Declaration

I hereby declare that this thesis describes my own research work carried out since my registration for the degree of Master of Philosophy in August, 1996, and that it has not previously been included in a thesis, dissertation or report presented to this or any other institution for a degree, diploma, or other qualification.

Pui-Erh Tong

August, 1998

ACKNOWLEDGMENT

I would like to express my heartful thanks to my supervisors Prof. Albert S. C. Chan and Dr. P. Li for their valuable advice, encouragement and discussion throughout the course of my work and for their valuable comments on the draft of this thesis. Their novel ideas and devoted attitude in research have made my study a rewarding experience.

I wish to give my special thanks to Dr. Zhang Fu-Yao for his profound concern and earnest teachings.

I wish also to thank Dr. Benzie for her valuable suggestions and recommendations of this thesis.

I am grateful to all my colleagues in our laboratory for their valuable advice, discussion and help. They are Associate Prof. Ren Chang-Yu, Prof. Li Xing-Shu, Prof. Cao Rong, Dr. Xue Guo-Ping, Dr. Chen Chih-Chiang, Dr. Yang San-Ming, Dr. Yang Li-Wei, Dr. Pai Cheng-Chao, Dr. Shi Ji-Cheng, Dr. Fan Qing-Hua, Dr. Yan Ming, Dr. Li Yue-Ming, Mr. Hu Wen-Hao, Mr. Lin Chi-Ching, Ms. Lin Ching-Wen, Ms. Tong Siu-Kuen, Ms. Huang Qiao-Hung, Mr. Su Li-Ming and Mr. Chen Yi-Xin.

I am obliged to all staff, especially the technical service crew, of the Department of Applied Biology and Chemical Technology for the rewarding experience I enjoyed.

I would like to acknowledge the Research Committee of The Hong Kong Polytechnic University for the award of studentship and the conference attendance grant.

I thank my family and my girl-friend, Stephanie for their support and concern in the past two years.

I thank all my friends for always being there for me.

Pui-Erh Tong

August, 1998

Abstract of thesis entitled "New Enantioselective Catalysts Based on Chiral Amino Alcohols"

Submitted by Pui-Erh Tong

For the Degree of Master of Philosophy

at The Hong Kong Polytechnic University in August 1998

Enantioselective catalysts based on chiral amino alcohols and their derivatives demonstrate unique features in asymmetric catalytic reactions because the chiral amino alcohols can be easily obtained through reduction of readily available chiral amino acids. The catalysts based on them have been applied in a large variety of asymmetric reactions such as asymmetric reduction, asymmetric diethylzinc addition, asymmetric trimethylsilylcyanation, asymmetric alkylation, asymmetric aldol reaction, etc. Because of their wide applications, ease of synthesis and recovery, new enantioselective catalysts based on chiral amino alcohols are worth exploring.

Several previous studies involved the use of 2-amino-1,2-diphenylethanol and 2-amino-2-phenylethanol as chiral ligands. In this study, the cyclohexyl analogs of these ligands have been sucessfully synthesized by hydrogenating the phenyl rings. Furthermore the properties of these new ligands in asymmetric borane reduction of prochiral ketones and asymmetric conjugate addition of diethylzinc to enones have been studied.

The objectives of this project are the design and synthesis of a series of new chiral amino alcohols containing cyclohexyl groups, their reactivity and enantioselectivity are compared with their phenyl counterparts.

Although a number of successful catalysts based on the use of chiral oxazaborolidines have been explored which give high e.e.'s (enantioselective excess) for the desired chiral alcohols, few examples focus on the investigation of steric and electronic effects of substituents on them. In this study, the phenyl rings on 2-amino-2-phenylethanol and 2-amino-1,2-diphenylethanol were hydrogenated to 2-amino-2-cyclohexylethanol and 2-amino-1,2-dicyclohexylethanol, respectively. The sterically more demanding cyclohexyl analogs are found to be consistently more effective than their phenyl counterparts (the former with e.e. value up to 94.7% and the biggest difference in e.e. between the former and the latter was 36.5%). Moreover, a supplement of the existing mechanism is proposed.

Recently the catalytic asymmetric conjugate addition of organometallic reagents to prochiral enones has been attempted. However the enantioselectivities of these processes are relatively low. In this study, the catalyst derived from N,N-dimethyl-2-amino-1,2-dicyclohexylethanol has been found to give good e.e.'s (up to 86.7% e.e.) for a wide variety of enones. Moreover, the enantioselectivity of this catalyst is significantly better than its phenyl analog (the biggest difference in e.e. between the former and the latter was 48.8%).

In conclusion, the modification of two existing chiral amino alcohols has been proved to be successful by hydrogenating their phenyl rings to cyclohexyl rings, this study has furnished the chemistry of using chiral amino alcohols as ligands in asymmetric catalytic reactions.

Contents

List of figures and tables included in this thesis

List of figures :

List of tables :

Chapter 1 Introduction

1.1 Chiral amino alcohols in asymmetric catalysis

1.1.1 General introduction

Chiral amino alcohols are playing an important role in asymmetric catalysis due to their ease of synthesis, recovery and most importantly, good reactivity and enantioselectivity in a wide variety of asymmetric reactions. A series of chiral amino alcohols and their derivatives have been developed as shown in fig. 1-1 and the chirality of these compounds has been utilized in many asymmetric processes. **1** is applied in asymmetric borane-reduction of ketones,[1] **2** is applied in asymmetric trimethylsilylcyanation of aldehydes,[2] **3** and **4** are applied in asymmetric addition of diethylzinc to aldehydes,[3] **3** and **5** are applied in asymmetric conjugate addition of diethylzinc to enones,[4] **6** is applied in asymmetric aldol reaction of aldehydes,[5] **7** and **8** are applied in asymmetric alkylation of carboxylic acids,[6] **9** is applied in asymmetric transfer hydrogenation of ketones,[7] **3** and **10** are applied in asymmetric Reformatsky reaction of aldehydes,[8] **11** is applied in asymmetric hydroformylation of styrene,[9] **12** is applied in asymmetric hydrogenation of activated ketones.[10]

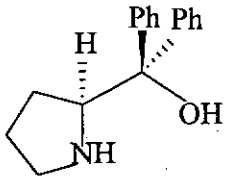
Recently, (1R,2S)-2-amino-1,2-diphenylethanol (**13**) was found to be a very effective chiral ligand in different kinds of asymmetric catalytic reactions, especially in asymmetric borane-reduction of ketones[11] and asymmetric transfer hydrogenation.[12] The derivatives[44] based on **13** (fig. 1-2) have also been synthesized and it has been found that most of them

demonstrate very good enantioselectivities in a variety of catalytic asymmetric reactions.

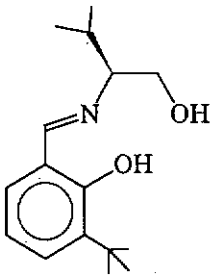
Although several reports have suggested that chiral ligands containing cyclohexyl groups give higher enantioselectivity than their phenyl analogs [35-37], this modification has not yet been applied to chiral amino alcohol. It may be due to the lack of convenient synthetic methods starting from existing chiral amino alcohols to their cyclohexyl counterparts. In this study, the synthesis of chiral amino alcohols containing cyclohexyl groups has been explored. The applications of these new chiral ligands to two asymmetric catalytic reactions : borane-reduction of ketones and conjugate addition of diethylzinc to enones have been systematically investigated. The reactivity and enantioselectivity have been compared to their phenyl analogs.

A brief review of the above two catalytic reactions is given in **1.1.2** and **1.1.3** of Chapter one. The review about modification of existing chiral ligands by hydrogenating the phenyl rings on them is given in **1.1.4** of Chapter 1. The objective of this work is given in **1.2**. Experimental plan and synthetic procedures are given in Chapter 2. It is divided into three parts : **2.1** Synthesis of new chiral amino alcohols containing cyclohexyl groups, describes the hydrogenation of phenyl rings on chiral amino alcohols and synthesis of their corresponding oxazaborolidines. **2.2** Synthesis of N-methylated and N,N-dimethylated chiral amino alcohols with 1,2- dicyclohexyl backbone and their Ni(II) catalysts for asymmetric conjugate addition. **2.3** gives detailed experimental procedures. Chapter 3

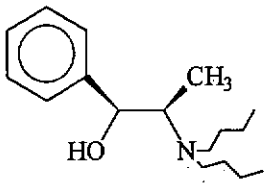
describes the catalytic properties of these modified ligands in the two asymmetric reactions, compared with their phenyl counterparts.



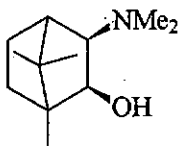
(S)-**1**



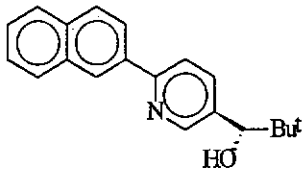
(S)-**2**



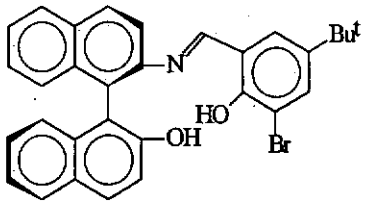
(1S,2R)-**3**



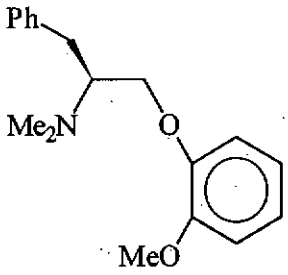
(1S,2R) -**4**



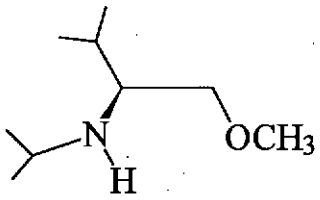
(S) -**5**



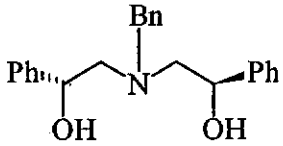
(S)-**6**



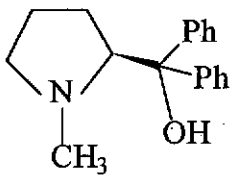
(S)- **7**



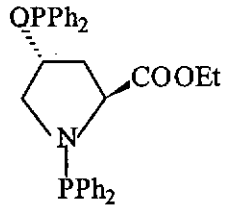
(S)-**8**



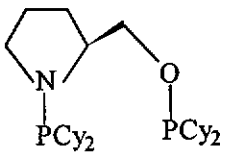
(R,R)-**9**



(S)-**10**



(2S,4R)-**11**



(S)-**12**

Fig. 1-1 Examples of highly effective chiral amino alcohols in various kinds of asymmetric catalytic reactions reported [1-10]

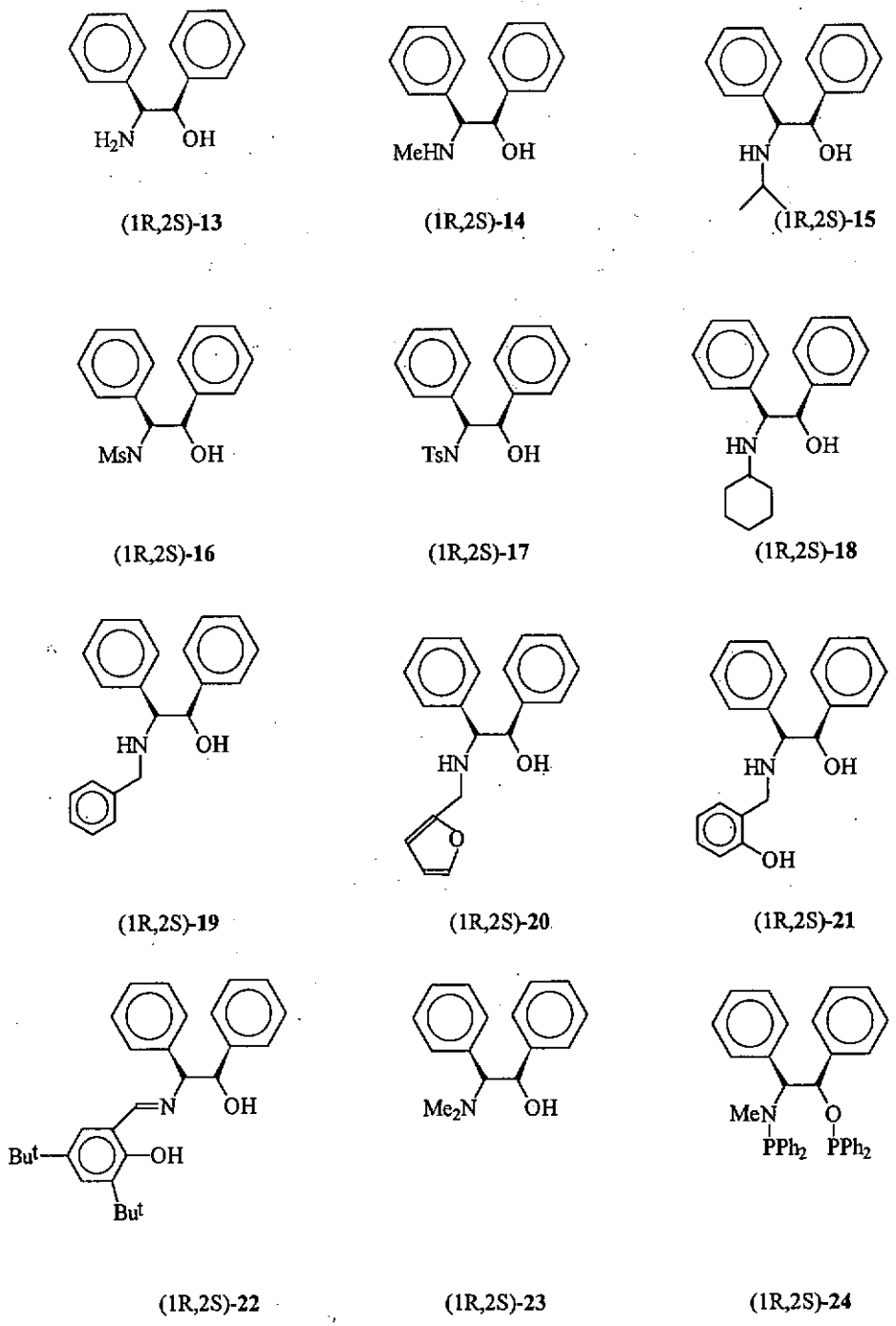
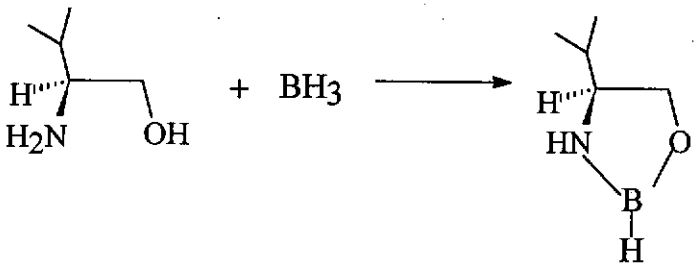


Fig. 1-2 Chiral 2-amino-1,2-diphenylethanol and some of its derivatives[44]

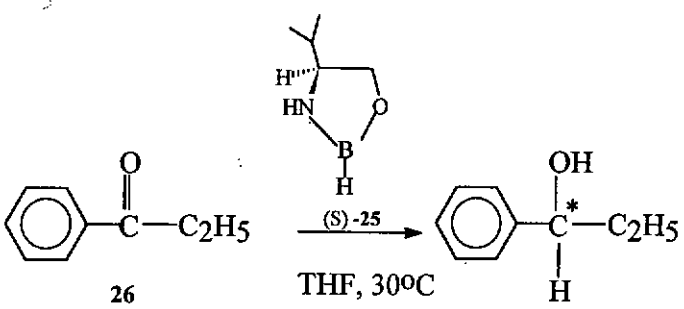
1.1.2 Asymmetric borane-reduction of prochiral ketones

Enantioselective reduction of prochiral ketones leading to chiral secondary alcohols is a topic of current interest.[13] One of the most successful methods was based on the use of chiral 1, 3, 2-oxazaborolidines as catalysts, a method which was developed by Itsuno et al.[14] as early as 1981. The amino alcohol which was derived from α-amino acid was used to prepare the oxazaborolidine complex **25** [Eq. 1]. A moderate e.e. value (60%) was obtained on reduction of propriophenone (**26**) and stoichiometric amount of ligand was needed [Eq. 2].



[Eq. 1

(S) -25



26

THF, 30°C

[Eq. 2]

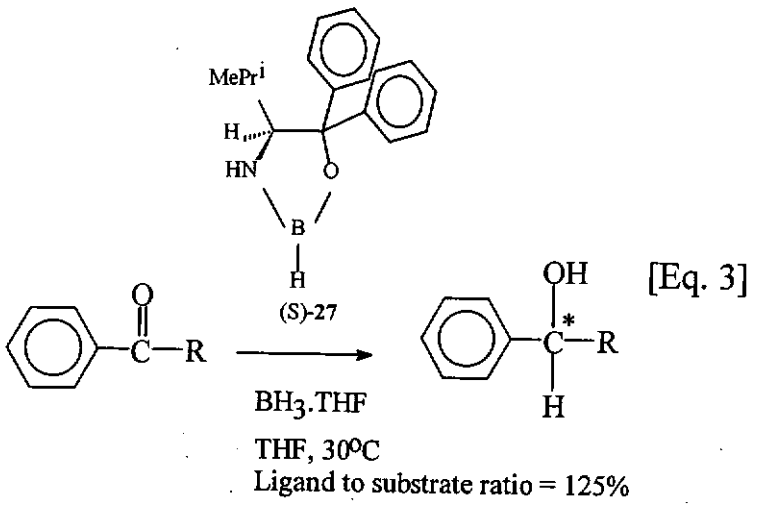
Ligand to substrate ratio =125%

e.e. = 60%

Yield = 100%

In 1985, the same group of chemists synthesized (S)-(-)-2-amino-3-methyl-1,1-diphenylpentanol as chiral auxiliary.[15] The enantioselectivities were significantly improved up to 99% for the reduction of various ketones

(Table 1-1), in the presence of (S)-oxazaborolidine catalyst (**27**). However, stoichiometric amount of chiral auxiliary still could not be avoided [Eq. 3].



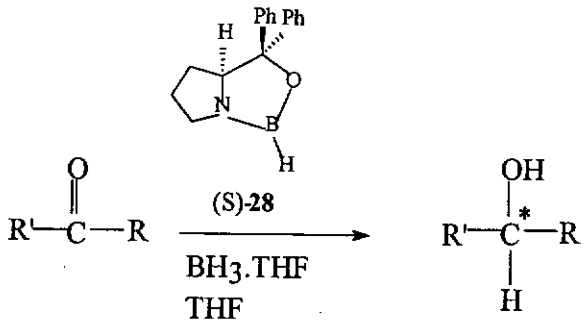
[Eq. 3]

Table 1-1 Asymmetric borane-reduction of ketones by (S)-27 [15]

R	e.e.(%)	conversion(%)
Me	94	100
Et	94	100
Pr^n	96	100
Bu^n	>99	100

The first break-through was achieved by Corey et al.[16] who successfully synthesized (S)-2-[diphenylhydroxymethyl]-pyrrolidine (**1**) as chiral ligand. The corresponding (S)-1, 3, 2-oxazaborolidine (**28**) catalyzed the asymmetric borane-reduction of carbonyl compounds giving very high e.e. values (up to 97.3%) (Table 1-2). (S)-**28** was only used in catalytic amount [Eq. 4].

Moreover, it also catalyzed the reduction of aliphatic ketones with high e.e. values.



[Eq. 4]

Table 1-2 Asymmetric borane-reduction of ketones by (S)-28 [1,16,17]

R	R'	temp(°C)	e.e.(%)	conversion(%)
C_6H_5	CH_3	2	96.6	100
C_6H_5	C_2H_5	-10	96.7	100
C_6H_5	CH_2Cl	32	95.3	100
t-Bu	CH_3	-10	97.3	100

In addition to the success in developing a catalytic asymmetric borane-reduction of carbonyl componds, Corey and his coworkers demonstrated that the absolute stereochemistry of the chiral alcohols produced could be predicted.[1, 17] The prediction was confirmed and cited by many other chemists [e.g.18]. It was based on the sizes of the two alkyl groups next to the carbonyl group of the prochiral ketones as well as the configuration of the chiral ligand. The concept is depicted below (Fig. 1-3).

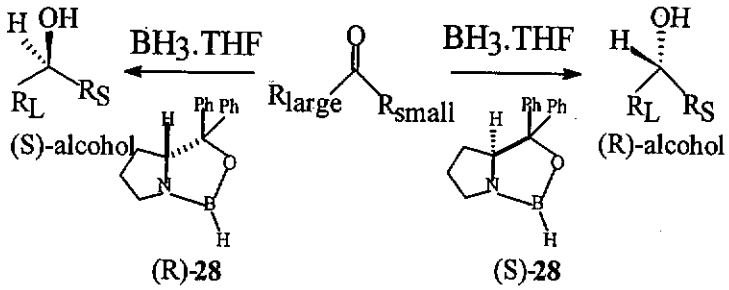
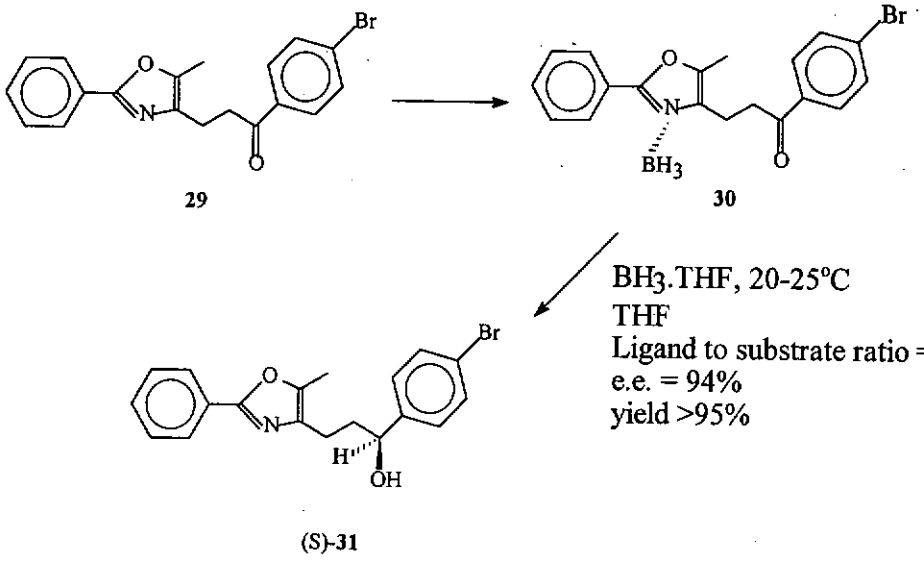


Fig. 1-3 The prediction of absolute stereochemistry of the resulting chiral alcohols produced in asymmetric borane-reduction of ketones developed by Corey et al [1, 17, 18]

The Corey's catalyst (**28**) was then investigated by many other groups of chemists. Quallich et al.[18] used this chiral catalyst (**28**) on the asymmetric reduction of ketones containing heteroatom. They also discovered that ketones, eg. **29** which contained heteroatoms are capable of coordinating with borane, particularly via nitrogen, thus the ketone could be reduced catalytically with oxazaborolidines to afford alcohols with high e.e.'s. They proved that the oxazole nitrogen was coordinating with borane competitively with the catalyst and once coordinated, the amine-borane **30** was inert under the reaction conditions. Therefore, a solution of oxazole and the catalyst in tetrahydrofuran was titrated in borane. Complete reaction was obtained with 1.7eq of borane, and the desired (S)-alcohol **31** was obtained in >90% e.e. [Eq. 5].



[Eq. 5]

(*S*)-31

Corey's catalyst also prompted a large number of investigations on the use of 1, 3, 2-oxazaborolidines as catalysts in asymmetric borane-reduction of prochiral ketones. The following is a summary of chiral oxazaborolidines synthesized by different chemists around the world (fig. 1-4).[19]

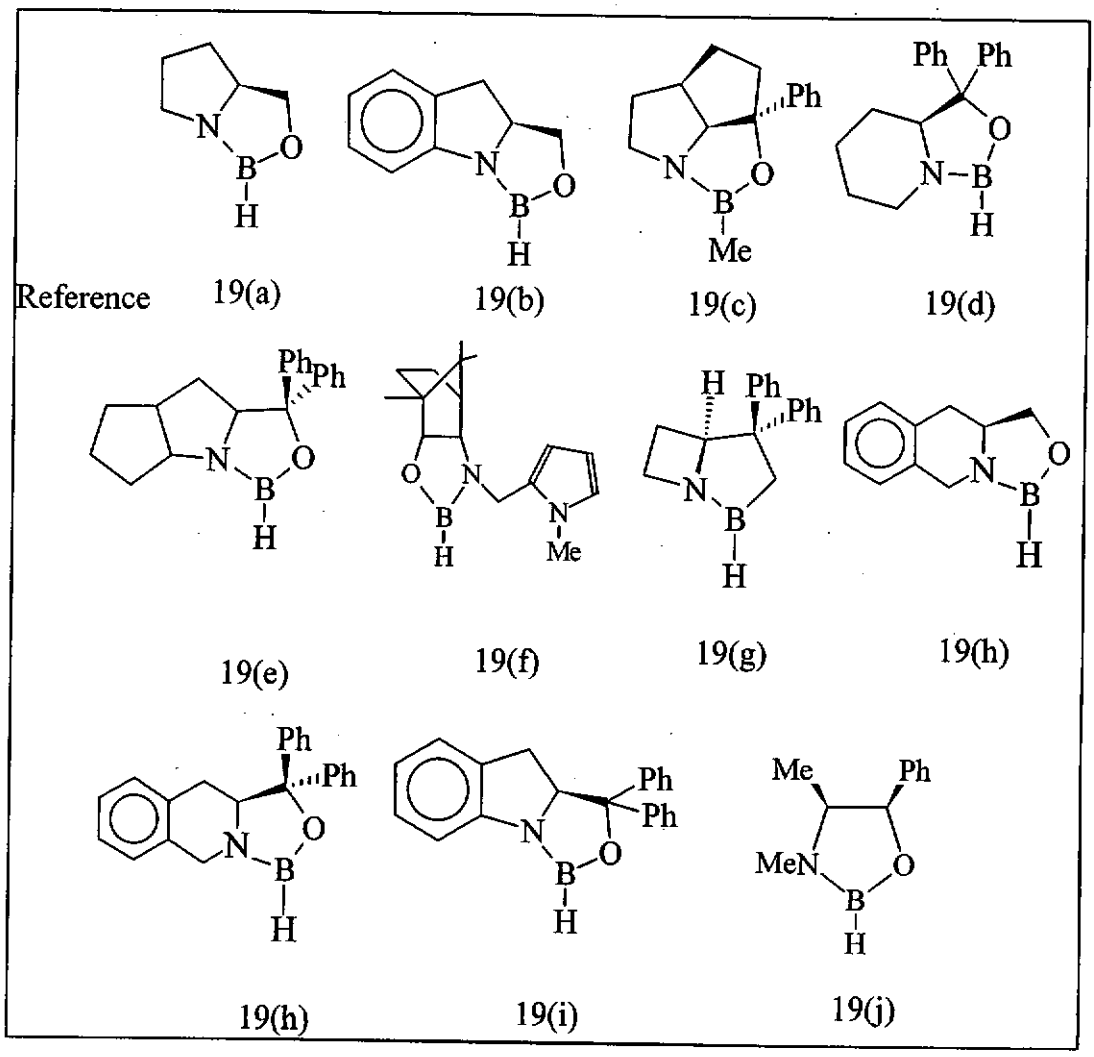
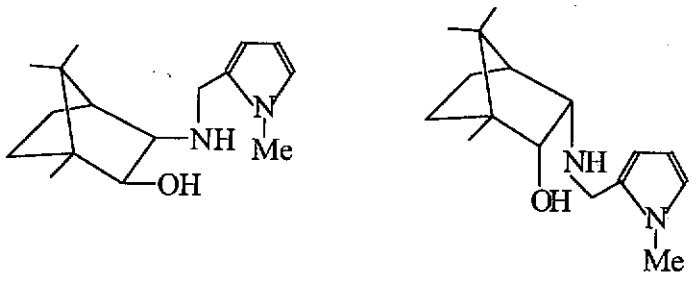


Fig. 1-4 Summary of various 1,3,2-oxazaborolidines reported by different chemists [19]

In many of these syntheses, it was difficult to synthesize both enantiomers of a product because both antipodes of a ligand were not always readily available. The products could only be prepared in both optical forms through tedious resolution from the single chiral auxilliary. Tanaka et al.[20] prepared both exo- and endo-2-hydroxy-3-(1-methyl-2-pyrrolyl)methylamino-bornanes, respectively (**32** and **33**) (fig 1-5). Their oxazaborolidines were found to be active catalysts for enantioselective borane reduction of prochiral aromatic ketones with predictable absolute stereochemistry. These two

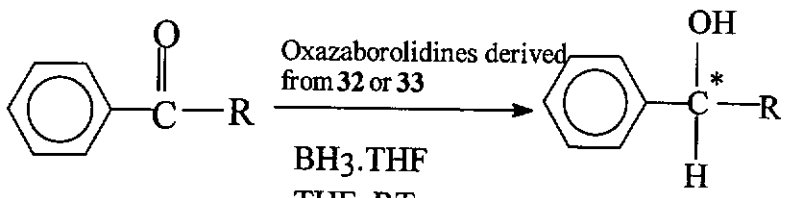
enantiomers could be readily prepared from D-camphor. However, only low to moderate e.e. values were obtained (Table 1-3).



exo-MPATH
32

eno-MPATH
33

Fig. 1-5 Exo and endo ligands prepared by Tanaka et al [20] for asymmetric borane-reduction of prochiral ketones with predictable stereochemistry



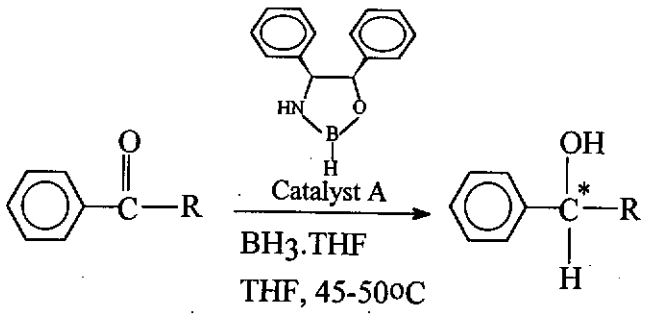
[Eq. 6]

Table 1-3 Asymmetric borane-reduction of ketones by exo-32 and endo-33 [20]

R	Cat*	ee(%)	Yield(%)	Configuration
Me	**32**	73	68	S
Me	**33**	73	62	R
Et	**32**	77	71	S
Et	**33**	79	65	R

Another successful chiral amino alcohol was 2-amino-1,2-diphenylethanol(**13**). In addition to its ease of synthesis and resolution, it could catalyze a wide variety of asymmetric reactions with good

enantioselectivities. The first application of oxazaborolidine **A** of (1R, 2S)-**13** [Eq. 7] in the enantioselective borane reduction of ketones was performed by Jiang et al.[11] It was found to be an efficient catalyst to provide good to excellent enenatioselectivities (up to >99%) for aromatic ketones (Table 1-4).

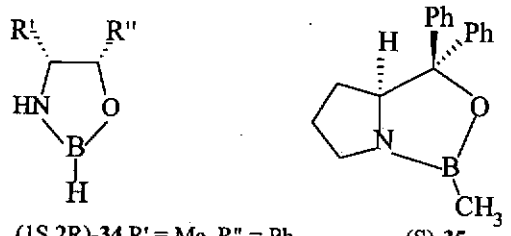


[Eq. 7]

Table 1-4 Asymmetric borane-reduction of ketones by catalyst A [11]

R	L/S(%)	e.e.(%)	Configuration
Me	20	>99	R
CH_2Br	5	>96	S

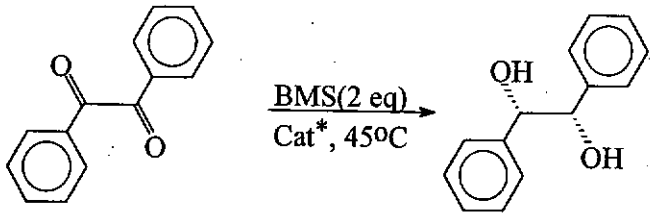
Owing to the promising performance of Corey's catalyst **28** and Jiang's catalyst **A**, in 1996, Joshi et al.[21] applied them to synthesize certain C_2-symmetrical diols (e.g. **36**) as shown in Eq. 8. For example, the reduction of benzil **36** under various conditions was known to provide predominantly the *erythreo* diastereomer in the absence of chiral catalyst. However, they discovered that oxazaborolidines (**A**, **34**, **35** in Fig. 1-6)-catalyzed the reduction with borane-methyl sulfide complex (BMS) provided a higher ratio of *threo / erythreo* diols (Table 1-5).



(1S,2R)-**34** R' = Me, R'' = Ph
(1S,2R)-**A** R' = R'' = Ph

(S)-**35**

Fig. 1-6 Three chiral oxazaborolidines applied in the asymmetric borane-reduction of benzil (**36**) developed by Joshi et al [21]



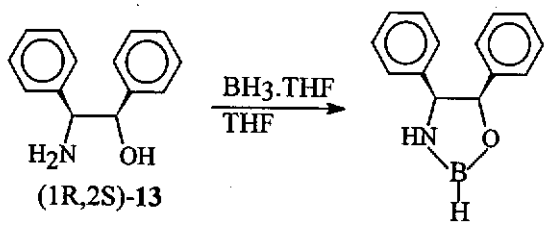
[Eq. 8]

36

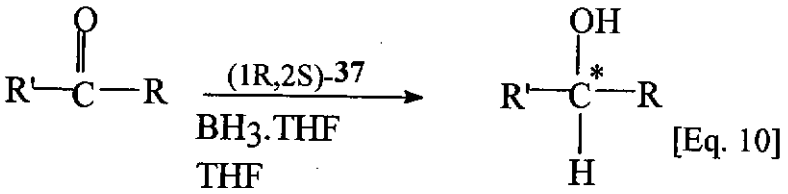
Table 1-5 Asymmetric borane-reduction of benzil (36) by A, 34, 35 [21]

Reagent	Solvent	catalyst	temp(°C)	time(min)	*threo : erythreo*
$NaBH_4$	MeOH	/	25	120	0 : 100
LAH	THF	/	0	30	4 : 96
$LiAl(O^tBu)_3H$	THF	/	0	120	20 : 80
BMS	THF	/	25	No reaction	/
BMS	THF	**34**	25	180	27 : 73
BMS	THF	**A**	25	60	42 : 58
BMS	THF	**35**	25	120	66 : 34
BMS	THF	**35**	45	15	87 : 13
BMS	THF	**35**	45	<5	88 : 12

Using oxazaborolidine of 2-amino-1,2-diphenylethanol (**A**) in asymmetric borane-reduction of ketones was also investigated by Chan et al[22] in 1996.[22] Organoaluminium compond (1R,2S)-**37** [Eq. 9] was found to be able to increased the rate significantly and in some cases slightly increased the enantioselectivity of the reaction as shown in Table 1-6. This finding offered a simple modification of the reaction system to make the asymmetric catalytic reduction of prochiral ketones a truly convenient synthetic method.



(1R,2S)-**13** (1R,2S)-A (1R,2S)-**37** [Eq. 9



Ligand to substrate ratio = 5% [Eq. 10]

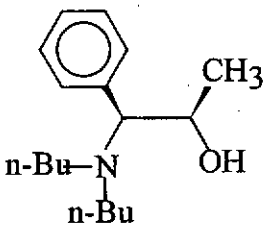
Table 1-6 Asymmetric borane-reduction of ketones by (1R,2S)-37 [22]

R	R'	$Al(i\text{-}Bu)_3$	Conversion(%)	e.e.(%)
Pheny	methy	No	77	75
		Yes	100	80
Phenyl	i-propyl	No	34	65
		Yes	78	65
Naphthyl	methyl	No	46	82
		Yes	100	81

Recently, many other novel chiral oxazaborolidines were synthesized containing heteroatoms,[23] intermolecular linkage,[24] bearing bulkier groups,[25] coordinating with transition metal,[26] etc. for asymmetric borane reduction. They have also been applied to other substrates to give many useful chiral compounds.[27]

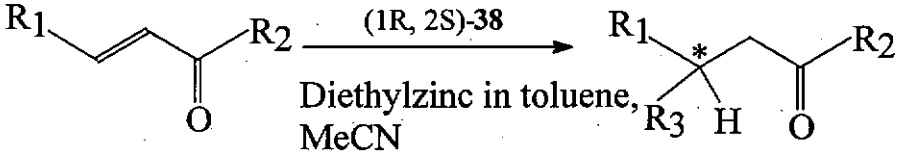
1.1.3 Asymmetric conjugate addition of diethylzinc to enones

Asymmetric conjugate addition of diethylzinc to enones was less explored when compared to asymmetric borane-reduction. On the other hand, enantioselective conjugate additions of organometallic reagents to prochiral enones afford optically active β-substituted ketones which attracted the concern of many chemists.[28] Luche et al.[29] found that Ni(II) salts facilitated the conjugate addition of dialkylzinc to enones. In 1988, Soai et al.[30] prepared a catalyst (1R,2S)-**38** from (1R,2S)-N,N-dibutylephedrine (**3**) as shown in Eq. 11. This catalyst was able to catalyze the conjugate addition of diethylzinc to give quantitative yield [Eq. 12]. Unfortunately, only poor to moderate enantioselectivities were obtained (Table 1-7).



(1R,2S)-**3**

+ $Ni(acac)_2$ $\xrightarrow[MeCN]{80^oC}$ (1R, 2S)-**38** [Eq. 11]

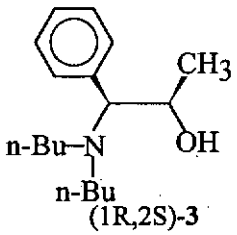


[Eq. 12

Table 1-7 Asymmetric conjugate addition of diethylzinc to enones by (1R,2S)-38 [30]

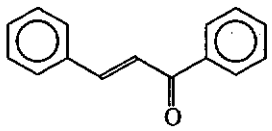
R_1	R_2	R_3	L/S(%)	e.e.(%)	Yield(%)
Ph	Ph	Me	60%	40	72
Ph	Ph	Et	50%	45	75
Ph	Ph	Et	6%	20	94
Ph	Me	Et	60%	12	63
Me	Ph	Et	50%	44	78

Soai et al.[4a] later reported that the enantioselectivity of these reactions could be improved significantly by using a combination of Ni(II)-2,2?dipyridyl as an achiral ligand in acetonitrile to form the catalyst [(1R,2S)-039] as shown in Eq. 13. A high enantioselectivity up to 90% was obtained in the conjugate addition of chalcone (**40**) [Eq. 14]. However, the activity of the catalyst was not very satisfactory. In some particular conditions, yield was high but e.e. was sacrified as shown in Table 1-8.

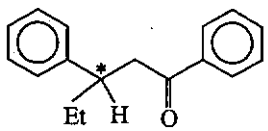


(1R,2S)-3

+ $Ni(acac)_2$ + 2,2'-dipyridyl $\xrightarrow[MeCN]{80^oC}$ (1R,2S)-**39** [Eq. 13


40

(1R,2S)-**39**
Diethylzinc in toluene, MeCN
-30°C, 12 hours



[Eq. 14

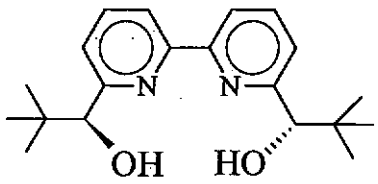
Ligand to substrate ratio = 17%

Table 1-8 Asymmetric conjugate addition of diethylzinc to chalcone (40) by (1R,2S)-39 [4(a)]

Achiral ligand	e.e.(%)	Yield(%)	Configuration
2,2-dipyridyl	90	47	R
Piperazine	87	44	R
2,2-bisquinoline		92	R

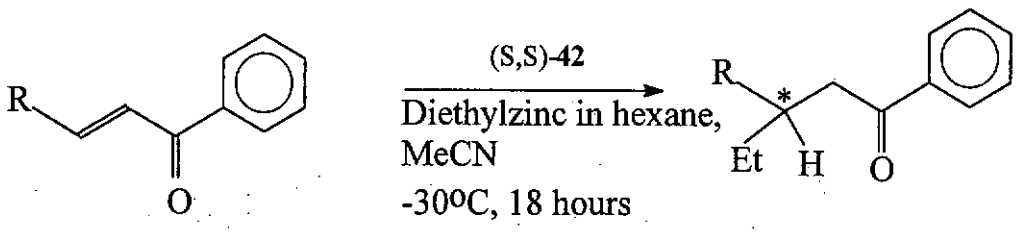
The reason for the tremendous enhancement of e.e. by adding 2,2-dipyridyl as achiral ligand has not yet been understood. It might be due to two reasons: firstly, the coordination of the achiral ligand to Ni(II) combined with chiral amino alcohol provide better discrimination of the face of substrate to coordinate on the metal, secondly, the achiral ligand may help to block the face for undesirable attack.

Based on the results of Soai et al.[30, 4a], Bolm and Ewald et al.[31] published the use of nickel-catalyzed asymmetric conjugate addition of organozinc reagents to enones using chiral 2,2?dipyridyl ligand (S,S)-n**41** [Eq. 15 and 16] and up to 74% e.e. was obtained (Table 1-9). Detailed investigation on the effect of catalyst concentration, ratio between Ni(II)$(acac)_2$, ligand and substrate were also performed.



(S,S)-**41**

$+ \ Ni(acac)_2 \xrightarrow[MeCN]{73^oC}$ (S,S)-**42** [Eq. 15

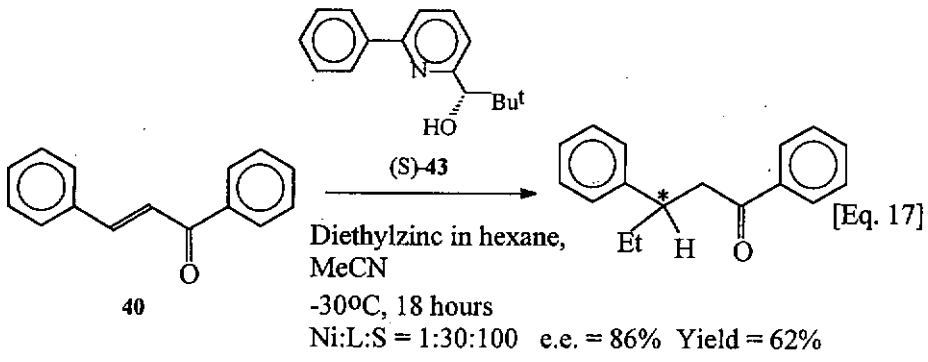


[Eq. 16

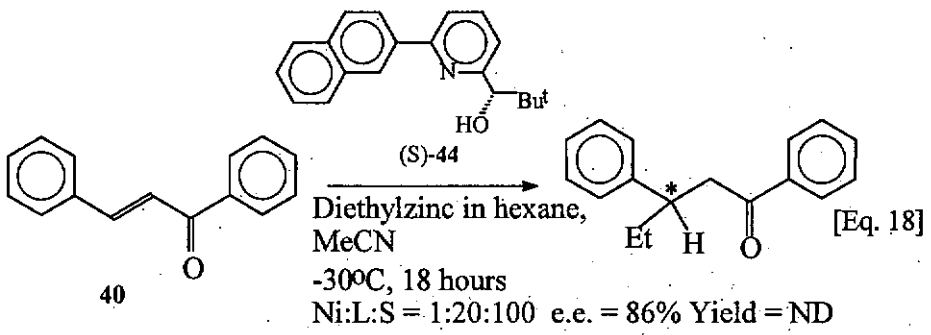
Table1-9 Asymmetric conjugate addition of diethylzinc to enones by (S,S)-42[31]

R	mol% $Ni(acac)_2$	Ratio Ni : Ligand : substrate	e.e.(%)	Yield(%)
C_6H_5	1	1:30:100	72	55
C_6H_5	1	1:20:100	72	75
C_6H_5	1	1:10:100	54	82
C_6H_5	1	1:5:100	20	74
C_6H_5	2	1:5:100	48	66
C_6H_5	2	1:5:100	18	73
C_6H_5	5	1:3:100	58	58
C_6H_5	5	1:1:100	18	69
4-OCH_3-1-C_6H_4	5	1:10:100	74	68
CH_3	5	1:5:100	2	76

Subsequently, Bolm el al.[4b] designed two more ligands (S)-**43** and (S)-**44** which catalyzed the asymmetric conjugate addition of diethylzinc to chalcone (**40**), giving e.e. up to 86% in moderate yield [Eq. 17 and Eq. 18].



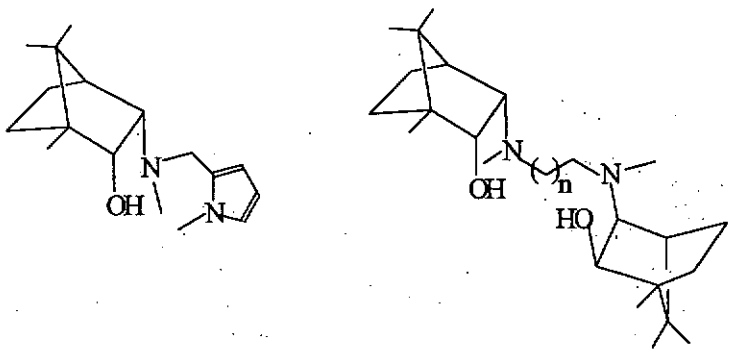
[Eq. 17]



[Eq. 18]

On the other hand, Bolm et al[4b] also suggested that asymmetric amplication occurs in their system. They claimed that it was due to the formation of dimeric nickel catalysts. If the nickel complexes with an unequal mixture of enantiomeric ligands, one can form SS (where S is the predominant enantiomer) and SR complexes. If the SR (meso enantiomer) is relatively unreactive as a catalyst, one would expect the enantioselectivity of the reaction to be higher than the enantiopurity of the ligand.

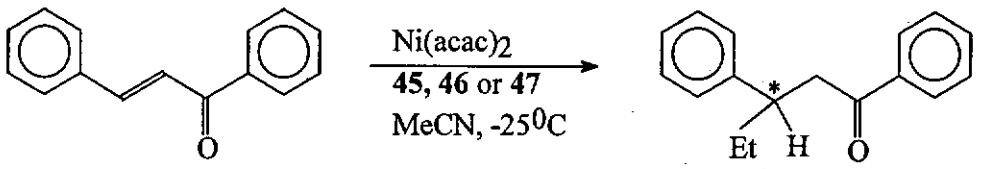
In addition to bidentate chiral amino alcohols, recently, a tridentate(**45**) and tetradentate (**46**, **47**) amino alcohol ligands were synthesized by Feringa et al.[32](fig. 1-7) The tetradentate ligands were not effective in the asymmetric conjugate addition. However, the tridentate ligand catalyzed the reaction with good e.e.(83%) as shown in Table 1-10.



45

46 n = 1
47 n = 2

Fig. 1-7 Tridentate (**45**) and tetradentate (**46** and **47**) ligands prepared by Feringa et al [32]



40

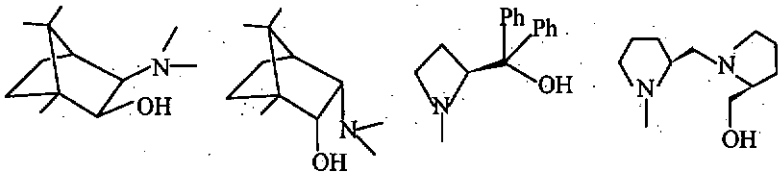
[Eq. 19

Table 1-10 Asymmetric conjugate addition of diethylzinc to chalcone (40) by 45, 46 and 47 [32]

Chiral ligand	L/S(%)	e.e.(%)	yield(%)	configuration
45	16	83	83	S
46	8	21	72	S
47	8	69	88	S

After a series of detailed investigations of this reaction with Ni(II) complex, Feringa et al.[33] also employed $Co(acac)_2$ in the presence of chiral ligands (**48** -**50**) as shown in fig 1-8 for the enantioselective conjugate addition of diethylzinc to chalcone (**40**). Enantioselectivity excess up to 83% was achieved when using chiral amino alcohol endo-**48** (Table 1-11).

However, the reaction was slow and a considerable amount of the reduced byproduct 1,3-diphenylpropan-1-one was detected.



exo-**48** endo-**48** (S)-**49** (S)-**50**

Fig. 1-8 Chiral amino alcohols employed in the $Co(acac)_2$ complex-catalyzed conjugate addition of diethylzinc developed by Feringa et al [33]

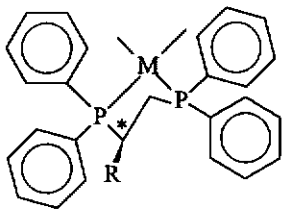
Table 1-11 Asymmetric conjugate addition of diethylzinc to chalcone (40) by chiral ligands 48-50 [33]

Ligand	Byproduct(%)	e.e.(%)	yield(%)
exo-**48**	5	67	61
endo-**48**	5	83	73
(S)-**49**	20	33	50
(S)-**50**	20	28	50

Since phosphine ligands play an important role in asymmetric catalytic reactions, Alexakis et al.[34] employed chiral bidentate aryl- and alkyl phosphines coordinated to copper(II)-triflate as catalysts for the asymmetric conjugate addition of diethylzinc to chalcone. However, only poor e.e. were obtained (0-7%).

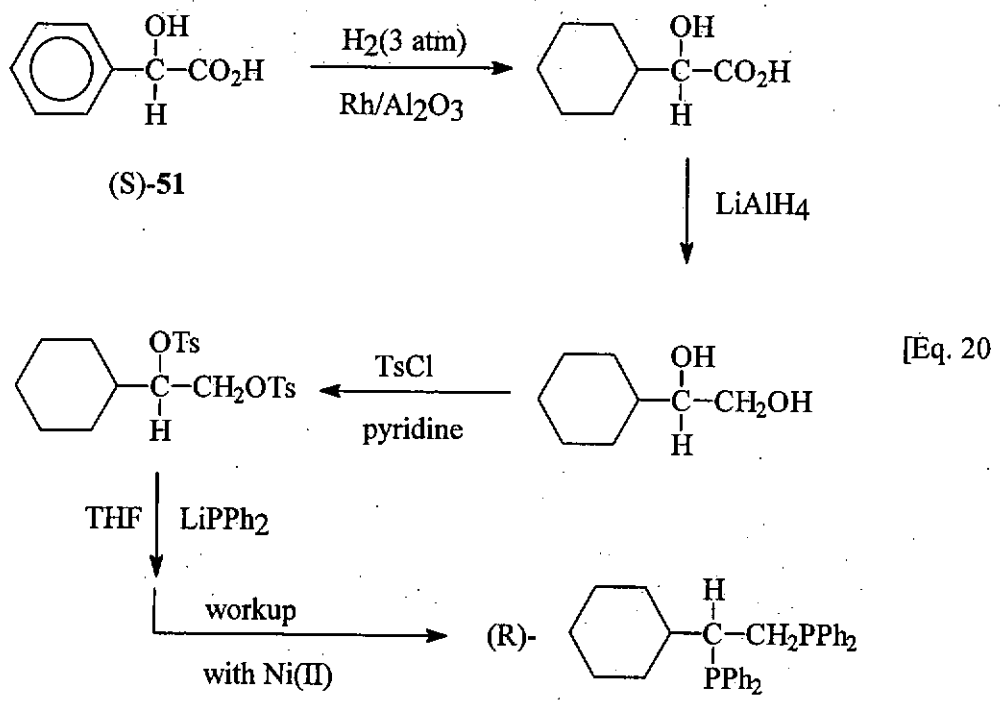
1.1.4 Chiral ligands containing cyclohexyl groups

The superiority of cyclohexyl group over phenyl group present in chiral ligands has been demonstrated by several studies [35-37]. It was generally due to two reasons: firstly, a very bulky 3-dimentional cyclohexyl group could stabilize the conformation of the catalyst complex to enhance effective enantiofacial discrimination, secondly, the less electron-withdrawing effect of cyclohexyl group than phenyl group induced higher availability of lone-pairs of electrons on the chiral ligand, thus, stabilizing the coordination between the ligand and metal. Two representative publications are selected here to elucidate this effect. The modification was firstly applied to chiral phosphine ligands in 1980 by Riley et al.[35] They investigated the chiral phosphine ligand containing cyclohexyl group in the asymmetric hydrogenation of amino-acid derivatives. The naturally occurring (S)-mandelic acid (**51**) was investigated as a potentially useful starting material because it was readily available for conversion to a chiral diphosphine by the established procedures [Eq. 20]. Furthermore, the phenyl ring could be reduced to a cyclohexyl ring, affording a very bulky three-dimensional group on the chiral chelate ring (fig. 1-9).



R = CH_3 **52** (Prophos)
R = cyclohexyl **53** (Cycphos)
R = phenyl **54** (phenphos)

Fig. 1-9 Preferred equatorial conformational structures of the known chiral chelate ring substituted, 1,2-bi(diphenylphosphino)ethane-type phosphine ligands [35]

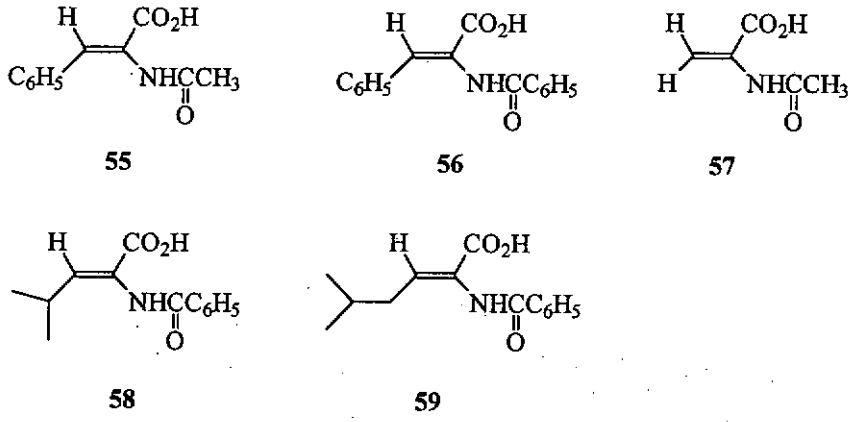


[Eq. 20

"Cycphos" [53]

Table 1-12 compares some results for the hydrogenation of amino acids derivatives in fig. 1-10 (**55** - **59**) with these three ligands (**52** - **54**). It is obvious that the cycphos ligand is a superior ligand with respect to enantioselectivity, while prophos is, in general, somewhat better than phenphos (Table 1-12). The observed results may be attributed to the fact that sterically rigid chelate ring would give the highest e.e. On the basis of such stereochemical argument, the bulkiest R group would provide the greatest steric barrier of inversion arising from the substituent's interaction with adjacent methylene protons. Thus, we might reasonably predict that the enantioselectivity would follow the order Cyphos>phenphos>prophos. Since the cyclohexyl group was the bulkiest R group, the superiority was

clearly demonstrated. However, the comparison between Prophos and Phenphos was not as clear.



55 56 57

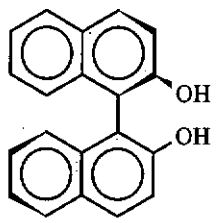
58 59

Fig. 1-10 Amino acid derivatives with different structures employed as substrates in the asymmetric hydrogenation by **52-54** [35]

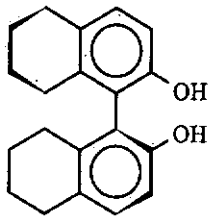
Table 1-12 Enantioselectivities(%) obtained in the asymmetric hydrogenation of amino acid derivatives by cycphos, prophos and phenphos [35]

Substrate	(R)-Cycphos (53)	(R)-Prophos (52)	(S)-Phenphos (54)
55	83	83	78
56	93	88	84
57	96	86	n.d.
58	91	79	n.d.
59	94	86	n.d.

Later on, Chan et al.[36] started a study of addition of triethylaluminium to aldehydes [Eq. 21] using 1,1'-bi-2-naphthol (BINOL) (**60**) and 5,5',6,6',7,7',8,8'-octahydro-1,1'-bi-2-naphthol (H_8-BINOL) (**61**) as chiral auxiliaries (Fig. 1-11).



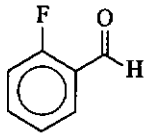
(R)-BINOL (**60**)



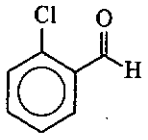
(S)-H_8-BINOL (**61**)

Fig.1-11 Structures of (R)-BINOL (**60**) and (S)-H_8-BINOL (**61**) developed by Chan et al [36]

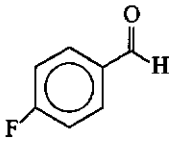
While the (R)-BINOL system provided good yields of chiral alcohols with moderate to good e.e. values, the (S)-H_8-BINOL system gave quantitative yields of the desired alcohols in excellent e.e.values for all of the aromatic aldehydes tested (Fig. 1-12). Part of the results are listed in table 1-13.



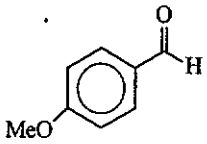
62



63

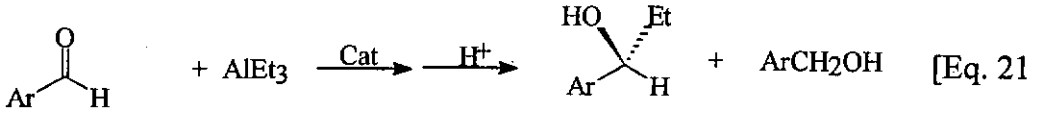


64



65

Fig. 1-12 Aldehydes with differently-substituted aromatic rings employed as substrates in the asymmetric triethylaluminium addition reaction by **60** and **61** [36]



[Eq. 21

Cat = Ti(O-*i*-Pr)$_4$ + Ligand

Table 1-13 Asymmetric addition of triethylaluminium to aldehydes by 60 and 61 [36]

Aldehyde	Ligand	Conversion(%)	selectivity(%)	e.e.(%)	configuration
62	(R)-BINOL	91.3	93.3	52	R
	(S)-H_8-BINOL	95.8	100	91	S
63	(R)-BINOL	95.1	91.6	62	R
	(S)-H_8-BINOL	95.8	100	90.6	S
64	(R)-BINOL	91.7	98.2	77.8	R
	(S)-H_8-BINOL	97.6	100	94.4	S
65	(R)-BINOL	93	80.2	67	R
	(S)-H_8-BINOL	97.9	100	92.8	S

Recently, Chan et al [37] established the generality of the advantage of the sterically more demanding H_8-binaphthyl backbone by asymmetric conjugate addition of dethylzinc to cyclic enones.

The above results reported imply that chiral ligands containing cyclohexyl groups are more efficient than their phenyl analogs. However, chiral amino alcohols containing cyclohexyl groups have not yet been explored.

1.2 Objectives

Chiral amino alcohols have played a pivotal role in catalytic asymmetric synthesis and their derivatives are expected to be of substantial interest for catalytic studies. On the other hand, several previous reports indicated that chiral ligands containing cyclohexyl groups gave higher reactivity and enantioselectivty than their phenyl analogs. Since there is no cyclohexyl derivatives of chiral amino alcohols have been applied in asymmetric catalytic reactions, it is highly desirable to design and synthesize a series of cyclohexyl derivatives of chiral amino alcohols and to test their application in the asymmetric synthesis of highly- valued pharmaceuticals and chiral intermediates.

The objectives of this project are the design and synthesis of a series of new chiral amino alcohols containing cyclohexyl groups, their reactivity and enantioselectivity are compared with their phenyl counterparts in two asymmetric catalytic reactions : the asymmetric borane-reduction of prochiral ketones and asymmetric conjugate addition of diethylzinc to enones. Details of the reactions and mechanisms are investigated.

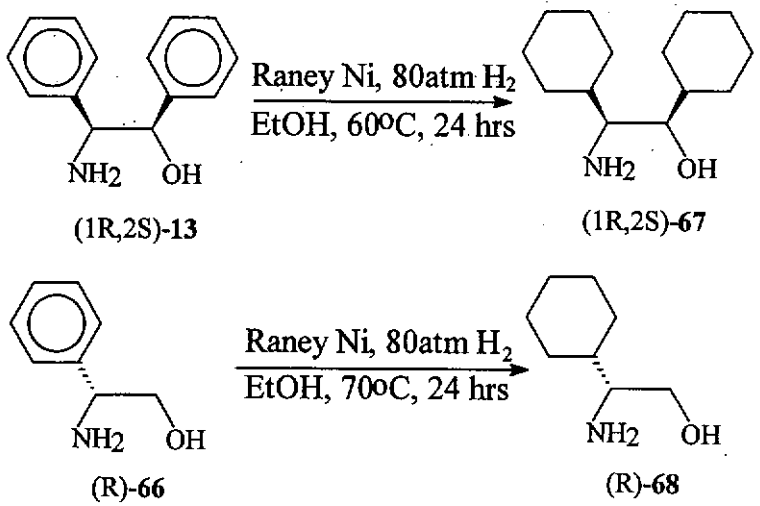
Chapter 2 Experimental Section

2.1 Synthesis of new、chiral amino alcohols containing cyclohexyl groups and their 1,3,2-oxazaborolidines

Several studies show that chiral ligands containing cyclohexyl groups as back bone are more effective asymmetric catalysts than their phenyl counterparts with respect to both reactivity and enantioselectivity.[35-37] In the past, the chiral ligands containing cyclohexyl groups were synthesized through multi-step reactions. Several methods were developed to modify the existing chiral ligands by directly hydrogenation of the phenyl rings.[35,38] However, these modifications have not yet been applied to the chiral amino alcohols. Thus the catalytic performance between chiral amino alcohols containing cyclohexyl groups and their phenyl analogs has not been systematically investigated.

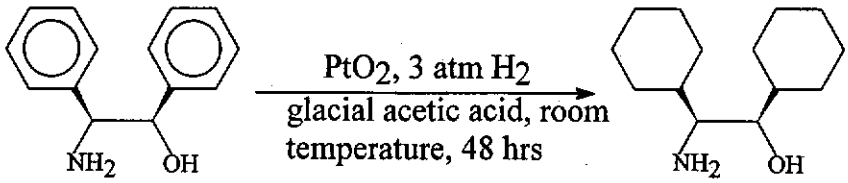
Several previous studies indicated that chiral 2-amino-1,2-diphenylethanol (**13**) was an useful ligand which gave reasonable enantioselectivites in a wide variety of asymmetric catalytic reactions.[11, 12] Therefore, it was chosen to be the target molecule. On the other hand, chiral 2-amino-2-phenylethanol (**66**) was also included in order to furnish the evidence of the modification. Chiral **13** can be purchased from commercial source while chiral **66** was synthesized by reduction of its corresponding amino acid- chiral phenylglycine without losing its optical

purity.[39] (1R,2S)-**13** and (R)-**66** were firstly hydrogenated to their cyclohexyl derivatives (1R,2S)-2-amino-1,2-dicyclohexylethanol (**67**) and (R)-2-amino-2-cyclohexylethanol (**68**) with Raney nickel as a catalyst [Eq. 22]. For product (1R,2S)-**67** and (R)-**68**, 90% and 79% yields were obtained, respectively (Method 2 on page 41).



[Eq. 22]

However, owing to the high temperature and hydrogen pressure adopted, using Raney Nickel as catalyst was not an economic and convenient method. It was desirable to develope another more practical method to hydrogenate (1R,2S)-**13** by using Platinum(II) Oxide [Eq. 23]. It was found that the method[38] utilized to hydrogenate BINOL(**60**) to H_8-BINOL(**61**) could be applied to hydrogenate **13**. A much lower hydrogen pressure and reaction temperature were used. Good yield (89%) was achieved (Method 1 on page 40). Through these novel synthetic routes [Eq. 22 and 23], chiral amino alcohols containing cyclohexyl groups can be prepared easily.

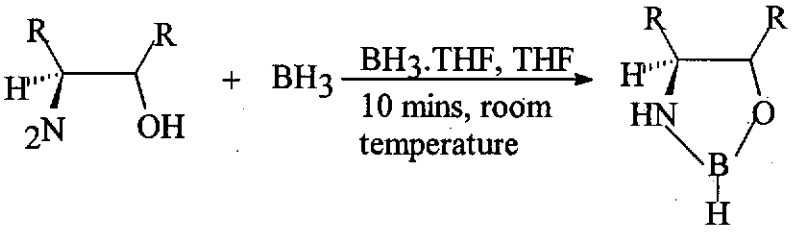


[Eq. 23

(1R,2S)-**13**

(1R,2S)-**67**

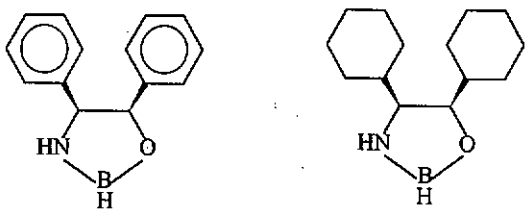
Asymmetric borane-reduction of prochiral ketones is one of the oldest asymmetric reactions and has been effectively catalyzed by many chiral amino alcohols. In order to determine whether ligands **67** and **68** performed better than their phenyl analogs, they were applied in this asymmetric reaction. The catalysts were prepared *in situ*, giving the 1, 3, 2-oxazaborolidines [Eq. 24]. Structures of these complexes were characterized based on the findings of Corey et al. [1, 17]



[Eq. 24

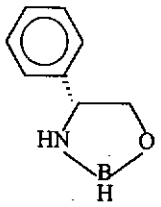
1,3,2-oxazaborolidine

Cat **A**, **B**, **C**, **D** were synthesized from ligands **13, 67, 66, 68** respectively as shown in fig. 2-1.

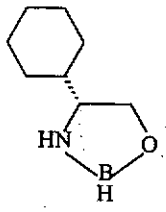


Cat **A**

Cat **B**



Cat **C**



Cat **D**

Fig. 2-1 Structures of prepared 1,3,2-oxazaborolidines derived from reported chiral amino alcohols with phenyl rings and new chiral amino alcohols with cyclohexyl rings.

The experimental procedures of asymmetric borane-reduction of prochiral ketones were basically based on those reported by Chan et al.[22]

2.2 Synthesis of N-methylated and N,N-dimethylated chiral amino alcohols with 1,2-dicyclohexyl backbone and their Ni(II) catalysts for asymmetric conjugate addition

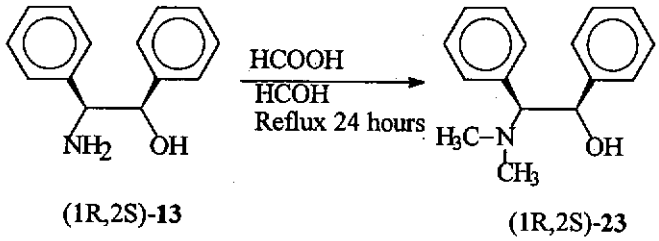
Enantioselective carbon-carbon bond formation has received an increasing interest because of its potential in the preparation of a variety of high-valued non-racemic chiral alcohols. For example, asymmetric conjugate addition of diethylzinc to enones afford optically active β-substituted ketones, which are synthetically useful. To the best of my knowledge, Soai *et al.*[4a] have obtained 90% e.e., the highest enantioselectivity by using (1R,2S)-**39** as catalyst. However, the reactivity of their system was not satisfactory [only 47% yield was obtained after 12-hour reaction. In some particular conditions, yield was high but e.e. was sacrified (table 1-8)]. Therefore, development of a more effective chiral catalyst towards the asymmetric conjugate addition reaction is highly desirable.

In previous studies, 2-amino-1,2-diphenylethanol (**13**) and its N,N-dimethylated derivative **23** were highly effective ligand in many asymmetric reactions, especially the asymmetric diethylzinc addition to aldehydes (up to 97% e.e. was obtained by using **23**).[40] However, **23** has not been applied to the asymmetric conjugate addition reaction due to its low enantioselectivity to a wide variety of enones. Therefore, modification of

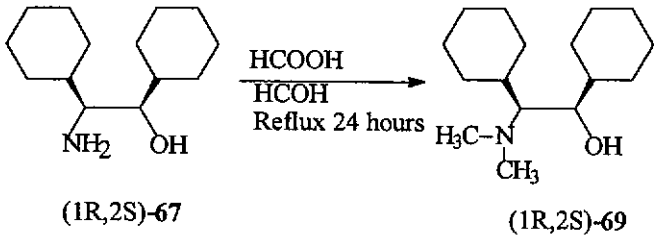
this ligand to give high e.e.'s in the asymmetric conjugate addition is worth investigating.

A more efficient chiral ligand has been synthesized- (1R,2S)-N,N-dimethyl-2-amino-1,2-dicyclohexylethanol (**69**), which contains a 1,2-dicyclohexyl moiety in the Nickel(II)-catalyzed conjugate addition of diethylzinc to enones. A comparison with its phenyl analog, (1R,2S)-N,N-dimethyl-2-amino-1,2-diphenylethanol (**23**) with respect to the reactivity and enantioselectivity was also investigated.

Ligand **23** and **69** were synthesized from (1R,2S)-2-amino-1,2-diphenylethanol (**13**) and (1R,2S)-2-amino-1,2-dicyclohexylethanol (**67**) respectively by refluxing with formic acid and formaldehyde [Eq. 25] for 24 hours. The preparation of **23** and **69** was based on the procedures reported by Jiang et al.[40] Ligands **23** and **69** were obtained with 74% and 83% yields respectively.

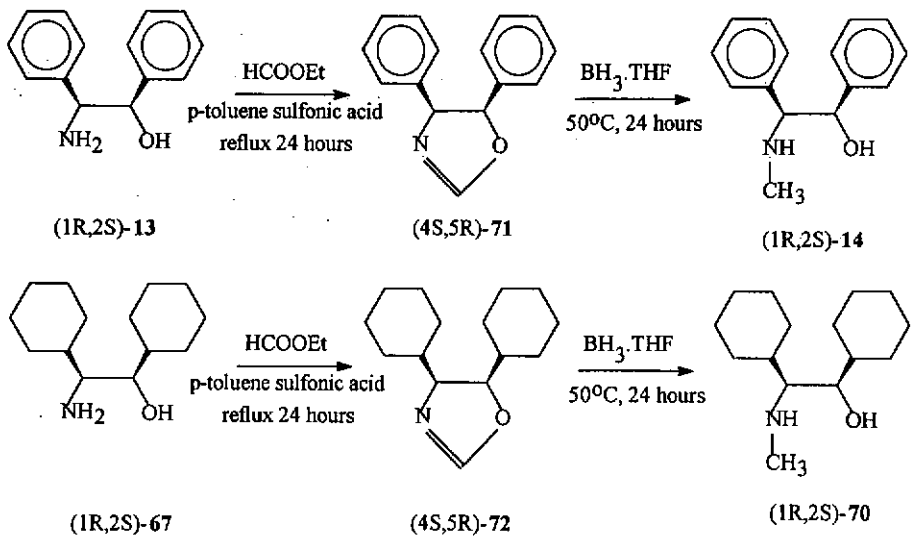


(1R,2S)-**13** (1R,2S)-**23** [Eq. 25]



(1R,2S)-**67** (1R,2S)-**69**

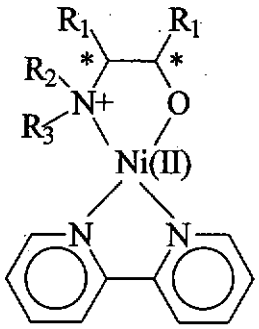
It was also of interest to observe the performance of mono-substituted chiral amino alcohols in the conjugate addition reaction to investigate the role played by the alkyl group on N atom. Therefore, (1R,2S)-**14** and (1R,2S)-**70** were prepared according to the following routes [Eq.26]. The route was basically based on the experimental procedures published by Jiang et al. [41]



[Eq. 26]

The catalysts were synthesized *in situ* by reacting ligand **23**, **69**, **14**, **70** with $Ni(acac)_2$ and 2,2-bipyridyl in acetonitrile. The suggested catalyst structure is shown in Fig. 2-2.

Ligand 23
Ligand 69
Ligand 14 + $Ni(acac)_2$ + 2,2-bipyridyl $\xrightarrow[MeCN]{reflux}$ Cat **1**
Cat **2**
Cat **3**
Cat **4**
Ligand 70



Cat **1** R_1= phenyl, R_2 = R_3 = methyl
Cat **2** R1= cyclohexyl, R_2 = R_3 = methyl
Cat **3** R_1= phenyl, R_2 = methyl, R_3 = H
Cat **4** R_1= cyclohexyl, R_2 = methyl, R_3 = H

Fig. 2-2 The suggested catalyst structure of Cat **1-4** forming *in situ*

The experimental procedures of asymmetric conjugate addition of diethylzinc to enones were basically based on those reported by Soai et al.[4a]

2.3 Experimental Procedures

Materials

The commercial reagents were used as received without further purification. All solvents were AR grade and purchased from Mallinckrodt. All solvents used in asymmetric borane reduction and asymmetric conjugate addition were dried using standard, published method and distilled before used.

List of reagents

2'-acetophenone (Aldrich, 99%)
2-amino-1,2-diphenylethanol (Aldrich, 99%)
2,2-bipyridyl Acros, 99%)
borane in THF (Acros, 1M solution in THF)
chalcone (Merck, 98%)
4'-chloroacetophenone (Aldrich, 97%)
3-chlorobenzaldehyde (Merck, 99%)
chloroform-d (Cambridge Isotope Laboratories, Inc., 99.8% atom D or Aldrich, 99.8% atom D with 0.03% v/v TMS)
diethylzinc (Aldrich, 1M solution in toluene)
3,3-dimethyl-2-butanone (Aldrich, 98%)
ethyl formate (Acros, 98%)
formaldehyde (Acros, 37 wt% solution in water, stabilized with 10-15% methanol)
formic acid (Acros, 96%)
3-fluorobenzaldehyde (Acros, 98%)
glacial acetic acid (Aldrich, 99.99%)
hydrochloric acid (Aldrich, 37%)
iodine (Merck, 99.5%)
magnesium sulfate (Riedel-deHaen, 99%)
(R)-mandelic acid (Acros, 99%)
2'-methoxyacetophenone (Aldrich, 99%)
1-naphthaldehyde (Aldrich, 97%)
(R)-Phenylglycine (Acros, 98%)
p- toluene sulfonic acid monohydrate (Aldrich, 98.5%)
platinum(IV) oxide (Aldrich, grade of Adam's catalyst)
propriophenone (Aldrich, 99%)

Raney nickel (Acros, 50% slurry in water, pore size- 50 μ, surface area- 80-100 m^2/g)

silica gel 60 (Merck, 230-400 mesh ASTM, particle sizes 0.040-0.063 mm)
sodium borohydride (Aldrich, 98%)
sodium chloride (Acros, 99%)
sodium hydrogen carbonate (Farco, 99.8%)
sodium hydroxide (Aldrich, 97%)
sodium sulfate (Acros, 99%)
m-tolualdehyde (Acros, 98%)

Instruments

NMR spectra were obtained on a BRUKER model AVANCE DPX 400 spetrometers (^1H : 400 MHz, ^{13}C : 101 MHz). ^{13}C chemical shifts are positive downfield (and negative upfield) from Me_4Si. Melting points were determined using a Electrothermal 9100 apparatus with sealed capillaries. Mass analyses were performed by V.G. Micromass, Fisons VG platform and Finnigan Model 95 ST. Optical rotations were measured on a Perkin-Elmer Model 341 polarimeter. GLC and HPLC analyses were performed using a Hewlett-Packard Model HP 5890 Series II GC and a Hewlett-Packard 1050, repectively.

Formation of (R)-2-amino-2-phenylethanol [(R)-**66**] [39]

A three-neck round bottom flask was fitted with a magnetic stirring bar, a reflux condenser and an additional funnel. The flask was charged with sodium borohydride (1.73 g, 45.75 mmol) and tetrahydrofuran (70 mL, predried over sodium). The remaining neck was sealed with a septum with a nitrogen line attached. The flask was cooled to 0°C in an ice bath. A solution of iodine (4.825 g, 19 mmol) dissolved in tetrahydrofuran (20 mL)

was poured into the additional funnel and added to the reaction vessel dropwise over 30 minutes. (R)-Phenylglycine (2.5 g, 19 mmol) was added in one portion, evoluting hydrogen gas vigorously. The flask was heated to reflux for 18 hours and cooled to room temperature. Methanol was added cautiously until the mixture became clear. After stirring for 30 minutes, the solvent was removed by rotatory evaporation leaving a white paste which was dissolved by addition of 40 mL of 20 % aqueous sodium hydroxide. The solution was then stirred for 4 hours and extracted with 3x150 mL of dichloromethane. The organic extracts were dried over anhydrous magnesium sulfate, and the white semi-solid was recrystallized with toluene for 1 day to give 1.9g of (R)-2-amino-2-phenylethanol (71 % yield).

The analytical data for (R)-2-amino-2-phenylethanol were as follows : ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.26 (m, 5H); 3.99 (q, 1H); 3.69 (dd, 1H); 3.53(dd, 1H).

Formation of (R)-2-amino-2-cyclohexylethanol [(R)-**68**]

A solution of (R)-2-amino-2-phenylethanol (0.5 g, 3.6 mmol) in 15 mL methanol and Raney-nickel catalyst were charged into a 50 mL autoclave equipped with a magnetic stirring bar. Eighty atmosphere of hydrogen gas was filled and the mixture was stirred at 80°C for 24 hours. After cooling to room temperature, the mixture was filtered to remove the solid catalyst. Evaporation of ethanol afforded the crude product, which was purified by crystallization with ethanol to give 0.41 g of (R)-2-amino-2-cyclohexylethanol (79% yield).

The analytical data for (R)-2-amino-2-cyclohexylethanol were as follows : m.p.: 180-182°C; $[\alpha]_D$ (*c*=1, methanol) : -9.4°; ^{1}H-NMR (400 MHz, CD_3OD) δ:3.79(dd, 1H); 3.61(dd, 1H); 2.96 (m, 1H); 1.32-1.09 (m, 11H), ^{13}C-NMR (101 MHz, CD_3OD) δ: 60.9, 59.7, 39.0, 30.4, 30.1, 27.3, 27.2 , M^+:144.

The enantiomeric excess of (R)-2-amino-2-cyclohexylethanol was determined as follows : 0.06 mmol of (R)-2-amino-2-cyclohexylethanol and 0.07 mmol of (R)-mandelic acid were dissolved in 1 mL of CD_3OD. This solution was used directly for the ^{1}H NMR analysis. Resonances for the proton at the stereogenic centre of rac-2-amino-2-cyclohexylethanol : δ=5.02 and 4.92 ppm (Δδ=0.1ppm). Based on this method [42] the enantiomeric excess of (R)-2-amino-2-cyclohexylethanol was established to be >99%.

Formation of (1R,2S)-2-amino-1,2-dicyclohexylethanol [(1R,2S)-**67**]

Method 1 :

A 50 mL autoclave with a magnetic stirring bar was charged with (1R,2S)-2-amino-1,2-diphenylethanol (0.2 g 0.9 mmol), 20 mg PtO_2 (0.02g , 0.09 mmol) and glacial acetic acid (10mL) under 3 atmosphere of H_2. The solution was stirred for 48 hours at room temperature. After releasing the hydrogen gas and removing the solid catalyst by filtration, the mixture was neutralized with aqueous $NaHCO_3$ solution followed by extraction with 20mL ethyl acetate three times. The combined extracts were dried with sodium sulfate and the solvent was removed with rotary evaporator to give

198 mg of crude product. The crude product was purified by crystallization with 70% ethanol aqueous solution to give 185 mg crystals of (1R,2S)-2-amino-1,2-dicyclohexylethanol (89% yield).

The analytical data for (1R,2S)-2-amino-1,2-dicyclohexylethanol were as follows : m.p.: 144-146°C; $[a]_D$= +8.0°(*c* = 1.0, ethanol); ^{1}H-NMR(400 MHz, $CDCl_3$) δ: 3.28(dd, 1H, *J* = 6.2 and 4.4 Hz); 2.59(dd, 1H, *J* = 6.1 and 4.3 Hz); 1.79-1.10(m,22H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ : 76.94, 57.87, 39.77, 30.85, 27.45, 27.42, 27.08, 26.97, 26.88, 26.71, 26.53 ppm. M^+:226.

The enantiomeric excess of (1R,2S)-2-amino-1,2-dicyclohexylethanol was determined by its N-methylated derivative [see preparation of (1R,2S)-N-methyl-2-amino-1,2-dicyclohexylethanol (1R,2S)-**70**].

Method 2 :

A solution of (1R,2S)-2-amino-1,2-diphenylethanol (0.2 g, 0.9 mmol) in 15 mL methanol and Raney-nickel catalyst were charged into a 50 mL autoclave equipped with a magnetic stirring bar. Eighty atmosphere of hydrogen gas was filled and the mixture was stirred at 60°C for 24 hours. After cooling to room temperature, the mixture was filtered to remove the solid catalyst. Evaporation of ethanol afforded the crude product. The crude product was purified by crystallization with ethanol to give 0.18 g of (1R,2S)-2-amino-1,2-dicyclohexylethanol (90% yield). The analytical data for (1R,2S)-2-amino-1,2-dicyclohexylethanol by method 2 were the same as those by method 1.

Formation of (4S,5R)-4,5-diphenyloxazoline [(4S,5R)-**71**] [41]

A one-neck 50 mL round bottom flask was fitted with a magnetic stirring bar and reflux condenser . The flask was charged with (1R,2S)-2-amino-1,2-diphenylethanol (0.2 g, 0.9 mmol) and p-toluene sulfonic acid (0.02 g, 0.1 mmol). Ethyl formate (4 mL) was added to dissolve the solids. The mixture was heated to reflux for 24 hours. The solution was then cooled down to room temperature and solvent was removed by rotatory evaporation to obtain a white solid. The solid was recrytallized with ethanol for one day to give 0.17g of (4S,5R)-4,5-diphenyloxazoline (85% yield).

The analytical data for (4S,5R)-4,5-diphenyloxazoline were as follows : ^{1}H-NMR(400 MHz, CD_3OD) δ : 8.16 (s, 1H); 7.46(m, 10H); 5.68(d, 1H); 5.37(d, 1H).

Formation of (1R,2S)- N-methyl-2-amino-1,2-diphenylethanol [(1R,2S)-**14**] [41]

A 50 mL one-neck round bottom flask was charged with (4S,5R) 4,5-diphenyloxazoline (0.1g, 0.4 mmol) and a magnetic stirring bar. Tetrahydrofuran (5mL, predried over sodium) was added to dissolve the solid. The mixture was cooled to 0°C followed by the injection of borane in tetrahydrofuran (1.5mL of 1M solution) under nitrogen protection. The mixture was reacted at 0°C for 3 hours and then at 50°C for 24 hours. After the reaction, the solution was cooled down to room temperature prior to the addition of hydrochloric acid (1mL of 2N solution) and methanol (1mL)

was added. The solution was concentrated by rotatory evaporation leaving a white solid. The solid was then dissolved in hot water (2mL) and transfered into a separatory funnel. Sodium hydroxide was added until pH was adjusted to 11. The solution was then extracted by 3x 10 mL dichloromethane. The organic extract was dried by anhydrous magnesium sulfate and the solvent was removed by rotatory evaporation to give a white solid, followed by dissolving it into hexane, particles which did not dissolved in hexane was removed by filtration. The solution was put aside and crystals were precipitated. The crystals were filtered to give 0.07g of (1R,2S) N-methyl-2-amino-1,2-diphenyl ethanol (77% yield).

The analytical data for (1R,2S) N-methyl-2-amino-1,2-diphenyl ethanol were as follows : ^{1}H-NMR(400 MHz, $CDCl_3$) δ: 7.27(m, 10H); 4.81(d, 1H); 3.77(d, 1H); 2.29(s, 3H).

Formation of (4S,5R)-4,5-dicyclohexyloxazoline [(4S,5R)-**72**]

A 50 ml one-neck round bottom flask was fitted with a magnetic stirring bar and a reflux condenser. The flask was charged with (1R,2S)-2-amino-1,2-dicyclohexylethanol(0.2 g, 0.9 mmol) and p-toluene sulfonic acid (0.02 g, 0.1 mmol). Ethyl formate (4 mL) was then added to dissolve the solids. The mixture was heated to reflux for 24 hours. After the reaction, the solution was cooled down to room temperature and the solvent was removed by rotatory evaporation to obtain a white solid. The solid was recrystallized in ethanol for one day, giving 0.17 g of (4S,5R)- 4,5-dicyclohexyloxazoline (82% yield).

The analytical data for (4S,5R)- 4,5-dicyclohexyloxazoline were as follows : ^{1}H-NMR(400 MHz, CD_3OD) δ: 8.2(s, 1H); 4.08(dd, 1H); 3.47(dd, 1H); 1.98-1.21(m, 22H).

Formation of (1R,2S)-N-methyl-2-amino-1,2-dicyclohexylethanol [(1R,2S)-**70**]

A 50 mL one-neck round bottom flask was charged with (4S,5R)-4,5-diphenyloxazoline (0.1g, 0.4 mmol) and a magnetic stirbar. Tetrahydrofuran (5mL, predried over sodium) was added to dissolve the solid. The mixture was cooled to 0°C, followed by the addition of borane in tetrahydrofuran (1.5mL of 1M solution , 1.5 mmol) by syringe under N_2 protection. The solution was reacted at 0°C for 3 hours and then 50°C for 24 hours. After the reaction, the mixture was cooled down to room temperature prior to the addition of hydrochloric acid (1mL of 2N solution) and methanol (1mL). The solution was concentrated by rotatory evaporation giving a white solid. The solid was then dissolved in hot water (2mL) and the aqueous solution was transfered into a separatory funnel. Sodium hydroxide was added until pH was adjusted to 11. The solution was extracted by 3x 10 mL dichloromethane. The solvent was removed by rotatory evaporation giving a white solid which was dissolved in hexane, particles which did not dissolved was filtered. The solution was put aside and crystals were precipitated. The crystals were filtered to give 60mg of (1R,2S)-N-methyl-2-amino-1,2-dicyclohexylethanol (61% yield).

The analytical data for (1R,2S)-N-methyl-2-amino-1,2-dicyclohexylethanol were as follows : m.p.: 55-57°C; $[a]_D$= +1.4 °(*c* = 1.0, ethanol); ^{1}H-NMR(400 MHz, $CDCl_3$) δ: 3.36(q, 1H); 2.40(s, 3H); 2.25(dd, 1H); 2.05(d,1H); 1.90(d, 1H); 1.75-1.05(m, 22H) ^{13}C-NMR (101 MHz, $CDCl_3$) δ : 73.8975, 66.1376, 39.6081, 38.1112, 35.7284, 31.9448, 30.2177, 29.1129, 28.2797, 27.0017, 26.7088, 26.5792, 26.1464, 26.0264 ppm. M^+:240

The enantiomeric excess of (1R,2S)-N-methyl-2-amino-1,2-dicyclohexylethanol was determined as follows : 0.06 mmol of (1R,2S)-N-methyl-2-amino-1,2-dicyclohexylethanol and 0.07 mmol of (R)-mandelic acid were dissolved in 1 mL of $CDCl_3$. This solution was used directly for the ^{1}H NMR analysis. Resonances for the proton at the stereogenic centre of rac-N-methyl-2-amino-1,2-dicyclohexylethanol: δ=3.43 and 3.36 ppm (Δδ=0.07ppm). Based on this method the enantiomeric excess of (1R,2S)-N-methyl-2-amino-1,2-dicyclohexylethanol was established to be >99%.

Formation of (1R,2S)- N,N-dimethyl-2-amino-1,2-diphenylethanol [(1R,2S)-**23**][40]

A 50 mL one neck round bottom flask containing a magnetic stirring bar was charged with (1R,2S)-2-amino-1,2-diphenylethanol (0.5 g, 2mmol), formic acid (5 mL), formaldehyde (2.5mL of 37% aqueous solution). The mixture was refluxed for 20 hours. After the reaction, the solution was cooled down to room temperature. Sodium hydroxide(80mL of 10% aqueous solution) was added and white solids precipitated. The solids was

filtered and dissolved in ethyl acetate (30ml). The solution was washed by saturated sodium chloride solution for three times. The organic phase was dried by anhydrous magnesium sulfate. The solvent was removed by rotatory evaporation giving a white solid. 0.36g of (1R,2S)- N,N-dimethyl-2-amino-1,2-diphenylethanol was obtained (74% yield).

The analytical data for (1R,2S)- N,N-dimethyl-2-amino-1,2-diphenylethanol were as follows : ^{1}H-NMR(400 MHz, $CDCl_3$) δ: 7.13-7.10(m, 6H); 6.99-6.97(m, 4H); 5.31(d, 1H); 3.2(d, 1H); 2.35(s, 6H).

Formation of (1R,2S)-N,N-dimethyl-2-amino-1,2-dicyclohexylethanol [(1R,2S)-**69**]

A 50 mL one neck round bottom flask was charged with (1R,2S)-2-amino-1,2-dicyclohexylethanol (0.2 g, 0.9mmol), formic acid (2 mL) and formaldehyde (1mL of 37% aqueous solution). The mixture was refluxed for 20 hours. After the reaction, the solution was cooled down to room temperature. Sodium hydroxide (40mL of 10% aqueous solution) was added and white solids precipitated. The solids was filtered and dissolved in ethyl acetate (30mL). The solution was washed with saturated sodium chloride solution for three times. The organic phase was dried by anhydrous magnesium sulfate, and the solvent was removed by rotatory evaporation giving a white solid. 0.19g of for (1R,2S) N,N-dimethyl-2-amino-1,2-dicyclohexylethanol was obtained (83% yield).

The analytical data for (1R,2S) N,N-dimethyl-2-amino-1,2-dicyclohexylethanol were as follows : m.p.: 72-74°C; $[a]_D$= + 3.0°(c = 1.0,

ethanol); ^{1}H-NMR(400 MHz, $CDCl_3$) δ:3.48(t, 1H); 2.28(s, 6H); 2.25(dd, 1H); 1.84-1.11(m, 22H) ^{13}C-NMR (101 MHz, $CDCl_3$) δ : 73.6158, 69.6347, 69.4601, 42.4081, 40.9957, 36.6137, 32.5980, 31.3912, 31.0284, 27.7390, 26.9797, 26.7667, 26.6837, 26.2913.ppm. M^+: 254.

Typical procedures of asymmetric borane-reduction of acetophenone [22]

Under nitrogen atmosphere, a solution of chiral amino alcohol (0.09 mmol) in 5 mL THF and a THF solution of borane (180 μL of a 1 M solution, 0.18 mmol) were mixed well in a 25 ml Schlenk flask with a magnetic stirring bar at ambient temperature for 10 minutes to form oxazaborolidine-catalyst (Cat **A-D**). After the addition of a 210 μL of acetophenone (1.8 mmol), a THF solution of borane (2.0 mL of a 1M solution, 2.0 mmol) was added and the mixture was allowed to stir at 50°C for 5 minutes. The configuration, conversion and enantioselectivity were determined by GLC with a Chromopack CP-Chirasil-DEX CB capillary column except 2'-methoxy-1-phenylethanol in which the configuration was determined by measuring its optical rotation and compared with literature value. Selectivity was >99% in all entries.

Typical procedures of asymmetric conjugate addition of diethylzinc to Chalcone [4a]

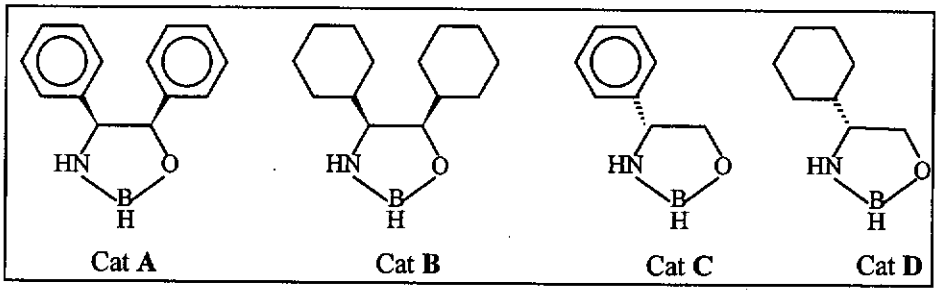
A mixture of $Ni(acac)_2$ (3.6 mg , 0.014mmol) and chiral amino alcohol (0.034mmol) in MeCN (0.2 mL) was stirred at 80°C for 1 hour under nitrogen atmosphere in a 25 mL schlenck flask. After the reaction, the solvent was removed under vacuum. 2,2'-Bipyridyl (2 mg , 0.014mmol)

and MeCN (0.2 mL) were added, and the mixture was stirred at 80°C for 1 hour. The resulting green solution (Cat **1-4**) was cooled to room temperature. Chalcone (40 mg , 0.2 mmol) was added, and the mixture was stirred for 20 minutes before cooling to -30°C. Diethylzinc (1M solution in toluene, 0.24 mmol) was added dropwise, and the resulting mixture was stirred at -30°C for 12 hours. The reaction was quenched with 1 M hydrochloric acid (0.6 ml) , and the product was extracted with ethyl acetate(3 mL). The configuration and enantioselectivity were determined by HPLC with a Daicel OD column. The conversion on chromatogram was calibrated against standard samples with known composition of substrate and product. Selectivity was >90% in all entries. Enones with substituted aromatic rings (**81-84**) were synthesized according to standard procedures.[45]

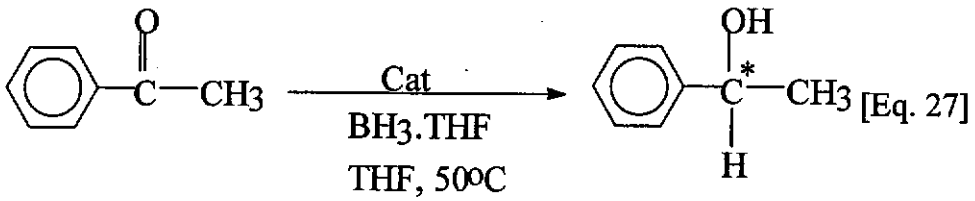
The use of $La(acac)_2$ to prepare the catalyst were followed the same procedures as above.

Chapter 3 Results and Discussion

3.1 Application of new chiral amino alcohols in the asymmetric borane-reduction of ketones



Having prepared the four new catalysts **A**, **B**, **C**, **D**, their catalytic properties were examined by employing them in the asymmetric borane-reduction of ketones [Eq. 27]. The results are shown in Table 3-1.



73 74

Table 3-1 Asymmetric borane-reduction of acetophenone (73)

Entry	Cat	L/S(%)	e.e.(%)	Conversion(%)	configuration
1	**A**	5	65.0	100	R
2	**B**	5	75.0	100	R
3	**A**	15	76.7	100	R
4	**B**	15	81.3	100	R
5	**A**	20	93.7	100	R
6	**B**	20	94.7	100	R
7	**C**	20	70.6	72.6	S
8	**D**	20	76.2	100	S

Substrate : BH_3.THF = 1 : 1.1 ; Different L/S ratio was performed by varying amount of substrate; Reaction time = 2 hours

Comparing entries 1-8 in Table 3-1, it was found that Cat **B** and **D** gave higher enantioselectivites than Cat **A** and **C**, respectively, in the reduction of acetophenone (**73**) to 1-phenylethanol (**74**) as shown in Eq. 27. These results confirmed the prediction that chiral amino alcohols containing cyclohexyl groups gave higher enantioselectivity than their phenyl counterparts. In addition, higher ligand to substrate ratio gave higher enantioselectivity. However, the improvement of e.e. by Cat **B** as compared to Cat **A** became less significant (entries 1-6). For example, when L/S = 5 %, the difference of e.e. between Cat **A** and **B** was as high as 10% (entries 1 and 2), but was only 1 % difference for L/S = 20% (entries 5 and 6). The variation of e.e. of Cat **A** and **B** with the increase of ligand to substrate ratio was shown in fig. 3-1.

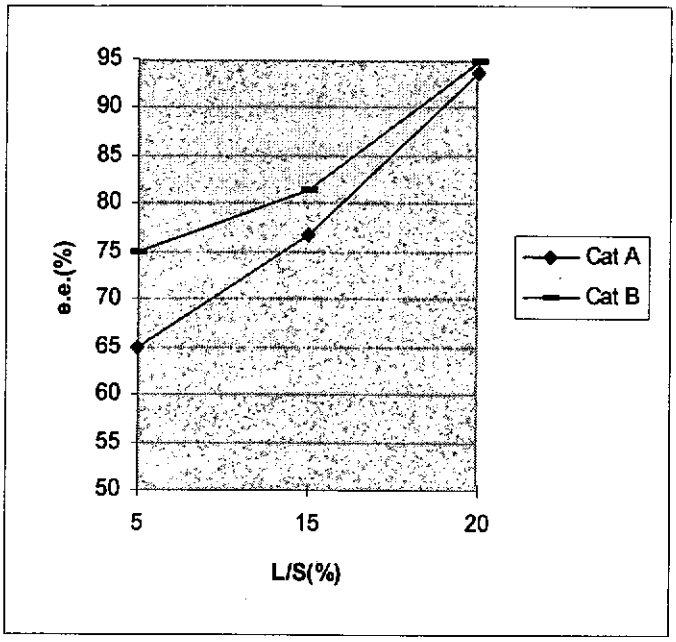
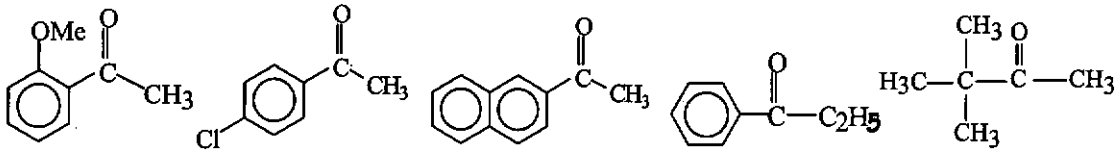


Fig. 3-1 The variation of e.e. of Cat **A** and Cat **B** with the increase of ligand to substrate ratio (L/S)

Moreover, since Cat **C** and Cat **D** were less reactive than **A** and **B**, use of Cat **D** has exhibited significant improvement on reaction conversion(entries 7 and 8 in Table 3-1).

Based on these preliminary results, a detailed study of this reaction with different ketones was performed.

2'-methoxyacetophenone (**75**), 4'-chloroacetophenone (**76**), 2'-acetonaphthone (**77**), propriophenone (**26**) and 3,3-dimethyl-2-butanone (**78**) were employed as substrates.



75 **76** **77** **26** **78**

Table 3-2 Enantioselective borane reduction of different prochiral ketones

Entry	Substrate	Cat	e.e.(%)	conversion(%)	configuration
1	**75**	A	69.2	100	S
2	**75**	B	78.1	100	S
3	**75**	C	54.4	78.4	R
4	**75**	D	79.1	100	R
5	**76**	A	59.3	100	R
6	**76**	B	67.4	100	R
7	**77**	A	73.0	100	R
8	**77**	B	76.4	100	R
9	**26**	A	61.8	100	R
10	**26**	B	67.9	100	R
11	**26**	C	24.5	100	S
12	**26**	D	61.0	100	S
13	**78**	A	39.8	15.6	R
14	**78**	B	44.4	14.0	R
15	**78**	C	7.0	11.2	S
16	**78**	D	30.8	14.9	S

Substrate: Ligand : BH_3.THF = 1 : 0.2 : 1.1 ; Ligand to substrate ratio = 20% ; reaction time = 2 hours

Table 3-2 shows a consistent improvement of enantioselectivity when using cyclohexyl groups on chiral ligands. In some cases, the enhancement of e.e. were significant (e.g. entries 3 and 4, 5 and 6, 11 and 12). All catalysts gave low conversions and enantioselectivities for aliphatic ketones (entries 13-16). The reaction for such poor reaction of aliphatic ketones **78** not yet fully understood, these results were formally similar to most of the chiral oxazaborolidines reported in the literature. Such a low reactivity towards reduction might be due to electron-donating ability of alkyl groups to the carbonyl groups so that the carbonyl carbon became less susceptible to the hydride transfer. In addition, lack of bulky substituent adjacent to the carbonyl group for enantiofacial selection might the cause for the lower e.e. Nevertheless, the superiority of Cat **B** and **D** over Cat **A** and **C** was still observed. For substrates **75** (entries 1-4), it was surprising to note that the configurations of the resulting 2'-methoxy-1-phenylethanol (**79** on fig. 3-5) were opposite to all corresponding entries of other substrates. Naturally, for chiral ligands with two chiral centres, (1R,2S)- ligands should give product with R configuration, for chiral ligands with one chiral centre, (R)- ligands should give product with S configuration.[1,17,18] These unusual results suggested a modified transition state for this reaction.

According to the mechanism of Corey et al.,[1] the borane reduction of prochiral ketones using chiral 1,3,2-oxazaborolidines as catalysts consists of four steps : I, formation of the borane adduct **c**; II, coordination of the ketone to borane adduct **c** giving **d** - a transition state; III, stereospecific

transformation of a hydride from BH_3 to the carbonyl carbon; IV, releasing of the product to regenerate the catalyst (fig. 3-2).

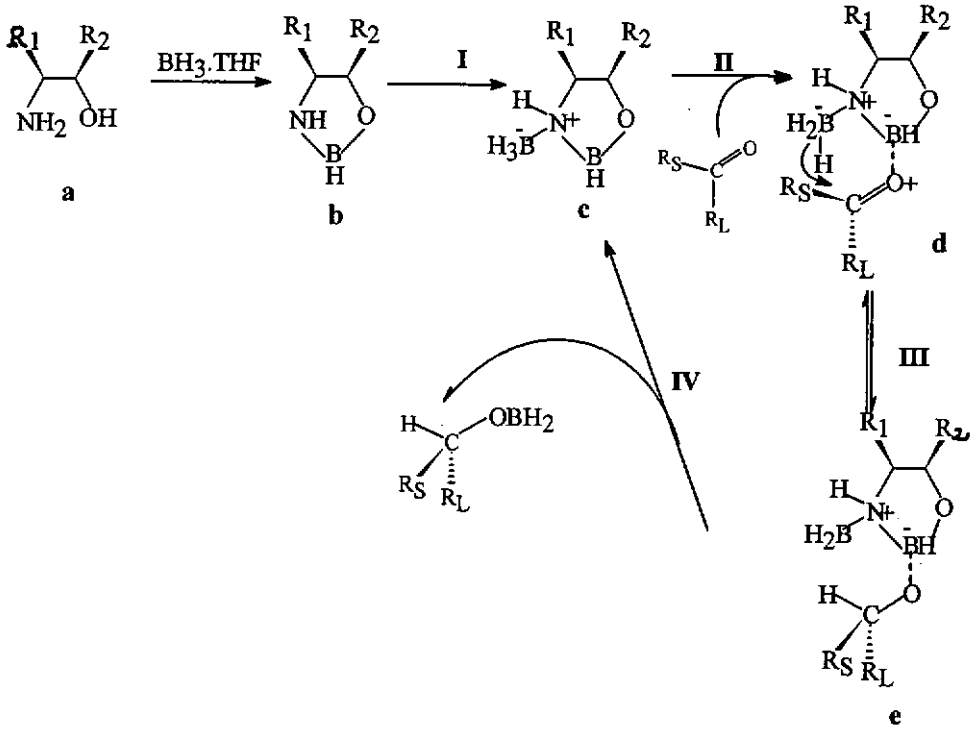


Fig. 3-2 Mechanism of asymmetric borane-reduction of ketones by 1,3,2-oxazaborolidine, demonstrating the four critical steps [1]

From the above mechanism, Corey and coworkers suggested that the absolute stereochemistry of the chiral alcohols produced could be predicted. It was based on the sizes of the two alkyl groups attached to the carbonyl group of the prochiral ketones as well as the configuration of the chiral ligand. The concept was depicted below (Fig. 3-3).

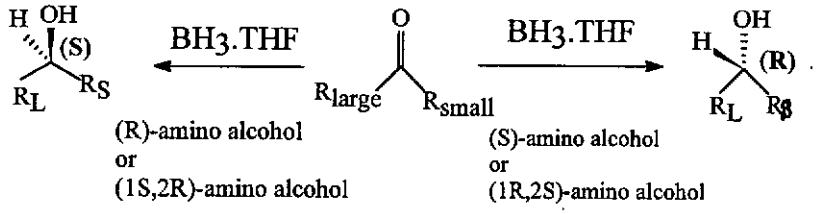
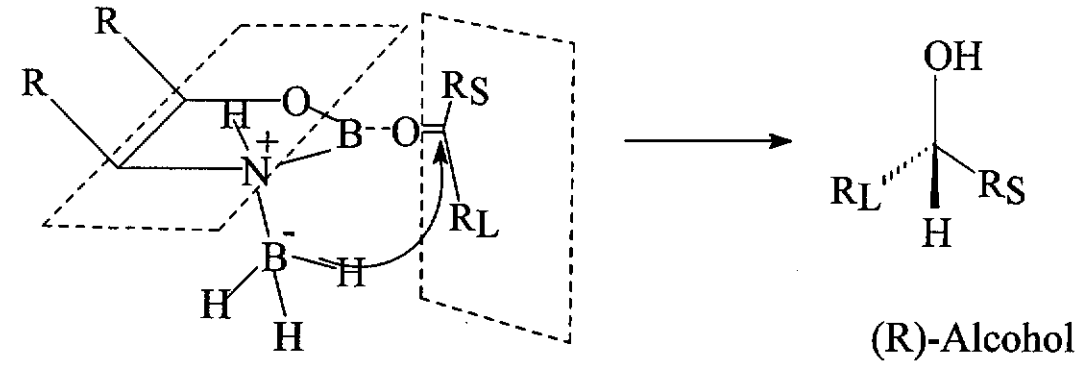
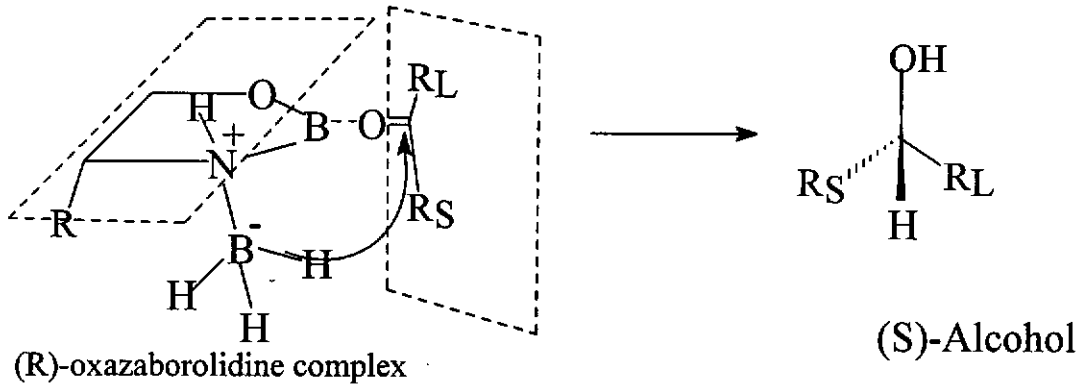


Fig. 3-3 The prediction of absolute stereochemistry of the resulting chiral alcohols developed by Corey et al [1,17,18]

For asymmetric borane-reduction of acetophenone (**73**) and most of the common prochiral ketones, the above mechanism was valid to predict the absolute configurations of the resulting chiral alcohols. The validity can be demonstrated by the two 3-dimensional transition states below.[43]



(1R,2S)-oxazaborolidine complex



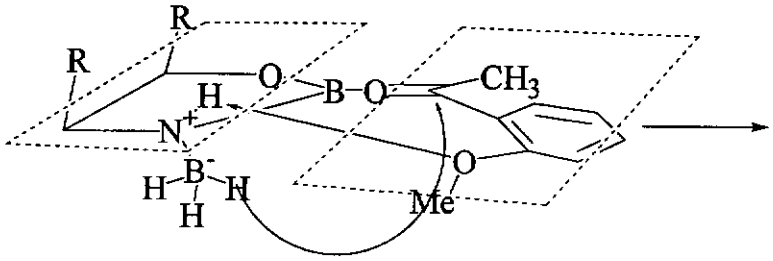
(R)-oxazaborolidine complex

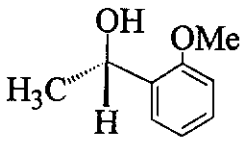
Fig. 3-4 Three-dimensional transition state of asymmetric borane-reduction of general ketones showing the perpendicular coordination between the substrate and oxazaborolidine catalysts [43]

From fig. 3-4, the ketone molecule was coordinated to the oxazaborolidine perpendicularly with the larger alkyl group (R_L) oriented oppositely to the large R groups on the ligand . This is the most stable transition state because these two bulky groups were the most distant.

Therefore, the enantiofacial attack of the hydride ion could be established.

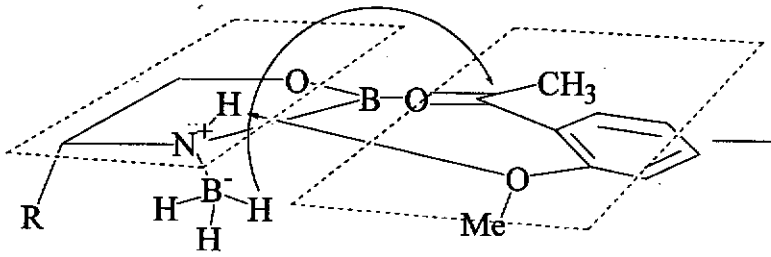
Unfortunately, the experimental results of entries 1-4 on Table 3-2 could not be explained based on above hypothesis, which the resulting 2'-methoxy-1-phenylethanol (**79**) of entries 1 and 2 in Table 3-2 should be R configuration and entries 3 and 4 should be S configuration. It indicated that the coordination-pattern of **75** with the chiral oxazaborolidines was not simply according to the steric-hindrances of various groups as suggested previously. Therefore, it is important to examine the role of *o*-methoxy group during the transition state.

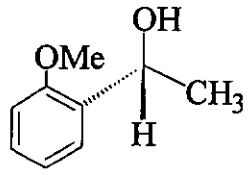




(S)-2'-methoxy-1-phenylethanol

(1R,2S)-oxazaborolidine complex





(R)-oxazaborolidine complex

(R)-2'-methoxy-1-phenylethanol

Fig. 3-5 Suggested 3-dimensional transition states of asymmetric borane-reduction of 2'-methoxyacetophenone (**75**) showing the planar coordination between **75** and oxazaborolidine catalysts

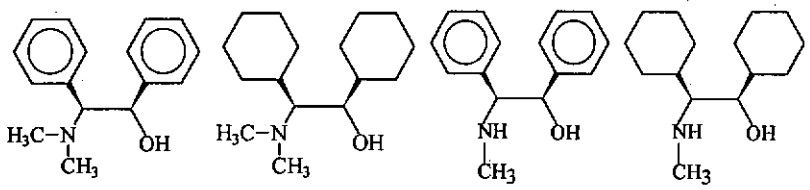
The above is the proposed 3-dimensional transition state of asymmetric borane-reduction of 2'-methoxyacetophenone **75** (Fig. 3-5). The lone pairs of electrons of the methoxy group could interact with the positively charged-N atom, thus, a horizontal coordination between the ketone and the oxazaborolidine was established. The enantiofacial attack was controlled by the steric hindrance of the bulky R groups on the hydride nucleophile. The above hypothesis explained the configurations obtained in entries 1-4 on table 3-2. In addition, we could observe that this kind of enantiofacial control was less effective than general perpendicular coordination.

From the above transition states (Fig. 3-4 and 3-5), the bulkier the R groups are, the more efficient is the enantiofacial discrimination, that is the reason why Cat **B** and **D** gave higher enantioselectivity than Cat **A** and **C**.

In summary, these findings add a new dimension to the chemistry of asymmetric borane-reduction as well as catalysts based on chiral amino alcohols. The modified ligands can be applied on a wide variety of asymmetric catalytic reactions and achieve impressive improvement.

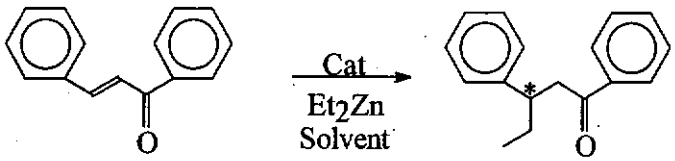
3.2 Application of new chiral amino alcohols in the asymmetric conjugate addition of diethylzinc to enones

Ligand derived :



Catalyst **1** **2** **3** **4**

Asymmetric conjugate addition of diethylzinc to chalcone (**40**) was studied using Cat **2**. Table 3-6 shows the effect of organic solvent on both conversion and enantioselectivity.



40 **80** [Eq. 28]

Table 3-3 Solvent effect of catalyst 2

Entry	Solvent	e.e.(%)	Conversion(%)	Configuration
1	THF	/	trace	/
2	Diethyl ether	/	trace	/
3	CH_2Cl_2	41.8	30.3	S
4	Toluene	45.8	21.4	S
5	MeCN	82.0	88.9	S

Cat = Cat 2; Substrate : Et_2Zn : $Ni(acac)_2$: ligand : 2,2-bipyridyl = 1 : 1.2 : 0.07 : 0.17 : 0.07; reaction time = 12 hours; reaction temperature = -30°C.

Results in Table 3-3 show that MeCN gives higher conversion and e.e. than CH_2Cl_2 and toluene for the alkylation of chalcone (**40**) to (S)-1,3-diphenylpentane-1-one (**80**). When THF and diethyl ether were used as solvents (entries 1 and 2), only trace amount of (S)-1,3-diphenylpentan-1-one (**80**) was detected. It was probably due their poor solubilities to the substrate and catalyst repectively. In addtion, reactions in CH_2Cl_2 and toluene(entries 3 and 4) gave only moderate e.e. and conversion indicated that a solvent with high polarity might be beneficial for this catalytic reaction.

Effect of Cat **1-4** on the asymmetric conjugate addition of diethylzinc to chalcone (**40**) was investigated in both toluene and acetonitrile (Table 3-4).

Table 3-4 Comparison of catalysts 1, 2, 3, 4 in the asymmetric conjugate addition of diethylzinc to chalcone (40)

Entry	Cat	Solvent	e.e.(%)	conversion(%)	configuration
1	**1**	Toluene	1.6	43.4	S
2	**2**	Toluene	45.8	21.4	S
3	**1**	MeCN	33.2	53.2	S
4	**2**	MeCN	82.0	88.9	S
5	**3**	MeCN	/	trace	/
6	**4**	MeCN	/	trace	/

Substrate : Et_2Zn : $Ni(acac)_2$: ligand : 2,2-bipyridyl = 1 : 1.2 : 0.07 : 0.17 : 0.07; reaction time = 12 hours; reaction temperature = -30°C

It was noted that the enantioselectivity of chiral catalyst was enhanced tremendously from Cat **1** to Cat **2** in both solvent systems. Cat **1** gave an almost racemic product in toluene (entry 1) and low enantioselectivity in MeCN (entry 3). Thus the advantage of the more sterically-demanding 1,2-dicyclohexyl backbone of Cat **2** was clearly demonstrated in this reaction. Beside the steric effect, ligand with cyclohexyl groups which had better electron-donating ability than its phenyl analogs probably stabilized the catalyst complex when coordinating to the electron-deficient Ni(II) metal. Since MeCN gave the best rate and enantioselectivity, it was chosen as the solvent for the subsequent study.

When using Cat. **3** and Cat **4**, only trace amount of (S)-1,3-diphenylpentan-1-one (**80**) was detected (entries 5 and 6). Although the detailed mechanism of this reaction was still not clear, the proton present on amino group of the ligand might play an important role to deactivate the catalyst. The two alkyl groups on N atom of Cat **1** and Cat **2** also helped to stabilize the rigidity of the catalyst complex.

Effect of ligand to substrate ratio of Cat **1** and Cat **2** on asymmetric conjugate addition of diethylzinc to chalcone (**40**) is shown in Table 3-5.

Table 3-5 Effect of ligand to substrate ratio of Cat 1 and 2 on asymmetric conjugate addition of diethylzinc to chalcone (40)

Entry	Cat	L/S(%)	e.e.(%)	conversion(%)	configuration
1	**1**	10	31.2	31.4	S
2	**2**	10	80.0	41.8	S
3	**1**	17	33.2	53.2	S
4	**2**	17	82.0	88.9	S
5	**1**	20	38.8	69.0	S
6	**2**	20	80.7	99.5	S
7	**1**	25	37.2	89.3	S
8	**2**	25	80.9	100	S

Et_2Zn : $Ni(acac)_2$: ligand : 2,2-bipyridyl = 7.1 : 0.41 : 1 : 0.41; Different L/S ratio was performed by varying amount of substrate; Reaction time = 12 hours; Reaction temperature = -30°C; Solvent = MeCN

The enantioselectivity of the reaction of both catalysts was found to be insensitive to the concentration of chiral ligand used in this catalytic reaction (entries 1, 3, 5, 7 and 2, 4, 6, 8). However, higher conversion was obtained with the increase of chiral ligand concentration. Furthermore, it was noted that the use of Cat **2** led to a substantial increase on conversion, while Cat **1** resulted in a graduate increase. The change of conversions of Cat **1** and Cat **2** with ligand to substrate ratio (L/S%) is demonstrated in Fig. 3-6. It can be explained by the significantly higher reactivity of Cat **2**, therefore, a plateau of converion against L/S(%) occured earlier than Cat **1**.

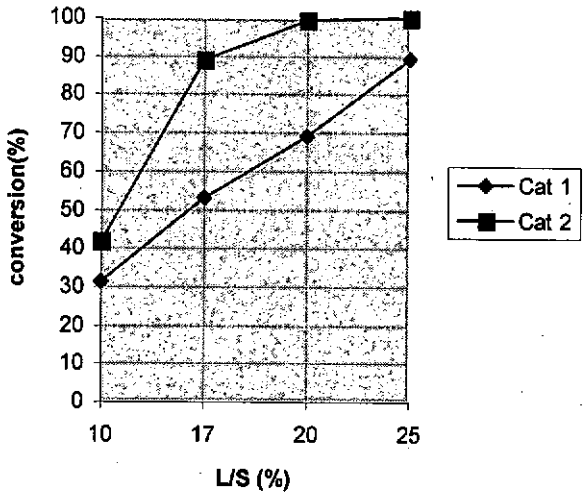


Fig. 3-6 Change of conversions of Cat **1** and Cat **2** with ligand to substrate ratio (L/S%)

Chiral catalysts containing rare-earth metals are attracting much interest recently. In the study of the asymmetric conjugate addition of diethylzinc to chalcone (**40**), we used $La(acac)_2$ as metal complex to prepare the chiral catalysts. Unfortunately, only low enantioselectivities were obtained (Table 3-6). However, the results still reflected the superiority of ligand **69** over ligand **23**.

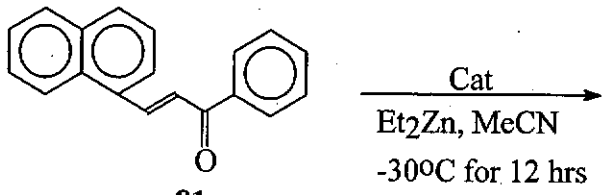
Table 3-6 The effect of using rare-earth metal $La(acac)_2$ to prepare the catalyst

Entry	Ligand	e.e.(%)	Conversion(%)	configuration
1	**23**	8.9	7.1	S
2	**69**	38.7	4.8	S

Substrate : Et_2Zn : $La(acac)_2$: ligand : 2,2-bipyridyl = 1 : 1.2 : 0.07 : 0.17 : 0.07; Reaction time = 12 hours; reaction temperature = -30°C

The superiority of Cat **2** over Cat **1** was further established by employing them in asymmetric conjugate addition of diethylzinc to various enones [Eq. 29-32].

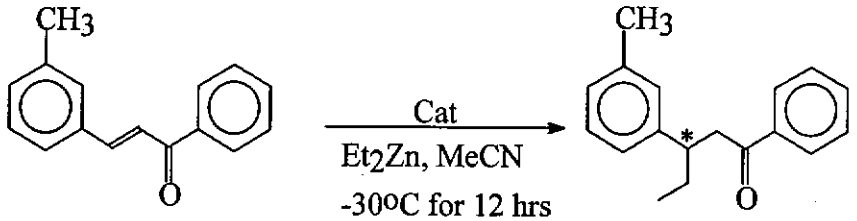
The results are shown in Table 3-7. Previous reports of employing enones with substituted aromatic rings as substrates was much less than those employing chalcone (**40**), therefore, it is valuable to explore and investigate this area.



[Eq. 29

81

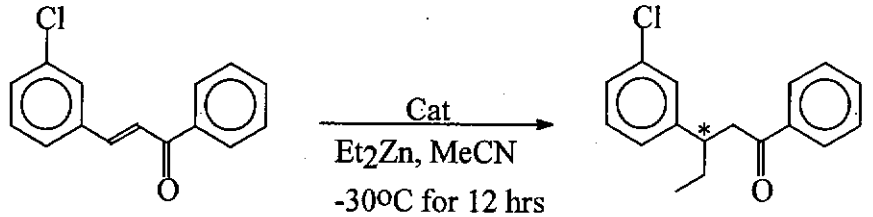
3-(1-Naphthalenyl)-1-phenyl-2-propen-1-one



[Eq. 30]

82

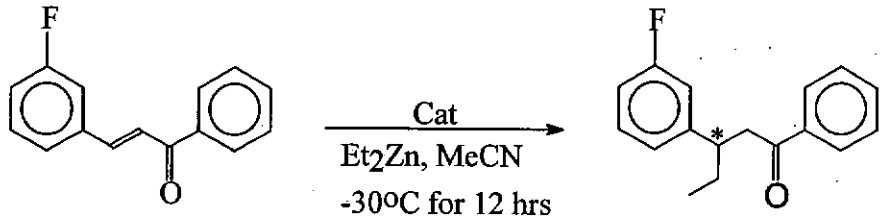
3-(3-Methylbenzyl)-1-phenyl-2-propen-1-one



[Eq. 31]

83

3-(3-Chlorobenzyl)-1-phenyl-2-propen-1-one

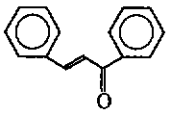
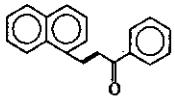
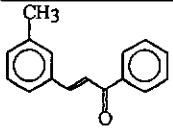
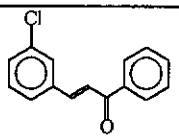
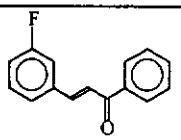


[Eq. 32]

84

3-(3-Fluorobenzyl)-1-phenyl-2-propen-1-one

Table 3-7 Asymmetric conjugate addition of diethylzinc to 40, 81-84

Substrate	e.e.(%)		conversion(%)		configuration
	Cat **1**	Cat **2**	Cat **1**	Cat **2**	
 **40**	33.2	82.0	53.2	88.9	S
 **81**	41.5	78.6	27.7	42.6	S
 **82**	60.0	79.8	14.0	31.1	S
 **83**	45.2	80.9	45.3	48.3	S
 **84**	41.1	86.7	27.5	36.4	S

Substrate : Et_2Zn : $Ni(acac)_2$: ligand : 2,2-bipyridyl = 1 : 1.2 : 0.07 : 0.17 : 0.07; reaction time = 12 hours; reaction temperature = -30°C.

Results in Table 3-7 demonstrate that Cat **2** is consistently better than Cat **1** regarding both the conversion and the enantioselectivity. On the other hand, the conversions of these enones (**81-84**) were generally lower than conjugate addition to chalcone (**40**). It was probably due to the presence of substituents on aromatic rings of the substrates caused steric hindrance for the attack of ethyl anion and the presence of substituents destabilized the coordination. It was also interesting to note that substituent

on the aromatic ring of enone had some effect on the enantioselectivity when Cat **1** was employed, but little effect was observed for Cat **2**.

Finally, these results again give an evidence of the generality of the advantage of the sterically more-demanding 1,2-dicyclohexyl backbone. On the other hand, an effective catalyst (Cat **2**) has been developed which is one of the best catalysts among all previous reported catalysts in the asymmetric conjugate addition of diethylzinc to enones.

Chapter 4 Conclusions

Summary :

1) Design and synthesis of a series of easily prepared chiral amino alcohols containing cyclohexyl groups. These new ligands can furnish the investigation of steric and electronic effects of substituents on chiral amino alcohols. This topic maybe significantly interesting both for its novelty and for its practical value.

2) Application of (1R,2S)-2-amino-2-cyclohexylethanol(**68**) and (R)-2-amino-1,2-dicyclohexylethanol(**67**) in the asymmetric borane-reduction of prochiral ketones has revealed that these newly synthesized ligands are consistently more effective than their phenyl counterparts.

3) A supplement of the existing mechanism of asymmetric borane-reduction has been proposed.

4) Application of (1R,2S)-N,N-dimethyl-2-amino-1,2-dicyclohexylethanol (**69**) in the asymmetric conjugate addition of diethylzinc to enones with high reactivity and enantioselectivty. Furthermore, this ligand has been found to be significantly more effective than its phenyl counterpart.

Claims to original research

1. Synthesis of (1R,2S)-2-amino-1,2-dicyclohexylethanol (**67**), (R)-2-amino-2-cyclohexylethanol(**68**), (1R,2S)-N,N-dimethyl-2-amino-1,2-dicyclohexyethanol (**69**) and (1R,2S)- N-methyl-2-amino-1,2-dicyclohexylethanol (**70**).
2. Application of (1R,2S)-**67** and (R)-**68** in asymmetric borane-reduction of ketones and application of (1R,2S)-**69** and (1R.2S)-**70** in the asymmetric conjugate addition of diethylzinc to enones.

Conclusions

The development of a new, highly efficient method for the production of chiral amino alcohols containing cyclohexyl groups (**67** and **68**) from their phenyl analogs opens up a new frontier for the development of more efficient synthetic methods. The application of the new 1,3,2-oxazaborolidines (Cat **B** and **D**) containing cyclohexyl groups in the asymmetric borane-reduction of prochiral ketones clearly demonstrates consistent superiority of these new chiral amino alcohols over their phenyl analogs. The supplement of existing mechanism of the asymmetric borane-reduction also furnishes the chemistry of this area. The tremendous improvement of reaction rate and enantioselectivity by employing new catalyst (Cat **2**) containing cyclohexyl group, in the asymmetric conjugate addition of enones, is of particularly high scientific and practical interest. The chemistry of asymmetric conjugate addition of enones with substituted aromatic rings has also been furnished. This finding establishes the generality of the advantage of the

sterically more demanding cyclohexyl groups, excellent opportunities are offered for upgrading many existing catalytic systems.

Recommendations

There are several prospects of this work which are valuable to be explored in the future :

1. The hydrogenation of phenyl rings of other existing chiral amino alcohols by similar procedures can be performed to achieve substantial exploration of this area.

2. The improvement of enantioselectivity in asymmetric borane-reduction by new catalysts containing cyclohexyl group was not significant enough, some other substrates/reaction conditions can be examined to achieve impressive improvement.

3. The generality of the suggested mechanism of the asymmetric borane-reduction of 2'-methoxyacetophenone (**75**) needs to be established by employing more different kinds of similar ketones e.g. ketones with aromatic ring containing hydroxy group.

4. The detailed mechanism of asymmetric conjugate addition has not been fully understood, the mechanistic study is valuable to be performed.

5. The low conversions of asymmetric conjugate addition of diethylzinc to enones with substituted -aromatic rings (**81-84**) can be improved after the establishment of the mechanism. Examining different ligands, metals, reaction conditions and different organozinc reagents will be potential to develop highly efficient catalysis.

References

1. US patent # 4,943,635 Corey, E. J. **1990**

2. Hayashi, M.; Miyamoto, Y.; Inoue, T.; Oguni, N. "Enantioselective trimethylsilylcyanation of some aldehydes by chiral titanium Schiff's base complex". *J. Chem. Soc., Chem. Commun.* **1991**, 1752-1753

3. (a) Soai, K.; Yokoyama, S.; Hayasaka, T. "Chiral *N,N*-Dialkylnorephedrines as catalysts of the highly enantioselective addition of dialkylzincs to aliphatic and aromatic aldehydes. The asymmetric synthesis of secondary aliphatic and aromatic alcohols of high optical purity". *J. Org. Chem.* **1991**, 56, 4264-4268

   (b) Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. "Catalytic asymmetric induction. Highly enantioselective addition of dialkylzincs to aldehydes". *J. Am. Chem. Soc.* **1986**, 108, 6071-6072

4. (a) Soai, K.; Hayasaka, T.; Ugajin, S. "Asymmetric synthesis of optically active β-substituted ketones by highly enantioselective catalytic conjugate addition of dialkylzinc reagents to enones using a catalyst system of nickel(II)-chiral ligand-achiral ligand in acetonitrile/toluene". *J. Chem. Soc., Chem. Commun.* **1989**, 516-517

   (b) Bolm, C. "Asymmetric amplification in nickel-catalyzed conjugate addition to chalcone". *Tetrahedron: Asymmetry* **1991**, 2, 701-704

5. (a) Carreira, E. M.; Singer, R. A.; Lee, W. S. "Catalytic enantioselective aldol addition with methyl and ethyl acetate *O*-Silyl enolates: A chiral

tridentate chelate as a ligand for titanium(IV)". *J. Am. Chem. Soc.* **1994**, 116, 8837-8838

(b) Singer, R. A.; Carreira, E. M. "Catalytic, enantioselective dienolate additions to aldehydes: preparation of optically active acetoacetate aldol adducts". *J. Am. Chem. Soc.* **1995**, 117, 12360-12361

6. Ando, A.; Shoir, T. "Asymmetric synthesis using chiral bases: Enantioselective α-alkylation of carboxylic acids". *J. Chem. Soc., Chem. Commun.* **1987**, 656-658

7. Evans, D. A.; Nelson, S. G.; Gagne, M. R.; Muci, A. R. "A chiral samarium-based catalyst for the asymmetric Meerwein-Ponndorf-Verley reduction". *J. Am. Chem. Soc.* **1993**, 115, 9800-9801

8. (a) Soai, K.; Kawase, Y. "Asymmetric synthesis of β-hydroxyesters by the enantioselective Reformatsky reaction in the presence of chiral aminoalcohols". *Tetrahedron : Asymmetry* **1997**, 2, 781-784

(b) Soai, K.; Hrirose, Y.; Sakata, S. "Highly enantioselective synthesis of β-hydroxy nitriles by the cyanomethylation of aldehydes using DPMPM as a chiral catalyst or ligand". *Tetrahedron : Asymmetry* **1992**, 3, 677-680

(c) Soai, K.; Oshio, A.; Saito, T. "Enantioselective Reformatsky reaction with ketones. Asymmetric reaction with ketones. Asymmetric synthesis of β-(tert-hydroxy)esters". *J. Chem. Soc. Chem. Commun.* **1993**, 811-812

9. Mutez, S.; Mortreux, A.; Petit, F. "Asymmetric hydroformylation of styrene on aminophosphinephosphinites modified platinum catalysts". *Tetrahedron Lett.* **1988**, 29, 1911-1914

10. Hatat, C.; Kokel, N.; Mortreux, A.; Petit, F. "New chiral mixed AMPP ligands and their use in asymmetric hydrogenation of activated ketones on rhodium catalysts". *Tetrahedron Lett.* **1990**, 31, 4139-4142

11. Jiang, Y.Z.; Yong, Q.; Mi, A. Q. "Enantioselective reduction of ketones catalyzed by new (4S,5R)-4,5-diphenyl-1,3,2-oxazaborolidine". *Tetrahedron : Asymmetry* **1994**, 5, 1211-1214

12. Takehara, J.; Hashiguch, S.; Fujii, A.; Inoue, S. I.; Ikariya, T.; Noyori, R. "Amino alcohols effects on the ruthenium(II)-catalyzed asymmetric transfer hydrogenation of ketones in propan-2-ol". *Chem. Commun.* **1996**, 233-234

13. Singh, V. K. "Practical and useful methods for the enantioselective reduction of unsymmetrical ketones". *Synthesis* **1992**, 605-617

14. Hirao, A.; Itsuno, S.; Nakahama, S.; Yamazaki, N. "Asymmetric reduction of aromatic ketones with chiral alkoxy-amine-borane complexes". *J. Chem. Soc. Chem. Commun.* **1981**, 315-317

15. Itsuno, S.; Nakano, M.; Miyazaki, K.; Masuda, H.; Ito, K. "Enantioselective reduction of ketones and oxime ethers with reagents prepared from borane and chiral amino alcohols". *J. Chem. Soc. Perkin Trans I* **1985**, 2039-2044

16. Corey, E. J.; Bakshi, R. K.; Shibata, S. "Highly enantioselective borane reduction of ketones catalyzed by chiral oxazaborolidines. Mechanism and synthetic implications". *J. Am. Chem. Soc.* **1987**, 109, 5551-5553

17. (a) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen C.; Singh, V. K. "A stable and easily prepared catalyst for the enantioselective reduction of ketones. Applications to multistep syntheses". *J. Am. Chem. Soc.* **1987**, 109, 7925-7926

(b) Corey, E. J.; Bakshi, R. K.; Shibata, S. "An efficient and catalytically enantioselective route to (S)-(-)-phenyloxirane". *J. Org. Chem.* **1988**, 53, 2861-2863

18. Quallich, G. J.; Woodall, T. M. "Enantioselective oxazaborolidine reduction of ketones containing heteroatoms". *Tetrahedron Lett.* **1993**, 34, 785-788

19. (a) Hirao, A.; Isuno, S.; Nakahama, S.; Yamazaki, N. "Asymmetric reduction of aromatic ketones with chiral alkoxy-amine-borane complexes". *J. Chem. Soc. Chem. Commun.* **1981**, 315-317

(b) Youn, I. K.; Lee, S. W.; Pak, C. S. "Asymmetric borane-reduction of ketones catalyzed by oxazaborolidine". *Tetrahedron: Asymmetry* **1988**, 29, 4453-4456

(c) Corey, E. J.; Chen, C. P.; Peichard, G. A. "(+)-1(S),5(R),8(S)-8-phenyl-2-azabicyclo[3.3.0]octane-8-ol N,O-methyl-boronate and its enantiomer, chiral chemzymes which serve as catalysts for their own enantioselective synthesis". *Tetrahedron Lett.* **1989**, 30, 5547-5550

(d) Rao, A. V. R.; Gurjar, M. K.; Sharma, P. A.; Kaiwar,V. "Enantioselective reductions of ketones with oxazaborolidines derived from (R) and (S)-α,α-diphenyl-2-piperidine methanol". *Tetrahedron Lett.* **1990**, 31, 2341-2344

(e) Wallbaum, S.; Martens, J. "Enantioselective catalytic reductions of ketones: Synthesis and application of a new structurally rigid bicyclic catalyst". *Tetrahedron: Asymmetry* ". **1991**, 2, 1093-1096

(f) Tanaka, K.; Matsui, J.; Suzuki, H. "Enantiocontrolled reduction of prochiral aromatic ketones with borane using diastereoisomeric secondary aminoalcohols as chiral catalysts". *J. Chem. Soc. Chem. Commun.* **1991**, 1311-1312

(g) Rao, A. V. R.; Gurjar, M. K.; Kaiwar, V. "Enantioselective catalytic reductions of ketones with new four membered oxazaborolidines: Application to (S)-Tetramisole". *Tetrahedron: Asymmetry,* **1992**, 3, 859-862

(h) Stingl, K.; Martens, J.; Wallbaum, S. "Enantioselective catalytic borane reductions of aromatic ketones: Synthesis and application of two chiral β-amino alcohols from (S)-porretine". *Tetrahedron: Asymmetry*, **1992**,3, 223-226

(i) Martens, J.; Dauelsberg, Ch.; Behnen, W.; Wallbaum, S. "Enantioselective catalytic borane reductions of achiral ketones : synthesis and application of two chiral β-amino alcohols from (S)-2-indolne carboxylic acid". *Tetrahedron: Asymmetry* **1992**, 3, 347-350

(j) Cho, B. T.; Chun, Y. S. "Asymmetric borane reduction of achiral ketones mediated by a chiral oxazaborolidine derived from (-)-ephedrine". *Tetrahedron: Asymmetry* **1992**, 3, 1539-1542

20. Tanaka, K.; Matsui, J.; Suzuki, H. "Enantiocontrolled reduction of prochiral aromatic ketones with borane using diastereoisomeric secondary aminoalcohols as chiral catalysts". *J. Chem. Soc. Chem. Commun.* **1991**, 1311-1312
21. Prasad, K. R. K.; Joshi, N. N. "Stereoselective reduction of benzils: A new convenient route to enantiomerically pure 1,2-diarylethanediols". *J. Org. Chem.* **1996**, 61, 3888-3889
22. Zhang, F. Y.; Yip, C. W.; Chan, A. S. C. "The acceleration of the catalytic asymmetric borane reduction of ketones by organoaluminium compounds". *Tetrahedron: Asymmetry* **1996**, 7, 3135-3140
23. (a) Shen, Z. X.; Lu, Z.; Zhang, Q.; Zhang, Y. W. "Enantioselective borane-reduction of prochiral ketones catalyzed by a chloro-containing chiral β-amino alcohol". *Tetrahedron: Asymmetry* **1997**, 8, 2287-2289

(b) Ito, H.; Sato, A.; Taguchi, T. "Enantioselective aromatic Claisen rearrangement". *Tetrahedron Lett.* **1997**, 38, 4815-4818

(c) Calmes, M.; Escale, F.; Paolini, F. "Viable use of 2-substituted thiazolidine-4-methanol diastereoisomeric mixtures during asymmetric borane-reduction of aromatic ketones". *Tetrahedron: Asymmetry* **1997**, 8, 3691-3697

24. (a) Le TouMelin, J. B.; Baboulene, M. "Chiral intramolecular amine-borane complexes as reducing agents for prochiral ketones". *Tetrhedron: Asymmetry* **1997**, 8, 1259-1265

(b) Li, X. S.; Zie, R. G. "Enantioselective reduction of prochiral ketones catalyzed by new (R)-4-(phenylmercapto)methyl-5,5-diphenyl-1,3,2-oxazaborolidine and bis-[(R,R)-5,5-diphenyl-1,3,2-oxazaborolidine methyl]disulfide from L-cystine". *Tetrahedron: Asymmetry* **1997**, 8, 2283-2285

25. Shen, Z. X.; Huang, W.; Feng, J. W.; Zhang, Y. W. "Chiral oxazaborolidines bearing a 1- or 2- naphthylmethyl group as catalysts for enantioselective borane reduction of ketones: experimental and quantum calculations". *Tetrahedron: Asymmetry* **1998**, 9, 1091-1095

26. Schmalz, H. G.; Jope, H. "On the oxazaborolidine-catalyzed borane-reduction of 1-tetralone-$Cr(CO)_3$ complexes: The control of the reagent over a strong substrate". *Tetrahedron* **1998**, 54, 3457-3464

27. (a) Corey, E. J.; Perez, A. G.; Lazerwth, E. "An enantioselective synthetic route to atractyligenin using the oxazaborolidine-catalyzed reduction of β-silyl- or β-Stannyl-substituted α,β-enones as a key step". *J. Am. Chem. Soc.* **1997**, 119, 11769-11776

(b) Dougherty, J. T.; Flisak, J. R.; Hayes, J.; Lantos, I.; Li, L.; Tucker, L. "Asymmetric reduction of ketoxime ethers to optically active O-substituted hydroxylamines with reagents prepared from borane and chiral amino alcohols". *Tetrahedron: Asymmetry* **1997**, 8, 497-499

28. Rossiter, B. E.; Swingle, N. M. "Asymmetric conjugate addition". *Chem. Rev.* **1992**, 92, 771-806

29. Greene, A. E.; Lansard, J. P.; Luche, J. L.; Petrier, C. "Efficient syntheses of (±)-β-cuparenone. Conjugate addition to organozinc reagents". *J. Org. Chem.* **1984**, 49, 931-932

30. Soai, K.; Yokoyama, S.; Hayasaka, T.; Ebihara, K. "Catalytic asymmetric induction in enantioselective conjugate addition of dialkylzincs to enones". *J. Org. Chem.* **1988**, 53, 4148-4149

31. Bolm, C.; Ewald, M. "Optically active bipyridines in nickel catalyzed enantioselective conjugate addition to enones". *Tetrahedron Lett.* **1990**, 31, 5011-5012

32. De Vries, A. H. M.; Imbos, R.; Feringa, B. L. "(+)-Camphor-derived tri- and tetradentate amino alcohols; synthesis and applications as ligands in the nickel catalyzed enantioselective conjugate addition of diethylzinc". *Tetrahedron: Asymmetry* **1997**, 8, 1467-1473

33. De Vries, A. H. M.; Feringa, B. L. "Enantioselective conjugate addition of diethylzinc to chalcone catalyzed by $Co(acac)_2$ and chiral amino alcohols". *Tetrahedron: Asymmetry* **1997**, 8, 1377-1378

34. Alexakis, A.; Burton, J.; Vastra, J.; Mangeney, P. "Asymmetric conjugate addition of diethylzinc to enones with chiral phosphine ligands". *Tetrahedron Asymmetry* **1997**, 8, 3987-3990

35. (a) Riley, D. P.; Shumate, R. E. "1,2-bis(diphenylphosphino)-1-cyclohexyethane. A new chiral phosphine ligand for catalytic chiral hydrogenations". *J. Org. Chem.* **1980**, 45, 5187-5193

(b) Oliver, J. D.; Riley, D. P. "Asymmetric hydrogenation catalysis. X-ray structural and catalytic studies of the rhodium(I) complex with (R)-cycphos". *Organometallics* **1983**, 2, 1032-1038

36. Chan, A. S. C.; Zhang, F. Y.; Yip, C. W. "Novel asymmetric alkylation of aromatic aldehydes with triethylaluminium catalyzed by titanium(1,1'-bi-2-naphthol) and titanium(5,5',6,6',7,7',8,8'-octa-hydro-1,1'-bi-2-naphthol)complexes". *J. Am. Chem. Soc.* **1997**, 119, 4081-4082

37. Zhang, F. Y.; Chan, A. S. C. "Enantioselective conjugate addition of diethylzinc to cyclic enones catalyzed by chiral copper complexes containing a new phosphorus ligand with an H_8-binaphthoxy moiety". *Tetrahedron Asymmetry* **1998**, 9, 1179-1182

38. Cram, D. J.; Helgeson, R. C.; Peacock, S. C.; Kaplan, L. J.; Domeier, L. A.; Moreau, P.; Koga, K.; Mayer, J. M.; Chao, Y.; Siegel, M. G.; Hoffman, D. H.; Sogah, G. D. Y. " Macrocyclic polyethers shaped by two rigid substituted dinaphthyl or ditetralyl units". *J. Org. Chem.* **1978**, 48, 1930-1946

39. Mckennon, J.; Meyers, A. I. "A convenient reduction of amino acids and their derivatives". *J. Org. Chem.* **1993**, 58, 3568-3571

40. Li, S. J.; Jiang, Y. Z. "New chiral catalysts for the stereocontrolled addition of benzaldehyde by diethylzinc". *Tetrahedron: Asymmetry* **1992**, 3, 1467-1474

41. Jiang, Y. Z.; Mi, A. Q.; Wang, Z. Y.; Li, S. J. "Syntheses of chiral ligands: 1,2-diphenyl-2-(*N*-alkyl)amino alcohols". *YOUJI HUAXUE*, **1994**, 14, 68-73

42. Reiners, I.; Martens, J. "Suitably designed chiral amino alcohols: synthesis and application to the catalytic enantioselective reduction of aryl alkyl ketones". *Tetrahedron: Asymmetry* **1997**, 8, 277-281

43. Corey, E. J.; Azimioara, M.; Sarshar, S. "X-ray structure of a chiral oxazaborolidine catalyst for enantioselective carbonyl reduction". *Tetrahedron: Lett.* **1992**, 33, 3429-3430

44. Chiang, Y. Z.; Feng, X. M. "Asymmetric catalytic reactions with amino alcohols as chiral ligands". *Chemistry (The Chinese Chem. Soc., Taipei)*, 55, 67-79

45. Furniss, B.S.; Hannaford, A.J.; Smith, P.W.G.; Tatchell, A.R. "Chapter 6 Aromatic compunds". Longman Scientific and Technical, United Kingdom, 1034

Appendix 1 ^{1}H-, ^{13}C-NMR spectra

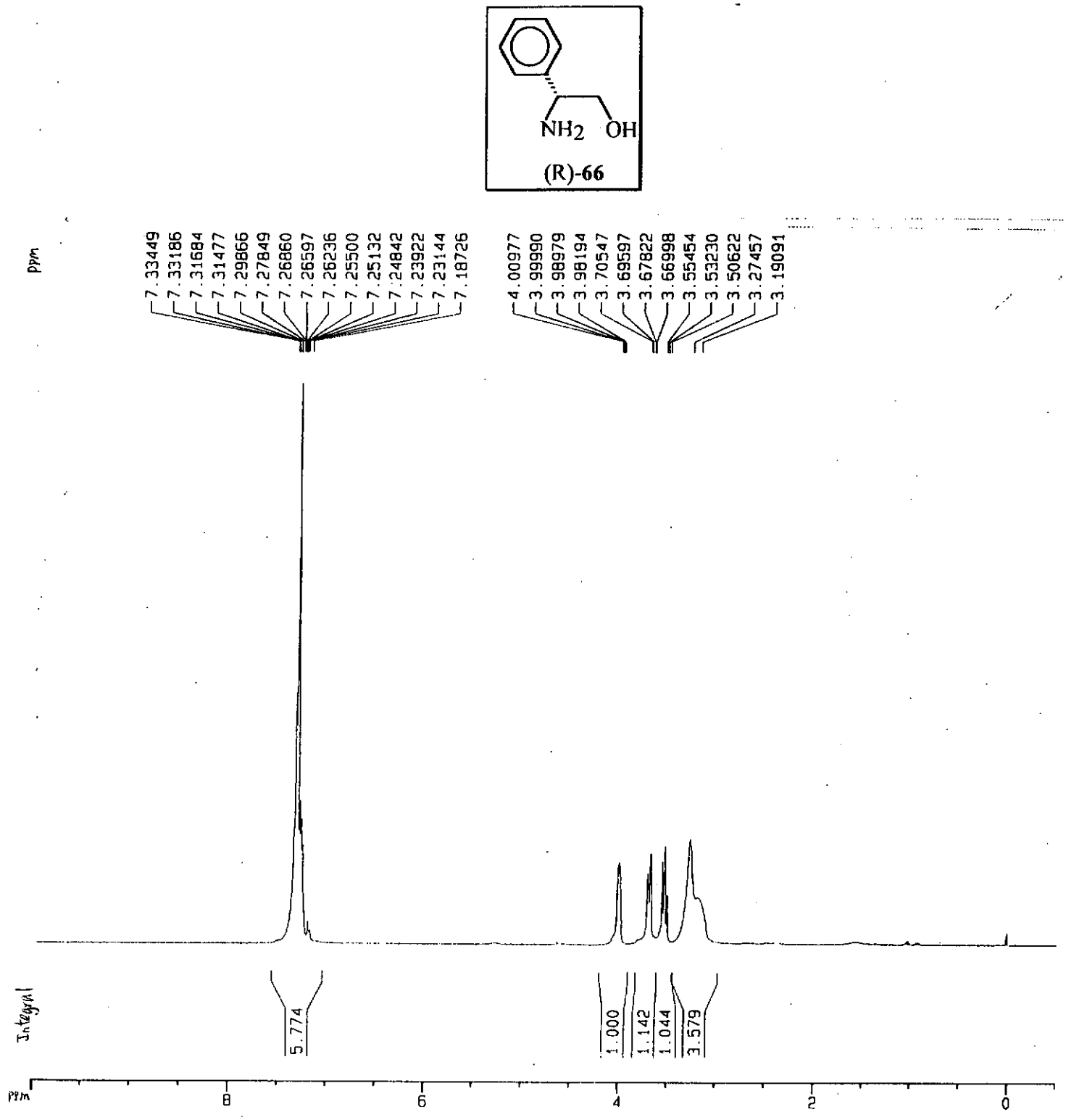


Fig. 4-1 ^{1}H NMR spectrum of (R)-**66**

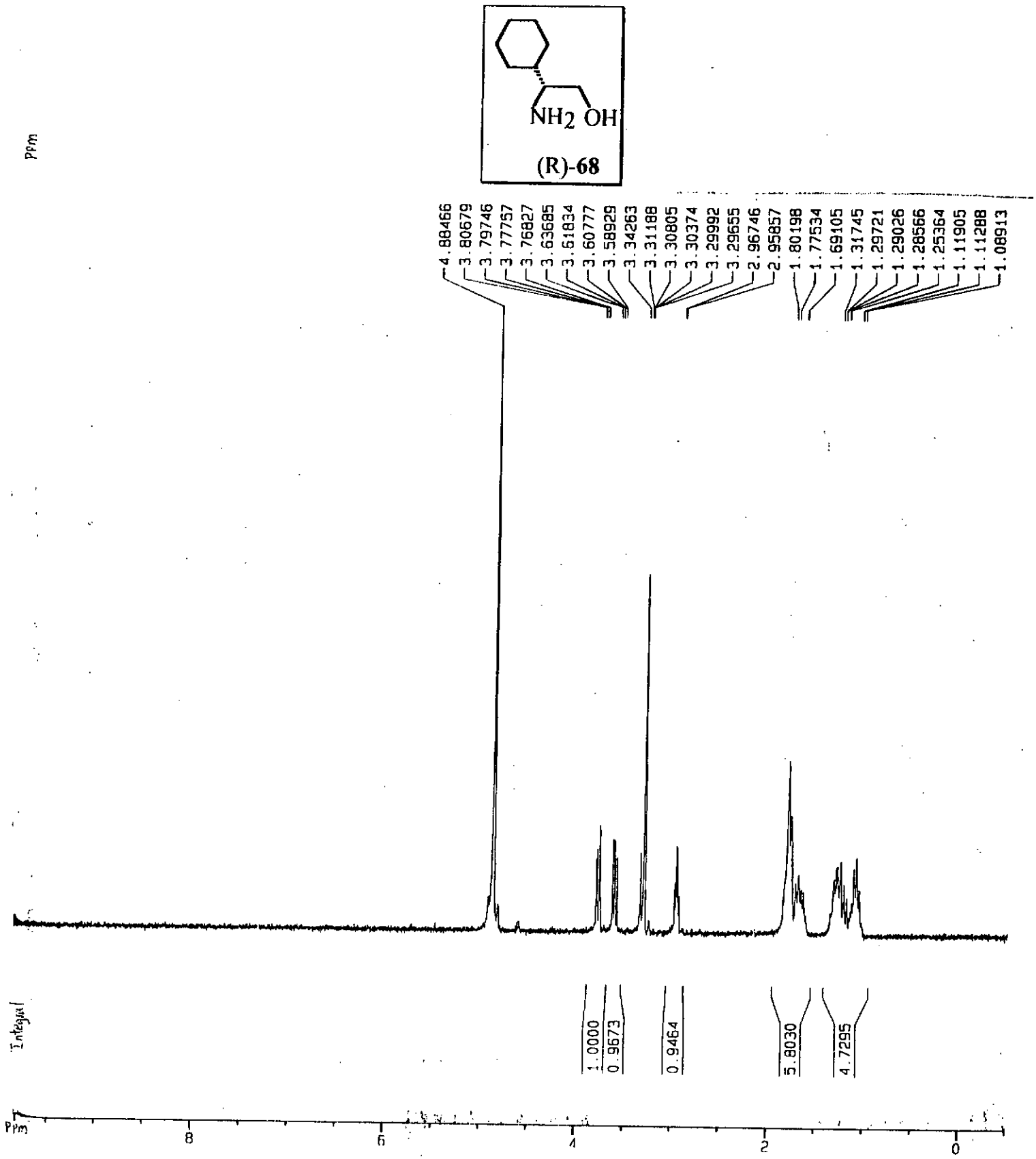
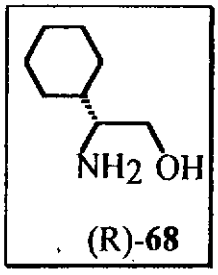


Fig. 4-2 ^{1}H NMR spectrum of (R)-**68**



(R)-**68**

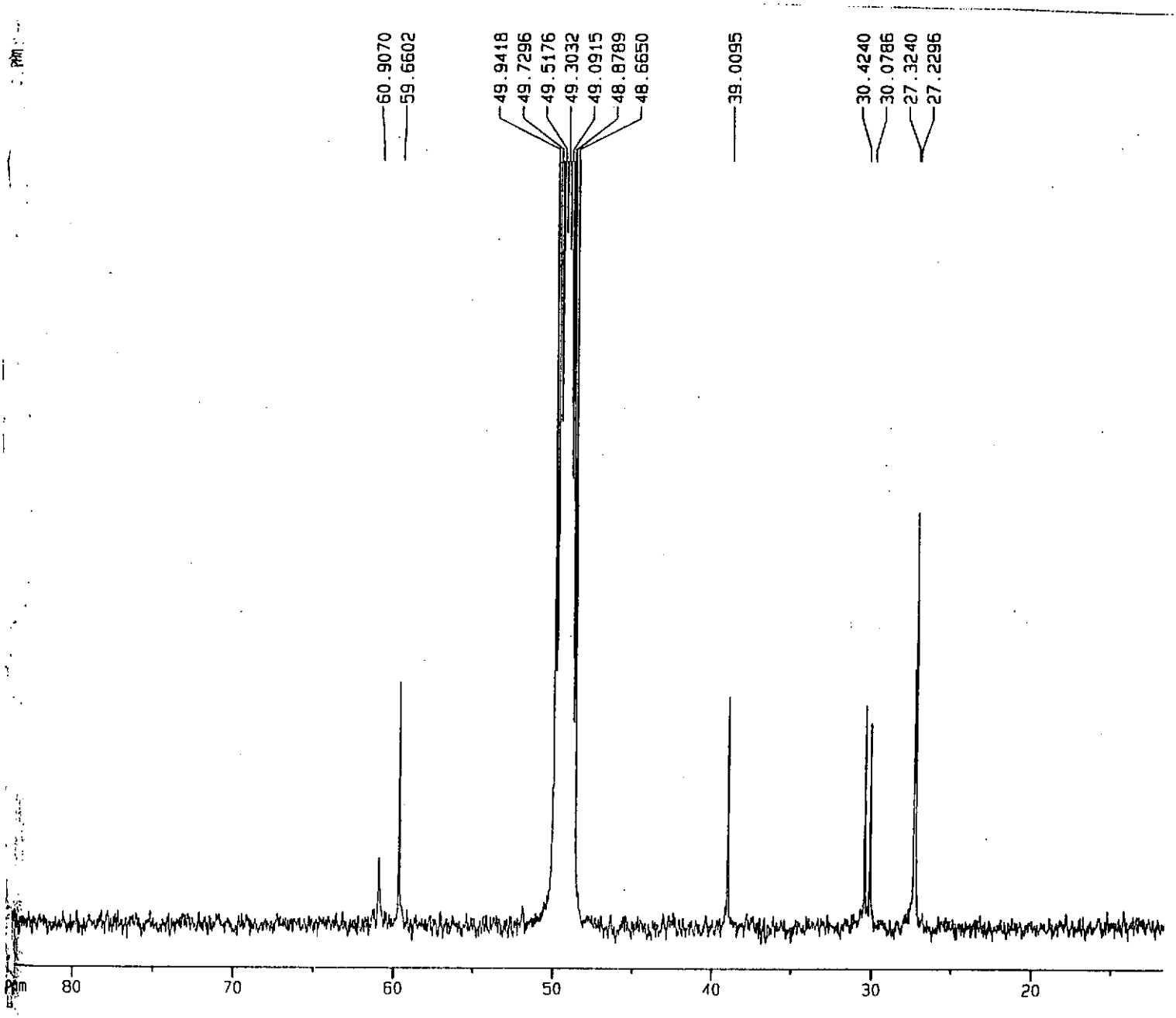
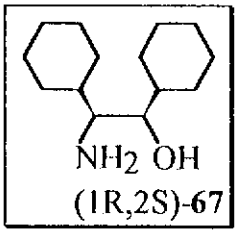


Fig. 4-3 ^{13}C NMR spectrum of (R)-**68**



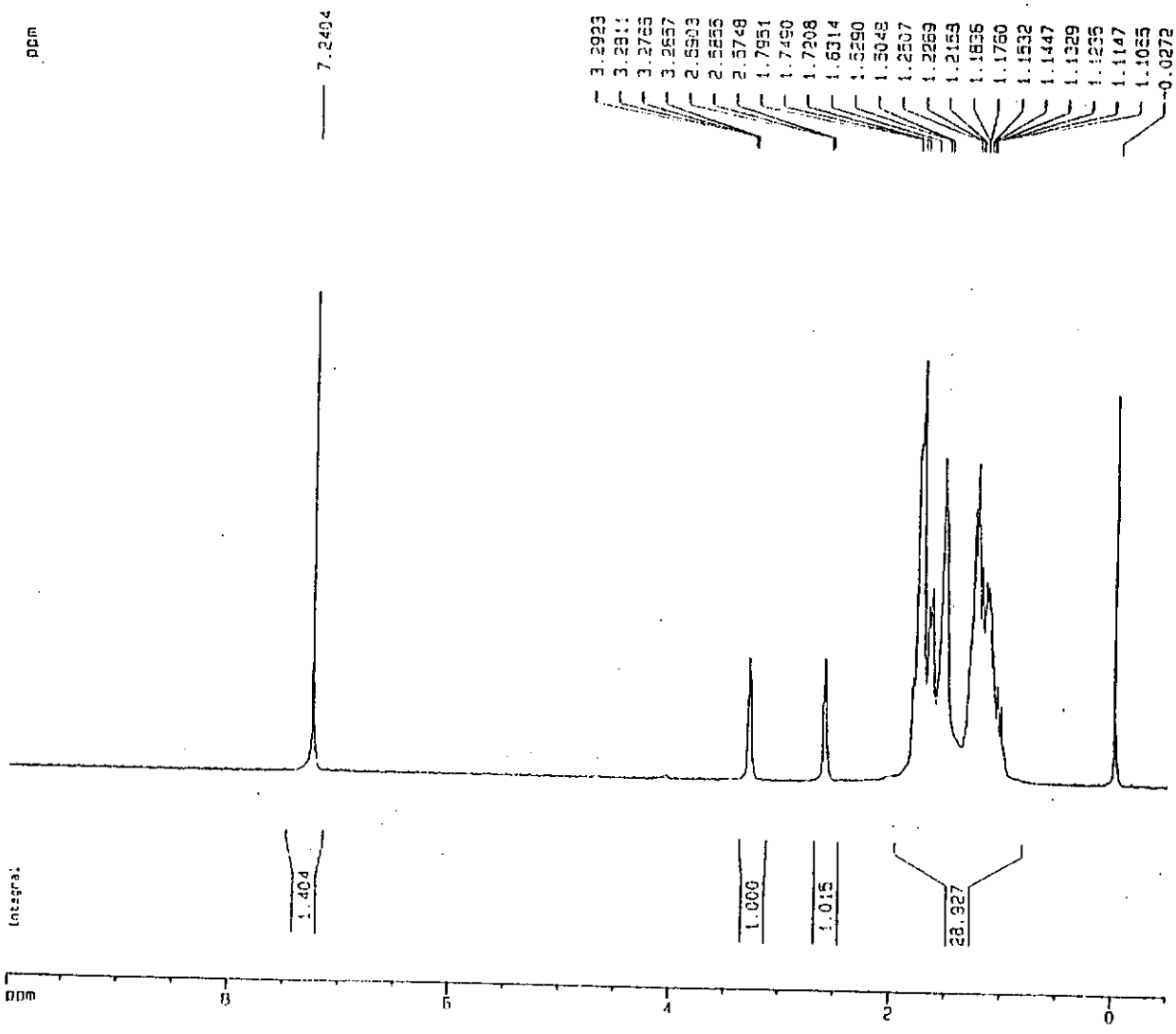
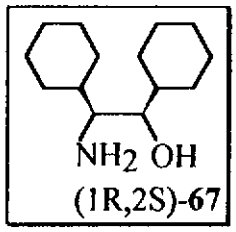


Fig 4-4 ^{1}H NMR spectrum of (1R,2S)-**67**



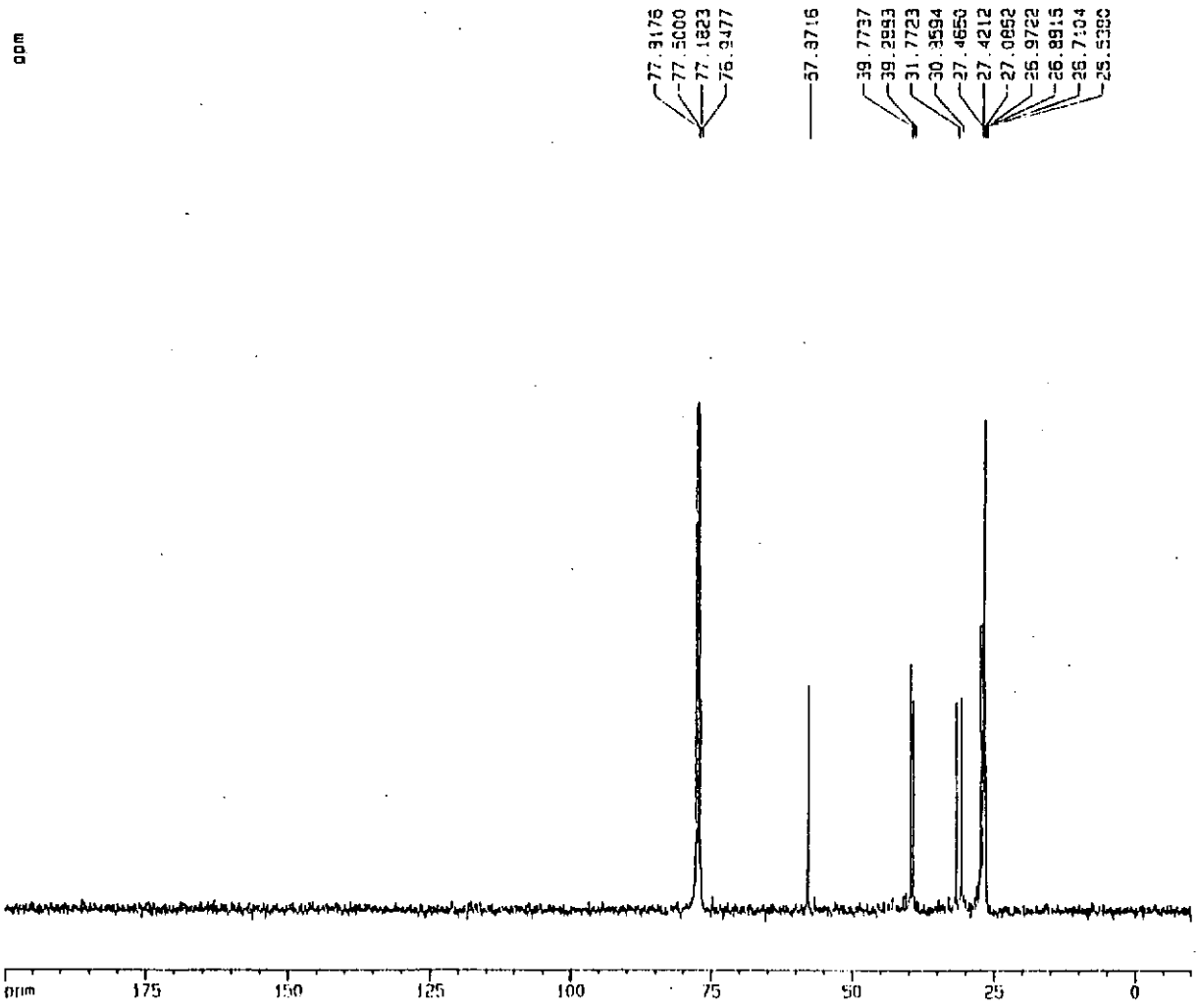
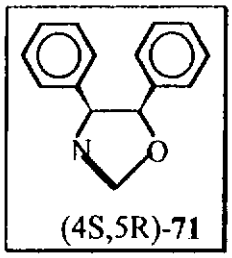


Fig. 4-5 ^{13}C NMR spectrum of (1R,2S)-**67**



(4S,5R)-**71**

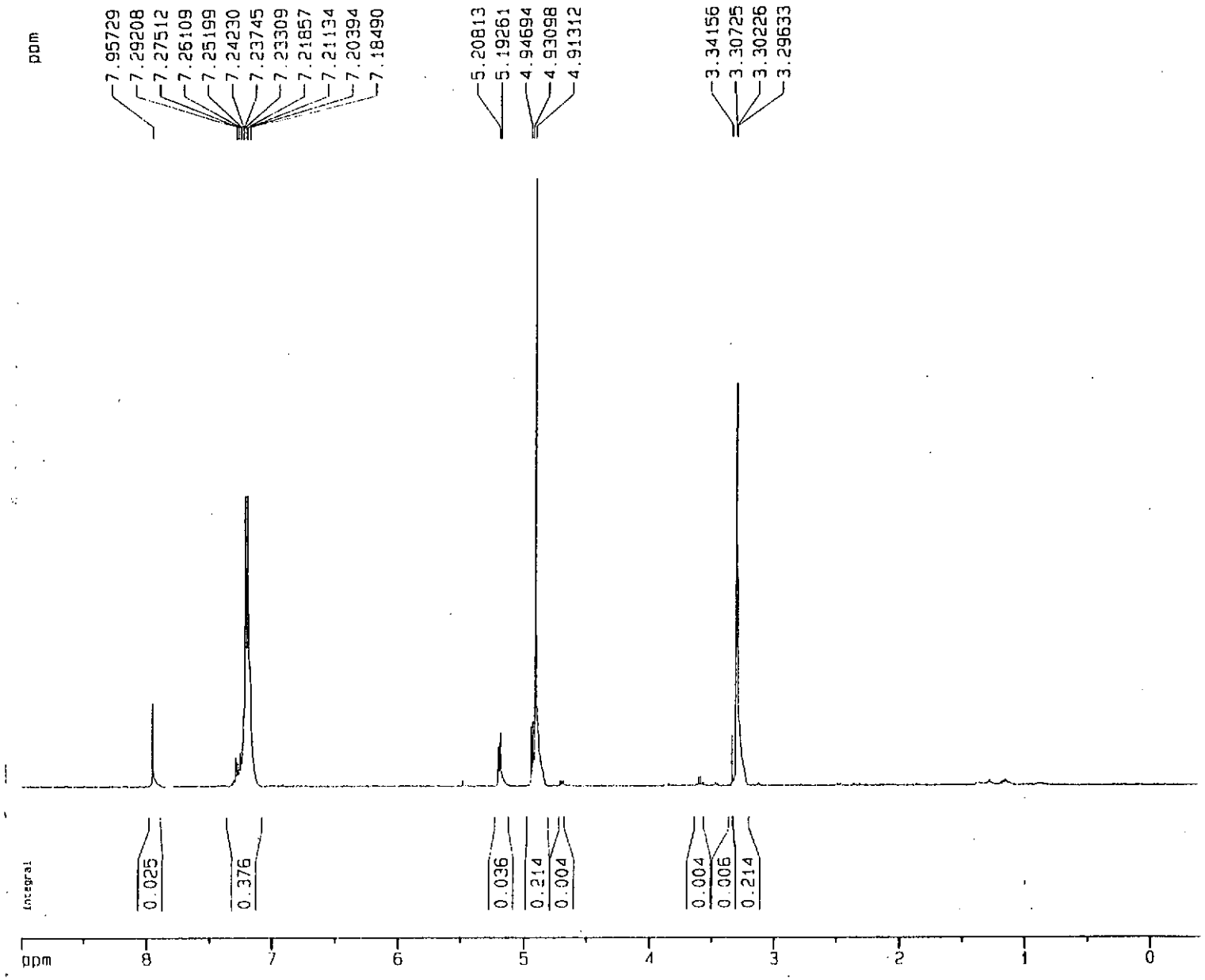
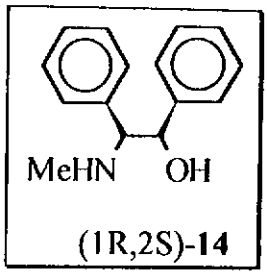


Fig. 4-6 ^{1}H NMR of (4S,5R)-**71**



(1R,2S)-**14**

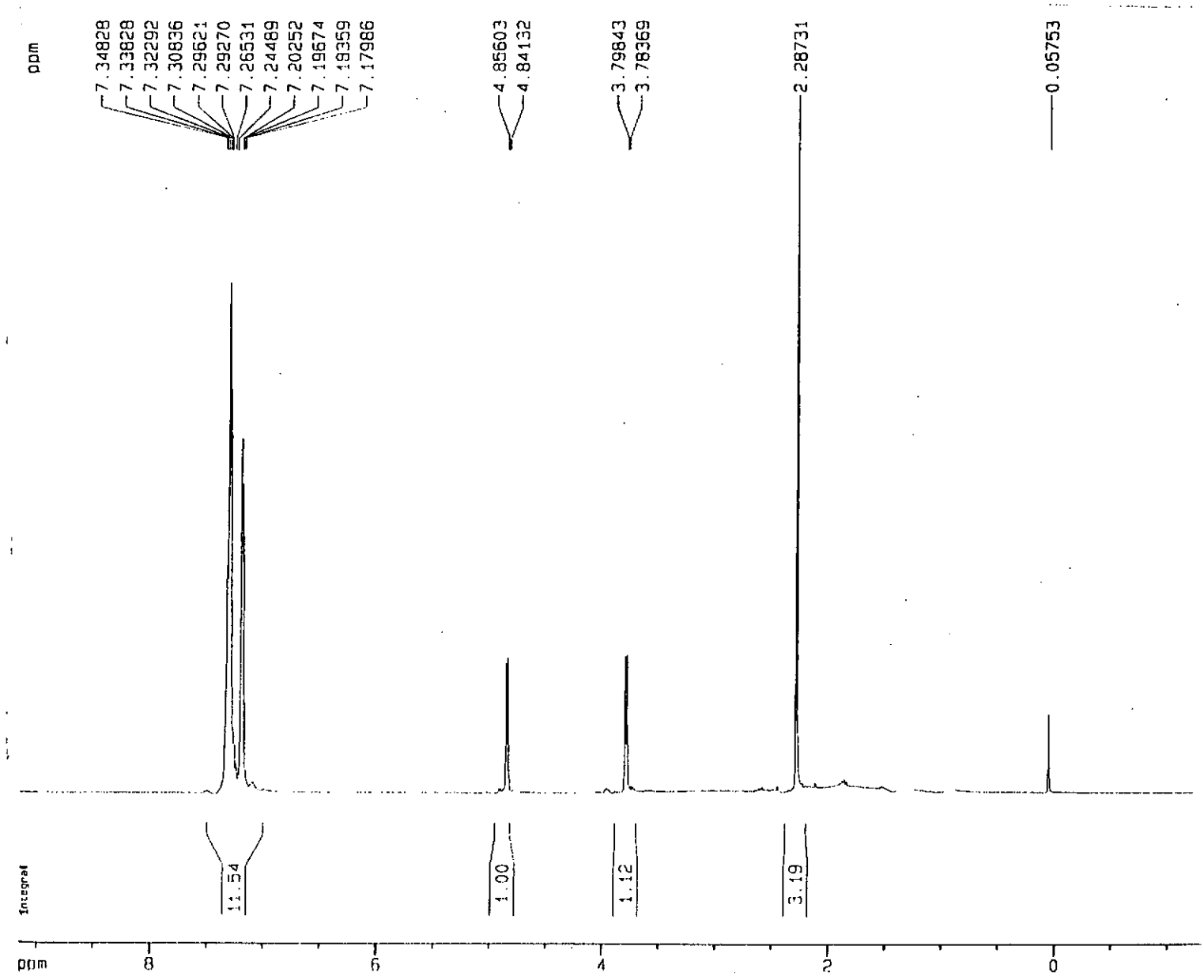
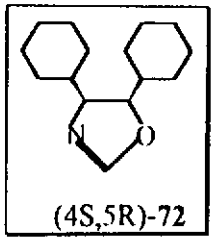


Fig. 4-7 ^{1}H NMR of (1R,2S)-**14**



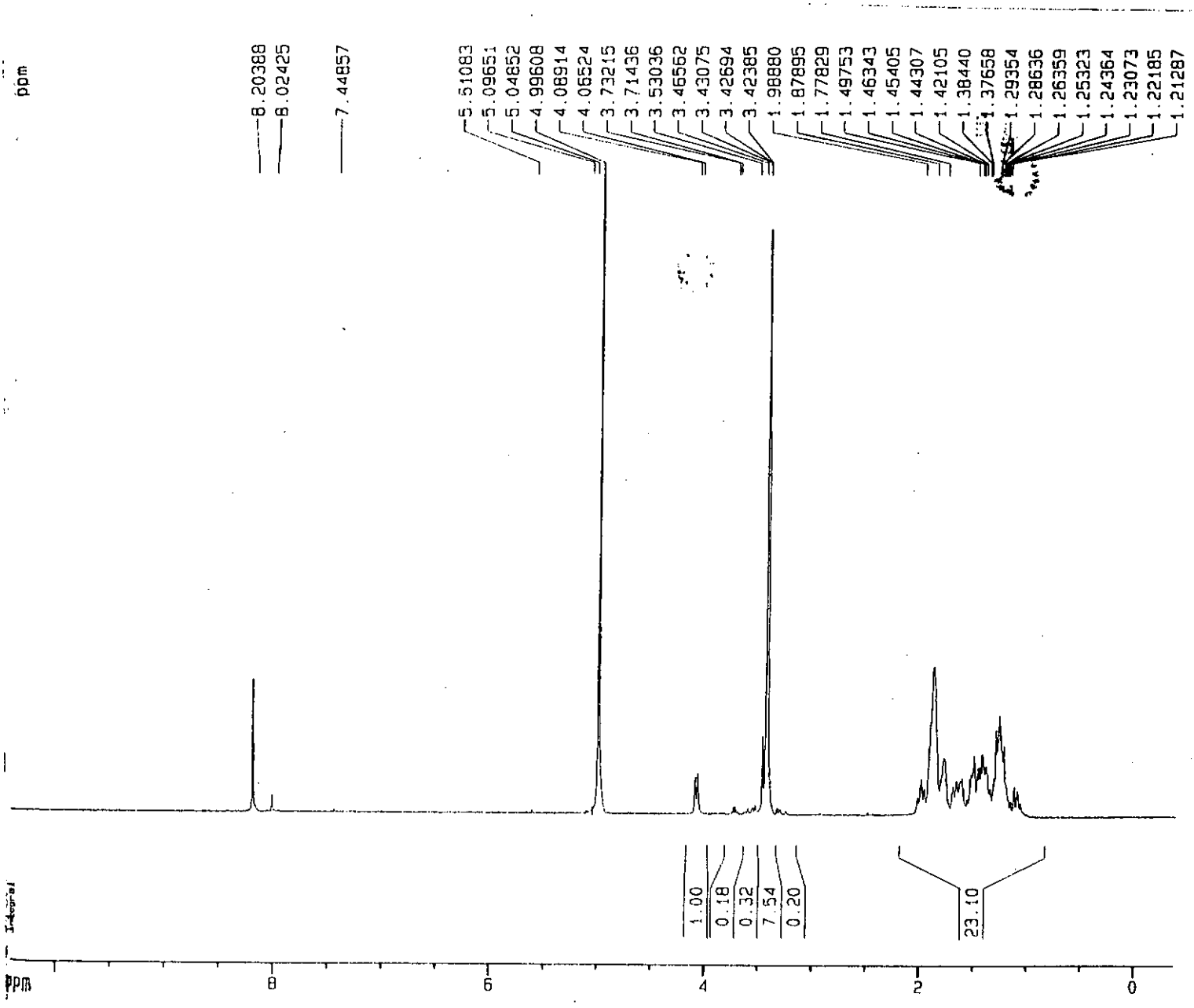


Fig. 4-8 ^{1}H NMR of (4S,5R)-**72**

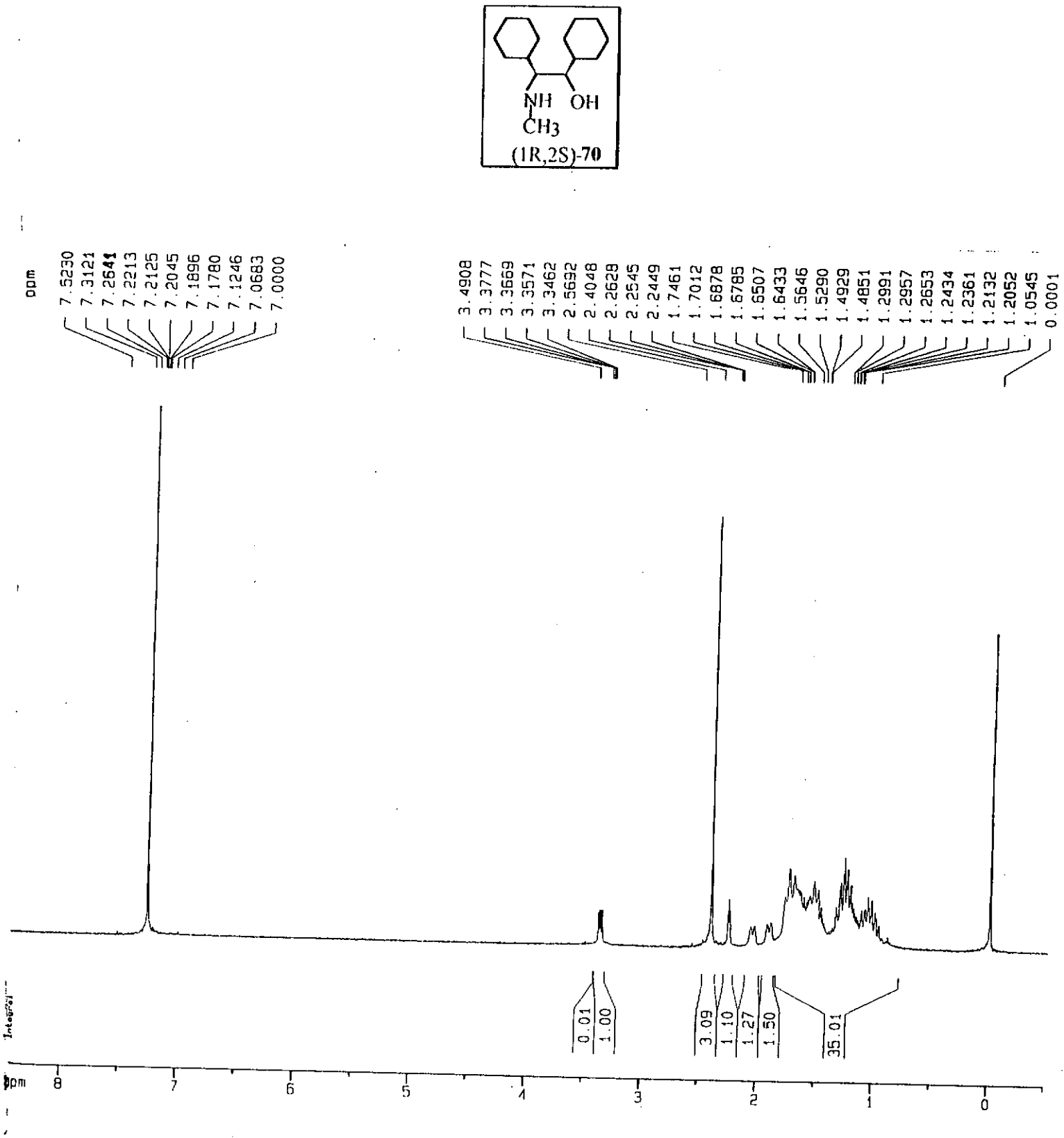


Fig. 4-9 ^{1}H NMR of (1R,2S)-**70**

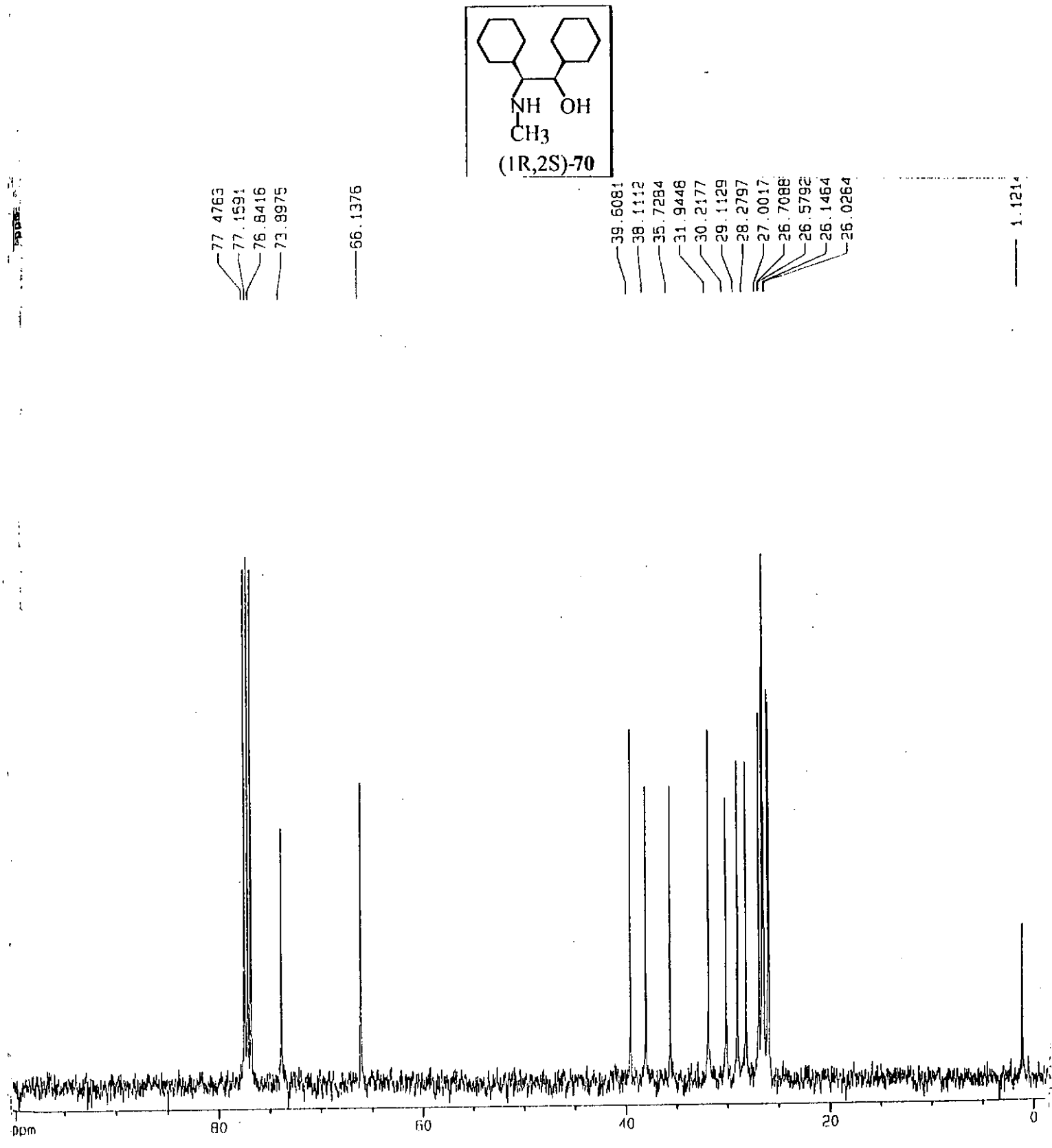


Fig. 4-10 ^{13}C NMR spectrum of (1R, 2S)-**70**

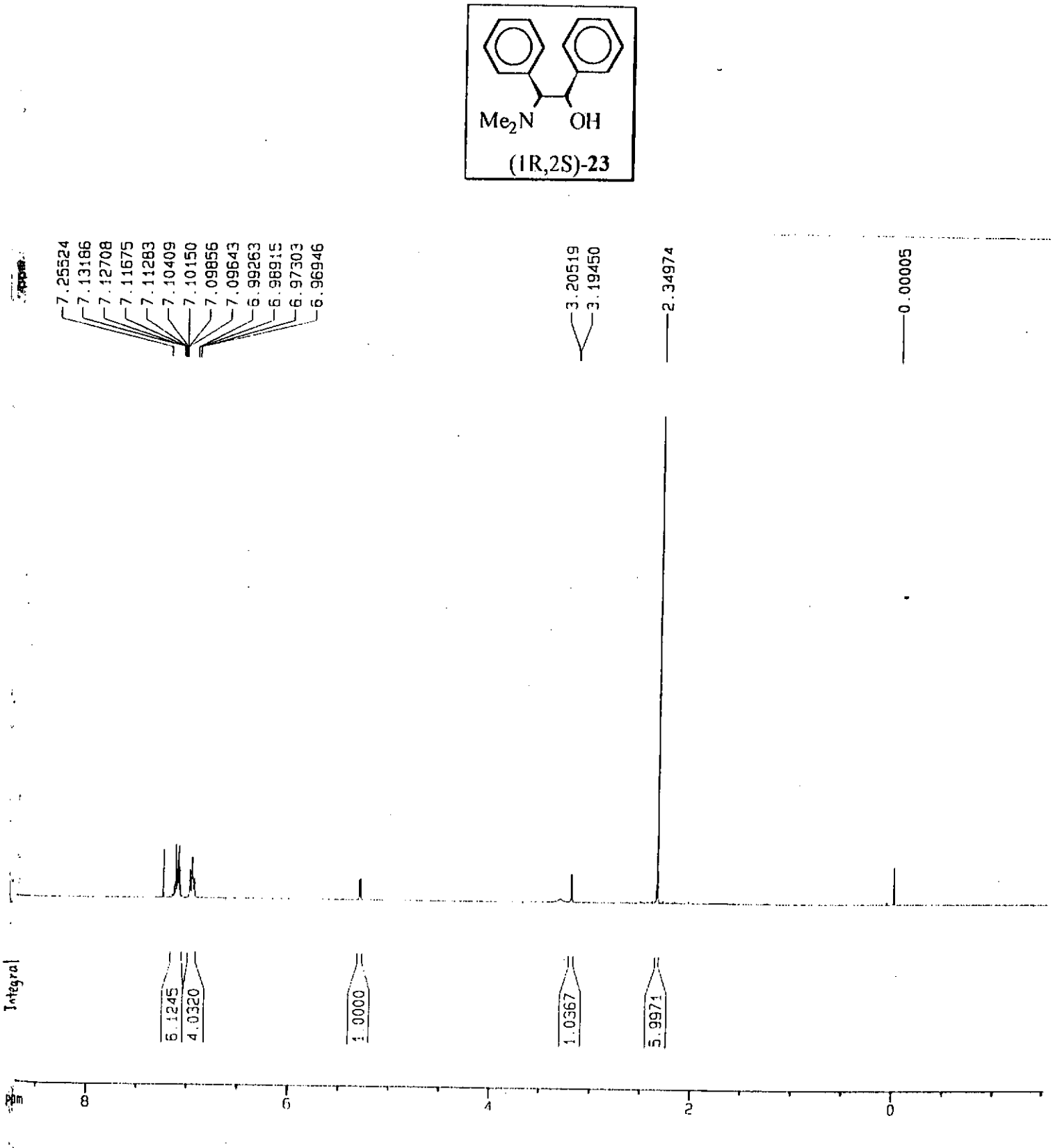


Fig. 4-11 ^{1}H NMR spetrum of (1R, 2S)-**23**

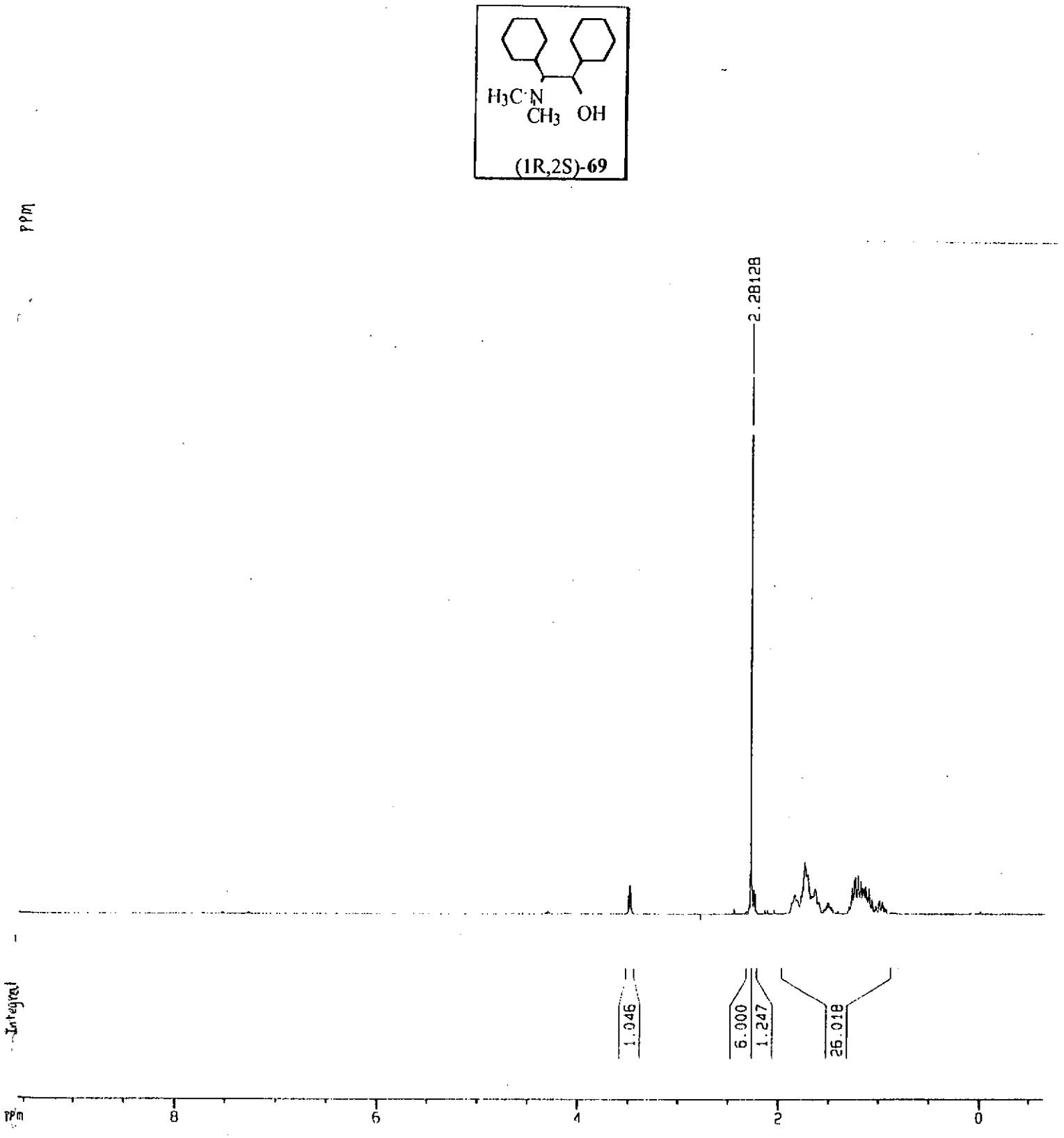


Fig. 4-12 ^{1}H NMR spectrum of (1R,2S)-**69**

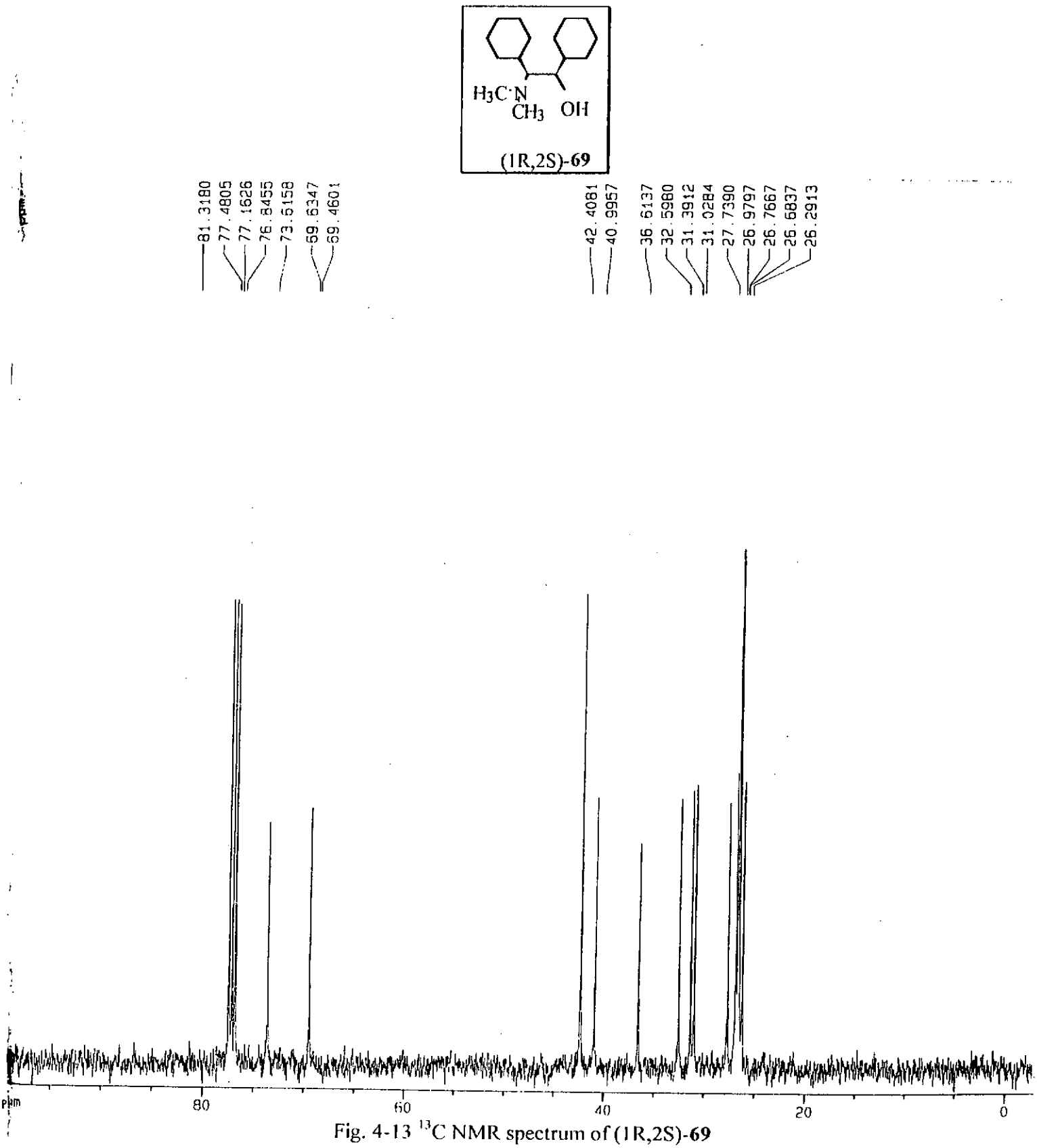


Fig. 4-13 ^{13}C NMR spectrum of (1R,2S)-**69**

Racemic **70** + (R)-Mandelic Acid
(0-8 ppm)

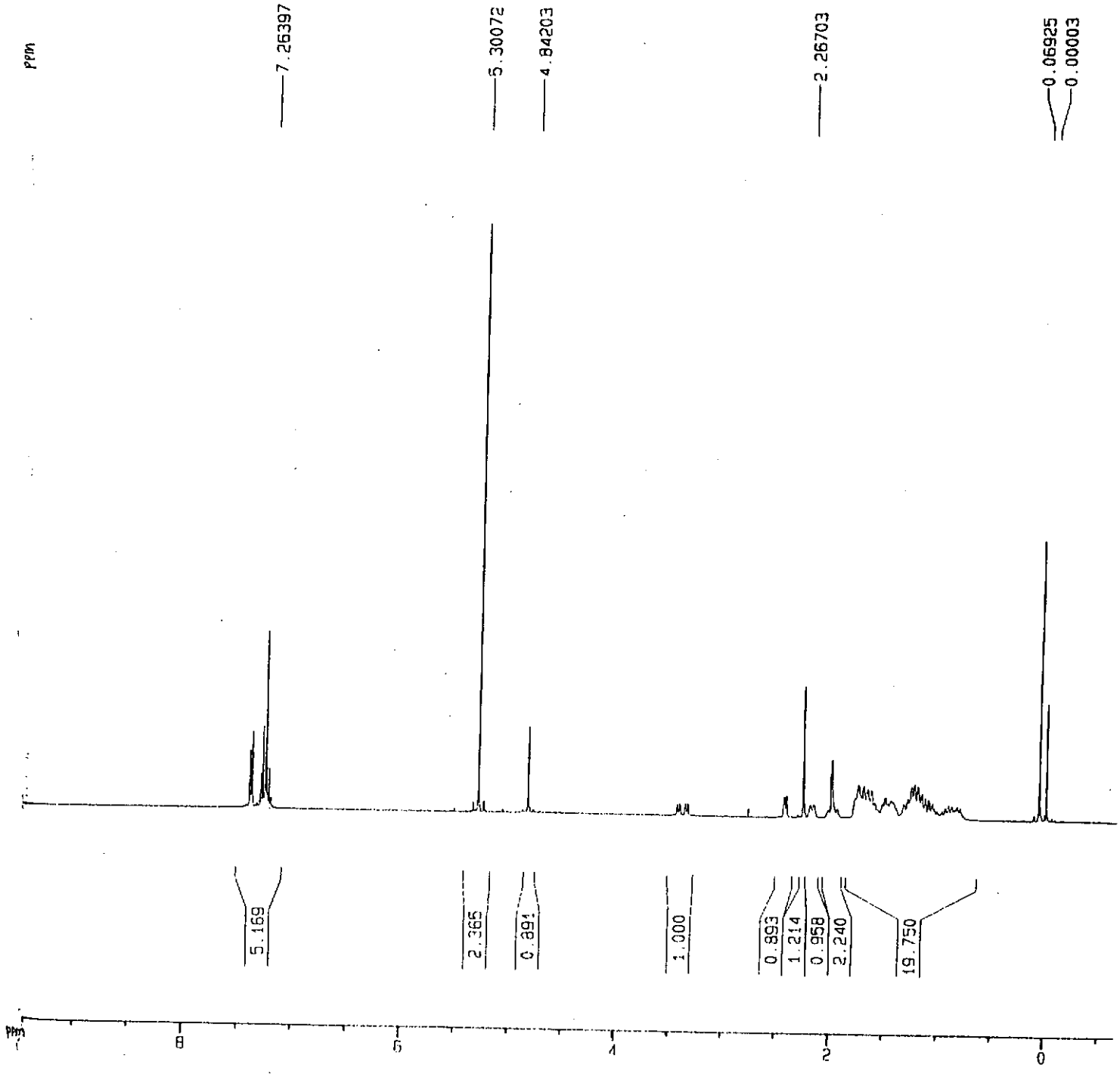


Fig. 4-14 ^{1}H NMR Spectrum of Rac-**70** + (R)-Mandelic Acid (0-8ppm)

Racemic **70** + (R)-Mandelic Acid
(Stereogenic centre)

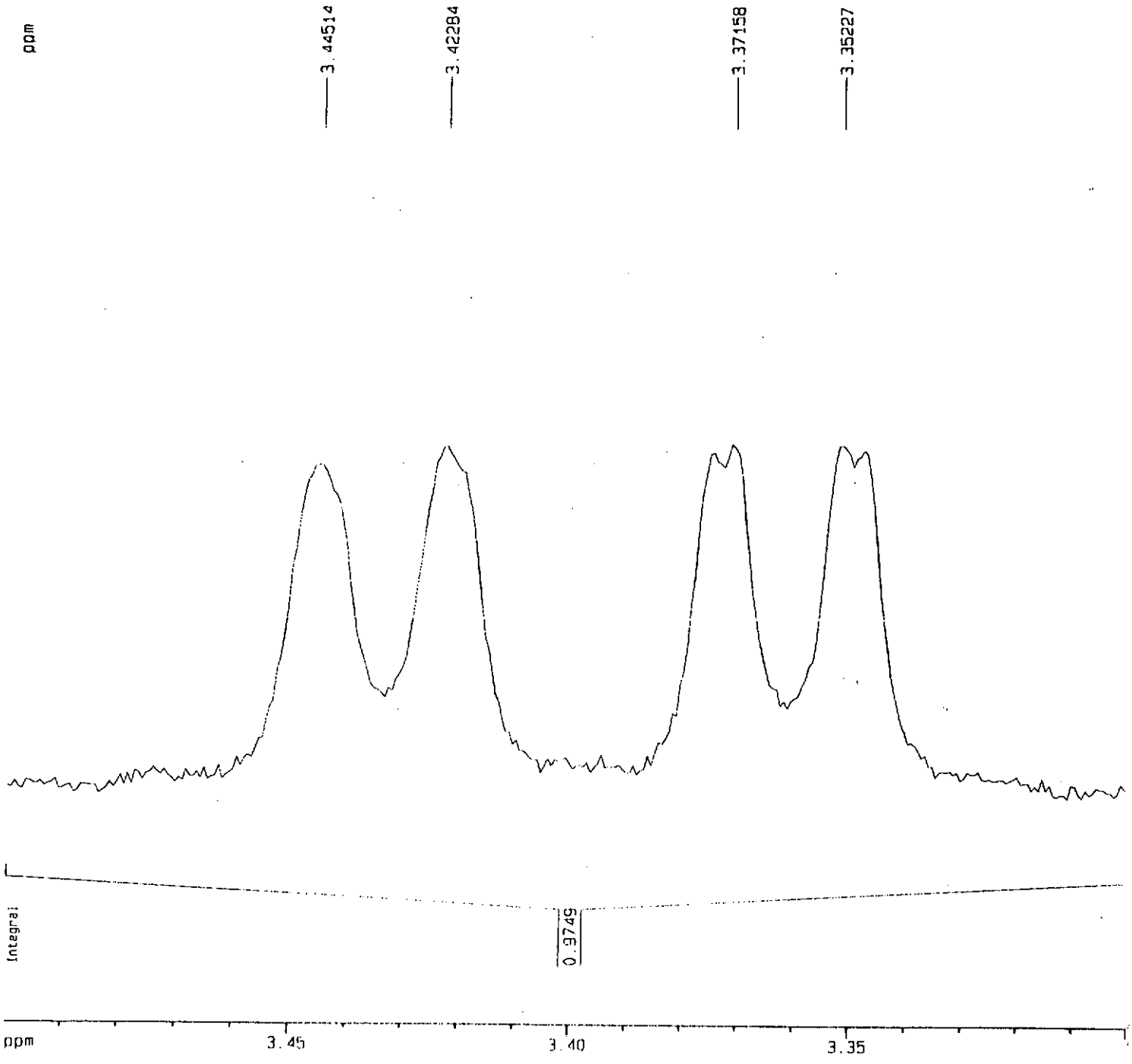
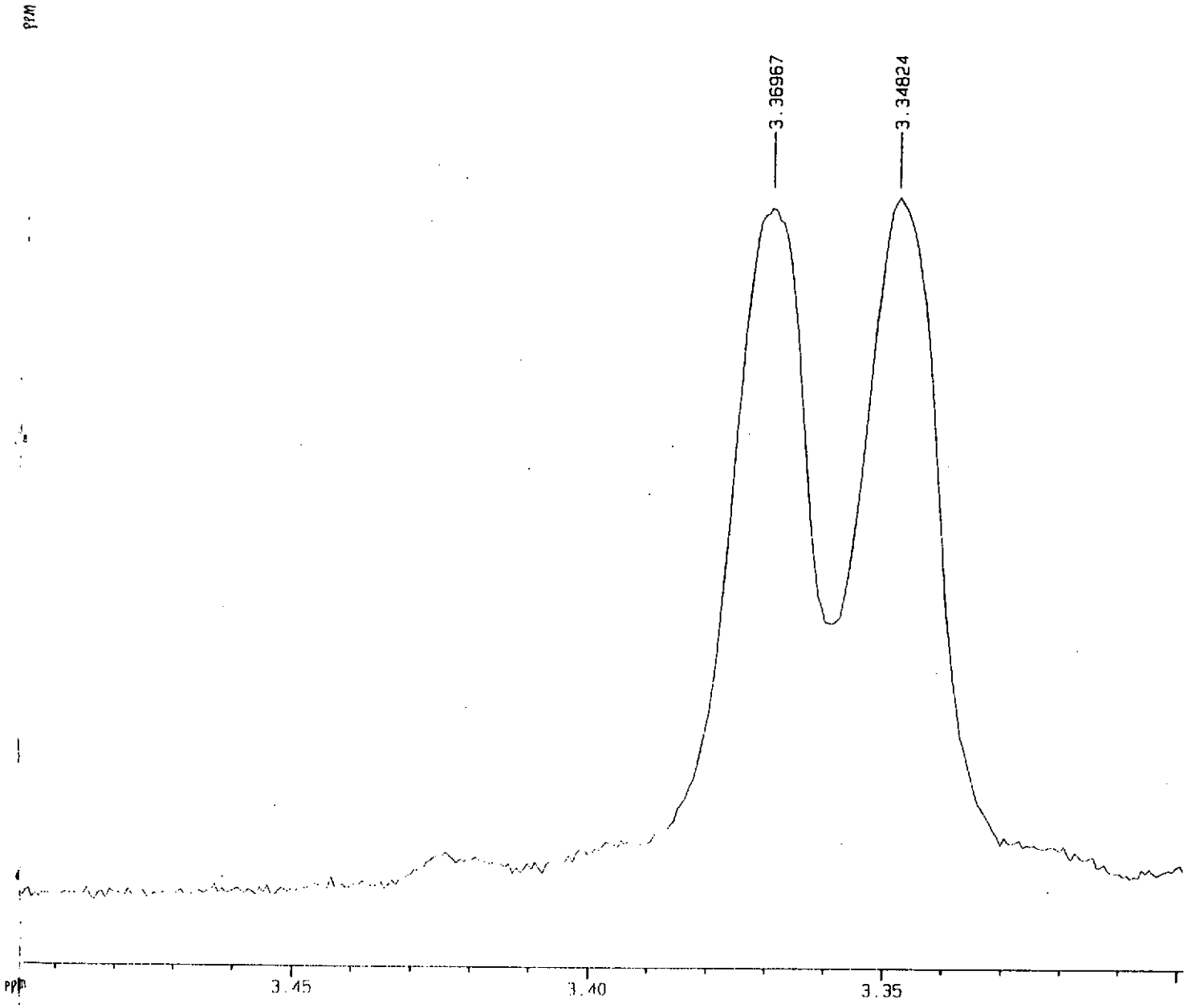


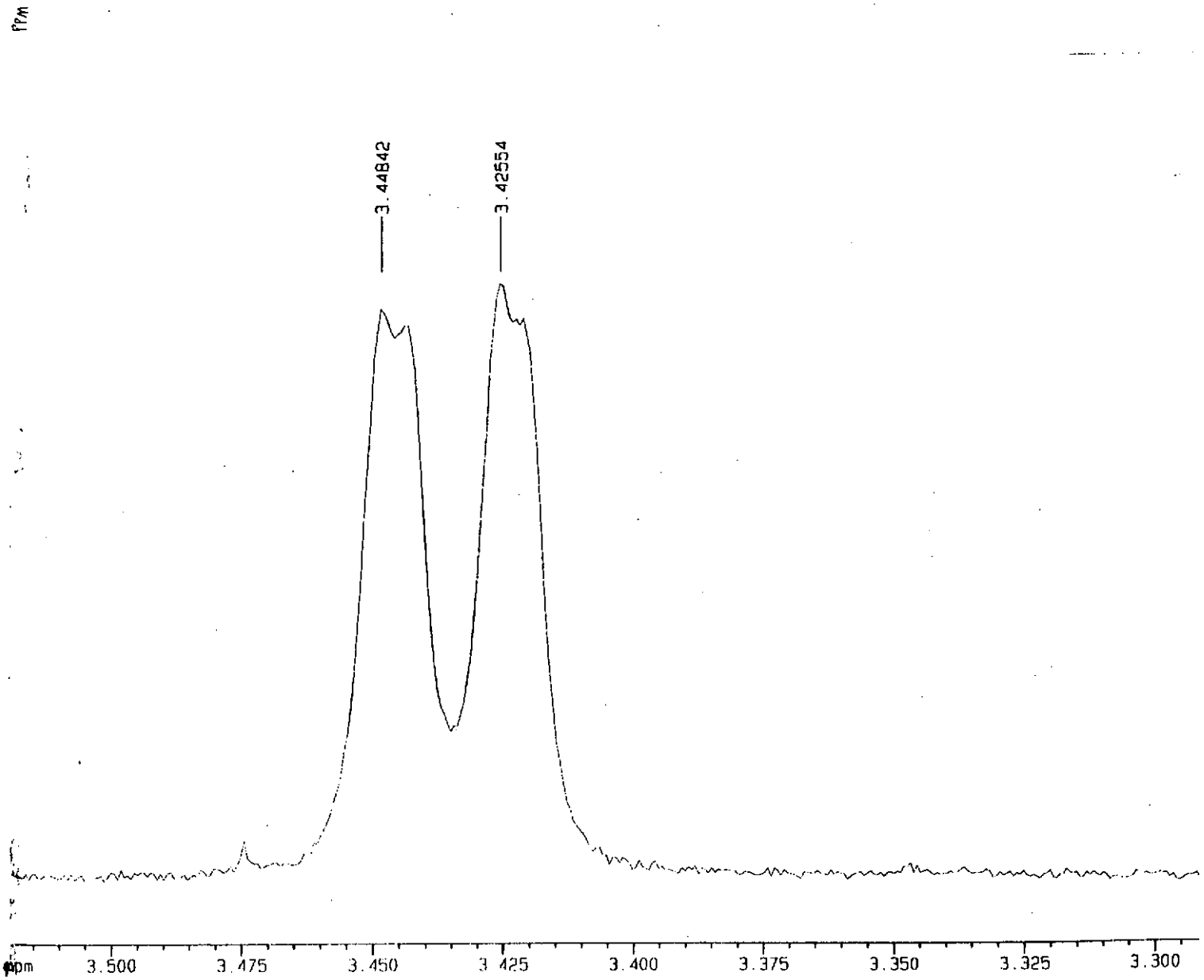
Fig. 4-15 ^{1}H NMR Spectrum of Rac-**70** + (R)-Mandelic Acid (Steregenic centre)

(1R, 2S)-**70** + (R)-Mandelic Acid
(Stereogenic centre)



4-16 ^{1}H NMR Spectrum of (1R,2S)-**70** + (R)-Mandelic Acid(Stereogenic centre)

(1S, 2R)-**70** + (R)-Mandelic Acid
(Stereogenic centre)



4-17 ^{1}H NMR Spectrum of (1S,2R)-**70** + (R)-Mandelic Acid(Stereogenic centre)

Appendix 2 Lists of conference papers and academic journal papers

Conference papers

1. Tong, P.E.; Li, P.; Zhang, F.Y.; Chan, A.S.C. "Synthesis of a series of novel chiral amino alcohols and their catalytic properties". *Proceedings of the 4th Symposium on Chemistry Postgraduate Research in Hong Kong*, Hong Kong, 19 April, 1997

2. Tong, P.E.; Zhang, F.Y.; Li, P.; Chan, A.S.C. "The effect of a series of novel chiral amino alcohols on the ruthenium(II)-catalyzed asymmetric transfer hydrogenation of ketones in propane-2-ol'. *Proceedings of the 214th American Chemical Society National Meeting*, Las Vegas, NV, USA, 7-11 September, 1997

3. Tong, P.E.; Li, P.; Zhang, F.Y.; Chan, A.S.C. "The synthesis and application of a series of new chiral amino alcohols in the asymmetric borane-reduction of ketones". *Proceedings of the 2nd Conference for Worldwide Chinese Young Chemists*, Hong Kong, 20-23 December, 1997

4. Tong, P.E.; Li, P.; Zhang, F.Y.; Chan, A.S.C. "The synthesis and application of a series of new chiral amino alcohols in the asymmetric borane-reduction of ketones". *Proceedings of the Symposium on Frontiers of Chemistry*, Hong Kong, 1997

5. Tong, P.E.; Li, P.; Zhang, F.Y.; Chan, A.S.C. "The synthesis and application of a series of new chiral amino alcohols in the asymmetric conjugate addition of diethylzinc to enones". *Proceedings of the 5th Symposium on Chemistry Postgraduate Research in Hong Kong*, Hong Kong, April 25, 1998

Academic journal papers

1. Tong, P.E.; Zhang, F.Y.; Li, P.; Chan, A.S.C. "Enantioselective borane-reduction of ketones catalyzed by new 1,3,2-oxazaborolidines containing cyclohexyl groups". *In preparation.*

2. Tong, P.E.; Zhang, F.Y.; Li, P.; Chan, A.S.C. "Enantioselective conjugate addition of diethylzinc to enones catalyzed by chiral nickel complexes containing a new chiral aminoalcohol with cyclohexyl groups". *In preparation.*