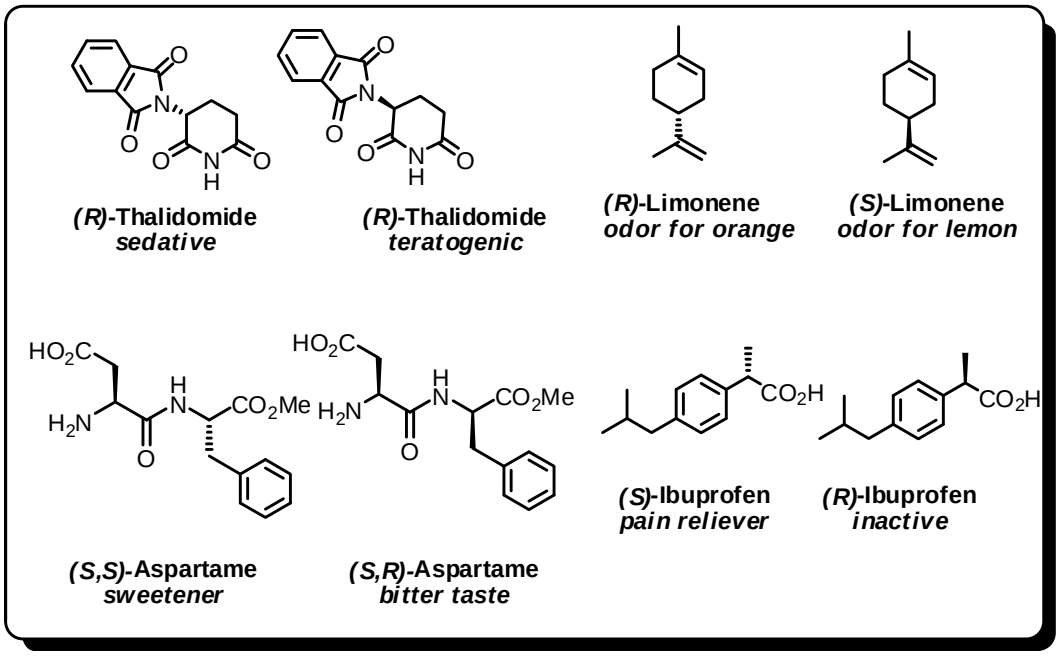


Figure 5. Structure and biological effects of enantiomers of some important chiral compounds

1.4. Application area of asymmetric catalysis

Asymmetric catalysis has found a large application area in asymmetric transformation reactions. There is a great number of widely used reactions which are involved in asymmetric catalysis [8]. In general terms and in a condensed way, these reactions can be categorized as;

i) Nucleophilic addition to carbonyl compounds involves organozinc additions to carbonyl compounds, cyanide addition to ketones and aldehydes, nucleophilic addition to imines,

ii) Reduction of alkenes: various asymmetric hydrogenation reactions (in presence of different transition metals such as ruthenium, rhodium, titanium, iridium), hydrosilyation, hydroboration, hydrocyanation reactions,

iii) Reduction of imines and ketones: hydrogenation, hydrosilyation, ketone reduction using borohydride reagents,

iv) Oxidation reactions: the most commonly used type is epoxidation reaction which is applied to alkenes, aldehydes allylic alcohols *etc*.,

v) Aldol type reactions,

vi) Cycloaddition reactions such as Diels-Alder reactions, cyclopropanation reactions *etc.*

1.4.1. Enantioselective carbon-carbon bond formation reactions by nuclephilic addition to carbonyl compounds and imines

Enantioselective carbon-carbon bond formation reactions have been employed as one of the most popular and useful reactions to produce optically active compounds. For this purpose, the most common and widely used method involves the dialkylzinc addition reactions, among the others. Since the subject of this thesis consists of nucleophilic addition of diethylzinc to aldehydes and imines, herein revealing information about related titles is given in details.

1.4.1.1. Dialkylzinc addition to aldehydes

1.4.1.1.1 History and Mechanism

The stereocontrol of absolute configuration in carbon-carbon bond formation reactions has been a great interest in synthetic organic chemistry. Enantioselective alkylation of carbonyl compounds using dialkylzinc reagents is one of the most popular and useful reactions to yield optically active secondary alcohols which are components of many biologically active compounds and are important intermediates in natural product synthesis [9]. Dialkylzinc reagents possessing sp hybridized structure have linear geometry and unreactive towards addition to carbonyl compounds due to the nonpolar alkyl-metal bonds [10]. Coordination of ligands to dialkylzinc converts this linear structure to tetrahedral form. The bond order of the Zn-C bond is reduced and the bond length increases. Consequently nucleophilicity of the alkyl group increases and nucleophilic attack to carbonyl

group of aldehyde takes place. Thus, ligands are effective on both activation of dialkylzinc reagent and stereochemical control of the reaction [11]. Unreactive and reactive structures for dialkylzinc molecule are depicted in Figure 6.

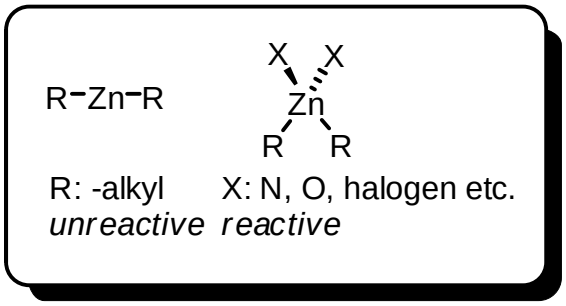


Figure 6. Unreactive and reactive dialkylzinc compounds.

The first example of diethylzinc addition to benzaldehyde was reported by Oguni and Omi in 1984 [12]. They obtained moderate enantioselectivity (49% ee) using catalytic amount of *(S)*-leucinol which is a 1,2-amino alcohol. After 2 years the first highly catalytic enantioselective addition of organozinc was achieved by Noyori and co-workers in 1986. A camphor derived chiral 1,2-amino alcohol, (-)-3-exo-dimethylaminoisobornenol [(-)-DAIB] was used to catalyze dialkylzinc addition to aldehydes (Figure 7).

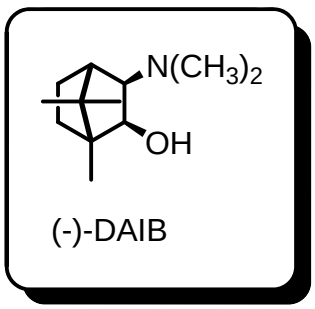
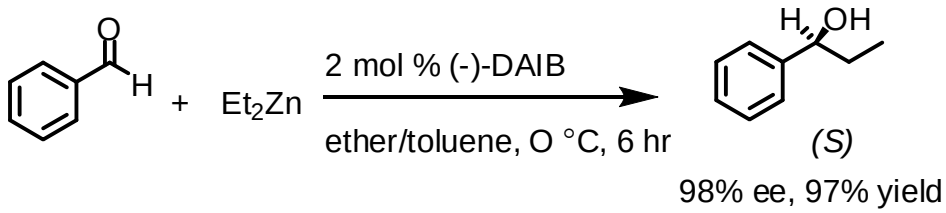


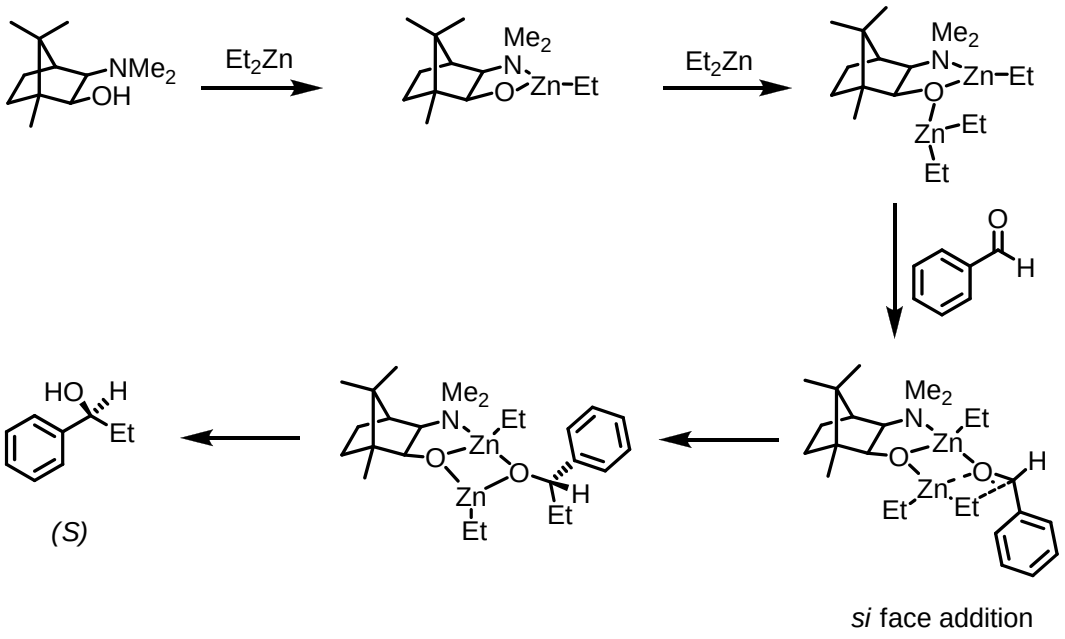
Figure 7. Noyori's catalyst

As represented in Scheme 1, 2 mol% of (-)-DAIB was subjected to diethylzinc addition to benzaldehyde to give *(S)*-1-phenylpropanol after aqueous work-up with 98% ee and 97% yield. The catalyst also worked well with other aromatic aldehydes but with aliphatic aldehyde, heptanal enantiomeric excess was moderate (61%) [13].



Scheme 1. Noyori's work

(-)-DAIB was also immobilized on polystyrene supports and used as efficient chiral catalysts by Itsuno and Frechet [14]. Using this polymer-bound chiral ligand in diethylzinc addition to benzaldehyde, they suggested a transition state model involving two zinc atoms bridged by the aldehyde oxygen. Corey and Hannon have proved that lithium chelates of amino alcohols are also good catalysts for this reaction and they have shown possible mechanisms for Noyori's reaction which are consistent with the ones provided by Itsuno and Frechet [15]. The mechanism of the reaction was also investigated by Noyori *et* al. and with the help of theoretical and experimental studies. It was found that for each aldehyde molecule two equivalent of dialkylzinc is responsible for alkylation [13]. Also Houk and co-workers performed theoretical calculations on the mechanism [16].



Scheme 2. Proposed mechanism for diethylzinc addition to benzaldehyde in Noyori's work.

As a consequence of all these studies it was found that firstly, the coordination of the zinc atom with oxygen and nitrogen, which act as donor atoms, forms a zinc alkoxide complex that can further coordinate with dialkylzinc and oxygen of the aldehyde molecule. Here, zinc alkoxide acts as a multifunctional catalyst. It acts as a Lewis acid to increase the electrophilicity of carbonyl group of aldehyde and as a Lewis base to facilitate the activation of dialkylzinc compound. In the case of Noyori's experiment, calculations showed that benzaldehyde undergoes anti coordination with respect to ligand molecule and the alkyl group attacks to the *si* face of the aldehyde to yield *(S)*-enantiomer. Scheme 2 shows the proposed mechanism for Noyori's reaction [14, 15, 16].

1.4.1.1.2. Chiral amino alcohols used as ligands

A great many of chiral ligands designed for dialkylzinc addition reactions are the derivatives of amino alcohols. The most widely used structure is 1,2-amino alcohols. In Figure 8, some examples of chiral 1,2-amino alcohols **1-6**, from literature are given respectively [17, 18, 19, 20, 21, 22].

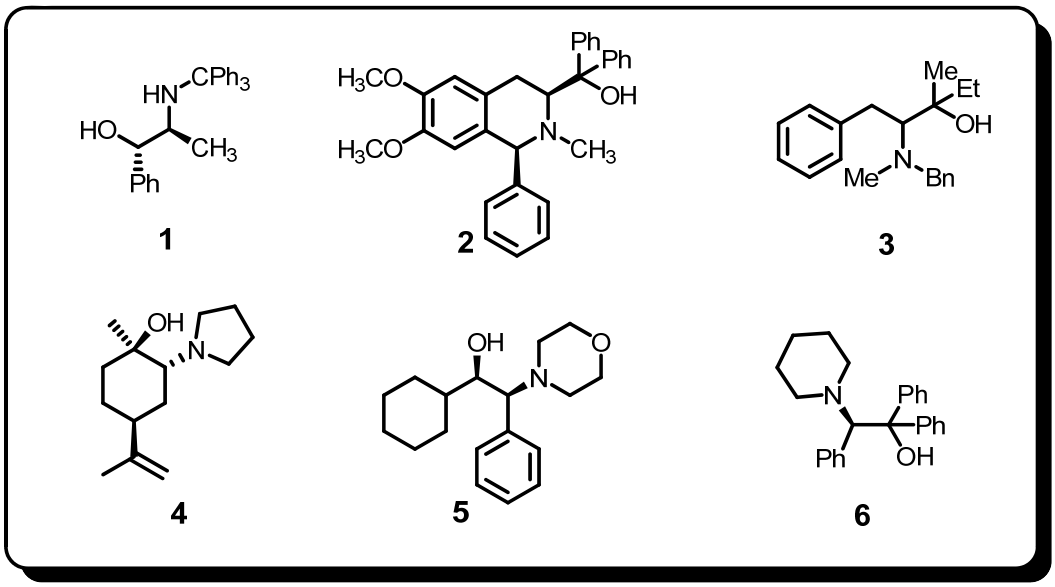


Figure 8. Chiral 1,2-amino alcohols used as chiral ligands in enantioselective diethylzinc addition to aldehydes.

The efficiencies of these ligands as catalysts in diethylzinc addition reaction are all tested using benzaldehyde as a model substrate. High enantioselectivities were reported for each ligand. The enantioselectivity may vary with the functional groups bounded to nitrogen or oxygen atom, sizes of these groups, other substituents on the molecule and their positions. The location of the chiral center which is the source of asymmetric induction is also another important factor. Other than 1,2-amino alcohols, 1,3-amino alcohols have also been found to be

effective ligands. Some examples of these chiral ligands showing high catalytic activity are given in Figure 9 [23].

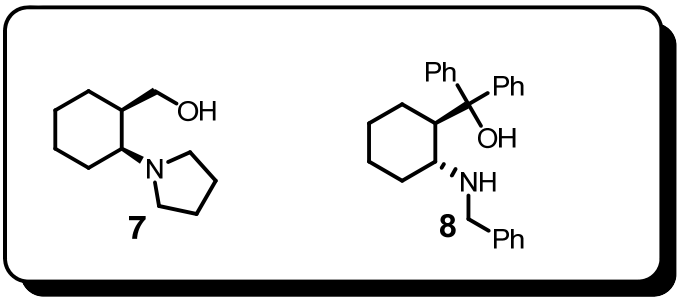


Figure 9. Examples of chiral 1,3-amino alcohols used as chiral ligands in enantioselective diethylzinc addition reactions.

Another class of amino alcohols that have been used as chiral ligands is 1,4-amino alcohols which have a more flexible structure than previously mentioned amino alcohols. Although in comparison with 1,2-amino alcohols the examples of this class are rare in literature in some cases excellent enantiomeric excess values were recorded. According to these examples, generally the best results were obtained with the ligands having alkyl substituents on nitrogen atom. Figure 10 shows some 1,4-amino alcohols from literature studies respectively [24, 25, 26, 27]. The first ligand **9** in the figure below is one of the first examples of this type and was synthesized by Tanyeli *et. al.* They used norbornene based amino alcohol and also its derivative having different substituents on hydroxyl bearing carbon atom, as chiral ligand. They achieved 97% enantiomeric excess value using 10 mol% ligand loading and employing benzaldehyde as substrate.

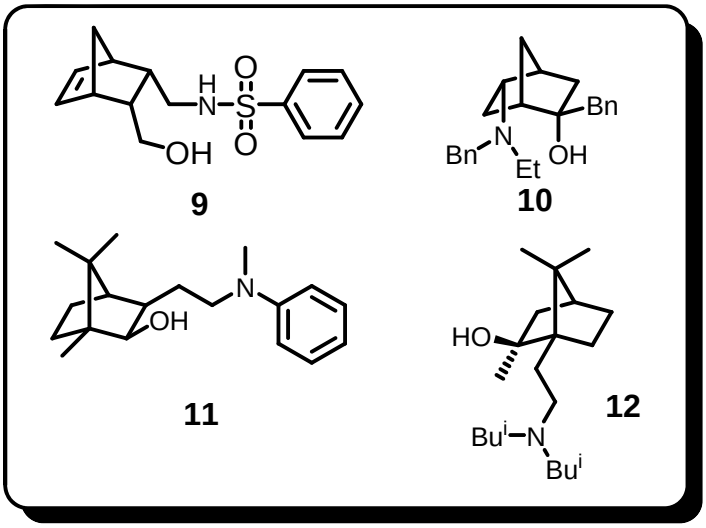


Figure 10. Examples of chiral 1,4-amino-alcohol ligands from literature.

Other than these amino alcohols there are also some examples out of type. Figure 11 shows a binaphthyl ligand with axial chirality and a ferrocene derived amino alcohol respectively which are both examined for their efficiencies in catalytic dialkylzinc addition to aldehydes [28, 29].

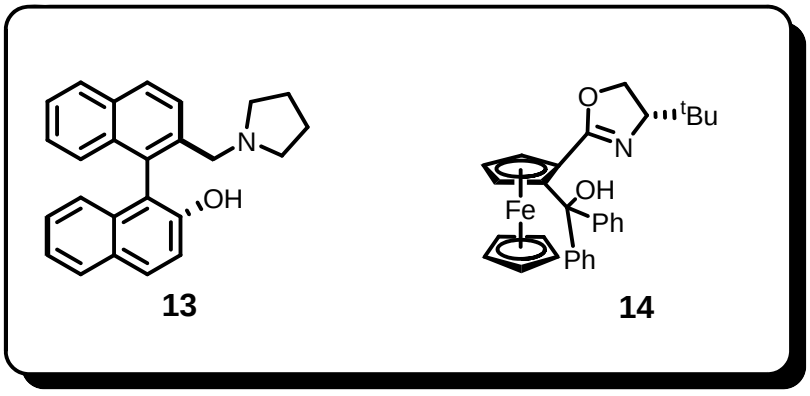


Figure 11. Binaphthyl and ferrocene based amino alcohols tested in dialkylzinc addition to aldehydes.

Another usage of amino alcohols is to develop immobilized catalysts like polymer-supported catalysts or dendrimeric catalysts. These heterogeneous

systems bring many advantages like easy of separation, reuseability many times without loss of optical activity. Figure 12 shows two examples for polymer supported chiral amino alcohols which are employed as efficient chiral ligands [30, 31].

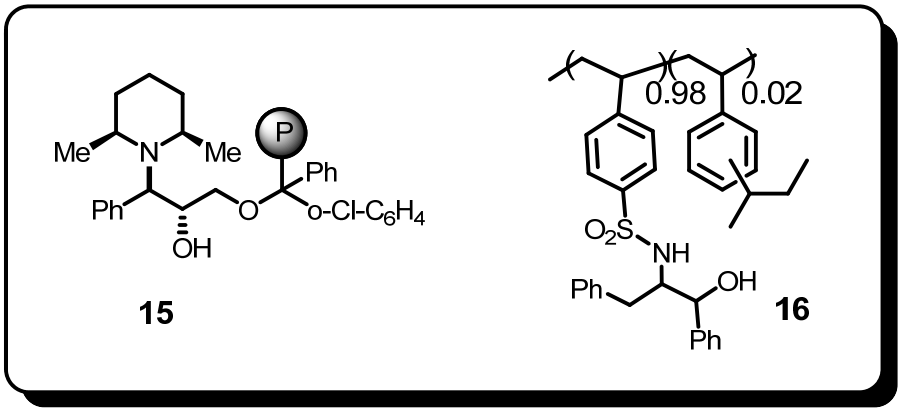


Figure 12. Some heterogenous polymer-supported amino alcohols with high catalytic activity in diethylzinc addition reactions.

1.4.1.1.3. Usage of chiral titanium complexes as catalysts

In enantioselective addition of dialkylzinc compounds to aldehydes the usage of chiral amino alcohols is said to be a breakthrough in organic synthesis. Since it was found that the actual catalyst is not the amino alcohol itself, but the chealate *in situ* formed with zinc reagent and amino alcohol, new catalyst systems are being developed [32]. Instead of the zinc complexes, Lewis acids were employed which were derived from chiral amino alcohols. These Lewis acids such as lithium salts [15], boron compounds, titanium compounds derived from chiral amino alcohols form complexetion with the carbonyl group and activate the system. A very efficient catalyst **17** for the diethylzinc addition to benzaldehyde was formed by Yoshioka *et al.* with the combination of 0.5-4 mol% of a bissulfonamide ligand **18** and 0.3-1.2 equivalent Ti(O*i*Pr)$_4$ [33]. It is notable that the aggregate **17** is a

stronger Lewis acid than Ti(O*i*Pr)$_4$ thus activates diethylzinc compound better. The hypothetical reactive species **19** is formed *in situ* with diethylzinc and carry out the ethylation of aldehydes (Figure 13).

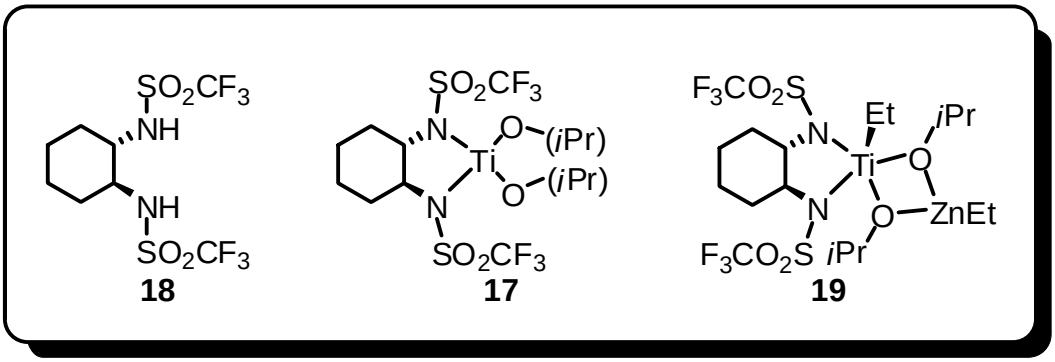


Figure 13. Chiral bissulfonamide ligand and its titanium complexes derived by Yoshioka *et al.*

Usage of Ti(O*i*Pr)$_4$ in stochiometric amounts in combination with chiral ligands has been widely used in literature [34]. Seebach *et al.* showed that tetraalkoxytitanium complexes (Ti-TADDOLates), shown in Figure 14, are also good catalysts for enantioselective ethylation of aldehydes [35].

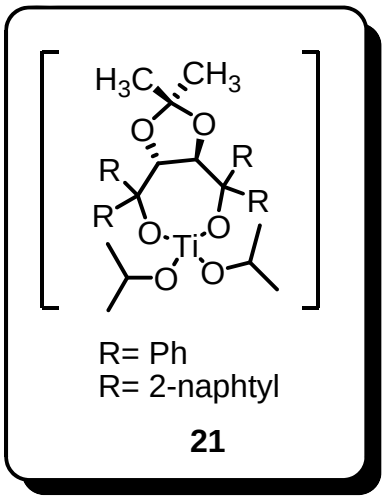


Figure 14. Catalyst provided by *Seebach* et al.

1.4.1.2. Enantioselective alkylation of C=N bonds using dialkylzinc reagents

Addition reaction of carbanions to carbon-nitrogen double bond of imines and imine derivatives has great interest because of the biological and synthetic importance of chiral nitrogen containing compounds. However, this reaction has some structural limitations including the poor electrophilicity of azomethine carbon atom. In order to increase the electrophilicity of imine carbon, *N*-alkylation to form reactive iminium salts, *N*-oxidation to form nitrones, *N*-acylation to form acylimines or *N*-sulfonation to give reactive sulfonimines can be done [36]. Some reactive azomethines are depicted in Figure 15. Recently, *N*-diphenylphosphinoylimines have withdrawn great attention. Their reactivities are lower than sulfonylimines so that they can easily be isolated and stored. Another advantage is that the phosphinamide product easily undergoes hydrolysis and deprotected even under mild conditions. In most of the studies that are carried out using phosphinoylimines, *P,P*-aryl or *P,P*-ethoxy substituted substrates are employed. There are still some limitations in the synthesis of these imines. Such as phosphinoyl imin formation is not achieved by aliphatic aldehydes [37, 38].

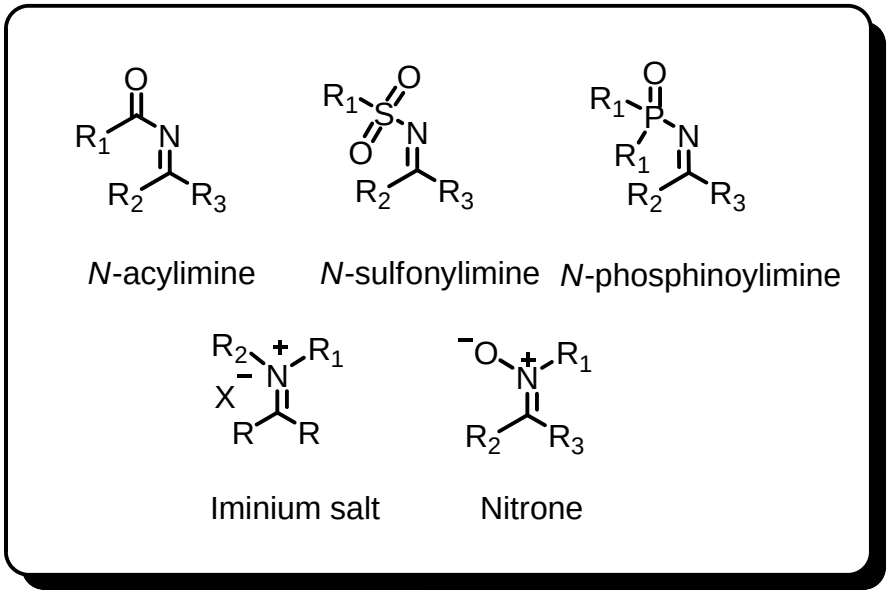
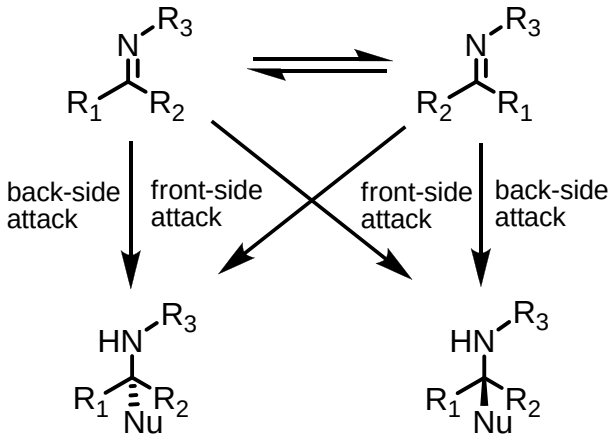


Figure 15. Azomethines

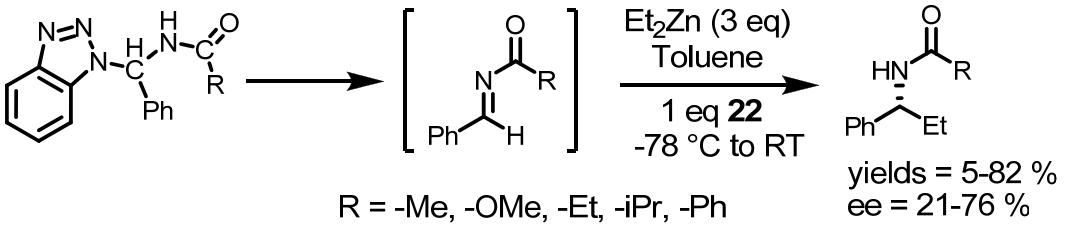
Another way to increase azomethine carbon reactivity is to use some Lewis acids such as $BF_3.OEt_2$ which coordinates to the nitrogen lone pair and activates the substrate. This method brings several by-products and another problem arises from the imine structure. Imines generally exist as mixtures of geometric isomers *E* and *Z*. These two forms are in equilibrium which leads to the formation of more than one transition state with the coordination of Lewis acids. As a result decrease in selectivity is seen as demonstrated in Scheme 3.



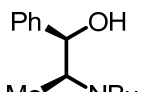
Scheme 3. Isomerization and Selectivity Relation

Another limitation comes out with the enolizable imines and imine derivatives which undergo deprotonation when they react with nucleophiles rather than addition to C=N bond. In order to overcome this problem imines derived from non-enolizable aryl or α,*β*-unsaturated aldehydes are used. Although there have been many reports on enantioselective diethylzinc addition to carbonyl compounds to generate chiral secondary alcohols, examples using their aza analogues are not well documented in literature [39]. Considering the biological importance of optically active amines as physiologically active compounds and pharmaceutical substances they are being synthesized *via* catalytic asymmetric reductions of imines or catalytic asymmetric carbon-carbon bond forming reactions [40]. Despite carbon-carbon bond formation is a convenient method to obtain optically active amines, the examples in literature are rare. Katritzky and co-workers

reported enantioselective diethylzinc addition to *N*-(amidobenzyl)benzotriazoles in 1992 (Scheme 4). These substrates act as masked *N*-acyl imines and the use of 1 equivalent of chiral amino alcohol (-) DBNE, *N,N*-dibutylnorephedrine **(22)** as chiral ligand gave *N*-(1-phenylpropyl)amides with enantiomeric excess values up to 76% [41].



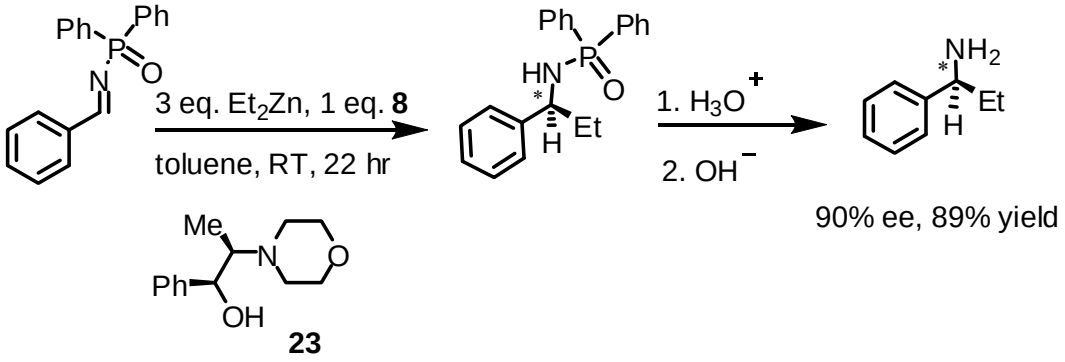
Chiral ligand:



22

Scheme 4. Katritzky's enantioselective diethylzinc addition reaction.

The pioneering work, describing the use of *N*-diphenylphosphinoylimines as electrophiles was published by Soai *et al.* in the same year [42]. In this publication, they achieved the first highly enantioselective alkylation of *N*-diphenylphosphinoylimines in presence of chiral amino alcohols using diethylzinc as alkylating reagent. They used morpholine derived β-amino alcohol **23** as chiral ligand and investigated the ligand loading effect and reactivity of three different substrates as shown in Scheme 5. They used of stoichiometric amount (1 eq.) of ligand and obtained 90% ee and 89% chemical yield. When 0.5 eq. ligand was used, enantioselectivity was still high with 85% ee. In case of catalytic amount (0.1 eq.) of ligand, they observed decrease in enantioselectivity and a sharp decrease in yield to 12%. The acidic hydrolysis of the product gave the enantiomerically enriched primary amines without loss of optical activity.



Scheme 5. The first highly enantioselective alkylation of *N*-diphenylphosphinoyl imines by Soai *et al.*

Andersson and *co*-workers also tested chiral bicyclic 1,2-amino alcohols **24-27** which are depicted in Figure 16, in the same reaction. They have similarly reported a systematic decrease in ee% value with decreasing chiral ligand amount. They have performed a large solvent screening and found out that in some solvents such as diethylether, THF, dichloromethane, the reaction did not even proceed and the results were good in many aromatic solvents such as toluene and chlorobenzene giving the best enantiomeric excess values and yields. Additionally, they specified results using different phosphinoyl imines as electrophiles. The imine derived from *p*-anisaldehyde gave the best result which is 98% ee [43].

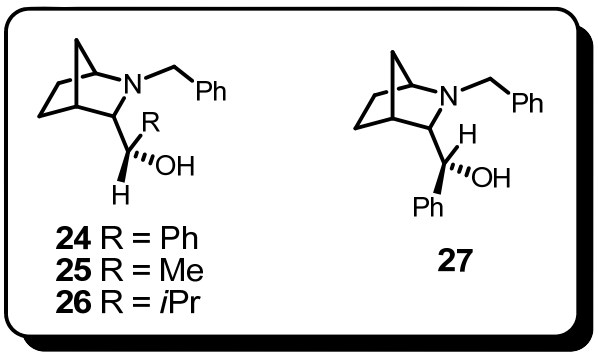


Figure 16. 1,2-chiral amino alcohols derived by Andersson *et. al.*

Since Soai's first study on alkylation of phosphinoyl imines, chiral amino alcohols [44], chiral dendrimers [45], chiral oxazolines [40], polymeric chiral amino alcohols have been employed as ligands for this reaction. Heterogeneous chiral ligands have also been used and brought out high enantiomeric excess values. The use of heterogeneous ligands provides easy separation of the products from the ligand. Figure 17 shows polymer supported chiral amino alcohol **28** and copolymeric structure **29**. The use of these hetergeneous ligands afforded high enantiomeric excess values (64-80%) and moderate yields (30-56%) with the use of alkylbenzenes (toluene, xylene etc.) as solvents [46].

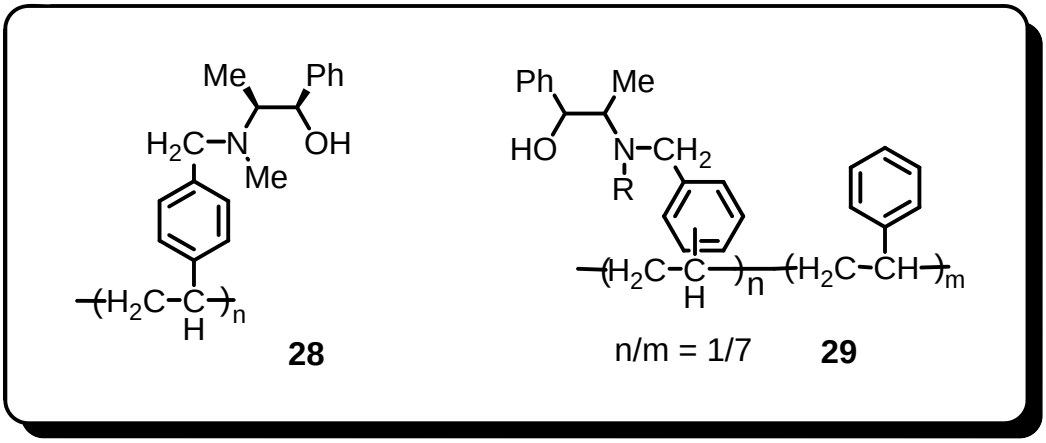


Figure 17. Heterogeneous chiral ligands used in enantioselective diethylzinc addition to *N*-diphenylphosphinoyl imines

1.5. Aim of the work

In a work by Yazıcıoğlu, Akhmedov and Tanyeli in 2008 [47], various novel *N*-(2-propylphenyl) substituted chiral amino alcohols were synthesized *via* a newly developed aromatization procedure. It has been well documented in literature that 1,2-amino alcohols with a similar backbone to aforementioned ligands afforded high enantioselectivities in diethylzinc addition reactions to aldehydes and imines [44]. These results prompted us to test the catalytic activity of our novel chiral ligands (Figure 18) in asymmetric transformation reactions.

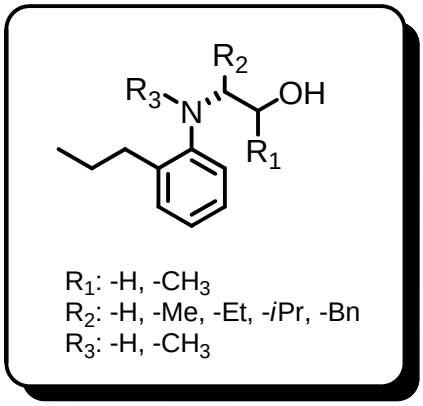


Figure 18. Structure of chiral amino alcohols

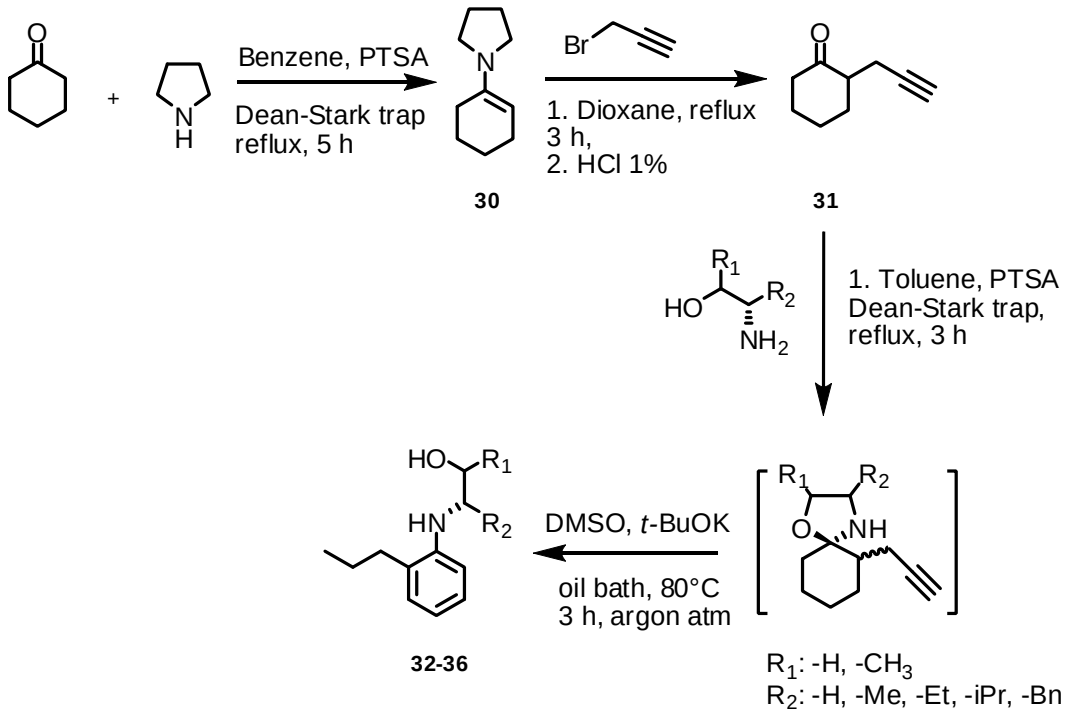
We aimed to enhance the chemical yield of target amino alcohol derivatives by modifying the previously reported procedure. We also planned to synthesize *N,N*-disubstituted analogues of these ligands *via* reductive methylation procedure. According to our strategy, we thought to test the effectiveness of these ligands in asymmetric diethylzinc addition to benzaldehyde and various *N*-diphenylphosphinoyl imines. During the course of these asymmetric transformations, various parameters which can affect the enantioselectivity, such as solvent, temperature, ligand loading and additive effect are going to be tested.

CHAPTER 2

RESULTS AND DISCUSSION

2.1. Synthesis of *N*-(2-propylphenyl) substituted chiral amino alcohols *via* an unusual aromatization reaction

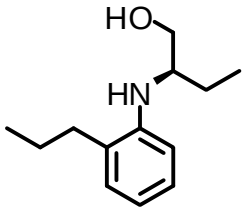
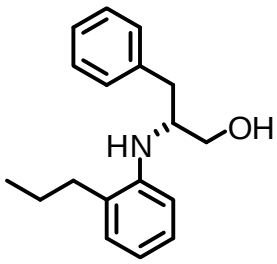
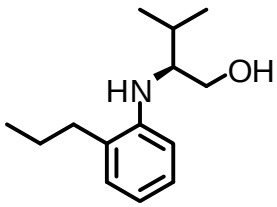
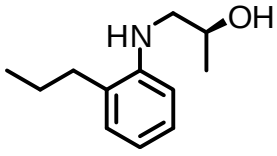
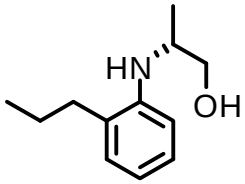
In literature, it is well known that the syntheses of aromatic amine compounds are mainly based on transition-metal catalyzed *N*-arylation or modifications on the benzene ring [48]. Alternative to these approaches, we developed a novel procedure for the synthesis of *N*-aryl substituted amino alcohols. In our synthetic strategy, cyclohexanone, propargyl bromide and various commercially available chiral amino alcohols were chosen as starting components. Synthetic route started with α-propargylation of cyclohexanone *via* the reaction of Stork-enamine species 1-cyclohexenylpyrrolidine **(30)** with propargyl bromide. The next step was the condensation of 2-(prop-2-ynyl)cyclohexanone **(31)** with the chiral amino alcohols under reflux. The final step was the key part of our synthetic route in which non-isolated oxazolidine type intermediate was subjected to *t*-BuOK treatment in DMSO at 80 °C to afford unusual aromatization products **32-36** (Scheme 6). We found out that temperature was the critical parameter for the unusual aromatization step. Above 80 °C, we observed some unidentified decomposition products whereas below this temperature, very low conversions were observed. The structures of the products were confirmed by ^{1}H and ^{13}C NMR spectroscopy. The spectra are given in appendix.



Scheme 6. Synthetic pathway for the aromatization reaction

The results are summarized in Table 1. The chemical yields given in parenthesis belong to the literature values [47]. By comparing the chemical yield results except product **36,** we observed increment in the chemical yields. This presumably depends upon the structure of the chosen cyclohexanone derivatives since the synthetic routes were carried out under the same conditions. We used α-propargylated derivative **31** as unsaturation source, whereas in the previous work 2-(2-bromoallyl)cyclohexanone was chosen for the same purpose.

Table 1. Structures and chemical yields of chiral amino alcohols

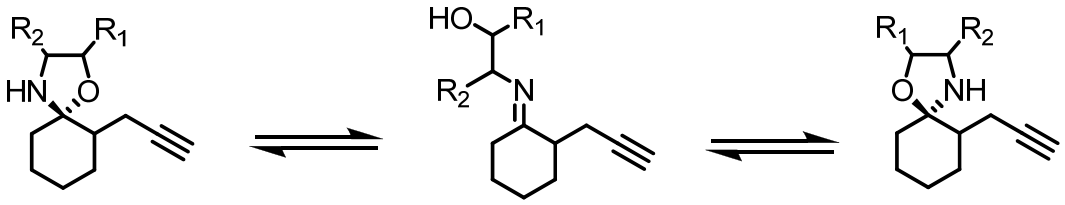
Compound Number	Ligand	Temp (°C)	Time (h)	Yield (%)[a, b]
32		80	3	**66** (56)
33		80	3	**42** (31)
34		80	3	**50** (35)
35		80	3	**45** (30)
36		80	3	**37** (45)

[a]Isolated yields.

[b]The yields in parentheses belong to literature values.

2.2. The mechanism of the unusual aromatization reaction

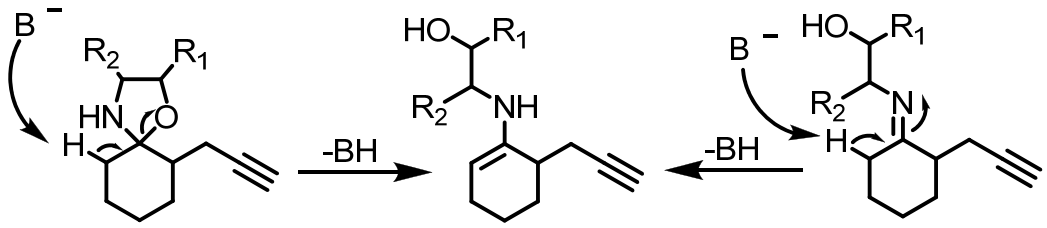
The mechanism of the reaction was investigated and proved by performing several experiments that support the proposed mechanism [47]. It was found that *"intramolecular unsaturation transfer"* occurs from propargyl unit and converts cyclohexane ring into a benzene ring. By the support of NMR analysis, it was proved that the first step gives the oxazolidine type condensation product which is in equilibrium with its tautomers as shown in Scheme 7.



R_1: -H, -Me
R_2: -H, -Me, -Et, -*i*Pr, -Bn

Scheme 7. Tautomeric equilibrium for oxazolidine intermediate

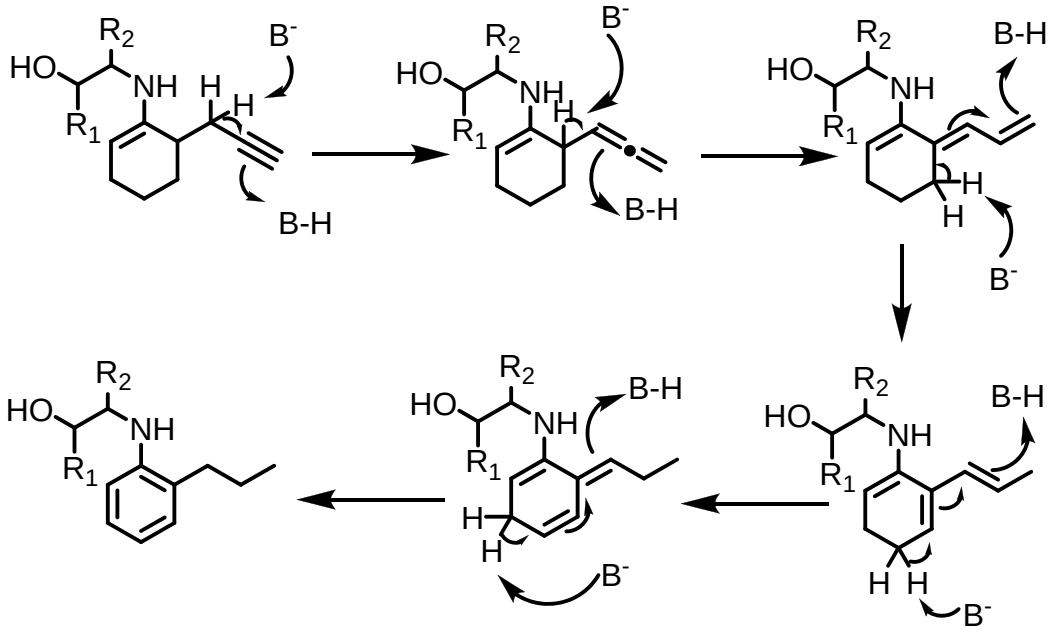
The second step occurs under strongly basic conditions in the presence of potassium *tert*-butoxide. The strong base abstracts one proton to convert oxazolidine or imine to its enamine structure as shown in Scheme 8.



R_1: -H, -Me
R_2: -H, -Me, -Et, -*i*Pr, -Bn
B: *t*BuOK

Scheme 8. Enamine formation step

Subsequent proton abstraction from methylene carbon adjacent to the acetylene unit forms allene. The next step is the formation of conjugate diene in the same way. The rearrangements occur until the double bonds are carried into the ring to form a resonance stabilized benzene ring (Scheme 9). The reaction ends up with the formation of the aromatized product.

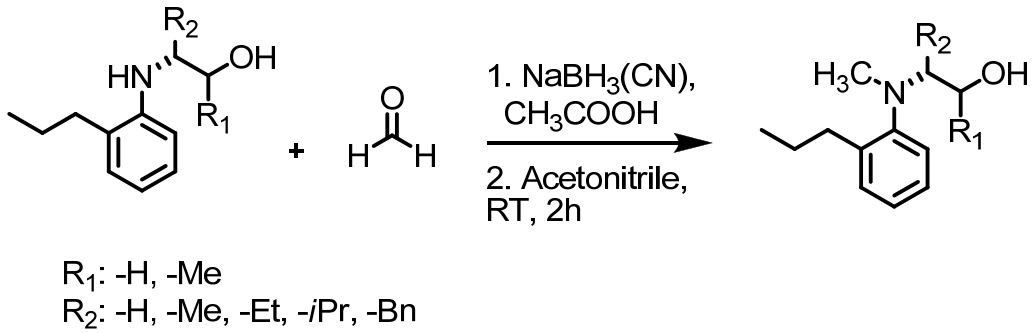


Scheme 9. Aromatization steps.

2.3. Modification of chiral ligands *via* reductive methylation

In literature it has been reported in many examples that enantioselectivity is directly related with the structures of the ligands [21,49]. We thought that the substituents on the benzene ring or on nitrogen atom would have influence on enantioselectivity. This directed us to make modifications on our chiral ligands. We subjected our ligands to *N*-methylation reaction to test the effect of tertiary

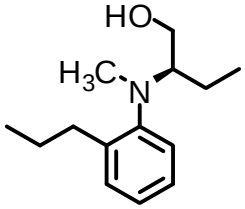
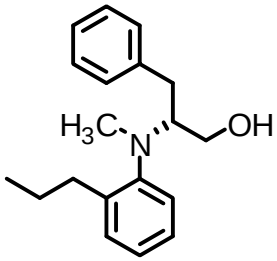
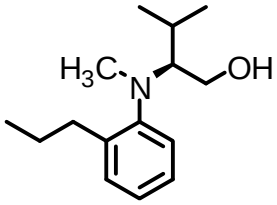
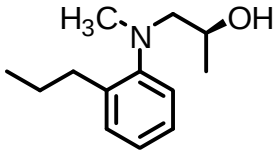
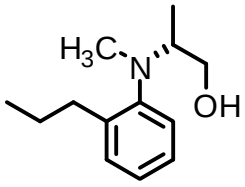
nitrogen units on enantioselectivity. In this procedure, formaldehyde was used as methyl source. The amino group of the ligand first reacted with the carbonyl group of formaldehyde to form a hemiaminal intermediate which was transformed to imine structure with the loss of water molecule. Subsequent reduction with sodium cyano borohydride in the presence of acetic acid directly afforded the resultant *N*-methylated amino alcohols. The reaction conditions are given in Scheme 10. The characterization of *N*-methylated ligands were done by ^{1}H, ^{13}C NMR and IR spectroscopy and also supported by HRMS results. All of these data are available in experimental part.



Scheme 10. Synthesis of *N,N*-disubstituted chiral amino alcohols

The results are summarized in Table 2.

Table 2. The structures and yields of *N*-methylated products

Compound Number	Ligand	Time (h)	Yield (%)[a]
37		2	**63**
38		2	**70**
39		2	**80**
40		2	**58**
41		2	**65**

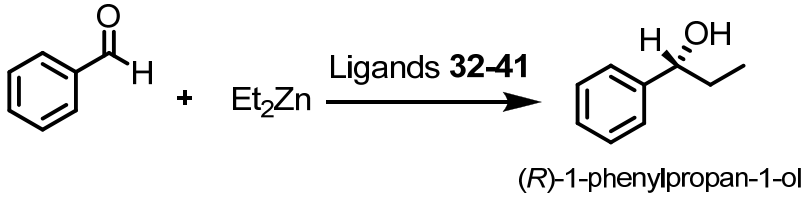
[a]Isolated yields.

2.4. Asymmetric trials

As previously mentioned our chiral ligands are potential ligands for enantioselective diethylzinc reactions. Accordingly, we tested these chiral ligands in diethylzinc addition to benzaldehyde and to various imines. In the further sections effect of different parameters on selectivity of the reaction will be discussed.

2.4.1. Diethylzinc addition to benzaldehyde

In the introduction part it was reported that enantioselective C-C bond formation reactions are important in organic synthesis and diethylzinc addition reaction to aldehydes is the most popular way to achieve this purpose. Therefore, benzaldehyde was chosen as an acceptor for diethylzinc addition. All the ligands **32-41** we have synthesized were used as chiral catalysts. The racemic form of the product, 1-phenylpropanol was synthesized using an achiral ligand *N,N*-dimethylethanolamine and used as reference for TLC monitoring and ee value determination using HPLC with a chiral column. All the ligands tested afforded *(R)*-1-phenylpropanol. The absolute configuration of the product was determined by comparing HPLC chromatogram with the literature data [50].



Scheme 11. Enantioselective diethylzinc addition to benzaldeyde in presence of chiral ligands **32-41**

Various parameters that would affect the enantioselectivity such as solvent effect, Lewis acid additive effect, temperature factor, loading effect of chiral ligand and diethylzinc were screened and the results are given in the following sections.

2.4.1.1. Ligand screening in different solvents

In all ligand screening experiments, chiral ligand amount was kept constant as 5 mol% and the reactions were carried out at 0 °C. Various common solvents such as toluene, hexane, THF, and diethylether were used. When the reactions were carried out in THF, all the ligands gave very poor results (Table 3). Ligand **32** afforded the highest chemical yield and ee as 20% and 16%, respectively.

Table 3. Ligand screening using THF

Entry	Ligand	Yield (%)[a]	Ee (%)[b]
1	**32**	20	16
2	**33**	6	12
3	**34**	10	7
4	**35**	3	2
5	**36**	12	14
6	**37**	4	5
7	**38**	4	2
8	**39**	10	5
9	**40**	-	-
10	**41**	15	15

[a]Isolated yields.

[b]Enantiomeric excess values were determined by HPLC analysis using OD-H chiral column.

Table 4 shows the ligand screening results in diethyl ether which are similar to the results obtained with THF. In this case ligand **36** afforded the best results as 20% ee and 27% chemical yield (Entry 5). The lowest enantioselectivity was obtained with ligand **35.** Among the ligands, ligand **41** gave the highest conversion as 31%, unfortunately low enantioselectivity (4% ee) was observed.

Table 4. Ligand screening using diethyl ether

Entry	Ligand	Yield (%)[a]	Ee (%)[b]
1	**32**	9	15
2	**33**	2	10
3	**34**	9	12
4	**35**	9	2
5	**36**	27	20
6	**37**	3	5
7	**38**	3	9
8	**39**	11	4
9	**40**	4	3
10	**41**	31	4

[a]Isolated yields.

[b]Enantiomeric excess values were determined by HPLC analysis using OD-H chiral column.

Further screening was performed using hexane and afforded relatively better results than previous solvents (Table 5). Higher conversion values than previous trials were obtained up to 43% (Entry 7). The best enantioselectivity (28% *ee*) was obtained with ligand **32** as in the case of THF. Although ligand **38** gave acceptable conversion value of 43%, it afforded to nearly racemic product (1% ee).

Table 5. Ligand screening using hexane

Entry	Ligand	Yield (%) [a]	Ee (%)[b]
1	**32**	40	28
2	**33**	40	13
3	**34**	35	13
4	**35**	15	16
5	**36**	32	16
6	**37**	7	2
7	**38**	43	1
8	**39**	15	9
9	**40**	23	11
10	**41**	15	5

[a]Isolated yields.

[b]Enantiomeric excess values were determined by HPLC analysis using OD-H chiral column.

In toluene, ligand **36** afforded the highest ee value (36% ee). The valinol derived ligand **34** gave an acceptable conversion value of 44% and 23% ee. As a summary of the solvent screening ligand **36** was found to be the relatively most appropriate ligand among the others (Table 6). Therefore, we decided to carry out the following screening experiments with ligand **36**.

Table 6. Ligand screening using toluene

Entry	Ligand	Yield (%)[a]	Ee (%)[b]
1	**32**	26	25
2	**33**	38	11
3	**34**	44	23
4	**35**	17	15
5	**36**	21	36
6	**37**	2	3
7	**38**	16	7
8	**39**	21	10
9	**40**	46	12
10	**41**	6	5

[a]Isolated yields.

[b]Enantiomeric excess values were determined by HPLC analysis using OD-H chiral column.

2.4.1.2. Effect of Lewis acid

As previously mentioned in the introduction part, in literature Lewis acids such as titanium compounds are widely used as additives in order to enhance the catalytic activity of chiral ligands [51]. This prompted us to use stoichiometric amount of $Ti(O\textit{i}Pr)_4$ in combination with 5 mol% of the best ligand **36** under former reaction conditions. The effect of $Ti(O\textit{i}Pr)_4$ was tested in various solvents as given in Table 7.

Table 7. Effect of Lewis Acid Ti(O*i*Pr)$_4$

Entry	Solvent	Additive[a]	Yield (%)[b]	Ee (%)[c]
1	THF	Ti(O*i*Pr)$_4$	47	*rac*
2	Toluene	Ti(O*i*Pr)$_4$	35	4
3	CH_2Cl_2	Ti(O*i*Pr)$_4$	35	*rac*
4	CH_2Cl_2	-	20	26

[a]Ti(O*i*Pr)$_4$ was used in 120 mol% amount.

[b]Isolated yields.

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

In contrast to the in literature data [51], the results of these trials were disappointing. By comparing the chemical yield results (entry 1 and 2) with previous results (Table 3, entry 5 and Table 6, entry 5), it was observed that chemical yields increased from 12% to 47% and 21% to 35% in THF and toluene respectively. Unfortunately, drastic decrease in enantioselectivity was observed. The reaction was also performed in dichloromethane (entry 3 and 4). In the presence of Ti(O*i*Pr)$_4$ (entry 3), 35% conversion with complete racemization was observed. Interestingly in the absence of Ti(O*i*Pr)$_4$ (entry 4), relatively lower conversion (20%) with 26% ee was obtained.values were increased. Consequently, titanium additive caused an unexpected negative effect on enantioselectivity in combination with chiral amino alcohol **36** in diethylzinc addition to benzaldehyde.

2.4.1.3. Effect of temperature

In order to improve the catalytic activity of the best performance ligand **36**, temperature was decreased to -10 °C with the expectation of increment in selectivity. Results are summarized in Table 8. We performed the experiments in toluene which showed superior selectivity to the other solvents. The ligand was used again in 5 mol% scale and the reaction was carried out both in presence and in absence of Ti(O*i*Pr)$_4$ to make comparison with the previous results.

Table 8. Effect of temperature for diethyzinc addition to benzaldehyde

Entry	Temp (°C)	Additive[a]	Yield (%)[b]	Ee (%)[c]
1	0	-	21	36
2	-10	-	27	8
3	0	$Ti(OiPr)_4$	35	4
4	-10	$Ti(OiPr)_4$	64	*rac*

[a]$Ti(OiPr)_4$ was used in 120 mol% amount.

[b]Isolated yields.

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

In contrast to our expectation, decrease in temperature gave even lower ee values. If entry 1 and entry 2 are compared yield was slightly affected positively by temperature whereas the ee value was decreased to 8%. Also with the trial in presence of additive the temperature decrease caused an increase in conversion and decrease in enantioselectivity (entry 4).

2.4.1.4. Effect of chiral ligand amount

In literature, ligand loading screening studies are frequently performed to examine the effect on enantioselectivity. In some cases increase in ligand amount causes a decrease in ee value [52]. Examples of increased or unchanged enantioselectivities are also present. This prompted us to see the effect of increase in chiral ligand amount in our reaction conditions. For this purpose, 10 mol% of best ligand **36** was employed at three different temperatures under optimized conditions.The results are summarized in Table 9.

Table 9. Ligand loading effect at different temperatures[a]

Entry	Mol (%) 36	Temp (°C)	Yield (%)[b]	Ee (%)[c]
1	5	0	21	36
2	10	0	37	32
3	5	-10	27	8
4	10	-10	43	15
5	10	RT	65	26

[a]The reactions were carried out in toluene.

[b]Isolated yields.

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

By using 10 mol% of **36**, in all trials increase in conversion was observed. At 0 °C, a slight decrease in enantioselectivity was recorded (entries 1 and 2). In comparison of entries 3 and 4, at -10 °C ee% value almost doubled (8% to 15%) with the increase in ligand amount. In the investigation of temperature effect it was observed that decrease in temperature always caused a decrease in ee values. Considering this observation, with 10 mol% ligand the reaction was carried out at room temperature (entry 5). The highest yield among all previous experiments was obtained as 65% whereas improve in enantioselectivity could not be achieved and was still low (26%).

2.4.1.5. Effect of diethylzinc amount

As pointed out in the introduction part, 2 equivalent of diethylzinc reagent is responsible for the reaction with 1 equivalent of benzaldehyde. So far, we employed 2 equivalent of Et_2Zn in all experiments and the poor results obtained with this amount developed the idea of using excess diethylzinc. Unfortunately, the use of excess Et_2Zn in the reaction medium inhibited the reaction and as seen in Table 10 afforded to racemic product with a very low conversion.

Table 10. Effect of Et_2Zn amount for diethyzinc addition reaction[a]

Entry	Equiv. of Et_2Zn	Yield (%)[b]	Ee (%)[c]
1	2	27	8
2	3	5	*rac*

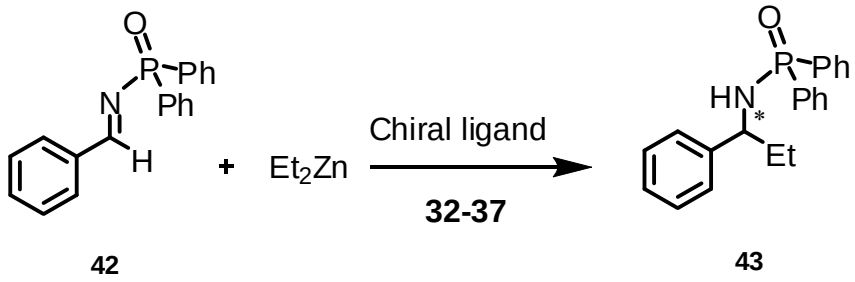
[a]The reactions were carried out at -10 °C using toluene as solvent. 5 mol% of chiral ligand **36** was used.

[b]Isolated yields were calculated after column chromatography.

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

2.4.2. Diethylzinc addition to *N*-diphenylphosphinoyl imines

As mentioned in the former sections, other than benzaldehyde *N*-diphenylphosphinoyl imines have been used as substrates in diethylzinc addition reactions in presence of chiral 1,2-amino alcohols similar to our ligands [44]. This triggered us to test our chiral ligands firstly with the imine derived from benzaldehyde as a model acceptor type substrate (Scheme 12).



42 43

Scheme 12. Diethylzinc addition to *N*-diphenylphosphinoyl benzalimine

N-Diphenylphosphinoyl benzalimine was synthesized by the condensation reaction of benzaldehyde and *P,P*-diphenylphosphinic amide in 70% chemical

yield according to literature procedure [53]. The structure of the substrate was confirmed by NMR analysis which is available in appendix. The racemic form of the product was synthesized in presence of achiral ligand *N,N*-dimethylethanolamine and used as reference for TLC and HPLC analysis. All reactions were monitored for 48 h. Diethylzinc has been used in excess amount as indicated in the literature [44,54]. The chiral ligands afforded the product either with *(R)* or *(S)* configuration.

2.4.2.1. Chiral ligand screening

In all diethylzinc addition to phosphinoyl imines studied in literature [44, 54], the first attempts were done by using stoichiometric amount of chiral ligand loading. For this purpose, the chiral ligands **32-37** were loaded in 1 eq. amount for ligand screening with the model substrate. All of the reactions were carried out at room temperature and in toluene, originated from literature studies. Table 11 shows the results for each ligand under optimized conditions. Although TLC monitoring showed high amount of addition product, the isolated yields were quite low in all cases. Since phosphinoyl amide is highly polar, it can strongly interact with the stationary phase. Generally acceptable enantioselectivities for the first trials were obtained except ligand **37,** which has methyl substituent on nitrogen (entry 6). Entry 3 showed the best results, highest ee and highest chemical yield values, 64% and 32% respectively. The ligand **33** resulted in a slightly lower enantioselectivity than **34**, giving 60% ee. These promising results prompted us to go on further screening of different conditions.

Table 11. Ligand optimization for Et_2Zn Addition to *N*-diphenylphosphinoyl benzalimine

Entry	Ligand	Yield (%)[a]	Ee (%)[b]	Configuration[c]
1	**32**	25	47	*(R)*
2	**33**	28	60	*(S)*
3	**34**	32	64	*(S)*
4	**35**	18	29	*(R)*
5	**36**	15	55	*(S)*
6	**37**	10	6	*(R)*

[b]Isolated yields.

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

[c]The absolute configuration of the products were determined by HPLC comparison with literature data.

2.4.2.2. Ligand loading effect

In literature the effect of ligand amount on enantioselectivity has been investigated in several studies. In all cases, decreasing in ee the was observed with decreasing amount of ligand. Our aim was to decrease chiral catalyst loading from stoichiometric amount to catalytic amount without any loss in enantioselectivity. For this purpose, the ligands **33** and **34** were chosen and catalyst loading was decreased from 1 eq. to 0.5 eq. Fortunately, we observed increase in enantioselectivity as 60 to 63% and 64 to 72% for ligand **33** and **34** respectively as given in Table 12 (entry 1,2,3, and 4). This observation directed us to continue screening with ligand **34**. When using only 0.25 equivalent of chiral ligand the ee value decreased to 60% which is still acceptable. However, with further decrease to 0.1 equivalent, a drastic decrease to 20% was observed in enantioselectivity.

Table 12. Ligand loading effect on enantioselectivity

Entry	Ligand	Ligand Equiv.	Yield (%)[a]	Ee (%)[b]
1	**33**	1	28	60
2	**33**	0.5	30	63
3	**34**	1	32	64
4	**34**	0.5	18	72
5	**34**	0.25	18	60
6	**34**	0.1	15	20

[a]Isolated yields.

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

2.4.2.3. Effect of temperature

Temperature effect for diethylzinc addition to diphenylphosphinoyl imines was also examined. The best ligands **33** and **34** were tested at 0 °C with stoichiometric amounts, using toluene as solvent. Table 13 shows the results including room temperature trials for comparison. Unfortunately, temperature lowering decreased the enantioselectivities in both cases (entry 2 and 4). Conversion values also decreased with decreasing temperature as expected.

Table 13. Effect of temperature

Entry	Ligand	Temp (°C)	Yield (%)[a]	Ee (%)[b]
1	**33**	RT	28	60
2	**33**	0	21	43
3	**34**	RT	32	64
4	**34**	0	24	61

[a]Isolated yields.

[b]Enantiomeric excess values were determined by HPLC analysis using AD chiral colum.

2.4.2.4. Solvent effect

In order to improve the enantioselectivity, another aromatic solvent BTF was alternatively used. It decreased both chemical yield and ee values as shown in Table 4.

Table 14. Solvent effect

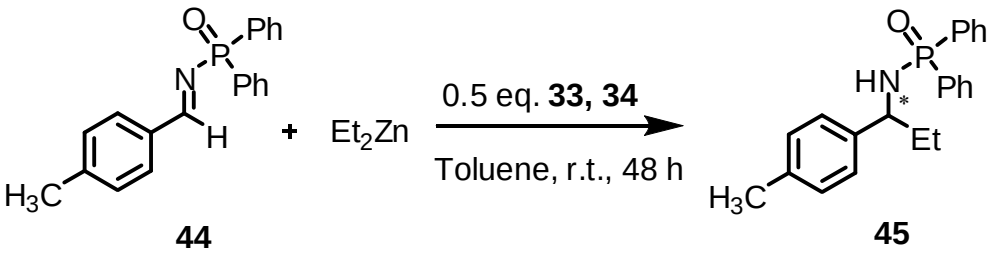
Entry	Solvent	Yield (%)[a]	Ee (%)[b]
1	Toluene	18	72
2	BTF	15	52

[a]Isolated yields.

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

2.4.2.5. Effect of different substrates

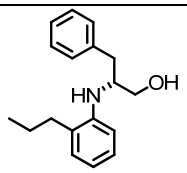
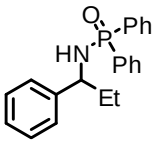
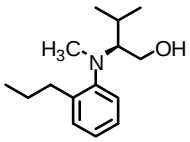
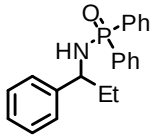
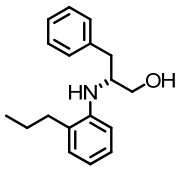
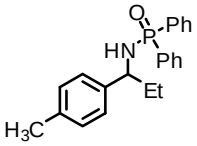
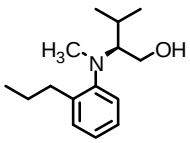
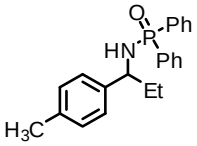
In order to improve enantioselectivity, we extended our study to other diphenylphosphinoyl imines by using the ligands **33** and **34**. A new substrate was derived from *p*-tolualdehyde according to literature procedure in 68% chemical yield [53]. The characterization of the substrate was done by ^{1}H and ^{13}C NMR analysis which is given in appendix. The reaction was carried out under previously optimized conditions (Scheme 13).



44 **45**

Scheme 13. Diethylzinc addition to *N*-diphenylphosphinoyl imines

Table 15. The comparison of the results for substrates derived from benzaldehyde and *p*-tolualdehyde

Entry	Ligand	Product	Yield(%)	Ee(%)
1	 **33**		30	63
2	 **34**		18	72
3	 **33**		50	60
4	 **34**		**61**	**80**

[a]Isolated yields.

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

In Table 15, the results for two different imine substrates are given for comparison. It is seen that the conversion values increase for both ligands evidently when imine derived from *p*-tolualdehyde is used as substrate. Using ligand **34,** ee value was increased from 72% to 80% whereas the ee value for ligand **33** was not apparently affected.

CHAPTER 3

CONCLUSION

In this work, the syntheses of various *N*-(2-propylphenyl) substituted chiral 1,2-amino alcohols were achieved using a newly developed procedure which is referred to as *''intramolecular unsaturation transfer''*. In this method commercially available cyclohexanone, propargyl bromide and various chiral amino alcohols were used as starting components. *N*-Methylated analogues of these amino alcohols were also synthesized. These amino alcohols can be potential chiral ligands for various asymmetric transformation reactions. Hence, in diethylzinc addition to benzaldehyde, various parameters including temperature, solvent, ligand amount, additive effect etc. were screened for all ligands. All of the ligands afforded to 1-phenylpropanol with *(R)* configuration. Unfortunately, the expected enantioselectivity could not be achieved. The highest enantioselectivity was obtained using 5 mol% of ligand **36** as 36% ee with yield of 21% under optimized conditions. The optimized temperature was found to be 0 °C at the end of temperature screening. The best performance solvent was found out as toluene. The diethylzinc addition to *N*-diphenylphosphinoyl imines was chosen as another asymmetric transformation reaction which can afford diphenylphosphinoyl amides. *N*-Diphenylphosphinoyl benzalimine was chosen as model substrate. With this substrate, chiral ligands **32-36** showed good enantioselectivities up to 72% ee, whereas ligand **37** which has methyl substituent on nitrogen gave poor enantioselectivity of 6% ee. The optimum ligand amount was found to be 5 mol% at the end of ligand loading studies. With imine derived from *p*-tolualdehyde 80% ee was obtained by using ligand **34**. As our further work different imines will be used as substrates for higher ee values.

CHAPTER 4

EXPERIMENTAL

^{1}H, ^{13}C NMR and ^{31}P spectra were recorded on a Bruker DPX 400 spectrometer in $CDCl_3$. Chemical shifts were expressed in ppm and tetramethylsilane (TMS) was used as internal standard; the ^{1}H NMR data are presented in the order value of the signal, peak multiplicity (abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad) and coupling constants in Hertz. ^{13}C NMR spectra were measured at 100 MHz and the chemical shifts were reported relative to $CDCl_3$ triplet centered at 77.0 ppm.

Reactions were monitored by thin layer chromatography using pre-coated silica gel plates (Merck Silica Gel 60F-254), visualized by UV-light and phosphomolybdic acid in ethanol. Crude mixtures were purified by flash column using thick-walled glass columns with a flash grade silicagel (Merck Silica Gel 60, particle size: 0.040-0.063 mm, 230-400 mesh ASTM). The relative portions of solvents are in volume: volume ratio used in column chromatography and TLC as eluent.

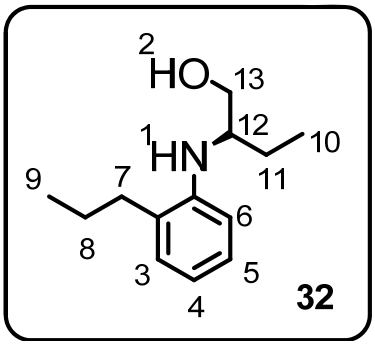
Optical rotations were measured in a 1 dm cell using a Rudolph Research Analytical Autopol III polarimeter and reported as $[\alpha]^{25}_{D}$ (c in g per 100 ml, solvent). HPLC measurements were performed with ThermoFinnigan Spectra System instrument using chiral columns. Solvents were dried prior to use. THF, hexane, toluene were distilled over Na/benzophenone, dichloromethane and DMSO was dried over CaH_2. All extracts were concentrated under vacuum by using rotary evaporator.

4.1. Synthesis of 2-(prop-2-ynyl)cyclohexanone (31)

Cyclohexanone (51.6 ml, 0.5 mol) and pyrrolidine (66.3 mL, 0.81 mol) were mixed in 100 mL round-bottomed flask in 75 mL benzene. A few crystals of PTSA was added and the mixture was stirred under reflux using a Dean-Stark trap for 5 hours. After the completion of the reaction benzene was evaporated. Then, $MgSO_4$ was added to resultant solution and kept for 1 day. The mixture was filtered, the enamine 1-cyclohexenylpyrrolidine (**30**) was purified by vacuum distillation. Compound (**30**) (33.86 g, 0.224 mol) and propargyl bromide (28.34 mL, 0.263 mol) were stirred in 250 mL dioxane under reflux. After 3 hours, 74 mL 0.33 M HCl solution was added and further heated under reflux for 1 hour. After completion of the reaction dioxane was evaporated and the organic phase was extracted with (3x150 mL) diethylether, dried over $MgSO_4$ for 1 day and then, filtered and evaporated to yield product **31** (17.3 g, 65% yield). The spectroscopic data are in accordance with the literature [55].

4.2. General procedure for the synthesis of *N*-(2-propylphenyl)substituted compounds

2-(prop-2-ynyl)cyclohexanone (31) (0.994 g, 7.3 mmol) was mixed with 1.5 eq. of *(R)*-2-aminobutan-1-ol (1.0 g, 11 mmol) in dry toluene and 10 mg of PTSA was added and stirred under reflux with a Dean-Stark trap for 3 h. Then, toluene was evaporated and 2 eq. potassium *tert*-butoxide (1.4 g, 14.6 mmol) was added in dry DMSO (10 mL). The reaction mixture was immersed in oil bath at 80 °C under argon gas and stirred for another 3 h. At the work-up stage, 10 mL of water was added and the organic phase was extracted with Et_2O (50x4 mL). The solvent was evaporated and the crude mixture was purified by flash column chromatography using EtOAc:Hexane (1:4) as eluent. The product *(R)*-2-(2-propylphenylamino)butan-1-ol (32) was obtained as a yellow oil (0.86 g, 56% yield).

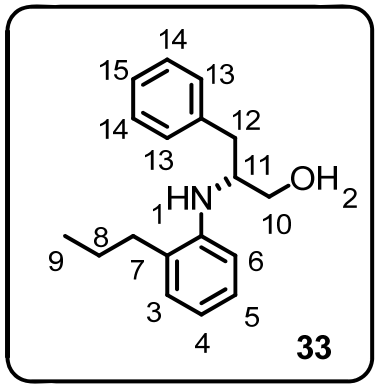


^{1}H-NMR (400 MHz, $CDCl_3$): δ ppm 6.93-7.00 (m, 2H, H_3, H_5), 6.56-6.59 (m, 2H, H_4, H_6), 3.63 (dd, J = 10.81 and 4.17 Hz, 1H, H_{13}), 3.46 (dd, J = 10.81 and 5.34 Hz, 1H, H_{13}), 3.31-3.37 (m, 1H, H_{12}), 2.37 (t, J = 7.7 Hz, 2H, H_7), 1.47-1.61 (m, 4H, H_8, H_{11}), 0.87-0.94 (m, 6H, H_9, H_{10}) (Figure A1)

^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 145.4, 129.6, 127.3, 126.8, 117.6, 111.5, 64.1, 58.6, 33.6, 25.2, 22.1, 14.5, 10.9 (Figure A2)

4.2.1. *(R)*-3-Phenyl-2-(2-propylphenylamino)propan-1-ol (33)

Starting from *(R)*-2-amino-3-phenyl-1-propanol, product **33** was obtained as a brown oil (0.83 g, 42% yield).

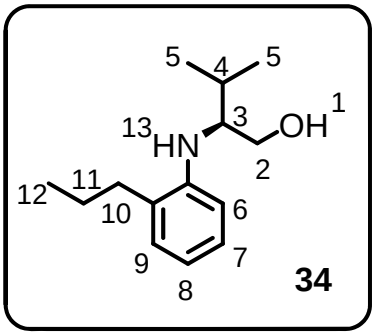


^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.16-7.20 (m, 2H, H_{14}), 7.08-7.12 (m, 3H, H_{13}, H_{15}), 6.99-7.03 (m, 1H, H_5), 6.93 (d, J = 6.1 Hz, 1H, H_3), 6.58-6.64 (m, 2H, H_4, H_6), 3.65-3.69 (m, 1H, H_{11}), 3.60 (dd, J = 10.8 and 4.2 Hz, 1H, H_{10}), 3.45 (dd, J = 10.7 and 4.4 Hz, 1H, H_{10}), 2.86 (dd, J = 13.7 and 5.5 Hz, 1H, H_{12}), 2.79 (dd, J = 13.7 and 7.4 Hz, 1H, H_{12}), 2.27 (t, J = 7.6 Hz, 3H, H_7), 1.42-1.47 (m, 2H, H_8), 0.87 (t, J = 7.4 Hz, 3H, H_9) (Figure A3)

^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 143.4, 136.9, 128.4, 128.2, 127.5, 126.0, 125.8, 125.5, 116.5, 110.1, 61.9, 54.4, 36.3, 32.2, 20.7, 13.2 (Figure A4)

4.2.2. *(S)*-3-Methyl-2-(2-propylphenylamino)butan-1-ol (34)

Starting from *(S)*-valinol, product **34** was obtained as a yellow oil (0.81 g, 50% yield).

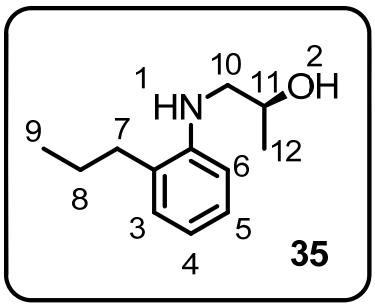


^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 6.90-7.00 (m, 2H, H_7, H_9), 6.55-6.61 (m, 2H, H_6, H_8), 3.68 (dd, J = 10.9 and 4.4 Hz, 1H, H_2), 3.50 (dd, J = 10.9 and 6.4 Hz, 1H, H_2), 3.29 (q, J = 6 Hz, 1H, H_3), 2.39 (t, 2H, J = 7.5 Hz, H_{10}), 1.88 (m, 1H, H_4), 1.59 (sext, J = 7.5 Hz, 2H, H_{11}), 0.89-0.96 (m, 9H, H_5, H_{12}) (Figure A5)

^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 145.8, 129.8, 127.7, 126.5, 117.5, 111.5, 62.7, 60.6, 33.8, 30.3, 22.2, 19.5, 14.6 (Figure A6)

4.2.3. *(S)*-1-(2-Propylphenylamino)propan-2-ol (35)

Starting from *(S)*-1-aminopropan-2-ol, product **35** was obtained as a yellow oil (0.64 g, 45% yield).

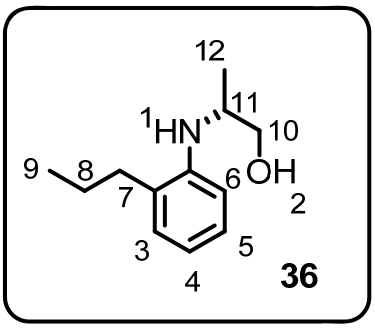


^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.02-7.07 (m, 1H, H_5), 6.99 (d, J = 7.2 Hz, 1H, H_3), 6.64 (t, J = 7.2 Hz, 1H, H_4), 6.58 (d, J = 8.0 Hz, 1H, H_6), 3.96-4.03 (m, 1H, H_{11}), 3.20 (dd, J = 12.8 and 3.6 Hz, 1H, H_{10}), 2.95 (dd, J = 12.8 and 8.4 Hz, 1H, H_{10}), 2.4 (t, J = 7.6 Hz, 2H, H_7), 1.58 (sext, J = 7.7 Hz, 2H, H_8), 1.20 (d, J = *6.3* Hz, 3H, H_{12}), 0.93 (t, J = 7.3 Hz, 3H, H_9) (Figure A7)

^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 145.9, 129.5, 127.1, 127.3, 117.8, 111.0, 66.7, 52.0, 33.5, 22.0, 21.2, 14.5 (Figure A8)

4.2.4. *(R)*-2-(2-Propylphenylamino)propan-1-ol (36)

Starting from *(R)*-2-aminopropan-1-ol, product **36** was obtained as a yellow oil (0.53 g, 37% yield).



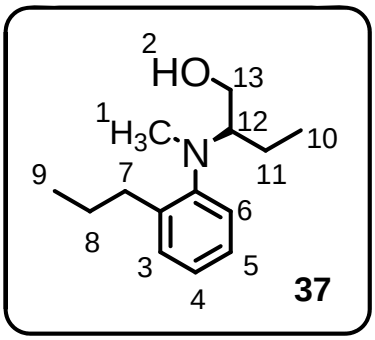
^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 6.98-7.07 (m, 2H, H_3, H_5), 6.61-6.65 (m, 2H, H_4, H_6), 3.67-3.70 (m, 2H, H_{10}), 3.46-3.50 (m, 1H, H_{11}), 2.38 (t, J = 7.6 Hz, 2H, H_7), 1.55-1.61 (m, 2H, H_8), 1.16 (d, J = 6.4 Hz, 3H, H_{12}), 0.94 (t, J = 7.2 Hz, 3H, H_9), (Figure A9)

^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 145.9, 130.4, 128.1, 128.0, 118.6, 112.5, 67.2, 51.6, 34.3, 22.9, 18.8, 15.3 (Figure A10)

4.3. Reductive methylation procedure

Sodium cyanoborohydride (0.18 g, 2.90 mmol) was added to a stirred solution of chiral ligand **32** (0.20 g, 0.965 mmol) and 37% aqueous formaldehyde (0.78 mL, 9.65 mmol) in 4 mL acetonitrile. To the resultant solution, acetic acid (0.1 mL) was added over 10 min and stirred for 2 h at room temperature. Subsequently, acetic acid (0.1 mL) was added and stirred for additional 30 min. The reaction mixture was poured into 75 mL diethyl ether and washed with 1 N KOH (3x20 mL) and finally with 20 mL brine. The organic phase was dried over Na_2CO_3 and then, the solvent was evaporated and the crude mixture was purified by flash column chromatography using EtOAc: Hexane (1:4) as eluent to afford the product, *(R)*-2-[methyl(2-propylphenyl)amino]butan-1-ol **(37)** (0.135 g, 63% yield).

$[\alpha]_D^{25}$= -0.9 (*c* 1.00, $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.04-7.11 (m, 2H, H_3, H_5), 6.93-6.97 (m, 2H, H_4, H_6), 3.67 (dd, J = 10.8 and 4.8 Hz, 1H, H_{13}), 3.48 (dd, J = 10.8 and 8.8 Hz, 1H, H_{13}), 2.89-2.97 (m, 1H, H_{12}), 2.65-2.70 (m, 1H, H_7), 2.55 (s, 3H, H_1), 2.43-2.51 (m, 1H, H_7), 1.49-1.61 (m, 3H, H_8, H_{11}), 1.30-1.38



(m, 1H, H_{11}), 0.90 (t, J = 7.2 Hz, 3H, H_{10}), 0.72 (t, J = 7.6 Hz, 3H, H_9) (Figure A11)

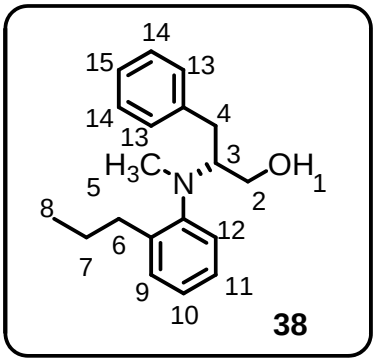
^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 151.1, 138.4, 130.6, 126.5, 124.4, 123.5, 65.9, 61.5, 33.6, 24.4, 19.6, 14.5, 11.5 (Figure A12)

IR cm^{-1} (CCl_4): 3431, 3016, 2958, 2932, 2871, 2800, 1489, 1449, 1250, 1217, 1083, 1047, 964, 749

HRMS: calculated for $C_{14}H_{24}NO$ $(M+H)^+$ 222.1858, found 222.1852

4.3.1. *(R)*-2-[Methyl(2-propylphenyl)amino]-3-phenylpropan-1-ol (38)

Starting from *(R)*-3-phenyl-2-(2-propylphenylamino)propan-1-ol **(33),** the product (38) was obtained as an orange oil (0.192 g, 70% yield).



$[\alpha]_D^{25}$= -81.5 (*c* 1.00, $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.04-7.17 (m, 6H, H_{10},H_{11},H_{13},H_{14}), 7.0 (t, J = 7.2 Hz, 1H, H_{15}), 6.91 (d, J = 7.6 Hz, 2H, H_9, H_{12}), 3.50 (d, J = 6.8 Hz, 2H, H_2), 3.19-3.25 (m, 1H, H_3), 2.83 (dd, J = 13.2 and 3.6 Hz, 1H, H_4), 2.67 (s, 3H, H_5), 2.43-2.58 (m, 3H, H_6, H_4), 1.50-1.63 (m, 2H, H_7), 0.89 (t, J = 7.2 Hz, 3H, H_8) (Figure A13)

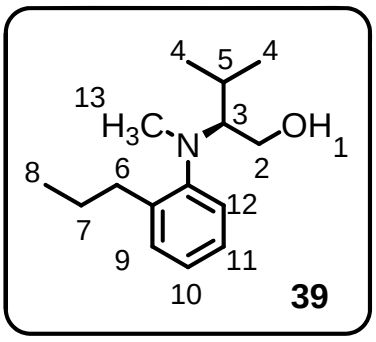
^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 149.3, 137.9, 137.3, 129.3, 127.9, 127.4, 125.3, 125.1, 123.4, 122.2, 65.1, 59.7, 34.1, 32.2, 31.9, 23.0, 13.1 (Figure A14)

IR cm^{-1} (CCl_4): 3405, 3058, 2994, 2961, 2929, 2870, 2805, 1598, 1481, 1449, 1429, 1095, 1085, 1065, 750, 724, 699

HRMS: calculated for $C_{19}H_{26}NO$ $(M+H)^+$ 284.2014, found 284.2007.

4.3.2. *(S)*-3-Methyl-2-[2-methyl(2-propylphenyl)amino]butan-1-ol (39)

Starting from *(S)*-3-methyl-2-(2-propylphenylamino)butan-1-ol **(34),** the product **(39)** was obtained as an orange oil (0.182 g, 80% yield).



$[\alpha]_D^{25}$= -23.3 (*c* 1.00, $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.07-7.10 (m, 2H, H_9, H_{11}), 7.01-7.05 (m, 1H, H_{10}), 6.88-6.91 (m, 1H, H_{12}), 3.60-3.70 (m, 2H, H_2), 2.87-2.92 (m, 1H, H_3), 2.67 (s, 3H, H_{13}), 2.59 (t, J = 8.4 Hz, 2H, H_6), 2.20 (brs, 1H, H_1), 1.89-1.97 (m, 1H, H_5), 1.55 (sext, J = 7.6 Hz, 2H, H_7), 0.91 (t, J = 7.2 Hz, 3H, H_8), 0.84 (d, J = 6.8 Hz, 6H, H_4) (Figure A15)

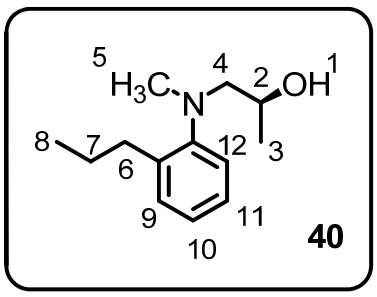
^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 150.3, 135.8, 129.3, 125.1, 122.1, 121.4, 68.0, 59.2, 34.4, 32.2, 27.1, 23.2, 20.4, 18.5, 13.2 (Figure A16)

IR cm^{-1} (CCl_4): 3421, 2956, 2871, 1489, 1464, 1448, 1256, 1081, 753

HRMS: calculated for $C_{15}H_{26}NO$ $(M+H)^+$ 236.2014, found 236.2011

4.3.3. *(S)*-1-[Methyl(2-propylphenyl)amino]propan-2-ol (40)

Starting from *(S)*-1-(2-propylphenylamino)propan-2-ol **(35),** the product **(40)** was obtained as an orange oil (0.116 g, 58% yield).



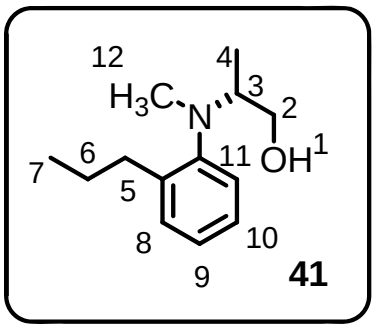
$[\alpha]_D^{25}$= -54.1 (*c* 1.00, $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 6.97-7.12 (m, 4H, H_9, H_{10}, H_{11}, H_{12}), 3.76-3.84 (m, 1H, H_2), 2.88 (dd, J = 12.4 and 3.2 Hz, 1H, H_4), 2.59-2.63 (m, 3H, H_4, H_6), 2.57 (s, 3H, H_5), 1.58 (sext, J = 7.2 Hz, 2H, H_7), 1.09 (d, J = 6.0 Hz, 3H, H_3), 0.92 (t, J = 7.2 Hz, 3H, H_8) (Figure A17)

^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 150.7, 137.3, 128.8 125.7, 123.7, 120.7, 63.8, 62.5, 42.8, 31.7, 23.0, 18.9, 13.3 (Figure A18)

IR cm^{-1} (CCl_4): 3457, 2959, 2931, 2870, 1597, 1490, 1450, 1147, 1110, 1059, 970, 763. HRMS: calculated for $C_{13}H_{22}NO$ $(M+H)^+$ 208.1701, found 208.1696

4.3.4. *(R)*-2-[Methyl(2-propylphenyl)amino]propan-1-ol (41)

Starting from *(R)*-2-(2-propylphenylamino)propan-1-ol **(36),** the product **41** was obtained as a orange oil (0.130 g, 65% yield).



$[\alpha]_D^{25}$= -46.6 (*c* 1.00, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.04-7.10 (m, 3H, H_8, H_9, H_{10}), 6.94-6.98 (m, 1H, H_{11}), 3.36-3.52 (m, 2H, H_2), 3.12-3.20 (m, 1H, H_3), 2.75 (brs, 1H, H_1), 2.42-2.49 (m, 1H, H_5), 2.52 (s, 3H, H_{12}), 2.66-2.72 (m, 1H, H_5), 1.49-1.62 (m, 2H, H_6), 0.88-0.92 (m, 6H, H_4, H_7) (Figure A19)

^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 152.7, 140.4, 132.2, 128.2, 126.3, 125.4, 65.7, 36.2, 35.2, 26.0, 16.2, 13.3 (Figure A20)

IR cm^{-1} (CCl_4): 3457, 29.59, 2931, 2870, 2796, 1490, 1450, 1147, 1110, 1059, 970, 763, 741

HRMS: calculated for $C_{13}H_{22}NO$ $(M+H)^+$ 208.1701, found 208.1699

4.4. General procedure for diethylzinc addition to benzaldehyde

Chiral ligand (0.05 eq.) was dissolved in 2 mL toluene in a well-dried Schlenk tube at room temperature under argon atmosphere and diethylzinc (2 eq. 1M in hexane) was added to this solution and stirred at room temperature for 30 min and then cooled to 0 °C. Benzaldehyde (1 eq.) was added to the mixture by syringe and the reaction was continued for 48 h at 0 °C. The reaction was quenched by the addition of 1 M HCl (10 mL) and extracted with EtOAc (2x25 mL). The combined organic phases were dried over $MgSO_4$, filtered off and the solvent was evaporated in vacuo. The crude mixture was purified by column chromatography (EtOAc:Hexane, 1:8) to yield the corresponding alcohol. HPLC analysis of 1-

phenylpropanol was done by using Chiral OD-H column at room temperature, *n*-hexane:2-propanol, 95:5, flow rate: 1 mL/min, 254 nm, t_1= 8.45 min *(R),* t_2= 9.50 min *(S)* (Figure A30).

4.4.1. Synthesis of *rac*-1-phenylpropanol

The procedure above was applied using an achiral ligand, *N,N*-dimethylethanol amine, to yield corresponding racemic alcohol. HPLC analysis: Chiral OD-H column, *n*-hexane:2-propanol, 95:5, flow rate: 1 mL/min, 254 nm, t_1= 9.11 min *(R),* t_2= 10.20 min *(S)* (Figure A29).

4.4.2. General procedure for diethylzinc addition to benzaldehyde in presence of Ti(O*i*Pr)$_4$

Chiral ligand (0.05 eq.) was dissolved in 2 mL toluene and Ti(O*i*Pr)$_4$ (1.2 eq.) was added to this solution and stirred for 1 h at room temperature. Diethylzinc (1.2 eq. 1 M in hexane) was added to this mixture and stirred for additional 30 min at room temperature. Then the reaction mixture was cooled to 0 °C. Finally, benzaldehyde (1 eq.) was added and the reaction was continued for 48 h at 0 °C. The reaction was quenched by the addition of 1 M HCl (10 mL) and extracted with EtOAc (2x25 mL). The combined organic phases were dried over $MgSO_4$, filtered off and the solvent was evaporated in vacuo. The crude mixture was purified by column chromatography (EtOAc:Hexane, 1:8) to yield the corresponding alcohol.

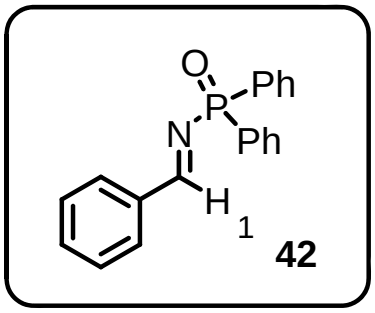
4.5. Synthesis of *N*-diphenylphosphinoyl imines

To an ice-cooled solution of diphenylphosphinamide (1 eq.) and aldehyde (1 eq.) in dry dichloromethane, anhydrous triethylamine (3.07 eq.) was added under argon atmosphere. Then titanium tetrachloride (0.55 eq.) was added dropwise and stirred for 3 hours. The reaction was monitored by TLC using EtOAc as eluent. After 3 h, the mixture was filtered through celite and washed with dichloromethane in

order to remove titanium dioxide. The filtrate gave the mixture of the product and triethylamine hydrochloride salt which was broken up by stirring the solution in 50 mL toluene at ambient temperature. The residual triethylamine hydrochloride salt was removed by suction filtration and the filtrate was evaporated to yield crude product. The purification was done by flash column chromatography using EtOAc as eluent to afford the imine product.

4.5.1. *(E)*-*N*-(4-Methylbenzylidene)-*P,P*-diphenylphosphinic amide (42)

Starting from benzaldehyde and diphenylphosphinic amide, the product **42** was obtained as a white solid (70% yield).



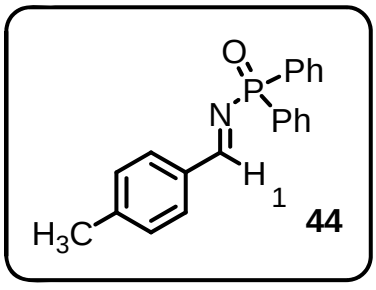
42

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 9.23 (d, $^{3}J_{PH}$ = 32 Hz, 1H, H_1), 7.92-7.83 (m, 6H, *Ar-H*), 7.46-7.34 (m, 9H, *Ar-H*) (Figure A21)

^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 172.4 (d, $^{2}J_{PC}$ = 10 Hz), 134.9, 134.7, 132.7, 132.5, 130.6, 130.5, 129.1, 127.8, 127.4, 127.3 (Figure A22)

4.5.2. *(E)*-*N*-(4-Methylbenzylidene)-*P,P*-diphenylphosphinic amide (44)

Starting from *p*-tolualdehyde and diphenylphosphinic amide, the compound **44** was synthesized as a white solid (68% yield).



44

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 9.20 (d, $^{3}J_{PH}$ = 32 Hz, 1H, H_1), 7.88-7.81 (m, 6H, *Ar-H*), 7.40-7.35 (m, 6H, *Ar-H*), 7.20-7.19 (m, 2H, *Ar-H*), 2.35 (s, 3H, H_6), (Figure A23)

^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 172.4 (d, $^{2}J_{PC}$ = 10 Hz), 143.4, 130.6, 130.5, 129.2, 128.6, 127.4, 127.3, 20.8 (Figure A24)

4.6. General procedure for diethylzinc addition to *N*-diphenylphosphinoyl imines

N-Diphenylphosphinoyl imine (0.1 mmol) was dissolved in 2 mL of toluene in a well-dried Schlenk tube at room temperature under argon atmosphere. The amino alcohol ligand (0.1 mmol) was added to this solution. After subsequent dropwise addition of diethylzinc (0.5 mmol, 1.1 M solution in toluene), the reaction was continued for 48 h at room temperature and quenched with 10 mL of aqueous satd. NH_4Cl and extracted with CH_2Cl_2 (2x25 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and filtered off. The crude product was purified by flash column chromatography using EtOAc as eluent to yield the corresponding amide.

HPLC analysis of chiral *P*,*P*-diphenyl-*N*-(1-phenylpropyl)phosphinic amide **(43)** amide: Chiral AD column, *n*-hexane:2-propanol, 80:20, flow rate: 1 mL/min, 254 nm, t_1=8.44 min *(R)*, t_2=10.97 min *(S)* (Figure A32)

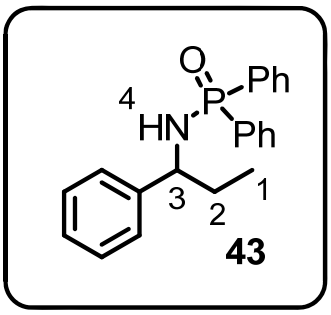
HPLC analysis of chiral *P*,*P*-diphenyl-*N*-(1-*p*-tolylpropyl)phosphinic amide **(45)**: Chiral AD column, *n*-hexane:2-propanol, 92:8, flow rate: 1 mL/min, 254 nm, t_1=26.4 min *(R)*, t_2= 33.4 min (*S)* (Figure A34)

4.6.1. Synthesis of *rac*-(43) and *rac*-(45)

The compounds *rac*-(**43**) and *rac*-(**45**) were synthesized by Grignard reaction. *N*-diphenylphosphinoyl imine (1 eq.) was dissolved in dry THF and cooled to 0 °C under argon atmosphere. Then EtMgBr (2 eq., 3M solution in diethylether) was added dropwise and the reaction was stirred for 3 h at room temperature. The reaction was quenched with saturated NH_4Cl solution and the organic phase is extracted with CH_2Cl_2. The solvent is evaporated to give the corresponding amide.

4.6.1.1. *P,P*-diphenyl-*N*-(1-phenylpropyl)phosphinic amide (43)

HPLC analysis: Chiral AD column, *n*-hexane:2-propanol, 80:20, flow rate: 1 mL/min, 254 nm, t_1=8.38 min *(R)*, t_2=11.03 min *(S)* (Figure A31)

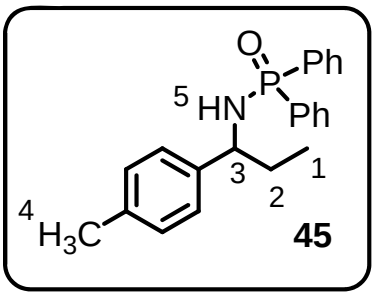


^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.78 (dd, J = 12 and 8 Hz, 2H, *Ar-H*), 7.67 (dd, J = 12 and 8 Hz, 2H, *Ar-H*), 7.14-7.40 (m, 9H, *Ar-H*), 7.07 (d, J = 6.8 Hz, 2H, *Ar-H*), 3.96-4.06 (m, 1H, H_3), 3.20 (brs, 1H, H_4), 1.89-1.99 (m, 1H, H_2), 1.70-1.81 (m, 1H, H_2), 0.72 (t, J = 7.6 Hz, 3H, H_1) (Figure A25)

^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 142.5, 139.8, 131.6, 131.5, 130.8, 130.7, 130.6, 130.5, 127.4, 127.3, 127.2, 127.1, 126.0, 125.4, 56.1, 31.5, 9.5 (Figure A26)

4.6.1.2. *P,P*-diphenyl-*N*-(1-*p*-tolylpropyl)phosphinic amide (45)

HPLC analysis: Chiral AD column, *n*-hexane:2-propanol, 92:8, flow rate: 1 mL/min, 254 nm, t_1=25.48 min *(R)*, t_2=31.97 min *(S)* (Figure A33)



^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.78 (dd, J = 11.8 and 8.3 Hz, 2H, *Ar-H*), 7.68 (dd, J = 11.9 and 8.2 Hz, 2H, *Ar-H*), 7.19-7.40 (m, 6H, *Ar-H*), 6.95-7.02 (m, 4H, *Ar-H*), 3.92-4.00 (m, 1H, H_3), 3.14-3.18 (m, 1H, H_5), 2.26 (s, 3H, H_4), 1.88-1.96 (m, 1H, H_2), 1.70-1.77 (m, 1H, H_2), 0.70 (t, J = 7.2 Hz, 3H, H_1) (Figure A27)

^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 140.6, 136.5, 132.9, 132.7, 132.6, 131.9, 131.8, 131.7, 131.6, 129.2, 128.5, 128.3, 128.2, 126.4, 57.0, 32.5, 21.1, 10.6 (Figure A28)

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APPENDIX A

SUPPORTING INFORMATION

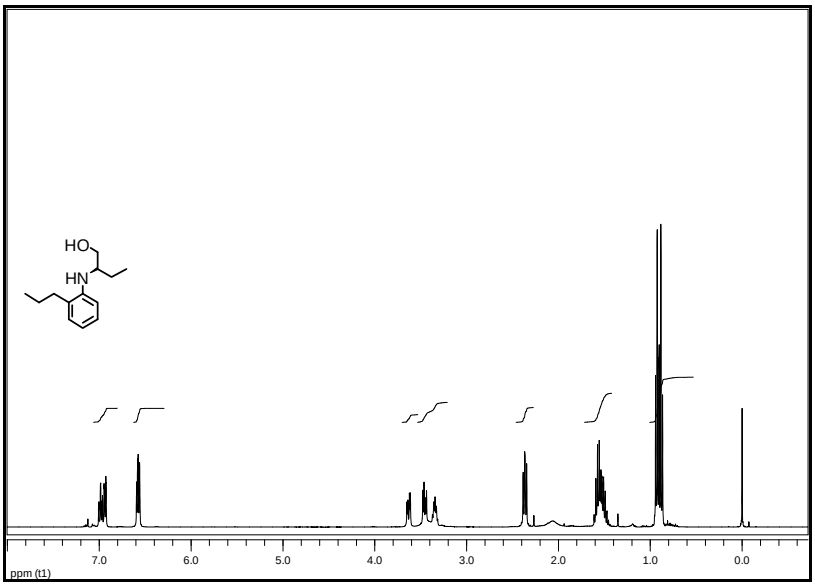

Figure A1. ^{1}H NMR spectrum of **32**

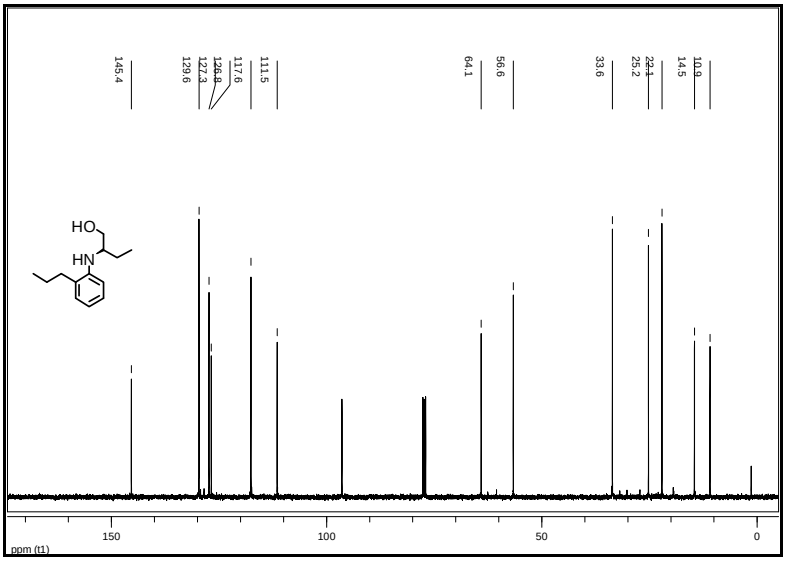

Figure A2. ^{13}C NMR spectrum of **32**

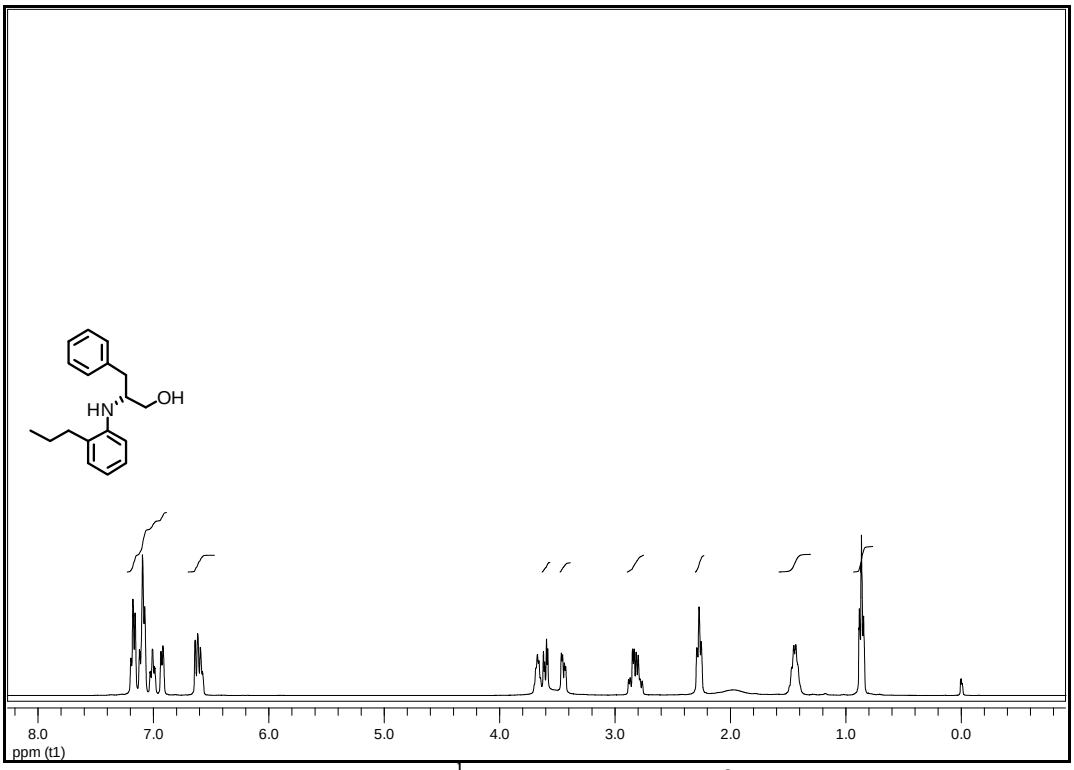

Figure A3. ^{1}H NMR spectrum of **33**

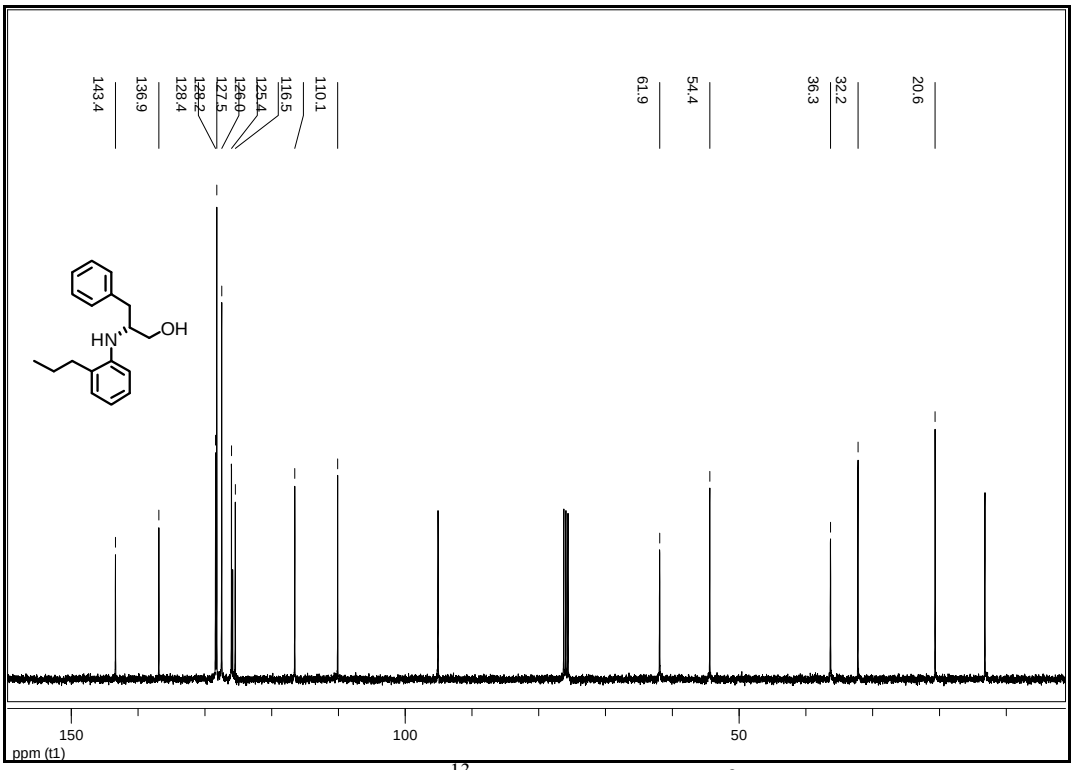

Figure A4. ^{13}C NMR spectrum of **33**

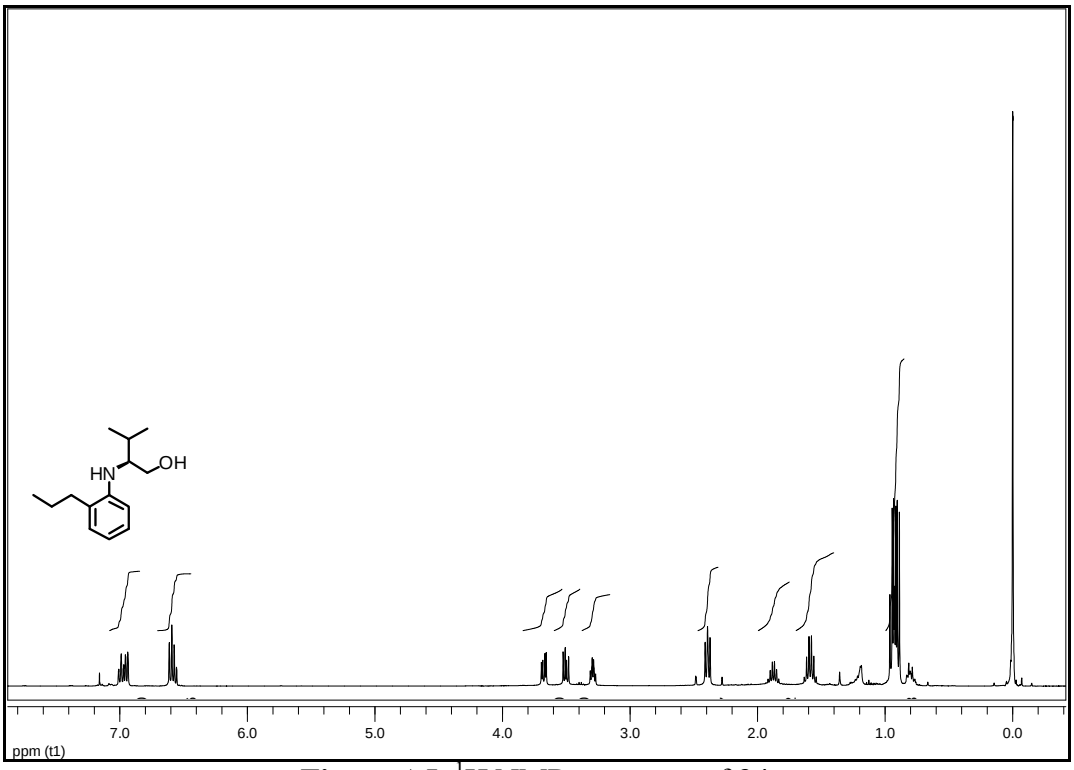

Figure A5. ^{1}H NMR spectrum of **34**

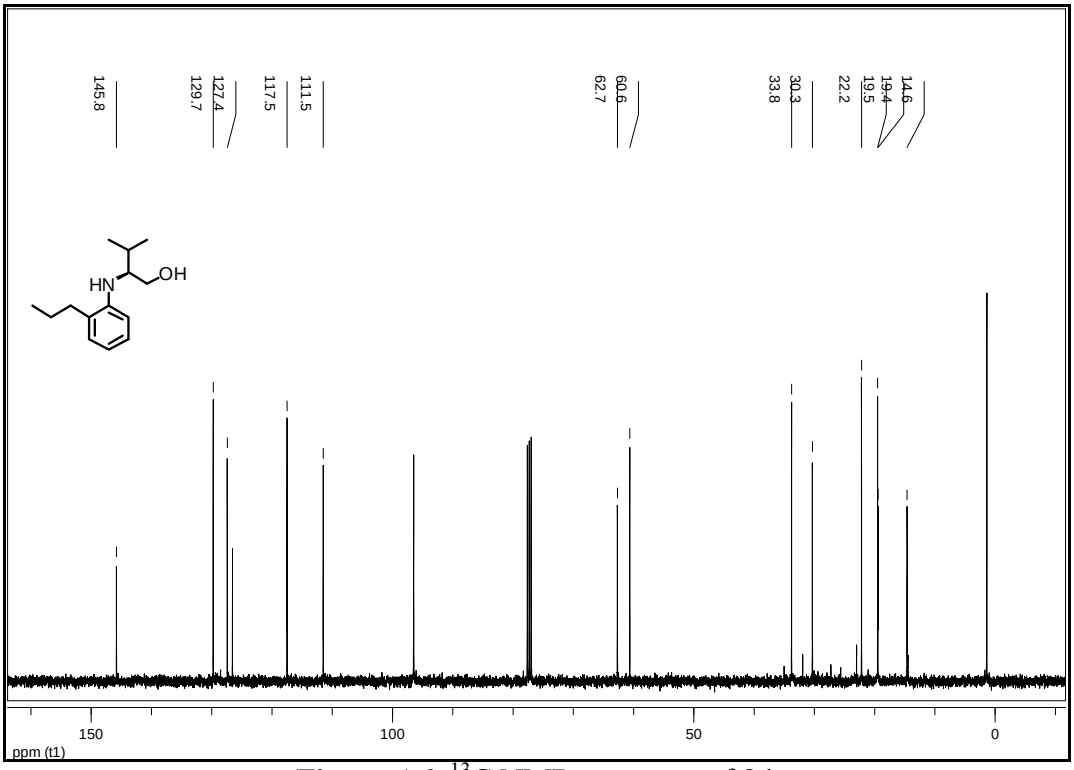

Figure A6. ^{13}C NMR spectrum of **34**

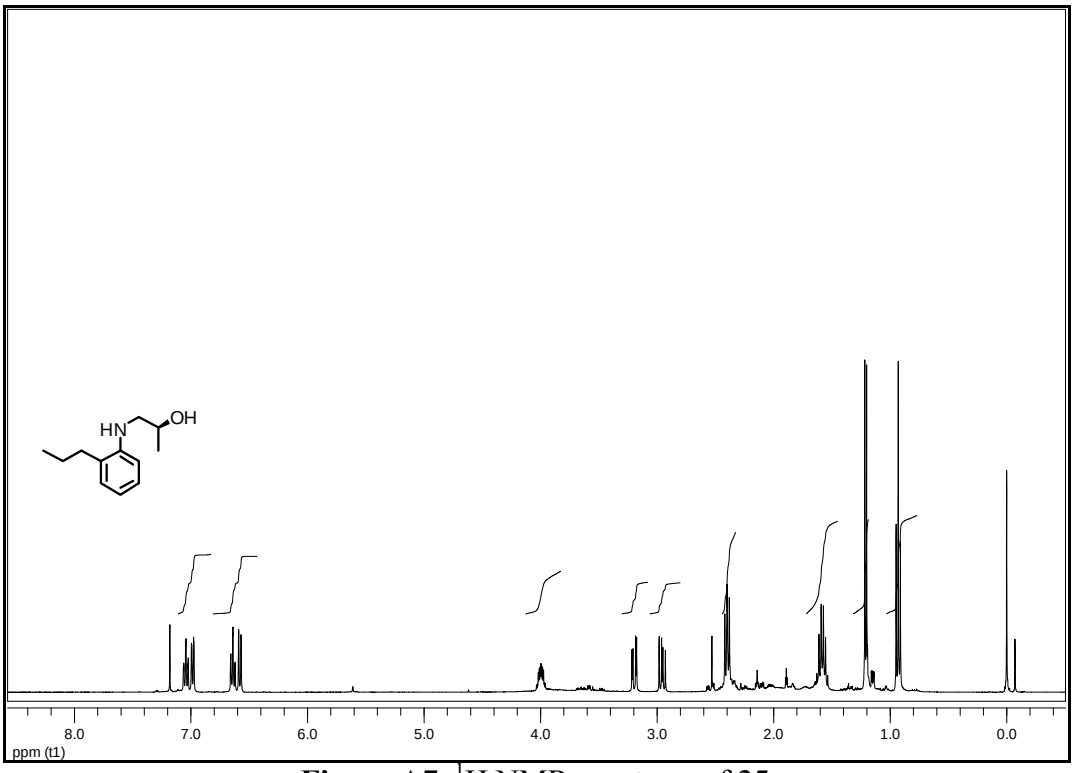

Figure A7. ^{1}H NMR spectrum of **35**

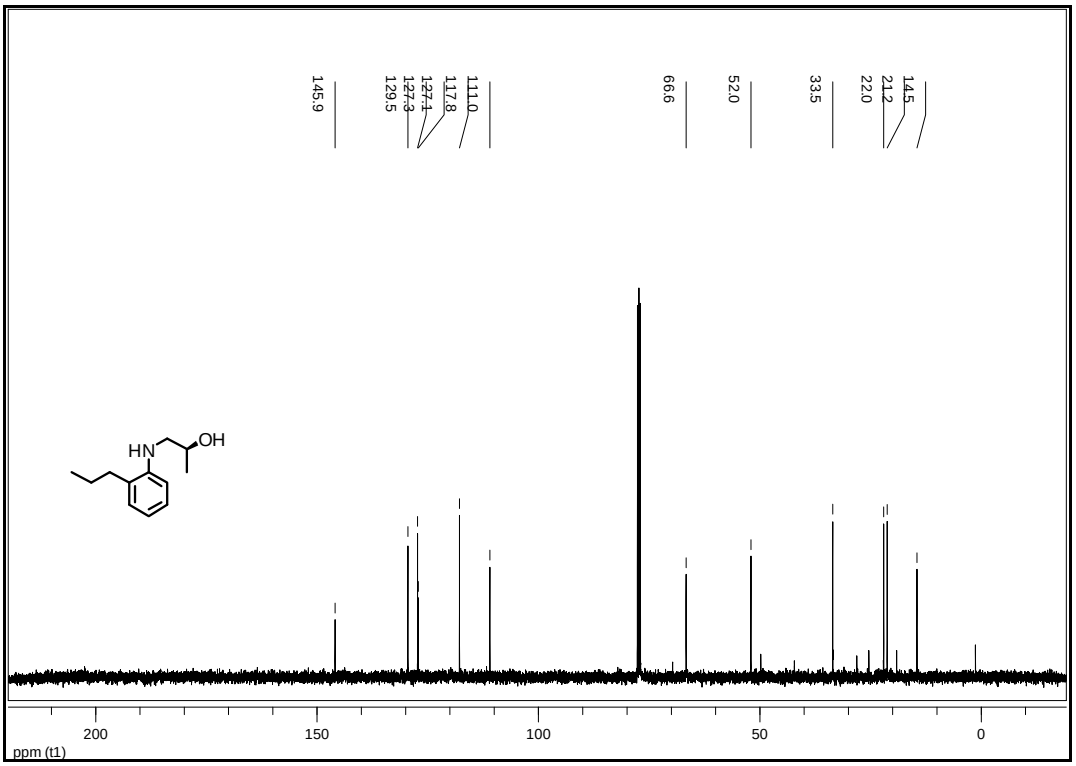

Figure A8. ^{13}C NMR spectrum of **35**

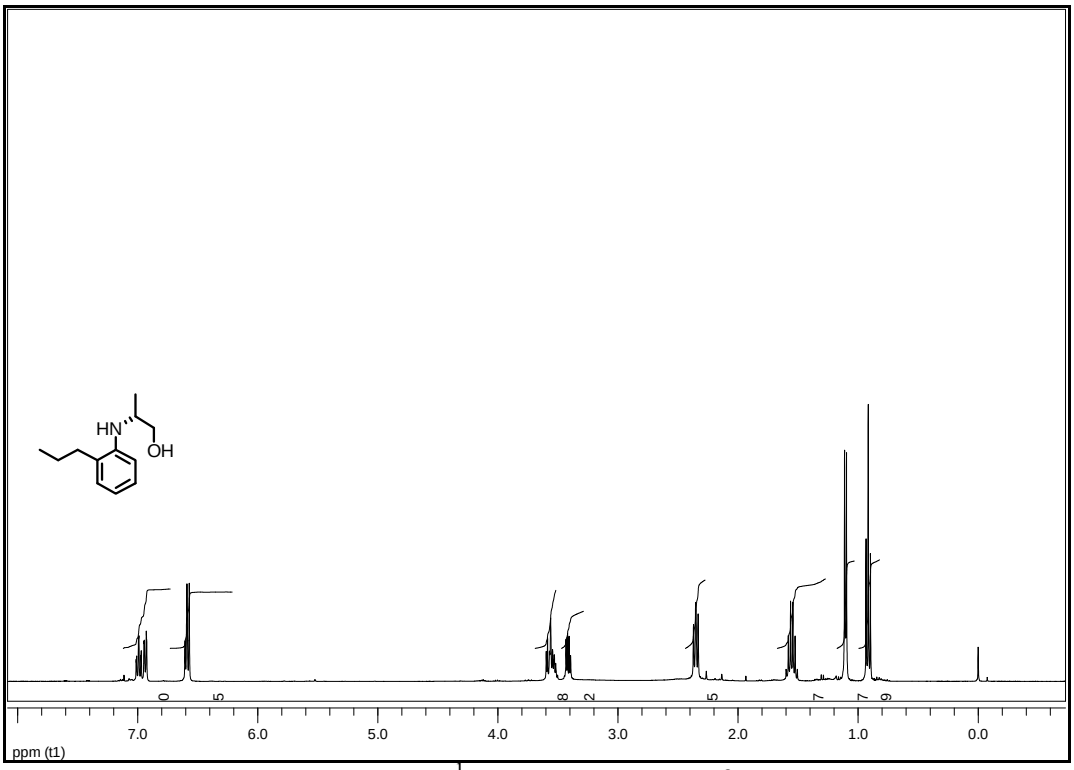

Figure A9. ^{1}H NMR spectrum of **36**

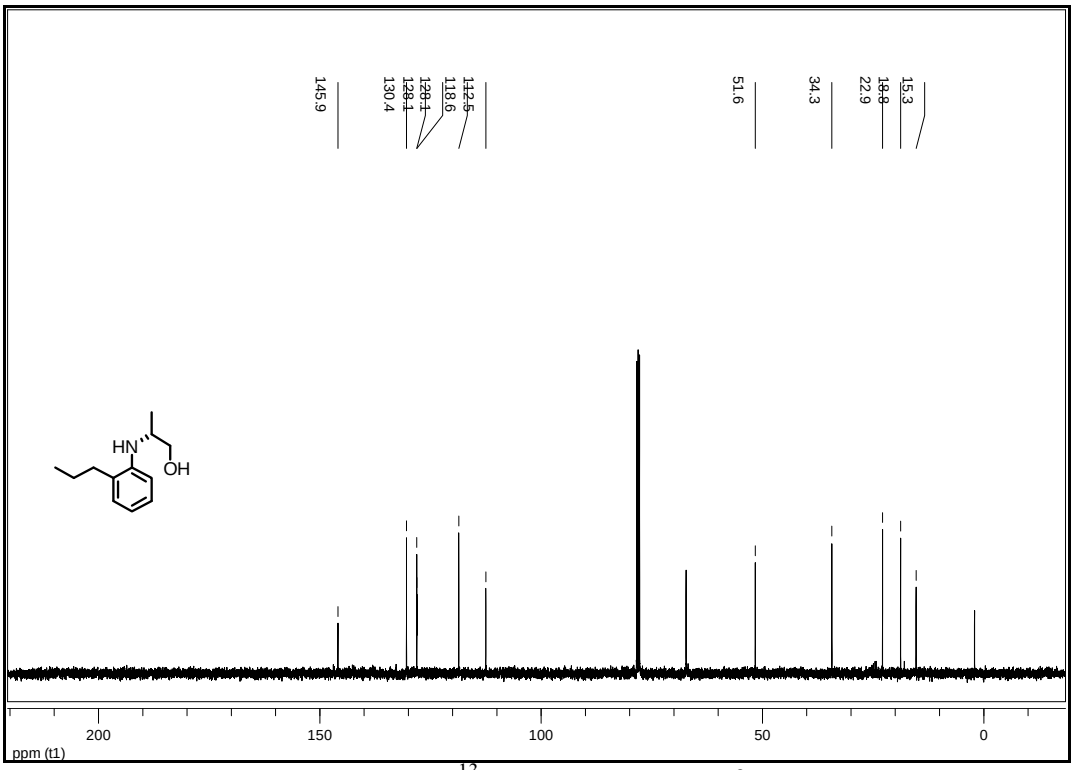

Figure A10. ^{13}C NMR spectrum of **36**

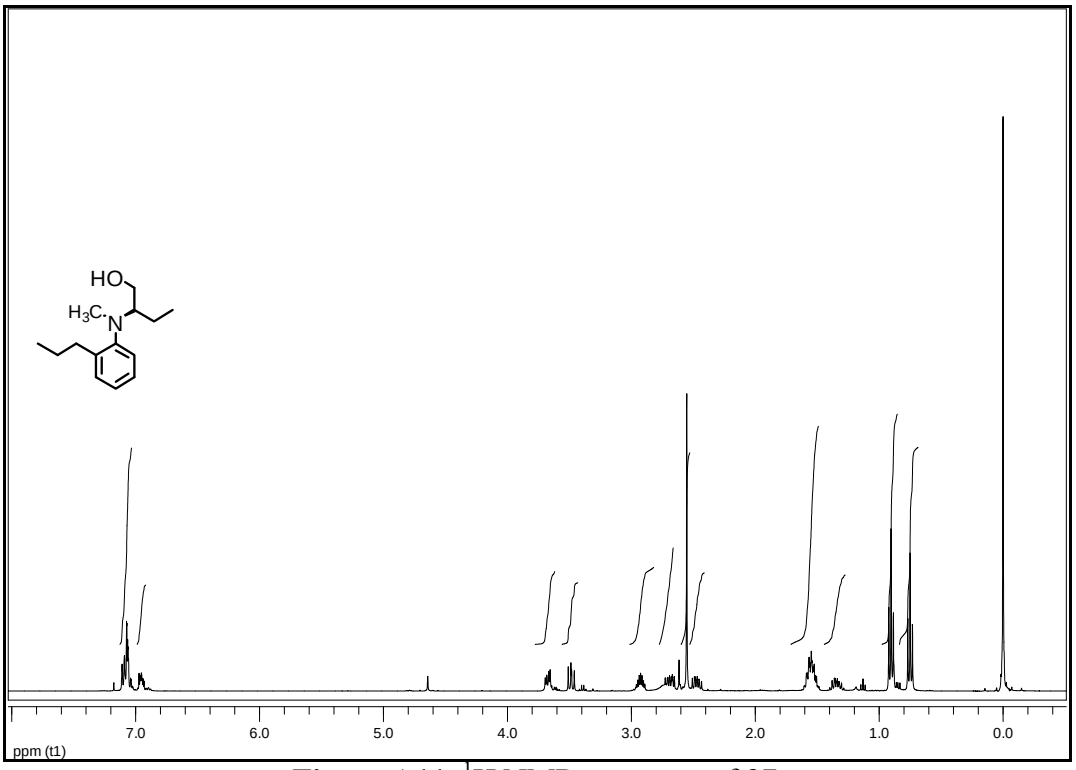

Figure A11. ^{1}H NMR spectrum of **37**

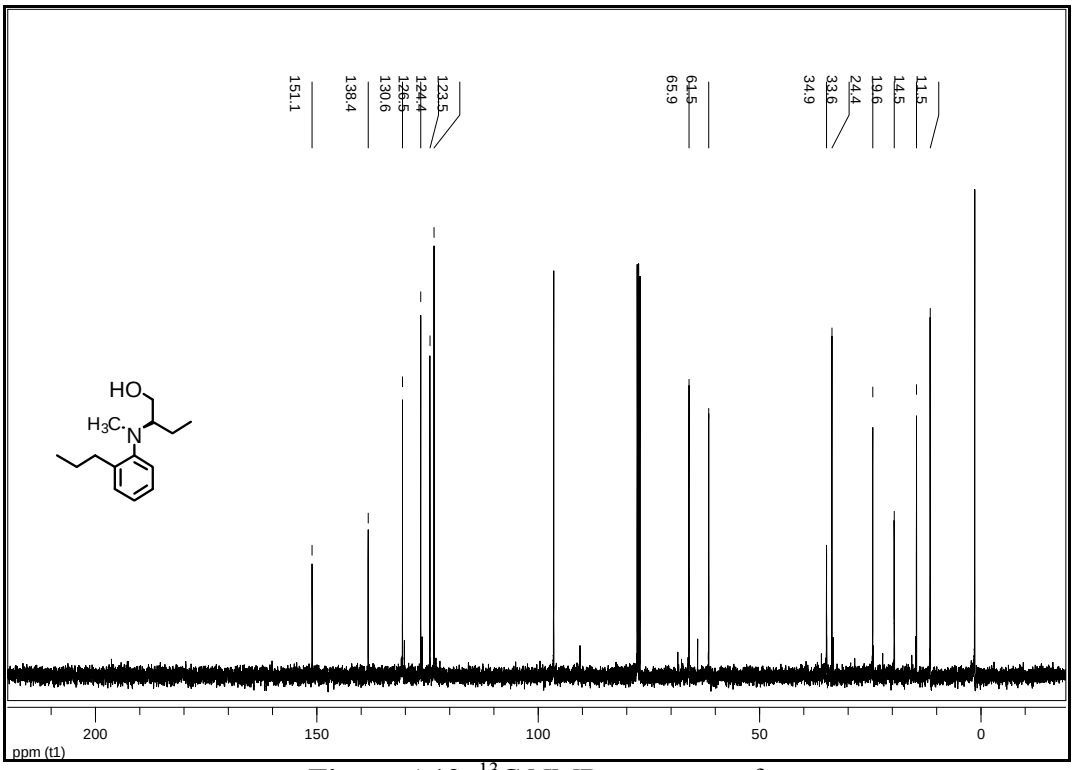

Figure A12. ^{13}C NMR spectrum of

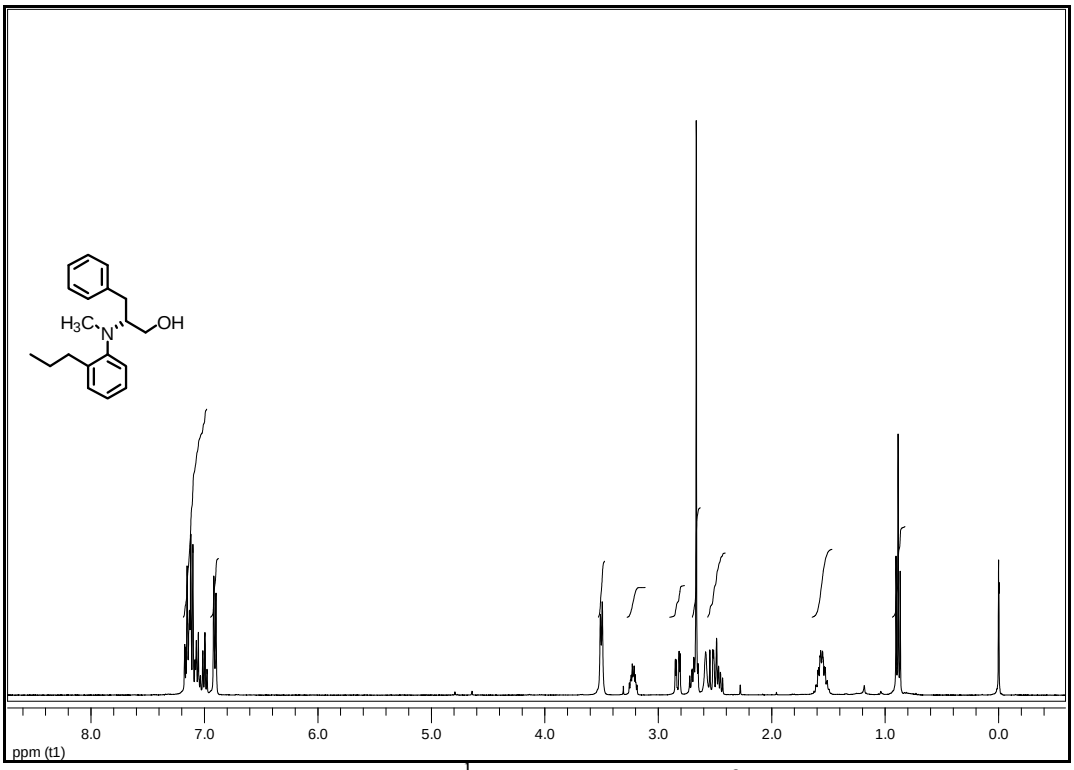

Figure A13. ^{1}H NMR spectrum of **38**

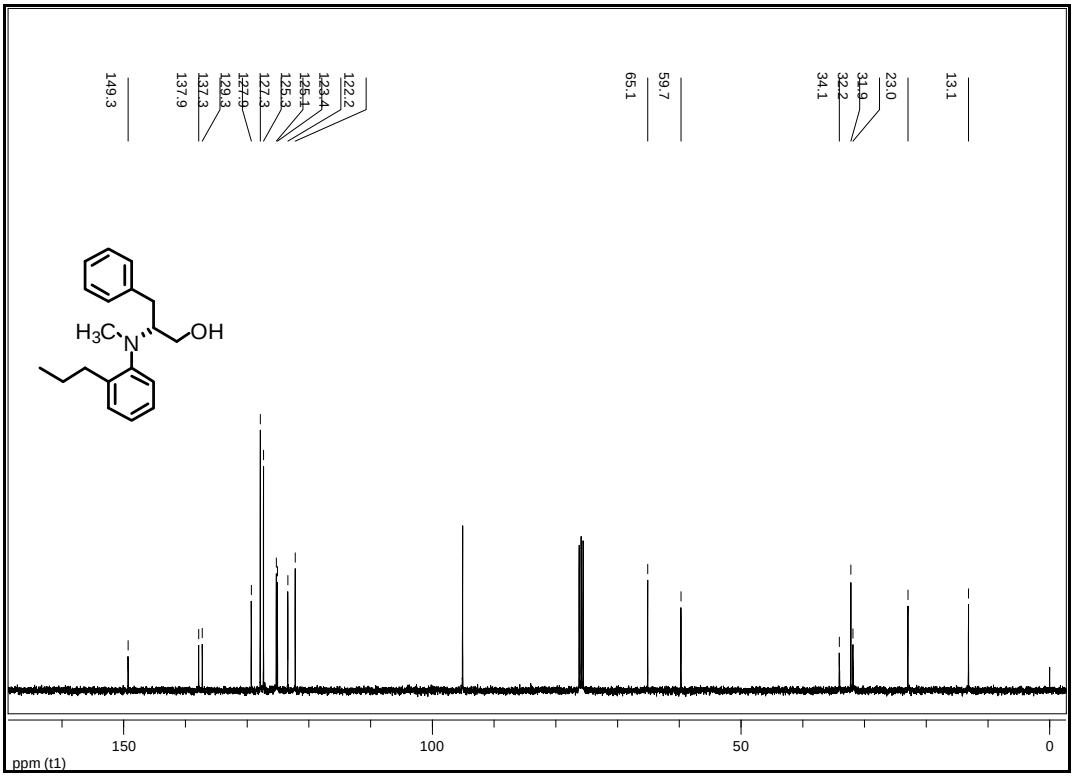

Figure A14. ^{13}C NMR spectrum of **38**

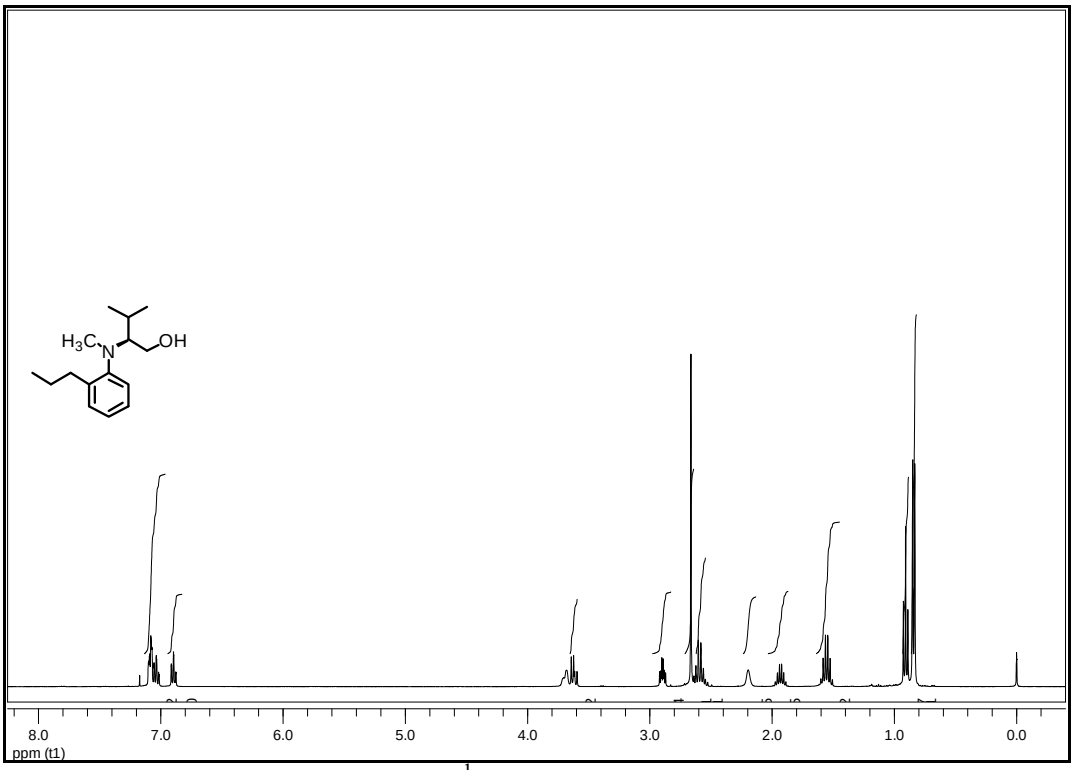

Figure A15. ^{1}H NMR spectrum of **39**

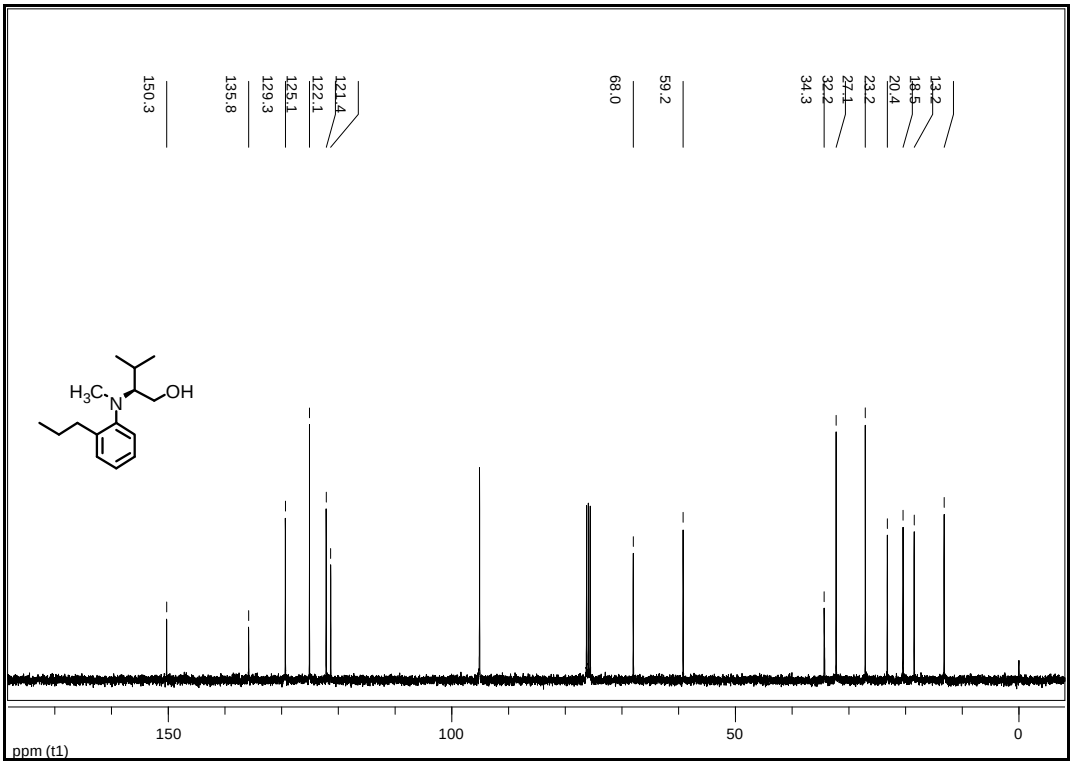

Figure A16. ^{13}C NMR spectrum of **39**

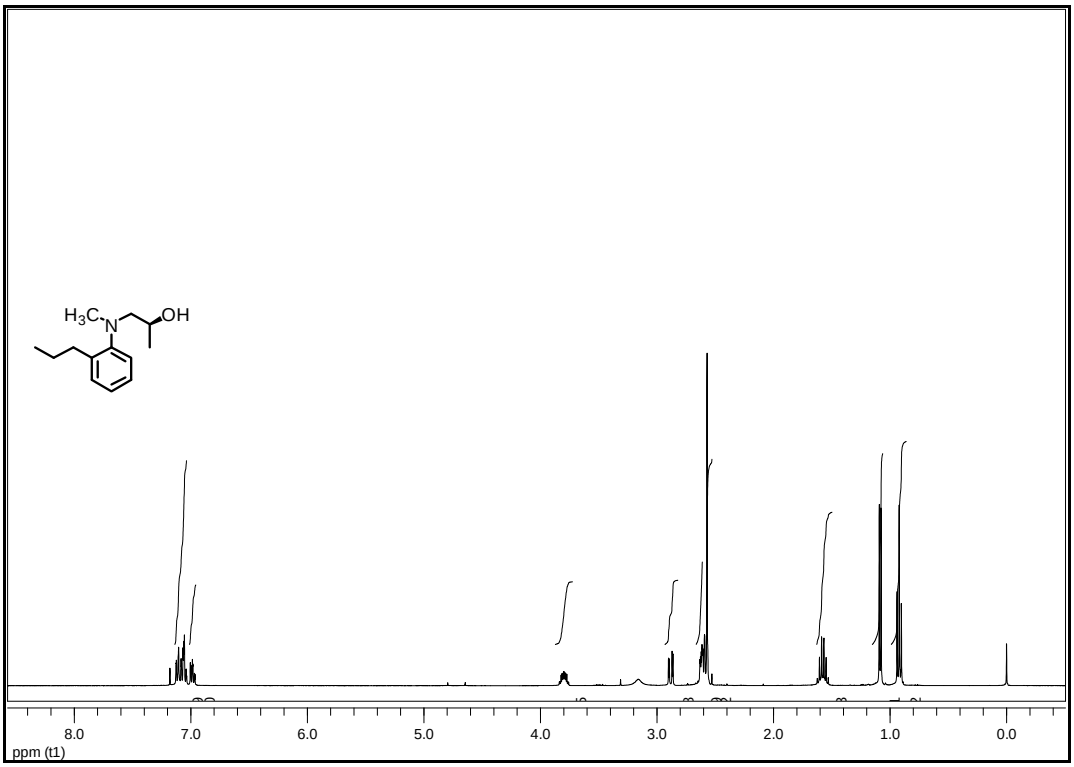

Figure A17. ^{1}H NMR spectrum of **40**

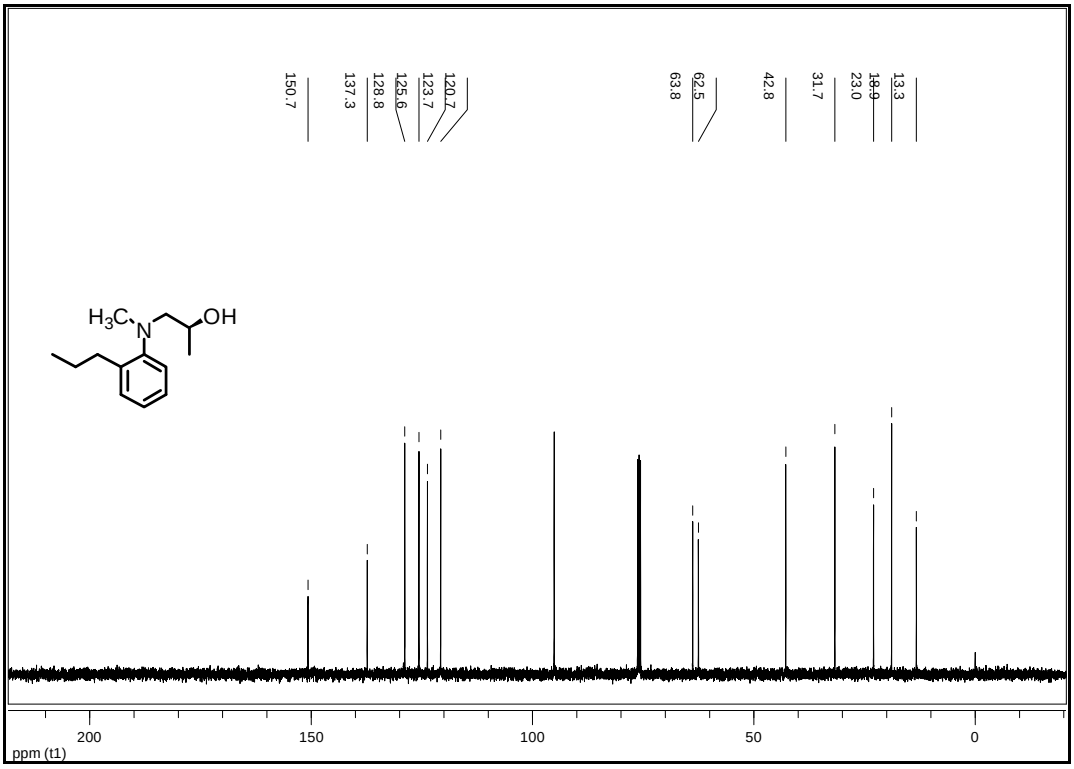

Figure A18. ^{13}C NMR spectrum of **40**

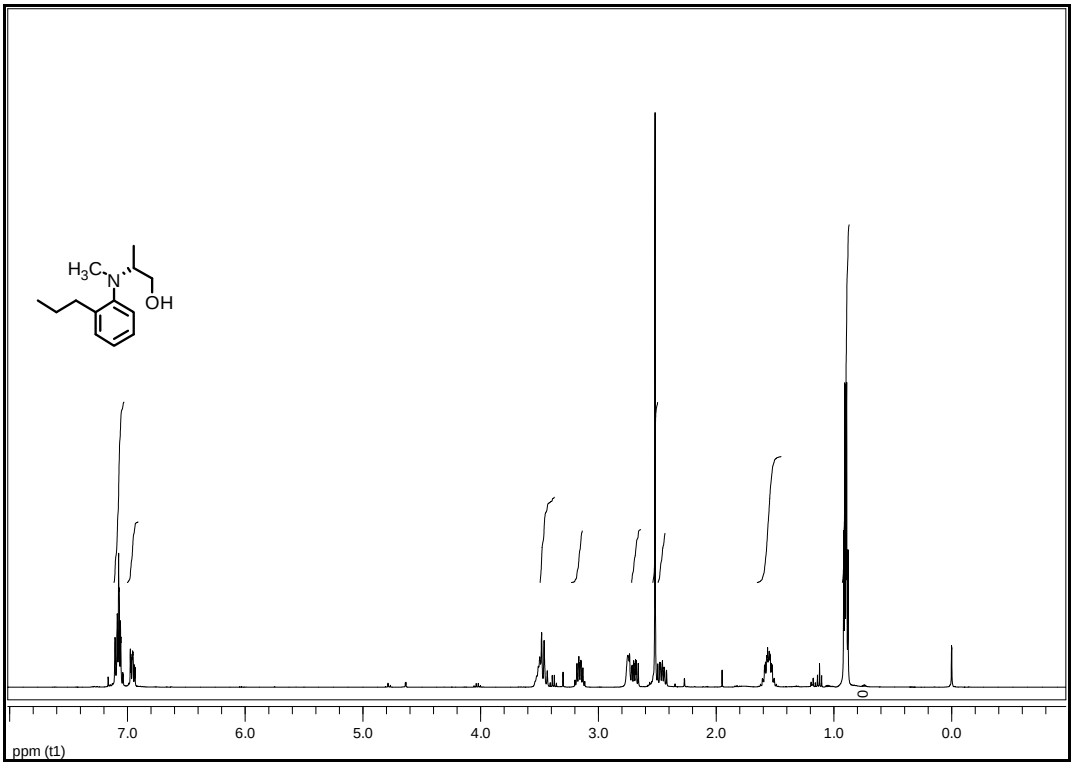

Figure A19. ^{1}H NMR spectrum of **41**

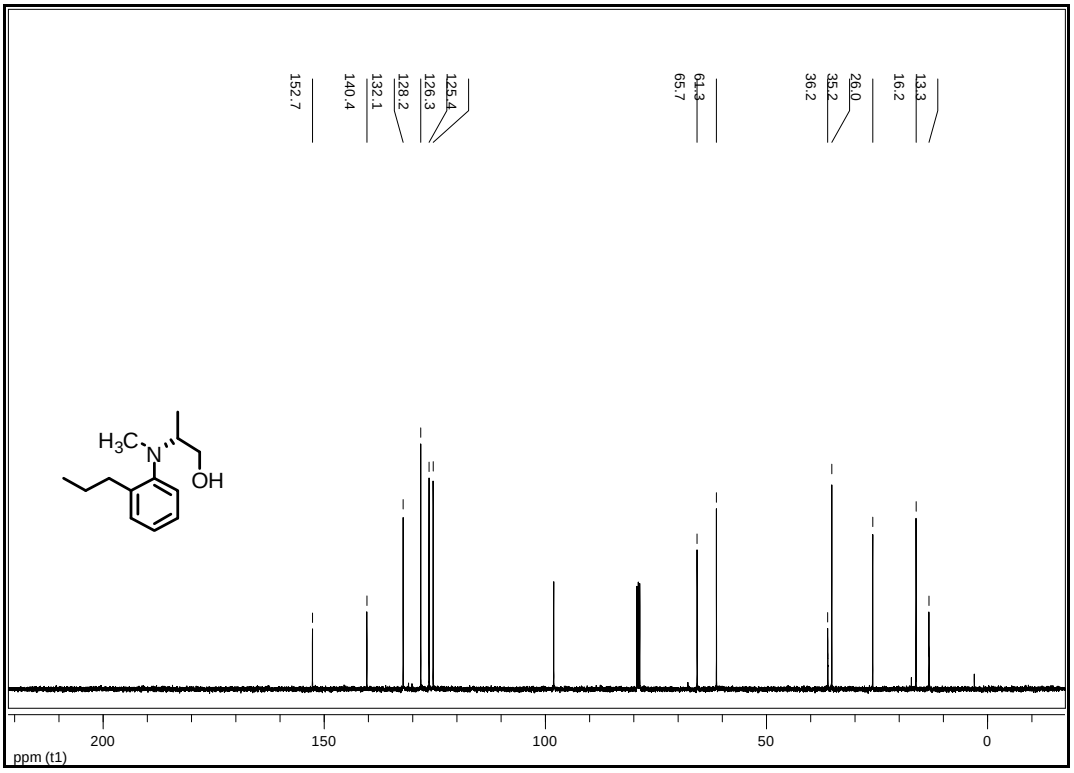

Figure A20. ^{13}C NMR spectrum of **41**

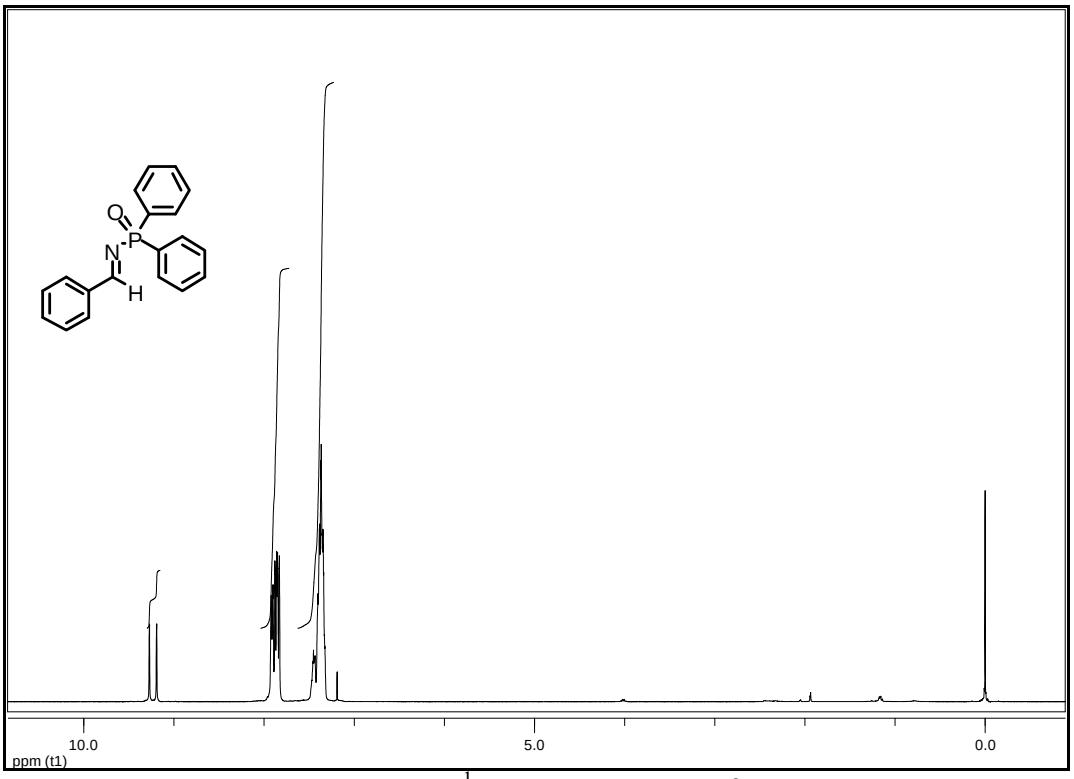

Figure A21. ^{1}H NMR spectrum of **42**

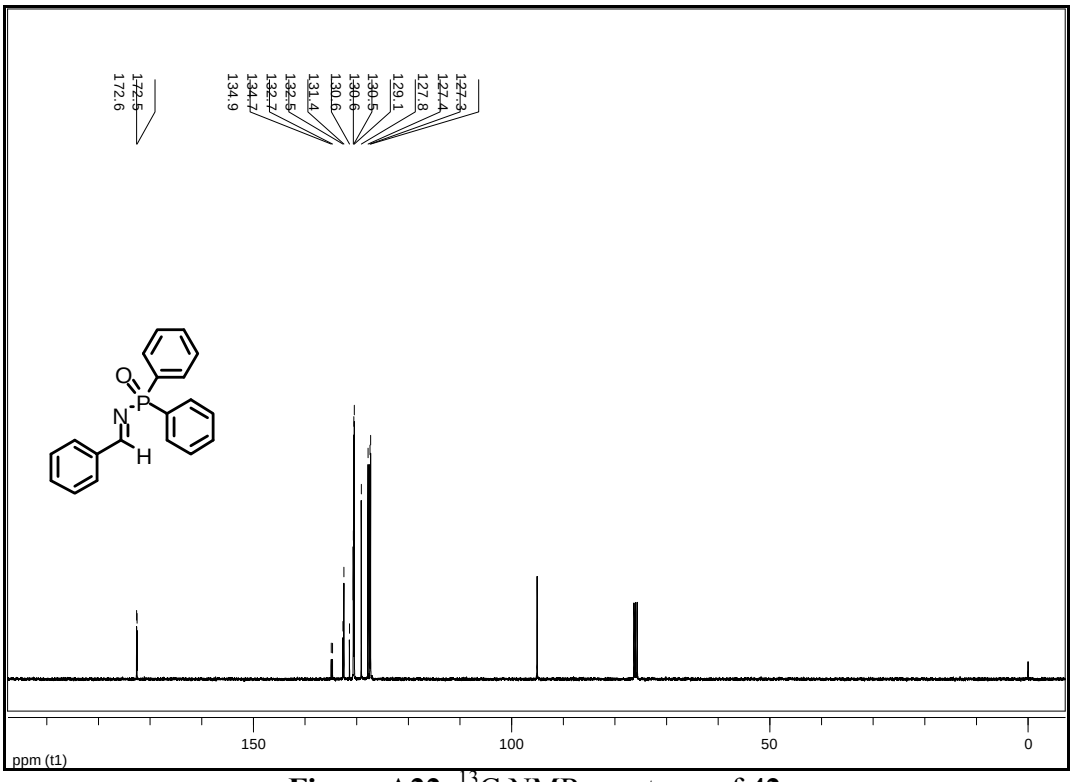

Figure A22. ^{13}C NMR spectrum of **42**

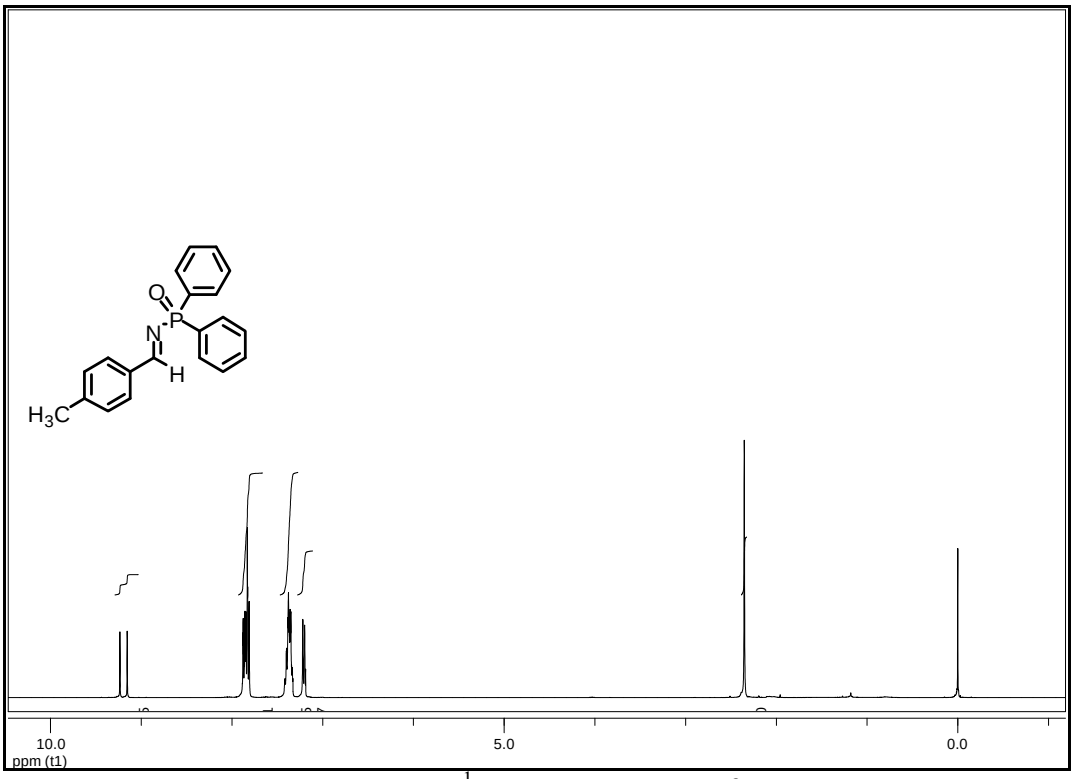

Figure A23. ^{1}H NMR spectrum of **44**

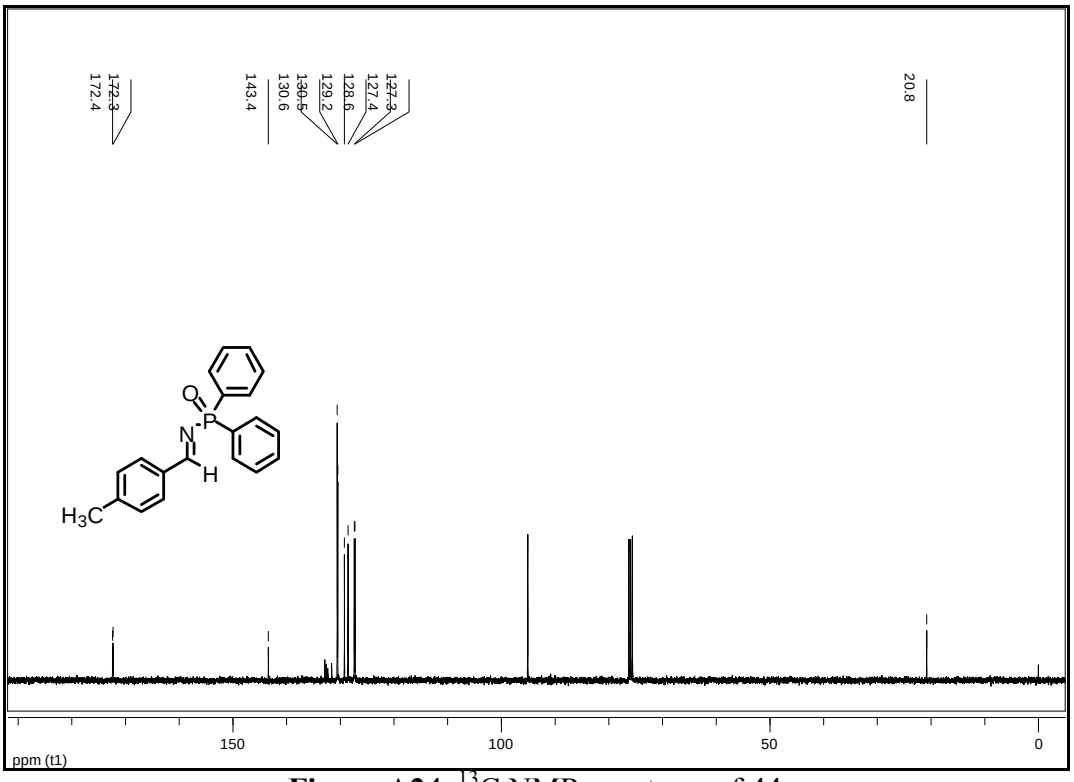

Figure A24. ^{13}C NMR spectrum of **44**

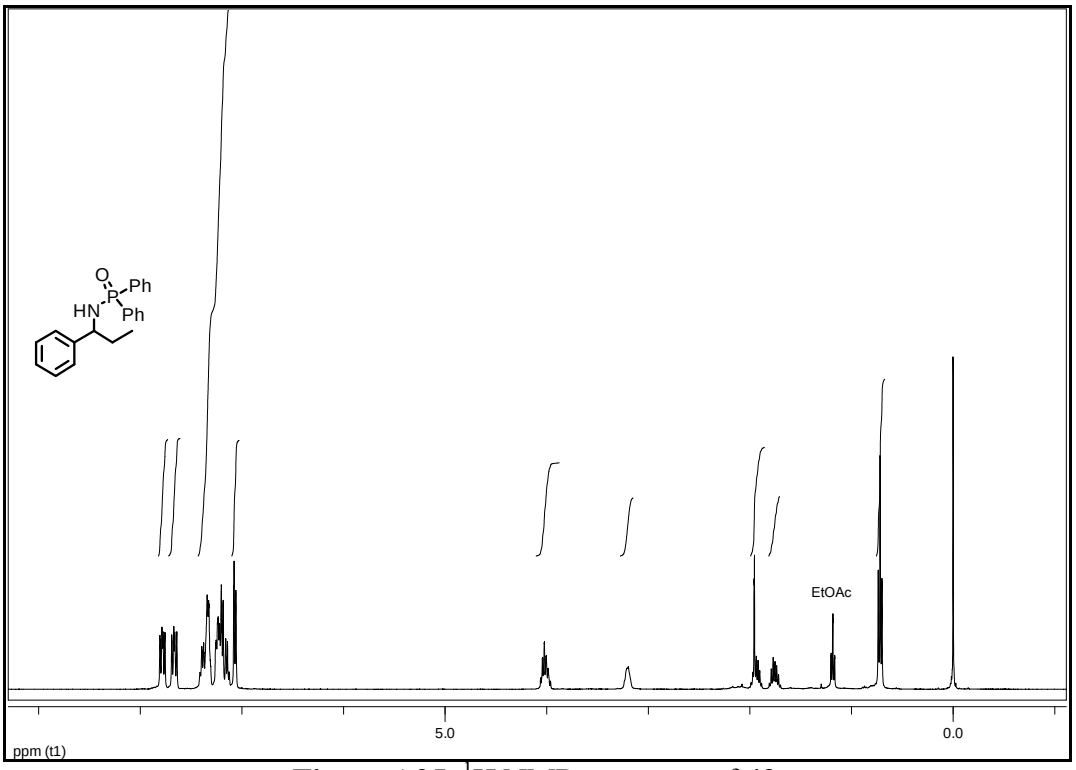

Figure A25. ^{1}H NMR spectrum of **43**

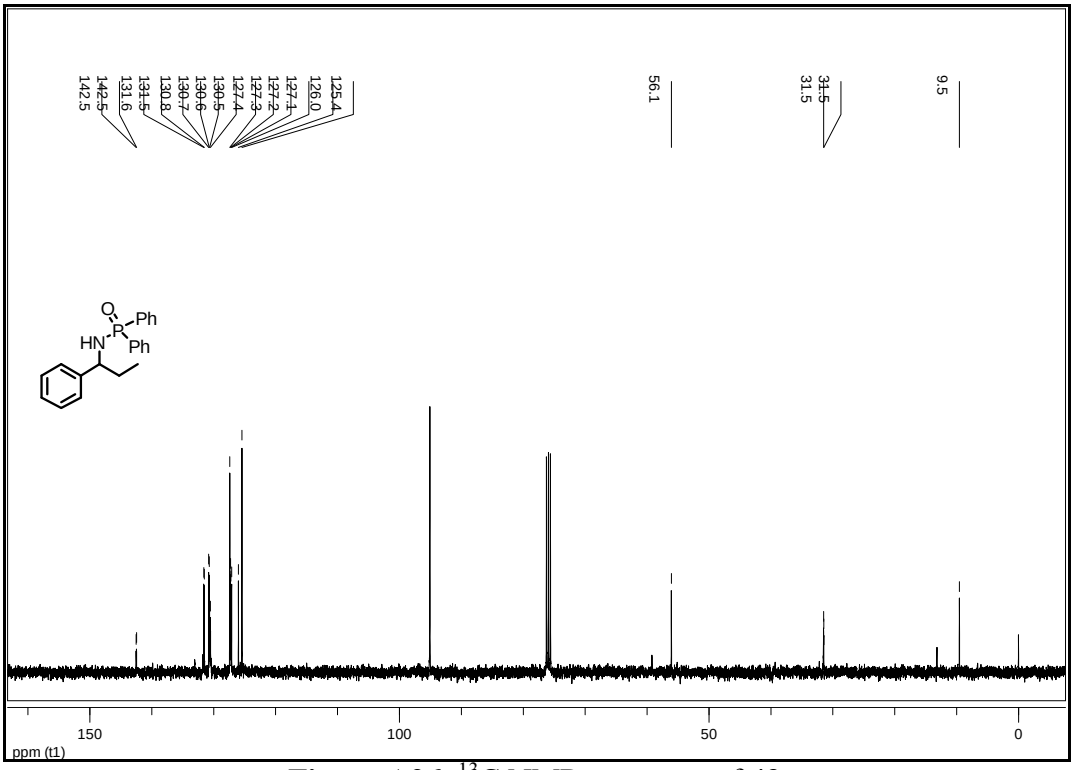

Figure A26. ^{13}C NMR spectrum of **43**

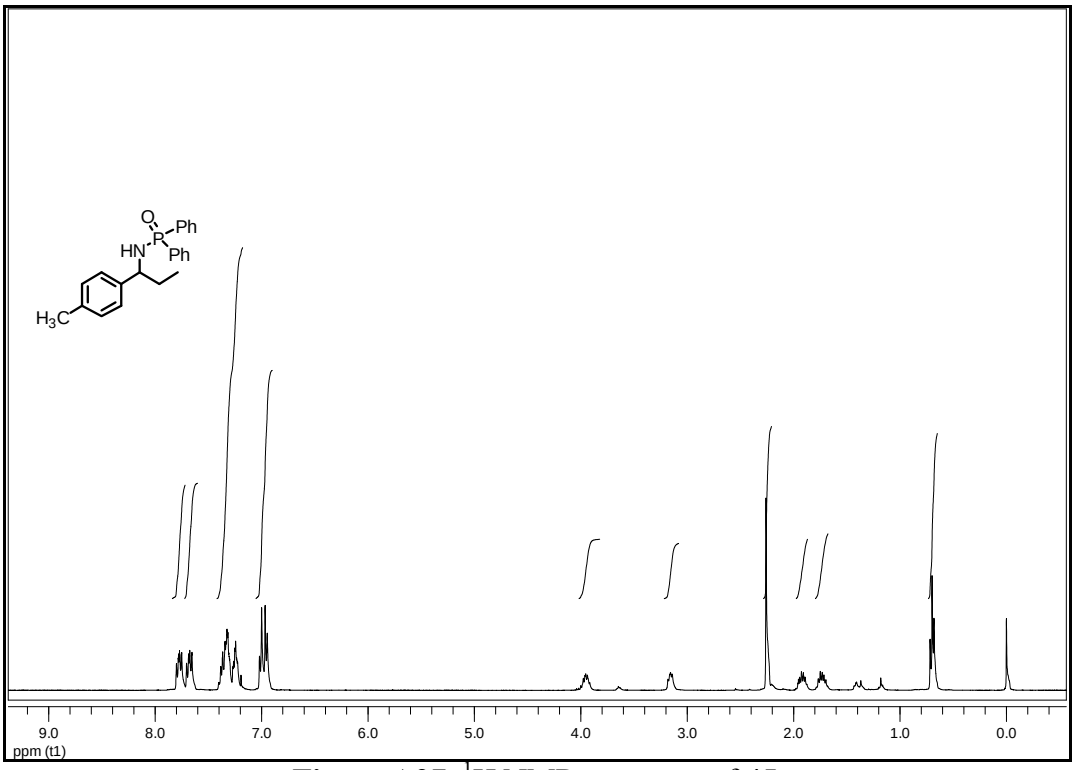

Figure A27. ^{1}H NMR spectrum of **45**

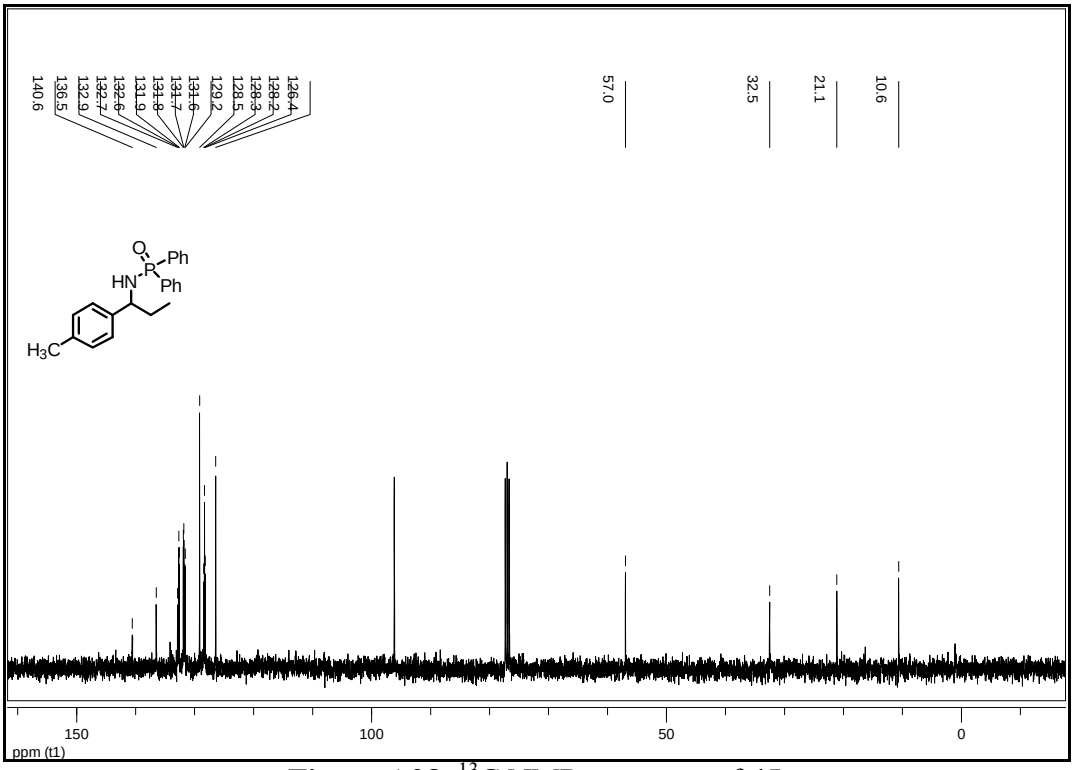

Figure A28. ^{13}C NMR spectrum of **45**

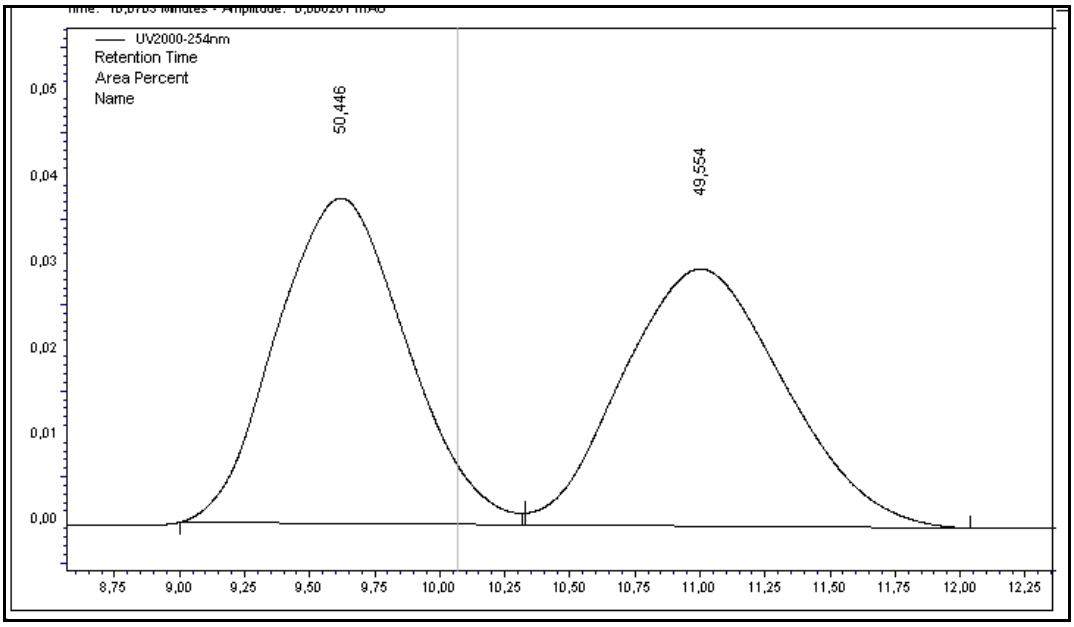

Figure A39. HPLC analysis of *rac* 1-phenyl propanol

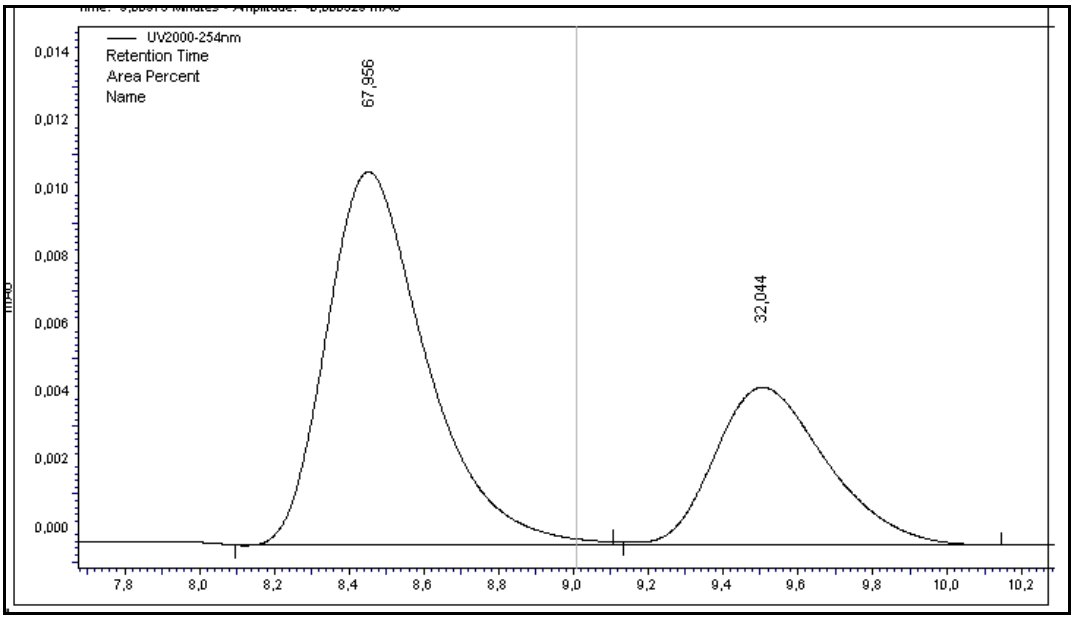

Figure A30. HPLC analysis of chiral 1-phenylpropanol (Table 6, entry 5)

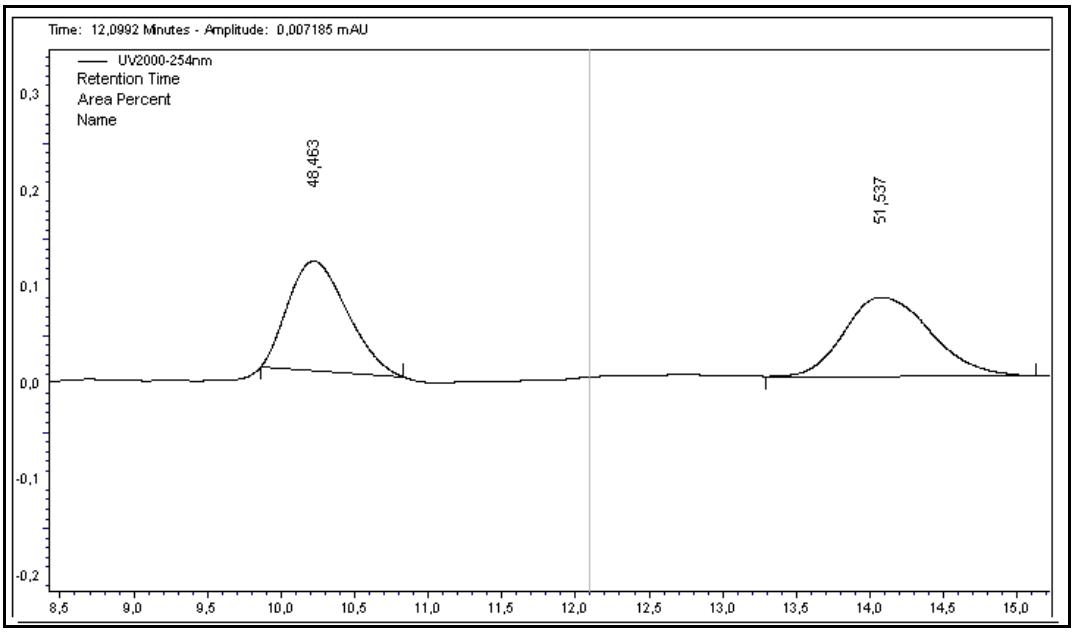

Figure A31. HPLC analysis of racemic *rac P,P*-diphenyl-*N*-(1-phenylpropyl)phosphinic amide **(43)**

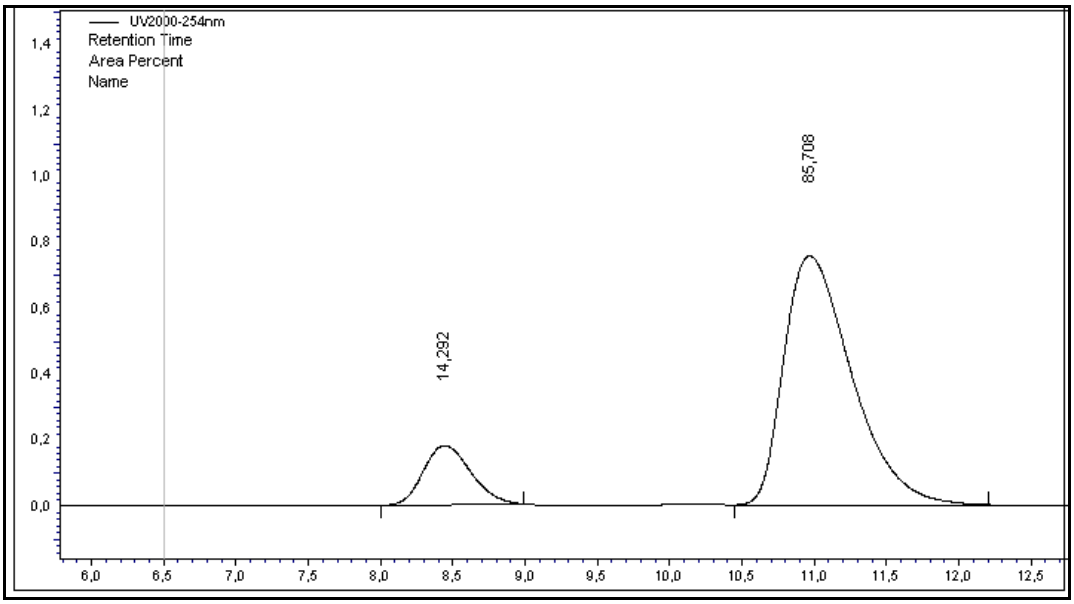

Figure A32. HPLC analysis of chiral **43** (Table 12, entry 4)

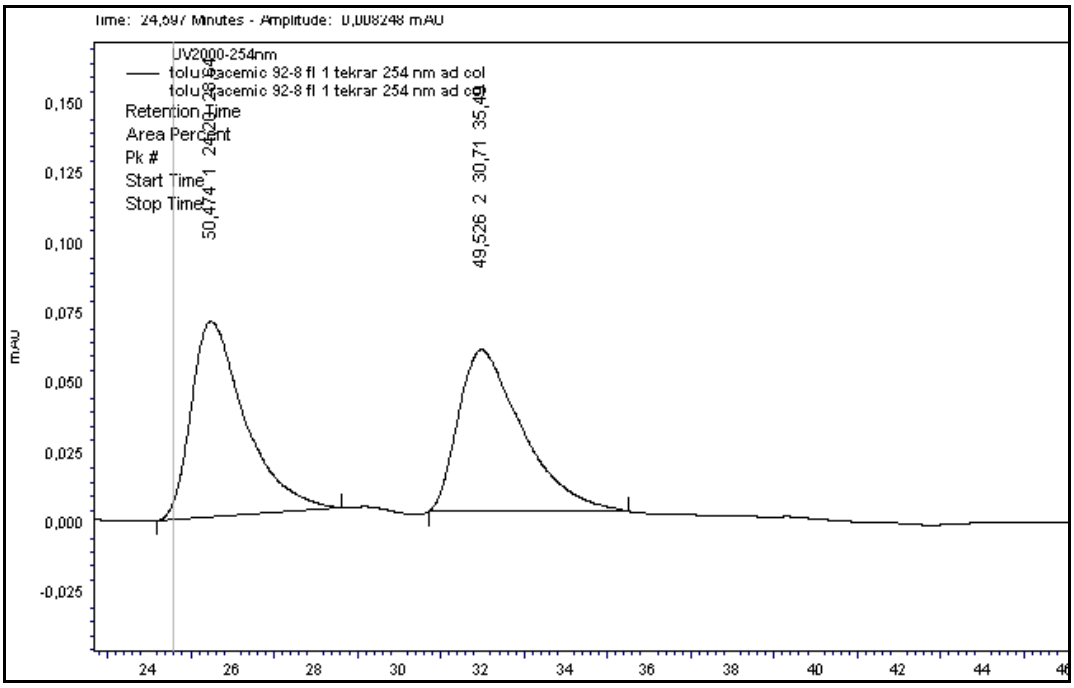

Figure A33. HPLC chromatogram of *rac P,P*-diphenyl-*N*-(1-*p*-tolylpropyl)phosphinic amide **(45)**

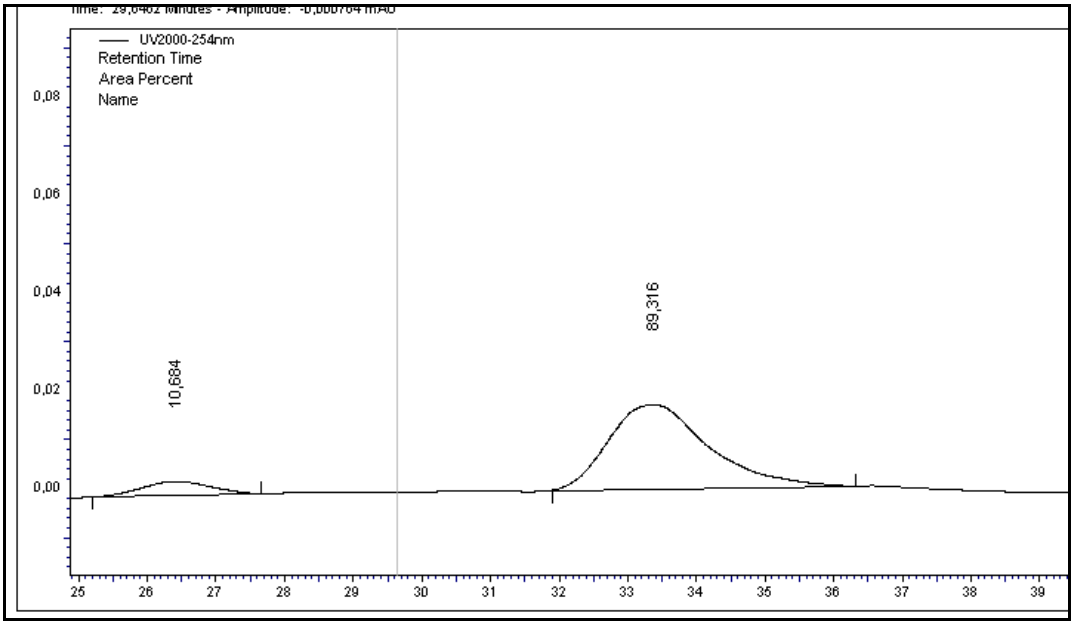

Figure A34. HPLC chromatogram of chiral **45** (Table 15, entry 2)