SYNTHESIS OF NOVEL CHIRAL PYRROLE DERIVATIVES AS CATALYST AND THEIR APPLICATIONS IN ASYMMETRIC SYNTHESIS

KATALİZÖR OLARAK YENİ KİRAL PİROL TÜREVLERİNİN SENTEZİ VE ASİMETRİK SENTEZLERDE UYGULAMALARI

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ANKARA

Gruduate School of Natural and Applied Sciences,

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

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APPROVEMENT

This thesis has been certified as thesis for the Degree of Doctor of Philosophy by the above Examining Committee Members on ...../...../2006.

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uzakları yakın eden sevdiklerime…

SYNTHESIS OF NOVEL PYRROLE DERIVATIES AS CATALYST AND THEIR APPLICATIONS IN ASYMMETRIC SYNTHESIS

Alime Ebru AYDIN

ABSTRACT

The carbon-carbon bond formation reactions, especially the catalytic asymmetric carbon-carbon bond formations, constitute an important part of organic synthesis. Developing new chiral ligands such as diamines, diols, aminothiols, aminosulfides and amino alcohols, to be used in asymmetric catalysis has attracted considerable attention in the last decades. Amino alcohol based chiral ligands are the most promising substances among them.

In this study, it was aimed to synthesize novel norephedrine and camphor based ligands with *N*-substituted chiral pyrrole to be used in the enantioselective addition of diethylzinc to aldehydes and chalcone.

In the first part of the study, *N*-substituted chiral pyrroles were synthesized from 5-chloropent-3-ene-2-one and commercially available chiral amine. The formylation of *N*-substituted chiral pyrroles was performed by the Vilsmeier Haack method. The reaction occured at the C-3 or C-2 of pyrrole, according to one- and two dimensional NMR analyses. The structure of 2-methyl-1-((1*R*)-1-phenylethyl)-1*H*-pyrrole-3-carbaldehyde was determined by single crystal X-ray analysis.

Novel chiral ligands were obtained in high yields from the reaction of *N*-substituted chiral pyrrole carbaldehydes with both enantiomers of norephedrine, and also with *exo*-3-amino-*exo*-2-hydroxy-1,7,7-trimethyl-bicyclo[2.2.1]heptane, *endo*-3-amino-*endo*-2-hydroxy-1,7,7-trimethyl-bicyclo[2.2.1]heptane prepared from camphor. The synthesized novel chiral ligands were characterized by NMR techniques.

In the last part of the study, the synthesized novel chiral ligands with multiple stereogenic centers were used as catalysts in the enantioselective addition reactions.

The enantioselective addition of diethylzinc to benzaldehyde and chalcone was chosen as a model reaction for the activity investigation of chiral ligands. The best enantiomeric excesses were obtained with (1*S*,2*R*)-2-((5-methyl-1-((1*S*)-1-phenylethyl)-1*H*-pyrrol-2-yl)methylamino)-1-phenylpropan-1-ol, (1*S*,2*R*)-2-((2-methyl-1-((1*S*)-1-phenylethyl)-1*H*-pyrrol-3-yl)methylamino)-1-phenylpropan-1-ol for the enantioselective addition of diethylzic to aldehydes. For enantioselective addition of diethylzinc to chalcone, (1*S*,2*R*)-2-((2-methyl-1-((1*R*)-1-phenylethyl)-1*H*-pyrrol-3-yl)methylamino)-1-phenylpropan-1-ol and 1,7,7-trimethyl-3-((5-methyl-1-((*R*)-1-phenylethyl)-1*H*-pyrrol-2-yl)methylamino)bicyclo[2,2,1]heptan-2-ol gave the best results.

In order to determine the optimum reaction conditions of enantioselective addition of diethylzinc to benzaldehyde and chalcone, effects of solvent, amount of ligand, temperature, and time were investigated.

The enantioselective additions of diethylzinc to , *ortho*-, *para*-substituted aromatic aldehydes with (1*S*,2*R*)-2-((5-methyl-1-((1*S*)-1-phenylethyl)-1*H*-pyrrol-2-yl)methyl amino)-1-phenylpropan-1-ol, (1*S*,2*R*)-2-((2-methyl-1-((1*S*)-1-phenylethyl)-1*H*-pyrrol-3-yl)methylamino)-1-phenylpropan-1-ol were performed to examine the substituent effect. The best results were obtained with *p*-trifluorobenzaldeyhe (88%, 83% ee).

The enantioselective additions of diethylzinc to benzaldeyhde with (1*S*,2*R*)-2-((5-methyl-1-((1*S*)-1-phenylethyl)-1*H*-pyrrol-2-yl)methylamino)-1-phenylpropan-1-ol, (1*S*,2*R*)-2-((2-methyl-1-((1*S*)-1-phenylethyl)-1*H*-pyrrol-3-yl)methylamino)-1-phenyl propan-1-ol were performed in the presence of $Ti(O\text{-}i\text{-}Pr)_4$ and additives such as BuLi, LiCl.

KEY WORDS: Enantioselective addition, *N*-substituted chiral pyrrole compounds, β-amino alcohol-based chiral ligands, norephedrine-based chiral ligands and camphor-based chiral ligands, 1,2- and 1,4-addition reaction of diethylzinc

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KATALİZÖR OLARAK YENİ PİROL TÜREVLERİNİN SENTEZİ VE ASİMETRİK SENTEZLERDE UYGULAMALARI

Alime Ebru AYDIN

ÖZET

Karbon-karbon bağ oluşum tepkimeleri özellikle katalitik asimetrik karbon-karbon bağ oluşumları organik sentezde önemli bir bölümü kapsar. Son zamanlarda diaminler, dioller, aminosülfürler, aminosülfitler ve amino alkoller gibi yeni kiral ligandların geliştirilmesi son derece önem kazanmıştır. Bu maddeler içinde, amino alkol temelli kiral ligandlar en çok umut verenlerdir.

Bu çalışmada, yeni norephedrin ve kafur temelli *N*-substituye kiral pirol yapısı içeren ligandların sentezi ve bunların katalizör olarak dietilçinkonun aldehitlere ve kalgona enantioseçimli katılmalarında kullanılması amaçlanmıştır.

Çalışmanın ilk bölümünde, 5-kloropent-3-en-2-on ve ticari olarak bulunan kiral aminlerden *N*-substitue kiral pirol bileşikleri sentezlendi. *N*-substitue kiral pirol bileşiklerinin formillenmesi Vilsmeier Haack metodu ile gerçekleştirildi. Bir ve iki boyutlu NMR analizlerine göre, tepkime pirolun C-3 veya C-2 pozisyonlarında gerçekleşmiştir. 2-Metil-1-(*R*)-1-feniletil)-1*H*-pirol-3-karbaldehidin yapısı X ışınları analizi ile belirlendi.

Yeni kiral ligandlar *N*-substituye kiral pirol karbaldehitlerin, norephedrinin her iki enantiomeri ve aynı zamanda kafurdan hazırlanan (*exo*-3-amino-*exo*-2-hidroksi-1,7,7-trimetilbisiklo[2.2.1]heptan,*endo*-3-amino-*endo*-2-hidroksi-1,7,7-trimetilbisiklo [2.2.1]heptan' ın tepkimesiyle yüksek verimlerle elde edildi. Sentezlenen yeni kiral ligandlar NMR teknikleriyle karakterize edildi.

Çalışmanın son bölümünde, sentezlenen çoklu stereojenik merkeze sahip kiral ligandlar enantioseçimli katılma tepkimelerinde katalizör olarak kullanıldı.

Benzaldehit ve kalgona dietilçinkonun enantioseçimli katılması, kiral ligandların aktivitelerinin araştırılması için model reaksiyon olarak seçildi. Aldehitlere

dietilçinkonun katılması tepkimesi için en iyi enantiomerik fazlalık (1*S*,2*R*)-2-((5-metil-1-((1*S*)-1-feniletil)-1*H*-pirol-2-yl)metilamino)-1-fenilpropan-1-ol, (1*S*,2*R*)-2-((2-metil-1-((1*S*)-1-feniletil)-1*H*-pirol-3-yl)metilamino)-1-fenilpropan-1-ol ile elde edildi. Kalgona dietilçinkonun enantioseçimli katılmasında ise (1*S*,2*R*)-2-((2-metil-1-((1*R*)-1-fenietil)-1*H*-pirol-3-yl)metilamino)-1-fenilpropan-1-ol and 1,7,7-trimetil-3-((5-metil-1-((*R*)-1-feniletil)-1*H*-pirol-2-yl)metilamino)bisiklo[2,2,1]heptan-2-ol en iyi sonuçları verdi.

Benzaldehit ve kalgona dietilçinkonun enantioseçimli katılmalarında optimum tepkime koşullarını belirlemek için çözücü, ligand miktarı, sıcaklık, süre etkileri araştırıldı.

Subsitutent etkisini belirlemek için *orto*-, *para*- substituye aromatik aldehitlere dietilçinkonun enantioseçimli katılmaları (1*S*,2*R*)-2-((5-metil-1-((1*S*)-1-feniletil)-1*H*-pirol-2-yl)metilamino)-1-fenilpropan-1-ol, (1*S*,2*R*)-2-((2-metil-1-((1*S*)-1-feniletil)-1*H*-pirol-3-yl)metilamino)-1-fenilpropan-1-ol ile gerçekleştirildi. En iyi sonuçlar *p*-triflorometilbenzaldehitle elde edildi (88% and 83% ee).

(1*S*,2*R*)-2-((5-metil-1-((1*S*)-1-feniletil)-1*H*-pirol-2-yl)metilamino)-1-fenilpropan-1-ol, (1*S*,2*R*)-2-((2-metil-1-((1*S*)-1-feniletil)-1*H*-pirol-3-yl)metilamino)-1-fenilpropan-1-ol ile benzaldehite dietilçinkonun enantioseçimli katılması Ti(O-*i*-Pr)$_4$ varlığında ve BuLi ve LiCl gibi katkı maddeleri kullanılarak yapıldı.

ANAHTAR KELİMELER: Enantioseçimli katılma, *N*-substitute kiral pirol bileşikleri, β-amino alkol temelli kiral ligandlar, norephedrine temelli kiral ligandlar ve kafur temelli kiral ligandlar, dietilçinkonun1,2- ve1,4- katılma tepkimeleri

Danışman: Prof. Dr. Canan ÜNALEROĞLU, Hacettepe Üniversitesi, Kimya Bölümü, Organik Kimya Anabilim Dalı.

Ortak Danışman: Prof. Dr. Ayhan S. Demir, Orta Doğu Teknik Üniversitesi, Kimya Bölümü, Organik Kimya Anabilim Dalı.

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ABBREVIATIONS

A, B	: reactant and substrate
M	: metallic species
X*	:chiral heteroatom ligand.
L*	:neutral or anionic chiral ligand
TBDMS	: *ter*-butyldimethylsily
ee	: enantiomeric excess
de	: diastereomeric excess

1. INTRODUCTION

Asymmetric synthesis has become a major aspect of modern organic chemistry. The importance of stereochemical purity in pharmaceutical products has been one driving force in the quest for improved control over the stereochemical outcome of organic reactions.

There has been intensive research into developing methods for producing - synthesising - one of the enantiomers rather than the other. The synthesis of enantiomerically pure compounds is one of the major challenges in organic synthesis. Organic chemists are now able to conduct various transformations in a stereocontrolled, enantioselective and atom-economic manner using asymmetric transition-metal catalysis. The importance of this field of chemistry was underlined by the granting of the Nobel Price in chemistry in 2001 to Dr. Knowles, Prof. Noyori and Prof. Sharpless for their contributions in enantioselective synthesis (Colacot, 2002).

The most attractive and challenging class of stereoselective synthesis methods revolve around asymmetric catalysis, using a small amount of catalyst, a large amount of desired product can be attained asymmetric often with enantiomeric excesses (ee' s) exceeding 95%. These reactions include asymmetric reductions, asymmetric oxidations and asymmetric carbon-carbon bond formations.

Especially the last category is one of the most fundamental operations for constructing organic molecules. Addition of organometallic reagents to carbonyl compounds provides a reliable way to form alcoholic products. Enantioselective addition of organometallic reagents to aldehydes and unsaturated enones afford optically active secondary alcohols. These compounds are useful intermediates for many pharmaceuticals and chemicals. The need for optically active drugs has increased in pharmaceutical and agrochemical fields in recent years and, therefore, chiral alcohols are increasingly being demanded, and it is important to provide enantiopure compounds.

In the present work, it was aimed to synthesize of novel β-amino alcohol ligands and to use them for the enantioselective synthesis of asymmetric compounds.

Novel β-amino alcohol ligands with multiple stereogenic centers prepared from *N*-substituted chiral pyrrole carbaldehyde and (1*R*,2*S*)-, (1*S*,2*R*)-norephedrine and *exo*-3-amino-*exo*-2-hdroxy-1,7,7-trimethylbicyclo[2.2.1]heptane, *endo*-3-amino-2-*endo*-1,7,7-trimethylbicyclo[2.2.1]heptane were applied to the catalytic asymmetric addition of diethylzinc to aldehydes and chalcone.

2. GENERAL INFORMATION

2.1. Chirality

Chirality plays an important role in chemical, biological, pharmaceutical, and material sciences (Soai, and Sato, 2002). Chemists working with perfumes, cosmetic, nutrients, flavors, pesticides, vitamins, and pharmaceuticals, as some examples, require access to enantiomerically pure compounds (Gawley and Aubé, 1996 , Crossley, 1992).

As the ability to produce enantiomerically pure compounds grows, scientists are aware of the difference in pharmacological properties that a chiral compound may have when compared with its enantiomer or even its racemate. All biological receptors are chiral, and as such can distinguish between the two enantiomers of a ligand or substrate. Enantiomeric compounds have different odors or tastes Thus, it is obvious that two enantiomers should be considered different compounds when screened for pharmacological activity.

It is well known that the pharmacological effect is restricted in most of the cases to one of the enantiomer. Nonetheless, only about 35% of drugs in 2000 are administered as pure enantiomers. There can be qualitative and quantitative differences in the activity of the enantiomers. Many studies have shown that two enantiomers of a chiral drug usually display different biological activities, and one enantiomer is sometimes detrimental. The pharmacologically inactive enantiomer can show unwanted side effects; in some cases antagonistic and even toxic effects are observed. A well known example of the dramatic difference in activity of enantiomers is thalidomide, commercially known as Softenon. Only one enantiomer gives desired therapeutic effect, whereas the other enantiomer causes severe fetal damage .

Nevertheless, even in the early 1990s, about 90% synthetic chiral drugs were still racemic – that is equimolar mixtures of both enantiomers, which reflects the difficulty in the practical synthesis of single-enantiomeric compounds (Borman, 1990). In 2000, the worldwide sales of single-enantiomer compound reached 123 billion $ and in 2001, single enantiomer pharaeceuticals accounted for 36% of the

US $ 410 billion drug industry (Stinson, 2001). The demand for chiral chemicals has been growing at an average rate of 9.4% with $ 15.1 billion per year Thus gaining access to enantiomerically pure compounds in the development of pharmaceuticals, agrochemicals, and flavors is a very significant endeavor.

2.2. Routes to enantiomerically pure products

There are several ways to obtain enantiomerically pure compounds, of which resolution of a racemic mixture, synthesis with compounds from the chirality pool, and asymmetric synthesis starting from prochiral substrates (Figure2.1)

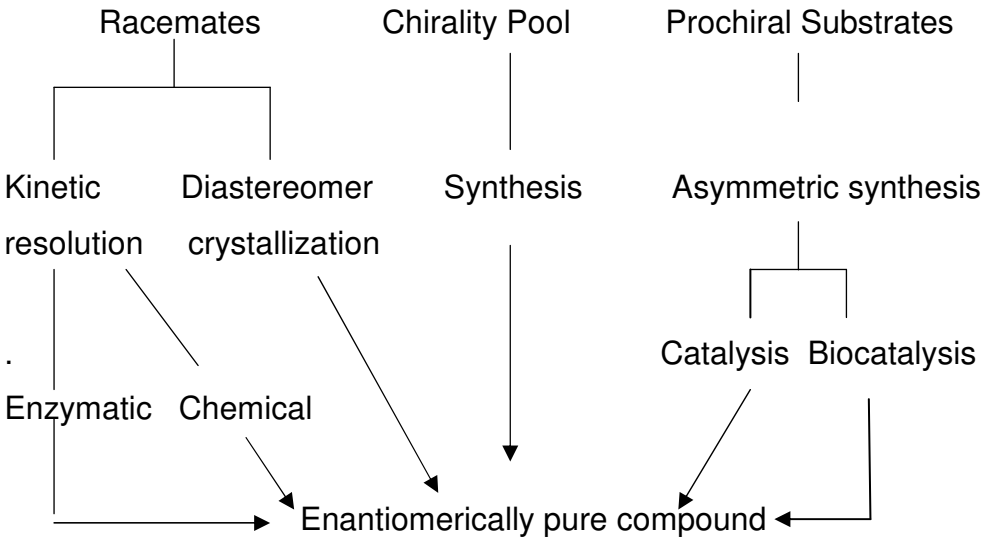


Figure 2.1. Routes to enantiomerically pure compounds.

Although significant advances in other routes to obtain enantiomerically pure compounds have been reported, the 'classical' resolution of racemates by diastereomeric crystallization still constitutes the most important method in industry. Separation is usually achieved through crystallization of diastereomers formed by derivatization of the mixture of enantiomers with a single enantiomer of another compound (Vries et al. 1998). However, the maximum yield of one enantiomer is 50%, unless the unwanted enantiomer can be recycled. Naturally occurring chiral compound (referred to as the chirality pool) can be used as starting materials for enantiomerically pure compounds or may be employed as

enantioselective agents (catalysts or ligands) in organic synthesis The lack of availability of both enantiomers of most natural compounds often is a limiting factor. Natural products very often have high enantiomeric purity, no further enrichment is usually necessary (Blaser, 2003).

In the early days, synthesis of enantiomerically pure compounds from prochiral precursors was considered possible only by using biochemical methods. Although powerful, those methods using enzymes, cell cultures, or (living) microorganisms are in most cases substrate specific. Organic synthesis, on the other hand, has revealed a variety of versatile stereoselective reactions that complement biological processes .

The 2001 Nobel Prize for Chemistry was awarded to William S. Knowles and Ryoji Noyori for their work on catalysed asymmetric hydrogenation reactions and to K. Barry Sharpless for the development of catalysed asymmetric oxidation. But here key reactions, allowing the synthesis of many more molecules of industrial and medical importance in pure enantiomeric form, such as the antibiotic levofloxacin and glycidol, a precursor of beta-blockers, which are widely used as cardiovascular drugs (Denmark and Fu, 2003).

Figure 2.2 shows a general principle of asymmetric catalysis which provides an ideal way for multiplying molecular chirality. A small amount of a well-designed chiral catalyst can combine A and B, which produces the chiral AB compound stereoselectively in a large quantity (Noyori, 2002).

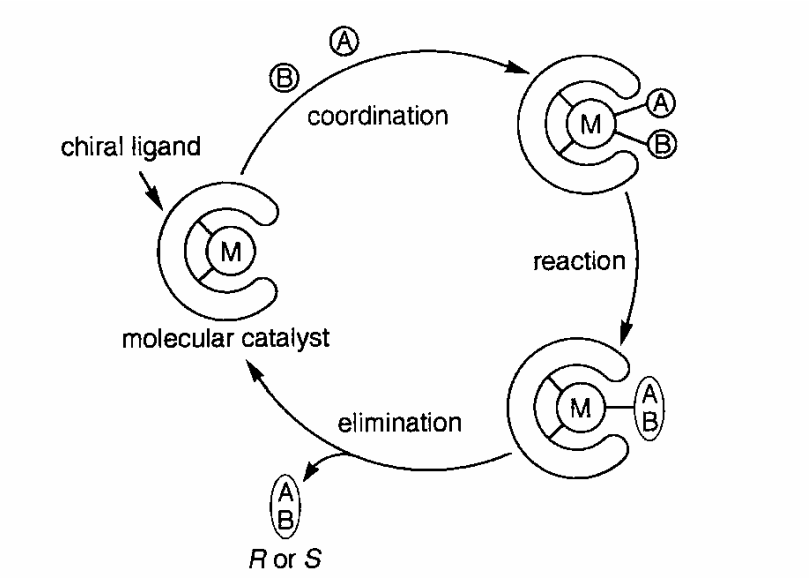


Figure 2.2. A general principle of asymmetric catalysis with chiral organometallic molecular catalysts.

2.3. Asymmetric Carbon-Carbon Bond Forming Reactions by Nucleophilic Addition to Carbonyl Groups

The carbon-carbon bond forming reaction, together with oxidation, reduction, and functional group transformation, is one of the most fundamental operation for constructing organic molecules. The most straightforward and commonly encountered example of this type of process is the addition of non-chiral nucleophiles to chiral aldehydes and ketones.

In the simplest case, addition of an achiral nucleophile to a prochiral aldehyde or ketone could give rise to two diastereoisomers from addition to either the lower or upper face of the carbonyl group **1** and **2** which are formed respectively. If the nucleophile is such that two chiral centers are produced in the reaction, then there are four possible diastereoisomeric products **3**, **4**, **5** and **6** (Figure 2.3). Product **3** and **4** arise from addition of the nucleophile on the upper face of the carbonyl group. Stereoisomers **5** and **6** represent the attack of the nucleophile on the lower face of the carbonyl group.

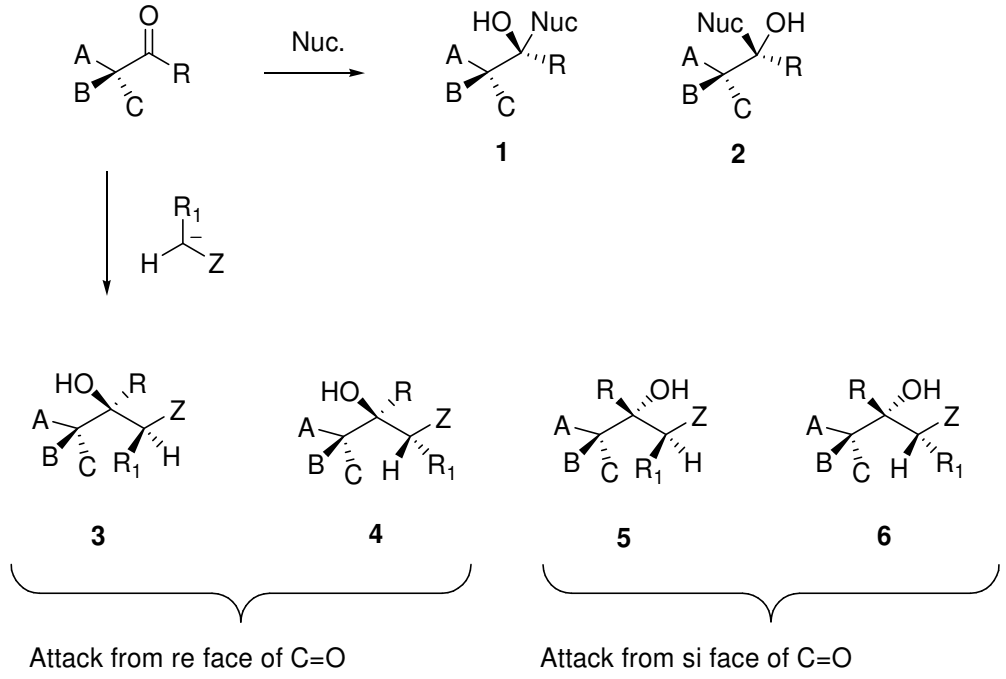


Figure 2.3. Addition of an achiral nucleophile to a prochiral aldehyde or ketone

Lewis acids such as BF_3, $AlCl_3$, MgX_2, $ZnCl_2$, $SnCl_4$, $TiCl_4$, $Ti(O\text{-}i\text{-}Pr)_4$, $Cu(OTf)_2$ and $Sc(OTf)_3$ have been used for a variety of carbon-carbon bond forming reactions in organic synthesis. Most often stoichiometric amounts of Lewis acids are employed. Undoubtedly, a most efficient way to create new carbon-carbon bonds enantioselectively would be to use catalytic amounts of a chiral Lewis acid in these reactions. In all cases, the complexation of a Lewis acid with a carbonyl or imine functionality would activate system. In the most cases chiral transition metal complexes, often prepared in situ, are employed as the catalysts. In the following, selected examples of successful catalytic asymmetric carbon-carbon bond formations will be highlighted.

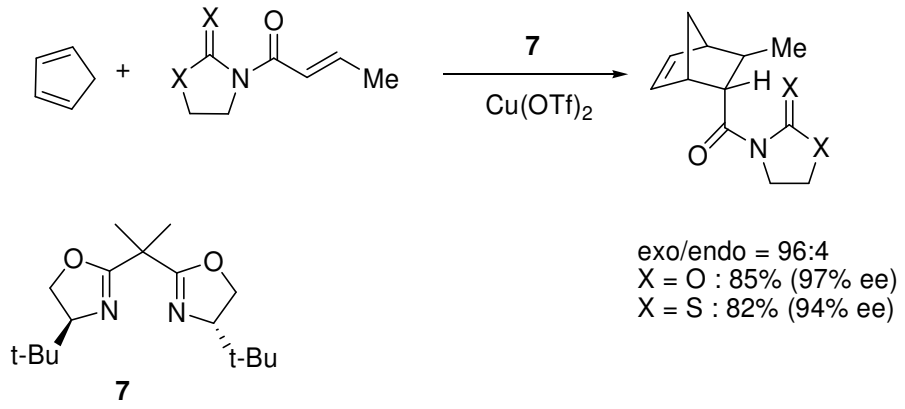
2.3.1. Asymmetric carbon-carbon bond formations

Asymmetric carbon-carbon bond formation has been one of the studied fields in synthetic organic chemistry over recent years. Some of them are summarized below.

2.3.1.1. Asymmetric Diels-Alder reactions

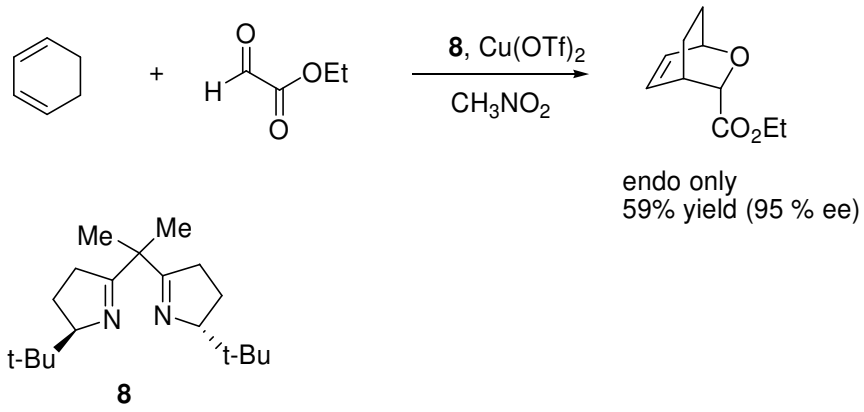
The Diels-Alder reaction is a classical reaction in organic synthesis and especially the very recent progress in the design of chiral Lewis acids has led to the development of effective catalysts for asymmetric Diels-Alder reactions. Several research groups have developed chiral Lewis acids by using various chiral ligands for asymmetric Diels-Alder reactions.

Evans (1993) designed C_2-symmetric bis(oxazoline)/Cu(II) complexes derived from chiral bis(oxazoline) **7** and $Cu(OTf)_2$, and applied them to asymmetric cycloadditions of acryloyl oxazolidinones and thiazolidine-2-thione analogues . (Scheme 2.1)



Scheme 2.1. Diels-Alder reaction catalysed by $Cu(OTf)_2$

Several chiral Lewis acid catalysts have been used for asymmetric hetero Diels-Alder reactions. Jϕrgensen (1996) applied chiral bis(oxazoline) **8**/Cu (II) catalyst to asymmetric hetero Diels-Alder reaction of glyoxylates with dienes. In this reaction, the use of polar solvents such as nitromethane and 2-nitropropane led to a signficant improvement of the catalytic efficiency (Scheme 2.2).



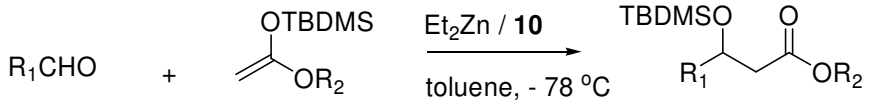
Scheme 2.2. Diels-Alder reaction catalysed by $Cu(OTf)_2$

2.3.1.2. Asymmetric aldol reactions

The aldol reaction is one of the most important organic reactions because it is a carbon-carbon bond forming reaction, which produces highly functionalized compounds with a pair of newly generated chiral centers.

In 1981, Masamune et al. and Evans et al. independently reported extremely stereoselective asymmetric aldol reactions by means of chiral boron enolates.

Mukaiyama' s group (1990) reported the catalytic asymmetric aldol reaction of ketene silyl acetals **9** promoted by chiral zinc complex. These complexes were prepared in situ form diethylzinc and sulfonamide ligand **10**, derived from optically amino acids, in a ratio of 1:2 . Although the enantioselectivities in the reaction with benzaldehyde and cyclohexanecarboxaldehyde were low moderate, high enantioselectivities of around 90% ee are obtainable with choral and bromal (Scheme 2.3).



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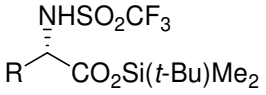


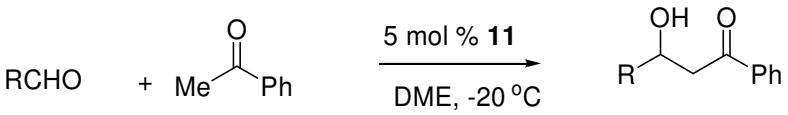
10

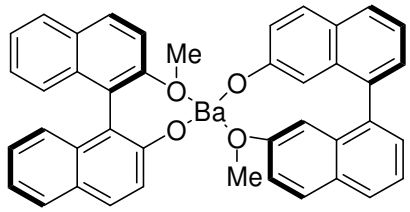
10a: R=$PhCH_2$
10b: R=*i*-Pr

entry	R^1	R^2	L	yield (%)	ee (%)
1	Ph	Et	**10a**	79	60
2	c-C_6H_{11}	Bn	**10a**	76	23
3	CCl_3	Bn	**10a**	70	72
4	CCl_3	Bn	**10b**	61	88
5	CBr_3	Bn	**10b**	66	93

Scheme 2.3. The catalytic asymmetric aldol reaction of ketene silyl acetals **9** promoted by chiral zinc complex

Shibasaki et al. (1998) examined catalysis of a complex, prepared from mono *O*-methyl ether of BINOL **11** and Ba(O-*i*-Pr)$_2$ in dimethoxyethane (DME). This complex is suggested to catalyze the addition of acetophenone to aldehydes, giving adducts in 77-99% yield and up to 70% ee (Scheme 2.4).



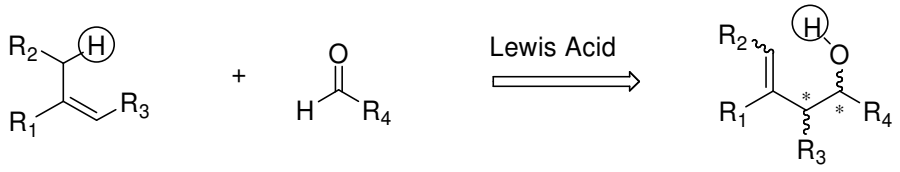


11

Scheme 2.4. The catalytic asymmetric aldol reaction of acetopenone to aldehydes

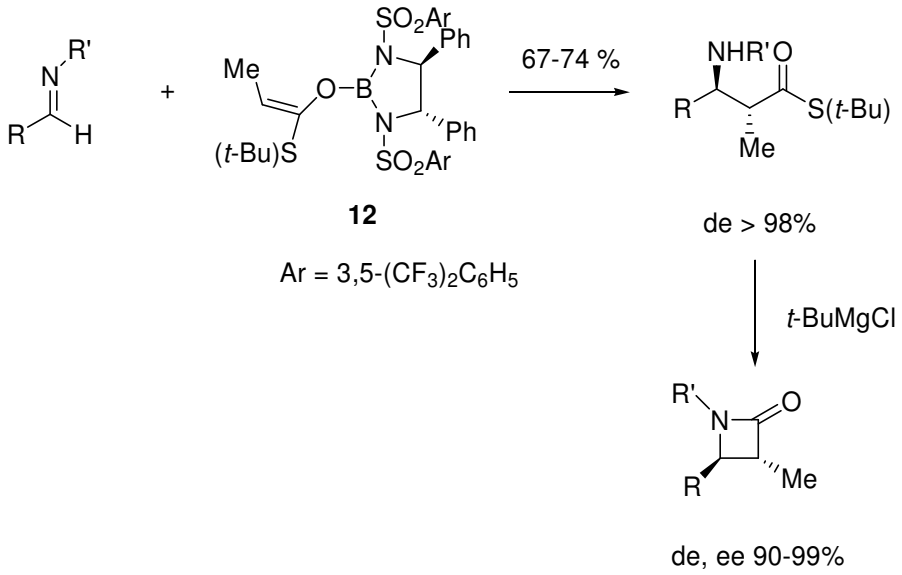
2.3.1.3. Asymmetric ene reactions

The class of ene reactions which involves a carbonyl compound as the enophile and what are refer to as the carbonyl-ene reaction, constitutes a useful synthetic method for the stereocontrolled construction of carbon skeleton using either stoichiometric or catalytic amount of various Lewis acids (Scheme 2.5)



Scheme 2.5. Carbonyl-ene reaction catalyzed by chiral Lewis acids.

The reactions of imines with ester enolates provide to β-lactams. Because of the importance of this class of antibiotics, much study has been devoted to this type of reaction (Maruoka et al., 1988). The prochiral imines and boron enolates of thiol esters Z-**12** designed by Corey et al. (1991) react at -78 °C, leading highly selectivity to *anti*-β-aminothioesters (Scheme 2.6)

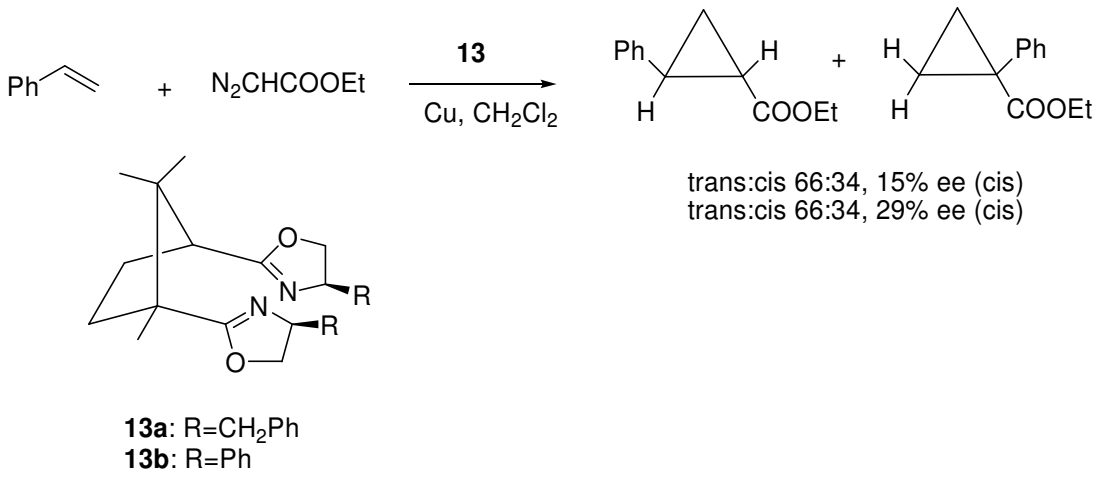


Scheme 2.6. Carbonyl-ene reaction of imines with ester enolates

2.3.1.4. Asymmetric cyclopropanation

An early example of metal-based homogeneous asymmetric catalysis dates from 1966. It involves an asymmetric cyclopropanation catalysed by a complex of copper (II) and a Schiff base derived from salicylaldehyde and α-phenylethyl amine.

Recently, novel bis(oxazoline) ligands from camphoric acids (Scheme 2.7) were applied Cu-catalyzed asymmetric cyclopropanation of styrene and diazoacetate. The reaction was carried out in CH_2Cl_2 at room temperature in the presence of 5 mol% Cu-bis(oxazoline) **13** complex. When ethyl diazoacetate was used the carbene source, the *cis*- and *trans*-cyclopropanecarboxylates were obtained with 18% ee and 15% ee using **13a**. In the presence of **13b**, the best result was obtained with 29% ee for *cis* product (You et al., 2005).

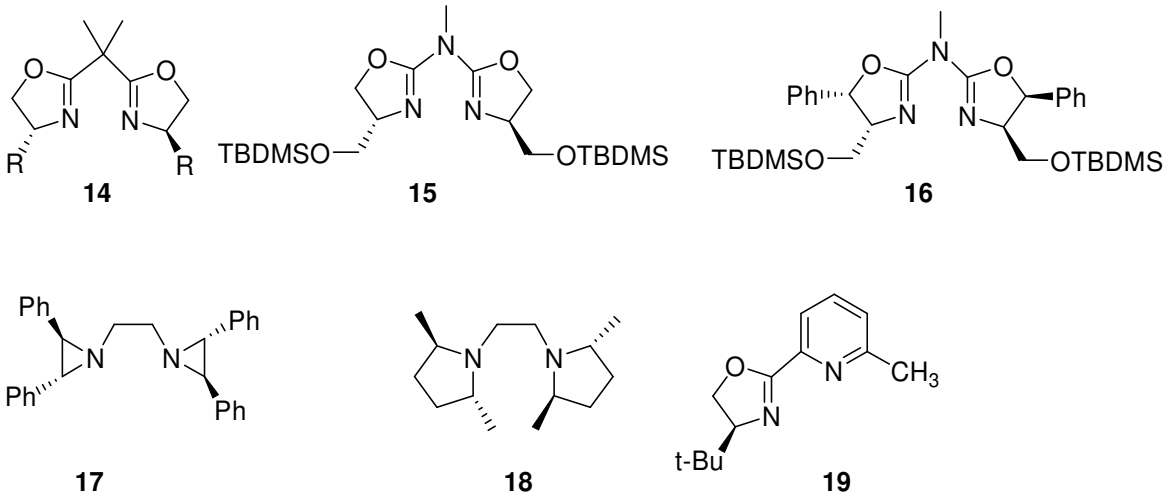


Scheme 2.7. Asymmetric cyclopropanation reaction

2.3.1.5. Asymmetric allylic alkylation

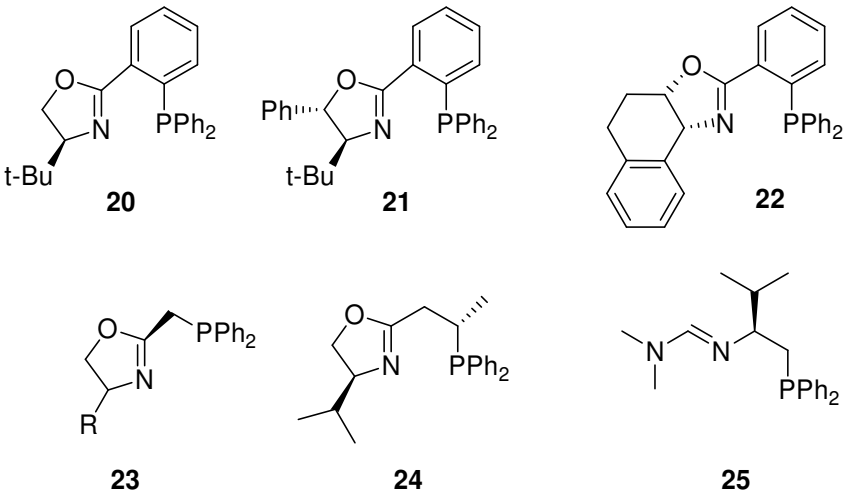
Since the first examples of inducing asymmetry at the allylic fragment with palladium catalyst in 1977 (Trost and Strege, 1977), the asymmetric allylic alkylation reaction has undergone a revolutionary development in recent years to establish its synthetic viability. New ligands of various types have been

synthesized and tested in reactions involving a wide range of substrates and nucleophiles. Scheme 2.8 and 2.9 show a selection of some ligands (**14**-**25**) that have been successfully used in the palladium-catalyzed asymmetric allylic alkylation reaction.



14 **15** **16** **17** **18** **19**

Scheme 2.8. Chiral dinitrogen ligands

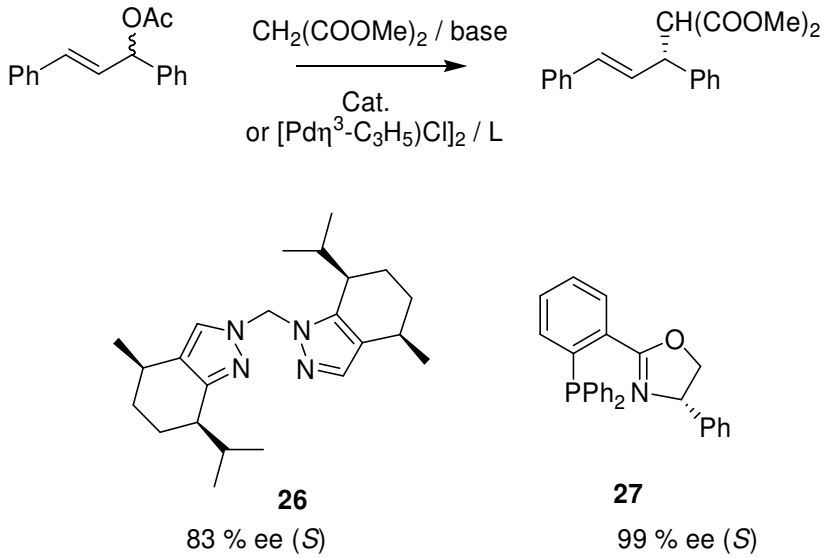


20 **21** **22** **23** **24** **25**

Scheme 2.9. Chiral P,N-chelate ligands

Highly enantioselective catalysts containing bis(dihydrooxazole), or 5-azasemicorrin ligands were used by Pfaltz et al. (1991). Under conditions where the nucleophile is generated in situ from dimethylmalonate, N,O-bis(trimethylsilyl)acetamide, and a cocatalytic amount of KOAc in CH_2Cl_2,

alkylation products were obtained in very high optical yields (up to 95% ee). Pfaltz and von Matt (1993) and Helmchen and Sprinz (1993), independently, developed (phosphinoaryl)dihydrooxazoles as P,N-ligands **26**, **27** which were shown to give more active highly selective catalysts in this reaction (Scheme 2.10).



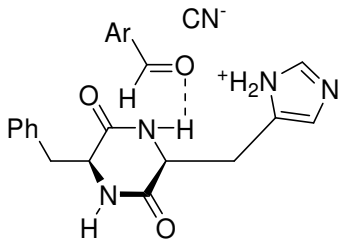
26
83 % ee (*S*)

27
99 % ee (*S*)

Scheme 2.10. Asymmetric allylic alkylation catalyzed by Pd complexes containing chelating P,N-ligands.

2.3.1.6. Hydrocyanation, silylcyanation

Asymmetric hydro- or silylcyanation of aldehydes can take place either with HCN or Me_3SiCN in the presence of a chiral catalyst. The reaction of HCN with aldehydes in the presence of a cyclic dipeptide, cyclo-[(*S*)-phenylalanino-(*S*)-histidine] **28** (or its (*R*,*R*)-enantiomer), promotes the highly enantioselective hydrocyanation of aromatic aldehydes (Scheme 2.11). This reaction may occur through an aldehyde-peptide complex in which the carbonyl group is activated by hydrogen-bonding and steric hindrance is minimized. The approach of the CN anion is directed by the histidine residue. Similar hydrosilylation of aliphatic aldehydes occurs with modest enantiomeric selectivity.



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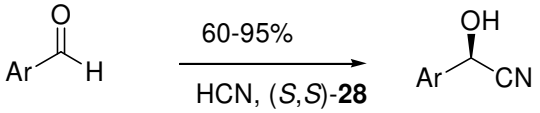
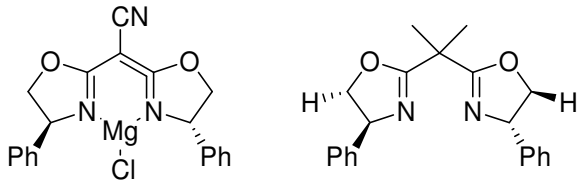


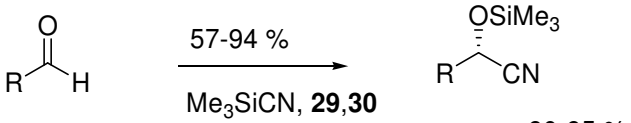
Ar= Ph, 3-$MeOC_6H_4$, 4-MeC_6H_4, 2-Np, 4-$PhOC_6H_4$

Scheme 2.11. Enantioselective hydrocyanation of aromatic aldehydes

Corey and Wang (1993) introduced asymmetric trimethylsilylcyanations in the presence of two oxazoline catalysts, **29** and **30** as shown in Scheme 2.12. High selectivities are observed in hydrogenations of aliphatic aldehydes at -78 °C, but unsaturated and aromatic aldehydes give lower selectivities. Aluminium complexes are less useful.



29 **30**



ee 90-95 %

R = n-C_6H_{13}, Et_2CH, c-C_6H11, tert-Bu

Scheme 2.12. Enantioselective silycyanantion of aliphatic aldehydes

2.4. Enantioselective Addition of Dialkyzinc to Aldehydes

Chirality is a major phenomenone in nature, and molecular asymmetry in particular is playing a crucial role in science and technology. A variety as significiant biological functions emerge through molecular recognition, which requires strict matching of chirality. Nonracemic molecules will also contribute to the creation of advanced materials possessing unique physical properties. Accordingly catalysis using chiral metal complexes, among others, provides a general, powerful tool in this context (Noyori and Kitamura, 1991).

The carbon-carbon bond forming reaction is one of the most fundamental operations for constructing organic molecules. Addition of organometallic reagents to carbonyl compounds provides a reliable way to form alcoholic products. Enantioselective addition of organometallic reagents to aldehydes affords optically active secondary alcohols. This reaction is the one of the most fundamental asymmetric reactions. The optically active secondary alcohols are components of many naturally occurring compounds, biologically active compounds, and materials such as liquid crystals. They are also important as synthetic intermediates of various functionalities such as halide, amine, ester, ether, etc. (Soai and Niwa, 1992a).

Organometallic chemistry dates back to the discovery of organozinc compounds by Frankland in 1849 (Erdik, 1981). However, the significance of organozinc chemistry remained underestimated for years. The Reformatsky reaction and Simmons-Smith reaction used zinc metal but, in simple alkylation to carbonyl compounds, organozinc compounds were replaced by Grignard reagents (Noyori and Kitamura, 1991) and organolithium compounds (Gilman et al.,1939). Recently, the chemistry of organoboron, -aluminium, -titanium, -lanthanide compounds has been developed. The enantioselective version of the reaction between organometallic reagents and carbonyl compounds, which leads to optically active alcohol, is desirable because of its general synthetic importance.
A non-racemic, chiral environment can be introduced into organometallic compounds in two ways, (Scheme 2.13).

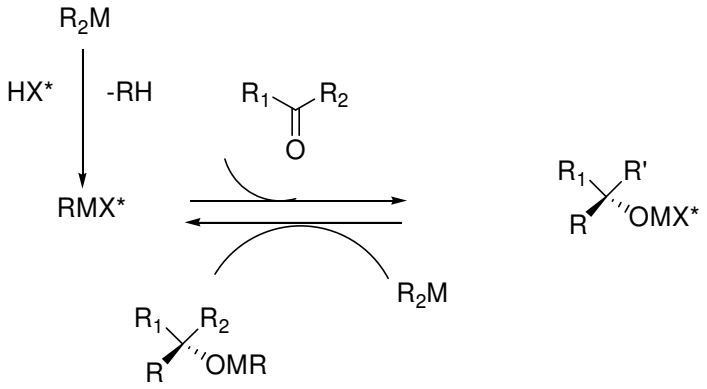
Scheme 2.13. Enantioselective addition of organometallic reagents to carbonyl compounds

One is the coordination of aprotic chiral solvents or complexing agents to the metallic center. The other is the modification of the organometallic reagent by protic chiral ancillaries, such as alcohols or amines, to give organometallic alkoxides or amides, respectively (Noyori et al., 1990). The organometallic compounds are amphiphillic in nature ; the nucleophilicity of the carbon moiety and Lewis acidity of the metallic center cooperate in the alkyl transfer reaction. Thus chiral ligand perturb the structure and stability of the transition state in many ways (Noyori and Kitamura, 1991).

In the last two decays, a number of highly enantioselective alkylation reactions of carbonyl compounds have been developed by proper combination of organometallic reagents and well-designed chiral ancillaries. Many important optically active compounds have been synthesized using various kind of chiral compounds as chiral catalysts for the enantioselective addition of organozinc reagents to aldehydes.

2.5. Catalytic Enantioselective Alkylation

Neutral or anionic heteroatom auxiliaries affect the reactivity of organometallic compounds. The addition of a chiral auxiliary could enhance the reactivity and at the same time control the stereochemical outcome of the reaction. Scheme 2.14 illustrates the possible pathway of the catalytic enantioselective alkylation of an organometallic reagent R_2M to a prochiral carbonyl substrate catalyzed by a protic chiral auxiliary, HX*.



Scheme 2.14. Enantioselective alkylation catalysed by protic auxiliary HX*

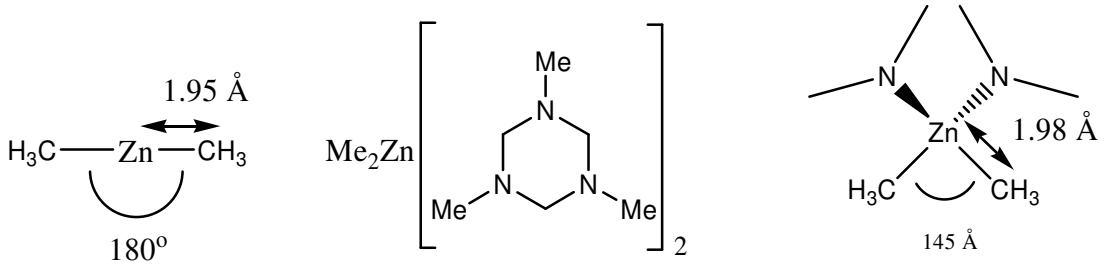
In order to obtain a high degree of enantioselection, the chiral anionic ligand X* must possess a suitable three-dimensional structure that differentiates between the diastereomeric transition states of the alkyl delivery step. First, the rate of the alkylation by the chiral modified organometallic compounds or reagent should substantially exceed that of the reaction of the original achiral reagent R_2M. Second, ligand X* must be readily detached from the initially formed metal alkoxide by the action of the alkyl donor or carbonyl substrate to establish the catalytic cycle. These considerations also apply to the reaction using aprotic modifiers (Noyori and Kitamura, 1991).

2.6. Origin of the Catalyst Efficiency

At least three factors are suitably coupled to achieve the ideal catalytic system :

The first is the structure/reactivity profile of organozinc compounds. Monomeric dialkylzinc compounds having an sp hybridized, linear geometry at Zn with a bond length 1.95 Å are inert to simple carbonyl compounds, because the alkyl-metal bond is rather nonpolar. However, the bond polarity can be enhanced by creating a bent geometry, where the Zn atom uses orbitals having a higher p character. When dimethylzinc makes a complex with a chiral ligand, the coordination chemistry of the Zn atom changes to the tetrahedral with a 145° carbon-zinc-carbon bond angle. The bond length between the zinc and carbon atoms becomes longer (1.98 Å). This means that the bond energy of the zinc and carbon bond

decreases and that the nucleophilicity of the methyl group of the dimethylzinc increases, (Scheme 2.15) (Noyori et al., 1989).



Scheme 2.15. Structure of dimethylzinc and its adduct with 1,3,5-trimethylhexahydro-1,3,5-triazine

The second important factor is the tendency of the alkyl zincoxide product to form the cubic tetrameric structure, which is removed from the reaction system. The tetramer neither alkylates aldehydes nor acts as a catalyst. (Noyori and Kitamura, 1991). The Zn alkoxides, which are soluble in hydrocarbon, do not bind to the chiral ligand (Itsuno and Féchet, 1987).

Third, the use of sterically congested chiral auxiliaries is essential for obtaining high reactivity.

2.7. Chiral Catalysts

A catalyst can effect both the reactivity and selectivity of organic transformations and afford the possibility of conducting organic synthesis in a highly controlled manner. Asymmetric synthesis of optically active compound via the intermolecular asymmetry/chirality transformations between a chiral catalyst and reactant are an important fascinating current topic in chemistry. Most of these are stereoselective organotransition-metal-mediated reactions. Therefore, the structures and reactivities are the dominant factors. With regard to the structure of the organometallic species, the geometry, hybridized state, polarity of the metal-ligand bond and vacant orbitals of the central metal all contribute to the complexing process of the organometallic fragment with chiral ligands. On the other hand,

chiral ligands take a more important role in the course of the asymmetric induction. So, they must contain appropriate electronegative donors so as to exhibit appropriate complexing capacities to accomplish the induction. Some well-studied chiral ligands which have appeared in the literature can be categorised as follows according to their donor atoms:

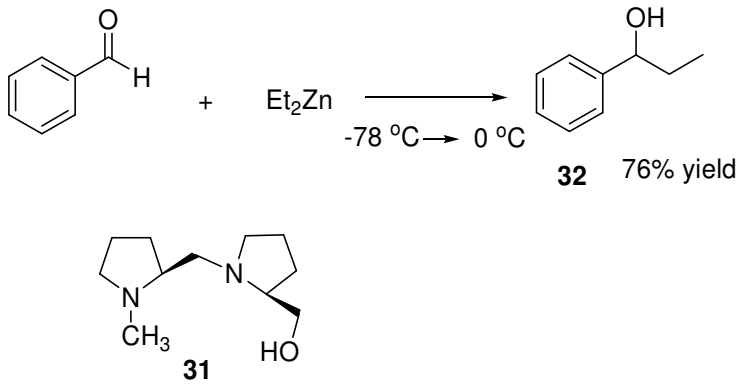
1. O-O class (dialcohols, diethers, and crown ethers)
2. N-N class (diamines, diamides, disulfonamides)
3. P-P class (diphosphine)
4. N-O class (β-amino alcohols, β-amino ethers)
5. Mixed class (class 1-4)
6. Others (such as, chiral complex where the stereogenic center is the metal itself) (ShengJian et al., 1992).

We can divide the chiral catalysts, that are used in the enantioselective addition of dialkylzincs to aldehydes, in to two main groups : homogeneus chiral catalysts and heterogeneous chiral catalysts.

2.7.1. Homogeneous Chiral Catalysts

2.7.1.1. Dialkylzinc additions to aldehydes catalyzed by chiral amino alcohol

The first clean nucleophilic addition of diethylzinc to benzaldehyde was reported by Mukaiyama et al. (1979) in the presence of *β*-amino alcohols **31** derived from (*S*)-proline (Scheme 2.16)

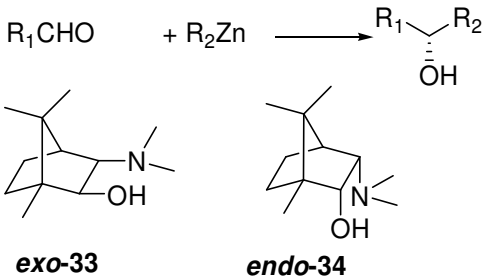


Scheme 2.16. Addition of diethylzinc to benzaldehyde using catalyst **31**

Carbon-carbon bond forming reaction is accelerated by the *β*-amino alcohol with 76% yield. No asymmetric induction was reported. But the formation of a carbon-carbon bond from dialkylzinc and aldehyde using *β*-amino alcohol suggests the possibility of asymmetric induction using the appropriate chiral *β*-amino alcohol Oguni and Omi (1984) used (*S*)-leucinol as a chiral catalyst and first obtained optically active alcohol with moderate optical purity (49% ee).

2.7.1.1.1. *β*-Tertiary amino alcohol

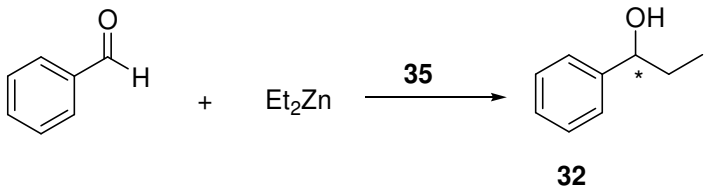
In 1986, Noyori et al. reported for the first a highly enantioselective alkylation catalyzed by (-)-3-*exo*-(dimethylamino)isoborneol ((-)-DAIB **33**), a camphor-derived, sterically congested, chiral *β*-dialkylamino alcohol (Scheme 2.17).



Scheme 2.17. Addition of diethylzinc to benzaldehyde using catalysts **33** and **34**

In the presence of 2 mol% of (-)-DAIB **33**, for example, the reaction of benzaldehyde and diethylzinc proceeds rapidly in toluene at 0 °C, and after 6 h the alcohol (*S*)-**32** is obtained in 97% yield with 98% ee. With the isomer of **33**, (+)-3-*endo*-(dimethylamino)isoborneol (**34**), the *R* alcohol in 95% ee is obtained. The catalyst is also effective for other aromatic aldehydes but the enantioselectivity for the aliphatic aldehydes is moderate (61% ee) (Noyori et al., 1986).

Yaozhong et al. (1992) found that the amino alcohol **35** (Scheme 2.18) and its enantiomer catalyzed the diethylzinc addition to benzaldehyde to give (*S*)-1-phenylpropanol or (*R*)-1-phenylpropanol with 97% ee.



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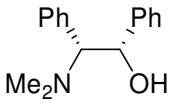
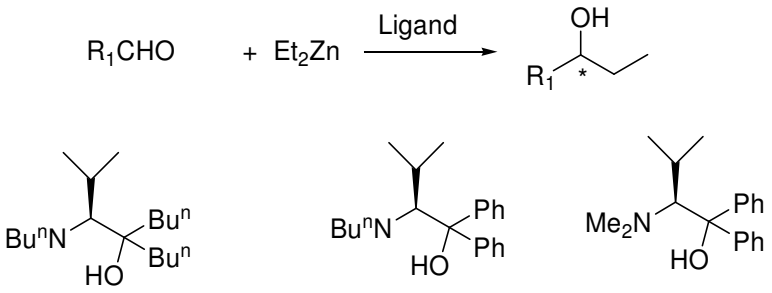


35

Scheme 2.18. Addition of diethylzinc to benzaldehyde using catalysts **35**

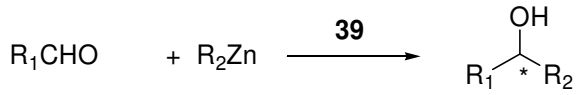
Luche et al. (1994, 1995) prepared the optically active β-amino alcohol **36**-**38** from L-valine and studied their use in diethylzinc additions. Ligand **36** with flexible butyl groups on both the nitrogen and hydroxyl carbon showed much better enantioselectivity (97% ee) than ligand **37** and **38** (2-75%) that contain rigid diphenyl substituents on the hydroxyl carbon. In the presence of 10 mol% of **36**, diethylzinc added to certain aliphatic and aromatic aldehydes to give the corresponding *R* alcohols with 82-97% ee (Scheme 2.19).

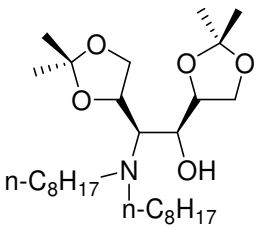


36 **37** **38**

Scheme 2.19. Addition of diethylzinc to benzaldehyde using catalysts **36**-**38**

Cho and Chun (1998) demonstrated that chiral β-dialkylamino alcohol **39** derived from D-mannitol are enantioselective catalysts in the addition of diethylzinc to both aliphatic and aromatic aldehydes; optically active secondary alcohols is up to 94% ee can be obtained in high yields (Scheme 2.20).

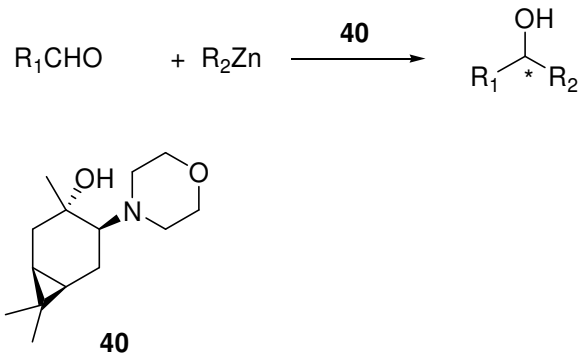




39

Scheme 2.20. Addition of diethylzinc to benzaldehyde using catalysts **39**

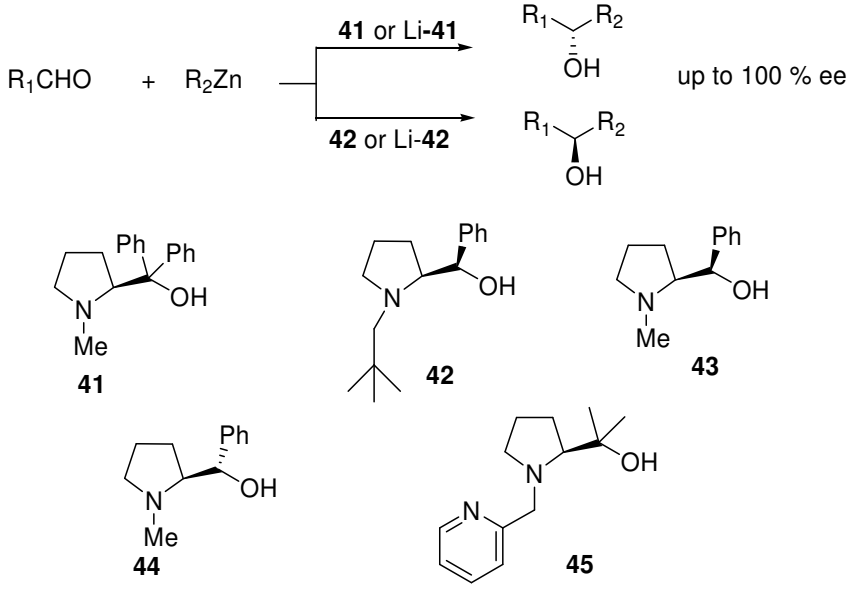
A (+)-3-carene derived aminoalcohol **40** was successfully used as a chiral ligand in the catalytic enantioselective 1,2-addition by Joshi and Malhotra (2003). They reported that temperature has a detrimental effect on the ee. A high ee and yield was obtained at room temperature. Interestingly, however, low conversion and low ee were observed at lower temperature. For most of the aldehydes studied a moderate to high enantioselectivity (72-98%) was obtained. They demonstrated the effective use of a sterically hindered, bicyclic aminoalcohol as a chiral catalyst, in the enantioselective addition of diethylzinc to various aldehydes (Scheme 2.21).



Scheme 2.21. Addition of diethylzinc to benzaldehyde using catalysts **40**

2.7.1.1.2. Proline derivatives

Soai et al. (1987a) synthesized a series of chiral pyrrolidinylmethanols **41**-**44** stereoselectively from (*S*)-proline. Optically active secondary alcohols (*R* and *S* enantiomers, respectively) in up to 100% ee were obtained in high yield from enantioselective addition of dialkylzincs to aldehydes catalyzed by 2-5 mol% of chiral pyrrolidinylmethanols (Scheme 2.22). The catalyst is also effective for aliphatic aldehydes (91% ee).



Scheme 2.22. Addition of diethylzinc to benzaldehyde using catalysts **41**-**45**

The sense of asymmetric induction and the degree of enantioselectivities were highly dependent on the structure of the catalyst. For instance, (*S*)-(+)-**41** catalyzes the addition of diethylzinc to benzaldehyde to afford (*S*)-1-phenylpropanol with 97% ee in 100% yield. On the other hand, (1*R*,2*S*)-(-)-phenyl(1-neopentylpyrrolidin-2-yl)methanol (**42**) catalyzes the reaction to afford *R* alcohols with 100% ee (Scheme 2.22).

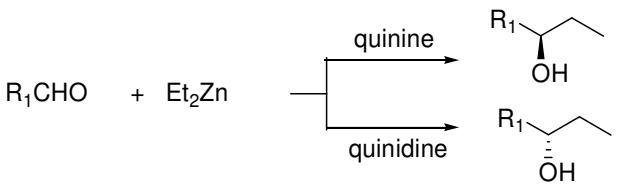
When lithium alkoxide of chiral (*S*)-DPMPM-**41** is used in the reaction of aromatic aldehydes, better enantioselectivities (up to 100% ee) are observed than when (*S*)-DPMPM-**41** itself is used. This situation is attributed to the stronger hard acid character of the lithium cation than zinc. Lithium cation may more easily coordinate with the oxygen atom, which is a hard base, of the approaching aldehyde than zinc does. Thus, this coordination may restrict the number of the possible stereochemical outcome of the reaction to obtain high enantioselectivity.

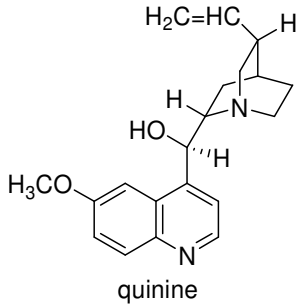
In the presence of 2 mol% **43** and **44**, optically active alcohols of up to 72% ee were obtained from enantioselective addition of diethylzinc to aldehydes (Soai, 1987a).

Chelucci et al. (1990) reported that the enantioselective addition of diethylzinc to aldehydes using prolinol derivative **45** as achiral catalyst. Lithium alkoxide of **45** catalyzed the reaction with benzaldeyde to afford *R* alcohol with 60% ee.

2.7.1.1.3. Cinchona alkoloids

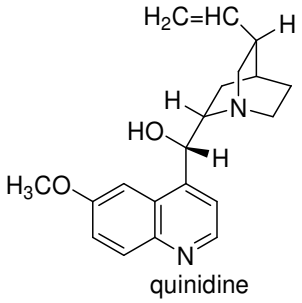
Smaardijk and Wynberg (1987) reported the enantioselective addition of diethylzinc to aromatic aldehydes using cinchona alkoloids as chiral catalysts, (Scheme 2.23)





quinine

46



quinidine

47

Scheme 2.23. Addition of diethylzinc to benzaldehyde using cinchona alkoloids as chiral catalysts **46** and **47**

Quinine catalyzes the reaction with benzaldehyde to afford (*R*)-1-phenylpropanol with 68% ee in 92% yield. When 2-ethoxybenzaldeyde is employed, the ee of the obtained alcohol reached 92%. The hydroxyl group of quinine is essential for this reaction. Since the same reaction with acetylquinine gives only 14% ee. On the other hand, quinidine affords (*S*)-1-phenylpropanol with 48% ee.

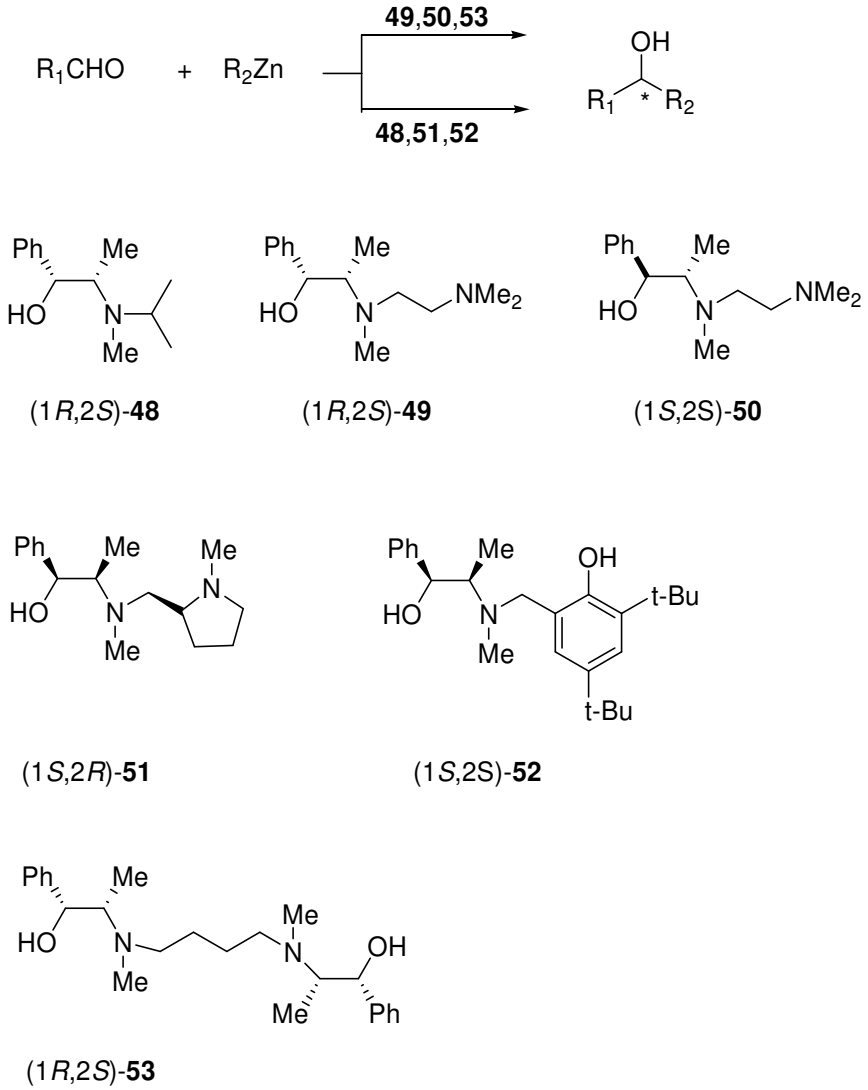
The temperature effect on the enantioselective addition of diethylzinc to benzaldehyde using quinine as chiral catalyst was worked by Buono et al. (1987). They reported that, unlike many other asymmetric syntheses, the reaction run for a short reaction time at elevated temperature (100 °C) affords alcohol with higher ee (73% ee) than that run at room temperature (64% ee).

2.7.1.1.4. Ephedrine derivatives

One of the advantages of the use of ephedrine as a chiral source in asymmetric synthesis is that both enantiomers are readily available. Thus both enantiomers of the chiral catalysts can be derived from ephedrine.

Chaloner et al. (1987) reported that (1*R*,2*S*)-*N*-isopropylephedrine (**48**), which is a chiral ligand for addition of diethylzinc to benzaldehyde to afford *R* alcohol with 80% ee in 72% chemical yield (Scheme 2.24). This is also effective for other aromatic aldehydes but no optical yield was reported for aliphatic ones. In the addition to aliphatic cyclohexanecarbaldehyde, only the racemic alcohol was obtained in 40% yield.

Chaloner and Langadianou (1990) reported also that, enantioselectivies depend on the amount of the diethylzinc. When an excess amount of diethylzinc was used in proportions to aldehydes, enantioselectivity increases. Because when dialkyzinc adds to aldehyde, alkyzinc alkoxide is formed in situ. This alkylzinc alkoxide may also form a complex with the chiral catalyst and may reduce the enantioselectivity of the chiral catalyst. When an excess amount of dialkylzinc is present, an enantioselective chiral complex may be more easily formed between dialkylzinc and the chiral catalyst.



Scheme 2.24. Addition of diethylzinc to benzaldehyde using ephedrine derivatives as chiral catalysts **48**-**53**

Corey and Hannon (1987) reported the enantioselective addition of diethylzinc to aldehyde using lithium salt of (1*R*,2*S*)-*N*-[2-(dimethylamino)ethyl]ephedrine (**49**) as chiral catalyst to afford (*R*)-1-phenylpropanol with 90% ee. When (1*S*,2*S*)-pseudoephedrine (**50**) was used as chiral catalyst , (*S*)-1-phenylpropanol with 91% ee was obtained. The reversal of the enantioselectivity shows that the enantioselectivity is dependent on the configuration of the alcohol part of the chiral catalyst.

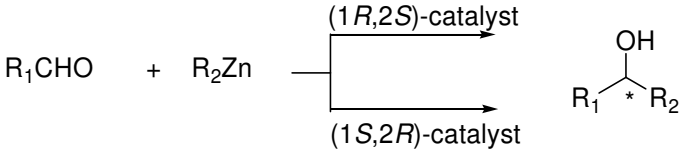
When the lithium salt of (*S*)-*N*-[1-methylpyrrolidin-2-yl)methyl] (**51**) derivative of (1*S*,2*R*)-ephedrine was employed as a chiral catalyst, (*S*)-1-phenylpropanol with

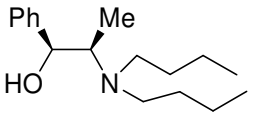
95% ee was obtained. Chiral phenol **52** derived from 2,4-di-*tert*-butylphenol and (1*S*,2*S*)-pseudoephedrine also catalyzed the addition of diethylzinc to benzaldehyde to afford (*S*)-1-phenylpropanol with 86% ee. Chiral diaminodiol **53**, derived from 2 mol of (1*R*,2*S*)-ephedrine with a trimethylene chain, has a C_2-symmetry axis. The dilithium salt of **53** catalyzes the ethylation of benzaldehyde to afford *R* alcohol with 85% ee in 59% yield.

2.7.1.1.5. Norephedrine derivatives

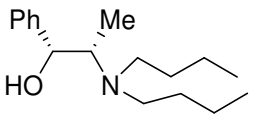
The chiral *N*,*N*-dialkylnorephedrine catalyzed the addition of dialkylzinc to aliphatic and aromatic aldehydes to afford optically active secondary alcohols with high enantioselectivity (Scheme 2.25) (Soai et al., 1987b and 1994b).

As shown in Scheme 2.25, these ligands, **54**-**57**, catalyzed the addition of dialkylzinc to aromatic (84% ee to 95% ee) and aliphatic aldehydes (53% ee to 100% ee). The optical purity of the product increases as the chain length of the *N*-alkyl substituents increases. (1*S*,2*R*)-*N*,*N*-Diallylnorephedrine (**56**) and (1*S*,2*R*)-1-phenyl-2-(1-pyrrolidinyl)propan-1-ol (**57**) were found to be the most effective catalyst (Soai et al., 1991a).

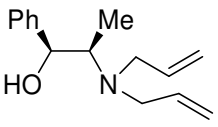




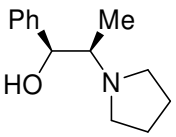
(1S,2R)-(-)-DBNE **54**



(1R,2S)-(+)-DBNE **55**



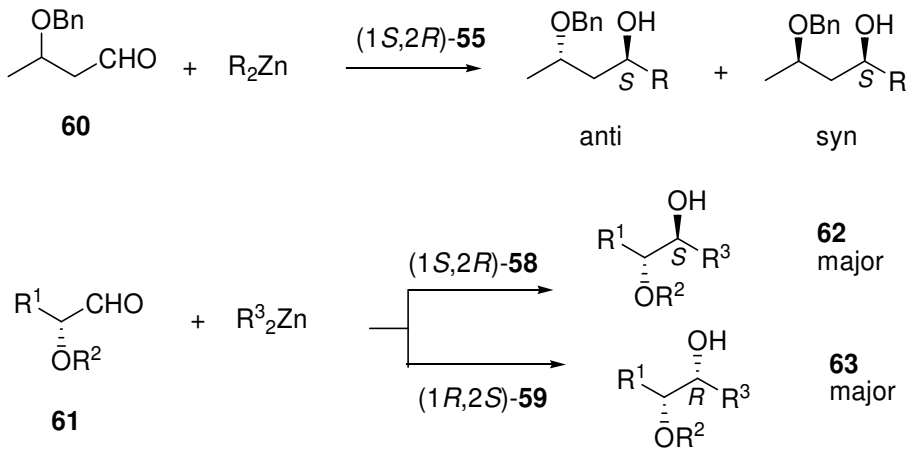
(1S,2R)-**56**



(1S,2R)-**57**

Scheme 2.25. Addition of diethylzinc to benzaldehyde using norephedrine derivatives as chiral catalysts **54**-**57**

Ligand (1*S*,2*R*)-**58** and (1*R*,2*S*)-**59** was used to catalyze the reaction of functionalized aldehydes such as *β*-alkoxy aldehyde **60** (Soai et al., 1992b and 1994a) and the *α*-alkoxy aldehyde **61** alkylzincs (Scheme 2.26). In the reaction of **60** with dialkyzinc in the presence of (1*S*,2*R*)-**55**, both the anti and syn products preferred a *S* configuration for the hydroxyl carbon. The ee' s of these products were in range of 61-85%. For the reaction of **61** with dialkyzincs (1*S*,2*R*)-**58** led to **62** as the major product with a *S* configuration for the hydroxyl carbon and (1*R*,2*S*)-**59** led to **63** as the major product with a *R* configuration. The ratio of these two diastereomeric products in the recations was in the range from 85/15 to 98/2. Thus, in the reaction of both **60** and **61**, the chiral configuration of the products was controlled by the chiral ligands rather than by the chiral center adjacent to the carbonyl group of the substrates.



R_1 = Me, Ph
R_2 = *t*-$BuPh_2Si$, Ph_3Si, *i*-Pr_3Si
R_3 = Me, Et

(1*S*,2*R*)-**58** (1*R*,2*S*)-**59**

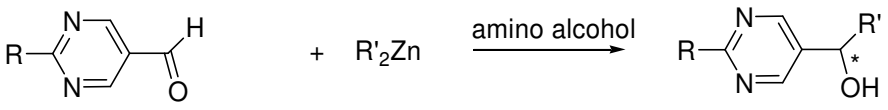
Scheme 2.26. Dialkylzinc additions to functional aldehydes catalyzed by **58**, **59**

The reaction of pyrimidine-5-carboxaldehydes **64** with dialkylzincs in the presence of several *β*-amino alcohols was studied by Soai et al (1997) (Scheme 2.27). They

found that ligand (1*S*,2*R*)-**58** catalyzed this recation to generate the corresponding (S)-pyrimidly alcohols **65** with up to 94% ee.

The amino alcohol ligands **66a-g** and (1*S*,2*R*)-**58** were examined for the diisopropylzinc addition to aldehydes among which (1*S*,2*R*)-**58** and **66a** were found to be most enantioselective (Soai et al., 1994).

These compounds catalyzed the reaction of a variety of aldehydes with diisopropylzinc with over 90% ee. Ligands **58** and **66** were used in a solvent-free system to catalyze the reaction of diethylzinc with aldeydes with 84-91% ee (Sato et al., 2000).

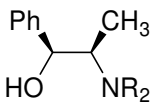


R = H, Me, Et, Ph

R' = Et, n-Bu

64

65

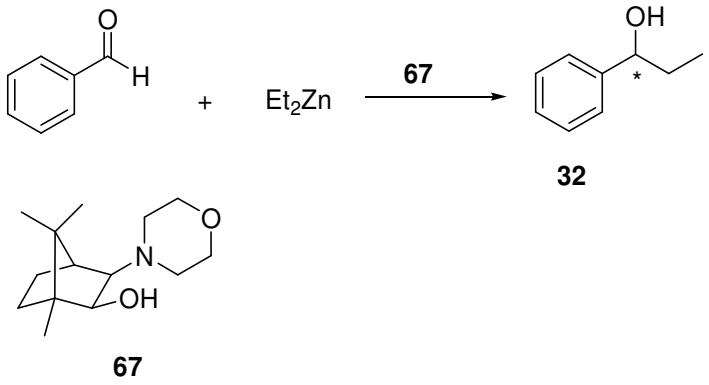


66a: R=^{i}Pr
66b: R=Me
66c: R=Et
66d: R=pentyl
66e: R=allyl
66f: R= -$(CH_2)_4$-
66g: R= -$CH_2CH_2OCH_2CH_2$

Scheme 2.27. Dialkyzinc addition to pyrimidine-5-carboxaldehydes

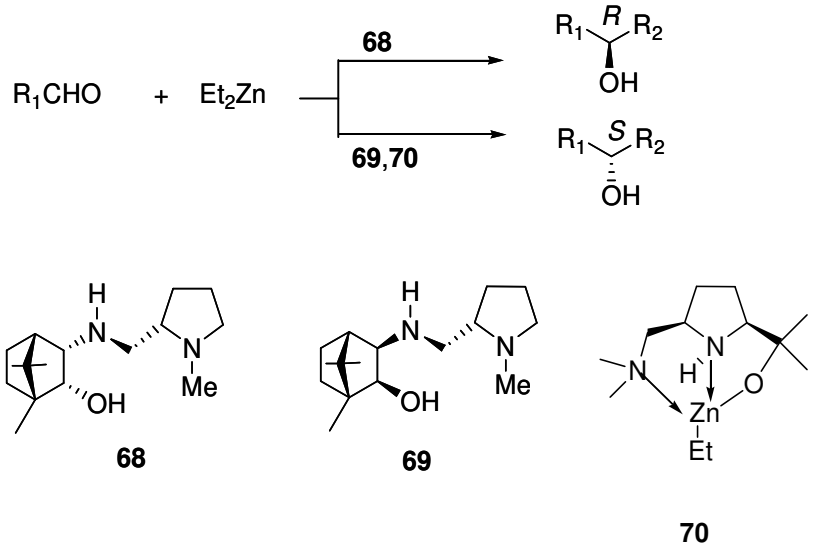
2.7.1.1.6. *β*-Secondary amino alcohols

(-)-DAIB **33** was first ligand that showed high enantioselectivity for organozinc additions. However, use of this ligand was limited to the reaction of only certain aromatic aldehydes. A modified DAIB ligand **67** (Scheme 2.28), was prepared by Nugent (1999). This compound contains a morpholine substituent and exhibited much more general enantioselectivity. For the reaction of diethylzinc with a number of aromatic as well as aliphatic aldehydes, the ee' s were observed in the range of 91-99%.



Scheme 2.28. Addition of diethylzinc to benzaldehyde using chiral catalysts **67**

Tanaka et al. (1989) reported that *N*-alkyl derivatives of *endo*-3-amino-*endo*-2-hydroxyborane **68** prepared from D-camphor catalyzes the addition of diethylzinc to benzaldehyde to afford (*R*)-1-phenylpropanol with 92% ee. On the other hand, *exo*-3-amino-*exo*-2-hydroxyborane (**69**) afforded (*S*)-1-phenylpropanol with 88% ee (Scheme 2.29).

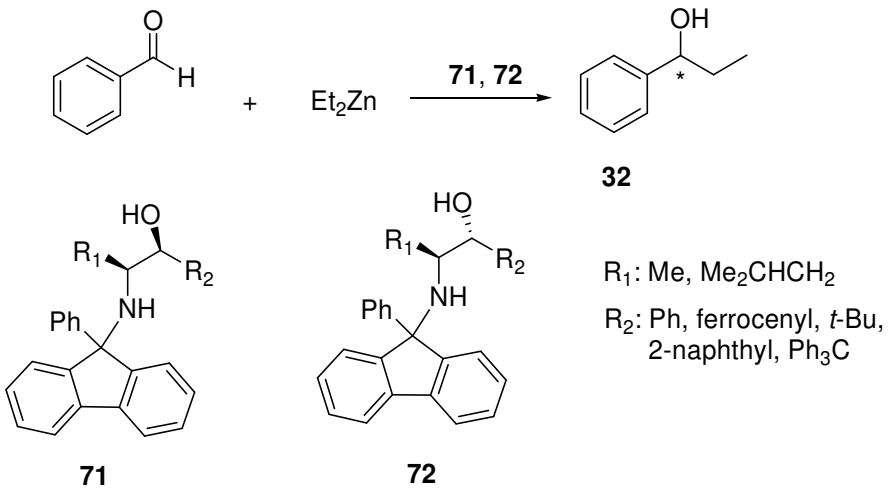


Scheme 2.29. Addition of diethylzinc to benzaldehyde using *β*-secondary amino alcohol as chiral catalysts **68**-**70**

Ethyl zinc alkoxide **70** derived from chiral diamino alcohol and diethylzinc has been used as a chiral catalyst for the enantioselective addition of diethylzinc to

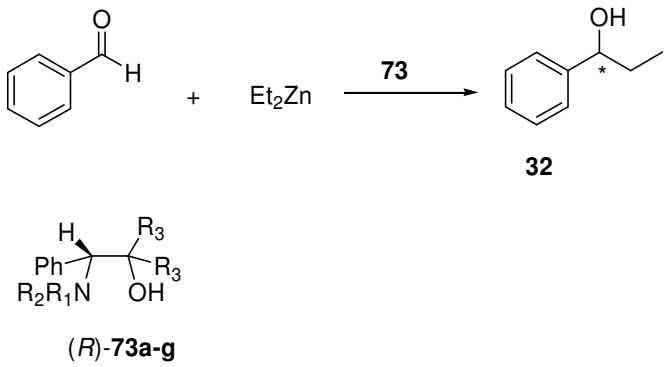
aromatic aldehyde, which afforded (*S*)-1-phenylpropanol with 94% ee in 95% yield (Corey et al., 1990).

Sardina et al. (2000) synthesized chiral secondary amino alcohol **71** and **72** for the dialkylzinc addition. Ligand **71** showed the highest enantioselectivity for the diethylzinc addition to benzaldehyde (97% ee). High enantioselectivity was also observed for both aromatic and aliphatic aldehydes. Ligand **72**, the diastereomers of **71**, generally showed lower enantioselectivity than **71** probably due to a unfavorable steric interaction between R_1 and R_2 in the intermediate formed by chelation of the amino alcohols with zinc (Scheme 2.30).



Scheme 2.30. Addition of diethylzinc to benzaldehyde using β-secondary amino alcohol as chiral catalysts **71**, **72**

Martens et al. (1996) reported that, the optically active β-amino alcohol derived from various amino acids with alkyl groups on the carbinol carbon atom, were used in the enantioselective alkylation reaction of benzaldehyde with diethylzinc (Scheme 2.31).

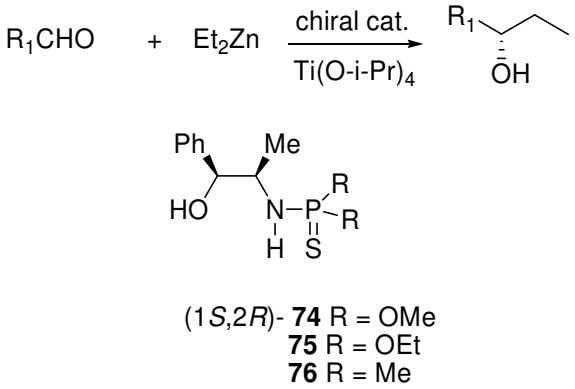


(*R*)-**73**	R_1	R_2	R_3
a	H	H	Me
b	H	H	Et
c	H	H	*n*-Prop
d	H	H	*n*-Bu
e	H	H	$CH_2CH{=}CH_2$
f	H	Me	Et
g	H	Me	Et

Scheme 2.31. Addition of diethylzinc to benzaldehyde using β-secondary amino alcohol as chiral catalyst **73**

The reactions in the presence of 10 mo% of the catalyst (*R*)-**73a-g** the enantioselectivities are ranging from 32-80% ee. The use of lithium alkoxides of the β-amino alcohols (*R*)-**73a-g** as catalysts [Li(*R*)-**73f** and Li(*R*)-**73g**] in the reaction of diethylzinc with benzaldehyde increases the enantioselectivity up to 96% ee.

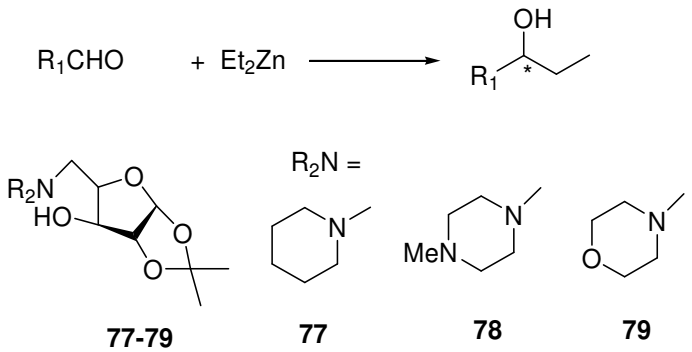
Soai et al. (1993) reported that chiral dialkyl thiophosphoamidates derived from norephedrine (which is available in either enantiomeric form) were highly enantioselective chiral catalysts for the addition of dialkylzincs to aldehydes in the presence of titanium (IV) isopropoxide (Scheme 2.32). In the presence of 15 mol% of **74** and 0.8 equiv of $Ti(O\text{-}i\text{-}Pr)_4$, the reaction of aromatic aldehydes and α,β-unsaturated aldehydes with diethylzinc produced chiral alcohols with 90-97% ee and good yields. The other ligands **75** and **76** gave slightly lower ee's (88% and 74%, respectivelly) for the reaction of diethylzinc with benzaldehyde.



Scheme 2.32. Addition of diethylzinc to benzaldehyde using dialkyl thiophosphoamidates derived from norephedrine as chiral catalysts

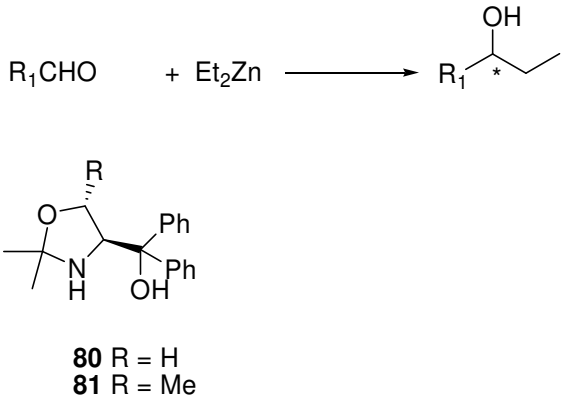
2.7.1.1.7. Chiral γ-amino alcohol

Cho et al. (1998) reported that enantioselective addition reaction of diethylzinc to aldehyde using γ-amino alcohols, 1,2-isopropylidene-5-deoxy-5-dialkylamino-α-D-oxylofuranoses as new chiral catalysts, which were prepared from 1,2-isopropylidene-5-*O*-*p*-toluenesulphonyl-α-D-xylofuranoses and the corresponding amines (Scheme 2.34). The optical yields of 1-phenylpropanol obtained are 87% ee with **77**, 78% ee with **78** and 96% ee with **79**. They reported that for aromatic aldehydes, consistently high optical yields, such as 89% ee for *o*-tolualdehyde, 88% ee for *p*-tolualdehyde. The catalyst **79** also is highly effective for the enantioselective addition aliphatic aldehydes, such as 93% ee for trimethylacetaldehyde, 76% ee for heptanal.



Scheme 2.33. Addition of diethylzinc to benzaldehyde using chiral γ-amino alcohol as chiral catalyst **77**-**79**

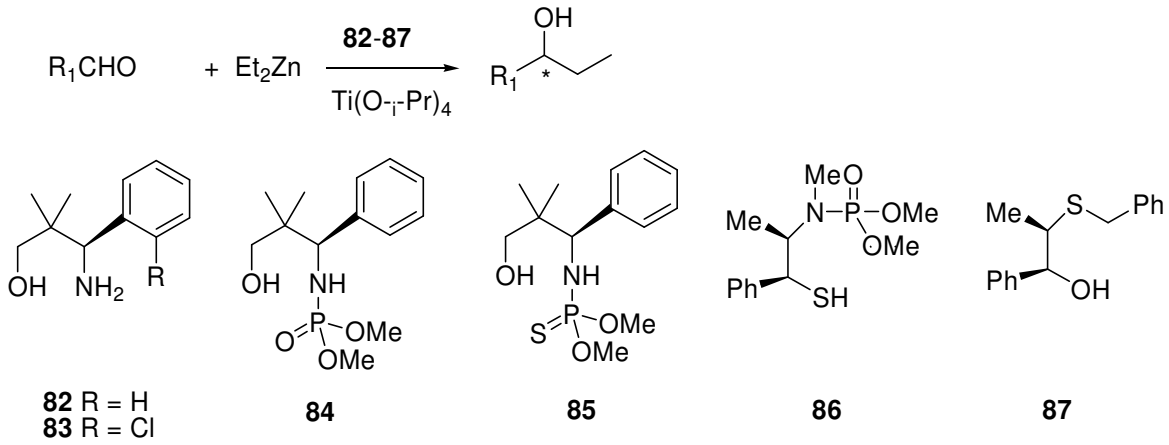
Starting from L-serine and L-threonine, (*S*)-diphenyl-(2,2-dimethyl-1,3-oxazolidin-4-yl)-methanol (**80**) and (4*S*,5*R*)-diphenyl-5-methyl-1,3-oxazolidin-4-yl) methanol (**81**) were prepared in good yields (Falorni et al., 1996). Enantioselective addition of diethylzinc to both aliphatic and aromatic aldehydes in the presence 6 mol% of **80** and **81** were carried out at several temperatures. The optically active secondary alcohols were obtained in *S* configuration with up to 100% ee, (Scheme 2.34).



80 R = H
81 R = Me

Scheme 2.34. Addition of diethylzinc to benzaldehyde using γ-amino alcohol as chiral catalyst

Hulst et al. (1996) synthesized ligand based on γ-amino alcohols **82** and **83** and the corresponding (thio)-phosphoramidates **84**-**87** (Scheme 2.35). They found that the phosphorylated ligands also catalyse the stereoselective alkylation of benzaldehyde using the titanium isopropoxide/diethlzinc reagent mixture. Ligands **84**, **85** and **86** gave the *S* product with an ee of 74%, 87% and 98%, respectively. The non-phosphorylated ligands **82** and **83** were appeared to be poor catalysts, as the product was obtained in low yield (11 and 14%) and low ee (17 and 26%). Ligand **87** failed to give any conversion at all.

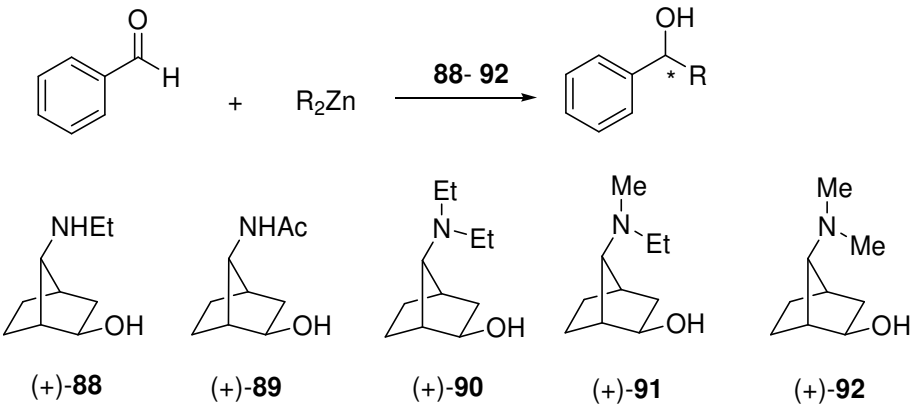


82 R = H
83 R = Cl

84 **85** **86** **87**

Scheme 2.35. Addition of diethylzinc to benzaldehyde using chiral γ-amino alcohol as chiral catalyst

Costa (2004) have synthesized a series of optically active bicyclic *syn*-1,3-amino alcohols as chiral ligand for the catalyzed enantioselective addition of dialkylzinc to benzaldehyde (Scheme 2.36). They have showed that homochiral *syn*-1,3-amino alcohols **90**, **91**, **92** are effective catalysts for the enantioselective addition of diethylzinc to benzaldehyde. When applying the *N*-ethylamino alcohol (+)-**88** and acetoamido alcohol (+)-**89**, a decrease in the enantioselectivity (55 and 63% ee) and yield (62 and 71%) was obtained, due to the formation of the benzyl alcohol as by product. They said that according to the literature (Noyori and Kitamura,1990,1991), the acidic protons on the nitrogen might cause complications due to different chiral intermediated while parallel reaction pathways could be involved, thus complicating the induction.

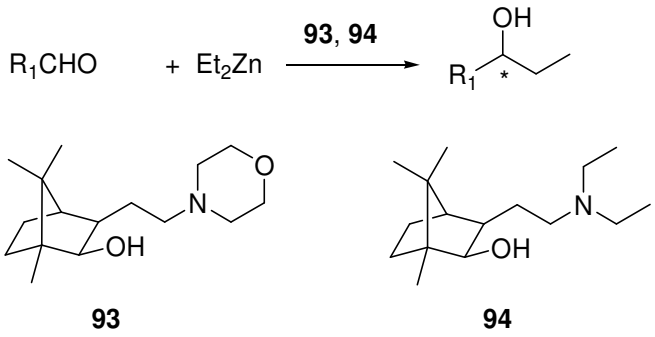


(+)-**88** (+)-**89** (+)-**90** (+)-**91** (+)-**92**

Scheme 2.36. Addition of diethylzinc to benzaldehyde using chiral γ-amino alcohol as chiral catalyst

2.7.1.1.8. Chiral δ-amino alcohol

(+)-Camphor derived enantiomerically pure 1,4-amino alcohols used as ligand in the addition reactions of n-BuLi, and *N*-BuMgBr to benzaldehyde and in the reaction of diethylzinc with benzaldehyde and hexanal by Knollmüller et al. (1998, 1999) (Scheme 2.37). This 1,4-amino alcohol showed lower enantioselectivity and activity. For the reaction of diethylzinc with benzaldehyde and hexanal, the alcohol products were obtained with 87% and 60% ee, respectively. Compound **94** gave the optically active alcohol with 78% ee for the reaction of diethylzinc with benzaldehyde.

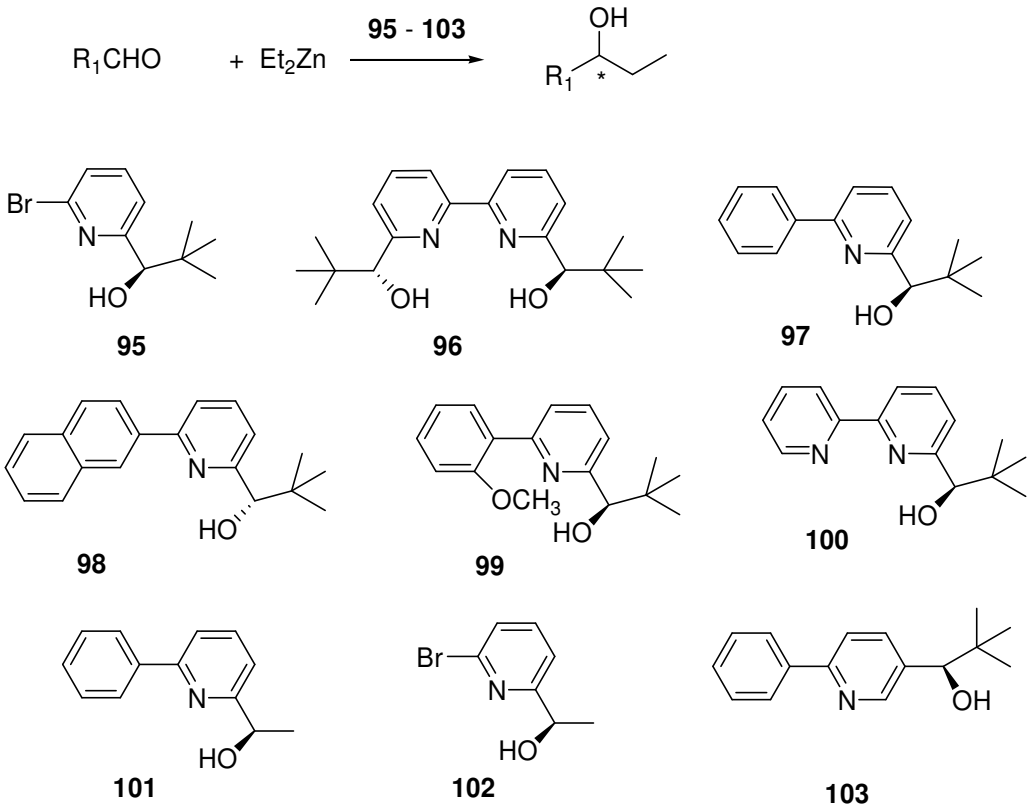


93 **94**

Scheme 2.37. Addition of diethylzinc to benzaldehyde using δ-amino alcohol as chiral catalyst.

2.7.1.2. Pyridyl alcohols

Enantioselective ethylation using a chiral (*R*,*R*)-bipyridyldiol (Scheme 2.38) which was reported by Bolm et al (1990) afforded optically active aromatic alcohols with 80-92 % ee' s, ethylation of heptanal gave (*R*)-3-nonaol with 70% ee. The C_2-symmetric bipyridine ligand **96** was synthesized via dimerization of **95** in the presence of a nickel complex. A 5 mol% amount of **96** was used to catalyze diethylzinc additions in toluene solution at 0 °C and found to show good enantioselectivity for aromatic aldehydes (90-97% ee) but much lower for aliphatic and α,β-unsaturated aldehydes (Bolm et., 1992a).



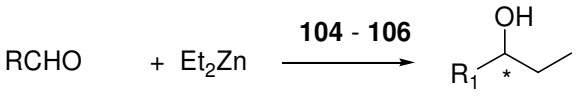
Scheme 2.38. Addition of diethylzinc to benzaldehyde using pyridyl alcohol as chiral catalyst

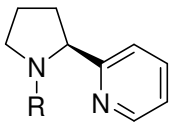
Compound **97** and **100** gave 93% and 95% ee, respectively, for the reaction of the diethylzinc with benzaldehyde . The bulky *tert*-butyl group on the hydroxyl carbon of these ligands was found to be very important since ligands **101** and **102** with less bulky methyl groups gave very low ee. In ligand **103**, the hydroxyl goup is far

away from the pyridine nitrogen, which prevents the formation of a chelate zinc complex. This also led to very low enantioselectivity (7% ee).

Chiral amines containing no hydroxyl or thiol groups but having multiple nitrogen atoms capable of chelate coordination were also found to be effective in the dialkylzinc additions to aldehydes.

A new type of chiral catalyst based on chiral 2-[(2*S*)-2-pyrrolidinyl]pyridines for the dialkylzinc-aldehyde addition was reported by Chelucci et al. (1991) (Scheme 2.39).



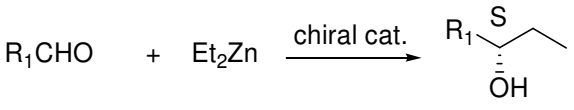


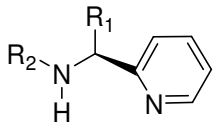
104 R = H
105 R = CH_3
106 R = Li

Scheme 2.39. Addition of diethylzinc to benzaldehyde using 2-[(2*S*)-2-pyrrolidinyl]pyridines as chiral catalyst

The pyridines **104** and **105** were prepared starting from natural (*S*)-proline. Enantioselective additions of diethylzinc to both aliphatic and aromatic aldehydes in the presence of catalytic amounts of **104**-**106** were carried out in different temperature. The nature of the substrate is significant for determining the steric course of the reaction at different temperatures. A lowering of the reaction temperature corresponded to a slight increment of the ee in aromatic aldehydes whereas in aliphatic aldehydes, lowering of the temperature resulted in the decreasing of the ee. All carbinols were obtained in *S* absolute configurations except (*E*)-3-phenylpropenal, which afforded an alcohol having *R* absolute configuration. Optical yields are ranging from 33% to up to 100% ee.

Falorni et al. (1992) demonstrated that chiral amino pyridines derived (**107**-**112**) from α-aminoacids are enantioselective catalysts in the addition of diethylzinc to both aliphatic and aromatic aldehydes; optically active secondary alcohols in up to 98% ee can be obtained in high yield (Scheme 2.40).





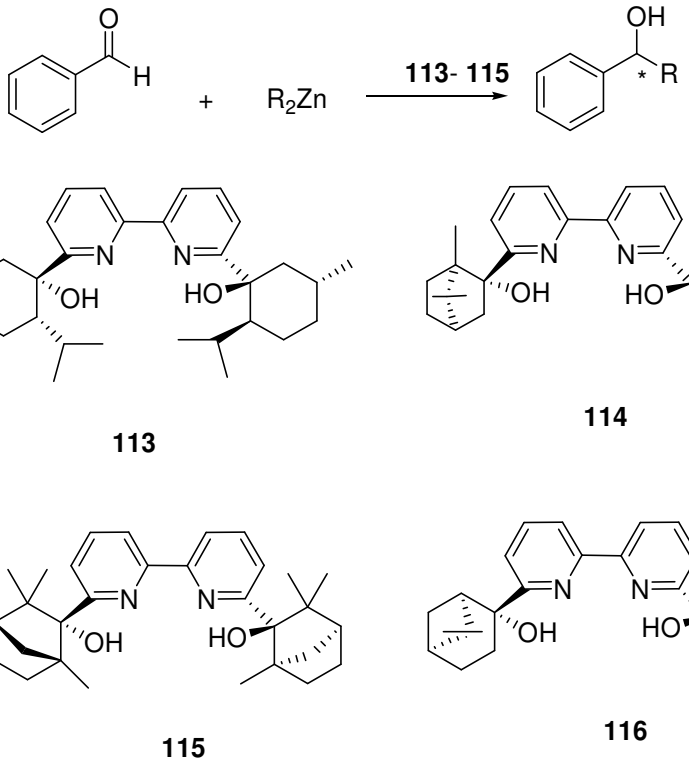
107 $R_1=R_2=CH_3$
108 R_1=i-Pr, $R_2=CH_3$
109 R_1=i-Bu, $R_2=CH_3$
110 R_1=i-Bu, R_2=H
111 R_1=s-Bu, $R_2=CH_3$
112 $R_1=CH_2Ph$, $R_2=CH_3$

Scheme 2.40. Addition of diethylzinc to benzaldehyde using amino pyridines derived from α-aminoacids as chiral catalyst

Enantioselective addition of diethylzinc to benzaldehyde in the presence of catalytic amounts (6 mol%) of **107**-**112** were carried out in ether at various temperature (35, 20, -10 °C). The optically active alcohols were obtained in *S* configuration. The best enatioselectivity was obtained with 73%, 72%, 78%, 98%, 90% ee, by using **107**, **109**, **110**, **111**, **112**, respectively. In most of cases a lowering of temperature corresponded to an enhancement of the ee. When **108** was used as catalyst at 35, 20, and -10 °C, the enantioselectivity decreased to 91%, 82%, 41% ee, respectively.

New C_2-symmetric chiral 2,2'-bipyridine diols were prepared from readily available homochiral materials such as menthone and camphor by Kwong et al. (1999). They tested their properties as catalysts for the addition of diethylzinc to benzaldehyde (Scheme 2.41). Catalyst **113** induces the formation of the *S* enantiomer in 82% ee while **114**, **115**, **116** induce the formation of *R* enantiomer in 92%, 77% and 79% ee, respectively. Temperature and solvent have great effects on both the rate and enantioselectivity. Lowering the temperature from 22 to 0 °C leads to slightly slower reactions but to an increase of asymmetric induction from 81% to 85% ee for **113** and from 92 to 95% ee for **114**. Toluene (92% ee), hexane

(92% ee) and THF (91% ee) gave similar results while CH_2Cl_2 (43% ee) and CH_3CN (23% ee) decreased the enantioselectivity and the rate as well. Changing the amount of catalyst from 2 to 8 mol% had only a small effect on the enantioselectivity. In the presence of 2, 5 and 8 mol% **114,** the enantiomeric excesses were 81%, 91%, 91%, respectively.



113 **114**

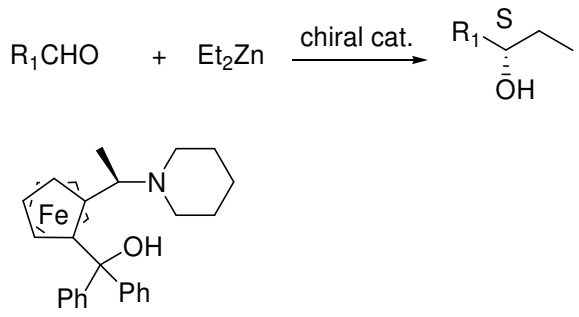
115 **116**

Scheme 2.41. Addition of diethylzinc to benzaldehyde using 2,2'-bipyridine diols as chiral catalyst

2.7.1.3. Chiral ferrocenyl amino alcohol

Butsugan et al. (1991) reported that, chiral 1,2-disubsitituted ferrocenyl amino alcohols can be used chiral catalyst in the addition of dialkylzincs to aldehydes. Ferrocenyl amino alcohol **117** catalyzed the addition of the diethylzinc to both aromatic and aliphatic aldehydes. Optical yields are vary from 70% to 100% ee. High ee' s (70-93% ee) were obtained by the addition of aliphatic aldehydes with the substituent not branched at the α-carbon, such as heptanal. However, the addition to aliphatic aldehydes with the subsitituent branched at the α-carbon,

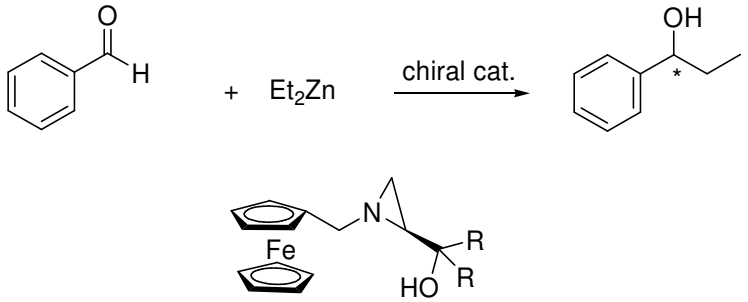
such as pivaldehyde, afforded the corresponding alcohols in very high ee' s (92-93% ee) (Scheme 2.42).



117

Scheme 2.42. Addition of diethylzinc to benzaldehyde using 1,2-disubsitiuted ferrocenyl amino alcohols as chiral catalyst

Wang et al. (2004) reported the synthesis of novel chiral ferrocenylaziridino alcohols **118**-**121** (Scheme 2.43) and their application in the addition of diethylzinc to aldehydes, where up to 98.8% ee was achieved. The reaction of diethylzinc with benzaldehyde was carried out in toluene in 0-20 °C in the presence of 3 mol% ligands **118**-**121**. The addition of diethylzinc to benzaldehyde led to 1-phenylpropanol in 71-98% yields with 1.3-92.7% ee. It shown that the enantioselectivity of the reaction was very sensitive to the structure of the chiral catalyst. When the ligands **118** and **119** were employed, (*S*)-1-phenylpropanol was obtained in low ee values (1.3% and 25.2%, respectively), while **120** gave the product with moderate enantioselectivity (40.4%). Chiral ligands **121** showed the best asymmetric induction (92.7% ee). Chiral ligands **121** was checked for the asymmetric addition of diethylzinc to a series of aromatic aldehydes. The best asymmetric induction as high as 98.8% ee was found by using *m*-chlorobenzaldehyde as substrate.



118 R=H
119 R=*i*-C_3H_7
120 R=C_2H_7
121 R=C_6H_5

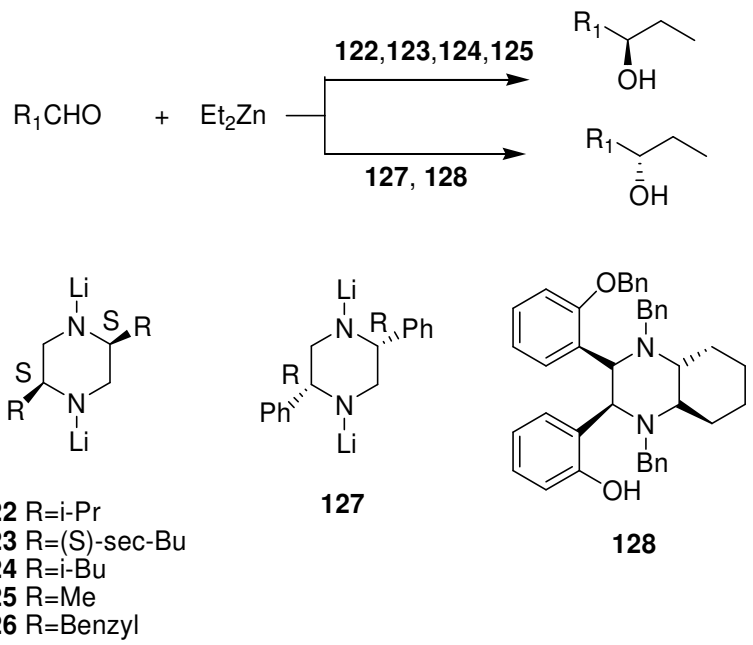
Scheme 2.43. Addition of diethylzinc to benzaldehyde using chiral ferrocenyl aziridino alcohols chiral catalyst

2.7.1.4. Chiral piperazine

A series of 2,5-disubstituted piperazines, as their lithium salts, have been synthesized and examined as chiral catalysts for the enantioselective addition of diethylzinc to benzaldehyde by Soai et al. (1987c) .

As shown in Scheme 2.44 chiral 2(*S*),5(*S*)-disubstituted piperazines that having branched substituents such as diisopropyl (**122**), di-(*S*)-*sec*-butyl (**123**), and diisobutyl (**124**) catalyzed the addtion reaction of diethylzinc to benzaldehyde. (*R*)-1-phenylpropanol was obtained with 89-91% ee. When 2(*S*),5(*S*)-dimethylpiperazine (**125**) was used as catalyst, the racemic alcohol was obtained. In the presence of **126**, (*R*)-1-phenylpropanol was obtained in 70% yield with 68% ee. (*S*)-1-phenylpropanol was obtained in 32% yield with 13% ee by using **127** as catalyst.

The piperazines derivative **128** was an efficients chiral catalysts for the enantioselective addition of diethylzinc to both aromatic and aliphatic aldehydes (81 to >99% ee' s) (Shono et al., 1991).



122 R=i-Pr
123 R=(S)-sec-Bu
124 R=i-Bu
125 R=Me
126 R=Benzyl

127

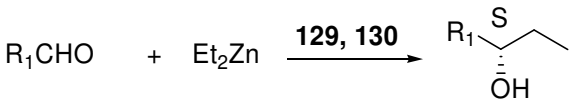
128

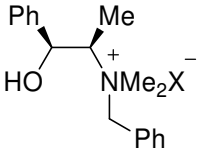
Scheme 2.44. Addition of diethylzinc to benzaldehyde using piperazines derivatives as chiral catalyst

2.7.1.5. Chiral quaternary ammonium salt

(1*S*,2*R*)-*N*-Benzyl-*N*-methylephedrinium halides (**129** and **130**), a chiral quaternary ammonium salt, is reported by Soai and Watanabe (1990a) to be an enantioselective catalyst for the addition of diethylzinc to aldehydes. Optically active alcohols can be synthesized in up to 73% ee (Scheme 2.45).

The effect of the solvents was important. The chiral quaternary ammonium catalyst in the solid state in hexane and benzene gives higher enantioselectivities than those in the solid state. The reaction of benzaldehyde with diethylzinc using a solid state catalyst in hexane affords an alcohol of 74% ee. The same reaction using a solution of chiral catalyst in DMF-hexane showed no enantioselectivity. This situation can be explained as, the oxygen or nitrogen atom of DMF strongly solvates the ammonium cation and may subsequently destroy the chiral complex of ammonium catalyst and diethylzinc.





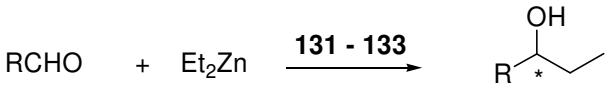
(1*R*,2*S*)-**129** X=Cl
130 X=Br

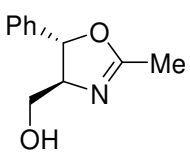
Scheme 2.45. Addition of diethylzinc to benzaldehyde using quaternary ammonium salts as chiral catalyst

2.7.1.6. Oxazolines

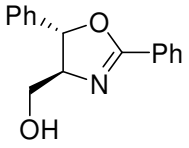
Chiral oxazolines can be easily prepared from amino alcohols. These compounds have been used for the asymmetric organozinc addition.

Williams et al. (1993) used the hydroxylmethyl oxazolines **131**-**133** to catalyze the diethylzinc addition to aromatic aldehydes, which gave 25-67% ee.





131



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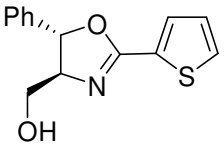


133

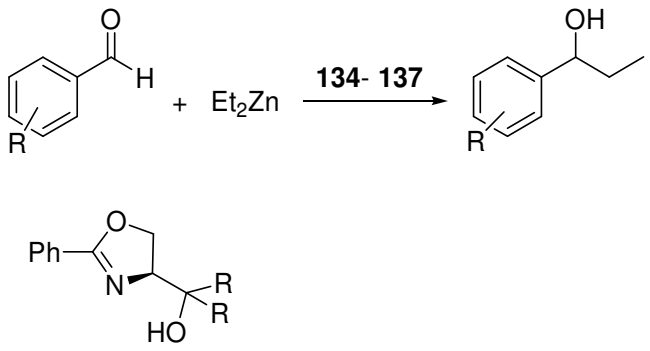
Scheme 2.46. Addition of diethylzinc to benzaldehyde using oxazolines as chiral catalyst

Several aromatic and aliphatic aldehydes have been alkylated with diethylzinc in the presence of the 4-hydroxyalkyl oxazolines **134**-**137** by Braga et al. (2003). These ligands were used as chiral auxiliary for the enantioselective addition of

diethylzinc to benzaldehyde. They studied the influence of substituents at the hydroxymethyl group. Oxazoline **135**, **136**, **137** with a more crowded sterical environment around the hydroxyl functionality suffered from a decrease in the reactivity and enantioselectivity. These ligands **134**, **135**, **136**, **137** give the *R* product with an ee of 95, 86, 55, and 77% , respectively.

They reported that electon donating substituents led to a decrease in enantiomeric excess while electron with-drawing substituents led to an increase.

Addition of diethylzinc to pentanal gave the secondary alcohol in a low yield and enantiomeric excess (25% ee). However, the reaction with hexanal resulted in an excellent enantiomeric excesses of more than 99%. (Scheme 2.47).



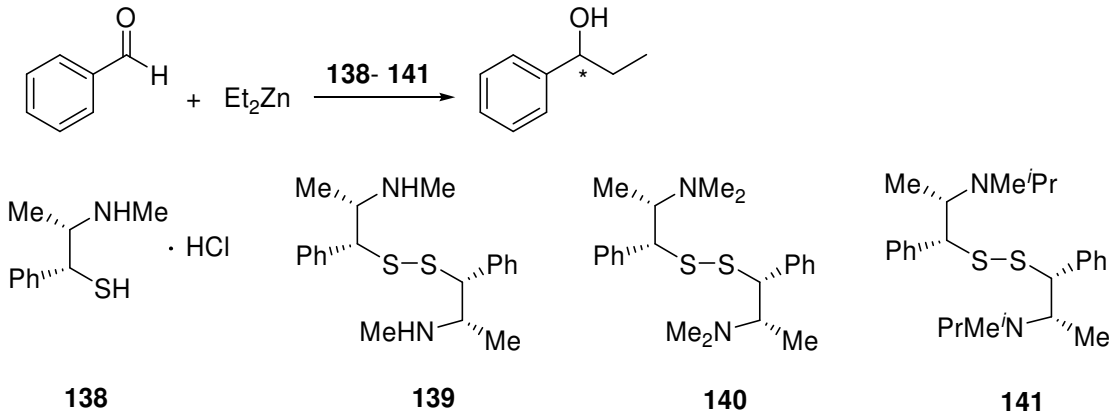
134 R=H
135 R=Me
136 R=Ph
137 R= Et

Aldehyde	Yield %	ee %
R=H	91	95 (*R*)
R=*p*-OMe	94	70 (*R*)
R=*o*-OMe	65	40 (*R*)
R=*p*-Me	65	89 (*R*)
R=*o*-Me	57	72 (*R*)
R=*p*-Cl	75	>99 (*R*)
R=*o*-Cl	90	>99 (*R*)

Scheme 2.47. The enantioselective addition of diethylzinc to substituted aromatic aldehydes employing of catalyst **134**

2.7.1.7. Amino thiols, disulfides ligands

Kellogg et al. (1995) prepared chiral amino thiols and disulfides from ephedrine for the reaction of diethyzinc with benzaldehyde. They found that the *N*-methyl ephedrine thiol HCl salt **138** and *N*-methyl ephedrine disulfides **139**-**140** and *N*-isopropyl ephedrine disulfides **141** exhibited good enantioselectivity (80-90 % ee).

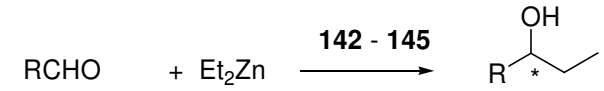


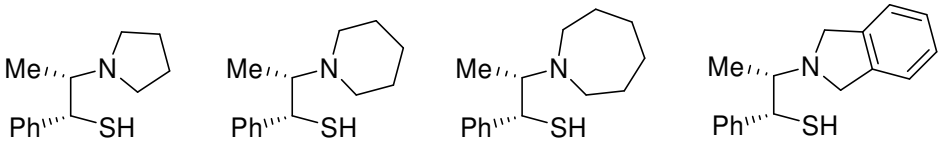
138 **139** **140** **141**

Scheme 2.48. Addition of diethylzinc to benzaldehyde using as chiral catalyst **138**-**141**

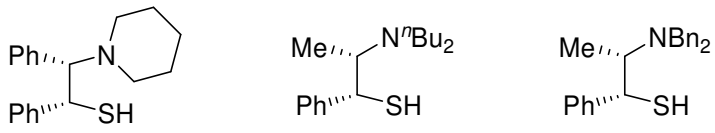
The amino thiols **142**-**148** with cyclic and acyclic amino substituents were used by Kang et al. (1996) for the diethylzinc addition to aldehydes. For example, in the presence of 5 mol% of **142**, the reaction of diethylzinc with various aldehydes in toluene at 0 °C proceeded with 78-99% ee, and the reaction of hexanal and cinnamaldehyde gave only 62-78% ee. Most of these ligands exhibited good enatioselectivity for 2-naphthaldehyde, cyclohexanecarboxaldehyde, and benzaldehyde but not as good for cinnamaldehydes.

In the presence of 5 mol% amino thiols **147** and **148** with acyclic amino substituetnts, the addition of diethylzinc to benzaldeyhde gave *R* alcohol with 99% and 72% ee, respectively.





142 **143** **144** **145**

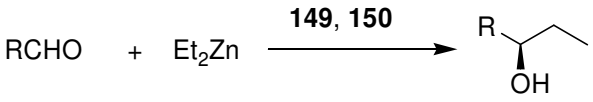


146 **147** **148**

Scheme 2.49. Addition of diethylzinc to benzaldehyde using amino thiols as chiral catalyst

2.7.1.8. Chiral 1,2- and 1,3-diols

Salvadori et al. (1990) reported that, (1*S*,2*S*)-1,2-diphenylethane-1,2-diol (**149**) which is a chiral diol with C_2 symmetry axis, catalyzes the addition of diethylzinc to aromatic aldehydes.



(1*S*,2*S*)-**149** (*R*)-**150**

Scheme 2.50. Addition of diethylzinc to benzaldehyde using 1,2-diols as chiral catalyst

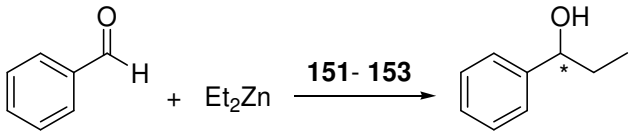
As shown in Scheme 2.51, when **149** was used as a catalyst, *R* alcohols up to 78% ee are obtained. On the other hand, (*R*)-1-phenylethane-1,2-diol (**150**), which

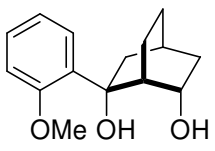
contains both primary and secondary alcohols, does not cause any asymmetric induction.

Optically pure 1,3-diols have been synthesized and used as catalysts in the enantioselective addition of diethylzinc to aromatic aldehydes by Frejd (2002). They obtained good enantiomeric excess in either toluene or mixtures of diethyl ether - hexane (2:3). At 0 °C the yield and enantiomeric excess were 89% and 92%, respectively. At -20 °C the yield was much lower (42%) and the enantiomeric excess was onyl 2% better than at 0 °C. At room temperature the yield was good (93%) but the enantiomeric excess was lowered 72%.

When using **151** the enantioselectivity was reversed but a fair yield and good enantiomeric excess of (*S*)-1-phenylpropanol was obtained. A lower yield was obtained in toluene, but enantiomeric excess was almost the same.

When applying a catalyst having a methyl group at the bridgehead position between the hydroxy groups as in **152** both yield and enantiomeric excess were lower than **153**.





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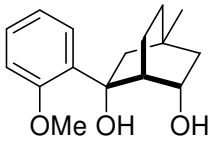

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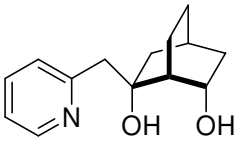


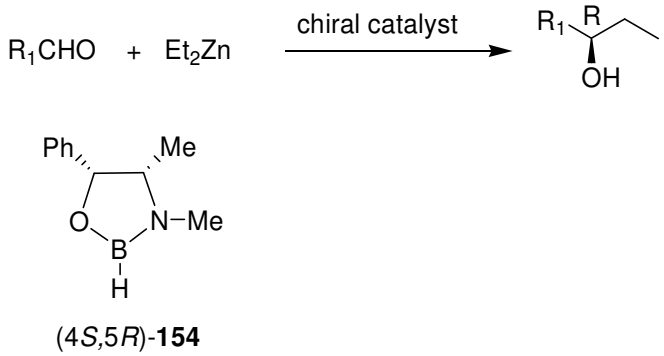
153

catalyst	solvent	ee %	yield %
151	hexane-Et_2O	92 (*R*)	89
	toluene	80	84
152	hexane-Et_2O	89 (*R*)	85
	toluene	56	76
153	hexane-Et_2O	83 (*S*)	80
	toluene	82	65

Scheme 2.51. Addition of diethylzinc to benzaldehyde using 1,3-diols as catalysts **151**-**153**

2.7.1.9. Chiral oxazaboralidine

Srebnik et al. (1989) reported that (4*S*,5*R*)-3,4-dimethyl-5-phenyl-1,3,2-oxazaborolidine (**154**), prepared from (1*R*,2*S*)-(-)-ephedrine and borane-methyl sulfide complex, is an efficient chiral catalyst for the addition of diethylzinc to aromatic aldehydes. This catalyst is the first example of a chiral boron compound for the addition of diethylzinc to aldehydes. The reaction of aromatic aldehydes afforded *R* alcohol up to 96% ee, whereas the ee of the addition to aliphatic aldehydes is moderate i.e 52% ee (Scheme 2.52).



(4*S*,5*R*)-**154**

Scheme 2.52. Addition of diethylzinc to benzaldehyde using catalysts (4*S*,5*R*)-**154**

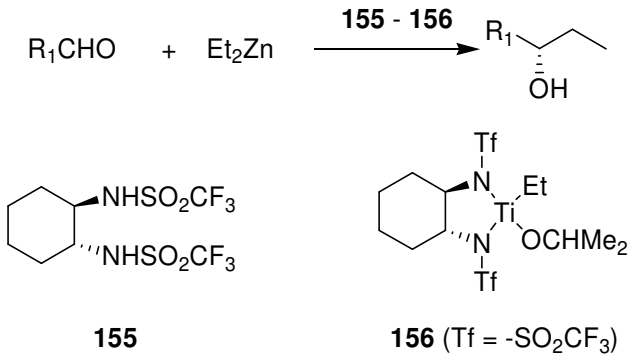
The role of the centered atom in the metalated oxaza ring system is important. When boron (86% ee) is replaced by aluminum, lithium, or zinc, the ee of the product dropped to 58%, 70%, and 71%, respectively.

2.7.1.10. Transition metal complex with chiral ligands

The chiral titanium complexes have been found to be highly effective in the addition of diethylzinc to aldehydes.

2.7.1.10.1. Titanium sulfonamide and phosphoramide complex

In the presence of titanium complexes such as Ti(O-*i*-Pr)$_4$, **155** can catalyze the reaction of a variety of alkylzinc as well as functionalized alkylzincs with many aldehydes with excellent enantioselectivity as demonstrated by Ohno et al. (1986). Optically active *S* alcohols with 98-99% ee' s were obtained from the enantioselective ethylation of benzaldehyde. In fact, alcohol 99% ee is obtained in 78% yield from the addition of diethylzinc to aliphatic hexanal (-20 °C, 5 h). The reaction of diethylzinc with benzaldehyde in the presence of Ti(O-*i*-Pr)$_4$, only, and without the disulfonamide is rather slow (24 h at room temperature). Therefore, the Lewis acidity of the Ti compound is considered to be increased by the electron-withdrawing disulfonamide. A key reactive species is considered to be ethyltitanium reagent **156** (Yoshioka et al., 1989) .



155 **156** (Tf = $-SO_2CF_3$)

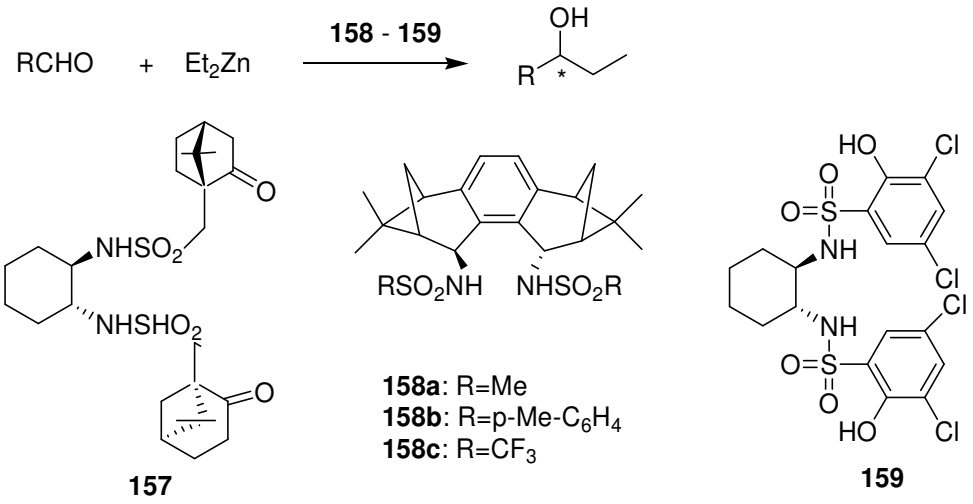
Scheme 2.53. Addition of diethylzinc to benzaldehyde using catalysts **155** and **156**

The titanium complexes of the optically pure chiral disulfonamides **157** and **158a**-**c** showed very good enantioselectivity for the reaction of diethylzinc with aldehydes.

Uang et al. (1998) found that in the presence of 20 mol% of **157** and 1.4 equiv of Ti(O-*i*Pr)$_4$, the enantioselectivity was in the range of 59-90% ee.

The titanium complexes of **158a**-**c** were found by Paquette and Zhou (1999) to have much higher enantioselectivity probably because of their more rigid bidentate structure. In the presence of 1 mol% of **158a**-**c** and 0.6-1.2 equiv of Ti(O-*i*Pr)$_4$, the reaction of diethylzinc with aromatic and aliphatic aldehydes proceeded with 81-98% ee.

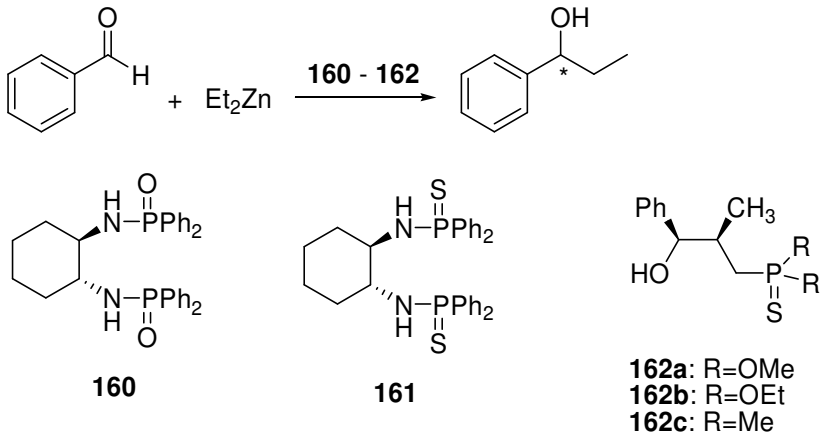
The sulfoamide ligand **159** containing phenol functions was prepared by Zhang et al. (1997). In the presence of 7 equiv of Ti(O-*i*Pr)$_4$ and 20 mol% of **159** at -23 °C in hexane, diethylzinc additions to various aldehydes were investigated. The reaction of certain aromatic aldehydes, α,β-unsaturated aldehydes, and cyclohexanecarbaldeyde showed up to 99% ee.



Scheme 2.54. Addition of diethylzinc to benzaldehyde using catalysts **157**, **158** and **159**

The phosphoramide **160** and thiophosphoramide **161** were prepared by Shi and Sui (1999). In the presence of 1.4 equiv Ti(O-*i*-Pr)$_4$, **160** catalyzed the reaction of diethylzinc with aldehydes with up to 83% ee but **161** onyl gave ≤50% ee.

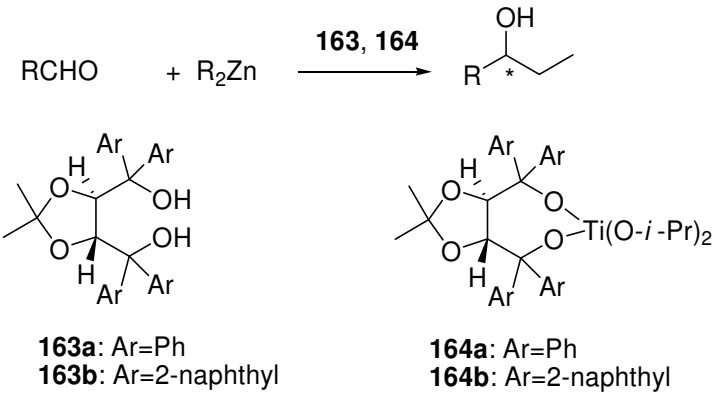
The thiophosphoramidate ligands **162a**-**c** in combination with Ti(O-*i*-Pr)$_4$ were used by Soai et al. (1993) to catalyze the diethylzinc addition to aldehydes. In the presence of 15 mol% **162a** and 0.8 equiv of Ti(O-*i*-Pr)$_4$, the reaction of aromatic aldehydes and α,β-unsaturated aldehydes with diethylzinc produced chiral alcohols with 90-97% ee and good yield. The reaction of dimethylzinc with benzaldehyde gave (*S*)-1-phenylethanol with 95% ee and 52% yield. Compounds **162b**,**c** gave slightly lower ee' s (88% and 74%, respectively) for the reaction of diethylzinc with benzaldehyde (Soai et al., 1993).



Scheme 2.55. Addition of diethylzinc to benzaldehyde using catalysts **160**, **161** and **162**

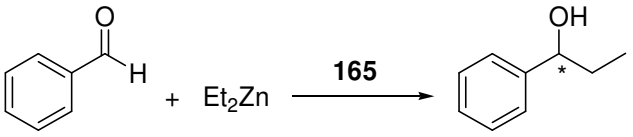
2.7.1.10.2. TADDOLs and Related Alcohol

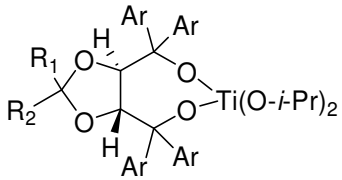
TADDOLs ($\alpha,\alpha,\alpha',\alpha'$,-tetraaryl-1,3-dioxolan-4,5-dimethanols) have been successfully employed as chiral auxiliaries for a variety of synthetic organic transformations including stoichiometric and catalytic nucleophilic additions to carbonyls. Seebach et al. (1991) carried out an extensive study on using the titanium complexes of TADDOLs such as **163** and **164** for asymmetric organozinc addition. They found that in the presence of 20 mol% of **163** or 10 mol% **164** and an excess amount of Ti(O-*i*-Pr)$_4$ (1.2-2.4 equiv), addition of dialkylzinc reagents to aromatic and aliphatic aldehydes were highly enantioselective (82-99% ee) in toluene at -76 to -20 °C.



Scheme 2.56. Addition of diethylzinc to benzaldehyde using catalysts **163** and **164**

Many TADDOL derivatives, e.g., **165a**-**d**, were prepared from tartrate esters and aryl Grignard reagents (Seebach et al., 1992). It was found that varying the aryl groups as well as the protecting acetal groups on TADDOL had little effect on the enantioselectivity for the diethylzinc addition to benzaldehydes. In general, over 90% ee was observed with 0.02-0.2 equiv of the chiral titanates and excess Ti(O-*i*-Pr)$_4$. Optically active *S* alcohols with 90-98% ee were obtained from the enantioselective ethylation of benzaldehyde.





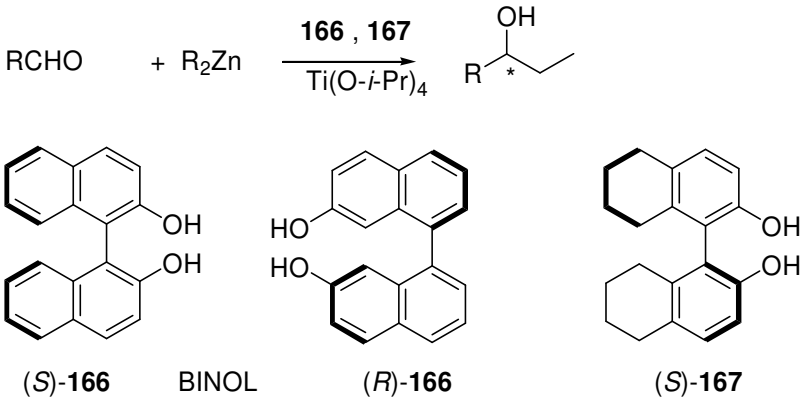
165a: R_1=R_2=Me, Ar=Ph
165b: R_1=R_2=Me, Ar=2-naphthyl
165c: R_1=R_2=Me, Ar=4-MeO-Ph
165d: R_1=R_2=Me, Ar=4-Ph-Ph
165e: R_1=R_2=Me, Ar=1-naphtyl
165f R_1=R_2=-$(CH_2)_5$-, Ar=Ph

Scheme 2.57. Addition of diethylzinc to benzaldehyde using catalysts **165**

2.7.1.10.3. BINOL-based ligands

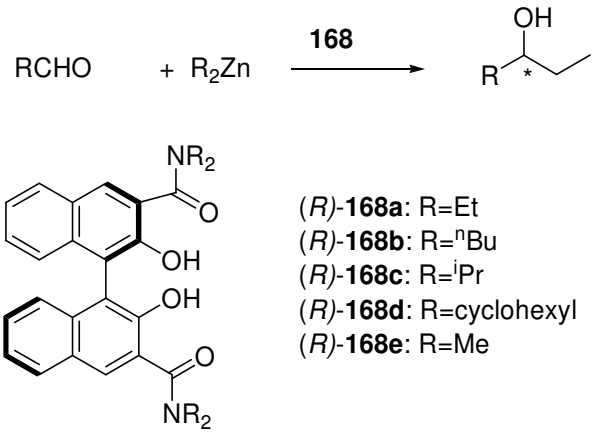
1,1'-Bi-2-naphthol (BINOL), *S*, or (*R*)-**166**, and its derivatives are axially chiral diols that have found extensive applications in asymmetric catalysis and others. In 1997, two research groups, Nakai (1997) and Chan (1997), independently reported the use of a titanium complex of (*S*)-**166** for the diethylzinc addition to aldehydes. It was found that the ratio of (*S*)-**166** and Ti(O-*i*-Pr)$_4$ had great effect on the enantioselectivity. A ratio of 1:7 [(*S*)-**166**/Ti(O-*i*-Pr)$_4$] gave the best result in methylene chloride and a ratio of 1:12 in toluene. In the presence of 20 mol% of (*S*)-**166** and 1.4 equiv of Ti(O-*i*-Pr)$_4$, the addition of diethylzinc to aromatic aldehydes, aliphatic aldehydes, and α,β-unsaturated aldehydes proceeded with up to 92% ee. The enantioselectivity for the recation of benzaldehyde was slightly better in CH_2Cl_2 than in toluene. All of the alcohol products generated from (*S*)-**166** had a *S* configuration.

When (*S*)-**166** was partially hydrogenated to (*S*)-**167**, a significant improvement in enantioselectivity was observed in many cases (Pu, 1998). With the use of excess Ti(O-*i*-Pr)$_4$, (*S*)-**167** catalyzed the diethylzinc addition to aromatic aldehydes with 85-99% ee. The enhanced enantioselectivity from (*S*)-**166** to (*S*)-**167** probably resulted from the increased steric interaction between the two tetrahydronaphtyl rings in (*S*)-**167**, which made the rotation around the pivotal 1,1'-bond more restricted.



Scheme 2.58. Addition of diethylzinc to benzaldehyde using catalysts (*S*)-, (*R)*-**166**, (*S*)-**167**

The BINOL derivatives (*R*)-**168a**-**e** containing amide functional groups at the 3-3'-positions were found by Katsuki et al. to be efficient catalysts for the diethylzinc addition without the use of a titanium complex.The reactions in polar solvents such as THF gave higher enantioselectivity as well as better chemical yield than those in nonpolar solvents such as toluene. Among these BINOL ligand, (*R*)-**168b,c** were the most enantioselective ones for the reaction of various aldehydes. Participation of the amide carbonyl groups in the coordination to the zinc centers of the intermediate in situ generated from the reaction of the ligands with diethylzinc was believed to be important for the high enantioselectivity. In the presence of 10 mol% of (*R*)-**168b** or (*R*)-**168c**, aromatic aldehydes, cyclohexanecarboxaldehydes, cinnamaldehyde, and phenylpropargyl aldehyde reacted with diethylzinc with 91-99% ee.



Scheme 2.59. Addition of diethylzinc to benzaldehyde using catalysts **168**

2.7.2. Heterogeneous chiral cataysts

Heterogeneous chiral catalysts have advantages over homogenous catalysts in their easier separation and recovery from the reaction mixture. The other advantage of heterogeneous catalyst is that they can be used several times without decreasing activity (König et al., 2003).

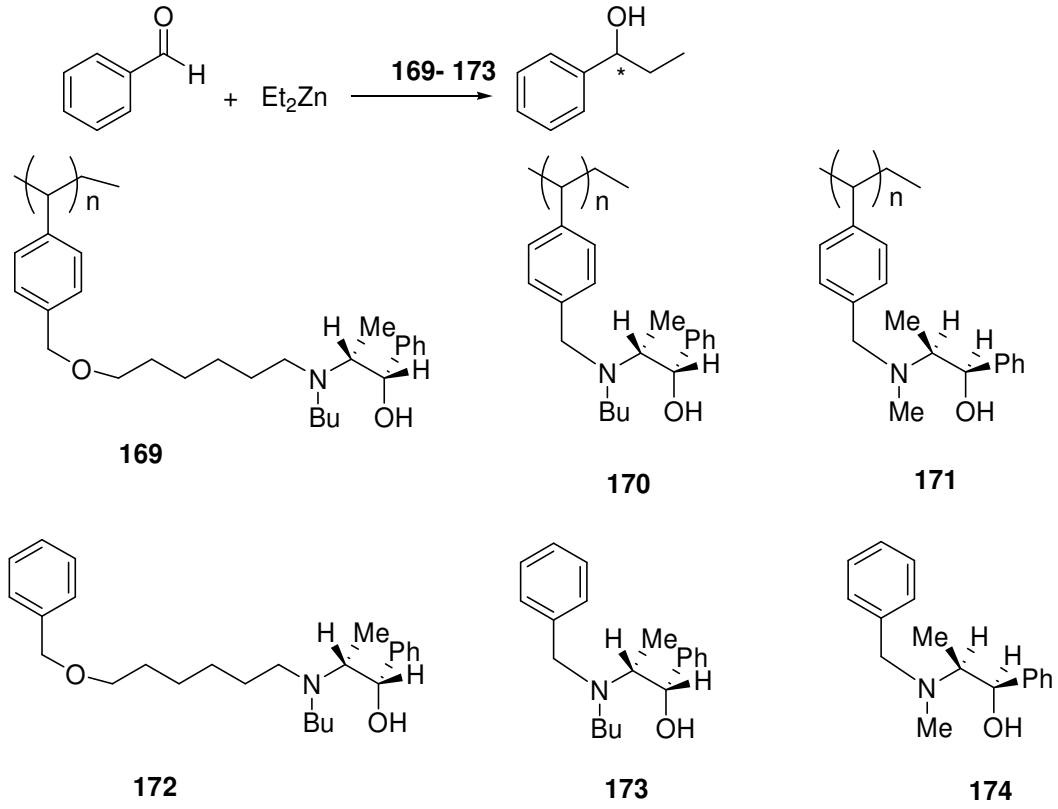
2.7.2.1. Macromolecules in organozinc additions

The use of polymer-based catalysts is very attractive for asymmetric catalysis because it allows easy recovery and reuse of the often quite expensive chiral catalysts. Polymer-based chiral catalysts also make it possible to carry out the asymmetric reactions in a flow system for continuous production. Three types of polymer-based chiral catalysts have been investigated in the asymmetric organozinc additions : (1) polymers anchored with chiral catalysts, (2) main chain chiral polymer catalysts, and (3) dentritic chiral catalyst.

2.7.2.1.1 Polymers anchored with chiral ligands

Soai and Watanabe (1991b, 1994c) studied the use of the polystyrene-supported ligands **169**-**171** for the reaction of diethylzinc with aldehydes. These polymers

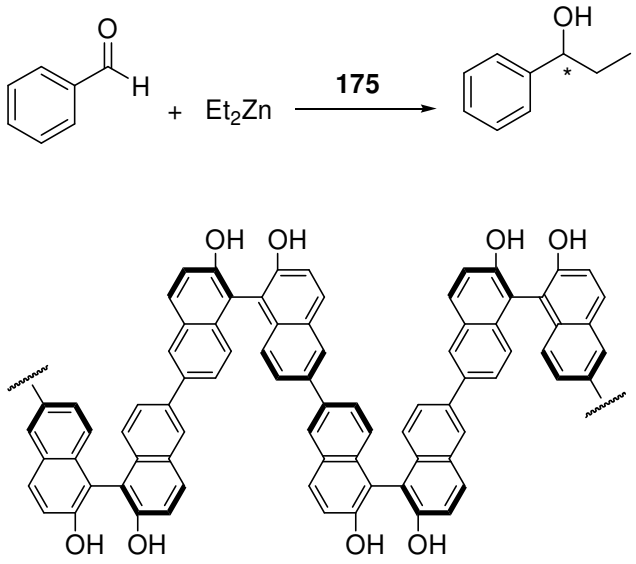
showed 82%, 17%, 89% ee, respectively, for the reaction of diethylzinc with benzaldehyde. The enantioselectivity of the polymers was lower compared to that of their corresponding monomers **172**, **173**, **174** which gave 99%, 89%, and 92% ee, respectively. For the reaction of aliphatic aldehydes, polymer **169** gave the highest enantioselectivity among the amino alcohol-based polymers. It catalyzed the reaction of diethylzinc with nonyl aldehyde with 71% ee. Its monomer ligand **172** gave 73% ee. The reactions using these polymer were carried out in hexane, which allowed the polymer ligands to be easily recycled by simple filtration, and the recovered polymers showed the same enantioselectivity as the original polymers.



Scheme 2.60. Addition of diethylzinc to benzaldehyde using polymer-based chiral catalysts

2.7.2.1.2. Main chain chiral polymer catalysts

A class of main chain chiral polymers based on optically active binaphthyls, such as (*R*)-**175**, was designed and synthesized for asymmetric catalysis by Pu et al. (1997). Polymer (*R*)-**175** was used to catalyze the reaction of benzaldehyde with diethylzinc (Pu et al., 1999). In the presence of this polymer, diethylzinc reacted with benzaldehyde at room temperature in methylene chloride to give 1-phenylpropanol with only 13% ee.



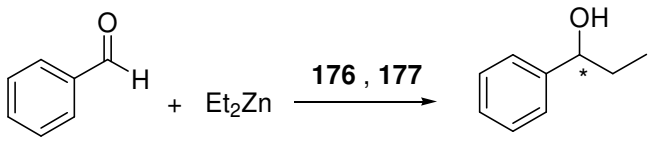
(*R*)-**175**

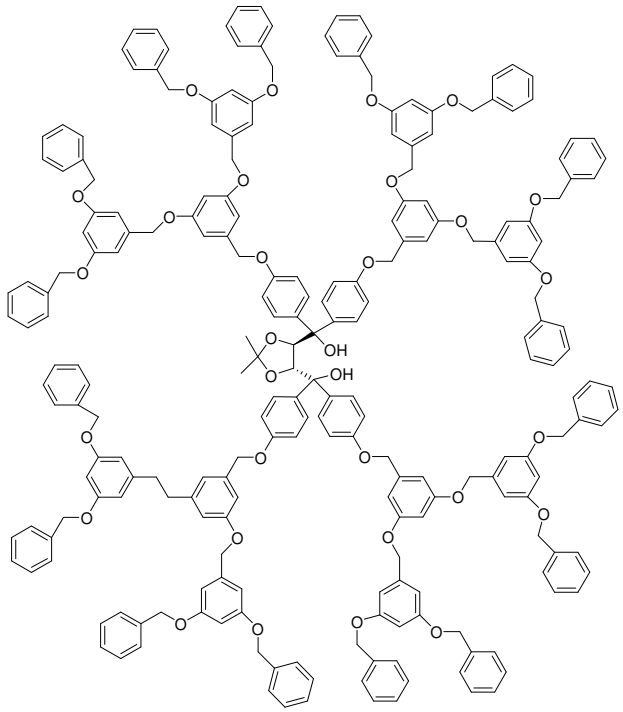
Scheme 2.61. Addition of diethylzinc to benzaldehyde using main chain chiral polymers based on optically active binaphthyls

2.7.2.1.3. Dendrimer ligands

Dendrimers are macromolecules that branch out from a center like trees. Seebach et al. synthesized dendritic TADDOL derivatives for the asymmetric organozinc addition. Compounds **176** and **177** had the TADDOL species in the periphery of the dendrimers, while dendritic ligands exhibited high enantioselectivity for the diethylzinc addition to benzaldehyde with the use of 20 mol% of the dendrimers

and 1.2. equiv of Ti(O-*i*-Pr)$_4$. These dendrimers showed 94-98% ee for the reaction of diethylzinc with benzaldehyde (Seebach, 1996).





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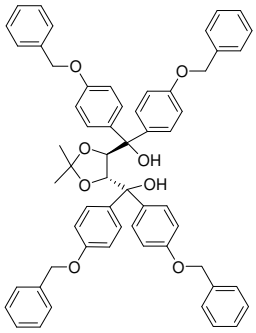


177

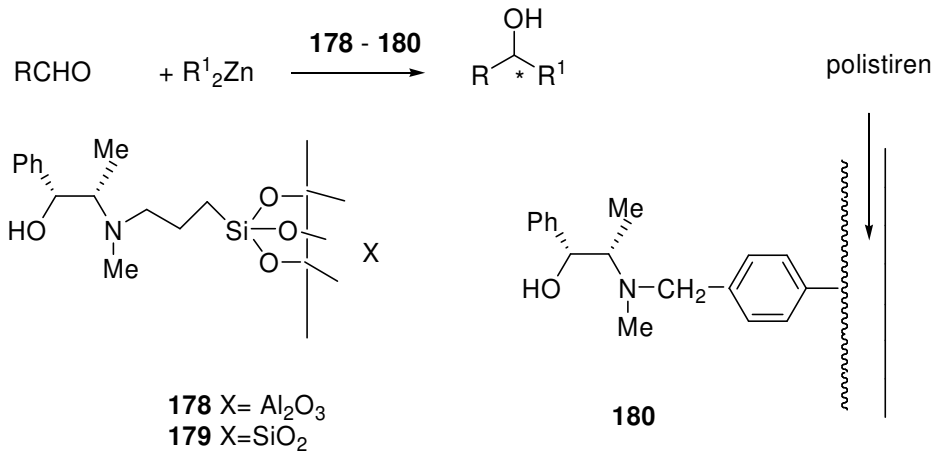
Scheme 2.62. Dendritic TADDOL derivatives for the asymmetric organozinc addition.

2.7.2.3. Organozinc additions on inorganic solid supports

Chiral catalysts were also anchored to inorganic supports for the reaction of dialkylzincs to aldehydes. Silica gel and alumina are widely used as the stationary phase in chromatographic separations.

Soai et al. (1990b) immobilized chiral *N*-alkylnorephedrine on (3-chloropropyl) silyl-functionalized alumina or silica gel using a silane coupling reagent (3-chloropropyl)-trimethoxysilane. Optically active secondary *R* alcohols were

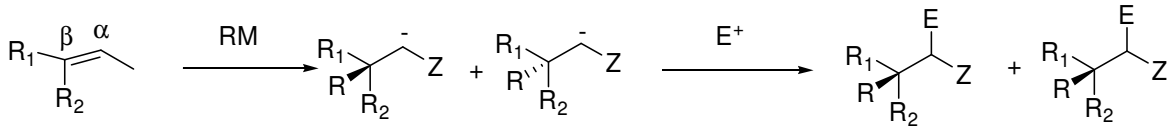
obtained by using (1*R*,2*S*)-**178** and (1*R*,2*S*)-**179**. Optical yields are not very high; 33-40% ee. (1*R*,2*S*)-Ephedrine immobilized on silica gel coated with polystrene **180** is also a chiral catalyst which affords optically active secondary alcohols in 36-56% ee.



Scheme 2.63. Inorganic supports for the reaction of dialkylzincs to aldehydes

2.7. Enantioselective Conjugate Addition Reactions

Conjugate addition reaction of carbon nucleophiles to α,β-unsaturated compounds is one of the most important carbon-carbon bond forming strategies in synthetic organic chemistry. In these reactions, the organic portion of an organometallic reagent add to the β-carbon of the electron-deficient alkene, giving first a stabilized carbanion and then after protonation or some other form of quenching, the β-substituted product (Scheme 2.64).



Scheme 2.64. Enantioselective conjugate addition reaction

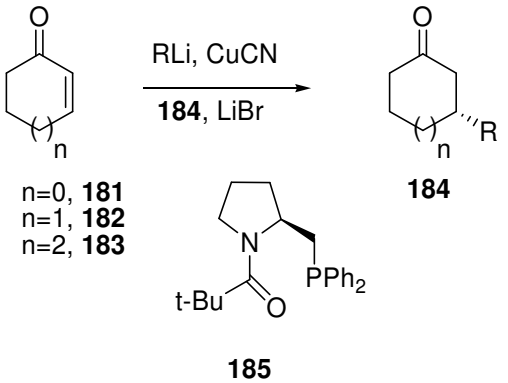
Substrates used in this reaction are usually α,β-unsaturated ketones, aldehydes, esters, amides, sulfoxides, or nitro compounds. Reactions involving organometallic

reagents are generally run under anhydrous, oxygen-free conditions. These reactions use a variety of organometallic reagents, the most common of which are organolithiums, Grignards, and cuprates. In particular, the exploitation of dialkylzinc reagents has been extremely successful in the development of highly enantioselective catalytic 1,4-additions in recent years (Sibi and Manyem, 2000). Enantioselective conjugate addition can be achieved in a number of ways :

(a) using a chiral non-transferable group attached to the nucleophile ;
(b) using an external chiral ligand, which complexes to the nucleophile ;
(c) using a chiral ligand that binds to the acceptor and dictates the approach of the nucleophile ;
(d) using a chiral Lewis acid (chiral ligand and metal salt) that activates the acceptor ;
(e) using a chiral entity that brings together both the acceptor and donor.

2.7.1. Addition of organocuprate reagents

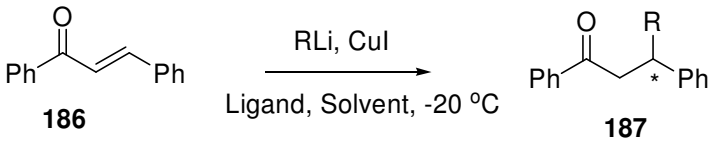
Organocuprates are some of the most important reagents for C-C bond forming reactions available to synthetic chemists. The additions of alkylcuprates were investigated by Tomioka et al. (1999) using chiral amidophosphines and CuCN (Scheme 2.65). In the absence of lithium salts, the addition of methylcopper proceeds with low selectivity. High enantioselectivities (68-95% ee) for **184** were obtained with high loading of the ligand **185** and lithium bromide.



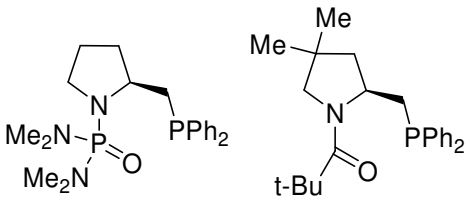
entry	N	R	yield (%)	ee (%)
1	1	Me	66	92
2	1	Et	89	91
3	1	Ph	63	73
4	0	Et	90	94
5	0	Bu	99	95
6	3	Me	46	68

Scheme 2.65. Enantioselective conjugate addition of lithium organocuprate to cyclic enone

They also studied the addition of lithium organocuprate to chalcone (**186**) in the presence of chiral amidophosphines **185**, **188**, and **189** by varying the substituent on nitrogen and the steric bulk on the pyrrolidinone ring, ligands of various potencies were prepared and tested (Scheme 2.66). Solvent dependence was two fold: donor solvents were required for enantioselectivity and the strength of the donor solvent was important for high ee' s and sense of stereoinduction. THF and DME gave the *R* enantiomer while ether, toluene and dimethyl sulfide gave the *S* enantiomer. As shown in Scheme 2.66, the best results were obtained with the second generation ligand **189** containing 3,3-dimethyl substituents (Tomioka et al., 1996).



186 **187**



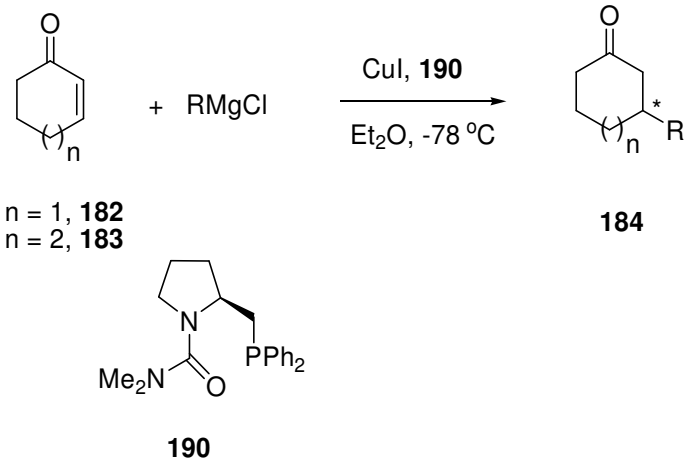
188 **189**

entry	ligand	R	solvent	yield (%)	ee (%)
1	**185**	Me	Ether	79	84 (*S*)
2	**185**	Me	THF	72	50 (*R*)
3	**185**	Bu	Ether	97	24 (*S*)
4	**185**	Bu	THF	39	30 (*R*)
5	**188**	Me	Ether	88	71 (*S*)
6	**188**	Me	THF	72	66 (*R*)
7	**189**	Me	Ether	99	90 (*S*)

Scheme 2.66. Enantioselective conjugate addition of lithium organocuprate to acyclic enone

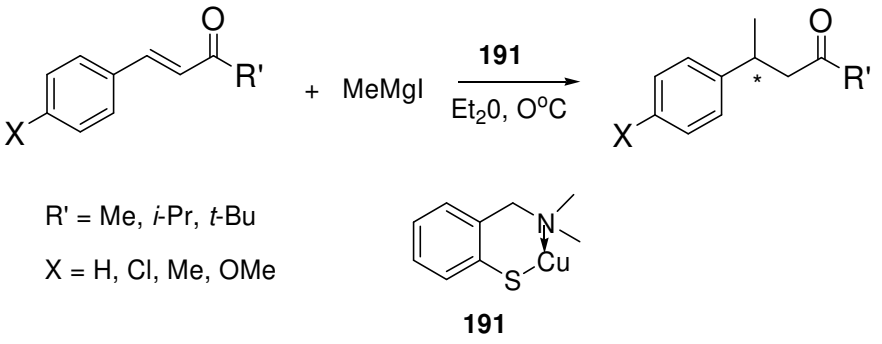
2.7.2. Addition of Grignard reagents

Tomioka and Kanai (1996) reported the use of a chiral bidentate phosphine ligand in the copper catalysed addition of Grignard reagents to cyclic enones. The additon of several *n*-alkylmagnesium chlorides to enones **182** or **183** in the presence of 8 mol% of CuI and 32 mol% of **190** gave 1,4-addition products in good yields and with relatively high enantioselectivities (70-92% ee) (Scheme 2.67).



Scheme 2.67. Enantioselective conjugate addition of Grignard reagents to cyclic enone.

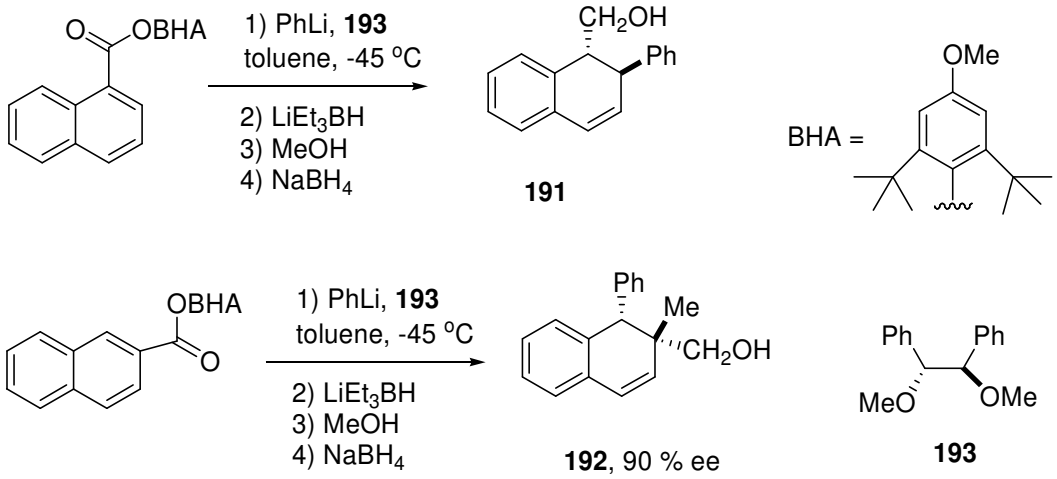
Koten et al. (1994) reported the use of chiral copper (I) arenethiolate (2-[1-(*R*)-dimethylamino)ethylphenylthiolate copper (I) **191** as a catalyst for the enantioselective addition of MeMgI to benzylideneacetone (Scheme 2.68). Using the optimal parameters found for MeMgI, the scope of this reaction examined for other Grignard reagent (*N*-BuMgI and *i*-PrMgI, 45 and 10% ee, respectively) and various acyclic enones. Substrates with different substituents on the aromatic ring and steric bulk next of the carbonyl group gave products with slightly lower enantioselectivities (45-72% ee).



Scheme 2.68. Enantioselective conjugate addition of Grignard reagents to enone.

2.7.3. Addition of organolithium reagents

α,β-Unsaturated esters undergo conjugate addition with alkyl and aryllithium reagents. Chemoselectivity (1,4- vs 1,2-addition) in these reactions can be controlled by increasing the steric bulk in the ester substituent. Shindo (1993) has successfully employed 2,6-di-ter-butyl-4-methoxyphenyl (BHA) esters in conjugate additions to give **191** and **192** with 84%, 90% ee, respectively.



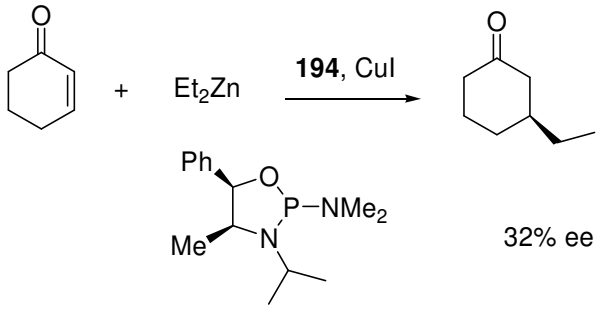
Scheme 2.69. Enantioselective conjugate addition of organolithium reagents to ester

2.7.4. Organozinc reagents

Organozinc reagents hold a special place in development of enantioselective conjugate addition of organometallic reagents. Organozinc reagents are much less basic than the other organometallic reagents employed in conjugate addition reaction. Diethylzinc addition to enones and other conjugate acceptors in the absence of additives, either ligands or other transition metal catalysts, is slow. Hence, this reaction has proved most suitable for the development of ligands and to test their efficiency in enantioselective conjugate addition and other reactions. Two distinct classes of catalysts have been pursued, nickel catalysts for acyclic enones and copper catalysts for cycloalkenones.

2.7.4.1. Copper catalyzed enantioselective conjugate addition of diethylzinc to cyclic enones

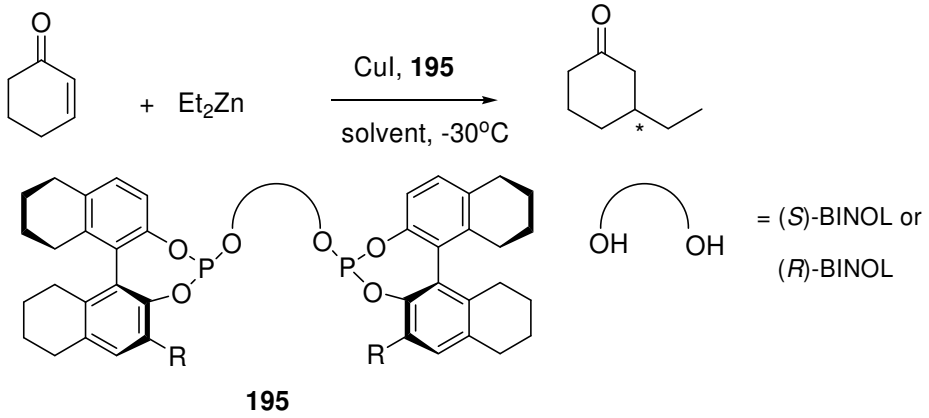
In 1993, Alexakis et al. published the first example of a copper catalyzed enantioselective 1,4-addition of diethylzinc to 2-cyclohexenone The use of 10 mol% of CuI and 20 mol% of trivalent phosphorous ligand **194** resulted in an enantioselectivity of 32%. Under the same conditions chalcone gave racemic material. (Alexakis et al., 1993).



194

Scheme 2.70. First copper catalyzed enantioselective 1,4-addition of diethylzinc published by Alexakis (1993)

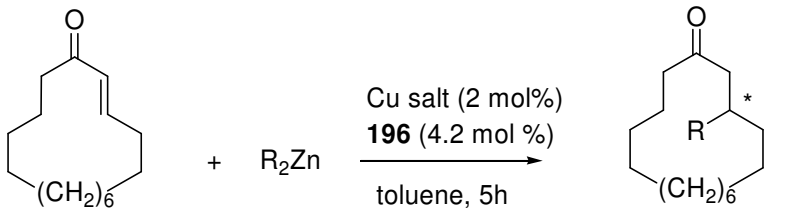
Liang et al. (2002) showed that when diethylzinc reacted with cyclic enones in the presence of chiral aryl diphosphite ligands, $Cu(OTf)_2$ and $Cu(OTf)_2.C_6H_6$, products were obtained with up to 99% ee. They found that the catalyst prepared in situ from $Cu(OTf)_2.C_6H_6$ (92% ee) was more effective than that from $Cu(OTf)_2$ (84% ee).



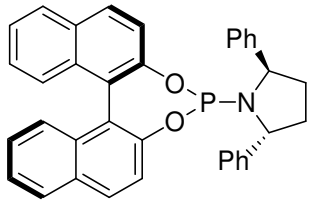
195

Scheme 2.71. Asymmetric Addition of diethylzinc to cyclic enones employing **193** as ligand.

Kim et al. (2002) established that a new binaphthol phosphoramidite ligand containing a chiral C_2-symmetric pyrrolidine moiety was an excellent ligand for chiral copper complexes which furnished high enantioselectivities in the asymmetric conjugate additions of organozinc reagents to macrocyclic and cyclic enones. The chiral ligand **196** had been applied to synthesis of (*R*)-(-)-muscone, a biologically intriguing natural product which had been synthesized. The highest enantioselectivity was obtained at -40 °C in toluene (95% ee). The enantioselectivity decreased considerably as the reaction temperature was elevated to -15 °C or 0 °C. Use of $(Cu(OTf)_2$.toluene complexes gave somewhat higher enantioselectivity than the $Cu(OTf)_2$ system.



55-95% ee
75-90% yield



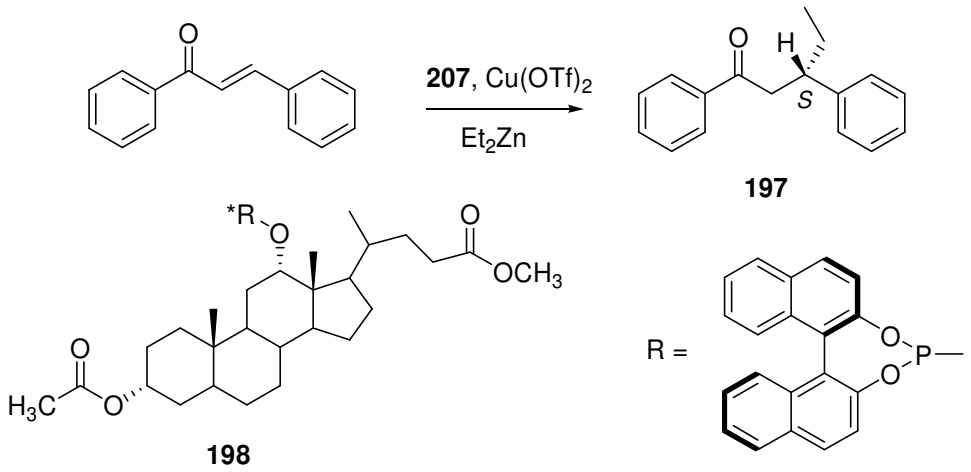
(*R*, *R*, *R*)-**196**

Cu salt	R	T (°C)	yield (%)	ee (%)
$(Cu(OTf)_2$	Me	-20	90	86 (R)
$(Cu(OTf)_2$	Me	-40	85	93 (R)
$(Cu(OTf)_2$	Me	-78	-	-
$(Cu(OTf)_2$.toluene	Me	-40	87	95 (R)
$(Cu(OTf)_2$.toluene	Et	-40	95	74 (R)

Scheme 2.72. The enantioselective conjugate addition of dialkylzinc to cyclic enones

2.7.4.2. Copper catalyzed enantioselective conjugate addition of diethylzinc to acyclic enones

Iuliano and Scafato (2003) reported the synthesis of different deoxycholic based phosphites obtained by reacting suitable monohydroxy derivatives of deoxycholic acid with *R*- and *S*-binaphthyl chlorophosphites and their screening for activity and enantioselectivity in the copper-catalyzed enantioselective conjugate addition of diethylzinc to acyclic enones. The conjugate addition of diethylzinc in the presence of the catalytic species obtained from **198** and $Cu(OTf)_2$ in molar ratio 1.2:1 at -20 °C affords the alkylated product in 87% yield with 59% ee, after 2 hours. This ligand showed 77% ee, respectively, for the reaction of diethylzinc with chalcone at -70 °C.

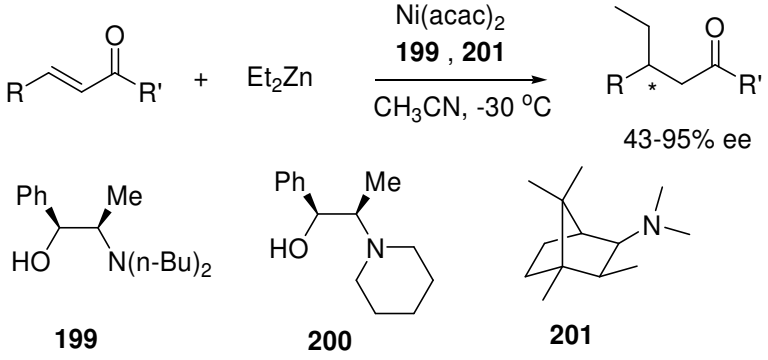


Scheme 2.73. Chiral ligands used as catalysts in the enantioselective conjugate addition of diethylzinc to chalcone.

2.7.4.3. Nickel catalyzed enantioselective conjugate addition of diethylzinc to acyclic enones

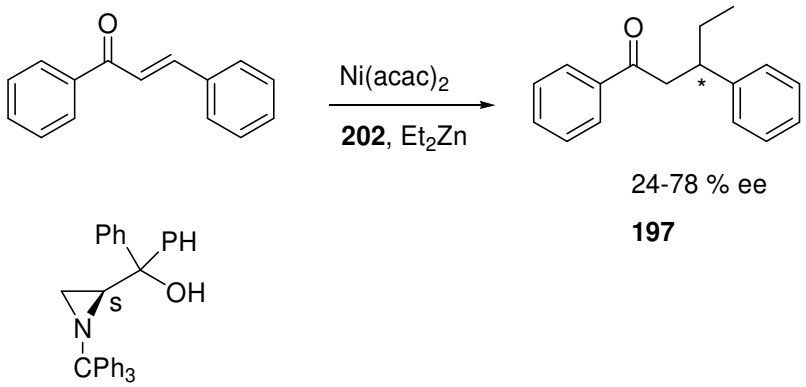
Several catalytic 1,4-additions of diethylzinc to acyclic enones employing chiral nickel complexes have been developed. The substrates and chiral catalysts are compiled in Scheme 2.74. Based on work of Grene and Luche et al. (1984) an enantioselective modification of the nickel catalysed alkyl transfer from diethylzinc to chalcone was found by Soai et al. (1991c).

The chiral catalyst, prepared in situ from $NiBr_2$ and (1*S*,2*R*)-*N*,*N*-di-n-butylnorephedrine (**199**), afforded (*R*)-1,3-diphenylpentan-1-one (**197**) in 32% yield with 48% ee. Higher yields (> 70 %) were achieved with $Ni(acac)_2$ instead of $NiBr_2$ (Soai et al., 1988), although large amounts of chiral ligand are required (Scheme 2.76). Preparation of the chiral catalyst from 6 mol% of $Ni(acac)_2$, 14 mol% chiral ligand **199** or **200** and 7 mol% 2,2'-bipyridine in acetonitrile raised the enantioselectivity up to 90% (Soai et al., 1989).



Scheme 2. 74. Enantioselective conjugate addition of diethylzinc to acyclic enones

Shadakshari and Nayak (2001) reported a new type of chiral auxiliary, *N*-trityl aziridine-2-(*S*)-(diphenyl)methanol (**202**), for the enantioselective conjugate addition to chalcones. They investigated the effect of temperature, ratio of ligand and solvent on the conjugate addition. The product was obtained in good yield (63-75%) with an ee of 78%, when the reaction was carried out -30 °C. The decrease in the enantioselectivity (27%) was observed when the reaction was carried out in acetonitrile at ambient temperature (25 °C). When the reaction was carried out in hexane in place of acetonitrile no reaction was observed and starting material was recovered quantitatively. Use of toluene yielded **197** in 67% yield with 28% ee. Similarly, **197** was isolated in good yield (65%), and good enantioselectivity (67% ee) using THF.



Scheme 2.75. Enantioselective conjugate addition of diethylzinc to chalcones in the presence chiral ligand **202**

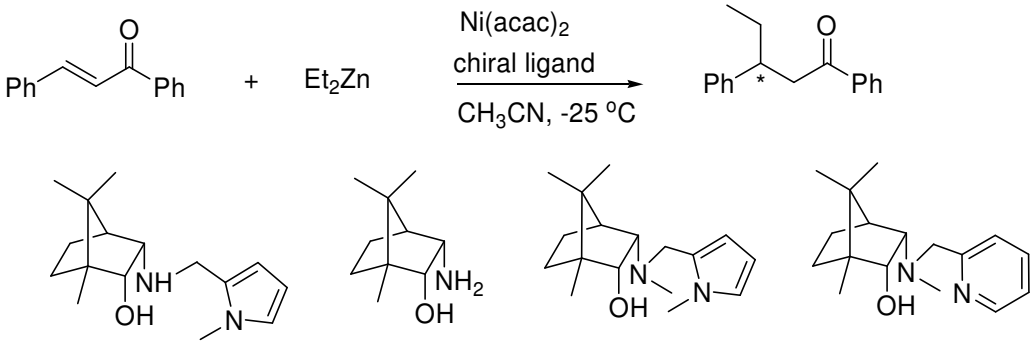
2.8. Pyrrole-Containing Chiral Ligands

Pyrrole ring is an important structural unit of many different biologically active compounds. The selective synthesis of unsymmetrically substituted pyrroles is an important area of the pyrrole chemistry. Chiral pyrrole derivatives of amines and amino acids have great importance because of their biologicall activities and their role in the synthesis of many different biologically active compounds (Jefford et al., 1991)

In addition to their biological activities, the chiral pyrrole derivatives of amines and amino acids can be used as chiral catalysts for the enantioselective reduction, and carbon-carbon bond forming reactions.

Feringa et al. (1997) synthesized several novel pyrrole-containing amino alcohol ligands, all derived (+)-camphor by using specific alkylation procedures. They used these ligands as chiral ligands in the nickel catalyzed conjugate additions of diethylzinc to chalcone and cyclohexenone as model substrates. The effect of additional coordinating groups in the chiral ligand on the enantioselectivity in the nickel catalyzed addition of diethylzinc to chalcone was examined. When the secondary amino alcohol **203** was employed as chiral ligand a relatively high enantioselectivity (57% ee) was observed for 1,4-product. Primary amino alcohols

like **204**, did hardyl show any enantioselectivity in their earlier study (ee <5%) (Feringa et al., 1994). High ee values (65-80%) were obtained by using the tertiary amine ligand **205** (7, 11, 16 mol%). At constant nickel ratio, enantioselectivity was increased by raising the amount of ligand **204** (Scheme 2.76). Pyridine substituted ligand **206** no enantioselectivity was observed.

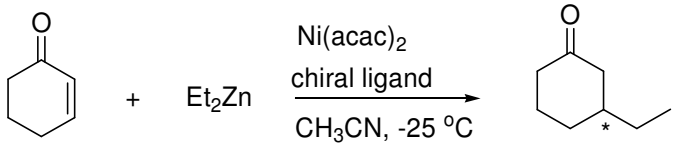


203 **204** **205** **206**

chiral ligand (mol %)	yield %	ee %
203(11)	75	57
204 (16)	85	4
205 (7)	78	65
20511)	91	80
205 (16)	83	83
206 (16)	67	0

Scheme 2.76. Pyrrole and pyridine containing ligands in the nickel addition of diethylzinc to chalcone

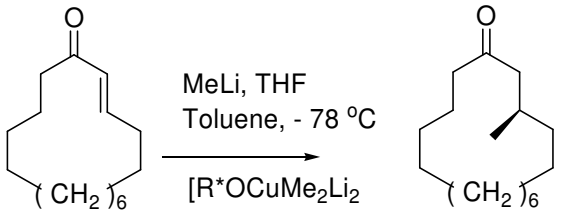
These ligands were examined as chiral ligand in the conjugate addition of diethylzinc to cyclohexenone. Ligand **203** and **204** were not able to induce selectivity exceeding 12% ee. The pyridine substituted ligand **206** did not result in optically active product (Scheme 2.77).



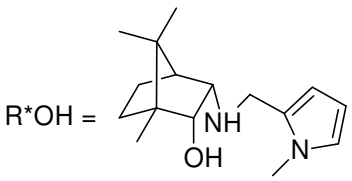
chiral ligand (mol %)	ee %
203 (11)	7
205 (16)	12
206 (7)	0

Scheme 2.77. Pyrrole and pyridine containing ligands in the nickel addition of diethylzinc to cyclohexenone

Tanaka et al. (1993) realized the chiral alkoxycuprate catalysed addition of MeLi to (*E*)-cyclopentadec-2-en-1-one affording (*R*)-(-)-muscone **207** with 99% ee (Scheme 2.78).



(*R*)-(-)-muscone, 99% ee

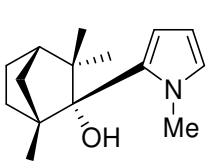


207

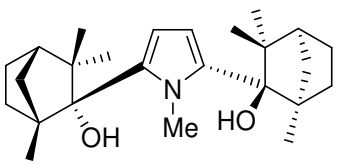
Scheme 2.78. Enantioselective conjugate addition of organolithium reagents to α,β-unsaturated enone

The chiral catalyst was prepared from amino alcohol ligand **207** by sequential addition of MeLi, CuI, and MeLi. The conditions for the catalyst preparation are very critial to reach high enantioselectivities. The use of 1 equivalent of THF, presumably as external ligand to the chiral cuprate, increase the ee significantly. Under optimised conditions, 36 mol% of chiral ligand **207** provides muscone virtually enantiomerically pure and in high yield.

Dimitrov et al. (1997) reported that new optically active amino alcohol in one step from (+)-camphor and (-)-fenchone (Scheme 2.79) catalyzes the enantioselective addition of diethylzinc to benzaldehyde. In the presence of 3 mol% **208** , *R*-conjugated alcohol was achieved with 10% ee. **209** furnished *S*-conjugated alcohol with 15% ee.



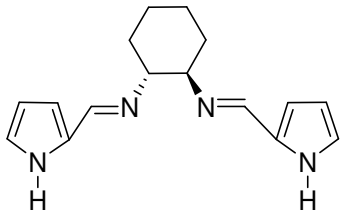
208



209

Scheme 2.79. Pyrrole and camphor containing ligands in the addition of diethylzinc to benzaldehyde.

König et al. (2003) presented some nitrogen-containing ligands with (1*R*,2*R*)-*trans*-diaminocyclohexane (Scheme 2.80) and their use in enantioselective reaction, such as alkene cyclopropanation, alkene epoxidation and addition of diethylzinc to benzaldehyde. In the presence of 5 mol% **210**, the addition of diethylzinc to benzaldehyde afforded *S* alcohols with 3% ee in 12% yield .



210

Scheme 2.80. Pyrrole containing ligands in the addition of diethylzinc to benzaldehyde.

3. THE AIM OF THE WORK

Catalytic asymmetric carbon-carbon formation is one of the most active research areas in organic synthesis. In this field, catalytic asymmetric addition of diethylzinc to aldehydes and chalcone using catalytic amount of chiral ligand have particularly attracted much attention. Therefore, great efforts have been devoted to the development of various types of chiral ligands for this reaction.

The aim of the work is the synthesis of novel norephedrine and camphor-based ligands with *N*-substituted chiral pyrrole. For this purpose, in the first part of the study, *N*-substituted pyrroles were synthesized from 5-chloropent-3-ene-2-one and commercially available chiral amine. The synthesized pyrrole compounds were formylated by Vilsmeier Haack method. The formylated products were used to synthesize novel norephedrine and camphor based ligands with *N*-substituted pyrrole.

In the second part of the work , it was aimed to examine the activities of these chiral ligands as chiral catalysts in the enantioselective addition of diethylzinc to aldehydes and chalcone. The effects of solvent, amount of ligand, time, and temperature were investigated to find the optimum reaction conditions by using the most efficient ligands. Absolute configurations and ee's of the addition products were determined by HPLC.

4. EXPERİMENTAL

The structure determination of the compounds in this study was done by the instruments mentioned below.

^{1}H-NMR (400 MHz) and ^{13}C-NMR (100 MHz) spectra were recorded with a Bruker Instrument DPX-400, 400 MHz High Performance Digital FT-NMR Spectrometer by using $CDCl_3$ as a solvent and tetramethylsilane (TMS) as internal standard respectively. Chemical shifts are as in part per million (δ) downfield from an internal standart TMS. Spin multiplicities are mentioned as: s (singlet), d (doublet), ddd (doublet of doublet of doublet), t (triplet), m (multiplet), b (broad).

All melting points were measured in sealed tubes using an electrothermal digital melting point apparatus (Gallenkamp).

Infrared spectra were recorded with Mattson 1000 series FTIR spectrometer.

Optical rotations were determined with AutoPol IV.

Enantiomeric excees were determined by HPLC, ThermoFinnigan equipped with an appropriate chiral phase column (Chiralcell OD and Chiralcell AD).

Elemental analysis were done by using a LECO CHNS-932.

X-Ray analysis was performed by using Enraf Nonius CAD4 Diffractometer

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

Solvents are higher grade, when necessary they were purified and dried with drying agents and by distillation.

All extracts were dried over anhydrous magnesium sulfate ($MgSO_4$) and solutions were concentrated under vacuum by performing rotary evaporator.

4.1. The synthesis of 5-chloropent-3-en-2-one (211)

Acetyl chloride (10.5 mmol) was added dropwise to a mixture of alumium chloride (11.2 mmol) suspension in dichlorometane (20 mL) at -20 °C. After 10 minutes, allyl chloride (7.5 mmol) dissolved in dichlorometane (5 mL) was added over 10 minutes at the same temperature. The mixture was stirred at – 20 °C for 1 hour and poured into 10 g ice with 10 mL water. The precipitate was dissolved with 1 N HCl and aqueous layer was extracted with dichlorometane (2x15 mL), the organic layers were washed with a 10% aqueous $NaHCO_3$ solution. Combined organic layers were dried over anhydrous $MgSO_4$. The crude product was checked by NMR and used without purification.

4.2. The Synthesis of Chiral Pyrrole Derivaties

4.2.1. The synthesis of 2-methyl-1-((1*R*)-1-phenylethyl)-1*H*-pyrrole ((*R*)-213) and 2-methyl-1-((1*S*)-1-phenylethyl)-1*H*-pyrrole ((*S*)-213)

In order to synthesize both enantiomers, same procedure was applied. For the synthesis of 2-methyl-1-((1*R*)-1-phenylethyl)-1*H*-pyrrole ((*R*)**-213**), (*R*)-phenylmethyl amine (**212**) was used, to synthesize 2-methyl-1-((1*S*)-1-phenylethyl)-1*H*-pyrrole (**212**) (*S*)-phenylmethyl amine (**212**) was used. The mixture of 5-chloropent-3-en-2-one (**211**) (4.89 g, 41.25 mmol), phenylmethyl amine (5 g, 41.25 mmol) and triethylamine (12.52 g, 123.75 mmol) in dry ether (50 mL) was refluxed for 8 hours. After this period 10 mL water was added to the solution. The water layer was extracted with ether (3 x 25 mL). Combined extracts were washed with brine and dried over anhydrous $MgSO_4$. The crude product was purified by column chromatography (Silica gel, EtOAc:hexane, 1:30).

2-Methyl-1-((1*R*)-1-phenylethyl)-1*H*-pyrrole ((*R*)-213): Light yellow solid, 6.87 g; 90% yield; mp:51-52 °C; R_f:0.47 (EtOAc:hexane, 1:3); $[\alpha]_D^{25}$ = +16.7 ° (c 1, $CHCl_3$); IR (KBr) ($\bar{\upsilon}_{max}$/cm^{-1}): 3100, 2970-2863, 1605-1440, 1100-1024, 762-700; ^{1}H-NMR: (400 MHz, $CDCl_3$) δ 1.79 (d, 3H, *J*=7.09 Hz, NCHC*H*$_3$), 2.06 (s, 3H, C*H*$_3$), 5.32 (q, 1H, *J*=7.08 Hz, NC*H*CH_3), 5.95 (broad s, 1H, C(3)*H*), 6.16 (broad s, 1H, C(4)*H*), 6.83 (broad s, 1H, C(5)*H*), 7.01 (d, 2H, *J*=7.37 Hz, Ar*H*), 7.24-7.35 (m, 3H, Ar*H*); ^{13}C-NMR: (100 MHz, $CDCl_3$) δ 12.26 (CH_3), 22.51 (CH_3), 54.85 (CH), 106.94 (CH, C-3 of pyrrole), 107.31 (CH, C(4) of pyrrole), 116.83 (CH, C(5) of pyrrole), 125.58 (CH), 127.05 (CH) 128.58 (CH), 128.60 (C, C(2) of pyrrole), 143.86 (C).

2-Methyl-1-((1*S*)-1-phenylethyl)-1*H*-pyrrole ((*S*)-213): Light yellow solid; 6.11 g; 80% yield; mp:51-52 °C; R_f:0.47 (EtOAc:hexane, 1:3); $[\alpha]_D^{25}$ = -16.7 ° (c 1, $CHCl_3$); IR (KBr) ($\bar{\upsilon}_{max}$/cm^{-1}): 3100, 2970-2863, 1605-1440, 1100-1024, 762-700; ^{1}H-NMR: (400 MHz, $CDCl_3$) δ 1.74 (d, 3H, *J*=7.09, NCHC*H*$_3$), 2.00 (s, 3H, C*H*$_3$), 5.18 (q, 1H, *J*=7.10 Hz, NC*H*CH_3), 5.80 (broad s,1H, C(3)*H*), 6.01 (broad s, 1H, C(4)*H*), 6.68 (broad s, 1H, C(5)*H*), 6.87 (d, *J*=7.48 Hz, Ar*H*), 7.10-7.28 (m, 3H, Ar*H*); ^{13}C-NMR: (100 MHz, $CDCl_3$) δ12.28 (CH_3), 22.53 (CH_3), 54.86 (CH), 106.97 (CH, C(3) of pyrrole), 107.34 (CH, C(4) of pyrrole), 116.85 (C, C(5) of pyrrole), 125.61 (CH), 127.06 (CH), 127.28 (CH), 128.62 (C, C-2 of pyrrole), 144.23 (C).

4.3. The Formylation of *N*-Substituted Pyrroles

In order to formylation of *N*-substituted pyrroles, Vilsmeir Haack formylation reaction was applied. Formylations of *N*-substituted pyrroles using DMF and $POCl_3$ were performed in pentane/Et_2O at 0 °C-room temperature or at 0 °C. Both of 3- and 5- formulated products were obtained by Vilsmeier Haack reaction. However by changing the reaction conditions (Method A and Method B) one of the formulated product can be obtained in higher yield.

4.3.1. General procedure for the formylation of *N*-substituted pyrroles

Method A : Pyrrole (6.22 g, 33.62 mmol) and dimethylformamide (2.49 g, 33.62 mmol) was dissolved in a mixture of 50 mL of pentane and 30 mL ether. This solution was cooled to 0 °C and $POCl_3$ (7.74 g, 50.43 mmol) was added with stirring over 1.5 hours. Stirring was continued for overnight at room temperature and iminium salt precipitates as a red oil and the upper layer was decanted. Then 4N NaOH (150 mL) was added to the red oil with stirring and cooling of the solution. After 1 hour, the aqueous mixture was extracted with chloroform (2x50 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated. The crude product was purified by column chromatography (EtOAc:hexane, 1:5, 1:3).

Method B : Pyrrole (0.185 g, 1 mmol) and dimethylformamide (0.740 g, 10 mmol) was dissolved in a mixture of 3 mL of pentane and 2 mL ether. This solution was cooled to 0 °C and $POCl_3$ (0.230 g, 10 mmol) was added with stirring over 1.5 hours. Stirring was continued for overnight at 0 °C and iminium salt precipitates as a red oil and the upper layer was decanted. Then 4N NaOH (15 mL) was added to the red oil with stirring and cooling of the solution. After 1 hour, the aqueous mixture was extracted chloroform (2x10 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated. The crude product was purified by column chromatography (Silica gel, EtOAc:hexane, 1:5, 1:3).

2-Methyl-1-((1*R*)-1-phenylethyl)-1*H*-pyrrole-3-carbaldehyde ((*R*)-214): Light yellow solid; 4.87 g; 68% yield for Method A; mp:107-108 °C; R_f:0.71 (EtOAc:hexane, 1:3); $[\alpha]_D^{25}$ = +21.1 (c 0.8, $CHCl_3$); IR (KBr) ($\bar{\upsilon}_{max}$/cm^{-1}): 3507-3134, 2987, 1650; ^{1}H-NMR: (400 MHz, $CDCl_3$) δ 1.85 (d, 3H, *J*=7.20 Hz, NCHC*H*$_3$), 2.43 (s, 3H, C*H*$_3$), 5.36 (q, 1H, *J*=7.20 Hz, C*H*CH_3), 6.60 (d, 1H, *J*=3.20 Hz, C(4)*H* of pyrrole), 6.75 (d, 1H, *J*=3.20 Hz, C(5)*H* of pyrrole), 7.04 (d, 2H, *J*=7.43 Hz, Ar*H*), 7.25-7.34 (m, 3H, Ar*H*), 9.85 (s, CHO); ^{13}C-NMR: (100 MHz, $CDCl_3$) δ 10.26 (CH_3), 21.99 (CH_3), 54.85 (CH), 108.64 (CH, C(4) of pyrrole), 118.65 (CH, C(5) of pyrrole), 122.76 (C, C(3) of pyrrole), 125.33 (CH), 126.70

(CH), 128.86 (CH), 137.08 (C, C(2) of pyrrole), 141.93 (C), 184.85 (C=O). Anal. Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.07; Found: C, 78.60; H, 7.24; N, 6.45.

5-Methyl-1-((1*R*)-1-phenylethyl)-1*H*-pyrrole-2-carbaldehyde ((*R*)-215): Brown oil; 1.5 g; 21% yield for Method A; R_f:0.87 (EtOAc:hexane, 1:3); $[\alpha]_D^{25}$ = +119.7 (c 11, $CHCl_3$); ^{1}H-NMR. (400 MHz, $CDCl_3$) δ 1.91 (d, 3H, *J*=7.20, NCHC*H*$_3$), 1.98 (s, 3H, C*H*$_3$), 6.00 (d, 1H, *J*=3.64 HZ, C(4)*H* of pyrrole), 6.88 (d, 1H, *J*=3.96 Hz, C(3)*H* of pyrrole), 6.98 (q, 1H, *J*=7.00 Hz NC*H*CH_3), 7.12 (d, 2H, *J*=7.34 Hz, Ar*H*) 7.24-7.33 (m, 3H, Ar*H*), 9.61 (s, CHO); ^{13}C-NMR. (100 MHz, $CDCl_3$) δ 14.25 (CH_3), 18.49 (CH_3), 53.17 (CH), 111.65 (CH, C(4) of pyrrole), 125.69 (CH, C(3) of pyrrole), 126.15 ppm (CH), 126.98 (CH), 128.42 (CH), 132.15 (C, C(2) of pyrrole), 140.77 (C, C(5) of pyrrole), 141.14 (C, C of phenyl), 178.24 (C=O).

2-Methyl-1-((1*S*)-1-phenylethyl)-1*H*-pyrrole-3-carbaldehyde ((*S*)-216): Light yellow solid**;** 5.01 g; 70% yield for Method A, 0.09 g, 43% yield for Method B; mp:107-108 °C; R_f:0.71 (EtOAc:hexane, 1:3); $[\alpha]_D^{25}$ = -21.9 (c 0.8, $CHCl_3$); IR (KBr) ($\bar{\upsilon}_{max}$/cm^{-1}): 3507-3134, 2987, 1650; ^{1}H-NMR: (400 MHz, $CDCl_3$) δ 1.86 (d, 3H, *J*=7.18 Hz , NCHC*H*$_3$), 2.44 (s, 3H, C*H*$_3$), 5.37 (q, 1H, *J*=7.07 Hz, NC*H*CH_3), 6.61 (d, 1H, *J*=3.23 Hz, C(4)*H* of pyrrole), 6.76 (d, 1H, *J*=3.26 Hz, C(5)*H* of pyrrole), 7.03 (d, 2H, *J*=7.33 Hz, Ar*H*), 7.26-7.37 (m, 3H, Ar*H*), 9.86 (s, C*H*O); ^{13}C-NMR: (100 MHz, $CDCl_3$) δ 10.42 (CH_3), 22.06 (CH_3), 54.91 (CH), 109.06 (CH, C(4) of pyrrole), 118.50 (CH, C(5) of pyrrole), 122.86 (C, C(3) of pyrrole), 125.63 (CH), 127.72 (CH), 128.92 (CH), 136.85 (C, C(2) of pyrrole), 141.80 (C), 185.18 (C=O). Anal. Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.07; Found: C, 78.55; H, 7.31; N, 6.30.

5-Methyl-1-((1*S*)-1-phenylethyl)-1*H*-pyrrole-2-carbaldehyde ((*S*)-217): Brown oil; 1.72 g; 24% yield for Method A, 0.111 g, 52% yield for Method B; R_f:0.87 (EtOAc:hexane, 1:3); $[\alpha]_D^{25}$ =-118.9 (c 11, $CHCl_3$); ^{1}H-NMR: (400 MHz, $CDCl_3$) δ 1.87 (d, 3H, *J*=7.09 Hz, CHC*H*$_3$), 1.95 (s, 3H, C*H*$_3$), 5.97 (d, 1H, *J*=3.87 Hz, C(4)*H* of pyrrole), 6.85 (d, 1H, *J*=3.91 Hz, C(3)*H* of pyrrole), 6.95 (q, 1H, *J*=7.02 Hz, C*H*CH_3), 7.08 (d, 2H, *J*=7.68 Hz, Ar*H*) 7.19-7.30 (m, 3H, Ar*H*), 9.43 (s, CHO); ^{13}C-

NMR: (100 MHz, $CDCl_3$) δ 14.23 (CH_3), 18.49 (CH_3), 53.21 (CH), 111.65 (CH, C-4 of pyrrole), 125.71 (CH, C(3) of pyrrole), 126.15 (CH), 126.99 (CH), 128.42 (CH), 132.17 (C, C(2) of pyrrole), 140.82 (C, C(5) of pyrrole), 141.16 (C, C of phenyl), 178.26 (C=O). Anal. Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.07; Found: C, 78.84; H, 6.86; N, 6.67.

4.4. General Procedure for the Synthesis of Novel Norephedrine-Based Ligands with *N*-Substituted Chiral Pyrrole

N-Substitueted pyrrole carbaldehyde (2.5 g, 11.74 mmol) was dissolved in 10 mL dry benzen. To this solution was added norephedrine (1.781 g, 11.74 mmol) in 10 mL dry benzen under argon. The mixture was refluxed under a Dean Stark trap for 3 days. Imine was concentrated to dryness without purification. Imine (4.28 g, 12.36 mmol) in dry ether (10 mL) was added to the suspension of LAH (0.53 g, 13.60 mmol) in dry ether (50 mL). After the addition was complete, the mixture was heated under argon for 10 hours (checking by TLC). The reaction mixture was quenched by sequential addition of water (15 mL), 15% NaOH (10 mL), and water (10 mL). The mixture was filtered off and white precipate was refluxed three times with ether. The mixture was filtered off, the organic layers was combined and dried over anhydrous $MgSO_4$. After evaporation of solvent, the crude product was purified by column chromatography.

(1*S*,2*R*)-2-((5-Methyl-1-((1*R*)-1-phenylethyl)-1*H*-pyrrol-2-yl)methylamino)-1-phenylpropan-1-ol ((1*S*,2*R*,*R*)-219): Brown oil; 2.78 g; 68% yield; R_f:0.32 (EtOAc:hexane, 1:1); $[\alpha]_D^{27}$=+20.6 (c 15.7, $CHCl_3$); IR (KBr) ($\bar{\upsilon}_{max}$/cm^{-1}): 3425, 3027, 2976, 2930-2864, 1467, 1451, 1405, 1291, 1112; ^{1}H-NMR: (400 MHz, $CDCl_3$) δ 0.81 (d, 3H, *J*= 6.40, NHCHC*H*$_3$), 1.97 (d, 3H, *J*=7.20 Hz, NCHC*H*$_3$), 2.08 (s, 3H, CH_3), 2.97-3.00 (m, 1H, NHC*H*CH_3), 3.78 (d, 1H, *J*=13.6 Hz, NHC*H*$_2$), 3.85 (d, 1H, *J*=13.6 Hz, NHC*H*$_2$), 4.71 (d, 1H, *J*= 4.00 Hz, C*H*OH), 5.71 (q, 1H, *J*=7.05 Hz, NC*H*CH_3), 5.85 (d, 1H, *J*= 2.48 Hz, C(4)*H* of pyrrole), 6.00 (d, 1H, *J*= 3.60 Hz, C(3)*H* of pyrrole), 7.09 (d, 2H, *J*=7.20 Hz, Ar*H*), 7.22-7.37 (m, 8H, Ar*H*); ^{13}C-NMR:

(100 MHz, $CDCl_3$) δ 14.18 (CH_3), 14.43 (CH_3, NHCHCH_3), 19.60 (CH_3, NCHCH_3), 44.01 ($NHCH_2$), 52.67 (CH, NCHCH_3), 57.82 (CH, NH$CHCH_3$), 73.05 (CHOH), 107.27 (CH, C(4) of pyrrole), 107.77 (CH, C-3 of pyrrole), 125.95 (CH), 126.03 (CH), 126.95 (CH), 126.98 (CH), 128.00 (CH), 128.58 (CH), 129.45 (C, C(2) of pyrrole), 130.31 (C, C(5) of pyrrole), 141.31 (C, C of phenyl), 142.47 (C, C of phenyl); Anal. Calcd for $C_{23}H_{15}N_2O$: C, 79.27; H, 8.10; N, 8.04; Found: C, 79.05; H, 7.94; N, 8.13.

(1*R*,2*S*)-2-((5-Methyl-1-((1*S*)-1-phenylethyl)-1*H*-pyrrol-2-yl)methylamino)-1-phenylpropanol ((1*R*,2*S*,*S*)-219): Brown oil; 2.98 g; 73% yield; R_f:0.32 (EtOAc:hexane, 1:1); $[\alpha]_D^{27}$ = -22.5 (c 14, $CHCl_3$); IR (KBr) ($\bar{\upsilon}_{max}$/cm^{-1}): 3428, 3087, 2974, 2930-2868,1495, 1449, 1406, 1333, 1291, 1110; ^{1}H-NMR: (400 MHz, $CDCl_3$) δ 0.78 (d, 3H, *J*= 6.40 Hz, NHCHC*H*$_3$), 1.94 (d, 3H, *J*=7.20 Hz, NCHC*H*$_3$), 2.04 (s, 3H, CH_3), 2.92-2.98 (m, 1H, NHC*H*CH_3), 3.74 (d, 1H, *J*=13.6 Hz, NHC*H*$_2$), 3.81 (d, 1H, *J*=13.6 Hz, NHC*H*$_2$), 4.62 (d, 1H, *J*= 3.60, C*H*OH), 5.72 (q, 1H, *J*=7.60 Hz, NC*H*CH_3), 5.82 (d, 1H, *J*= 3.20 Hz, C(4)*H* of pyrrole), 5.97 (d, 1H, *J*= 3.20 Hz, C(3)*H* of pyrrole), 7.10 (d, 2H, *J*=7.20 Hz, Ar*H*), 7.19-7.30 (m, 8H, Ar*H*); ^{13}C-NMR: (100 MHz, $CDCl_3$) δ 14.20 (CH_3), 14.59 (CH_3, NHCHCH_3), 19.80 (CH_3, NCHCH_3), 44.07 ($NHCH_2$), 52.60 (CH, NCHCH_3), 57.79 (CH, NH$CHCH_3$), 73.13 (CHOH), 107.23 (CH, C(3) of pyrrole), 107.70 (CH, C(4) of pyrrole), 125.88 (CH), 126.05 (CH), 126.89 (CH), 126.99 (CH), 127.91 (CH), 128.56 (CH), 129.43 (C, C(2) of pyrrole), 130.31 (C, C(5) of pyrrole), 141.13 (C, C of phenyl), 142.50 (C, C of phenyl).

(1*S*,2*R*)-2-((5-Methyl-1-((1*S*)-1-phenylethyl)-1*H*-pyrrol-2-yl)methylamino)-1-phenylpropan-1-ol ((1S,2R,S)-220): Brown oil; 2.94 g; 72% yield; R_f: 0.32 (EtOAc:hexane, 1:1); $[\alpha]_D^{27}$ = +28.2 (c 11, $CHCl_3$); IR (KBr) ($\bar{\upsilon}_{max}$/cm^{-1}): 3059, 3054, 2973, 2927, 1493, 1449, 1407, 1291, 1108; ^{1}H-NMR: (400 MHz, $CDCl_3$) δ 0.81 (d, 3H, *J*=6.52 Hz, NHCHC*H*$_3$), 1.96 (d, 3H , *J*=7.24 Hz, NCHC*H*$_3$), 2.05 (s, 3H, C*H*$_3$,), 2.93-2.98 (m, 1H, NHC*H*CH_3), 3.75 (d, 1H, *J*=13.6 Hz, NHC*H*$_2$), 3.82 (d, 1H, *J*=13.6 Hz, NHC*H*$_2$), 4.71 (d, 1H, *J*=3.48 Hz, C*H*OH), 5.73 (q, 1H, *J*=7.12 Hz, NC*H*CH_3), 5.83 (d, 1H, *J*=3.08 Hz, C(4)*H* of pyrrole), 5.98 (d, 1H, *J*=3.24 Hz,

C(3)*H* of pyrrole), 7.11 (d, 2H, *J*=7.36 Hz, Ar*H*), 7.19-7.38 (m, 8H, Ar*H*); ^{13}C-NMR: (100 MHz, $CDCl_3$) δ 14.21 (CH_3), 14.61 (CH_3, $NHCHCH_3$), 19.81 (CH_3, $NCHCH_3$), 44.08 ($NHCH_2$), 52.61 (CH, $NCHCH_3$), 57.79 (CH, $NHCHCH_3$), 73.15 (CHOH), 107.25 (CH, C(4) of pyrrole), 107.71 (CH, C(3) of pyrrole), 125.90 (CH), 126.07 (CH), 126.90 (CH), 126.99 (CH), 127.93 (CH), 128.57 (CH), 129.43 (C, C(2) of pyrrole), 130.34 (C, C(5) of pyrrole), 141.17 (C, C of phenyl), 142.52 (C, C of phenyl).

(1*R*,2*S*)-2-((5-Methyl-1-((1*R*)-1-phenylethyl)-1*H*-pyrrol-2-yl)methylamino)-1-phenylpropan-1-ol ((1*R*,2*S*,*R*)-220): Brown oil; 2.86 g; 70% yield; R_f:0,31 (EtOAc:hexane, 1:1); $[\alpha]_D^{27}$=-31.0 (c 10, $CHCl_3$), IR (KBr) ($\bar{\upsilon}_{max}$/cm^{-1}): 3425, 3060, 2974, 2930-2868, 1495, 1449, 1407, 1291, 1112; ^{1}H-NMR: (400 MHz, $CDCl_3$) δ 0.80 (d, 3H, *J*= 6.40 Hz, $NHCHC*H*_3$), 1.96 (d, 3H, *J*=7.20 Hz, $NCHC*H*_3$), 2.03 (s, 3H, $C*H*_3$), 2.96-3.00 (m, 1H, $NHC*H*CH_3$), 3.77 (d, 1H, *J*=13.6 Hz, $NHC*H*_2$), 3.84 (d, 1H, *J*=13 .6 Hz, $NHC*H*_2$), 4.71 (d, 1H, *J*= 3.60 Hz, C*H*OH), 5.69 (q, 1H, *J*=7.20 Hz, $NC*H*CH_3$), 5.82 (d, 1H, *J*= 3.20 Hz, C(4)*H* of pyrrole), 5.99 (d, 1H, *J*= 3.20 Hz, C(4)*H* of pyrrole), 7.08 (d, 2H *J*= 7.20 Hz, Ar*H*), 7.18-7.28 (m, 8H, Ar*H*); ^{13}C-NMR: (100 MHz, $CDCl_3$) δ 14.16 (CH_3), 14.39 (CH_3, $NHCHCH_3$), 19.59 (CH_3, $NCHCH_3$), 44.00 ($NHCH_2$), 52.67 (CH, $NCHCH_3$), 57.82 (CH, $NHCHCH_3$), 73.00 (CHOH), 107.26 (CH, C(4) of pyrrole), 107.79 (CH, C(3) of pyrrole), 125.93 (CH), 126.00 (CH), 126.94 (CH), 126.97 (CH), 127.99 (CH), 128.57 (CH), 129.47 (C, C(2) of pyrrole), 130.23 (C, C(5) of pyrrole), 141.25 (C, C of phenyl), 142.44 (C, C of phenyl).

(1*R*,2*S*)-2-((2-Methyl-1-((1*R*)-1-phenylethyl)-1*H*-pyrrol-3-yl)methylamino)-1-phenylpropan-1-ol ((1*R*,2*S*,*R*)-221): White soild; 2.90 g; 70% yield; mp:101-102 °C; R_f:0.24 (EtOAc:MeOH:hexane, 1:1:6), $[\alpha]_D^{25}$ = -3.2 (c 13, $CHCl_3$); IR (KBr) ($\bar{\upsilon}_{max}$/cm^{-1}): 3060, 3027, 2977, 2900-2830,1486, 1444, 1411, 1322, 1241, 1132; ^{1}H-NMR: (400 MHz, $CDCl_3$) δ 0.80 (d, 3H, *J*= 6.52 Hz, $NHCHC*H*_3$), 1.84 (d, 3H, *J*=7.08 Hz, $NCHC*H*_3$), 2.09 (s, 3H, CH_3), 2.98-3.04 (m, 1H, $NHC*H*CH_3$), 3.71 (d, 1H, *J*=12.8 Hz, $NHC*H*_2$), 3.78 (d, 1H, *J*=12.8 Hz, $NHC*H*_2$), 4.80 (d, 1H, *J*= 3.68 Hz, C*H*OH), 5.28 (q, 1H, *J*=7.08 Hz, $NC*H*CH_3$), 6.14 (d, 1H, *J*= 2.92 Hz, C(4)*H* of pyrrole), 6.78 (d, 1H, *J*= 2.92 Hz, C(5)*H* of pyrrole), 6.96 (d, 2H, *J*=7.20 Hz, Ar*H*),

7.23-7.32 (m, 8H, Ar*H*); ^{13}C-NMR: (100 MHz, $CDCl_3$) δ 9.93 (CH_3), 14.58 (CH_3, $NHCHCH_3$), 22.51 (CH_3, N-$CHCH_3$), 43.33 ($NHCH_2$), 55.09 (CH, $NCHCH_3$), 57.84 (CH, $NHCHCH_3$), 72.38 (CHOH), 107.56 (CH, C(4) of pyrrole), 116.26 (CH, C(5) of pyrrole), 118.63 (C, C(3) of pyrrole), 125.56 (CH), 125.88 (CH), 125.96 (CH), 126.76 (CH), 127.14 (CH), 127.93 (CH), 128.67 (C, C(2) of pyrrole), 141.54 (C, C of phenyl), 143.70 (C, C of phenyl).

(1*S*,2*R*)-2-((2-Methyl-1-((1*S*)-1-phenylethyl)-1*H*-pyrrol-3-yl)methylamino)-1-phenylpropan-1-ol ((1*S*,2*R*,*S*)-221): White solid; 2.82 g; 69% yield; mp:99.5-100.5 °C; R_f:0.24 (EtOAc:MeOH:hexane, 1:1:6); $[\alpha]_D^{25}$ = +3.7 (c 11, $CHCl_3$); IR (KBr) ($\bar{\upsilon}_{max}$/cm^{-1}): 3093, 3054, 2977, 2900-2699, 1488, 1450, 1441, 1326, 1121, 1133; ^{1}H-NMR. (400 MHz, $CDCl_3$) δ 0.81 (d, 3H, *J*= 6.80 Hz, NHCHC*H*$_3$), 1.84 (d, 3H, *J*=7.20 Hz, NCHC*H*$_3$), 2.08 (s, 3H, CH_3), 3.00-3.06 (m, 1H, NHC*H*CH_3), 3.71 (d, 1H, *J*=12.8 Hz, NHC*H*$_2$), 3.76 (d, 1H, *J*=12.8 Hz, NHC*H*$_2$), 4.79 (d, 1H, *J*= 3.60 Hz, C*H*OH), 5.28 (q, 1H, *J*=7.20 Hz, NC*H*CH_3), 6.14 (d, 1H, *J*= 3.20 Hz, C(4)*H* of pyrrole), 6.77 (d, 1H, *J*= 2.80 Hz, C(5)*H* of pyrrole), 6.97 (d, 2H, *J*=7.20 Hz, Ar*H*) 7.20-7.32 (m, 8H, Ar*H*); ^{13}C-NMR: (100 MHz, $CDCl_3$) δ 9.91 (CH_3), 14.63 (CH_3, $NHCHCH_3$), 22.47 (CH_3, N-$CHCH_3$), 43.39 ($NHCH_2$), 55.08 (CH, $NCHCH_3$), 57.86 (CH, $NHCHCH_3$), 72.44 (CHOH), 107.57 (CH, C(4) of pyrrole), 116.25 (CH, C(5) of pyrrole), 118.75 (C, C(3) of pyrrole), 125.56 (CH), 125.83 (CH), 125.97 (CH), 126.74 (CH), 127.13 (CH), 127.92 (CH), 128.65 (C, C(2) of pyrrole), 141.58 (C, C of phenyl), 143.71 (C, C of phenyl). Anal. Calcd for $C_{23}H_{15}N_2O$ C, 79.27; H, 8.10; N, 8.04; Found: C, 79.17; H, 7.99; N, 8.04.

(1*R*,2*S*)-2-((2-Methyl-1-((1*S*)-1-phenylethyl)-1*H*-pyrrol-3-yl)methylamino-1-phenylpropan-1-ol ((1*R*,2*S*,*S*)-222): Brown oil; 2.86 g; 70% yield; R_f:0.25 (EtOAc:MeOH:hexane, 1:1:6); $[\alpha]_D^{25}$ = -4.5 (c 9.2, $CHCl_3$); IR (KBr) ($\bar{\upsilon}_{max}$/cm^{-1}): 3060, 3027, 2977, 2900-2830, 1492, 1450, 1323, 1219, 1131; ^{1}H-NMR: (400 MHz, $CDCl_3$) δ 0.83 (d, 3H, *J*= 6.52 Hz, NHCHC*H*$_3$), 1.84 (d, 3H, *J*=7.08 Hz, NCHC*H*$_3$), 2.08 (s, 3H, C*H*$_3$), 2.99-3.05 (m, 1H, NHC*H*CH_3), 3.72 (d, 1H, *J*=12.8 Hz, NHC*H*$_2$), 3.77 (d, 1H, *J*=12.8 Hz, NHC*H*$_2$), 4.81 (d, 1H, *J*=3.72 Hz, C*H*OH), 5.28 (q, 1H, *J*=7.16 Hz, NC*H*CH_3), 6.15 (d, 1H, *J*= 2.96 Hz, C(4)*H* of pyrrole), 6.78

(d, 1H, *J*= 2.92 Hz, C(5)*H* of pyrrole), 6.97 (d, 2H *J*= 7.08 Hz, Ar*H*), 7.23-7.33 (m, 8H, Ar*H*); ^{13}C-NMR: (100 MHz, $CDCl_3$) δ 9.92 (CH_3), 14.50 (CH_3, NHCHCH_3), 22.47 (CH_3, NCHCH_3), 43.34 (CH_2), 55.09 (CH, NCHCH_3), 57.87 (CH, NHCHCH_3), 72.47 (CHOH), 107.60 (CH, C(4) of pyrrole), 116.29 (CH, C(5) of pyrrole), 118.57 (C, C(3) of pyrrole), 125.57 (CH), 125.90 (CH), 125.98 (CH), 126.75 (CH), 127.13 (CH), 127.93 (CH), 128.66 (C, C(2) of pyrrole), 141.59 (C, C of phenyl), 143.17 (C, C of phenyl).

(1*S*,2*R*)-2-((2-Methyl-1-((1*R*)-1-phenylethyl)-1*H*-pyrrol-3-yl)methylamino)-1-phenylpropan-1-ol ((1*S*,2*R*,*R*)-222): Brown oil; 2.98 g; 73% yield; R_f: 0.25 (EtOAc:MeOH:hexane, 1:1:6); $[\alpha]_D^{25}$ = +5.6 (c 7.3, $CHCl_3$); IR (KBr) ($\bar{\upsilon}_{max}$/cm^{-1}): 3060, 3027, 2975, 2900-2830, 1489, 1446, 1320, 1216, 1130; ^{1}H-NMR: (400 MHz, $CDCl_3$) δ 0.82 (d, 3H, *J*= 6.52 Hz, NHCHCH_3), 1.83 (d, 3H, *J*=7.08 Hz, NCHCH_3), 2.08 (s, 3H, CH_3), 2.98-3.04 (m, 1H, NHCHCH_3), 3.72 (d, 1H, *J*=12.8 Hz, NHCH_2), 3.78 (d, 1H, *J*=12.8 Hz, NHCH_2), 4.80 (d, 1H, *J*= 3.68 Hz, CHOH), 5.28 (q, 1H, *J*=7.00 Hz, NCHCH_3), 6.14 (d, 1H, *J*= 2.88 Hz, C(4)*H* of pyrrole), 6.77 (d, 1H, *J*= 2.92 Hz, C(5)*H* of pyrrole), 6.96 (d, 2H, *J*=7.32 Hz, Ar*H*), 7.21-7.31 (m, 8H, Ar*H*); ^{13}C-NMR: (100 MHz, $CDCl_3$) δ 9.91 (CH_3), 14.56 (CH_3, NHCHCH_3), 22.47 (CH_3, NCHCH_3), 43.36 (CH_2), 55.09 (CH, NCHCH_3), 57.86 (CH, NHCHCH_3), 72.45 (CHOH), 107.58 (CH, C(4) of pyrrole), 116.27 (CH, C(5) of pyrrole), 118.67 (C, C(3) of pyrrole), 125.57 (CH), 125.86 (CH), 125.97 (CH), 126.75 (CH), 127.13 (CH), 127.92 (CH), 128.65 (C, C(2) of pyrrole), 141.59 (C, C of phenyl), 143.71(C, C of phenyl).

4.5. The Synthesis of Novel Camphor-Based Ligands with *N*-Substituted Chiral Pyrrole

exo- and *endo*-3-Amino-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol were used for synthesis of novel pyrrole-based derivatives of camphor. These amino alcohols were prepared from camphor.

4.5.1. The synthesis of 3-hydroxyimino-2-*oxo*-1,7,7-trimethylbicyclo[2.2.1] heptane (223)

Na (1 g, 43.48 mmol) and *t*-BuOH (10 mL) were refluxed until Na dissolves completely (about 3 hours) under N_2. A solution of camphor (5 g, 32.89 mmol) in dry THF (5 mL) was added to solution of *t*-BuONa at -30 °C under N_2. The mixture was stirred at the same temperature for 10 min, treated with BuONO (4.07 g, 39.47 mmol) and stirred at room temperature for 12 hours. The residue was diluted in water (15 mL). The aqueous layer was extracted with ether (3x30 mL). The aqueous layer was cooled and acidified with 5% aqueous HCl (pH=4) and extracted with Et_2O (3x30 mL) and dried over anhydrous $MgSO_4$. After evaporation of solvent the crude product was purified by column chromatography.

3-Hydroxyimino-2-*oxo*-1,7,7-trimethylbicyclo[2.2.1]heptane (223): Light yellow solid; 5.66 g; 95% yield; mp:113.9-114.5°C; R_f:0.51 (EtOAc:hexane, 1:3); ^{1}H-NMR: (400 MHz, $CDCl_3$) δ 0.90 (s, 3H, CH_3, C(1)), 1.02 (s, 3H, CH_3, C(7)), 1.04 (s, 3H, CH_3, C(7)), 1.58-1.63 (m, 2H, CH_2, H-5$_{endo}$, H-6$_{endo}$), 1.77-1.82 (m, 1H, CH_2, H-6$_{exo}$), 2.02-2.08 (m, 1H, CH_2, H-5$_{exo}$), 3.28 (d, 1H, *J*=4.40 Hz, C*H*, C(4)*H*), 9.70 (broad s, 1H, NO*H*),); ^{13}C-NMR: (100 MHz, $CDCl_3$) δ 9.03 (CH_3), 17.73 (CH_3), 20.73 (CH_3), 23.80 (C(5)), 30.67 (C(6)), 44.90 (C(4)), 46.61 (C(7)), 58.43 (C)1)), 159.24 (C=NOH), 203.48 (C=O).

4.5.2. The synthesis of 3-*exo*-amino-2-*exo*-hdroxy-1,7,7-trimethylbicyclo [2.2.1]heptane ((2-*exo*,3-*exo*)-224)

A solution of 3-hydroxyimino-2-oxo-1,7,7-trimethylbicyclo[2.2.1]heptane (**223**) (5.05 g, 27.90 mmol) in 150 mL dry Et_2O was added dropwise to a stirred suspension of LAH (3.62 g, 91.23 mmol) in dry Et_2O during 1 hour at 0 °C. The mixture was heated under reflux for 6 hours. The reaction mixture was quenched by addition of water (15 mL) and filtered off. White precipate was refluxed three times with Et_2O (3x25 mL). The mixture was filtered off, organic layers combined and dried over anhydrous $MgSO_4$. After evoparation of solvent, the crude product was purified by sublimation.

3-*exo*-Amino-2-*exo*-hdroxy-1,7,7-trimethylbicyclo[2.2.1]heptane ((2-*exo*,3-*exo*)-224): White solid; 3.60 g; 76.40% yield; mp:181.3-182.8 °C, R_f:0.27; ^{1}H-NMR: (400 MHz, $CDCl_3$) δ 0.80 (s, 3H, CH_3, C(1)), 0.94 (s, 3H, CH_3, C(7)), 1.08 (s, 3H, CH_3, C(7)), 1.40-1.46 (m, 2H, CH_2, H-5$_{endo}$, H-6$_{endo}$), 1.62 (d, 1H *J*=4.23 Hz, C*H*, C-4), 1.65-1.68 (m, 1H, CH_2, H-6$_{exo}$), 1.83-1.86 (m, 1H, CH_2, H-5$_{exo}$), 3.10 (d, 1H, *J*=7.34 Hz, C*H*NH_2), 3.46 (d, 1H, *J*=7.36 Hz, C*H*OH), 3.66 (broad s, 3H, N*H*$_2$ and O*H*); ^{13}C-NMR: (100 MHz, $CDCl_3$) 11.80 (CH_3, C(1)), 21.67 (CH_3, C(7)), 22.33 (CH_3, C(7)), 27.29 (C(5)), 33.47 (C(6)), 47.10 (C(4)), 49.25 (C(7)), 53.02 (C(1)), 57.79 (C(2)), 79.07 (C(3)).

4.5.3. The synthesis of *endo*-3-amino-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (225)

3-Hydroxyimino-2-oxo-1,7,7-trimethylbicyclo[2.2.1]heptane (**223**) (3 g, 16.57 mmol) was dissolved in NaOH (15mL of 30%) and then zinc dust (3.60 g, 55.01 mmol) was added in small quantities, when the deep yellow colour of the solution almost completely disappears. The oily precipitate was extracted with ether and organic phase dried over anhydrous $MgSO_4$, and evaporated. The crude product was purified by recrystallization.

***endo*-3-Amino-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (225):** White solid; 2.55 g; 92% yield; R_f:0.22 (EtOAc:hexane, 1:1); ^{1}H-NMR: (400 MHz, $CDCl_3$) δ 0.93 (s, 3H, CH_3, C(1)), 0.93 (s, 3H, CH_3, C(7)), 1.03 (s, 3H, CH_3, C(7)), 1.30-1.34 (m, 1H, CH_2, C(6)*H*), 1.40 (s, 2H, NH_2), 1.71-1.83 (m, 3H, C(5)*H*, C(6)*H*), 2.11 (t, 1H, *J*=4.40 Hz, C(4)*H*) 3.47 (d, 1H, *J*=4.80 Hz, C*H*NH_2); ^{13}C-NMR: (100 MHz, $CDCl_3$) δ 9.54 (CH_3, C(1)), 18.52 (CH_3, C(7)), 19.13 (CH_3, C(7)), 19.80 (C(5)), 32.12 (C(6)), 43.93 (C(4)), 49.29 (C(7)), 59.28 (C(1)), 58.57 (C(3)), 213.12 (C(2)).

4.5.4. The synthesis of 3-*endo*-amino-2-*endo*-hydroxy-1,7,7-trimethylbicyclo [2.2.1]heptane ((2-*endo*,3-*endo*)-224)

endo-3-Amino-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (**225**) (2.50 g, 14.97 mmol) was dissolved in dry ether (125 mL). To the solution was slowly added LAH (1.56 g, 41.17 mmol) in dry ether (200 mL) at 0 °C. The mixture was refluxed for 16 h. After cooling to room temperature, water (10mL) and then aqueous 5% NaOH (15 mL) were cautiously added at 0 °C. The organic layer was separated, the aqueous layer was extracted with ether (3x20 mL). The organic layers were washed with water, dried over $MgSO_4$, and evaporated. The reduction of the carbonyl group of **225** led to a mixture of (*endo*, *endo*)-**224** and (*exo*,*endo*9-**224**. The mixture of amino alcohols **224** (2.00 g, 11.83 mmol) in aqueous 6 M HCl was heated at 100 °C for 23 h. After cooling to room temperature, the mixture was washed with CH_2Cl_2 (4x30 mL), made basic with aqueous 50% NaOH (75 mL) and extracted with ether (3x30 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, and evaporated. The residue was sublimed to give pure (2-*endo*,3-*endo*)-**224**.

3-*endo*-Amino-2-*endo*-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptane ((2-*endo*,3-*endo*)-224) : White solid; 1.57 g; 62% yield; mp:163.5-164.7 °C; R_f:0.23 (EtOAc:hexane, 1:1); ^{1}H-NMR: (400 MHz, $CDCl_3$) δ 0.89 (s, 3H, CH_3, C(1)), 0.93 (s, 3H, CH_3, C(7)), 0.97 (s, 3H, CH_3, C(7)), 1.07 (d, 1H, *J*=4.80 Hz, C(4)*H*), 1.42-1.47 (m, 2H, CH_2, C(5)*H* and C(6)*H*), 1.71-1.73 (m, 1H, CH_2, C(6)*H*), 1.83-1.86 (m,

1H, CH_2, C(5)*H*), 2.27 (broad s, 3H, NH_2 and O*H*), 3.49 (ddd, 1H, *J*=9.4 Hz, 4.4, 1.2 Hz, C*H*NH_2, C(3)*H*), 3.58 (dd, 1H, *J*=9.2 Hz, 1.6 Hz, C*H*OH, C(2)*H*).

4.6 General Procedure for the Synthesis of Novel Camphor-Based *N*-Substituted Chiral Pyrrole Ligands

exo- and *endo*-3-Amino-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol (**224**) (0.57 g, 3.37 mmol) and *N*-substitueted pyrrole carbaldehyde (0.72 g, 3.37 mmol) were dissolved in dry benzene and refluxed under Dean-stark trap for 2 days. Imine was concentrated to dryness without purification. Imine (1.20 g, 3.30 mmol) in dry ether (10 mL) was added to the suspension of LAH (0.15 g, 3.96 mmol) in dry ether (50 mL) After the addition was complete, the mixture was heated under argon for 10 hours (checking by TLC). The reaction mixture was quenched by sequential addition of water (15 mL), 15% NaOH (10 mL), and water (10 mL). The mixture was filtered off and white precipate was refluxed three times with ether. The mixture was filtered off, the organic layers was combined and dried over anhydrous $MgSO_4$. After evaporation of solvent, the crude product was purified by column chromatography.

(2-*exo*,3-*exo*)-1,7,7-Trimethyl-3-((2-methyl-1-((*R*)-1-phenylethyl)-1*H*-pyrrol-3-yl)methylamino)bicyclo[2,2,1]heptan-2-ol ((2-*exo*,3-*exo*,*R*)-225): Brown oil; 0.89 g; 72% yield; R_f:0.42 (EtOAc:MeOH:hexane,1:1:6); $[\alpha]_D^{26}$ = +8.43 (9.7, $CHCl_3$); IR (KBr) ($\bar{\upsilon}_{max}$/cm^{-1}): 3062, 3028, 2907, 2876, 1321; ^{1}H-NMR: (400 MHz, $CDCl_3$) δ 0.81 (s, 3H, CH_3, C(1)), 0.98 (s, 3H, CH_3, C(7)), 1.08 (s, 3H, CH_3, C(7)), 1.03-1.10 (m, 2H, H-5$_{endo}$, H-6$_{endo}$), 1.42-1.47 (m, 1H, H-6$_{exo}$), 1.58 (d, *J*=4.32, 1H, C(4)*H*), 1.71-1.75 (m, 2H, 1H, H-5$_{exo}$), 1.84 (d, 3H, *J*=6.99 Hz, CH_3, NCHC*H*$_3$), 2.07 (s, 3H, CH_3, pyrrole), 2.79 (d, 1H, *J*=7.23 Hz, C*H*NH, C(3)*H*), 3.42 (d, 1H, *J*=7.21 Hz, C*H*OH, C(2)*H*), 3.62 (s, 2H, NHC*H*$_2$), 5.27 (q, 1H, *J*= 6.92 Hz, NC*H*CH_3), 6.13 (d, 1H, *J*=2.69 Hz, C*H*, C(4)*H* of pyrrole), 6.77 (d, 1H, *J*=2.72 Hz, C(5)*H* of pyrrole), 6.96 (d, 2H, *J*=7.47 Hz, Ar*H*), 7.21-7.32 (m, 3H, Ar*H*.); ^{13}C-NMR: (100 MHz, $CDCl_3$) δ 9.70 (CH_3, C-2 of pyrrole), 11.37 (CH_3, C(1)), 21.34 (CH_3, C(7)), 21.97 (CH_3, C(7)), 22.34 (CH_3, $CHCH_3$), 27.29 (C(5)), 32.85 (C(6)), 46.41 ($NHCH_2$), 46.82 (C(7)), 48.66 (C(1)), 51.95 (C(4)), 54.87 (CH, $NCHCH_3$), 65.44 (CHNH,

C(3)), 78.44 (CHOH, C(2)), 107.31 (CH, C(4)*H* of pyrrole), 116.00 (CH, C(5) of pyrrole), 118.61 (C, C(3) of pyrrole), 125.36 (CH), 125.91 (CH), 126.96 (CH), 128.49 (C(2) of pyrrole), 143.66 (C, C of pheny).

(2-*exo*,3-*exo*)-1,7,7-Trimethyl-3-((2-methyl-1-((*S*)-1-phenylethyl)-1*H*-pyrrol-3-yl)methylamino)bicyclo[2,2,1]heptan-2-ol ((2-*exo*,3-*exo*,*S*)-225): Brown oil; 0.86 g; 70% yield; R_f:0.42 (EtOAc:MeOH:hexane, 1:1:6); $[\alpha]_D^{26}$=-9.22 (8.9, $CHCl_3$); IR (KBr) ($\bar{\upsilon}_{max}$/cm^{-1}): 3060, 3026, 2948, 2922-2878, 1318; ^{1}H-NMR: (400 MHz, $CDCl_3$) δ 0.70 (s, 3H, CH_3, C(1)), 0.87 (s, 3H, CH_3, C(7)), 0.96 (s, 3H, CH_3, C(7)), 0.92-0.99 (m, 2H, H-5$_{endo}$, H-6$_{endo}$), 1.31-1.36 (m, 1H, H-6$_{exo}$), 1.49 (d, 1H, *J*=4.45, C*H*, C(4)*H*), 1.58-1.64 (m, 2H, 1H, H-5$_{exo}$), 1.73 (d, 3H, *J*=7.04, CH_3, CHC*H*$_3$), 1.96 (s, 3H, CH_3, pyrrole), 2.70 (d, 1H, *J*=7.25, NHC*H*, C(3)*H*), 3.33 (d, 1H, *J*=7.23, C*H*OH, C(2)*H*), 3.51 (s, 2H, NHC*H*$_2$), 5.17 (q, 1H, *J*= 7.05, NC*H*CH$_3$), 6.01 (d, 1H, *J*=2.91, C*H*, C(4)*H* of pyrrole), 6.66 (d, 1H, *J*=2.93, (C(5)*H* of pyrrole), 6.85 (d, 2H, *J*=7.33, Ar*H*), 7.11-7.31 (m, 3H, Ar*H*.); ^{13}C-NMR: (100 MHz, $CDCl_3$) δ 10.29 (CH_3, C(2) of pyrrole), 11.87 (CH_3, C(1)), 21.84 (CH_3, C(7)), 22.47 (CH_3, C(7)), 22.82 ($CHCH_3$), 27.79 (C(5)), 33.38 (C(6)), 47.22 ($NHCH_2$), 47.98 (C(7)), 49.22 (C(1)), 52.25 (CH, C(4)), 55.45 (CH, $NCHCH_3$), 65.97 (NHCH, C(3)*H*), 78.99 (OHCH, C(2)*H*), 108.07 (CH, C(4)*H* of pyrrole), 116.60 (CH, C(5)*H* of pyrrole), 118.89 (C, C(3) of pyrrole), 125.96 (CH), 126.35 (CH), 127.51 (CH), 129.00 (C, C(2) of pyrrole), 144.04 (C, C of phenyl).

(2-*endo*,3-*endo*)-1,7,7-Trimethyl-3-((5-methyl-1-((*R*)-1-phenylethyl)-1*H*-pyrrol-2-yl)methylamino)bicyclo[2,2,1]heptan-2-ol ((2-*endo*,3-*endo*,*R*)-226): Brown oil; 0.90 g; 73% yield; R_f:0.42 (EtOAc:hexane, 1:1); $[\alpha]_D^{25}$=-32.17 (c 7.20, $CHCl_3$); ^{1}H-NMR: ($CDCl_3$) δ 0.79 (s, 3H, CH_3, C(1)), 0.97 (s, 3H, CH_3, C(7)), 1.01 (s, 3H, CH_3, C(7)), 1.03-1.10 (m, 2H, H-5$_{endo}$, H-6$_{endo}$), 1.40-1.47 (m, 1H, H-6$_{exo}$), 1.58 (d, 1H, *J*=4.40, C*H*, C(4)), 1.69-1.76 (m, 2H, 1H, H-5$_{exo}$), 1.94 (d, 3H, *J*=7.20 Hz, NCHC*H*$_3$), 1.98 (s, 3H, CH_3, pyrrole), 2.79 (d, 1H, *J*=1.36, NHC*H*, C(3)*H*), 3.40 (d, 1H, *J*=1.37, C*H*OH, C(2)*H*), 3.66 (d, 1H, *J*=13.6 Hz, NHC*H*$_2$), 3.79 (d, 1H, *J*=13.6 Hz, NHC*H*$_2$), 5.60 (q, 1H, *J*= 7.20, NC*H*CH$_3$), 5.80 (d, 1H, *J*=3.60, C*H*, C(4)*H* of pyrrole), 5.98 (d, 1H, *J*=3.20, C*H*, C(3)*H* of pyrrole), 7.02 (d, 2H, *J*=7.40, Ar*H*), 7.22-7.32 (m, 3H, Ar*H*.); ^{13}C-NMR: (100 MHz, $CDCl_3$) δ 11.40 (CH_3, C(2) of

pyrrole), 14.13 (CH_3, C(1)), 19.52 (CH_3, C(7)), 21.33 (CH_3, C(7)), 22.03 ($CHCH_3$), 27.29 (C(5)), 32.99 (C(6)), 46.59 ($NHCH_2$), 47.53 (C(7)), 48.83 (C(1)), 51.56 (C(4)), 52.68 (CH, $NCHCH_3$), 65.76 (NHCH, C(3)*H*), 78.83 (CHOH, C(2)*H*), 107.35 (CH, C(4)*H* of pyrrole), 107.62 (CH, C(5)*H* of pyrrole), 125.88 (CH), 126.93 (CH), 128.50 (CH), 129.53 (C, C(2) of pyrrole),130.53 (C, C(3) of pyrrole), 142.42 (C, C of phenyl).

(2-*endo*,3-*endo*)-1,7,7-Trimethyl-3-((5-methyl-1-((*S*)-1-phenylethyl)-1*H*-pyrrol-2-yl)methylamino)bicyclo[2,2,1]heptan-2-ol ((2-*endo*,3-*endo*,*S*)-226): Brown oil; 0.86 g; 70% yield; R_f:0.42 (EtOAc:hexane, 1:1); $[\alpha]_D^{25}$ = -32.69 (c 6.92, $CHCl_3$); ^{1}H-NMR: (400 MHz, $CDCl_3$) δ 0.68 (s, 3H, CH_3, C(1)), 0.84 (s, 3H, CH_3, C(7)), 0.88 (s, 3H, CH_3, C(7=), 0.90-0.99 (m, 2H, H-5$_{endo}$, H-6$_{endo}$), 1.30-1.36 (m, 1H, H-6$_{exo}$), 1.47 (d, 1H, *J*=4.45, C*H*, C-4), 1.59-1.69 (m, 2H, 1H, H-5$_{exo}$), 1.84 (d, 3H, *J*=7.23, CHC*H*$_3$), 1.88 (s, 3H, CH_3, pyrrole), 2.68 (d, 1H, *J*=1.42, NHC*H*), 3.30 (d, 1H, *J*=1.41, C*H*OH), 3.56 (d, 1H, *J*=13.5 Hz, NHC*H*$_2$), 3.69 (d, 1H, *J*=13.5 Hz, NHC*H*$_2$), 5.50 (q, 1H, *J*= 7.14, NC*H*CH$_3$), 5.70 (d, 1H, *J*=3.28, C*H*, C-4 of pyrrole), 5.88 (d, 1H, *J*=3.36, C*H*, C-3 of pyrrole), 6.92 (d, 2H, *J*=7.92, Ar*H*), 7.13-7.31 (m, 3H, Ar*H*.); ^{13}C-NMR: (100 MHz, $CDCl_3$) δ 11.37 (CH_3, C(2) of pyrrole), 14.111 (CH_3, C(1)), 19.51 (CH_3, C-7), 21.31 (CH_3, C-7), 22.01 (CH*C*H$_3$), 27.28 (C-5), 33.00 (C-6), 46.58 (CH_2), 47.52 (C-7), 48.83 (C-1), 51.56 (C-4), 52.69 (CH, $NCHCH_3$), 65.78 (NHCH, C(3)), 78.88 (CHOH, C(2)), 107.33 (CH, C(4) of pyrrole), 107.61 (CH, C(5) of pyrrole), 125.88 (CH), 126.92 (CH), 128.50 (CH), 129.53 (C, C(2) of pyrrole), 130.56 (C, C(3) of pyrrole), 142.25 (C, C of phenyl).

4.7. The enantioselective Addition Reactions in the Presence of Chiral Ligands

One of the purpose of this study is to examine the catalytical activity of synthesized novel chiral amino alcohol derivatives as a chiral catalyst on the chemical and optical outcome of the diethylzinc addition reactions of benzaldehyde and conjugate additions of diethylzinc to enones. We focused our attention on these reactions in the second part of study. Benzaldehyde and chalcone were chosen as model substrates for enantioselective addition reactions. Several common factors such as, solvent, reaction temperature, amount of ligand, reaction time which are known to affect the enantioselectivity of the catalyst system, have been examined.

4.7.1. The enantioselective diethylzinc addition to prochiral aldehydes

4.7.1.1. General procedure for the synthesis of 1-phenylpropanol (32)

a) A 25 mL three-necked vessel was dried under vacuum by applying the Schlenk technique for five times. Chiral ligand (0.05 mmol, 5 mol%) was dissolved dry solvent (5 mL) under the argon atmosphere. After cooling to 0 °C, diethylzinc (2 mL, 2 mmol, 1M in hexane) was added with a syringe over a period of 5 min. The mixture was stirred for 6 hours at the same temperature. Benzaldehyde (0.10 mL, 1 mmol) was added at 0 °C. The reaction mixture was stirred for 16 hours at room temperature and monitored by TLC. The reaction was quenched with 10 mL of 1 N HCl solution. The organic layer was separated and aques layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with 10 mL of brine, dried over anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (Silica gel, EtOAc:hexane, 1:6; R_f:0.5 (EtOAc:hexane, 1:2)).

b) The addition of diethylzinc reaction was performed with different a molar ratio of Ti(O-*i*-Pr)$_4$/Ligand (5, 10, 15). A 25 mL three-necked vessel was dried under vacuum by applying the Schlenk technique for five times. Chiral ligand (0.05 mmol) was dissolved in 5 mL dry toluene at room temperature under argon

atmosphere. Ti(O-*i*-Pr)$_4$ (0.071 g, 0.25 mmol) was added with a syringe and the mixture was stirred for 1 hour. The mixture was cooled to 0 °C and diethylzinc (2 mL, 2 mmol, 1M in hexane) was added with a syringe over a period of 5 min. The mixture was stirred at room temperature for 30 min, and then benzaldehyde (0.10 mL, 1 mmol) was added at 0 °C. The reaction mixture was stirred for 16 hours at room temperature and monitored by TLC. The mixture reaction was quenched with saturated NH_4Cl solution, extracted with CH_2Cl_2 (2x25 mL) and dried over anhydrous $MgSO_4$. The crude product was purified by flash column chromatography (Silica gel, EtOAc:hexane, 1:6; R_f:0.5, (EtOAc:hexane, 1:2)).

c) A 25 mL three-necked vessel was dried under vacuum by applying the Schlenk technique for five times. To an ice-cooled solution of chiral ligand (0.184 mmol) in 5 mL dry toluene was added butyllithium (0.368 mmol, 0.245 mL, 1.6 M in hexane) under argon atmosphere. After 10 min of stirring, diethylzinc (6.2 mmol, 6.2 mL, 1 M in hexane) was added with a syringe over a period of 5 min. The mixture was stirred at room temperature for 30 min, and benzaldehyde (0.32 mL, 3.05 mmol) was added at 0 °C. The reaction mixture was stirred for 16 hours at room temperature and monitored by TLC. The reaction mixture was queched with 1 N HCl (10mL). The mixture was extracted with CH_2Cl_2 (3x20 mL), the organic layer was dried over anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (Silica gel, EtOAc:hexane, 1:6; R_f:0.5, (EtOAc:hexane, 1:2)).

d) A 25 mL three-necked vessel was dried under vacuum by applying the Schlenk technique for five times. To an ice-cooled solution of chiral ligand (0.184 mmol) and LiCl (0.08 g, 1.84 mmol) in 5 mL dry toluene was added butyllithium (0.368 mmol, 0.245 mL of 1.6 M in hexane) under argon atmosphere. After 10 min, diethylzinc (6.2 mmol, 6.2 mL of 1 M hexane solution) was added with a syringe over a period of 5 min. The mixture was stirred at room temperature for 30 min, and benzaldehyde (0.32 mL, 3.05 mmol) was added at 0 °C. The reaction mixture was stirred for 16 hours at room temperature and monitored by TLC. The reaction mixture was queched with 1 N HCl (10 mL). The mixture was extracted with

CH_2Cl_2 (3 x 20 mL), the organic layer was dried over anhydrous $MgSO_4$, and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (Silica gel, EtOAc:hexane, 1:6; R_f:0.5, (EtOAc:hexane, 1:2)).

e) A 25 mL three-necked vessel was dried under vacuum by applying the Schlenk technique for five times. To an ice-cooled solution of chiral ligand (0.184 mmol) and LiCl (0.08 g, 1.84 mmol) in 5 mL dry toluene was added diethylzinc (6.2 mmol, 6.2 mL of 1 M hexane solution) was added with a syringe over a period of 5 min. The mixture was stirred at room temperature for 30 min, and benzaldehyde (0.32 mL, 3.05 mmol) was added at 0 °C. The reaction mixture was stirred for 16 hours at room temperature and monitored by TLC. The reaction mixture was quenched with 1N HCl (10 mL). The mixture was extracted with CH_2Cl_2 (3x20 mL), the organic layer was dried over anhydrous $MgSO_4$, and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (Silica gel, EtOAc:hexane, 1:6; R_f:0.5, (EtOAc:hexane, 1:2)).

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1-Phenylpropanol (32): R_f = 0.32 (EtOAc:hexane, 1:5); ^{1}H-NMR: (400 MHz, $CDCl_3$) δ 0.94 (t, 3H, *J*= 7.60 Hz, C*H*$_3$), 1.71-1.85 (m, 2H, C*H*$_2$CH$_3$), 2.12 (s, 1H, OH), 4.56 (t, 1H, *J*=6.80 Hz, C*H*), 7.24-7.236 (m, 5H, Ar*H*), ^{13}C-NMR: (100 MHz, $CDCl_3$) δ 10.53 (CH_3), 32.29 (CH_2), 76.43 (CH), 126.37 (CH), 127.89 (CH), 128.91 (CH), 145.01(C); HPLC analysis: Chiralcell OD column eluted with hexane:2-propanol (98:2) at 1 mL/min using UV detection (254nm), R_t:17 min. for (*R*) , 19 min. for (*S*).

4.7.1.2. The enantioselective diethylzinc addition to substituted aromatic aldehydes

In order to determine the effect of the substitutents on the enantioselectivity, *ortho*-, *meta*- and *para* substituted aldehydes such as *o*- and *p*-metoxy benzaldehyde, *o*-chlorobenzaldehyde, *p*-trifluoromethylbenzaldehyde were used in

the enantioselective diethylzinc addition reaction. The procedure is given as follows.

A 25 mL three-necked vessel was dried under vacuum by applying the Schlenk technique for five times. Chiral ligand (0.05 mmol) was dissolved dry solvent (5 mL) under the argon atmosphere. After cooling to 0 °C, diethylzinc (2 mL, 2 mmol) 1M in hexane) was added with a syringe over a period of 5 min. The mixture was stirred for 6 hours at the room temperature. Substituted benzaldehyde (1 mmol) was added at 0 °C. The mixture was stirred for 8-20 hours at room temperature and monitored by TLC. The reaction was quenched by the addition of 10 mL of 1 N HCl solution. The layers were separated and aques layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with 10 mL of brine, dried over anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography. (Silica gel, EtOAc.hexane, 1:6).

1-(4-Metoxyphenyl)propan-1-ol (227): R_f:0.32 (EtOAc:hexane, 1.5); ^{1}H-NMR ($CDCl_3$): δ 0.87 (t, 3H, *J*=7.40 Hz, C*H*$_3$), 1.63-1.80 (m, 2H, C*H*$_2$CH$_3$), 1.90 (broad s, 1H, O*H*), 3.77 (s, 3H, OC*H*$_3$), 4.47 (t, 1H, *J*=6.64 Hz, C*H*), 6.81 (d , 2H, *J*= 8.68 Hz Ar*H*), 7.17 (d, 2H, *J*= 8.64 Hz, Ar*H*); HPLC analysis: Chiralcell OD column eluted with hexane:2-propanol (97:3) at 1 mL/min using UV detection (254nm), R_t:35 min for (*R*) , 39 min for (*S*).

1-(2-Metoxyphenyl)propan-1-ol (228): R_f:0.32 (EtOAC:hexane ; 1.5); ^{1}H-NMR ($CDCl_3$): δ 0.94 (t, 3H, *J*=7.20 Hz, C*H*$_3$), 1.73-1.80 (m, 2H, C*H*$_2$CH$_3$), 2.53 (broad s, 1H, O*H*), 3.83 (s, 3H, OC*H*$_3$), 4.76 (t, 1H, *J*=6.51 Hz, C*H*), 6.82 (d, 1H, *J*= 8.20 Hz, Ar*H*), 6.89-6.93 (m, 1H, Ar*H*), 7.16-7.20 (m, 1H, Ar*H*), 7.27 (d, 1H, *J*=7.52 Hz, Ar*H*); HPLC analysis: Chiralcell OD column eluted with hexane:2-propanol (98:2) at 1 mL/min using UV detection (254nm), R_t:28 min for (*S*), 39 min for (*R*).

1-(4-Trifluoromethylphenyl)propanol-1-ol (229): R_f:0.31 (EtOAc:hexane, 1.5); ^{1}H-NMR ($CDCl_3$): δ 0.96 (t, 3H, *J*=7.60 Hz, C*H*$_3$), 1.73-1.85 (m, 2H, C*H*$_2$CH$_3$), 1.99 (broad s, 1H, O*H*), 4.67 (t, 1H, *J*=6.40 Hz, C*H*), 7.46 (d, 2H, *J*=8.40 Hz, Ar*H*), 7.62 (d, 2H, *J*=8.00 Hz, Ar*H*); HPLC analysis: Chiralcell OD column eluted with

hexane:2-propanol (95:5) at 0.8 mL/min using UV detection (254nm), R_t:9.11 min for (*S*), 10.92 min for (*R*).

1-(4-Chlorophenyl)propan-1-ol (230): R_f:0.32 (EtOAc:hexane, 1.5); ^{1}H-NMR ($CDCl_3$): δ 0.91 (t, 3H, *J*=7.40 Hz, C*H*$_3$), 1.69-1.83 (m, 2H, C*H*$_2$CH$_3$), 2.21 (broad s, 1H, O*H*), 4.54 (t, 1H, *J*=7.10, C*H*), 7.24 (d, 2H, *J*=8.48 Hz, Ar*H*), 7.30 (d, 2H, *J*=8.44, Ar*H*); HPLC analysis: Chiralcell OD column eluted with hexane:2-propanol (97:3) at 0.5 mL/min using UV detection (254nm), R_t:23 min for (*R*), 25 min for (*S*).

4.7.2. Conjugate addition of diethylzinc to chalcone using nickel acetylacetonate (Niacac)$_2$ as metal salt in the presence of chiral ligand

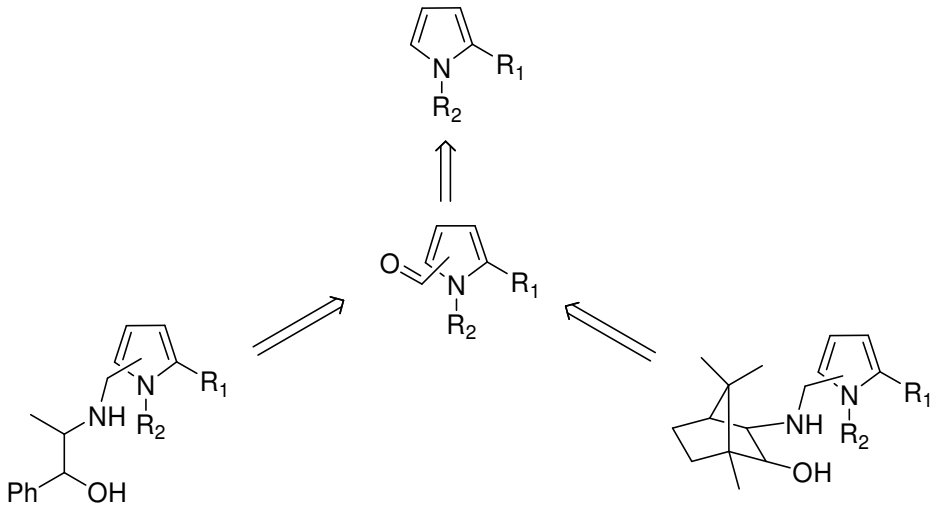
A solution of Ni(acac)$_2$ (0.013 g, 0.05 mmol) and chiral ligand (0.0348 g, 0.1 mmol) in 3 mL acetonitrile was stirred and refluxed for 1 hour under argon atmosphere. The solution was cooled to room temperature and chalcone (0.104 g, 0.5 mmol) was added. The mixture was cooled to -35 °C and diethylzinc (0.75 mmol, 0.75 mL of 1 M hexane solution) was added with a syringe over a period 5 min. The colour changed from bright green to dark brown red. The reaction mixture was stirred at –35 °C for 6 hours and monitored by TLC. The mixture was quenched with 1 N HCl (10 mL) and extracted with CH_2Cl_2 (3x20 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. Evaporation of the solvent gave crude product was purified by column chromatography (silica gel, EtOAc:hexane, 1:20).

1,3-Diphenylpentan-2-one (187): R_f:0.55 (EtOAc:hexane, 1:5); ^{1}H-NMR ($CDCl_3$): δ 0.85 (t, 3H, *J*=7.40 Hz, CH_2CH_3), 1.67-1.71 (m, 1H, C*H*$_2$CH$_3$), 1.80-1.83 (m, 1H, C*H*$_2$CH$_3$), 3.22-3.30 (m, 3H, C*H*C*H*$_2$), 7.18-7.29 (m, 5H, Ar*H*), 7.43-7.45 (m, 2H, Ar*H*), 7.52-7.55 (m, 1H, Ar*H*), 7.90-7.92 (m, 2H, Ar*H*); HPLC analysis: Chiralcell OD column eluted with hexane:2-propanol (99.5:0.5) at 1 mL/min using UV detection (254 nm), R_t:14.11 min. for (*S*) , 15.35 min. for (*R*) and Chiralcell AD column eluted with hexane:2-propanol (99:1) at 1 mL/min using UV detection (254nm), R_t:14.51 min for (*S*) , 17.82 min for (*R*).

5. EXPERIMENTAL RESULTS AND DISCUSSION

An enantioselective reaction through a catalytic process is recognized as one of the most challenging problems in organic synthesis. Catalytic enantioselective carbon-carbon bond forming reactions are important organic synthesis processes. The development of enantioselective catalysts is also one of the most important challenges in modern organic chemistry. For this purpose, a wide variety of chiral catalysts, i.e., amino alcohols, diamines, diols, disulfonamides, phosphor containing ligands have been synthesized. These new chiral ligands have been successfully applied in the catalytic enantioselective reactions to give enantiopure product in good yield and with high enantioselectivity.

In the first part of the work, it is aimed to synthesise norephedrine- and camphor-based ligands with *N*-substituted chiral pyrrole as outlined in retrosynthetic pathway (Scheme 5.1).



Scheme 5.1. Retrosynthetic pathways to the catalysts

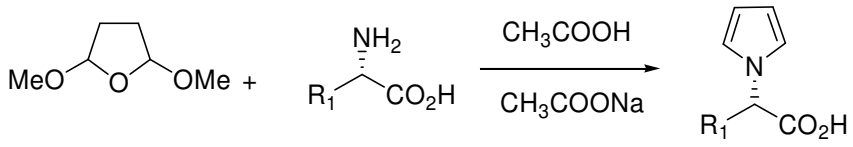
Synthesized ligands were used as chiral catalysts for the enantioselective additon of diethylzinc to prochiral aldehydes and chalcone in the second part of the work.

5.1. The Synthesis of *N*-Substituted Chiral Pyrrole Derivatives

Pyrrole derivatives are important starting materials for synthesis many different biologically active compounds (Jefford et al., 1991; Sardina et al., 1996).

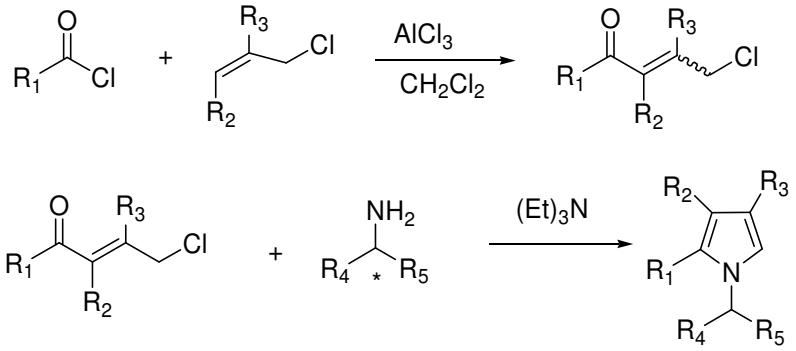
Pyrroles have traditionally been prepared *via* the condensation reaction of 1,4-dicarbonyl compounds with ammonia or primary amines, a reaction known as the Paal-Knorr pyrrole synthesis (Knorr, 1884).

N-Substituted chiral pyrrole derivatives have been prepared by the condensation of amino acids with 2,5-dimetoxytetrahydrofuran (Scheme 5.2). Racemization problem can be seen in this method when the reaction was performed in the acetic acid or acetic acid containing sodium acetate (Jefford et al., 1996). This method is also applied to the conversion of β-amino alcohols into their pyrrole derivatives. However optical yields were low and all pyrroles suffered racemization (Jefford et al., 1994).



Scheme 5.2. Condensation of amino acids with 2,5-dimetoxytetrahydofuran

There are many procedure in literature for the synthesize of pyrrole compounds. The most useful and efficient method reported by Demir et al (1997). They developed a new and efficient method for the synthesis of *N*- and 2-substituted chiral pyrroles from amines, amino alcohols and amino acids (Scheme 5.3).

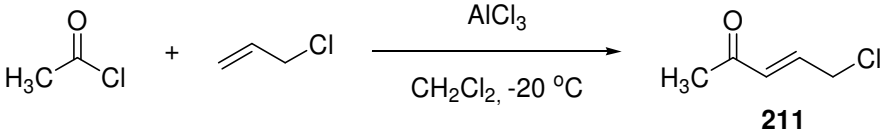


Scheme 5.3. The synthesis of chiral pyrroles.

This useful and efficient method was preferred in our study since starting compounds are easily available, substrate range is so broad, and the most important feature is that; no racemization occurs during the formation of pyrrole ring.

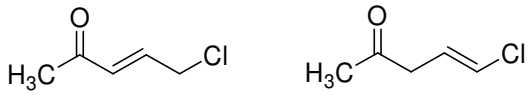
5.1.1. Synthesis of 5-chloropent-3-en-2-one (211)

5-Chloropent-3-en-2-one (**211**) was chosen as starting material for the pyrrole ring construction (Scheme 5.4).



Scheme 5.4. The synthesis of 5-chloropent-3-en-2-one (**211**)

The synthesis of the 5-chloropent-3-en-2-one (**211**), was carried out by addition of 3-chloropropene to acetyl chloride in the presence of aluminium chloride suspension in CH_2Cl_2 at -20 °C. The reaction gives two different isomers (Scheme 5.5). As it will be shown in the formation of the pyrrole rings, both **211a** and **211b** give same reaction with amines to yield pyrrole ring . So, the crude product was used without purification



211a **211b**

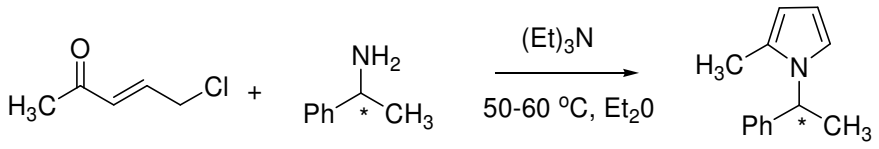
Scheme 5.5. Isomers of 5-chloropent-3-en-2-one (**211a**-**b**)

The reaction yield **211** depends on the reaction temperature. The temperature of the reaction should be between -15 °C and -20 °C during reactions. Increasing of the reaction temperature caused decomposition and polymerization of the product.

5.1.2. The synthesis of 2-methyl-1-((1*R*)-1-phenylethyl)-1*H*-pyrrole ((*R*)-213) and 2-methyl-1-((1*S*)-1-phenylethyl)-1*H*-pyrrole ((*S*)-213)

2-Methyl-1-((1*R*)-1-phenylethyl)-1*H*-pyrrole ((*R*)-**213**) and 2-methyl-1-((1*S*)-1-phenylethyl)-1*H*-pyrrole ((*S*)-**213**) were prepared from (*R*)-phenyl ethylamine and (*S*)-phenyl ethylamine, respectively.

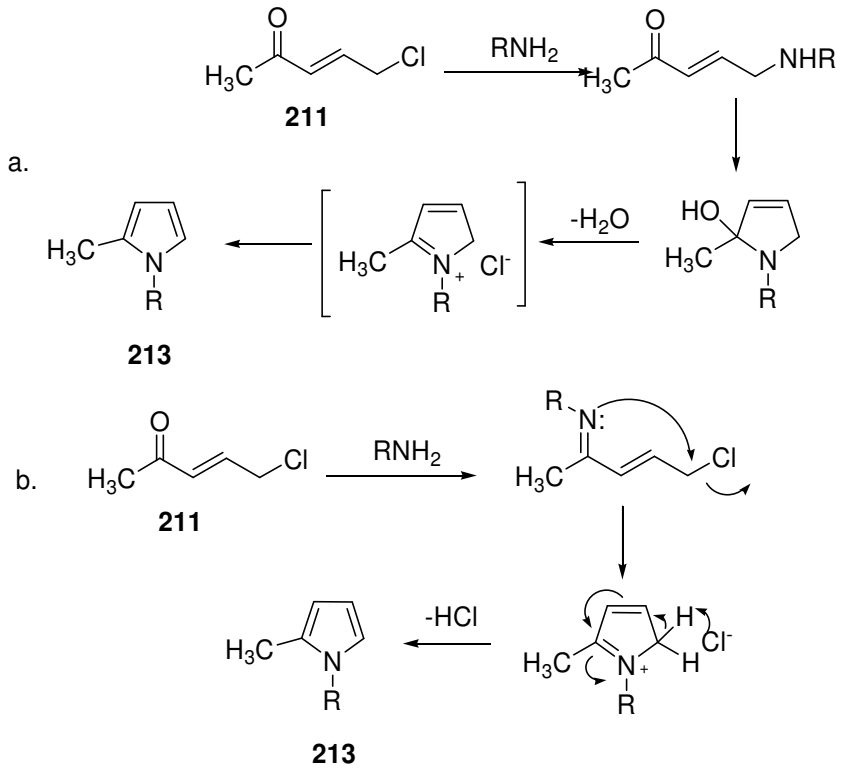
As shown in Scheme 5.6., 5-chloropent-3-en-2-one (**211**) and phenylethylamine refluxed in the presence of triethylamine at 50-60 °C in ether, and crude product was purified by using flash column chromatograpy.



211 *(R)*-**212** *(S)*-**212** *(R)*-**213** *(S)*-**213**

Scheme 5.6. The synthesis of chiral *N*-subsituted pyrrole

The proposed mechanism for the pyrrole ring construction is shown in Scheme 5.7a and Scheme 5.7b.



Scheme 5.7. Proposed mechanism for synthesis of pyrroles.

As shown in Scheme 5.7a, the chloride is replaced with amine and aminoketone is formed. The condensation reaction of amine with carbonyl compound followed by water elimination should afford pyrrole ring. As shown in Scheme 5.7b, it is possible that first the condensation reaction occurs to give imine. The intramolecular substitution reaction and followed by elimination of HCl should give pyrrole ring.

The products (*R*)-**213** and (*S*)-**213** were obtained as colourless solids in 90% and 85% chemical yields, respectively. Specific rotation of (*R*)-**213** and (*S*)-**213** are $[\alpha]_D^{25}$=+16.7 (c 1, CH_3OH) and $[\alpha]_D^{25}$=-16.9 (c 1, CH_3OH), respectively.

^{1}H-NMR and ^{13}C-NMR spectrum of (*R*)-**213** and (*S*)-**213** were given in Figure 5.1. and 5.2.

The ^{1}H-NMR spectrum (Figure 5.1) shows a doublet at 1.79 ppm for methyl protons, a singlet at 2.06 ppm for methyl protons at C(2)*H* of pyrrole ring, a

quartet 5.32 ppm for methine proton of ethyl group. The signals at 5.95 ppm, 6.16 ppm, 6.83 ppm belong to the C(3)*H*, C(4)*H* and C(5)*H* of pyrrole ring, respectively. The phenyl ring protons appear as a doublet at 7.01 ppm and a multiplet between 7.24-7.35 ppm.

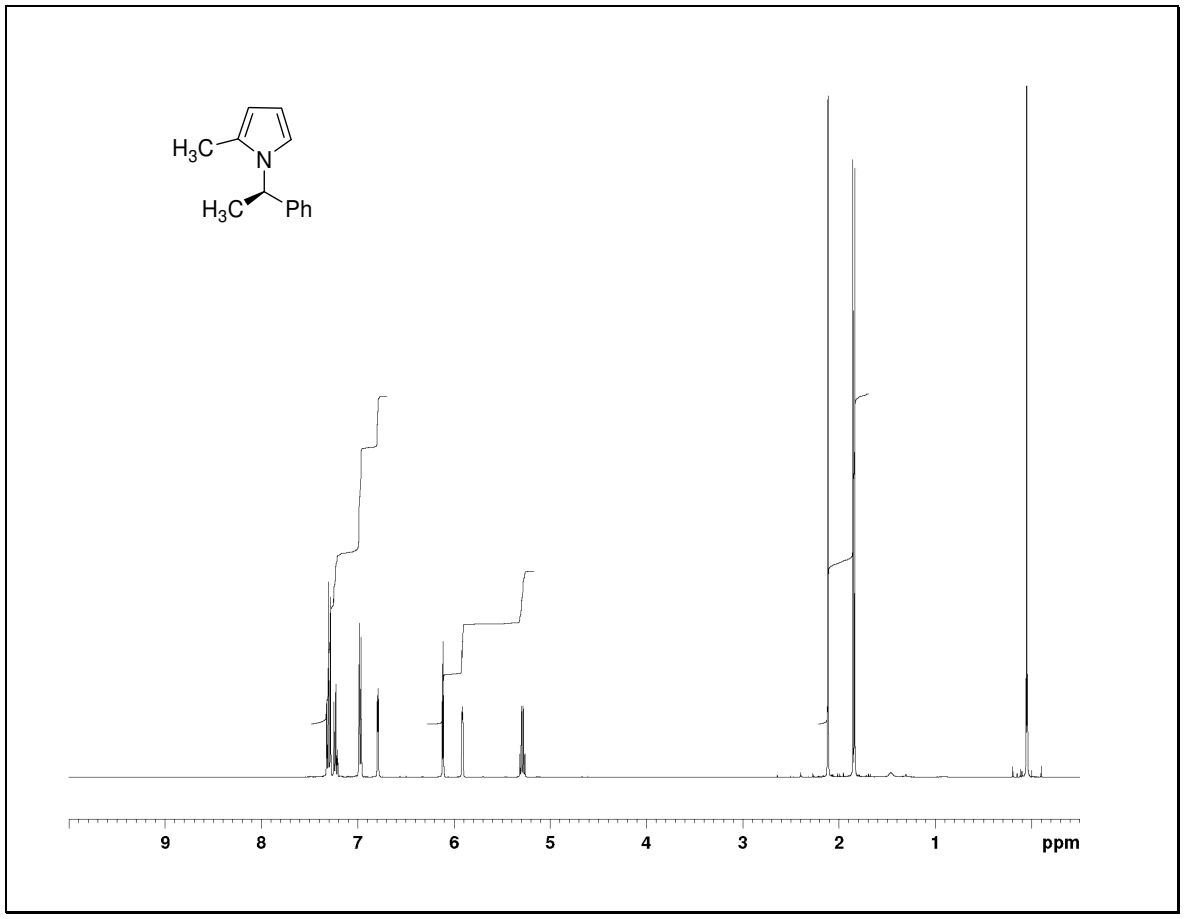


Figure 5.1. The ^{1}H-NMR spectrum of 2-methyl-1-((1*R*)-1-phenylethyl)-1*H*-pyrrole ((*R*)-**213**)

The ^{13}C-NMR spectrum (Figure 5.2) of compound (*R*)-**213** shows signals at 12.26 ppm for the methyl carbon attached to the pyrrole ring. The methyl carbon of the ethyl group exhibits a signal at 22.51 ppm. The signal at 54.85 ppm belongs to the methine carbon of ethyl group. The carbons of the pyrrole ring exhibit signals at 106.94 ppm for C(3), 107.31 ppm for C(4), 116.83 ppm for C(5) for, 128.60 ppm for C(2). The carbons of the phenyl ring show signals at 125.58 ppm (CH), 127.05 ppm (CH), 128.58 ppm (CH), 143.86 ppm (C).

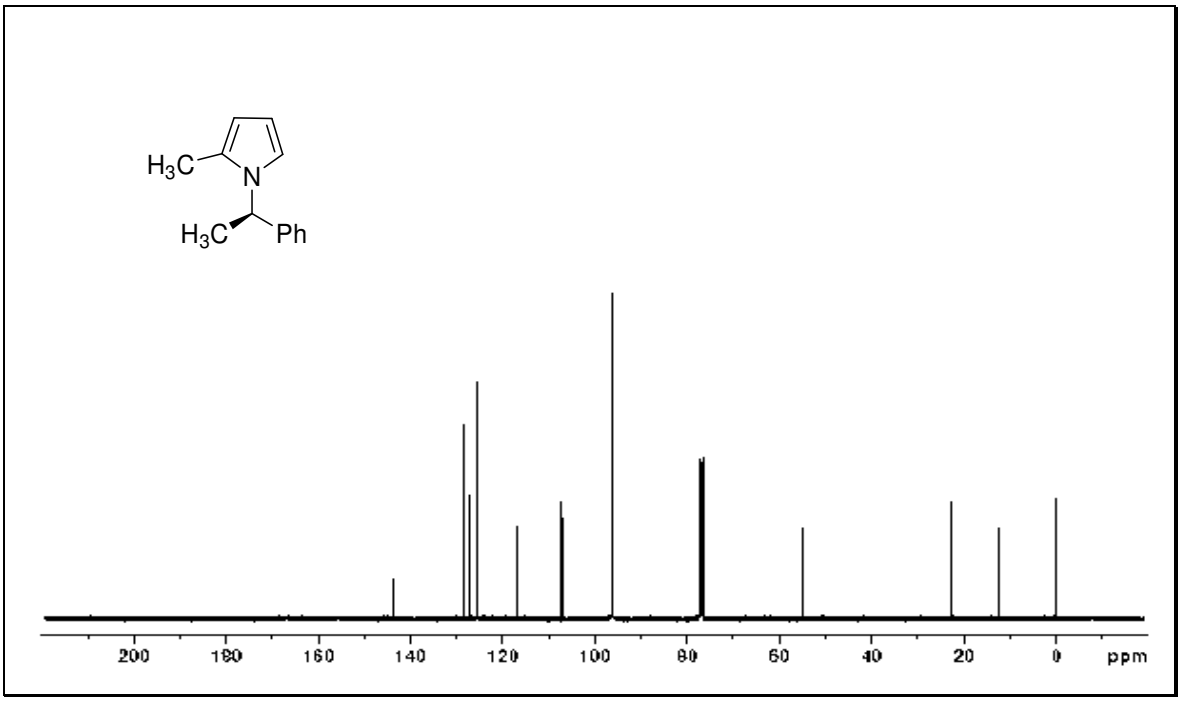


Figure 5.2. The ^{13}C-NMR spectrum of 2-methyl-1-((1*R*)-1-phenylethyl)-1*H*-pyrrole ((*R*)-**213**)

^{1}H-NMR and ^{13}C-NMR spectrum of the other enantiomer (*S*)-**213** are given Figure 5.3 and 5.4.

As shown in Figure 5.3., the ^{1}H-NMR spectrum of (*S*)-**213** gives signals of pyrrole ring at 5.80 ppm for C(3)*H*, 6.01 ppm for C(4)*H*, 6.68 ppm for C(5)*H*. The phenyl ring protons appear as a doublet at 6.87 ppm and a multiplet between 7.10-7.28 ppm.

The ^{13}C-NMR spectrum also supports the suggested structure. Characteristic signals of pyrrole ring appear at 106.97 ppm, 107.34 ppm, 116.85 ppm, 128.62 ppm belong to C(3), C(4), C(5), C(2), respectively.

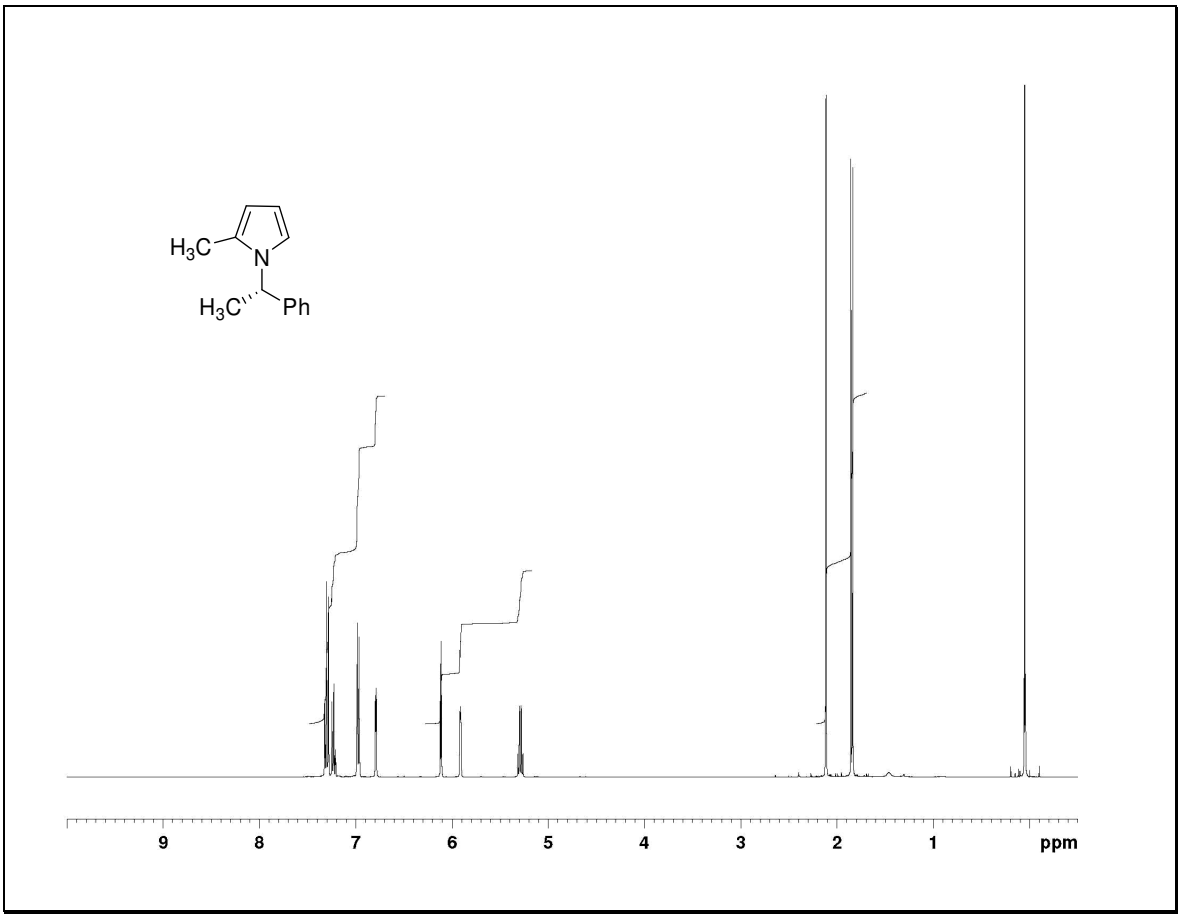


Figure 5.3. The ^{1}H-NMR spectrum of 2-methyl-1-((1*S*)-1-phenylethyl)-1*H*-pyrrole ((*S*)-**213**)

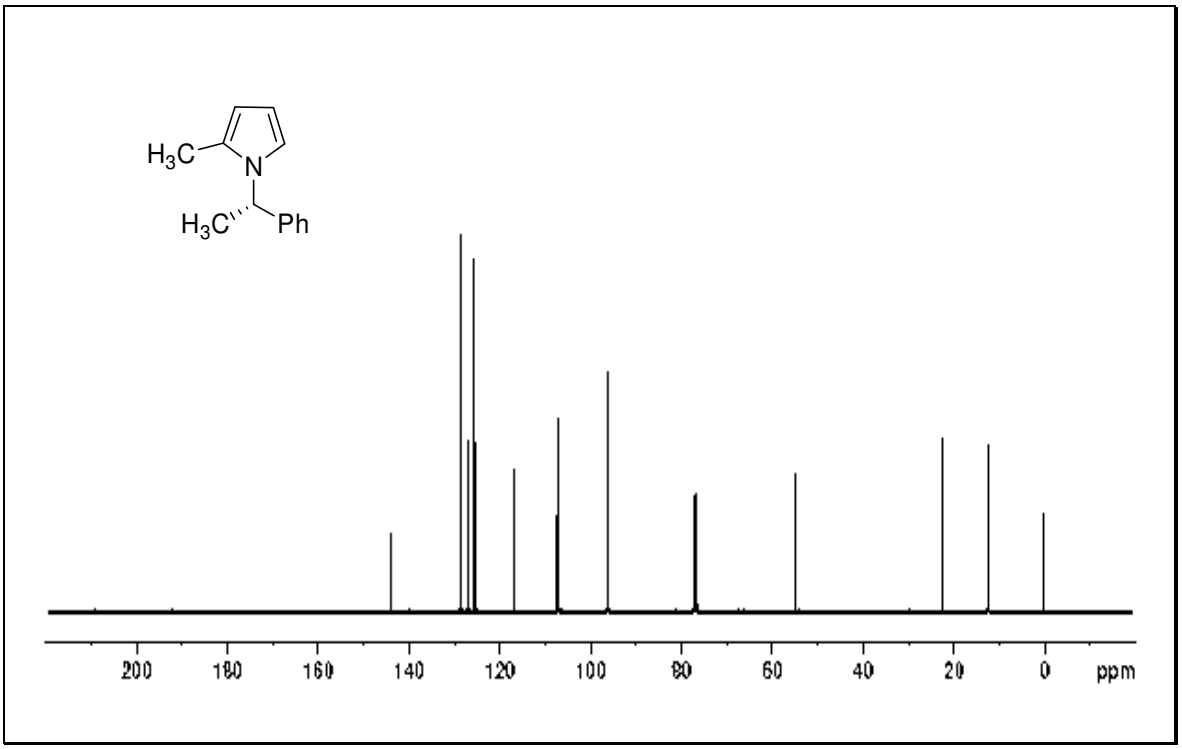


Figure 5.4. The ^{13}C-NMR spectrum of 2-methyl-1-((1*S*)-1-phenylethyl)-1*H*-pyrrole ((*S*)-**213**)

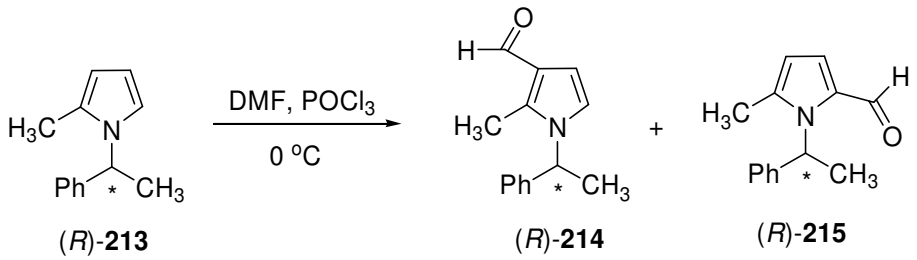
5.2. The Formylation of *N*-Substituted Chiral Pyrroles

The formylation of *N*-substituted pyrrole compounds ((*R*)-**213** and (*S*)-**213**) were performed by Vilsmeier Haack reaction (Scheme 5.8 and 5.9). *N*-Substituted pyrrole compound and DMF were dissolved in a mixture of n-pentane and ether. This solution was cooled to 0 °C and $POCl_3$ was added dropwise with stirring over 1 hour. Stirring continued for 12 hours at room temperature (checking by TLC). The compounds were identified by one and two dimensional NMR techniques and X-ray spectroscopy. The formylation position of product was determined with the aid of a heteronuclear multiple bond correlation (HMBC) spectrum, homonuclear correlation (^{1}H-^{1}H COSY). Formylation reaction was occurred at C(2) and C(3) according to COSY spectra of the products. C(3) formulated product was obtained a main product in 68-70% yield by using equal moles of (*R*)-**213**, DMF and $POCl_3$ at 0 °C-room temperature. C(2) formulated product was formed in 21-24% yield.

We examined different reaction conditions to increase the yield of C(2) formulated product. (*S*)-**217** formed with high yield (52%) where molar ratio of pyrrole, DMF and $POCl_3$ was 1:10:10 at 0 °C.

5.2.1. The synthesis of 2-methyl-1-((1*R*)-1-phenylethyl)-1*H*-pyrrole-3-carbaldehyde ((*R*)-214) and 5-methyl-1-((1*R*)-1-phenylethyl)-1*H*-pyrrole-2-carbaldehyde ((*R*)-215)

2-Methyl-1-((1*R*)-1-phenylethyl)-1*H*-pyrrole ((*R*)-**213**) was converted into its formylated derivatives using Vilsmeier Haack formylation reaction. (Scheme 5.8). The reaction produced 2- and 3- formyl pyrrole compounds which were separated by flash column chromatography. 2-Methyl-1-((1*R*)-1-phenylethyl)-1*H*-pyrrole-3-carbaldehyde ((*R*)-**214**) [68% yield, $[\alpha]_D^{25}$= +21.1 (c 11, $CHCl_3$)] and 5-methyl-1-((1*R*)-1-phenylethyl)-1*H*-pyrrole-2-carbaldehyde ((*R*)-**215**) [21% yield, $[\alpha]_D^{25}$= +119.7 (c 11, $CHCl_3$] were obtained.



(*R*)-**213** (*R*)-**214** (*R*)-**215**

Scheme 5.8. The formylation of 2-methyl-1-((1*R*)-1-phenylethyl)-1*H*-pyrrole ((*R*)-**213**)

Characterization of 2-methyl-1-((1*R*)-1-phenylethyl)-1*H*-pyrrole-3-carbaldehyde ((*R*)-**214**) and 5-methyl-1-((1*R*)-1-phenylethyl)-1*H*-pyrrole-2-carbaldehyde ((*R)*-**215**) was achieved by ^{1}H-NMR, ^{13}C-NMR, COSY, HMBC spectroscopy.

The ^{1}H-NMR spectrum of 2-methyl-1-((1*R*)-1-phenylethyl)-1*H*-pyrrole-3-carbaldehyde ((*R*)-**214**) (Figure 5.5.) shows a doublet at 1.85 ppm for the methyl protons of the ethyl gorup. The singlet at 2.43 ppm is for the other methyl protons

that is bounded to pyrrole ring. The quartet at 5.36 ppm is due to methine proton of ethyl group. Typical doublets of pyrrole ring protons appear at 6.60 ppm (C(4)*H*) and 6.75 ppm (C(5)*H*). The phenyl ring protons appear as doublet at 7.04 ppm and a multiplet between 7.25 and 7.34 ppm. Characteristic aldehyde proton signal appears at 9.85 ppm as singlet.

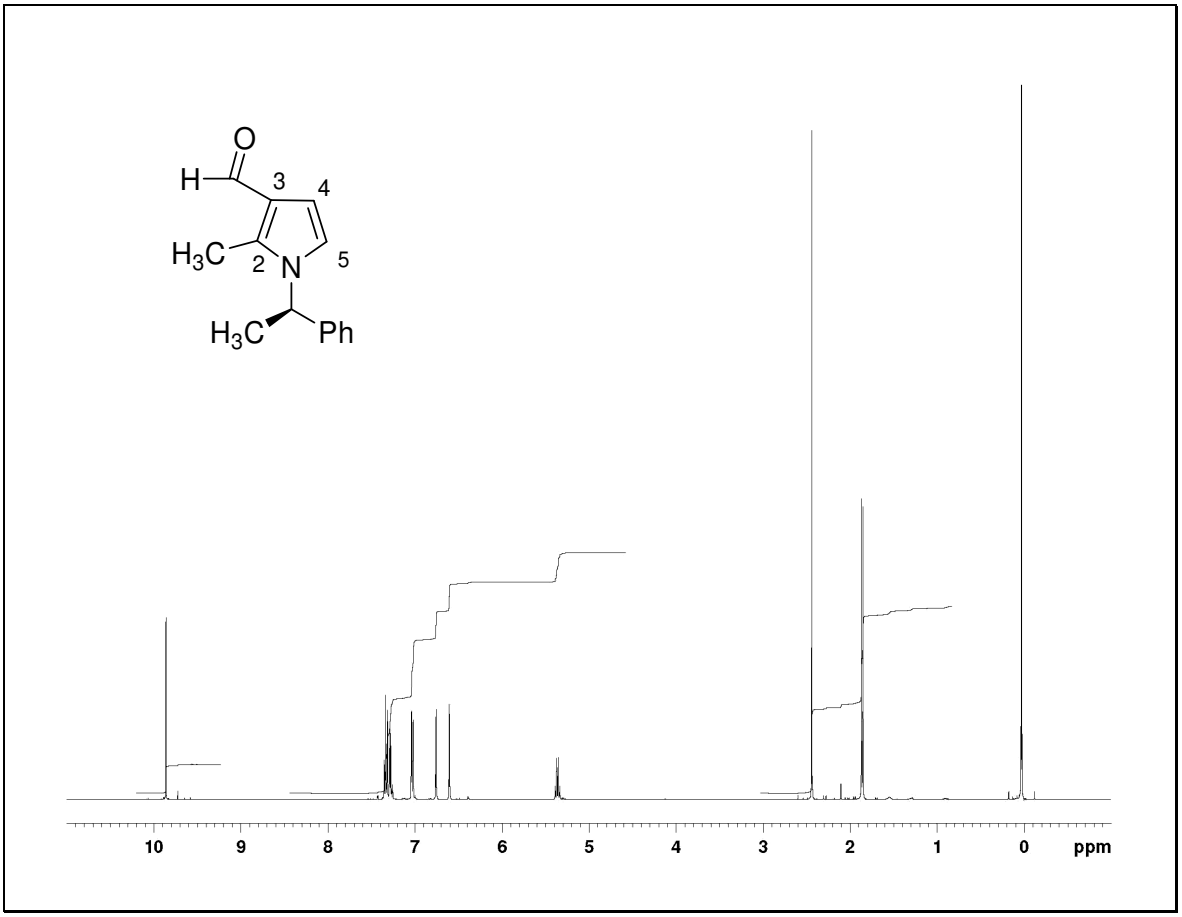


Figure 5.5. The ^{1}H-NMR spectrum of 2-methyl-1-((1*R*)-1-phenylethyl)-1*H*-pyrrole-3-carbaldehyde ((*R*)-**214**)

The ^{1}H-NMR spectrum of 5-methyl-1-((1*R*)-1-phenylethyl)-1*H*-pyrrole-2-carbaldehyde ((*R*)-**215**) (Figure 5.6.) shows a doublet at 1.91 ppm for the methyl protons of the ethyl groups. The methyl protons attached to the pyrrole ring exhibit singlet at 1.98 ppm. Interestingly methine proton of ethyl group shifted from 5.36 to 6.98 ppm because of the interaction between methine proton of the ethyl group and carbonyl oxygen. The two doublet, at 6.00 ppm (C(4)*H*) and 6.88 ppm (C(3)*H*)

belong to the pyrrole protons. The phenyl protons give doublet at 7.12 ppm and multiplet between 7.22-7.34 ppm. The carbonyl proton exhibit singlet at 9.61 ppm.

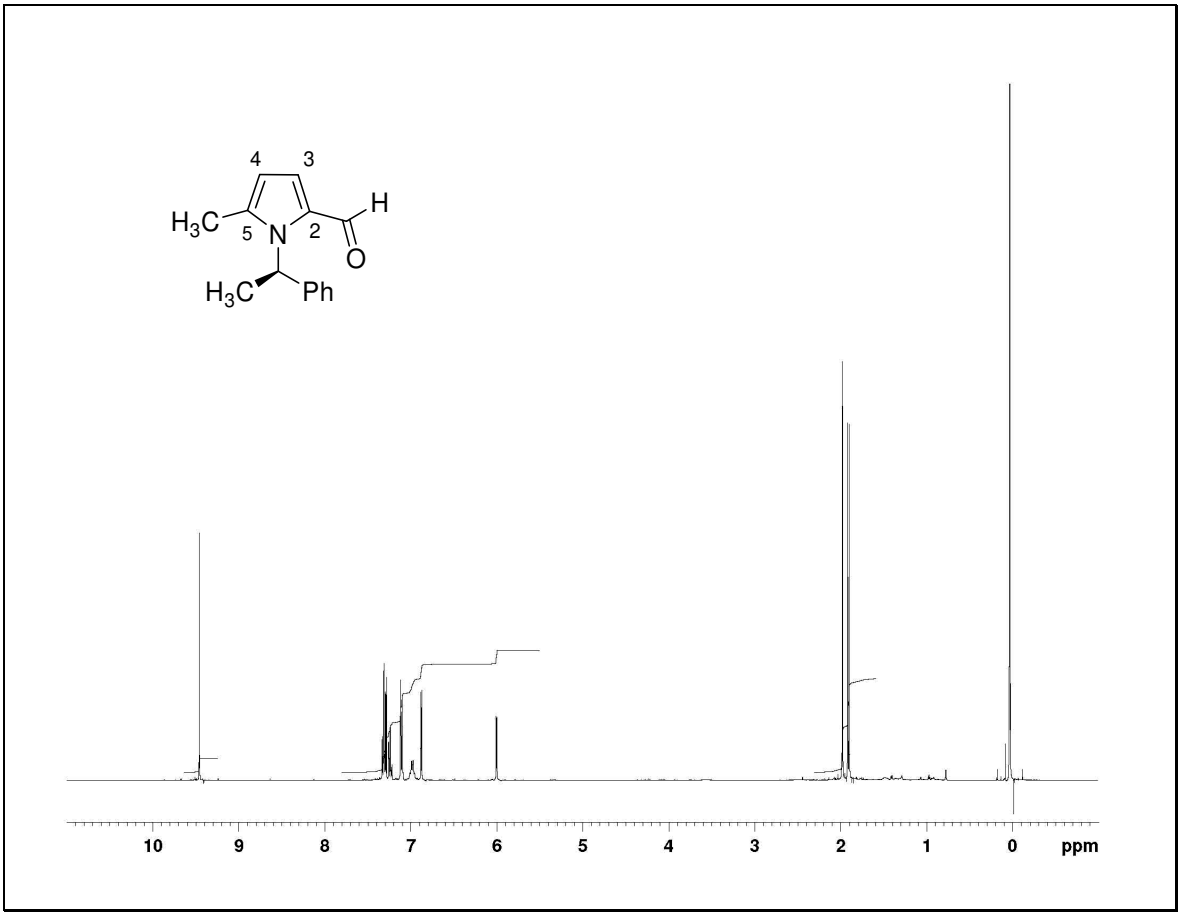


Figure 5.6. The ^{1}H-NMR spectrum of 5-methyl-1-((1*R*)-1-phenylethyl)-1*H*-pyrrole-2-carbaldehyde ((*R*)-**215**)

In order to determine the formylation position of pyrrole ring, COSY spectrum of the compounds were taken. As shown in Fgure 5.7, pyrrole protons at 6.60 ppm for C(4)*H* and 6.75 ppm for C(5)*H* have interaction with each other.

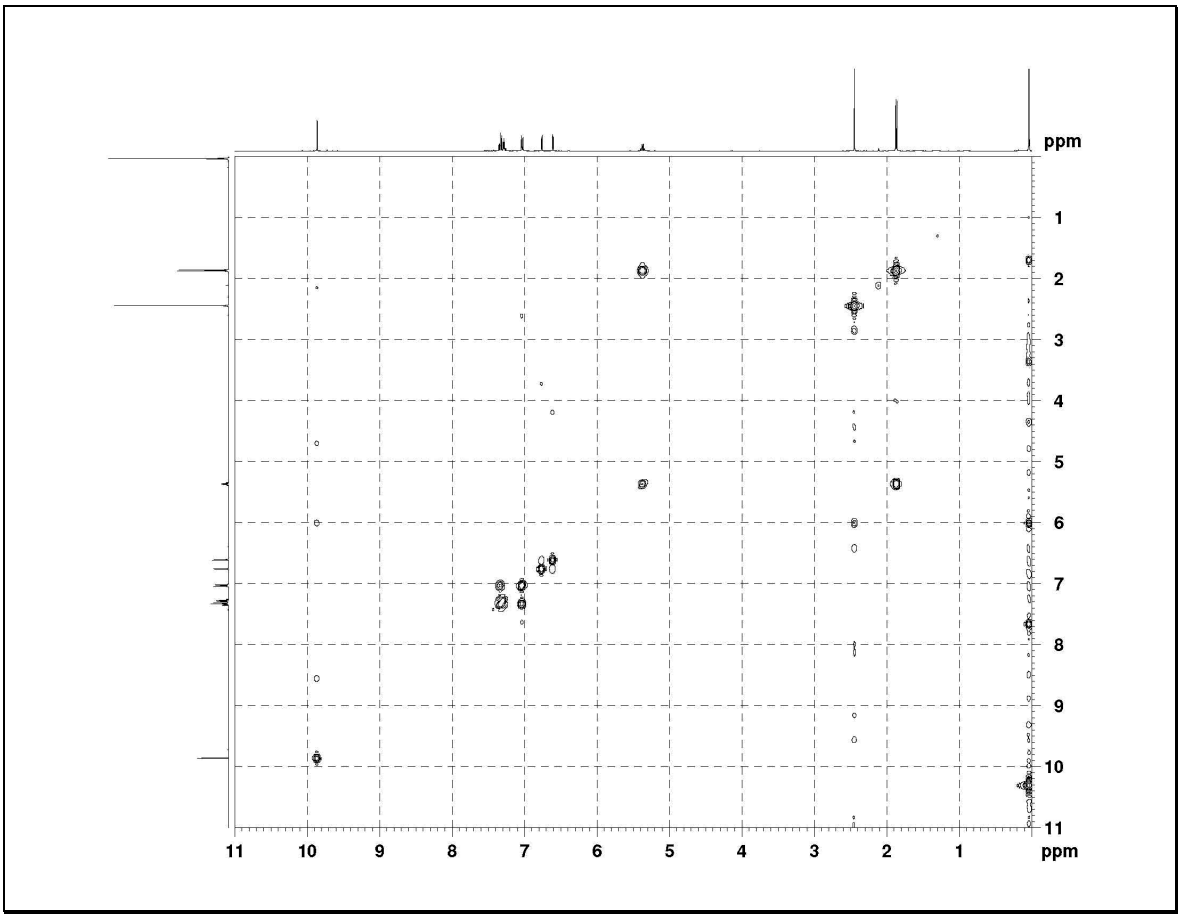


Figure 5.7. The COSY spectrum of 2-methyl-1-((1*R*)-1-phenylethyl)-1*H*-pyrrole-3-carbaldehyde ((*R*)-**214**)

The COSY spectrum (Figure 5.8) of (*R*)-**215** showed that the doublet at 6.00 ppm for C(4)*H* and 6.88 ppm for C(3)*H* correlates with each other so they are neighbour protons. Formylation reaction might be occurred at C(2) or C(3) of pyrrole. To define the certain position of formyl group, the other NMR techniques were applied.

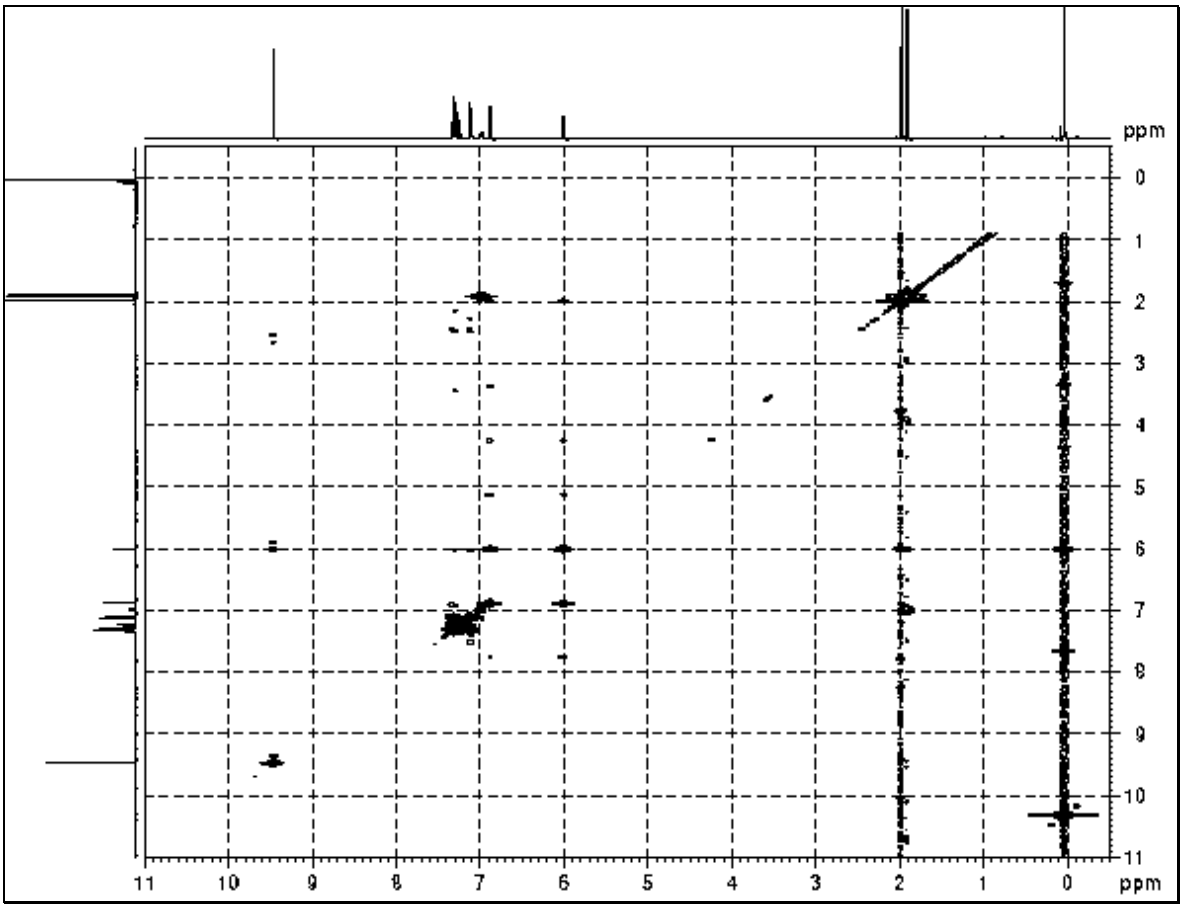


Figure 5.8. The COSY spectrum of 5-methyl-1-((1*R*)-1-phenylethyl)-1*H*-pyrrole-2-carbaldehyde ((*R*)-**215**)

The ^{13}C-NMR spectrum (Figure 5.9) of the (*R*)-**214** shows signal at 10.26 ppm for methyl carbon attached to pyrrole ring. The signal at 21.99 ppm is due to the methyl carbon of ethyl group. The signal at 54.85 ppm indicates the methine carbon of the ethyl group. The signals of pyrrole ring can be seen at 108.64 ppm for C(4) and 118.65 ppm for C(5). The signals at 122.76 ppm and 137.08 ppm which belong to the quaternary carbons (C(3), C(2)) of pyrrole, according to APT spectrum (Figure 5.10). The phenyl carbons exhibit signals at 125.33 ppm, 126.70 ppm, 128.86 and 141.93 ppm. Characteristic carbonyl carbon appears at 184.85 ppm.

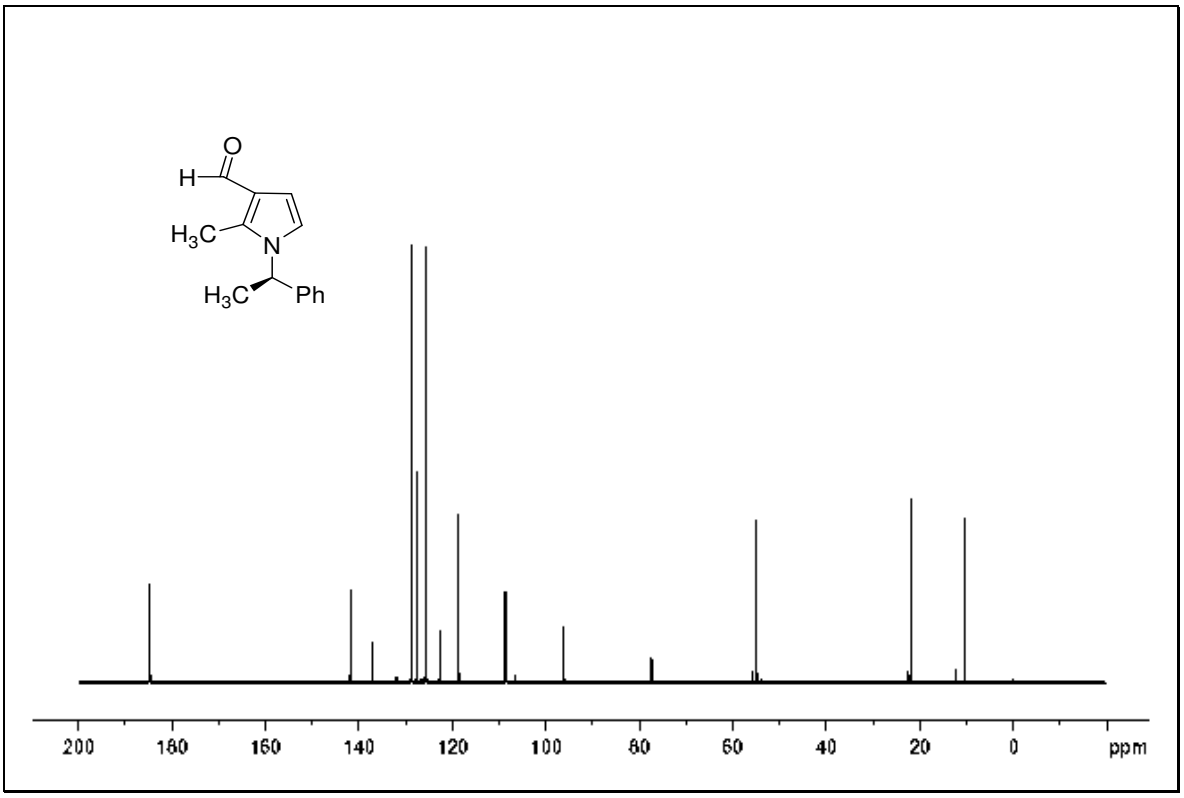


Figure 5.9. The ^{13}C-NMR spectrum of 2-methyl-1-((1*R*)-1-phenylethyl)-1*H*-pyrrole-3-carbaldehyde ((*R*)-**214**)

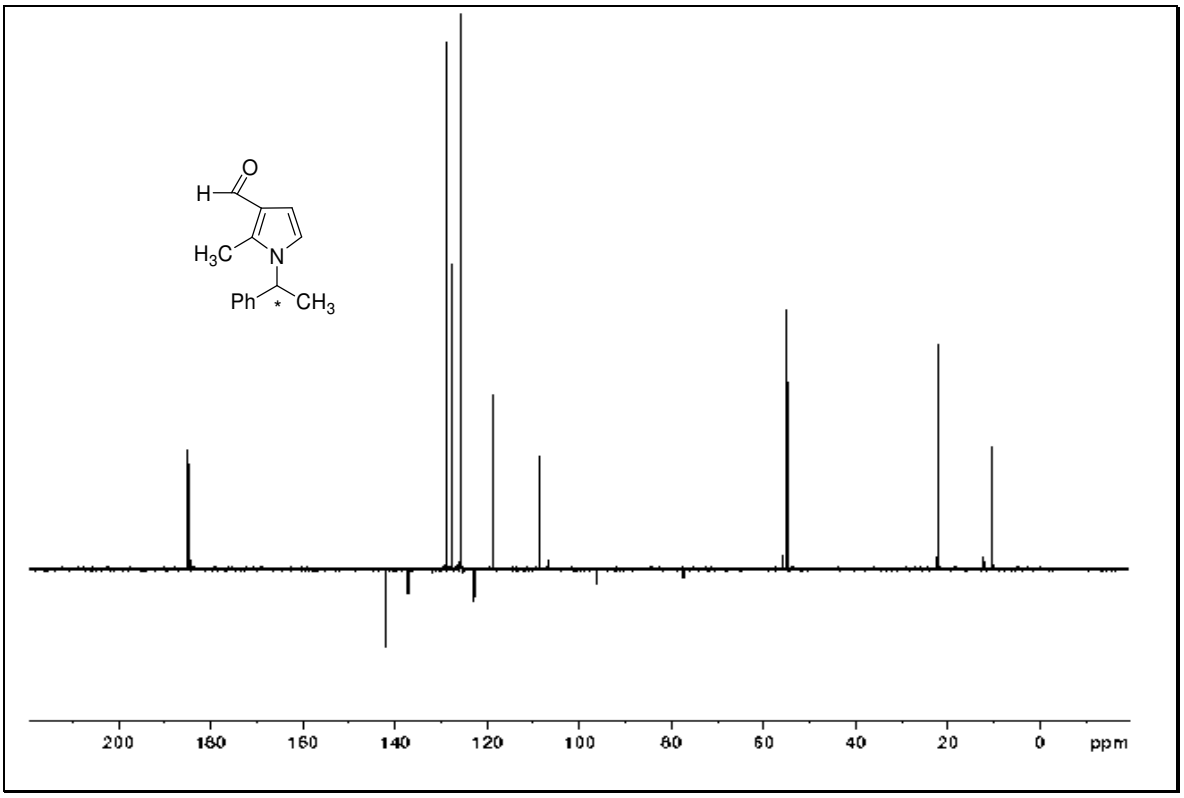


Figure 5.10. The APT spectrum of 2-methyl-1-((1*R*)-1-phenylethyl)-1*H*-pyrrole-3-carbaldehyde ((*R*)-**214**)

The position of formylated carbon of (*R*)-**214** were assigned using HMBC techniques

As shown in HMBC spectrum (Figure 5.11) the hydrogen of the aldehyde at 9.85 ppm showed crosspeak signals to the C(4) of pyrrole ring resonating at 108.64 ppm, quaternary carbon resonating at 137.08 ppm and the other quaternary carbon resonating at 122.76 ppm for C(3). According to the spectrum, aldehyde proton showed no correlation with the C(5) of the pyrrole ring resonating at 118.65 ppm.

In additional, pyrrole proton resonating at 6.60 ppm showed correlation with the three carbons resonating at 118. 65 ppm for C(5), 122.76 ppm for C(3), at 137.08 ppm for C(2) in Figure 5.11.

As shown in Figure 5.11, the correlation peaks were observed between methyl proton on pyrrole ring resonating at 2.43 ppm and the quaternary carbons resonating at 122.76 ppm for C(3), 137.08 ppm for C(2). No correlation were observed between methyl protons on pyrrole and pyrrole carbon C(4).

This result shows that given structure of (*R*)-**214** are in good agreement with HMBC spectrum.

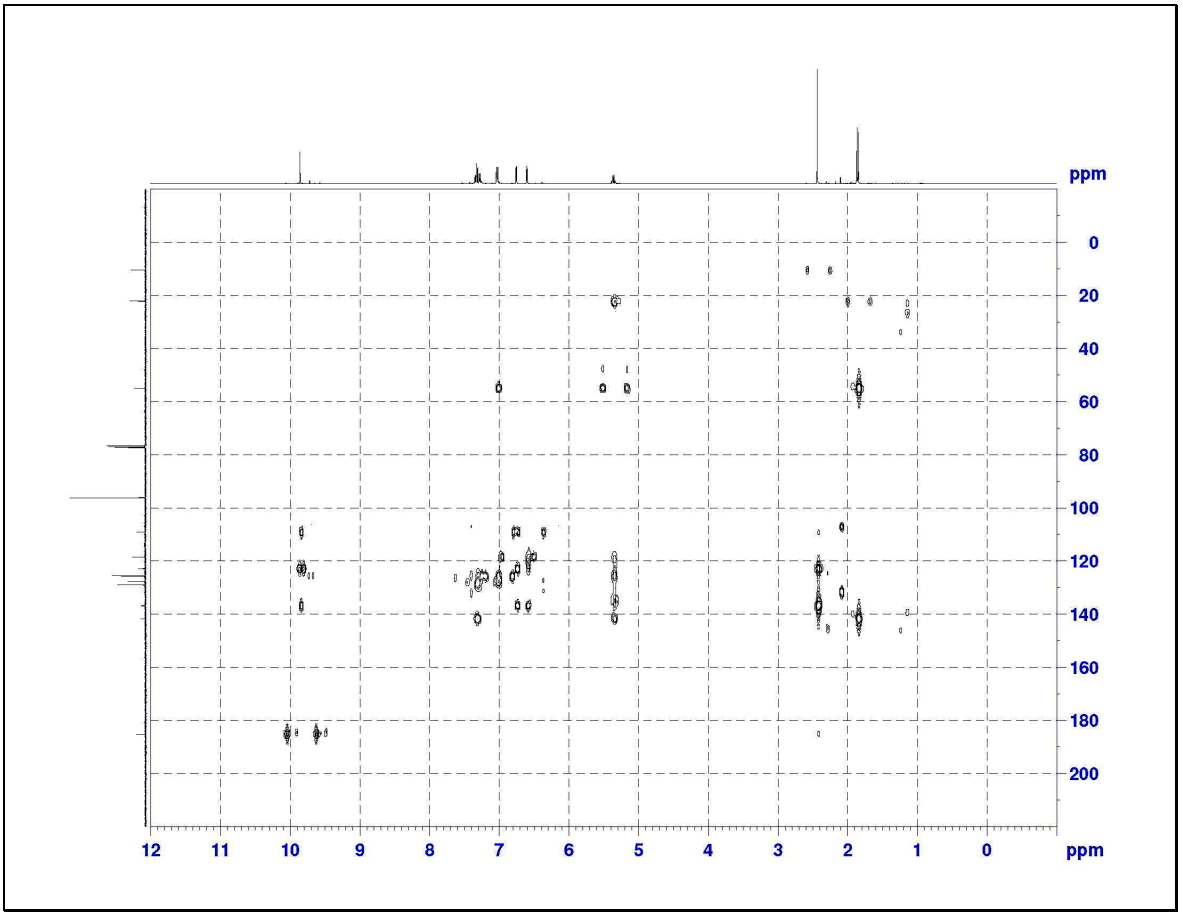


Figure 5.11. The HMBC spectrum of 2-methyl-1-((1*R*)-1-phenylethyl)-1*H*-pyrrole-3-carbaldehyde ((*R*)-**214**)

The ^{13}C-NMR spectrum (Figure 5.12) of the compound (*R*)-**215** exhibits signals at 14.25 ppm and 18.49 ppm for the methyl carbons attached to the pyrrole ring and the ethyl group, respectively. The signal at 53.17 ppm is due to the methine carbon of the ethyl gorup. Pyrrole carbons appear at 111.65 ppm for C(4)*H*, 125.69 ppm for C(3)*H*. The signals at 132.15 ppm, 140.70 ppm, 141.14 ppm

belong to pyrrole C(2), C(5) and the quaternary phenyl carbon, respectively. These signals were determined with the help of APT spectrum in Figure 5.13 and HMBC spectrum in Figure 5.14. The signals at 126.15 ppm, 126.98 ppm, 128.42 ppm, belong to the carbons of the phenyl ring. Characteristic carbonyl carbon appears at 178.24 ppm.

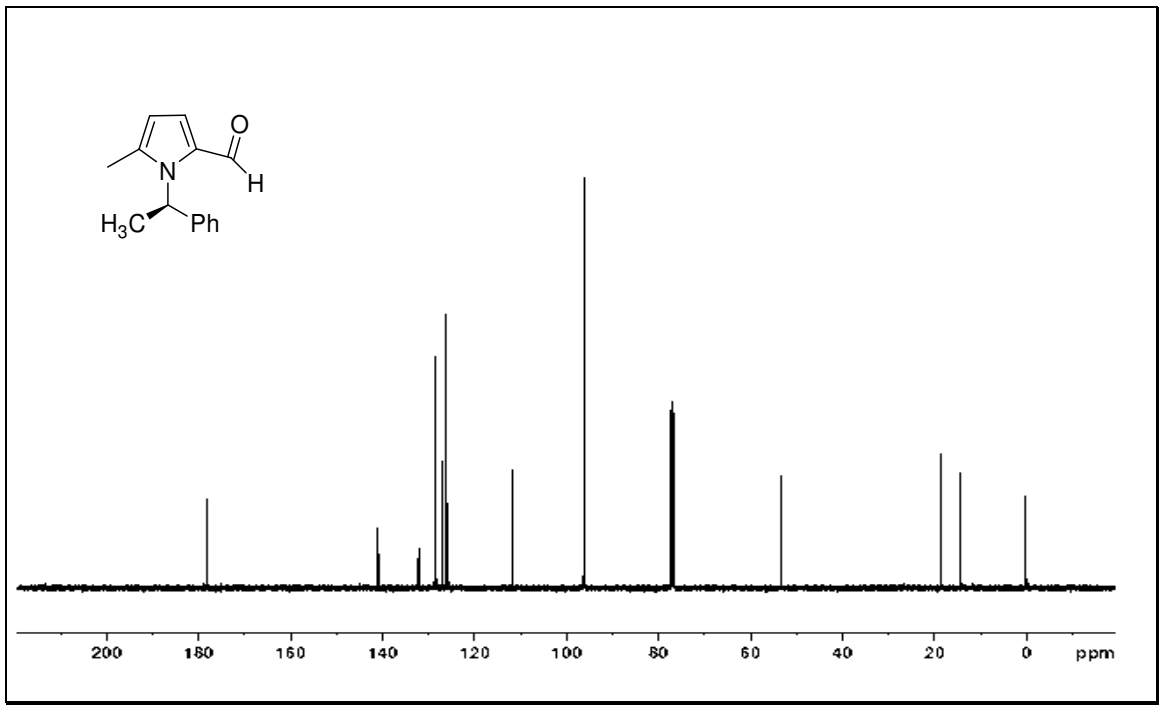


Figure 5.12. The ^{13}C-NMR spectrum of 5-methyl-1-((1*R*)-1-phenylethyl)-1*H*-pyrrole-2-carbaldehyde ((*R*)-**215**)

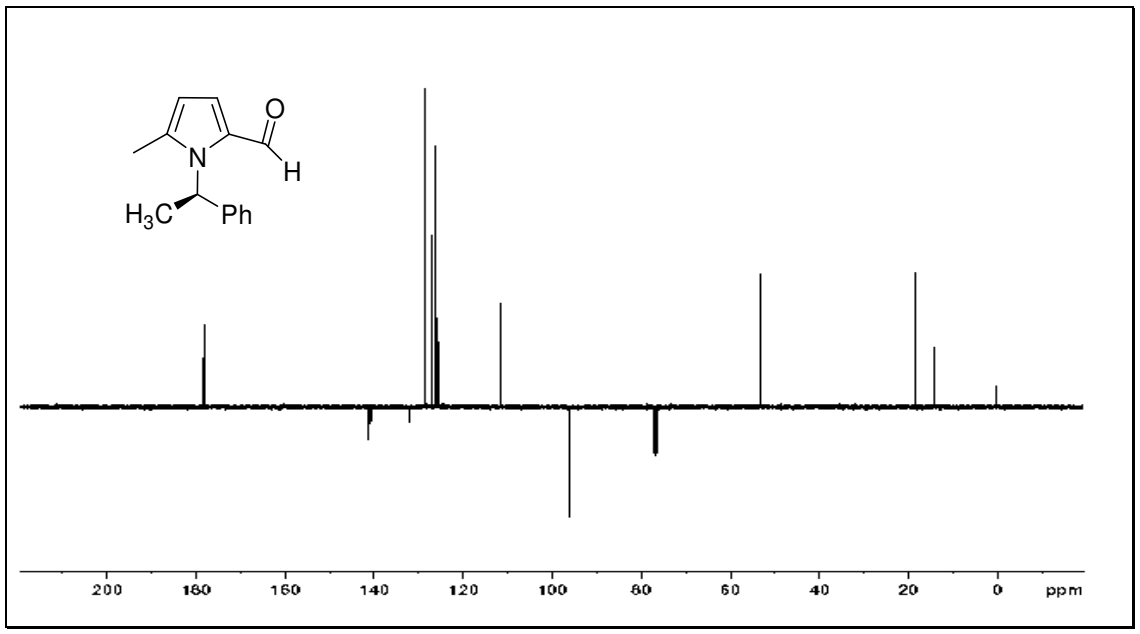


Figure 5.13. The APT spectrum of 5-methyl-1-((1*R*)-1-phenylethyl)-1*H*-pyrrole-2-carbaldehyde ((*R*)-**215**)

The HMBC spectrum of (*R*)-**215** (Figure 5. 14) showed the correlation between the carbonyl carbon resonating at 178.24 ppm and proton of pyrrole ring at (C(3)*H* resonating at 6.98 ppm.

The peak of methyl proton on pyrrole ring resonating at 1.98 ppm has cross-peaks with carbons of pyrrole ring resonating at 111.65 ppm for C(4), 125.69 ppm for C(3), 140.77 ppm for C(5) and 132.15 ppm for C(2) . Pyrrole proton resonating at 6.98 ppm showed correlation with carbons resonating at 111.65 ppm for C(4), 132.15 ppm for C(2) and 140.77 ppm for C(5).

This result shows that the HMBC spectrum of (*R*)-**215** is also consistent with the structure.

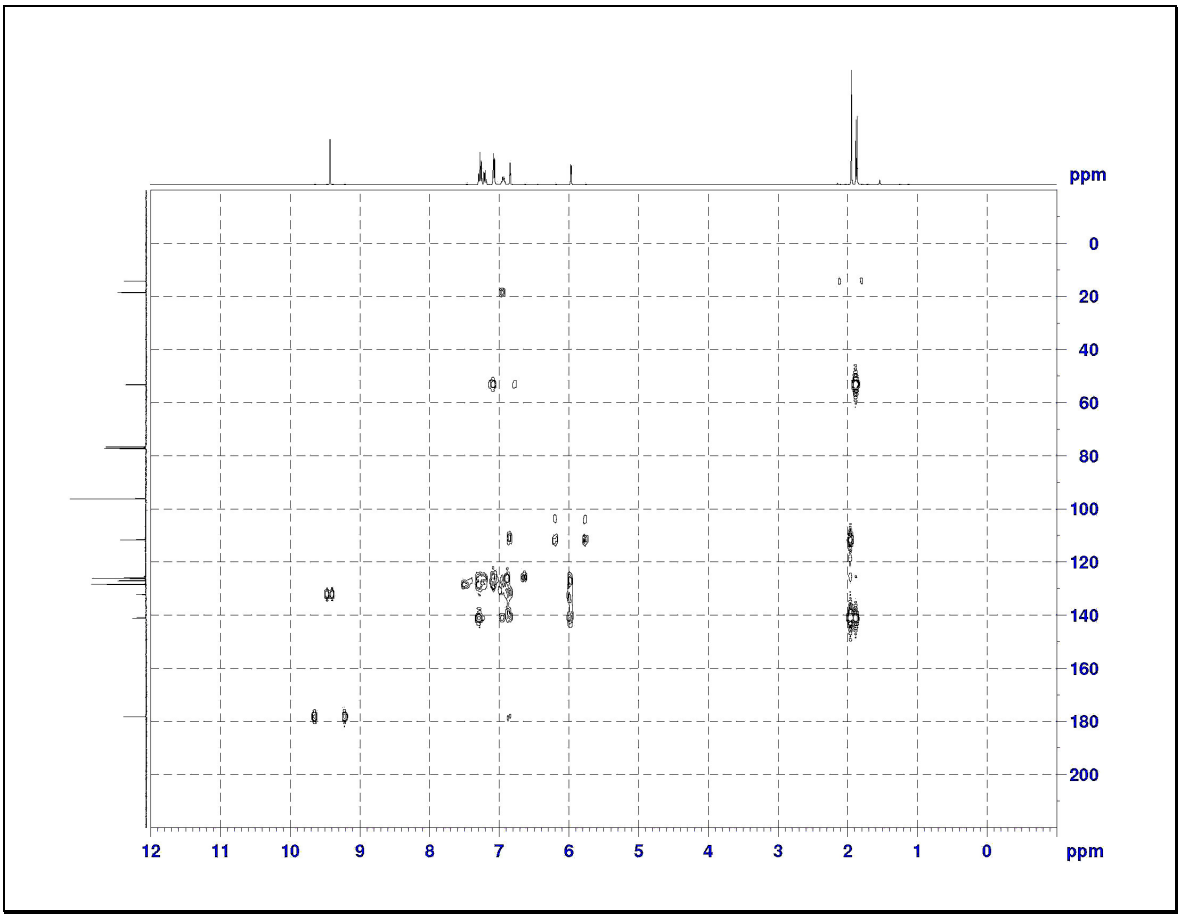


Figure 5.14. The HMBC spectrum of 5-methyl-1-((1*R*)-1-phenylethyl)-1*H*-pyrrole-2-carbaldehyde ((*R*)-**215**)

Formylation position of (*R)*-**214** was determined by one-, two dimentional NMR techniques. The structure was also charaterized by single crystal X-Ray analysis. The recrystallization of 2-methyl-1-((1*R*)-1-phenylethyl)-1*H*-pyrrole-3-carbaldehyde ((*R*)-**214**) from EtOAc:hexane system at room temperature, gave white crystals. As shown in Figure 5.15., X-ray analysis was indicated that the formylation was occurred at C(3) of pyrrole.

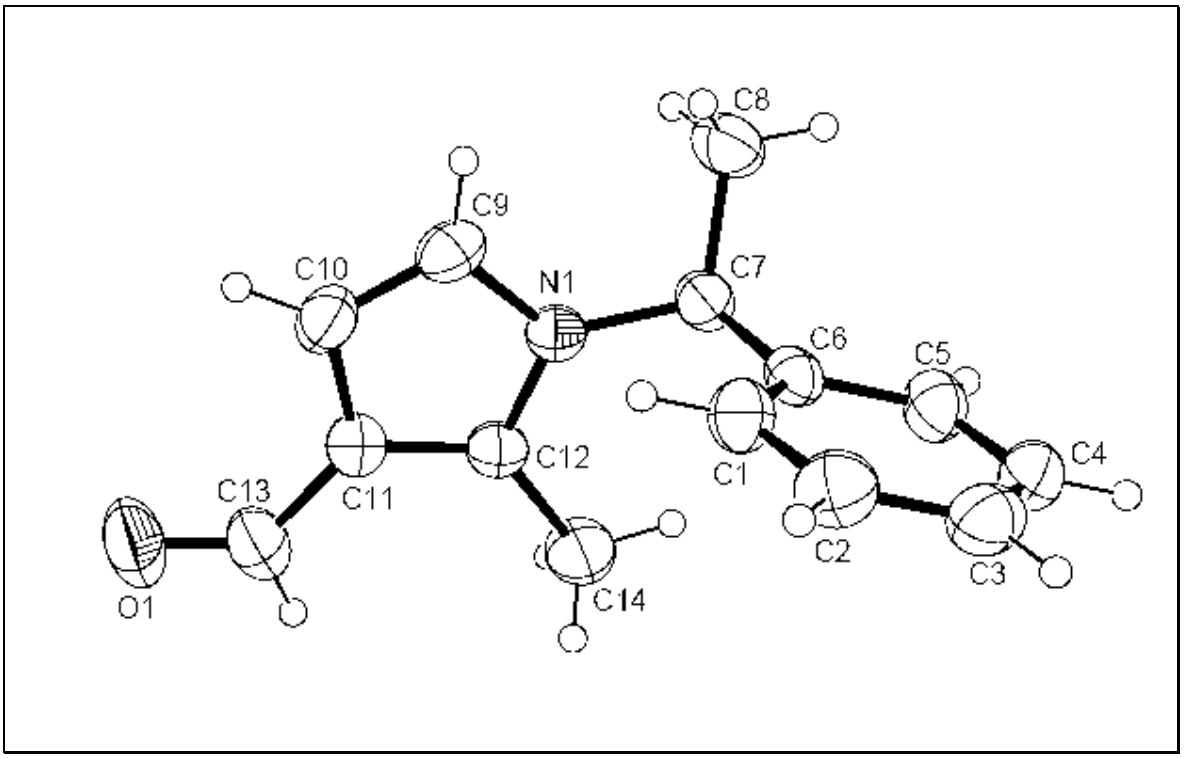


Figure 5.15. X-Ray crystallography result of (*R*)-**214**

Figure 5.16 shows the obtained unit cell, from X-Ray analysis of the (*R*)-**214**.

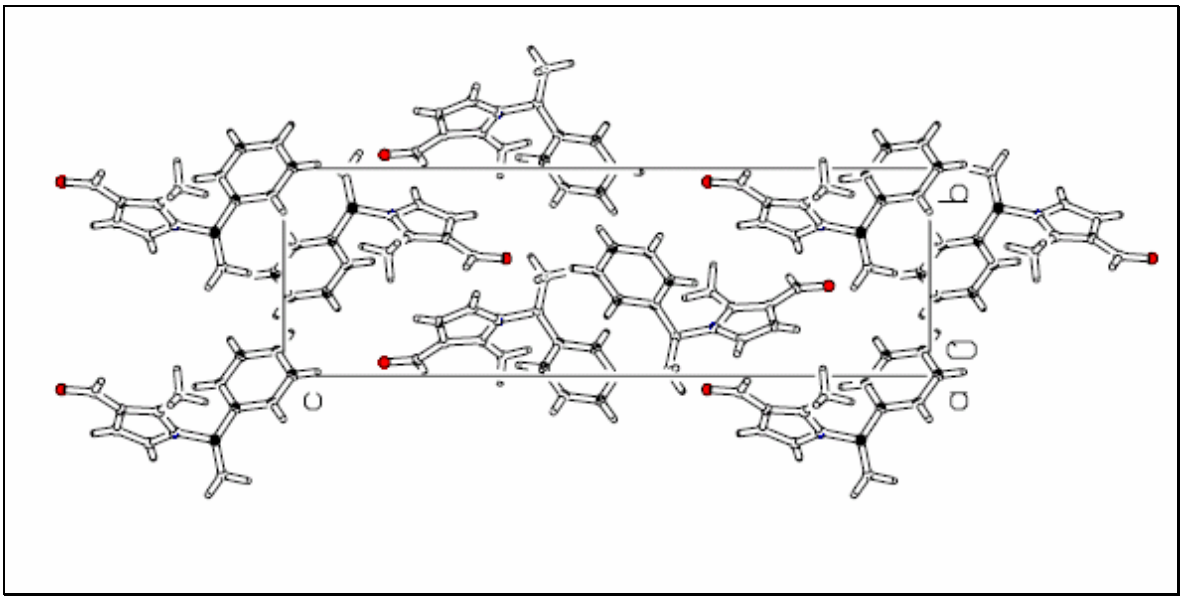
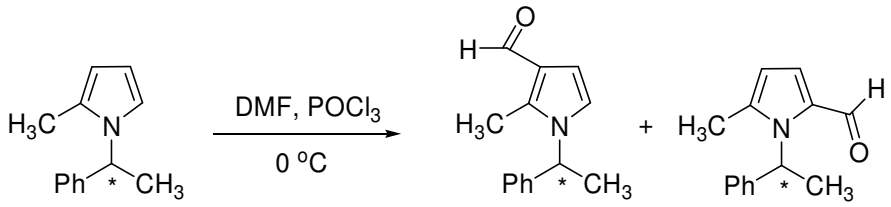


Figure 5.16. Obtained unit cell apperance of (*R*)-**214**

5.2.2.Synthesis of 2-methyl-1-((1*S*)-1-phenylethyl)-1*H*-pyrrole-3-carbaldehyde ((*S*)-216) and 5-methyl-1-((1*S*)-1-phenylethyl)-1*H*-pyrrole-2-carbaldehyde ((*S*)-217)

The treatment of (*S*)-**213** with Vilsmeier Haack reagents afforded 3-methyl-1-((1*S*)-1-phenylethyl)-1*H*-pyrrole-3-carbaldehyde ((*S*)-**216**) and 5-methyl-1-((1*S*)-1-phenylethyl)-1*H*-pyrrole-2-carbaldehyde ((*S*)-**217**) in 70% and 24% yield, respectively as shown in Scheme 5.9. When method B was applied, (*S*)-**216** and (*S*)-**217** was obtained in 52% and 43% yield, respectively.



Scheme 5.9. The formylation of 2-methyl-1-((1*S*)-1-phenylethyl)-1*H*-pyrrole ((*S*)-**213**)

The specific rotation values were $[\alpha]_D^{25}$ = -21.9 (c 11, $CHCl_3$) for (*S*)-**216** and $[\alpha]_D^{25}$ =-118.9 (c 11, $CHCl_3$) for (*S*)-**217**.

Characterization of (*S*)-**216** and (*S*)-**217** was achieved by ^{1}H-NMR and ^{13}C-NMR spectroscopy.

As shown in Figure 5.17, the quartet is observed at 5.37 ppm for methine proton of ethyl group. The typical pyrrole protons appear at 6.61 ppm for C(4)*H* and at 6.76 ppm C(5)*H* as doublets. The doublet at 7.03 ppm and multiplet 7.26-7.37 ppm belong to the protons of phenyl ring. The carbonyl proton exhibits singlet at 9.86 ppm.

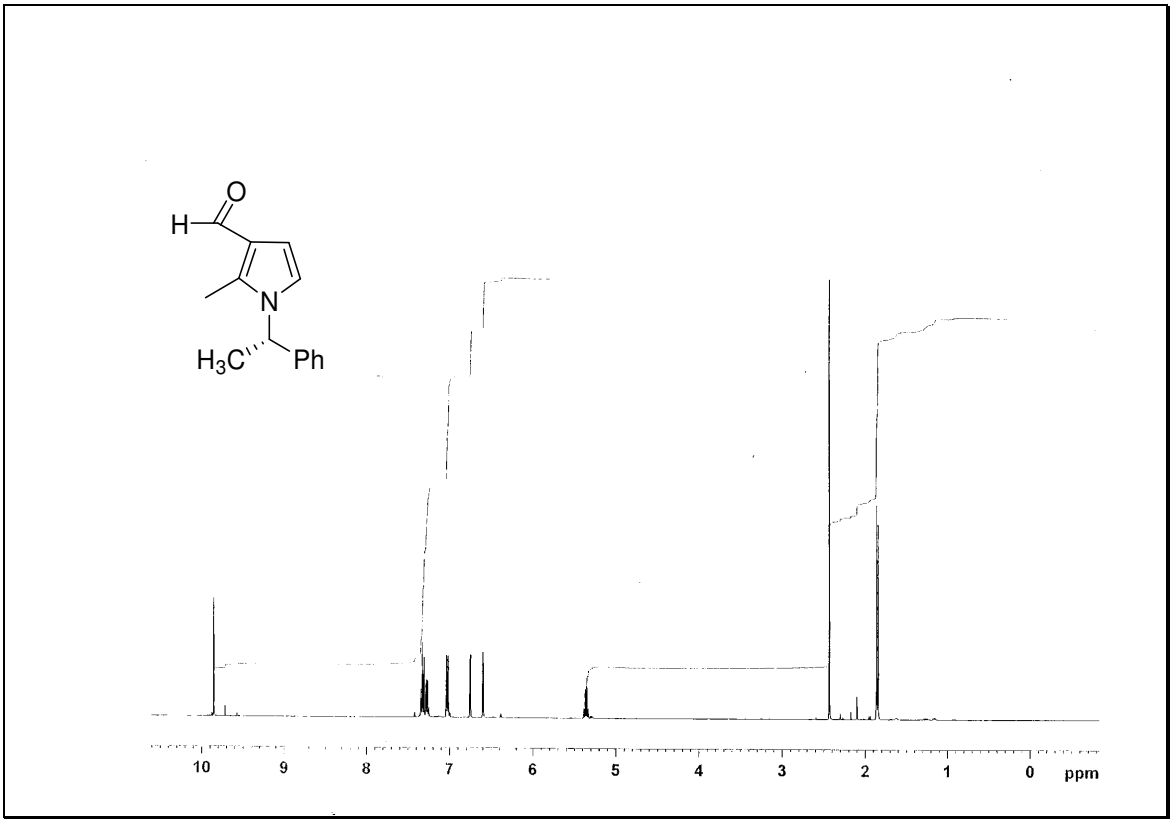


Figure 5.17. The ^{1}H-NMR spectrum of 2-methyl-1-((1*S*)-1-phenylethyl)-1*H*-pyrrole-3-carbaldehyde ((*S*)-**216**)

The ^{13}C-NMR spectrum of the 2-methyl-1-((1*S*)-1-phenylethyl)-1*H*-pyrrole-3-carbaldehyde ((*S*)-**216**) (Figure 5.18) exhibit signals at 109.06 ppm for C(4) and 118.50 ppm for C(5). The signals at 122.86 ppm and 136.85 ppm are due to the quaternary carbons at C(3) and C(2) of the pyrrole ring, respectively. The carbons of the phenyl ring exhibit signals 125.63 ppm, 127.72 ppm, 128.92 ppm and 141.80 ppm. Carbonyl carbon shows a signal at 185.18 ppm.

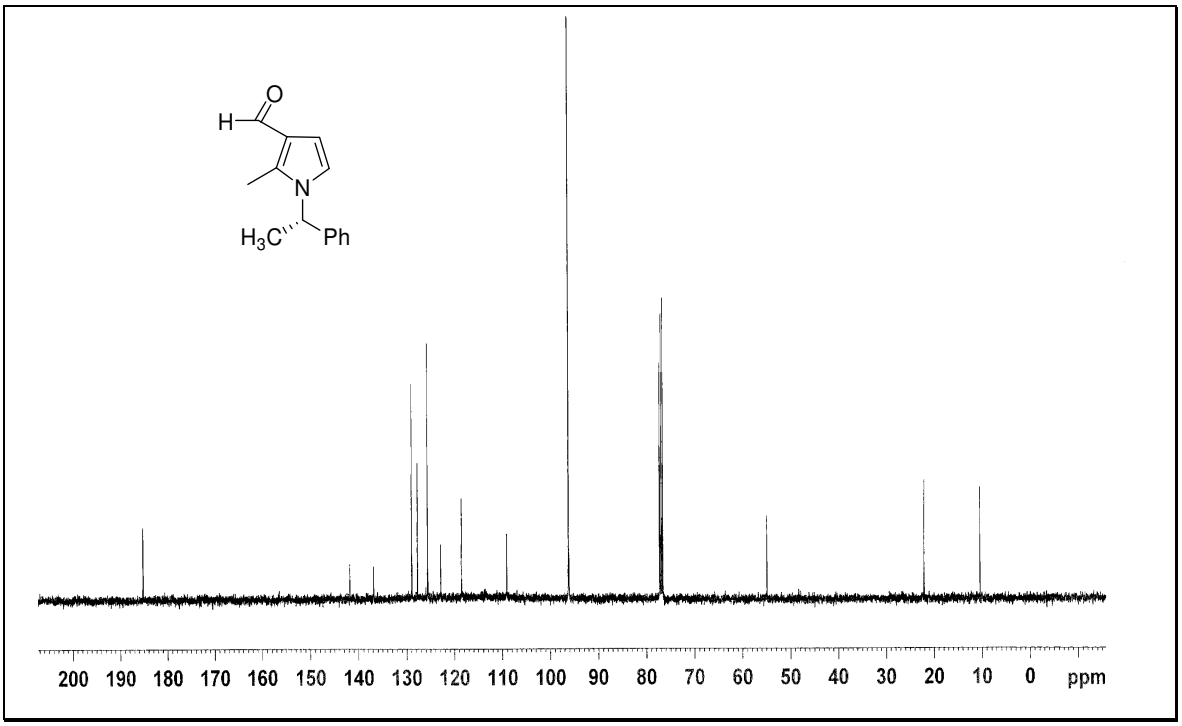


Figure 5.18. The ^{13}C-NMR spectrum of 2-methyl-1-((1*S*)-1-phenylethyl)-1*H*-pyrrole-3-carbaldehyde ((*S*)-**216**)

The ^{1}H-NMR spectrum of the 5-methyl-1-((1*R*)-1-phenylethyl)-1*H*-pyrrole-2-carbaldehyde ((*S*)-**217**) (Figure 5.19) shows doublet at 1.87 ppm for the methyl protons of the ethyl group and the singlet at 1.95 ppm for the methyl protons attached to pyrrole ring. The quartet at 6.95 ppm is due to the methine proton of ethyl group. Signals at 5.97 ppm (C(4)*H*) and 6.85 ppm (C(3)*H*) belong to the pyrrole ring. The carbonyl proton exhibits singlet at 9.43 ppm.

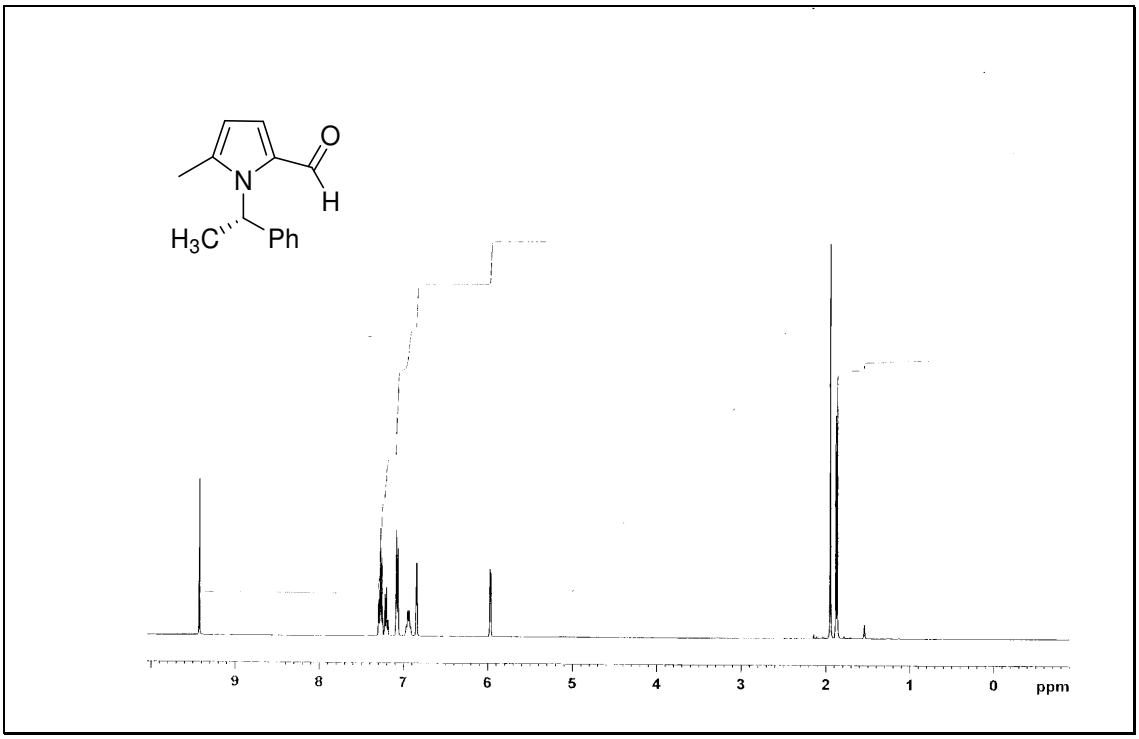


Figure 5.19. The ^{1}H-NMR spectrum of 5-methyl-1-((1*S*)-1-phenylethyl)-1*H*-pyrrole2-carbaldehyde ((*S*)-**217**)

The ^{13}C-NMR spectrum of the 5-methyl-1-((1*S*)-1-phenylethyl)-1*H*-pyrrole-2-carbaldehyde ((*S*)-**217**) (Figure 5.20) shows signals at 111.65 ppm (C(4)), 125.71 ppm (C(3)) for carbons of the pyrrole ring. The signals at 132.17 ppm and 140.82 ppm belong to the quaternary carbons at C(2) and C(5) of the pyrrole ring, respectively. The signals at 126.15 ppm, 126.99 ppm, 128.42 ppm, 141.16 ppm belong to the carbons of the phenyl ring. The carbonyl carbon exhibits signal at 178.26 ppm.

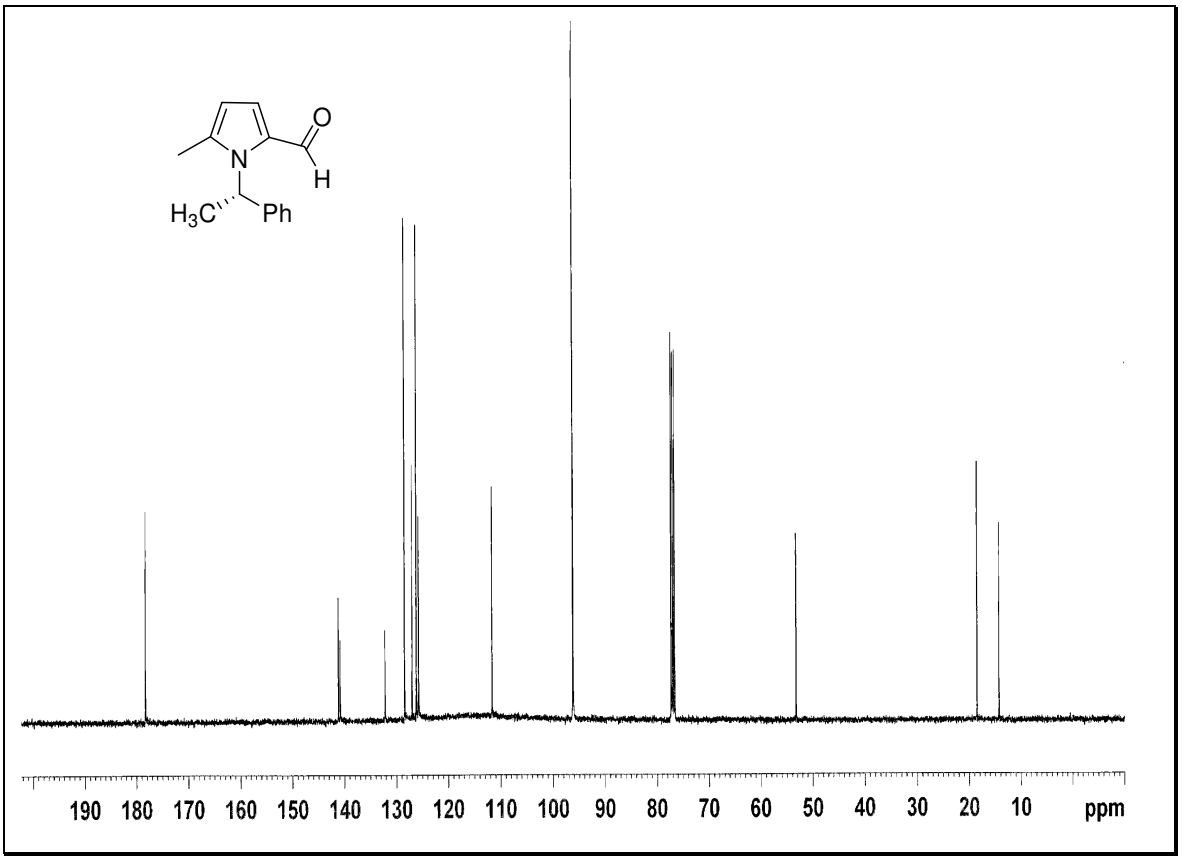
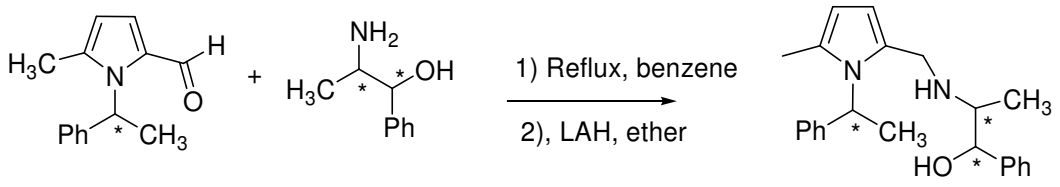


Figure 5.20. The ^{13}C-NMR spectrum of 5-methyl-1-((1*S*)-1-phenylethyl)-1*H*-pyrrole2-carbaldehyde ((*S*)-**217**)

5.3. General Procedure for the Synthesis of Novel Norephedrine-Based Ligands with *N*-Substituted Chiral Pyrrole

In this study, (-)-(1*R*,2*S*)-norephedrine and (+)-(1*S*,2*R*)-norephedrine (**218**) were chosen as amino alcohol for synthesis of novel chiral ligands. There are several examples in the literature for the usage of norephedrine derivatives as a chiral catalyst in the enantioselective C-C bond forming reactions (Soai et al, 1987, 1991, Pélinski et al, 2000). The optical yields of the reactions were reported very high. In addition to their catalytical activity, norephedrine derivatives are used as starting materials for the synthesis of the many biologically active compounds. The other reason of the use of norephedrine as chiral source in asymmetric synthesis is that, both enantiomers are readily available. Thus by using enantiomers of the norephedrine, both enantiomers of the chiral catalyst can be synthesized.

The synthesis of stereoisomers have been accomplished by applying the given route in Scheme 5.10 and Scheme 5.11.

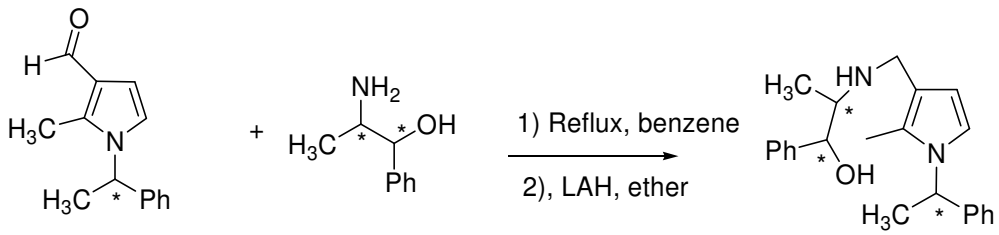


(*R*)-**215**
(*S*)-**217**

(1*R*, 2S)-**218**
(1*S*, 2*R*)-**218**

(1*S*, 2*R*, R)-**219**
(1*R*, 2*S*, S)-**219**
(1*S*, 2*R*, *S*)-**220**
(1*R*, 2*S*, *R*)-**220**

Scheme 5.10. The synthesis of compounds **219** and **220**



(*R*)-**214**
(*S*)-**216**

(1*R*, 2S)-**218**
(1*S*, 2*R*)-**218**

(1*R*, 2*S*, *R*)-**221**
(1*S*, 2*R*, *S*)-**221**
(1*R*, 2*S*, *S*)-**222**
(1*S*, 2*R*, *R*)-**222**

Scheme 5.11. The synthesis of compounds **221** and **222**

5.3.1. The Synthesis of (1*S*,2*R*)-2-((5-methyl-1-((1*R*)-1-phenyl-ethyl)-1*H*-pyrrol-2-yl)methylamino)-1-phenylpropan-1-ol ((1*S*,2*R*,*R*)-219) and (1*R*,2*S*)-2-((5-methyl-1-((1*S*)-1-phenylethyl)-1*H*-pyrrol-2-yl)methylamino)-1-phenylpropan-1-ol ((1*R*,2*S*,*S*)-219)

(1*S*,2*R*)-2-((5-Methyl-1-((1*R*)-1-phenylethyl)-1*H*-pyrrol-2-yl)methylamino)-1-phenylpropan-1-ol ((1*S*,2*R*,*R*)-**219**) was prepared from (1*R*,2*S*)-norephedrine (**218**) and 5-methyl-1-((*R*)-1-phenylethyl)-1-pyrrole-2-carbaldehyde ((*R*)-**215**). As shown in Scheme 5.9, (1*S*,2*R*)-**218** and (*R*)-**215** in dry benzene was refluxed under N_2 by using Dean-Stark trap for 10 hours The imine was reduced with $LiAlH_4$ in dry ether under N_2. After purification of the crude product by flash column

choromatography, (1*S*,2*R,R*)-**219** was obtained in 68% yield as brown oil ($[\alpha]_D^{27}$ = +20.6 (c 15.7, $CHCl_3$)).

The characterization of (1*S*,2*R,R*)-**219** was performed by using spectroscopic methods as ^{1}H-NMR, ^{13}C-NMR, DEPT, HMQC spectrums.

^{1}H-NMR spectrum of the (1*S*,2*R,R*)-**219** (Figure 5.21) exhibits a doublet at 0.81 ppm for the methyl protons on norephedrine moiety. The other doublet at 1.97 ppm is due to the methyl protons on the *N*-substituted group. The singlet at 2.08 ppm belong to methyl protons connected to pyrrole ring. The multiplet between 2.97 ppm and 3.00 ppm is due to methine proton attached to NH group on norephedrine moiety. The one of the diastereotopic methylene proton appears at 3.78 ppm as doublet. The other doublet at 3.85 ppm is due to the other diastereotopic methylene proton. The methine group which connected to hydroxyl group appear at 4.71 ppm. The quartet at 5.71 ppm for methine group of *N*-substituted ethyl group. Typical pyrrole ring protons appear 5.85 ppm for C(4)*H*, 6.00 ppm for C(3)*H* as doublet. Signals of phenyl protons appear at 7.09 ppm as doublet and between 7.22 and 7.37 ppm as multiplet.

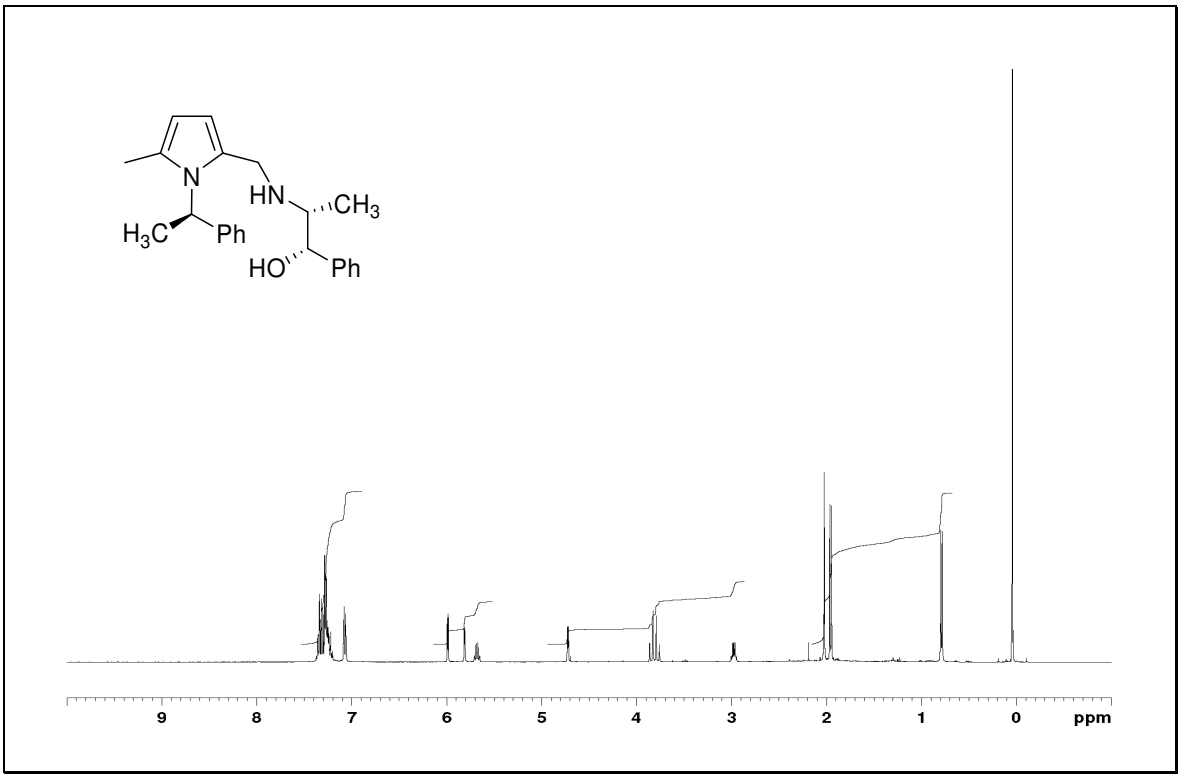


Figure 5.21. The ^{1}H-NMR spectrum of (1*S*,2*R*)-2-((5-methyl-1-((1*R*)-1-phenylethyl)-1*H*-pyrrol-2-yl)methylamino)-1-phenylpropan-1-ol ((1*S*,2*R*,*R*)-**219**)

The ^{13}C-NMR spectrum of the (1*S*,2*R,R*)-**219** (Figure 5.22) exhibits signals 14.18 ppm for the methyl carbon attached to pyrrole ring and the signal at 14.43 ppm is for the methyl carbon attached to norephedrine moiety. The methyl carbon of ethyl group appears at 19.60 ppm. The methylene carbon exhibits a signal at 44.01 ppm (determined with help of DEPT spectrum (Figure 5.23) and HMQC spectrum (Figure 5.24)). The signal at 52.67 ppm belongs to the methine carbon of ethyl group. The other methine carbon attached to NH on norephedrine moiety exhibits a signal at 57.82 ppm. The methine carbon attached to hydroxy group appears at 73.05 ppm. The signals at 107.27 ppm, 107.77 ppm are due to pyrrole ring carbon C(4) and C(3), respectively. The phenyl carbons exhibit signals at 125.95 ppm, 126.03 ppm, 126.95 ppm, 126.98 ppm, 128.00 ppm, and 128.58 ppm. The signals at 129.45 ppm and 130.31 ppm which belong to quaternary carbon of pyrrole at C(2) and C(5), respectively. The other quaternary carbons of phenyl ring appear at 141.31 ppm and 142.47 ppm.

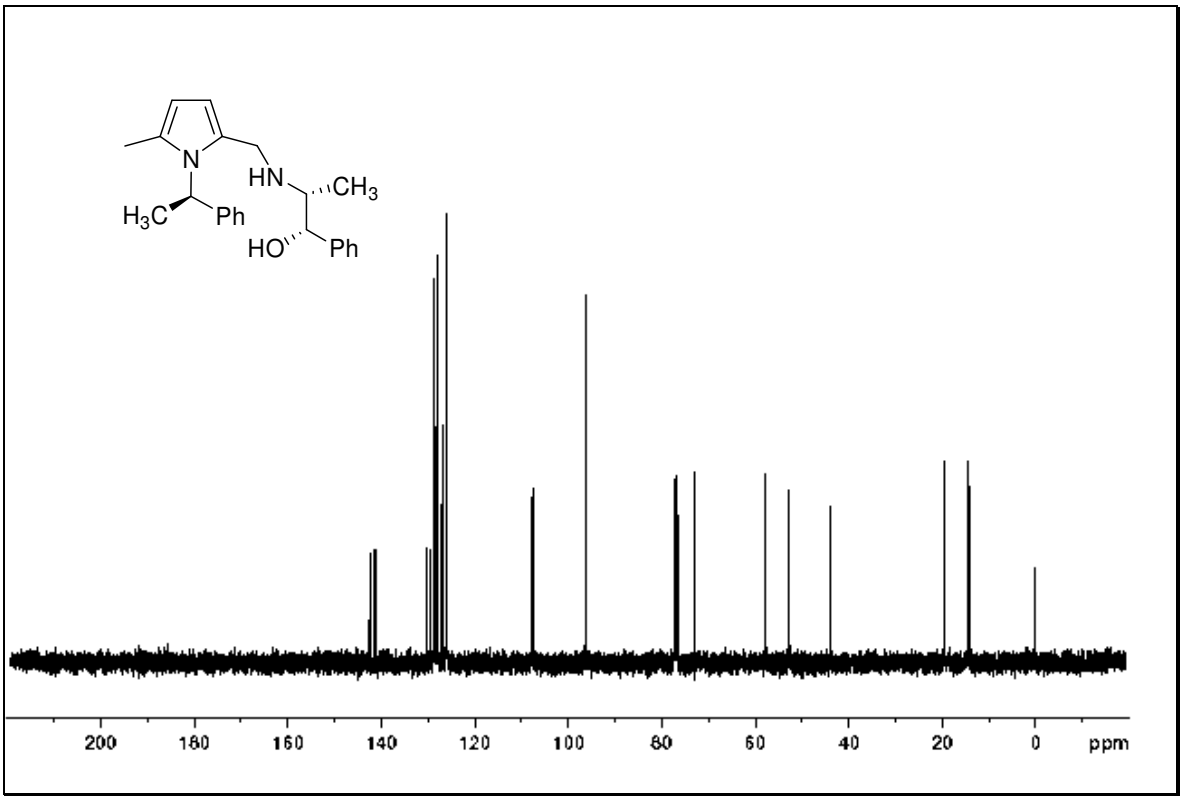


Figure 5.22. The ^{13}C-NMR spectrum of (1*S*,2*R*)-2-((5-methyl-1-((1*R*)-1-phenylethyl)-1*H*-pyrrol-2-yl)methylamino)-1-phenylpropan-1-ol ((1*S*,2*R*,*R*)-**219**)

The DEPT spectrum (Figure 5.23) of (1*S*,2*R*,*R*)-**219** shows the presence of one methylene carbon in the structure.

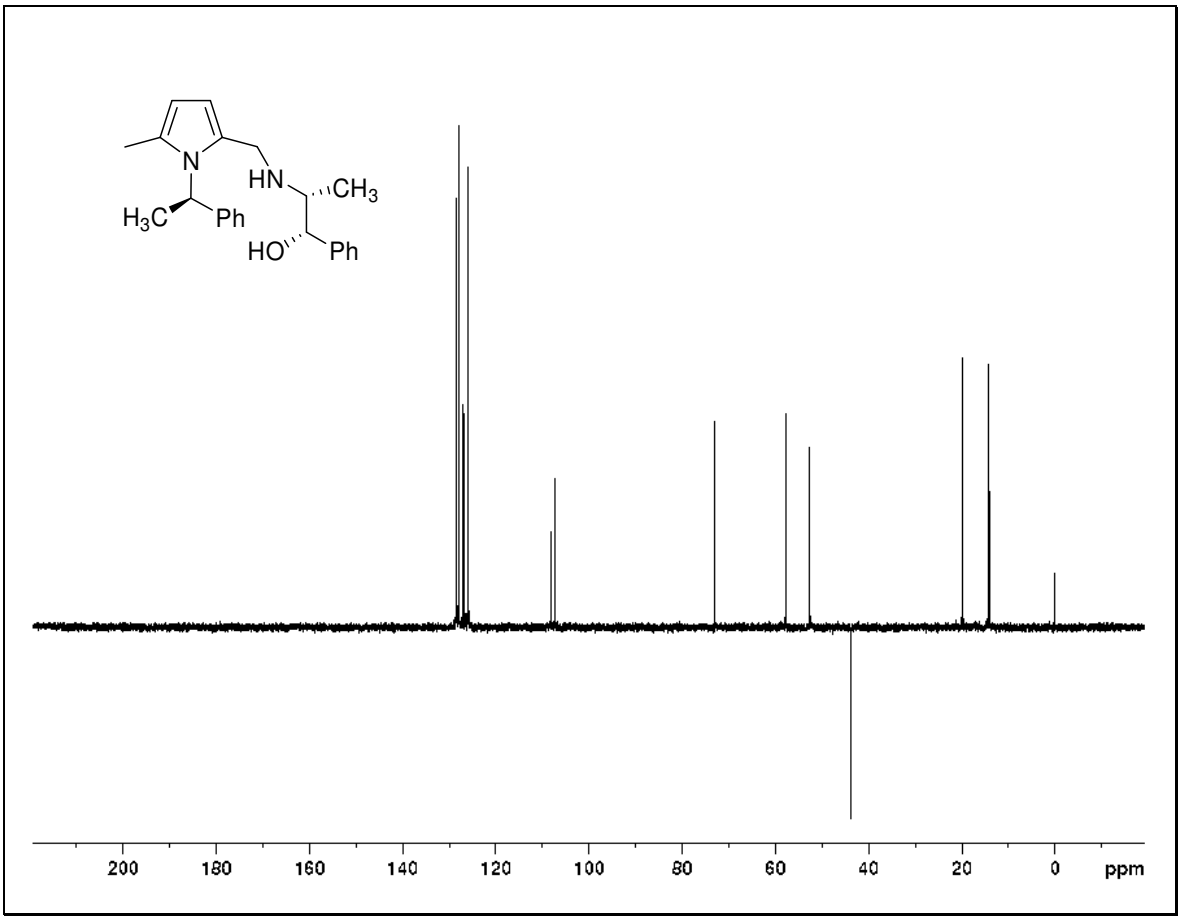


Figure 5.23. The DEPT spectrum of (1*S*,2*R*)-2-((5-methyl-1-((1*R*)-1-phenylethyl)-1*H*-pyrrol-2-yl)methylamino)-1-phenylpropan-1-ol ((1*S*,2*R*,*R*)-**219**)

The structure of (1*S*,2*R*,*R*)-**219** was confirmed by HMQC techique which allowed to determining which protons and carbons were directyl attached to each other. As shown in Figure 5.24, three methine protons which resonated at 2.97-3.00 ppm, 4.71 ppm, 5.71 ppm were correlated to carbons at 57.82 ppm, 73.05 ppm, 52.67 ppm, respectively. In addition, the methylene protons resonated at 3.81 ppm correlated to carbon at 44.01 ppm.

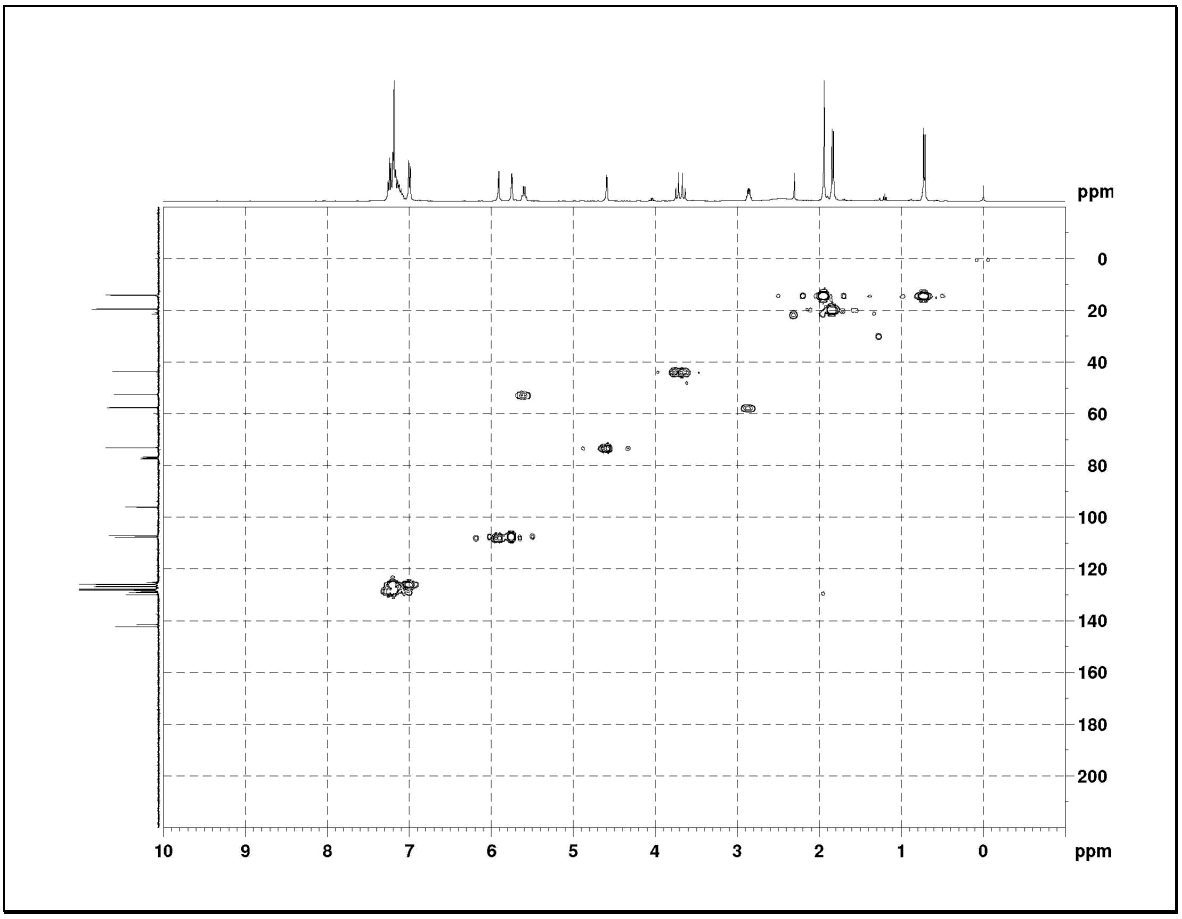


Figure 5.24. The HMQC spectrum of (1*S*,2*R*)-2-((5-methyl-1-((1*R*)-1-phenyl-ethyl)-1*H*-pyrrol-2-yl)methylamino)-1-phenylpropan-1-ol ((1*S*,2*R*,*R*)-**219**)

Under the same reaction condition, the reaction of (1*R*,2*S*)-**218** and 5-methyl-1-((*S*)-1-phenylethyl)-1*H*-pyrrole-2-carbaldehyde ((S)-**217**) gave the other enantiomer, (1*R*,2*S*,*S*)-**219**, in 73% yield as brown oil. The specific rotation value was obtained as $[\alpha]_D^{27}$ = -22.5 (c 14, $CHCl_3$).

The structure of (1*R*,2*S*,*S*)-**219** is identified by ^{1}H-NMR and ^{13}C-NMR spectroscopy (Figure 5.25 and Figure 5.26)

The ^{1}H-NMR spectrum of (1*R*,2*S*,*S*)-**219** (Figure 5.25) shows a multiplet between 2.92 ppm and 2.98 ppm for methine proton attached to NH on the norephedrine moiety. The one of the diastereotopic methylene proton appears at 3.74 ppm as

doublet. The other doublet at 3.81 ppm is due to the other diastereotopic methylene proton. The doublet at 4.62 ppm belongs to methine proton attached to hydroxy group. The methine proton of the ethyl group substituted to pyrrole nitrogen appears at 5.72 ppm as quartet. The signals at 5.82 ppm and 5.97 ppm are due to pyrrole protons of pyrrole ring at C(4)*H* and C(3)*H*, respectively.

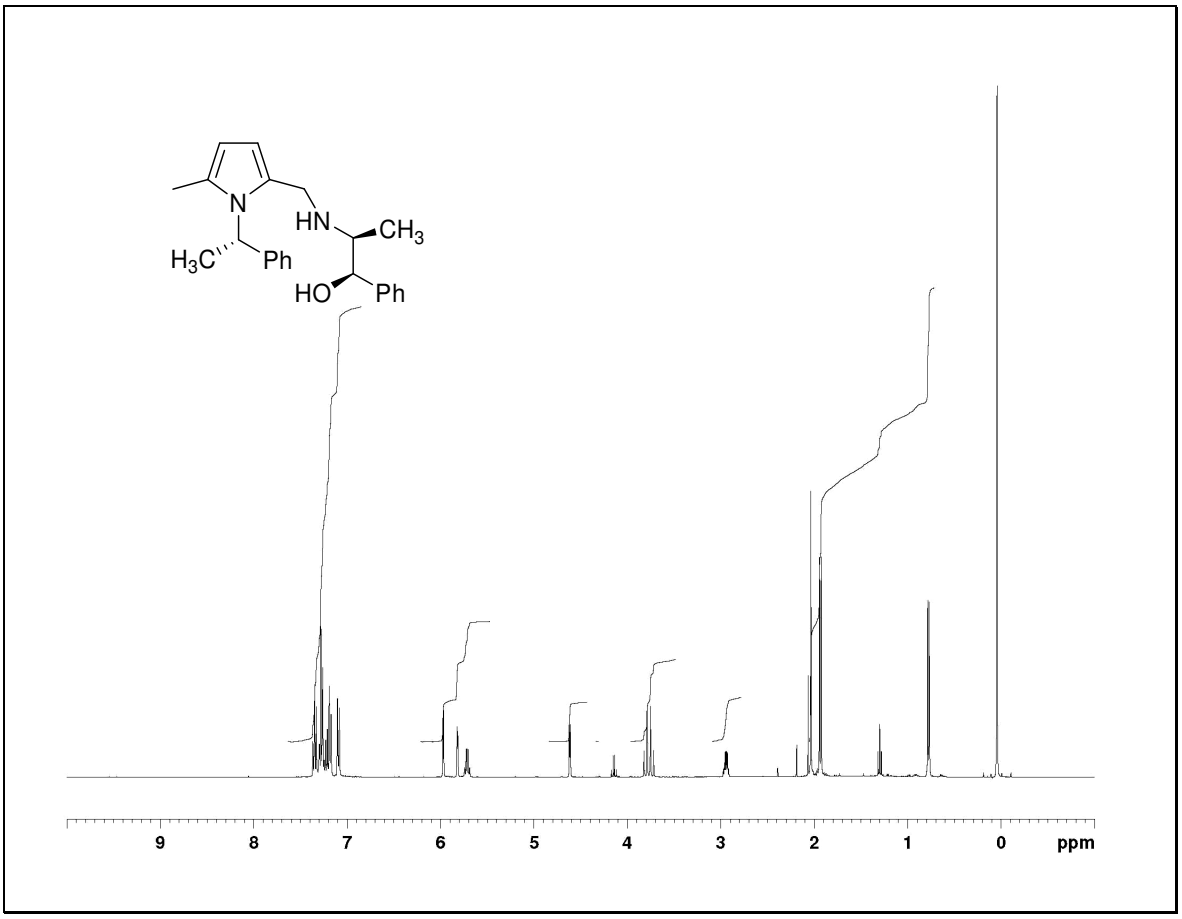


Figure 5.25. The ^{1}H-NMR spectrum of (1*R*,2*S*)-2-((5-methyl-1-((1*S*)-1-phenylethyl)-1*H*-pyrrol-2-yl)methylamino)-1-phenylpropan-1-ol ((1*R*,2*S*,*S*)-**219**)

The ^{13}C-NMR spectrum of (1*R*,2*S*,*S*)-**219** (Figure 5.29) exhibits signals at 44.07 ppm, 52.60 ppm which belong to the methylene carbon, and the methine carbon of the ethyl group, respectively. The signal at 73.13 ppm is for the methine carbon attached to hydroxyl group. The carbons of pyrrole ring exhibit signals at 107.23 ppm (C-4), 107.70 ppm for C(3), 129.47 ppm for C(2), 130.23 ppm for C(5). Signals of phenyl ring can be seen at 125.88 ppm, 126.05 ppm, 126.89 ppm, 126.99 ppm, 127.91 ppm, 128.56 ppm, 141.13 ppm, 142.50 ppm.

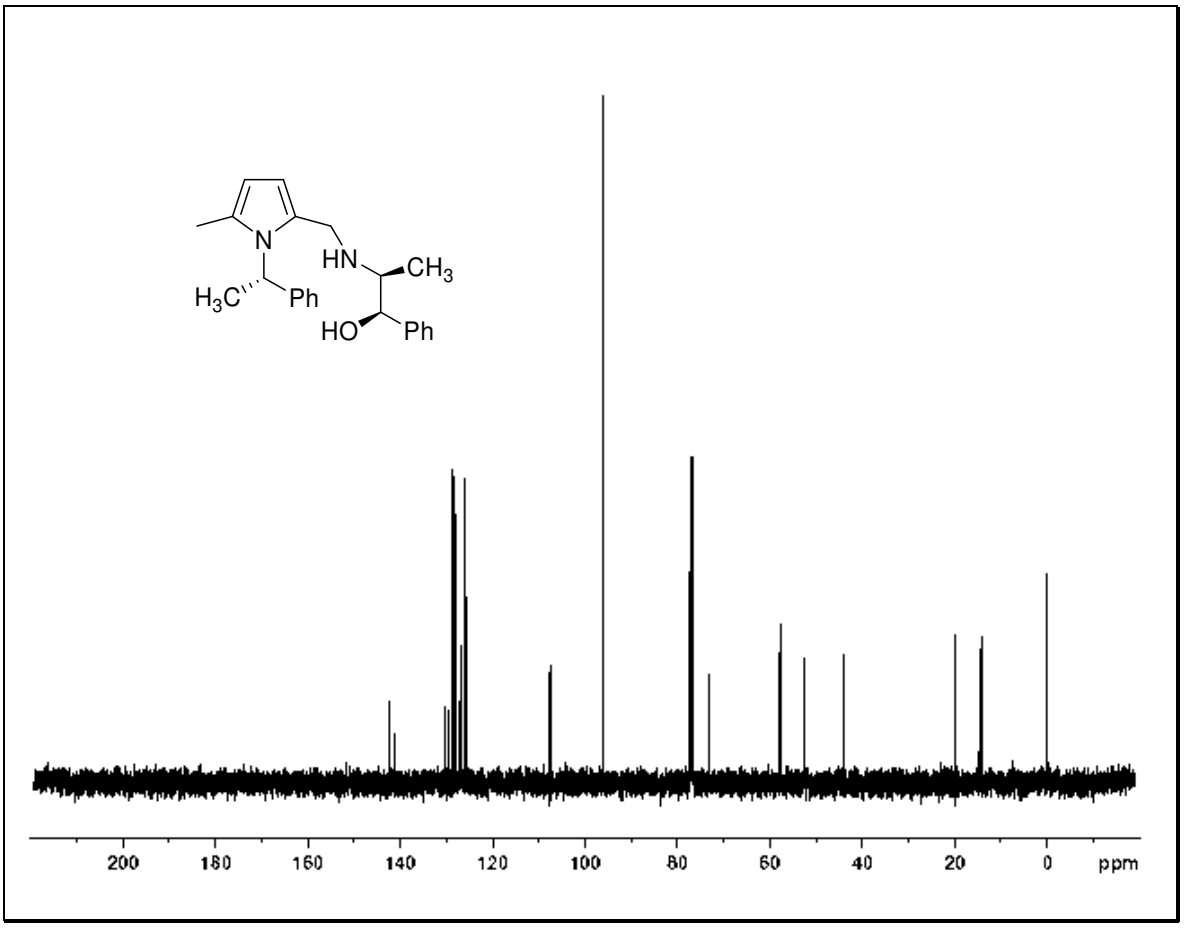


Figure 5.26. The ^{13}C-NMR spectrum of (1*R*,2*S*)-2-((5-methyl-1-((1*S*)-1-phenylethyl)-1*H*-pyrrol-2-yl)methylamino)-1-phenylpropan-1-ol ((1*R*,2*S*,*S*)-**219**)

5.3.2. The synthesis of (1*S*,2*R*)-2-((5-methyl-1-((1*S*)-1-phenylethyl)-1*H*-pyrrol-2-yl)methylamino)-1-phenylpropan-1-ol ((1*S*,2*R*,*S*)-220) and (1*R*,2*S*)-2-((5-methyl-1-((1*R*)-1-phenylethyl)-1*H*-pyrrol-2-yl)methylamino)-1-phenylpropan-1-ol ((1*R*,2*S*,*R*)-220)

The reaction of (1*S*,2*R*)-**218** with 5-methyl-1-((1*S*)-1-phenylethyl)-1*H*-pyrrole-2-carbaldehyde ((*S*)-**219**) afforded (1*S*, 2*R*)-2-((5-methyl-1-((1*S*)-1-phenylethyl)-1*H*-pyrrol-2-yl)methylamino)-1-phenylpropan-1-ol ((1*S*,2*R*,*S*)-**220**) in 72% yield as brown oil. The specific rotation value was determined as $[\alpha]_D^{27}$ = +28.2 (c 11, $CHCl_3$).

The characterization of (1*S*,2*R,S*)-**220** and (1*R*,2*S,R*)-**220** were achieved by ^{1}H-NMR and ^{13}C-NMR spectroscopy.

The ^{1}H-NMR spectrum of (1*S*,2*R*,*S*)-**220** (Figure 5.27) shows a multiplet between 2.93 ppm and 2.98 ppm for methine proton attached to NH group. The one of the diastereotopic methylene proton appears at 3.75 ppm as doublet. The other doublet at 3.82 ppm is due to the other diastereotopic methylene proton.The protons of methine group attached to hydroxyl group appears at 4.71 ppm as doublet. The methine proton of the ethyl group attached to pyrrole nitrogen appears at 5.73 ppm as quartet. The signals at 5.83 ppm and 5.98 ppm are due to pyrrole protons ring of C(4)*H*, and C(3)*H*, respectively.

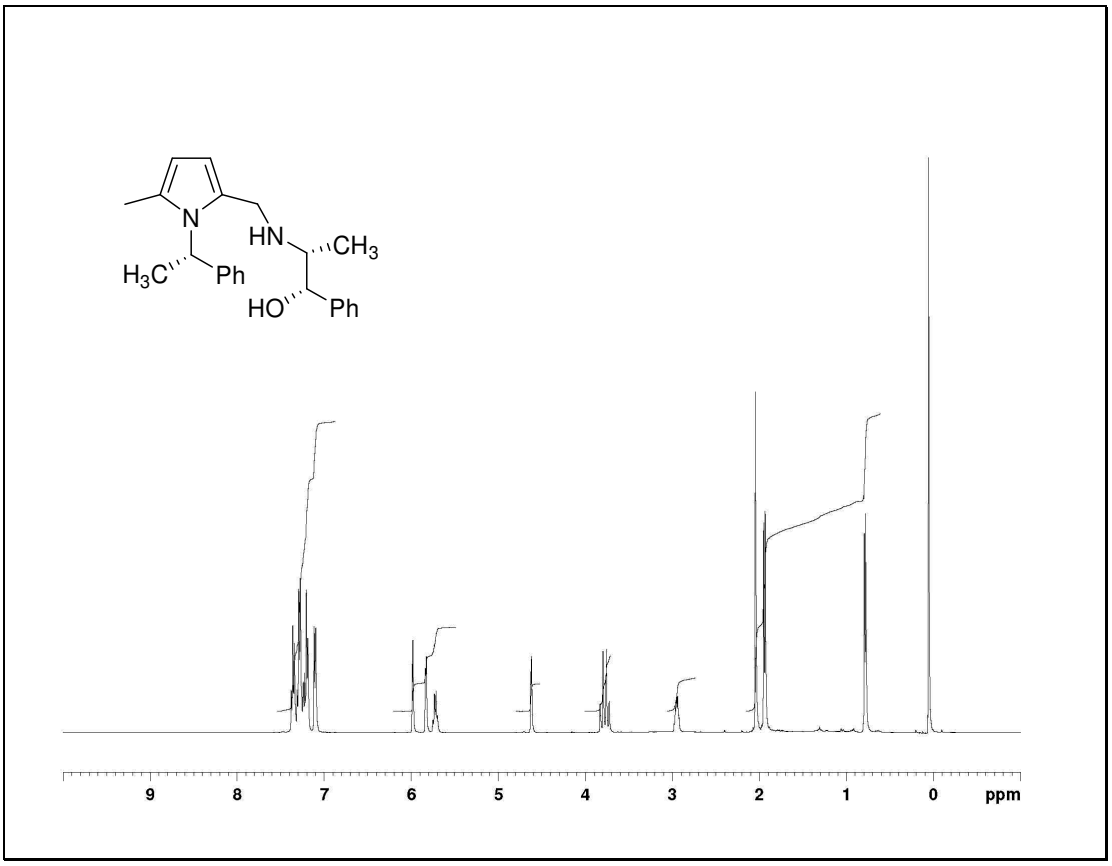


Figure 5.27. The ^{1}H-NMR spectrum of (1*S*,2*R*)-2-((5-methyl-1-((1*S*)-1-phenylethyl)-1*H*-pyrrol-3-yl)methylamino)-1-phenylpropan-1-ol ((1*S*,2*R*,*S*)-**220**)

The ^{13}C-NMR spectrum of (1*S*,2*R*,*S*)-**220** (Figure 5.28) also confirms the struccture. The methylene carbon exhibits a signal at 44.08 ppm. The signal at 52.61 ppm belongs to the methine carbon of ethyl group on pyrrole ring. The signal at 57.79 ppm is due to the methine carbon attached to NH group on norephedrine moeity. The carbons of pyrrole ring can be seen 107.25 ppm, 107.71 ppm, 129.43 ppm, 130.34 ppm, C(4)*H*, C(3)*H*, C(2)*H*, C(5)*H*, respectively. The signals at 125.90 ppm, 126.07 ppm, 126.90 ppm, 126.99 ppm, 127.93 ppm, 128.57 ppm, 141.17 ppm, 142.52 ppm are due to carbons of phenyl rings.

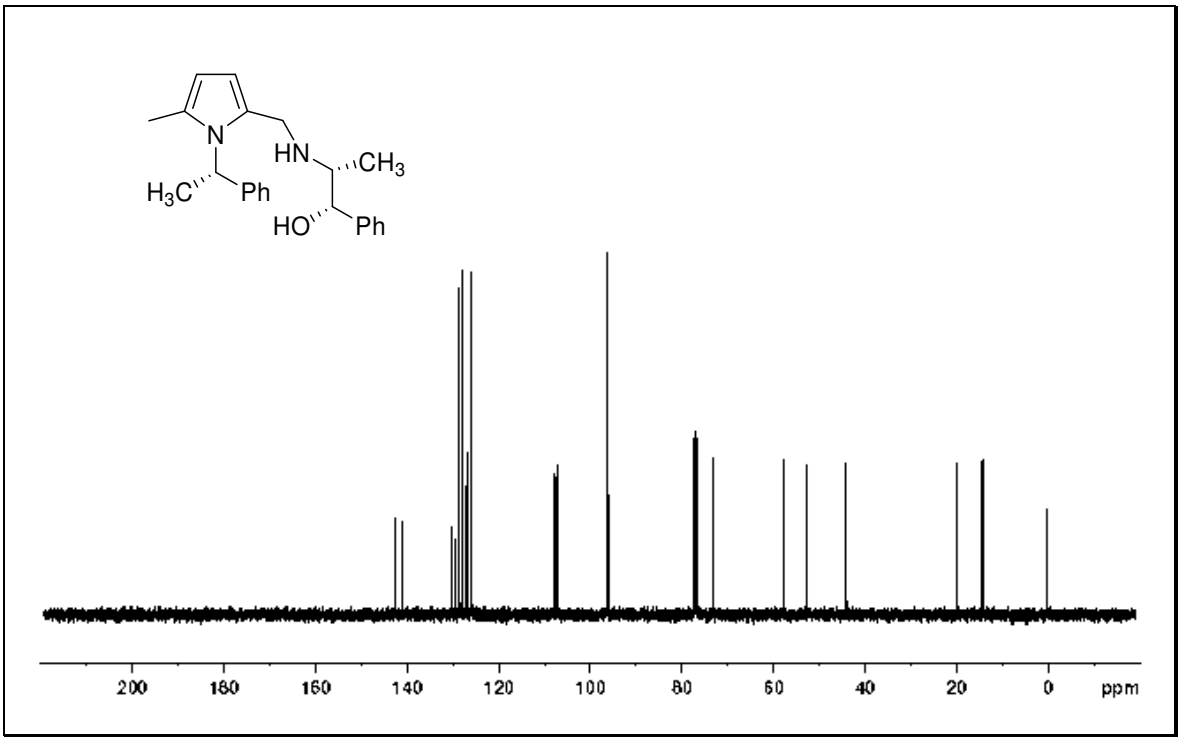


Figure 5.28. The ^{13}C-NMR spectrum of (1*S*,2*R*)-2-((5-methyl-1-((1*S*)-1phenylethyl) -1*H*-pyrrol-3-yl)methylamino)-1-phenylpropan-1-ol ((1*S*,2*R*,*S*)-**220**)

Under the same reaction condition, (1*R*,2*S*)-**218** and 5-methyl-1-((*R*)-1-phenylethyl)-1-pyrrole-2-carbaldehyde ((1*R*)-**217**) gave the other enantiomer of the product, (1*R*,2*S*,*S*)-**220** in 70% yield as brown oil. The specific rotation value was obtained $[\alpha]_D^{27}$ =-31.00 (c 10, $CHCl_3$).

As shown in ^{1}H-NMR spectrum (Figure 5.29) of (1*R*,2*S*,*R*)-**220**, the multiplet between 2.96 ppm and 3.00 ppm belongs to the methine proton attached to NH group. The one of the diastereotopic methylene proton appears at 3.77 ppm as doublet. The other doublet at 3.84 ppm is due to the other diastereotopic methylene proton.The doublet at 4.71 ppm belongs to proton of methine group attached to hydroxyl group. The quartet at 5.69 ppm belongs to the methine proton of the ethyl group on pyrrole ring. The typical doublets at 5.82 ppm and 5.99 ppm are due to the methine protons on pyrrole ring, C(4)*H* and C(3)*H*, respectively.

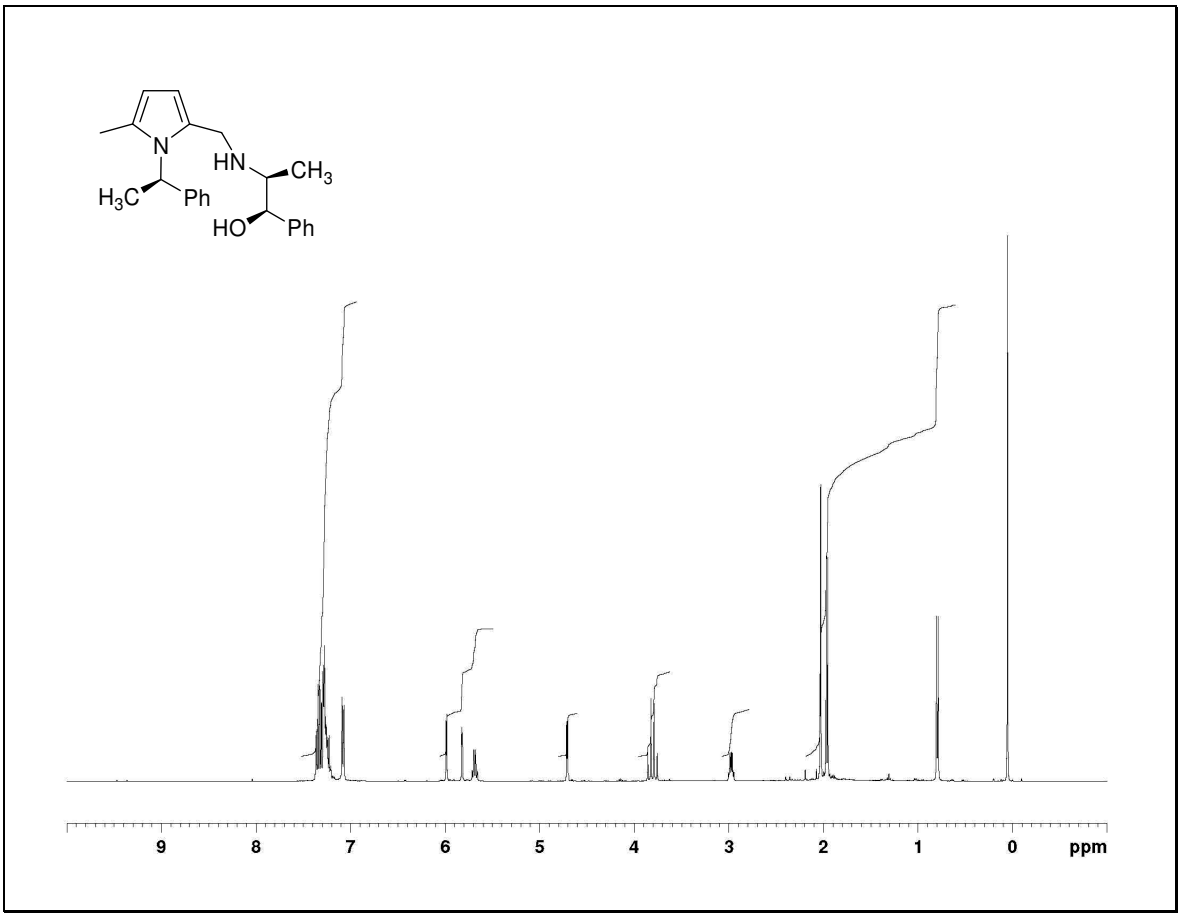


Figure 5.29. The ^{1}H-NMR spectrum of (1*R*,2*S*)-2-((5-methyl-1-((1*R*)-1-phenylethyl)-1*H*-pyrrol-3-yl)methylamino)-1-phenylpropan-1-ol ((1*R*,2*S*,*R*)-**220**)

The ^{13}C-NMR spectrum of (1*R*,2*S*,*R*)-**220** (Figure 5.30) exhibits signals at 44.00 ppm for methylene carbon, and at 52.67 ppm for methine carbon attached to ethyl group on pyrrole ring. The signal at 57.82 ppm belongs to the methine carbon attached to NH group on norephedrine moeity. The signal at 73.00 ppm is for the

methine carbon attached to hydroxyl group. The carbons of pyrrole ring exhibit signals at 107.26 ppm for C(4), 107.79 ppm for C(3), 129.47 ppm for C(2), 130.23 ppm for C(5). Phenyl protons appear at 125.93 ppm, 126.00 ppm, 126.94 ppm, 126.99 ppm, 127.99 ppm, 128.57 ppm, 141.24 ppm, 142.44 ppm.

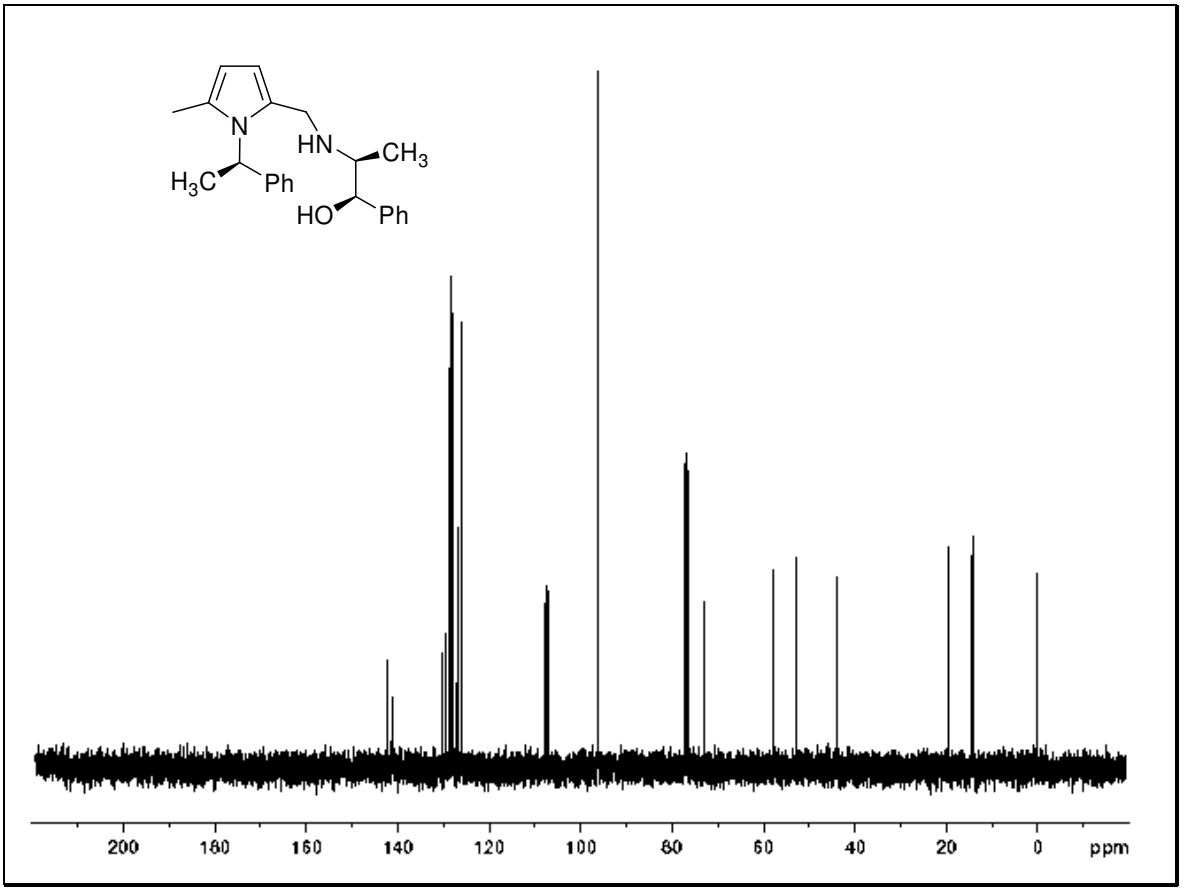


Figure 5.30. The ^{13}C-NMR spectrum of (1*R*, 2*S*)-2-((5-methyl-1-((1*R*)-1-phenylethyl)-1*H*-pyrrol-3-yl)methylamino)-1-phenylpropan-1-ol ((1*R*,2*S*,*R*)-**220**)

5.3.3. The synthesis of (1*R*,2*S*)-2-((2-methyl-1-((1*R*)-1-phenylethyl)-1*H*-pyrrol-3-yl)methylamino)-1-phenylpropan-1-ol ((1*R*,2*S*,*R*)-221) and (1*S*,2*R*)-2-((2-methyl-1-((1*S*)-1-phenylethyl)-1*H*-pyrrol-3-yl)methylamino)-1-phenylpropan-1-ol ((1*S*,2*R*,*S*)-221)

The reaction of 3-methyl-1-((1*R*)-1-phenylethyl)-1*H*-pyrrole-2-carbaldehyde ((*R*)-**216**) with (1*R*,2*S*)-**218** was performed in dry benzene by refluxing under Dean-Stark trap for 3 days. The obtained imine was reduced with $LiAlH_4$ in dry ether under N_2. After purification of the crude product by column chromatography, (1*R*,2*S*,*R*)-**221** was obtained in 70% yield.

The structure of the (1*R*,2*S*,*R*)-**221** were identified by ^{1}H-NMR, ^{13}C-NMR, spectroscopy. As shown in Figure 5.44 and Figure 5.45 spectrum of compound is accordance with its structure.

The ^{1}H-NMR spectrum of the (1*R*,2*S*,*R*)-**221** (Figure 5.31) exhibits a doublet at 0.80 ppm for the methyl protons on norephedrine moiety. The doublet at 1.84 ppm belongs to methyl group protons of the other ethyl group attached to pyrrole nitrogen. The singlet at 2.09 ppm is due to methyl protons attached to pyrrole ring. The multiplet between 2.98 ppm and 3.04 ppm is due to methine proton that is attached to NH group. The one of the diastereotopic methylene proton appears at 3.71 ppm as doublet. The other doublet at 3.78 ppm is due to the other diastereotopic methylene proton. The proton of methine group attached to hydroxyl group appears at 4.80 ppm as a doublet. Methine proton of ethyl group appears at 5.28 ppm as a quartet. Typical doublets of pyrrole ring protons appear at 6.14 ppm (C(4)*H*), 6.78 ppm (C(5)*H*). The doublet at 6.96 ppm and the multiplet between 7.23 ppm and 7.32 ppm are due to the phenyl protons.

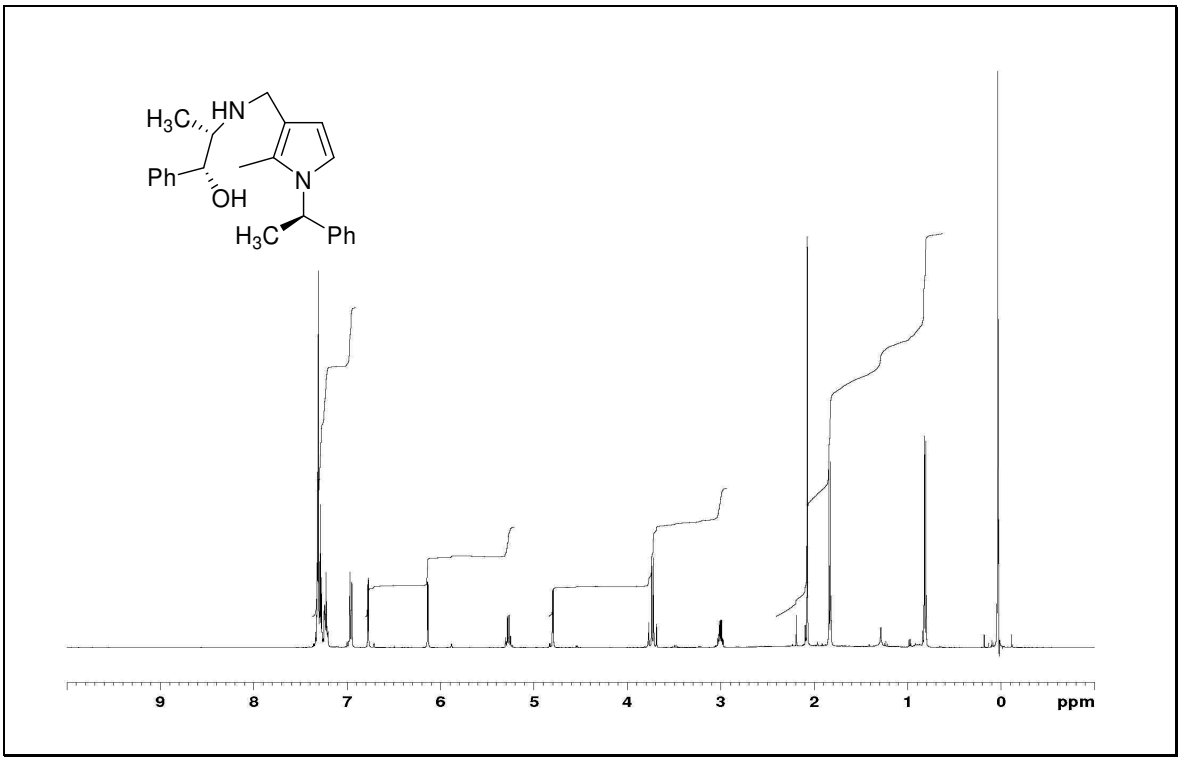


Figure 5.31. The ^{1}H-NMR spectrum of (1*R*,2*S*)-2-((2-methyl-1-((1*R*)-1-phenylethyl)-1*H*-pyrrol-3-yl)methylamino)-1-phenylpropan-1-ol ((1*R*,2*S*,*R*)-**221**)

The ^{13}C-NMR spectrum of the the compound (1*R*,2*S*,*R*)-**221** (Figure 5.32) exhibits a signal 9.93 ppm for the methyl carbon connected to pyrrole ring and the signal at 14.58 ppm is for the methyl carbon of ethyl group on norephedrine moeity. The signal at 22.51 ppm is due to the methyl carbon of ethyl group on pyrrole nitrogen. The methylene carbon exhibits a signal at 43.33 ppm. The signal at 55.09 ppm is due to the methine carbon of ethyl group connected to pyrrole ring. The other methine on norephedrine moiety exhibits a signal 57.84 ppm. The signal at 72.38 ppm is for the methine carbon attached to hydroxy group on norephedrine moiety. The signals at 107.56 ppm for C(4), 116.26 ppm for C(5), 118.63 ppm for C(3), 128.67 ppm for C(2) are due to the carbons of pyrrole ring. The phenyl carbons exhibit signals at 125.56 ppm, 125.61 ppm, 125.88 ppm, 126.76 ppm, 127.14 ppm, 127.94 ppm. The signals at 141.54 ppm and 143.70 ppm which belong to quaternary carbon of phenyl rings.

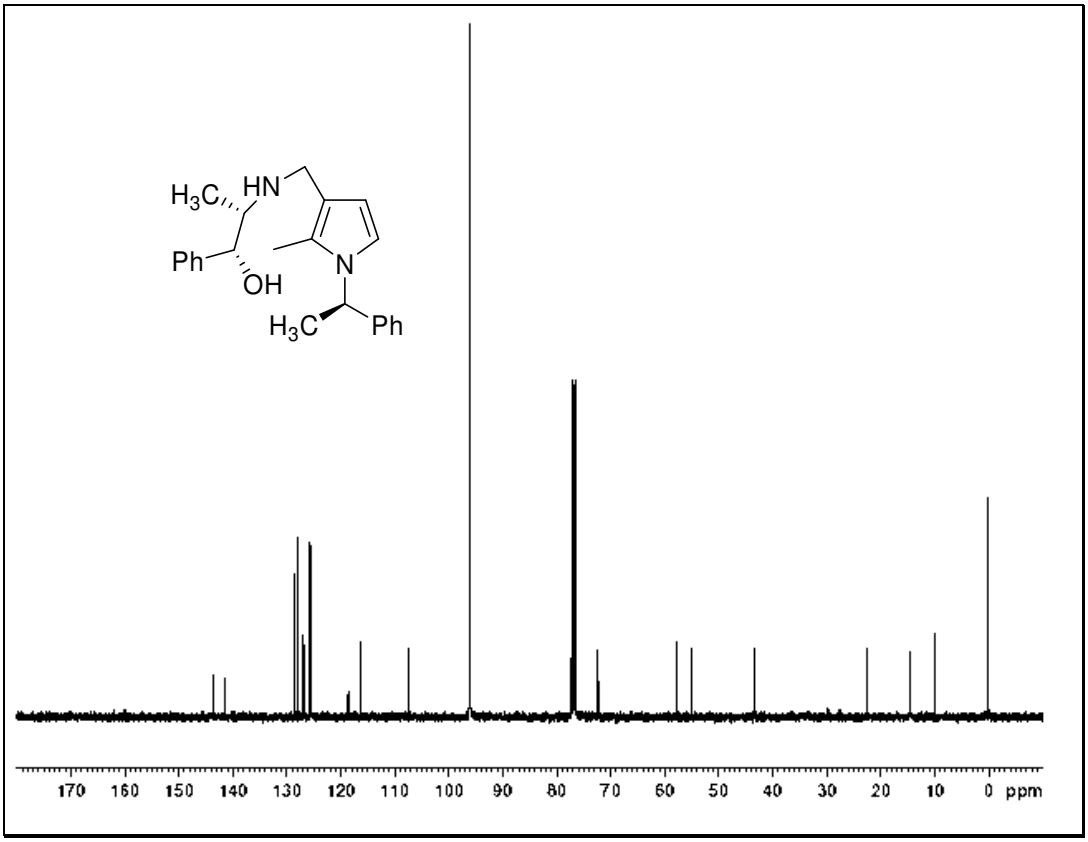


Figure 5.32. The ^{13}C-NMR spectrum of (1*R*, 2*S*)-2-((2-methyl-1-((1*R*)-1-phenylethyl)-1*H*-pyrrol-3-yl)methylamino)-1-phenylpropan-1-ol ((1*R*,2*S*,*R*)-**221**)

Under the same reaction condition, (1*S*,2*R*)-**218** and 2-methyl-1-((*S*)-1-phenylethyl)-1-pyrrole-3- carbaldehyde ((S)-**216**) gave the other enantiomer of the product; (1*S*,2*R*,*S*)-**221** in 69 % yield.

The enantiomers of synthesized compound have similar optical rotation values with opposite sign [(1*R*,2*S*,*R*)-**221** $[\alpha]_D^{25}$ = -3.2 (c 13, $CHCl_3$), (1*S*,2*R*,*S*)-**221** $[\alpha]_D^{25}$ = +3.7 (c 11, $CHCl_3$)

The charaterization of (1*S*,2*R*,*S*)-**221** was performed by ^{1}H-NMR and ^{13}C-NMR spectroscopy.

As shown in ^{1}H-NMR spectrum (Figure 5.33) of (1*S*,2*R*,*S*)-**221**, the multiplet between 3.00 ppm and 3.06 ppm belongs to the methine proton of the ethyl group

attached to NH group. The one of the diastereotopic methylene proton appears at 3.71 ppm as doublet. The other doublet at 3.76 ppm is due to the other diastereotopic methylene proton. The doublet at 4.79 ppm belongs to proton of methine group attached to hydroxyl group. The quartet at 5.28 ppm belongs to the methine proton of the ethyl group on pyrrole ring. The typical doublets at 6.14 ppm and 6.77 ppm are due to the pyrrole protons of C(4)*H* and C(5)*H*, respectively.

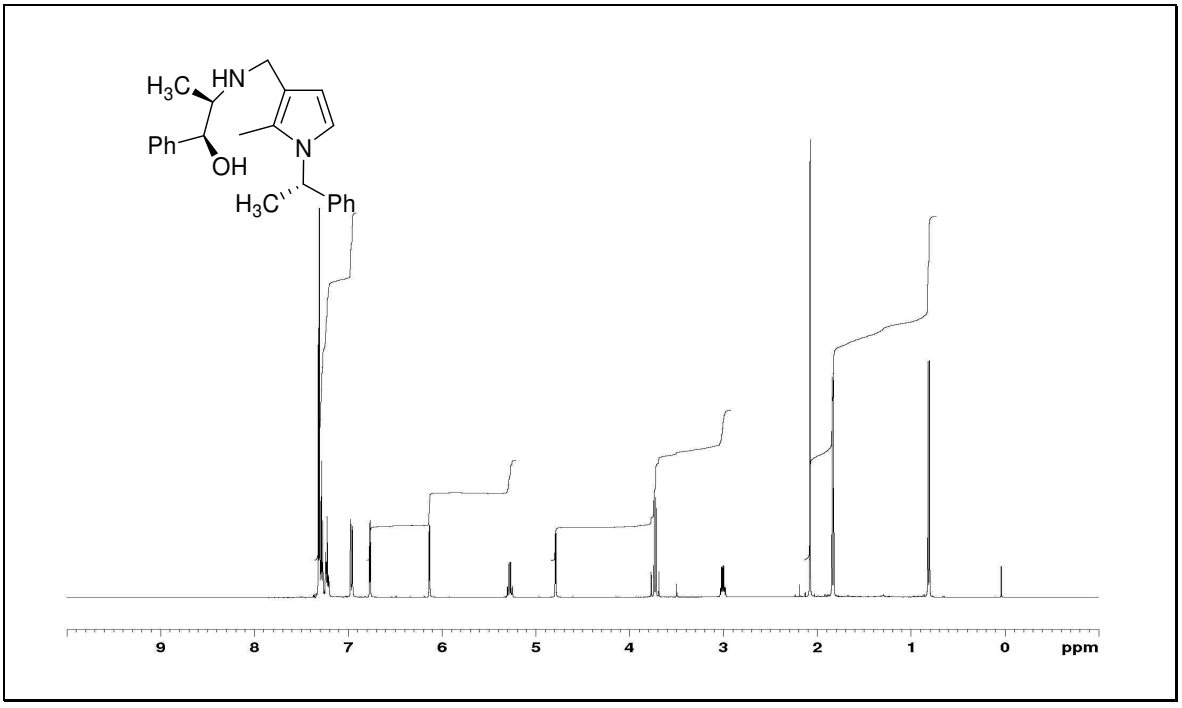


Figure 5.33. The ^{1}H-NMR spectrum of (1*S*,2*R*)-2-((2-methyl-1-((1*S*)-1-phenylethyl)-1*H*-pyrrol-3-yl)methylamino)-1-phenylpropan-1-ol ((1*S*,2*R*,*S*)-**221**)

The ^{13}C-NMR spectrum of (1*S*,2*R*,*S*)-**221** (Figure 5.34) is agreement with structure. The methylene carbon exhibits a signal at 43.39 ppm. The signal at 55.08 ppm belongs to methine carbon of ethyl group on pyrrole ring. The methine carbon attached to NH group on norephedrine moeity appears at 57.86 ppm. The signal at 72.44 ppm is for the methine carbon attached to hydroxyl group. The carbons of pyrrole ring exhibit signals at 107.57 ppm for C(4), 116.25 ppm for C(5), 118.75 ppm for C(3), 128.65 ppm for C(2). The signals of phenyl carbons appear at 125.90 ppm, 126.07 ppm, 126.90 ppm, 126.99 ppm, 127.93 ppm, 128.57 ppm, 141.17 ppm, 142.52 ppm.

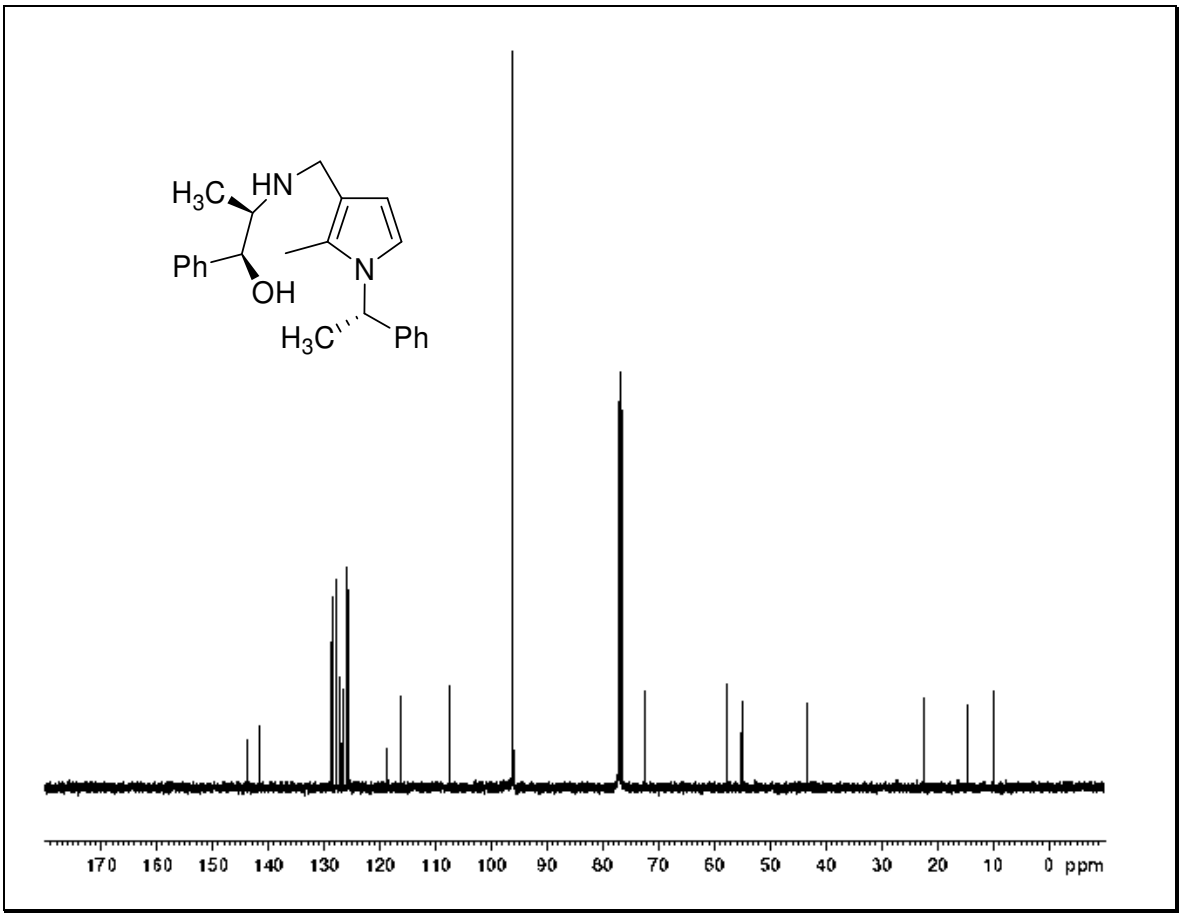


Figure 5.34. The ^{13}C-NMR spectrum of (1*S*, 2*R*)-2-((2-methyl-1-((1*S*)-1-phenylethyl)-1*H*-pyrrol-3-yl)methylamino)-1-phenylpropan-1-ol ((1*S*,2*R*,*S*)-**221**)

5.3.4. The synthesis of (1*R*,2*S*)-2-((2-methyl-1-((1*S*)-1-phenylethyl)-1*H*-pyrrol-3-yl)methylamino)-1-phenylpropan-1-ol ((1*R*,2*S*,*S*)-222) and (1*S*,2*R*)-2-((2-methyl-1-((1*R*)-1-phenylethyl)-1*H*-pyrrol-3-yl)methylamino)-1-phenylpropan-1-ol ((1*S*,2*R*,*R*)-222)

Synthesis of (1*R*,2*S*)-2-((2-methyl-1-((1*S*)-1-phenylethyl)-1*H*-pyrrol-3-yl)methyl amino)-1-phenylpropan-1-ol ((1*R*,2*S*,S)-**222**) and (1*S*,2*R*)-2-((2-methyl-1-((1*R*)-1-phenylethyl)-1*H*-pyrrol-3-yl)methylamino)-1-phenylpropan-1-ol ((1*S*,2*R*,*R*)-**222**) were obtained as brown oil in 70 and 73% yield, respectively. Specific rotation values were determined as $[\alpha]_D^{25}$ = -4.50 (c 9.2, $CHCl_3$)) for (1*R*,2*S*,S)-**222** and $[\alpha]_D^{25}$ =+5.60 (c 7.3, $CHCl_3$ for (1*S*,2*R*,*R*)-**222**

The characterization of products were carried out by ^{1}H-NMR and ^{13}C-NMR spectroscopy.

The ^{1}H-NMR spectrum of (1*R*,2*S*,*S*)-**222** (Figure 5.35) shows a multiplet between 2.99 ppm and 3.05 ppm for methine proton attached to NH group. The one of the diastereotopic methylene proton appears at 3.72 ppm as doublet. The other doublet at 3.77 ppm is due to the other diastereotopic methylene proton.The proton of methine group attached to hydroxyl group appears at 4.81 ppm as doublet. The methine proton of the ethyl group on pyrrole ring appears at 5.28 ppm as quartet. The signals at 6.15 ppm and 6.78 ppm are due to pyrrole protons of C(4)*H* and C(5)*H*, respectively.

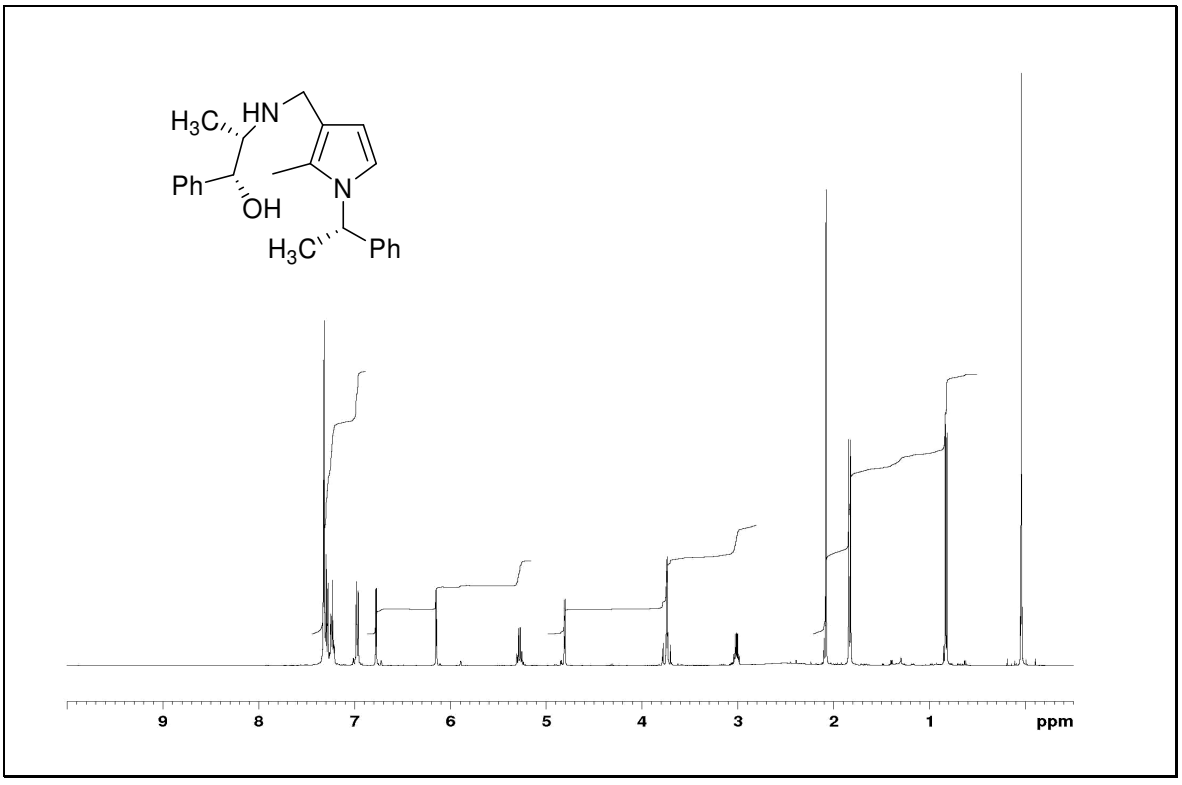


Figure 5.35. The ^{1}H-NMR spectrum of (1*R*,2*S*)-2-((2-methyl-1-((1*S*)-1-phenylethyl)-1*H*-pyrrol-3-yl)methylamino)-1-phenylpropan-1-ol ((1*R*,2*S*,*S*)- **222**)

As shown in Figure 5.36, the ^{13}C-NMR spectrum of (1*R*,2*S*,*S*)-**222** consistents with the structure. The methylene carbon exhibits a signal at 43.34 ppm. The signal at 55.09 ppm belongs to the methine carbon of the ethyl group on pyrrole ring. The

methine carbon attached to NH group on norephedrine moiety apperas at 57.86 ppm. The signal at 72.47 ppm belongs to the methine carbon attached to hydroxyl group. The carbons of pyrrole ring exhibit signals at 107.60 ppm for C(4), 116.29 ppm for C(5), 118.57 ppm for C(3), 128.66 ppm for C(2). The phenyl carbons appear at 125.57 ppm, 125.90 ppm, 125.98 ppm, 126.75 ppm, 127.13 ppm, 127.93 ppm, 141.59 ppm, 143.71 ppm.

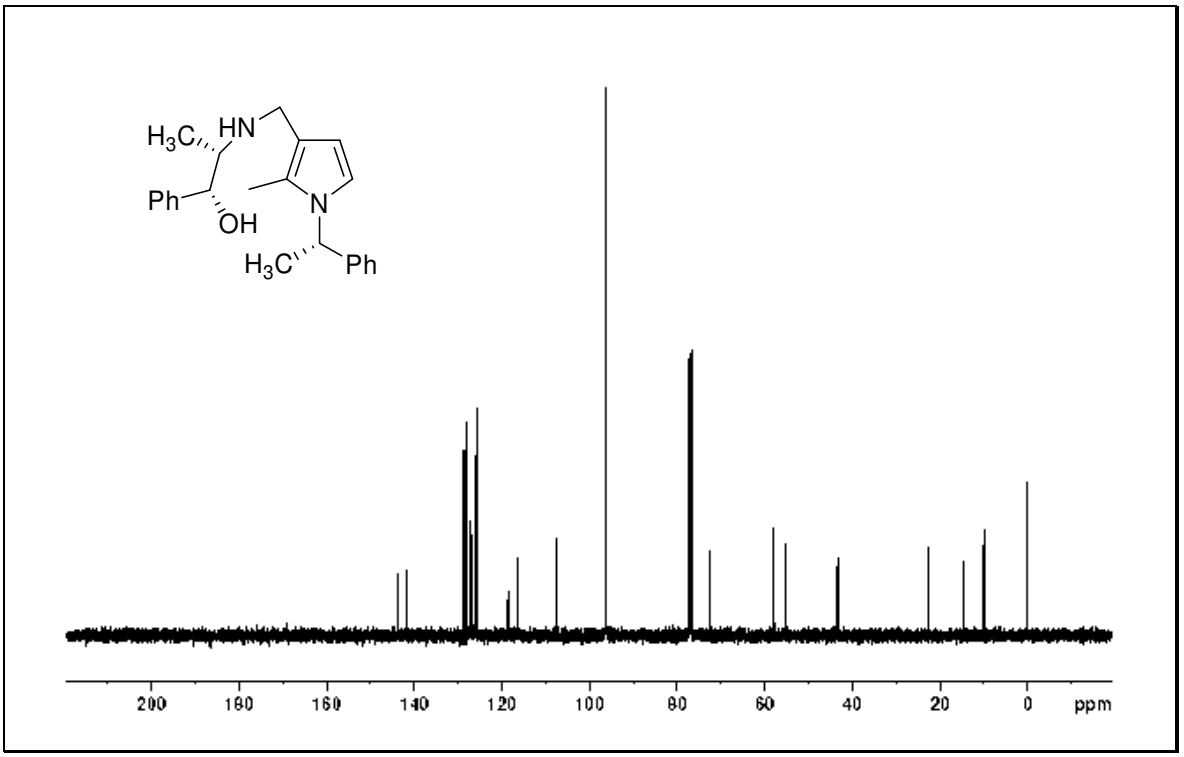


Figure 5.36. The ^{13}C-NMR spectrum of (1*R*,2*S*)-2-((2-methyl-1-((1*S*)-1-phenylethyl)-1*H*-pyrrol-3-yl)methylamino)-1-phenylpropan-1-ol ((1*R*,2*S*,*S*)-**222**)

The ^{1}H-NMR spectrum of (1*S*,2*R*,*R*)-**222** (Figure 5.37) exhibits a multiplet between 2.98 ppm and 3.04 ppm for methine proton of the ethyl group attached to NH group. The one of the diastereotopic methylene proton appears at 3.71 ppm as doublet. The other doublet at 3.76 ppm is due to the other diastereotopic methylene proton. The methine group connected to hydroxy group appears at 4.80 ppm as doublet. The methine proton of the ethyl group on pyrrole ring appears at 5.28 ppm as quartet. The signals at 6.14 ppm and 6.77 ppm belong to pyrrole protons of C(4)*H* and C(5)*H*, respectively.

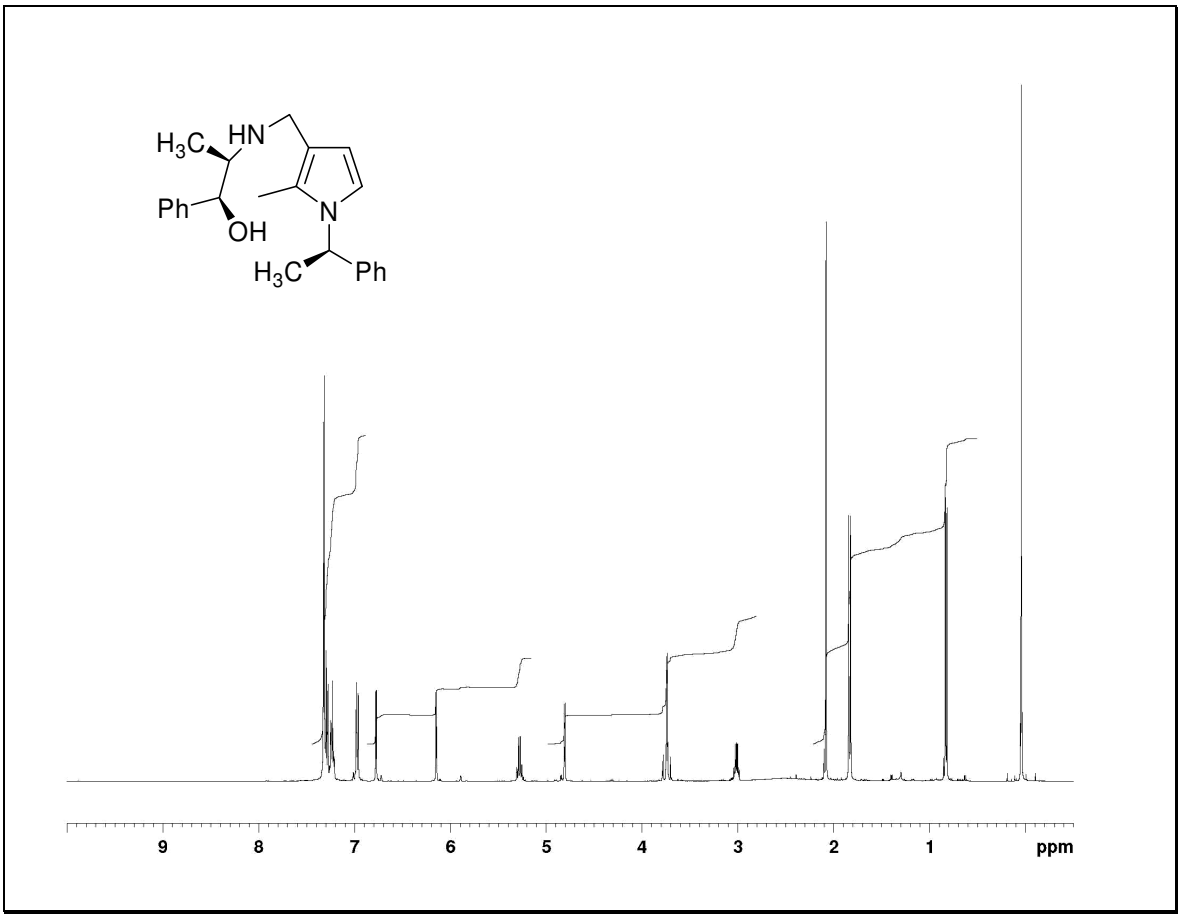


Figure 5.37. The ^{1}H-NMR spectrum of (1*S*,2*R*)-2-((2-methyl-1-((1*R*)-1-phenylethyl)-1*H*-pyrrol-3-yl)methylamino)-1-phenylpropan-1-ol ((1*S*,2*R*,*R*)-**222**)

The ^{13}C-NMR spectrum of (1*S*,2*R*,*R*)-**222** was given in Figure 5.38. It shows signals at 43.36 ppm for methylene carbon, at 55.09 ppm for methine carbon of the ethyl group on pyrrole ring, at 55.47 ppm for methine carbon attached to NH group on norephedrine moiety. The signal at 72.45 ppm is for the methine carbon attached to hydroxyl group. The carbons of pyrrole ring exhibit signals at 107.58 ppm for C(4), 116.27 ppm for C(5), 118.67 ppm for C(3), 128.65 ppm for C(2). The signals at 125.57 ppm, 125.86 ppm, 125.97 ppm,126.75 ppm, 127.13 ppm, 127.92 ppm, 141.59 ppm, 143.71 ppm belong to the phenyl carbons.

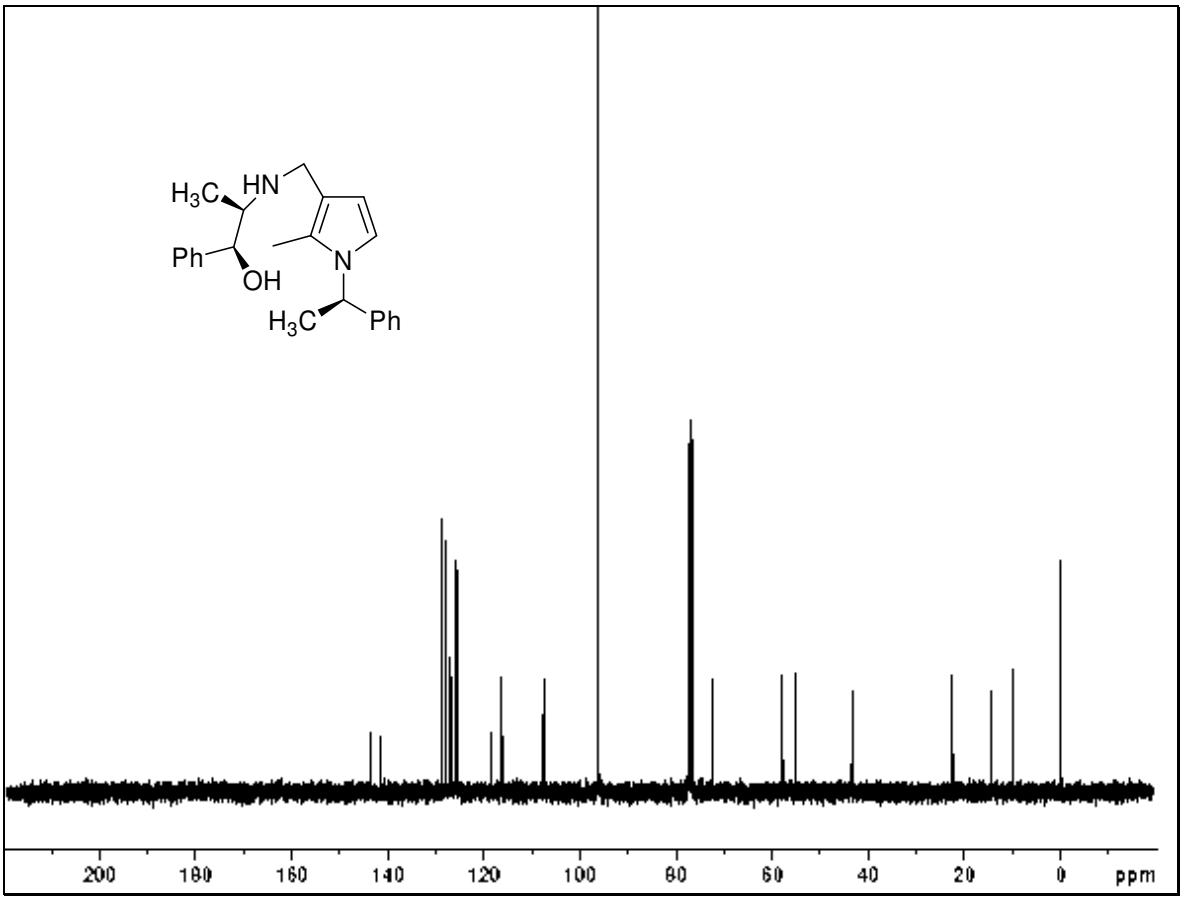


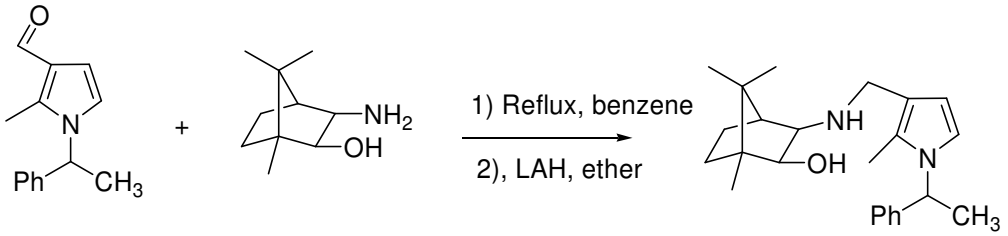
Figure 5.38. The ^{13}C-NMR spectrum of (1*S*,2*R*)-2-((2-methyl-1-((1*R*)-1-phenylethyl)-1*H*-pyrrol-3-yl)methylamino)-1-phenylpropan-1-ol ((1*S*,2*R*,*R*)-**222**)

5.4. The Synthesis of Novel Camphor-Based Ligands with *N*-Substituted Chiral Pyrrole

(+)-Camphor, readily available from natural sources or produced synthetically from pinene, has found extensive use as chiral ligand in natural compounds. Derivatives of camphor have been used frequently as catalyst in asymmetric synthesis. The most striking example is probably (-)-*cis*-*exo*-*N*,*N*-dimethyl-3-aminoborneol ((-)-DAIB) **33**, introduced by Noyori (1986), as excellent chiral catalyst in the addition of dialkylzinc reagent to several aldehydes.

In this part of the work, it is aimed to synthesize novel camphor-based ligands with *N*-substituted chiral pyrrole. For this purpose, *exo*- and *endo*- amino alcohols were prepared and used in the synthesis of novel camphor-based chiral ligands .

The synthesis of chiral ligand have been accomplished by applying the synthetic route given in Scheme 5.12 and Scheme 5.13.

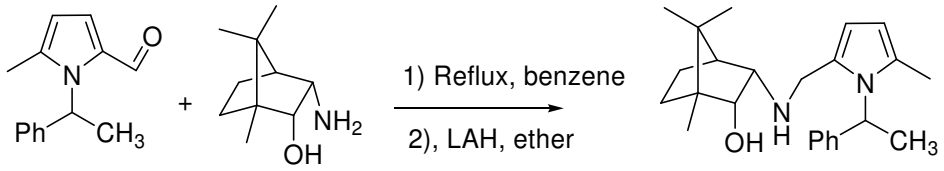


(*R*)-**214**
(*S*)-**216**

(2-*exo*,3-*exo*)-**224**

(2-*exo*,3-*exo*,*R*)-**225**
(2-*exo*,3-*exo*,*S*)-**225**

Scheme 5.12. The synthesis of (2-*exo*,3-*exo*,*R*)-**225** and (2-*exo*,3-*exo*,*S*)-**225**



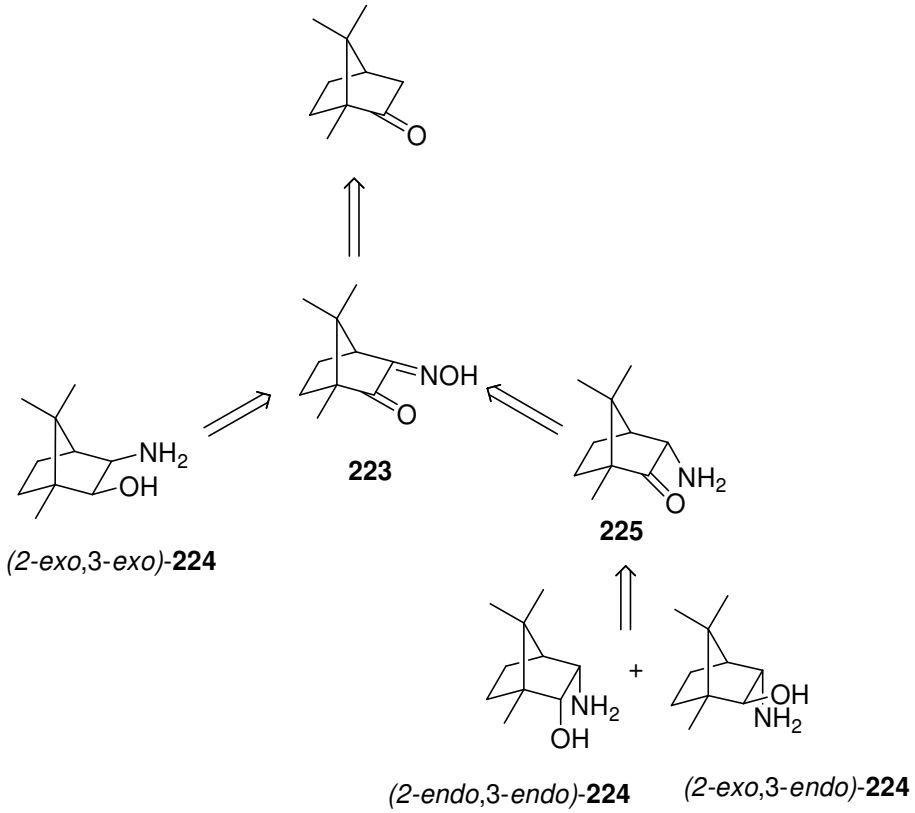
(*R*)-**215**
(*S*)-**217**

(2-*endo*,3-*endo*-**224**

(2-*endo*,3-*endo*,*R*)-**226**
(2-*endo*,3-*endo*,*S*)-**226**

Scheme 5.13. The synthesis of (2-*endo*,3-*endo*,*R*)-**226** and (2-*endo*,2-*endo*,*S*)-**226**

3-*exo*-Amino-2-*exo*-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptane ((2-*exo*,3-*exo*) **224**) and *endo*-3-amino-*endo*-2-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptane ((2-*endo*,3-*endo*)-**224**) were prepared from camphor according to the synthetic plan given in Scheme 5.14.



Scheme 5.14. Retrosynthetic pathway for **224**

5.4.1. The synthesis of 3-hydroxyimino-2-oxo-1,7,7-trimethylbicyclo[2.2.1] heptane (223)

According to retrosynthetic pathway, camphor was converted to 3-hydroxyimino-2-oxo-1,7,7-trimethylbicyclo[2.2.1]heptane (**223**) using the procedure given in literature (Costa et al., 2001). The reaction of camphor with *tert*-butyl nitrite in dry THF in the presence of *ter*-sodyum butylate gave **223** in high yield (95%).

Characterization of 3-hydroxyimino-2-oxo-1,7,7-trimethylbicyclo[2.2.1]heptane (**223**) was performed by ^{1}H-NMR and ^{13}C-NMR spectroscopy.

^{1}H-NMR spectrum of 3-hydroxyimino-2-oxo-1,7,7-trimethylbicyclo[2.2.1]heptane (**223**) (Figure 5.39) exhibits three singlet at 0.90 ppm, 1.02 ppm and 1.04 ppm for the methyl protons. *endo*- Methylene protons at C(5) and C(6) exhibit multiplet between 1.58 ppm and 1.63 ppm. The multiplet between 1.77 ppm and 1.82 ppm is due to the *exo*- methylene proton at C(6). The other multiplet between 2.02 ppm and 2.08 ppm belongs to *exo*- methylene proton at C(5). The doublet at 3.28 ppm belongs to the bridgehead proton of C(4). The typical broad singlet of oxime proton appears at 9.70 ppm.

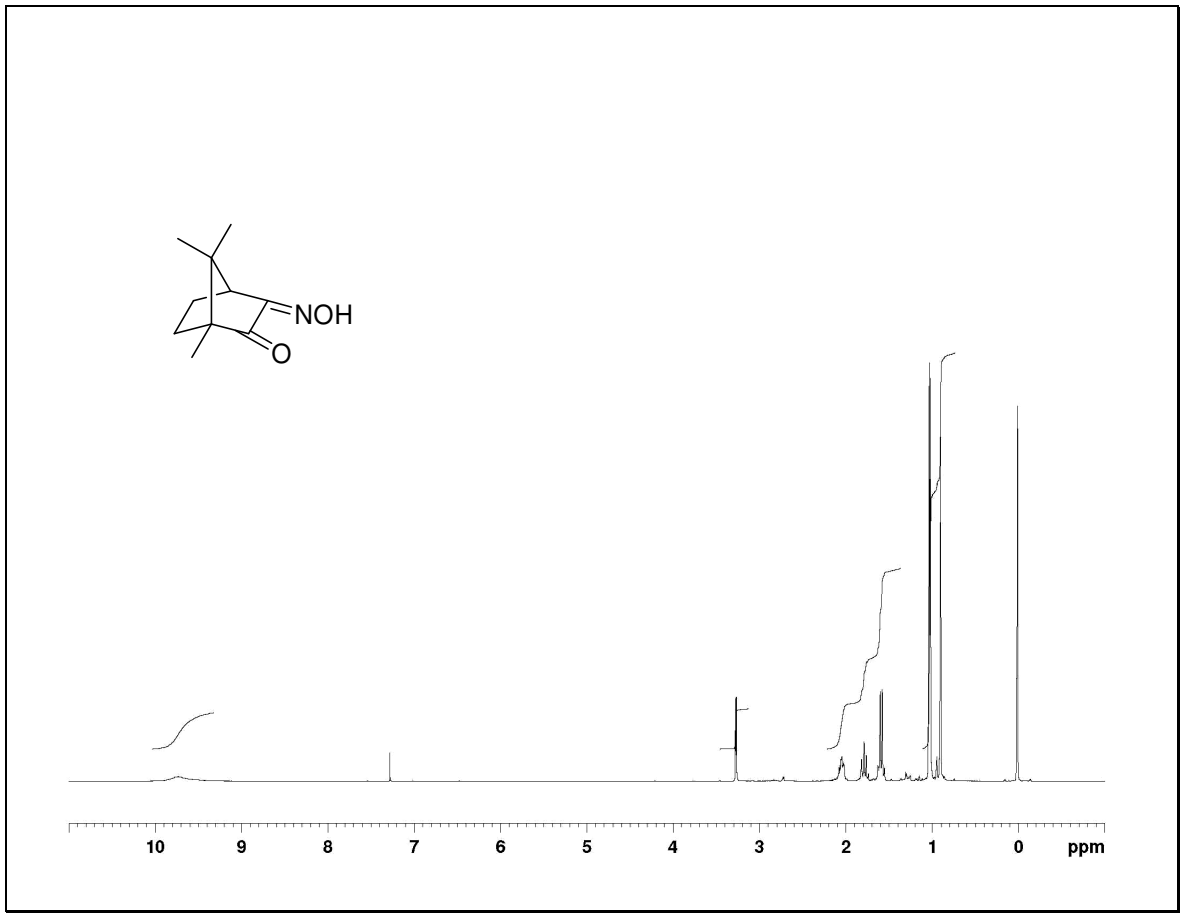


Figure 5.39. The ^{1}H-NMR spectrum of 3-hydroxyimino-2-oxo-1,7,7-trimethylbicyclo [2.2.1]heptane (**223**)

^{13}C-NMR spectrum of 3-hydroxyimino-2-oxo-1,7,7-trimethylbicyclo[2.2.1]heptane (**223**) (Figure 5.40) exhibits signals at 9.03 ppm, 17.73 ppm and 20.73 ppm for methyl group. The signals at 23.80 ppm for C(5) and 30.67 ppm for C(6) is due to the methylene carbons. The methine carbon shows signals at 44.90 ppm for C(4).

Oxime and carbonyl carbons show signals at 159.24 ppm and 203.48 ppm, respectively.

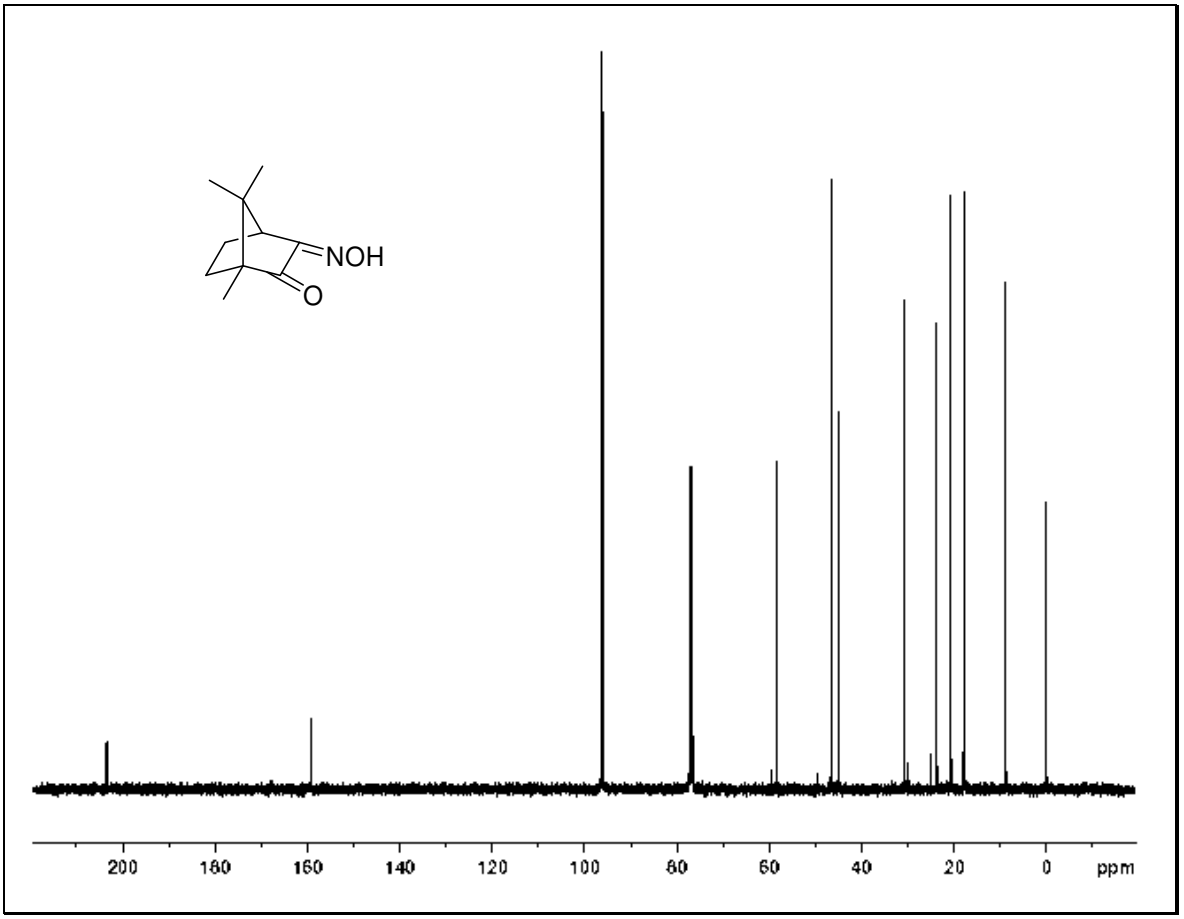


Figure 5. 40. The ^{13}C-NMR spectrum of 3-hydroxyimino-2-oxo-1,7,7-trimethylbicyclo[2.2.1]heptane (**223**)

5.4.2. The synthesis of 3-*exo*-amino-2-*exo*-hydroxy-1,7,7-trimethylbicyclo [2.2.1]heptane ((2-*exo*,3-*exo*)-224)

3-*exo*-Amino-2-*exo*-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptane ((2-*exo*,3-*exo*)-**224**) was obtained readily from the reduction of 3-hydroxyimino-2-oxo-1,7,7-trimethylbicyclo[2.2.1]heptane (**223**) with $LiAlH_4$ by refluxing in dry ether with 76% yield, according to literature procedure (Cooper et al., 1970). The product was purified by sublimation.

Characterization of 3-*exo*-amino-2-*exo*-hydroxy-1,7,7-trimethylbicyclo[2.2.1] heptane ((2-*exo*,3-*exo*)-**224**) was achieved by ^{1}H-NMR and ^{13}C-NMR spectroscopy.

The ^{1}H-NMR spectrum of the compound (2-*exo*,3-*exo*)-**224** (Figure 5.41) exhibits three singlet at 0.80 ppm, 0.94 ppm, 1.08 ppm for the methyl groups attached to C(1), C(7) and C(7), respectively. *endo*-Methylene protons at C(5) and C(6) exhibit multiplet between 1.40 ppm and 1.46 ppm. The multiplet between 1.65 ppm and 1.68 pmm belongs to *exo*-methylene proton at C(6). *exo*-Methylene proton at C(5) can be seen as multiplet between 1.83 ppm and 1.86 ppm. The two doublet at 3.10 ppm and 3.46 ppm which belong to methine protons at C*H*NH_2 and C*H*OH, respectively. The methine proton of C(4) appears at 1.62 ppm as doublet. The coupling constant $J_{2,3}$ is 7.36 Hz indicating that two protons are located in the *cis* pozition.

Reduction of **223** in the given reaction condition resulted in the formation of *exo* product for which the structure is in agreement with the known structure of (2-*exo*,3-*exo*)-**224** in the literature (Cooper et al., 1970).

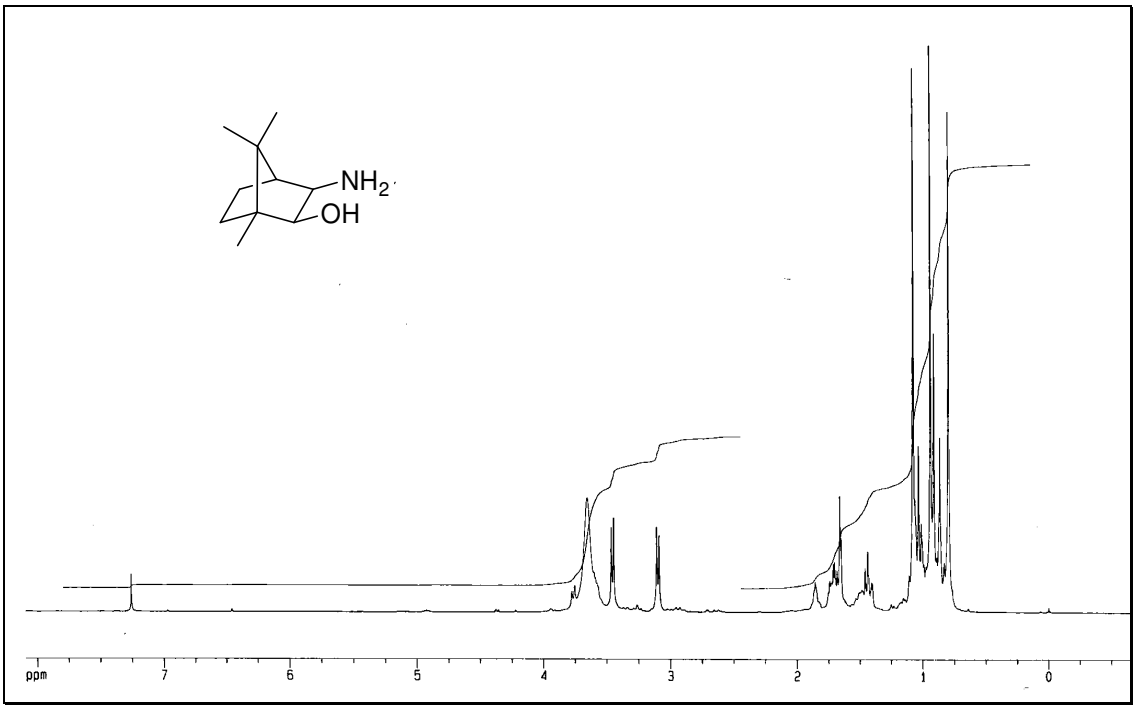


Figure 5.41. The ^{1}H-NMR spectrum of 3-*exo*-amino-2-*exo*-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptane ((2-*exo*,3-*exo*)-**224**)

The ^{13}C-NMR spectrum of spectrum of 3-*exo*-amino-2-*exo*-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptane ((2-*exo*,3-*exo*)-**224**) (Figure 5.42) exhibits signals at 11.80 ppm, 21.67 ppm, 22.33 ppm for methyl protons at C(1), C(7) and C(7), respectively. The methylene carbons exhibit signals at 27.29 ppm for C(5) and 33.47 ppm for C(6). The methine carbon at C(4) shows a signal at 47.10 ppm The quaternary carbons exhibit signals at 49.25 ppm for C(7), 53.02 ppm for C(1). The signals at 57.79 ppm and 79.07 ppm which belong to the methine carbons of C(3) and C(2), respectively.

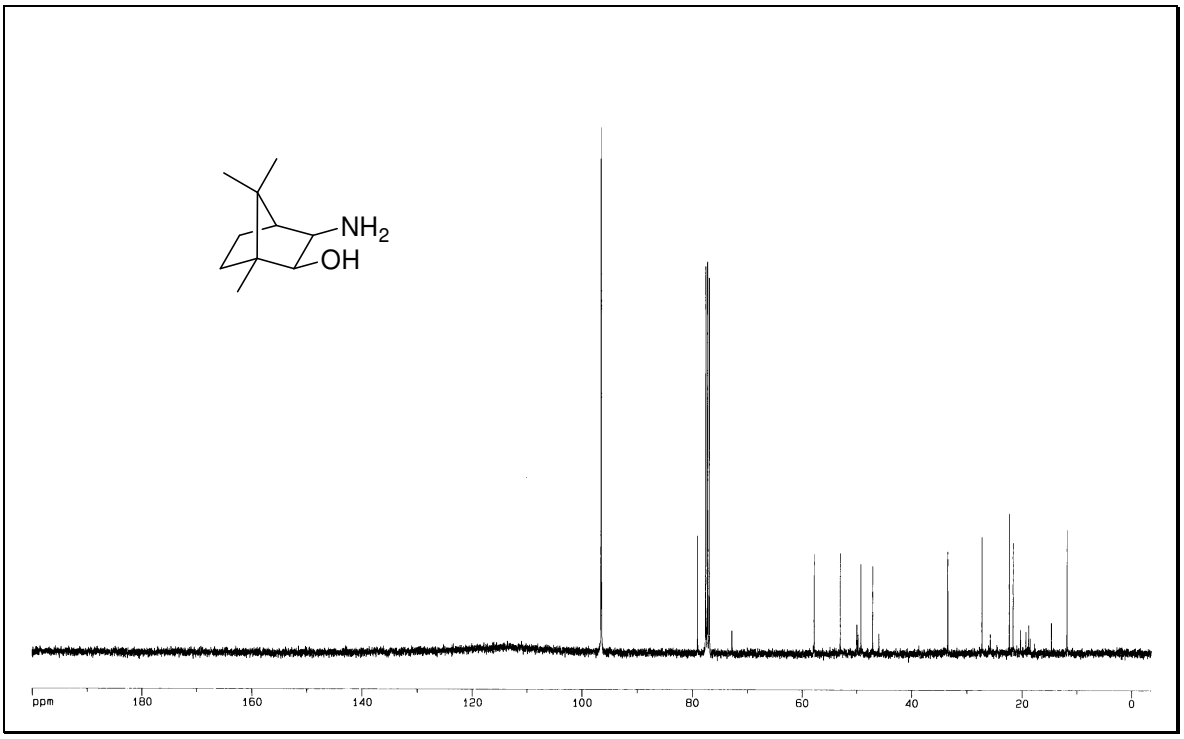


Figure 5.42. The ^{13}C-NMR spectrum of 3-*exo*-amino-2-*exo*-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptane ((2-*exo*,3-*exo*)-**224**)

5.4.3. The synthesis of 3-*endo*-amino-2-exo-hdroxy-1,7,7-trimethylbicyclo [2.2.1]heptane ((2-*endo*,3-*endo*)-224)

According to the given retrosynthetic pathway in Scheme 5.14, 3-*endo*-amino-2-*endo*-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptane ((2-*endo*,3-*endo*)-**224**) was synthesized from oxime **223**.

Firstly, oxime **223** was converted to *endo*-3-amino-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (**225**) with zinc dust in alkali solution and the compound **225** was obtained in 93% yield.

endo-3-Amino-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (**225**) was characterized by ^{1}H-NMR and ^{13}C-NMR spectroscopy.

The ^{1}H-NMR spectrum of compound **225** (Figure 5.43) shows a doublet at 3.47 ppm for the methine at C*H*NH_2. The singlet at 1.40 ppm belongs to amino group. Its structure is in agrrement with the known structure of **225** in the literature (Hénin et al., 1993).

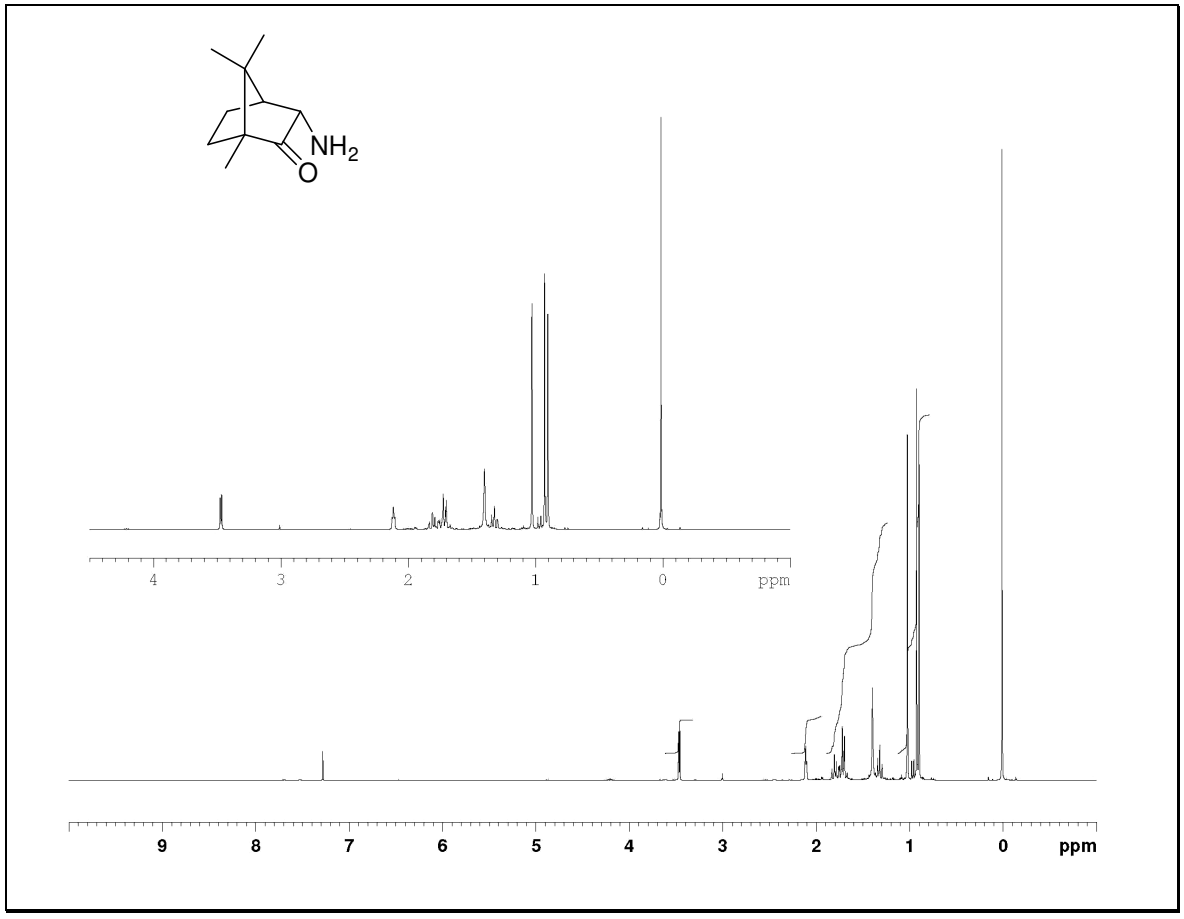


Figure 5.43. The ^{1}H-NMR spectrum of *endo*-3-amino-1,7,7-trimethylbicyclo[2.2.1] heptan-2-one (**225**)

The ^{13}C-NMR spectrum of compound **225** (Figure 5.44) shows signals at 19.80 ppm, 32.12 ppm for methylene carbons, C(5) and C(6), respectively. The signal at 43.93 ppm is due to methine carbon at C(4). The signal at 58.57 ppm belong to methine carbon attached to amino group. The carbonyl carbon appears at 213.12 ppm.

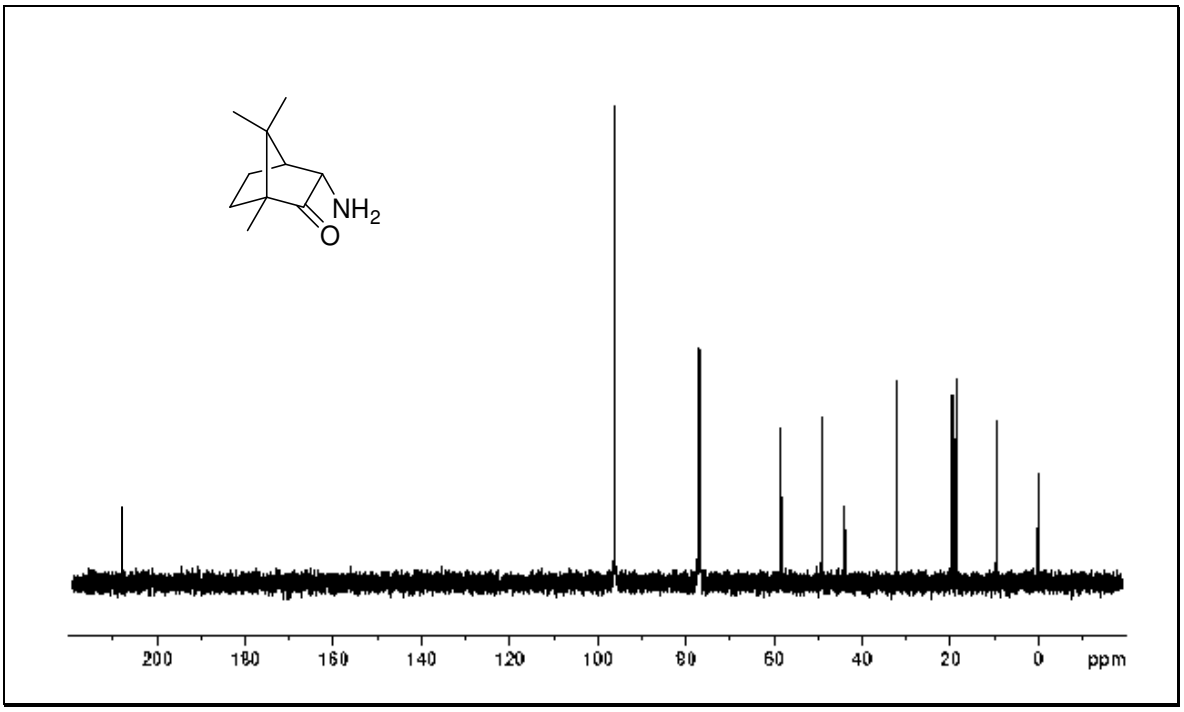


Figure 5.44. The ^{13}C-NMR spectrum of *endo*-3-amino-1,7,7-trimethylbicyclo [2.2.1]heptan-2-one (**225**)

For the synthesis of 3-*endo*-amino-2-*endo*-hydroxy-1,7,7-trimethylbicyclo[2.2.1] heptane ((2-*endo*,3-*endo*)-**224**), the carbonyl group of the compound **225** was reduced with $LiAlH_4$ in dry ether. And the mixture of (2-*endo*,3-*endo*)-**224** and (2-*exo*,3-*endo*)-**224** was obtained. The treatment of mixture with acids under hydrolysis conditions allowed isolation of (2-*endo*,3-*endo*)-**224**. The product was sublimed to give pure (2-*endo*,3-*endo*)-**224**.

The characterization of the compound (2-*endo*,3-*endo*)-**224** was achieved by ^{1}H-NMR. spectroscopy.

As shown Figure 5.45, the methine proton attached to C(2) gives doublet of doublet at 3.58 ppm with 9.2 Hz and 1.6 Hz. The other doublet of doublet of doublet at 3.49 with 9.2 Hz, 4.4. Hz and 1.2 Hz for the methine proton attacahed to C-3. According to coupling constatnt, two protons are cis to each other.

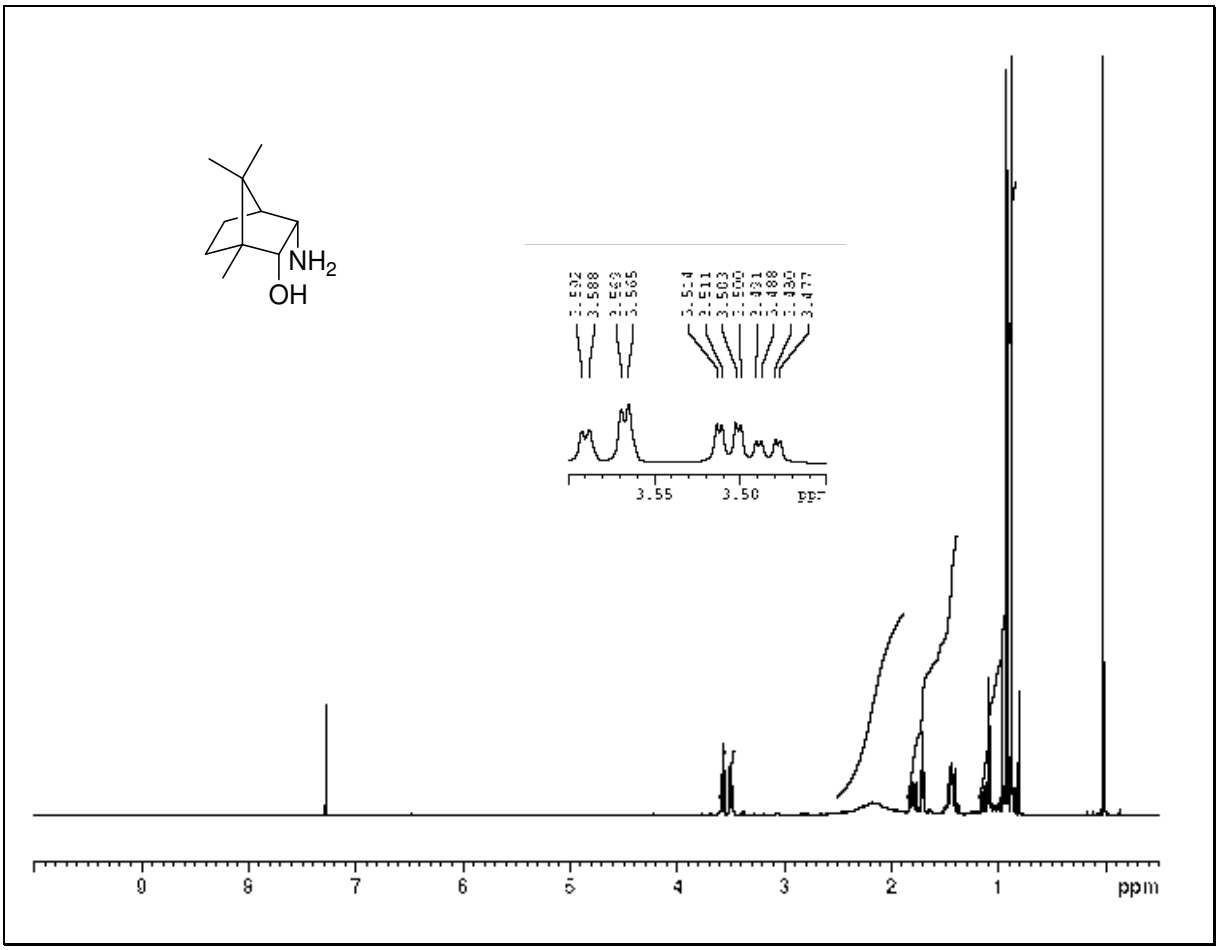


Figure 5.45. The ^{1}H-NMR spectrum of 3-*endo*-amino-2-*endo*-hdroxy-1,7,7-trimethylbicyclo[2.2.1]heptane ((2-*endo*,3-*endo*)-**224**)

5.4.4.General procedure for the synthesis of novel camphor-based ligands with *N*-substituted chiral pyrrole

Novel camphor-based ligands with *N*-substituted chiral pyrrole were synthesized from *exo*- and *endo*- amino alcohols prepared from camphor and *N*-substituted chiral pyrrole carbaldeyhes. For the synthesis of chiral ligands, *exo*- and *endo*-amino alcohols and pyrrole carbaldeyhes in dry benzen were refluxed under Dean-Stark trap. The imine was reduced with $LiAlH_4$ in dry ether. The crude products was purified by flash column chromatography.

5.4.4.1.The synthsesis of (2-*exo*,3-*exo*)-1,7,7-trimethyl-3-((2-methyl-1-((*R*)-1-phenylethyl)-1*H*-pyrrol-3-yl)methylamino)bicyclo[2,2,1]heptan-2-ol ((2-*exo*,3-*exo*,*R*)-225) and (2-*exo*,3-*exo*)-1,7,7-trimethyl-3-((2-methyl-1-((*S*)-1-phenylethyl)-1*H*-pyrrol-3-yl)methylamino)bicyclo[2,2,1]heptan-2-ol ((2-*exo*,3-*exo*,*S*)-225)

1,7,7-Trimethyl-3-((2-methyl-1-((*R*)-1-phenylethyl)-1*H*-pyrrol-3-yl)methylamino) bicyclo[2,2,1]heptan-2-ol ((2-*exo*,3-*exo*,*R*)-**225**) was prepared from *exo*-amino alcohol ((2-*exo*,3-*exo*)-**224**) and 2-methyl-1-((1*R*)-1-phenylethyl)-1*H*-pyrrole-3-carbaldehyde (*R*)-**214** as given procedure above.

The compound (2-*exo*,3-*exo*,*R*)-**225** was obtained in 72% yield as brown oil. The specific rotation was determined as $[\alpha]_D^{25}$ = +8.43 (c 9.7, $CHCl_3$).

The characterization of (2-*exo*,3-*exo*,*R*)-**225** was performed by ^{1}H-NMR and ^{13}C-NMR spectroscopy.

The ^{1}H-NMR spectrum of the (2-*exo*,3-*exo*,*R*)-**225** (Figure 5.46) shows a singlet at 0.81 ppm for methyl proton attached to C(1) on camphor moiety. The singlet at 0.98 ppm and is due to the methyl proton attached to C(7). The singlet at 1.08 ppm for the methyl protons attached to C(7) overlaps with multiplet between 1.02 ppm and 1.10 ppm which belong to *endo* protons of methylene group of C(5) and C(6). The multiplet between 1.42 ppm and 1.47 ppm is due to *exo*- proton of methylene group attached to C(6). The doublets at 1.58 ppm and 1.84 ppm are due to bridgehead proton at C(4) and methyl protons of ethyl group on pyrrole nitrogen, respectively. The *exo*- proton of methylene group on C(5) exhibits multiplet between 1.71 ppm and 1.75 ppm. The singlet at 2.07 belongs to the methyl protons on pyrrole ring. Two doublets at 2.79 ppm (*J*=7.23 Hz), and 3.42 ppm (*J*=7.21 Hz) which belong to methine protons attached to C(3) and C(2), respectively. The other singlet at 3.62 ppm belogs to methylene protons (NHCH_2) . The methine proton of ethyl group on pyrrole nitrogen exhibits a quartet at 5.27 ppm. The doublets of pyrrole ring appear at 6.13 ppm (C(4)*H*) and 6.77 ppm

(C(5)*H*). The doublet at 6.96 ppm and the multiplet between 7.21 ppm and 7.32 ppm are belong to the phenyl ring.

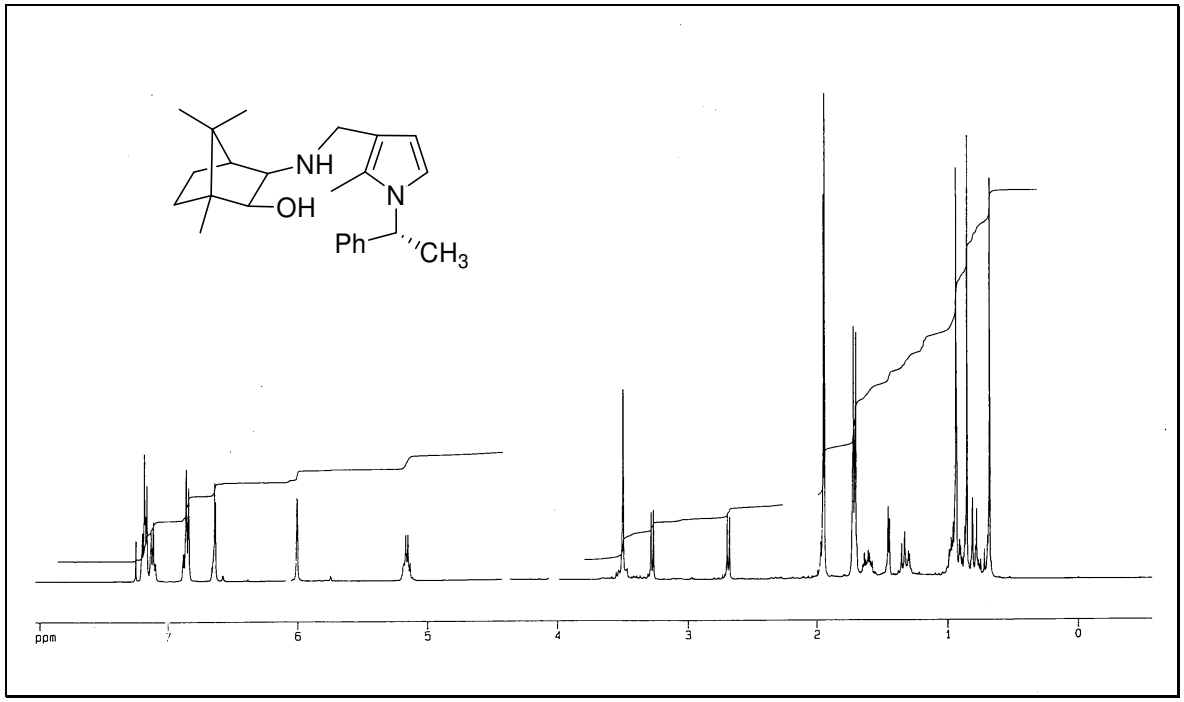


Figure 5.46. The ^{1}H-NMR spectrum of (2-*exo*,3-*exo*)-1,7,7-trimethyl-3-((2-methyl-1-((*R*)-1-phenylethyl)-1*H*-pyrrol-3yl)methylamino)bicyclo[2,2,1]heptan-2-ol ((2-*exo*,3-*exo*,*R*)-**225**)

The ^{13}C-NMR spectrum of the (2-*exo*,3-*exo*,*R*)-**225** (Figure 5.47) exhibits signals at 9.70 ppm for the methyl carbon on pyrrole ring, at 11.37 ppm, 21.34 ppm and 21.97 ppm for methyl carbons attached to C(1), C(7), respectively. The methyl carbon of ethyl group on pyrrole nitrogen exhibits a signal at 22.34 ppm. The methylene carbons at C(5) and C(6) appear at 27.29 ppm and 32.85 ppm, respectively. The methylene carbon attached to NH group exhibits a signal at 46.41 ppm. The signals at 46.82 ppm, 48.66 ppm, 51.95 ppm are due to C(1), C(7) and C(4), respectively. The methine carbons attached to C(3) and C(2) exhibit signals at 65.44 ppm and 78.44 ppm, respectively. The pyrrole carbons appear at 107.31 ppm for C(4), 116.00 ppm for C(5), 118.61 ppm for C(3), 128.49 ppm for C(2). The phenyl carbons exhibit signals at 125.36 ppm, 125.91 ppm, 126.96 ppm, 143.66 ppm.

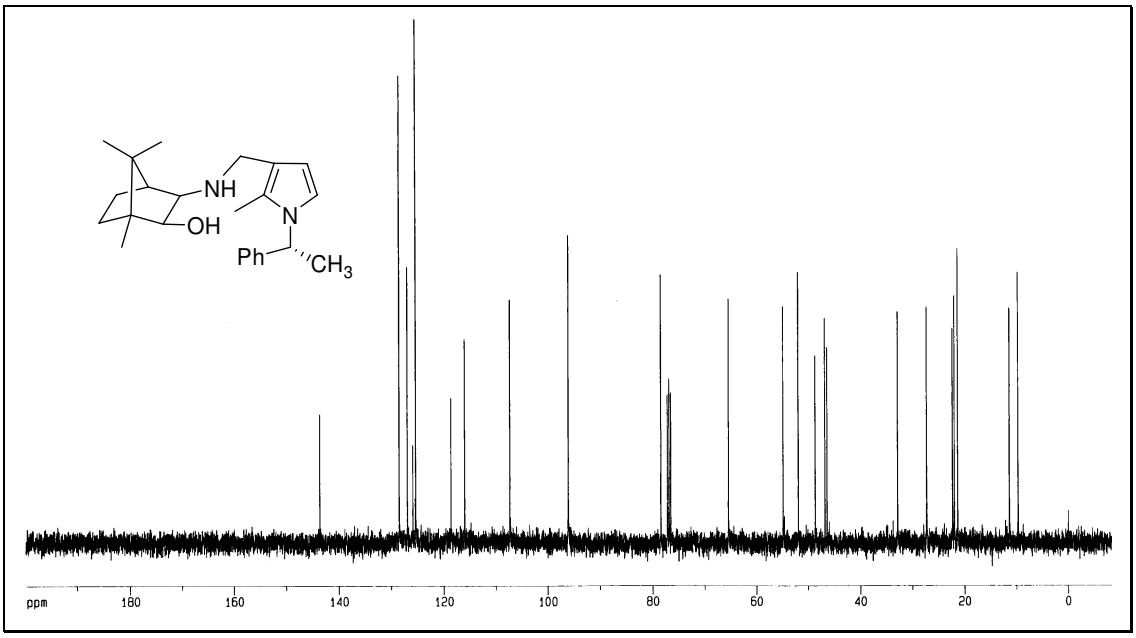


Figure 5.47. The ^{13}C-NMR spectrum of (2-*exo*,3-*exo*)-1,7,7-trimethyl-3-((2-methyl-1-((*R*)-1-phenylethyl)-1*H*-pyrrol-3yl)methylamino)bicyclo[2,2,1]heptan-2-ol ((2-*exo*,3-*exo*,*R*)-**225**)

Under same reaction conditions, (2-*exo*,3-*exo*)-1,7,7-trimethyl-3-((2-methyl-1-((*S*)-1-phenylethyl)-1*H*-pyrrol-3yl)methylamino)bicyclo[2,2,1]heptan-2-ol ((2-*exo*,3-*exo*,*S*)-**225**) was synthesized from 3-*exo*-amino-2-*exo*-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol ((2-*exo*,3-*exo*)-**224**) and 2-methyl-1-((1*S*)-1-phenylethyl)-1*H*-pyrrole-3-carbaldehyde ((*S*)-**216**) (70% yield and $[\alpha]_D^{25}$ = -9.22 (c 8.9, $CHCl_3$)

The characterization of (2-*exo*,3-*exo*,*S*)-**225** was performed by ^{1}H-NMR and ^{13}C-NMR spectroscopy.

The ^{1}H-NMR spectrum of (2-*exo*,3-*exo*,*S*)-**225** (Figure 5.48) shows two doublets at 1.49 ppm and 1.73 ppm are due to bridgehead proton (C(4)*H*) and methyl protons of ethyl group, respectively. The methyl protons on pyrrole ring appear at 1.96 ppm as singlet. Two doublets at 2.70 ppm (*J*=7.25 Hz), and 3.33 ppm (*J*=7.23 Hz) which belong to methine protons attached to C(3)*H* and C(2)*H*, respectively. The singlet at 3.51 ppm belongs to methylene protons at NHCH_2. The methine

proton of ethyl group on pyrrole nitrogen exhibits a quartet at 5.17 ppm. The doublets of pyrrole ring appear at 6.01 ppm for C(4)*H* and 6.77 ppm for C(5)*H*. The doublet at 6.66 ppm and the multiplet between 7.11-7.31 ppm are belong to the phenyl ring.

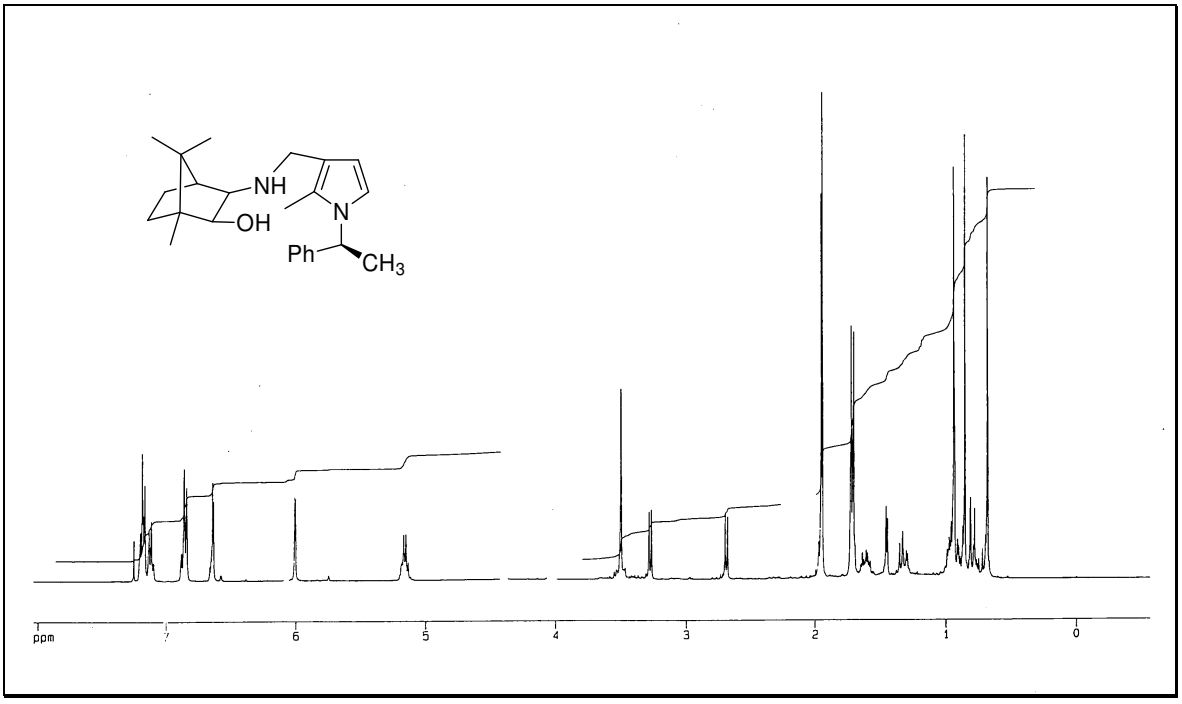


Figure 5.48. The ^{1}H-NMR spectrum of (2-*exo*,3-*exo*)-1,7,7-trimethyl-3-((2-methyl-1-((*S*)-1-phenylethyl)-1*H*-pyrrol-3yl)methylamino)bicyclo[2,2,1]heptan-2-ol ((2-*exo*,3-*exo*,*S*)-**225**)

The ^{13}C-NMR spectrum of (2-*exo*,3-*exo*,*S*)-**225** (Figure 5.49) exhibits signals at 10.29 ppm for the methyl carbon on pyrrole ring, at 11.87 ppm, 21.84 ppm and 22.47 ppm for methyl carbons attached to C(1), C(7), respectively. The methyl carbon of ethyl group on pyrrole nitrogen exhibits a signal at 22.82 ppm. The methylene carbons at C(5) and C(6) appear at 27.79 ppm and 33.38 ppm, respectively. The methylene carbon attached to NH group exhibits a signal at 47.22 ppm. The signals at 47.98 ppm, 49.22 ppm, 52.25 ppm are due to C(7), C(1) and C(4), respectively. The methine carbon of ethyl group on pyrrole nitrogen appears at 55.45 ppm. The methine carbons attached to C(3) and C(2) exhibit signals at 65.97 ppm and 78.99 ppm, respectively. The pyrrole carbons appear at 108.07 ppm for C(4), 116.60 ppm for C(5), 118.89 ppm for C(3), 129.00 ppm for

C(2). The phenyl carbons appear at 125.96 ppm, 126.35 ppm, 127.51 ppm, 144.04 ppm.

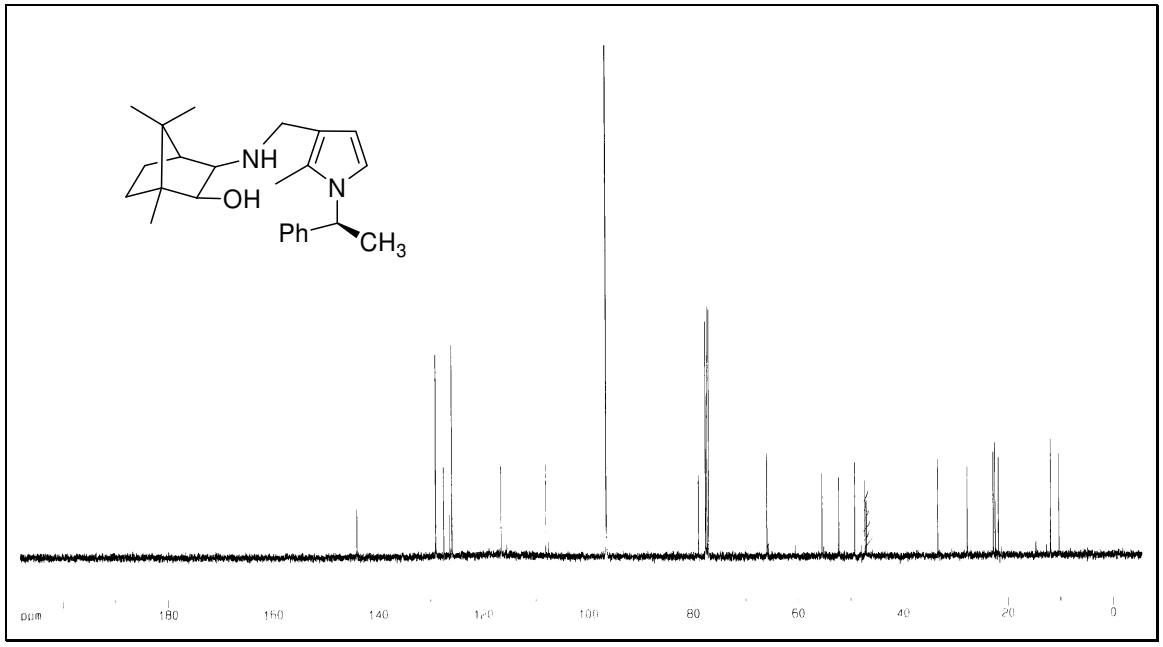


Figure 5.49. The ^{13}C-NMR spectrum of (2-*exo*,3-*exo*)-1,7,7-trimethyl-3-((2-methyl-1-((*S*)-1-phenylethyl)-1*H*-pyrrol-3-yl)methylamino)bicyclo [2,2,1]heptan-2-ol ((2-*exo*,3-*exo*,*S*)-**225**)

5.4.4.2. The synthesis of (2-*endo*,3-*endo*)-1,7,7-trimethyl-3-((5-methyl-1-((*R*)-1-phenylethyl)-1*H*-pyrrol-2-yl)methylamino)bicyclo[2,2,1]heptan-2-ol ((2-*endo*, 3-e*ndo*,*R*)-226) and (2-*endo*,3-*endo*)-1,7,7-trimethyl-3-((5-methyl-1-((*S*)-1-phenylethyl)-1*H*-pyrrol-2-yl)methylamino)bicyclo[2,2,1]heptan-2-ol ((2-*endo*, 3-*endo*,*S*)-226)

(2-*endo*,3-*endo*)-1,7,7-Trimethyl-3-((5-methyl-1-((*R*)1-phenylethyl)-1*H*-pyrrol -2-yl)methylamino)bicyclo[2,2,1]heptan-2-ol ((2-*endo*,3-*endo*,*R*)-**226**) was prepared from *endo*-amino alcohol **224** and 5-methyl-1-((1*R*)-1-phenylethyl)-1*H*-pyrrole-2-carbaldehyde (*R*)-**215** as given procedure above.

The compound (2-*endo*,3-*endo*,*R*)-**226** was obtained in 73% as brown oil. The specific rotation was determined as $[\alpha]_D^{25}$ = -32.17 (c 7.20, $CHCl_3$).

The characterization of the compound (2-*endo*,3-*endo*,*R*)-**226** was performed by ^{1}H-NMR and ^{13}C-NMR spectroscopy.

The ^{1}H-NMR spectrum of the compound (2-*endo*,3-*endo*,*R*)-**226** (Figure 5.50) shows a singlet at 0.79 ppm for methyl proton attached to C(1) on camphor moiety. The singlet at 0.97 ppm is due to the methyl proton attached to C(7). The singlet at 1.00 ppm is for the methyl protons attached to C(7). The multiplet between 1.03 ppm and 1.10 ppm belong to *endo* protons of methylene group of C(5) and C(6). The multiplet between 1.40 ppm and 1.47 ppm is due to *exo*-proton of methylene group attached to C(6). The doublets at 1.58 ppm belongs to brigdehead proton (C(4)). The *exo*- proton of methylene group on C(5) exhibits multiplet between 1.69 ppm and 1.76 ppm. The doublet at 1.94 ppm is due to the methyl protons of ethyl group. The singlet at 1.98 ppm belongs to the methyl protons on pyrrole ring. Two doublets at 2.79 ppm (J=1.36 Hz), and 3.40 ppm (J=1.36 Hz) which belong to methine protons attached to C(3) and C(2), respectively. The one of the diastereotopic methylene proton appears at 3.66 ppm as doublet. The other doublet at 3.79 ppm is due to the other diastereotopic methylene proton. The methine proton of ethyl group exhibits quartet at 5.60 ppm. The doublets of pyrrole ring appear at 5.80 ppm for C(4)*H* and 5.98 ppm for C(3)*H*. The doublet at 7.02 ppm and the multiplet between 7.22 ppm and 7.32 ppm are belong to the phenyl ring.

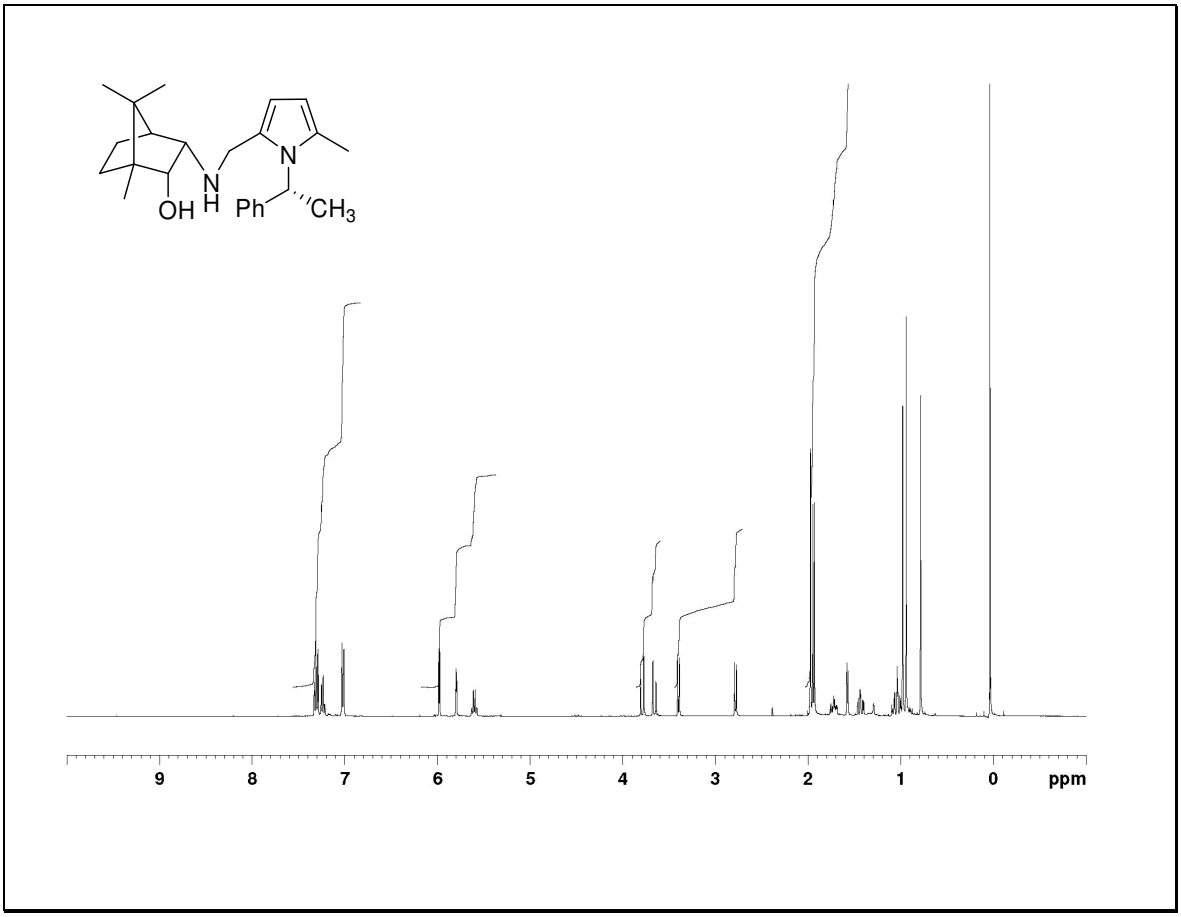


Figure 5.50. The ^{1}H-NMR spectrum of (2-*endo*,3-*endo*)-1,7,7-trimethyl-3-((5-methyl-1-((*R*)1-phenylethyl)-1*H*-pyrrol-2-yl)methylamino)bicyclo[2,2,1]heptan-2-ol ((2-*endo*,3-*endo*,*R*)-**226**)

The ^{13}C-NMR spectrum of (2-*endo*,3-*endo*,*R*)-**226** (Figure 5.51) exhibits signals at 11.40 ppm for the methyl carbon on pyrrole ring, at 14.13 ppm, 19.52 ppm and 21.33 ppm for methyl carbons attached to C(1), C(7), respectively. The methyl carbon of ethyl group on pyrrole nitrogen exhibits a signal at 22.03 ppm. The methylene carbons at C(5) and C(6) appear at 27.29 ppm and 32.99 ppm, respectively. The methylene carbon attached to NH group appears at 46.59 ppm. The signals at 47.53 ppm, 48.83 ppm, 51.56 ppm are due to C(1), C(7) and C(4), respectively. The signal at 52.68 ppm belongs to the methine carbon of the ethyl group on pyrrole nitrogen. The methine carbons attached to C(3) and C(2) exhibit signals at 65.76 ppm and 78.83 ppm, respectively. The pyrrole carbons exhibits signals at 107.35 ppm for C(4), 107.62 ppm for C(5), 129.53 ppm for C(2), 130.53

ppm for C(3). The phenyl carbons appear at 125.88 ppm, 126.93 ppm, 128.50 ppm, 142.42 ppm.

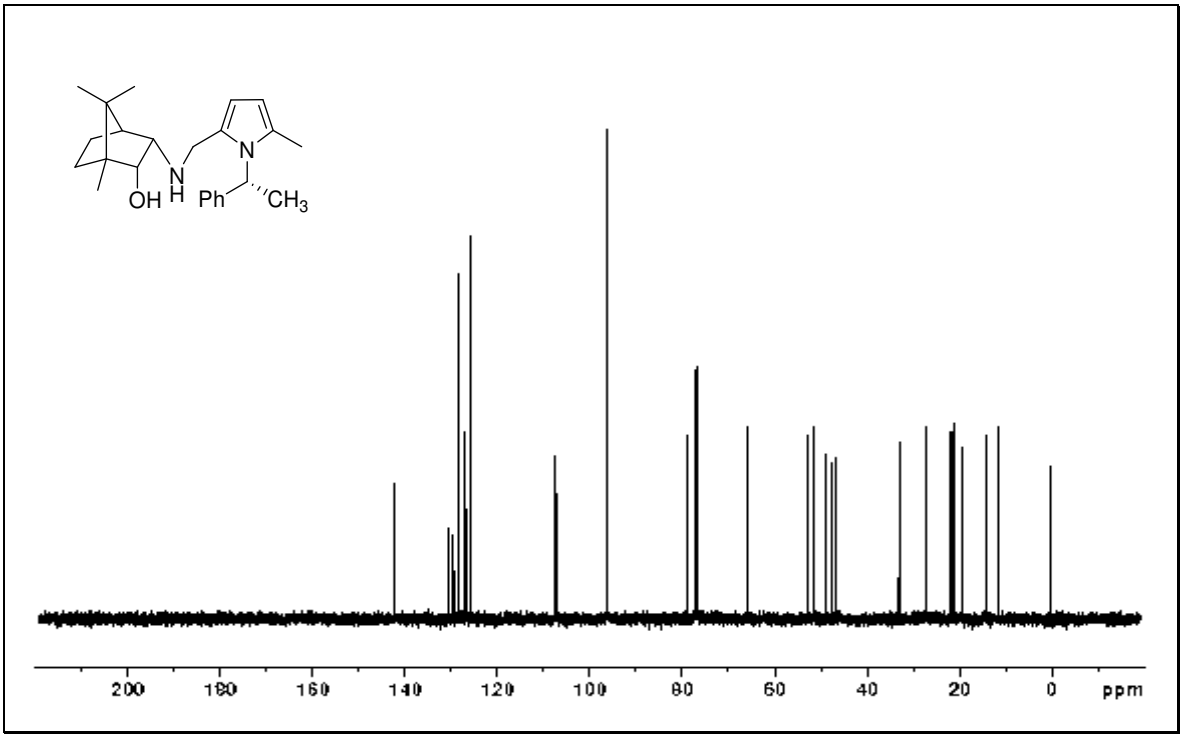


Figure 5.51. The ^{13}C-NMR spectrum of (2-*endo*,3-*endo*)-1,7,7-trimethyl-3-((5-methyl-1-((*R*)1-phenylethyl)-1*H*-pyrrol-2-yl)methylamino)bicyclo[2,2,1]heptan-2-ol ((2-*endo*,3-*endo*,*R*)-**226**)

Under the same reaction conditions, (2-*endo*,3-*endo*)-1,7,7-trimethyl-3-((5-methyl-1-((*S*)1-phenylethyl)-1*H*-pyrrol-2-yl)methylamino)bicyclo[2,2,1]heptan-2-ol ((2-*endo*,3-*endo*,*S*)-**226**) was synthesized from *endo*-3-amino-*endo*-2-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol (**224**) and 5-methyl-1-((1*S*)-1-phenylethyl)-1*H*-pyrrole-2-carbaldehyde ((*S*)-**217**) with 72% yield ($[\alpha]_D^{25}$ = -32.69 (c 6.92, $CHCl_3$)).

The characterization of compound ((2-*endo*,3-*endo*,*S*)-**226**) was performed by ^{1}H-NMR and ^{13}C-NMR spectroscopy.

The ^{1}H-NMR spectrum of (2-*endo*,3-*endo*,*S*)-**226** (Figure 5.52) shows two doublets at 1.47 ppm and 1.84 ppm are due to bridgehead proton (C(4)*H*) and

methyl protons of ethyl group, respectively. The methyl protons on pyrrole ring appear at 1.91 ppm as singlet. Two doublets at 2.68 ppm (*J*=1.42 Hz), and 3.30 ppm (*J*=1.41 Hz) which belong to methine protons attached to C(3)*H* and C(2)*H*, respectively. The one of the diastereotopic methylene proton appears at 3.56 ppm as doublet. The other doublet at 3.69 ppm is due to the other diastereotopic methylene proton.The methine proton of ethyl group exhibits quartet at 5.50 ppm. The doublets of pyrrole ring appear at 5.70 ppm and 5.88 ppm. The doublet at 6.92 ppm and the multiplet between 7.13 ppm and 7.31 ppm are belong to the phenyl ring.

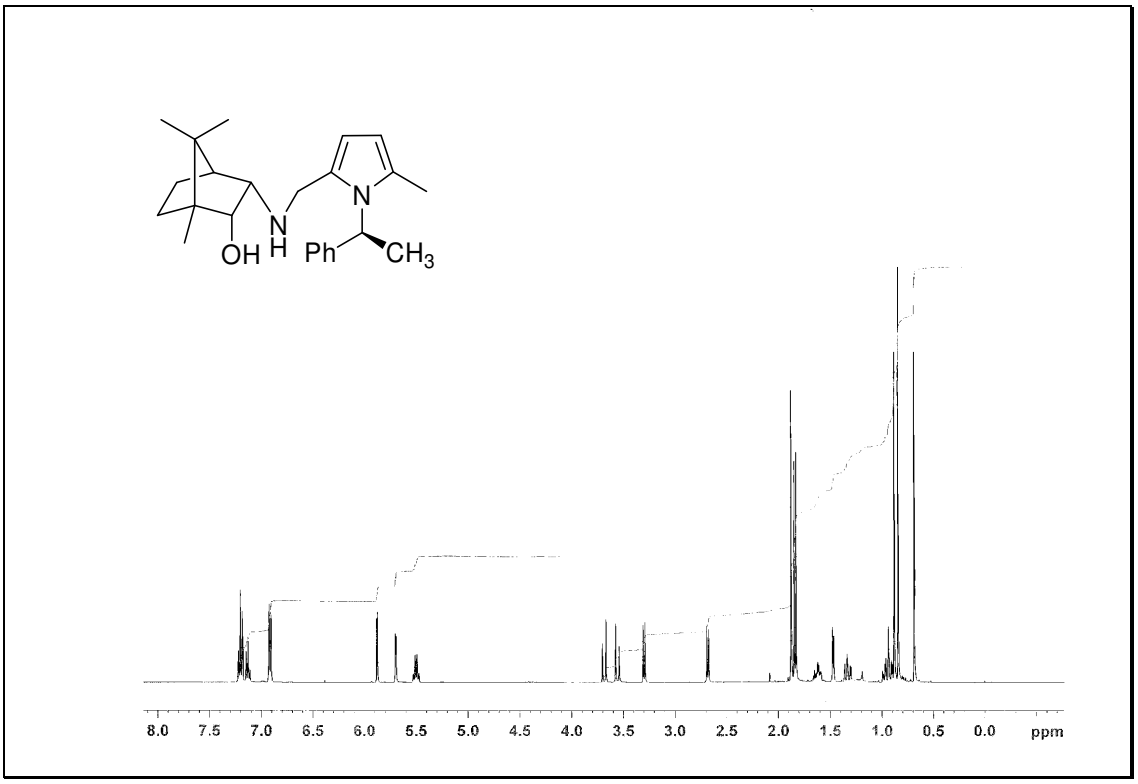


Figure 5.52. The ^{1}H-NMR spectrum of (2-*endo*,3-*endo*)-1,7,7-trimethyl-3-((5-methyl-1-((*S*)1-phenylethyl)-1*H*-pyrrol-2-yl)methylamino)bicyclo[2,2,1]heptan-2-ol ((2-*endo*,3-*endo*,*S*)-**226**)

The ^{13}C-NMR spectrum of ((2-*endo*,3-*endo*,*S*)-**226** (Figure 5.53) exhibits signals at 11.37 ppm for the methyl carbon on pyrrole ring, at 14.11 ppm, 19.51 ppm and 21.31 ppm for methyl carbons attached to C(1), C(7), respectively. The signal at

22.01 ppm belongs to the methyl carbon of ethyl group on pyrrole nitrogen The methylene carbons at C(5) and C(6) appear at 27.28 ppm and 33.00 ppm, respectively. The methylene carbon attached to NH group appears at 46.58 ppm. The signals at 47.52 ppm, 48.83 ppm, 51.56 ppm are due to C(1), C(7) and C(4), respectively. The signal at 52.69 ppm belongs to the methine carbon of the ethyl group on pyrrole nitrogen. The methine carbons attached to C(3) and C(2) exhibit signals at 65.78 ppm and 78.88 ppm, respectively. The pyrrole carbons exhibits signals at 107.33 ppm for C(4), 107.61 ppm for C(5), 129.53 ppm for C(2), 130.56 ppm for C(3). The signals at 125.88 ppm, 126.92 ppm, 128.50 ppm, 142.25 ppm belong to phenyl carbons.

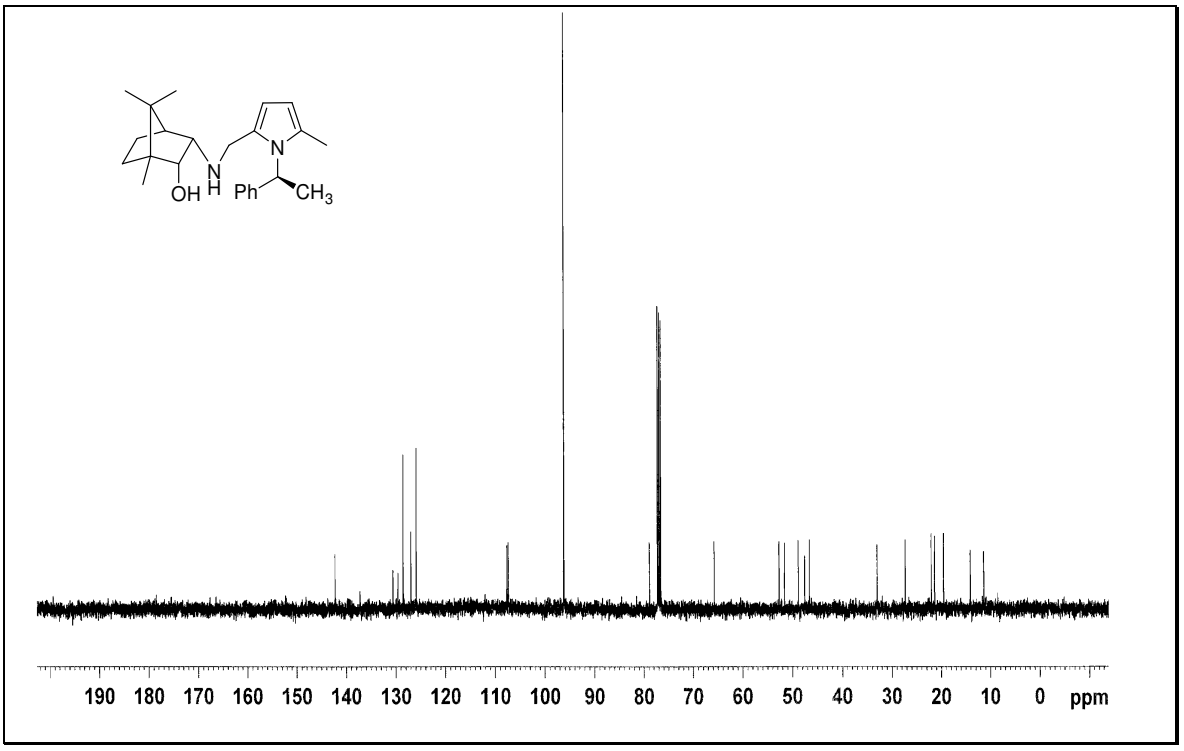
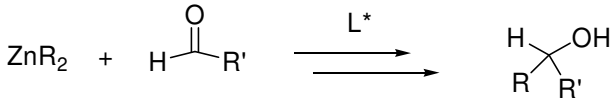


Figure 5.53. The ^{13}C-NMR spectrum of (2-*endo*,3-*endo*)-1,7,7-trimethyl-3-((5-methyl-1-((*S*)1-phenylethyl)-1*H*-pyrrol-2-yl)methylamino)bicyclo[2,2,1]heptan-2-ol ((2-*endo*,3-*endo*,*S*)-**226**)

5.5. Enantioselective Addition of Diethylzinc to Aldehydes

The synthesis of optically active secondary alcohols through the enantioselective addition of organometallic reagents to aldehydes has been widespread use in stereoselective organic synthesis. Among the organometallic reagents, dialkylzincs have received special attention due to the development of chiral catalysts that enable the important of chemoselectivity, activity, and enantioselectivity of the addition. Enantioselective addition of dialkyzinc reagents to aldehydes leads optically active secondary alcohols. These optically active alcohols obtained using chiral catalysts are part of many naturally occuring compounds, biologically active compounds, and materials such as liquid crystals. They are also important as synthetic intermediates of various functionalities such as halide, amine, ester, ether, etc. (Soai et al., 1992). The additions of organozinc reagents to aldehydes in the presence of small amounts of chiral ligands (L*) are among the most succesful catalytic reactions of this type (Scheme 5.15)



Scheme 5.15. The additions of organozinc reagents to aldehydes in the presence of chiral ligands (L*)

Most of the studies have focused on the use of β-amino alcohols as chiral catalysts derived from natural products, such as camphor, α-amino acids and norephedrine, etc. Also several kind of synthetic chiral amino alcohol derivatives have proved to be efficient chiral catalysts and may afford high asymmetric induction in such reactions. Among the various organometallic compounds, diorganozinc acts as an ideal alkyl donor for catalytic asymmetric alkylation. When dimethylzinc or diethylzinc, for instance, is mixed with aldehyde in toluene at or below room temperature, a yellow colorination occurs owing to reversible donor-acceptor complexation. With the enhanchement of nucleophilicity of dialkylzinc and the usage of chiral compounds as catalyst, many important optically active compounds

have been synthesized by the enantioselective addition of organozinc reagents to aldehydes (Noyori and Kitamura, 1991).

Donor atoms such as nitrogen and oxygen of the chiral ligands coordinate the metal atoms of the organometallic reagent to form chiral complexes which differentiate the enantioface of the aldehydes. Majority of the catalysts employed for the reaction are based on amino alcohols. The mechanism of the reaction involves an assembly of the tricoordinated zinc alkoxide, the aldehyde and the diethylzinc as shown in Figure 5.54. It is presumed that diethylzinc coordinates to oxygen atom of the catalyst.

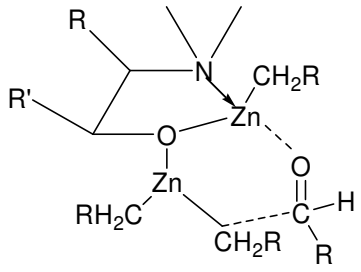


Figure 5. 54. Coordination of ZnR_2 to aldehyde and amino alcohol

In this part of the study, novel norephedrine- and camphor-based ligands with *N*-substituted chiral pyrrole are used as catalysts in the enantioselective addition of diethylzinc to prochiral aldehydes.

5.5.1. The enantioselective addition of diethylzinc to benzaldehyde in the presence novel norephedrine-based ligands with *N*-substituted chiral pyrrole

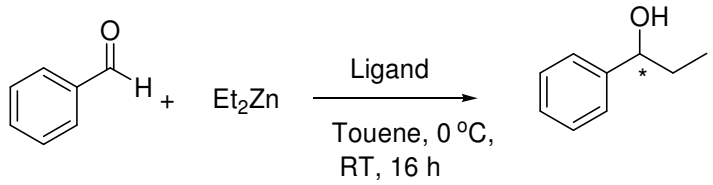
One of the purposes of this study is to examine the catalytical activity of synthesized novel norephedrine- and camphor-based ligands with *N*-substitted chiral pyrrole ligands in the diethylzinc addition reactions to prochiral aldehydes. Since benzaldehyde has been the most extensively studied previously, we chose the enantioselective addition of diethylzinc to benzaldeyhe to examine activity of ligands, so that the result can be easily compared with those from previous studies.

In order to select the most efficient ligand, the addition of diethylzinc to benzaldehyde was performed in dry toluene at 0 °C - room temperature.

After selecting the most efficient ligand, we investigated the effect of a variety of reaction conditions including ligand ratio, solvent, reaction time, temperature and additive.

5.5.1.1.The enantioselective addition of diethylzinc to benzaldehyde in the presence of different ligands

Addition reactions of diethylzinc to benzaldehyde were performed by using the synthesized ligands as catalyst to observe the effect of on enantioselectivity. The enantioselective addition of diethylzinc to benzaldehyde was carried out in the presence of 10 mol and 5 mol% ligands in toluene under argon atmosphere at 0 °C and room temperature (Table 5.1 and 5.2).



Scheme 5.16. The enantioselective addition of diethylzinc to benzaldehyde

When (1*S*,2*R*,*R*)-**219** and (1*R*,2*S*,*S*)-**119** were used as chiral ligand in the addition of diethylzinc to benzaldehyde, the optically active alcohols were obtained with *S* configuration in 53% yield with 51% ee and *R* configuration in 58% yield with 43% ee, respectively.

In the presence of (1*S*,2*R*,*S*)-**220** and (1*R*,2*S*,*R*)-**220**, the optically alcohol was obtained with *S* configuration in 65% yield with 68% ee and *R* configuration in 63% yield with 57% ee, respectively.

Table 5.1. The addition of diethylzinc to benzaldehyde with novel synthesise ligands

		5 mol% ligand		
entry	ligand	yield[a] (%)	ee [b] (%)	conf.
1	(1*S*,2*R*,*R*)-**219**	53	51	*S*
2	(1*R*,2*S*,*S*)-**219**	58	43	*R*
3	(1*S*,2*R*,*S*)-**220**	65	68	*S*
4	(1*R*,2*S*,*R*)-**220**	63	57	*R*
5	(1*S*,2*R*,*S*)-**221**	66	75	*S*
6	(1*R*,2*S*,*R*)-**221**	58	69	*R*
7	(1*R*,2*S*,*S*)-**222**	34	46	*R*
8	(1*S*,2*R*,*R*)-**222**	46	51	*S*

[a] Yields were calculated after column chromatography.

[b] The ee values were determined by HPLC with a Chiralcel OD column;
2% 2-propanol in hexane, flow flow rate:1mL/min, UV detection (254nm)
R_t :17 min. for (*R*) , 19 min. for (*S*).

In the presence of (1*S*,2*R*,*S*)-**221**, *S* alcohol was obtained in 66% yield with 75% ee. Performing the same reaction with (1*R*,2*S*,*R*)-**221** gave *R* alcohol in 58% yield with 69% ee. The use of (1*R*,2*S*,*S*)-**222** (5 mol%) as a chiral ligand afforded optically active secondary alcohol with *S* configuration in 34% yield with 46% ee, whereas the other enantiomer, (1*S*,2*R*,*R*)-**222**, gave the optically active alcohol in *R* configuration in 46% yield with 51% ee.

Since (1*S*,2*R*,*S*)-**220** and (1*S*,2*R*,*S*)-**221** gave the highest enantioselectivity in the enantioselective addition of diethylzinc to benzaldehyde, we used these ligands to determine the optimum reaction condition for addition reaction.

As shown in Table 5.1., the reversal of the enantioselectivity shows that the enantioselectivity is dependent on the configuration of norephedrine. The configuration of substituent on pyrrole nitrogen has no effect on the configuration of the product.

The characterization of the obtained optically active alcohol was achieved by ^{1}H-NMR and ^{13}C-NMR.

The ^{1}H-NMR spectrum of **32** (Figure 5.55) shows a triplet at 0.94 ppm for methyl protons, between 1.71 ppm and 1.85 ppm a multiplet for methylene protons, a broad singlet at 2.12 ppm for hydroxy proton, triplet at 4.56 ppm for methine proton, a multiplet is seen between 7.24 ppm and 7.36 ppm for aromatic protons.

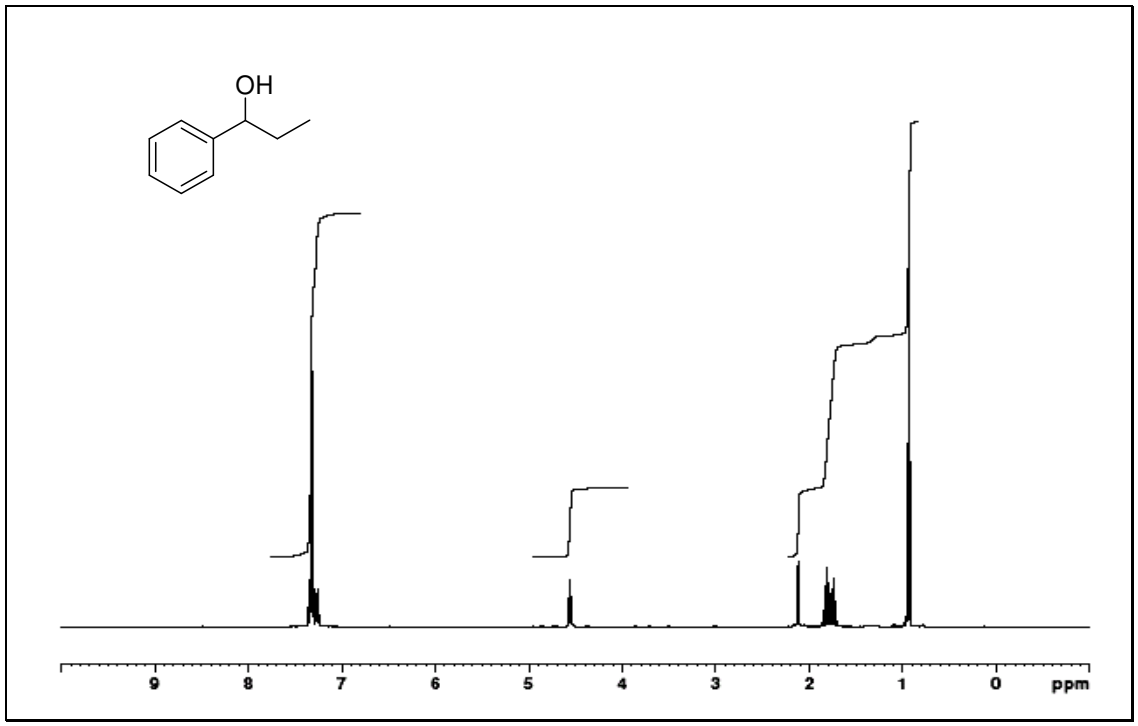


Figure 5.55. The ^{1}H-NMR spectrum of 1-phenyl propanol (**32**)

5.5.1.2. Effect of amount of ligand on the enantioselective diethylzinc addition to benzaldehyde

In order to determine the optimal amount of the ligand for the addition of diethylzinc to benzaldehyde, experiments with variable quantities of (1*S*,2*R*,*S*)-**221** were carried out in dry toluene at 0 °C-room temperature.

When the amount of (1*S*,2*R*,*S*)-**221** was increased from 2.5 to 20 mol% , the enantiomeric excess was decreased to 76% from 41% ee, respectively. Changing the amount of (1*S*,2*R*,*S*)-**221** from 2.5 to 5 mol% had only a small effect on the enantioselectivity. (75%, 76% ee). The results indicated that 5mol % of ligand is the optimum amount for this reaction..

Table 5.2. Effect of amount of ligand on the enantioselective addition reaction.

		(1*S*,2*R*,*S*)-**221**		
entry	mol (%)	yield (%)	ee (%)	conf.
1	2.5	50	76	*S*
2	5	66	75	*S*
3	7.5	83	66	*S*
4	10	85	58	*S*
5	20	85	41	*S*

As shown in Table 5.2, the selectivity of the reaction was highly dependent on the amount of ligand and enantioselectivity was decreased by raising the amount of ligand.

5.5.1.3. Effects of solvents on the enantioselective addition of diethylzinc to benzaldehyde

To study the effect of solvent on enantioselectivity, the addition reactions were performed in various solvents and mixture of solvents, the results of which is summarized in Table 5.3. In the presence of 5 mol% ligand (1*S*,2*R*,*S*)-**220** and (1*S*,2*R*,*S*)-**221**, the highest enantioselectivity were obtained in toluene at 0 °C-room temperature.

Table 5.3. The effect of solvent on the enantioselective addition of diethylzinc to benzaldehyde

		(1*S*,2*R*,*S*)-**220**			(1*S*,2*R*,*S*)-**221**		
entry	Solvent	yield (%)	ee(%)	conf.	yield (%)	ee (%)	conf.
1	toluene	65	68	*S*	66	75	*S*
2	CH_2Cl_2	62	58	*S*	71	72	*S*
3	toluene:CH_2Cl_2	57	62	*S*	41	69	*S*
4	toluene:hexane	72	62	*S*	82	72	*S*
5	toluene:THF	5	4	*S*	5	31	*S*
6	hexane	37	49	*S*	*		

*(1*S*,2*R*,*S*)-**221** was no dissolved in hexane.

The addition reaction in toluene gave the best enantioselectivity.

5.5.1.4. Effect of reaction temperature on the enantioselective addition of diethylzinc to benzaldehyde

(1*S*,2*R*,*S*)-**220** and (1*S*,2*R*,*S*)-**221** were used to investigate the effect of temperature on the enantioselective addition of diethylzinc to benzaldehyde.

As shown in Table 5.5, in the presence 5 mol% (1*S*,2*R*,*S*)-**221,** the similar enantioselectivities (75% and 74% ee) were obtained in dry toluene at 0 °C - room temperature and 0 °C. When the same reaction was performed at -20 °C with (1*S*,2*R*,*S*)-**221** and (1*S*,2*R*,*S*)-**220**, *S* alcohol was obtained in 77% yield with 10% ee and 73% yield with 12% ee, respectively. At -78 °C, addition reaction was not formed.

Table 5.4. The effect of different reaction temperature on the enantioselective addition of diethylzinc to benzaldehyde

		(1*S*,2*R*,*S*)-**220**		(1*S*,2*R*,*S*)-**221**		
entry	T °C	yield (%)	ee (%)	yield (%)	ee (%)	conf.
1	0-RT	65	68	66	75	*S*
2	0	69	65	68	74	*S*
3	-20	73	12	77	10	*S*
4	-78	-	-	-	-	-

5.5.1.5. The effect of the reaction time on the enantioselective addition of diethylzinc to benzaldehyde

The effect of the reaction time on the enantioselective addition of diethylzinc to benzaldehyde was investigated.

Table 5.5. Effect of reaction time on the enantioselective addition of diethylzinc to benzaldehyde

		(1*S*,2*R*,*S*)-**220**		(1*S*,2*R*,*S*)-**221**		
entry	time (h)	yield(%)	ee(%)	yield(%)	ee(%)	conf.
1	6	69	42	72	48	*S*
2	16	65	68	66	75	*S*
3	48	72	61	70	71	*S*
4	72	74	55	76	59	*S*

The enantioselectivity decreased with increasing reaction time from 16 to 72 hours. The 1,2-addition product after 16 hours was obtained with 68% and 75% ee, using (1*S*,2*R*,*S*)-**220** and (1*S*,2*R*,*S*)-**221**, respectively. After 48 hours, enantiomeric excesses were only 61% and 71%. The higher conversion was obtained after 72 hours, but enantioselectivity decreased.

5.5.2. The optimum reaction condition for the enantioselective addition to benzaldehyde

For determination of the optimum conditions on the enantioselective addition of diethylzinc to benzaldehyde, several common factors such as structure of ligand, ligand ratio, solvent, reaction temperature, time which are known to affect to enantioselectivity of the catalyst system have been examined.

The optimum reaction conditions are .

The high enantiomeric excesses were obtained with 5 mol % of (1*S*,2*R*,*S*)-**220** and (1*S*,2*R*,*S*)-**221**.

Toluene was determined as a suitable solvent for this reaction.

The optimum reaction temperature range was 0 °C -room temperature.

The optimum reaction time was determined as 16 hours.

5.5.3. The enantioselective addition of diethylzinc to benzaldehyde in the presence of Ti(O-*i*-Pr)$_4$ and additives

It is reported that the chiral catalyst in the presence of Ti(O-*i*-Pr)$_4$ has an enhancement effect on enantioselectvity (Wu, et al., 2003). For this reason, a series of experiments have been performed by using different Ti(O-*i*-Pr)$_4$/ligand ratios. The reactions were carried out in dry toluene at 0 °C-room temperature in the presence (1*S*,2*R*,*S*)-**220** and (1*S*,2*R*,*S*)-**221**.

As shown in Table 5.6, the enantioselectivity decreased in the presence of different Ti(O-*i*-Pr)$_4$/ligand ratio. When diethylzinc addition to benzaldehyde was achieved in the absence of Ti(O-*i*-Pr)$_4$, *S* alcohol was formed with 68% and 75% ee by using (1*S*,2*R*,*S*)-**220** and (1*S*,2*R*,*S*)-**221**, respectively.

The enantioselective diethylzinc addition to benzaldehyde under the same reaction condition was carried out with BuLi, LiCl, a mixture of BuLi and LiCl. When LiCl

was used as additive in the presence of (1*S*,2*R*,*S*)-**220** and (1*S*,2*R*,*S*)-**221**, *S* alcohol was obtained with 61% and 70% ee, respectively. In the presence of BuLi as additive, *S* alcohol was obtained with 57% ee with (1*S*,2*R*,*S*)-**220** and 64% ee with (1*S*,2*R*,*S*)-**221**. When a mixture of BuLi and LiCl was used as additive, S alcohol was formed with 60% ee with (1*S*,2*R*,*S*)-**221**, and with 51% ee with (1*S*,2*R*,*S*)-**220**.

The results in Table 5.6 show that of the enantioselective addition to benzaldehyde in the presence of Ti(O-*i*-Pr)$_4$, and with additives as BuLi, LiCl are not effective in the increase of enantioselectivity.

Table 5.6. Enantioselective addition of diethylzinc to benzaldehyde catalysed by Ti(O-*i*- Pr)$_4$ / Ligand system and ligands with additive.

entry	ligand	Ti(O-*i*Pr)$_4$/Ligand	Additive	yield (%)	ee (%)	conf.
1	(1*S*,2*R*,*S*)-**220**	5	-	70	58	S
2	(1*S*,2*R*,*S*)-**220**	15	-	73	52	S
3	(1*S*,2*R*,*S*)-**220**	100	-	76	43	S
4	(1*S*,2*R*,*S*)-**220**	-	LiCl	40	61	*S*
5	(1*S*,2*R*,*S*)-**220**	-	BuLi	92	57	*S*
6	(1*S*,2*R*,*S*)-**220**	-	(LiCl+BuLi)	82	51	*S*
7	(1*S*,2*R*,*S*)-**221**	5	-	74	62	S
8	(1*S*,2*R*,*S*)-**221**	15	-	75	56	*S*
9	(1*S*,2*R*,*S*)-**221**	100	-	78	48	*S*
10	(1*S*,2*R*,*S*)-**221**	-	LiCl	65	70	*S*
11	(1*S*,2*R*,*S*)-**221**	-	BuLi	98	64	*S*
12	(1*S*,2*R*,*S*)-**221**	-	(LiCl+BuLi)	96	60	*S*

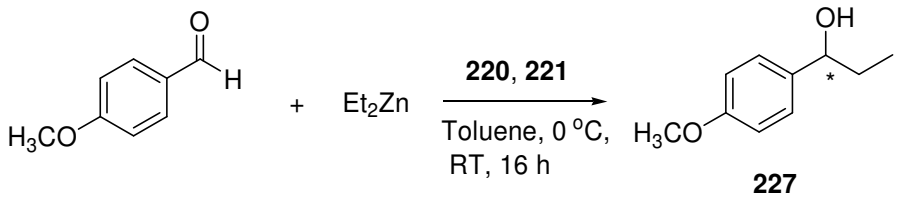
5.5.4. The enantioselective addition of diethylzinc to substituted aromatic aldehydes

The effect of the electron donating and electron withdrawing groups at the *ortho*-, *meta*-, *para*- positions of the benzaldehyde on the outcome of the enantioselective diethylzinc addition reaction was also investigated. The enantiomeric excess and absolute configuration of the alcohol were determined by HPLC analysis and comparing the given results in the literature.

5.5.4.1. Enantioselective addition of diethylzinc to *p*-methoxybenzaldehyde

In order to investigate the effect of *p*-substituent on benzene ring of aldehydes, *p*-methoxy benzaldehyde was chosen.

Alkylation of *p*-methoxy benzaldehyde in the presence of 5 mol% (1*S*,2*R*,*S*)-**220** and (1*S*,2*R*,*S*)-**221** (Scheme 5.16) gave (*S*)-1-(*p*-methoxyphenyl)propanol in 32% yield with 26% ee and in 30% yield with 38% ee, respectively (Scheme 5.17).



Scheme 5.17. The enantioselective addition of diethylzinc to *p*-methoxy benzaldehyde

The characterization of the product was done by ^{1}H-NMR spectroscopy (Figure 5.56). The spectrum of **227** shows a triplet at 0.87 ppm for methyl protons, a multiplet between 1.63 ppm and 1.80 ppm for methylene protons, a broad singlet at 1.90 ppm for hydroxyl proton, a singlet at 3.77 ppm for methoxy protons, triplet at 4.47 ppm for methine proton, The aromatic protons appears at 6.81 ppm and 7.19 ppm as doublets.

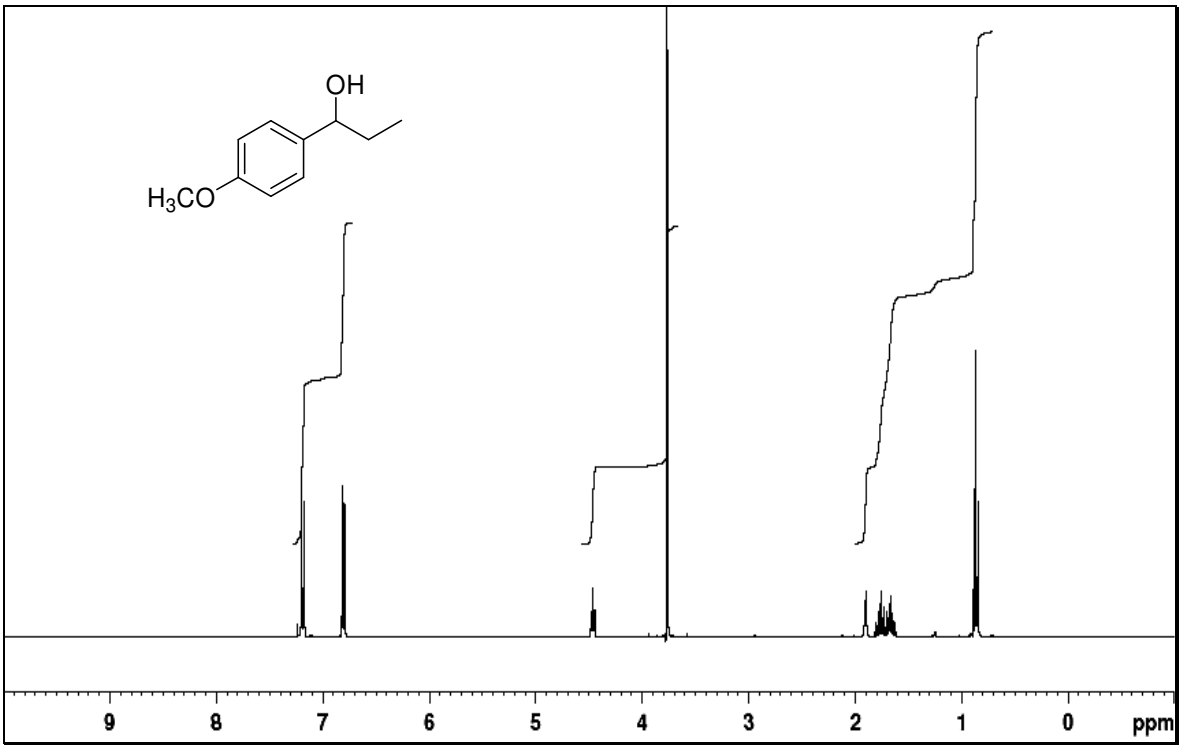
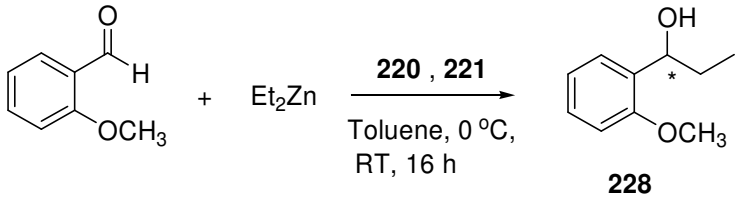


Figure 5.56. The ^{1}H-NMR spectrum of 1-(*p*-methoxyphenyl)propanol (**227**)

5.5.4.2. Enantioselective addition of diethylzinc to *o*-methoxybenzaldehyde

The effect of the electron donating group at the *ortho*- position on the chemical yield and enantioselectivity of the reaction was examined with *o*-methoxy benzaldehyde.

Under the optimum reaction condition, 1-(*o*-methoxyphenyl)propanol was obtained in 74% yield with 50% ee and in 67% yield with 48% ee in the presence of (1*S*,2*R*,*S*)-**220** and (1*S*,2*R*,*S*)-**221**, respectively (Scheme 5.18).



228

Scheme 5.18. The enantioselective addition of diethylzinc to *o*-methoxy benzaldehyde

The product **228** was characterizated by ^{1}H-NMR spectrum which is shown in Figure 5.57.

The ^{1}H-NMR spectrum of **228** shows a triplet at 0.94 ppm for methyl protons, a multiplet 1.71 ppm and 1.85 ppm for methylene protons, a broad singlet at 2.53 ppm for hydroxyl proton, a singlet at 3.83 ppm for metoxy protons, a triplet at 4.76 ppm for methine proton. The two doublet at 6.82 ppm and 7.27 ppm , the multiplets between 6.89-6.93 ppm, 7.16-7.20 ppm which belong to aromatic protons.

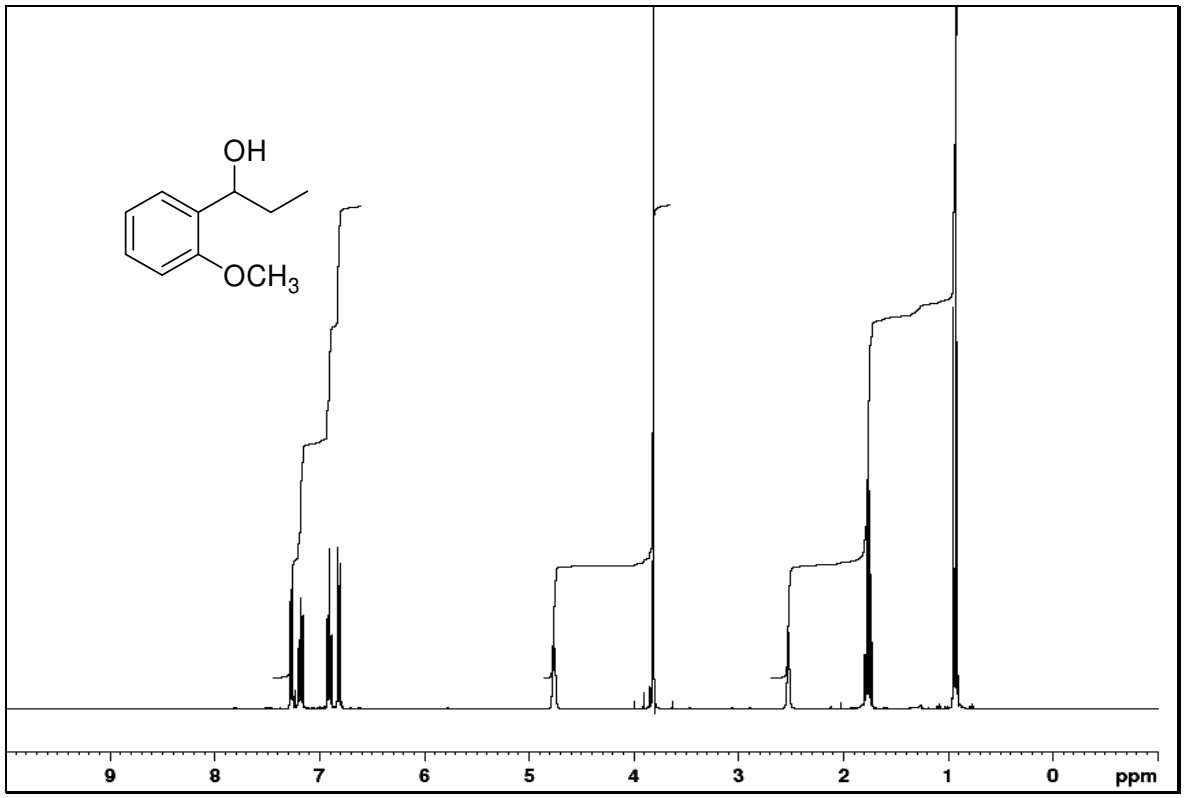


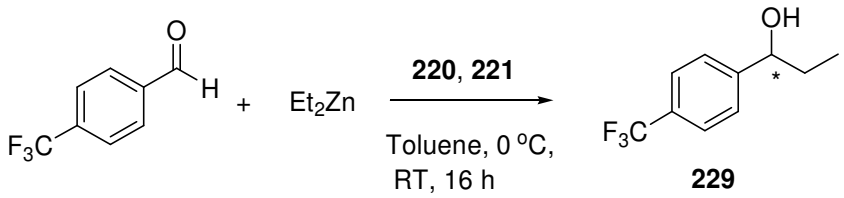
Figure 5.57. The ^{1}H-NMR spectrum of 1-(*o*-methoxyphenyl)propanol (**228**)

The results show that electron donating substitutents decrease the enantioselectivity.

5.5.4.3. Enantioselective addition of diethylzinc to *p*-trifluoromethylbenzaldehyde

The effect of the electron withdrawing group on the chemical yield and enantiomeric excess of the reaction was examined with *p*-trifluoromethylbenzaldehyde.

Addition of diethylzinc to *p*-trifluoromethylbenzaldehyde was performed by using (1*S*,2*R*,*S*)-**220** and (1*S*,2*R*,*S*)-**221** and the highest enantioselectivity was obtained with *R* configuration in 88% ee and 83% ee, respectively (Scheme 5.19).



Scheme 5.19. The enantioselective addition of diethylzinc to *p*-trifluoromethylbenzaldehyde

Identification of **229** was performed by ^{1}H-NMR spectroscopy (Figure 5.58).

Expected signals for methyl protons were observed at 0.96 ppm as a triplet, the methylene proton between 1.73 ppm and 1.85 ppm as a multiplet, hydroxyl proton at 1.99 ppm as a broad singlet, methine proton at 4.67 ppm as a triplet The aromatic protons appears at 7.46 ppm and 7.62 ppm as doublets.

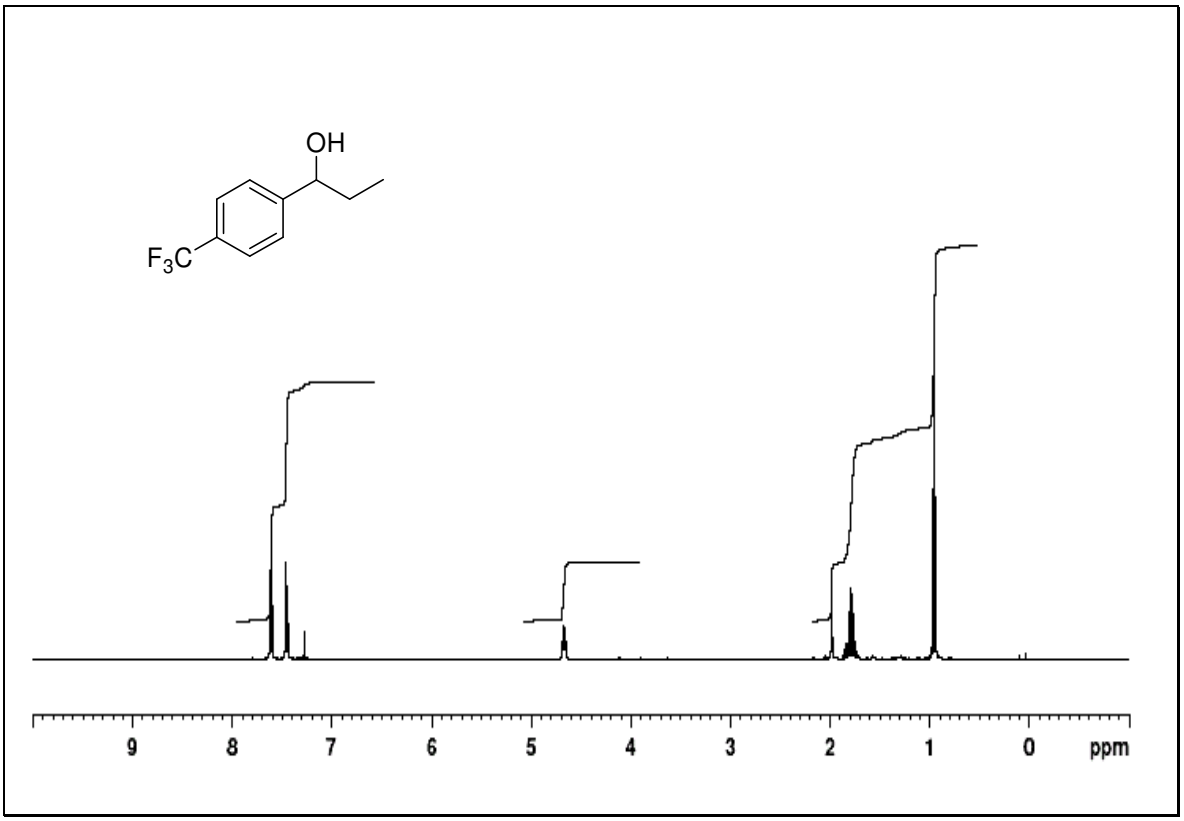
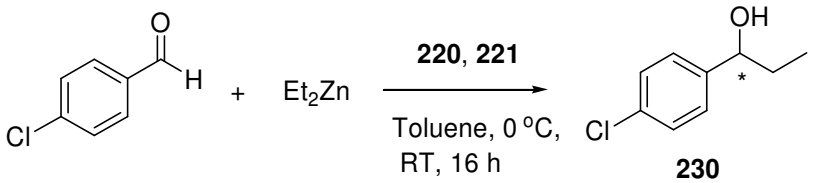


Figure 5.58. The ^{1}H-NMR spectrum of 1-(*p*-trifluromethylphenyl)propanol (**229**)

5.5.4.4. Enantioselective addition of diethylzinc to *p*-chlorobenzaldehyde

In the presence of (1*S*,2*R*,*S*)-**220** and (1*S*,2*R*,*S*)-**221**, the enantioselective addition to *p*-chloro benzaldehyde was afforded 1-(*p*-chlorophenyl)propanol **230** with 48% ee and 72% ee, respectively (Scheme 5.20).



Scheme 5.20. The enantioselective addition of diethylzinc to *p*-chloro benzaldehyde

The characterization of the product was done by ^{1}H-NMR spectroscopy (Figure 5.59).

The ^{1}H-NMR spectrum of **230** shows a triplet at 0.91 ppm for methyl protons, a multiplet between 1.60 and 1.83 ppm for methylene protons, a broad singlet at 2.21 for hydroxyl proton, triplet at 4.54 ppm, for methine proton. Two doublets at 7.24 ppm and 7.30 ppm which belong to aromatic protons.

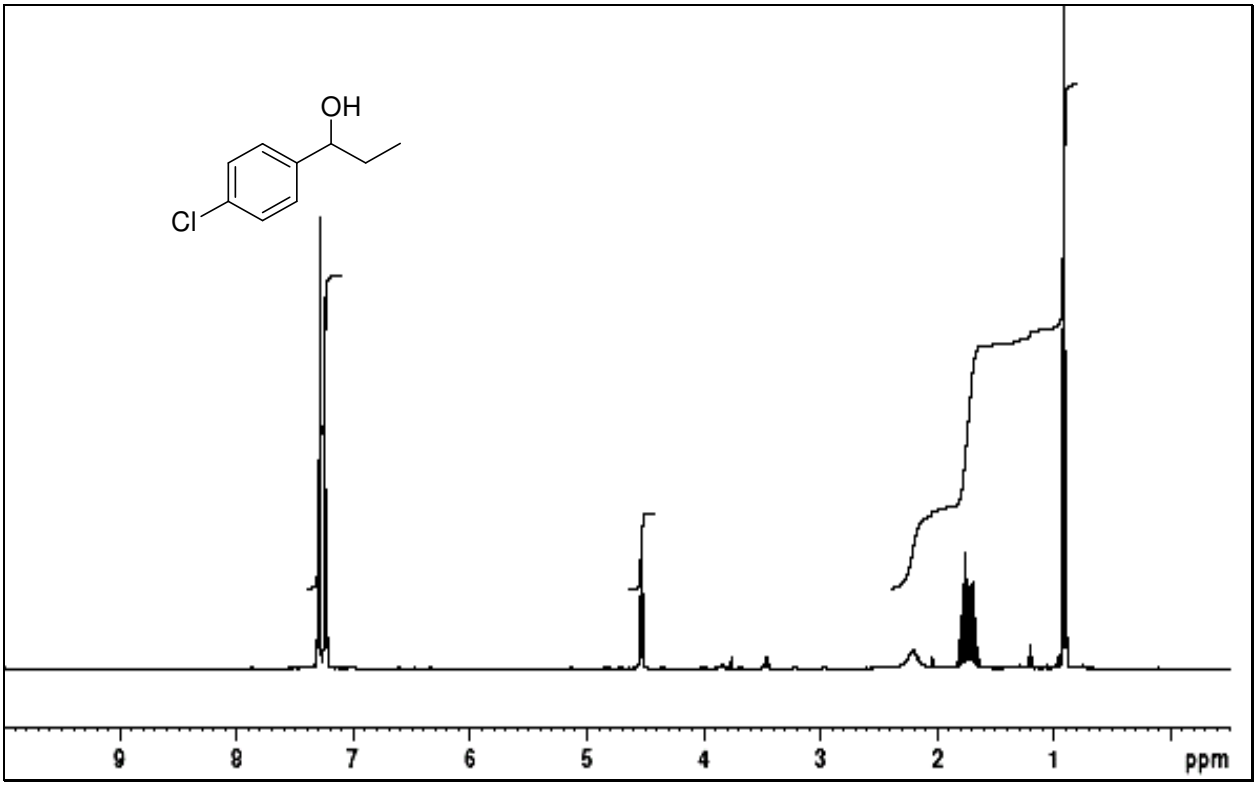


Figure 5.59. The ^{1}H-NMR spectrum of 1-(*p*-chlorophenyl)propanol (**230**)

The results are summarized in Table 5.7.

Table 5.7. The diethylzinc addition to various substituted aromatic aldehyde with chiral ligand (1*S*,2*R*,*S*)-**221** and (1*S*,2*R*,*S*)-**220** in toluene

entry	ligand	aldehyde	time(h)	yield[a] (%)	ee[b] (%)	conf.
1	(1*S*,2*R*,*S*)-**220**	benzaldehyde	16	65	68	*S*
2	(1*S*,2*R*,*S*)-**220**	*p*-methoxybenzaldehyde	16	32[c]	26	*S*
3	(1*S*,2*R*,*S*)-**220**	*o*-methoxybenzaldehyde	16	74[d]	50	*S*
4	(1*S*,2*R*,*S*)-**220**	*p*-chlorobenzaldehyde	16	76[e]	48	*S*
5	(1*S*,2*R*,*S*)-**220**	*p*-trifluoromethylbenzaldehyde	16	75[f]	88	*R*
6	(1*S*,2*R*,*S*)-**221**	benzaldehyde	16	70	75	*S*
7	(1*S*,2*R*,*S*)-**221**	*p*-methoxybenzaldehyde	20	30	38	*S*
8	(1*S*,2*R*,*S*)-**221**	*o*-methoxybenzaldehyde	8	67	48	*S*
9	(1*S*,2*R*,*S*)-**221**	*p*-chlorobenzaldehyde	16	98	72	*S*
10	(1*S*,2*R*,*S*)-**221**	*p*-trifluoromethylbenzaldehyde	16	72	83	*R*

[a] Yields were calculated after column chromatography.

[b] The ee values were determined by HPLC with a Chiracel OD column.

[c] 3% 2-propanol in hexane, flow flow rate:1 mL/min, UV detection (254nm) R_t: 35 min. for (*R*) , 39 min for (*S*).

[d] 2% 2-propanol in hexane, flow flow rate:1 mL/min, UV detection (254nm) R_t: 28 min. for (*S*), 39 min for (*R*).

[e] 3% 2-propanol in hexane, flow flow rate:0.5 mL/min, UV detection (254nm) R_t: 23 min. for (*S*), 25 min for (*R*).

[f] 5% 2-propanol in hexane, flow flow rate:0.8 mL/min, UV detection (254nm) R_t: 9.11 min. for (*S*), 10.92 min for (*R*).

p-Methoxybenzaldehyde and *o*-methoxybenzaldehyde gave low enantioselectivity of 26% and 50%, by using (1*S*,2*R*,*S*)-**220** and (1*S*,2*R*,*S*)-**221**, respectively. *p*-Trifluoromethylbenzaldehyde gave the highest enantioselectivity. 1-(*p*-Chlorophenyl)propanol (**230**) was obtained with 48% and 72% ee by using (1*S*,2*R*,*S*)-**220** and (1*S*,2*R*,*S*)-**221**, respectively.

As can be seen from Table 5.7, electron donating substituents led to a decrease in enantioselectivity while electron with-drawing substituents led to an increase.

5.6. The Mechanism of Enantioselective Addition of Diethylzinc to Aldehydes in the Presence of the Ligand

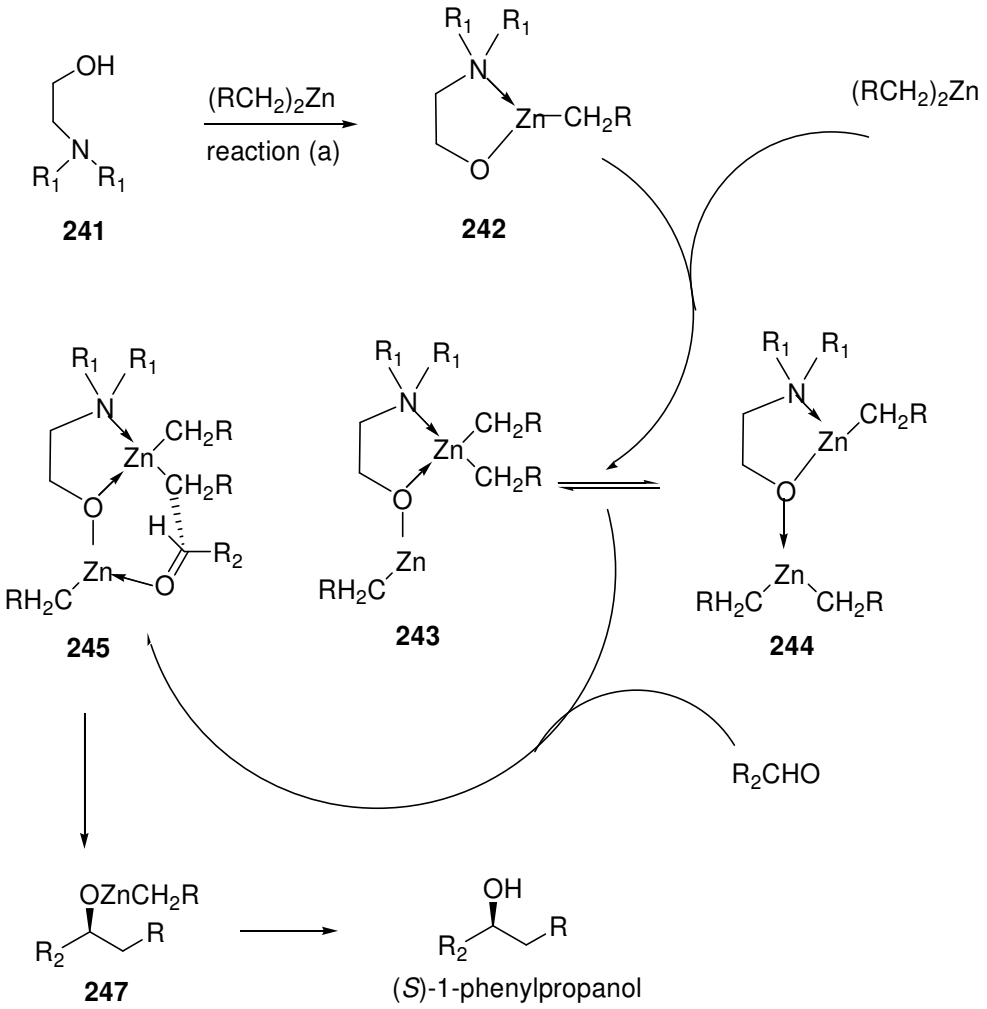
The enantioselective addition of diethylzinc reagents to aldehydes catalysed by chiral ligands has received widespread attention because it is an efficient method for generating optically active secondary alcohols.

The reason for the high reactivity of organozinc reagents in the presence of chiral ligands such as amino alcohols may be explained as follows. Monomeric dialkylzinc with sp-hybridised linear geometry at zinc are inert to carbonyl compounds because the alkyl-metal bond are rather nonpolar. However, the bond polarity can be enhanced by creating a bent geometry in which the zinc atom uses molecular orbitals of a higher p character. In particular, coordinatively unsaturated bent compounds with an electronegative substituent such as alkyl, N, O, halogen, bearing the high donor ability of the alkyl group R and an acceptor character at zinc center (Soai et al., 1992). In this way, the nucleophilicity of the alkyl group increases and the addition becomes possible.

The mechanism by which amino alcohols catalyse asymmetric addition of diethylzinc reaction has been discussed by Noyori (1991) and the accepted mechanism is outlined in Scheme 5.21. Essentially amino alcohol first react with diethylzinc, reaction (a), to generate the catalyst **242**. The zinc centre in the catalyst **242** behaves as a Lewis acid and binds to a lone pair on the oxygen atom of the carbonyl group, thus activating the latter to nucleophilic attack. A second molecule of diethylzinc binds to a lone pair of oxygen atom in the catalyst **242**, thus enhancing the nucleophilic properties of the ethyl groups. It is believed that it is the alkyl group of the dialkylzinc and not that of the alkoxy ethylzinc that adds to aldehydes.

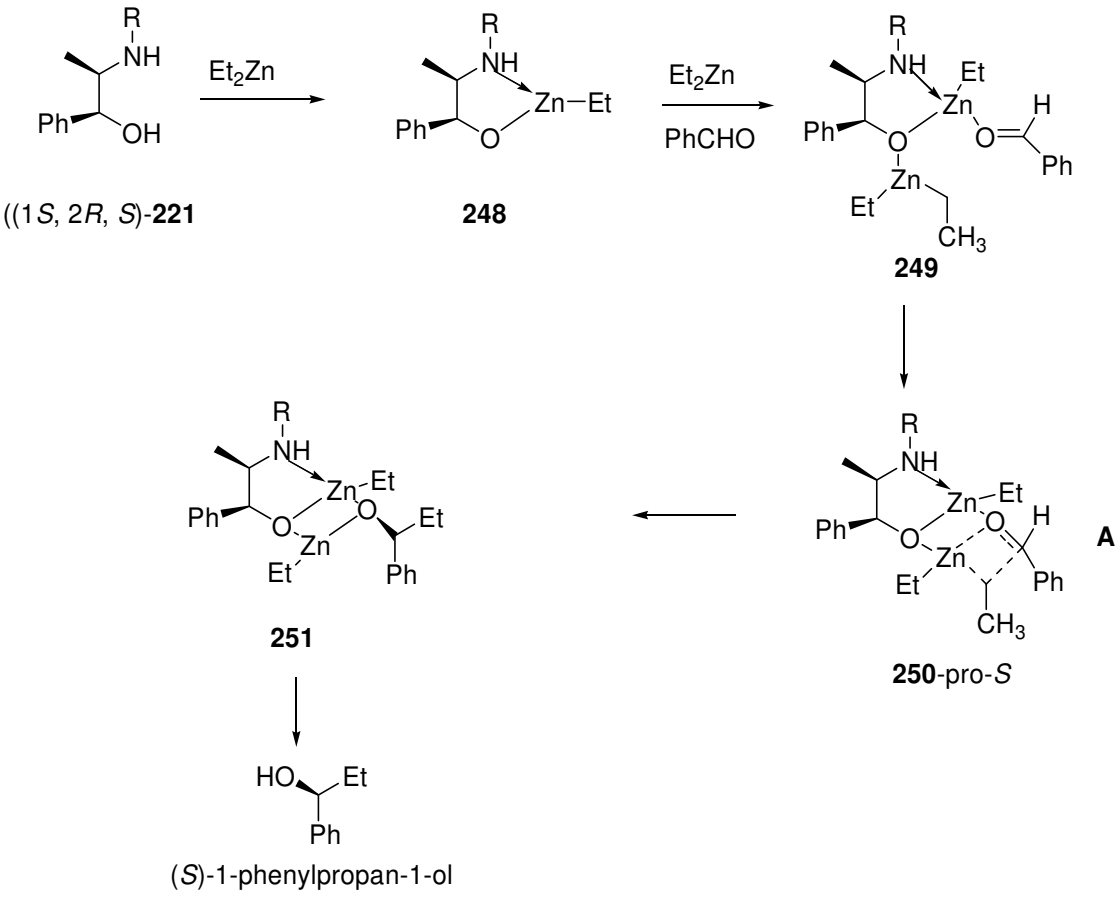
Benzaldehyde coordinates to the face of complex **243** in two ways: *anti* (the two unrecating ethyl groups on zinc atoms are *anti)* or *syn* (the two unrecating ethyl groups are *syn*) and ethyl migrates to the *re*-face or *si*-face. The amino alcohols attacking directly the *si*-face leading the (*S*)-1-phenylpropanol, and amino alcohols attack directly to the *re*-face leading the (*R*)-1-phenylpropanol. As shown in

Scheme 5.21, the benzaldehyde is attacked at the *si*-face via a six-center transitation (**245**) to afford chiral alkylzinc alkoxide **247**.



Scheme 5.21. Mechanism proposed by Noyori for the addition of dialkylzinc compounds to aldehydes in the presence of amino alcohol

The proposed mechanism for (1*S*,2*R*,*S*)-**221** in Scheme 5.22 is based on the Noyori dinuclear zinc complexes. Transition state structure **A**, which leads to the formation of the *S* enantiomer, is favored, because it avoids axial positioning of the aldehyde phenyl group and any destabilizing interaction with the ethyl group attached to the zinc atom.



Scheme 5.22. The suggested mechanism for the addition of diethylzinc to benzaldehyde in the presence of (1*S*,2*R*,*S*)-**221**.

5.7. The Enantioselective Conjugate Addition of Diethylzinc to Chalcone in the Presence Chiral Ligands

Conjugate addition reactions of carbon nucleophiles to α,β-unsaturated compounds are among the most widely used methods for carbon-carbon bond formation in organic synthesis.

Enantioselective carbon-carbon formation using organozinc reagents has become one of the most successful areas of asymmetric synthesis in the last two decades (Soai et al., 1992 and Rossiter et al., 1992). Although dialkylzinc reagent react extremely sluggish with carbonyl compounds, effective catalysis has been achieved by several ligands and transition metal complexes.

Several catalytic conjugate addition of diethylzinc to acyclic enone employing chiral nickel complexes have been developed. A variety of chiral ligand have subsequently been used in nickel-catalyzed conjugate addition; these include chiral (bi)pyridines, amino alcohols, β-hydroxysulfoximines, proline amides, arene-chromium amino alcohols, thiazolidin-4-ones and diamines.

5.7.1. The enantioselective conjugate addition of diethylzinc to chalcone in the presence of norephedrine-based ligands with *N*-substituted chiral pyrrole

In this part of the work, the performance of the synthesized chiral ligands were tested in the enantioselective addition of diethylzinc to chalcone.

Firstly, we examined the enantioselective conjugate addition of diethylzinc to chalcone to find the most efficient ligand. According to the procedure of Bolm (1992), a solution of 1 mol% ($Ni(acac)_2$) and 20 mol% chiral ligand in 5 mL acetonitrile was heated at reflux under Argon atmosphere for 1 hour, and chalcone was added at room temperature followed by diethylzinc at -30 °C. The product (1,3-diphenylpentan-1-one) **186** was isolated by flash column chromatography and enantiomeric excess was determined by HPLC analysis.

After determining the most efficient ligand, the effect of different reaction parameters such as reaction temperature, reaction time, solvent, amount of ligand, different nickel-to-ligand ratio were investigated.

5.7.1.1. Enantioselective conjugate addition of diethylzinc to chalcone in the presence of different ligands

The enantioselective conjugate addition of diethylzinc to chalcone was performed by using synthesized novel chiral ligands to find the most efficient ligand. The reaction was carried out according to given procedure above.

The results are summarized in Table 5.8. (1*S*,2*R*,*R*)-**222** and (1*R*,2*S*,*R*)-**220** gave in 70% yield with 53% ee and 72% yield with 49% ee, respectively. The compound **186** was obtained in 80% yield with 42% ee.

(1*R*,2*S*,*R*)-**221** and (1*S*,2*R*,*S*)-**221** showed low enantioselectivity as 36% and 32% ee, respectively. The use of (1*S*,2*R*,*R*)-**219** and (1*R*,2*S*,*S*)-**219** as chiral ligand afforded **186** in 83% yield with 26% ee and 81% yield with 28% ee, respectively. When (1*S*,2*R*,*S*)-**220** was used as chiral ligand, **186** was obtained with 36% ee.

Table 5.8. The enantioselective conjugate addition to chalcone with novel chiral ligands

entry	ligand	yield[a] (%)	ee[b] (%)	conf.
1	(1*S*,2*R*,*R*)-**222**	70	53[c]	*R*
2	(1*R*,2*S*,*S*)-**222**	80	42[c]	*S*
3	(1*R*,2*S*,*R*)-**221**	93	36[c]	*S*
4	(1*S*,2*R*,*S*)-**221**	60	32[c]	*R*
5	(1*S*,2*R*,*S*)-**220**	79	36[d]	*R*
6	(1*R*,2*S*,*R*)-**220**	72	49[d]	*S*
7	(1*S*,2*R*,*R*)-**219**	83	26[d]	*R*
8	(1*R*,2*S*,*S*)-**219**	81	28[d]	*S*

[a] Yields were calculated after column chromatography.

[b] The ee values were determined by HPLC.

[c] Chiralcell OD column eluted with n-hexane:2-propanol (99.5:0.5) at 1 mL/min using UV detection (254 nm), R_t:14.11 min. for (*S*) , 15.35 min. for (*R*)

[d] Chiralcell AD column eluted with n-hexane:2-propanol (99:1) at 1 mL/min using UV detection (254nm), R_t:14.51 min for (*S*) , 17.82 min for (*R*).

The best result was obtained with (1*S*,2*R*,*R*)-**222**. This ligand was used to determine the optimum reaction conditions.

The results in Table 5.9 show that the enantioselectivity is dependent on the configuration of the norephedrine moiety and the configuration of substituent on pyrrole nitrogen has no effect on configuration of 1,3-diphenylpentan-2-one.

The characterization of 1,3-diphenylpentan-1-one (**186**) was performed by ^{1}H-NMR.

The ^{1}H-NMR spectrum of **186** (Figure 5.60) shows a triplet at 0.85 ppm for methyl protons, two multiplet between 1.67 -1.71 ppm and 1.80-1.83 ppm for methylene protons (C(4)*H*. The methine and methylene protons appear between 3.22 and 3.30 ppm as multiplet. The phenyl protons can be seen between 7.18-7.29 ppm (alkyl substituted phenyl), 7.43-7.45 ppm, 7.52-7.7.55 and 7.90-7.92 ppm (carbonyl substitted phenyl) as multiplets.

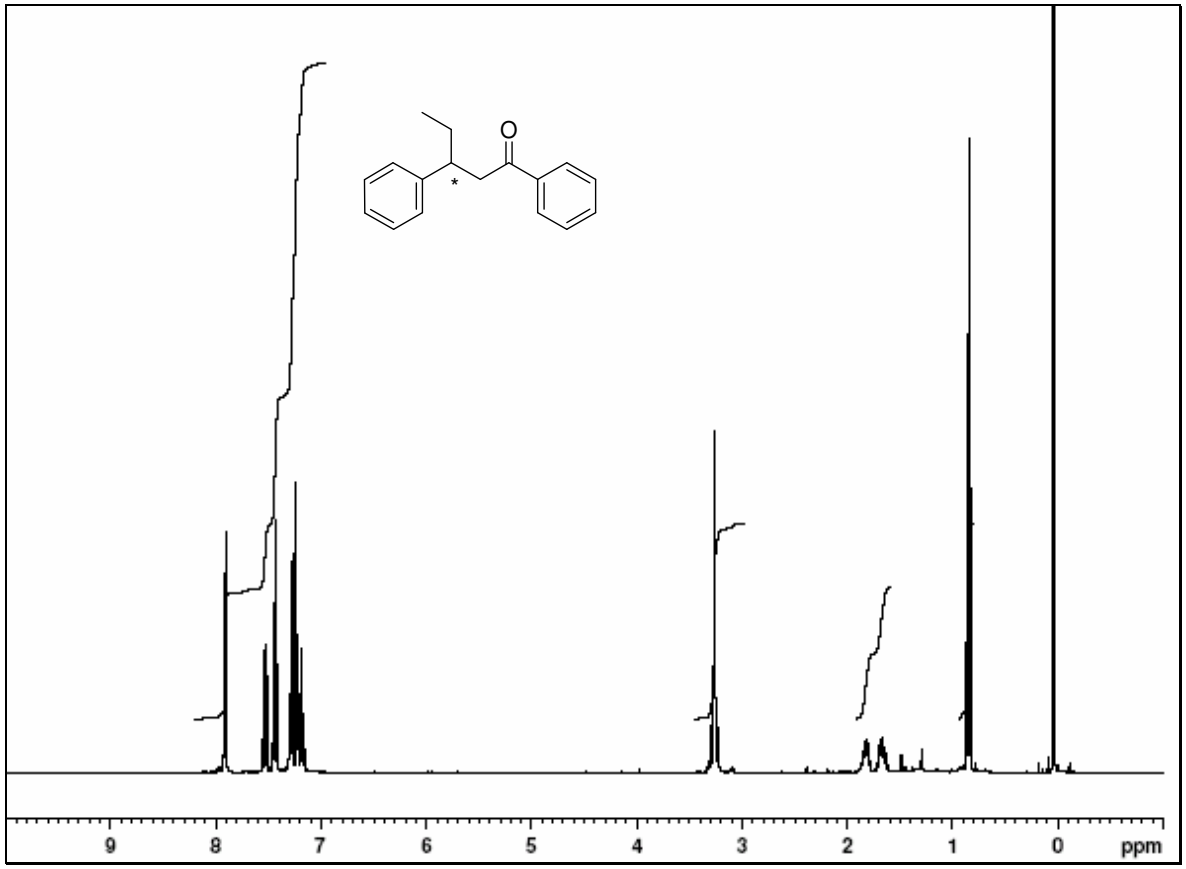


Figure 5.60. The ^{1}H-NMR spectrum of 1,3-diphenylpentan-1-one (**186**)

5.7.1.2. The effect of reaction temperature and time on the enantioselective addition of diethylzinc to chalcone

In order determine the optimum reaction temperature, the reaction was carried out at different temperature by using 1 mol% $Ni(acac)_2$ and 20 mol% (1*S*,2*R*,*R*)-**222** in dry acetonitrile.

High enantioselectivity was obtained at -30 °C and -45 °C. Reducing the reaction temperature -30 °C to -45 °C did not significantly affect enantioselectivity. If reaction was performed at 0 °C, the product was obtained with 11% ee. At -78 °C, no product was observed under same reaction conditions. The highest enantioselectivty was obtained at -30 °C for 6 hours (Table 5.9).

Table 5.9. Effect of different reaction temperature and time on the enantiomeric excess of 1,3-diphenyl-1-pentanone (**186**)

Entry	ligand	T (°c)	time (h)	yield (%)	ee (%)	conf.
1	(1*S*,2*R*,*R*)-**222**	0	6	70	11	*R*
2	(1*S*,2*R*,*R*)-**222**	-30	6	70	53	*R*
3	(1*S*,2*R*,*R*)-**222**	-45	6	76	52	*R*
4	(1*S*,2*R*,*R*)-**222**	-30	24	65	47	*R*

5.7.1.3. The effect of solvent on the enantioselective addition of diethylzinc to chalcone

To determine the effect of solvent on the enantioselectivty, the enantioselective conjugate addition of diethylzinc to chalcone was performed in various solvent and a mixture of solvents. In the presence of 1 mol% $Ni(acac)_2$ and 20 mol% (1*S*,2*R*,*R*)-**222**, the high enantioselectivity was obtained in acetonitrile at -30 °C.

The results was summarized at Table 5.10.

Table 5.10. Effect of solvent on the enantiomeric excess of 1,3-diphenyl-1-pentanone (**186**)

	(1*S*,2*R*,*R*)-**222**			
entry	solvent	yield (%)	ee (%)	conf.
1	CH_3CN	70	53	*R*
2	CH_2Cl_2	6	2	*R*
3	toluene	70	17	*R*
4	toluene-THF	74	14	*R*
5	hexane-THF	82	6	*R*
6	CH_3CN -THF	86	27	*R*
7	DMF	83	19	*R*

5.7.1.4. The enantioselective conjugate addition in the different amount of chiral ligand

In order determine the optimum amount of chiral ligand, the conjugate addition reaction was carried out by using different amount of (1*S*,2*R*,*R*)-**222**.

When the amount of (1*S*,2*R*,*R*)-**222** was raised from 10 to 20 molar ratio, the enatioselectivity was increased from 27% to 53% ee. In the presence of 30 mol% (1*S*,2*R*,*R*)-**222**, the enantioselectivity was not changed.

Table 5.11. Effect of different amount of (1*S*,2*R*,*R*)-**222** on the enantiomeric excess of 1,3-diphenyl-1-pentanone (**186**) in the presence of 1 mol% $Ni(acac)_2$

entry	ligand (%)	yield (%)	ee (%)	conf.
1	(1*S*,2*R*,*R*)-**222** (10)	61	27	*R*
2	(1*S*,2*R*,*R*)-**222** (20)	93	53	*R*
3	(1*S*,2*R*,*R*)-**222** (30)	60	53	*R*

5.7.2. The optimum reaction condition for the enantioselective conjugate addition to chalcone

For determination of the optimum reaction conditions on the enantioselective conjugate addition of diethylzinc to chalcone, several common factors such as structure of ligand, the choise of solvent, reaction temperature, time, ligand ratio, nickel-to-chiral ligan ratio which are known to affect to enantioselectivity of the catalyst system have been examined.

The optimum reaction conditions are :

The most efficient ligand was (1*S*,2*R*,*R*)-**222**. The high enantiomeric excesses were obtained with 20 mol% ligands and 1 mol% $Ni(acac)_2$.

Acetonitrile was determined as a suitable solvent for this reaction.

The optimum reaction temperature was determined as -30 °C.

The optimum reaction time was determined as 6 hours.

5.7.3. The enantioselective conjugate addition of diethylzinc to chalcone in the presence of camphor-based ligands with *N*-substituted chiral pyrrole

The enantioselective conjugate addition of diethylzinc to chalcone was performed in acetonitrile at -30 °C in the presence of **234**, **235** and $Ni(acac)_2$.

When (2-*exo*,3-*exo*,*R*)-**234** was used as chiral ligand in the enantioselective addition of diethylzinc to chalcone, *S*-configurated alcohol formed in 36% yield and 35% ee.

The use of other enantiomer of ligand (2-*exo*,3-*exo*,*R*)-**234**; ((2-*exo*,3-*exo*,*S*)-**234** afforded the *R* alcohol in 34% yield with 34% ee.

The conjugate addition of diethylzinc to chalcone in the presence of (2-*endo*,3-*endo*,*R*)-**235** and (2-*endo*,3-*endo*,*S*)-**235** afforded (*S*)-1-phenylpropanol-1-ol in 52% with 71% ee, (*R*)-1-phenylpropanol-1-ol 65% yield with 81% ee, respectively.

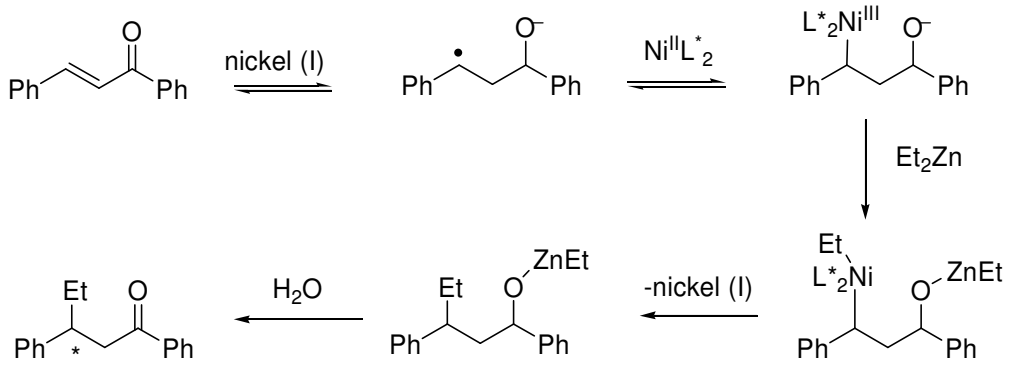
Table 5.12. Enantioselective conjugate addition of diethylzinc to chalcone catalyzed by (2-*exo*,3-*exo*,*R*)- **234** and (2-*endo*,3-*endo*,*R*)-**235**

entry	ligand (mol%)	Yield (%)	ee (%)	conf.
1	(2-*exo*,3-*exo*,*R*)- **234**	36	35	*S*
2	(2-*exo*,3-*exo*,*S*)- **234**	34	34	*R*
3	(2-*endo*,3-*endo*,*R*)-**235**	52	81	*S*
4	(2-*endo*,3-*endo*,*S*)-**235**	65	71	*R*

5.8. The Mechanism of Enantioselective Conjugate Addition of Diethylzinc to Chalcone in the Presence of the Ligand

For the enantioselective conjugate addition of diethylzinc to chalcone in the presence of chiral ligand and $Ni(acac)_2$, the mechanism proposed by Bolm, et al (1992b).

According to Bolm, the diethylzinc was used to reduce $Ni(acac)_2$ to nickel (I) and nickel (0), of which nickel (I) is most likely to be responsible for an efficient catalysis. Electron transfer from nickel (I) to the substrate, followed by attack of the ketyl radical upon the nickel (II) species, thus generated forms a nickel (III) intermediate. Alkyl transfer form zinc to the nickel center followed by reductive elimination gives the zinc enolate of the 1,4-product and regenerates the catalytically active nickel (I) species (Scheme 5.23).



Scheme 5.23. Proposed mechanism of the enantioselective nickel cataysed conjugate addition

The reaction of diethylzinc with chalcone in the presence of the ligand- Ni complexes delivered *R* enantiomer of the addition product. This can be explained on the basis of a mechanism proposed by Bolm et al. A catalytically active Ni^{I} species undergoes an electron transfer reaction chalcone and a transmetallation with diethylzinc giving a Ni^{III} enolate complex

6. CONCLUSIONS

The design and development of effective catalysts which show high reactivity and stereoselectivity play an important role in asymmetric synthesis.

In this study, we synthesized novel norephedrine- and camphor–based chiral ligands with *N*-substituted chiral pyrrole and characterised by spectroscopic techniques. These novel chiral ligands were used in the catalysis of enantioselective addition of diethylzinc to aldehydes and to chalcone. In the synthesis of these ligands, *N*-substituted chiral pyrrole carbaldehyde and both enantiomers of norephedrine, *exo*-3-amino-*exo*-2-hydroxy-1,7,7-trimethylbicyclo [2.2.1]heptane (**224**), *endo*-3-amino-*endo*-2-hydroxy-1,7,7-trimethylbicyclo[2.2.1] heptane (**224**) were used.

The synthesis of these novel ligands were carried out as follows:

- ✓ *N*-substituted pyrroles were synthesized from the commercially available enantiomers of phenylethyl amine, and 5-chloropent-3-ene-2-one (**211**).

- ✓ Formylation of *N*-substituted pyrroles were performed by Vilsmeier Haack reaction. C-3 and C-2 formulated products of pyrrole were obtained. These products were characterised by one- and two-dimensional NMR techniques. The structure of 2-methyl-1-((1*R*)-1-phenylethyl)-1*H*-pyrrole-3-carbaldehyde ((*R*)- **214** was determined by single crystal X-ray analysis.

- ✓ *exo*-3-Amino-*exo*-2-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptane (**224**), *endo*-3-amino-*endo*-2-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptane (**224**) were prepared from (+)-Camphor.

- ✓ Novel chiral ligands with multiple stereogenic centres were synthesized from the reaction of *N*-substituted pyrrole carbaldehyde with norephedrine and also with *exo*-3-amino-*exo*-2-hydroxy-1,7,7-trimethylbicyclo[2.2.1] heptane (**224**), *endo*-3-amino-*endo*-2-hydroxy-1,7,7-trimethylbicyclo[2.2.1] heptane (**224**). The synthesized chiral ligands and yields are;

- (1*S*, 2*R*)-2-((5-Methyl-1-((1*R*)-1-phenylethyl)-1*H*-pyrrol-2-yl)methylamino)-1-phenylpropan-1-ol ((1*S*,2*R*,*R*)-**219**) 68%
- (1*R*, 2*S*)-2-((5-Methyl-1-((1*S*)-1-phenylethyl)-1*H*-pyrrol-2-yl)methylamino)-1-phenylpropan-1-ol ((1*R*,2*S*,*S*)-**219**) 73%
- (1*S*,2*R*)-2-((5-Methyl-1-((1*S*)-1-phenylethyl)-1*H*-pyrrol-2-yl)methylamino)-1-phenylpropan-1-ol ((1*S*,2*R*,*S*)-**220**) 72%
- (1*R*, 2*S*)-2-((5-Methyl-1-((1*R*)-1-phenylethyl)-1*H*-pyrrol-2-yl)methylamino)-1-phenylpropan-1-ol ((1*R*,2*S*,*R*)-**220**) 70%
- (1*R*, 2*S*)-2-((2-Methyl-1-((1*R*)-1-phenylethyl)-1*H*-pyrrol-3-yl)methylamino)-1-phenylpropan-1-ol ((1*R*,2*S*,*R*)-**221**) 70%
- (1*S*, 2*R*)-2-((2-Methyl-1-((1*S*)-1-phenylethyl)-1*H*-pyrrol-3-yl)methylamino)-1-phenylpropan-1-ol ((1*S*,2*R*,*S*)-**221**) 69%
- (1*R*, 2*S*)-2-((2-Methyl-1-((1*S*)-1-phenylethyl)-1*H*-pyrrol-3-yl)methylamino)-1-phenylpropan-1-ol ((1*R*,2*S*,*S*)- **222**) 70%
- (1*S*, 2*R*)-2-((2-Methyl-1-((1*R*)-1-phenylethyl)-1*H*-pyrrol-3-yl)methylamino)-1-phenylpropan-1-ol ((1*S*,2*R*,*R*)- **222**) 73%
- 1,7,7-Trimethyl-3-((2-methyl-1-((*R*)1-phenylethyl)-1*H*-pyrrol-3-yl)methylamino)bicyclo[2,2,1]heptan-2-ol ((2-*exo*,3-*exo*,*R*)-**234**) 72%
- 1,7,7-trimethyl-3-((2-methyl-1-((*S*)-1-phenylethyl)-1*H*-pyrrol-3-yl)methylamino)bicyclo[2,2,1]heptan-2-ol ((2-*exo*,3-*exo*,*S*)-**234**) 70%
- 1,7,7-Trimethyl-3-((5-methyl-1-((*R*)-1-phenylethyl)-1*H*-pyrrol-2-yl)methylamino)bicyclo[2,2,1]heptan-2-ol ((2-*endo*,3-*endo*,*R*)-**235**) 73%
- 1,7,7-trimethyl-3-((5-methyl-1-((*S*)-1-phenylethyl)-1*H*-pyrrol-2-yl)methylamino)bicyclo[2,2,1]heptan-2-ol((2-*endo*,3-*endo*,*S*)-**235**) 70%

Asymmetric addition of diethylzinc to aldehydes and chalcone was chosen as a model reaction for the activity investigation of chiral ligands.

The best enantiomeric excesses in the addition of diethylzinc to benzaldeyde were obtained in the presence of 5 mol% (1*S*,2*R*,*S*)-**220** and (1*S*,2*R*,*S*)-**221**, 68% ee and 75% ee, respectively. .

The effects of solvent, amount of ligand, reaction time and temperature on the enantioselectivity were examined by using (1*S*,2*R*,*S*)-**220** and (1*S*,2*R*,*S*)-**221**.

The optimum reaction conditions are :

Toluene was determined as a suitable solvent for this reaction.

The optimum reaction temperature range was 0 °C -room temperature.

The optimum reaction time was determined as 16 hours.

The results showed that the stereochemistry of norephedrine plays an important role on the configuration of the addition product, but the stereogenic center on the substituent of pyrrole nitrogen has no effect.

The asymmetric addition of diethylzinc with (1*S*,2*R*,*S*)-**220** and (1*S*,2*R*,*S*)-**221** was performed in a different molar ratio of Ti(O-*i*-Pr)$_4$/Ligand (5, 15, 100). The increasing Ti(O-*i*-Pr)$_4$/Ligand ratio lowered the enantioselectivity.

The addition reaction of diethylzinc to benzaldehyde was carried out using additives such as BuLi, LiCl. However, the additives did not obviously affected enantioselectivity.

With the most efficient chiral ligands ((1*S*,2*R*,*S*)-**220** and (1*S*,2*R*,*S*)-**221**)), the effect of substituent on the enantioselective addition of diethylzinc to aldehydes was investigated. The best enantioselectivity was obtained with *p*-trifluoromethylbenzaldehyde (88% ee).

The synthesized chiral ligands were employed in the enantioselective conjugate addition of diethylzinc to chalcone. The best enantioselectivity was obtained with (1*S*,2*R*,*R*)-**222** (53% ee) and (2-*endo*,3-*endo*)-**235** (81% ee).

The effects of a variety of reaction conditions including, solvent, temperature, reaction time were investigated by using (1*S*,2*R*,*R*)-**222** .

The most efficient ligand was (1*S*,2*R*,*R*)-**222**. The high enantiomeric excesses were obtained with 20 mol% ligands and 1 mol% $Ni(acac)_2$.

Acetonitrile was determined as the most suitable solvent for this reaction.

The optimum reaction temperature was determined as -30 °C.

The optimum reaction time was determined as 6 hours.

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