SYNTHESIS, RESOLUTION AND APPLICATIONS OF 3-AMINO-2,2-DIMETHYL-1,3-DIPHENYLPROPAN-1-OL, A NOVEL CONFORMATIONALLY RESTRICTED 1,3-AMINOALCOHOLS

THESIS

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IN

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Under the supervision of

DR. N. N. JOSHI

BY

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Dedicated to my beloved parents
And
My late grandmother

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CERTIFICATE

The research work presented in thesis entitled "**Synthesis, resolution and applications of 3-amino-2,2-dimethyl-1,3-diphenylpropan-1-ol, a novel conformationally restricted 1,3-aminoalcohols"** has been carried out under my supervision and is a bonafide work of **Mr. Manmath Nagnath Patil**. This work is original and has not been submitted for any other degree or diploma of this or any other university.

October, 2010

Dr. N. N. Joshi
(Research Supervisor)

National Chemical Laboratory, Pune (India).

DECLARATION

I hereby declare that the thesis entitled **"Synthesis, resolution and applications of 3-amino-2,2-dimethyl-1,3-diphenylpropan-1-ol, a novel conformationally restricted 1,3-aminoalcohols"** submitted for Ph. D. degree to the University of Pune has been carried out at National Chemical Laboratory, under the supervision of **Dr. N. N. Joshi**. This work is original and has not been submitted in part or full by me for any degree or diploma to this or any other university.

October, 2010 Manmath N. Patil

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Finally I thank God for giving me strength to carry out this work.

Manmath

CONTENTS

Abbreviations

AcOH	Acetic acid
Ar	Aromatic
aq	Aqueous
BINOL	2,2'-Dihydroxy-1,1'-binaphthol
Bn	Benzyl
^{i}Bu	Iso-butyl
^{n}Bu	n-butyl
^{n}BuLi	n-butyllithium
^{s}Bu	secondary butyl
^{t}Bu	tertiary butyl
Bz	Benzoyl
Cat.	Catalytic
^{o}C	Temperature in degrees Centigrade
DCM	Dichloromethane
DEPT	Distortionless Enhancement by Polarization Transfer
DIBAL-H	Diisobutylaluminium hydride
DMAP	4-Dimethylaminopyridine
DME	Dimethoxy ethane
DMF	*N,N*-Dimethylformamide
DMS	Dimethyl sulphate
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
dr	Distereomeric ratio
eq	equation
equiv.	Equivalent
er	Enantiomeric ratio
Et	Ethyl
Et_3N	Triethyl amine
EtOAc	Ethyl acetate
EtOH	Ethyl alcohol

g	gram/s
GC	Gas Chromatography
h	hour/s
HIV	Human immunodeficiency virus
HPLC	High Performance Liquid Chromatography
Hz	Hertz
IR	Infrared
LA	Lewis acid
LAH	Lithium aluminium hydride
LB	Lewis base
LDA	Lithium diisopropyl amide
M	Molar
Me	Methyl
MeOH	Methanol
min.	minute(s)
mL	millilitre/s
mmol	millimole
m.p.	Melting point
MS	Mass spectroscopy
MsCl	Methanesulfonyl chloride
NaH	Sodium hydride
NMR	Nuclear magnetic resonance
ORTEP	Oak Ridge Thermal Ellipsoid Plot
PCC	Pyridinium chlorochromate
PE	Pet ether
Ph	Phenyl
PMHS	Polymethylhydrosilaxane
PMP	p-methoxyphenyl
^{i}Pr	Isopropyl
PTSA	*para*-Toluene sulfonic acid
Py	Pyridine
rt/RT	room temperature
TABH	Tetramethylammonium triacetoxyborohydride
TBAF	Tetrabutylammonium Fluoride

TBH	Tri-tert-butoxyaluminium hydride
TEBA	Triethyl benzyl ammonium chloride
TFA	Trifluoroacetic acid
TFAA	Trifluroacetic anhydride
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMH	Trimethoxy aluminium hydride
TMSCl	Trimethyl silyl chloride
TMSCN	Trimethyl silyl cyanide
Ts	Tosyl
UV	Ultraviolet

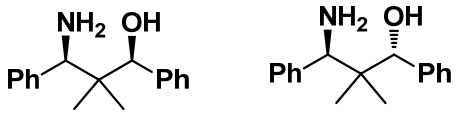
GENERAL REMARKS

- Independent compound numbering, scheme numbers and reference numbers have been employed for abstract, as well as each chapter (Chapter 1-3).
- All the solvents and reagents were purified and dried according to procedures given in D. D. Perin's "Purification of Laboratory Reagents." All reactions were carried out under argon atmosphere using freshly distilled solvents, unless otherwise specified. Yields refer to isolated product. Column chromatographic separations were carried out by gradient elution using silica gel (100-200 mesh/230-400 mesh) using light petroleum ether-ethyl acetate as the eluent, unless otherwise mentioned. Petroleum ether used in the experiments was of 60-80 °C boiling range.
- TLC was performed on E-Merck pre-coated silica gel 60 F_{254} plates and the spots were rendered visible by exposing to UV light, iodine, charring or staining with ninhydrin, *p*-anisaldehyde or phosphomolybdic acid solutions in ethanol.
- All the melting points reported are uncorrected and were recorded using Buchi melting point B-540 apparatus.
- IR spectra were recorded on Shimadzu FTIR instrument, for solid in chloroform and neat in case of liquid compounds and are measured in cm^{-1}.
- ^{1}H NMR spectra were recorded on Bruker ACF 200 MHz, AV200 MHz, MSL 300 MHz, AV 400 MHz, DRX 500 MHz spectrometers using tetramethylsilane (TMS) as an internal standard in $CDCl_3$. Chemical shifts have been expressed in parts per million (ppm) on δ scale downfield from TMS. The abbreviations s, bs, d, t, and m refer to the singlet, broad singlet, doublet, triplet, quartet and multiplet respectively. Coupling constants whenever mentioned have been given in MHz.
- ^{13}C NMR spectra were recorded at 50 MHz and 75 MHz with $CDCl_3$ (δ = 77 ppm) as the reference.
- Microanalytical data were obtained using a Carlo-Erba CHNS-O EA 1108 Elemental Analyzer.
- Optical rotations were obtained on Bellingham & Stanley ADP-220 Polarimeter. Specific rotations, $[\alpha]_D$ are reported in deg, and the concentration (c) is given in g/100 mL in the specific solvent.

Abstract

Enantioselective homogeneous metal catalysis is an important method for the preparation of enantiomerically pure compounds. To achieve the highest levels of reactivity and selectivity in catalytic enantioselective reactions, several reaction parameters must be optimized. Amongst these, the selection and design of the chiral ligands is the most crucial step. Hence the design and synthesis of chiral ligands for catalytic asymmetric synthesis is of great interest.

Aminoalcohols and their derivatives have been used extensively in asymmetric synthesis, both as chiral auxiliaries as well as chiral ligands. A wide variety of aminoalcohols, mostly 1,2-aminoalcohols have been reported in the literature. Only a few examples of the use of chiral 1,3-aminoalcohols are known. With the exception of the ones derived from camphor, most 1,3-aminoalcohols posses flexible backbone and provide poor enantioselectivity. Thus the design and synthesis of novel 1,3-aminoalcohol containing rigid backbone, is an important endeavor. The present work deals with synthesis and applications of *syn*- and *anti*-3-amino-2,2-dimethyl-1,3-diphenylpropan-1-ol, **1** and **2** respectively.



1 **2**

The thesis entitled, **"Synthesis, resolution and applications of 3-amino-2,2-dimethyl-1,3-diphenylpropan-1-ol, a novel conformationally restricted 1,3-aminoalcohols"** is divided into three chapters.

Chapter 1: Synthesis and applications of 1,3-aminoalcohols: Literature survey

This chapter provides background to the present work by reviewing the literature on synthesis of several aminoalcohols and their applications in various enantioselective reactions.

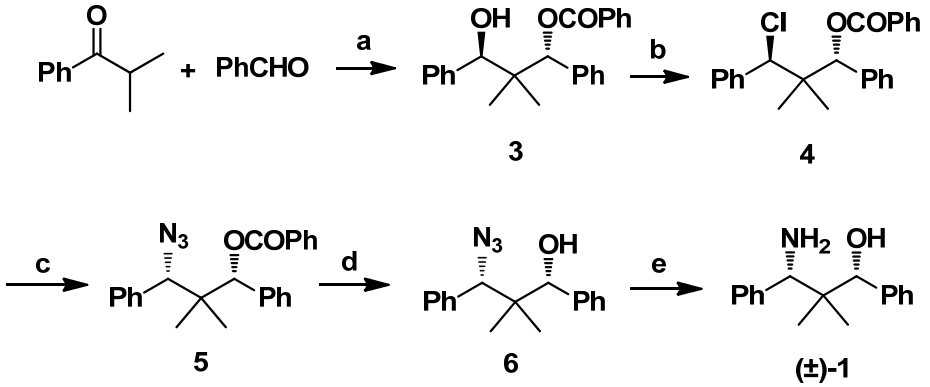
Chapter 2: Synthesis and resolution of *syn*- and *anti*-3-amino-2,2-dimethyl-1,3-diphenylpropan-1-ols

This chapter has been divided into three sections. **Section-2A** describes a diastereoselective synthesis of both *syn*- and *anti*-3-amino-2,2-dimethyl-1,3-diphenylpropan-1-ols by employing sequence of nucleophilic substitution reaction on corresponding γ-hydroxybenzoate **3** and **9** respectively. **Section-2B** describes a short route for the synthesis of *syn*- and *anti*-3-amino-2,2-dimethyl-1,3-diphenylpropan-1-ols through a highly diastereoselective reduction of β-hydroxy oxime, a common intermediate **13**. While **Section-2C** deals with the resolution of *syn*- and *anti*-3-amino-2,2-dimethyl-1,3-diphenylpropan-1-ols to obtain optically pure aminoalcohols.

Section-2A: Diastereoselective synthesis of *syn*- and *anti*-3-amino-2,2-dimethyl-1,3-diphenylpropan-1-ols

1. Synthesis of *syn*-(±)-1

Synthesis of the *syn*-aminoalcohol (**1**) is depicted in scheme 1.

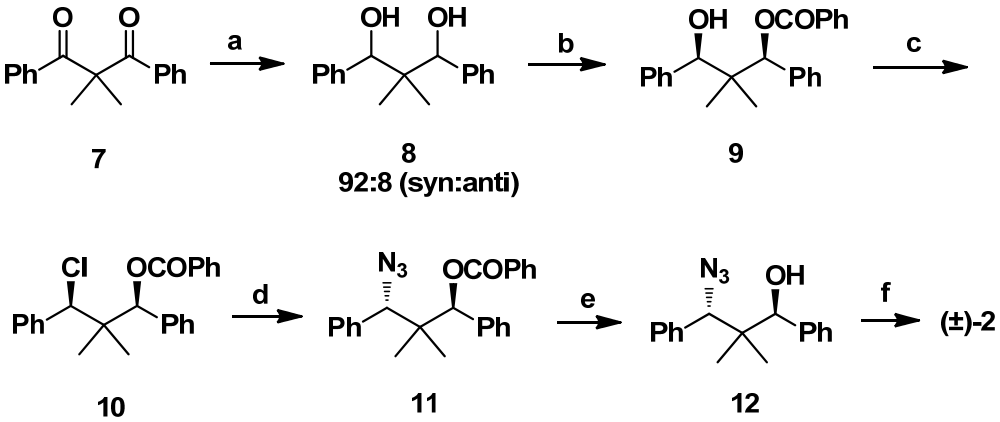


Scheme 1. Synthesis of compound **1**. Reagents and conditions: (a) LiO^tBu, THF, 0 ^oC to rt, 73%; (b) $SOCl_2$, DCM, rt, 83%; (c) NaN_3, DMF, reflux, 83%; (d) KOH, MeOH; (e) H_2-Pd/C, MeOH, 90% (over two steps).

First and the crucial step of the scheme is an Aldol-Tishchenko reaction between isobutyrophenone and benzaldehyde in the presence of LiO^tBu. The resulting γ-hydroxybenzoate **3** was treated with thionyl chloride to obtain the *anti*-chlorobenzoate **4** with retention of configuration. Compound **4** was then converted to azidobenzoate **5** by treatment with sodium azide in DMF with an inversion of the configuration. The resulting *syn*-azidobenzoate **5** was first hydrolyzed to azidoalcohol **6**, followed by hydrogenation to obtain *syn*-1,3-aminoalcohol **1** in high overall yield.

2. Synthesis of *anti*-(±)-2:

The same strategy was used for the preparation of *anti*-1,3-aminoalcohol **2**, as shown in scheme 2. The required *syn*-hydroxybenzoate **9**, which is the key intermediate for further transformation, was prepared from the meso 1,3-diol **8**. 1,3-Diketone **7** was reduced using $LiBH_4/TiCl_4$ to obtain 1,3-diol in 92:8 ratio (*syn*:*anti*). The mixture was converted to pure *syn*-hydroxybenzoate **9** by treatment with one equivalent of PhCOCl followed by crystallization. The hydroxybenzoate **9** was then converted to *anti*-1,3-aminoalcohol **2** in high overall yield by using the same sequence of reactions.

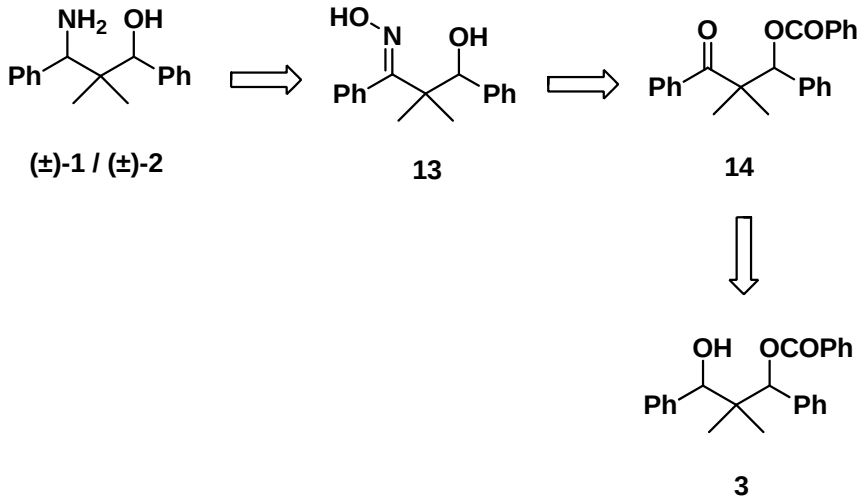


Scheme 2. Synthesis of compound **2**. Reagents and conditions: (a) $LiBH_4$, $TiCl_4$, 82%; (b) BzCl, Pyridine, DCM, rt, 71%; (c) $SOCl_2$, DCM, rt, 78%; (d) NaN_3, DMF, reflux, 81%; (e) KOH, MeOH; (f) H_2-Pd/C, MeOH, 90% (over two steps).

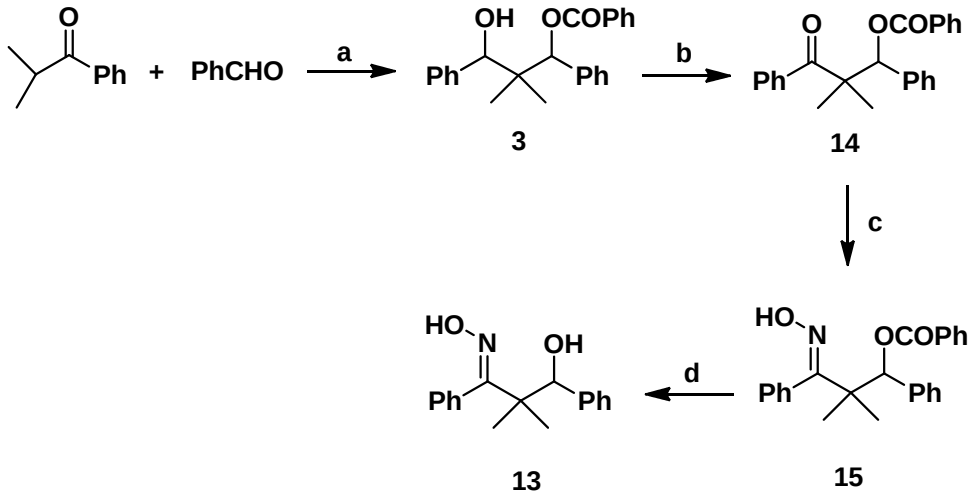
Section-2B: Reduction of *β*-hydroxy oxime: A short route to the synthesis of *syn*- and *anti*-3-amino-2,2-dimethyl-1,3-diphenylpropan-1-ols.

The retrosynthetic analysis as shown in scheme 3, reveals that both *syn*- and *anti*-1,3-aminoalcohols can be synthesized through a distereoselective reduction of common intermediate i.e. *β*-hydroxy oxime **13.**

Scheme 3. Retrosynthetic analysis



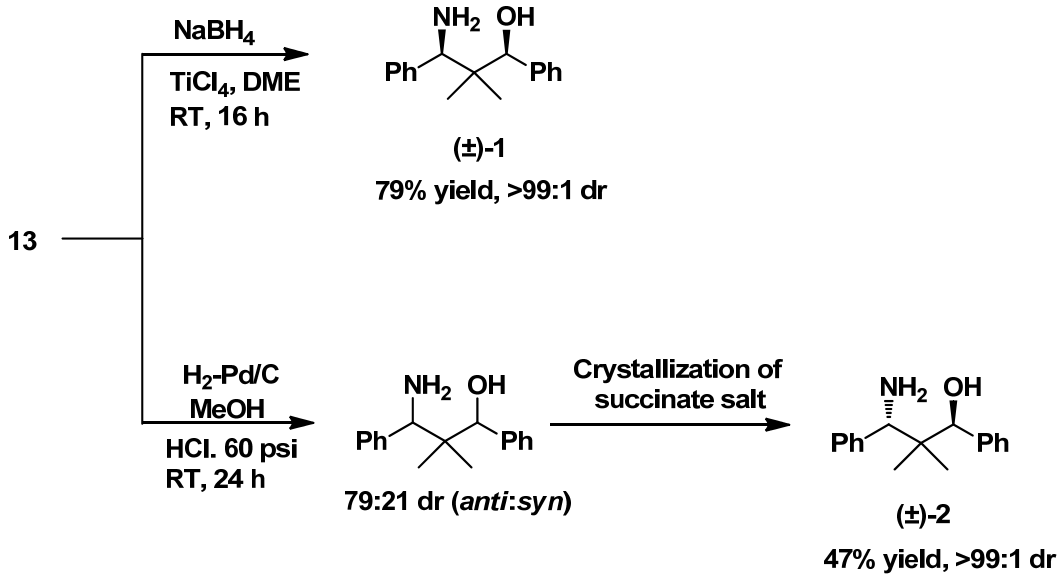
The required *β*-hydroxy oxime **13** was prepared from *γ*-hydroxybenzoate **3** over three steps with excellent overall yield (Scheme 4). The *γ*-hydroxybenzoate **3** was prepared employing Aldol-Tishchenko reaction. The resulting *γ*-hydroxybenzoate **3** was then oxidized into corresponding keto benzoate **14** by chromic acid and the latter was oximated to give oxime benzoate **15** by reacting with $NH_2OH.HCl$ / CH_3COONa, which upon hydrolysis with methanolic KOH afforded the *β*-hydroxy oxime **13.**



Scheme 4. Synthesis of compound **13**. Reagents and conditions: (a) LiO^tBu, THF, 0 ^oC-rt, 73%; (b) $K_2Cr_2O_7$, dil. H_2SO_4, Et_2O, rt, quant.; (c) $NH_2OH.HCl$, CH_3COONa, Ethanol, reflux, quant.; (d) KOH, MeOH, rt, 81%;

Hydrogenation using H_2-Pd/C in methanol at 60 psi in the presence of one equivalent of hydrochloric acid reduces the oxime **13** to 1,3-aminoalcohol in 80% yield with 79:21 (*anti*:*syn*) distereoselectivity. The desired *anti*-isomer **2** was separated by crystallization of succinate salt of this mixture. While $NaBH_4$ in the presence of $TiCl_4$ reduces the oxime **13** with exclusive formation of *syn*-1,3-aminoalcohol **1** in high yield as shown in scheme 5.

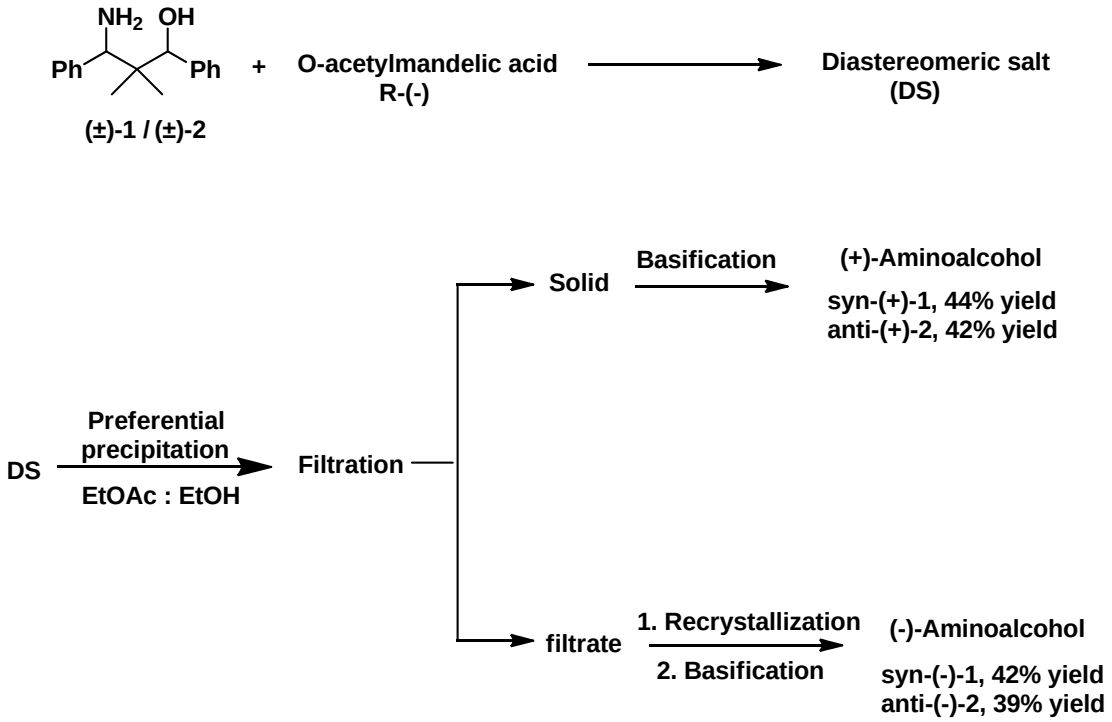
Scheme 5. Reduction of *β*-hydroxy oxime **13**



Section-2C: Resolution of *syn*- and *anti*-3-amino-2,2-dimethyl-1,3-diphenylpropan-1-ols.

We examined various mono- as well as dibasic acids for the resolution of (±)-**1**. Unfortunately we could not separate the diastereomeric salts prepared from almost all commonly used chiral acids. Finally the resolution could be accomplished through preferential precipitation of the salts from R-(-)-O-acetyl mandelic acid. The precipitated solid after basification with aqueous ammonia was found to be enantiopure (+)-**1** while (-)-**1** was recovered from the filtrate. The same protocol was also used for the resolution of (±)-**2** (Scheme 6).

Scheme 6. Resolution of aminoalcohols

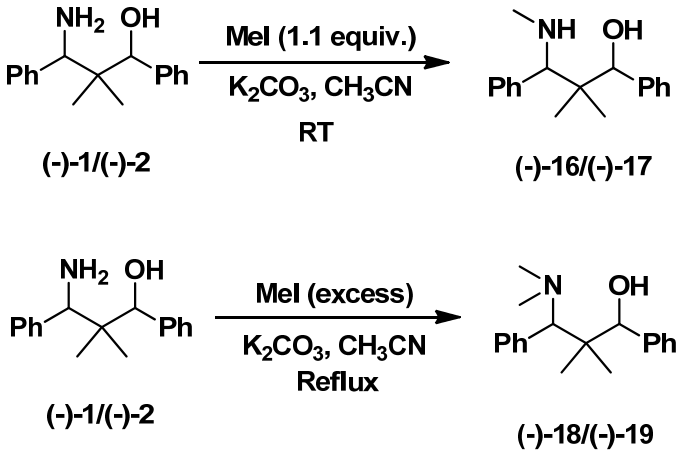


Optical purity of all the four stereoisomers of 3-amino-2,2-dimethyl-1,3-diphenylpropan-1-ol was determined by chiral HPLC and found to be more than 99%. The absolute configuration was established by anomalous dispersion effects in X-ray diffraction measurements on the crystal of the hydrobromide salts and it was found to be **(*R*,*S*), (*S*,*R*), (*R*,*R*),** and **(*S*,*S*)** for (+)-**1**, (-)-**1**, (+)-**2** and (-)-**2** respectively.

Chapter 3: Applications of 3-amino-2,2-dimethyl-1,3-diphenylpropan-1-ol

A standard test for the stereodifferentiating efficacy of an aminoalcohol is in its performance during few standard asymmetric reactions, like the addition of diethylzinc to aldehyde oxazaborolidine-catalyzed reduction of ketone etc. This chapter is divided in to three sections. **Section-3A** describes a detailed study on enantioselective addition of diethylzinc to aldehydes. **Section-3B** deals with enantioselective addition of trimethylsilyl cyanide to benzaldehyde. While **Section-3C** describes oxazaborinane-catalyzed reduction of prochiral ketone. We also prepared the methyl derivatives of (-)-**1** and (-)-**2** for the above mentioned reactions. The derivatives **16-19** were obtained by judicious methylation as shown in scheme 7.

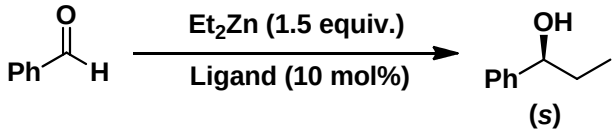
Scheme 7. Synthesis of ligands **16-19**



Section-3A: Enantioselective addition of Et_2Zn to aldehydes

Enantioselective addition of Et_2Zn to aldehyde is one of the most widely studied reactions in recent times. The reaction provides enantiomerically pure chiral secondary alcohols which are important intermediates for the synthesis of bioactive compounds and various natural products. We first examined the methyl derivatives of (-)-**1** and (-)-**2** as ligands for the addition of Et_2Zn to benzaldehyde. The test reaction involving Et_2Zn and benzaldehyde was carried out in toluene-hexane using 10 mol% of the ligand. The results are summarized in Table 1.

Table 1. Enantioselective addition of Et_2Zn to benzaldehyde



entry	ligand	time (h)	yield[a] (%)	er[b]
1	(-)-**16**	4	69	92:8
2	(-)-**17**	4	70	70:30
3	(-)-**18**	1	90	97:3
4	(-)-**19**	2	80	80:20
5[c]	(-)-**18**	2	86	97:3

[a] Isolated yield. [b] Determined by chiral HPLC analysis. [c] reaction carried out at 0 ^oC.

As expected, better enantioselectivity was realized with dimethyl derivative than the monomethyl derivative. The highest degree of enantioselectivity (97:3 er) was observed with *syn*-*N*,*N*-dimethyl aminoalcohol (-)-**18** (entry 3). Unexpectedly, the

corresponding *anti*-derivative provided only moderate yield and moderate enantioselectivity.

Several aromatic and aliphatic aldehydes were also examined for the reaction with ligand (-)-**18**. High level of enantioselection was observed in all the cases.

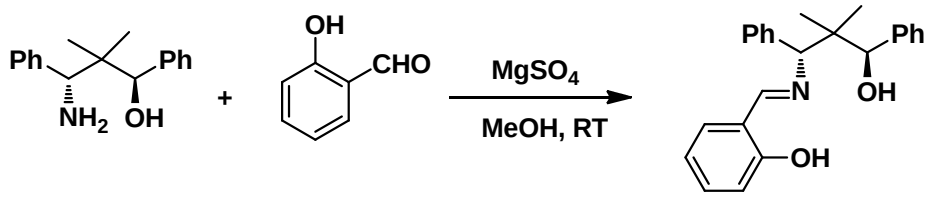
Section-3B: Addition of trimethylsilyl cyanide to benzaldehyde

Enantioselective addition of trimethylsilyl cyanide to aldehydes is one of the important carbon-carbon bond forming reactions since chiral cyanohydrins serve as valuable synthetic intermediates. The reaction can be catalyzed by Lewis acid as well as Lewis base.

1. Lewis acid catalyzed trimethylsilyl cyanation

Chiral Schiff bases (**20,** and **21**) were prepared by the condensation of aminoalcohol (+)-**2** with 2-hydroxy benzaldehyde (salicylaldehyde) and 3,5-di-*tert*-butyl-2-hydroxy benzaldehyde respectively (Scheme 8).

Scheme 8. Preparation of Schiff base **20** and **21**



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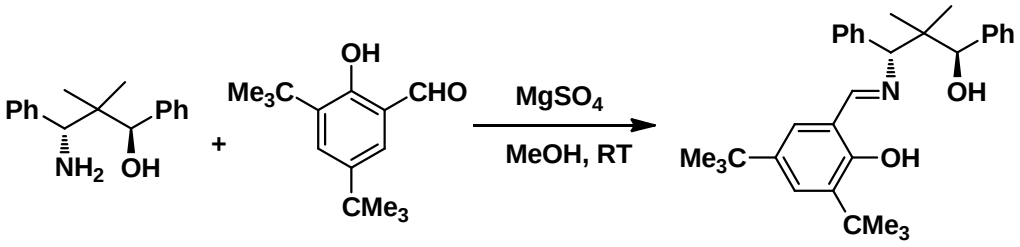
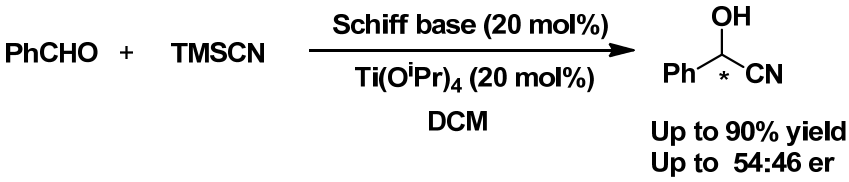


21

The reaction of benzaldehyde with trimethylsilyl cyanide was then examined using 20 mol% of the catalyst prepared *in situ* by the reaction of Schiff bases **20** and **21** with $Ti(O^iPr)_4$ in DCM. The resulting complex efficiently catalyzed the trimethylsilyl cyanation of benzaldehyde, but with poor enantioselectivity (eq 1).

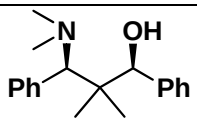
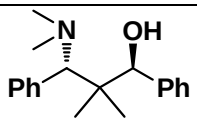
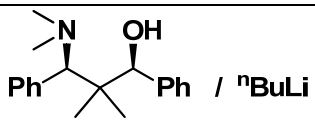
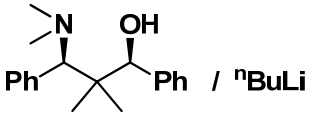
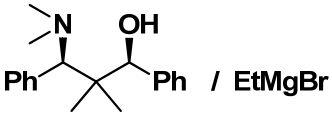


(1)

2. Lewis base catalyzed trimethylsilyl cyanation

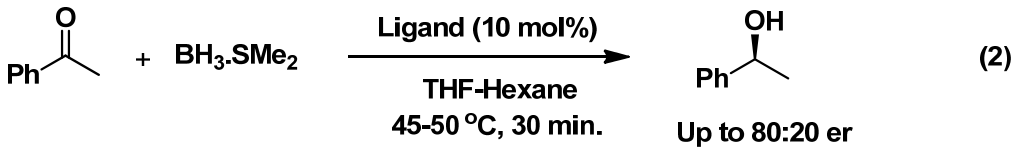
Dimethyl aminoalcohol based Lewis bases were also examined for this reaction. Although excellent yield was observed in many cases, enantiomeric excess was insignificant (Table 2).

Table 2. Lewis base catalyzed TMSCN addition to PhCHO

entry	Lewis base	condition	yield (%)	er
1	 (-)-18	DCM, 0 °C-RT	17	-
2	 (-)-19	DCM, 0 °C-RT	~15	-
3	 (-)-18	Toluene, 0 °C 1 h	92	-
4	 (-)-18	Toluene, -78 °C 24 h	79	-
5	 (-)-18	MTBE/THF 0 °C, 6 h	90	-

Section-3C: Borane reduction of acetophenone

Asymmetric borane reduction originally described by Itsuno and later studied extensively by Corey is one of the most effective approaches for preparing optically active secondary alcohols. Here we evaluated amino alcohols (-)-**1**, (-)-**2**, (-)-**16** and (-)-**17** as chiral ligands for the enantioselective reduction of acetophenone with borane. The oxazaborinane catalyst was prepared by treating the aminoalcohol with borane according to the procedure published by our group earlier. Baring aminoalcohol **1** (er 80:20), the results with other derivatives were disappointing (eq 2).



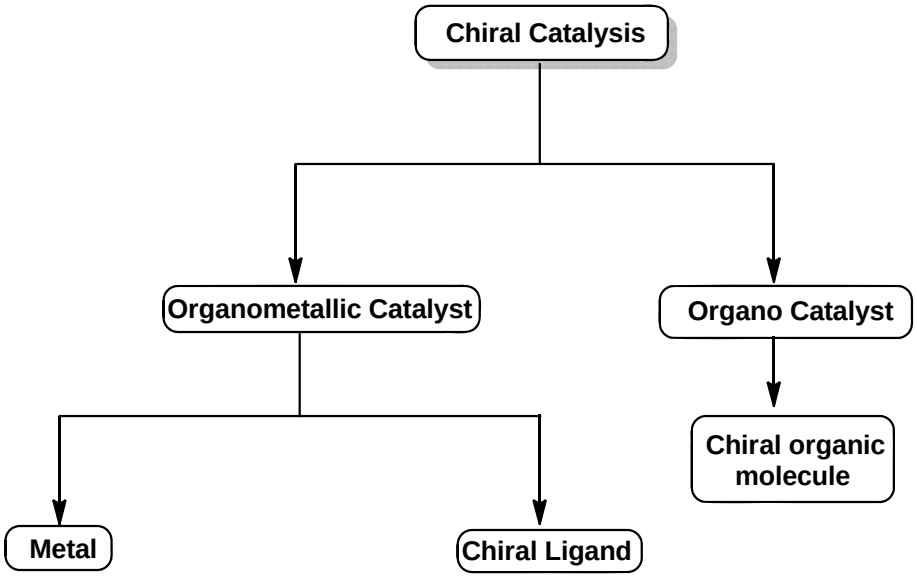
(2)

CHAPTER 1

Synthesis and applications of 1,3-aminoalcohols: Literature survey

Introduction

Discovering efficient methods for gaining access to enantiomerically pure pharmaceuticals, agrochemicals, and flavors has been a great challenge for chemists. Amongst various methods for preparing enantiopure compounds, enantioselective homogeneous metal catalysis is an appealing strategy, as reflected by the many publications in this field and the award of the Noble prize in 2001 to W. S. Knowles, R. Noyori, and K. B. Sharpless.[1] A transition metal complex containing a chiral ligand catalyzes the transformation of a prochiral substrate in such a way that one stereochemical path is preferentially followed. To achieve the highest levels of reactivity and selectivity in catalytic enantioselective reactions, several reaction parameters must be optimized. In this context, selection of an appropriate chiral ligands is the most crucial step.[2] Hence the design and synthesis of chiral ligands for catalytic asymmetric synthesis is of great interest.



A good chiral ligand should possess several characteristics.[3]

i) It must be co-ordinated to the metal during the step in which the chiral center is created on the substrate and not exert merely a chiral medium effect. That means the bond between the coordinating atoms with the metal center should not break during the course of the reaction.

ii) The catalytic activity in presence of the chiral ligand should be much better relative to that of the achiral catalyst. In other words, the rate of formation of the desired product should suppress the formation of the undesired compounds.

iii) The structure of the ligand should allow for various chemical modifications to be made in order to permit the synthesis of the variants. In this way optimal ligand substrate matches can be sought.

iv) The synthesis of the ligands must be relatively easy.

v) It is desirable to get both the antipodes of the ligand.

. Various chiral ligands, like phosphorus containing ligands[4] (phosphines), oxygen containing ligands[5] (alcohols and diols) and nitrogen containing ligands[6] (amines, aminoalcohols and diamines) have been used with appropriate metals in asymmetric synthesis. Phosphine containing ligands are not very desirable for practical applications mainly because of the high cost and poor recyclability due to oxidation. Nitrogen containing ligands offer many advantages, such as the ease of preparation by resolution of racemates, high stability, and easy separation. Furthermore some nitrogen containing ligands also act as excellent organocatalyst.[7]

Amongst the nitrogen containing ligands, aminoalcohols are of particular interest. Aminoalcohols and their derivatives have been used extensively in asymmetric synthesis both as chiral auxiliaries and chiral ligands.[2,6e,8] The two heteroatoms allow flexibility as one or both can be bound to Lewis acid, transition metal, or achiral starting material. Besides acting as chiral ligands, aminoalcohols are important and versatile synthetic intermediate for many biologically active compounds and natural products.[9] A wide variety of aminoalcohols, mostly 1,2-aminoalcohols have been prepared and used as chiral catalyst for many enantioselective reactions, specially C-C bond forming reactions.[2,6e,8d,g] While only a few examples of the use of 1,3-aminoalcohols have been reported.[10,11,12,13] However there has been increasing interest in the preparation and applications of 1,3-aminoalcohols.[14] These are important synthetic intermediates for many natural products such as nucleoside, antibiotics and alkoloids.[9e-i] 1,3-Aminoalcohols also posses relevance in the development of new enzyme inhibitors and HIV protease inhibitor e.g. ritonqvir and lopinavir.[15,26b]

The present chapter will focus on reviewing the literature on synthesis and applications of 1,3-aminoalcohols.

1. Synthesis of 1,3-aminoalcohols

Various methodologies are available for the synthesis of 1,3-aminoalcohols. These include cycloaddition of olefin to nitrones and nitrile oxides,[16,21] the addition reaction to β-alkoxyimines,[17] the reduction of β-aminoketones,[18,19f] β-hydroxy oximes,[10k,19] β-hydroxy nitrile[10g,h,20] and the isoxazoline,[21] double reduction of enamines,[22] the addition of azaenolate to aldehydes[23] and the addition of organometallic reagents to the β-aminocarbonyl compounds.[18a,24]

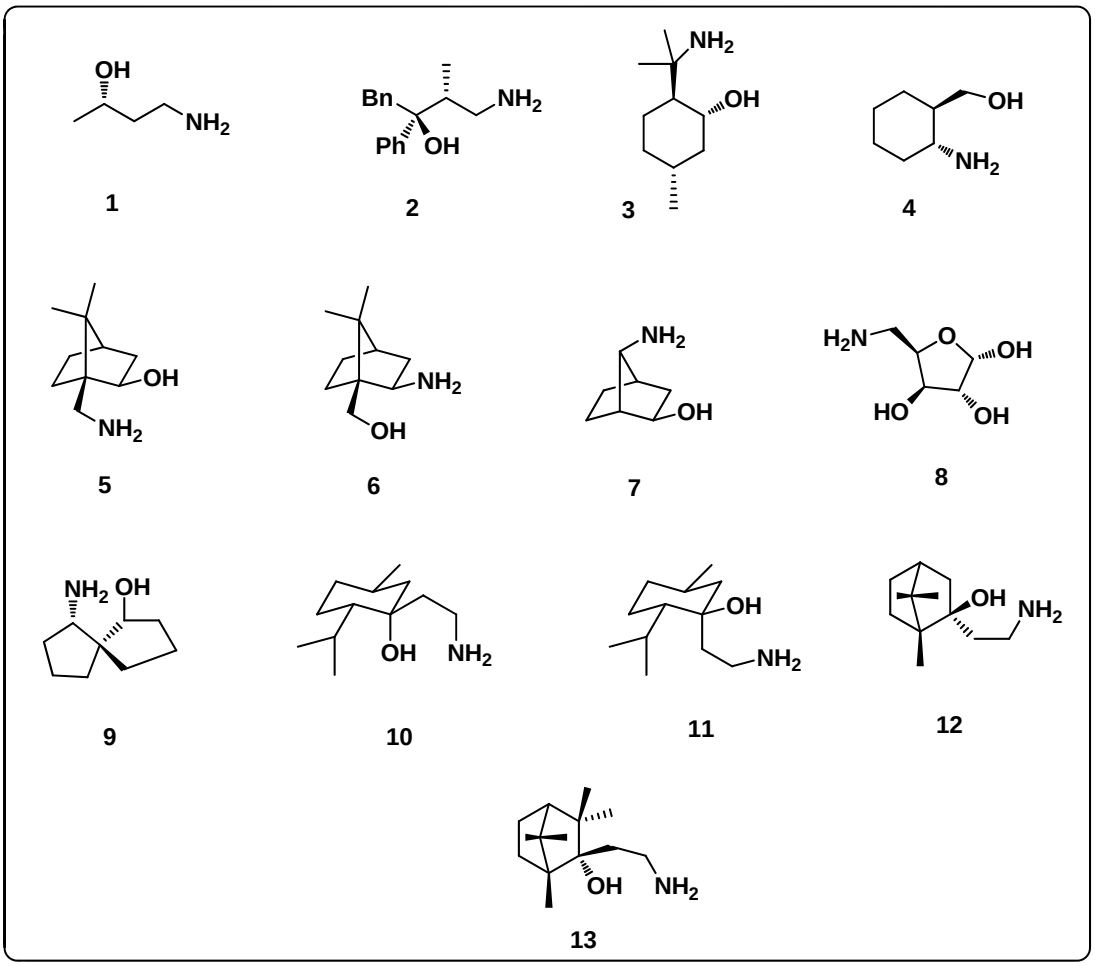


Figure 1. 1,3-aminoalcohols

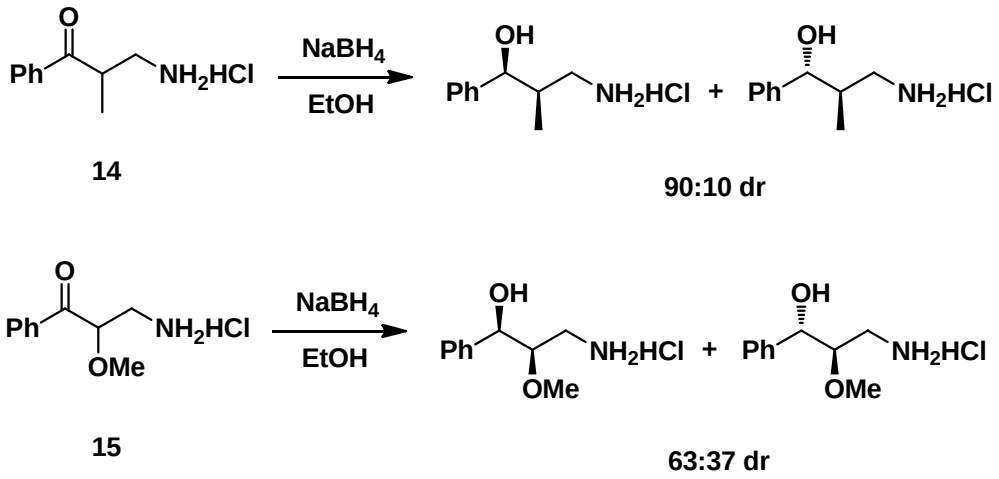
There are many 1,3-aminoalcohols known in the literature as shown above (Figure 1), which were prepared by applying different methodologies. Some of the important methodologies are discussed below.

1.1. Reduction

1.1.1 Reduction of aminoketone

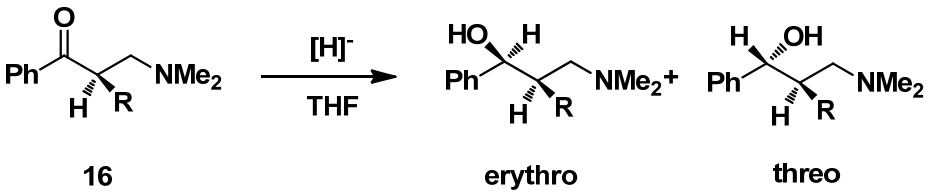
Yamada *et al*.[18b] in 1967 reported a simple method for the reduction of acyclic α-aminoketones and β-aminoketones using $NaBH_4$ in ethanol. In the case of reduction of β-aminoketones (**14** and **15**) moderate to good diastereoselectivity was observed (Scheme 1).

Scheme 1. Reduction of α-substituted β-aminoketones



Later in early 1970 and late 1980, various approaches were developed for the diastereoselective reduction of acyclic and cyclic β-aminoketones.[18a] Angiolini *et al*.[18c] in 1970 had reported the reduction of α- substituted β-amino propiophenones (**16**) using lithium aluminium hydride ($LiAlH_4$), lithium trimethoxyaluminium hydride (TMH), and lithium tri-*tert*-butoxyaluminium hydride (TBH). Low to good diastereoselectivity was achieved by altering the parameters. The outcome of the diastereoselectivity was explained by mechanistic study. Usually phenyl group at α-position assists diastereoselectivity. The result of reduction is shown in Table 1.

Table 1. Reduction of **16** with $LiAlH_4$

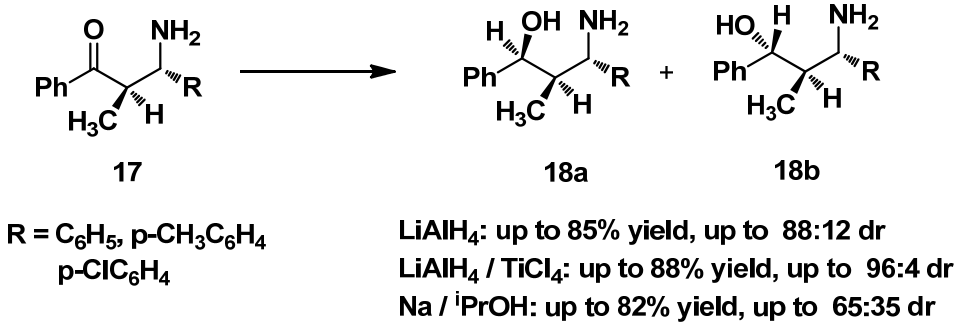


R	$LiAlH_4$[a]	TMH[a]	TBH[a]
CH_3	60:40	50:50	50:50
CH_2Ph	54:46	82:18	82:18
Ph	87:13	98:2	92:8

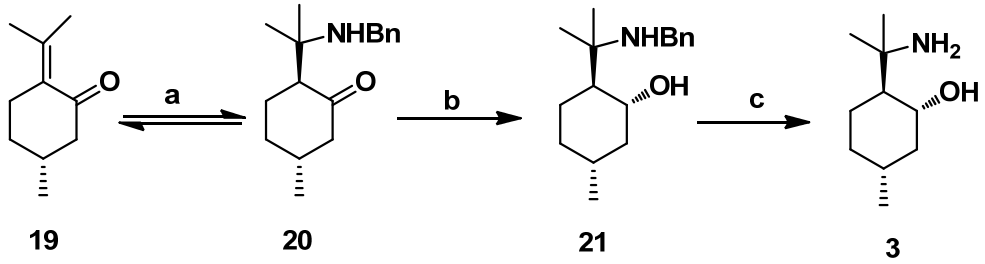
[a] erythro:threo ratio

Barluenga *et al.*[18d] in 1985 reported the diastereoselective synthesis of 1,3-aminoalcohol (**18**) with three chiral centers in a very good yield by the reduction of *β*-aminoketones **17** (Scheme 2).

Scheme 2. Reduction of **17**



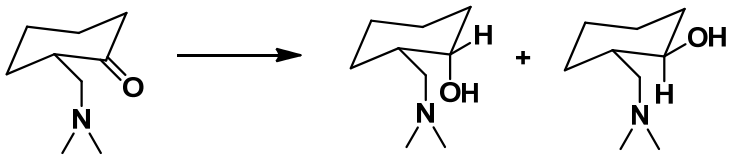
In 1987, He and Eliel[29] reported the synthesis of 8-amino menthol (**3**) from (+)-pulegone (**19**). Conjugate addition of benzyl amine to **19** gave aminoketone intermediate **20**, which upon reduction with sodium borohydride followed by deprotection of benzyl group and crystallization gave diastereomerically pure aminoalcohol **3** in 35% yield (Scheme 3).



Scheme 3. Reagents and conditions: (a) $BnNH_2$; (b) $NaBH_4$, EtOH:H_2O (4:1); (c) HCO_2NH_4, 10% Pd/C, MeOH.

Reduction of 2-dimethylaminomethylcyclohexane, a cyclic *β*-aminoketone **22** was reported by Costes *et al.*[18e] Low diastereoselectivity was obtained using various metal hydride reagents (Scheme 4).

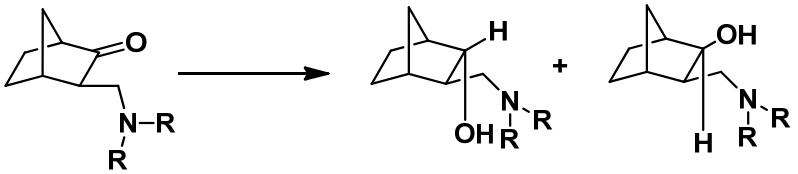
Scheme 4. Reduction of **22**



22 low diastereoselectivity: $NaBH_3CN$, $LiAlH_4$, $NaBH_4$, $LiBH_4$, KBH_4

Krieger *et al*.[18f] reported the reduction of cyclic aminoketone (**23**), using $LiAlH_4$ and $NaBH_4$ with low diastereoselectivity (Scheme 5).

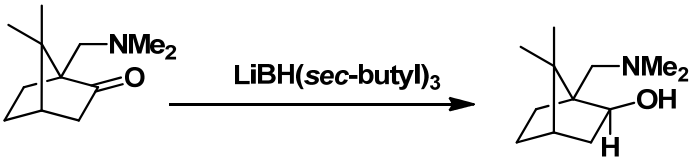
Scheme 5. Reduction of **23**



23 $LiAlH_4$, $NaBH_4$: low diastereoselectivity

However the reduction of 10-dimethylaminobornan-2-one (**24**), a hindered cyclic *β*-aminoketone with lithium tris[*sec*-butyl]borohydride gave only one isomer (Scheme 6).

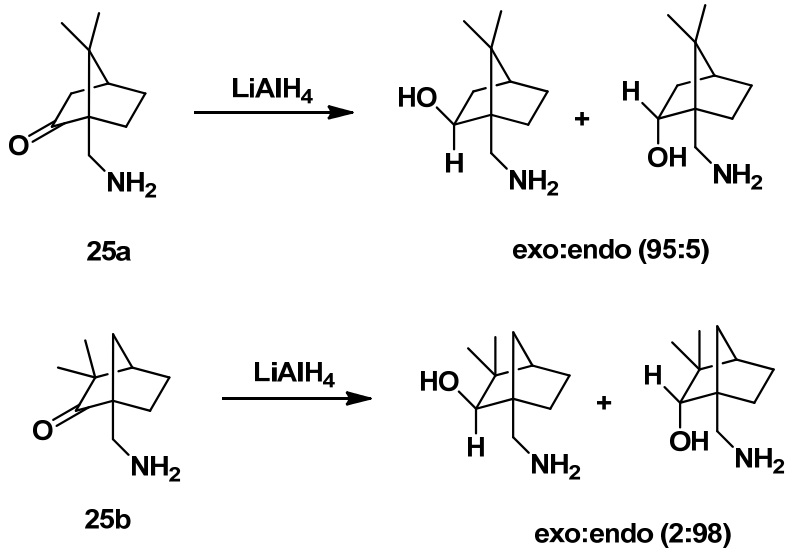
Scheme 6. Reduction of **24**



24

Martínez and co-workers[19f] in 1998 studied the reduction of bridgehead-substituted 2-norbornanones (**25**). Excellent diastereoselectivity was observed using $LiAlH_4$ as a reducing agent (Scheme 7).

Scheme 7. Reduction of **25** with LAH



There are many cyclic *β*-aminoketones, which were reduced to corresponding 1,3-aminoalcohols (Figure 2).

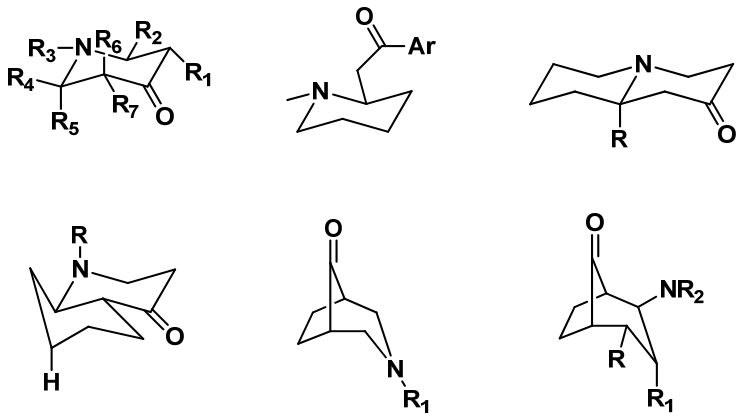


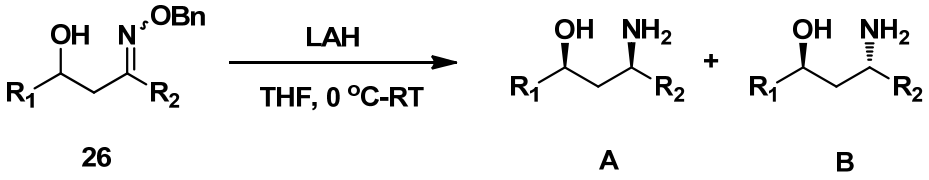
Figure 2

1.1.2. Reduction of *β*-hydroxy oxime and *β*-hydroxy oximino ether

Hydroxy oxime is an intermediate mainly utilized for the preparation of *syn*- and *anti*-1,3-aminoalcohols through stereoselective reduction directed by hydroxyl group. Narasaka *et al*.[19a] in 1984 reported the stereoselective preparation of acyclic *syn*-1,3-aminoalcohols by the reduction of oximino benzyl ether **26** with $LiAlH_4$. *Syn*-1,3-aminoalcohol was found to be the major product in both (**E**)- and (**Z**)-oximino benzyl ether reduction (Table 2). The stereoselectivity of the reduction was explained based on the hypothesis that the reaction of **26** with $LiAlH_4$ would generate the aluminium alcoholate and the intramolecular reduction would proceed through

cyclic transition state to result in the formation of a *syn*-1,3-aminoalcohol as a major product.[19b-c]

Table 2. Reduction of **26**

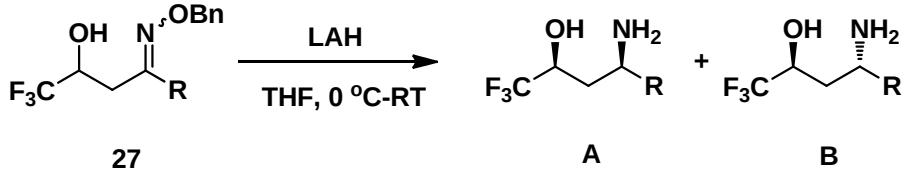


26 A B

R_1	R_2	A:B	
		From (Z)-oxime	From (E)-oxime
^{n}Bu	^{n}Bu	95:5	77:23
^{i}Bu	^{i}Bu	95:5	77:23
$PhCH_2CH_2$	$PhCH_2CH_2$	91:9	79:21
$PhCH_2CH_2$	CH_3	88:12	78:22
Ph	CH_3	88:12	85:15
Ph	Ph	85:15	88:12

Later in 1987, Kitazume *et al*.[19d] used the same approach and reduced various *β*-hydroxy oximino ether possessing trifluromethyl group. *Syn*-1,3-aminoalcohol was found to be the major product when reduction was carried on mixture of (E)- and (Z)-oximino benzyl ether **27** (Table 3). The author proposed the same mechanism as described by Narasaka *et al*. earlier.[19c]

Table 3. Reduction of **27**

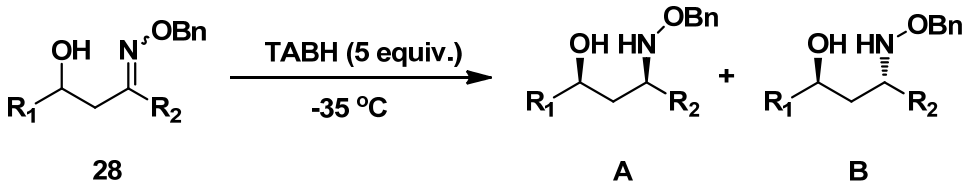


27 A B

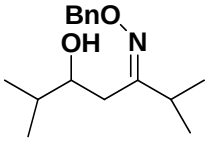
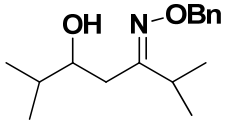
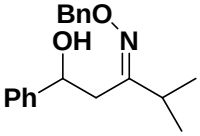
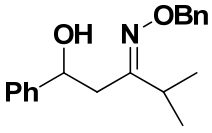
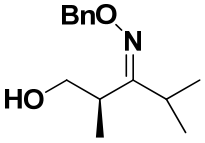
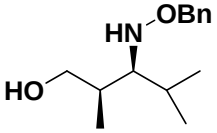
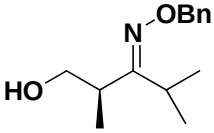
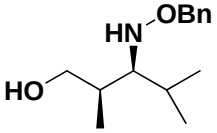
entry	R	A:B
1	Ph	87:13
2	CH_2CH_2Ph	79:21
3	CH_2CHMe_2	82:18
4	$(CH_2)_5CH_3$	83:17

In 1992, Williams *et al.*[19e] reported the tetramethyl ammonium triacetoxyborohydride (TABH) mediated reduction of pure (E)- and (Z)-oximino benzyl ether (**28**) in anhydrous acetic acid-acetonitrile (1:1) at -35 ^{o}C. (Z)-oxime afforded smooth conversion to the 1,3-*anti* product while the corresponding (E)-oxime gave mostly the 1,3-*syn* product. Diastereoselectivity originated from the geometry of starting oximino ether (Table 4).

Table 4. TABH mediated reduction of **28**

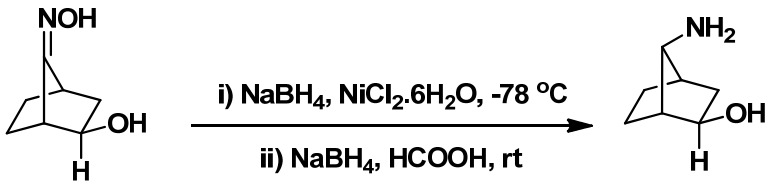


28 A B

Substrate	yield (%)	A:B
	~100	33:67
	94	91:9
	92	1:100
	95	65:35
	93	
	92	

Costa *et al.*[10k] synthesized (+)- and (-)-*syn*-1,3-aminoalcohol (**7**) with norbornane framework through a diastereoselective reduction of the corresponding *β*-hydroxy oxime (**29**) using $NaBH_4/NiCl_2.6H_2O$ followed by treatment with $NaBH_4$ in formic acid (Scheme 8).

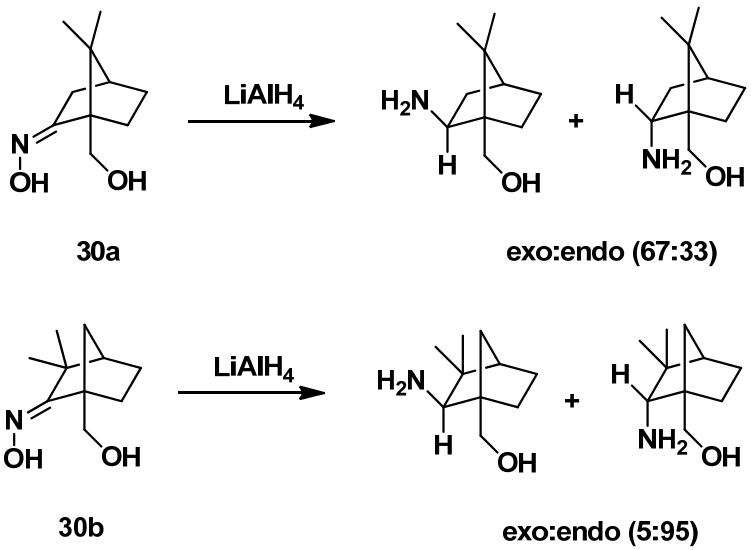
Scheme 8. Reduction of **29**



29 **(+)-7**

Martínez *et al.*[19f] studied the reduction of bridgehead-substituted 2-norbornanoximes (**30**). Good to excellent diastereoselectivity was observed using $LiAlH_4$ as a reducing agent (Scheme 9).

Scheme 9. Reduction of **30** with $LiAlH_4$

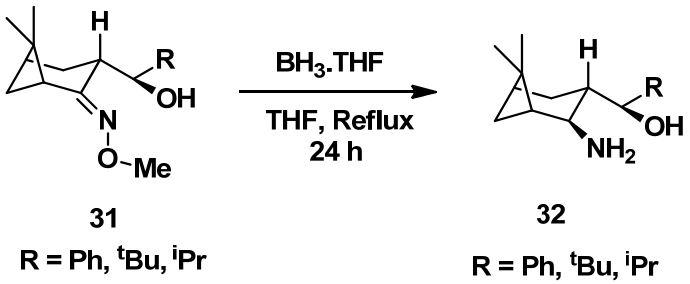


30a **exo:endo (67:33)**

30b **exo:endo (5:95)**

Mauduit *et al.*[19g] reported the synthesis of a new 1,3-aminoalcohol (**32**) by the reduction of corresponding *β*-hydroxy oxime methyl ether (**31**) using BH_3.THF as a reducing agent. The exclusive *syn*-aminoalcohol was obtained with good yield (Scheme 10).

Scheme 10. Synthesis of **32**



31
R = Ph, ^{t}Bu, ^{i}Pr

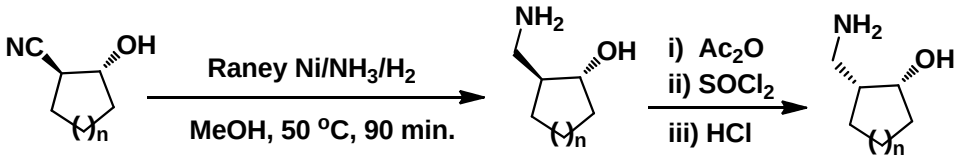
32
R = Ph, ^{t}Bu, ^{i}Pr

1.1.3. Reduction of *β*-hydroxynitrile

Reduction of *β*-hydroxynitriles is one of the important method used for the preparation of 1,3-aminoalcohols.[20]

Fulop *et al*.[20a] in 1991 reported a simple method for the preparation of both *trans*- and *cis*-2-amino methyl cycloalkanols (**34** and **35**) starting from common intermediate i.e. *trans*-2-hydroxycycloalkanecarbonitrile **33**. Reduction of the nitrile using Raney Nickel gave *anti*-1,3-aminoalcohol, which was further converted into *syn*- isomer as shown in scheme 11.

Scheme 11. Reduction of *β*-hydroxynitrile **33**



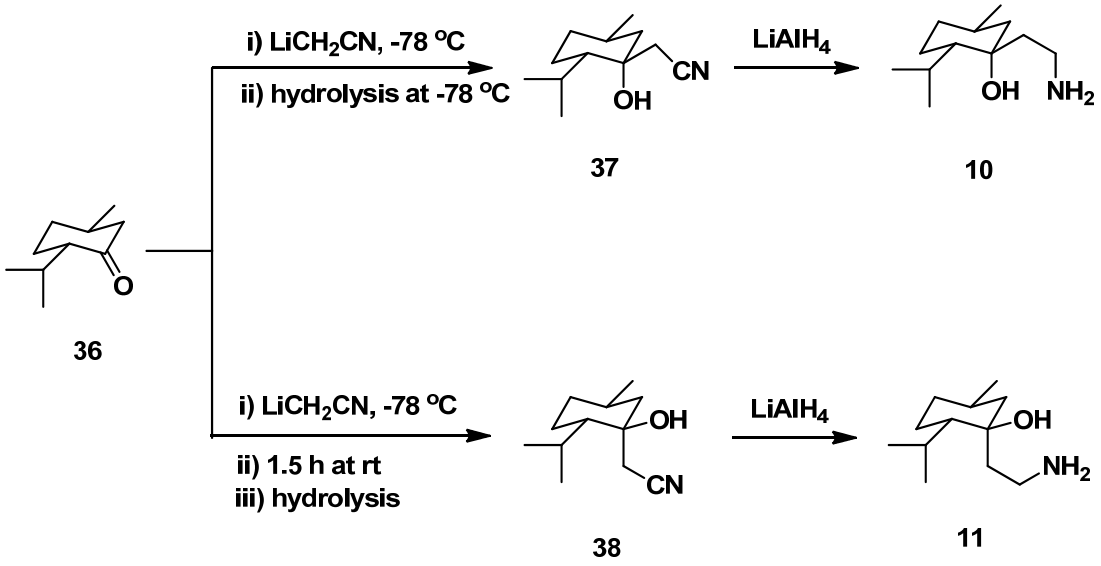
33
n = 1, 2

34
n = 1, 2

35
n = 1, 2

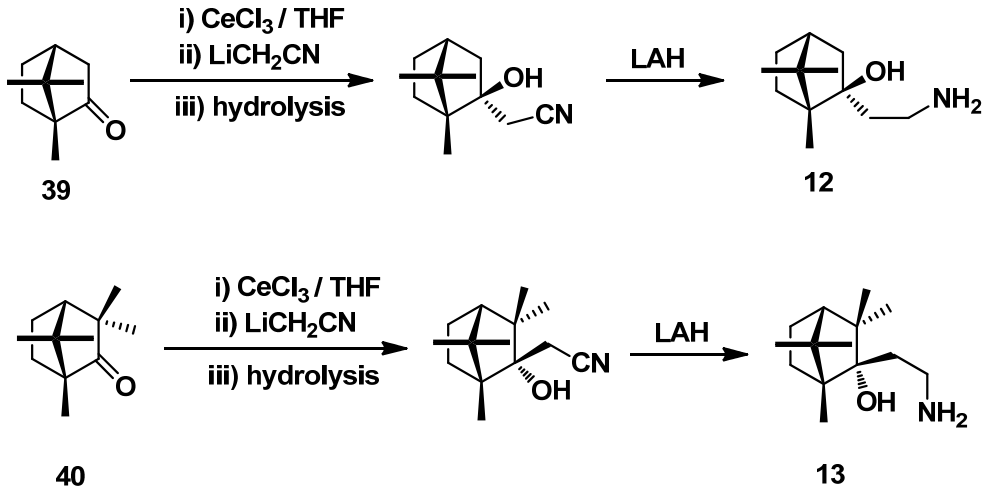
Dimitrov *et al*.[10g] in 2001 reported the diastereoselective preparation of novel chiral 1,3-aminoalcohol (**10** and **11**) with a menthane skeleton by the reduction of corresponding *β*-hydroxynitrile **37** and **38** using $LiAlH_4$ as a reducing agent. The *β*-hydroxynitrile was prepared by highly diastereoselective addition of $LiCH_2CN$ to (-)-menthone **36** (Scheme 12).

Scheme 12. Synthesis of **10** and **11**



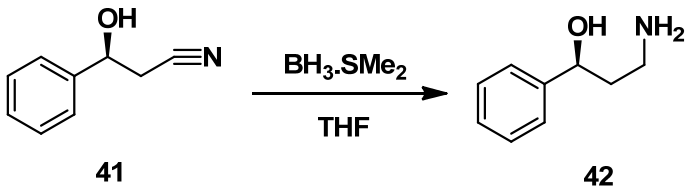
The same author later described the synthesis of chiral 1,3-aminoalcohols (**12** and **13**) derived from (+)-camphor **39** and (-)-fenchone **40** using similar sequence of reactions[10h] (Scheme 13).

Scheme 13. Synthesis of **12** and **13**



Kamal *et al*.[20b] in 2004 reported a simple approach for the preparation of acyclic 1,3-aminoalcohols. Chiral *β*-hydroxynitrile (**41**) obtained through resolution, was reduced with $BH_3.SMe_2$ to obtain the corresponding aminoalcohol **42** (Scheme 14).

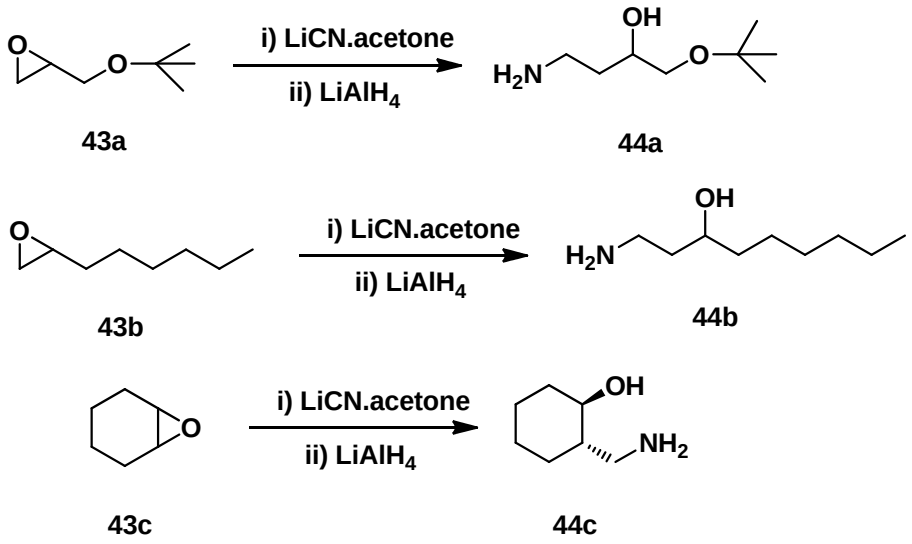
Scheme 14. Synthesis of **42**



41 **42**

Ciaccio *et al.*[20c] developed a methodology for one pot preparation of 1,3-aminoalcohols (**44**) starting from the epoxide **43**, without isolating the intermediate *β*-hydroxynitrile. The reaction of epoxide with LiCN.acetone complex followed by *in situ* reduction using $LiAlH_4$ gave the corresponding 1,3-aminoalcohol (Scheme 15).

Scheme 15. One pot preparation of 1,3-aminoalcohol.

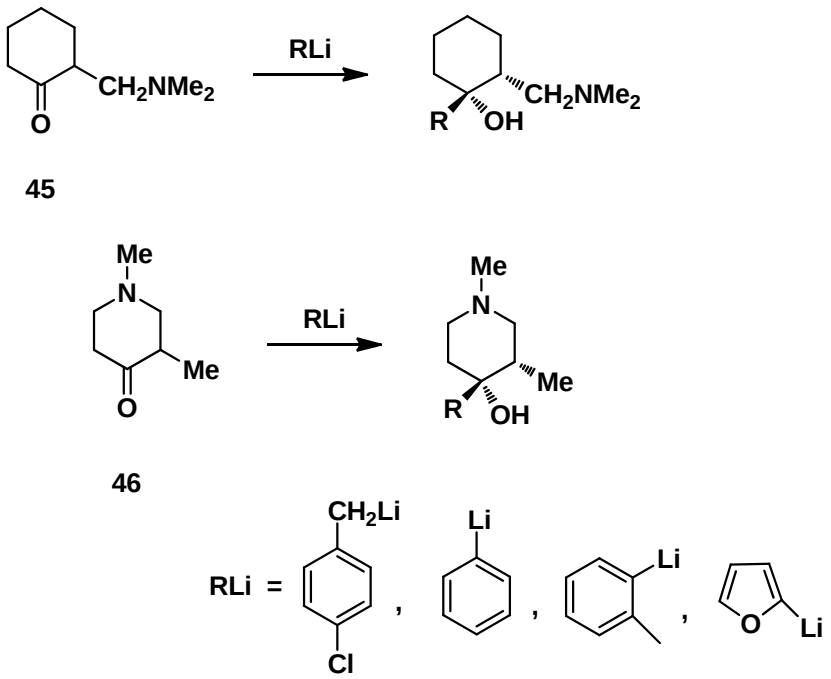


1.2. Addition of organometallic reagents to *β*-aminocarbonyl compounds

1.2.1. Addition to *β*-aminoketone

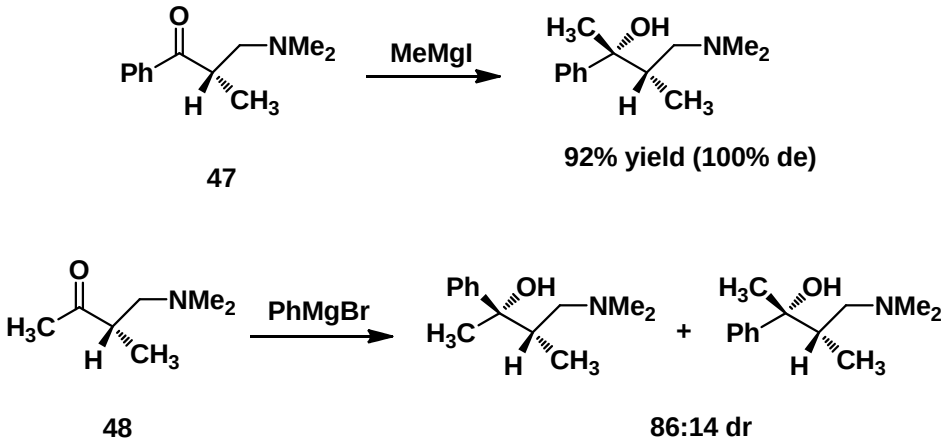
Casy *et al.*[24a] studied the addition reaction of organolithium reagents to 2-dimethylaminomethylcyclohexanone (**45**) and 4-piperidone (**46**). The reaction produces only one stereoisomer (Scheme 16).

Scheme 16. Addition of organolithium reagents



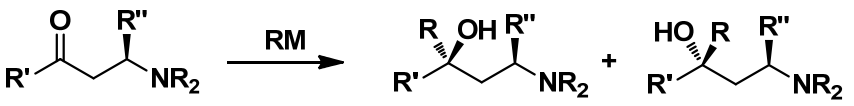
Later Tramontini *et al*.[24b] reported the addition of Grignard reagents to various *β*-aminoketones. Usually good to excellent diastereoselectivity were observed for many substrates. Two representative examples are given in scheme 17.

Scheme 17. Addition of Grignard reagent to *β*-aminoketone



Fouquey *et al*.[24c] reported the addition reaction between organometallic reagents and various *β*-substituted aminoketones (**49**). Low to good diastereoselectivity were observed in the addition reaction (Scheme 18).

Scheme 18. Addition of organometallic reagents



49

Low to good diastereoselectivity with good yield

R' = Me, Et, Ph

R'' = H, Me, Et, Ph

$-NR_2$ = -NHMe, $-NMe_2$, 

RM = MeLi, EtLi, MeMgI, EtMgBr, PhMgCl, PhMgBr, PhMgI

In figure 3, is shown a few *β*-aminoketones which were converted to the corresponding 1,3-aminoalcohols by the addition of organometallic reagents.

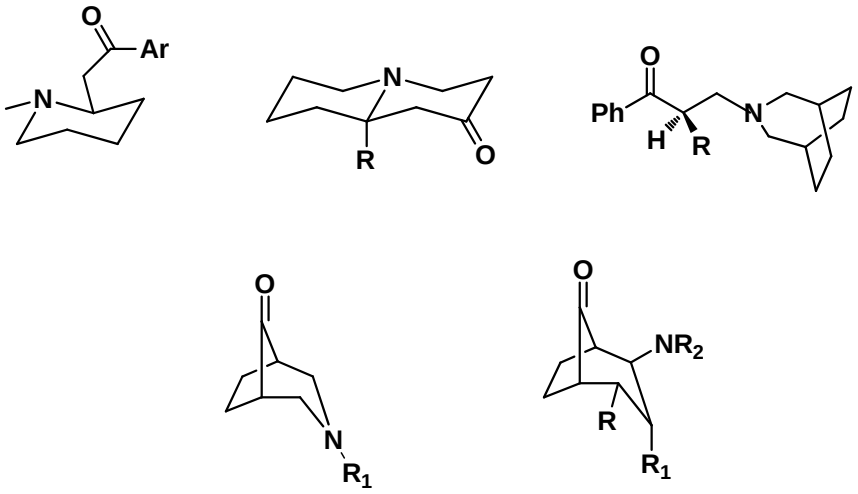


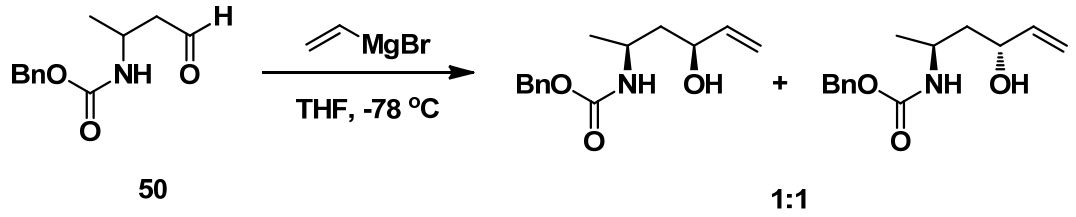
Figure 3

1.2.2. Addition to *β*-aminoaldehyde

The addition of organometallic reagents to *β*-aminoaldehyde is very rarely used for the preparation of 1,3-aminoalcohols mainly because it always required the protection of amino group before to perform the addition reaction and hence lack of practical utility.

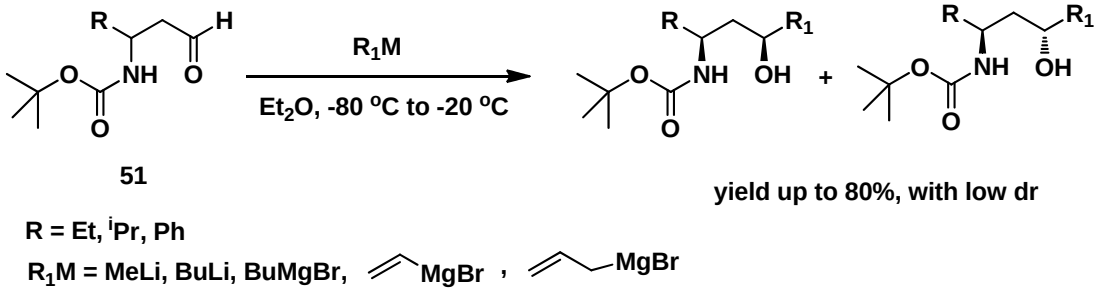
Holmes *et al*.[24d] in 1996 reported the addition of vinylmagmesium bromide to N-protected aminoaldehyde (**50**) in THF at -78 ^{o}C, resulting in a 1:1 mixture of two diastereomers (Scheme 19).

Scheme 19. Addition of vinylmagnesium bromide



Later in 2000, Vaultier *et al*.[24e] studied this reaction in details. Various N-protected aminoaldehydes (**51**) were alkylated using organomagnesium and organolitium reagents. Low diastereoselectivity was observed in these addition reactions (Scheme 20).

Scheme 20. Alkylation of **51**

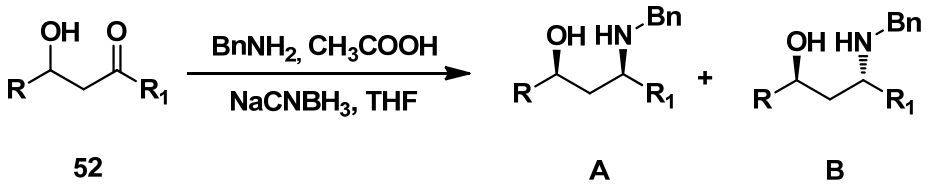


1.3. Miscellaneous methods

1.3.1. Reductive amination of 3-hydroxy ketone

Larchevtque *et al*.[25a] in 1997 developed a methodology for the stereoselective preparation of *syn*-1,3-aminoalcohols through reductive amination of 3-hydroxy ketone (**52**). Excellent diastereoselectivity was observed in the reaction (Table 5).

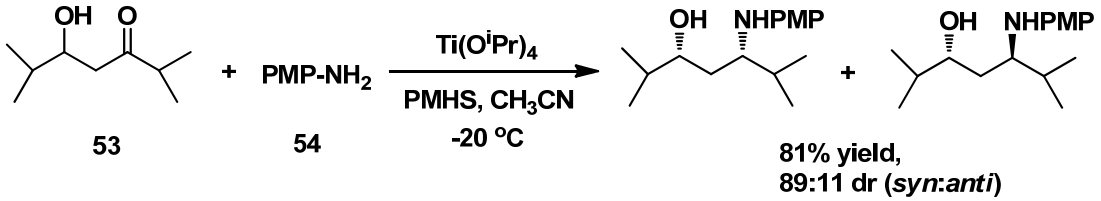
Table 5. Reductive amination of 3-hydroxy ketone **52**



entry	R	R_1	temp. (^oC)	yield (%)	A:B
1	CH_2Ph	Ph	20	77	81:19
2	CH_2Ph	Ph	-15	79	98:2
3	Ph	Ph	0	77	84:16
4	^iPr	Ph	-25	72	91:9
5	^iBu	Ph	0	79	95:5
6	^iPr	^iPr	0	75	92:8
7	^iPr	^iPr	-15	40	85:15

Later Menche *et al.*[25b] reported an efficient method for the diastereoselective preparation of *syn*-1,3-aminoalcohols through directed reductive amination of *β*-hydroxy ketones. The reaction between *β*-hydroxy ketone (**53**) and para-anisidine (**54**) was carried out in the presence of various Lewis acids and hydride reagents. The combination of $Ti(O^iPr)_4/NaBH_4$ provided moderate yield and diastereoselectivity when the reaction was performed at room temperature. By using polymethylhydrosilaxane (PMHS) as a hydride source in the presence of $Ti(O^iPr)_4$ gave improved yield and selectivity (81% yield, 89:11 dr) at -20 ^oC temperature (Scheme 21).

Scheme 21. Reductive amination of *β*-hydroxy ketone



Chelation controlled six-membered transition state (Figure 4) was proposed for the observed *syn*-selective reduction.

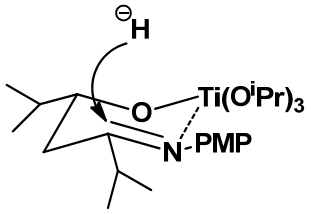


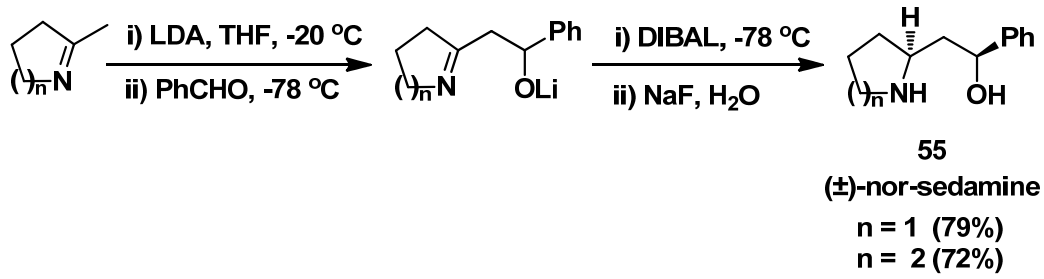
Figure 4. Transition state

Authors further applied this methodology for the preparation of variety of *syn*-1,3-aminoalcohols as well as demonstrated the importance of this methodology in the preparation of hydroxyl-amine core of the pharmaceutically used HIV-protease inhibitors ritonavir and lopinavir.

1.3.2. Addition of azaenolate to aldehyde

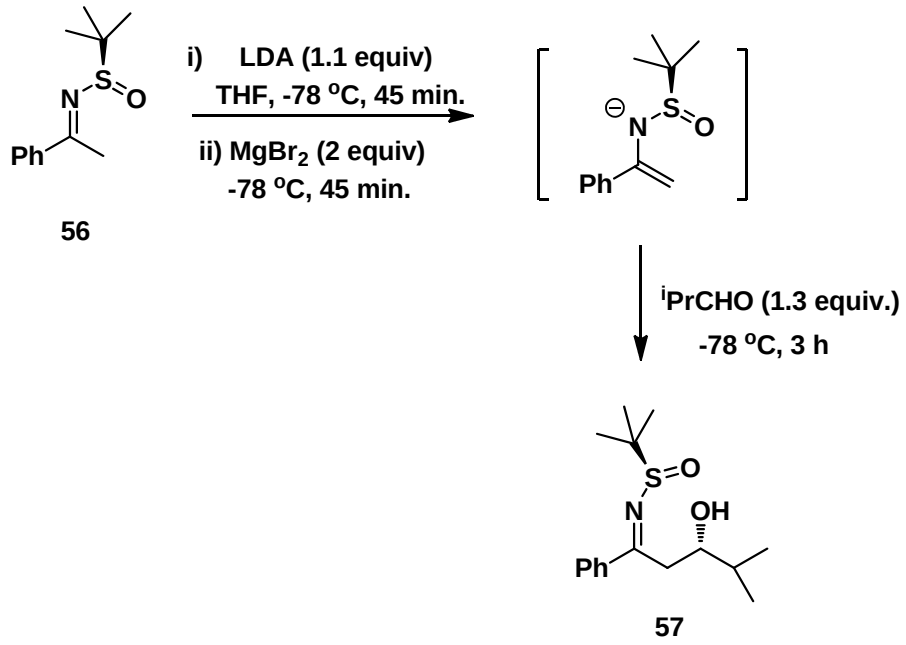
Vaultier *et al*.[23] reported the synthesis of (±)-nor-sedamine, a 1,3-aminoalcohol (**55**) by employing addition of azaenolate to benzaldehyde, followed by reduction with DIBAL-H (Scheme 22).

Scheme 22. Synthesis of (±)-nor-sedamine **55**



1.3.3. Diastereoselective reduction of *β*-hydroxy-*N*-sulfinyl ketimine

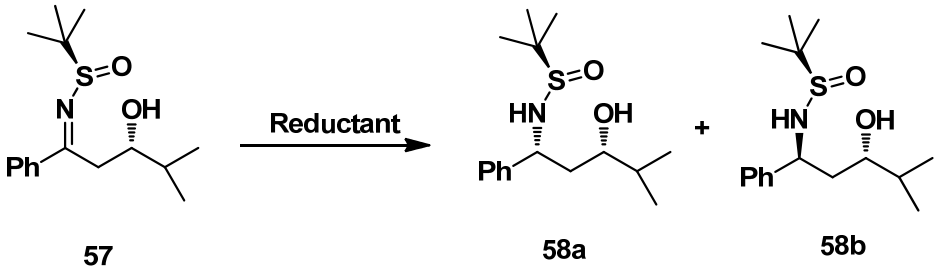
Scheme 23. Synthesis of intermediate **57**



In 2002 Ellman *et al*.[26] reported a very efficient method for the synthesis of both *syn*- and *anti*-1,3-aminoalcohols starting from common intermediate, i.e. *β*-

hydroxy-*N*-sulfinyl ketimine (**57**). The intermediate **57** was prepared by highly diastereoselective addition of a metalated *tert*-butanesulfinyl imine (**56**) to aldehydes in the presence of metal salts (Scheme 23). A number of reducing agents were examined to reduce the intermediate **57** into *N*-sulfinyl-1,3-aminoalcohol diastereoselectively. The *syn*-product (**58a**) was obtained with the highest selectivity (96:4 *syn*:*anti*) by the reduction with catecholborane at -10 ^{o}C. Alternatively, reduction of **57** with $LiBHEt_3$ at -78 ^{o}C provided the *anti*-product (**58b**) in good yield (Table 6).

Table 6. Reduction of **57**



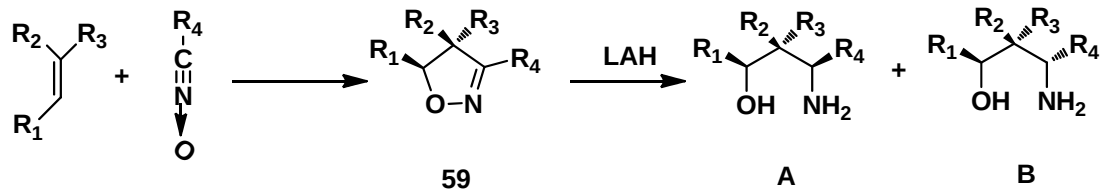
57 **58a** **58b**

reductant	solvent	yield (%)	dr (*syn*:*anti*)
$NaBH_4$	THF	45	34:66
$NaCNBH_4$	THF/AcOH	78	83:17
Catecholborane	THF	88	96:4
$LiBHEt_3$	THF	83	1:99
$LiBH(^{s}Bu)_3$	THF	83	1:99

1.3.4. Reduction of isoxazoline

Jager *et al*.[21] reported the synthesis of 1,3-aminoalcohol by the reduction of isoxazoline (**59**). The isoxazoline was prepared by 1,3-dipolar cycloaddition of nitrile oxides to alkenes which was then converted to 1,3-aminoalcohol by reduction. Good diastereoselectivity was obtained using $LiAlH_4$ (Scheme 24 and Table 7).

Scheme 24. Synthesis of 1,3-aminoalcohol



59 **A** **B**

Table 7. Reduction of **59** with $LiAlH_4$

sr. no.	R_1	R_2	R_3	R_4	yield (%)	A:B
1	CH_3	H	H	Ph	79	87:13
2	Ph	H	H	Ph	98	95:5
3	H	CH_3	H	Ph	82	69:31
4	CH_3	CH_3	H	Ph	65	90:10
5	CH_3	H	CH_3	Ph	89	72:28
6	$-(CH_2)_3-$		H	Ph	97	95:5

2. Applications of 1,3-aminoalcohols

Optically pure 1,3-aminoalcohols have found a variety of applications in asymmetric synthesis as chiral ligands, as chiral auxiliaries and as chiral building blocks.[14,9e,i,15] Ease of preparation of 1,3-aminoalcohols as discussed earlier, is advantageous for their use in asymmetric synthesis. Herein the applications of few important 1,3-aminoalcohols in various asymmetric transformations have been discussed. These include enantioselective addition reactions to carbonyl compounds,[10,11,12] Diels-Alder reaction,[13] ring opening reactions[48] etc (Figure 5).

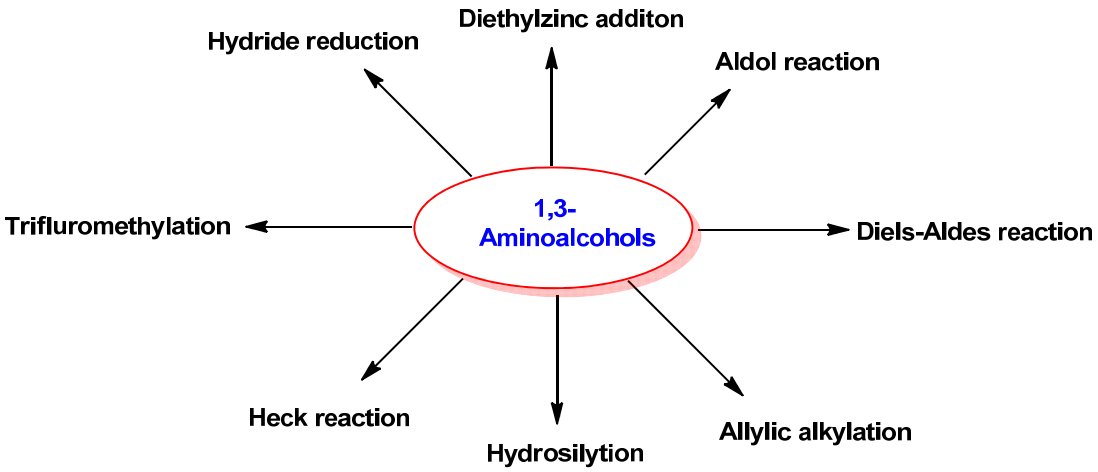


Figure 5

2.1. Enantioselective addition to carbonyl compounds

Over the last 20 years there has been virtually an explosive growth in the discovery of organic reactions that exert control over bond construction. A multitude of chiral reagents and catalysts are now available that can differentiate the enantiotopic atom, group or face in achiral molecule and are capable of exercising precise control over stereoselection.

One of the research directions that hold great influence in this area is the stereoselective addition of nucleophiles to a carbonyl group. It would be a major accomplishment to be able to dictate the direction of the attack of any given nucleophile (Nu) to a predefined enantioface exclusively through the agency of a chiral catalyst. In these reactions, defined stereochemical outcome can be controlled through the proper agency of a chiral auxiliary (stoichiometric) or a chiral catalyst (catalytic). Enantioselective addition of organometallic reagents to aldehydes,[10] asymmetric reduction of prochiral ketones,[11] aldol reactions[12] and addition of trifluromethane to aldehydes[46] are among the important reactions used for the preparation of chiral alcohols as discussed below.

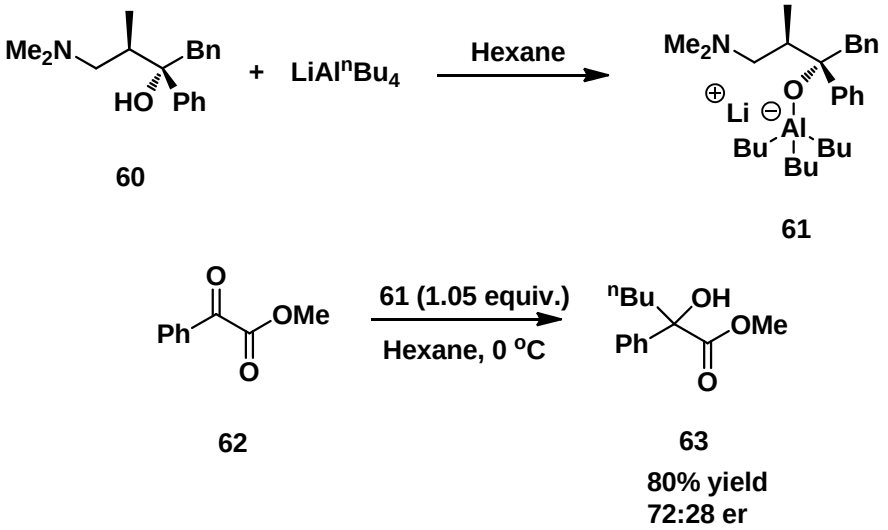
2.1.1. Enantioselective addition of organometallic reagents to carbonyl compounds

Enantioselective addition of organometallic reagents to carbonyl compounds affords optically active alcohols. The reaction is one of the fundamental asymmetric reactions. The use of 1,3-aminoalcohols in this reaction is described below.

i) Stoichiometric approach

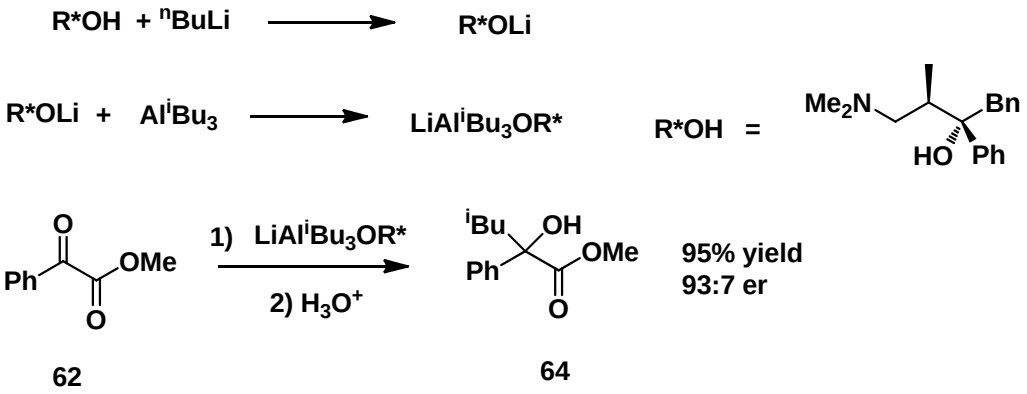
In 1980, Abenhaim *et al*.[27] demonstrated the preparation of chiral alkylating agent **61** by treating the aminoalcohol **60** with $LiAl^{n}Bu_4$. **61** Reacted with phenylglyoxylic acid methyl ester (**62**) in hexane at 0 ^{o}C to give the expected *α*-butyl-*α*-hydroxy ester (**63**) with a good chemical yield and with up to 72:28 er (Scheme 25). It is worth noting that 1,3-aminoalcohol **60** was more successful as a ligand than (-)-*N*-Methyl ephedrine.

Scheme 25: Alkylation of **62**



Later in 1985, the same author reported this reaction with improved selectivity.[28] Replacing the lithium alkyl aluminate with $LiAl^{i}Bu_3OR^*$ affected the enantioselective addition of an isobutyl group to α-keto ester. Compound **64** was generated in 95% yield with 93:7 er (Scheme 26).

Scheme 26. Alkylation of **62** with $LiAl^{i}Bu_3OR^*$



Eliel and He[29] reported the addition of Grignard and organolithium reagents to 2-α-benzoyl-*N*-benzyl-4,4,7-α-trimethyl-*trans* octahydro-1,3-benzoxazine, a chiral auxiliary **65a** derived from the condensation of corresponding 1,3-aminoalcohol **21** with phenylglyoxal. In all the addition reactions, just one diastereomer **66** was observed by ^{1}H and ^{13}C NMR. Hydrolysis of the oxazine adduct **66** with dilute acid cleaved the auxiliary, which upon selective oxidation produced enantiomerically pure α-hydroxy acids **67** (Scheme 27 and Table 8).

Scheme 27. Preparation of α-hydroxy acid **65**

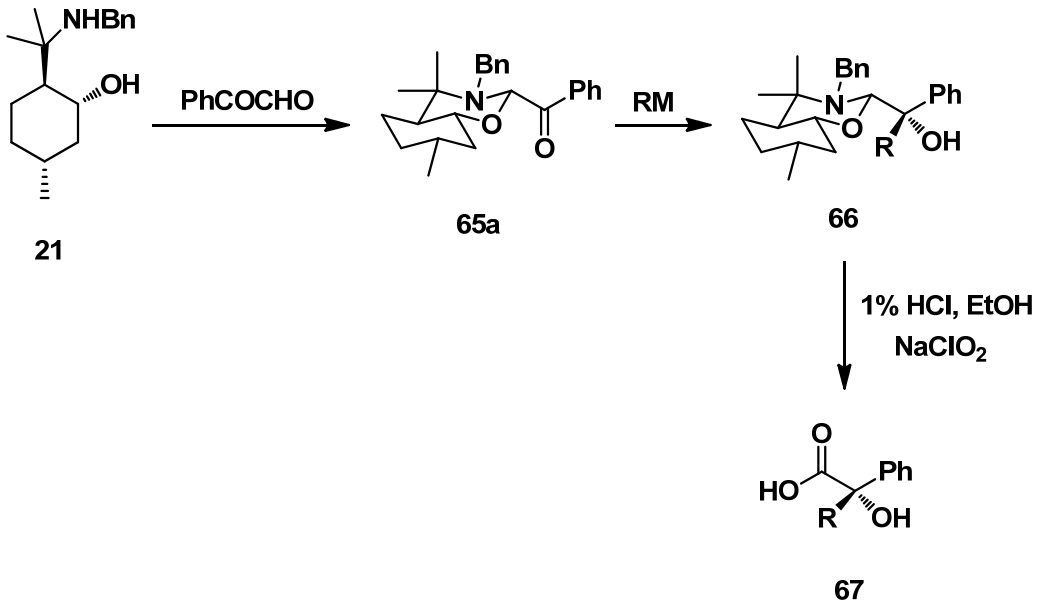
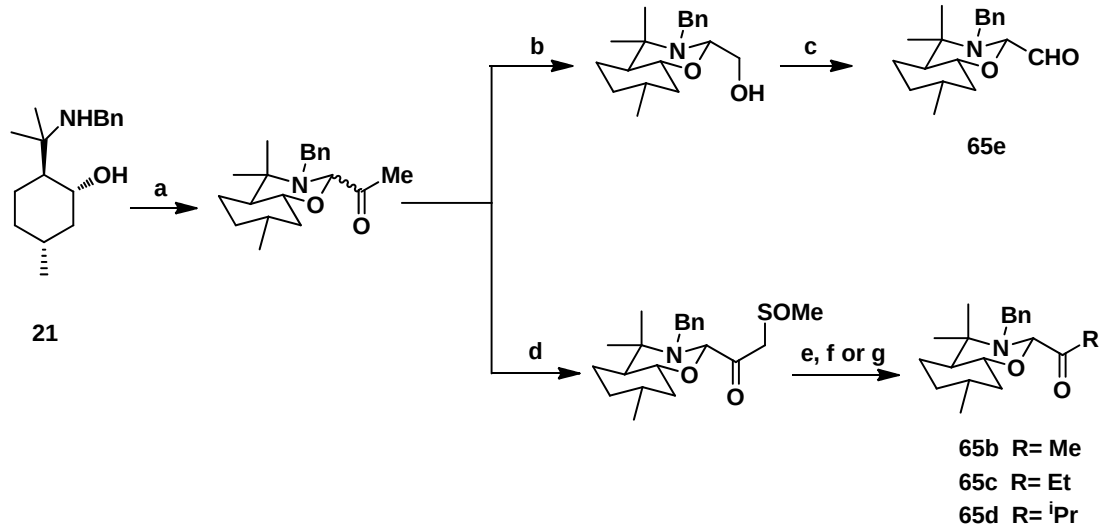


Table 8. Preparation of α-hydroxy acid **67**

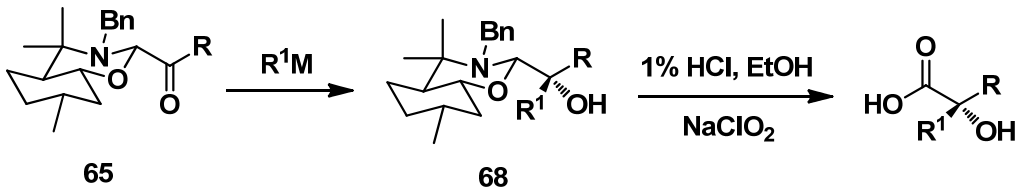
RM	temp (^{o}C)	yield (%)	er
MeMgBr	**20**	**44**	**99:1**
MeMgBr	**-70**	**-**	**99:1**
MeLi	**-70**	**47**	**97:3**
EtMgBr	**5**	**77**	**99:1**
HC≡CMgBr	**20**	**63**	**99:1**
1NP-MgBr	**20**	**23**	**91:9**

In an expansion of this work, Eliel and He[30] in 1990 reported the synthesis of oxazine **65b-e** via an indirect approach (Scheme 28). Various nucleophile were added to **65b-e**, giving product **68** with high yield and diastereoselectivity. Sterics at that site did not appear to play a key role in controlling the direction of addition of MeMgBr to the carbonyl carbon. Exchange the R and R^1 groups allowed access to enantiomeric pairs of the product by using only one enantiomer of the chiral auxiliary.



Scheme 28. Reagents and conditions: (a) MeOCH(OH)COOMe; (b) Vitride, toluene; (c) DMSO, TFAA, Et_3N; (d) NaDMSO; (e) Al-Hg; (f) excess NaDMSO, MeI (1 equiv.), Al-Hg; (g) excess NaDMSO, excess MeI, Al-Hg.

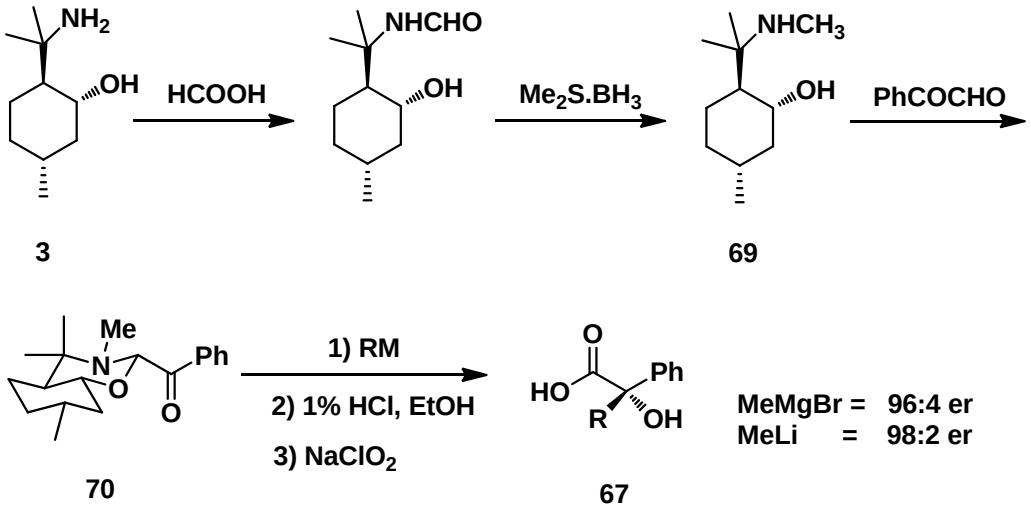
Table 9. Addition of nucleophile



SM(65)	R^1M	R	R^1	yield (%)	dr
b	EtMgBr	Me	Et	97	92:8
b	^{i}PrMgCl	Me	iPr	~100	96:4
b	PhMgBr	Me	Ph	81	95:5
c	MeMgBr	Et	Me	93	96:4
d	MeMgBr	iPr	Me	~100	94:6
e	MeMgBr	H	Me	81	95:5
e	PhMgBr	H	Ph	~100	84:16

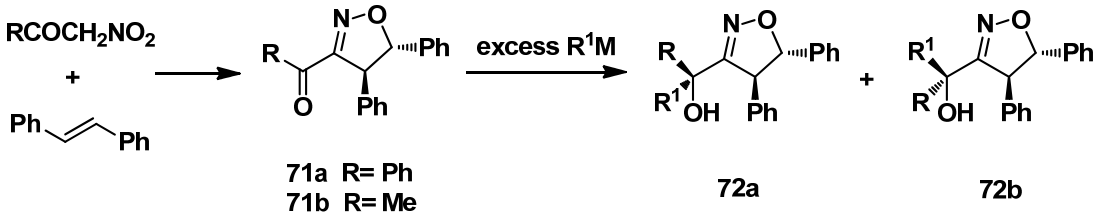
Eliel and He,[30] also reported the preparation of 8-methyl aminomenthol **69**, from which ketone **70** was made. Reaction of oxazine **70** with nucleophile was slightly less selective than the corresponding benzylated system (Scheme 29).

Scheme 29. Addition of nucleophile to **70**



In 1984, Wade *et al*.[31] reported a highly diastereoselective addition of organolithium and Grignard reagents to 3-acyl isoxazoline **71**. When ketone **71a** and **71b** were reacted with an excess of the organometallic reagents, they provided diastereomeric alcohols **72a** and **72b** respectively. Diastereofacial selectivity is highly metal dependent (Table 10).

Table 10. Addition of organometallic reagents to **69**



SM	R^1M	yield (%)	72a:72b
71a	MeLi	94	99.5:0.5
71a	MeMgBr	77	2:98
71b	PhLi	82	1:99
71b	PhMgBr	71	99:1

ii) Catalytic approach

Eventhough there have been successful methods reported for the enantioselective addition of organolithium and Grignard reagents using chiral 1,3-aminoalcohols, these methods require at least a stoichiometric amount of chiral ligands. A catalytic enantioselective addition of organometallic reagents to aldehydes is a challenging problem. A possible pathway to achieve enantioselective alkylation by the addition of organometallic reagent R_2M to carbonyl compounds in the presence of catalytic amount of protic auxiliary is represented below[32] (Figure 6).

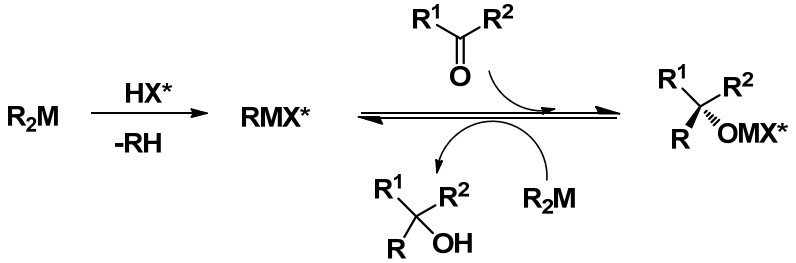


Figure 6

To achieve high chiral efficiency, the anionic ligand x* must have a suitable three dimensional structure which can differentiate between the diastereomeric transition states of the alkyl transfer step. Unlike in stoichiometric reagents, the rate of the reaction of the alkyl transfer from chirally modified reagent should substantially exceed that of non-catalyzed original achiral reagent R_2M. Furthermore, X* should detach readily from the initially formed metal alkoxide by the action of alkyl donor or carbonyl substrate to establish the catalytic cycle.

In this context, diorganozinc reagents serve as ideal donors. Monomeric dialkylzincs having a *sp*-hybridized linear geometry are inert to 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 possesses a higher *p* character (Figure 7).

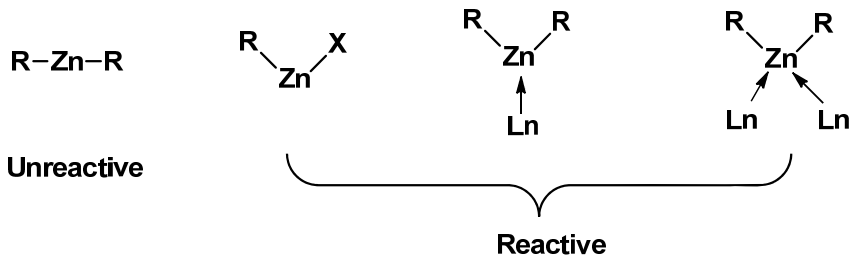
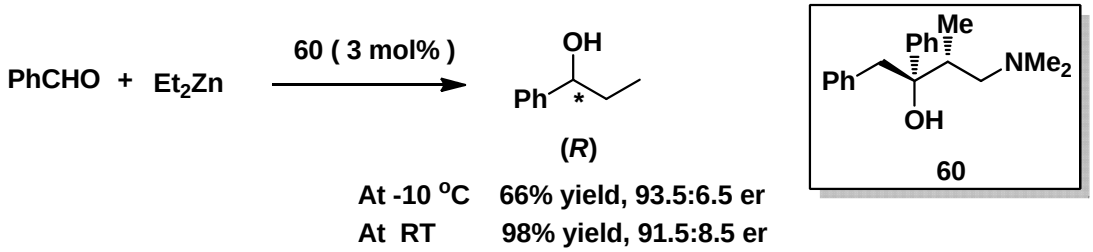


Figure 7

A coordinatively unsaturated bent compound, particularly with an electronegative substituent, has a strong donor property for the alkyl group and acceptor character at the Zn atom. Such auxiliary-induced structural perturbation would increase the reactivity toward carbonyl substrates. In addition, since alkylzincalkoxides usually form stable cubic tetramers in hydrocarbons, liberation of chiral anionic ligands from the initial alkylation products may be facilitated. Thus chiral ligands not only control the stereochemistry of the organozinc addition, but also activate the zinc reagents. Overall, organozinc chemistry provides an opportunity for stereoselective alkylation based on catalytic asymmetric induction. The validity of such a consideration was first shown in 1984 by Oguni and Omi[33] reporting that reaction of diethylzinc and benzaldehyde was aided by a catalytic amount of (*S*)-leucinol to give (*R*)-l-phenylpropanol in 74.5:25.5 er. Since the initial work of Oguni and Omi[33] with (*S*)-leucinol, followed by Noyori's[34] work with DAIB, a number of chiral ligands have been developed.[35] Aminoalcohol react with dialkylzinc to generate a zinc-based chiral Lewis acid complex which can further co-ordinate with both the aldehyde substrates and the dialkylzinc reagents to conduct the catalytic addition. Thus, the *in situ* generated zinc complex is a multifunctional catalyst. It acts as a Lewis acid to activate the carbonyl substrates and also as a Lewis base to activate the organozinc reagents. The chiral environment of the ligand controls the stereoselectivity. A wide variety of amino alcohols, mostly 1,2-aminoalcohols have been prepared and used as chiral catalyst for enantioselective addition of Et_2Zn to aldehyde.[35] Whereas, only a few examples of the use of chiral 1,3-aminoalcohols have been reported.[10]

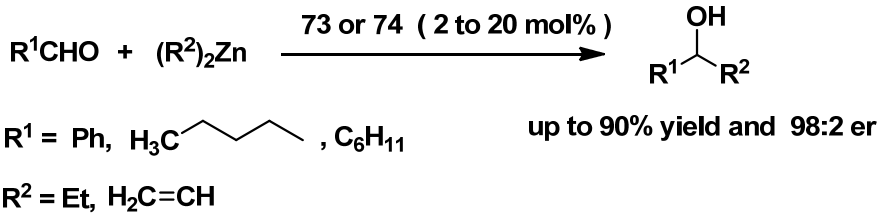
In 1987 Buono and co-workers[10a] reported the use of (2*S*,3*R*)-4-(Dimethylamino)-1,2-diphenyl-3-methyl-2-butanol (**60**, **Chirald**), a 1,3-aminoalcohol for the enantioselective addition of diethylzinc to benzaldehyde. Up to 93.5:6.5 er with 66% yield was obtained at -10 ^{o}C temperature using 3 mol% loading of catalyst. Increasing the temperature to room temperature, enantiomeric excess decreased slightly but the yield was increased dramatically (91.5:8.5 er, 98% yield) (Scheme 30). It is worth noting that the result obtained with chirald was better than (-)-*N*-methyl ephedrine.

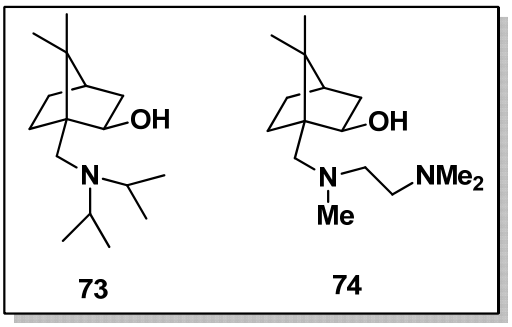
Scheme 30. Enantioselective addition of Et_2Zn to aldehyde catalyzed by **60**



Oppolzer *et al.*[10b] in 1988 reported the application of novel bi- and tri-dentate ligands (**73** and **74**), derived from camphor-10-sulfonic acid for the enantioselective addition of diethylzinc and divinylzinc to aldehydes. Excellent enantioselectivity and yield were observed for the addition of both diethyl and divinylzinc to various aromatic and aliphatic aldehydes (Scheme 31).

Scheme 31. Enantioselective addition of Et_2Zn to aldehyde

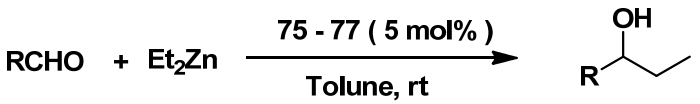




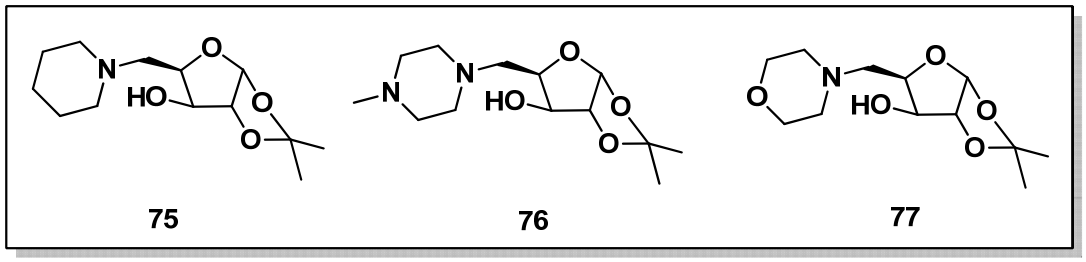
Cho *et al.*[10c] in 1994 reported the enantioselective addition of diethylzinc to aldehydes using 1,2-isopropylidene-5-deoxy-5-dialkylamino-α-D-xylofuranoses **75-77** prepared from α-D-xylose. This is the first example where carbohydrate derived ligand was used for the enantioselective addition of diethylzinc to aldehydes. Reaction was carried out at room temperature using 5 mol% catalyst and the corresponding

alcohol was obtained in up to 96% yield with 98:2 er. For addition to benzaldehyde, **77** offered the best chiral induction giving product with 98:2 er (Scheme 32).

Scheme 32. Enantioselective addition of Et_2Zn to aldehyde catalyzed by **75-77**

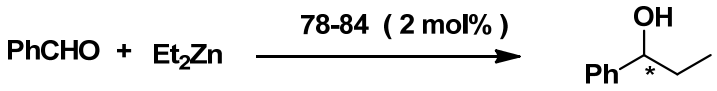


up to 96% yield and 98:2 er

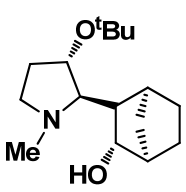


Later in 1997 Cicchi and co-workers[10d] reported a series of new 1,3-aminoalcohols (**78-84**) for the enantioselective addition of diethylzinc to benzaldehyde. The results were satisfactory for conversion but the obtained enantioselectivity was low (Scheme 33).

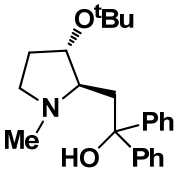
Scheme 33. Enantioselective addition of Et_2Zn to aldehyde catalyzed by **78-84**



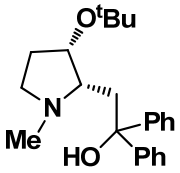
up to 100% yield and 77:23 er



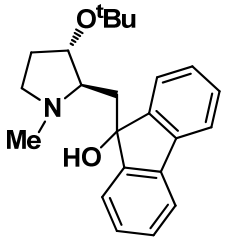
78



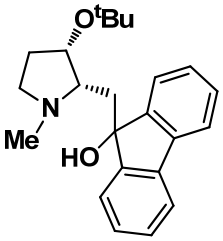
79



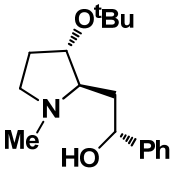
80



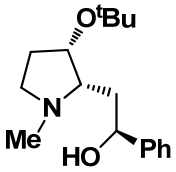
81



82



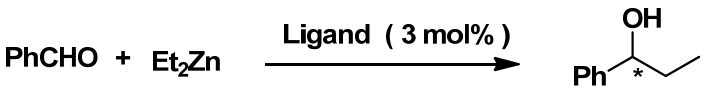
83

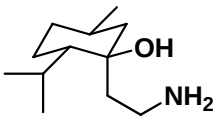


84

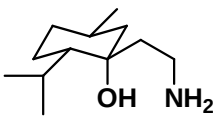
Dimitrov *et al.*[10g,h] in 2001 reported the enantioselective addition of diethylzinc to benzaldehyde using 1,3-aminoalcohols derived from (-)-menthone, (+)-camphor and (-)-fenchone. Using 3 mol% of catalyst, the yield of ethylated product was satisfactory while enantioselectivity was moderate (Scheme 34).

Scheme 34. Enantioselective addition of Et_2Zn to benzaldehyde

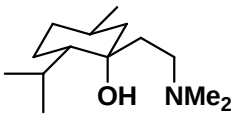




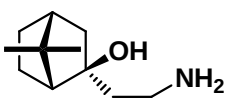
50:50 er



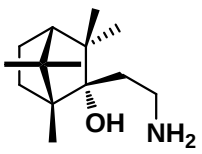
60:40 er



88.5:11.5 er

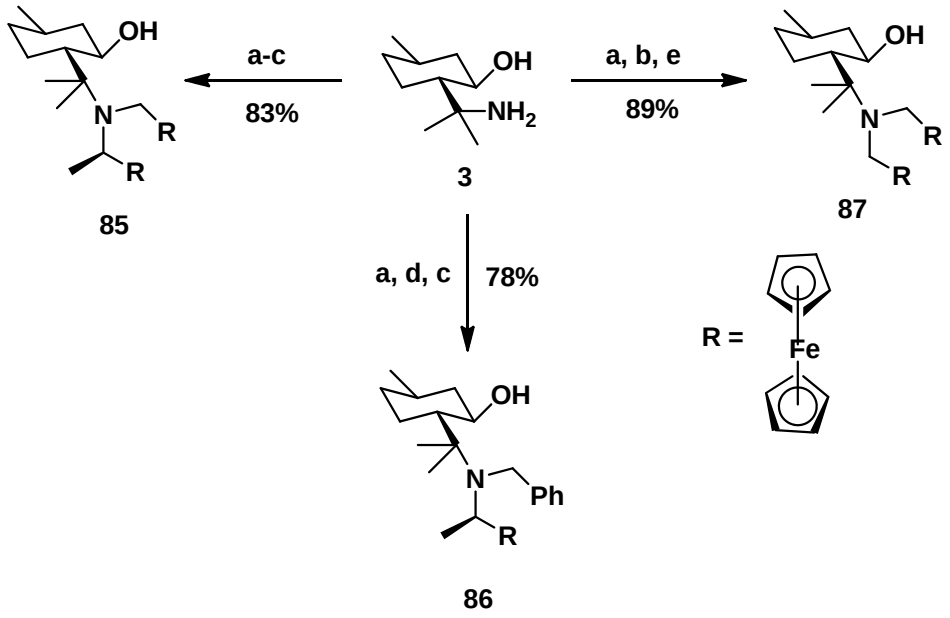


54.5:46.5 er



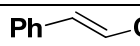
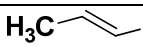
64:36 er

8-Aminomenthol derivatives have also been used as ligands for asymmetric dialkylzinc addition to aldehydes. Specifically, Pedrosa *et al.*[10i] prepared ferrocenyl derivatives **85**, **86**, and **87** in good yield from **3** (Scheme 35). None of these compounds were effective ligands on their own; however, when pretreated with MeMgBr, the results were much better. Ligands **85** and **86** both gave excellent yields of ethylated product with moderate enantioselectivity (75:25 er for both ligands) while ligand **87** gave product in good yield with 98:2 er. Given this success, **87** was used to catalyze Et_2Zn addition to a variety of aromatic and aliphatic aldehydes, giving alcohols with 80:20 to 98:2 er (Table 11).

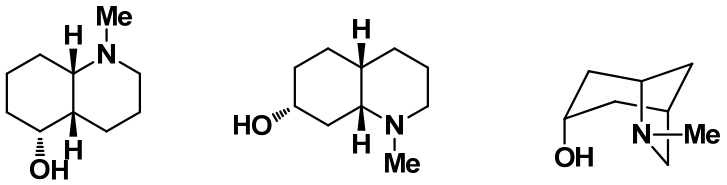


Scheme 35. Reagents and conditions: (a) ferrocenecarboxaldehyde, CH_2Cl_2, rt; (b) ferrocenyl CH_2NMe_3I, K_2CO_3, reflux; (c) MeMgBr, PhH, rt; (d) BnBr, K_2CO_3, MeCN, reflux; (e) DIBAL-H, PhMe, 0 °C.

Table 11. Et_2Zn addition catalyzed by **87**

entry	aldehyde	yield (%)	er
1	PhCHO	87	97.5:2.5
2	*p*-$OMeC_6H_4CHO$	65	85:15
3	*p*-ClC_6H_4CHO	76	97.5:2.5
4		78	54:46
5		70	84:16
6	$CH_3(CH_2)_4CHO$	73	88.5:11.5
7	FecCHO	90	86.:13.5

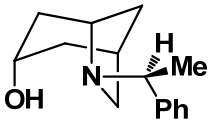
Kozlowski and co-workers[10j] in 2003 described theoretical and experimental studies of asymmetric addition of organozinc to benzaldehyde catalyzed by *cis*-decalin based γ-aminoalcohols, **88-92** (Figure 8).



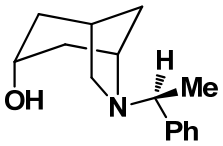
88

89

90



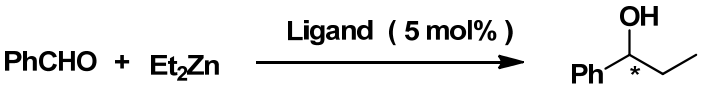
91



92

Figure 8

Table 12. Et_2Zn addition catalyzed by **88-92**



entry	solvent	ligand	er (*R*:*S*)
1	Toluene	88	47:53
2	THF / Toluene	89	61:39
3	Toluene	90	73:27
4	THF / Toluene	89	85:15
5	Toluene	90	67:33
6	Toluene	91	53:47
7	Toluene	92	63:37

Ligands **88-92** were investigated in the addition of diethylzinc to benzaldehyde (Table 12). Low to moderate enantioselectivity could be attributed to low energy difference between the diastereomeric reaction pathways for these γ-aminoalcohols. Ligand **89** provide better enantioselectivity when compared to ligand **87**. The equilibrium ratio of **89**-in / **89**-out (12:1) is higher than **88**-in / **88**-out (2.4:1) which explains the higher enantioselection for ligand **89** (Figure 9). Conformationally

constrained analogue (**90**) would be expected to give the (*S*)-product, instead provided the (*R*)-product with low selectivity. Further incorporation of *N*-alkyl groups with additional stereogenic centers (**91**, **92**) in place of the *N*-methyl group of **90** did not improve the selectivity.

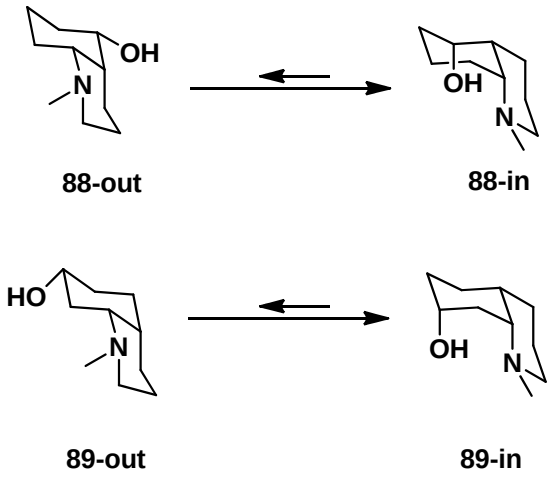


Figure 9

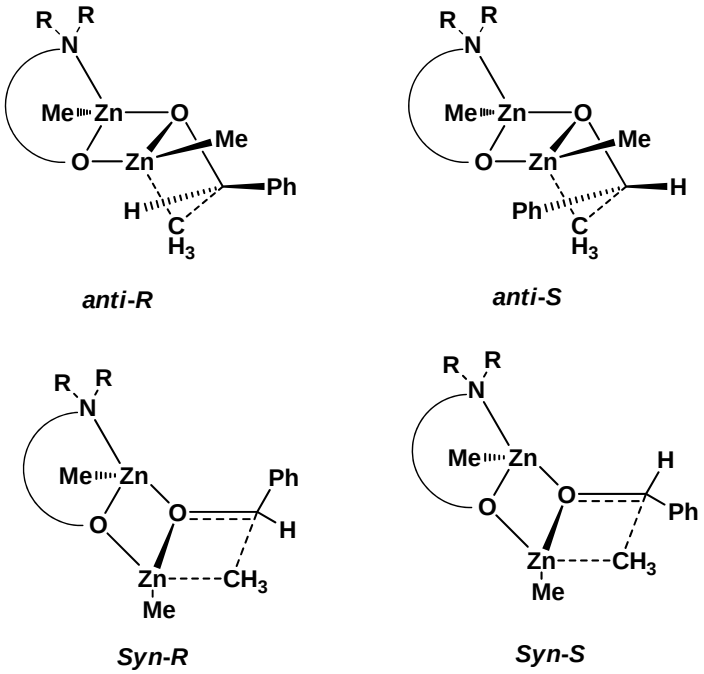


Figure 10. 6/4/4 Transition state

These experimental results were further explained by calculations on the transition structure of **88-90.** Two different transition structures, namely, 6/4/4 tricyclic transition structure (Figure 10) originally described by Noyori *et al*.[33] and 6/6 bicyclic six membered transition structure (Figure 11) originally described by Norrby

et al.[36] were studied by using different theoretical methods. The three different methods (HF, B3LYP and MP2) employed in this study, for all the cases studied (ligand **88, 89**, and **90**) the *anti R*-transition structure leading to (*R*)-alcohol was found to be the most stable.

As reported by Norrby *et al*.[36] that the PM3 bicyclic transition structure for certain *β*-aminoalcohols are lower in energy than the tricyclic structure. In case of *γ*-aminoalcohol **88-90** also, 6/6 bicyclic transition structure at PM3 level are 4-8 kcal/mol lower in energy compared to 6/4/4 analogues.

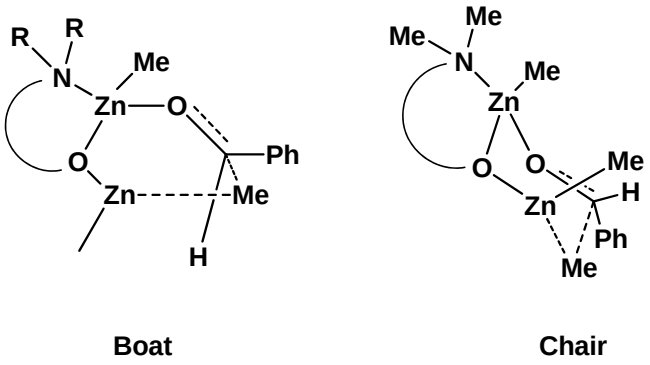
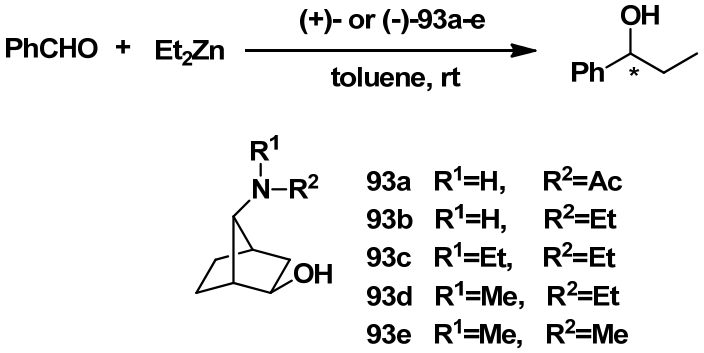


Figure 11. 6/6 bicyclic six-membered transition state

In the HF/LanL2DZ calculations, the 6/6 transition structures were found to be higher in energy than their 6/4/4 analogues. Overall, PM3 calculations are not reliable for anticipating the selectivity. Among the quantum chemical calculations examined (HF, DFT, MP2), MP2 proved most useful in estimating the selectivity for the *γ*-aminoalcohol which explains the tricyclic *μ*-oxo (6/4/4) rather than the bicyclic six-membered (6/6) transition structures.

Costa and de Oliveira[10k] recently reported the synthesis of (+)- and (-)-*syn*-1,3-aminoalcohols **93a-e** with norbornane framework and used as catalysts. Moderate to excellent enantioselectivities (77:23 to 95:5 er) were reported (Table 13). The configuration of the carbon bearing the hydroxyl moiety was found to influence the absolute stereochemistry of 1-phenylpropanol. At 20 mol% loading, catalyst (-)-**93c** was found to be the most efficient, giving (*S*)-1- phenylpropanol in 99% yield and 96:4 er (entry 5, Table 13).

Table 13. Diethylzinc addition catalyzed by **93**



entry	ligand (93)	mol (%)	time (h)	yield (%)	er	config.
1	(+)-a	20	3	71	82:18	*R*
2	(+)-b	20	8	62	77:23	*R*
3	(+)-c	8	18	94	93:7	*R*
4	(-)-c	8	18	90	89:11	*S*
5	(-)-c	20	1	99	96:4	*S*
6	(+)-d	20	1	96	93:7	*R*
7	(-)-e	8	20	91	89:11	*S*
8	(+)-e	8	20	93	91:9	*R*
9	(+)-e	20	1	98	93:7	*R*

The 6/4/4 transition structure (Figure 12) was proposed for the result obtained by these 1,3-aminoalcohols.

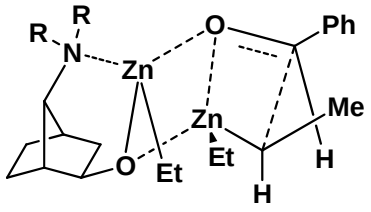
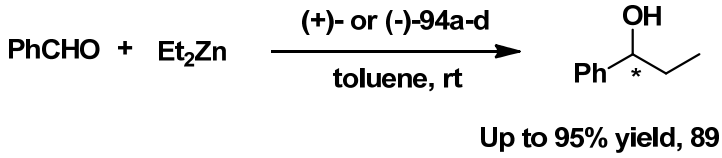


Figure 12. Transition state

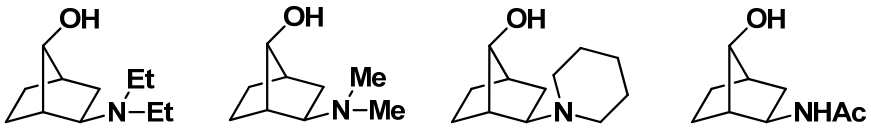
Inspired by these results, the same group later[101] in 2006, synthesized a new chiral *γ*-aminoalcohols (+)-and (-)-*syn*-2-amino-7-hydroxy norbornane derivatives **94a-d** which presents the functional groups in opposite positions as compared to **(+)-**

93. The catalyst afforded 1- phenylpropanol in high yields (83-98%) and moderate enantioselectivity (70:30-89:11 er). At 20 mol % loading, catalyst **94c** was found to be the most efficient, giving 1- phenylpropanol in 95% yield and 89:11 er (Scheme 36).

Scheme 36. Diethylzinc addition catalyzed by **94**



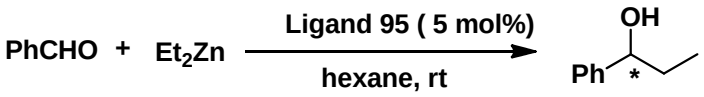
Up to 95% yield, 89:11 er



94a **94b** **94c** **94d**

Aoyama *et al*.[10m] in 2005 described the enantioselective addition of diethylzinc to various aldehydes catalyzed by (1*R*,2*R*)-10-Dialkylaminoisoborneols **95a-j**, derived from (+)-ketopinic acid. For the addition to benzaldehyde, **95j** with 9-azabicyclo[3.3.1]nonan-9-yl group as an amino moiety offered the best chiral induction, giving product with 97:3 er (Scheme 37). This ligand was therefore used for Et_2Zn addition to various aldehydes, giving alcohols in good yield with good to excellent enantioselectivity (Table 14).

Scheme 37. Diethylzinc addition catalyzed by **95**



Up to 99% yield, 97:3 er

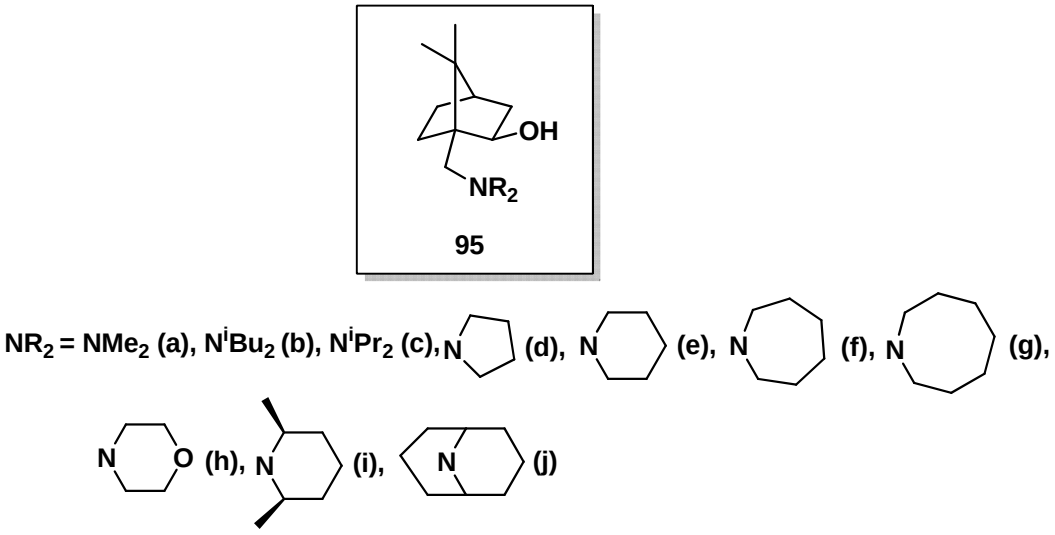
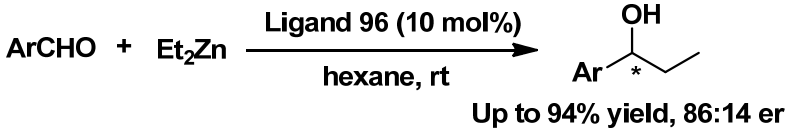


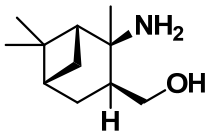
Table 14. Enantioselective addition of diethylzinc to aldehydes using **95j**

entry	aldehyde	time (h)	yield (%)	er
1	*p*-tolualdehyde	3	99	96.5:3.5
2	*p*-chlorobenzaldehyde	3	99	96:4
3	*o*-tolualdehyde	3	99	97.5:2.5
4	1-naphthaldehyde	3	94	95.5:4.5
5	Ph–CHO	3	86	89.5:10.5
6	$PhCH_2CH_2CHO$	3	82	92:8

In 2006 Fulop and co-workers[10n] prepared 1,3-aminoalcohols **96a-d**, from (+)- and (-)-pinene and used as ligands for addition of diethylzinc to various aromatic aldehydes. Low to good enantioselectivities (up to 86:14 er) were reported (Scheme 38). The obtained results were explained by theoretical calculations using molecular modelling at the ab initio level.

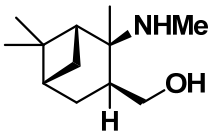
Scheme 38. Enantioselective addition of diethylzinc to aldehydes catalyzed by **96**



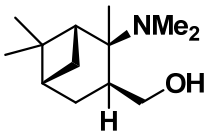


96a

96b



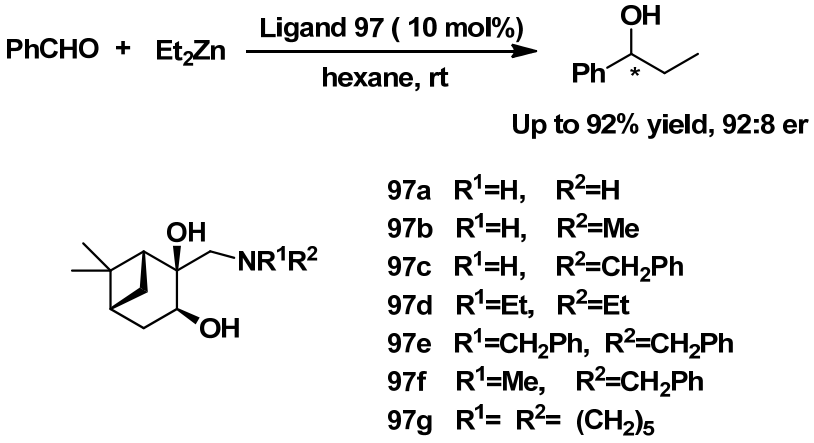
96c



96d

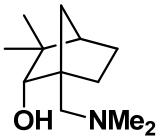
Later[10o] in 2008, the same group prepared aminodoils **97a-g**, from (-)-pinene via α-pinene oxide and examined their catalytic efficiency. These catalyst afforded 1-phenylpropanol in high yields (60-92%) and good enantioselectivity (up to 92:8 er) as shown in scheme 39.

Scheme 39. Enantioselective addition of diethylzinc to aldehydes catalyzed by **97**

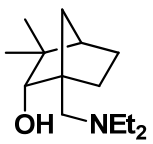


In 2007 Vilar and co-workers[10p] reported norbornane-based γ-aminoalcohols **98-101** (Figure 13) catalyzed enantioselective addition of diethylzinc to benzaldehyde and compared their results with corresponding β- and δ-aminoalcohols (**102 and 103**) with the same structural features (Table 15 and Figure 14). Due to the lower energy difference between two diastereomeric transition states, γ-aminoalcohols provides less stereodifferentiation when compared to their β- and δ-homologues.

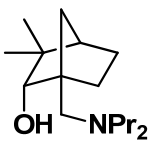
98



99



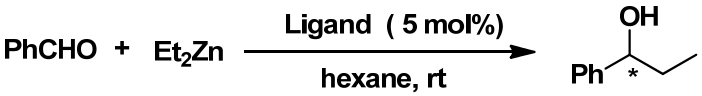
100



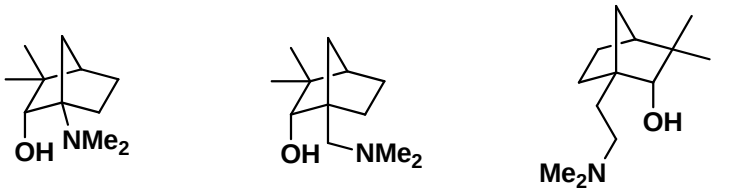
101

Figure 13

Table 15. Enantioselective addition of diethylzinc to PhCHO catalyzed by **98-101**



ligand	yield (%)	er
98	**94**	**66:34**
99	**97**	**73.5:26.5**
100	**99**	**83:17**
101	**80**	**55.5:44.5**



102
83.5:16.5 er (*R*)

99
73.5:26.5 er (*R*)

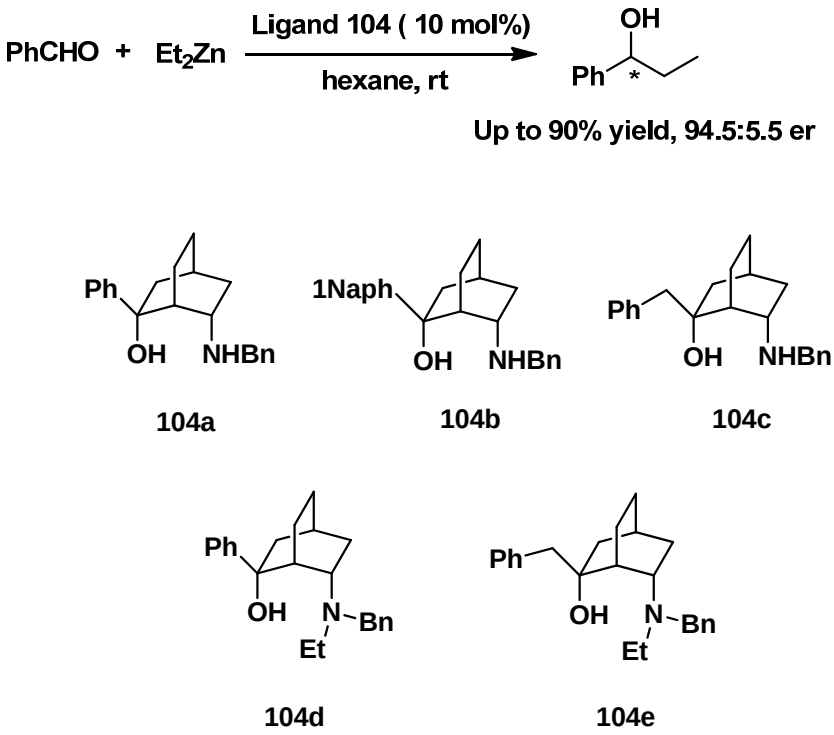
103
83.5:16.5 er (*S*)

Figure 14

Better results are obtained by increasing the steric hindrance around the nitrogen atom upto a critical steric congestion point, determined by both nitrogen substituent bulkiness and chelate ring-size. As a consequence, the enantioselectivity was found to vary in a non-systematic manner upon increasing both the catalyst chelate ring-size, from five to seven-membered, and the bulkiness of the nitrogen substituents.

Very recently Frejd *et al.*[10q] reported few bicyclic *γ*-aminoalcohols (**104a-e**) and studied their catalytic properties in enantioselective addition of diethylzinc to benzaldehyde. These *γ*-aminoalcohols afforded 1- phenylpropanol in high yields (up to 90%) with moderate to good enantioselectivity (74:26-94.5:5.5 er) (Scheme 40).

Scheme 40. Enantioselective addition of diethylzinc to PhCHO catalyzed by **104**



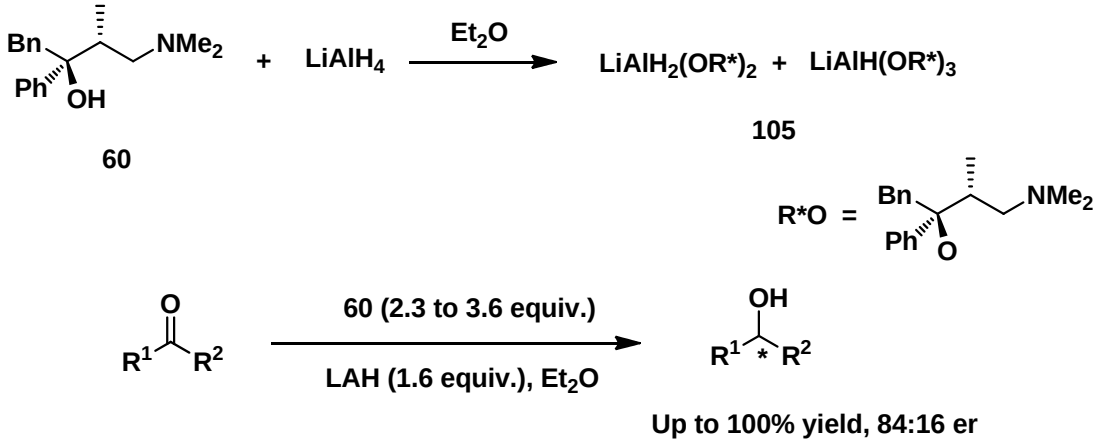
2.1.2. Asymmetric reduction of prochiral ketone

The reduction of prochiral ketones with an optically active reducing agent is a conceptually simple approach to enantiomerically enriched secondary alcohols. The reduction is discussed by two approaches as follows.

i) Lithium aluminium hydride mediated reduction: Stoichiometric approach

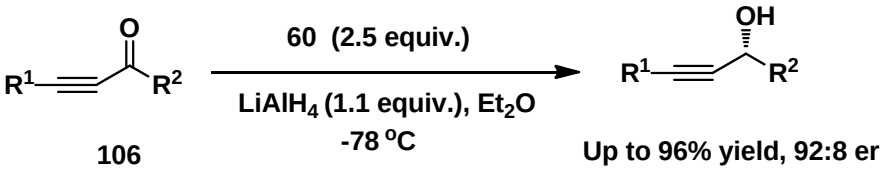
Yamaguchi *et al*.[37] in 1972 first time reported the use of 1,3-aminoalcohol in the asymmetric reduction of prochiral ketone in the presence of lithium aluminium hydride. (+)-(2*S*,3*R*)-4-dimethylamino-l,2-diphenyl-3-methyl-2-butanol (**60**, **Darvon alcohol**) was reacted with $LiAlH_4$ to generate chiral reducing agents (**105**), which was used to reduce acetophenone to corresponding alcohol. Reaction with fresh reagent in Et_2O at -65 ^oC gave (*R*)-alcohol (88:12 er) quantitatively after 3 minutes. The reaction with reagents that had been stirred overnight gave (*S*)-alcohol (83:17 er) with 40% conversion. Similar results were observed for the reduction of other ketones although the enantioselectivity was not as good (Scheme 41). Author postulated the existence of a rapidly formed *R*-selective reagent which could be converted to a more stable *S*-selective reagent over time, as one of the reason behind the time dependent reversal selectivity.

Scheme 41. Reduction of ketone using LAH in the presence of **60**



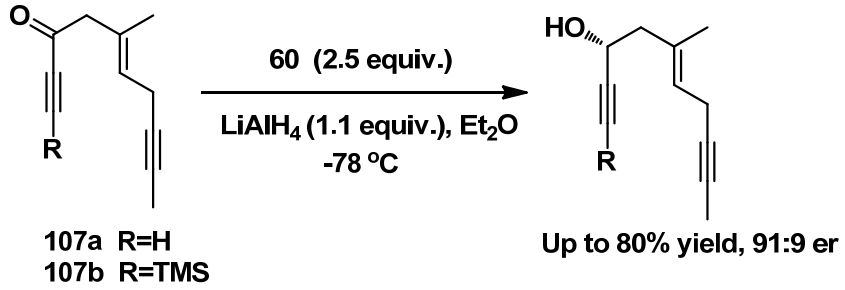
Five years later, Brinkmeyer and Kapoor[38] used this methodology to reduce acetylenic ketones **106** to propargylic alcohols. Up to 92:8 er was obtained with excellent yield (Scheme 42).

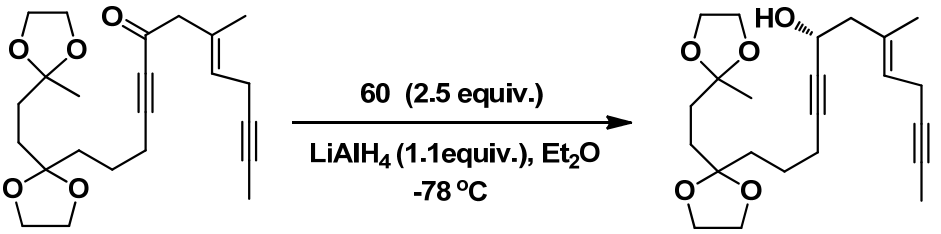
Scheme 42. Reduction of **106**



This chemistry was applied for the asymmetric synthesis of 11*R*-hydroxyprogesterone, a key intermediate in commercial production of hydrocortisone acetate. Asymmetric reduction of **107c** using **60** with $LiAlH_4$ gave cyclization precursor in which the key chiral center at C-11 has been set (Scheme 43).

Scheme 43. Reduction of **107**

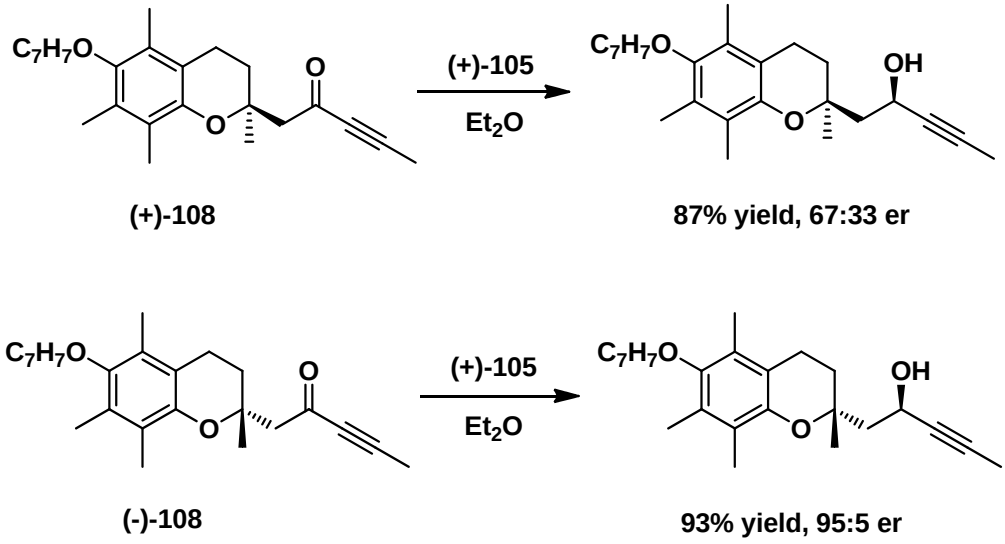




107c **95% yield, 92:8 er**

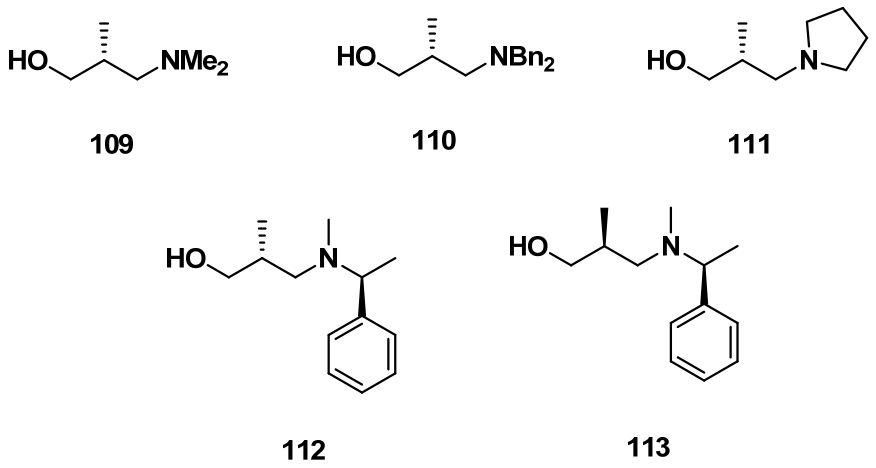
In 1980 Cohen *et al*.[39] expanded upon this work in their studies toward asymmetric synthesis of Vitamin E. Applying the strategy of matched and mismatched pairs, Cohen et al.[39] took note of the fact that enantiomer (-)-**108** gave the best selectivity observed (Scheme 44). As such, they prepared *ent*-**105** from (-)-**60**, and it reduced (+)-**108** with 95:5 er and 96% yield. They also prepared chiral reducing agents from 1,3-aminoalcohols **109-113** (Figure 15) and $LiAlH_4$. However the reduction using these reagents gave no better than 68:32 er.

Scheme 44. Reduction of **108**



(+)-108 **87% yield, 67:33 er**

(-)-108 **93% yield, 95:5 er**



109 110 111

112 113

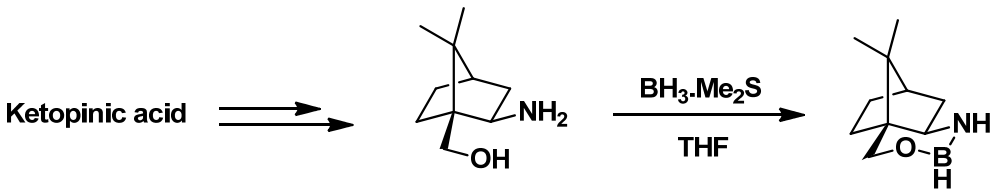
Figure 15

ii) Borane reduction: Catalytic approach

Asymmetric borane reduction originally described by Itsuno[40] and later studied extensively by Corey[41] is one of the most effective approaches for preparing optically active secondary alcohols. In this context *β*-aminoalcohol derived oxazoborolidine catalyzed reduction has emerged as the most prominent methodology.[42]

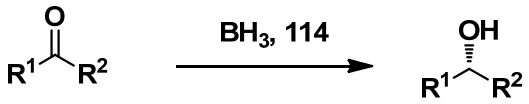
Chan *et al.*[11] in 1999 reported ketopinic acid derived 1,3-aminoalcohol, (1*S*,2*R*)-1-hydroxylmethyl-2-amino-7,7-dimethyl bicyclo[2,2,1]heptane (**6**) and used as the ligand. Reaction of **6** with BH_3 gave **114** (Scheme 45), which was used *in situ* to catalyze reduction of ketones to secondary alcohols. Increasing reaction temperature from 0 to 50 °C improved the enantioselectivity of alcohols from 58:42 to 94:6 er (Table 16).

Scheme 45. Preparation of **114**



6 114

Table 16. Borane reduction

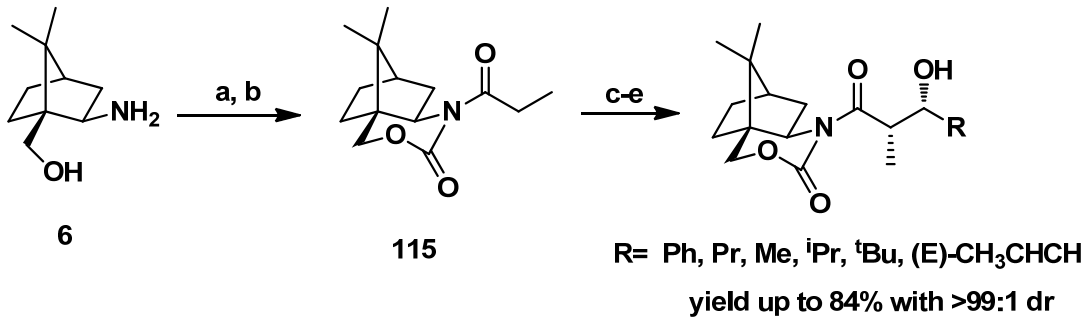


entry	ketone	er	configuration
1	ethyl phenyl ketone	83.5:16.5	*S*
2	ω-bromo acetophenone	83.5:16.5	*R*
3	*p*-chloroacetophenone	86.5:13.5	*S*
4	acetophenone	93:7	*S*

2.1.3. Chiral auxiliary mediated aldol reaction

The stereoselective aldol reaction employing a chiral auxiliary is an important methodology in organic synthesis. It has been known that stereoselectivity of the aldol reaction is dependent on several factors such as enolate geometry, metal, substrate, and others.[43] The aldol reaction of boron enolates employing amino acid-derived chiral auxiliaries developed by Evans and co-workers,[44] has been widely used.

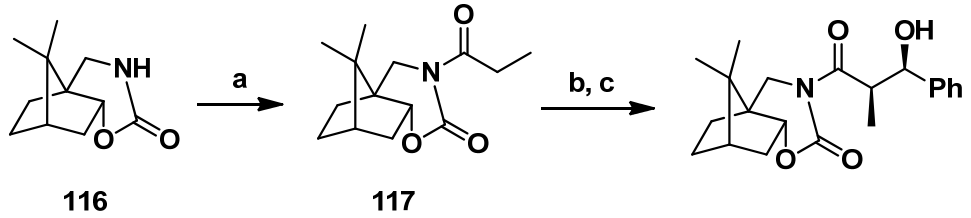
Ahn and co-workers[12a] in 1992 employed camphor derived chiral auxiliary (**115**) for aldol reactions (Scheme 46). Treatment of **115** with $TiCl(O^iPr)_3$ generated *Z*-enolates which were later treated with a variety of aldehydes to give "chelation-controlled" *syn*-aldol products with excellent diastereoselectivity.



Scheme 46. Reagents and conditions: (a) $(Cl_3CO)_2CO$, -OH; (b) ^{n}BuLi, EtCOCl; (c) LDA, -78 °C; (d) $TiCl(O^iPr)_3$ (3 equiv.), -45 °C; (e) RCHO (2 equiv.), -78 °C.

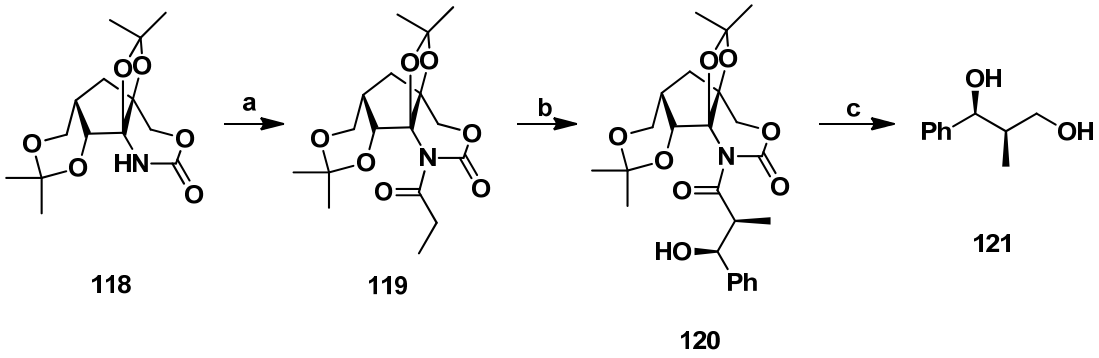
Later in 1997 Sadler and co-workers[12b] reported the use of the 1,3-oxazin-2-one **116** as a chiral auxiliary for aldol reaction. The oxazinone **116** was converted to propionamide **117**, followed by treatment with Bu_2BOTf and quenching the resulting

enolate with benzaldehyde to obtain *syn*-aldol product as a single diastereomer (Scheme 47).



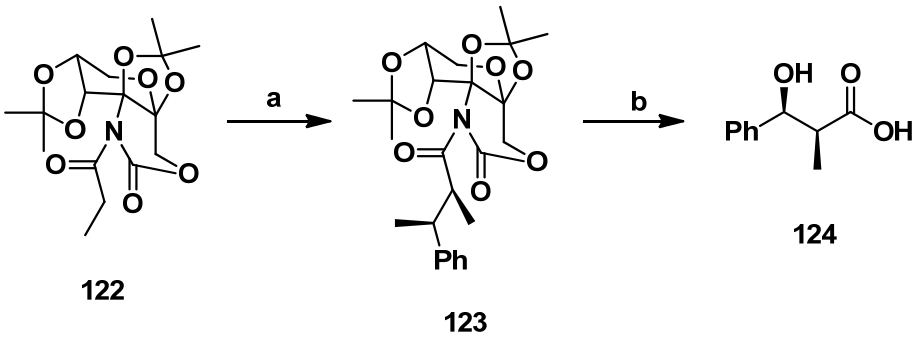
Scheme 47. Reagents and conditions: (a) EtMgBr, then EtCOCl, THF, -78 °C; (b) Bu_2BOTf, $^{i}Pr_2NEt$, CH_2Cl_2, 0 °C; (c) PhCHO, CH_2Cl_2, -78 °C.

Banks and co-workers[12c] in 1994 used gulonic acid derivative **118** as a chiral auxiliary for asymmetric aldol reactions. Treatment of **118** with propionyl chloride afforded amide **119**. Reaction of **119** with LDA at -78 °C generated the enolate, which was quenched with benzaldehyde to give aldol product **120** in 88% yield with 91:9 dr. Reductive cleavage of the auxiliary from **120** gave alcohol **121** in moderate yield (Scheme 48).



Scheme 48. Reagents and conditions: (a) ^{n}BuLi, hexanes, THF, -78 °C, EtCOCl; (b) LDA, THF, -78 °C, PhCHO; (c) $LiBH_4$, THF, H_2O, 0 °C.

The same group later reported fructose derivative **122** as a chiral auxiliary for aldol reactions.[12d] LDA was used to generate the enolate, which was later treated with benzaldehyde gave **123** in good yield with 89:11 dr. Cleavage of the auxiliary gave acid **124** in high yield (Scheme 49).



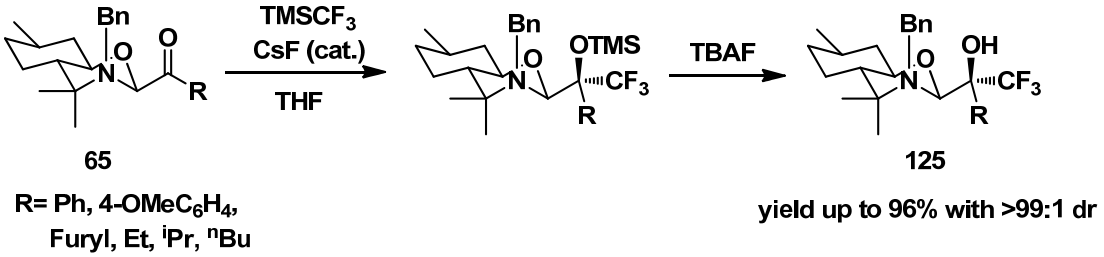
Scheme 49. Reagents and conditions: (a) LDA, THF, 0 °C, PhCHO; (b) LiOH, H_2O_2,

2.1.4. Nucleophilic addition of $TMSCF_3$

Organofluorine compounds show remarkable physical, chemical, and biological properties. Also Trifluoromethylated derivatives have special lipophilicity and metabolic characteristics.[45] For these reasons, their synthesis has attracted considerable attention. One of the most useful methods to introduce a trifluoromethyl group consists on the nucleophilic addition of $TMSCF_3$ to carbonyl compounds.

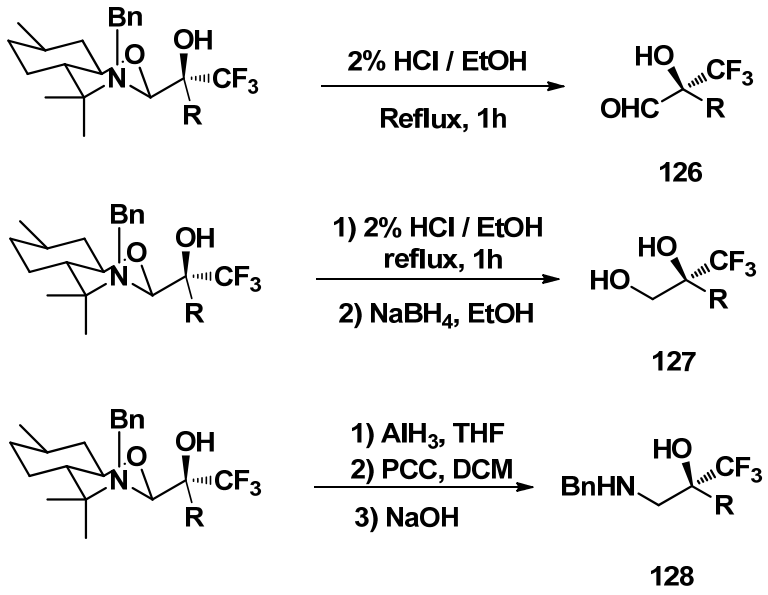
Pedrosa *et al*.[46] in 2006 reported the diastereoselective addition of $TMSCF_3$ to 2-acyl-1,3-perhydrobenzoxazines **65** in the presence of a catalytic amount (2.5 mol%) of tetrabutylammonium fluoride (TBAF) or CsF at 0 °C using Et_2O or THF as a solvent. The use of THF as solvent and CsF as catalyst allows for the trifluoromethylation of both aromatic and aliphatic derivatives, leading to **125** in excellent yields and high diastereoselectivity (Scheme 50).

Scheme 50. Addition of $TMSCF_3$ to **65**



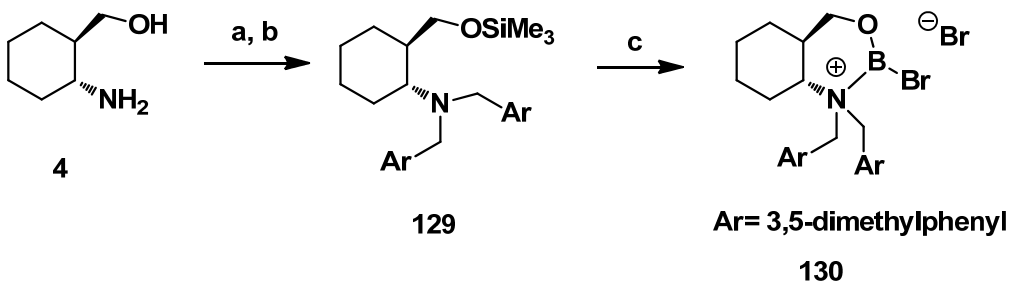
The chiral auxiliary was then removed via three procedures, giving *R*-hydroxyaldehyde **126**, 1,2-diols **127**, or 1,2-aminoalcohols **128** (Scheme 51).

Scheme 51. cleavage of chiral auxiliary



2.2. Diels-Alder reaction

Corey *et al.*[13] in 1996 reported the enantioselective Diels-Alder reaction catalyzed by Lewis acid derived from cyclohexane-based 1,3-aminoalcohol (**4**). Lewis acid **130** was prepared *in situ* by reacting **129** with BBr_3 (Scheme 52). Pretreatment of Lewis acid **130** with $AgB[3,5\text{-}(CF3)_2C_6H_3]_4$ enhanced dissociation of bromide from the boron, giving a more active catalyst (method B) than when no silver salt was included in catalyst formation (method A). When performing Diels-Alder reactions on the highly reactive cyclopentadiene, this pretreatment was not necessary (Table 17). Less reactive dienes **131a-d** however, did not react using method A, but gave excellent yields of adducts using method B. In all cases, the adducts were formed with greater than 90:10 er (Table 18).



Scheme 52. Reagents and conditions: (a) $Ba(OH)_2$, 3,5-dimethylbenzyl bromide, EtOH, reflux; (b) TMSCI, DMAP; (c) BBr_3.

Table 17. Enantioselective Diels-Alder reaction of 1,3-cyclopentadiene with α,β-unsaturated aldehydes in CH_2Cl_2 at -94 °C catalyzed by cationic Lewis Acid **130**

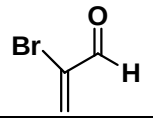
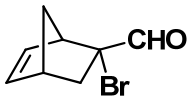
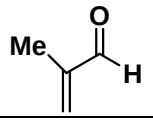
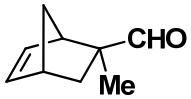
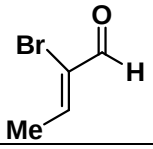
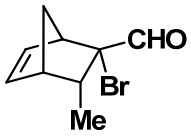
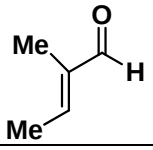
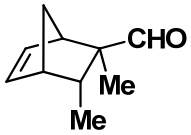
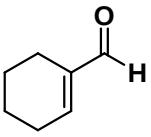
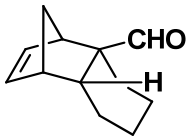
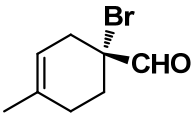
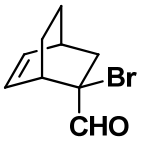
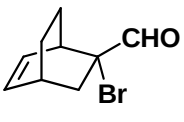
dienophile	method	exo:endo	yield (%)	er	product
	A	94:6	99	97.5:2.5	
	B	91:9	99	99:1	
	A	88:12	99	95:5	
	B	89:11	98	93.5:6.5	
	A	>98:2	99	95.5:4.5	
	B	>98:2	99	98:2	
	A	>98:2	88	94.5:5.5	
	B	>98:2	97	94.5:5.5	
	A	>98:2	99	98:2	
	B	>98:2	97	91:9	

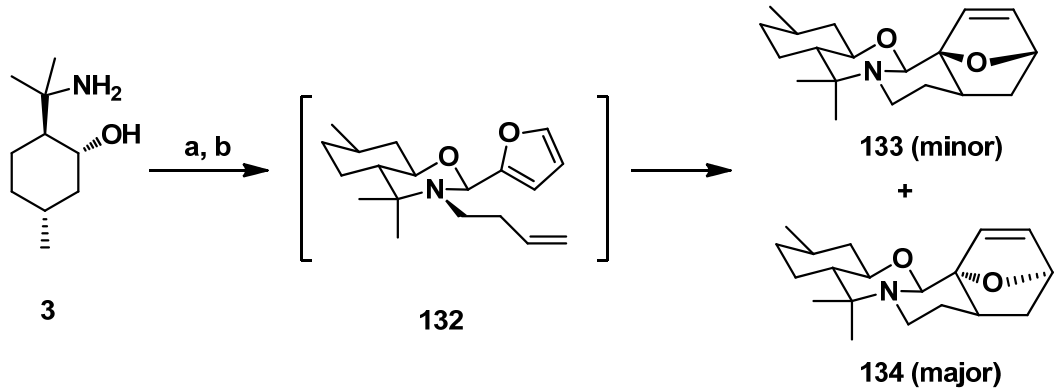
Table 18. Diels-Alder reaction of 1,3-dienes with 2-bromoacrolein using method B.

diene (131a-d)	product	yield (%)	er
		99	97:3
		99	98:2
		99 exo:endo (4:96)	96.5:3.5
		99 exo:endo (91:9)	99:1

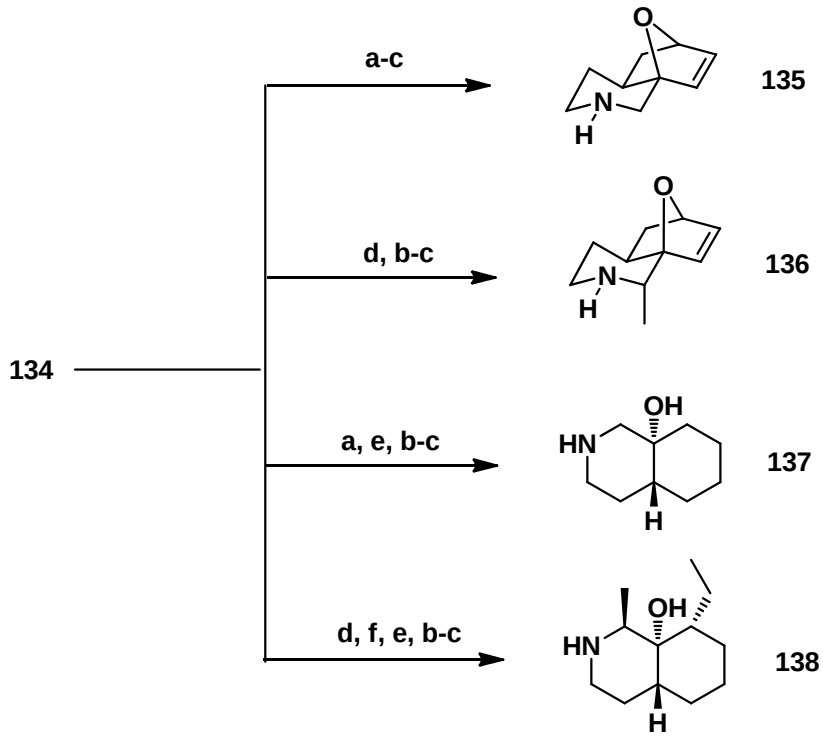
Chiral auxiliary mediated Diels-Alder reactions are also reported in the literature, one representive example is discussed below.

1,3-aminoalcohol **3** has also been used as a chiral auxiliary for intramolecular Diels-Alder reactions of furan dienes (IMDAF reactions). Pedrosa *et al*.[47] studied

IMDAF reactions using unactivated dienophiles. In 1998, they reported the synthesis of enantiopure substituted decahydroisoquinolines. Alkylation of **3** followed by condensation with neat 2-furaldehyde gave a 9:1 mixture of **133** and **134** via intermediate **132** (Scheme 53). Chromatographic separation of the diastereomers gave **134** which, upon cleavage of the auxiliary, could be converted to epoxyisoquinoline **135** or **136** or decahydroisoquinolines **137** or **138** (Scheme 54). Minor diastereomer **133** could be used to prepare the opposite enantiomers of **135**-**138**.



Scheme 53. Reagents and conditions: (a) $H_2C{=}CHCH_2CH_2Br$, K_2CO_3, PhMe, reflux; (b) 2-furaldehyde, reflux, 4 days.

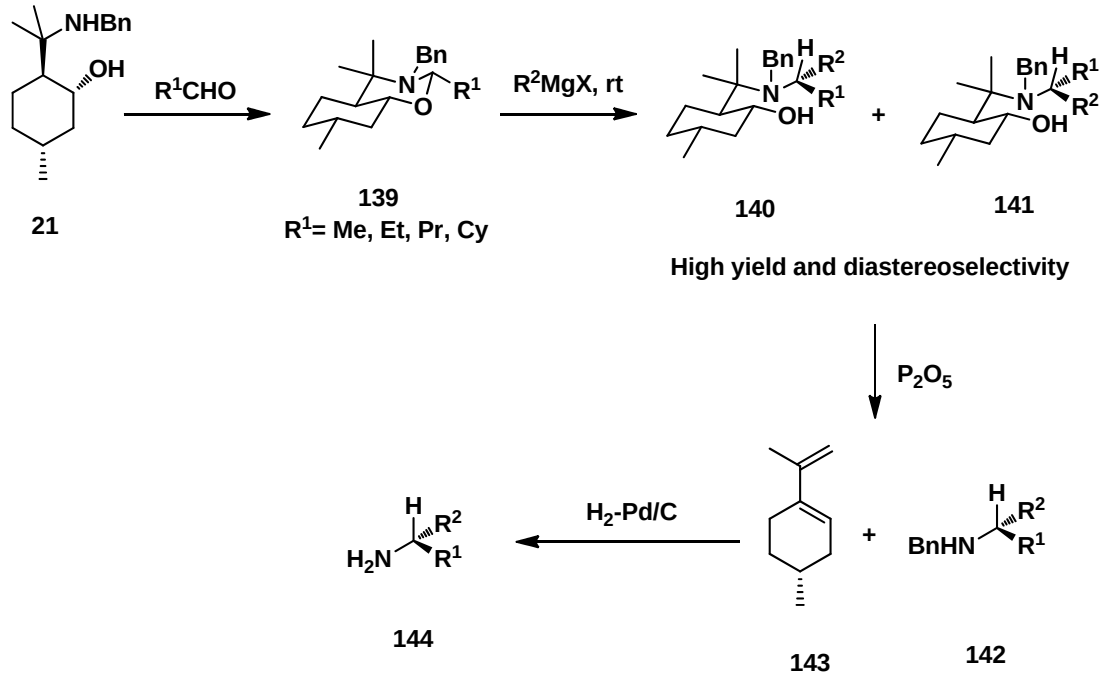


Scheme 54. Reagents and conditions: (a) $LiAlH_4$ (5 equiv), $AlCl_3$ (2 equiv), THF, -10 °C; (b) PCC; (c) KOH, MeOH, THF; (d) Me_3Al, PhMe, rt; (e) PtO_2, H_2, EtOH; (f) Et_3Al, PhMe, rt.

2.3. Ring opening reaction: Asymmetric synthesis of amines

Pedrosa *et al*.[48] used **21** as a chiral auxiliary for the addition of Grignard reagents. Instead of the more typical nucleophilic attack on a carbonyl, the oxazine linking the substrate to the auxiliary was opened directly, allowing asymmetric synthesis of amines. Condensation of aldehydes with **21** gave thermodynamic diastereomers **139**, in which R^1 was equatorial (Scheme 55). The oxazine was then opened in an SN_2-like reaction by alkyl magnesium bromides, giving **140** as a major product. Alkyl magnesium iodides, on the other hand, reacted with retention at the electrophilic carbon, giving alkylation product **141** as a major product (Scheme 55). The diastereoselectivity of these reactions was generally good for reagents other than *c*-PrMgBr and EtMgX, with yields ranging from moderate to good. Removal of the auxiliary was achieved by elimination with P_2O_5 to give amine **142** and diene **143**. The benzyl group of the **142** was removed by hydrogenolysis, giving excellent yields of amines **144**. These reactions proceeded without any apparent racemization.

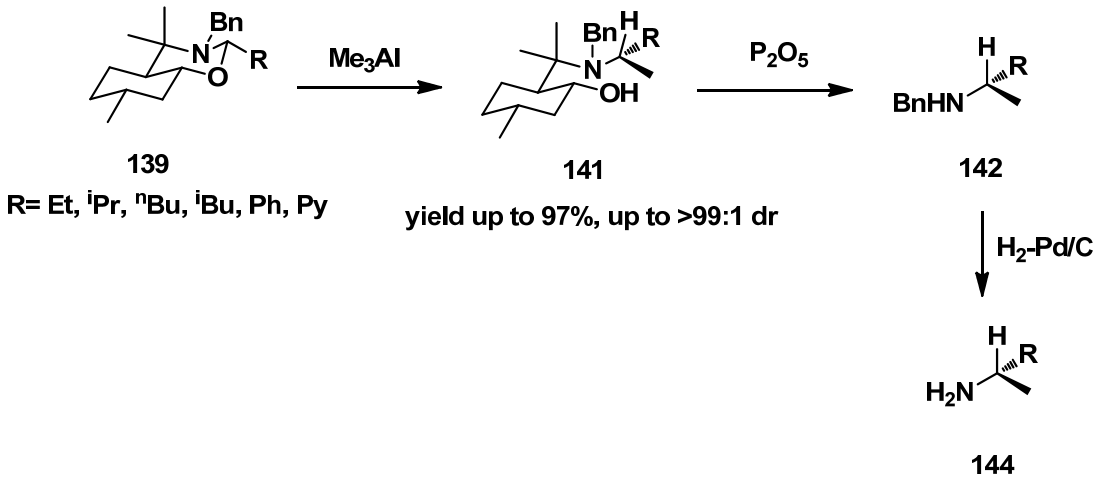
Scheme 55. Preparation of chiral amine



Oxazines **139** were also treated with Me_3Al to give similar addition products. Whereas the Grignard reagents reacted with inversion at the reacting carbon, the stereochemistry at that center was retained using Me_3Al. Thus MeMgBr and Me_3Al

were complementary reagents giving opposite enantiomers of amine using the same auxiliary (Scheme 56).

Scheme 56. Addition of Me_3Al to **139**



139

R= Et, ^{i}Pr, ^{n}Bu, ^{i}Bu, Ph, Py

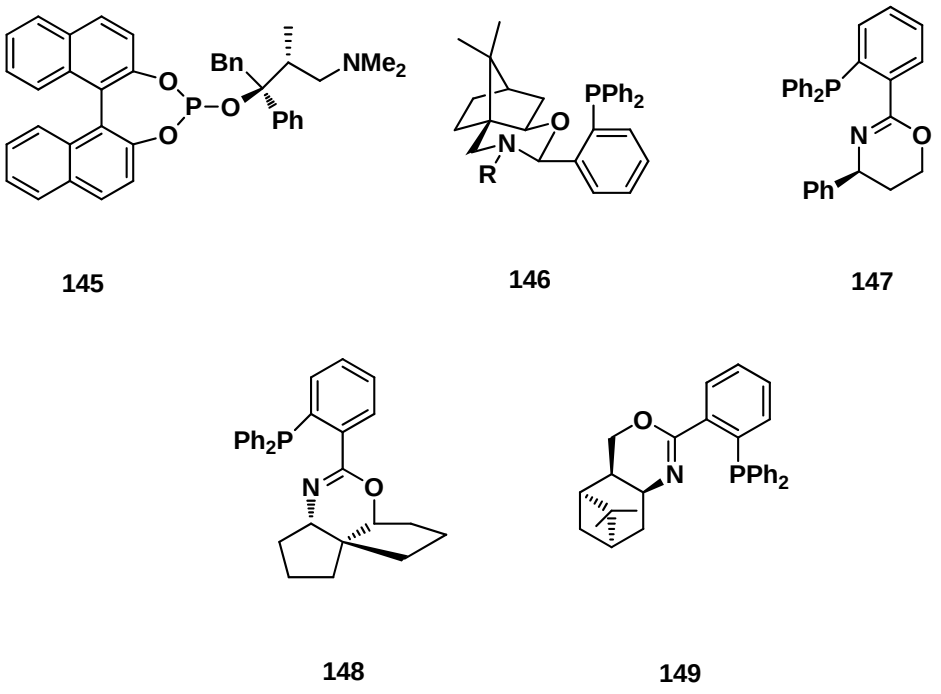
141

yield up to 97%, up to >99:1 dr

142

144

Various 1,3-aminoalcohols were used as a starting material for the preparation of phosphorus containing ligands (Figure 16) which were further evaluated as a chiral catalysis in transition metal catalyzed reactions, e.g. allylic alkylation,[49] heck reaction,[50] hydrosilylation,[49] and catalytic hydrogenation.[51]



145 **146** **147**

148 **149**

Figure 16

Concluding Remarks:

- ✓ Various efficient methodologies are known for the synthesis of variety of 1,3-aminoalcohols. Some of these are derived from common natural products such as menthol, camphor, and sugars. 1,3-Aminoalcohols and their derivatives have been used as a chiral ligands and chiral auxiliaries for a variety of enantioselective reactions.
- ✓ From the above account, it is obvious that these molecules could not gain the popularity of their 1,2-counterparts. The reasons could be lack of simple methodologies for their synthesis, as well as less impressive enantioselection. Further developments will need to address these issues. We believe that suitably designed 1.3-aminoalcohols can prove to be valuable additions for asymmetric synthesis.

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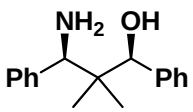
CHAPTER-2

Synthesis and resolution of *syn*- and *anti*-3-amino-2,2-dimethyl-1,3-diphenylpropan-1-ols

Introduction

As we have discussed in chapter **1**, the design and synthesis of chiral ligands is of great importance in asymmetric synthesis. In this context, nitrogen containing ligands[1] proved to be a excellent ligand for various asymmetric reactions mainly because of ease of preparation, high stability, and the easy separation. It is always possible that the interaction of the ligand with the metals could be widely varied by preparing various types of derivatives like amides, sulfonamides or imines. Amongst these ligands, aminoalcohols are particularly important. Aminoalcohols and their derivatives were used extensively in asymmetric synthesis both as chiral auxiliaries and chiral ligands.[1c,f,2] A wide variety of aminoalcohols, mostly 1,2-aminoalcohols have been reported in the literature.[1c,f,2d,g-j] Only a few examples of the use of chiral 1,3-aminoalcohols are known.[3,4,5] With the exception of the ones derived from camphor,[4b,k,m,5a] most 1,3-aminoalcohols posses flexible backbone and provide poor enantioselectivity.[4d,e,g,h,l,p] Further, majority of these amino alcohols are based on naturally occurring skeletons and thus have limited number of structural variations. Thus the synthesis of new ligands having rigid backbone with simple synthetic pathway is highly desirable. We have designed a new conformationally restricted 1,3-aminoalcohols, namely, *syn*- and *anti*-3-amino-2,2-dimethyl-1,3-diphenylpropan-1-ol, **1** and **2** respectively.



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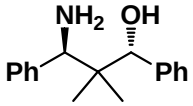


2

These molecules would offer particular advantage for selectivity due to conformational rigidity induced by two methyl groups present at beta position.

This chapter deals with the diastereoselective synthesis and resolution of both *syn*- and *anti*-3-amino-2,2-dimethyl-1,3-diphenylpropan-1-ols. It has been divided into three sections.

Section-2A: Diastereoselective synthesis of *syn*- and *anti*-3-amino-2,2-dimethyl-1,3-diphenylpropan-1-ols.

Section-2B: Reduction of *β*-hydroxy oxime: A short route to the synthesis of *syn*- and *anti*-3-amino-2,2-dimethyl-1,3-diphenylpropan-1-ols.

Section-2C: Resolution of *syn*- and *anti*-3-amino-2,2-dimethyl-1,3-diphenylpropan-1-ols.

Section-2A

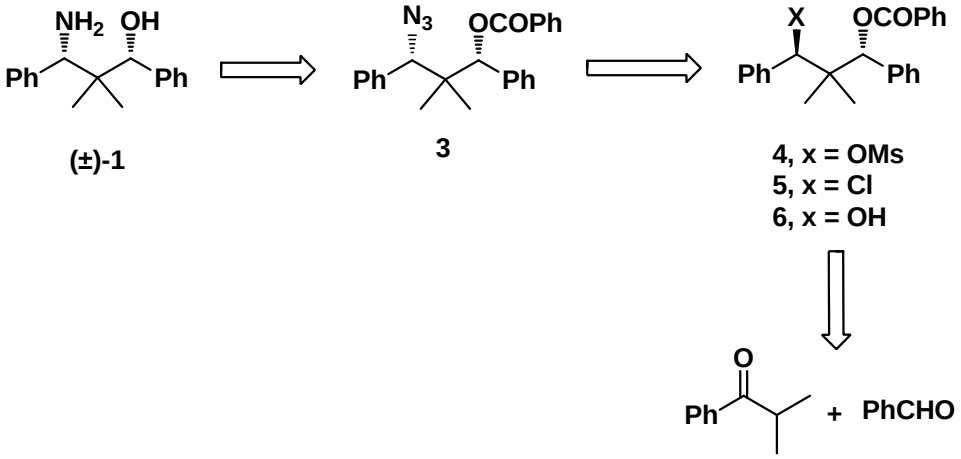
Diastereoselective synthesis of *syn*- and *anti*-3-amino-2,2-dimethyl-1,3-diphenylpropan-1-ols.

Introduction

Conversion of hydroxyl group to amine through azide using nucleophilic substitution reactions ($R-OH \rightarrow R-X \rightarrow R-N_3 \rightarrow R-NH_2$) is one of the general method used for the introduction of amine moiety.[6] By converting the hydroxyl group to good leaving group (x = Cl. OTs, OMs etc) followed by SN^2 displacement with azide and reduction of azide afforded corresponding amine compound. We designed the synthesis of *syn*-1,3-aminoalcohol (**1**) considering these sequence of reactions as shown in retrosynthetic analysis (Scheme 1).

1. Diastereoselective synthesis of *syn*-1,3-aminoalcohol (1)

Scheme 1. Retrosynthetic analysis



In the synthetic direction, it was anticipated that the aminoalcohol **1** could be obtained by the hydrolysis followed by the reduction of intermediate **3**. The intermediate **3** could be obtained by the SN^2 reaction between sodium azide and compound **4** or **5**. The compound **4** or **5** could be easily prepared from *γ*-hydroxybenzoate **6** by simple functional group transformation. The *γ*-hydroxybenzoate in turn could obtain using Aldol-Tishchenko[7] reaction between isobutyrophenone and benzaldehyde.

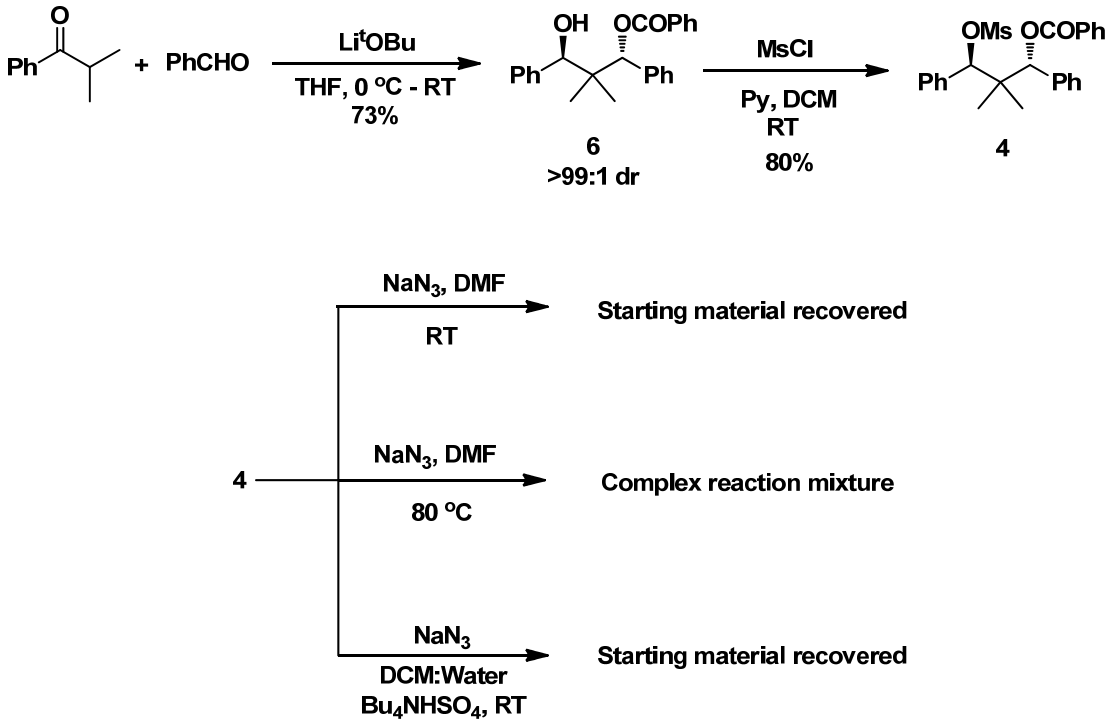
The retrosynthetic analysis outlined in scheme 1 identified compound **6** as a potential synthetic intermediate and its synthesis would be crucial step.

Result and discussion

According to retrosynthetic plan *γ*-hydroxybenzoate **6** was prepared using Aldol-Tishchenko[7] reaction between isobutyrophenone and benzaldehyde. Isobutyrophenone when reacted with benzaldehyde in the presence of LiO^tBu in THF

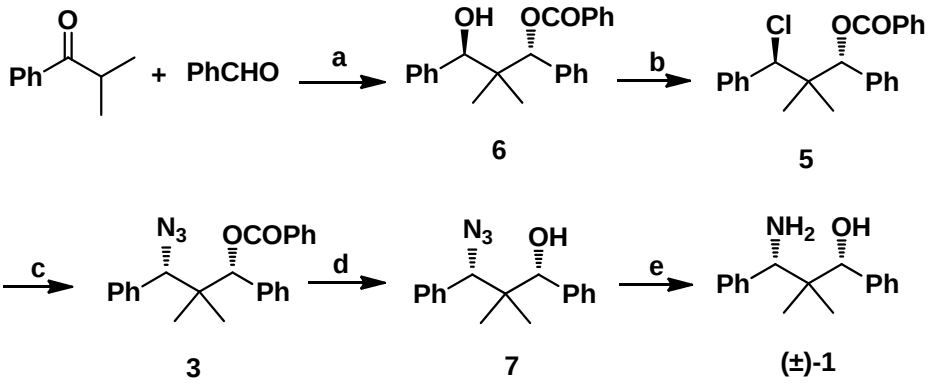
at room temperature afforded *anti*-diastereomer of γ-hydroxybenzoate in 73% yield with >99:1 dr (confirmed by ^{1}H NMR which shows two singlet for two benzylic protons). Once we have the compound **6** in hand, the hydroxyl group of **6** was converted to mesyl group by treating the compound **6** with methanesulfonyl chloride in the presence of pyridine. The disappearance of peak due to hydroxyl group and a new peak for O=S=O st. frequency in IR spectrum and appearance of peak at δ 2.67 ppm (s, 3H) in the ^{1}H NMR spectrum indicated the formation of the product **4**. At this stage we tried various reaction conditions to convert mesyl benzoate **4** to azidobenzoate **3**. When reaction was carried out at room temperature using sodium azide as nucleophile in DMF as solvent, reaction does not proceed at all. Increasing reaction temperature resulted in decomposition of the starting material which showed complex TLC pattern. Further, use of phase transfer catalyst also did not help as starting material remained unreacted (Scheme 2).

Scheme 2.



We then prepared the chlorobenzoate **5** in 83% yield by treating the compound **6** with thionyl chloride in DCM at room temperature. Compound **5** was then treated with sodium azide at room temperature. However the reaction does not proceed at this temperature. Increasing the reaction temperature to reflux, azidobenzoate **3** was obtained in 83% yield with inversion of configuration. The structure of **3** was

confirmed by NMR as well as IR spectra. The *syn*-azidobenzoate **3** was then hydrolysed using methanolic KOH at room temperature giving the corresponding azidoalcohol **7**, which upon hydrogenation using H_2-Pd/C afforded *syn*-1,3-aminoalcohol **1** in 90% yield. The formation of product was confirmed by the disappearance of peak due to -N_3 st. frequency (2104 cm^{-1}) and appearance of two peaks for primary amine in IR spectrum. The structure was further confirmed by NMR, Mass and CHN analysis. Thus synthesis of aminoalcohol **1** was completed in 45% overall yield starting from isobutyrophenone (Scheme 3).

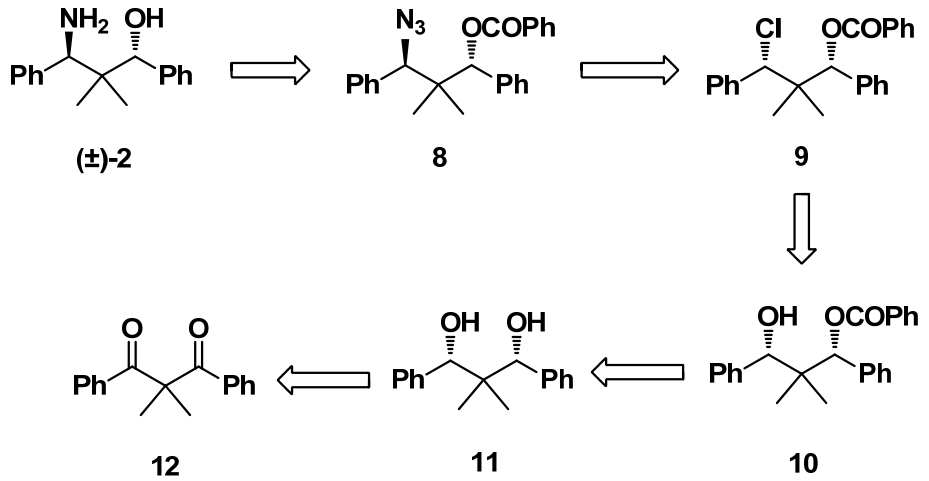


Scheme 3. Synthesis of compound **1**. Reagents and conditions: (a) LiO^tBu, THF, 0 ^oC to rt, 73%; (b) $SOCl_2$, DCM, rt, 83%; (c) NaN_3, DMF, reflux, 83%; (d) KOH, MeOH; (e) H_2-Pd/C, MeOH, 90% (over two steps).

2. Diastereoselective synthesis of *anti*-1,3-aminoalcohol (2)

The same strategy was applied for the preparation of *anti*-1,3-aminoalcohol **2**, as shown in retrosynthetic analysis (Scheme 4).

Scheme 4. Retrosynthetic analysis

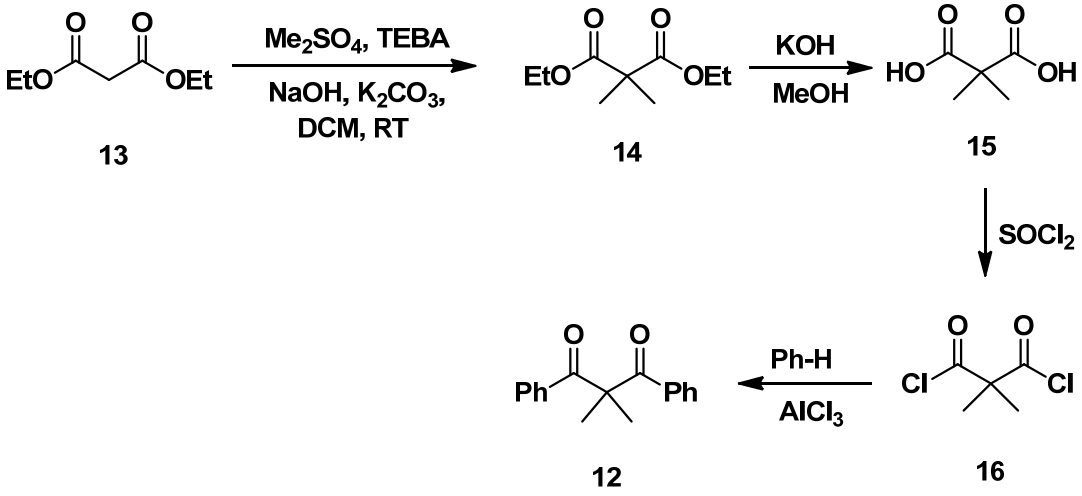


Retrosynthetic analysis reveals that, for the synthesis of *anti*-aminoalcohol **2**, *syn*-γ-hydroxybenzoate **10** could be taken as the key intermediate from which aminoalcohol **2** could be accessed employing simple transformation as discussed in retrosynthesis analysis for **1**. The required key intermediate **10** could be easily prepared from 1,3-diol **11**, which in turn could be obtained by diastereoselective reduction of 1,3-diketone **12**.

Result and discussion

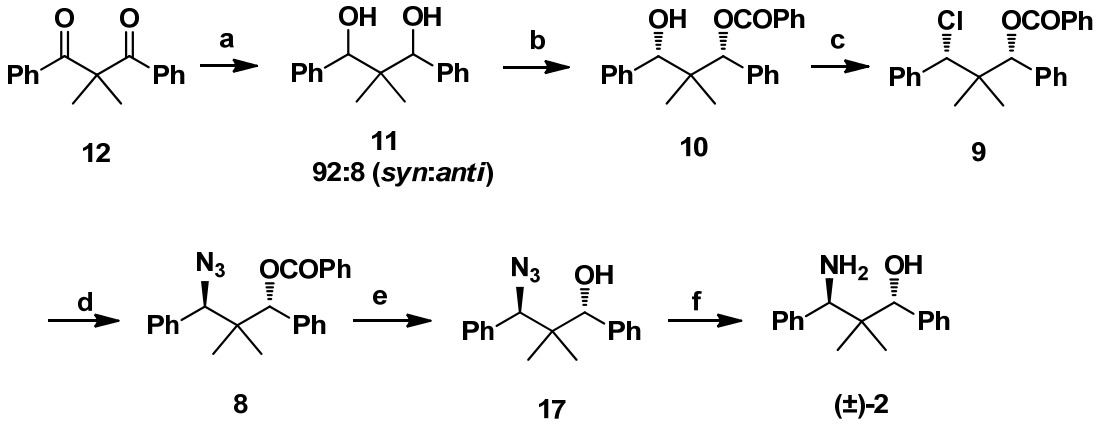
According to retrosynthetic analysis depicted in scheme 4, 1,3-diketone **12** was required for the synthesis of *syn*-γ-hydroxybenzoate **10**, which is the key intermediate. The required 1,3-diketone[8] **12** was prepared in four steps starting from cheap and commercially available starting materials. Diethylmalonate **13** was first dimethylated at C-2 position using dimethylsulfate under phase-transfer condition to provide 2,2-dimethyl diethylmalonate **14**. Saponification followed by thionyl chloride treatment provided the corresponding acid chloride **16**. Friedel-Craft reaction between **16** and benzene produced the diketone **12,** as shown in scheme 5.

Scheme 5. Preparation of **12**



As the observed diastereoselectivity was low in $NaBH_4$-mediated reduction of diketone **12**, we used Maier's[9] method for the reduction of diketone **12**. When the reduction was carried out using $LiBH_4/TiCl_4$, the diol **11** was obtained in 82% yield with 92:8 *syn*:*anti* diastereomeric ratio. The mixture was converted to pure *syn*-hydroxybenzoate **10** in 71% yield by treatment with one equivalent of PhCOCl

followed by crystallization. The structure of **10** was confirmed by IR and NMR spectra. Two singlets at δ 4.49 and 6.10 ppm in NMR spectrum confirm the structure. Treatment of **10** with $SOCl_2$ formed chlorobenzoate **9** in 79% yield. The *anti*-azidobenzoate **8** was obtained in 81% yield by treating the compound **9** with sodium azide. Hydrolysis of **8** using methanolic KOH, followed by hydrogenation provided the corresponding *anti*-1,3-aminoalcohol **2** in 33% overall yield (Scheme 6). The formation of product was confirmed by IR, NMR, Mass and CHN analysis.



Scheme 6. Synthesis of compound **2**. Reagents and conditions: (a) $LiBH_4$, $TiCl_4$, 82%; (b) BzCl, Pyridine, DCM, rt, 71%; (c) $SOCl_2$, DCM, rt, 79%; (d) NaN_3, DMF, reflux, 81%; (e) KOH, MeOH; (f) H_2-Pd/C, MeOH, 90% (over two steps).

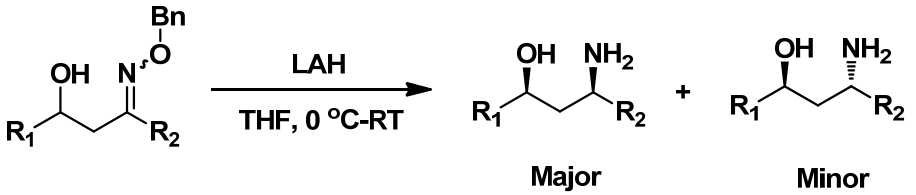
Section-2B

Reduction of *β*-hydroxy oxime: A short route to the synthesis of *syn*- and *anti*-3-amino-2,2-dimethyl-1,3-diphenylpropan-1-ols.

Introduction

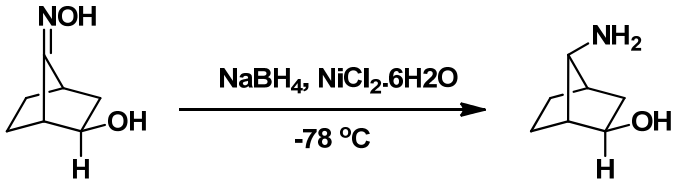
Hydroxyl group directed stereoselective reduction of *β*-hydroxy oxime is an important methodology for the preparation of *syn*- and *anti*-1,3-aminoalcohols.[10,11]

Narasaka *et al*.[10a,b,c] in 1986 first time reported the *syn*-selective reduction of *β*-hydroxy oximino benzyl ether (eq 1).



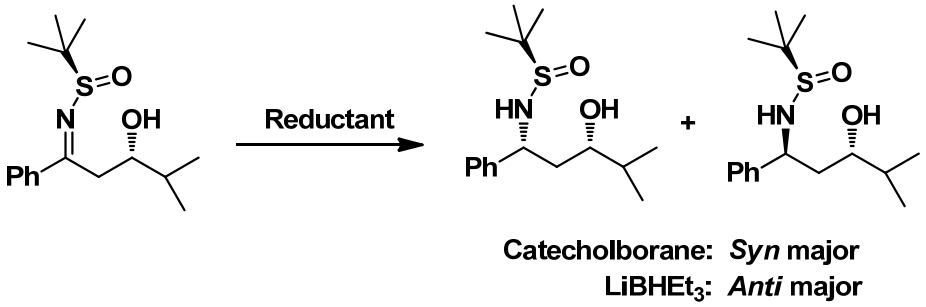
(1)

Costa *et al*.[10g] also reported *syn*-selective reduction of *β*-hydroxy oxime (eq 2).



(2)

In 2002, Ellman *et al*.[11] reported a very efficient method for the synthesis of both *syn*- and *anti*-1,3-aminoalcohols starting from a common intermediate, i.e. *β*-hydroxy-*N*-sulfinyl ketimine. The *syn*-product was obtained with the highest selectivity (96:4 *syn*:*anti*) by the reduction with catecholborane. Alternatively, reduction with $LiBHEt_3$ provided the *anti*-product in good yield (eq 3).



(3)

In the literature various methods are available for *syn*-selective reduction of *β*-hydroxy oxime but synthesis of both *syn*- and *anti*-isomer of aminoalcohol from *β*-hydroxy oxime, a common intermediate was not reported. Though Ellman *et al.*[11]

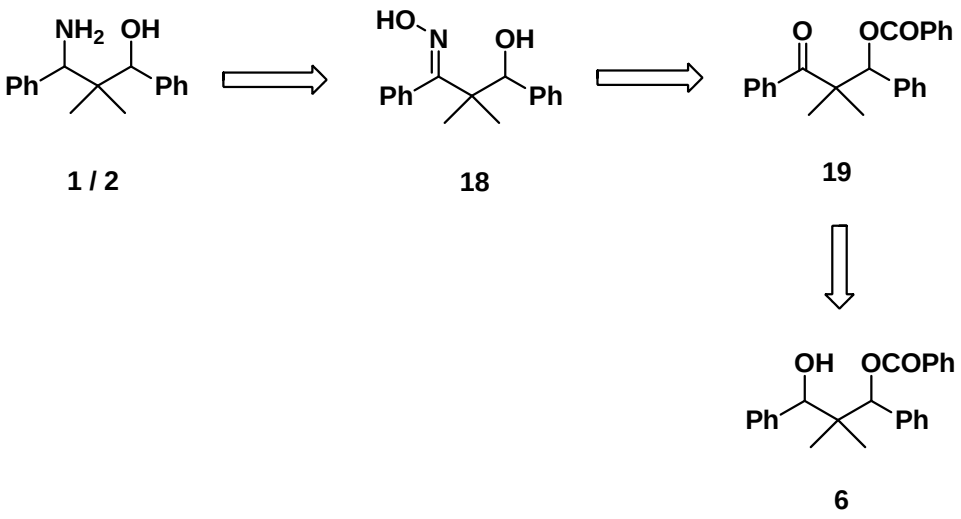
reported the synthesis of both *syn*- and *anti*-1,3-aminoalcohols starting from a common intermediate, they used *β*-hydroxy-*N*-sulfinyl ketimine as a starting material.

We have developed a new protocol for the preparation of both *syn*- and *anti*-aminoalcohols through stereoselective reduction of *β*-hydroxy oxime, a common intermediate.

Result and discussion

To avoid the use of azide chemistry and increase the overall yield by reducing the number of steps, we conceived a new route to both aminoalcohols **1** and **2** as shown in retrosynthetic analysis (Scheme 7).

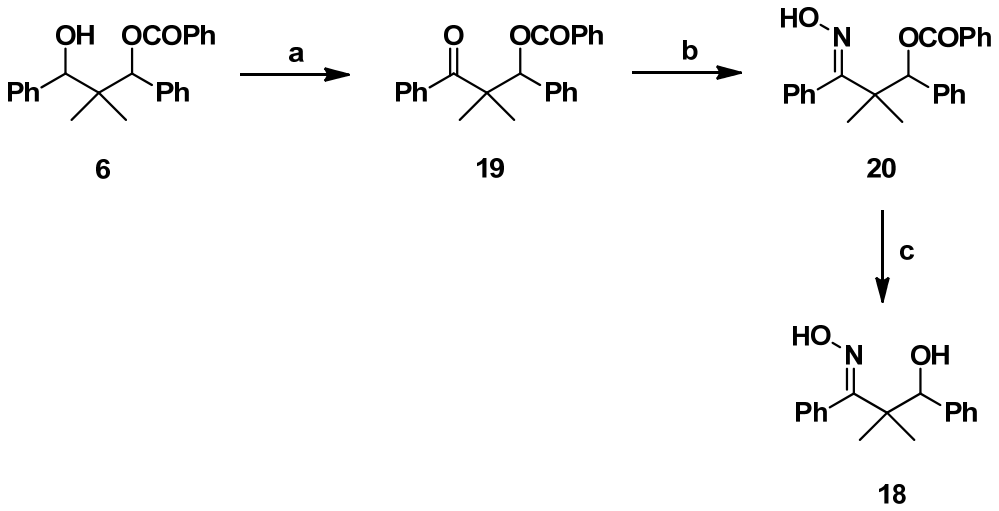
Scheme 7. Retrosynthetic analysis



1 / 2 **18** **19** **6**

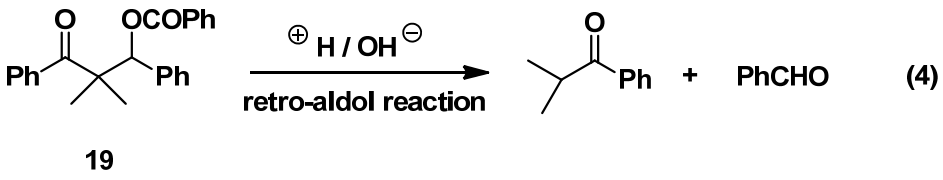
As depicted in retrosynthetic analysis, aminoalcohol **1** and **2** could be obtained from *β*-hydroxy oxime **18** by the reduction using appropriate reducing agent. The intermediate *β*-hydroxy oxime **18** could obtain from keto benzoate **19** by oximation followed by hydrolysis. While the later could be obtained by oxidation of **6**.

According to retrosynthetic plan shown in scheme 7, the required *β*-hydroxy oxime **18** was prepared from *γ*-hydroxybenzoate **6** over three steps with excellent overall yield (Scheme 8).



Scheme 8. Synthesis of compound **18**. Reagents and conditions: (a) $K_2Cr_2O_7$, dil. H_2SO_4, Et_2O, rt, quant.; (b) $NH_2OH.HCl$, CH_3COONa, Ethanol, reflux, quant.; (c) KOH, MeOH, rt, 81%;

The *γ*-hydroxybenzoate **6** was oxidized using chromic acid solution in ether:water to obtain the corresponding keto benzoate **19** in almost quantitative yield. The disappearance of peak due to hydroxyl group and a new appearance of peak at 1787 cm^{-1} for –C=O st. frequency in IR spectrum, and disappearance of one singlet in the benzylic region in the ^1H NMR spectrum indicated the formation of the product. Here we tried various conditions to carry out hydrolysis of compound **19** to hydroxy ketone but could not obtain the expected product. In basic as well as in acidic conditions **18** underwent retro-aldol reaction to yield isobutyrophenone and benzaldehyde (eq 4). Instead of hydrolysis we first made the oxime of **19** by treating with $NH_2OH.HCl$ in the presence of sodium acetate. The oxime benzoate **20** was obtained in almost quantitative yield, which upon hydrolysis in methanolic KOH gave *β*-hydroxy oxime **18** in excellent yield. The product was confirmed by IR, NMR and CHN analysis.

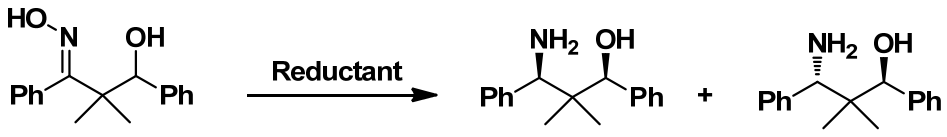


19

Our next job was to reduce the *β*-hydroxy oxime **18** to corresponding *syn*- and *anti*-aminoalcohol. First we tried to reduce the oxime **18** under hydrogenation

condition (Table 1). The reduction using H_2-Pd/C in methanol at 60 psi pressure did not proceed. Also H_2/Raney-Ni and $HCOONH_4$-Pd/C in methanol failed to give the reduced product. Hydrogenation using H_2-Pd/C in the presence of one equivalent acetic acid did provide the product, but did not go to completion. Finally we observed that hydrogenation in the presence of one equivalent of hydrochloric acid reduces the oxime **18** to 1,3-aminoalcohol in 80% yield with 79:21 (*anti*:*syn*) distereoselectivity (determined by ^{1}H-NMR). The desired *anti*-isomer **2** was separated by crystallization of the succinate salt from ethanol:ethyl acetate (47% yield, >99:1 dr).

Table 1. Reduction of *β*-hydroxy oxime **18**



18 ***Syn*** ***Anti***

entry	reductant	yield (%)[a]	dr (*syn*:*anti*)[b]
1	$LiAlH_4$	71	47:53
2	$NaBH_3CN$/Aq. $TiCl_3$	68	55:45
3	$NaBH_4/NiCl_2.6H_2O$	c	-
4	$NaBH_4/TiCl_4$	79	>99:1
5	H_2-Pd/C, MeOH	c	-
6	$HCOONH_4$, Pd/C	c	-
7	H_2, Raney-Ni	c	-
8	H_2-Pd/C, AcOH (1 equiv.)	c	-
9	H_2-Pd/C, HCl (1 equiv.)	80	21:79

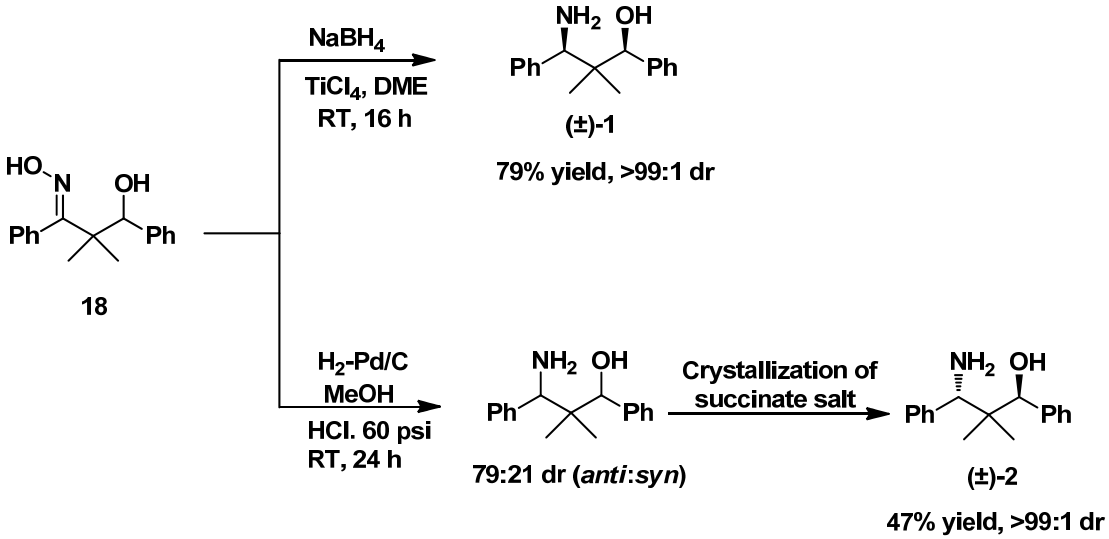
[a]Isolated yield, [b]Determined by ^{1}H-NMR, [c]Very slow or no reaction

For *syn*-1,3-aminoalcohol, we tried to reduce the oxime **18** with various hydride reagents (Table 1). $LiAlH_4$[10c,f] in THF as well as $NaBH_3CN$[12] in aqueous $TiCl_3$ reduced the oxime **18** in moderate yield and low diastereoselectivity. The reduction does not proceed at all using $NaBH_4$ in the presence of $NiCl_2.6H_2O$.[10g] We thought that a strong chelating agent would work to proceed the reduction stereoselectively. Finally we were successful to reduce the oxime **18** by $NaBH_4$ in the presence of $TiCl_4$.[13] The reduction proceeds smoothly using 2 equivalent of $TiCl_4$

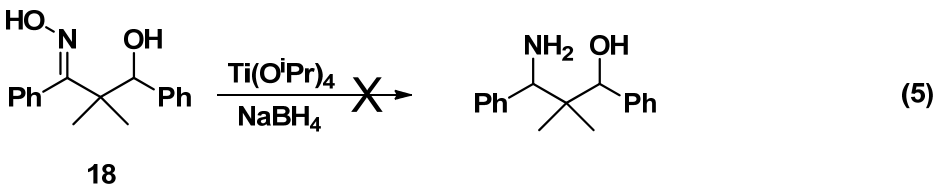
with excess of $NaBH_4$ at room temperature with exclusive formation of *syn*-1,3-aminoalcohol **1** in high yield (79%).

In conclusion *syn*-aminoalcohol **1** was obtained by hydride transfer reagent while under hydrogenation condition, *anti*-isomer **2** was obtained as a major product (Scheme 9).

Scheme 9. Reduction of *β*-hydroxy oxime **18**

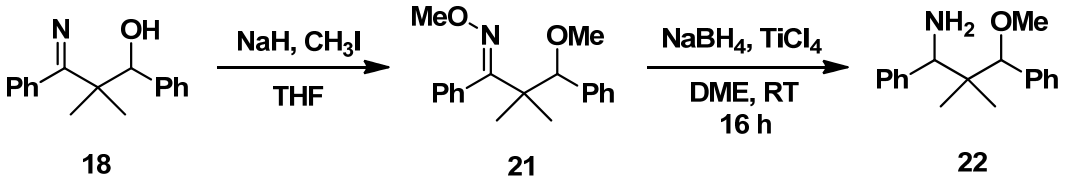


The observed *syn*-diastereoselectivity in hydride reagents is similar to that reported by other groups.[10,14] However the reduction with $NaBH_4/TiCl_4$ is not easy to explain because the combination can involve several reactive species including $Ti(BH_4)_3$, B_2H_6, and which would vary with stoichiometry of the reactant.[15] Reduction does not proceed when *β*-hydroxy oxime **18** was first treated with $Ti(O^iPr)_4$ followed by with $NaBH_4$ (eq 5), which ruled out Ti(IV)-mediated reduction as in the case with reductive amination.[14]



To check the influence of hydroxyl group in the reduction, both the hydroxyl groups of *β*-hydroxy oxime **18** were converted to corresponding methyl ether **21**, which was then subjected to reduction under identical condition (Scheme 10).

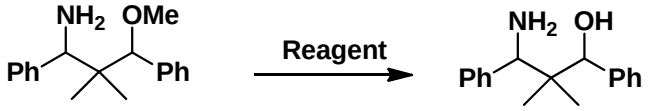
Scheme 10. Reduction of **21**



18 **21** **22**

The reduction of *β*-methoxy oximino ether **21** proceeded smoothly affording single diastereomer of amino methyl ether **22**. To know the relative stereochemistry of product, we tried to convert the amino methyl ether to the corresponding known aminoalcohol via demethylation. However, none of the known reagents for demethylation worked in the present case (Table 2). Using BBr_3 in DCM at -78 ^oC to -25 ^oC, complex reaction mixture was observed as benzyl cleavage took place (Table 2, entry 5).

Table 2. Demethylation of **22**



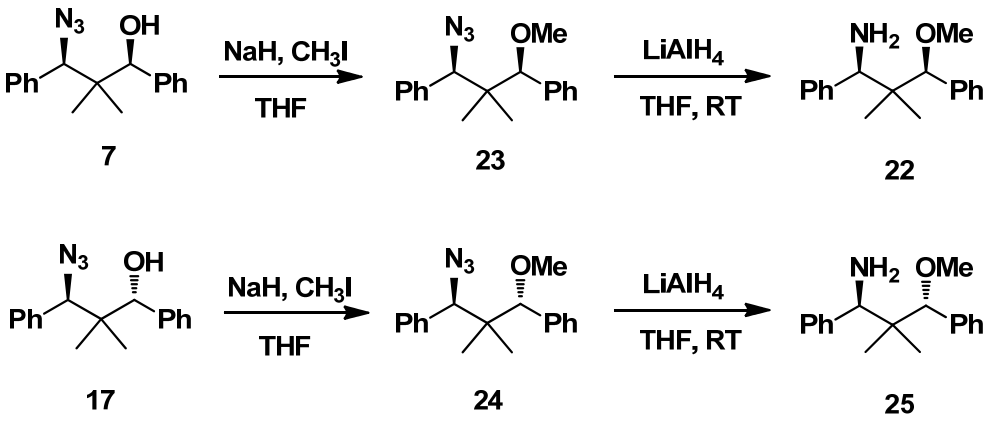
22 **1 or 2**

entry	reagent and condition	results
1	Me_3SiCl, NaI, CH_3CN rt, 24 h	Starting matarial recovered
2	$LiAlH_4$, CCl_4, THF rt to reflux	„
3	HBr (aqueous), reflux	„
4	$AlCl_3$, toluene reflux, 16 h	„
5	BBr_3, DCM -78 ^oC to -25 ^oC, 4 h	Complex reaction mixture

We then changed the approach, since we had both *syn*- and *anti*-azidoalcohol (**7** and **17**) in hand, it was possible to convert them to corresponding amino methyl ether.

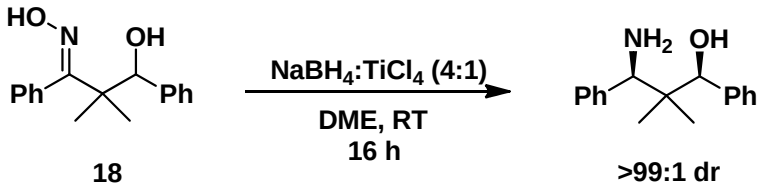
This would indirectly reveal relative stereochemistry of amino methyl ether **22**. Both the azidoalcohols were converted to amino methyl ether as shown in scheme 11.

Scheme 11. Preparation of amino methyl ether



We compared the ^{1}H-NMR spectra which indicated that the product obtained in the reduction of *β*-methoxy oximino ether **21** has *syn*-stereochemistry.

The reduction of *β*-hydroxy oxime **18** was also carried out using 1:4 ratio of $TiCl_4$:$NaBH_4$ (eq 6). It was observed that rate of reaction is increased, but yield and diastereoselectivity were comparable when compared with reduction usng 1:2 ratio of $TiCl_4$:$NaBH_4$.



(6)

With these preliminary experiments, the mechanism of the $TiCl_4$:$NaBH_4$ mediated reduction still remains ambiguous.

As for the *anti*-selectivity in the hydrogenation, it can be explained based on the mechanism proposed for *α*-hydroxy oxime.[16]

Section-2C

Resolution of *syn*- and *anti*-3-amino-2,2-dimethyl-1,3-diphenylpropan-1-ols.

Introduction

A resolution is a separation whose point of departure is a racemate and whose conclusion at least one of the enantiomers present in the initial mixture, is recovered.[17] Several resolution techniques are available, including

a) Resolution by direct crystallization

b) Resolution through formation and separation of diastereomers

c) Crystallization-induced asymmetric transformations leading to total formation of the initial racemate into a single enantiomer.

Among these, the resolution through formation and separation of diastereomers is the most general and widely used technique. In this type of reaction, the substrate to be resolved is treated with one enantiomer of a chiral substance (the resolving agent).

There are two types of diastereomeric separation

i) Separation of enantiomer via covalent diastereomer

ii) Separation of enantiomer via diastereomeric salt

The resolution of alcohols and diols is usually done by using 1st method i.e. resolution through formation and separation of covalent diastereomers. The resolution of acids and bases on the other hand is best done through the corresponding diastereomeric salts. A good resolving agent should possess several characteristics.

1) Ready availability

2) Stability in use

3) Low price and ease of preparation

4) Ease of recovery and reuse

5) Low molecular weight

6) Availability in high enantiomeric purity

7) Availability of both enantiomer

8) Reasonable solubility

Pasteur[18] in 1853 discovered this type of resolution by the formation of salt between a racemic acid and an optically active base. This type of resolution has been mainly based on solubility differences of the solids.

Resolution of aminoalcohols can be done by making i) covalent diastereomers like diastereomeric amide using chiral acid, diastereomeric carbamate using chloroformate ester of an optically active alcohol, through Schiff bases using chiral

aldehyde or ii) diastereomeric salt using chiral acid. We describe herein the resolution of aminoalcohol **1** and **2** through the corresponding diastereomeric salt.

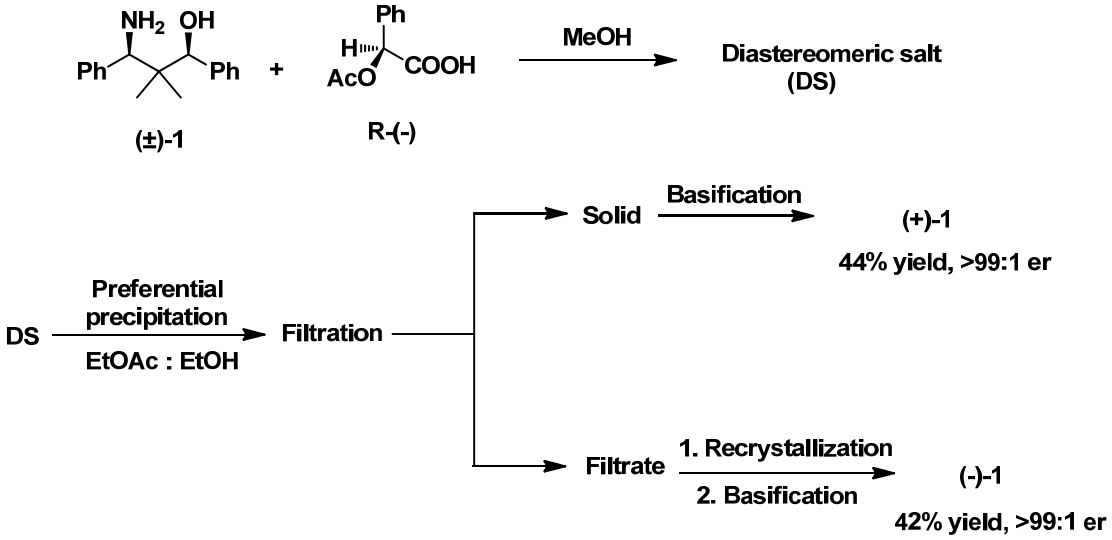
Result and discussion:

We examined various monobasic and dibasic optically pure acids for the resolution of the aminoalcohols **1** and **2**.

Resolution of (±)-1

First we tried to resolve *syn*-1,3-aminoalcohol, through the salts prepared from all commonly used chiral acids,[17] namely, (+)-tartaric acid, (-)-mandelic acid, (-)-camphanic acid, (-)-camphorsulfonic acid and (+)-glutamic acid. The Salts obtained from (-)-mandelic acid and (-)-camphanic acid failed to crystallize due to gummy nature while other salts crystallized with both the isomers. Finally we were successful to resolve the aminoalcohol **1** using R-(-)-O-acetyl mandelic acid (Scheme 12).

Scheme 12. Resolution of (±)-**1**



The diastereomeric salt was prepared using one equivalent of R-(-)-O-acetyl mandelic acid in methanol at room temperature. We tried to crystallize the obtained salt from various solvents but the yield was unsatisfactory. It was observed during crystallization that the corresponding salt is highly soluble in ethanol while insoluble in ethyl acetate, we therefore decided to use a combination of the two. Excellent yield

for both the isomers eventually obtained by preferential precipitation using ethanol:ethyl acetate (~15:85). The salt was dissolved in minimum amount of hot ethanol and diluted with ethyl acetate. The resulting solution was stirred at room temperature for 1 h, to obtain one of the diastereomeric salt as white precipitate. The mixture was filtered to obtain solid salt in 44% yield with a melting point 196-197 ^{o}C and $[\alpha]_D$ -66 (*c* 1, MeOH). It was recrystallized and its melting point and $[\alpha]_D$ checked again. Since these values were unchanged, we assumed that it was single diastereomer. The second isomer of salt was isolated from mother liquor. It was recrystallized from ethanol: ethyl acetate in 42% yield [mp 160-161 ^{o}C, $[\alpha]_D$ -42 (*c* 1, MeOH)]. After basification of diastereomeric salts using aqueous ammonia, (+)-isomer of aminoalcohol **1** was obtained from the precipitated salt while (-)-isomer was isolated from the salt left in the mother liquor.

Optical purity of (+)-**1** and (-)-**1** isomer of *syn*-3-amino-2,2-dimethyl-1,3-diphenylpropan-1-ol was determined by chiral HPLC and found to be more than 99%. Finally the absolute configuration was established by anomalous dispersion effects in X-ray diffraction measurements on the crystal of the hydrobromide salts. It was found to be **(*R*,*S*),** and **(*S*,*R*)** for (+)-**1**, and (-)-**1** respectively. The ORTEP diagram for compound **(-)-1** is shown in Figure 1.

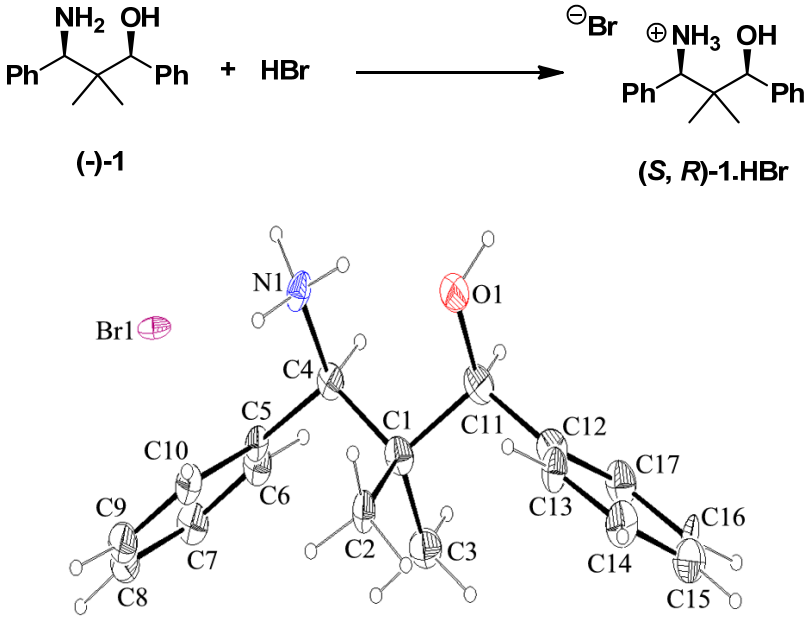


Figure 1. ORTEP diagram for **(-)-1.HBr**

The structure of (+)-**1** and (-)-**1** isomer of aminoalcohol with absolute configuration is shown in figure 2.

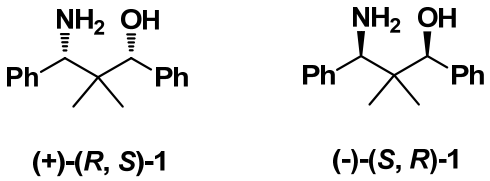
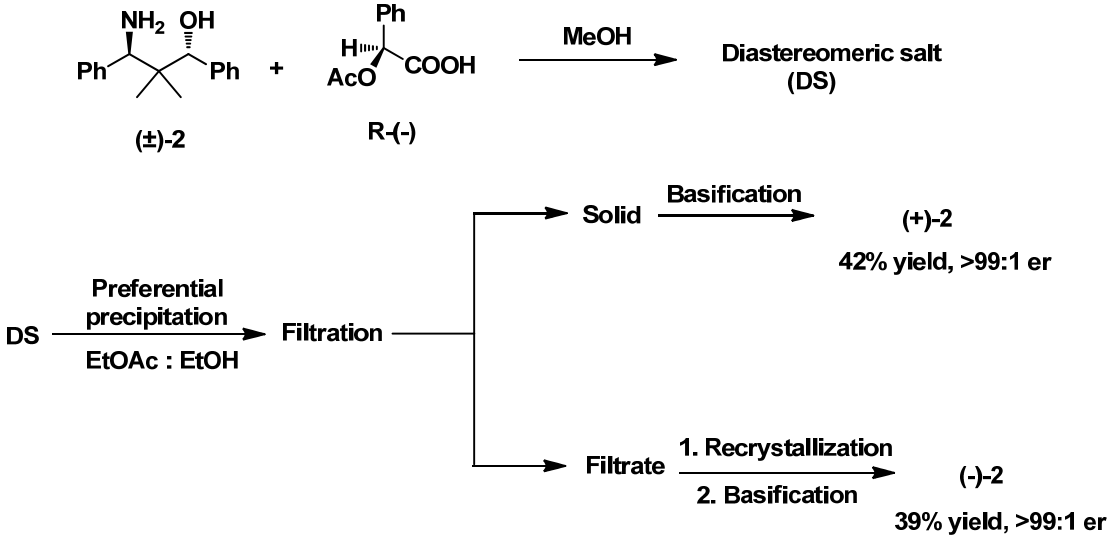


Figure 2

Resolution of (±)-2

The same protocol was also applied for the resolution of **2** (Scheme 13). The precipitated solid after basification with aqueous ammonia was found to be enantiopure (+)-**2** while (-)-**2** was recovered from the filtrate.

Scheme 13. Resolution of (±)-**2**



Optical purity of (+)-**2** and (-)-**2** isomer of anti 3-amino-2,2-dimethyl-1,3-diphenylpropan-1-ol was determined by chiral HPLC and found to be more than 99%. The absolute configuration was established by anomalous dispersion effects in X-ray diffraction measurements on the crystal of the hydrobromide salts and it was found to be **(R,R),** and **(S,S)** for (+)-**2**, and (-)-**2** respectively. The ORTEP diagram for compound **(-)-2** is shown in Figure 3.

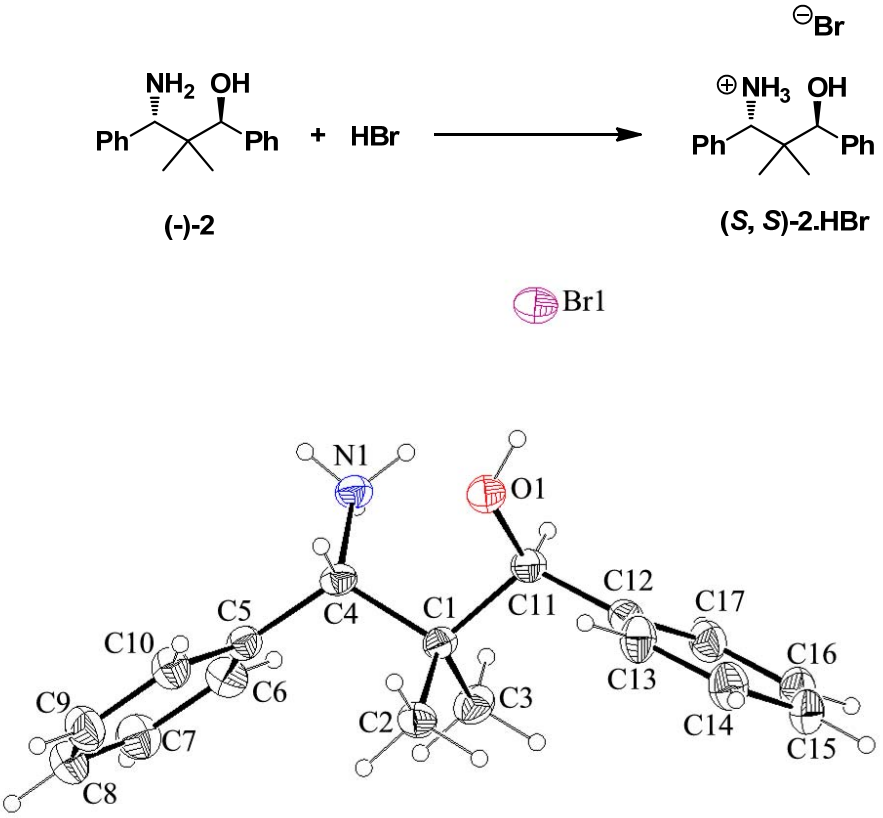


Figure 3. ORTEP diagram for **(-)-2.HBr**

The structure of (+)-**2** and (-)-**2** isomer of aminoalcohol with absolute configuration is shown in figure 4.

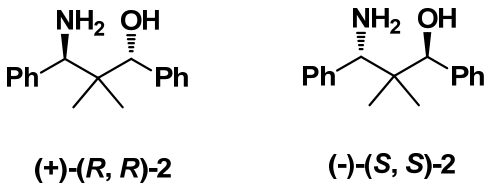


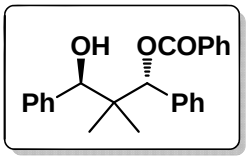
Figure 4

Conclusions

- ✓ We have synthesized both *syn*- and *anti*-isomer of 3-amino-2,2-dimethyl-1,3-diphenylpropan-1-ols starting from the corresponding *γ*-hydroxy benzoates.
- ✓ We also developed a short route for the synthesis of both the aminoalcohols by the stereoselective reduction of *β*-hydroxy oxime, a common intermediate.
- ✓ Both *syn*- and *anti*-isomer of 3-amino-2,2-dimethyl-1,3-diphenylpropan-1-ols were resolved in excellent yield and optical purity using R-(-)-O-acetyl mandelic acid.
- ✓ The absolute configuration was established by X-ray diffraction measurements on the crystal of the hydrobromide salts.

Experimental section

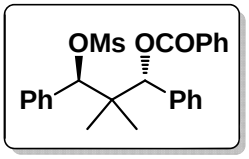
***Anti*-(±)-3-hydroxy-2,2-dimethyl-1,3-diphenylpropyl benzoate (6)**



A cooled solution of anhydrous *tert*-butanol (4.78 mL, 50 mmol) in 25 mL anhydrous THF was treated with ^{n}BuLi (50 mmol, 55.5 mL, 0.9M solution in cyclohexane) followed by isobutyrophenone (7.5 mL, 50 mmol). The mixture was allowed to stir for 10 minutes. Benzaldehyde (12.7 mL, 125 mmol) dissolved in anhydrous THF (60 mL) was then added dropwise over a period of 60 minutes. The mixture was allowed to stir at room temperature for 16 h. The reaction mixture was quenched by the addition of 1N HCl (70 mL) and product was extracted with ethyl acetate (2 x 200 mL). Combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (230-400 mesh) using ethyl acetate:petroleum ether as the eluent to obtain **6** as a white solid.

Yield	**:** 13.2 g, (73%)
TLC data	**:** R_f (10% EtOAc/PE): 0.32
Melting point	**:** 138-139 ^{o}C
dr	**:** >99:1 (by ^{1}H NMR)
IR ($CHCl_3$)	**:** 3608, 1716 cm^{-1}
^{1}H NMR ($CDCl_3$)	**:** δ 0.81 (s, 3H), 0.87 (s, 3H), 2.16 (s, 1H), 4.76 (s, 1H), 6.37 (s, 1H), 7.26-8.17 (m, 15H).
^{13}C NMR ($CDCl_3$)	**:** δ 17.8, 19.2, 42.9, 76.9, 80.0, 127.3, 127.5, 127.7, 128.1, 128.2, 128.5, 129.7, 130.2, 133.2, 137.9, 141.1, 166.0.
Analysis for	**:** $C_{24}H_{24}O_3$
Calculated (%)	**:** C, 79.97; H, 6.71
Found (%)	**:** C, 80.13; H, 6.56

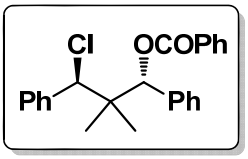
***Anti*-(±)-2,2-dimethyl-3-(methyl sulfonyloxy)-1,3-diphenylpropyl benzoate (4)**



6 (1.08 g, 3 mmol) was dissolved in anhydrous DCM (3 mL). To the stirred solution, pyridine (0.64 mL, 8 mmol) followed by mesyl chloride (0.46 mL, 6 mmol) were added dropwise. It was then stirred for 24 h at room temperature. The reaction mixture was diluted with DCM (15 mL) and washed with 1 N HCl, water, saturated aqueous $NaHCO_3$, water followed by brine. It was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (100-200 mesh) followed by crystallization from ethyl acetate: petroleum ether (1:9) to obtain **4** as a white solid.

Yield	**:** 1.05 g, (80%)
TLC data	**:** R_f (10% EtOAc/PE): 0.2
Melting point	**:** 146-148 ^oC
dr	**:** >99:1 (by ^1H NMR)
IR ($CHCl_3$)	**:** 1722, 1499, 1452 cm^{-1}
^1H NMR ($CDCl_3$)	**:** δ 0.91 (s, 3H), 1.0 (s, 3H), 2.67 (s, 3H), 5.78 (s, 1H), 6.09 (s, 1H), 7.28-8.14, (m, 15H).

***Anti*-(±)-3-chloro-2,3-dimethyl-1,3-diphenylpropyl benzoate (5)**

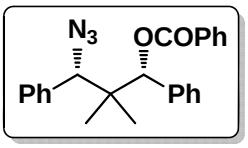


6 (10.8 g, 30 mmol) was dissolved in anhydrous DCM (30 mL) and treated dropwise with thionyl chloride (6.5 mL, 90 mmol). The reaction was monitored by the evolution of gas (HCl and SO_2). After stirring for 24 h at room temperature, DCM and excess thionyl chloride were evaporated under rotavapour. The residue was dissolved in DCM (75 mL), washed with water, saturated aqueous $NaHCO_3$, and brine. The solution was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by filtration column through a short column of silica gel (100-200 mesh)

followed by crystallization from ethyl acetate: petroleum ether (1:9) to obtain **5** as a white solid.

Yield	**:** 9.45 g, (83%)
TLC data	**:** R_f (10% EtOAc/PE): 0.54
Melting point	**:** 167-168 ^oC
dr	**:** >99:1 (by ^1H NMR)
IR ($CHCl_3$)	**:** 3018, 1722, 1452 cm^{-1}
^1H NMR ($CDCl_3$)	**:** δ 0.94 (s, 3H), 0.97 (s, 3H), 5.25 (s, 1H), 6.33 (s, 1H) 7.29-8.17, (m, 15H).
^{13}C NMR ($CDCl_3$)	**:** δ 18.4, 19.9, 43.7, 69.1, 79.8, 127.7, 127.8, 128.0, 128.5, 129.3, 129.5, 130.3, 133.1, 137.7, 138.5, 164.9.
Analysis for	**:** $C_{24}H_{23}ClO_2$
Calculated (%)	**:** C, 76.08; H, 6.12
Found (%)	**:** C, 75.99; H, 6.30

***Syn*-(±)-3-azido-2,3-dimethyl-1,3-diphenylpropyl benzoate (3)**

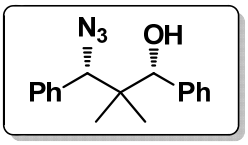


A mixture of chlorobenzoate **5** (11.37 g, 30 mmol), sodium azide (5.85 g, 90 mmol) and DMF (70 mL) was stirred under reflux for 3 days. The reaction mixture was cooled to room temperature, poured into ice water and extracted with ether (3 x 200 mL). Combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (230-400 mesh) using ethyl acetate-petroleum ether as the eluent followed by crystallization to obtain **3** as a white solid.

Yield	**:** 9.65 g, (83%)
TLC data	**:** R_f (10% EtOAc/PE): 0.54
Melting point	**:** 145-146 ^oC
dr	**:** >99:1 (by ^1H NMR)
IR ($CHCl_3$)	**:** 3018, 2104, 1720 cm^{-1}

^{1}H NMR ($CDCl_3$)	: δ 0.85 (s, 3H), 1.20 (s, 3H), 4.45 (s, 1H), 5.81 (s, 1H), 7.22-8.12 (m, 15H)
^{13}C NMR ($CDCl_3$)	**:** δ 19.1, 19.3, 42.8, 71.7, 79.8, 127.8, 128.0, 128.2, 128.3, 128.5, 128.8, 129.5, 130.3, 133.1, 135.9, 137.4, 165.0.
Analysis for	**:** $C_{24}H_{23}N_3O_2$
Calculated (%)	**:** C, 74.78; H, 6.01; N, 10.90
Found (%)	**:** C, 74.48; H, 5.77; N, 10.61

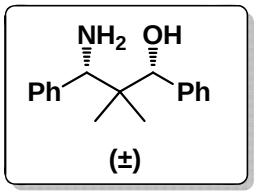
***Syn*-(±)-3-azido-2,3-dimethyl-1,3-diphenylpropan-1-ol (7)**



A mixture of **3** (9.8 g, 25.45 mmol) and KOH (4.2 g, 75 mmol) was stirred in methanol (100 mL) for 24 h at room temperature. Methanol was then removed on a rotary evaporator. Water was added and the reaction mixture was extracted with DCM (2 x 100 mL). Combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (230-400 mesh) using ethyl acetate-petroleum ether as the eluent followed by crystallization from ethyl acetate: petroleum ether (1:9) to obtain **7** as a white solid.

Yield	**:** 6.4 g, (89%)
TLC data	**:** R_f (10% EtOAc/PE): 0.45
Melting point	**:** 89-91 ^oC
dr	**:** >99:1 (by ^{1}H NMR)
IR ($CHCl_3$)	**:** 3608, 3018, 2104 cm^{-1}
^{1}H NMR ($CDCl_3$)	**:** δ 0.61 (s, 3H), 1.09 (s, 3H), 1.85 (s, 1H), 4.40 (s, 1H), 4.71 (s, 1H), 7.26-7.40 (m, 10H).
^{13}C NMR ($CDCl_3$)	**:** δ 17.7, 19.1, 43.1, 72.7, 78.2, 127.6, 127.7, 127.9, 128.0, 128.9, 136.9, 141.2.
Analysis for	**:** $C_{17}H_{19}N_3O$
Calculated (%)	**:** C, 72.57; H, 6.81; N, 14.94
Found (%)	**:** C, 72.34; H, 6.96; N, 15.29

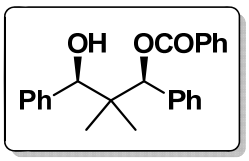
***Syn*-(±)-3-amino-2,3-dimethyl-1,3-diphenylpropan-1-ol (1)**



A solution of **7** (5.2 g, 18.5 mmol) in methanol (50 mL) was hydrogenated at room temperature and at 50 psi pressure using 10% Pd/C (250 mg) for 1 h. Usual work-up provided (±)-3-amino-2,3-dimethyl-1,3-diphenylpropan-1-ol **1** as a white solid.

Yield	**:** 4.71 g, (quantitative)
TLC data	**:** R_f (40% MeOH/EtOAc): 0.45
Melting point	**:** 168-170 ^oC
dr	**:** >99:1 (by ^1H NMR)
IR ($CHCl_3$)	**:** 3388, 3018, 1215 cm^{-1}
^1H NMR ($CDCl_3$)	**:** δ 0.39 (s, 3H), 0.94 (s, 3H), 4.02 (s, 1H), 4.84 (s, 1H), 7.23-7.38 (m, 10H).
^{13}C NMR ($CDCl_3$)	**:** δ 11.8, 24.8, 41.1, 66.2, 84.9, 127.0, 127.2, 127.3, 127.5, 128.0, 128.4, 141.6, 143.5.
Analysis for	**:** $C_{17}H_{21}NO$
Calculated (%)	**:** C, 79.96; H, 8.29; N, 5.49
Found (%)	**:** C, 79.95; H, 8.28; N, 5.27

***Syn*-(±)-3-hydroxy-2,2-dimethyl-1,3-diphenylpropyl benzoate (10)**

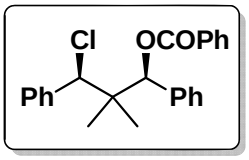


The diol **11** (as a mixture of *syn*:*anti* in 92:8, 6.4 g, 25 mmol)[9] was dissolved in anhydrous DCM (75 mL). To the stirred solution, pyridine (2 mL, 25mmol) followed by benzoyl chloride (2.9 mL, 25 mmol) were added dropwise. It was then stirred for 16 h at room temperature. The reaction mixture was diluted with DCM (100 mL) and washed with 1N HCl, water, saturated aqueous $NaHCO_3$, water, and brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by "flash chromatography" on silica gel (230-400 mesh) using ethyl acetate: petroleum ether as

the eluent followed by crystallization from ethyl acetate: petroleum ether (1:9) to obtain **10** as a white solid.

Yield	**:** 6.4 g, (71%)
TLC data	**:** R_f (10% EtOAc/PE): 0.32
Melting point	**:** 151-153 ^oC
dr	**:** >99:1 (by ^1H NMR)
IR ($CHCl_3$)	**:** 3612, 3489, 3018, 1714 cm^{-1}
^1H NMR ($CDCl_3$)	**:** δ 0.84 (s, 3H), 1.19 (s, 3H), 2.00 (s, 1H), 4.49 (s, 1H), 6.10 (s, 1H), 7.26-8.11 (m, 15H)
^{13}C NMR ($CDCl_3$)	**:** δ 18.0, 19.2, 43.1, 77.8, 80.3, 127.6, 127.7, 127.73, 127.8, 127.84, 127.9, 128.4, 129.6, 130.6, 132.9, 138.1, 141.2, 165.3.
Analysis for	**:** $C_{24}H_{24}O_3$
Calculated (%)	**:** C, 79.97; H, 6.71
Found (%)	**:** C, 80.26; H, 6.38

***Syn*-(±)-3-chloro-2,3-dimethyl-1,3-diphenylpropyl benzoate (9)**



The same procedure was followed as described for the compound **5**. Reaction was performed with 15.5 g (43.05 mmol) of compound **10**.

Yield	**:** 12.8 g, (78%)
TLC data	**:** R_f (10% EtOAc/PE): 0.54
Melting point	**:** 136-137 ^oC
dr	**:** >99:1 (by ^1H NMR)
IR ($CHCl_3$)	**:** 3018, 1722, 1452 cm^{-1}
^1H NMR ($CDCl_3$)	**:** δ 0.95 (s, 3H), 1.35 (s, 3H), 4.84 (s, 1H), 5.91 (s, 1H) 7.27-8.12 (m, 15H)

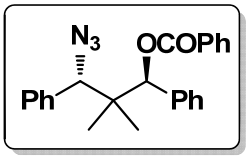
^{13}C NMR ($CDCl_3$) **:** δ 19.4, 19.8, 44.4, 69.7, 79.9, 127.8, 127.9, 128.0, 128.1, 128.2, 128.5, 129.0, 129.6, 130.3, 133.2, 137.4, 138.0, 165.0.

Analysis for **:** $C_{24}H_{23}ClO_2$

Calculated (%) **:** C, 76.08; H, 6.12

Found (%) **:** C, 75.76; H, 6.33.

***Anti*-(±)-3-azido-2,3-dimethyl-1,3-diphenylpropyl benzoate (8)**



The same procedure was followed as described for the compound **3**. Reaction was performed with 7.4 g (19.5 mmol) of compound **9**.

Yield **:** 6.1 g, (81%)

TLC data **:** R_f (10% EtOAc/PE): 0.54

Melting point **:** 154-155 ^oC

dr **:** >99:1 (by ^{1}H NMR)

IR ($CHCl_3$) **:** 3018, 2104, 1720 cm^{-1}

^{1}H NMR ($CDCl_3$) **:** δ 0.78 (s, 3H), 0.90 (s, 3H), 4.82 (s, 1H), 6.2 (s, 1H), 7.26-8.18 (m, 15H)

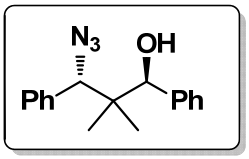
^{13}C NMR ($CDCl_3$) **:** δ 18.5, 19.3, 42.2, 71.3, 79.4, 127.8, 128.0, 128.1, 128.11, 128.5, 129.0, 129.6, 130.3, 133.1, 136.6, 137.7, 165.1.

Analysis for **:** $C_{24}H_{23}N_3O_2$

Calculated (%) **:** C, 74.78; H, 6.01; N, 10.90

Found (%) **:** C, 75.06; H, 5.76; N, 10.75

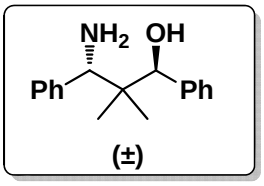
***Anti*-(±)-3-azido-2,3-dimethyl-1,3-diphenylpropan-1-ol (17)**



The same procedure was followed as described for the compound **7**. Reaction was performed with 5.74 g (15 mmol) of compound **8**.

Yield	**:** 3.79 g, (90%)
TLC data	**:** R_f (10% EtOAc/PE): 0.45
Melting point	**:** 135-136 ^oC
dr	**:** >99:1 (by ^1H NMR)
IR ($CHCl_3$)	**:** 3608, 3018, 2104 cm^{-1}
^1H NMR ($CDCl_3$)	**:** δ 0.68 (s, 3H), 0.72 (s, 3H), 1.92 (s, 1H, -OH), 4.88 (s, 1H), 4.97 (s, 1H), 7.26-7.38 (m, 10H)
^{13}C NMR ($CDCl_3$)	**:** δ 18.9, 19.3, 42.2, 71.7, 77.9, 127.4, 127.6, 127.9, 128.0, 128.03, 129.0 136.9, 141.4.
Analysis for	**:** $C_{17}H_{19}N_3O$
Calculated (%)	**:** C, 72.57; H, 6.81; N, 14.94
Found (%)	**:** C, 72.63; H, 6.80; N, 15.20

***Anti*-(±)-3-amino-2,3-dimethyl-1,3-diphenylpropan-1-ol (2)**



The same procedure was followed as described for the compound **1**. Reaction was performed with 3.37 g (12 mmol) of compound **17**.

Yield	**:** 3.06 g, (quantitative)
TLC data	**:** R_f (40% MeOH/EtOAc): 0.45
Melting point	**:** 137-139 ^oC
dr	**:** >99:1 (by ^1H NMR)
IR ($CHCl_3$)	**:** 3018, 1597 cm^{-1}

^{1}H NMR ($CDCl_3$) **:** δ 0.67 (s, 3H), 1.00 (s, 3H), 4.04 (s, 1H), 4.65 (s, 1H), 7.24-7.42 (m, 10H)

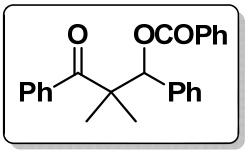
^{13}C NMR ($CDCl_3$) **:** δ 20.7, 23.6, 40.0, 65.9, 79.5, 126.8, 127.2, 127.6, 128.1, 128.2, 141.1, 141.7.

Analysis for **:** $C_{17}H_{21}NO$

Calculated (%) **:** C, 79.96; H, 8.29; N, 5.49

Found (%) **:** C, 79.84; H, 8.18; N, 5.33

2,2-dimethyl-3-oxo-1,3-diphenylpropyl benzoate (19)



To a cooled solution of **6** (20 g, 55 mmol) in diethyl ether (100 mL), was added cold chromic acid solution (75 mmol, 227 mL of 0.33M solution) with vigorous stirring. After the addition stirring was continued at room temperature for 12 h. The reaction mixture was dilute with diethyl ether (100 mL), and the ether layer was separated. The aqueous layer was extracted with ether (3 x 75 mL). Combined ether layer was washed with saturated aqueous $NaHCO_3$, water followed by brine. The extract was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by filtration column through a short column of silica gel (100-200 mesh) to obtain **19** as a white solid.

Yield **:** 19.69 g, (quantitative)

TLC data **:** R_f (10% EtOAc/PE): 0.34

Melting point **:** 87-89 ^oC

IR ($CHCl_3$) **:** 3018, 1787, 1724, 1600 cm^{-1}

^{1}H NMR ($CDCl_3$) **:** δ 1.35 (s, 3H), 1.44 (s, 3H), 6.52 (s, 1H), 7.29-8.03 (m, 15H)

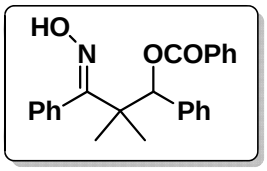
^{13}C NMR ($CDCl_3$) **:** δ 21.1, 23.2, 52.2, 79.7, 127.0, 127.6, 127.9, 128.0, 128.1, 128.4, 129.5, 129.9, 130.7, 133.1, 136.8, 139.2, 164.8, 207.6.

Analysis for **:** $C_{24}H_{22}O_3$

Calculated (%) **:** C, 80.42; H, 6.19

Found (%) **:** C, 80.56; H, 5.86

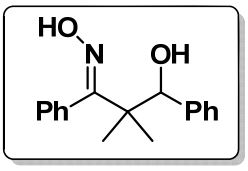
3-(hydroxyimino)-2,2-dimethyl-1,3-diphenylpropyl benzoate (20)



A suspension of **19** (19.7 g, 55 mmol), $NH_2OH.HCl$ (13.86 g, 165 mmol), and sodium acetate (11.46 g, 165 mmol) in ethanol (180 mL) was stirred under reflux temperature for 36 h. Evaporated all ethanol to dryness, water (200 mL) was added and the product was extracted with DCM (1 x 200 ml, 2 x 100 ml). Combined dichloromethane layer was washed with saturated aqueous $NaHCO_3$, water followed by brine. It was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by filtration column through a short column of silica gel (100-200 mesh) to obtain **20** as a white solid.

Yield	**:** 20.51 g, (quantitative)
TLC data	**:** R_f (20% EtOAc/PE): 0.32
Melting point	**:** 135-137 ^oC (EtOAc/PE)
IR ($CHCl_3$)	**:** 3298, 3018, 1720, 1602, 1585 cm^{-1}
^1H NMR ($CDCl_3$)	**:** δ 1.09 (s, 3H), 1.38 (s, 3H), 6.04 (s, 1H), 7.15 (s, 1H, -OH), 7.01-8.12 (m, 15H)
^{13}C NMR ($CDCl_3$)	**:** δ 20.6, 24.4, 44.8, 79.6, 127.5, 127.8, 127.9, 128.3, 128.4, 128.43, 129.7, 130.1, 132.7, 133.1, 136.9, 164.1, 165.1.
Analysis for	**:** $C_{24}H_{23}NO_3$
Calculated (%)	**:** C, 77.19; H, 6.21; N, 3.75
Found (%)	**:** C, 76.98; H, 6.40; N, 3.43

3-hydroxy-2,2-dimethyl-1,3-diphenylpropan-1-one oxime (18)

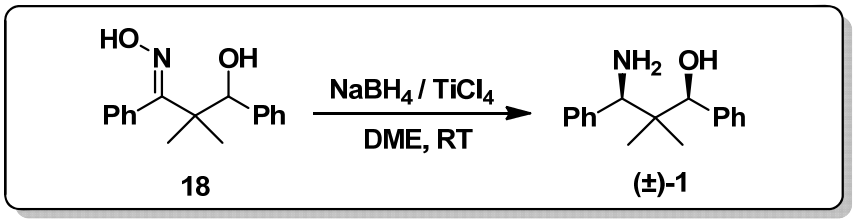


A mixture of **20** (20.5 g, 55 mmol) and KOH (8.4 g, 150 mmol) was stirred in methanol (250 mL) for 16 h at room temperature. Methanol was then evaporated on a rotary evaporator. Water was added and the product was extracted with DCM (1 x

200 mL, 2 x 100 mL). Combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by crystallization from ethanol to obtain **18** as a white solid.

Yield	**:** 12.00 g, (81%)
TLC data	**:** R_f (40% EtOAc/PE): 0.35
Melting point	**:** 193-196^oC
IR ($CHCl_3$)	**:** 3282, 3238, 3086, 2969 cm^{-1}
^1H NMR ($CDCl_3$)	**:** δ 0.97 (s, 3H), 1.08 (s, 3H), 3.79 (s, 1H), 4.96 (s, 1H), 7.09-7.44 (m, 10H) 7.26 (s, 1H, -OH).
^{13}C NMR ($CDCl_3$)	**:** δ 19.3, 25.0, 45.6, 78.6, 127.5, 127.6, 128.2, 128.3, 128.4, 132.7, 140.1, 166.8.
Analysis for	**:** $C_{17}H_{19}NO_2$
Calculated (%)	**:** C, 75.81; H, 7.11; N, 5.20
Found (%)	**:** C, 75.36; H, 7.54; N, 5.55

Reduction of 18 with $NaBH_4/TiCl_4$



A solution of **18** (1.34 g, 5 mmol) in anhydrous 1,2-dimethoxyethane (15 mL) was added dropwise to an ice-cooled, stirred mixture of $TiCl_4$ (1.2 mL, 11 mmol) and $NaBH_4$ (0.83 g, 22 mmol) in anhydrous 1,2-dimethoxyethane (15 mL). After the addition, ice-bath was removed and stirring was continued at room temperature for 44 h. The reaction mixture was then quenched by the addition of ice-cold water, followed by 10% NaOH. The resulting suspension was filtered and the solid was washed with dichloromethane. Combined filtrate was transferred to a separating funnel and dichloromethane layer was separated. The organic portion was washed with brine dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by crystallization from toluene to obtain **1** as a white solid.

Yield	**:** 1.00 g, (79%)

TLC data : R_f (40% MeOH/EtOAc): 0.45

Melting point : 168-170 ^oC

dr : >99:1 (by ^1H NMR)

IR ($CHCl_3$) : 3388, 3018, 1215 cm^{-1}

^1H NMR ($CDCl_3$) : δ 0.39 (s, 3H), 0.94 (s, 3H), 4.02 (s, 1H), 4.84 (s, 1H), 7.23-7.38 (m, 10H).

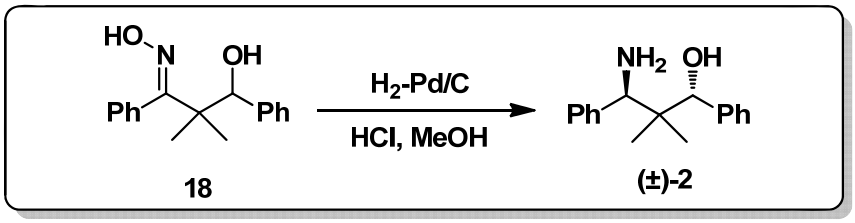
^{13}C NMR ($CDCl_3$) : δ 11.8, 24.8, 41.1, 66.2, 84.9, 127.0, 127.2, 127.3, 127.5, 128.0, 128.4, 141.6, 143.5.

Analysis for : $C_{17}H_{21}NO$

Calculated (%) : C, 79.96; H, 8.29; N, 5.49

Found (%) : C, 79.95; H, 8.28; N, 5.27

Preparation of *anti*-(±)-3-amino-2,3-dimethyl-1,3-diphenylpropan-1-ol (2)



In a solution of **18** (2.69 g, 10 mmol) in methanol (100 mL) was added 1 mL concentrated HCl, the resulting mixture was hydrogenated at room temperature in the presence of 10% Pd/C (250 mg). The catalyst was removed by filtration and methanol was evaporated under rotavapour. The obtained crude salt was dissolved in water, washed with ether to remove neutral impurity and basified with aqueous ammonia to obtain aminoalcohol (2.04 g, 90%) as a 79:21 mixture (*anti*:*syn*).

The mixture was converted to the corresponding succinate salt by treating with one equivalent of succinic acid in methanol at room temperature. Methanol was evaporated and the obtained salt was crystallized using ethanol:ethyl acetate (1:9). The salt was basified using aqueous ammonia to obtain the desired *anti*-aminoalcohol **2** as a white solid.

Yield : 1.2 g, (47%)

TLC data : R_f (40% MeOH/EtOAc): 0.45

Melting point : 137-139 ^oC

dr : >99:1 (by ^1H NMR)

IR ($CHCl_3$) : 3018, 1597 cm^{-1}

^{1}H NMR ($CDCl_3$) : δ 0.67 (s, 3H), 1.00 (s, 3H), 4.04 (s, 1H), 4.65 (s, 1H), 7.24-7.42 (m, 10H)

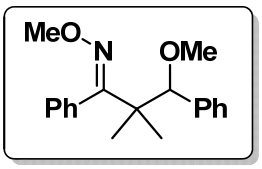
^{13}C NMR ($CDCl_3$) : δ 20.7, 23.6, 40.0, 65.9, 79.5, 126.8, 127.2, 127.6, 128.1, 128.2, 141.1, 141.7.

Analysis for : $C_{17}H_{21}NO$

Calculated (%) : C, 79.96; H, 8.29; N, 5.49

Found (%) : C, 79.84; H, 8.18; N, 5.33

3-methoxy-2,2-dimethyl-1,3-diphenylpropan-1-one o-methyl oxime (21)



To a cooled suspension of NaH (0.279 g, 6 mmol) in THF (3 mL), compound **18** (0.538 g, 2 mmol) dissolved in THF (8 mL) was added. The resulting solution was stirred at room temperature for 1 h and at 50 ^oC for 30 minutes. The reaction mixture was cooled to 0 ^oC and treated with methyl iodide (0.37 mL, 6 mmol). After the addition, the ice-bath was removed and reaction mixture was stirred at room temperature for 8 h. The reaction was quenched by the addition of water (1 mL). The reaction mixture was evaporated to dryness and the product was extracted by trituration with ethyl acetate (2 x 25 mL). Combined organic layer was washed by brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash chromatography on silica gel (230-400 mesh) using ethyl acetate:petroleum ether as a eluent to obtain **21** as a white solid.

Yield : 0.51 g, (86%)

TLC data : R_f (5% EtOAc/PE): 0.6

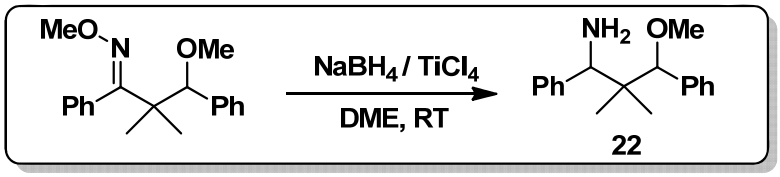
Melting point : 72-74 ^oC

IR ($CHCl_3$) : 3018, 2937, 1599, 1467 cm^{-1}

^{1}H NMR ($CDCl_3$) : δ 0.95 (s, 3H), 1.14 (s, 3H), 3.13 (s, 3H), 3.80 (s, 3H), 4.11 (s, 1H), 7.10-7.41 (m, 10H)

^{13}C NMR ($CDCl_3$) : δ 19.5, 24.9, 45.3, 56.6, 61.7, 87.5, 127.5, 127.6, 127.9, 129.0, 134.5, 137.6, 164.2.

3-methoxy-2,2-dimethyl-1,3-diphenylpropan-1-amine (22)



The same procedure was followed as described for the reduction of compound **18**. The reaction was performed with 0.297 g (1 mmol) of compound **21**.

Yield **:** 0.2 g, (74%)

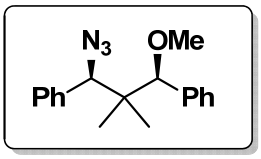
TLC data **:** R_f (40% EtOAc/PE): 0.35

Nature **:** Thick liquid

IR ($CHCl_3$) **:** 3385, 3323, 3028, 2972, 1600 cm^{-1}

^{1}H NMR ($CDCl_3$) **:** δ 0.59 (s, 3H), 1.04 (s, 3H), 1.60 (s, 2H, $-NH_2$), 3.10 (s, 3H), 3.76 (s, 1H), 4.18 (s, 1H), 7.20-7.35 (m, 10H)

(*Syn*-(±)-1-azido-3-methoxy-2,2-dimethylpropane-1,3-diyl)dibenzene (23)



The same procedure was followed as described for the compound **21**. The reaction was performed with 0.056 g (0.2 mmol) of compound **7**.

Yield **:** 0.052 g, (88%)

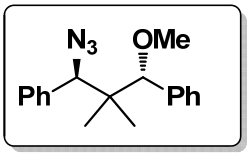
TLC data **:** R_f (5% EtOAc/PE): 0.5

Nature **:** Sticky solid

IR ($CHCl_3$) **:** 3018, 2980, 2102 cm^{-1}

^{1}H NMR ($CDCl_3$) **:** δ 0.64 (s, 3H), 1.08 (s, 3H), 3.09 (s, 3H), 3.63 (s, 1H), 4.75 (s, 1H), 7.16-7.39 (m, 10H)

(*Anti*-(±)-1-azido-3-methoxy-2,2-dimethylpropane-1,3-diyl)dibenzene (24)



The same procedure was followed as described for the compound **21**. The reaction was performed with 0.056 g (0.2 mmol) of compound **17**.

Yield **:** 0.054 g, (91%)

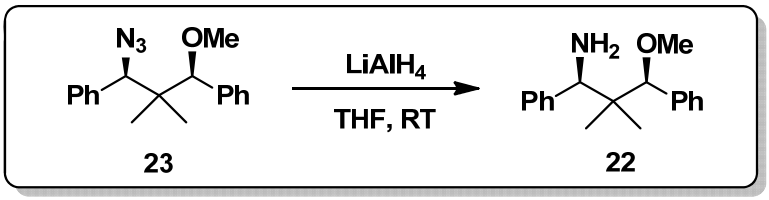
TLC data **:** R_f (5% EtOAc/PE): 0.5

Melting point **:** 113-115 ^oC

IR ($CHCl_3$) **:** 3018, 2980, 2102 cm^{-1}

^1H NMR ($CDCl_3$) **:** δ 0.58 (s, 3H), 0.60 (s, 3H), 3.29 (s, 3H), 4.39 (s, 1H), 5.08 (s, 1H), 7.26-7.34 (m, 10H)

***Syn*-(±)-3-methoxy-2,2-dimethyl-1,3-diphenylpropan-1-amine (22)**



To a suspension of $LiAlH_4$ (0.0042 g, 1 mmol) in THF (2 mL), **23** (0.044 g, 0.15 mmol) dissolved in THF (1 mL) was added. The resulting solution was stirred at room temperature for 6 h. It was quenched by the addition of 10% NaOH (few drops). The resulting suspepsion was filtered. The solid was washed with diethyl ether. Combined filtrate was transferred to a separating funnel and the ether layer was separated. The aqueous layer was extracted with diethyl ether (2 x 10 mL). Combined ether layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatoghaphy on silica gel (100-200 mesh) using ethyl acetate:petroleum ether as the eluent to obtain **22** as a sticky mass.

Yield **:** 0.031 g, (77%)

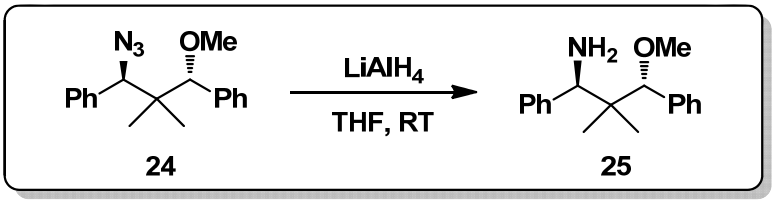
TLC data **:** R_f (40% EtOAc/PE): 0.35

Nature **:** Sticky mass

IR (Neat) **:** 3385, 3323, 3028, 2972, 1600 cm^{-1}

^{1}H NMR ($CDCl_3$) **:** δ 0.59 (s, 3H), 1.04 (s, 3H), 1.60 (s, 2H, -NH_2), 3.10 (s, 3H), 3.76 (s, 1H), 4.18 (s, 1H), 7.18-7.35 (m, 10H)

***Anti*-(±)-3-methoxy-2,2-dimethyl-1,3-diphenylpropan-1-amine (25)**



24 25

The same procedure was followed as described for the reduction of compound **23**. The reaction was performed with 0.044 g (0.15 mmol) of compound **24**.

Yield **:** 0.033 g, (82%)

TLC data **:** R_f (40% EtOAc/PE): 0.34

Nature **:** Sticky solid

IR ($CHCl_3$) **:** 3385, 3315, 3016, 1217 cm^{-1}

^{1}H NMR ($CDCl_3$) **:** δ 0.70 (s, 3H), 0.72 (s, 3H), 1.95 (s, 2H, -NH_2), 3.23 (s, 3H), 4.14 (s, 1H), 4.24 (s, 1H), 7.23-7.34 (m, 10H)

Resolution of (±)-1

The aminoalcohol **1** (2.55 g, 10 mmol) and R-(-)-O-acetylmandelic acid (1.94 g, 10 mmol) were dissolved in methanol (20 mL). The resulting clear solution was evaporated to dryness under reduced pressure. The salt was dissolved in minimum amount of hot ethanol (5 mL) and diluted with ethyl acetate (30 mL). The resulting solution was stirred at room temperature for 1 h, to obtain white precipitate of one of the diastereomeric salt. The mixture was filtered to obtain the solid salt (2 g, 44%), mp 196-197 ^oC, $[\alpha]_D$ -66 (*c* 1, MeOH). The second isomer of the salt was isolated from the mother liquor by evaporation followed by recrystallization from ethanol: ethyl acetate (1:9), (1.9 g, 42%), mp 160-161 ^oC, $[\alpha]_D$ -42 (*c* 1, MeOH). Basification of the salts was carried out using aqueous ammonia. **(+)-1** isomer of aminoalcohol was obtained from the precipitated salt while **(-)-1** isomer was isolated from the salt left in mother liquor.

Yield of (+)-1 isomer **:** 1.12 g (44%)
Melting point **:** 170-171 ^{o}C
$[\alpha]_D$ **:** +42 (*c* 1, $CHCl_3$)
er **:** >99:1 (Kromasil-5-Amycoat column, 2-propanol:PE:TFA).
Absolute configuration **:** 1*R*,3*S*
Yield of (-)-1 isomer **:** 1.06 g (42%)
Melting point **:** 170-171 ^{o}C
$[\alpha]_D$ **:** -42 (*c* 1, $CHCl_3$)
er **:** >99:1 (Kromasil-5-Amycoat column, 2-propanol:PE:TFA).
Absolute configuration **:** 1*S*,3*R*

Resolution of (±)-2

The aminoalcohol **2** (1.27 g, 5 mmol) and R-(-)-O-acetylmandelic acid (0.97 g, 5 mmol) were dissolved in methanol (15 mL).

The same procedure was then followed as described for the resolution of **(±)-1**

Precipitated salt was obtained in 42% yield (0.95 g), mp 175-177 ^{o}C, $[\alpha]_D$ -60 (*c* 1, MeOH).

Salt from mother liquor, 39% yield (0.9 g), mp 160-162 ^{o}C , $[\alpha]_D$ -44 (*c* 1, MeOH).

Basification was carried out as described for above.

Yield of (+)-2 isomer **:** 0.52 g (42%)
Melting point **:** 142-143 ^{o}C
$[\alpha]_D$ **:** +40 (*c* 1, $CHCl_3$)
er **:** >99:1 (Kromasil-5-Amycoat column, 2-propanol:PE:TFA).
Absolute configuration **:** 1*R*,3*R*
Yield of (-)-2 isomer **:** 0.49 g (39%)
Melting point **:** 141-142 ^{o}C
$[\alpha]_D$ **:** -40 (*c* 1, $CHCl_3$)
er **:** >99:1 (Kromasil-5-Amycoat column, 2-propanol:PE:TFA).
Absolute configuration **:** 1*S*,3*S*

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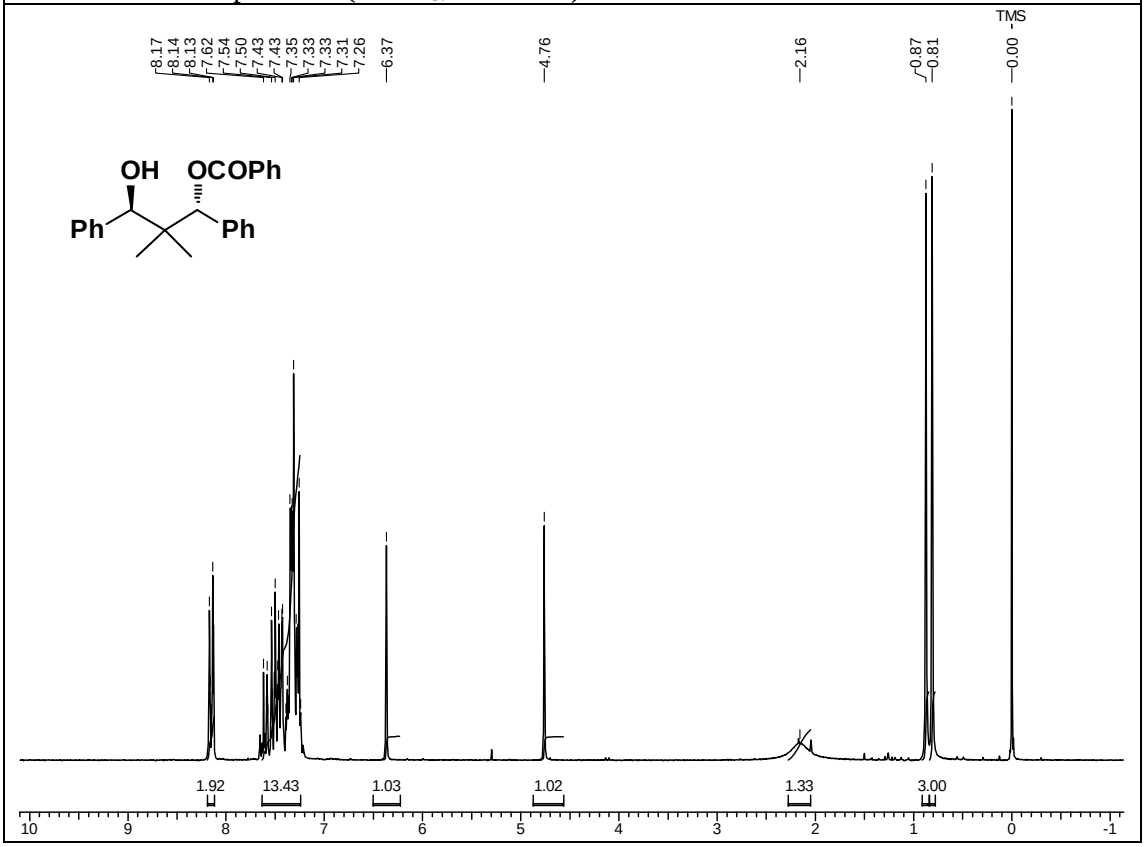
NMR Spectra,

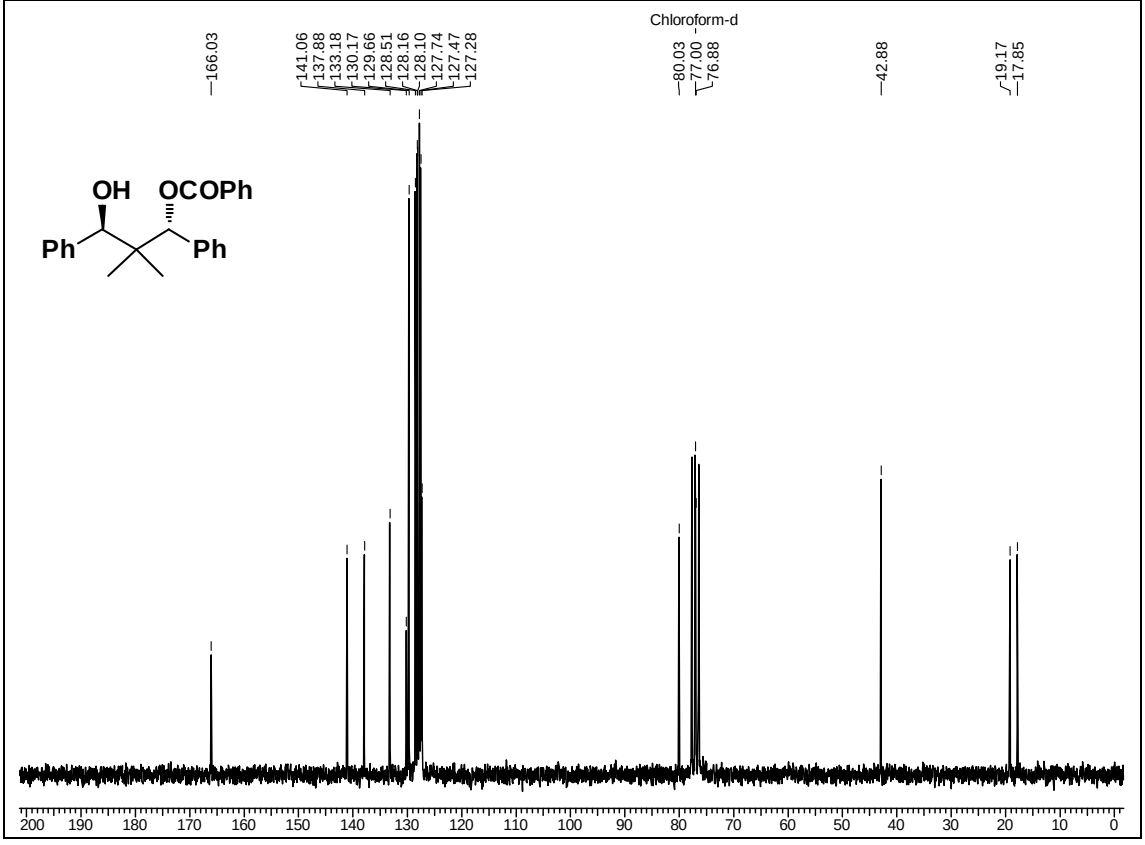
HPLC Chromatogram

And Crystallographic Data

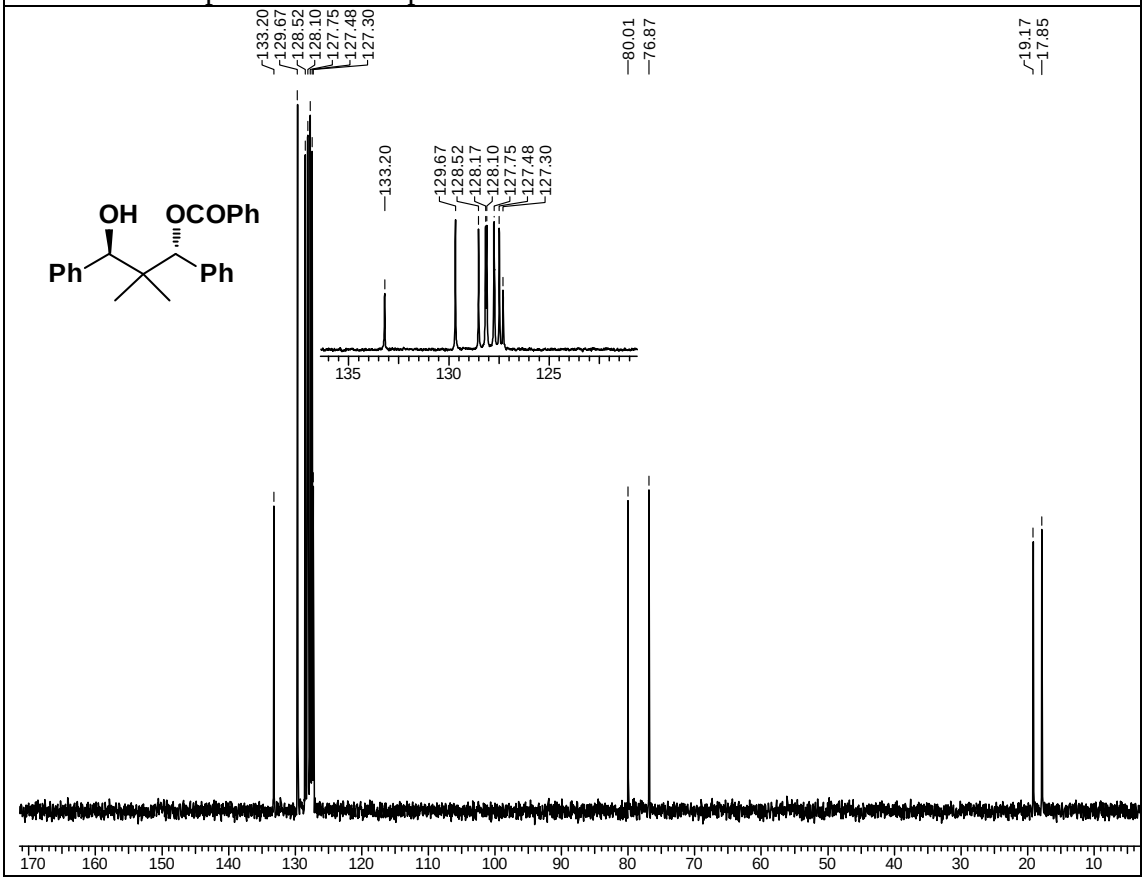
^{1}H-NMR of compound **6** ($CDCl_3$, 200MHz)



^{13}C-NMR of compound **6** ($CDCl_3$, 50.32MHz)



DEPT NMR Spectrum of compound **6**



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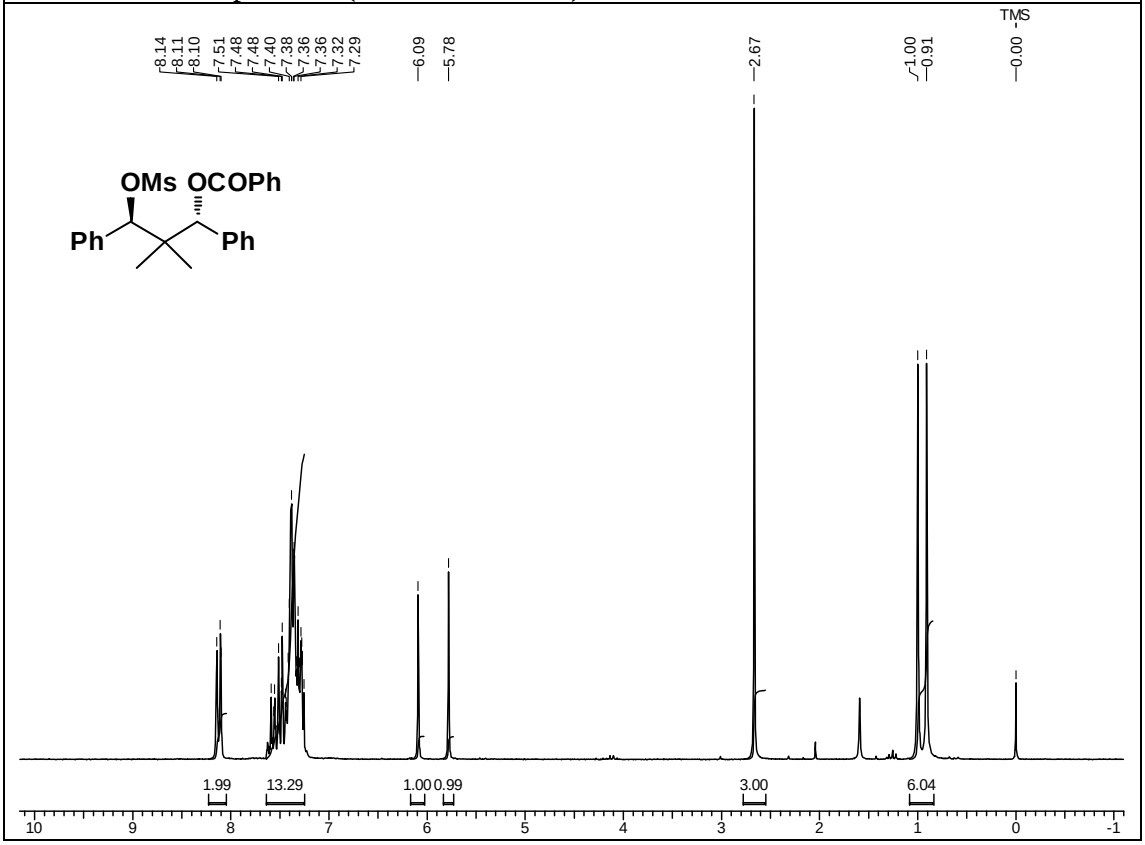

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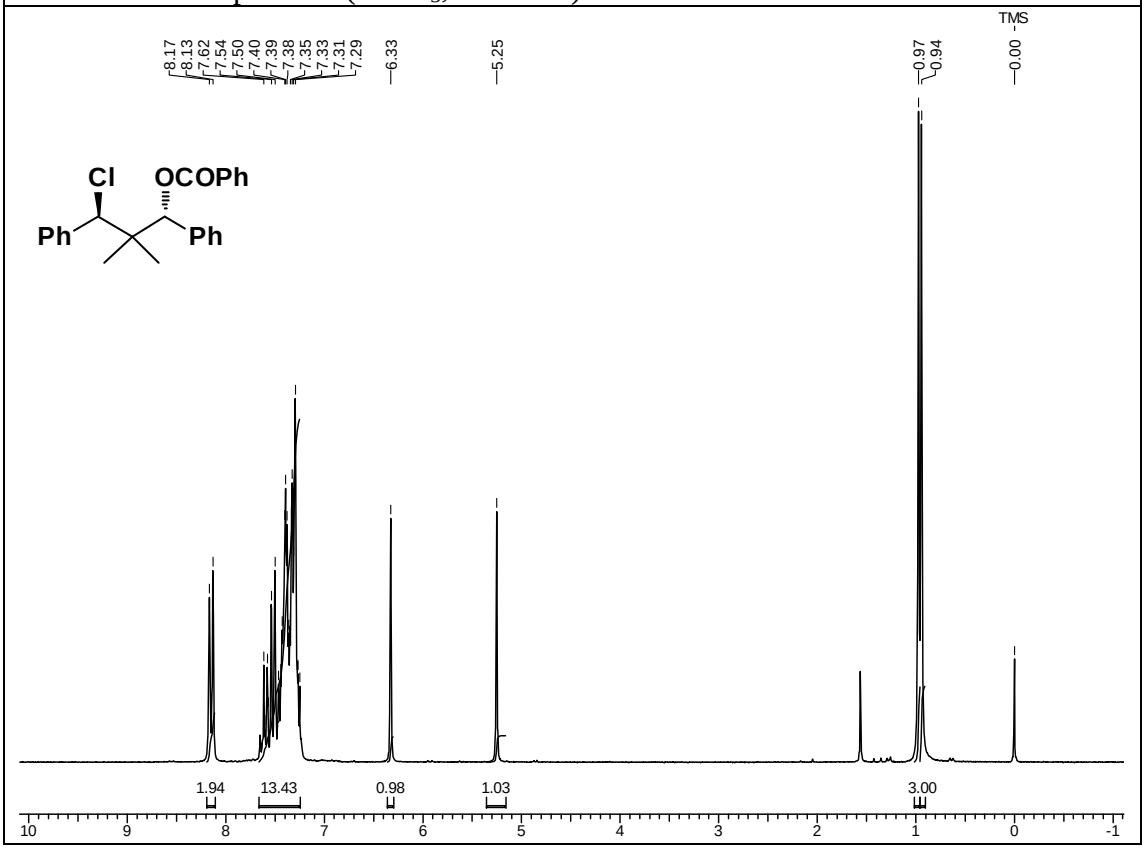
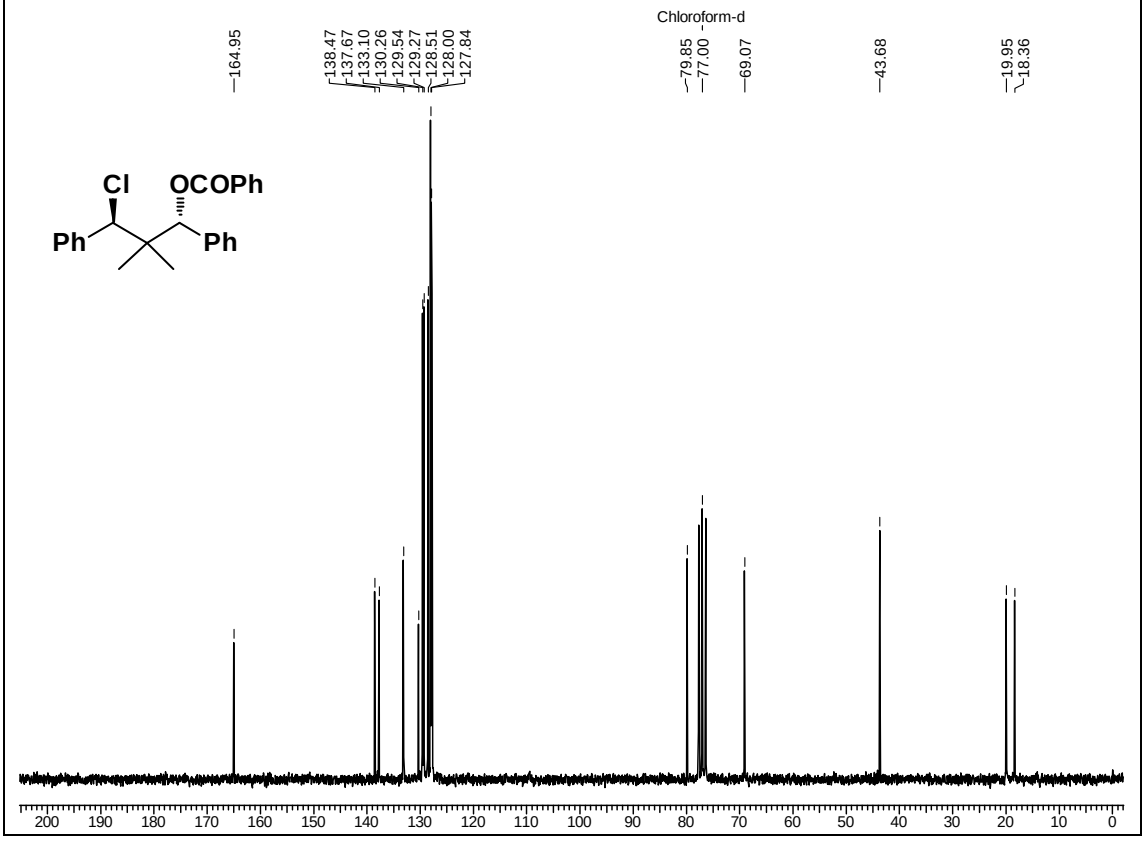
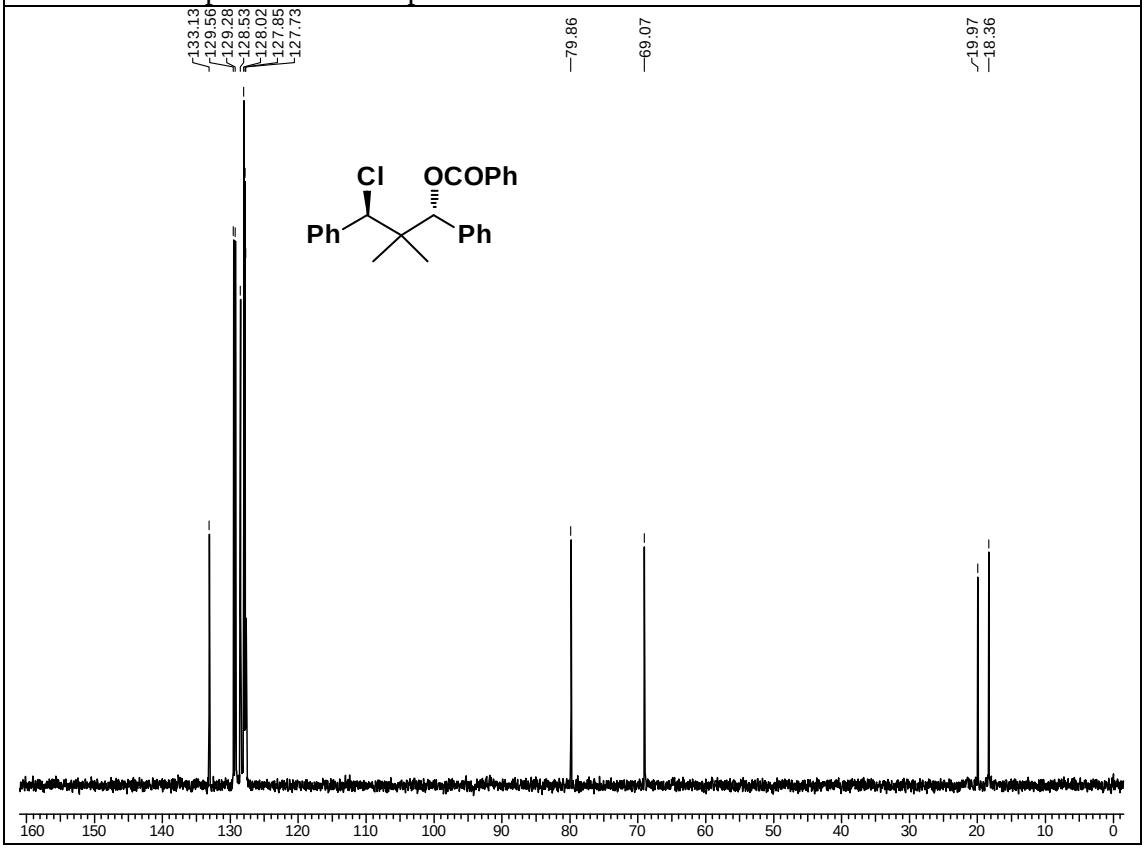


^{13}C-NMR of compound **5** ($CDCl_3$, 50.32MHz)



DEPT NMR Spectrum of compound **5**



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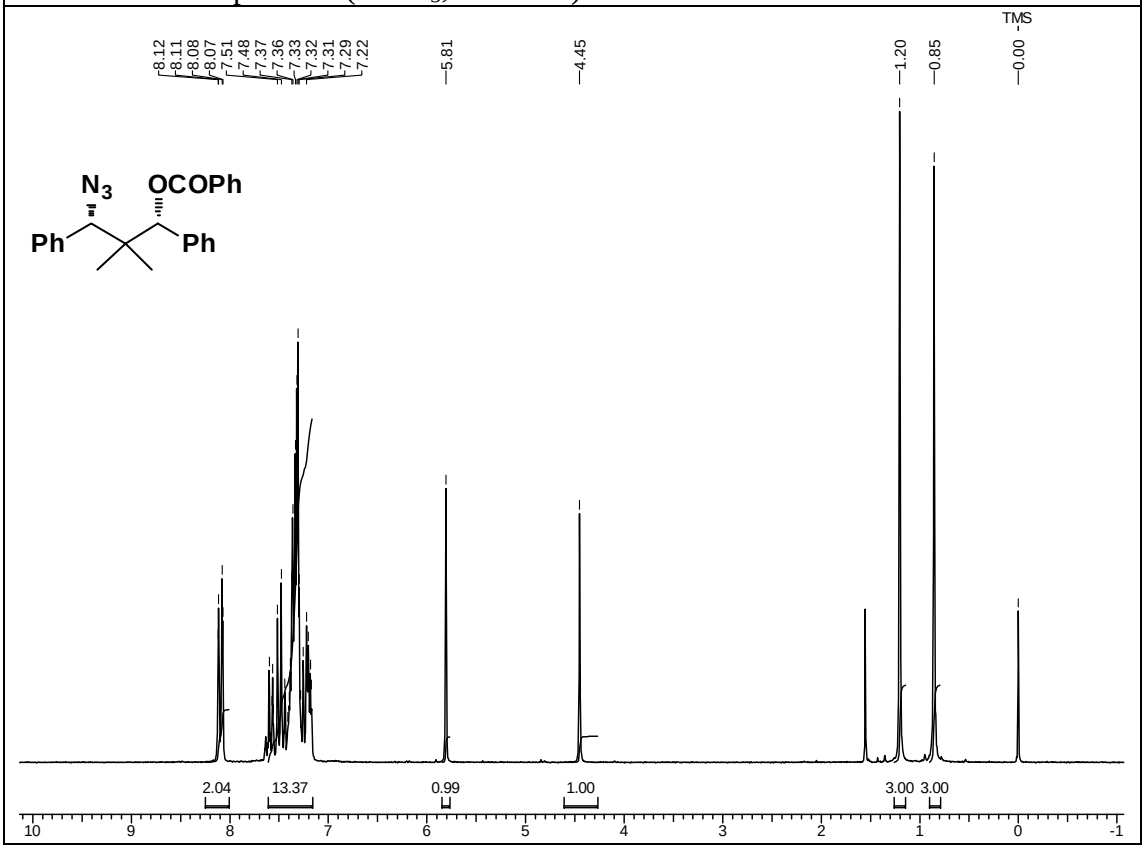
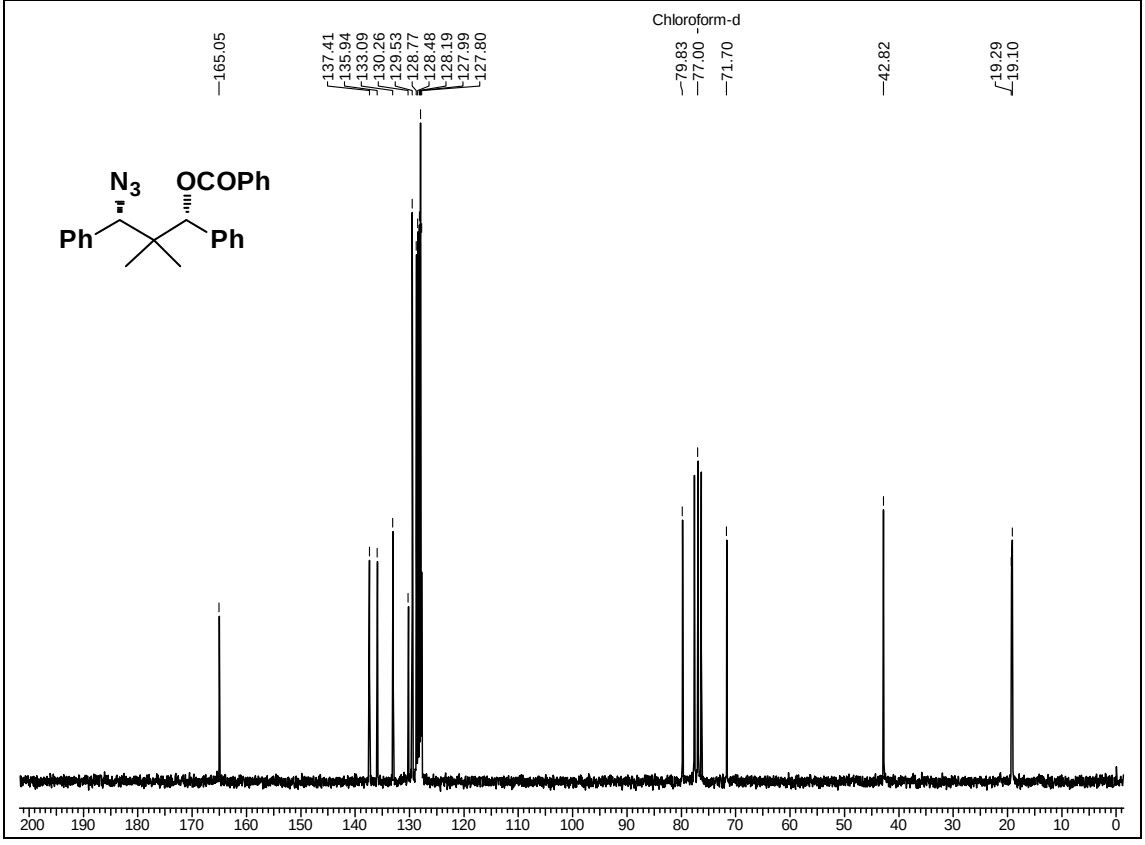
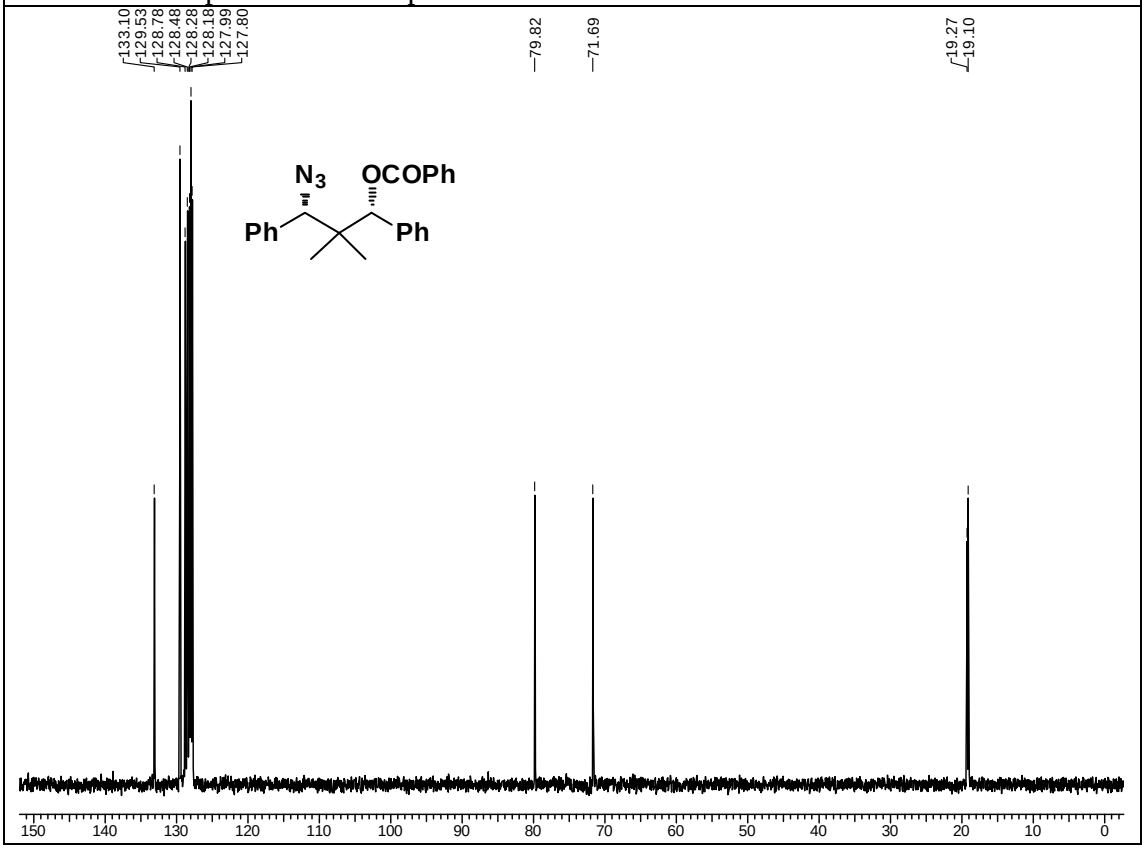


^{13}C-NMR of compound **3** ($CDCl_3$, 50.32MHz)



DEPT NMR Spectrum of compound **3**



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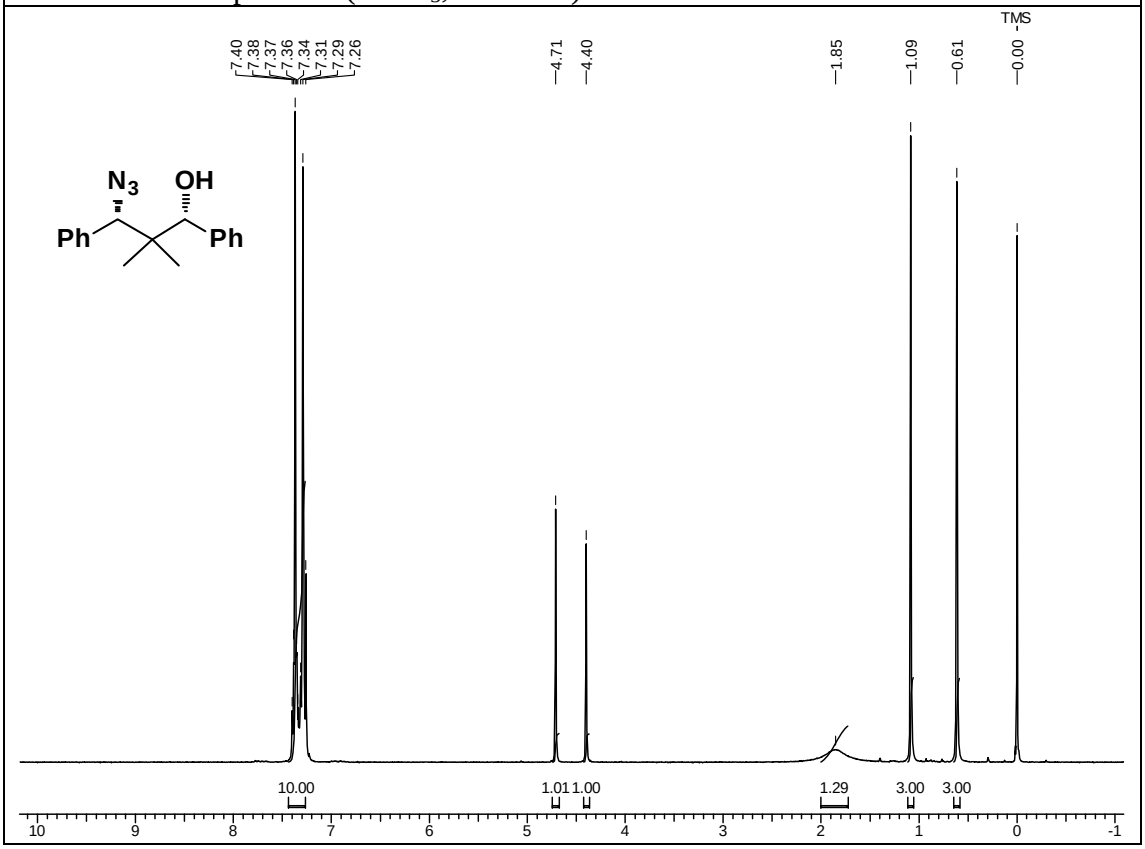
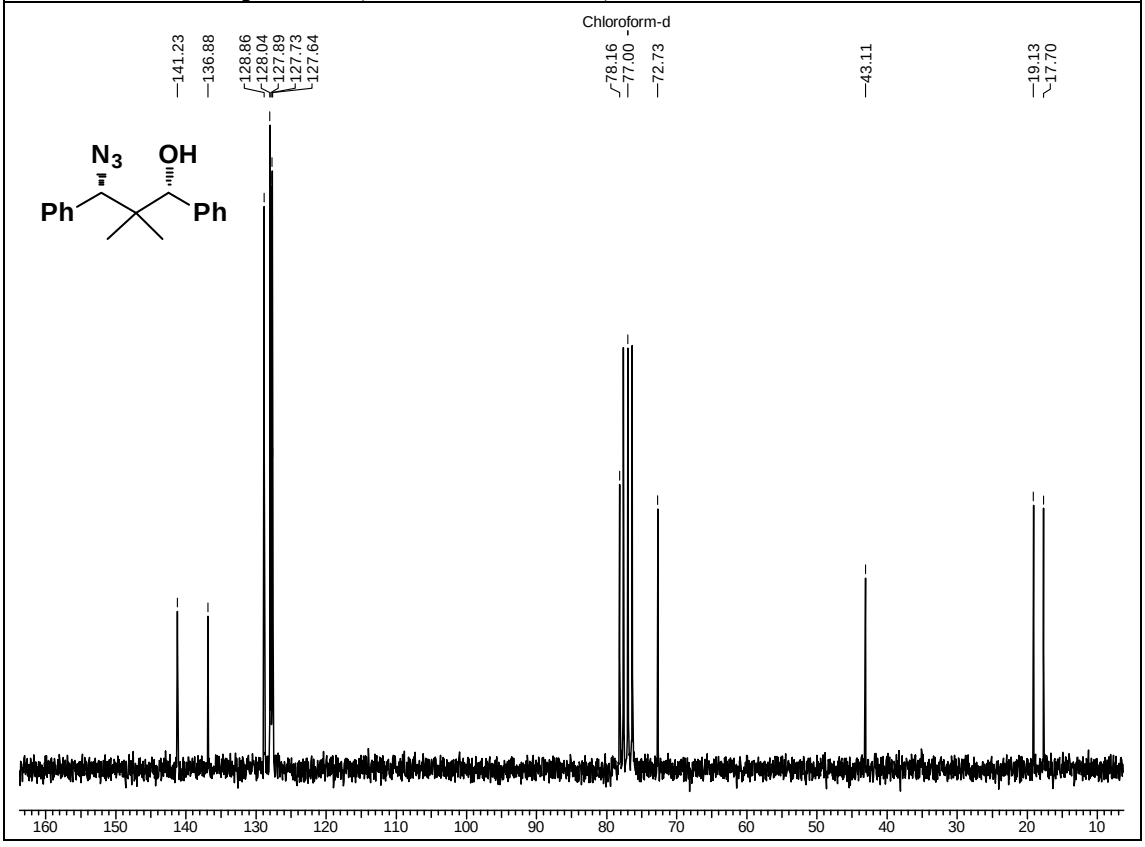
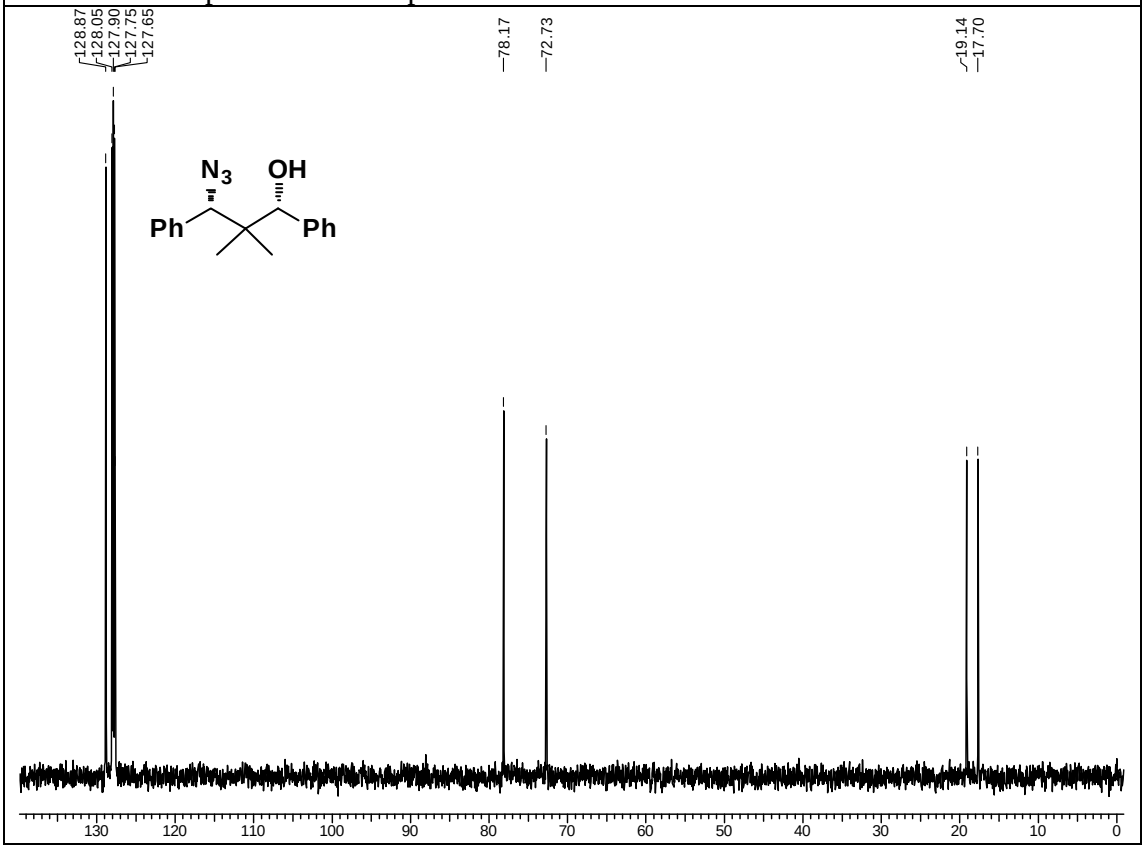


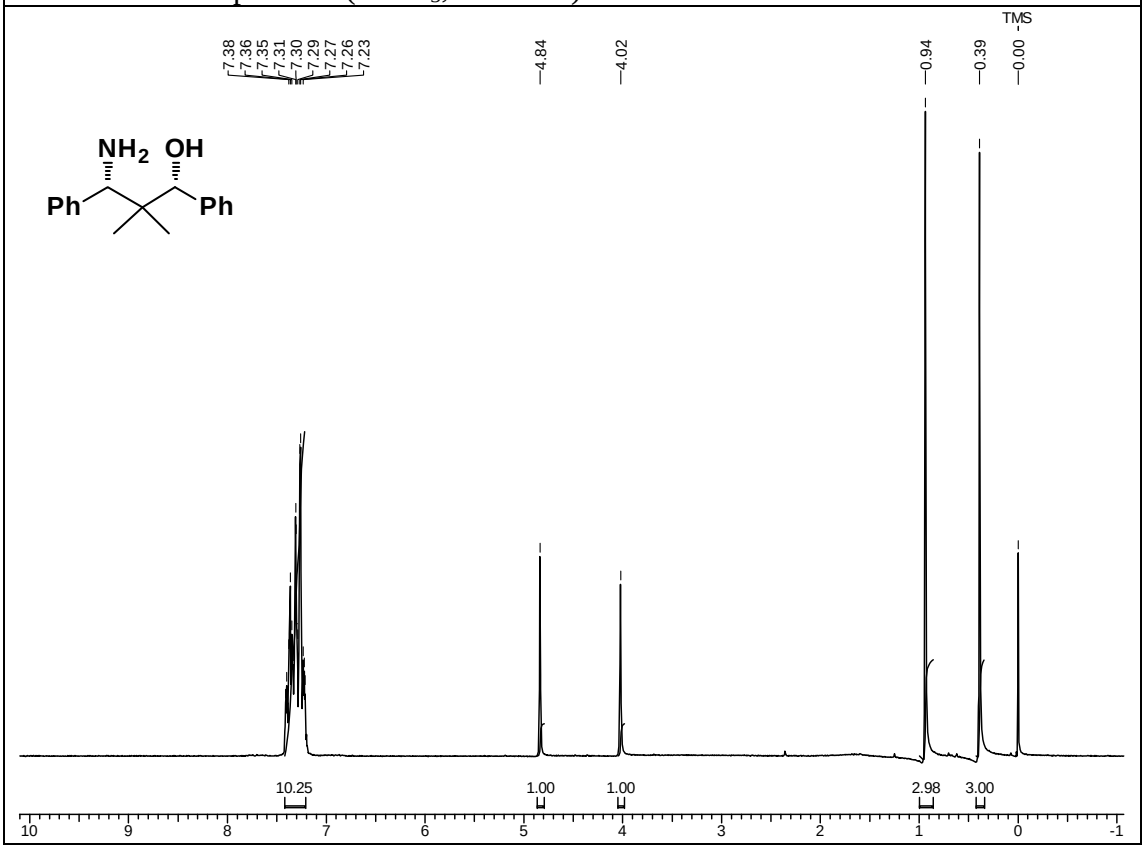
^{13}C-NMR of compound **7** ($CDCl_3$, 50.32MHz)



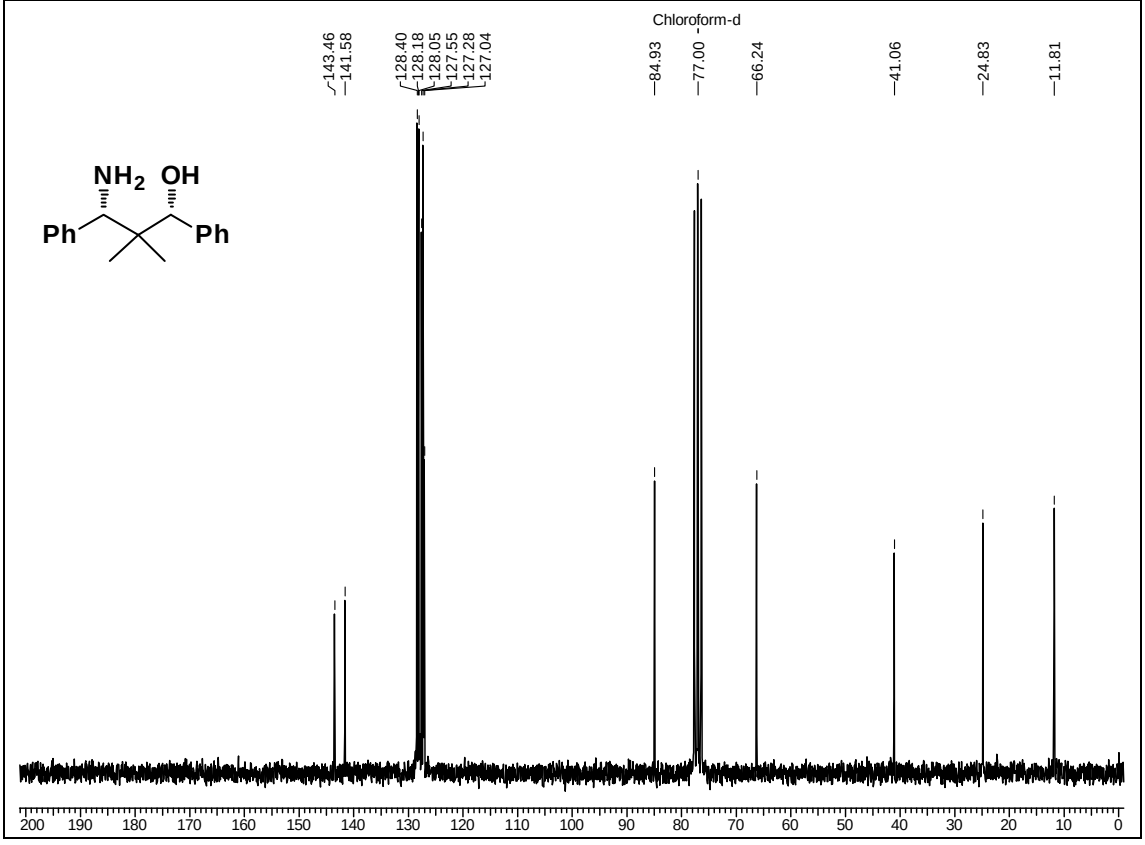
DEPT NMR Spectrum of compound **7**



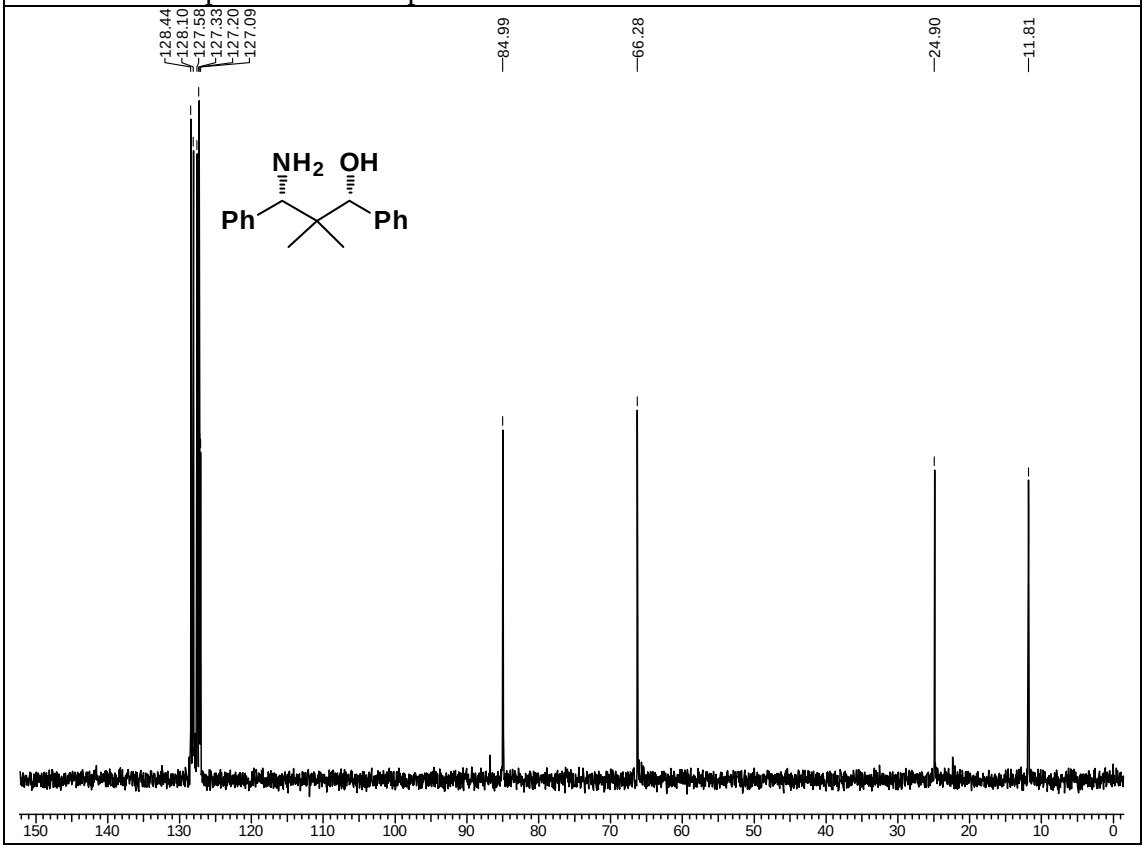
^{1}H-NMR of compound **1** ($CDCl_3$, 200MHz)



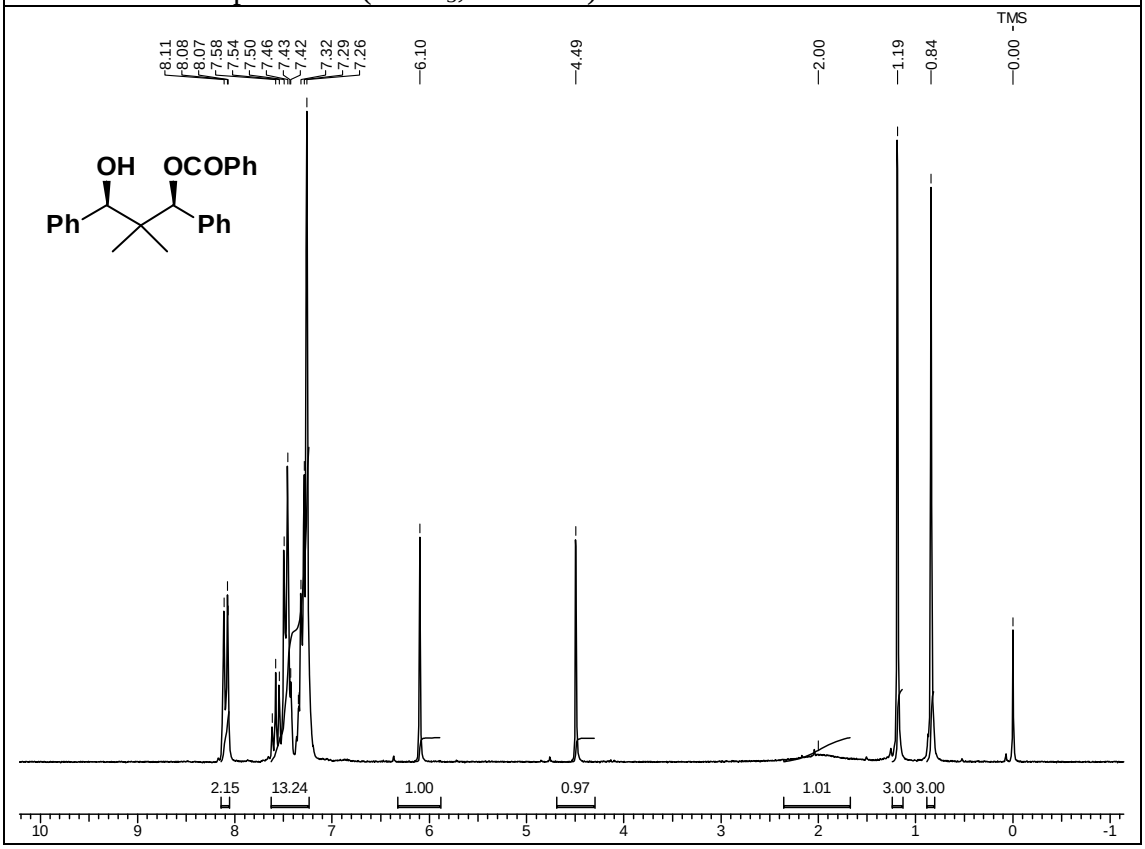
^{13}C-NMR of compound **1** ($CDCl_3$, 50.32MHz)



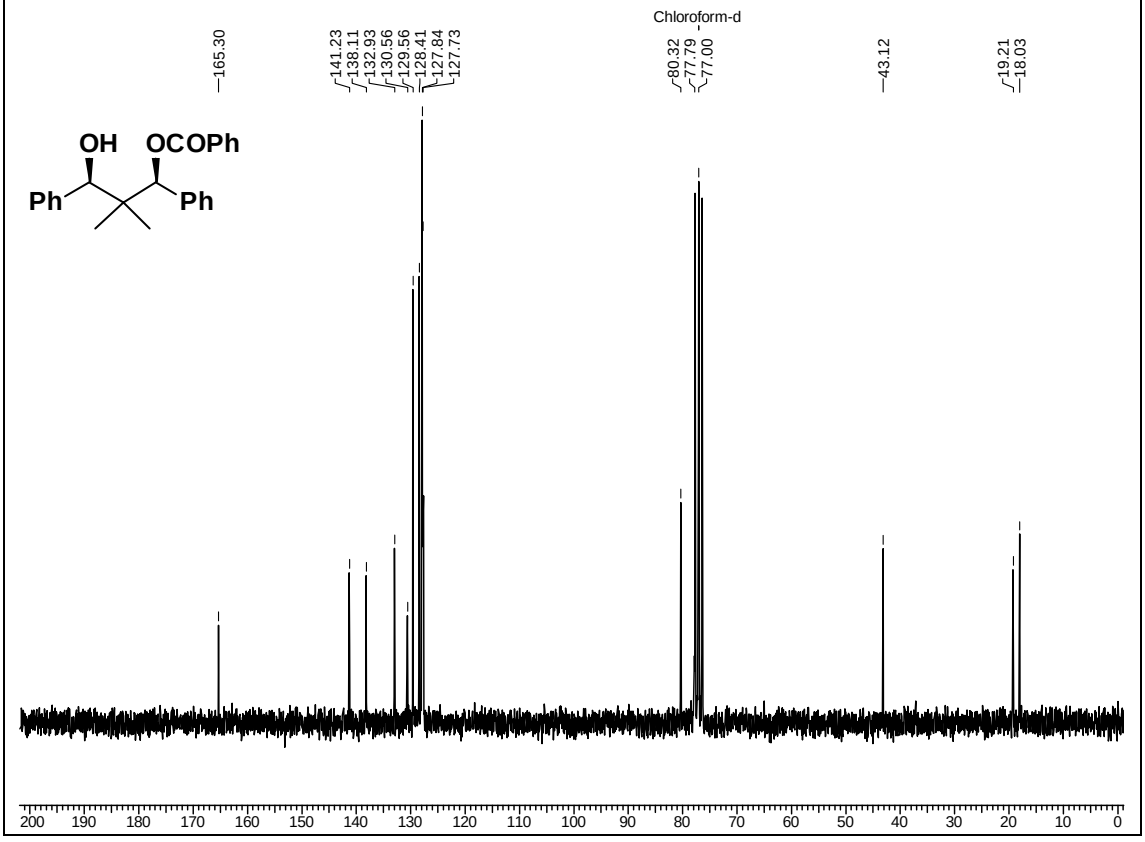
DEPT NMR Spectrum of compound **1**



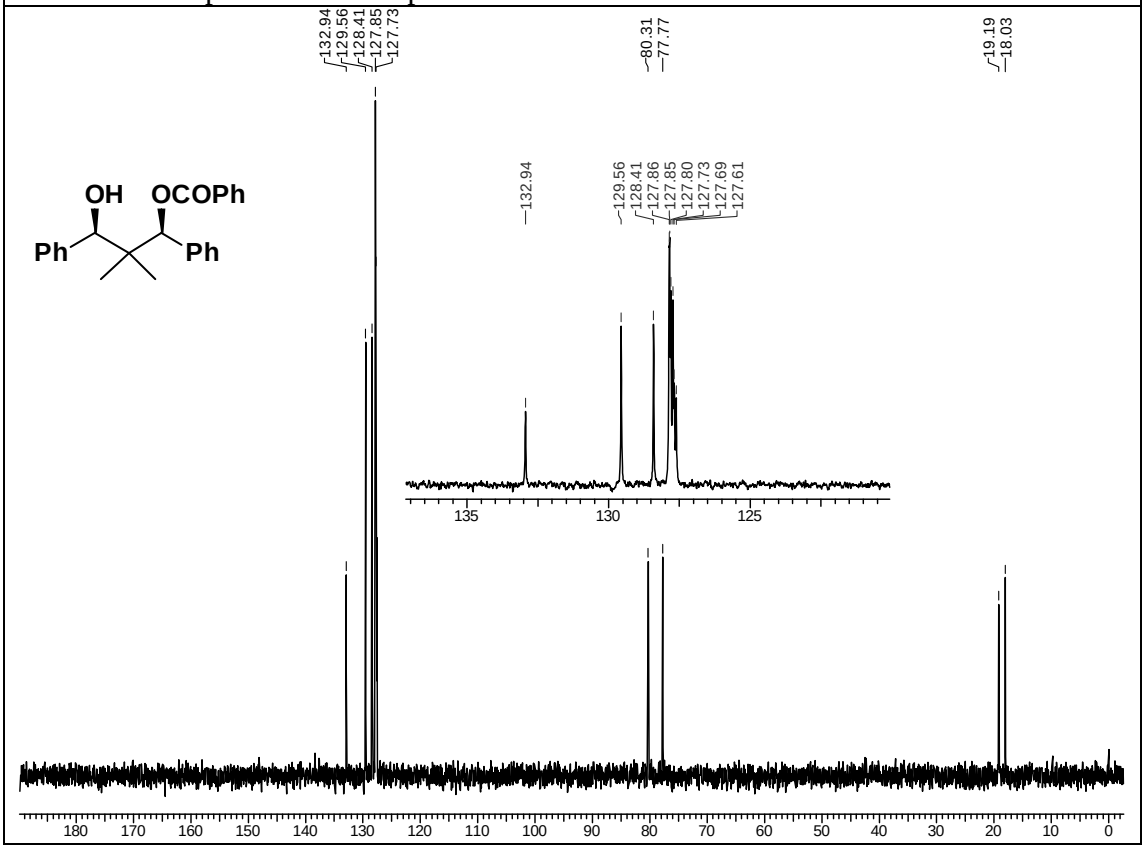
^{1}H-NMR of compound **10** ($CDCl_3$, 200MHz)



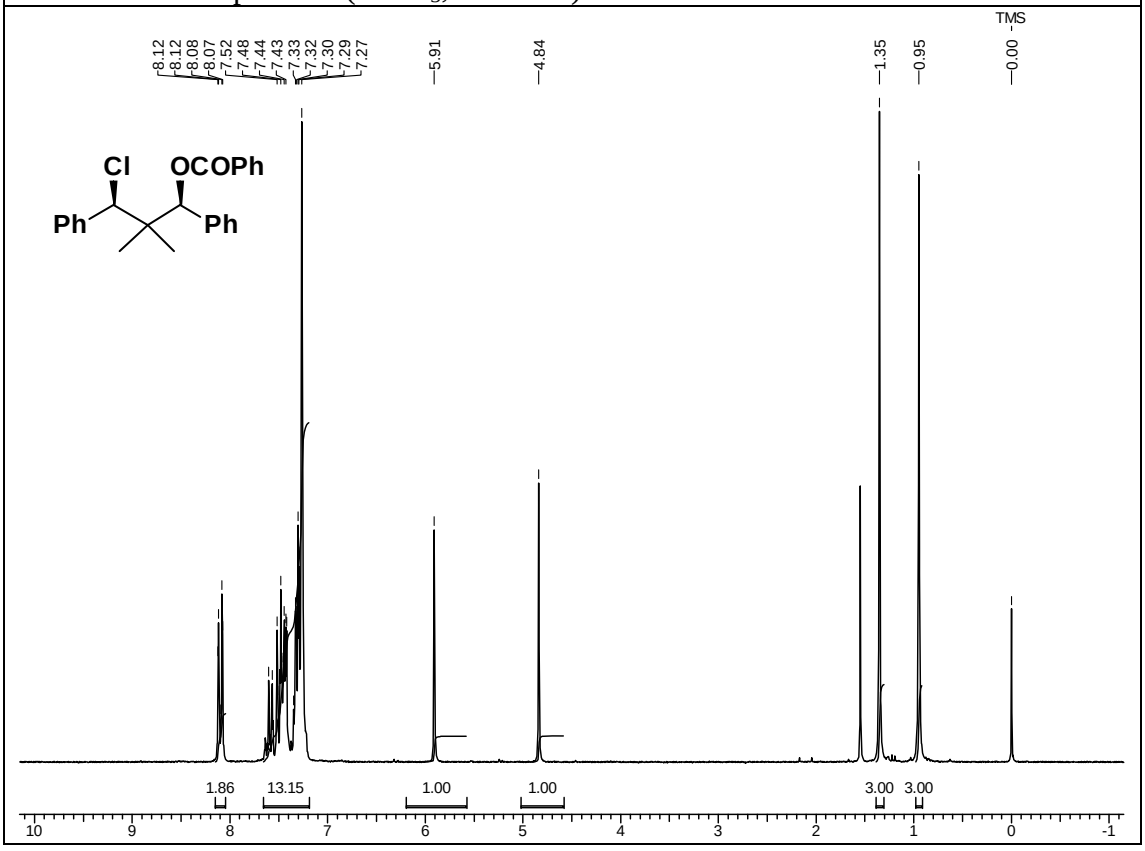
^{13}C-NMR of compound **10** ($CDCl_3$, 50.32MHz)



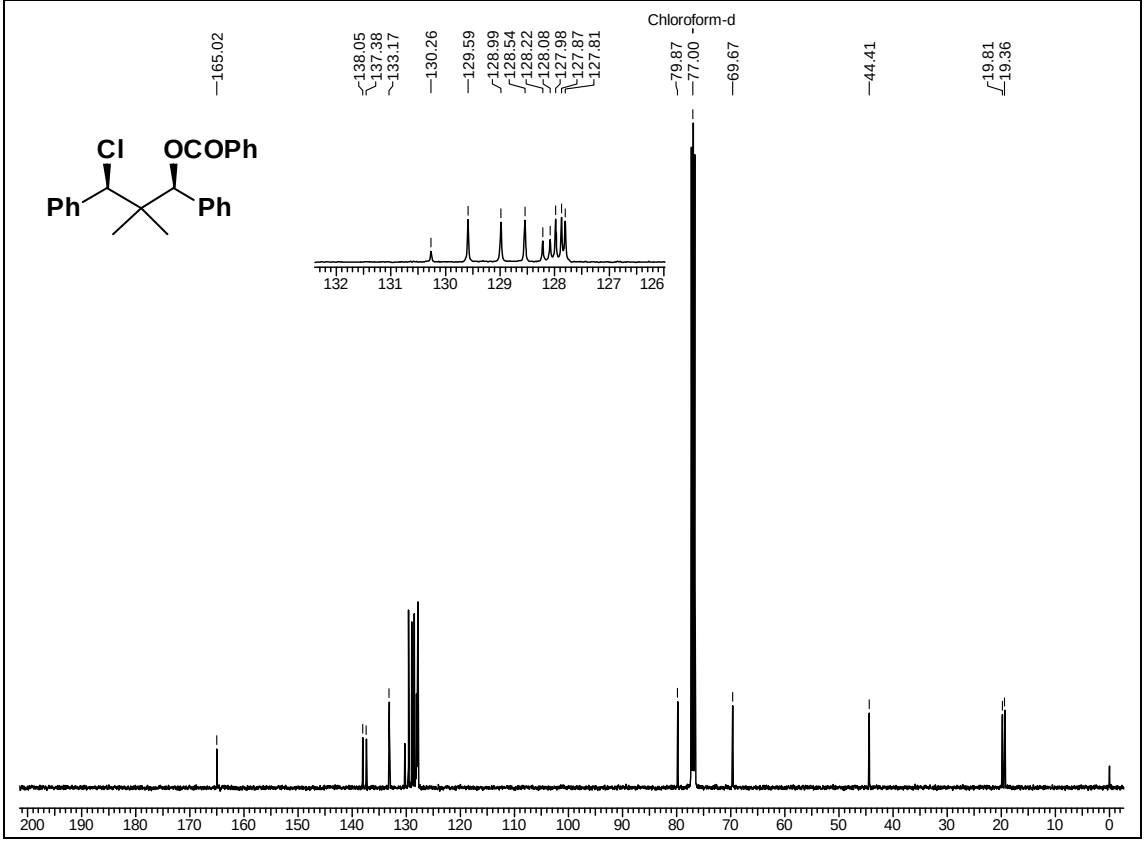
DEPT NMR Spectrum of compound **10**



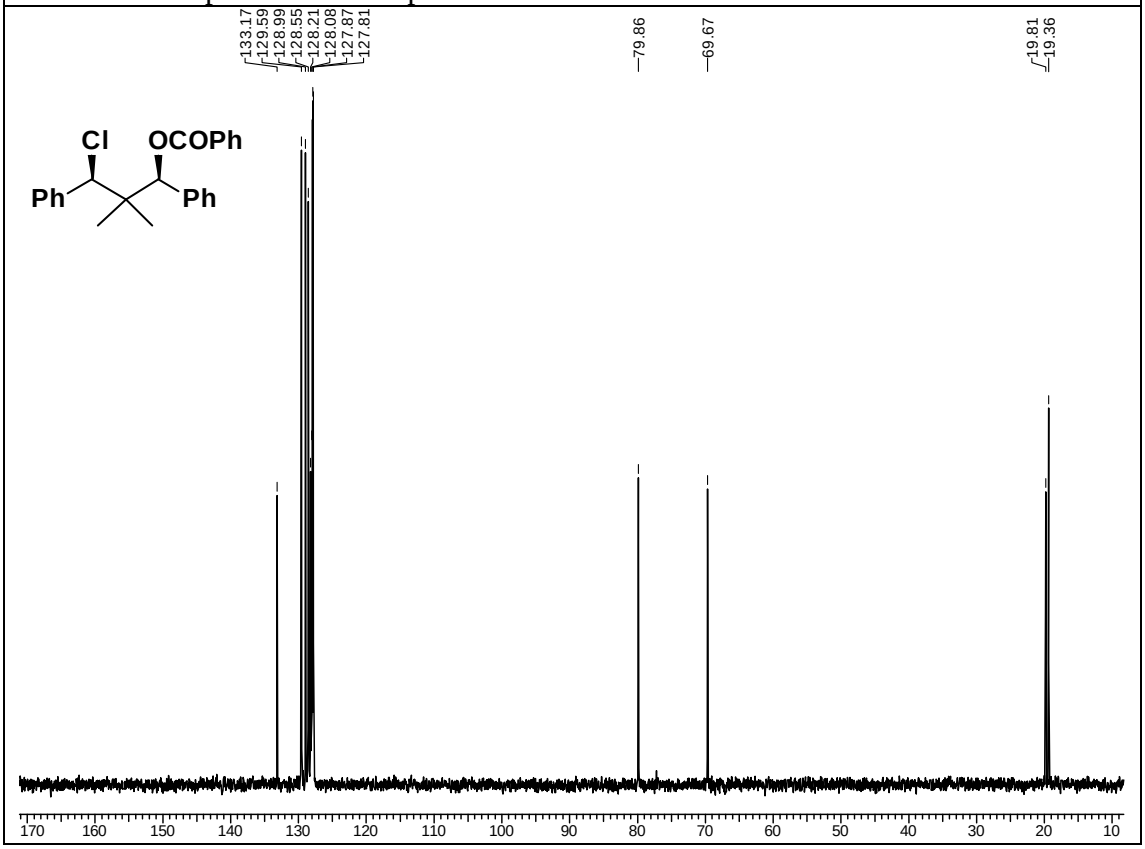
^{1}H-NMR of compound **9** ($CDCl_3$, 200MHz)



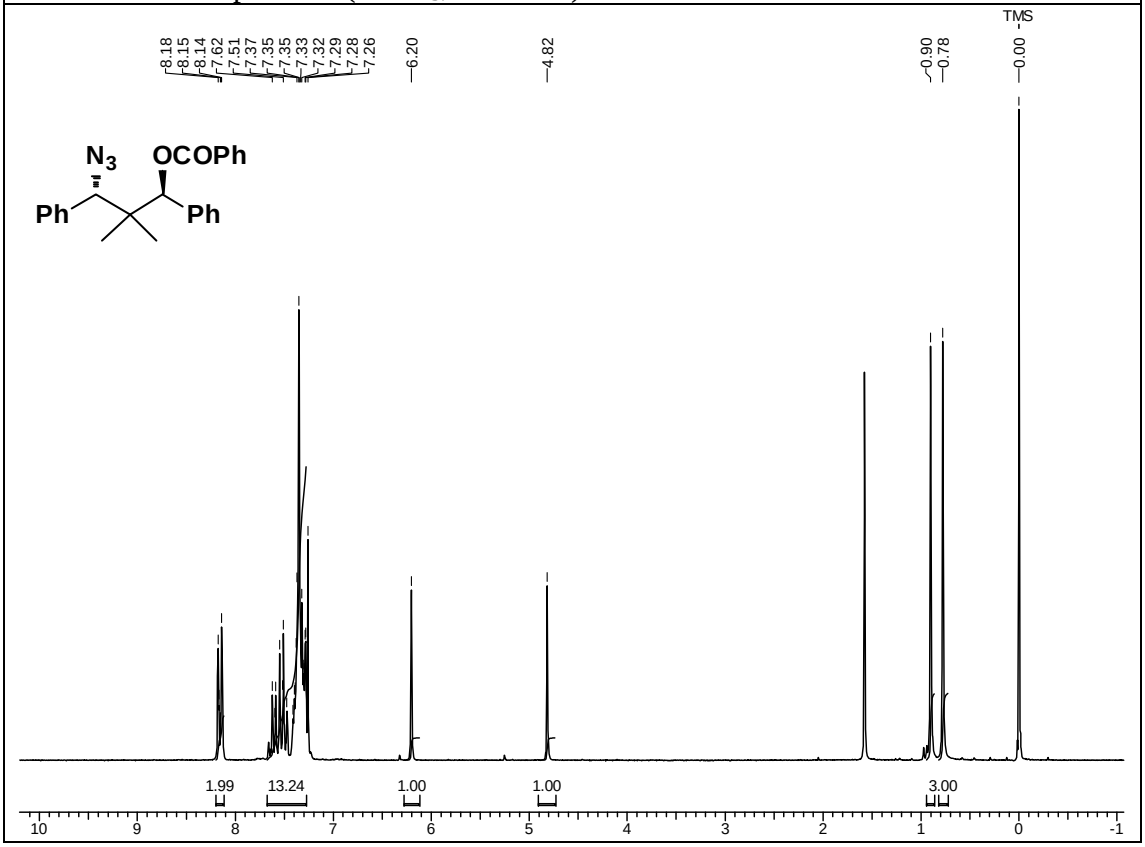
^{13}C-NMR of compound **9** ($CDCl_3$, 50.32MHz)



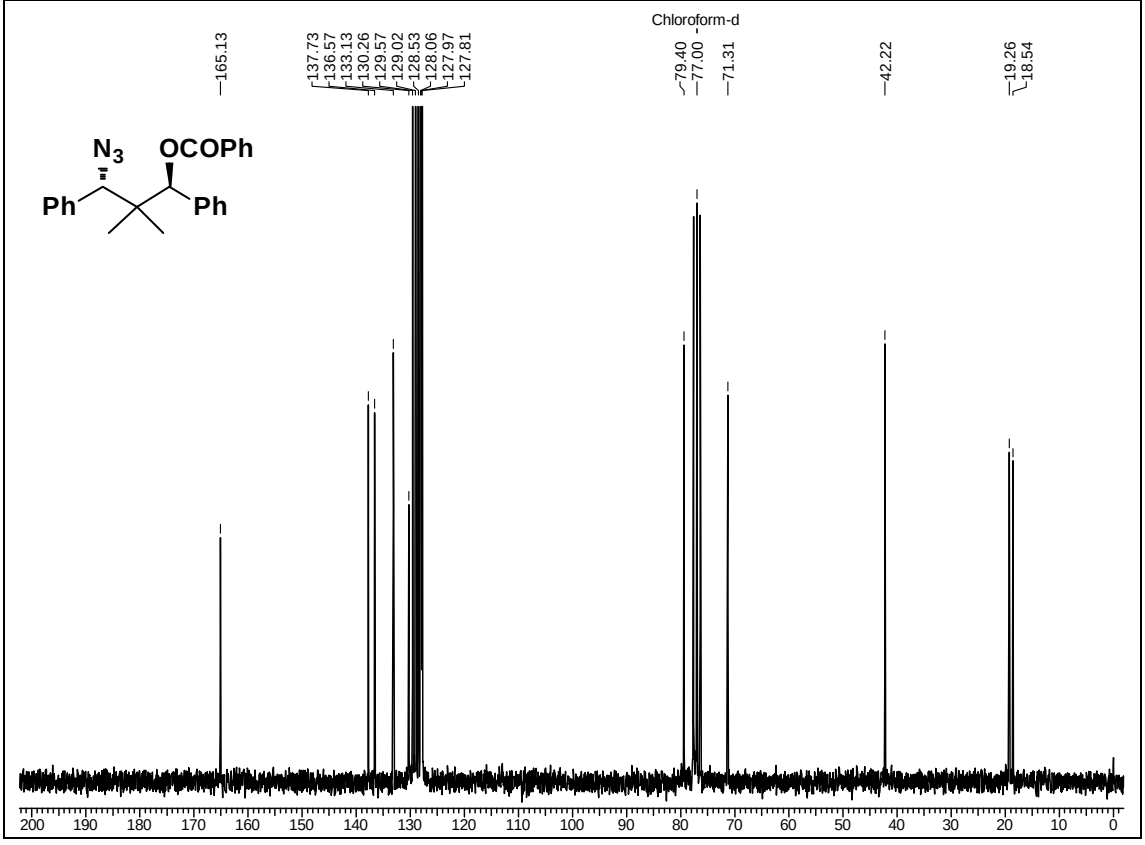
DEPT NMR Spectrum of compound **9**



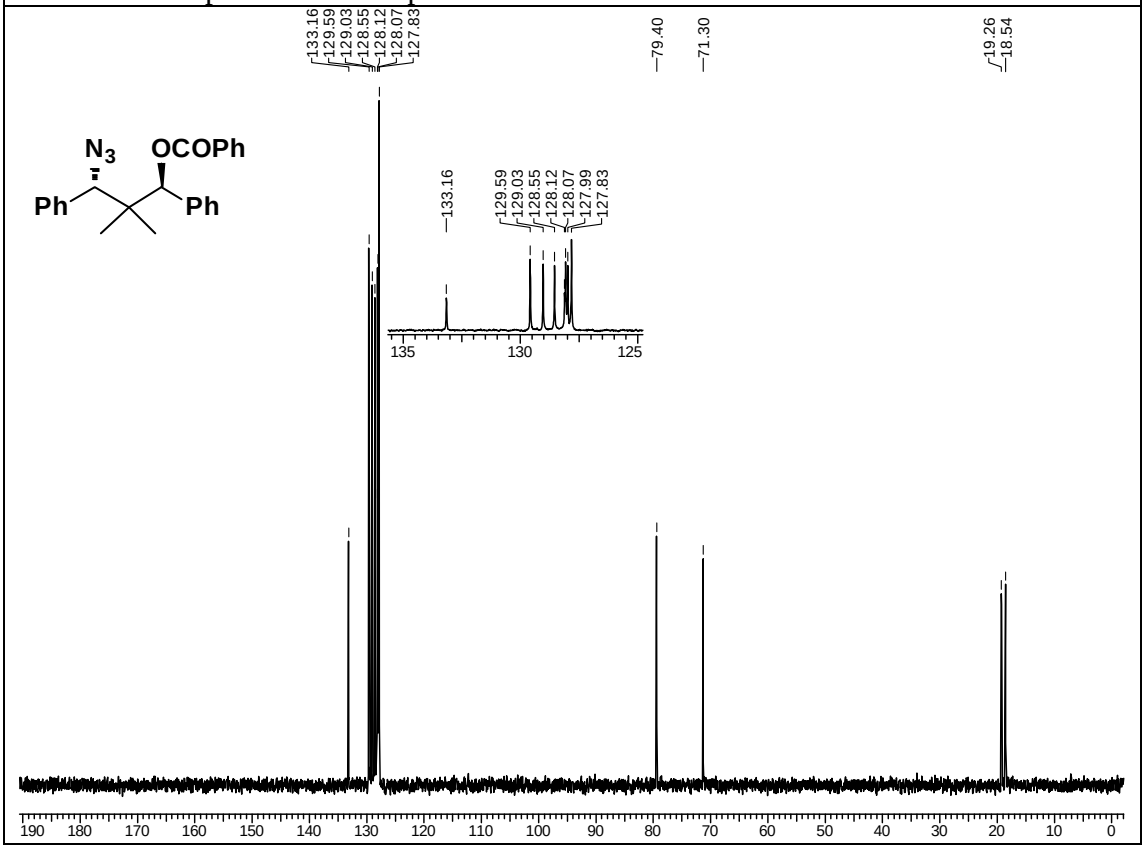
^{1}H-NMR of compound **8** ($CDCl_3$, 200MHz)



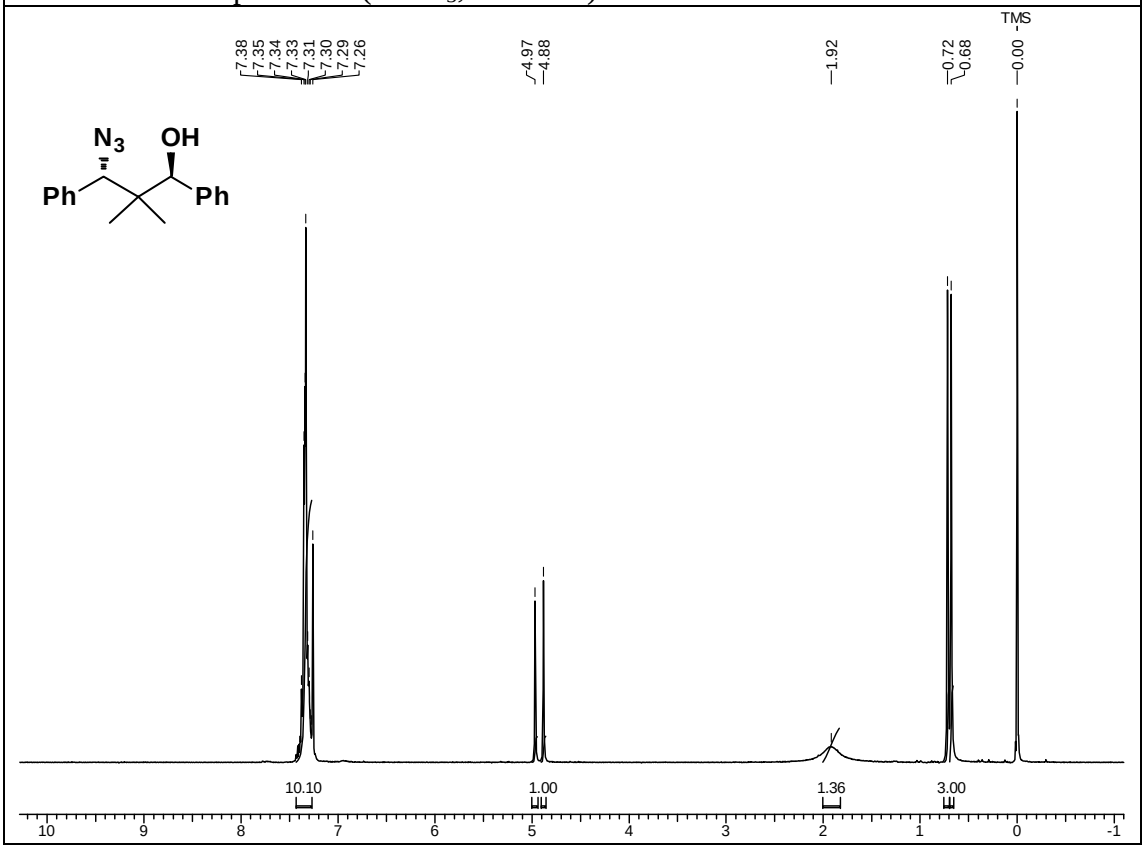
^{13}C-NMR of compound **8** ($CDCl_3$, 50.32MHz)



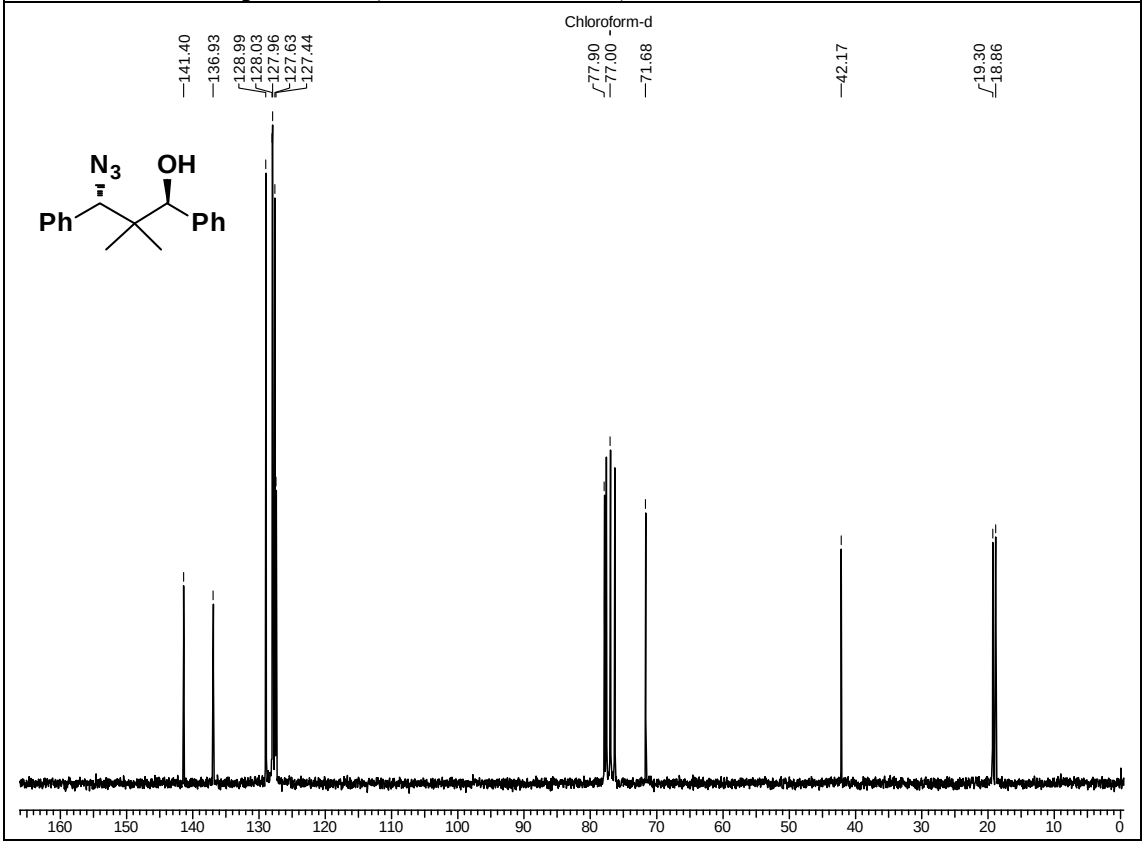
DEPT NMR Spectrum of compound **8**



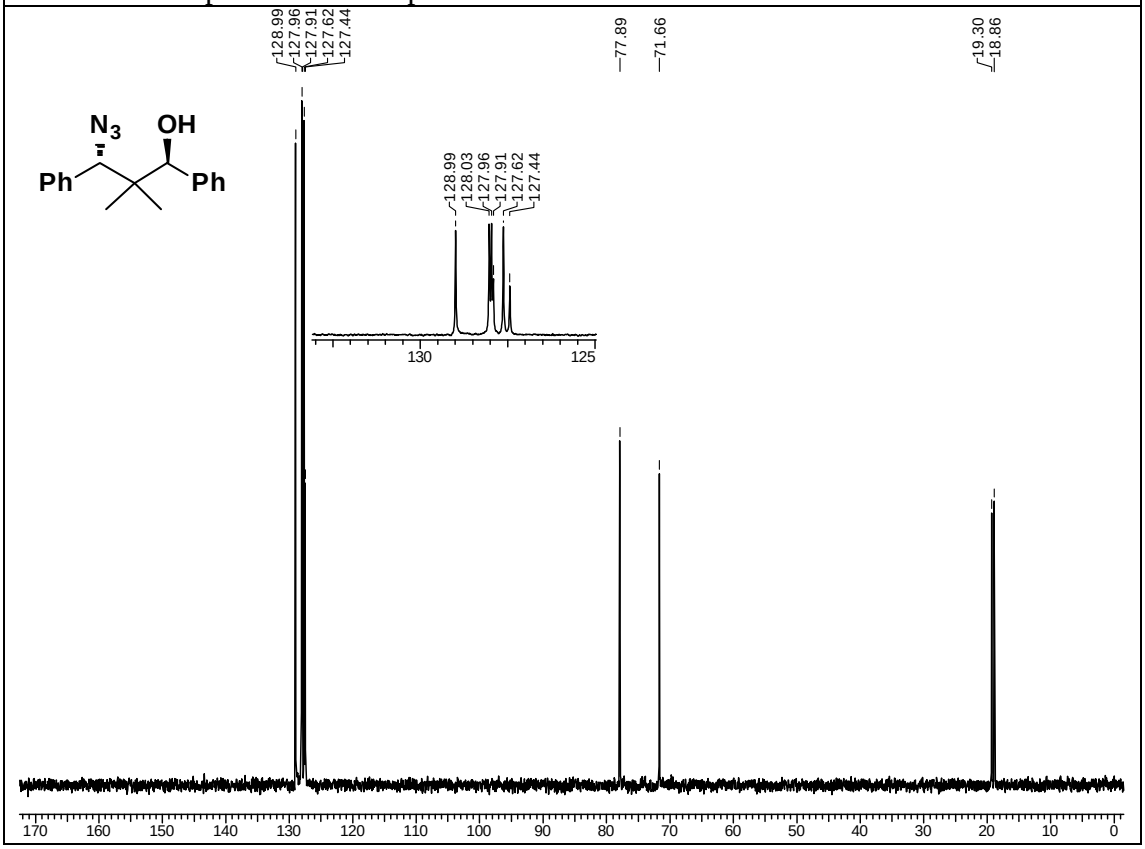
^{1}H-NMR of compound **17** ($CDCl_3$, 200MHz)



^{13}C-NMR of compound **17** ($CDCl_3$, 50.32MHz)



DEPT NMR Spectrum of compound **17**



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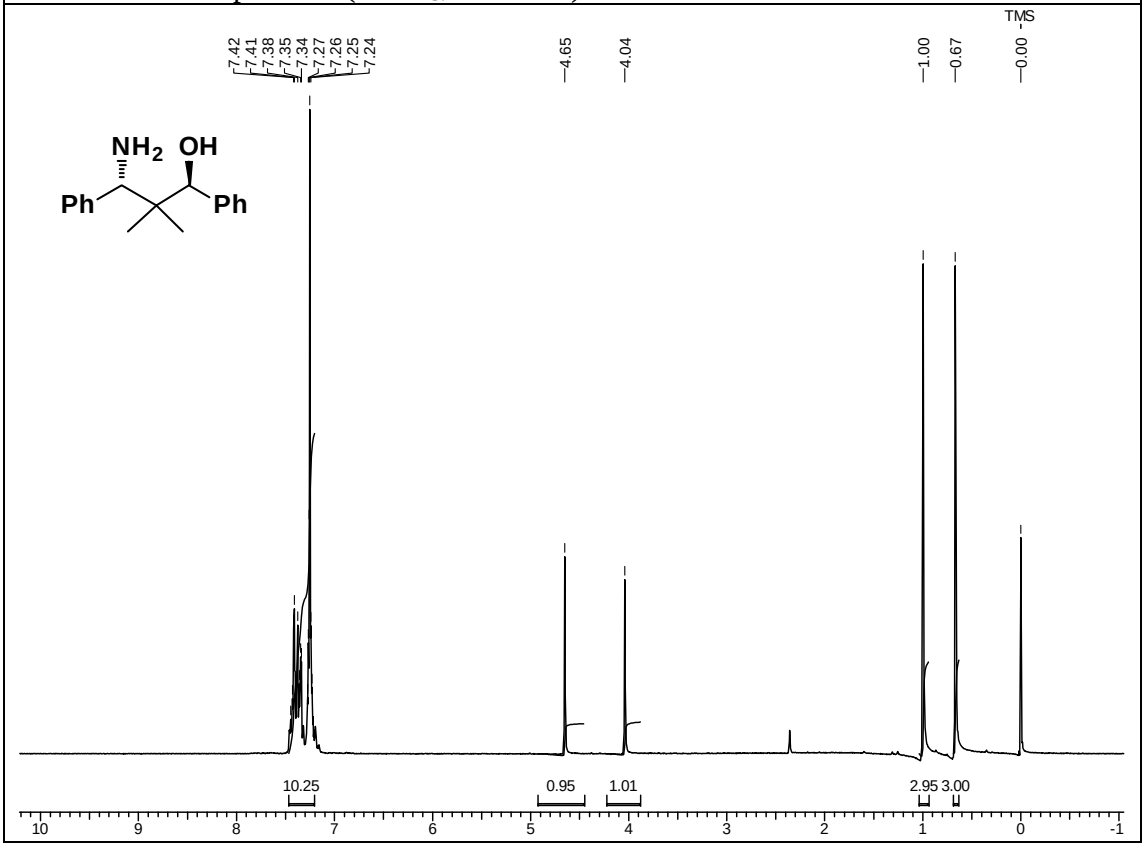
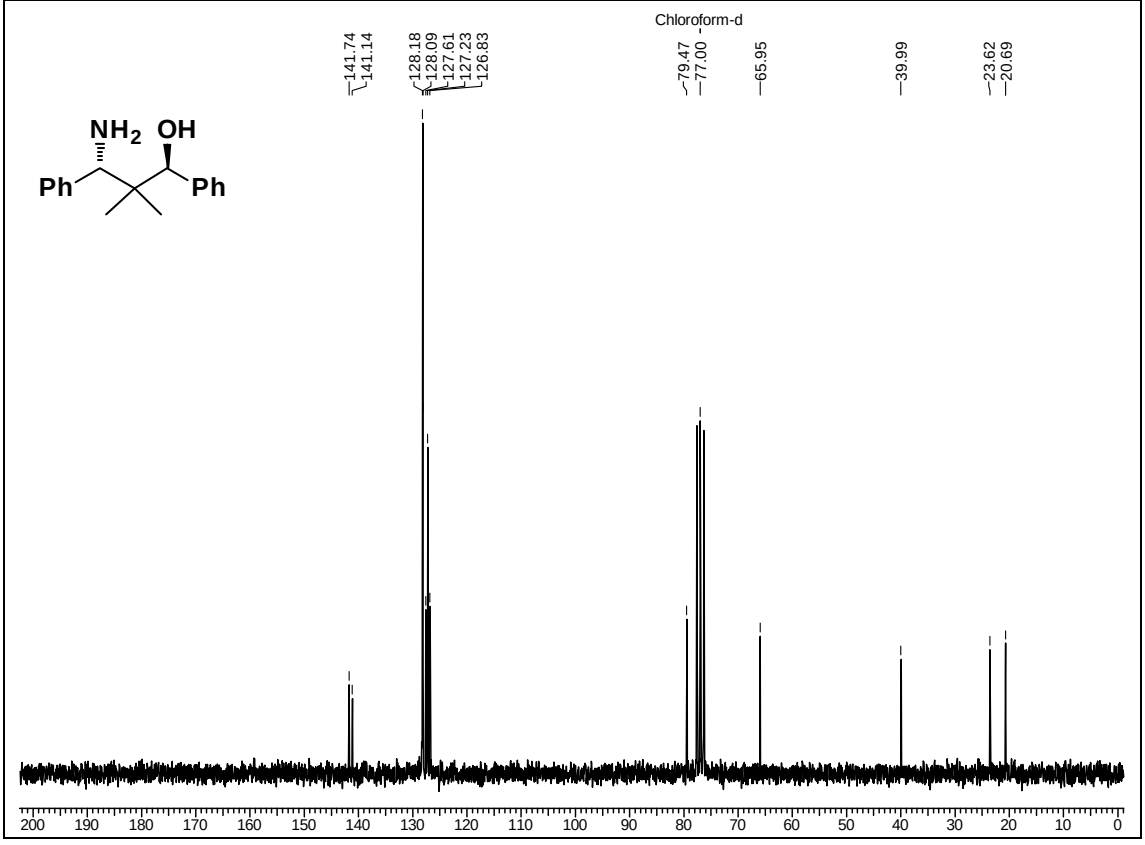
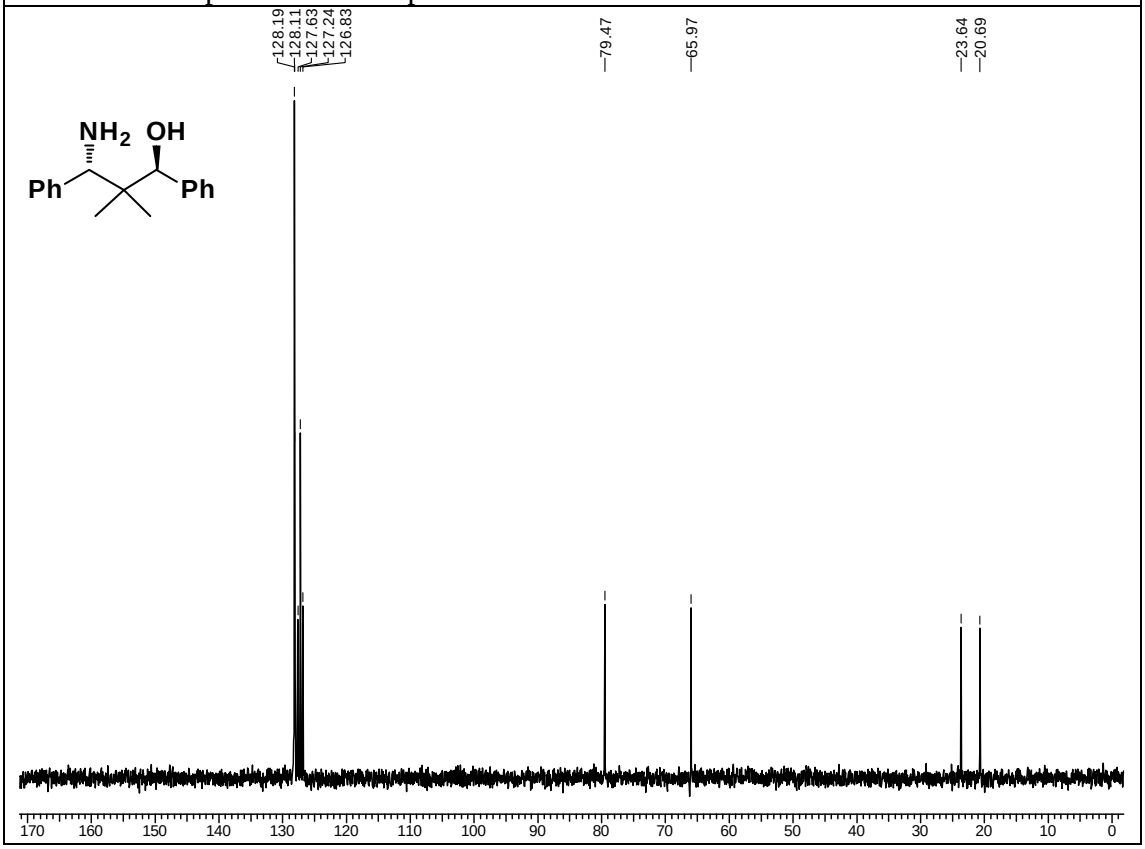


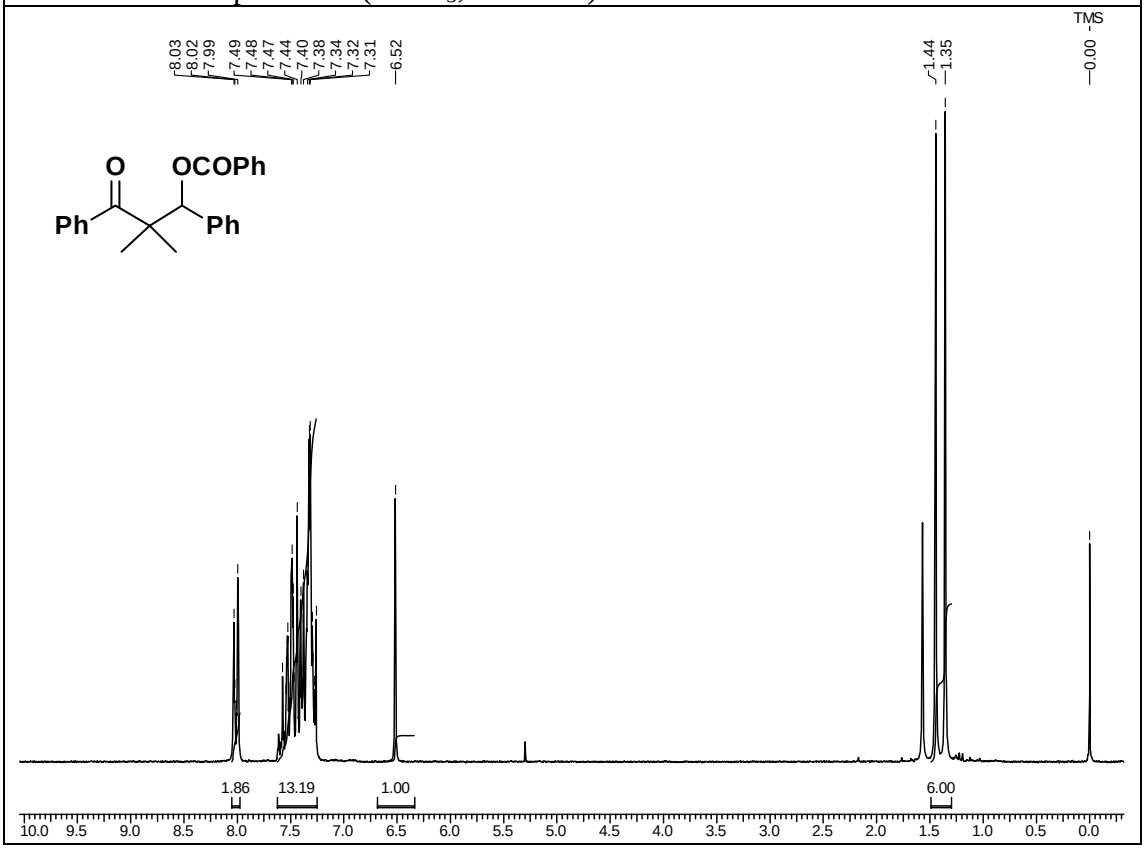
^{13}C-NMR of compound **2** ($CDCl_3$, 50.32MHz)



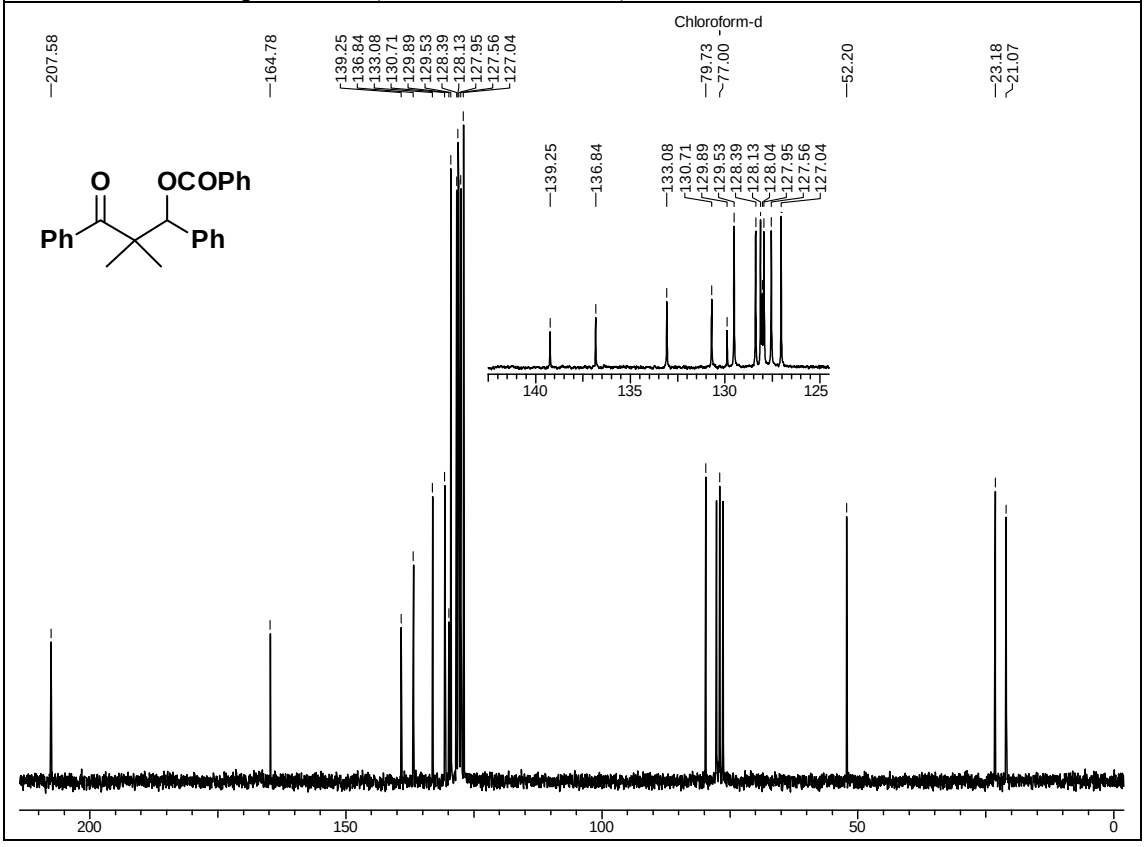
DEPT NMR Spectrum of compound **2**



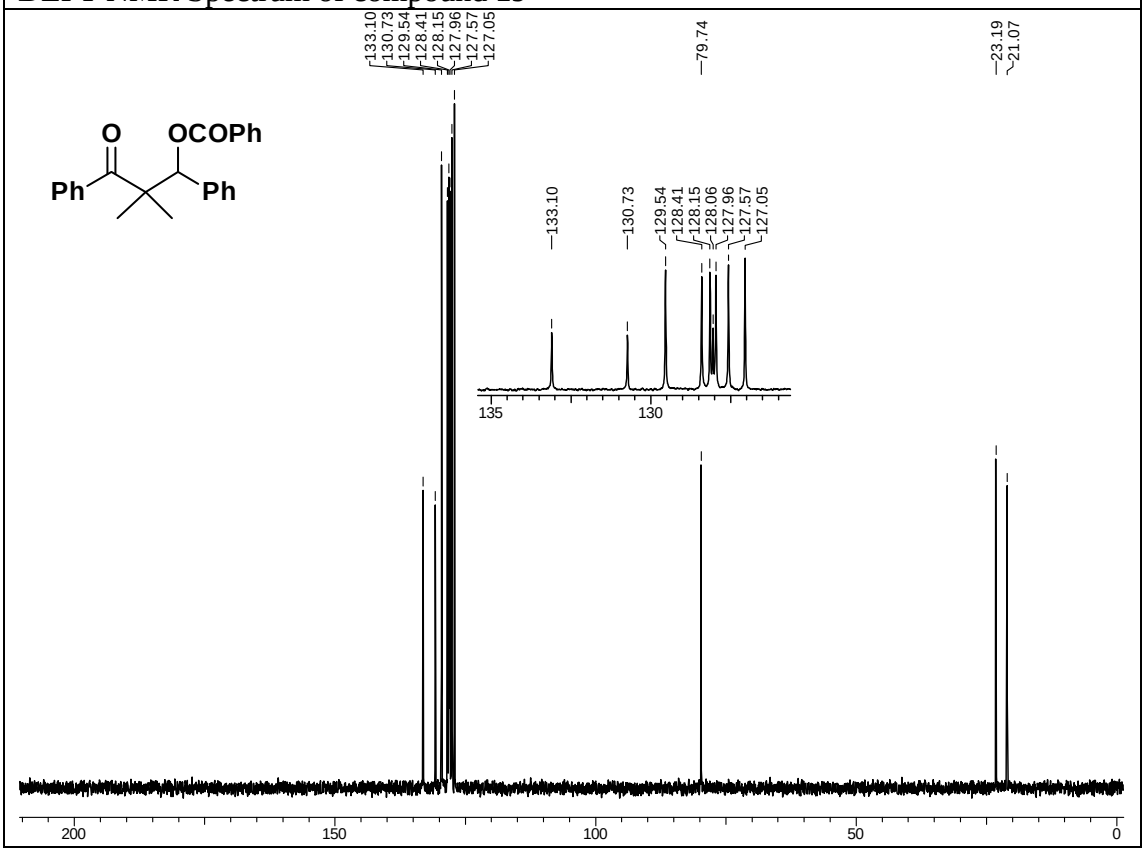
^{1}H-NMR of compound **19** ($CDCl_3$, 200MHz)



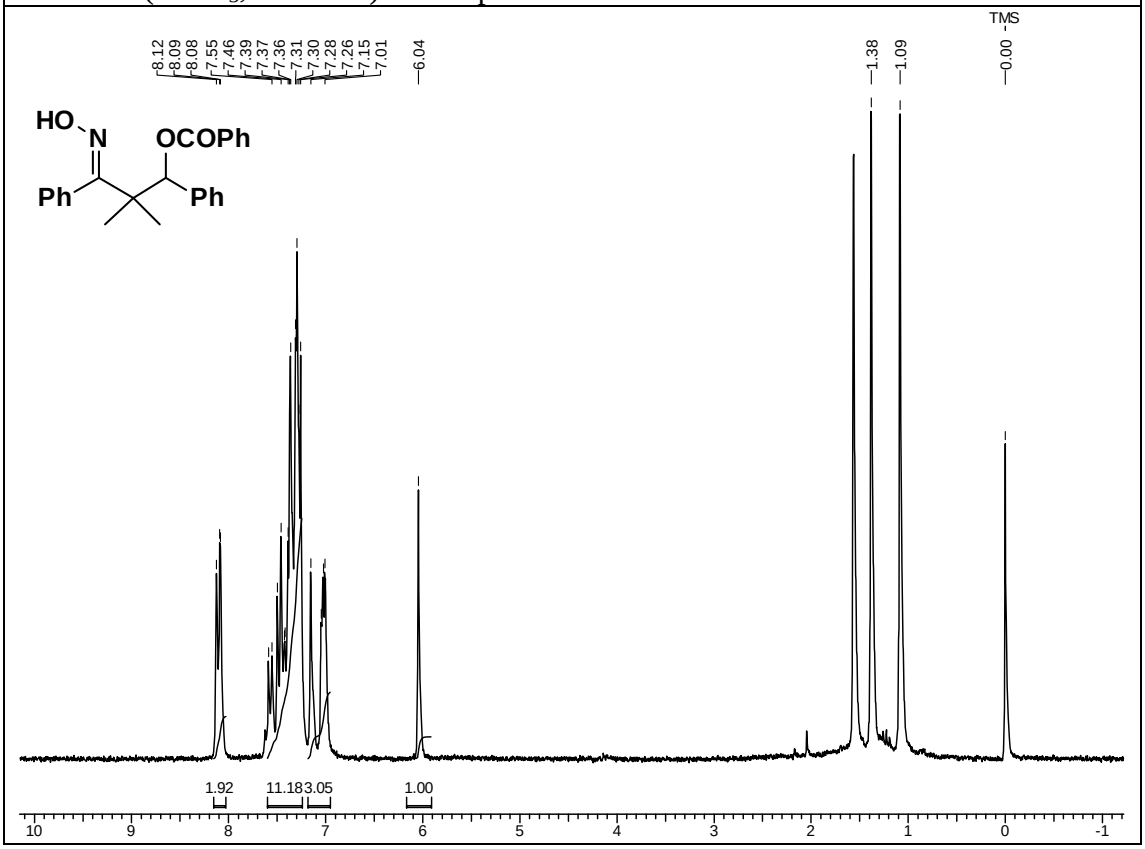
^{13}C-NMR of compound **19** ($CDCl_3$, 50.32MHz)



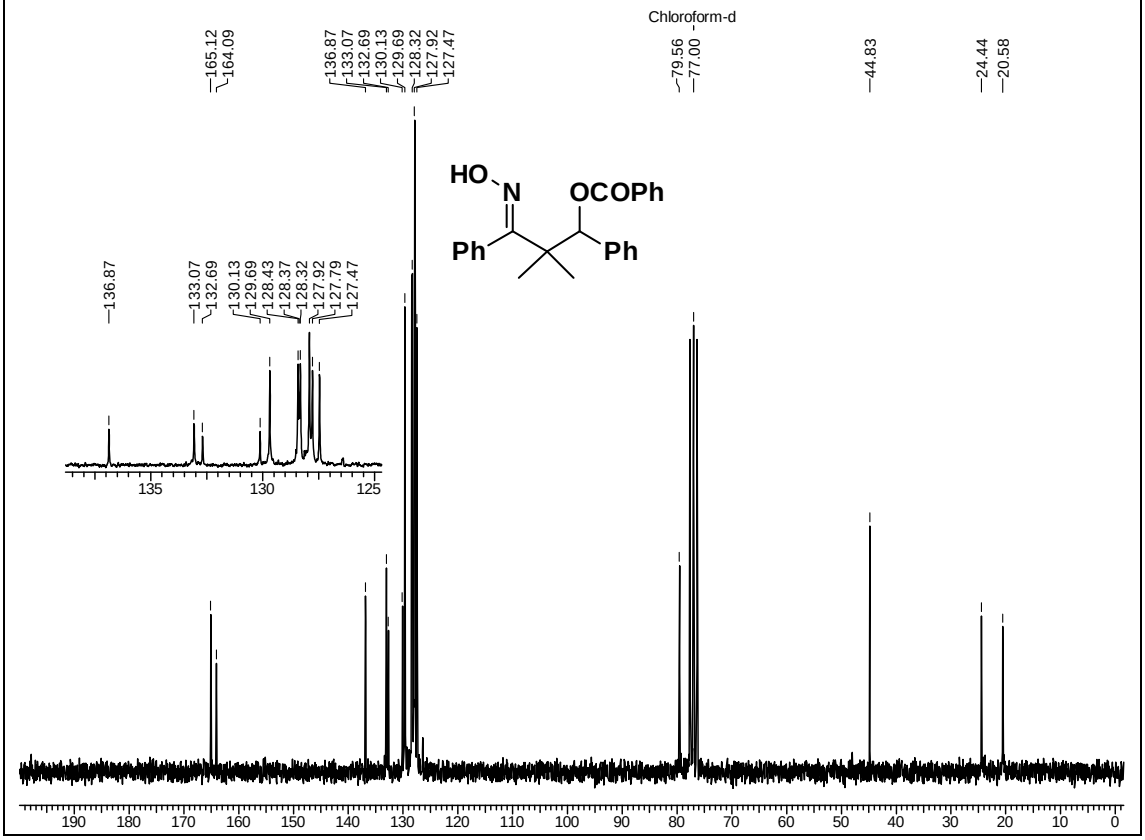
DEPT NMR Spectrum of compound **19**



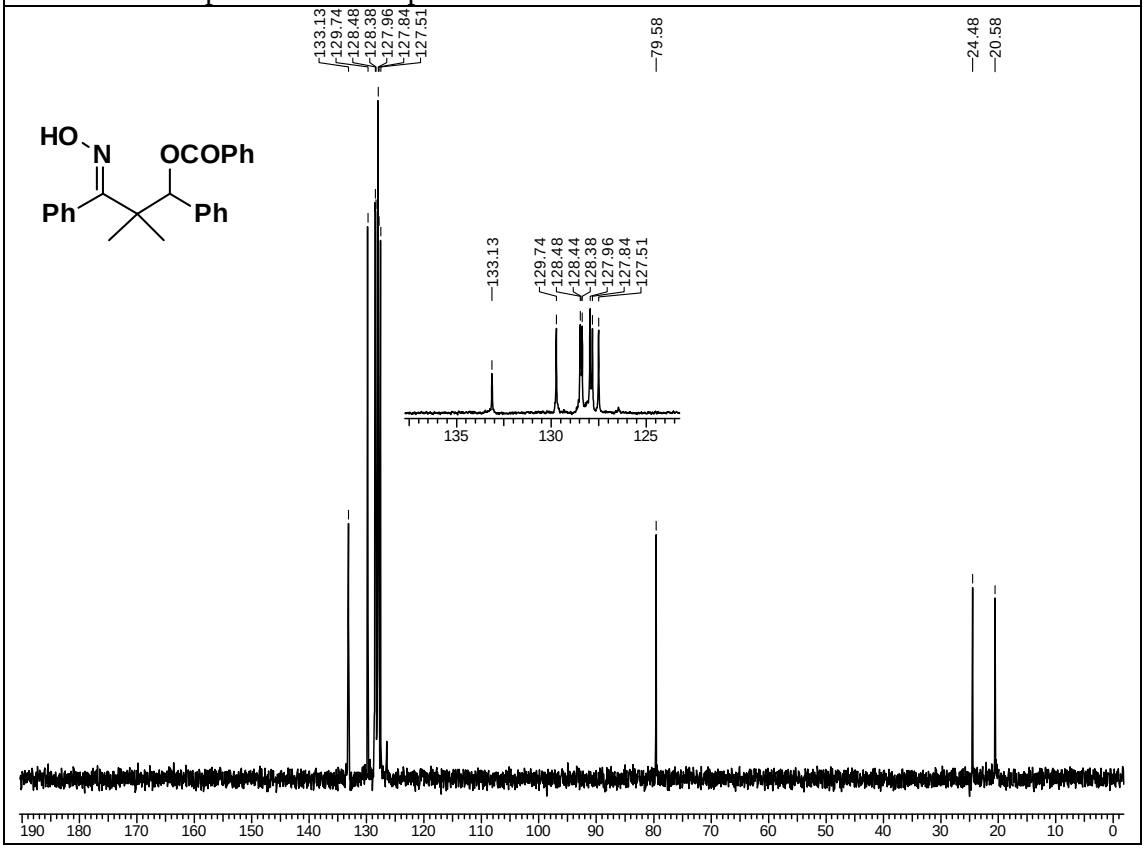
^{1}H-NMR ($CDCl_3$, 200MHz) of compound **20**



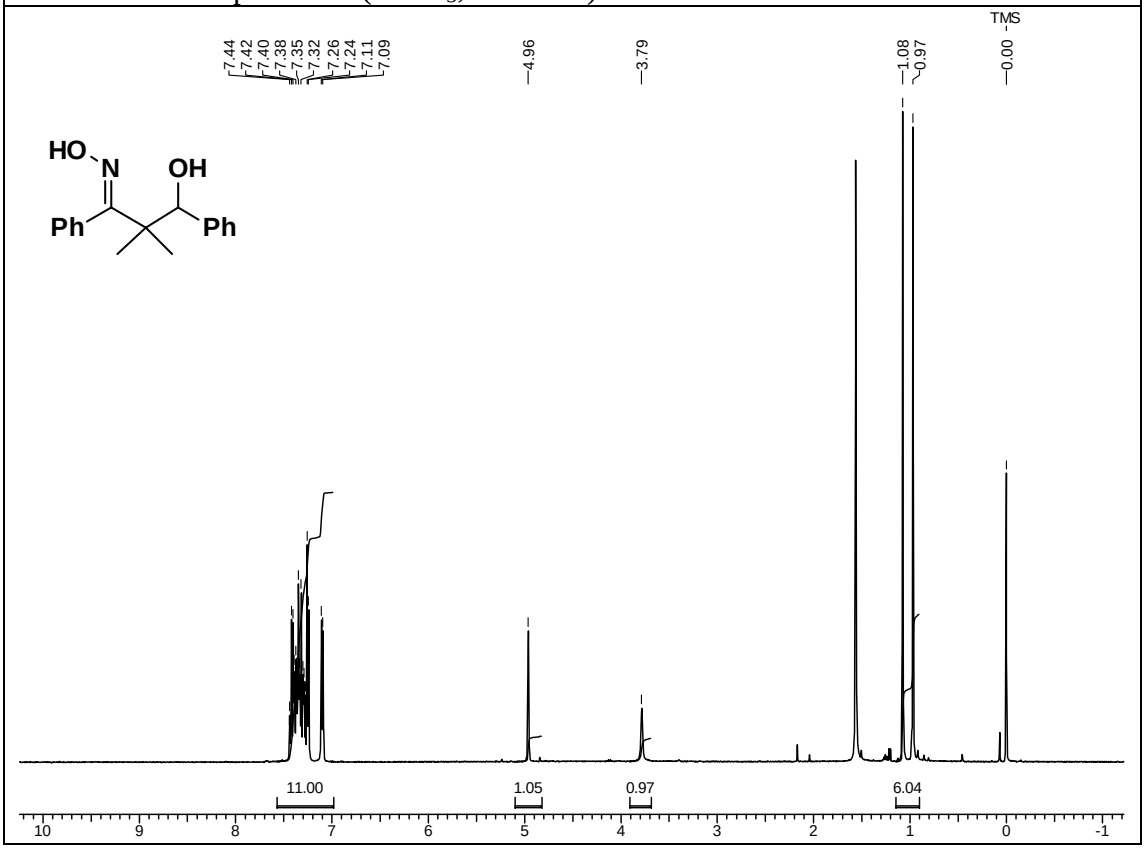
^{13}C-NMR of compound **20** ($CDCl_3$, 50.32MHz)



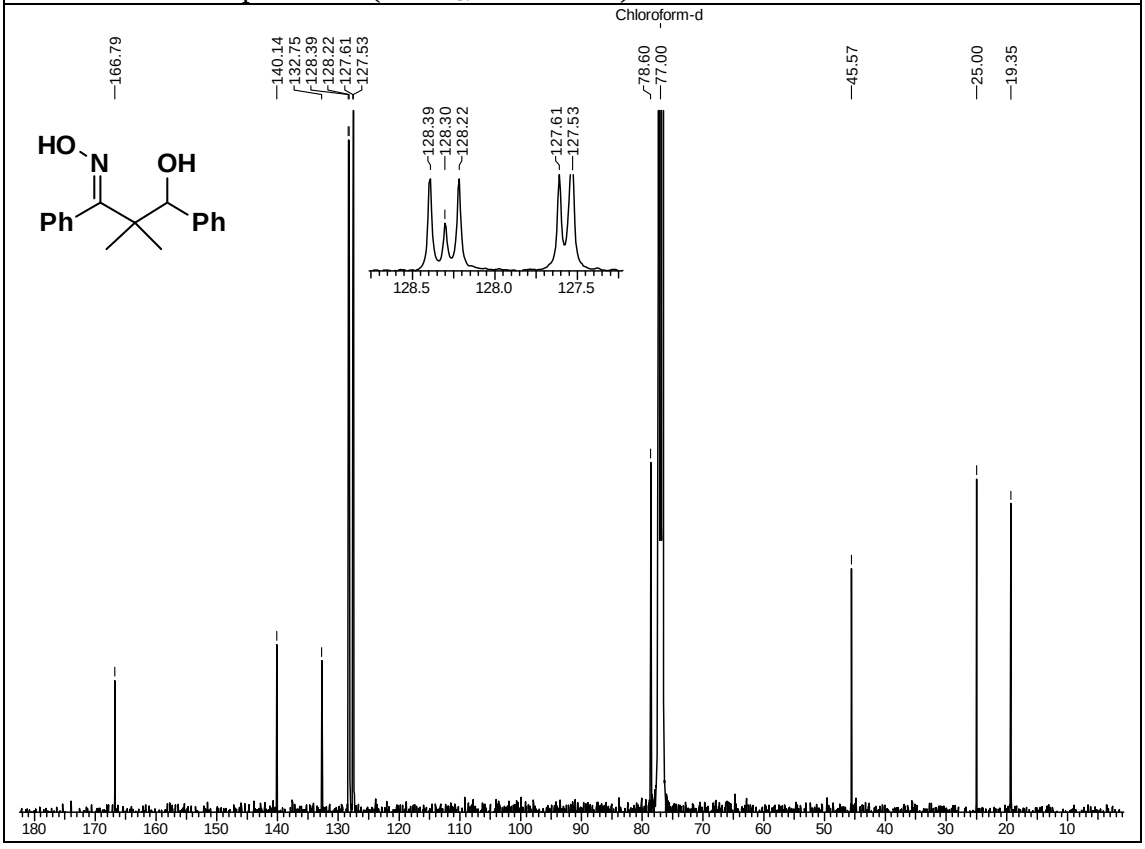
DEPT NMR Spectrum of compound **20**



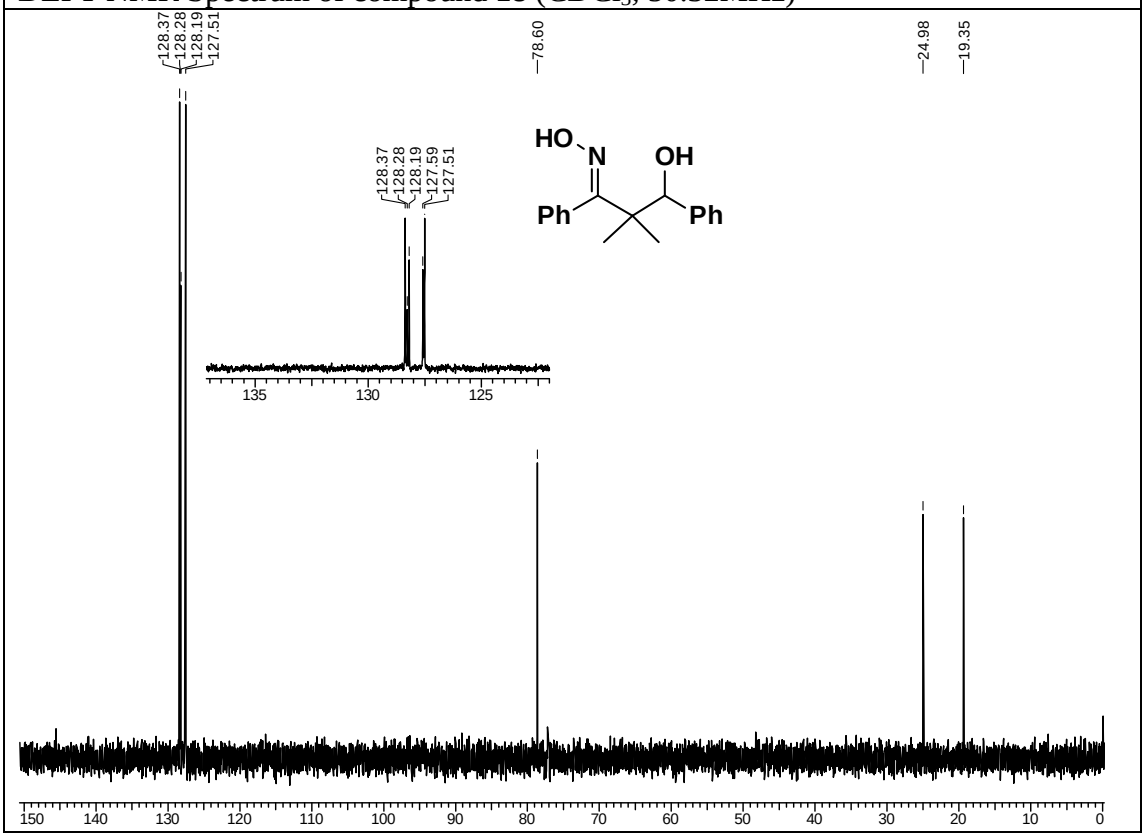
^{1}H-NMR of compound **18** ($CDCl_3$, 200MHz)



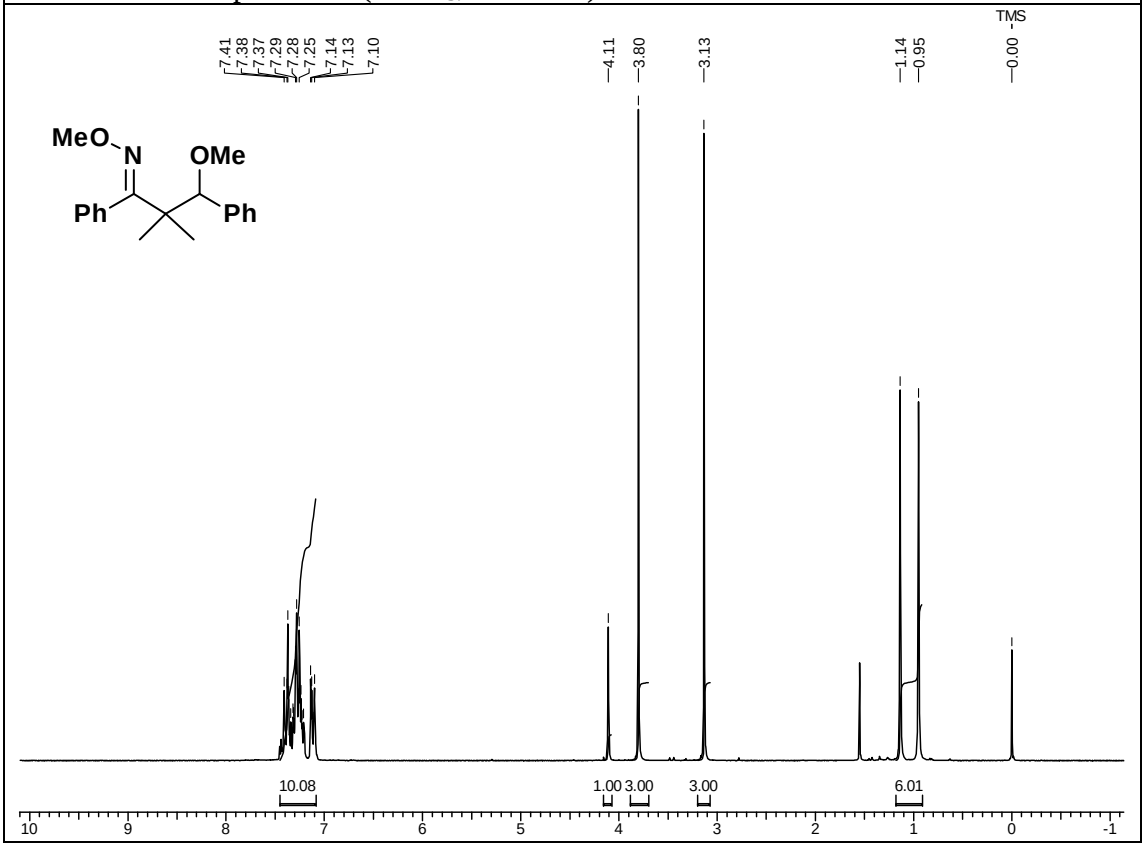
^{13}C-NMR of compound **18** ($CDCl_3$, 50.32MHz)



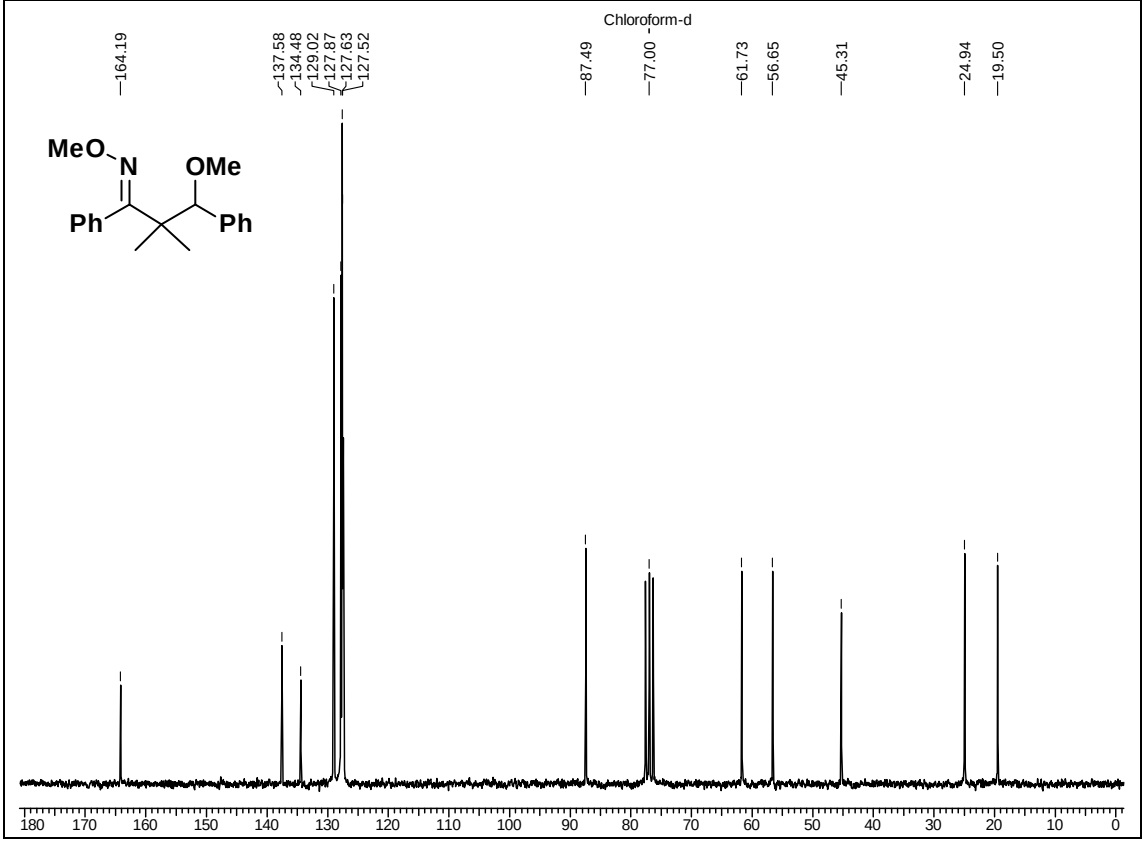
DEPT NMR Spectrum of compound **18** ($CDCl_3$, 50.32MHz)



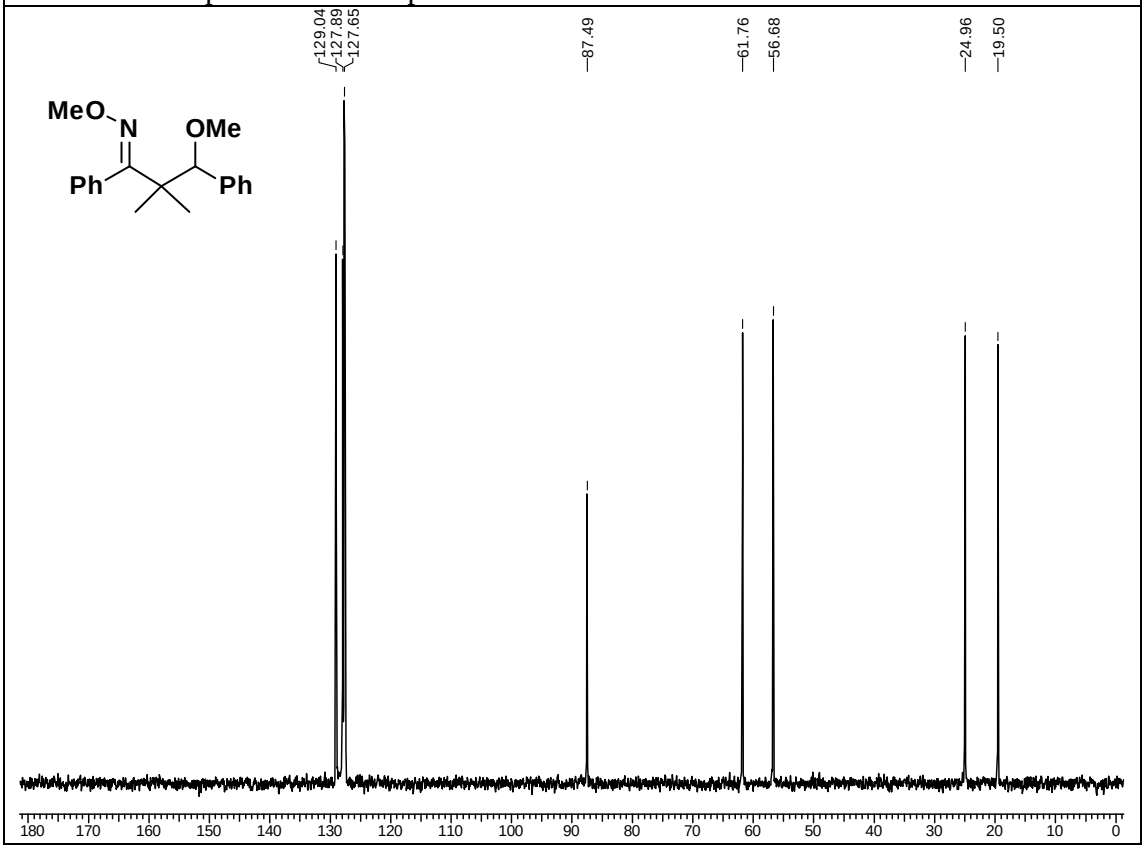
^{1}H-NMR of compound **21** ($CDCl_3$, 200MHz)



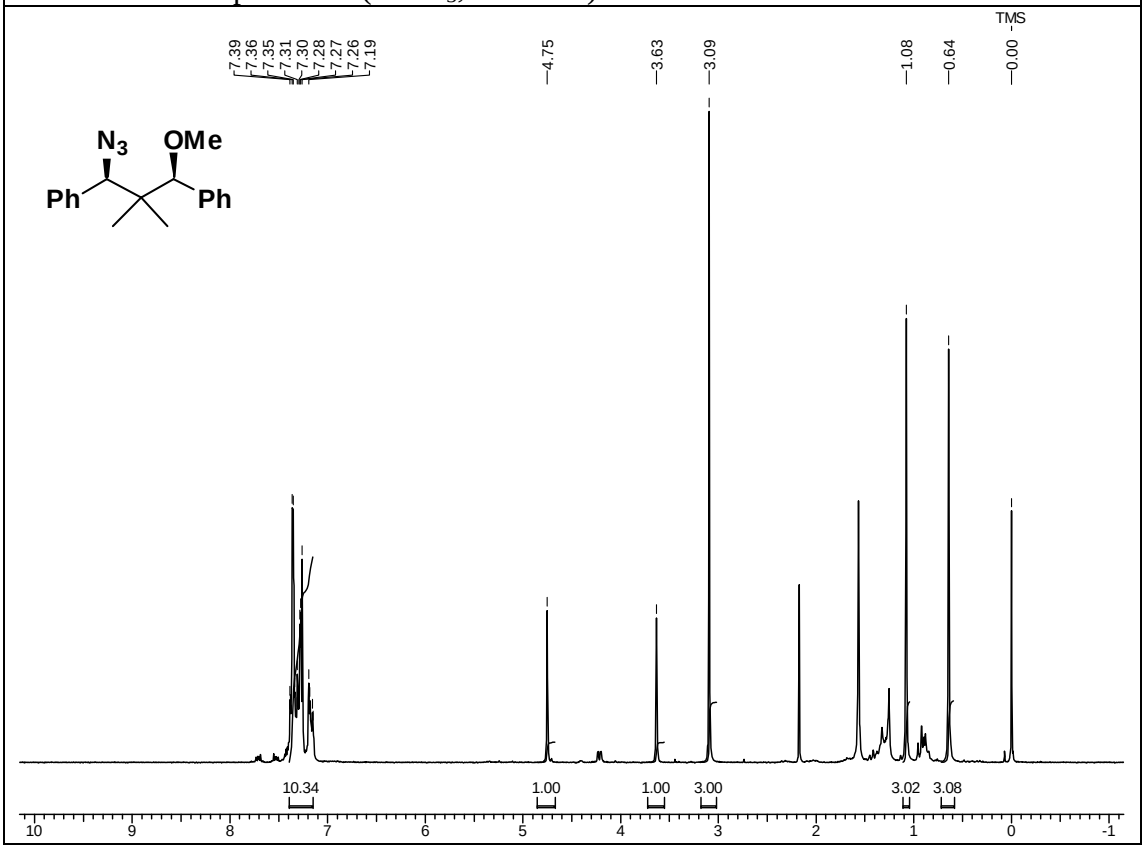
^{13}C-NMR of compound **21** ($CDCl_3$, 50.32MHz)



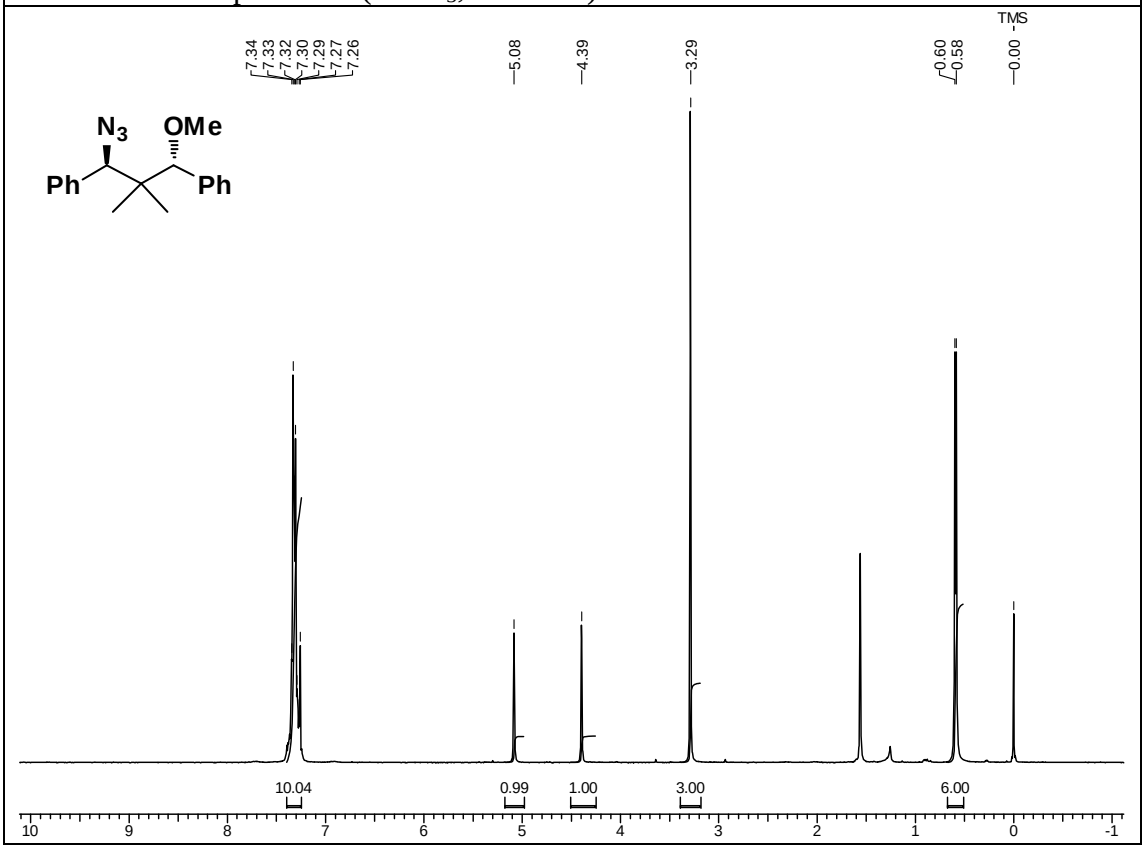
DEPT NMR Spectrum of compound **21**



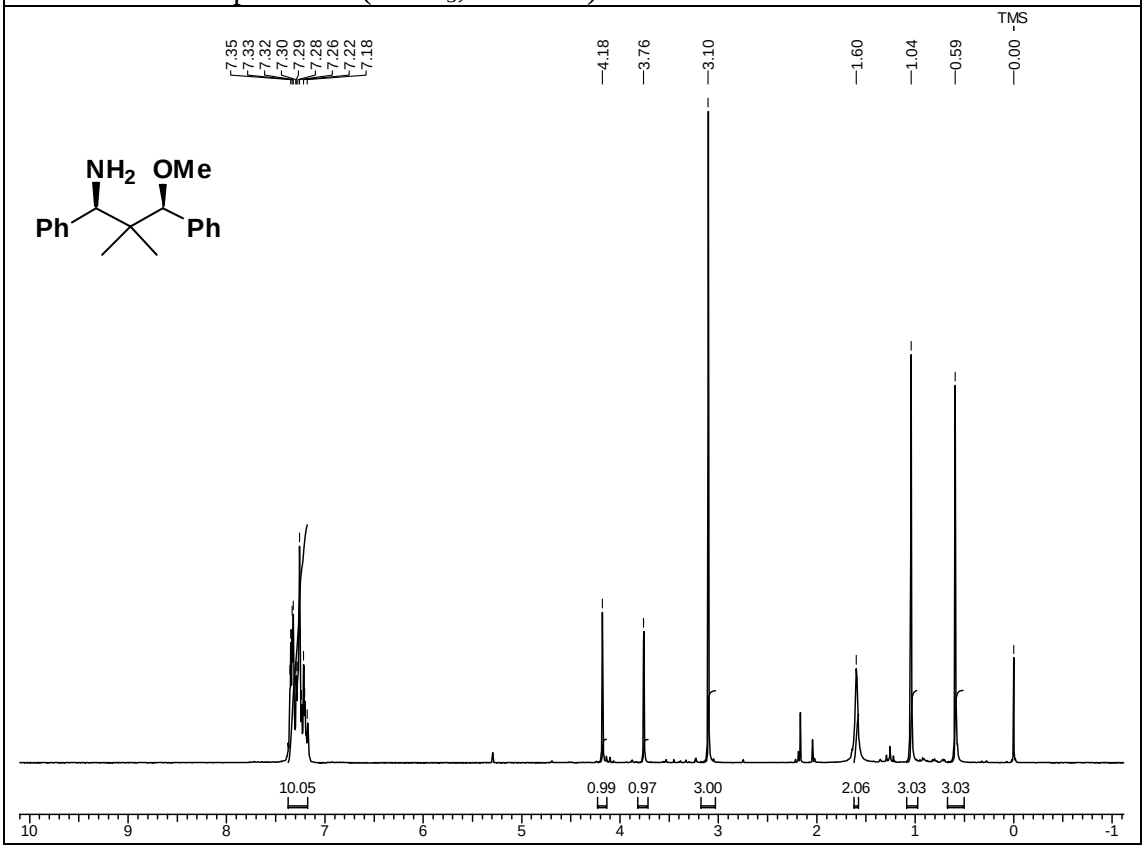
^{1}H-NMR of compound **23** ($CDCl_3$, 200MHz)



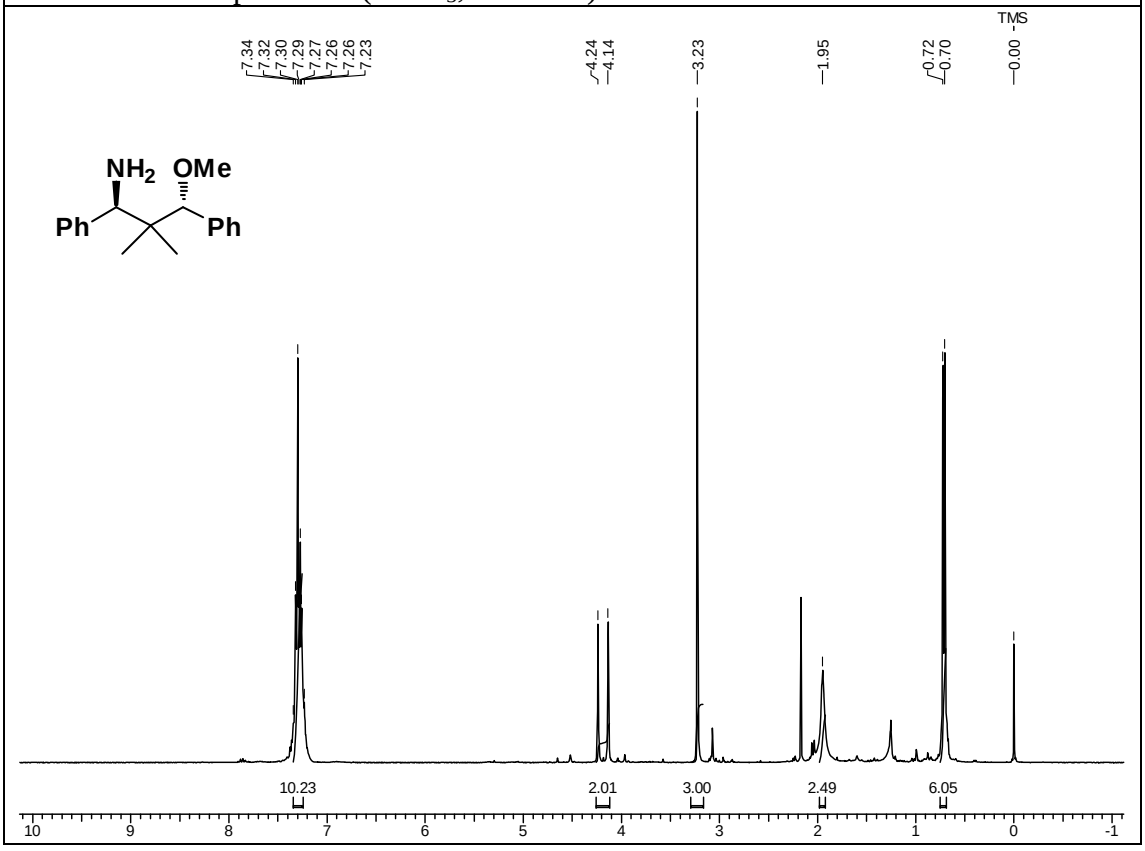
^{1}H-NMR of compound **24** ($CDCl_3$, 200MHz)



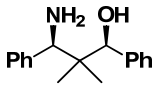
^{1}H-NMR of compound **22** ($CDCl_3$, 200MHz)



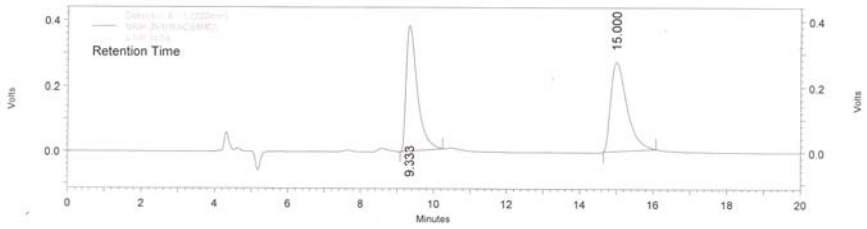
^{1}H-NMR of compound **25** ($CDCl_3$, 200MHz)



Determination of enantiomeric excess for chiral aminoalcohols

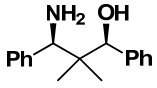


(±)-1

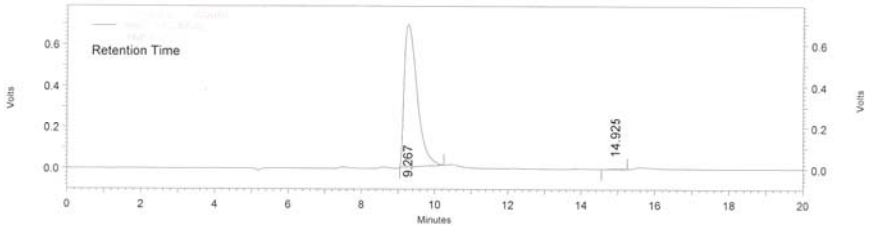


Detector A - 1
(220nm)

Pk #	Retention Time	Area	Area %	Height	Height Percent
1	9.333	8202619	49.398	383461	58.46
2	15.000	8402456	50.602	272443	41.54
Totals		16605075	100.000	655904	100.00



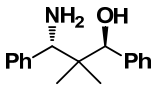
(-)-1



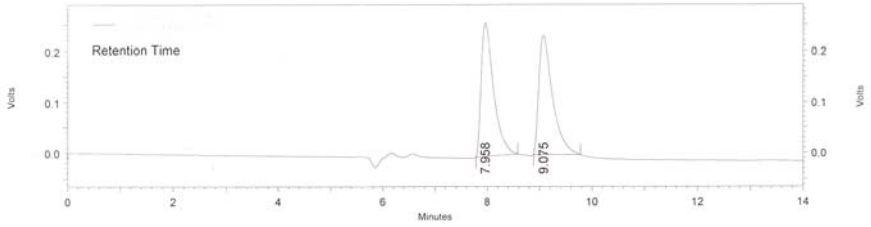
Detector A - 1
(220nm)

Pk #	Retention Time	Area	Area %	Height	Height Percent
1	9.267	16864978	99.801	688840	99.75
2	14.925	33685	0.199	1703	0.25
Totals		16898663	100.000	690543	100.00

>99:1 er, Kromasil-5-Amycoat column; ^{i}PrOH:PE:TFA (20:80:0.1); 0.7 mL/min.; 220 nm. Retention time: t_R = 9.267 min, t_R = 14.925 min.

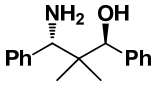


(±)-2

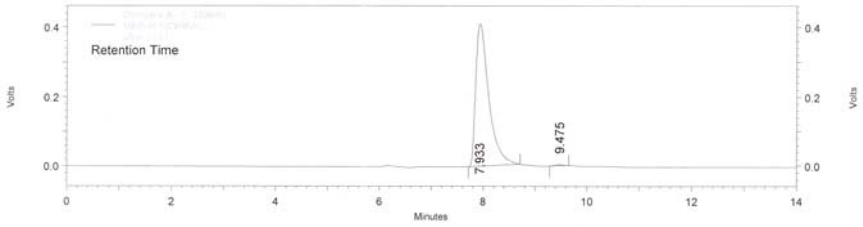


Detector A - 1
(220nm)

Pk #	Retention Time	Area	Area %	Height	Height Percent
1	7.958	4324079	50.213	261454	52.89
2	9.075	4287329	49.787	232888	47.11
Totals		8611408	100.000	494342	100.00



(-)-2



Detector A - 1
(220nm)

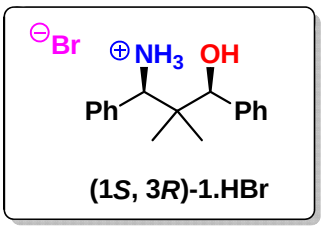
Pk #	Retention Time	Area	Area %	Height	Height Percent
1	7.933	7276053	99.505	410565	99.34
2	9.475	36185	0.495	2733	0.66
Totals		7312238	100.000	413298	100.00

99:1 er, Kromasil-5-Amycoat column; ^{i}PrOH:PE:TFA (20:80:0.1); 0.7 mL/min.; 220 nm. Retention time: t_R = 7.933 min, t_R = 9.475 min.

X-ray analysis of single crystal

X-ray intensity data were collected on a Bruker SMART APEX CCD diffractometer with omega and phi scan mode, $\lambda_{MoK\alpha}$ = 0.71073 Å at T = 100(2) for compound (-)-1 and 297(2) K for compound (-)-2. All the data were corrected for Lorentzian, polarisation and absorption effects using Bruker's SAINT and SADABS programs. The crystal structures were solved by direct method using SHELXS-97 and the refinement was performed by full matrix least squares of F^2 using SHELXL-97 (Sheldrick, G. M. *Acta Cryst.,* **2008**, A*64*, 112). Hydrogen atoms for compound (-)-1 were included in the refinement as per the riding model, whereas for the compound (-)-2, H-atoms H1, H4, H11 and H1A, H1B, H1C bonded to O1, C4, C11 and N1 atoms respectively were located in the difference Fourier and refined isotropically. Other H-atoms for the structure (-)-2 were included in the refinement as per the riding model. Furthermore, the bromine atom of the compound (-)-1 showed statistical disorder over three positions even at 100(2) K. The reasonable model was obtained by splitting the bromine into three components Br1, Br1A and Br1B with site occupancies 0.8, 0.1 and 0.1 respectively, thus the site occupancy factor for the disordered Br atom was constrained to unity.

1. Hydrobromide salt of (-)-1



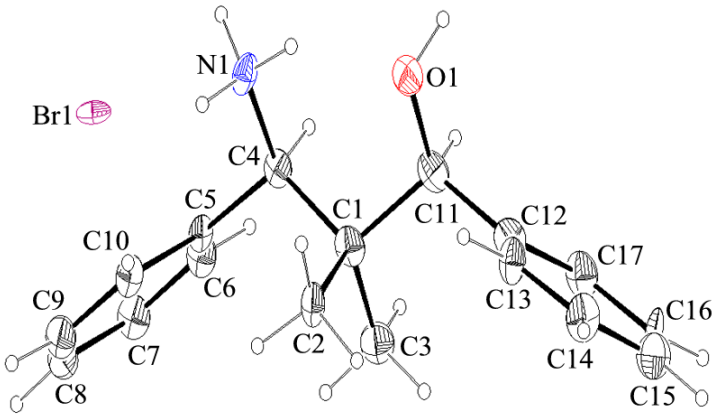


Table 1. Crystal data and structure refinement for (-)-**1**.

Empirical formula	$C_{17}H_{22}BrNO$
Formula weight	336.27
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system, space group	Orthorhombic, $P2_12_12_1$
Unit cell dimensions	a = 6.009(4) Å, α = 90°.
	b = 11.318(8) Å, β = 90°.
	c = 23.288(15) Å, γ = 90°.
Volume	1583.6(18) Å
Z, Calculated density	4, 1.410 Mg/m^3
Absorption coefficient	2.592 mm^{-1}
F(000)	696

Crystal size	0.30 x 0.09 x 0.06 mm
Theta range for data collection	1.75 to 25.00 deg.
Limiting indices	-7<=h<=6, -13<=k<=13, - 17<=l<=27
Reflections collected / unique	7396 / 2764 [R(int) = 0.0523]
Completeness to theta = 25.00	99.6 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.8537 and 0.5102
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2764 / 0 / 193
Goodness-of-fit on F^2	1.103
R indices (all data)	R1 = 0.0526, wR2 = 0.1190
Absolute structure parameter	0.035(18)
Largest diff. peak and hole	0.579 and -0.813 e. $Å^{-3}$

Table 2. Bond lengths [Å] and angles [deg] for (-)-1.

O(1)-C(11)	1.421(7)
C(1)-C(3)	1.531(8)
C(1)-C(11)	1.548(8)
C(1)-C(2)	1.553(8)
C(1)-C(4)	1.556(8)
C(4)-N(1)	1.496(7)
C(4)-C(5)	1.507(8)
C(5)-C(10)	1.391(8)

C(5)-C(6)	1.401(8)
C(6)-C(7)	1.380(8)
C(7)-C(8)	1.400(9)
C(8)-C(9)	1.377(9)
C(9)-C(10)	1.387(8)
C(11)-C(12)	1.508(8)
C(12)-C(17)	1.387(8)
C(12)-C(13)	1.413(8)
C(13)-C(14)	1.372(8)
C(14)-C(15)	1.393(9)
C(15)-C(16)	1.378(9)
C(16)-C(17)	1.401(9)
C(3)-C(1)-C(11)	108.0(5)
C(3)-C(1)-C(2)	108.8(5)
C(11)-C(1)-C(2)	110.5(5)
C(3)-C(1)-C(4)	108.1(5)
C(11)-C(1)-C(4)	109.9(4)
C(2)-C(1)-C(4)	111.3(5)
N(1)-C(4)-C(5)	110.5(4)
N(1)-C(4)-C(1)	111.5(4)
C(5)-C(4)-C(1)	115.8(4)
C(10)-C(5)-C(6)	118.2(5)
C(10)-C(5)-C(4)	122.7(5)
C(6)-C(5)-C(4)	119.1(5)
C(7)-C(6)-C(5)	121.4(5)

C(6)-C(7)-C(8)	119.4(5)
C(9)-C(8)-C(7)	119.6(5)
C(8)-C(9)-C(10)	120.7(6)
C(9)-C(10)-C(5)	120.5(5)
O(1)-C(11)-C(12)	110.8(5)
O(1)-C(11)-C(1)	108.8(4)
C(12)-C(11)-C(1)	115.2(5)
C(17)-C(12)-C(13)	118.0(5)
C(17)-C(12)-C(11)	121.2(5)
C(13)-C(12)-C(11)	120.8(5)
C(14)-C(13)-C(12)	121.5(5)
C(13)-C(14)-C(15)	119.7(6)
C(16)-C(15)-C(14)	119.9(6)
C(15)-C(16)-C(17)	120.4(5)
C(12)-C(17)-C(16)	120.5(5)

Table 3. Torsion angles [deg] for (-)-1.

C(3)-C(1)-C(4)-N(1)	177.8(4)
C(11)-C(1)-C(4)-N(1)	-64.5(6)
C(2)-C(1)-C(4)-N(1)	58.3(6)
C(3)-C(1)-C(4)-C(5)	50.4(6)
C(11)-C(1)-C(4)-C(5)	168.1(4)
C(2)-C(1)-C(4)-C(5)	-69.1(6)
N(1)-C(4)-C(5)-C(10)	-48.2(7)

C(1)-C(4)-C(5)-C(10)	79.7(7)
N(1)-C(4)-C(5)-C(6)	133.4(5)
C(1)-C(4)-C(5)-C(6)	-98.7(6)
C(10)-C(5)-C(6)-C(7)	-0.3(8)
C(4)-C(5)-C(6)-C(7)	178.2(5)
C(5)-C(6)-C(7)-C(8)	-0.1(9)
C(6)-C(7)-C(8)-C(9)	1.4(9)
C(7)-C(8)-C(9)-C(10)	-2.2(8)
C(8)-C(9)-C(10)-C(5)	1.8(8)
C(6)-C(5)-C(10)-C(9)	-0.6(8)
C(4)-C(5)-C(10)-C(9)	-178.9(5)
C(3)-C(1)-C(11)-O(1)	175.3(5)
C(2)-C(1)-C(11)-O(1)	-65.7(6)
C(4)-C(1)-C(11)-O(1)	57.5(6)
C(3)-C(1)-C(11)-C(12)	-59.6(6)
C(2)-C(1)-C(11)-C(12)	59.4(6)
C(4)-C(1)-C(11)-C(12)	-177.4(5)
O(1)-C(11)-C(12)-C(17)	-136.2(5)
C(1)-C(11)-C(12)-C(17)	99.8(6)
O(1)-C(11)-C(12)-C(13)	41.2(7)
C(1)-C(11)-C(12)-C(13)	-82.9(6)
C(17)-C(12)-C(13)-C(14)	-0.2(8)
C(11)-C(12)-C(13)-C(14)	-177.6(6)
C(12)-C(13)-C(14)-C(15)	-1.4(9)
C(13)-C(14)-C(15)-C(16)	2.3(9)

C(14)-C(15)-C(16)-C(17)	-1.6(9)
C(13)-C(12)-C(17)-C(16)	0.8(8)
C(11)-C(12)-C(17)-C(16)	178.2(5)
C(15)-C(16)-C(17)-C(12)	0.1(9)

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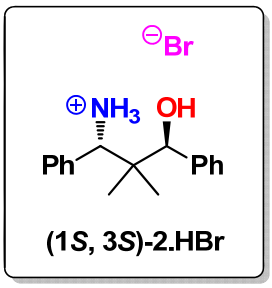
2. Hydrobromide salt of (-)-2



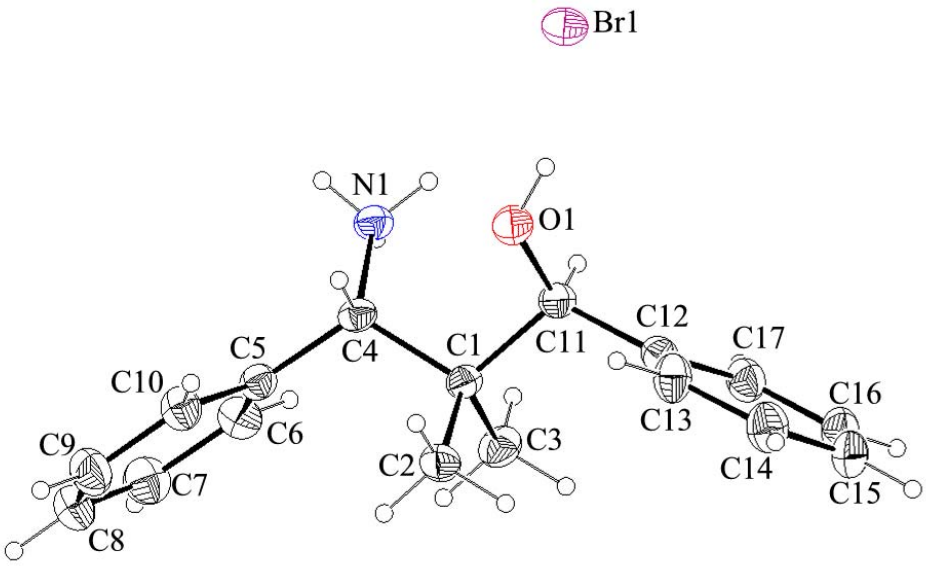


Table 1. Crystal data and structure refinement for (-)-2.

Empirical formula	$C_{17}H_{22}BrNO$
Formula weight	336.27

Temperature	297(2) K
Wavelength0	.71073 Å
Crystal system, space group	Monoclinic, $P2_1$
Unit cell dimensions	a = 11.288(3) Å α = 90°.
	b = 6.1140(14) Å β= 114.187(3)°
	c = 12.697(3) Å γ = 90°.
Volume	799.3(3) $Å^3$
Z, Calculated density	2, 1.397 Mg/m^3
Absorption coefficient	2.567 mm^{-1}
F(000)	348
Crystal size	0.51 x 0.18 x 0.10 mm
Theta range for data collection	1.76 to 26.00°.
Limiting indices	-13<=h<=13, -7<=k<=7, -15<=l<=15
Reflections collected / unique	6240 / 3015 [R(int) = 0.0151]
Completeness to theta = 26.00	99.7 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7833 and 0.3514
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3015 / 2 / 207
Goodness-of-fit on F^2	1.056
Final R indices [I>2sigma(I)]	R1 = 0.0369, wR2 = 0.0945
R indices (all data)	R1 = 0.0380, wR2 = 0.0956
Absolute structure parameter	-0.010(11)
Largest diff. peak and hole	0.571 and -0.176 $e.Å^{-3}$

Table 2. Bond lengths [Å] and angles [deg] for (-)-2.

O(1)-C(11)	1.435(4)
N(1)-C(4)	1.510(4)
C(1)-C(2)	1.532(5)
C(1)-C(3)	1.541(6)
C(1)-C(4)	1.553(4)
C(1)-C(11)	1.555(4)
C(4)-C(5)	1.517(5)
C(5)-C(6)	1.385(5)
C(5)-C(10)	1.401(5)
C(6)-C(7)	1.405(6)
C(7)-C(8)	1.361(7)
C(8)-C(9)	1.389(7)
C(9)-C(10)	1.383(5)
C(11)-C(12)	1.512(4)
C(12)-C(13)	1.389(5)
C(12)-C(17)	1.405(6)
C(13)-C(14)	1.388(6)
C(14)-C(15)	1.374(6)
C(15)-C(16)	1.376(6)
C(16)-C(17)	1.394(5)
C(2)-C(1)-C(3)	109.0(3)
C(2)-C(1)-C(4)	106.9(3)
C(3)-C(1)-C(4)	112.4(3)

C(2)-C(1)-C(11)	111.3(3)
C(3)-C(1)-C(11)	108.4(3)
C(4)-C(1)-C(11)	109.0(2)
N(1)-C(4)-C(5)	109.0(3)
N(1)-C(4)-C(1)	112.2(3)
C(5)-C(4)-C(1)	115.7(3)
C(6)-C(5)-C(10)	118.6(3)
C(6)-C(5)-C(4)	123.3(3)
C(10)-C(5)-C(4)	118.1(3)
C(5)-C(6)-C(7)	120.4(3)
C(8)-C(7)-C(6)	120.1(4)
C(7)-C(8)-C(9)	120.3(3)
C(10)-C(9)-C(8)	119.9(4)
C(9)-C(10)-C(5)	120.5(4)
O(1)-C(11)-C(12)	110.8(3)
O(1)-C(11)-C(1)	106.9(3)
C(12)-C(11)-C(1)	114.9(2)
C(13)-C(12)-C(17)	118.5(3)
C(13)-C(12)-C(11)	121.9(4)
C(17)-C(12)-C(11)	119.6(3)
C(14)-C(13)-C(12)	120.8(4)
C(15)-C(14)-C(13)	120.1(4)
C(14)-C(15)-C(16)	120.4(4)
C(15)-C(16)-C(17)	120.1(4)

C(16)-C(17)-C(12)	120.0(4)

Table 3. Torsion angles [deg] for (-)-2.

C(2)-C(1)-C(4)-N(1)	173.5(3)
C(3)-C(1)-C(4)-N(1)	-67.0(4)
C(11)-C(1)-C(4)-N(1)	53.1(4)
C(2)-C(1)-C(4)-C(5)	-60.6(4)
C(3)-C(1)-C(4)-C(5)	58.9(4)
C(11)-C(1)-C(4)-C(5)	179.0(3)
N(1)-C(4)-C(5)-C(6)	46.6(4)
C(1)-C(4)-C(5)-C(6)	-80.9(4)
N(1)-C(4)-C(5)-C(10)	-132.8(3)
C(1)-C(4)-C(5)-C(10)	99.6(4)
C(10)-C(5)-C(6)-C(7)	-1.3(5)
C(4)-C(5)-C(6)-C(7)	179.2(4)
C(5)-C(6)-C(7)-C(8)	-0.4(6)
C(6)-C(7)-C(8)-C(9)	1.3(7)
C(7)-C(8)-C(9)-C(10)	-0.5(7)
C(8)-C(9)-C(10)-C(5)	-1.3(6)
C(6)-C(5)-C(10)-C(9)	2.2(5)
C(4)-C(5)-C(10)-C(9)	-178.3(3)
C(2)-C(1)-C(11)-O(1)	-72.9(3)
C(3)-C(1)-C(11)-O(1)	167.3(3)

C(4)-C(1)-C(11)-O(1)	44.7(4)
C(2)-C(1)-C(11)-C(12)	50.5(5)
C(3)-C(1)-C(11)-C(12)	-69.4(4)
C(4)-C(1)-C(11)-C(12)	168.1(3)
O(1)-C(11)-C(12)-C(13)	33.4(4)
C(1)-C(11)-C(12)-C(13)	-87.8(4)
O(1)-C(11)-C(12)-C(17)	-145.3(3)
C(1)-C(11)-C(12)-C(17)	93.5(4)
C(17)-C(12)-C(13)-C(14)	-0.9(6)
C(11)-C(12)-C(13)-C(14)	-179.7(3)
C(12)-C(13)-C(14)-C(15)	-0.7(6)
C(13)-C(14)-C(15)-C(16)	1.6(7)
C(14)-C(15)-C(16)-C(17)	-0.9(6)
C(15)-C(16)-C(17)-C(12)	-0.8(6)
C(13)-C(12)-C(17)-C(16)	1.7(5)
C(11)-C(12)-C(17)-C(16)	-179.6(3)

CHAPTER-3

Applications of 3-amino-2,2-dimethyl-1,3-diphenylpropan-1-ol

Introduction

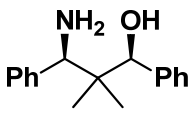
As we discussed in chapter **1**, 1,3-aminoalcohols are of importance as a chiral auxiliaries as well as ligands in various asymmetric reactions.[1] Many synthetically useful C-C bond forming reactions e.g. Aldol reaction,[2] Diels-Alder reaction,[3] addition of diethylzinc to aldehydes[4] etc have been promoted with high stereoselectivity employing 1,3-aminoalcohol as a ligand or auxiliary. Beside this, 1,3-aminoalcohols are important synthetic intermediates for several biologically active natural products.[5] In the literature, many of the known 1,3-aminoalcohols are used as a chiral auxiliary,[2,3b-h,6] while the use of 1,3-aminoalcohols as a chiral ligand is limited.[3a,4,7] After the successful synthesis of optically active title 1,3-aminolacohols, we decided to use these as a chiral ligand for three reactions, namely, enantioselective addition of diethylzinc to aldehydes, addition of trimethylsilyl cyanide to aldehydes and borane reduction of prochiral ketone. We had the following reasons for the present study.

i) Although various 1,3-aminoalcohols are reported to catalyze addition of diethyzinc to aldehydes, with the exception of the ones derived from camphor,[4b,k,m] most 1,3-aminoalcohols posses flexible backbone and provide poor enantioselectivity.[4d,e,g,h,l,p] Further successful aminoalcohols are based on naturally occurring skeletons with limited structural variation, and accessibility of single enantiomer.

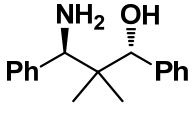
ii) Borane reduction of prochiral ketones catalyzed by 1,3-aminoalcohols has been rarely studied (only one example was reported with moderate success).[7]

iii) Though 1,2-aminoalcohols have been successfully examined as a chiral inducer in trimethylsilyl cyanation reaction,[8,9] no report exists for 1,3-aminoalcohol.

In this context, we envisaged that the aminoalcohols **1** and **2** are likely to provide better selectivity due to steric and electronic reasons.



1



2

This chapter is divided into three sections.

Section-3A: Enantioselective addition of Et_2Zn to aldehydes

Section-3B: Addition of trimethylsilyl cyanide to benzaldehyde

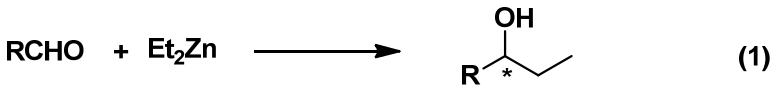
Section-3C: Borane reduction of acetophenone

Section-3A

Enantioselective addition of Et_2Zn to aldehydes

Introduction

The enantioselective addition of diethylzinc to aldehydes (eq 1) is one of the most studied carbon-carbon bond forming reactions in synthetic organic chemistry.[4,10] This reaction constitutes a fundamental tool for the synthesis of enantiopure or enantiomerically enriched secondary alcohols.



(1)

Different types of chiral ligands e.q. diols, aminoalcohols, diamines and aminothiols have been investigated for this reaction. Among these, *β*-aminoalcohols have been most studied.[10] In 1987, Buono and co-workers[4a] for the first time reported the use of (2*S*,3*R*)-4-(Dimethylamino)-1,2-diphenyl-3-methyl-2-butanol **(Chirald)**, a 1,3-aminoalcohol for the enantioselective addition of diethylzinc to benzaldehyde (Figure 1).

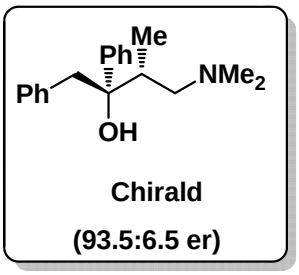


Figure 1

Since this initial report, various 1,3-aminoalcohols have been prepared and examined as a chiral ligands. Most of these aminoalcohols are derived from natural products like (+)-camphor,[4b,h,k,m] (-)-menthone,[4g] (-)-fenchone[4h] or α-D-xylose[4c] etc. A few of them are shown in figure 2 mentioning the enantioselectivity obtained for the addition of diethylzinc to aldehydes. With the exception of the ones derived from camphor,[4b,k,m] most 1,3-aminoalcohols posses flexible backbone and provide poor enantioselectivity. In the case of camphor derived ligand, the structural rigidity of the chiral aminoalcohol plays an important role by limiting the diastereomers of the catalyst.

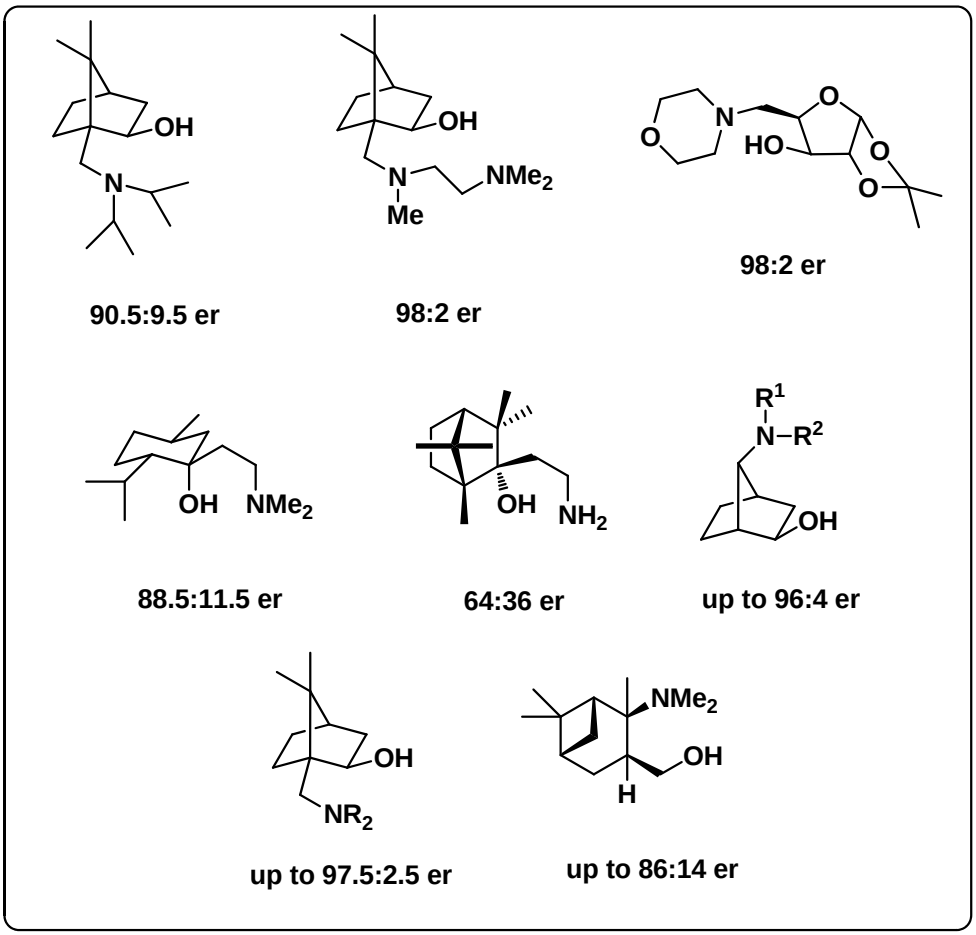


Figure 2

In this section, we have described a highly enantioselective addition of diethylzinc to aldehydes catalyzed by methyl derivatives of the title aminoalcohol (figure 3).

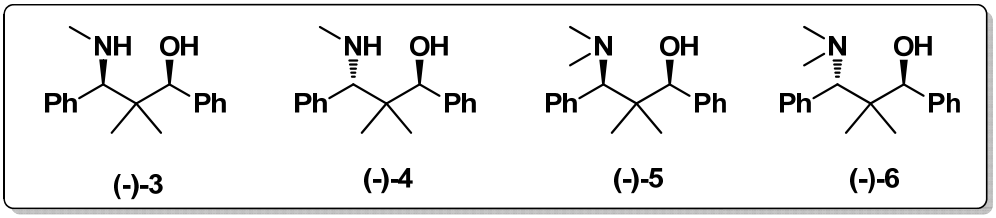
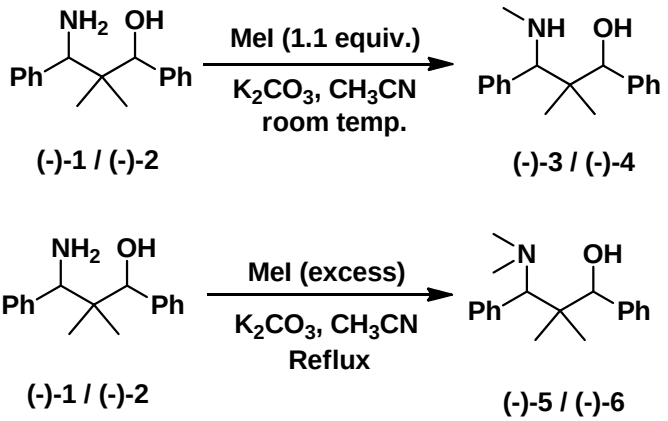


Figure 3

Result and discussion

It is well known that *N*-alkylated aminoalcohols are better ligands compared to its parent aminoalcohol. Therefore we first prepared methyl derivatives (monomethyl and dimethyl derivatives, ligands **3-6**) by judicious methylation as shown in scheme 1.

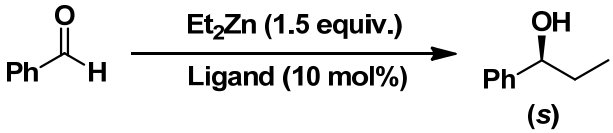
Scheme 1. Preparation of ligand **3-6**



All four ligands were prepared by alkylation of aminoalcohols **(-)-1** and **(-)-2** with methyl iodide in the presence of K_2CO_3 as a base and acetonitrile as a solvent. Ligands (-)-**3** and (-)-**4** were obtained when reaction was carried out at room temperature using 1.1 equivalent of methyl iodide while dimethyl aminoalcohols, (-)-**5** and (-)-**6** were obtained at reflux temperature using excess methyl iodide (2.5 equiv.). The identity of two products was confirmed by IR, NMR, and CHN analysis.

The test reaction involving Et_2Zn and benzaldehyde was carried out in toluene-hexane using 10 mol% of the ligand. The results are summarized in Table 1.

Table 1. Enantioselective addition of Et_2Zn to benzaldehyde



entry	ligand	time (h)	yield[a] (%)	er[b]
1	(-)-**3**	4	69	92:8
2	(-)-**4**	4	70	70:30
3	(-)-**5**	1	90	97:3
4	(-)-**6**	2	80	80:20
5[c]	(-)-**5**	2	86	97:3

[a] Isolated yield. [b] Determined by chiral HPLC analysis. [c] reaction carried out at 0 °C.

As expected, better enantioselectivity was realized with dimethyl derivative than the monomethyl derivative. In the case of monomethyl derivative, a decrease in enantioselectivity and yield was observed. The highest degree of enantioselectivity

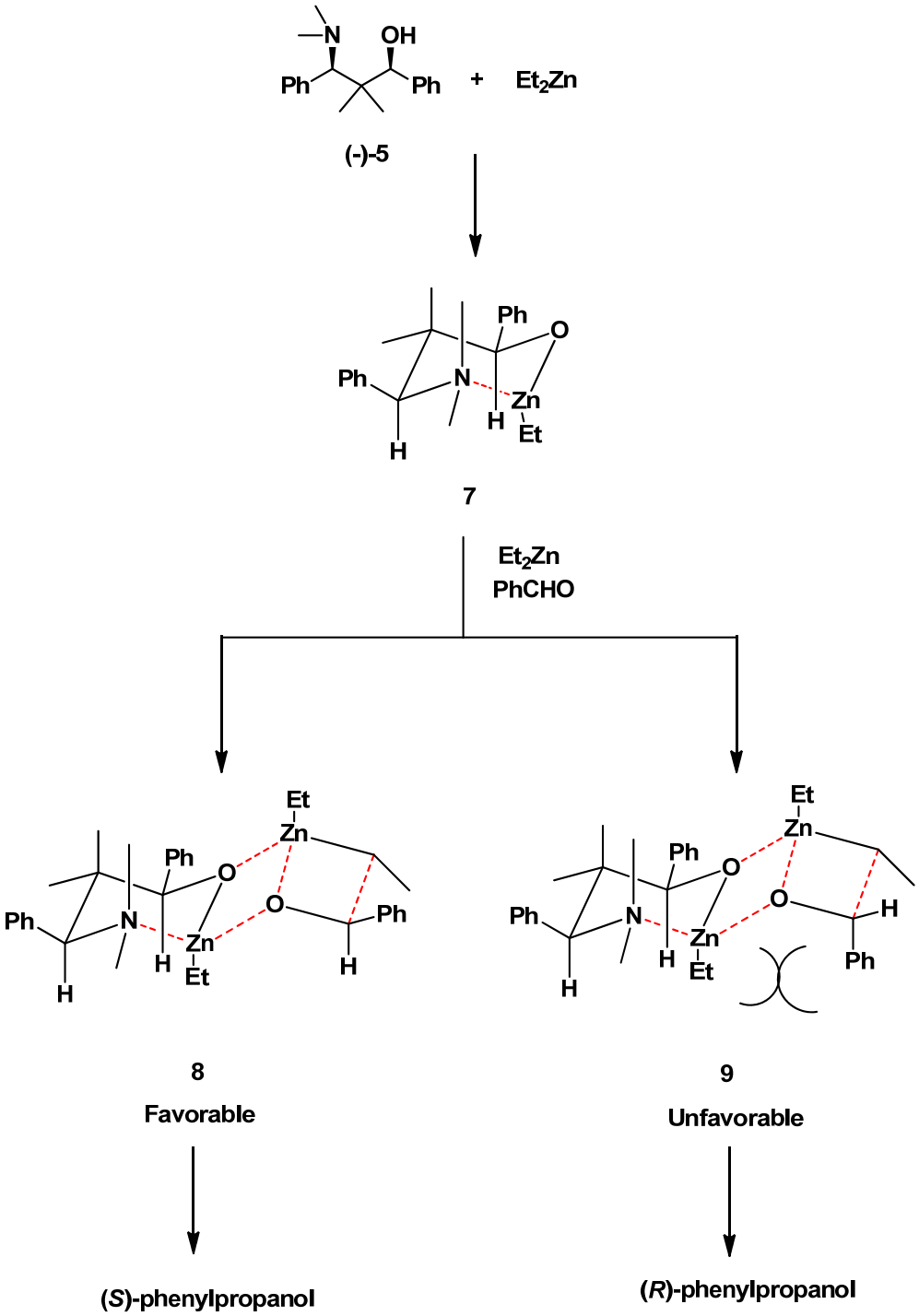
(97:3 er) was observed with *syn*-*N*,*N*-dimethyl aminoalcohol (-)-**5** (entry 3). Unexpectedly, the corresponding *anti*-derivative provided only moderate yield and moderate enantioselectivity. In the case of the ligand (-)-**5**, the reaction was complete within 1 h at room temperature with 100% conversion. It was found that lowering the temperature decreased the reaction rate, but yield and enantioselectivity were comparable (entry 3 and 5).

Mechanism

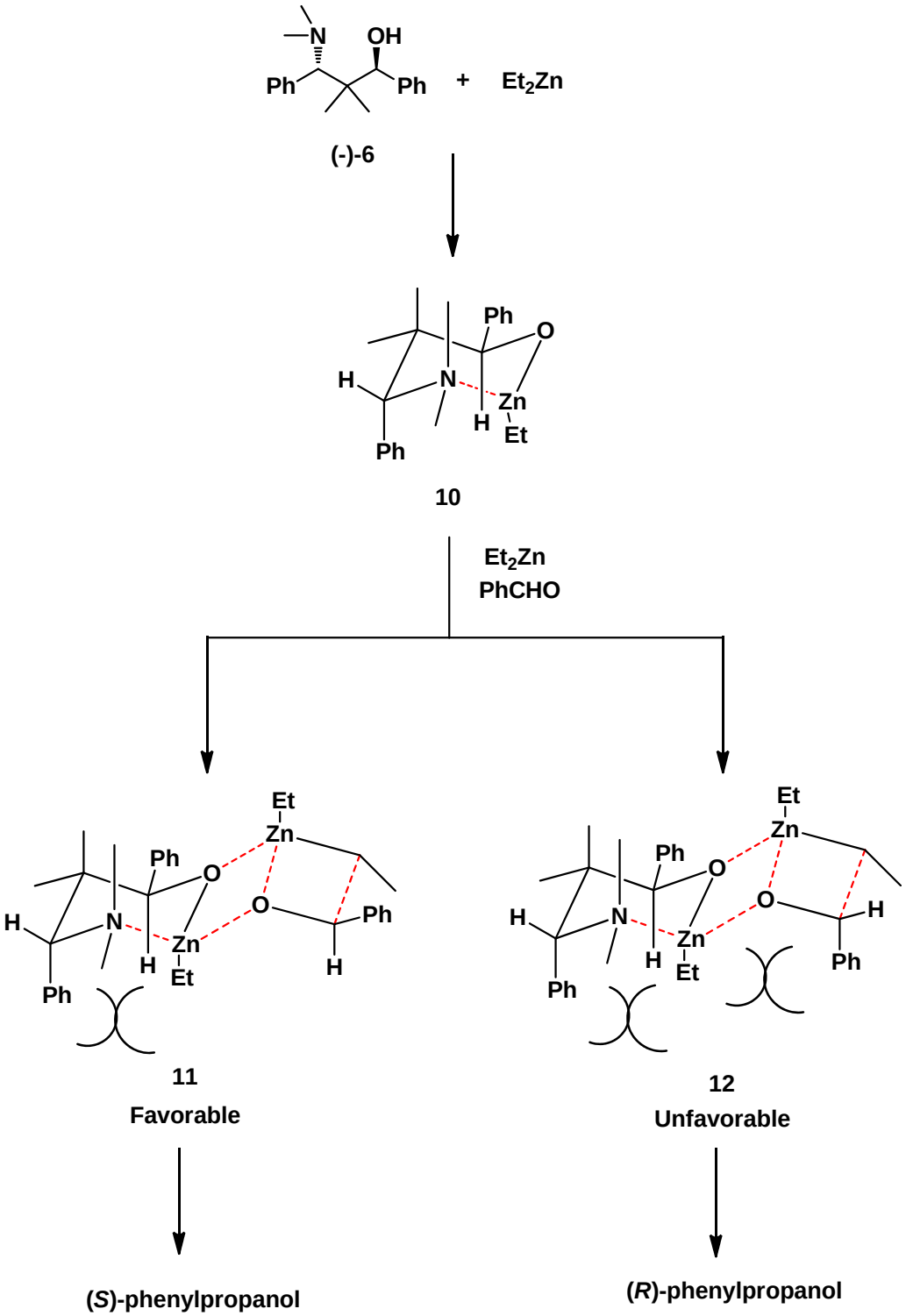
Several studies on the mechanism of the asymmetric diethylzinc addition to aldehydes catalyzed by aminoalcohols have been reported.[10c,d,11] These studies explain the origin of the asymmetric induction, revealing the intermediates and the transition states involved in the reaction. Noyori and Yamakawa[11] proposed the 5/4/4 tricyclic transition structure for observed stereoselectivity in the case of *β*-aminoalcohol catalyzed reaction. In case of 1,3-aminoalcohol, the reaction mechanism has been less studied, Panda *et al.*[4j] has been carried out transition structure calculations using various theoretical methods (HF, DFT, MP2) to explain the reason for the selectivity for 1,3-aminoalcohol and proposed 6/4/4 tricyclic transition structure. We therefore use the mechanism depicted in scheme 2 to explain the observed enantioselectivity and configuration obtained with our aminoalcohol.

Scheme 2. Mechanism

i) Involving *syn*-*N*,*N*-dimethyl aminoalcohol (-)-**5**



ii) Involving *anti*-*N*,*N*-dimethyl aminoalcohol (-)-**6**

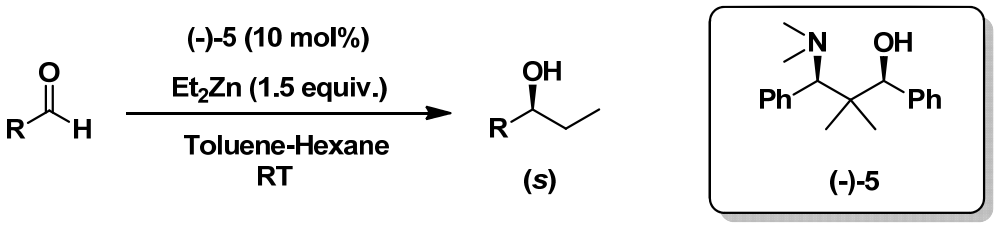


Aminoalcohol **5** and **6** first react with Et_2Zn formed zinc alkoxide by liberating ethane. The resulting Zn-alkoxide then co-ordinates with nitrogen lone pair to form six-membered ring **7** and **10** respectively. High selectivity obtained in case of *syn*-aminoalcohol **5** can be explained by the 6/4/4 tricyclic transition state **8** and **9**. The transition state **9** which is responsible for the formation of (*R*)-alcohol through the *re*-face attack of ethyl group to benzaldehyde is unfavorable due to the steric interaction between ethyl group and phenyl group. However, the transition state **8** with lower energy due to the absence of such steric interaction, is favorable and gives (*S*)-alcohol by the *si*-face attack of ethyl group to benzaldehyde.

The moderate enantioselectivity obtained in the case of *anti*-aminoalcohol **6** is further explained by comparing the tricyclic transition structure **11** and **12** with **8**. Due to the presence of two steric interactions between ethyl group and phenyl group, the transition state **12** is unfavorable. Although **11** is favored, it still possesses one 1,3-interaction between ethyl and phenyl group which results in moderate selectivity.

To extend the scope of the optimal ligand (-)-**5**, several aromatic and aliphatic aldehydes were examined (Table 2). High level of enantioselection was observed in all the cases. The sterically hindered α-napthaldehyde (entry 4) was alkylated with 97:3 er. Even the less reactive cyclohexanecarboxaldehyde (entry 6), was alkylated with excellent enantioselectivity and yield (96:4 er, 90% yield). However hydrocinnamaldehyde, an aliphatic aldehyde (entry 7), provided moderate enantioselectivity although with excellent yield (88:12 er, 90% yield).

Table 2. Enantioselective addition of Et_2Zn to aldehydes catalyzed by **(-)-5**[a]



entry	aldehyde	time (h)	yield (%)	er
1	*o*-tolualdehyde	1.5	87	96:4[b]
2	*p*-tolualdehyde	1.5	88	95:5[b]
3	*p*-chlorobenzaldehyde	1	86	95:5[c]
4	*α*-naphthaldehyde	2	88	97:3[b]
5	*β*-naphthaldehyde	2	89	98:2[b]
6	cyclohexanecarboxaldehyde	3	84	96:4[c]
7	hydrocinnamaldehyde	2	90	88:12[b]

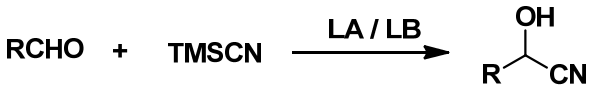
[a] All the reactions were conducted at room temperature using 10 mol% ligand and 1.5 equiv Et_2Zn. [b] Determined by chiral HPLC analysis. [c] Determined by chiral GC analysis

Section-3B

Addition of trimethylsilyl cyanide to benzaldehyde

Introduction

Enantioselective addition of trimethylsilyl cyanide (TMSCN) to a carbonyl compound is one of the important reactions in organic chemistry.[8,9,12] The product of the reaction, optically active cyanohydrins, serve as valuable synthetic precursors for α-hydroxy carboxylic acids, α-amino carboxylic acids, β-hydroxy amines and several other classes of organic compounds. The reaction can be catalyzed by Lewis acid[8,9,12] as well as Lewis base[13] (eq 2).



(2)

1. Lewis acid catalyzed trimethylsilyl cyanation

Various Lewis acid catalysts[9] have been developed for the enantioselective addition of TMSCN to carbonyl compounds (Figure 4). Various chiral ligands e.g. diols,[14] 1,2-diamines,[15] 1,2-aminoalcohols[8] were successfully employed as a chiral source, while boron[16] and titanium[8,9,12] are the most studied metals for this reaction.

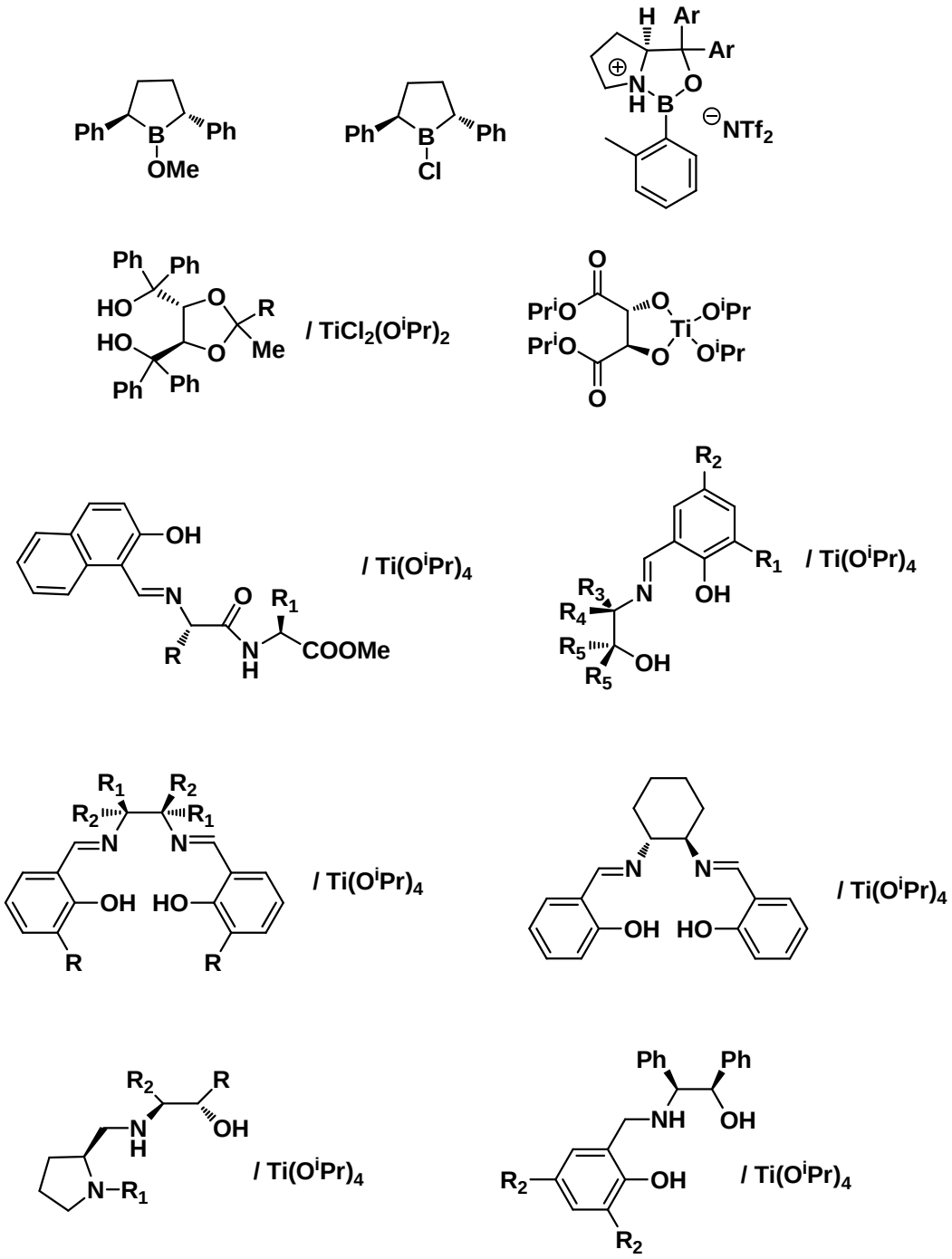


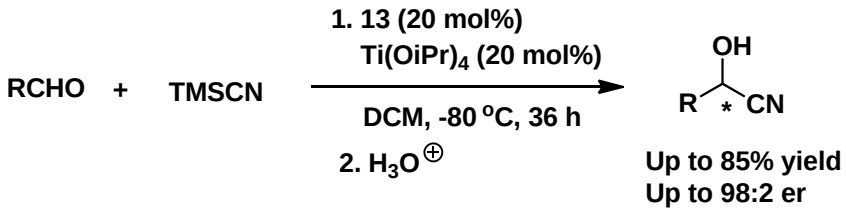
Figure 4

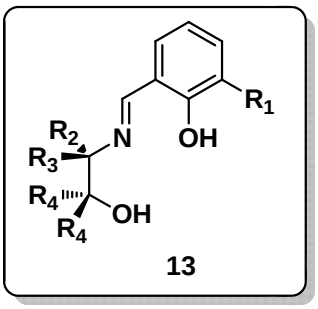
Enantioselective addition of TMSCN to aldehydes catalyzed by *β*-aminoalcohol derived Schiff base-Ti(O^iPr)$_4$ complex is discussed below. The groups of Inoue and Oguni have reported pioneering work in this area.

Oguni and co-workers[8a] in 1991 reported the use of *β*-aminoalcohol derived Schiff base in combination with Ti(O^iPr)$_4$ for trimethylsilyl cyanation. The complex formed from Schiff base and titanium isopropoxide was found to catalyze the

formation of aromatic and aliphatic cyanohydrin silyl ethers with 82.5:17.5-98:2 er and in 58-85% yield (Scheme 3).

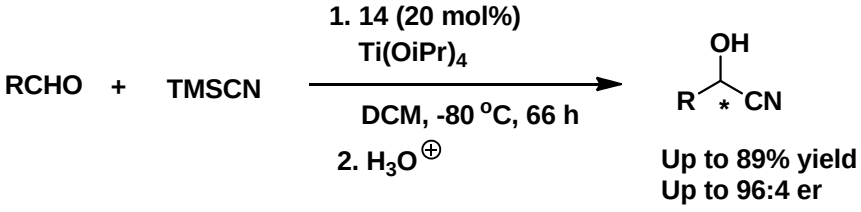
Scheme 3

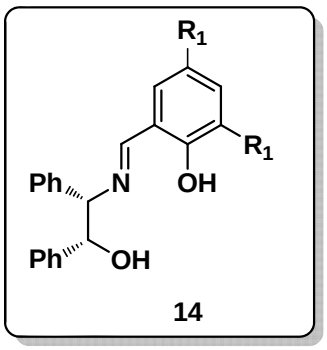




Later, Jiang and co-workers[8c,d] reported similar approach using 2-amino-1,2-diphenylethanol derived Schiff base **14**. It was found that a 2:1 ratio of Schiff base to titanium isopropoxide gave the highest enantioselectivity with good yield (Scheme 4).

Scheme 4

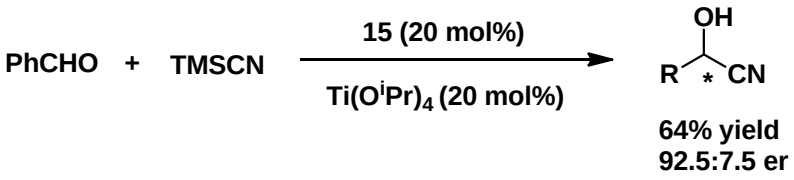


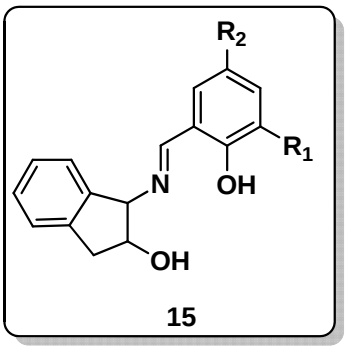


Walsh and Somanathan[8e] reported a library of ligands (**15**) derived from *cis*-1-amino-2-indanol and salicylaldehyde derivative. Using 20 mol% of the titanium

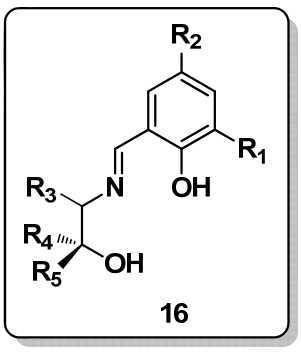
complex formed from Schiff base **15**, cyanation of benzaldehyde was done in good yield with high enantioselectivity (Scheme 5).

Scheme 5



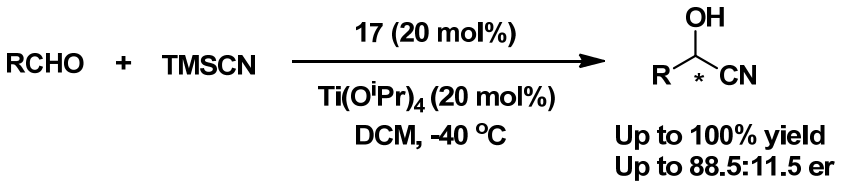


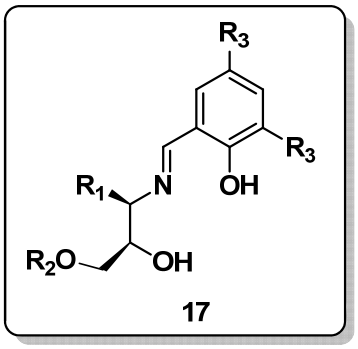
Somanathan and Cole[8f] studied the influence of substituents in Oguni's ligands. They prepared a range of Schiff bases with varing substituents on position R_1-R_5 in ligand **16**. However, attempts to improve the existing system were not particularly successful.



Pericas and co-workers[8g] examined another range of substituents based on Oguni's ligands. The *in situ* formed titanium complexes of ligand **17** were tested for their activity (Scheme 6).

Scheme 6





The transition state shown in figure 5 was proposed to explain the results. The key feature of this transition state is that the oxygen linked to the R_2 group participates in the cyanide bonding process whilst the metal ion acts as Lewis acid.

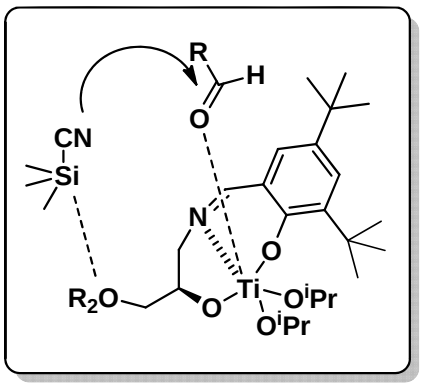
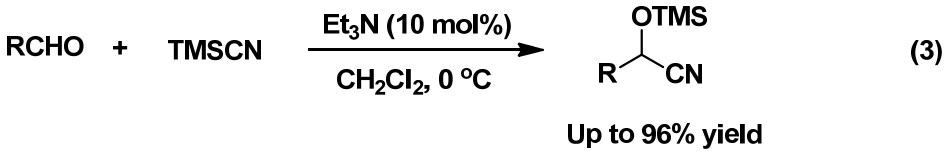


Figure 5. Transition state

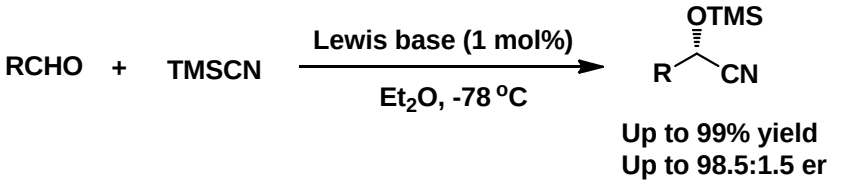
2. Lewis base catalyzed trimethylsilyl cyanation

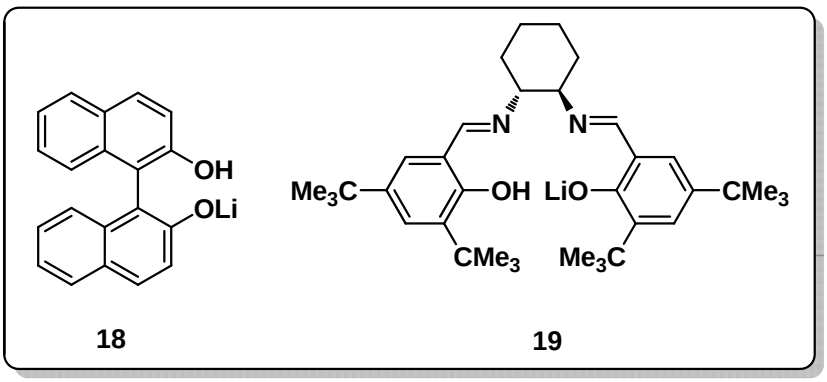
Cyanosilylation can be effectively catalyzed by Lewis bases such as amines, phosphines, metal alkoxides, arsines etc. Mukaiyama *et al.*[17] in 1991 first time explore this concept. The reaction was carried out in the presence of Lewis base to afford the corresponding cyanohydrin trimethylsilyl ethers (eq 3). Et_3N and $^nBu_3P$ were found to be excellent catalysts. It was considered that an amine may co-ordinate to TMSCN to form the intermediate penta co-ordinate silicate which reacts with aldehydes to give the corresponding cyanohydrin trimethylsilyl ethers.



The addition of trimethylsilyl cyanide to aldehydes catalyzed by chiral Lewis base has been reported in 2000 by Holmes and Kagan[18] using monolithium slats of either (*S*)-(-)-BINOL (**18**) or (*R*,*R*)-(-)-*N*,*N*'-bis(3,5-di-*tert*-butyl salicylaldehyde)-1,2-cyclohexanediamine (**19**). The silylated cyanohydrines were obtained in up to 99% yield and with up to 98.5:1.5 er using as little as 1 mol% of the catalyst (Scheme 7).

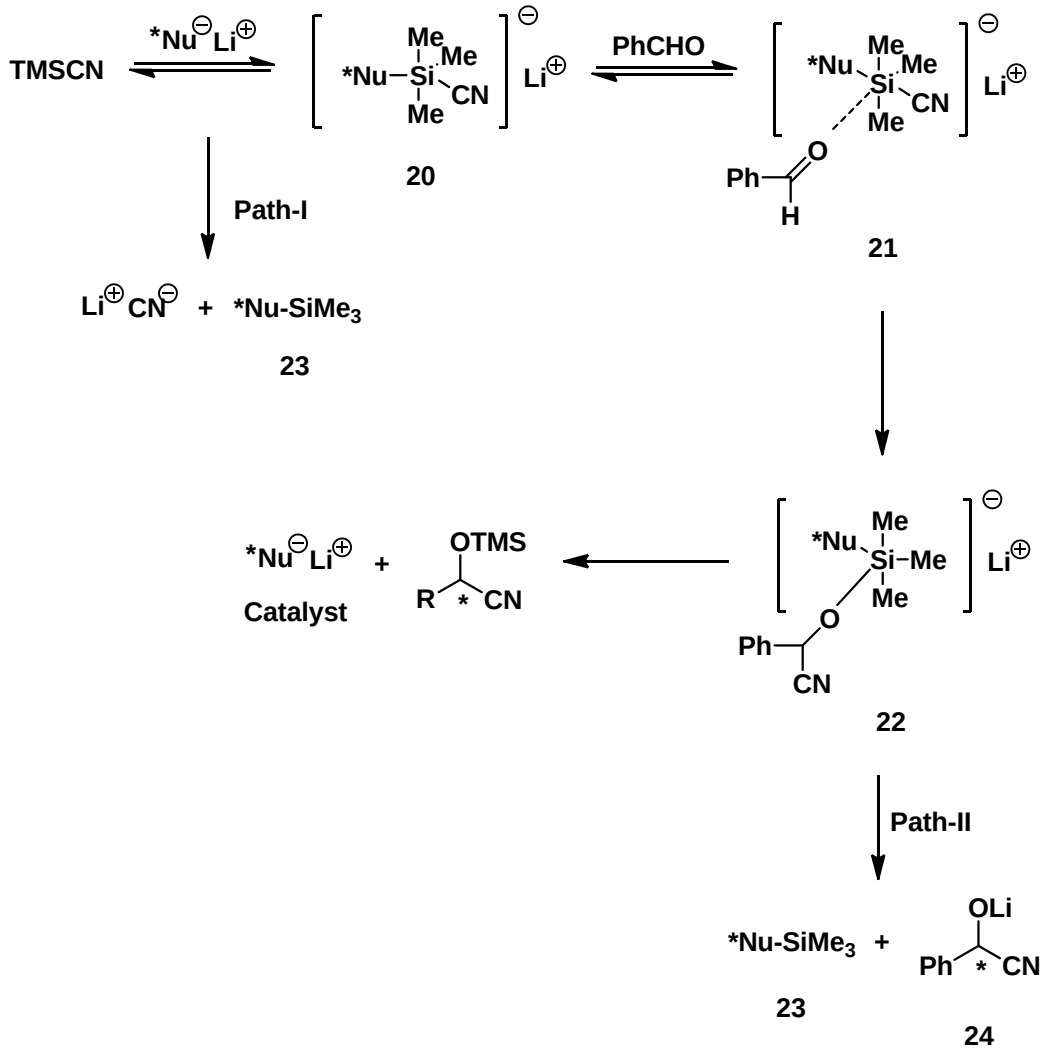
Scheme 7.





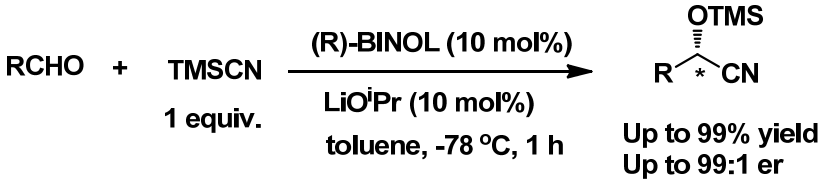
Author proposed the mechanism as shown in scheme 8. Two potential problems are highlighted in scheme 8. The first is the rapid ionization of the TMSCN by the catalyst to give silylated compound (**23**) and a cyanide ion. The cyanide ion can act as a non-enantioselective carrier in the catalytic cycle. Secondly, after the enantioselective transfer of cyanide the resulting complex (**22**) can collapse to eliminate the alkoxide formed (**24**) instead of the catalyst. This gives silylated compound **23** and hence poisoning of the catalyst. Both these problems were overcome by the authors using the catalysts **18** and **19**.

Scheme 8. Mechanism



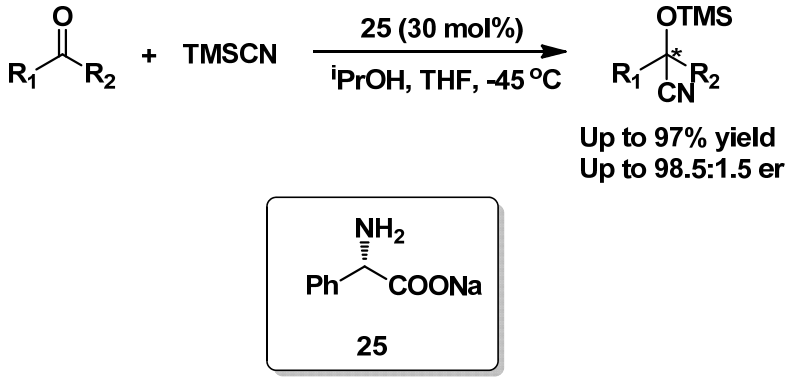
Later Ishihara *et al.*[19] has shown a substantial effect of the lithium source on the yield and enantioselectivity of the addition of TMSCN to aromatic aldehydes. When the lithium hydroxide or lithium alkoxide were used instead of ^{n}BuLi highly effective lithium binaptholate aqua or alcohol complexes were formed which provides silylated cyanohydrins with excellent yield and enantioselectivities (Scheme 9).

Scheme 9.



Feng et al.[20] reported the use of sodium phenylglycinate **25** as a catalyst for cyanosilylation of ketone with enantioselectivities in the range of 77.5:22.5-98.5:1.5 er. Neither lithium nor potassium salts nor the salts of other amino or hydroxyl acids were active as catalyst **25** in this reaction (Scheme 10).

Scheme 10.



Later other catalysts were developed for base catalyzed trimethylsilyl cyanation from the various research groups.[21] A few of them are shown in figure 6.

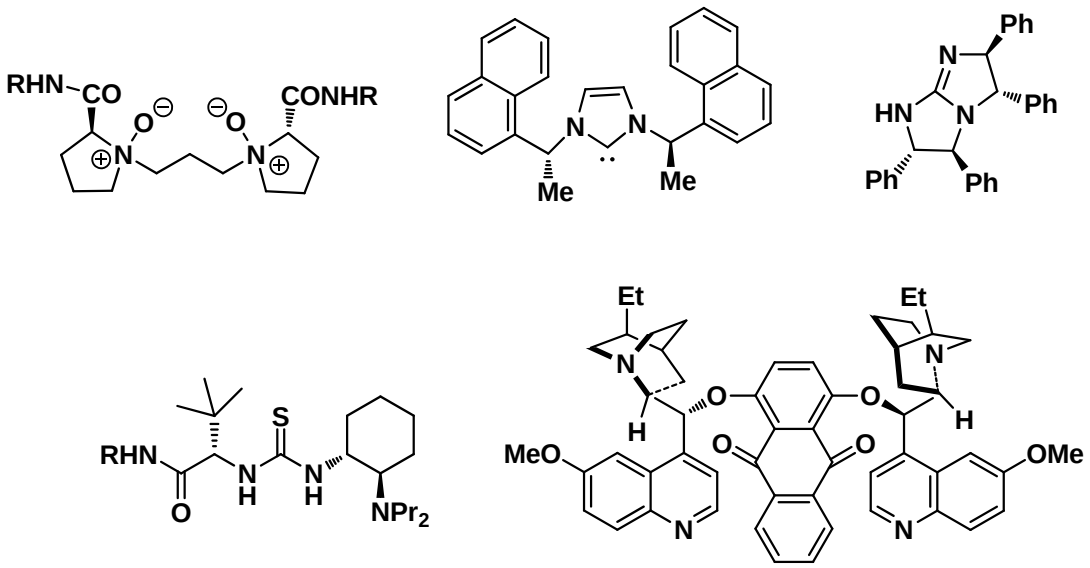
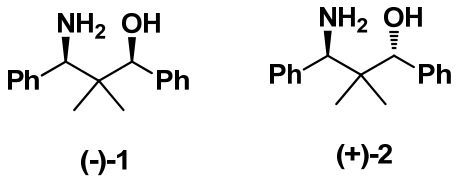


Figure 6

Present work

We studied the trimethylsilyl cyanation of aldehyde catalyzed by both Lewis acids and Lewis bases derived from aminoalcohols (-)-**1** and (+)-**2**.



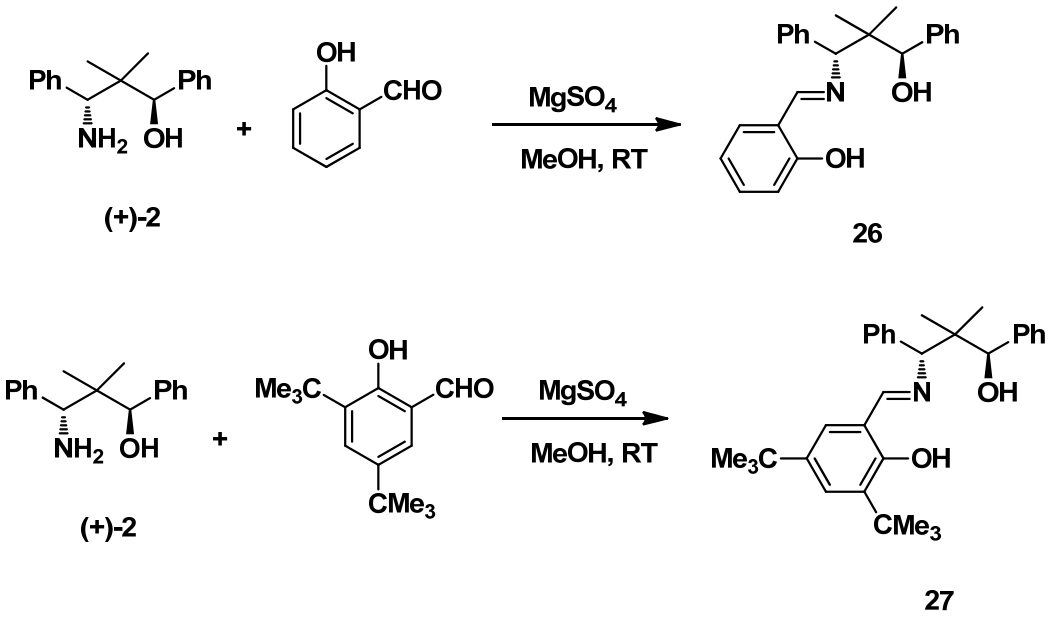
(-)-1 (+)-2

Results and discussion

1. Lewis acid catalyzed trimethylsilyl cyanation

We prepared the Schiff bases (**26** and **27**) to study the Lewis acid catalyzed addition of TMSCN to aldehyde in the presence of $Ti(O^iPr)_4$. The bases were prepared in good yield by the condensation of aminoalcohol (+)-**2** with 2-hydroxy benzaldehyde (salicylaldehyde) and 3,5-di-*tert*-butyl-2-hydroxy benzaldehyde respectively (Scheme 11).

Scheme 11. Preparation of Schiff bases **26** and **27**.



The reaction of benzaldehyde with trimethylsilyl cyanide was then examined at different temperature using 20 mol% of the catalyst prepared *in situ* by the reaction of Schiff bases **26** and **27** with $Ti(O^iPr)_4$ in CH_2Cl_2. The resulting complex efficiently catalyzed the reaction, but with poor enantioselectivity (Table 3).

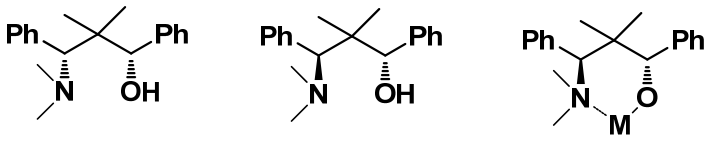
Table 3. Addition of TMSCN to benzaldehyde

entry	Schiff base	temp (^{o}C)	time (h)	yield (%)	er
1	**26**	**0**	**2**	**83**	**-**
2	**27**	**0**	**2**	**90**	**-**
3	**26**	**-78**	**36**	**31**	**-**
4	**27**	**-78**	**36**	**27**	**54:46**

The stereochemical outcome could be explained by assuming that the reaction proceeds through an open transition state. Since the chiral centre in such case would be away from the reaction site, the product would have poor enantioselectivity.

2. Lewis base catalyzed trimethylsilyl cyanation

To study the Lewis base catalyzed trimethylsilyl cyanation of aldehydes, we examined *N*,*N*-dimethyl-1,3-aminoalcohol based Lewis bases (Figure 7).

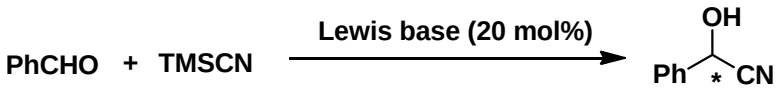


(-)-5 **(-)-6** **28, M = Li**
29, M = Mg

Figure 7

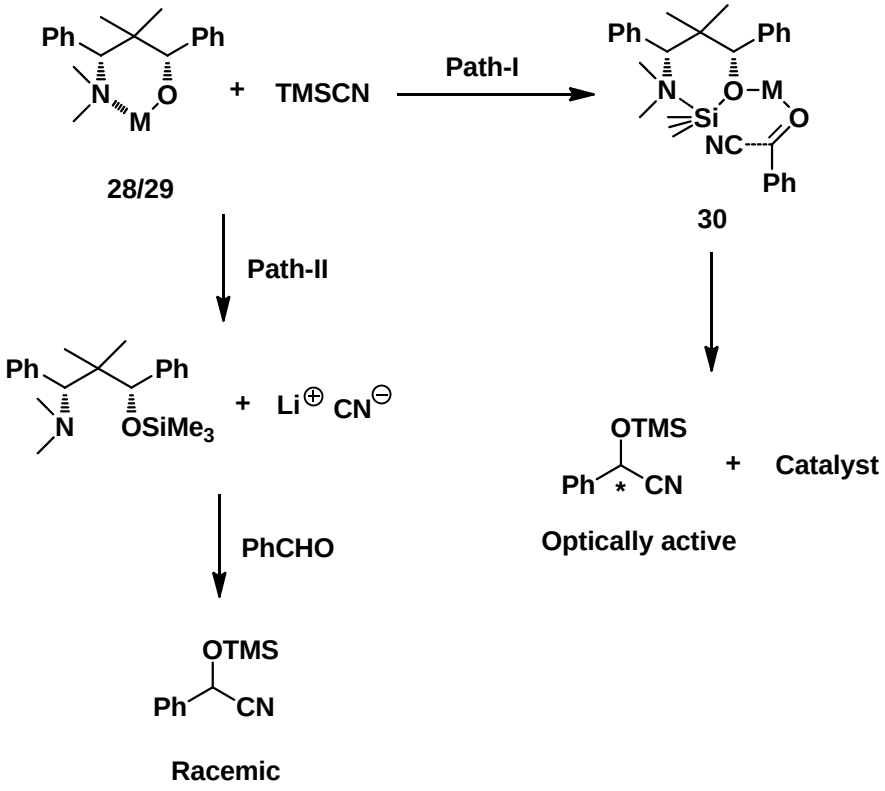
The idea was to activate silicon of trimethylsilyl cyanide through lone pair electron of nitrogen and oxygen. First the trimethylsilyl cyanation of benzaldehyde was performed using 20 mol% of ligand (-)-**5** and (-)-**6** in CH_2Cl_2. However the product was obtained in low yield. We then thought of using stronger base derived from these aminoalcohols. Lithium and magnesium alkoxides were prepared *in situ* by treating the aminoalcohol (-)-**5** with ^{n}BuLi and EtMgBr respectively. It was found that these metal alkoxides (**28** and **29**) rapidly catalyze the reaction between benzaldehyde and TMSCN. Although excellent yields were obtained, enantiomeric excess was disappointing (Table 4).

Table 4. Lewis base catalyzed trimethylsilyl cyanation



entry	Lewis base	solvent	temp (^oC)	time (h)	yield (%)	er
1	(-)-5	CH_2Cl_2	RT	16	17	-
2	(-)-6	CH_2Cl_2	RT	16	15	-
3	30	Toluene	0	1	92	-
4	30	Toluene	-78	24	79	-
5	31	MTBE/THF	0	6	90	-

Scheme 12. Mechanism



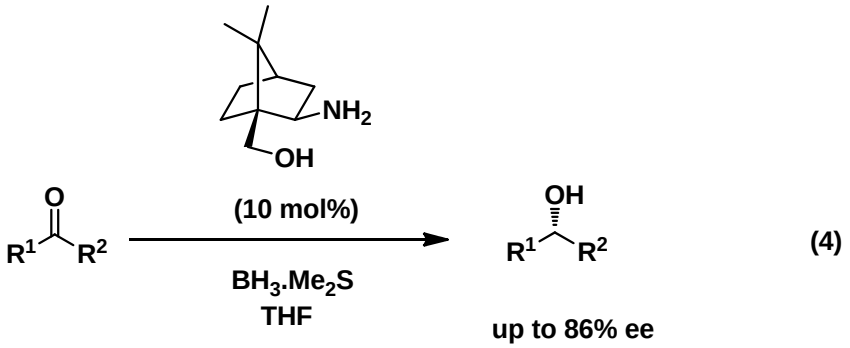
The formation of racemic product observed in this reaction could be explained by considering the mechanism as shown in scheme 12. Two pathways are possible for this reaction. If the reaction proceeds through path I, i.e. through a six-membered transition state **30**, optically active trimethylsilyl ether of cyanohydrins will be formed. While path II is responsible for the formation of racemic product. In the present case the reaction must be proceeding through path II, which is simple $CN^{\ominus}$ catalyzed trimethylsilyl cyanation.

Section-3C

Borane reduction of acetophenone

Introduction

Oxazoborolidine-catalyzed reduction of prochiral ketones has emerged as the most prominent methodology in synthetic organic chemistry.[22] After the initial report by Itsuno *et al.*[22a] and later detailed study by Corey *et al.*,[22b] various 1,2-aminoalcohols have been used as chiral inducers. However there is only one report for the use of 1,3-aminoalcohol as chiral ligand in the borane reduction of ketone (eq 4).[7]



In this section we described the reduction of acetophenone using aminoalcohols (-)-**1,** (-)-**2,** (-)-**3** and (-)-**4** (Figure 8) in the presence of $BH_3.SMe_2$ as a hydride source.

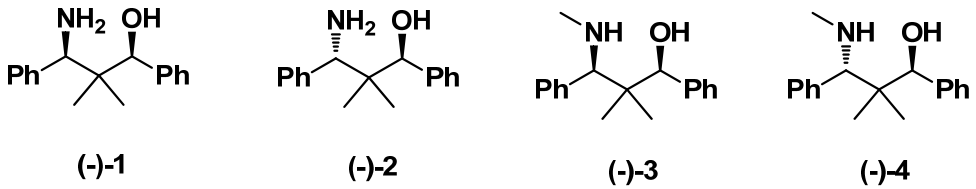
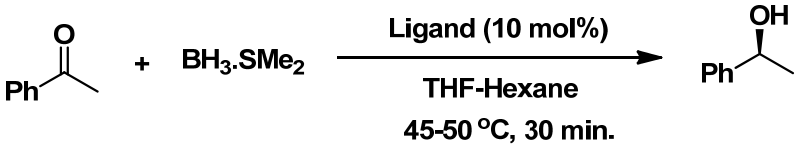


Figure 8

Result and discussion

The oxazaborinane catalyst (**31**) was prepared according to the procedure published by our group earlier.[23j] The aminoalcohol was stirred with one equivalent of borane dimethylsulfide complex at 45-50 ^{o}C for 1 h. The catalyst thus formed reduced acetophenone within 30 minutes. Baring aminoalcohol **1** (er 80:20), the results with other derivatives were disappointing (Table 5).

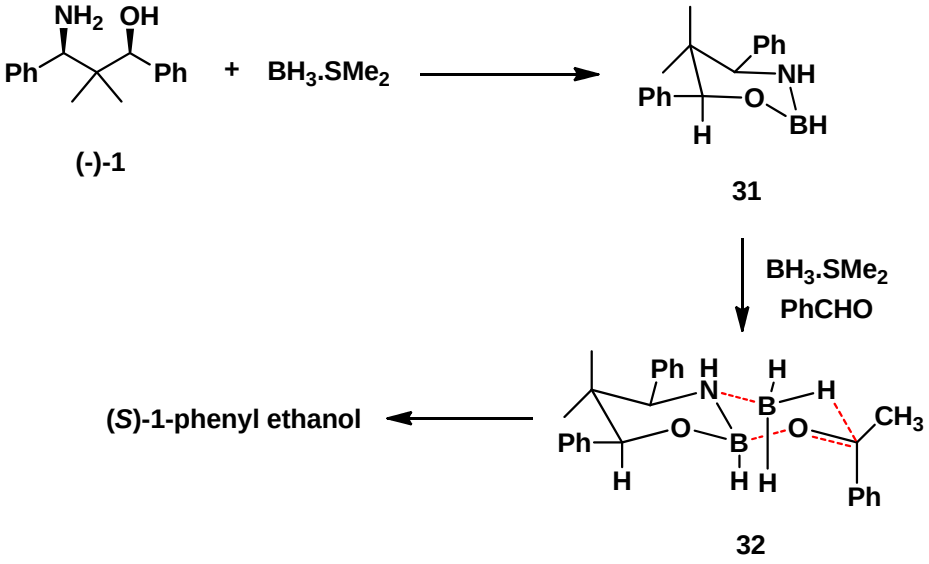
Table 5. Reduction of acetophenone



entry	ligand	yield (%)	er
1	(-)-1	86	80:20
2	(-)-2	84	-
3	(-)-3	89	-
4	(-)-4	86	-

The obtained stereochemical outcome in this reaction could be explained by considering the mechanism as shown in scheme 13.

Scheme 13. Mechanism



First the aminoalcohol reacts with borane to form oxazaborinane catalyst (**31**). Lewis basic nitrogen then co-ordinates with another equivalent of borane followed by acetophenone co-ordination with Lewis acidic boron of oxazaborinane. Hydride transfer then takes place from the *Si*-face of the carbonyl group through a six-membered transition state (**32**) which results in the formation of (*S*)-1-phenyl ethanol as a major product.

Conclusions

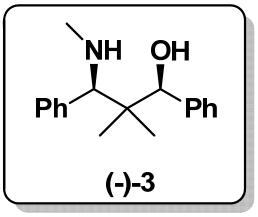
- ✓ *N*,*N*-dimethyl derivative of (*S*,*R*)-3-amino-2,2-dimethyl-1,3-diphenylpropan-1-ol, *syn*-(-)-**5** was found to be excellent ligand for enantioselective addition of diethylzinc to aldehydes.
- ✓ In the Lewis acid as well as Lewis base catalyzed trimethylsilyl cyanation, although excellent yields were obtained in many cases, enantiomeric excess was poor.
- ✓ *In situ* generated oxazaborinane catalyst derived from (*S*,*R*)-3-amino-2,2-dimethyl-1,3-diphenylpropan-1-ol, *syn*-(-)-**1** provided moderate enantioselectivity in the borane reduction of acetophenone.

Experimental section

General procedure for the preparation of *N*-methyl -1,3-aminoalcohol

A suspension of **1** (0.255 g, 1 mmol), K_2CO_3 (0.206 g, 1.5 mmol), methyl iodide (0.07 mL, 1.1 mmol) in acetonitrile (4 mL) was stirred at room temperature for 10 h. The reaction mixture was filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (230-400 mesh) using ethyl acetate: petroleum ether as the eluent to obtain corresponding monomethyl derivative of 1,3-aminoalcohol.

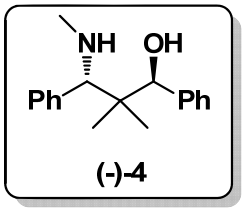
***Syn*-(1*S*,3*R*)-2,2-dimethyl-3-(methylamino)-1,3-diphenylpropan-1-ol, (-)-3**



(-)-3

Yield	**:** 0.200 g, (75%)
TLC data	**:** R_f (20% EtOAc/PE): 0.2
Melting point	**:** 118-120 ^oC
$[\alpha]_D$	**:** -80 (*c* 1, $CHCl_3$).
er	**:** >99:1
IR ($CHCl_3$)	**:** 3019, 1454 cm^{-1}
^1H NMR ($CDCl_3$)	**:** δ 0.36 (s, 3H), 0.90 (s, 3H), 2.27 (s, 3H), 3.63 (s, 1H), 4.82 (*s*, 1H) 7.20-7.39 (m, 10H).
^{13}C NMR ($CDCl_3$)	**:** δ 23.9, 26.1, 42.0, 43.6, 73.9, 84.0, 126.8, 127.4, 127.5, 127.6, 128.0, 131.2, 133.0, 142.2.
Analysis for	**:** $C_{18}H_{23}NO$
Calculated (%)	**:** C, 80.26; H, 8.61; N, 5.20
Found (%)	**:** C, 79.93; H, 8.44; N, 5.23

***Anti*-(1*S*,3*S*)-2,2-dimethyl-3-(methylamino)-1,3-diphenylpropan-1-ol, (-)-4**



(-)-4

Yield : 0.190 g, (71%)

TLC data : R_f (20% EtOAc/PE): 0.2

Melting point : 132-134 ^oC

$[\alpha]_D$: -30 (*c* 1, $CHCl_3$).

er : >99:1

IR ($CHCl_3$) : 3194, 3020, 2978, 1454 cm^{-1}

^1H NMR ($CDCl_3$) : δ 0.70 (s, 3H), 0.99 (s, 3H), 2.25 (s, 3H), 3.55 (s, 1H), 4.57 (*s*, 1H) 7.18-7.32 (m, 10H)

^{13}C NMR ($CDCl_3$) : δ 12.4, 24.9, 33.9, 41.0, 75.4, 85.0, 127.1, 127.3, 127.5, 128.2, 128.4, 138.5, 141.5.

Analysis for : $C_{18}H_{23}NO$

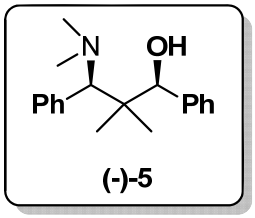
Calculated (%) : C, 80.26; H, 8.61; N, 5.20

Found (%) : C, 80.36; H, 8.77; N, 4.91

General procedure for the preparation of *N*,*N*-dimethyl -1,3-aminoalcohol

A suspension of **1** (0.255 g, 1 mmol), K_2CO_3 (0.414 g, 3 mmol), methyl iodide (0.16 mL, 2.5 mmol) in acetonitrile (5 mL) was stirred under reflux for 16 h. The residue was purified by flash chromatography on silica gel (230-400 mesh) using ethyl acetate:petroleum ether as the eluent to obtain corresponding *N*,*N*-dimethyl derivative of 1,3-aminoalcohol.

***Syn*-(1*S*,3*R*)-2,2-dimethyl-3-(dimethylamino)-1,3-diphenylpropan-1-ol, (-)-5**



(-)-5

Yield : 0.2 g, (71%)

TLC data : R_f (20% EtOAc/PE): 0.24

Melting point : 106-107 ^{o}C

$[\alpha]_D$: -42 (*c* 1, $CHCl_3$).

er : >99:1

IR ($CHCl_3$) : 3016, 1465 cm^{-1}

^{1}H NMR ($CDCl_3$) : δ 0.37 (s, 3H), 1.27 (s, 3H), 2.35 (s, 6H), 3.75 (s, 1H), 4.80 (*s*, 1H) 7.26-7.39 (m, 10H)

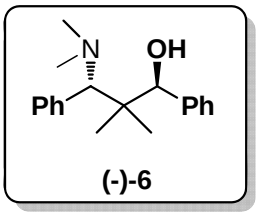
^{13}C NMR ($CDCl_3$) : δ 15.3, 25.5, 42.1, 43.7, 81.1, 85.8, 127.0, 127.2, 127.7, 127.9, 128.5, 131.1, 133.0, 141.1.

Analysis for : $C_{19}H_{25}NO$

Calculated (%) : C, 80.52; H, 8.89; N, 4.94

Found (%) : C, 80.63; H, 9.15; N, 4.83.

***Anti*-(1*S*,3*S*)-2,2-dimethyl-3-(dimethylamino)-1,3-diphenylpropan-1-ol, (-)-6**



(-)-6

Yield : 0.2 g, (71%)

TLC data : R_f (20% EtOAc/PE): 0.24

Melting point : 116-118 ^{o}C

$[\alpha]_D$: -102 (*c* 1, $CHCl_3$).

er : >99:1

IR ($CHCl_3$) : 3016, 1465 cm^{-1}

^{1}H NMR ($CDCl_3$) : δ 0.48 (s, 3H), 1.57 (s, 3H), 2.35 (s, 6H), 3.56 (s, 1H), 4.67 (*s*, 1H) 7.14-7.43 (m, 10H).

^{13}C NMR ($CDCl_3$) : δ 15.2, 25.4, 42.0, 43.7, 81.1, 86.1, 127.0, 127.1, 127.6, 127.8, 128.5, 131.1, 133.1, 141.1.

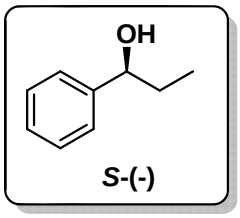
Analysis for : $C_{19}H_{25}NO$

Calculated (%) : C, 80.52; H, 8.89; N, 4.94

Found (%) : C, 80.35; H, 9.00; N, 4.76.

General procedure for enantioselective diethylzinc addition to aldehyde.

To a solution of ligand (-)-**5** (0.113 g, 0.4 mmol) in toluene (2 mL) was added diethylzinc (6 mmol, 4 mL of 1.5 M solution in hexane) and the reaction mixture was stirred at room temperature for 30 min. The resulting solution was cooled to 0 °C, and benzaldehyde (0.4 mL, 4 mmol) was added. The resulting yellow solution was stirred at room temperature until the coloration disappeared and TLC indicated complete absence of benzaldehyde (approximately 1 h). The reaction mixture was then cautiously quenched with MeOH (1 mL) followed by 2 N HCl (5 mL) and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic portion was washed with water followed by brine and dried over anhydrous Na_2SO_4. The residue obtained after evaporation of the solvent was purified by flash column chromatography followed by Kugelrohr distillation to obtain pure (*S*)-(-)-1-phenyl-1-propanol.



Yield **:** 0.470 g, (86%)

$[\alpha]_D$ **:** - 46.3 (*c* 5.1, $CHCl_3$) [Lit[23] -45.45 (*c* 5.15, $CHCl_3$)]

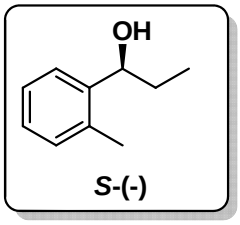
er **:** 97:3 (by HPLC)

IR ($CHCl_3$) **:** 3362, 2967, 1495 cm^{-1}

HPLC **:** Chiracel OD-H column, ^{i}PrOH:*n*-Hexane (2:98), flow rate 0.5 mL/min, detection at 254 nm., t_R = 26.68 min and 32.70 min.

^{1}H NMR ($CDCl_3$) **:** δ 0.92 (t, *J* = 6.9 Hz, 3H), 1.71-1.84 [m, 3H (CH_2 and -OH)], 4.60 (t, *J* = 6.9 Hz, 1H), 7.26-7.36 (m, 5H).

(*S*)-(-)-1-(o-Tolyl)-1-propanol



The reaction was performed with 0.46 mL (4 mmol) of ***o*-tolualdehyde.**

Yield **:** 0.525 g, (87%)

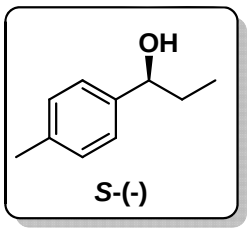
$[\alpha]_D$ **:** - 60.0 (*c* 4, benzene) [Lit[10e] -56.18 (*c* 4, benzene)]

er **:** 96:4 (by HPLC)

HPLC **:** Kromasil-5-Amycoat column, EtOH:*n*-Hexane (2:98), flow rate 0.5 mL/min, detection at 220 nm., t_R = 19.94 min and 22.70 min.

^{1}H NMR ($CDCl_3$) **:** δ 0.98 (t, *J* = 7.4 Hz, 3H), 1.71-1.80 [m, 3H (CH_2 and -OH)], 2.34 (s, 3H), 4.87 (t, *J* = 6.4 Hz, 1H), 7.14-7.48 (m, 4H).

(*S*)-(-)-1-(p-Tolyl)-1-propanol



The reaction was performed with 0.47 mL (4 mmol) of ***p*-tolualdehyde.**

Yield **:** 0.530 g, (88%)

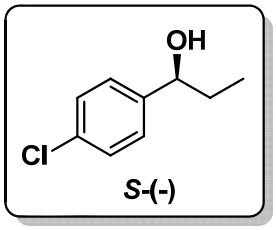
$[\alpha]_D$ **:** - 39.4 (*c* 5, benzene) [Lit[10e] -37.18 (*c* 5, benzene)]

er **:** 95:5 (by HPLC)

HPLC **:** Chiracel OD-H column, ^{i}PrOH:*n*-Hexane (0.5:99.5), flow rate 0.5 mL/min, detection at 254 nm., t_R = 77.32 min and 89.317 min.

^{1}H NMR ($CDCl_3$) **:** δ 0.91 (t, *J* = 7.4 Hz, 3H), 1.7-1.83 [m, 3H (CH_2 and -OH)], 2.35 (s, 3H), 4.56 (t, *J* = 6.7 Hz, 1H), 7.07-7.26 (m, 4H).

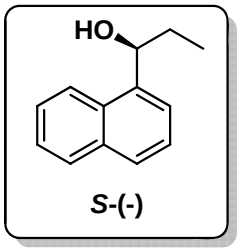
(*S*)-(-)-(p-Chlorophenyl)-1-propanol



The reaction was performed with 0.562 g (4 mmol) of **4-chloro benzaldehyde.**

Yield	**:** 0.590 g, (87%)
$[\alpha]_D$	**:** - 28.3 (*c* 5.15, benzene) [Lit[10e] -28.3 (*c* 5, benzene)]
er	**:** 95:5 (by GC)
GC	**:** Cp-cyclodextrin-B-2,3,6-m-19 capillary column, at 100 ^{o}C (1 min), 10 deg./min, 120 ^{o}C (30 min), t_R = 21.184 min and 21.686 min.
^{1}H NMR ($CDCl_3$)	**:** δ 0.91 (t, *J* = 7.4 Hz, 3H), 1.68-1.81 [m, 3H (CH_2 and -OH)], 4.59 (t, *J* = 6.5 Hz, 1H), 7.25-7.32 (m, 4H).

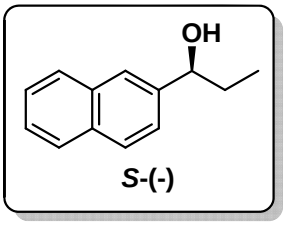
(*S*)-(-)-(*α*-Napthyl)-1-propanol



The reaction was performed with 0.4 mL (3 mmol) of ***α*-naphthaldehyde.**

Yield	**:** 0.490 g, (88%)
$[\alpha]_D$	**:** - 51.4 (*c* 2.53, $CHCl_3$) [Lit[10e] -50.53 (*c* 2.5, $CHCl_3$)]
er	**:** 97:3 (by HPLC)
HPLC	**:** Chiracel OD-H column, ^{i}PrOH:*n*-Hexane (4:96), flow rate 0.5 mL/min, detection at 254 nm., t_R = 33.775 min and 63.883 min.
^{1}H NMR ($CDCl_3$)	**:** δ 1.04 (t, *J* = 7.4 Hz, 3H), 1.77 (bs, 1H, -OH), 1.89-2.04 (m, 2H), 5.41 (t, *J* = 7.3 Hz, 1H), 7.44-8.14 (m, 7H).

(*S*)-(-)-(*β*-Napthyl)-1-propanol



The reaction was performed with 0.468 g (3 mmol) of ***β*-naphthaldehyde.**

Yield **:** 0.495 g, (89%)

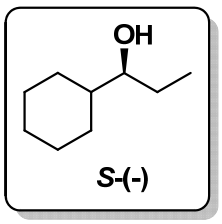
$[\alpha]_D$ **:** - 28.4 (*c* 3.44, benzene)
[Lit[10e] -28.24 (*c* 3.4, benzene)]

er **:** 97.5:2.5 (by HPLC)

HPLC **:** Chiracel OD-H column, ^{i}PrOH:*n*-Hexane (4:96), flow rate 0.5 mL/min, detection at 254 nm., t_R = 39.692 min and 47.183 min.

^{1}H NMR ($CDCl_3$) **:** δ 0.94 (t, *J* = 7.5 Hz, 3H), 1.78 (bs, 1H, -OH), 1.82-1.96 (m, 2H), 4.77 (t, *J* = 6.57 Hz, 1H), 7.42-7.86 (m, 7H).

(*S*)-(-)-(Cyclohexyl)-1-propanol



The reaction was performed with 0.484 mL (4 mmol) of **cyclohexanecarbaldehyde.**

Yield **:** 0.480 g, (84%)

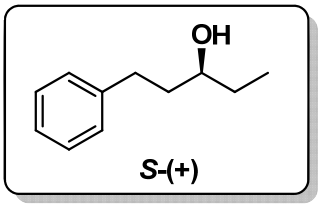
$[\alpha]_D$ **:** - 5.5 (*c* 1.09, $CHCl_3$) [Lit[24] +5.4 (*c* 0.61, $CHCl_3$)]

er **:** 96:4 (by GC)

GC **:** Cp-cyclodextrin-B-2,3,6-m-19 capillary column, at 100 ^{o}C (1 min), 10 deg./min, 120 ^{o}C (30 min), t_R = 18.998 min and 19.715 min.

^{1}H NMR ($CDCl_3$) **:** δ 0.95 (t, *J* = 7.3 Hz, 3H), 1.02-1.82 (m, 14H), 3.24-3.33 (m, 1H).

(*S*)-(+)-1-phenylpentan-3-ol



The reaction was performed with 0.526 mL (4 mmol) of **hydrocinnamaldehyde.**

Yield **:** 0.590 g, (90%)

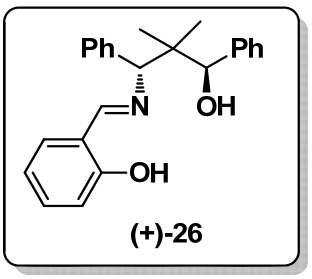
$[\alpha]_D$ **:** +24 (*c* 5, ethanol) [Lit[10e] +26.8 (*c* 5, ethanol)]

er **:** 88:12 (by HPLC)

HPLC **:** Chiracel OD-H column, ^{i}PrOH:*n*-Hexane (2:98), flow rate 0.5 mL/min, detection at 220 nm., t_R = 37.417 min and 63.308 min.

^{1}H NMR ($CDCl_3$) **:** δ 0.95 (t, *J* = 7.46 Hz, 3H), 1.43-1.57 (m, 4H), 1.69-1.83 (m, 2H), 2.66-2.82 (m, 2H), 3.53-3.60 (m, 1H), 7.18-7.33 (m, 5H).

Preparation of Schiff base (+)-26



The aminoalcohol (+)-**2** (0.255 g, 1 mmol) was dissolved in methanol (3 mL). To this stirred solution $MgSO_4$ (0.360 g, 3 mmol) followed by salicylaldehyde (0.1 mL, 1 mmol) were added. The resulting yellowish solution was stirred for 8 h at room temperature. The reaction mixture was diluted with DCM and filtered. The solvent was evaporated under reduced pressure and the obtained residue was purified by crystallization from ethyl acetate:pet ether to obtain (+)-**26** as a yellow solid.

Yield **:** 0.270 g, (75%)

TLC data **:** R_f (10% EtOAc/PE): 0.2

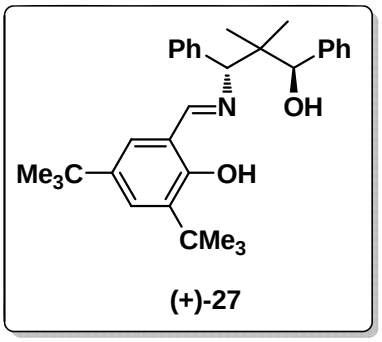
Melting point **:** 178-180 ^{o}C

$[\alpha]_D$ **:** +124 (*c* 1, $CHCl_3$).

IR ($CHCl_3$) **:** 3615, 3609, 3021, 1626, 1215 cm^{-1}

^1H NMR ($CDCl_3$) **:** δ 0.81 (s, 3H), 0.83 (s, 3H), 4.58 (s, 1H), 4.82 (s, 1H), 5.30 (s, 1H, -OH), 6.8-7.40 (m, 14 H), 8.54 (s, 1H), 14.08 (s, 1H, phenolic –OH).

Preparation of Schiff base (+)-27



(+)-27

The same procedure was followed as described for compound **26**. The reaction was performed with 0.255 g (1 mmol) of compound (+)-**2**.

Yield **:** 0.360 g, (76%)

TLC data **:** R_f (10% EtOAc/PE): 0.4

Melting point **:** 156-158 ^oC (MeOH)

$[\alpha]_D$ **:** +118 (*c* 1, $CHCl_3$).

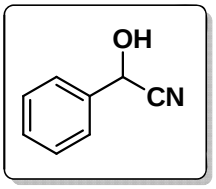
IR ($CHCl_3$) **:** 3615, 3428, 3005, 2967, 1629, 1215 cm^{-1}

^1H NMR ($CDCl_3$) **:** δ 0.81 (s, 3H), 0.84 (s, 3H), 129 (s, 9H), 1.51 (s, 9H), 4.62 (s, 1H), 4.80 (s, 1H), 5.30 (s, 1H, -OH), 7.11-7.41 (m, 12H), 8.55 (s, 1H), 14.10 (s, 1H, phenolic –OH).

General procedure for Lewis acid catalyzed trimethylsilyl cyanation of benzaldehyde

To a solution of Schiff base (+)-**26** (0.072 g, 0.2 mmol) in DCM (1 mL) was added $Ti(O^iPr)_4$ (0.2 mmol, 0.2 mL of 1 M solution in DCM), and the reaction mixture was stirred at room temperature for 2 h. The resulting solution was cooled to 0 ^oC and benzaldehyde (0.1 mL, 1 mmol) followed by trimethylsilyl cyanide (0.28 mL, 2.28 mmol) were added. The resulting solution was stirred at 0 ^oC until TLC indicated complete absence of benzaldehyde (approximately 2 h). The reaction

mixture was diluted with ethyl acetate (50 mL) and 1N HCl (10 mL) was added. The mixture was stirred vigrously until TLC indicated total conversion of trimethylsilyl ether to the corresponding cyanohydrin (30 min). Ethyl acetate layer was separated, washed with water followed by with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (230-400 mesh) using ethyl acetate:petroleum ether as the eluent to obtain 2-hydroxy-2-phenylacetonitrile.



Yield **:** 0.110 g, (83%)

Nature **:** Liquid

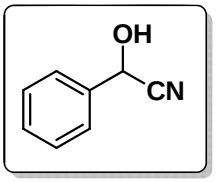
$[\alpha]_D$ **:** 0 (*c* 2, $CHCl_3$).

IR ($CHCl_3$) **:** 3417, 3252, 1495 cm^{-1}

^{1}H NMR ($CDCl_3$) **:** δ 2.89-2.92 (d, *J* = 6.9 Hz, 1H), 5.53-5.56 (d, *J* = 6.8 Hz, 1H), 7.43-7.57 (m, 5 H)

General procedure for Lewis base catalyzed trimethylsilyl cyanation of benzaldehyde

The aminoalcohol (-)-**5** (0.056 g, 0.2 mmol) was dissolved in anhydrous toluene (2 mL). The solution was cooled to 0 ^oC and ^{n}BuLi (0.2 mmol, 0.11 mL of 1.8 M solution in cyclohexane) was added. The mixture was allowed to stir for 30 min. Benzaldehyde (0.1 mL, 1 mmol) followed by trimethylsilyl cyanide (0.25 mL, 2 mmol) were added. The mixture was allowed to stirr at 0 ^oC until TLC indicated complete absence of benzaldehyde (approximately 1 h). The reaction mixture was quenched by the addition of 1N HCl (10 mL) and product was extrcted with ethyl acetate (2 x 20 mL). Combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (230-400 mesh) using ethyl acetate:petroleum ether as the eluent to obtain 2-hydroxy-2-phenylacetonitrile



Yield **:** 0.122 g, (92%)

Nature **:** Liquid

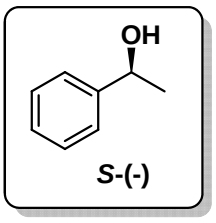
$[\alpha]_D$ **:** 0 (*c* 2, $CHCl_3$).

IR ($CHCl_3$) **:** 3417, 3252, 1495 cm^{-1}

^{1}H NMR ($CDCl_3$) **:** δ 2.89-2.92 (d, *J* = 6.9 Hz, 1H), 5.53-5.56 (d, *J* = 6.8 Hz, 1H), 7.43-7.57 (m, 5 H)

General procedure for Asymmetric reduction of acetophenone.

To a solution of ligand (-)-**1** (0.051 g, 0.2 mmol) in THF (1 mL) was added $BH_3.SMe_2$ solution (2 mmol, 1.42 mL of 1.4 M solution in toluene), and the reaction mixture was stirred at 45-50 ^oC temperature for 1 h under argon atmosphere. A solution of acetophenone (0.23 mL, 2 mmol) in anhydrous THF (1 mL) was then added dropwise over a period of 25-30 min. After the addition was over, the reaction mixture was stirred at the same temperature for another 30 minutes. The reaction mixture was cooled to room temperature and cautiously quenched with MeOH (0.5 mL). Solvent was evaporated under reduced pressure and the residue was dissolved in ether. The ether layer was washed with 2N HCl followed by brine and dried over anhydrous Na_2SO_4. The residue obtained after the removal of ether was purified by filtration column on silica gel (100-200 mesh) to obtain pure (*S*)-(-)-l-phenyl ethanol.



Yield **:** 0.210 g, (86%)

$[\alpha]_D$ **:** -26.6 (*c* 3, MeOH) [Lit[22j] -45.9 (*c* 3, MeOH)]

er **:** 80:20

^{1}H NMR ($CDCl_3$) **:** δ 1.5 (d, *J* = 7.2 Hz, 3H), 2.25 (bs, 1H, -OH), 4.85 (q, *J* = 7.2 Hz, 1H), 7.2-7.4 (m, 5H).

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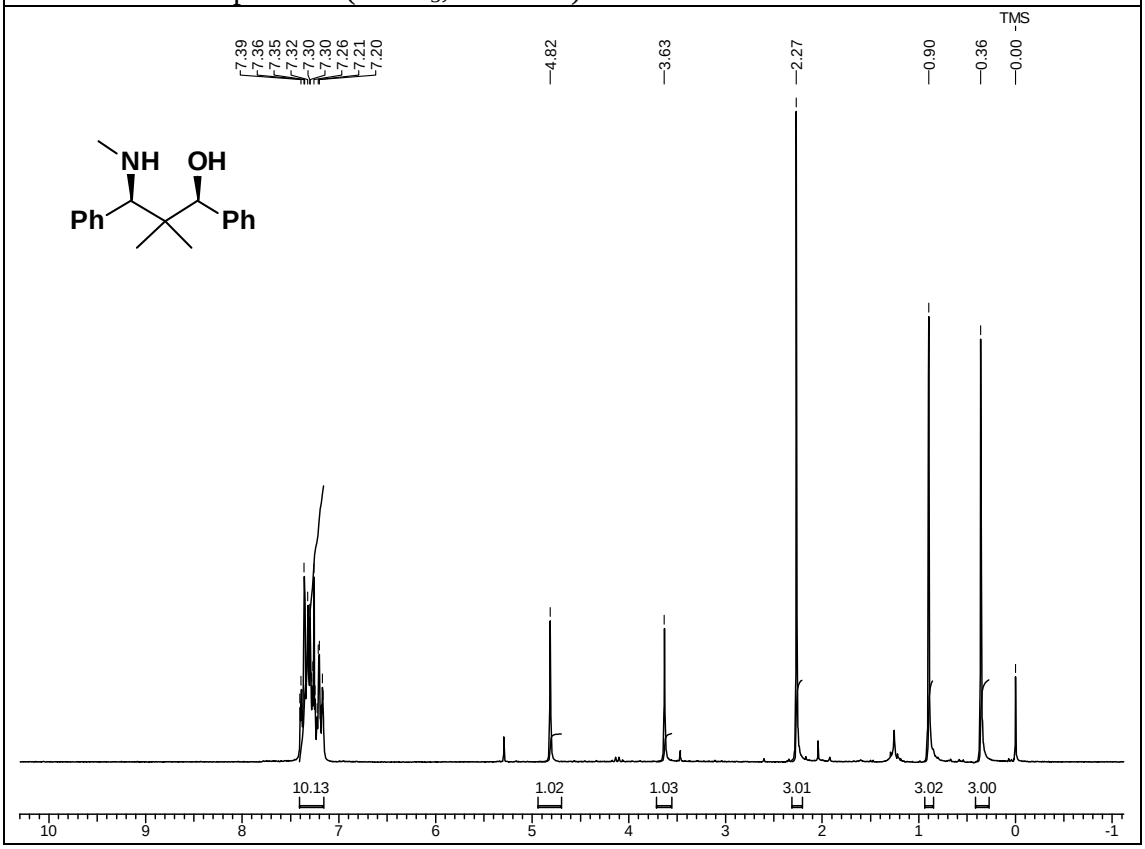
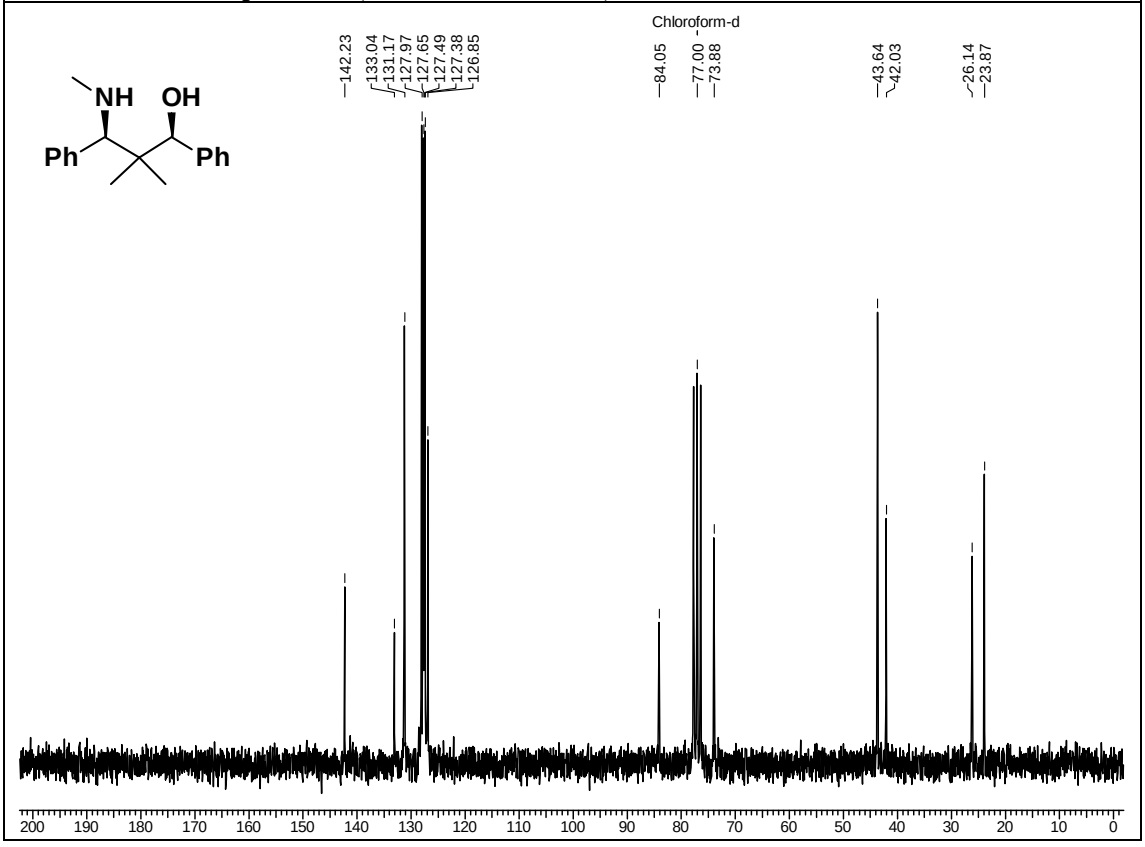
NMR Spectra And

HPLC Chromatogram

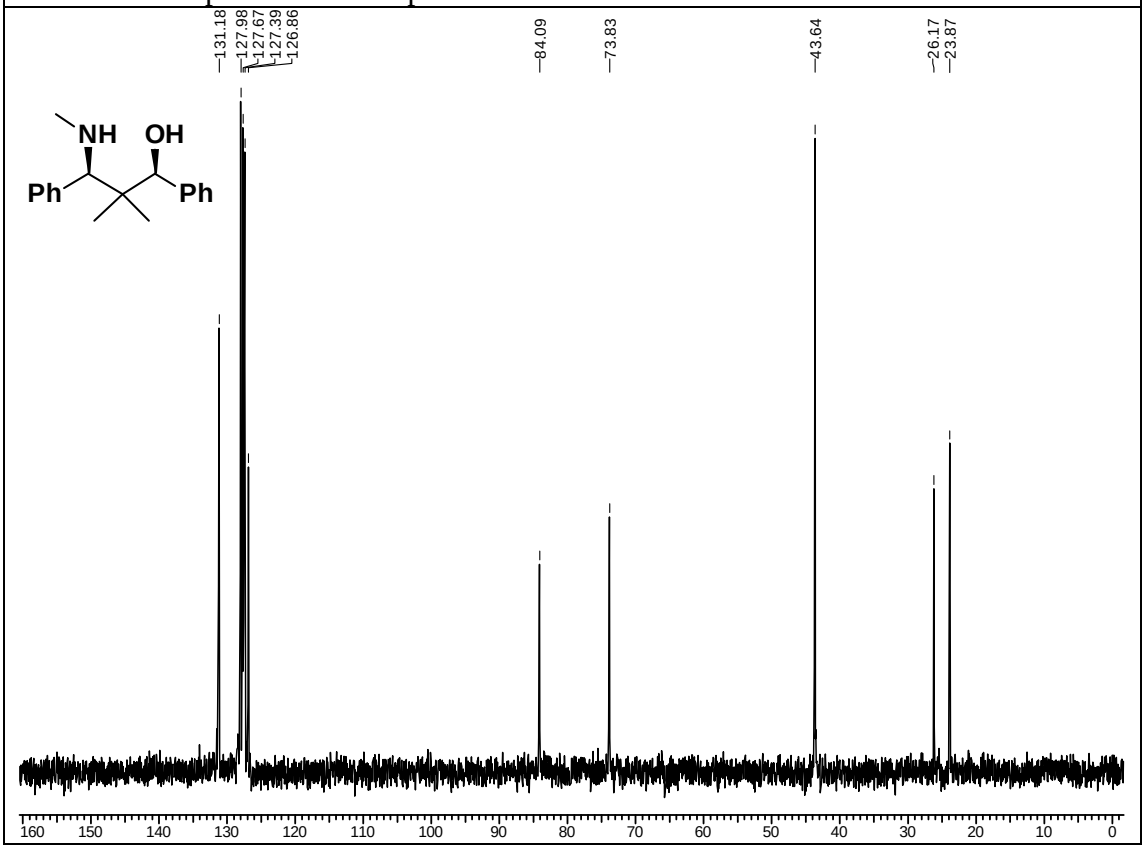
^{1}H-NMR of compound **3** ($CDCl_3$, 200MHz)



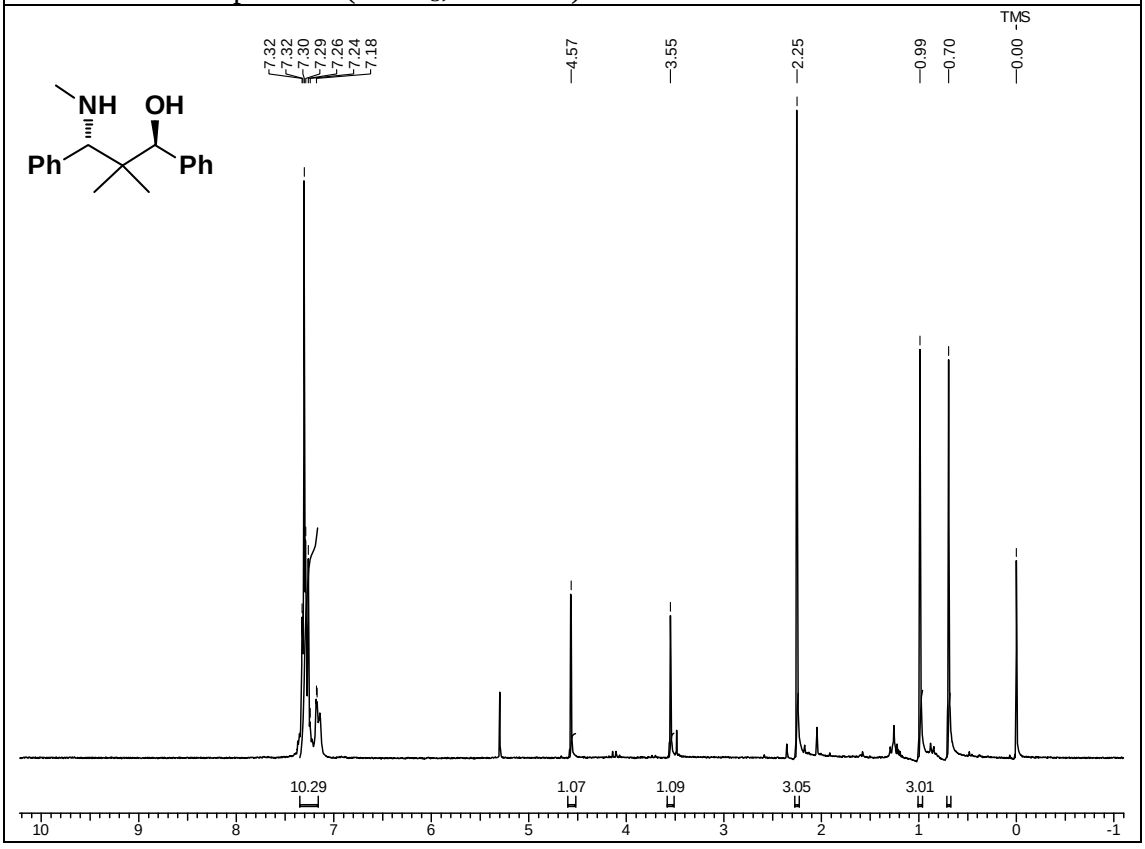
^{13}C-NMR of compound **3** ($CDCl_3$, 50.32MHz)



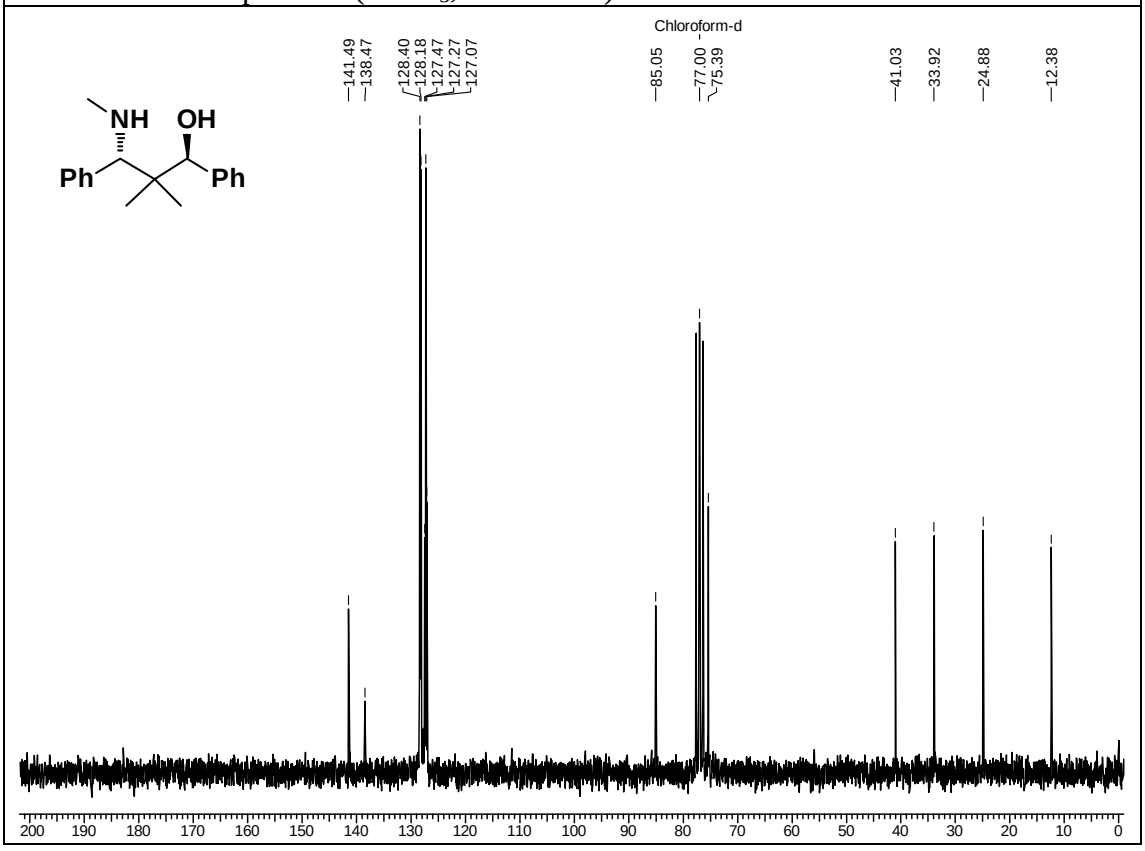
DEPT NMR Spectrum of compound **3**



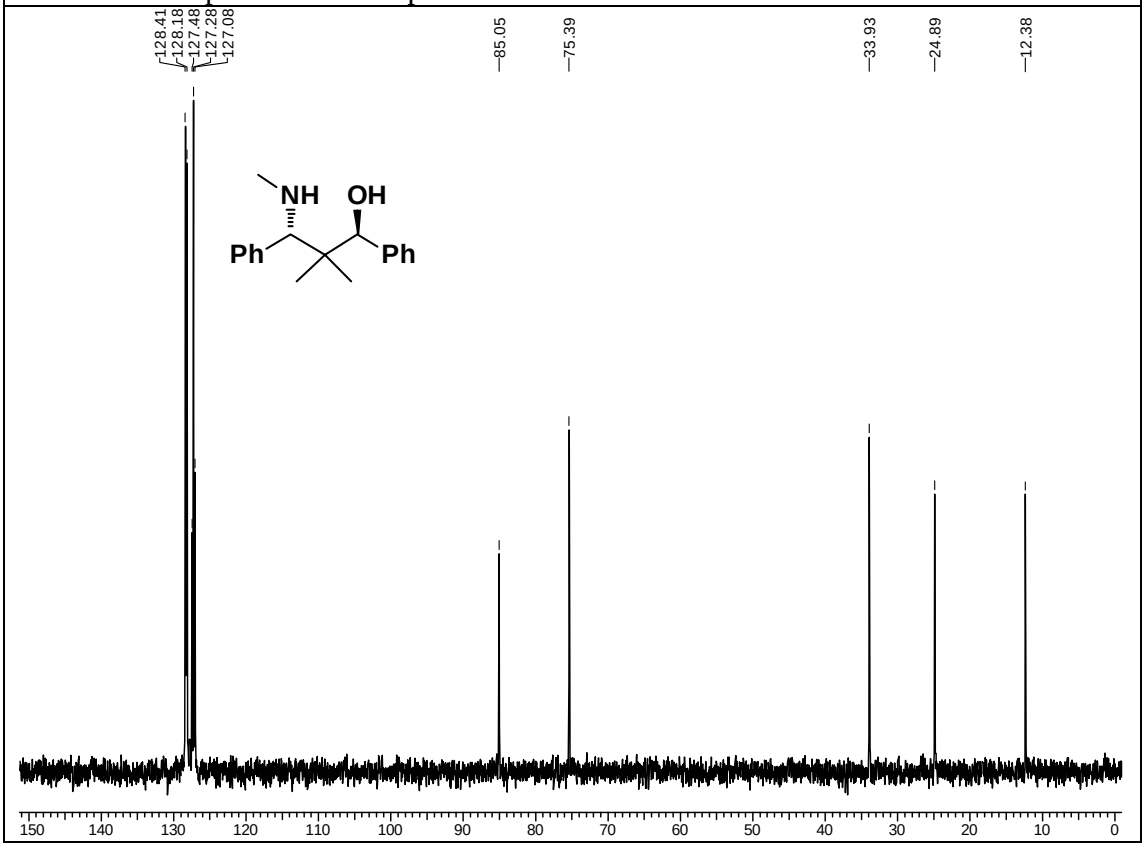
^{1}H-NMR of compound **4** ($CDCl_3$, 200MHz)



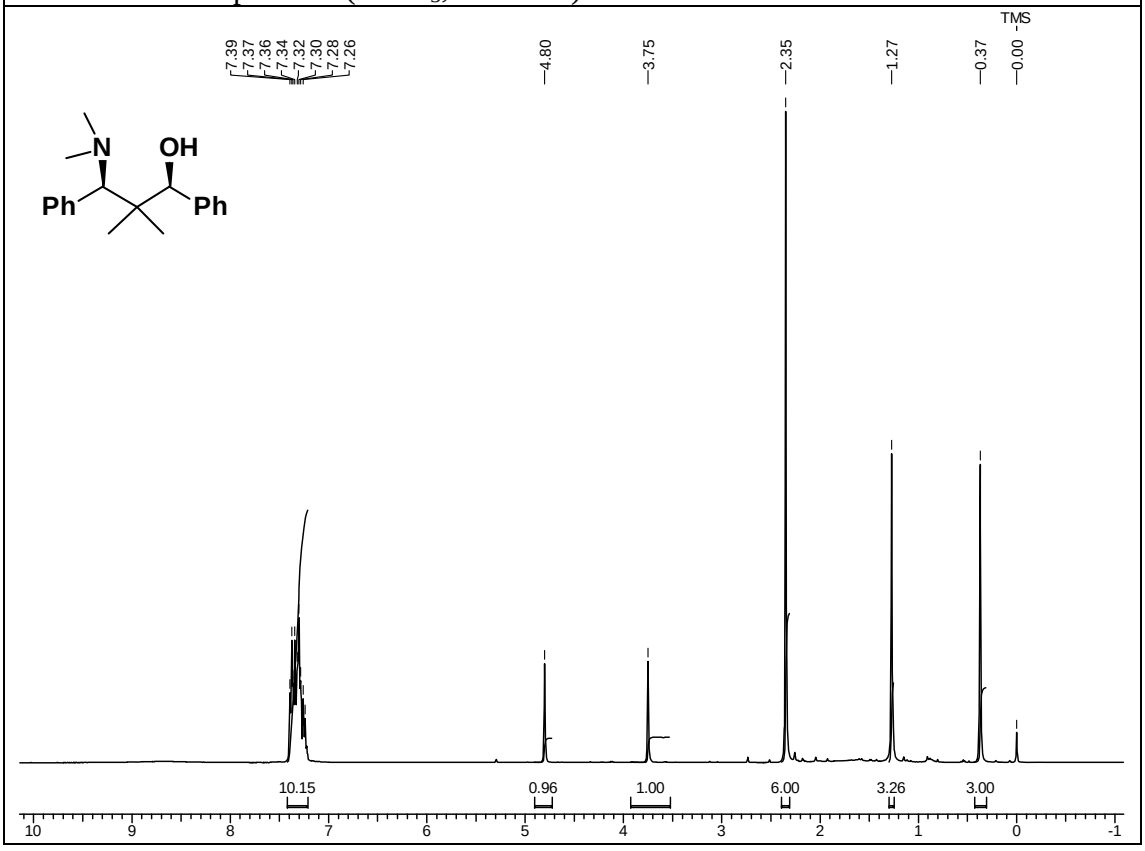
^{13}C-NMR of compound **4** ($CDCl_3$, 50.32MHz)



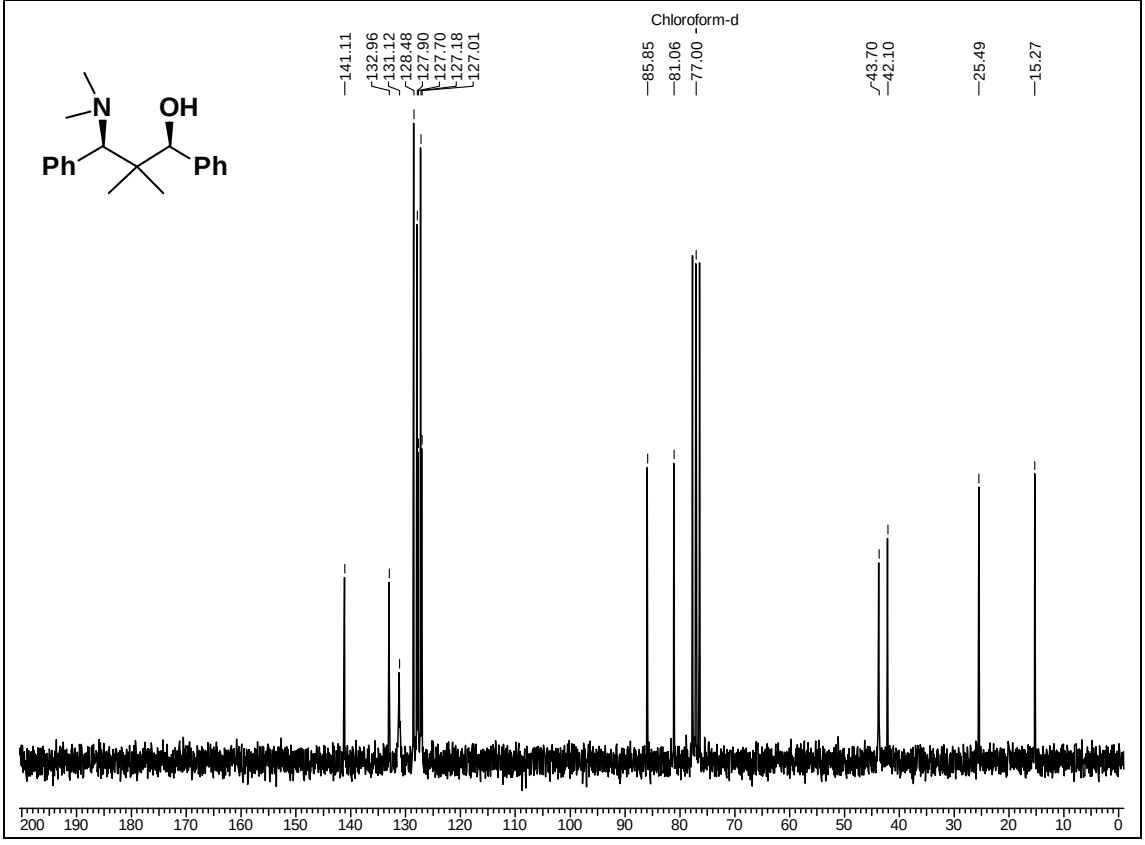
DEPT NMR Spectrum of compound **4**



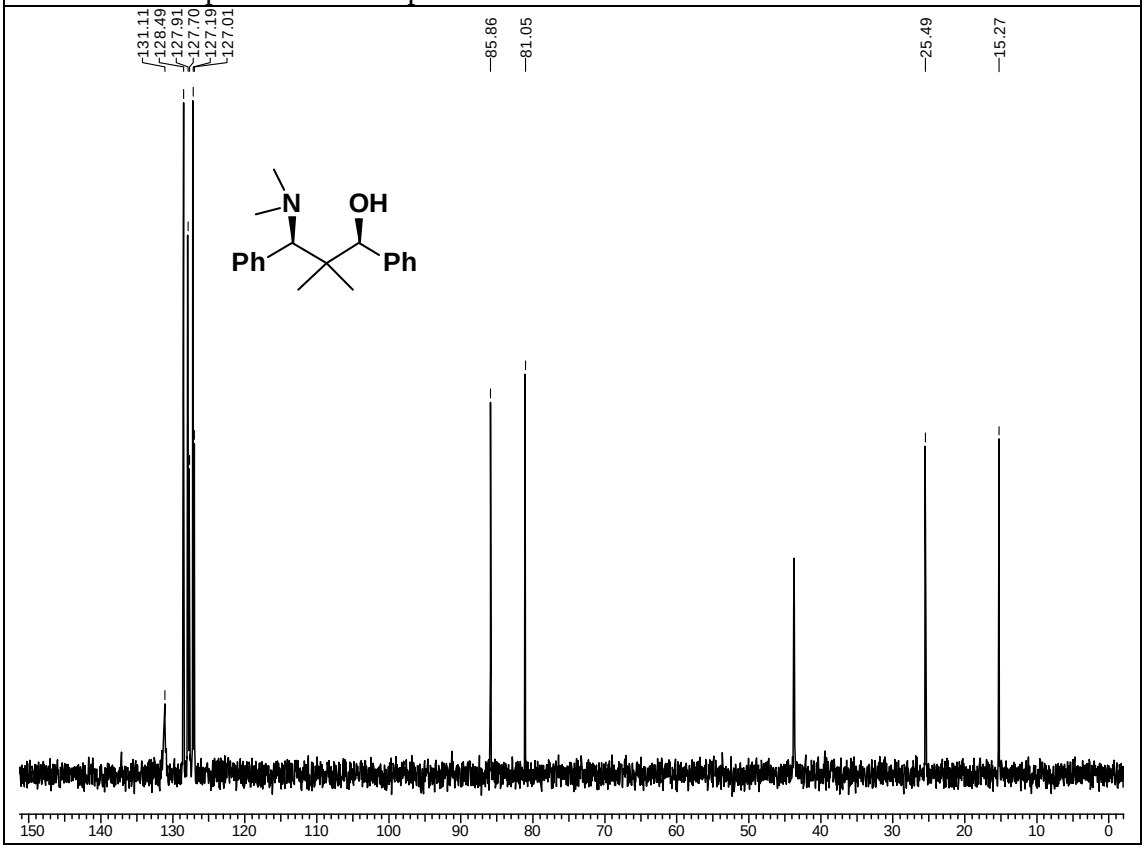
^{1}H-NMR of compound **5** ($CDCl_3$, 200MHz)



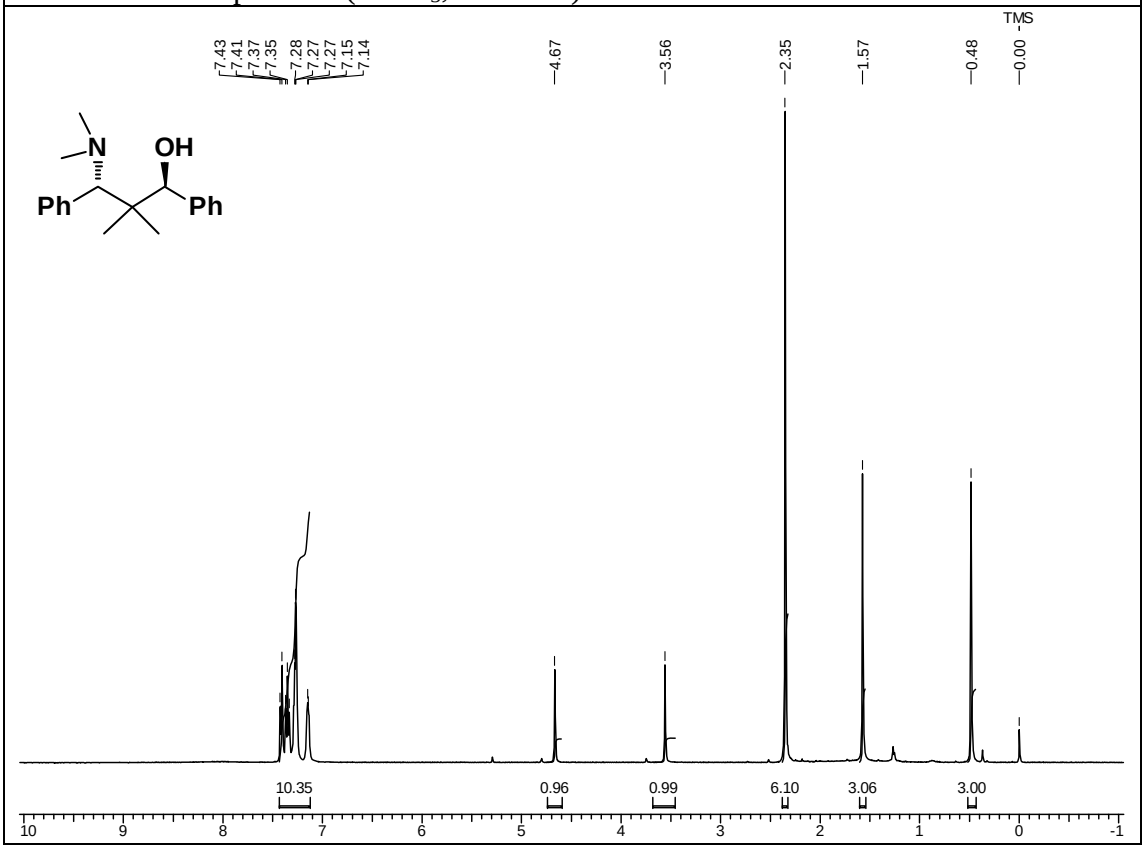
^{13}C-NMR of compound **5** ($CDCl_3$, 50.32MHz)



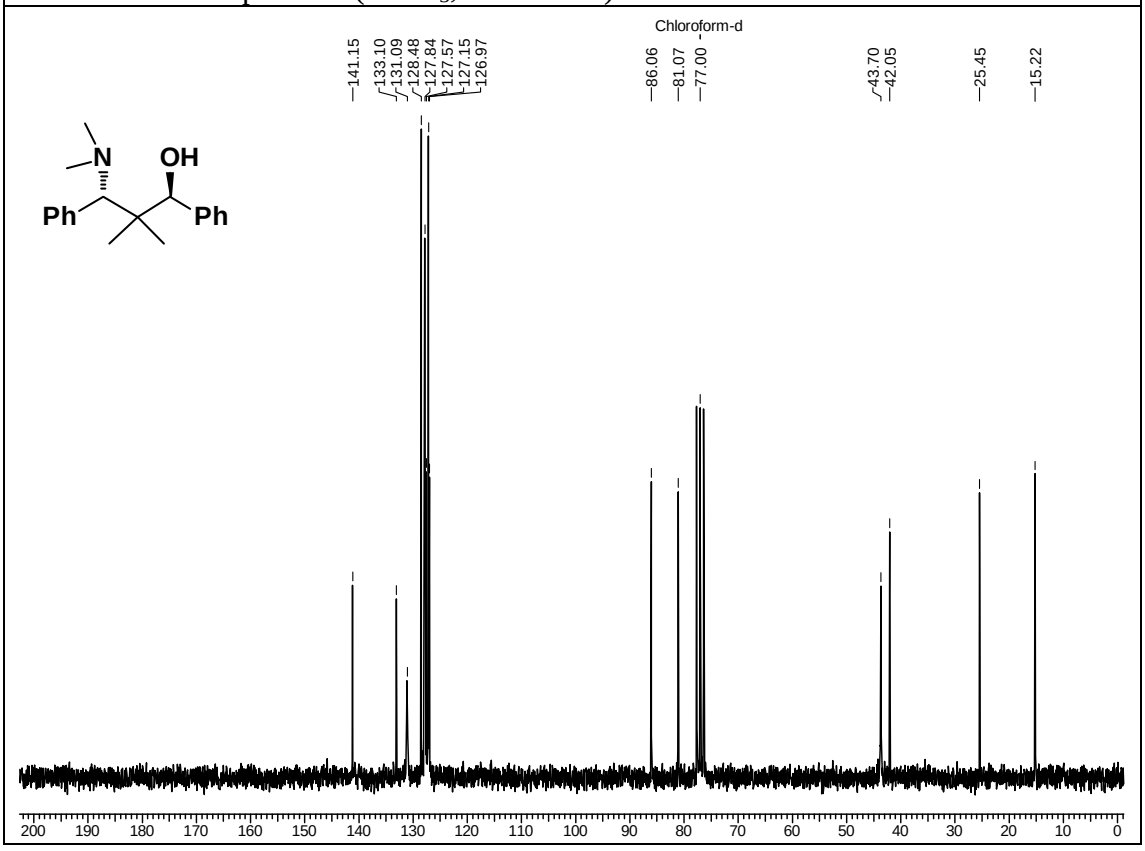
DEPT NMR Spectrum of compound **5**



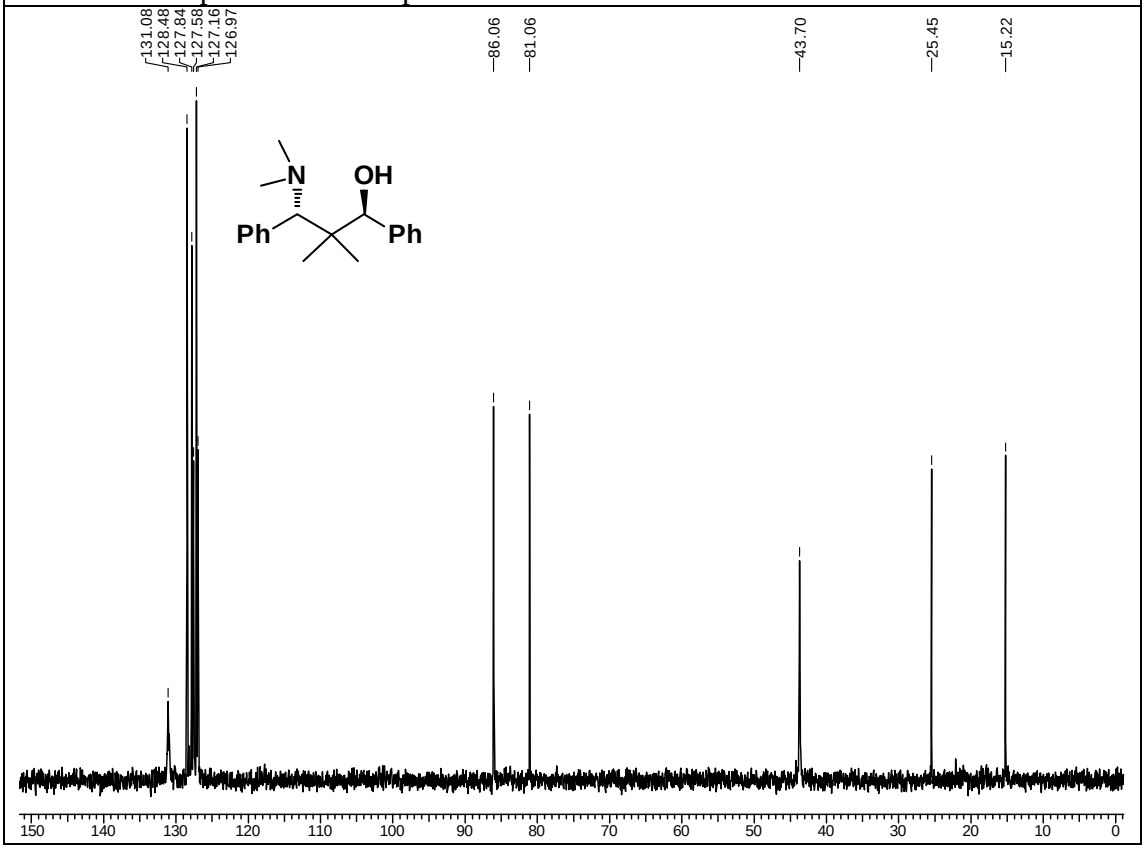
^{1}H-NMR of compound **6** ($CDCl_3$, 200MHz)



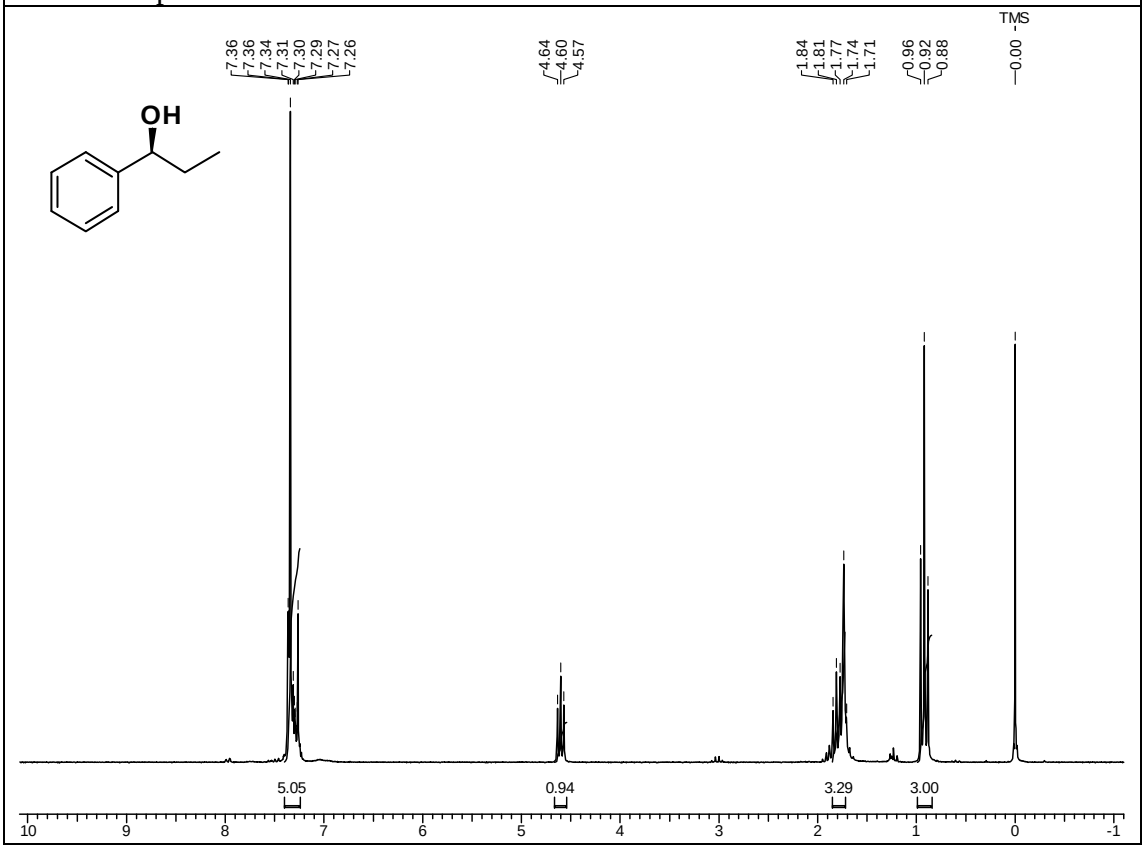
^{13}C-NMR of compound **6** ($CDCl_3$, 50.32MHz)



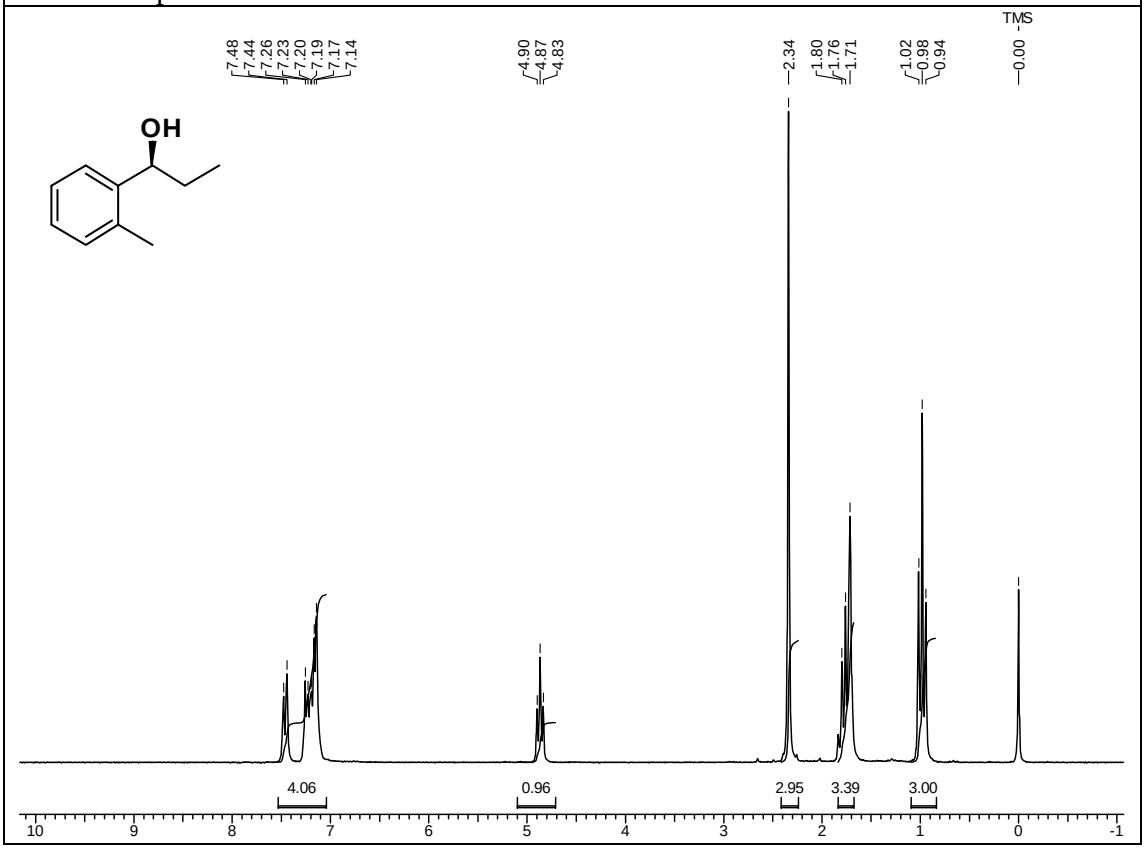
DEPT NMR spectrum of compound **6**



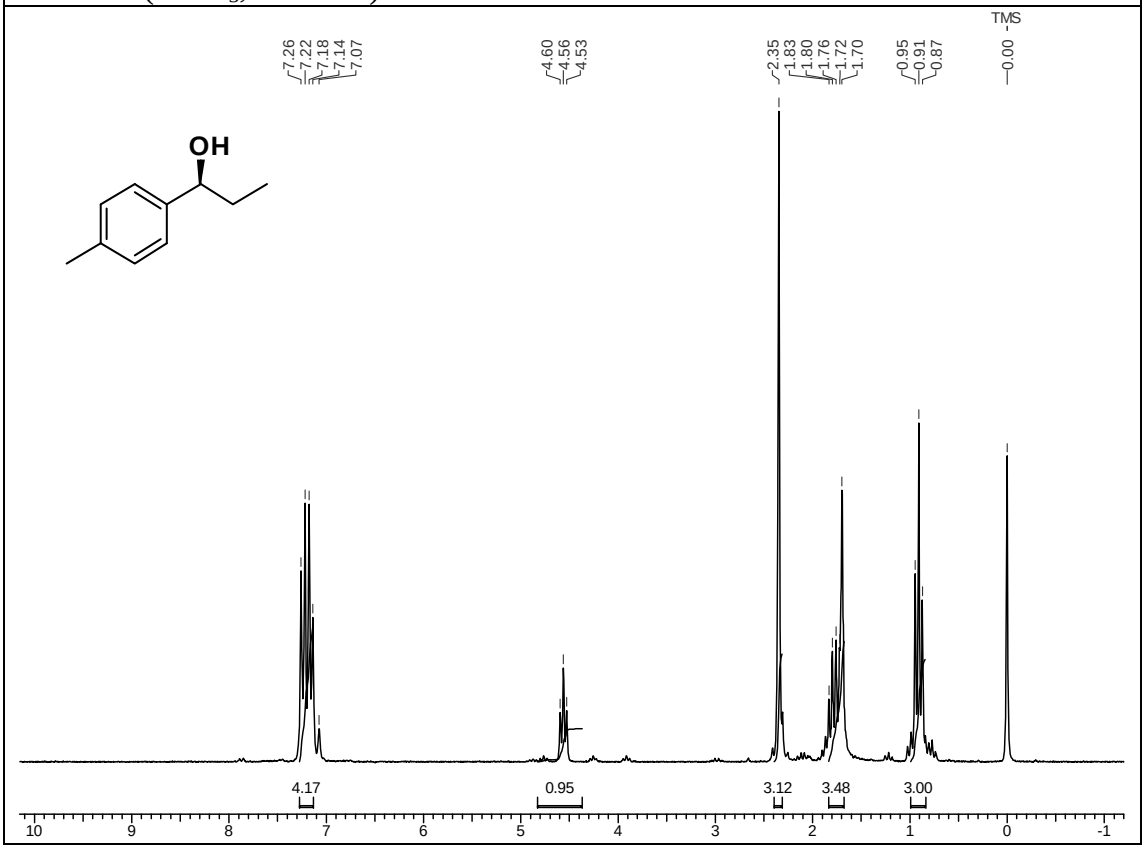
^{1}H-NMR spectrum



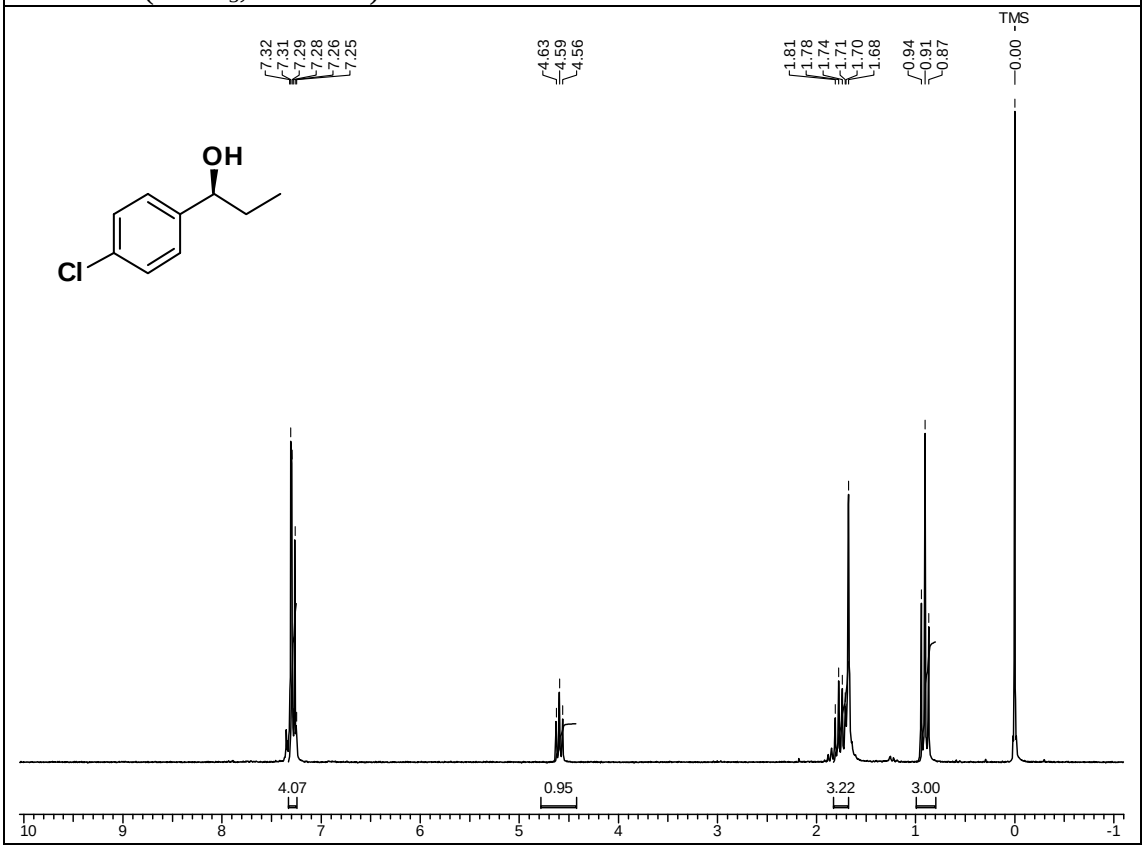
^{1}H-NMR spectrum



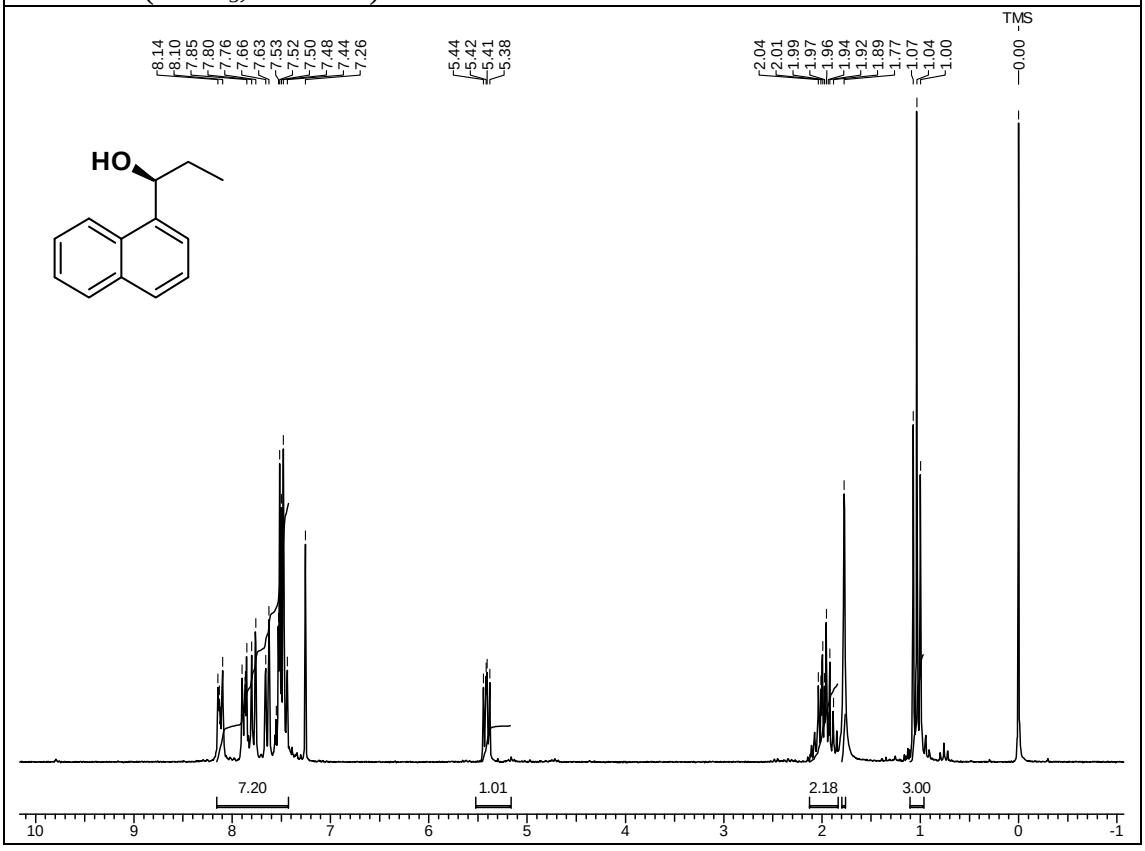
^{1}H-NMR ($CDCl_3$, 200MHz)



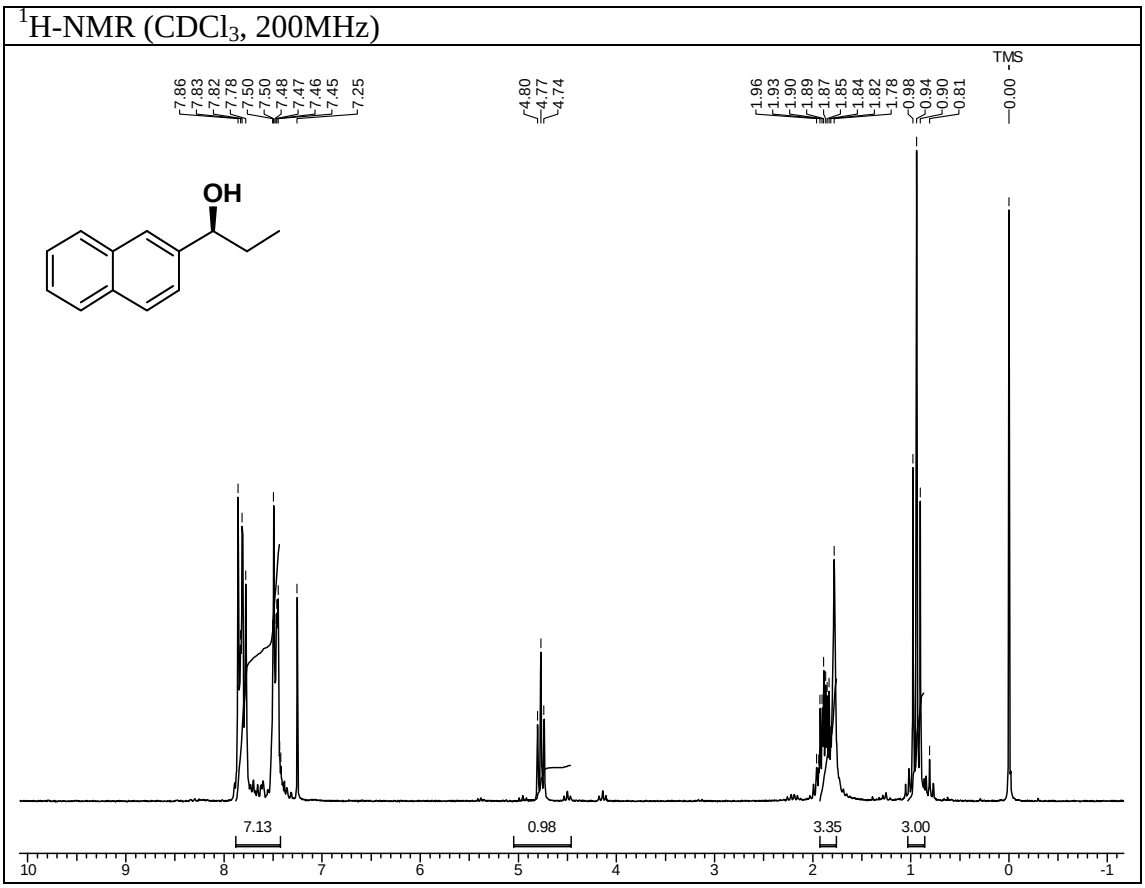
^{1}H-NMR ($CDCl_3$, 200MHz)



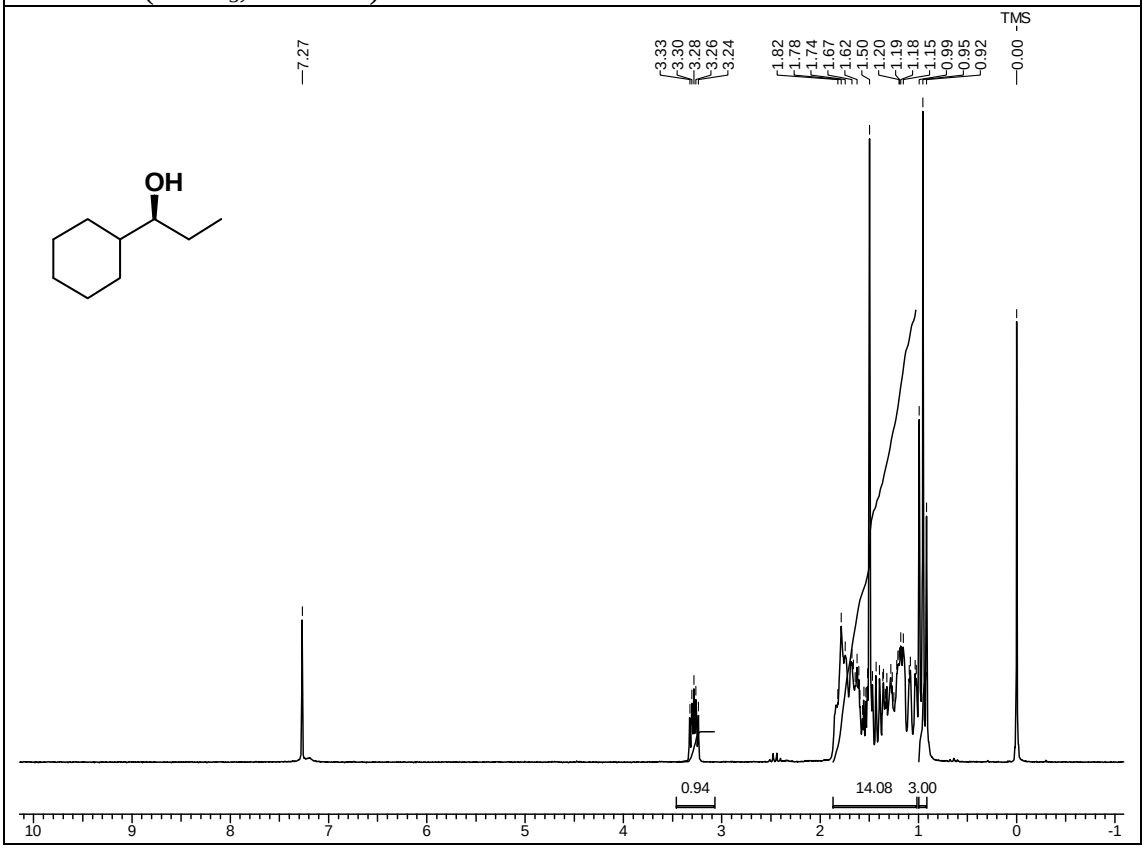
^{1}H-NMR ($CDCl_3$, 200MHz)



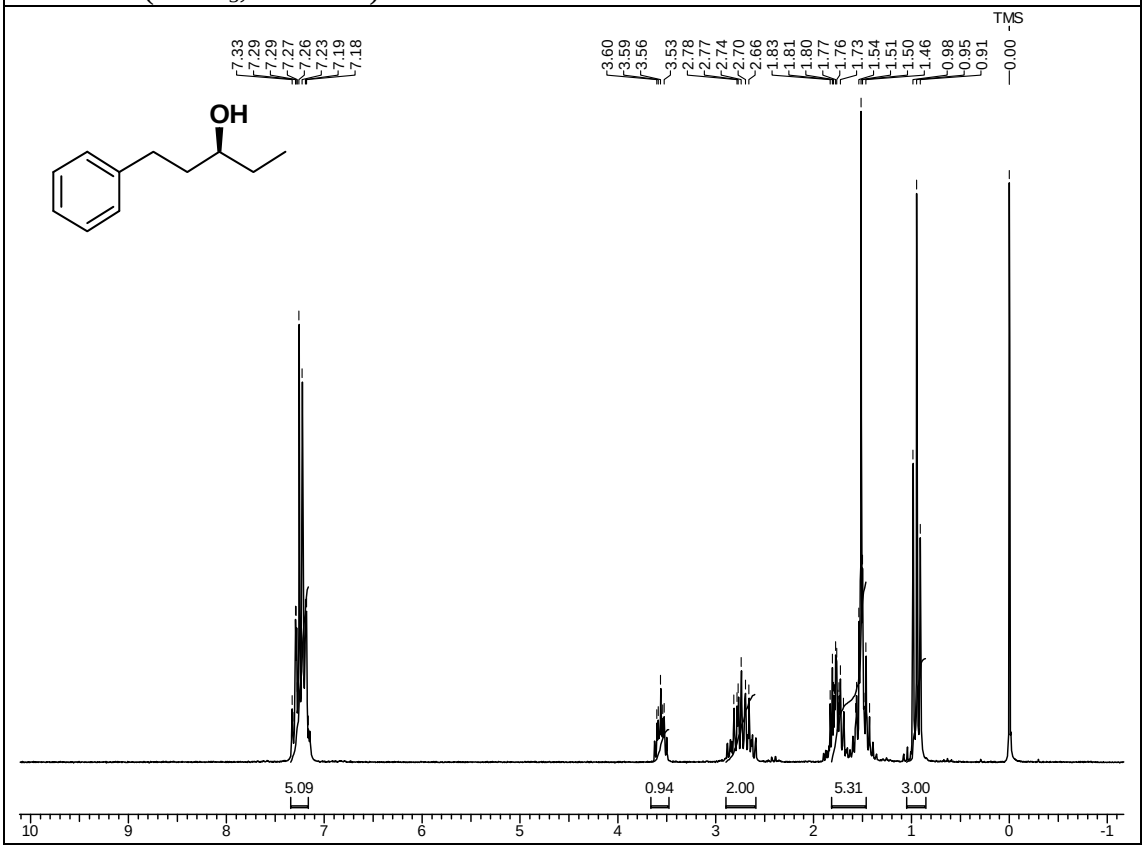
^{1}H-NMR ($CDCl_3$, 200MHz)



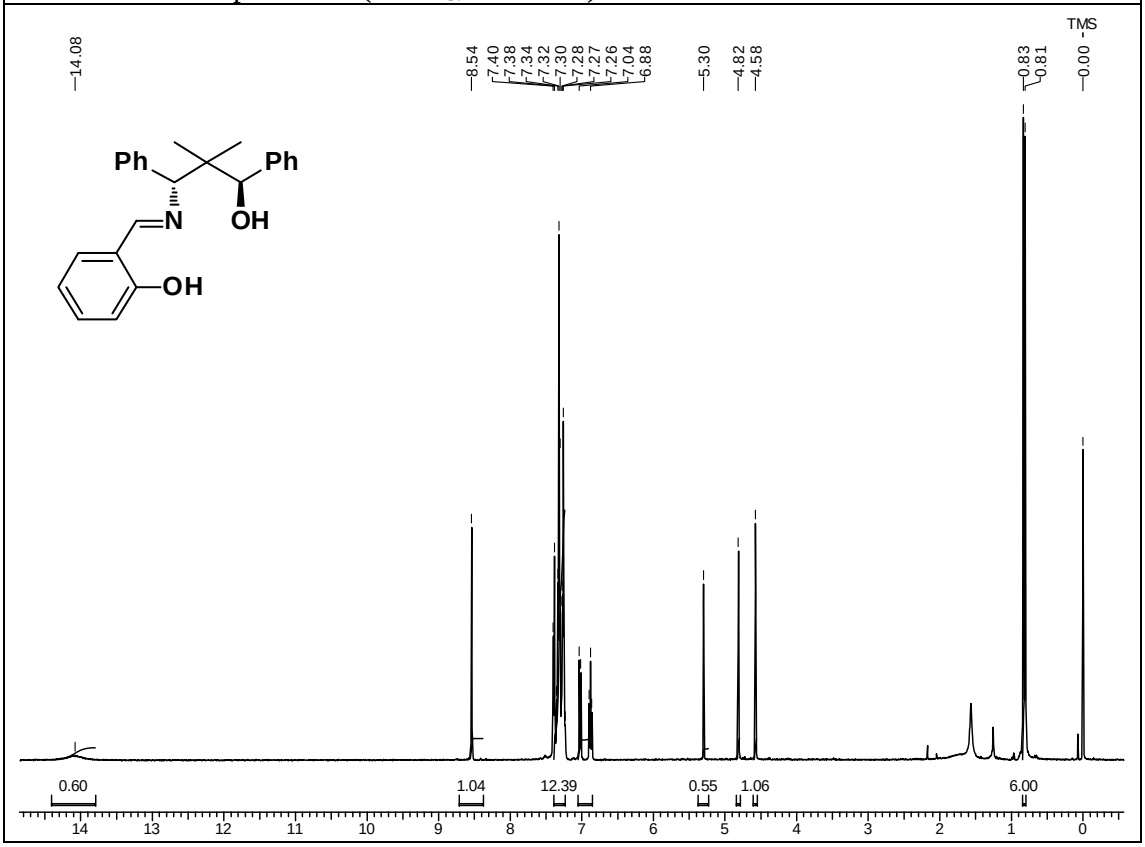
^{1}H-NMR ($CDCl_3$, 200MHz)



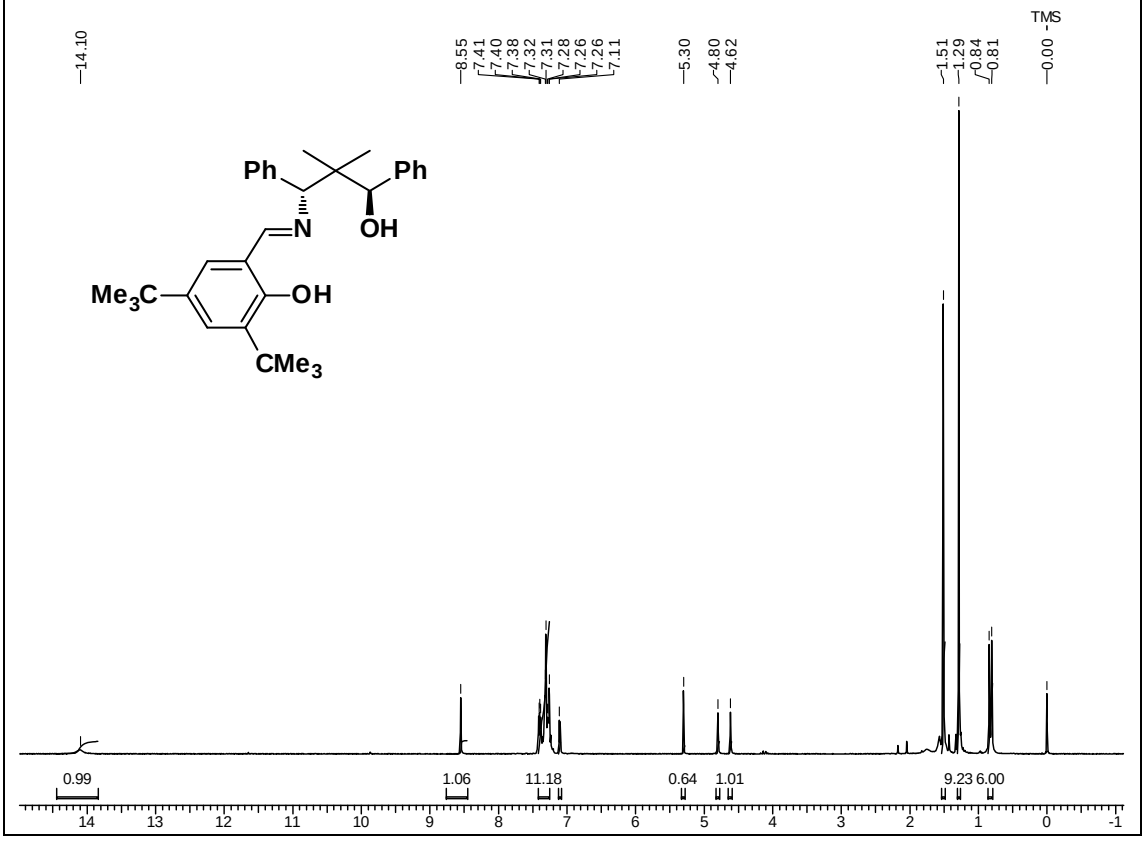
^{1}H-NMR ($CDCl_3$, 200MHz)



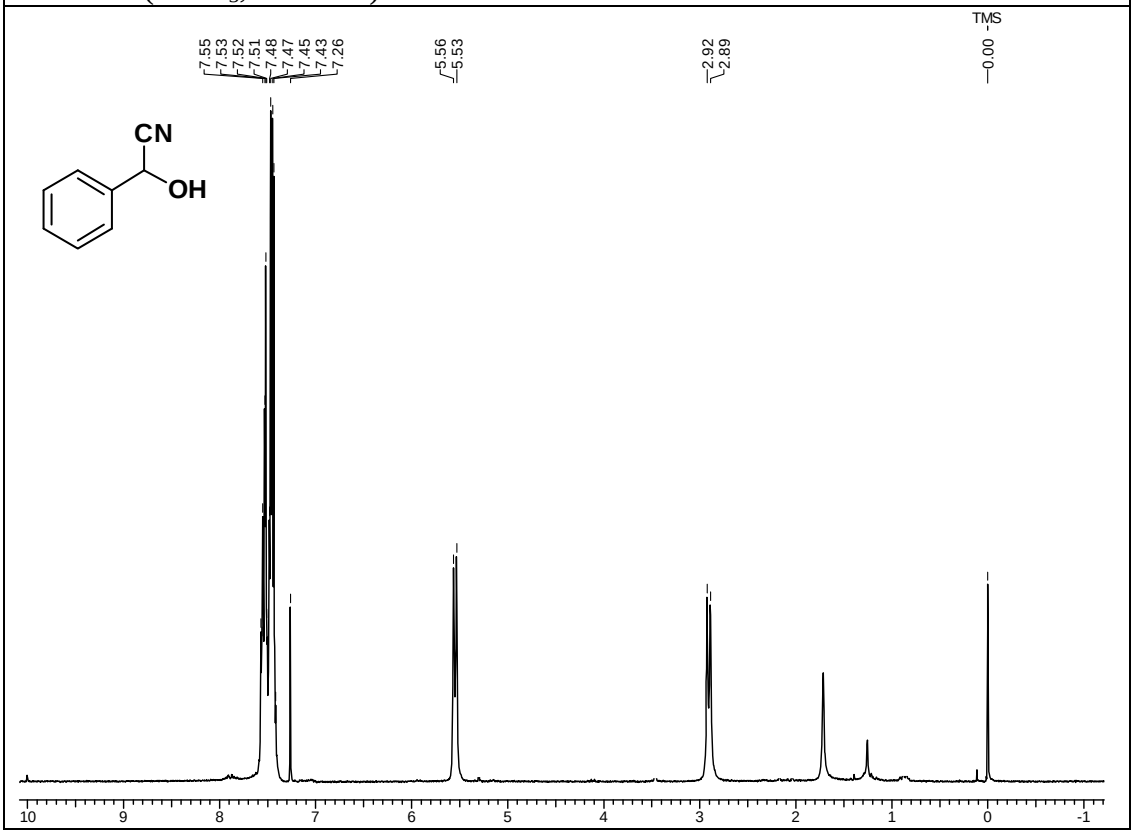
^{1}H-NMR of compound **26** ($CDCl_3$, 200MHz)



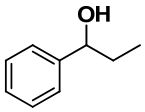
^{1}H-NMR of compound **27** ($CDCl_3$, 200MHz)



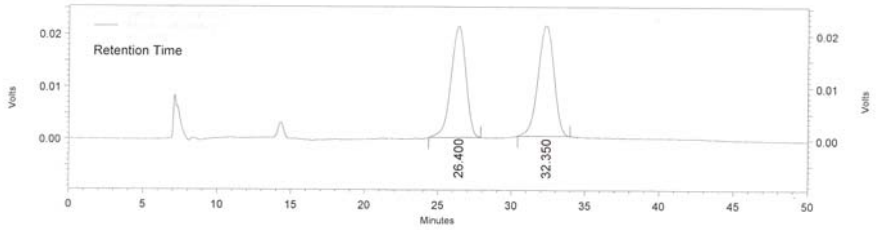
^{1}H-NMR ($CDCl_3$, 200MHz)



Determination of enantiomeric excess for Et_2Zn addition product

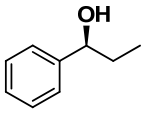


(±)

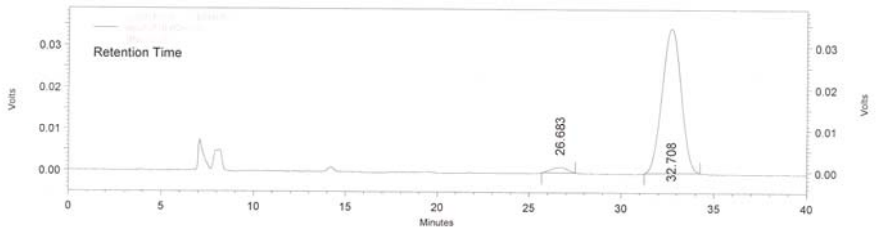


Detector A - 1
(254nm)

Pk #	Retention Time	Area	Area %	Height	Height Percent
1	26.400	1497853	48.486	21277	50.17
2	32.350	1591421	51.514	21130	49.83
Totals		3089274	100.000	42407	100.00



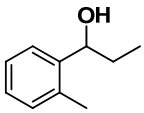
S-(-)



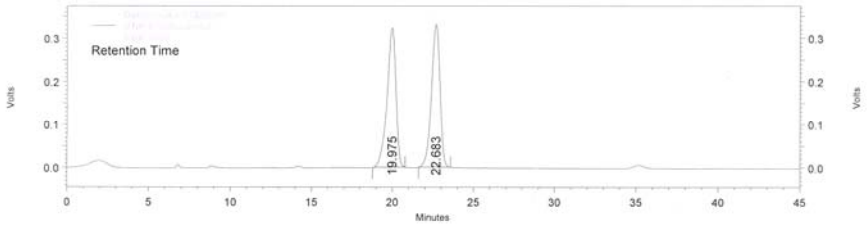
Detector A - 1
(254nm)

Pk #	Retention Time	Area	Area %	Height	Height Percent
1	26.683	82847	3.246	1352	3.76
2	32.708	2469452	96.754	34623	96.24
Totals		2552299	100.000	35975	100.00

97:3 er, Chiracel OD-H column; ^{i}PrOH:*n*-Hexane (2:98); 0.5 mL/min.; 254 nm. Retention time: t_R = 26.683 min, t_R = 32.708 min.

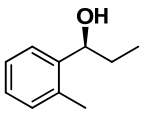


(±)

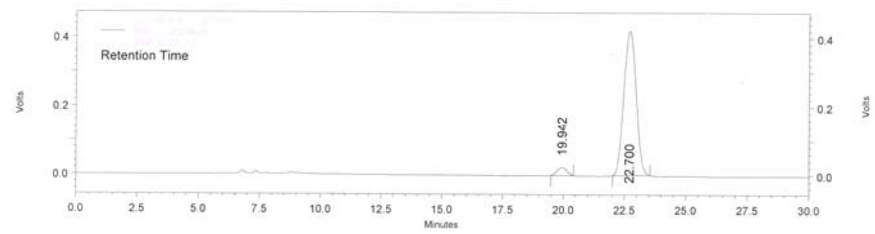


Detector A - 1
(220nm)

Pk #	Retention Time	Area	Area %	Height	Height Percent
1	19.975	12305208	50.216	323459	49.41
2	22.683	12199155	49.784	331238	50.59
Totals		24504363	100.000	654697	100.00



S-(-)

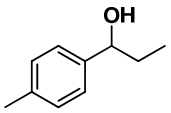


Detector A - 1
(220nm)

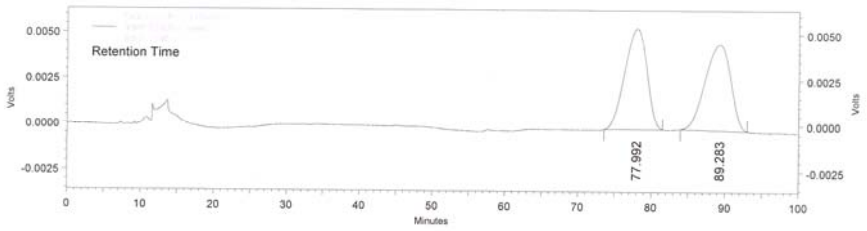
Pk #	Retention Time	Area	Area %	Height	Height Percent
1	19.942	645574	4.195	23386	5.26
2	22.700	14742106	95.805	421241	94.74
Totals		15387680	100.000	444627	100.00

96:4 er, Kromasil-5-Amycoat column; EtOH:*n*-Hexane (2:98); 0.5 mL/min.; 220 nm.

Retention time: t_R = 19.942 min, t_R = 22.70 min.

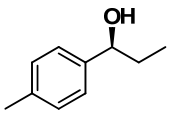


(±)

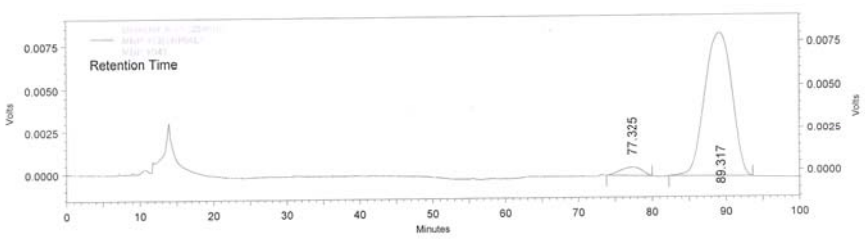


Detector A - 1
(254nm)

Pk #	Retention Time	Area	Area %	Height	Height Percent
1	77.992	1152768	50.320	5522	53.86
2	89.283	1138101	49.680	4731	46.14
Totals		2290869	100.000	10253	100.00



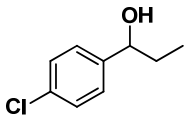
S-(-)



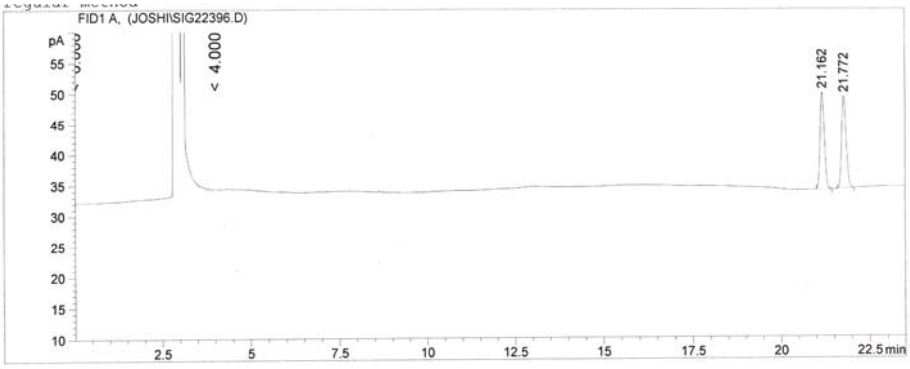
Detector A - 1
(254nm)

Pk #	Retention Time	Area	Area %	Height	Height Percent
1	77.325	105531	4.649	526	5.91
2	89.317	2164326	95.351	8368	94.09
Totals		2269857	100.000	8894	100.00

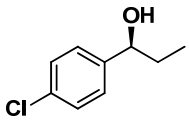
95:5 er, Chiracel OD-H column; ^{i}PrOH:*n*-Hexane (0.5:99.5); 0.5 mL/min.; 254 nm. Retention time: t_R = 77.325 min, t_R = 89.317 min.



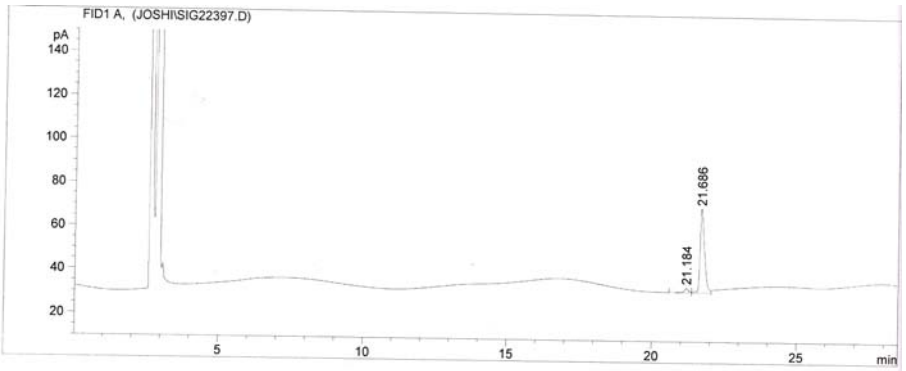
(±)



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	21.162	BB	0.1318	135.08836	15.95500	49.77854
2	21.772	BB	0.1408	136.29033	15.16953	50.22146
Totals :				271.37869	31.12452	

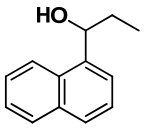


S-(-)

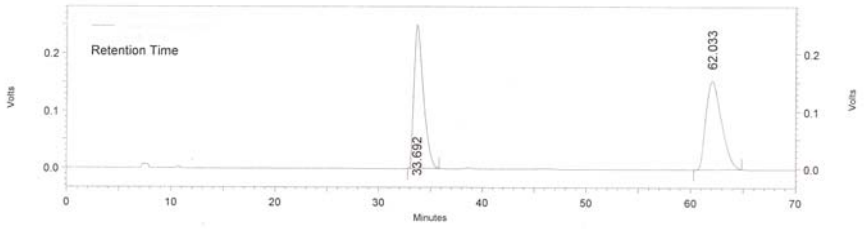


Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	21.184	VV	0.1616	20.44768	1.89899	4.78068
2	21.686	VV	0.1590	407.26746	38.62247	95.21932
Totals :				427.71513	40.52146	

95:5 er; GC analysis (Cp-Cyclodextrin-B-2,3,6-M-19 capillary column), at 100 ^{o}C (1 min.), 10 deg./min., 120 ^{o}C (30 min.), Retention time: t_R = 21.184 min, t_R = 21.686 min.

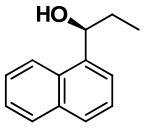


(±)

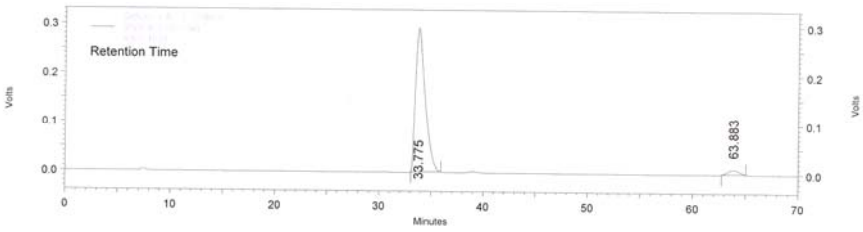


Detector A - 1
(254nm)

Pk #	Retention Time	Area	Area %	Height	Height Percent
1	33.692	15810270	49.759	249858	61.73
2	62.033	15963252	50.241	154922	38.27
Totals		31773522	100.000	404780	100.00



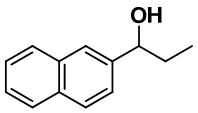
S-(-)



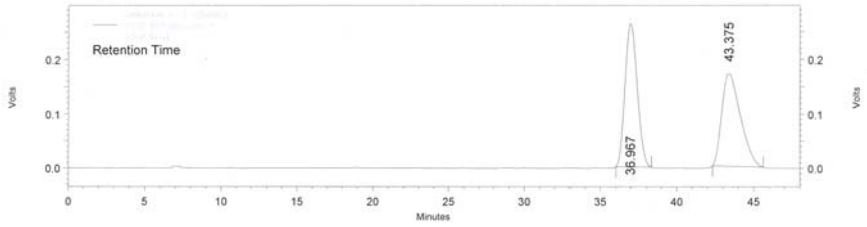
Detector A - 1
(254nm)

Pk #	Retention Time	Area	Area %	Height	Height Percent
1	33.775	18876381	96.553	293599	97.03
2	63.883	673971	3.447	8975	2.97
Totals		19550352	100.000	302574	100.00

97:3 er, Chiracel OD-H column; ^{i}PrOH:*n*-Hexane (4:96); 0.5 mL/min.; 254 nm. Retention time: t_R = 33.775 min, t_R = 63.883 min.

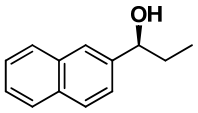


(±)

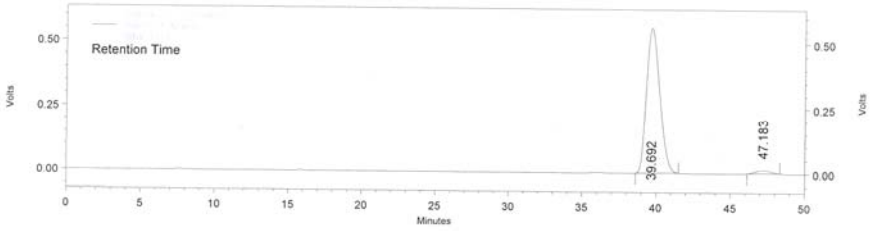


Detector A - 1
(254nm)

Pk #	Retention Time	Area	Area %	Height	Height Percent
1	36.967	14657041	50.468	262819	60.63
2	43.375	14385217	49.532	170646	39.37
Totals		29042258	100.000	433465	100.00



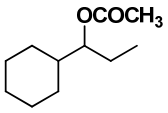
***S*-(-)**



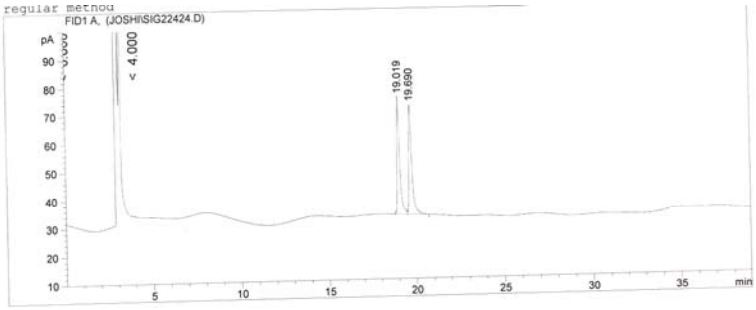
Detector A - 1
(254nm)

Pk #	Retention Time	Area	Area %	Height	Height Percent
1	39.692	34968899	97.512	560609	97.88
2	47.183	892243	2.488	12139	2.12
Totals		35861142	100.000	572748	100.00

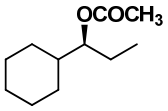
97.5:2.5 er, Chiracel OD-H column; ^{i}PrOH:*n*-Hexane (4:96); 0.5 mL/min.; 254 nm. Retention time: t_R = 39.692 min, t_R = 47.183 min.



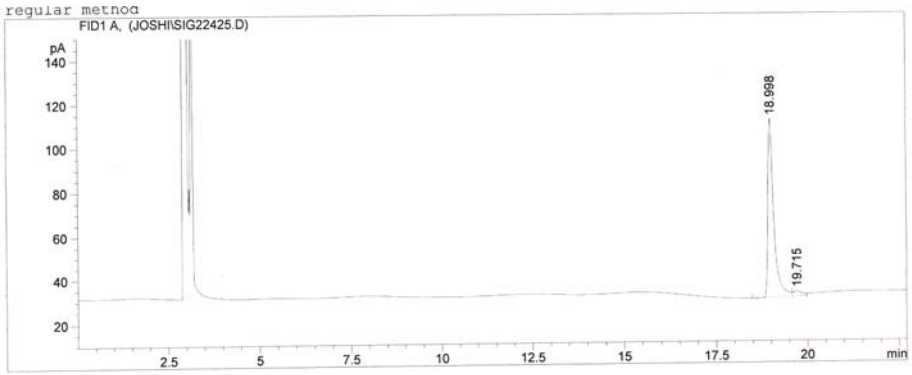
(±)



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	19.019	PV	0.1592	453.23935	42.25035	49.24873
2	19.690	VB	0.1759	467.06738	39.52060	50.75127
Totals :				920.30673	81.77094	

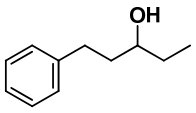


S-(-)

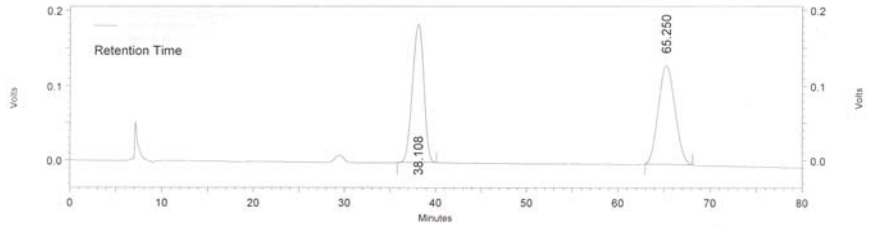


Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	18.998	VV	0.1649	921.42261	82.12567	95.81315
2	19.715	VV	0.2193	40.26435	2.50790	4.18685
Totals :				961.68696	84.63357	

96:4 er; GC analysis (Cp-Cyclodextrin-B-2,3,6-M-19 capillary column), at 100 ^{o}C (1 min.), 10 deg./min., 120 ^{o}C (30 min.), Retention time: t_R = 18.998 min, t_R = 19.715 min.

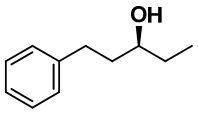


(±)

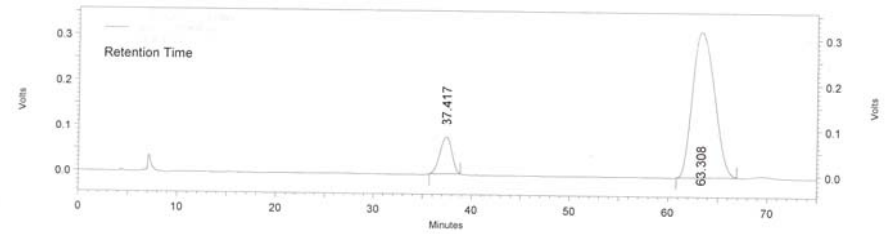


Detector A - 1
(220nm)

Pk #	Retention Time	Area	Area %	Height	Height Percent
1	38.108	16123020	49.090	184318	58.15
2	65.250	16720986	50.910	132638	41.85
Totals		32844006	100.000	316956	100.00



***S*-(+)**



Detector A - 1
(220nm)

Pk #	Retention Time	Area	Area %	Height	Height Percent
1	37.417	6818068	12.146	80978	20.18
2	63.308	49317604	87.854	320208	79.82
Totals		56135672	100.000	401186	100.00

88:12 er, Chiracel OD-H column; ^{i}PrOH:*n*-Hexane (2:98); 0.5 mL/min.; 220 nm. Retention time: t_R = 37.417 min, t_R = 63.308 min.