STEREOSELECTIVE CARBONYL ADDITION REACTIONS

A THESIS

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CHEMISTRY

BY

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PUNE -411 008

DECEMBER 1996

..... to my Parents and to the memory of my beloved Uncle

CERTIFICATE

This is to certify that the work incorporatd in the thesis entitled **"Stereoselective Carbonyl Addition reactions"** submitted by **Mr. K. Ramakrishna Prasad** was carried out by him under my supervision at National Chemical Laboratory, Pune. Such material as has been obtained from other sources has been duly acknowledged.

N. N. Joshi

Date: Dec. 23, 1996

National Chemical Laboratory,

Pune - 411 008.

(Dr. N. N. Joshi)

Research Guide

Acknowledgments

It gives me a great pleasure to place on record my deep sense of gratitude to my mentor **Dr. N. N. Joshi** *for introducing me to this enthrilling field of Asymmetric Synthesis. The work presented here would have not been accomplished without his unfailing attention, constructive criticism and constant encouragement. I owe him much not only for his help in the scientific matters but also for his care and concern all the time.*

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I would like to specially thank Seshu,Venkata Satya Siva Rajasekharam, Raghunath, Nagesh for taking trouble in bringing out the thesis. I will be failing in my duties if I forget to thank my well wishers Sreedhar, Subhash, Suresh, Rajasekhar Kavuluru and Jamadagni for their inspiration and moral strength all the time.

I thank University Grants Commission (UGC), New Delhi for the financial assistance and Director, NCL for allowing me to work in this laboratory.

What I am and what I intend to be is because of the unfailing love, affection and encouragement of my parents and family members which can not be expressed in any form.

K. RAMAKRISHNA PRASAD

CONTENTS

Abbreviations

DAIB	:	(-)-3-*exo*-(dimethylamino)-*iso*borneol
DPMPM	:	(+)-diphenyl-(N-methylpyrrolidin2-yl) methanol
DBNE	:	N,N-dibutyl norephedrine
BH_3.THF	:	borane-tetrahydrofuran complex
$BH_3.SMe_2$	:	borane-dimethylsulfide complex
BMS	:	borane-dimethylsulfide complex
ee	:	enantiomeric excess
Et_2O	:	diethyl ether
CH_2Cl_2	:	dichloromethane
$CHCl_3$	:	chloroform
$CDCl_3$	:	deuterated chloroform
EtOAc	:	ethyl acetate
EtOH	:	ethanol
MeOH	:	methanol
LAH	:	lithium aluminum hydride
$NaBH_4$	:	sodium borohydride
$LiAl(O^tBu)_3H$	:	lithium tri *tert* butoxy aluminum hydride
$LiAl(O^tBu)_2H_2$	:	lithium di *tert* butoxy aluminum hydride
DIP-Cl	:	diisopinocampheyl chloroborane
$Eu(hfc)_3$	:	tris-[3-(heptafluoropropyl hydroxymethylene)-(-)camphorato] europium derivative
MTPA	:	∝-methoxy-∝-trifluoromethyl-phenylacetic acid.

General Remarks

All the melting points are uncorrected and determined in centigrade scale on Yamaco micro melting point apparatus.

Infrared spectra were recorded on a ATI (Mattson) RS-1 spectrophotometer. Solid samples were recorded in Nujol or Chloroform and liquids as neat.

^{1}H-NMR spectra were recorded at 200 MHz or 300 MHz using tetramethylsilane as an internal standard in $CDCl_3$ on a Bruker-AC-200 or Bruker-MSL- 300 machine.

^{13}C-NMR spectra were recorded at 50 MHz with $CDCl_3$ (δ=77ppm) as the reference.

Chemical shifts are reported in parts per million (ppm) on δ scale. The abbreviations s, d, t, q, m, refer to the singlet, doublet, triplet, quartet and multiplet respectively. Coupling constants whereever mentioned, have been given in Hz.

Mass spectra were recorded on Fenningan-MAT-1020B instrument at an ionization volatge of 70 eV.

TLC was performed on Merck precoated silicagel 60F 254 plates.

Column chromatography was performed on silicagel (200-400 mesh) supplied by Merck.

Optical rotations were measured on a JASCO DIP-181 digital polarimeter.

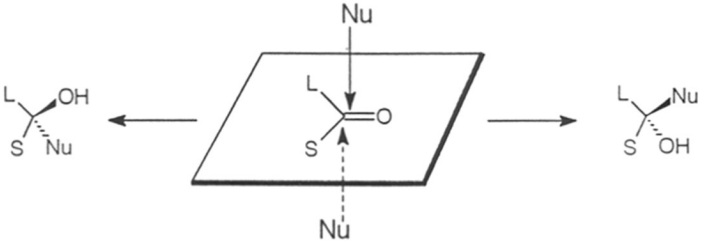
GC analysis was performed on a Shimadzu GC-17A fitted with a 5% PhMe Silicone column (25 x 0.2 mm).

HPLC analysis was performed on a Shimadzu LC-10AD equipped with SPD-10A UV-VIS detector using special grade solvents.

ABSTRACT

Stereoselective Carbonyl Addition Reactions

Carbon - Carbon bond forming reaction is the backbone of organic synthesis. Notable developments that have occurred in the past decade are for the enantioselective formation of C -C bond. One of the emerging research directions that hold great promise in this area is the stereoselective addition of nucleophiles to a carbonyl group. It would be a major accomplishment to be able to dictate the direction of attack of any given nucleophile (Nu) to a predefined enatioface exclusively through the agency of a chiral catalyst.



A multitude of chiral reagents and catalysts now exist that are capable of exercising nearly perfect control over stereochemical bond construction, once thought to be impossible to achieve *via* non enzymatic methods. Amongst these stereochemical addition reactions the addition of organometallic reagents to aldehydes and the reduction of prochiral ketones where the hydride is delivered selectively, constitute the most reliable methods for the synthesis of chiral hydroxy compounds.

Chapter 1 : Introduction.

This chapter provides background to the present work by reviewing the literature on catalytic stereoselective addition of carbon nucleophiles and hydride to a carbonyl substrate.

Chapter 2 : Enatioselective addition of diethylzinc to arylaldehydes.

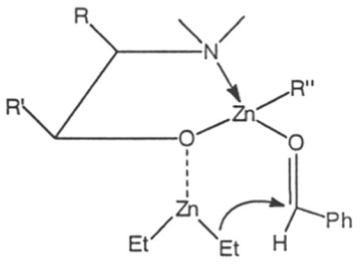
The enantioselective version of the reaction between organometallic reagents and carbonyl compounds which leads to optically active alcohols is desirable because of its general synthetic importance. In this context the addition of diethylzinc to aldehydes in the presence of suitable ligands has emerged as an important synthetic operation.

This chapter is divided into the following three sections.

Section 2a : Catalysts based on C_2- symmetric diols.

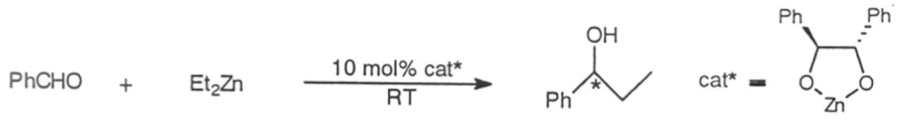
Since the discovery that β- amino alcohols catalyze the addition of diethylzinc to benzaldehyde, the past decade has seen virtually an explosive growth in this area. The majority of the catalysts employed are based on amino alcohols. In its simplest form, the mechanism of the reaction involves an assembly

of the coordinated zinc alkoxide, aldehyde and diethylzinc as shown below. It is presumed that the diethylzinc coordinates to the oxygen atom of the catalyst. We reasoned that if this is indeed true, then the catalyst need not be an amino alcohol, in fact a C_2- symmetric dialkoxide should function as an effective catalyst.



Amongst the various dialkoxides examined, the zinc dialkoxide derived from 1, 2- diphenylethane diol catalyzed the addition of diethylzinc to benzaldehyde with an impressive enantioselectivity (89%). We extended the scope of the addition to other aromatic aldehydes which were smoothly alkylated with good yield and %*ee* (Table-1).

Table - 1 : (*1S, 2S*) - Stilbene Diol as the Chiral Auxiliary

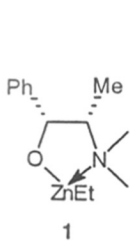


Entry	Aldehyde	Time (h)	%Yield	%*ee*	Config
1	benzaldehyde	18	98	89	R
2	*p*- fluorobenzaldehyde	9	95	70	R
3	*p*- methylbenzaldehyde	14	98	82	R
4	*p*- chlorobenzaldehyde	24	85	69	R
5	β- naphthaldehyde	20	94	84	R

Section 2b : Catalysts based on amino alcohols.

Eventhough there are a number of studies directed towards the structural modifications of amino alcohols for the enhancement of the enantioselectivity, the effect of structural modifications around the metal centre chelated to the nucleophilic oxygen atom of the carbonyl group has not been studied. In this section we present our results dealing with this aspect.

We prepared catalysts **1-4** and examined them for the enantioselective addition of diethylzinc to benzaldehyde.



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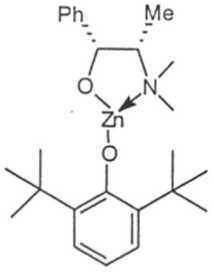

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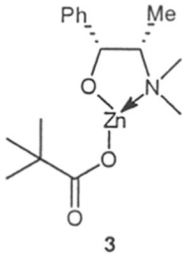

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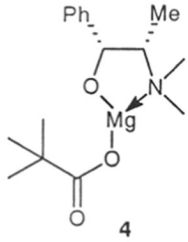

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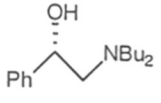
The catalyst **1** which has less steric bulk on the zinc atom catalyzed the addition with 83% *ee*. The increase of steric hindrance around the metal centre with a 2, 6- di *tert* butyl phenoxy moiety (catalyst **2**) decreased the enantioselectivity slightly (80%*ee*). The presence of a pivaloyl moiety in **3** decreased the enantioselectivity drastically (20%). In all the cases examined, the catalysts derived from magnesium provided lower enantioselectivity.

We have also synthesized a series of di- and tridentate amino alcohols which are structural analogues of the most successful DBNE ligand.



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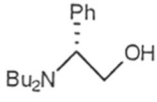

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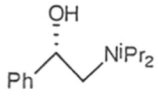

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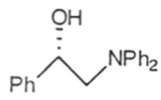

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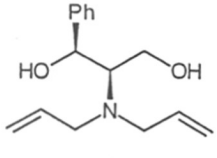

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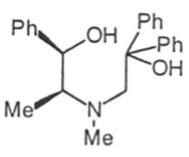

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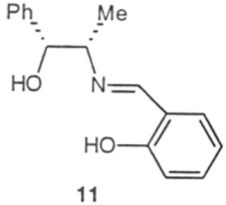


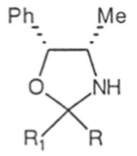
11

Catalyst derived from **5** provided the product with 77% *ee* whereas the **ligand 6** failed to catalyze the reaction. The tridentate ligand **10** catalyzed the reaction with poor selectivity (21%*ee*). The Schiff base complex **11** did catalyze the reaction, but the enantiomeric excess was only 30%.

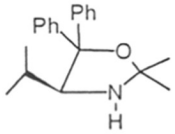
Section 2c : Catalysts based on oxazolidines.

As discussed earlier, the presence of a di- or tricoordinated zinc that chelates to the carbonyl oxygen and a tetracoordinated zinc that transfers the alkyl group, are the prime factors for achieving high enantioselectivity. With this view we anticipated that oxazolidines which are readily available by the ketalization of amino alcohols with aldehydes or ketones will satisfy these conditions. In this section the preparation of various oxazolidines and their application as ligands for diethylzinc addition to benzaldehyde is presented.

The zinc amides of oxazolidines **12-14** derived from norephedrine catalyzed the addition of diethylzinc to benzaldehyde in 50-83% *ee*. The zinc amide from α,α-diphenylvalinol catalyzed the reaction in up to 100% *ee*. Oxazolidine derived from simple valinol however provided moderate (40% *ee*) but surprisingly with the reversal of stereoselectivity. A reasonable mechanism was formulated to explain the outcomes.



12 = R = R_1 = Me
13 = R = H, R_1 = ^{t}Bu
14 = R = H, R_1 = Me



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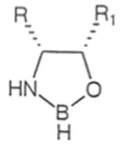
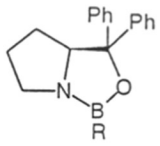
Chapter 3 : Stereoselective reduction of ketones.

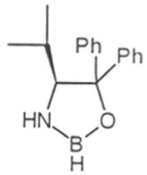
Asymmetric reduction of prochiral ketones is an actively studied area in synthetic organic chemistry. In order to gain an insight into the various factors that control the efficiency of chiral oxazaborolidine catalysts, following investigation was undertaken with a series of related structures.



16 = R = R_1 = Ph
17 = R = Me, R_1 = Ph



18 = R = Me
19 = R = H



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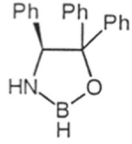

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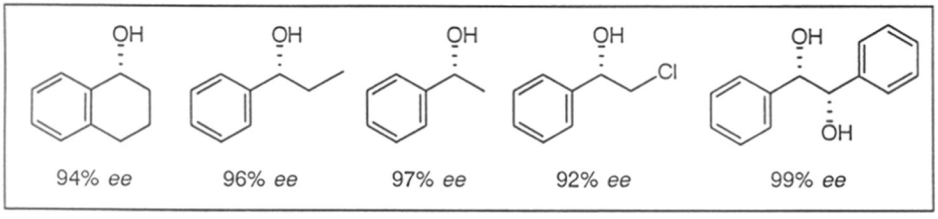
This chapter is divided into the following two sections.

Section 3a : An optimized *in situ* procedure for the oxazaborolidine catalyzed enantioselective reduction of ketones.

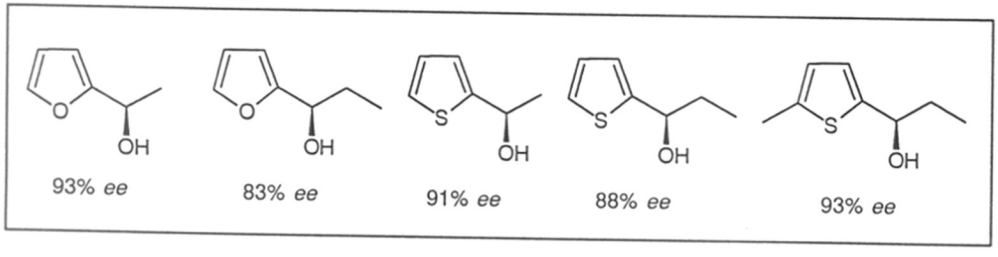
To begin with, we studied the reduction of acetophenone with three representative oxazaborolidines **19-21**. Since there is no or little difference in the enantioselectivity of the product alcohol with the change in the substituents on boron atom, we opted for the most easily accessible B-H substitution. It was found that the best procedure to obtain B-H substituted oxazaborolidine *in situ,* is to stir the amino alcohol with large excess of $BH_3.SMe_2$ at 45°C for 16h. The reaction was examined at various temperatures *viz* 0°C,

25°C, 45°C, and it was surprising to find that the best results were obtained at 45°C. We attribute the rate enhancement to the formation of catalytically active monomeric species of oxazaborolidine. At lower temperature, the non-active dimeric structure predominates.

Thus optimized reduction conditions were successfully used for the reduction various other aromatic ketones which provided the enantiomeric excess comparable to the best known so far.



This protocol was also applied for the reduction 2- acyl furans and 2-acyl thiophenes to obtain chiral 2- furyl and thienyl carbinols which are intermediates in the synthesis of variety of natural products. So far these compounds have been prepared by Sharpless kinetic resolution and enzymatic resolutions which suffer from an inherent disadvantage that the maximum yield can be 50%.

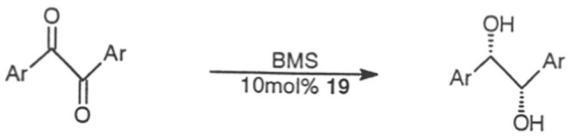


Section 3b : Stereoselective reduction of 1, 2 diketones.

Eventhough there are a number of methods available for the reduction of simple prochiral ketones, the reduction of functionalized ketones is scantily addressed in the literature. We present in this section the stereoselective reduction of symmetrical diketones to give the corresponding C_2- symmetric diols which are important chiral auxiliaries in asymmetric synthesis.

The diastereoselective reduction of 1, 2- diketones was performed with various reducing agents *viz.* $LiAlH_4$, $NaBH_4$, $BH_3.SMe_2$ etc. It was found that these reagents provide predominantly *erythro* (meso) isomer. We were surprised to find that oxazaborolidine catalyzed reduction of benzil provided an excess of the *threo* isomer. This led us to investigate the stereoselective reduction of 1,2- diaryl diketones. The catalyst structure and the temperature proved crucial in governing the diastereoselectivity. Of the four representative oxazaborolidines **16-18** the one derived from α,α-diphenyl prolinol provided the corresponding diol in 88:12 diastereomeric ratio and a very high enantioselectivity (>99%). The reaction worked well with a variety of 1,2- diaryl diones as evident from Table - 2.

Table - 2 : Stereoselective Reduction of Benzils



entry	Ar	yield (threo : erythro)	config	%*ee*
1	phenyl	85 (88:12)	S, S	>99
2	4- anisyl	80 (89:11)	S, S	>99
3	4- tolyl	83 (85:15)	S, S	>99
4	3- tolyl	82 (84:16)	S, S	>99
5	2- furyl	70 (89:11)	S, S	>99
6	2- thienyl	80 (92:8)	S, S	>99

CHAPTER - 1

Introduction

Chirality is a major phenomenon in nature and molecular asymmetry in particular is playing a crucial role in science and technology[1]. A variety of biological processes emerging through molecular recognition requires strict matching of chirality. The synthesis of optically active compounds is a subject with a long history, dating back more than a hundred years to the seminal work of Louis Pasteur. He was first to recognize that optical activity is a result of molecular asymmetry and the first to separate (in 1848) the enantiomers of a racemate. In recent years interest in the synthesis of pure enantiomers has gained new impetus as a result of increasing awareness of the importance of optical purity in the context of biological activity. The growing awareness of the importance of chirality in conjunction with biological activity has resulted in a steadily increasing effort being devoted to the development of methods for the synthesis of optically active compounds. Discovery of truly efficient methods for obtaining chiral substances is a challenge for synthetic organic chemist.

Carbon - Carbon bond forming reaction is the backbone of organic synthesis. Important advances that have occurred in recent years are for the formation of C-C bond stereoselectively[2]. Until the early 1970's the resolution of racemates by classical methods was the primary method to obtain optically active compounds. Practical access to optically active compounds was considered possible only by enzymatic methods which has limited scope because of the lock and key specificity. On the other hand, synthetic organic chemists have discovered a variety of versatile selective reactions that compliments the biological processes. The chemists approach involving the use of small amount of catalyst to produce naturally occurring and non-natural optically active compounds in large holds great promise in this area.

Over the past decade there has been virtually an explosive growth in the discovery of organic reactions that exert perfect control over bond construction. A multitude of chiral reagents and catalysts are now available that can differentiate the enantiotopic atom, group or face in the achiral molecule and are capable of exercising precise control over stereoselection, once thought to be impossible to achieve *via* non - enzymatic methods.

One of the research directions that hold great influence in this area is the stereoselective addition of nucleophiles to a carbonyl group. It would be a major accomplishment to be able to dictate the direction of the attack of any given nucleophile (Nu) to a predefined enantioface exclusively through the agency of a chiral catalyst (fig. 1).

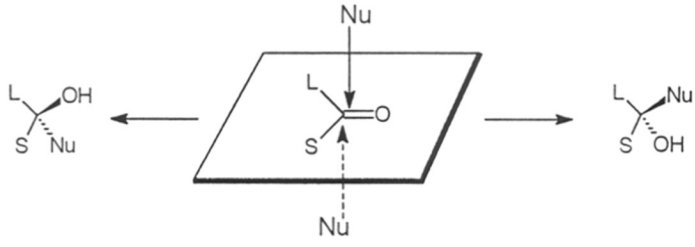


fig. 1

In these reactions, defined stereochemical outcome can be controled through the proper agency of a chiral auxiliary (stoichiometric) or a chiral catalyst (catalytic). Such reactions whether designed by keen insight or discovered by serendipity, have provided a new dimension to the art and science of molecular building. Amongst these stereoselective reactions, the addition of organometallic reagents to aldehydes and the reduction of prochiral ketones, constitute the most reliable methods for the synthesis of hydroxy compounds[3].

This chapter provides the background to the present work by reviewing the CATALYTIC stereoselective addition of carbon nucleophiles and hydride to a carbonyl substrate. Due to the vastness of the literature, the coverage has been restricted to ligand mediated dialkylzinc reagents and borane as the nucleophiles.

Enantioselective Addition of Organozinc Reagents to Aldehydes

Except for dialkylzinc reagents, it has not been possible so far to add any other organometallic reagents to carbonyl group in a catalytic enantioselective fashion. The following account is therefore restricted to the addition of organozinc compounds. Reactivity of organometallic compounds is profoundly affected by neutral, anionic, hetero or aromatic auxiliaries. In certain cases the addition of small amount of chiral auxiliary could enhance the reactivity and at the same time control the stereochemical outcome. A possible pathway to achieve enantioselective alkylation from a dialkyl metal R_2M to a carbonyl substrate by a catalytic amount of protic auxiliary is represented below (fig. 2).

fig. 2

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

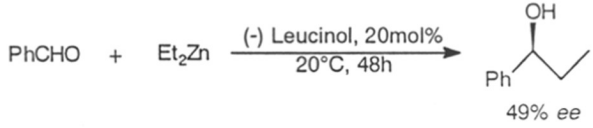
Eventhough there have been successful examples of alkylation by organomagnesium or lithium compounds using a stoichiometric or even excess amount of chiral auxiliary, the control of kinetic requirements outlined above with catalytic amount

of the chiral auxiliary was not easily obtained. Certain catalysts may accelerate the nucleophilic alkylation, but the rates of catalyzed and non-catalyzed reactions is not large enough to provide a practical asymmetric catalysis. In this context, dialkylzinc reagents act as a perfect donor of alkyl group for the catalytic asymmetric synthesis, generating a novel domain of asymmetric catalysis.

As such, diorganozinc compounds are less reactive towards aldehydes in hydrocarbon or ethereal solvents. This can be attributed to the fact that Zn-Carbon bond can be regarded as occupying two equivalent Sp- hybridized molecular orbitals, resulting in a linear geometry of the molecule. If one of the organic group in a diorganozinc compound is replaced by an electronegative substituent like a halogen atom or by a group bound to zinc *via* an electronegative atom like oxygen/nitrogen, both the acceptor character of zinc and the donor character of the zinc bound nucleophile are enhanced. This formation of coordinatively bent structure enhances the reactivity of alkyl group towards carbonyl compounds.[4]

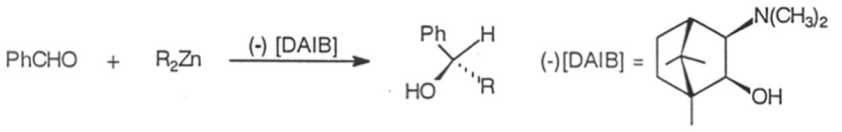
(i) Chiral amino alcohols as catalysts:

The major finding in the alkylation of aldehydes with diethylzinc was made by Oguni and Omi, who demonstrated that various additives enhanced the reactivity of diethylzinc to aldehydes[5]. Particularly the use of 20 mol % *S*-(-) leucinol gave product with 49% *ee* and 96% yield for the reaction with benzaldehyde (scheme 1).



scheme 1

The first truly catalytic enantioselective addition of diethylzinc to aromatic aldehydes was reported by Noyori *et. al.*[6] A camphor derived sterically congested chiral β- dialkylamino alcohol (**1**) *viz.* (-)-3-*exo*-(dimethylamino) isoborneol [(-) **DAIB**] catalyzes the addition of diethylzinc to benzaldehyde. In the presence of 2 mol % of **1**, the reaction proceeded rapidly at 0°C in toluene and 1-phenylpropanol was obtained in 98% *ee* and 97% yield (scheme 2).



1

scheme 2

This reaction has been extended to a range of alkylating agents and aldehyde substrates. *Para* substituted benzaldehydes and cinamaldehyde can also be alkylated with high enantioselectivity. However, moderate enantioselectivity was observed in the addition of Et_2Zn to *n*-hexanal. Methylation of benzaldehyde proceeds 20 times more slowly than ethylation.

Extensive investigation by Noyori's group led to the elucidation of exact mechanism of the amino alcohol catalyzed alkylation of aldehydes[7]. The reaction of benzaldehyde with diethylzinc does not proceed in toluene without DAIB. No alkylation takes place with a stoichiometric amount of DAIB. But a catalytic amount of DAIB promotes the alkylation smoothly. A complex formed from equimolar amount of dialkylzinc and DAIB by elimination of an alkane can not alkylate the aldehyde, but does catalyze the addition of alkyl group to aldehydes with dialkylzinc present in excess. The researchers postulated a catalytic cycle for the ligand accelerated reaction (fig. 3) on the basis of ^{1}H-NMR studies, single crystal X- ray analysis, molecular weight determination of certain intermediates, kinetic experiments, alkyl scrambling experiments, etc.

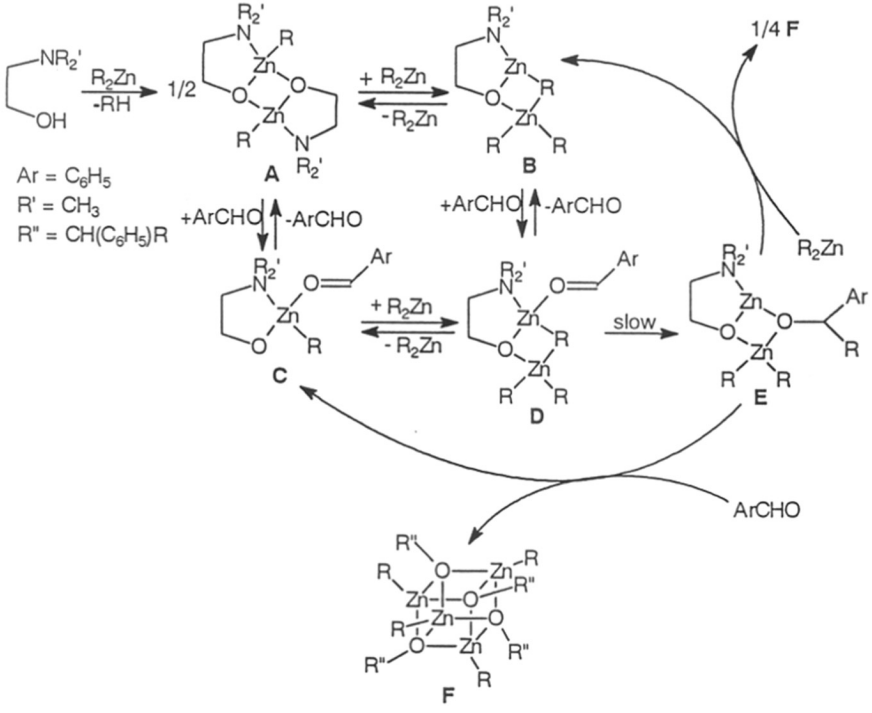
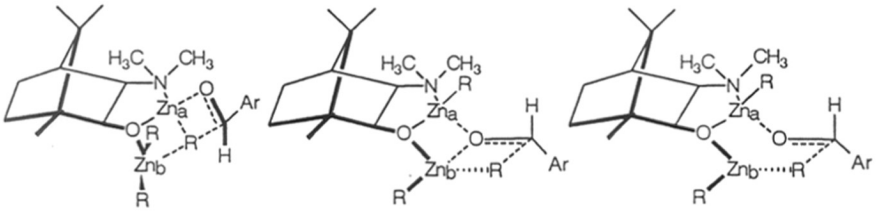


fig. 3

Diethylzinc and PhCHO (1:1) mixture gives two independent signals in ^{1}H-NMR for both the components in ^{1}H-NMR. Reaction of DAIB with Me_2Zn in a 1:1 ratio in toluene evolves methane to give a single dimeric compound **A** (R=CH_3) among the three possible isomers. This complex may be in equilibrium with a coordinatively unsaturated monomeric species which cannot transfer the alkyl group, but can act as catalyst precursor. The dinuclear framework **A** is ruptured spontaneously upon the addition of 1 equivalent of benzaldehyde leading to a monomeric complex **C**. Dimethylzinc also breaks the dimeric structure of **A** to give complex **B** which upon addition of 1 eq. of RCHO gives complex **D**. There is a rapid equilibrium between **C** → **D** → **B.** The alkyl transfer step **D** → **E** is slow and the complex **E** is very stable for days, which slowly dissociates to cubic Zn- alkoxide tetramer **F** and the catalyst precursor **A**. Upon exposure

to benzaldehyde or dimethylzinc, **E** undergoes instantaneous decomposition to **F** completing the catalytic cycle.

The sterically demanding DAIB auxiliary plays a pivotal role in the effective and selective creation of chiral Zn chelate complexes (fig. 4).



2 **3** **4**

fig. 4

Transition states **3** and **4** are favored over **2** which suffers serious interactions between Zn_a-R and Ar group. The configuration of the product alcohol depends on the configuration of the α-position of the amino alcohol. It is consistently observed that α-*S* configurated β-dialkylamino alcohol always produces *S*- enriched alkylated products while α-*R* derivatives lead predominantly to *R*- enriched products. Stereochemical information from the auxiliary defines the chirality of the bridgehead atoms in transition states **2/ 3/ 4**, leading to the alkylated products.

Chirality Amplification:

In most of the catalytic asymmetric reactions, the extent of asymmetric induction differs with the optical purity of the auxiliary used. The addition of dialkylzinc to aldehydes produces the products with higher *% ee* than that of starting chiral auxiliary. This "chirality amplification" phenomenon is demonstrated by the use of 8

mol% of 15% *ee* DAIB as a catalyst yielding (S)- 1- phenylpropanol in 95% *ee* and 92% yield[8].

Such amplification phenomenon is anticipated to be from strict chirality matching, where the actual catalyst exist as a dimer. Homochiral dimerization results in the C_2- chiral 2*S*, 2'*S* or 2*R*, 2'*R* dimer, whereas heterochiral dimerization results in the *meso* compound (2*S*,2'*R*). It was found that the *meso* dimer is unreactive and stable, whereas the less stable homochiral dimer catalyzes the reaction.

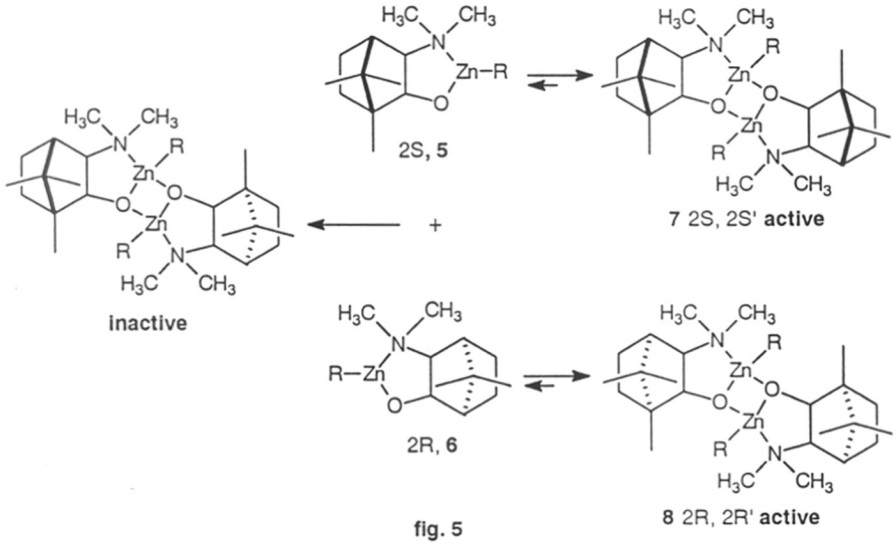
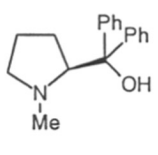


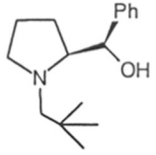
fig. 5

When partially resolved (-)- DAIB was utilized, the minor (+) isomer present gets converted into *meso* achiral dimer by taking equivalent amount of (-)- isomer and does not dissociate. The major (-)- isomer gets converted to the homochiral dissociable pair and catalyzes the reaction (fig. 5).

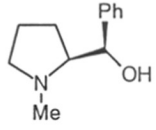
Catalysts derived from proline:



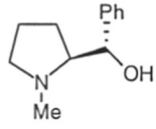
9
(Soai *et.al.*)



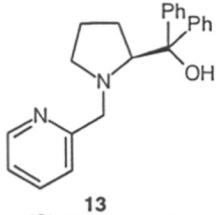
10
(Soai *et.al.*)



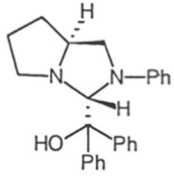
11
(Soai *et.al.*)



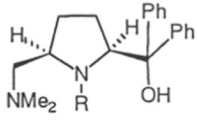
12
(Soai *et.al.*)



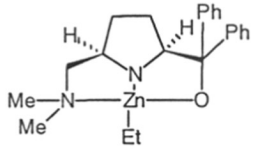
13
(Chelucci *et. el.*)



14
(Asami and Inoue)



15, R = H
16, R = Me



17
(Corey *et. al.*)

A series of chiral pyrrolidine methanols derived from *S*(-)- proline were successfully utilized for the enantioselective transfer of alkyl group to the aldehyde and optically active secondary alcohols in upto 100% *ee* were obtained by Soai *et. al.*[9]

(+)-Diphenyl (N- Methyl pyrrolidin- 2- yl) methanol (DPMPM) **9** where the carbon bearing the hydrogen group is not chiral, catalyzes the addition of dialkylzinc to aryl/ α, β-unsaturated and aliphatic aldehydes to give (*S*)- alcohol in very high enantiomeric excess. The lithium salts also catalyzes the addition in very high *ee*'s. On the other hand (1*R*,2'*S*)-(-)-phenyl (1-neopentylpyrrolidin-2-yl)methanol **10** catalyzes the reaction to afford (*R*) alcohols in high *ee* (upto 100%).

In S-(+)-DPMPM (**9**) the sense of asymmetric induction was determined by the configuration of the asymmetric carbon bearing the amino group whereas in other chiral pyrrolidine methanols (**10-12**) the configuration of the carbon atom bearing the hydroxyl group determines the sense of enantioselectivity.

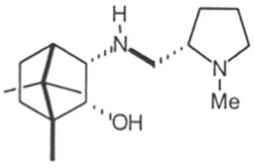
Thus, it was found that *erythro* (-)- **11** afforded product alcohol of (*R*)- configuration while *threo* (-)- **12** afford (*S*)-alcohol. By employing pyrrolidine

methanols or their metal salts of an appropriate structure derived from proline, both the enantiomers of secondary alcohols were obtained.

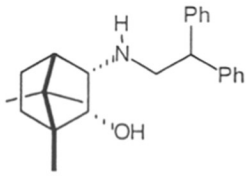
Optically active pyridine ligand **13** from proline were utilized by Chelucci *et. al.*[10] for the enantioselective addition of diethylzinc to benzaldehyde affording the product alcohol in 60% *ee*. Asami and Inoue found that chiral hydroxy aminol **14** derived from (-)- proline catalyzed the enantioselective addition of diethylzinc to benzaldehyde with very high enantioselectivities in *ee*'s upto 96%. The solvent has very little or no effect in the enantioselectivity.[11]

Corey *et. al.*[12] utilized amino alcohols **15** and **16** derived from proline for the enantioselective addition of diethylzinc to benzaldehyde in *ee*'s upto 94%. The reaction of **15** with 1 eq. of Et_2Zn smoothly evolved 1 eq. ethane to give the complex **17** which was fully characterised by X-ray and is the active catalyst for the alkyl transfer step.

Tanaka *et. al.*[13] demonstrated the use of **18** and **19** as efficient auxiliaries in the ethylation of benzaldehyde affording 1-phenyl propan-1-ol in upto 97% *ee*.

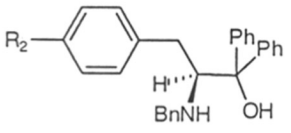


18



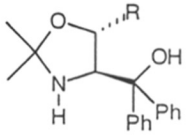
19

Auxiliaries derived from aminoacids other than proline:



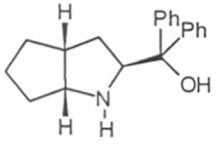
20 R_2 = H
21 R_2 = H

(Soai *et.al.*)

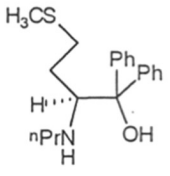


31 R = H
32 R = Me

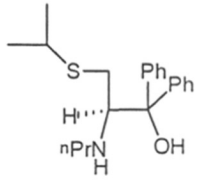
(Falorni *et. al.*)



22



23



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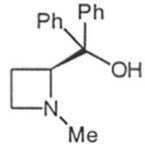
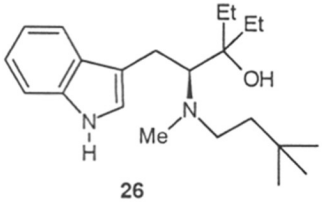


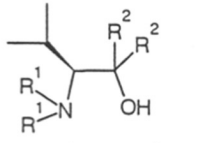
25

(Wallabaum and Martens)



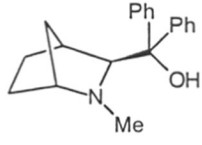
26

(Dai *et.al.*)



27 = R^1 = Me, R^2 = Ph
28 = R^1 = Me, R^2 = nBu
29 = R^1 = R^2 = nBu

(Delair *et.al.*)



30

(Nakano *et.al.*)

Soai *et. al.*[14] found that the *tertiary* amino alcohol (**20**) derived from phenyl alanine catalyzes the addition of diethylzinc to benzaldehyde in 94% *ee*. The substitution at *para* position by a OCH_2Ph group in the catalyst (**21**) catalyzed the addition to afford (*S*)-(-)-1-phenyl propan-1-ol in 96% *ee*.

Wallabaum and Martens[15] utilized the β-amino alcohol (1*R*, 3*R*, 5*R*) 3-(diphenyl hydroxymethyl)-2-azabicyclo[3, 3, 0]octane **22** derived from a bicyclic proline analogue as a catalyst in the ethylation of benzaldehyde to get *R*(+)-1- phenyl- 1-propanol in 100% *ee*.

The same group later reported[16] the use of **23**, **24** and **25** as the auxiliaries derived from L-cystine, limethionine and pipecolinic acid respectively for the enantioselective addition of diethylzinc to benzaldehyde. They found that **23** catalyzes the addition of Et_2Zn to PhCHO to afford (*S*)-(-)1-phenyl propanol in 93% *ee*. The lithium alkoxide of **24** in 5 mol% was more effective than the parent amino alcohol (**24**) to afford the (*S*)-(-)- 1-phenyl propanol in 94% *ee* (*Vs* 60% *ee*). Interestingly, when 10 mol% of lithium alkoxide was used, the enantioselectivity dropped to 68%. The use of (**25**) as catalyst provided 100% *ee* for *para* chloro benzaldehyde.

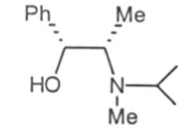
Dai *et. al.*[17] have shown that the β- amino alcohol **26** derived from alkaloid Abrine which contains an indole ring, smoothly alkylates the aromatic aldehydes in upto 100% *ee*. A $-CH_2CH_2{}^tBu$ substituent at nitrogen atom is essential for getting high induction. The change in substitution from $-CH_2CH_2Ph$ to $-CH_2-CH_2{}^iPr$ and finally to $-CH_2CH_2{}^tBu$ increased the enantiomeric excess of the product from 13% to 29% to 60%.

Delair *et. al.*[18] have recently utilized valine derived auxiliaries for the enantioselective addition of diethylzinc to benzaldehyde in 97% *ee*. The change in substitution on the nitrogen as well as on the benzylic carbon effects the enantioselectivity of the alcohol. Thus, the catalyst **27** afforded the product alcohol in 73% *ee*, whereas **28** provided 75% *ee*. The lipophilic amino alcohol **29** with a tetrabutyl substitution position afforded (*R*)-(+)- phenylpropanol in 97% *ee*.

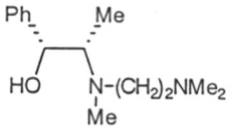
An enantioselectivity of 92% was reported by Nakano *et. al.*[19] in the ethylation of 2-naphthaldehyde with diethylzinc in presence of N-methyl 2-azanorbornyl methanol **30** as a catalyst. Moderate selectivity 76% was observed in the ethylation of benzaldehyde.

Falorni *et. al.*[20] recently reported the use of (*S*)-diphenyl-(2,2)-dimethyl-1,3-oxazolidin-4-yl)methanol (**31**) and (4*S*,5*R*)-diphenyl-(2,2)-dimethyl-5-methyl-1,3-oxazolidin-4-yl)methanol (**32**) derived from L- serine and L- threonine in the enantioselective addition of Et_2Zn to aldehydes. Benzaldehyde was smoothly ethylated with 100% *ee* whereas aliphatic heptanal was alkylated with 84% *ee*.

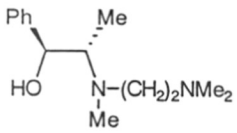
Ligands derived from ephedrine:



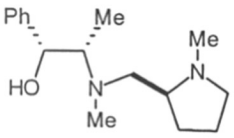
33
(Chalomer *et. al.*)



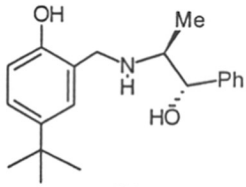
34
(Corey and Hannon)



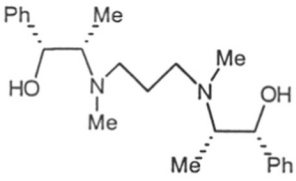
35
(Corey and Hannon)



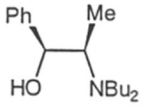
36
(Corey and Hannon)



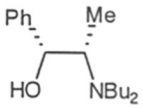
37



38 (Soai *et. al.*)

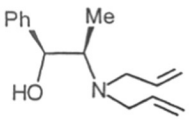


39
(1*S*, 2*R*)- (+)- DBNE

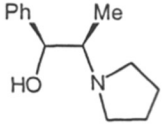


40
(1*R*, 2*S*)- (-)- DBNE

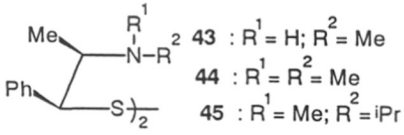
(Soai. *et.al*)



41
(Soai *et. al*)

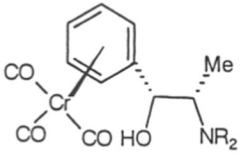


42
(Soai *et. al*)

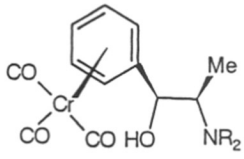


43 : R^1 = H; R^2 = Me
44 : R^1 = R^2 = Me
45 : R^1 = Me; R^2 = iPr

(Hof *et. al.*)

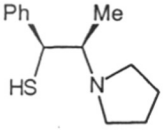


46

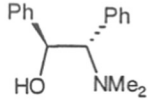


47 R = Me/Bu

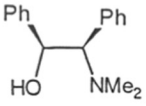
(Jones and Heaton)



48
(Kang *et. al*)

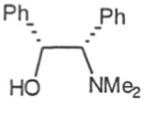


49

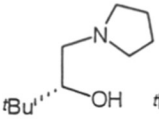


50

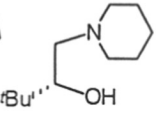
(Noyori *et.al*)



51
(Lisheng *et.al.*)



52



53

(Oguni *et. al.*)

Due to the easy availability of both the enantiomers of ephedrine and norephedrine derivatives, the synthesis of a variety of catalysts in both the enantiomeric forms has an advantage in asymmetric synthesis.

Chalomer *et. al.*[21] found that (1*R*,2*S*)-N-*iso*propylephedrine (**33**) catalyzes the addition of diethylzinc to benzaldehyde to afford (*R*)-1-phenyl propanol with 80% *ee*. They have also found that the enantioselectivities of product alcohols increases with increase in the amount of diethylzinc in proportion to aldehydes. When the molar ratio of diethylzinc to cyclohexane carboxaldehyde was 4.5, *ee* of the product alcohol reached 97%.

The enhancement of enantiomeric excess when excess amount of diethylzinc was utilized was attributed to the assumption that when dialkylzinc adds to aldehyde, alkylzinc alkoxide is formed *in situ*. This alkyl zinc alkoxide may also form a complex with the chiral catalyst and may reduce the enantioselectivity of the chiral catalyst. Therefore when an excess amount of dialkylzinc is present, an enantioselective chiral complex may be more easily formed between dialkylzinc and chiral catalyst.

Corey and Hannon[22] reported that the lithium salt of **34** derived from (1*R*,2*S*)-ephedrine catalyzes the addition of diethylzinc to benzaldehyde to afford *R*(+)-1-phenylpropan-1-ol in 90% *ee*. They have also observed[23] that the lithium salt of ligand **35** catalyzes the addition of diethylzinc to benzaldehyde to produce the (*S*)-phenylpropanol in 91% *ee*. The reversal of enantioselectivity in the product alcohols shows that the chirality of the benzylic alcohol stereocenter of the catalyst correlates with the chirality of the predominant isomer. A molecular model was formulated for this observation (fig. 6).

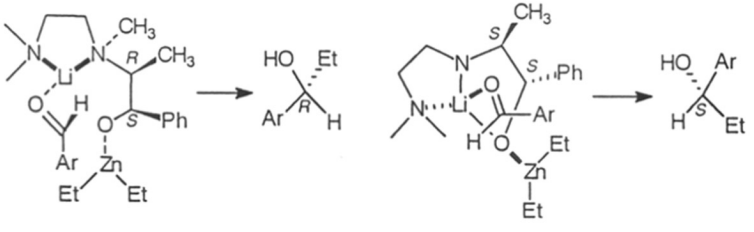
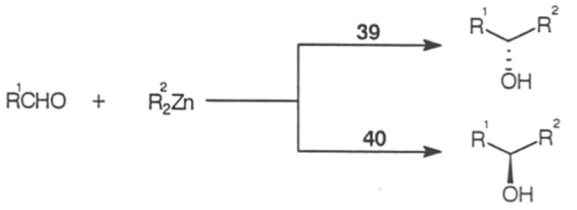


fig. 6

When the lithium salt of **36** derived from (1*S*,2*R*)- ephedrine was utilized, the product alcohol was obtained in 95% *ee*. When a chiral *tertiary* amino phenolic alcohol **37** derived from (1*S*,2*S*)-pseudoephedrine was employed as a catalyst the product alcohol was obtained in 86% *ee*.

A chiral diamino diol **38** possessing a C_2-axis of symmetry derived from ephedrine was utilized as a catalyst by Soai *et. al.*[24] for the enantioselective addition of diethylzinc to benzaldehyde. The dilithium salt of **38** catalyzed the reaction to yield (*R*)-1-phenyl 1-propanol in 85% *ee*.

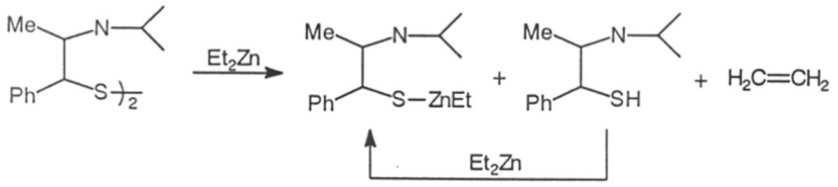
Extensive investigations by Soai *et. al.*[25] on the chiral N,N-dialkyl norephedrine derivatives as the catalysts for the enantioselective addition of dialkylzincs to aromatic as well as aliphatic aldehydes led to the development of N,N-dibutyl norephedrines (**39, 40**) as efficient auxiliaries for this reaction (scheme 3).



scheme 3

They found that these catalysts transfers alkyl group from dimethyl, diethyl and diisopropylzinc reagents to the aromatic as well as aliphatic aldehydes in high enantiomeric excesses. (1*S*,2*R*)-N,N-diallyl norephedrine (**41**) and (1*S*,2*R*)-1-phenyl-2-(1-pyrrolidinyl) propan-1-ol (**42**) were also effective catalysts. It was found that the enantioselectivity of the addition of dialkylzincs to aldehydes is very sensitive to the structure of the chiral catalyst. The optical purity of the product in the addition of Et_2Zn to 3-methylbutanal increases up to the chain length of four carbons. Catalysts with N-alkyl substituents possessing more than four carbons gave alcohols of lower optical purity.

Hof *et. al.*[26] have demonstrated the use of sulfur derivatives of ephedrine **43, 44, 45** for the enantioselective addition of diethylzinc to benzaldehyde to afford (*R*)-1-phenyl-1-propanol in 90% enantiomeric excess. The thioalkoxide formed by the *in situ* cleavage of the disulfide bond of the catalyst with excess diethylzinc was believed to be the active catalytic species (scheme 4).



scheme 4

Jones and Heaton demonstrated[27] the utility of chiral tricarbonyl (η^6-arene) chromium (0) complexes (**46, 47**) derived from norephedrine as efficient catalysts for the enantioselective addition of diethylzinc to aldehydes. The uncomplexed catalyst gave product alcohols with diminished enantiomeric excess whereas complexed catalysts gave product alcohols with very high inductions. The origin of extremely high selectivity observed in these reactions can be attributed to a possible transition state assembly as shown in fig. 7.

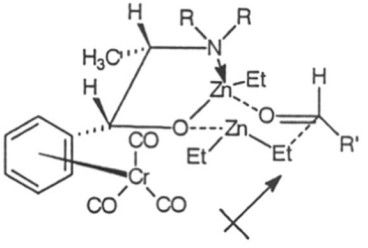


fig. 7

The chiral zinc metallocycle coordinates the incoming aldehyde in such a way that the alkyl group of the aldehyde is shielded by N,N-dialkyl group. An incoming alkylzinc coordinates to oxygen of the metallocycle and is stabilized by attractive dipole-dipole interactions with the chromium tricarbonyl group which in turn helps to stabilize the six membered chain like transition state.

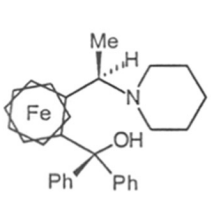
Recently, Kang *et. al.* reported[28] the use of (1*R*,2*S*)-1-phenyl- 2-piperdinopropane-1-thiol (**48**) derived from corresponding ephedrine as a successful catalyst for the enantioselective addition of diethylzinc to α-branched aldehydes with very high inductions (100% *ee*). However, aliphatic aldehyde and α,β-unsaturated aldehydes could only be ethylated in moderate enantioselectivity (62-77% *ee*).

Noyori *et. al.*[8] have utilized the amino alcohols **49** and **50** for the enantioselective addition of diethylzinc to benzaldehyde. They observed that α-stereogenic centre appears to be more influential than the β-stereogenic centre. Thus (1*S*,2*S*)-**49** and (1*S*,2*R*)-**50** exhibit the same asymmetric orientation with the latter in higher enantioselectivity (81% *ee Vs* 94% *ee*). Substituent on nitrogen also effects the enantioselectivity. The substitution of ethyl instead of methyl in **50** increased the enantioselectivity from 73% to 94%.

A high enantioselection of 97% was achieved by Lisheng Jian *et. al.*[29] in the addition of diethylzinc to benzaldehyde utilising (1*R*,2*S*)-N,N-dimethylamino-1,2-diphenylethane diol (**51**). The utilisation of the (1*S*,2*R*) antipode of the catalyst afforded other enantiomer of the product.

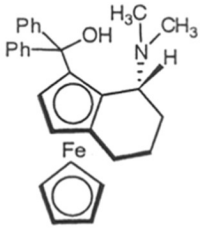
High asymmetric amplification phenomena was observed by Oguni *et. al.*[30] in the ethylation of benzaldehyde using sterically constrained β-amino alcohols **30, 52** & **53**. when the catalyst **53** of 20% *ee* was utilized as an auxiliary 1-phenyl-1-propanol was obtained in 83% *ee*. Similarly, the utilisation of 77% *ee* of **52** provided the product alcohol in 94% *ee*.

Chiral ferrocenyl amino alcohols as the ligands:



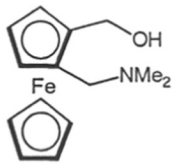
54

(Watanabe *et. al.*)



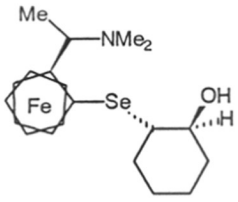
55

(Wally *et. al*)



56

(Nicolsi *et. al.*)



57

(Fukuzawa *et.al.*)

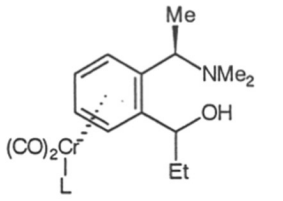
Watanabe *et. al.*[31] have successfully utilized chiral 1, 2- disubstituted ferrocenyl amino alcohols for the enantioselective addition of diethylzinc to aromatic and highly branched aliphatic aldehydes. The amino alcohols derived from (*R*)- and (*S*)- N, N-dimethyl-1- ferrocenyl ethylamines catalyze the ethylation smoothly. Of the variety of amino alcohols examined, **54** is found to be the best affording alcohols of high enantiomeric purity.

Wally *et. al.*[32] employed the ferrocenyl amino alcohol (**55**) as a catalyst for the enantioselective ethylation of aldehydes. 94% Enantioselectivity was obtained in the ethylation of *para* tolualdehyde, whereas 87% *ee* was observed in the case of benzaldehyde. β-Branched aliphatic aldehydes were also ethylated with good enantioselectivity (up to 85% *ee*).

Nicolosi *et. al.*[33] utilized the alcohol (**56**) which has only planar chirality and no chiral centre in the molecule as a catalyst for the enantioselective addition of diethylzinc to benzaldehydes. The resulting 1-phenyl-propanol was found to be of 82% *ee*.

Fukuzawa and Tsuzuki employed[34] a chiral ferrocenylseleno amino alcohol **57** as a catalyst for the enantioselective addition of diethylzinc to aryl aldehydes. The catalyst **57** was used as a 1:1 diastereomeric mixture affording 94% *ee* of 1-phenyl-1-propanol.

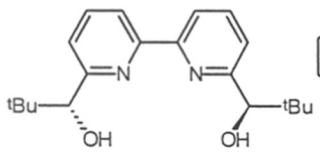
A chiral (η^6-arene) chromium complex **58** with an amino and a hydroxy group in the two *ortho* benzylic positions was derived from α-phenethylamine and was utilized as a chiral ligand in the enantioselective addition of Et_2Zn to benzaldehyde[35]. The catalyst **58** smoothly catalyzed the addition of Et_2Zn to benzaldehyde in 97% *ee*. Unsubstituted complex (R = H) at the α-position exhibited very low selectivity. Complexes with α'-(*S*)- configuration at the benzylic alcohol moiety gave products with (*S*)- configuration.



58 (Uemera *et. al.*)

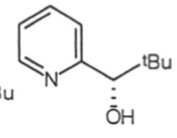
The substitution with methyl, phenyl (R_1=R_2=Me or Ph) lowered the enantioselectivity. The free amino alcohol without chromium complex lowered the *ee* to 24%. The stereogenic α'-(*R*)- centre at the benzylic alcohol complexes also gave the (*S*)- isomer. It was found that the stereogenic centre at the α-position of benzylic hydroxyl moiety is essential to afford product alcohols of high selectivity. The face chirality of the (arene) chromium complex determines the absolute configuration of the product.

Chiral pyridyl alcohols as ligands:

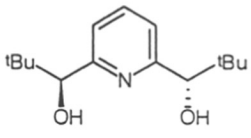


59

(Bolm *et. al.*)

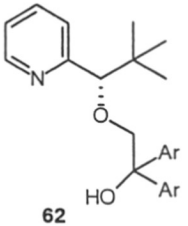


60

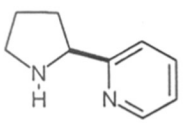


61

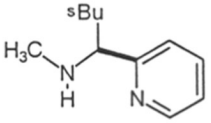
(Ishizaki *et. al)*



62

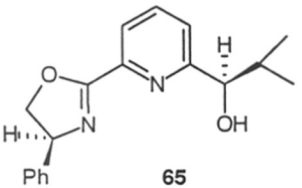


63



64

(Conti *et. al.*)



65

(Macedo and Moberg)

Bolm *et. al.*[36] were the first to report the use of a chiral bipyridine ligand **59** which catalyzes the enantioselective addition of diethylzinc to aryl aldehyde. A 97% enantioselectivity was observed in the reaction of diethylzinc with benzaldehyde. Lowering of the temperature as well as increase in the concentration of the catalyst from 5 mol% to 10mol% has little or no effect on the enantioselectivity.

Ishizaki *et. al.*[37] found that the ligands **60** and **61** catalyze the addition of diethylzinc to benzaldehyde in moderate *ee*'s (66% and 68% respectively). The modification of the ligand **60** to a tridentate ligand **62** enhanced the enantioselectivity to 93%.

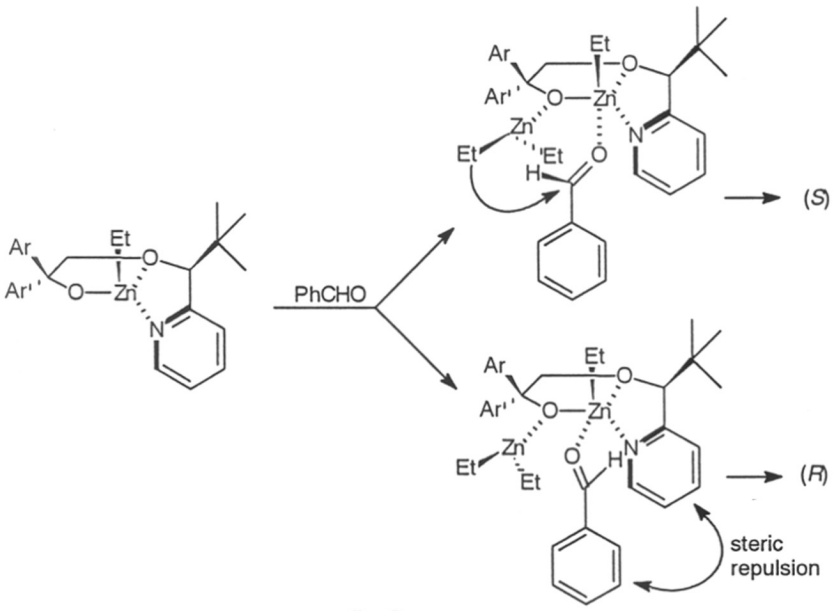
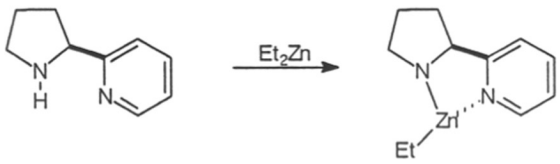


fig. 8

The significant increase in the enantioselectivity by the use of a tridentate pyridyl ligand than the free pyridyl alcohol was explained by a transition state. The formation of (*S*)- alcohol through a pentacoordinated Zn atom is more favourable than the transition state for (*R*)- alcohol which involves steric repulsion (fig. 8).

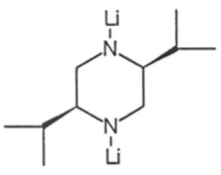
Chelucci *et. al.*.[38] successfully utilized optical active pyridyl amines **63** and **64** for the enantioselective addition of diethylzinc to aryl aldehydes in very high *ee*'s (upto 100%). Selectivity upto 100% was also achieved in ethylation arylaldehyde with substitution on the benzene ring. Cyclohexane carboxaldehyde was ethylated with 90% *ee*, whereas other aliphatic aldehydes were ethylated in moderate enantioselectivity (upto 67%). The substitution of H with a methyl on the pyrrolidine moiety showed no induction, and also the lithium salt of **63** surprisingly provided no induction. An enantioselectivity of 98% for benzaldehyde was realized with catalyst **64**. The presence of a hydrogen atom on the nitrogen of the pyrrolidine ring is essential for enantioselection and suggests the formation of stoichiometric complex between the dialkylzinc and the ligand, thereby providing an effective chiral environment for the reaction.



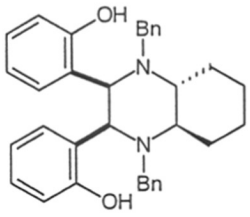
Recently Macedo and Moberg utilized[39] pyridineoxazoline alcohol (**65**) as ligand for the ethylation of aldehydes and reported 84% *ee* for ethylation of benzaldehyde.

Chiral piperazines as catalysts:

Chiral 2,5-disubstituted piperazines are readily available by the reduction of the corresponding 2,5-diketopiperazines derived from α-amino acids.

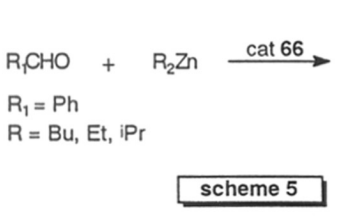


66
(Soai *et. al.*)



67
(Shono *et. al.*)

Soai *et. al.*[40] examined a variety of 2,5-disubstituted piperazines and found that (2*S*,5*S*)-diisopropylpiperazine (**66**) catalyzed the reaction to afford (*R*)-1-phenyl-1-propanol in 89-91% *ee*. When the piperazine was used without lithiation, the enantioselectivity dropped to 81%. Substituents smaller than isopropyl did not afford optically active alcohol. The piperazine derivative was not only effective for diethylzinc but also impressive for diisopropyl and dibutyl zinc affording corresponding alcohols in 92% and 96% *ee* (Scheme 5).



scheme 5

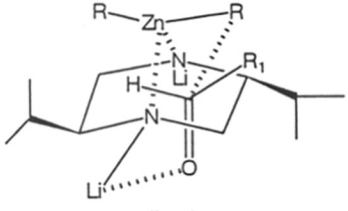


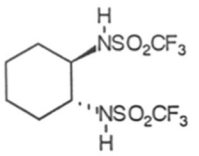
fig. 9

Soai *et. al.* postulated the probable stereochemical course of the reaction, as shown in fig. 9. The zinc atom of the dialkylzinc is chelated to two nitrogen atoms of the piperazine ring which has a boat like configuration with both the *iso*propyl groups occupying pseudoequitorial positions. The configuration of dialkylzinc becomes tetrahedral and becomes more reactive. Because of the C_2-symmetry of the complex, the number of possible transition states are reduced. The aldehyde approaches the complex

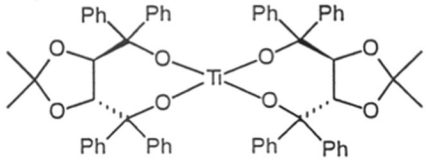
from a direction avoiding the bulky isopropyl substituent and reacts *via* a six centered transition state involving bulky phenyl group at equitorial position.

Shono *et. al.*[41] synthesized a chiral tetrasubstituted piperazine (**67**) and utilized the auxiliary for the enantioselective addition of Et_2Zn to aromatic and aliphatic aldehydes in 81 to 99% *ee*.

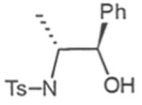
Chiral transition metal complexes as ligands:



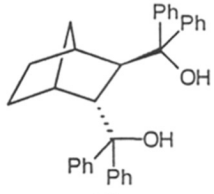
68
(Yoshioka *et. al.*)



69
(Schimdt and Seebach)



70
(Ito *et. al*)



71
(Dreisbach et. al)

Yoshioka *et. al.*[42] found that the chiral orthotitanate complex prepared *in situ* from titanium tetraisopropoxide and bis trifluoromethane sulfonamide of *trans*-1,2-cyclohexane diamine (**68**) works as a highly enantioselective catalyst for the addition of diethylzinc to aliphatic and aromatic aldehydes. The turnover of the catalyst reaches to about 2000. The reaction of benzaldehyde with $Ti(O^iPr)_4$ in the absence of chiral sulfonamide is very slow. Therefore, the Lewis acidity of the titanium is considered to be increased by electron withdrawing disulfonamide. The enantiomeric excess was increased with decrease in the amount of $Ti(O^iPr)_4$. Use of the excess of Et_2Zn also

increased the enantiomeric excess of the product alcohol. The probable mechanism involves the formation of a chiral ethyl titanium reagent (**C**) in the system (fig. 10).

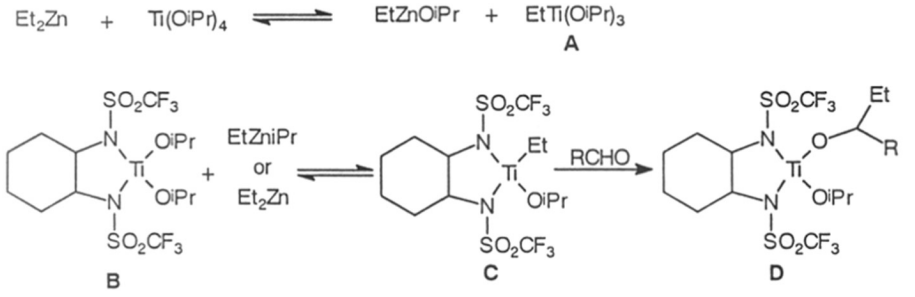
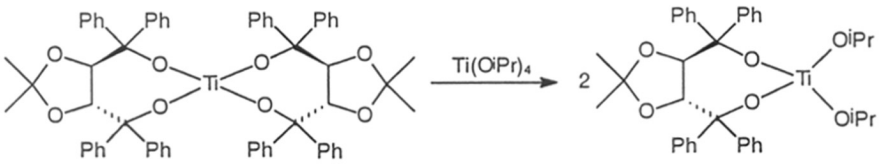


fig. 10

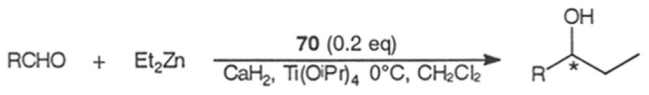
Alkyl titanium reagents are known to react with aldehydes. Chiral titanium species (**C**) might initially be generated by the reaction of chiral titanate **B** and achiral titanate species **A** or Et_2Zn and further be regenerated from dialkoxytitanate **D** establishing the catalytic cycle.

Schmidt and Seebach reported[43] the enantioselective addition of diethylzinc to aldehydes using a chiral spirotitanate **69** prepared from the corresponding diol derived from tartaric acid. The addition of 0.05-20 equivalents of **69** to a mixture of diethylzinc and anisaldehyde (1.2:1) in toluene gave the product alcohol in 98% *ee* with (*R*)- configuration. However by the addition of 10 fold excess of $Ti(O^iPr)_4$, the induction was reversed and the chiral product alcohol with (*S*)- configuration in upto 99% *ee* was obtained. The reaction can also be carried out in donor solvents like ether and THF. The method is also applicable to aliphatic and α,β-unsaturated aldehydes. The mixing of a chiral spirotitanate **69** with $Ti(O^iPr)_4$ causes an exchange of the alkoxy ligands presumably leading to the formation of a monocyclic titanate with two isopropoxy groups. It was shown that the spirotitanate derived from diol accelerates the reaction rate more efficiently than $Ti(O^iPr)_4$ (scheme 6).



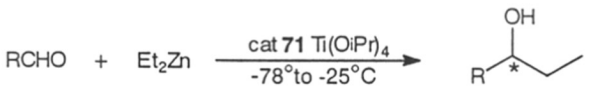
scheme 6

Ito. *et. al.* utilized[44] a chiral titanium reagent modified with N-sulfonylated aminoalcohol for the enantioselective addition of diehtylzinc to benzaldehyde. The use of 0.2 eq of **70** and 1.2 eq of $Ti(O^iPr)_4$ in presence of CaH_2 catalyzed the ethylation affording (*S*)- 1- phenyl- 1- propanol in 97% *ee* and 97% yield. The *ee*'s were good for cinnamaldehyde as well as for aliphatic aldehydes (90% *ee*) (scheme 7).



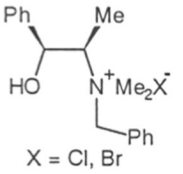
scheme 7

Recently Dreisbach *et. al.* have reported[45] the use of **71** derived from (1*S*,2*R*,3*R*,4*R*)- bicyclo [2,2,1] heptane-2,3-dicarboxylic acid as an auxiliary in the presence of $Ti(O^iPr)_4$ as a catalyst for the enantioseletive ethylation of aldehydes. The use of 2.2 eq of $Ti(O^iPr)_4$ was recommended for high enantioselection. In the ethylation of benzaldehyde, 97% *ee* was obtained with ehter as a solvent. The ethylation of *para* substituted aldehydes proceeded smoothly whereas α- substituted and α, β- unsaturated aldehydes provided low *ee*'s (scheme 8).

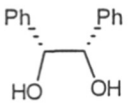


scheme 8

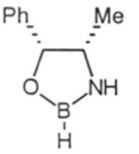
Miscellaneous catalysts:



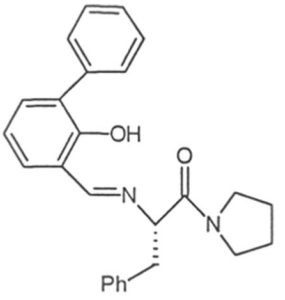
72
(Soai *et. al*)



73
(Rosini *et. al*)

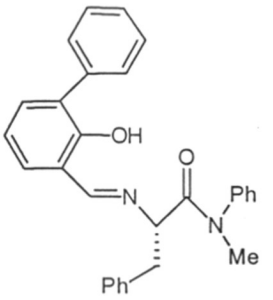


74
(Joshi *et. al.*)

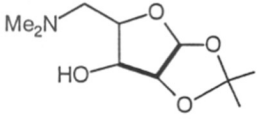


75

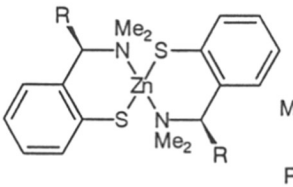
(Mori *et. al.*)



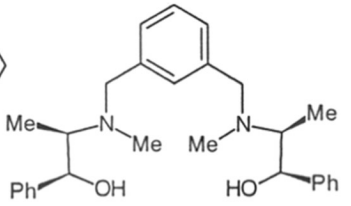
76



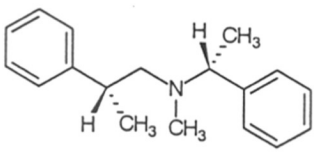
77
(Cho & Kim)



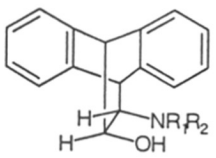
78
(Rijnberg *et. al.*)



79
(Andreas *et.al.*)



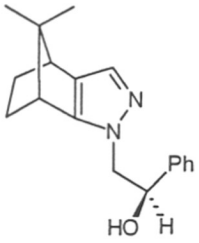
80
(Iuliano *et. al.*)



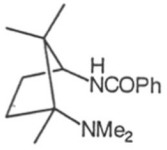
81 $R_1 = R_2 = Me$

82 $R_1 = SO_2CF_3$; $R_2 = Me$

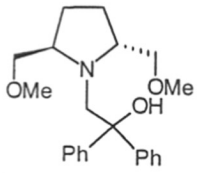
(Kimura *et. al.*)



83 (Kotsuki *et. al.*)



84 (Urabe *et. al.*)

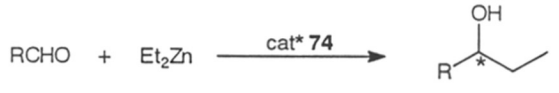


85 (Shi *et. al.*)

Soai. *et. al.* have demonstrated[46] that (1*S*, 2*R*) N- benzyl ephedrinium halides (**72**) also catalyze the addition of diethyl zinc to aldehydes to afford optically active alcohols in moderate *ee*'s 74%. The effect of the solvent was important. The chiral quaternary salts in solid state in hexane exhibited much more selectivity than in solution state. Very little solvation of the ammonium cation in hexane is essential for the asymmetric induction. The use of DMF as solvent destroys the chiral complex of ammonium cation.

Rosini. *et. al.* has reported[47] that 1,2-diphenylethanediol (**73**) catalyzes the addition of diethylzinc to aryl aldehydes up to 78% *ee*. On the other hand 1-phenylethane-1,2-diol does not catalyze the addition.

A very high enantioselectivity (>95%) in the reaction of diehtylzinc to a vareity of arylaldehyes using an oxazaborolidine (**74**) derived from (1*R*,2*S*)-(-)-ephedrine was reported by Joshi. *et. al.*[48] This was the first example of a chiral boron compound utilized for this reaction. However aliphatic aldehydes showed moderate (52%) enantiomeric excess. The repalcement of boron with aluminium, lithium or zinc lowered the *ee* of the product (scheme 9).



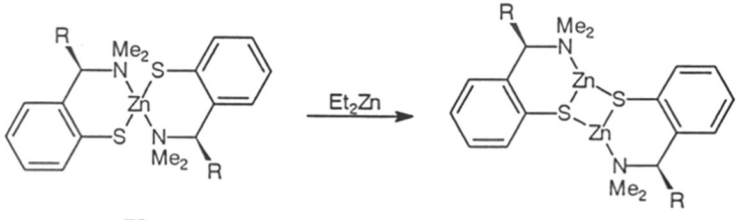
scheme 9

>95% *ee*

Mori. *et. al.* found[49] that the addition of diehtylzinc to aryl aldehydes was catalyzed by the peptide or α- amino acid amide containing schiffbase at N- terminal ((**75**, **76**) to afford product alcohols in up to 93% *ee*.

Cho and Kim reported[50] 1,2-diisopropylidine-5-deoxy-5-dialkylamino,α-D-xylofuranose (**77**) derived from α-D-xylose as the catalysts for the enatioselective addition of dietylzinc to aldehydes. Good enantioselectivities (up to 96%) were observed for aliphatic and aromatic aldehydes.

Rijnberg *et. al.* successfully utilized[51] (N, S) chelated zinc complex **78** in the addition of diethylzinc to aldehydes. The air-stable zinc bis [(2(*R*)-1-dimethylamino)ehtyl] phelyl thiolate complex catalyzes the addition in excellent selectivities. The product alcohols obtained were of (*S*)- configuration. The authors have postulated that the complex **78** itself is not the actual catalyst in the reaction, but the ethylzinc thiolate complex **78a** which was readily formed from the reaction of **78** with Et_2Zn (scheme 10).



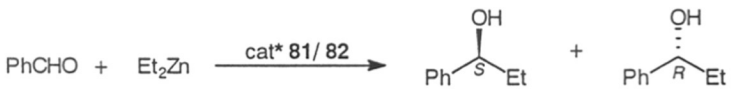
78 **78a**

scheme 10

A moderate *ee* of 70% in the addtionof diethylzinc to benzaldehyde was provided by a *meta*- xylene β- hydroxy derivative (**79**)[52].

Iuliano. *et. al.* has reported[53] the additon of Et_2Zn to benzaldehyde in presence of (1*R*,2*S*)-1-phenethylamino-1-phenethanol (**80**) affording (*R*)- phenyl propanol in 88% *ee*.

Kimura. *et. al.* found[54] that β- amino alcohols **81** & **82** sterically constrained by a diazabicyclo [2,2,2] ring system serve well as chiral catalysts for enantioselective addition of Et_2Zn to benzaldehdyes (up to 98% *ee*). A dramatic difference in the enantioselectivity was observed between the catalysts **81** & **82**. The use of N, N-dimehtyl derivative **81** as catalysts provided (*S*)-1- phenyl-1-propanol in 96% *ee* in the ethylation of benzaldehyde whereas sulfonamide **82** afforded (*R*)- alcohol in 98% *ee* (scheme 11).



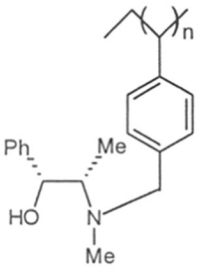
cat 81	**98**	**2**
cat 82	**1**	**99**

scheme 11

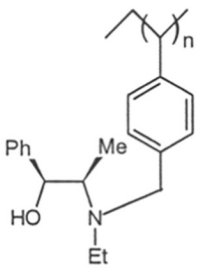
A chiral pyrazole derivative **83** was utilized by Kotsuki *et. al.*[55] for the ethylation of benzaldehyde in 93% *ee*. Urabe *et. al.*[56] found that (1*R*,3*S*) **84** derived from (+)-camphoric acid catalyzed the enantioselective addition of diethylzinc to benzaldehyde in 93% *ee*.

Recently Shi. *et. al.*[57] utilized a C_2-Symmetric pyrrolidine auxiliary **85** for the enantioselective addition of diethylzinc to aldehydes. A 91% *ee* was reported for benzaldehyde and 96% for *para* tolualdehyde in the ethylation.

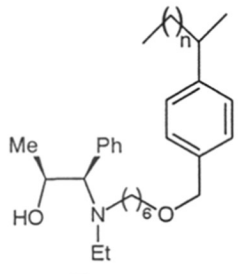
Polymer supported catalysts:



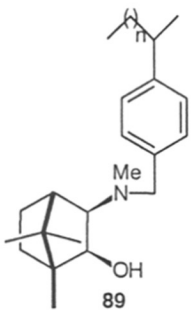
86



87
(Soai *et al.*)



88



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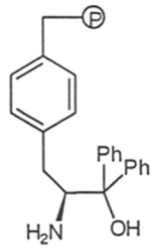
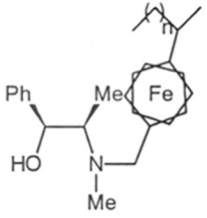


90

(Itsuno and Frechet)



91
(Watanabe *et. al*)

Enantioselective addition of diehtylzinc to aromatic aldehdyes in the presence of a polymer supported (1*R*, 2S) ephedrine was reported by Soai *et. al*[58]. The enantiomeric excess of the product alcohols were up to 83% *ee*. Although **86** was effective for aromatic aldehdyes, the enantioselectivity was low for aliphatic aldehydes. The same group has demonstrated[59] that the use of polymer supported N-ethyl norephdrine **87** gave better enantioselectivities in the ethylation of alipahtic aldehydes.

Polymer supported (1*S*,2*R*)-DBNE containing hexamethylene spacer (**88**) was successfully utilized by Soai. *et. al.*[60] for the enantioselective alkylation of both aromatic and aliphatic aldehydes (60- 92% *ee*).

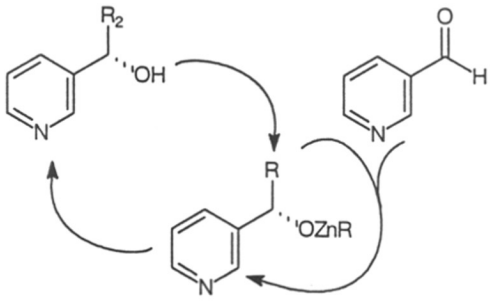
Itsuno and Frechet reported[61] very high enantioselectivity tin the addition of diehtylzinc to arylaldehdyes (up to 99% *ee*) by utilizing a polymer supported DAIB (**89**) catalysts. The same group has reported that cross linked polymers binding an amino alcohol (**90**) catalyzed the enantioselective ehtylation to afford products in up to 99% *ee*. It was proposed that the primary amino group of the chiral amino alcohol reacts with the aldehyde to form a schiff base which accelarates the ethylation of aldehydes.

Watanabe *et. al.* reported[62] 72% *ee* for the ethylation of benzaldehyde with diethylzinc catalyzed by a chiral polymer containing N- ferrocenylephedrine (**91**).

Asymmetric auto-catalytic reactions:

If the stereochemical structure of the product and the chiral catalyst are the same (chiral self re- catalyst), the reaction becomes a self- reproducing system for chiral molecules. An asymmetric "self catalytic reaction" is an ideal reaction because the amount of chiral catalyst that is product itself increases during the reaction.

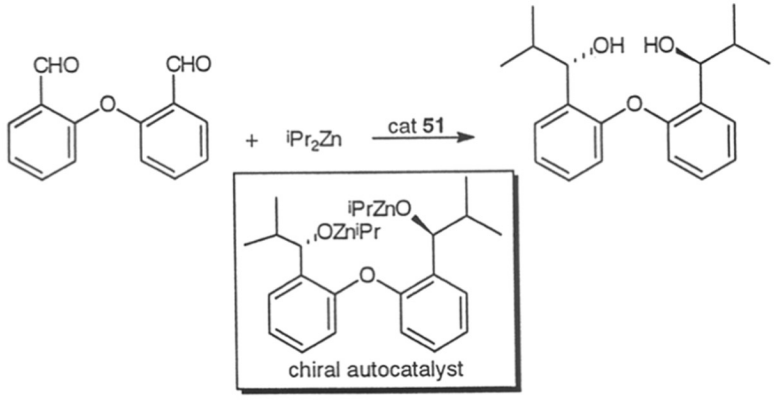
Soai *et. al.*[63] reported that optically active 3- pyridylalkyl alcohols produced themselves in the same configuration during the addition of diethylzinc reagents to 3- pyridine carboxaldehyde with 35% *ee* (fig. 11).



R = iPr, 35% *ee*

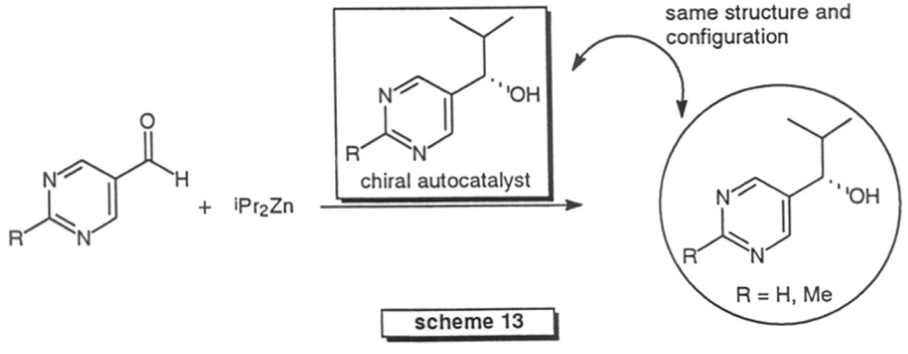
fig. 11

Recently, the same group[64] has shown that bis [2-(1-hydroxyalkyl)-phenyl] ether acts as an asymmetric autocatalyst. The catalyst was synthesized by addition of $^{i}Pr_2Zn$ to the required aldehyde in the presence of DBNE (scheme 12).



scheme 12

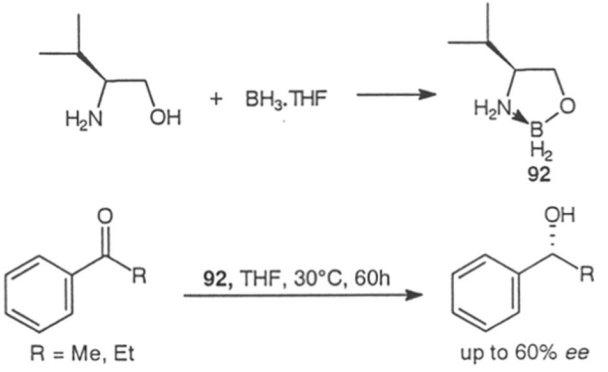
Yet another example of high enantioselective auto-catalysis was reported[65] for chiral pyrimidyl alcohol. When 2-methyl pyrimidine-5-carbaldehyde and $^{i}Pr_2Zn$ were reacted in the presence of (*S*)- 2-methyl-1-(2-methyl-5-pyrimidyl)- 1-propanol of 99.9% *ee*, the *ee* of the newly formed product reached 98.2% *ee* (scheme 13).



scheme 13

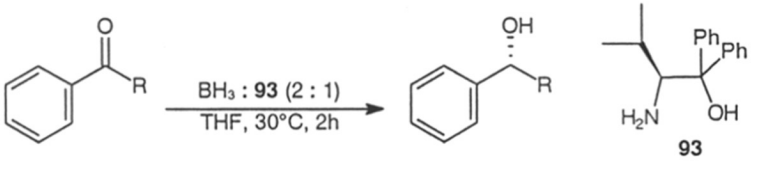
Oxazaborolidine Catalyzed Reduction of Ketones

In 1981 Itsuno *et. al.*[66] reported the reduction of prochiral ketones using an amino alcohol - borane complex as a catalyst. They speculated that the amino alcohol reacts with borane to give complex **92** which reduces prochiral ketones in up to 60% *ee*. (scheme 14)



scheme 14

Further studies by Itsuno *et. al.*[67] concluded that the asymmetric reduction of aromatic and aliphatic ketones with reagents prepared from borane and chiral amino alcohol such as α-α-diphenyl valinol **93** provides very high enantioselectivities (up to 90%). The stereoselectivity depends upon the molar ratio of borane and amino alcohol derivatives. The highest selectivity is obtained with a ratio of borane to amino alcohol 2:1 (scheme 15).

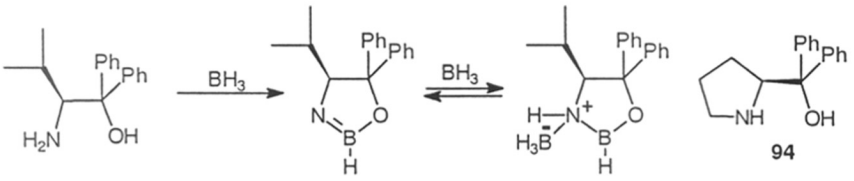


scheme 15

The reduction of aliphatic ketones provided alcohols in 55-79%*ee* and the best being the reduction of 'BuCOMe in 79% *ee*. Despite the high

enantioselectivities obtained in the reductions, the main drawback of this method is the use of a quantitative amount of the auxiliary **93.** The problem was partially overcome by the use of polymer supported amino alcohols[68].

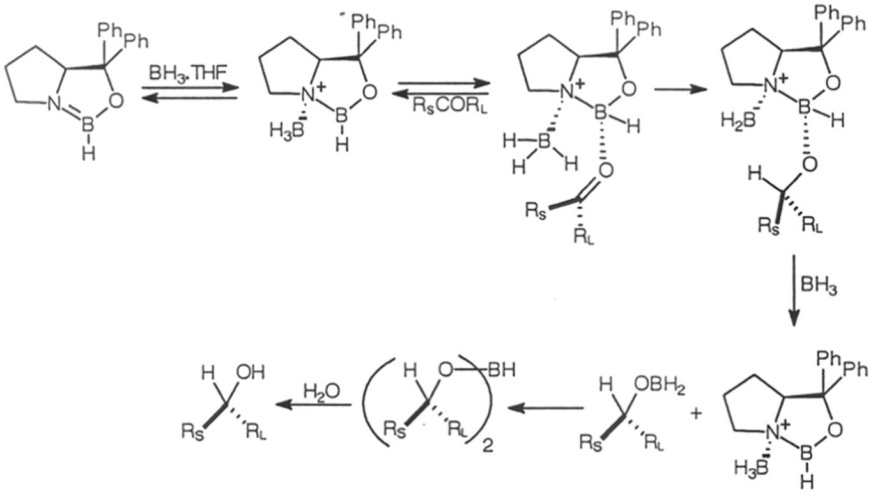
Corey *et. al.*[69] extensively examined the Itsuno's reagent and solved it's structure. They developed, isolated and identified the active catalyst and also elucidated the mechanism of the reaction. It was found that a faster reaction occurs between diphenylvalinol and 2 eq of borane in THF at 35°C to give 2 eq of H_2 and the corresponding oxazaborolidine. The oxazaborolidine was isolated by sublimation under reduced pressure. Most importantly, it was found that a catalytic amount of oxazaborolidine (10mol%) leads to optically active alcohols in high *ee*'s (up to 95%) (scheme 16). An even better catalyst for the reduction of ketones is the oxazaborolidine prepared from (*S*)-2-(diphenyl hydroxymethyl)- pyrrolidine (**94**).



94

scheme 16

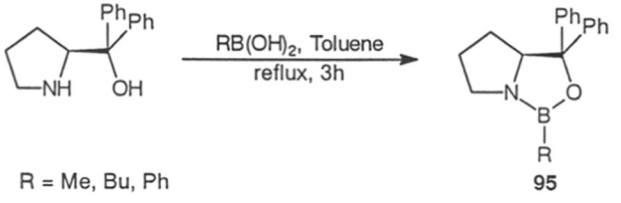
As for the mechanism, the oxazaborolidine catalyst behaves like an enzyme in the sense that it binds with ketone and borane both, and brings them closer. After the reduction is over, it releases them and itself becomes free. That is why the term "Chemzyme" was coined for these oxazaborolidines (scheme 17).



scheme 17

Complex formed by the reaction of oxazaborolidine and BH_3 is ideally structured as an effective reagent for carbonyl reduction in which Lewis acidic ring boron coordinates to the oxygen atom *anti* to the larger carbonyl appendage. The hydrogen transfer thus take place from the NBH_3^* unit to the carbonyl carbon *via* a six membered cyclic transition state as shown in scheme 17. This mechanistic picture explains well the stereochemistry of the reductions.

Corey *et. al.*[70] later prepared the B- alkyl oxazaborolidines from corresponding amino alcohol and alkyl boronic acids. These were found to be less moisture senesitive and reduce prochiral ketones with very high *ee*'s (scheme 18).



R = Me, Bu, Ph

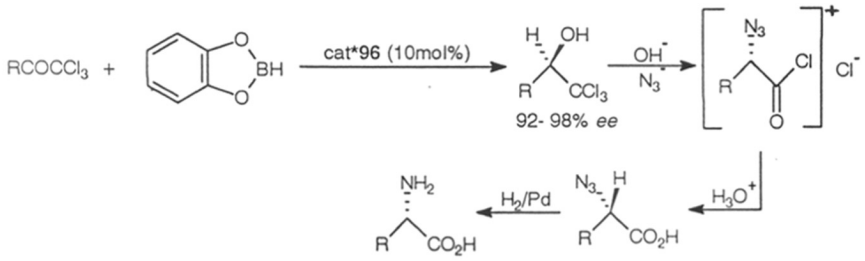
95

scheme 18

The oxazaborolidine catalyzed reduction was extended to a vareity of ketones *viz.* α- haloketones[71], α, β- unsaturated ketones[72], α- fluoro

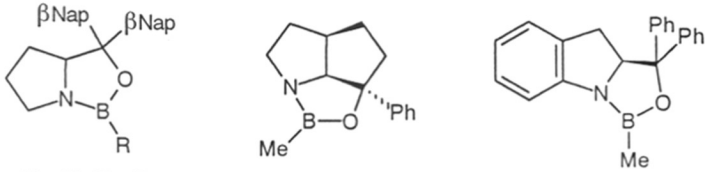
ketones etc. The catalysts with B-H and B-Me substitution are not effective at lower temperatures. B-Bu catalyst can be used at -78°C in conjunction with catecholborane for the reduction of α,β-unsaturated ketones which normally undergo side reactions when reduced with BH_3.

This methodology was elegantly applied[73] for the synthesis of α-hydroxy acids and α- amino acids in very high enantioselectivities (scheme 19).



scheme 19

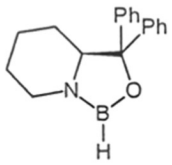
Corey's group also synthesized[74,75] other oxazaboroliidnes **96 -98** for the reduction of prochiral ketones and dueterated aldehydes to afford optically active alcohols in up to 99% *ee*.



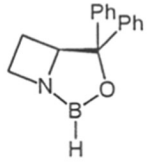
After the pioneering work of Itsuno and Corey, there has been a flood of papers describing the preparation and application of various oxazaborolidines[76]. However, no catalyst is effective for all the type of ketones.

Ramarao *et. al.*[77] synthesized a six membered amino alcohol to obtain 7,7-diphenyl- 8- oxa-1-aza-9-borabicyclo [4,3,0] nonane **99** which shows moderate *ee* in the enantioselective reduction of prochiral ketones. The same group

reported[78] the use of oxazaborolidine from a 4 membered α, α-diphenyl-2-azetidine methanol **100** and observed high enantioselectivity (up to 95% *ee*).



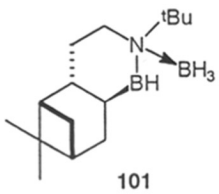
99



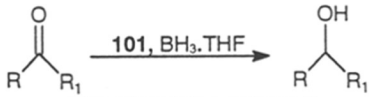
100

Martens *et. al.*[79] simultaneously reported that an *in situ* prepared oxazaborolidine **100** reduced acetophenone and propiophenone in 98 and 99%*ee* respectively.

Midland and Kabsuki utilized[80] an azabora cyclohexanone derived from the terpene Nopol. Moderate enantioselectivity in the reduction of acetophenone (77%) and 'BuCOMe (82% *ee*) was realized (scheme 20).



101

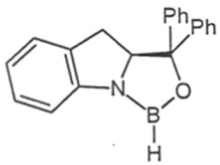


101, BH_3.THF

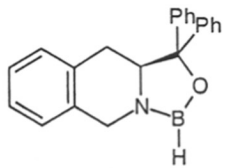
R	R_1	*ee*
Me	Ph	77%
Me	^{t}Bu	82%

scheme 20

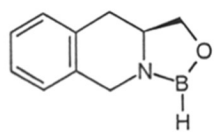
Martens *et. al.*[81,82] found that the oxazaborolidine **102- 104** derived from (*S*)-α,α-diphenyl (indolin-2-yl) methanol and (*S*)-α,α-diphenyl (1,2,3,4) tetrahydro isoquinolin-3-yl) methanol **104** catalyzes the reduction of prochiral ketones with moderate to good enantioselectivities.



102



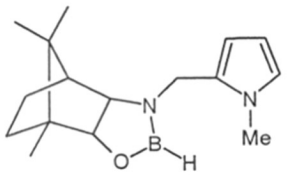
103



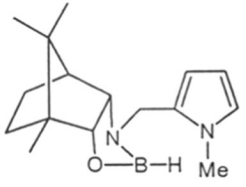
104

91% enantioselectivity was observed in the reduction of acetophenone in presence of 10mol% of catalyst **102** wheres **103** provided a low selectivity of 51%. Interestingly, the oxazaborolidine with no alkyl substitution α- to alcohol showed greater enantioselection (71%) in the reduction of acetophenone.

Tanaka *et. al.*[83] found that *exo* and *endo*- 2-hydroxy-3-(1-methyl-2-pyrrolyl) methylamino boranes **105, 106** are efficient catalysts for the enantioselective reduction of prochiral aromatic ketones.The reduciton of propiophenone in the presence of 5 mol% of *exo* ligand **105** afforded (*S*)- 1- phenyl propanol in 77% *ee* whereas the *endo* analogue **106** provided (*R*)-1- phenyl propanol in 79% *ee* (scheme 21).



105



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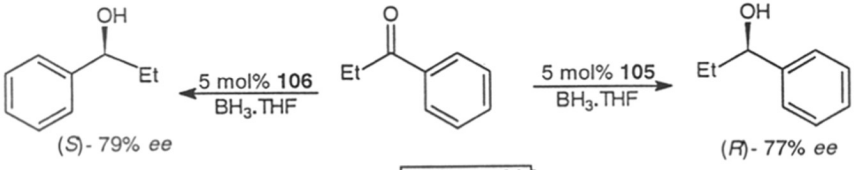
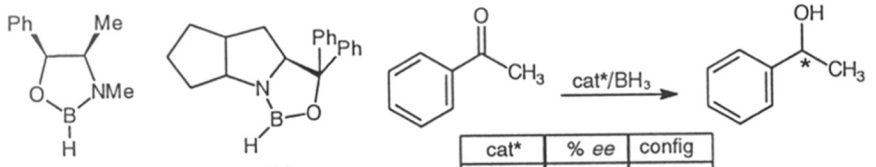


(*S*)- 79% *ee*

(*R*)- 77% *ee*

scheme 21

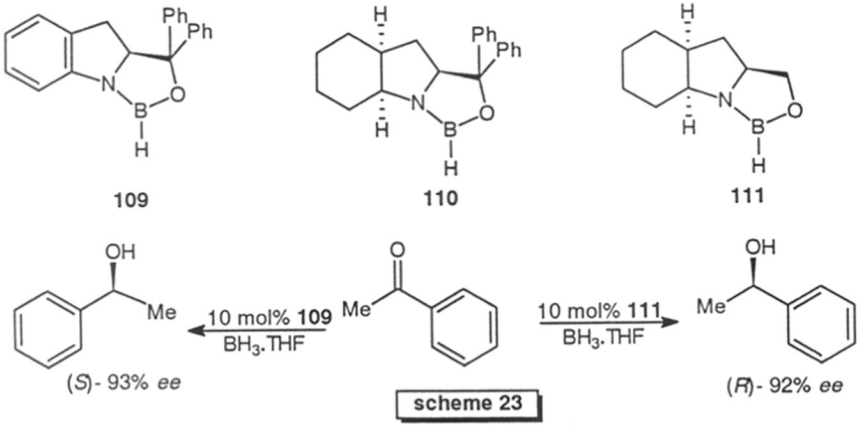
Cho and Chun found[84] that the oxazaborolidines derived from (-)-ephedrine **107** catalyzes the reduction of prochiral ketones to afford optically active alcohols in 41- 83% *ee*. Acetophenone was reduced in 83% *ee*. Wallabaum and Martens utilized[85] oxazaborolidine **108** derived from a bicyclic analogue of proline for the reduction of prochiral ketones to affords alcohols in moderate *ee*'s. (up to 61%) (scheme 22).



cat*	% *ee*	config
107	83	*R*
108	61	*S*

scheme 22

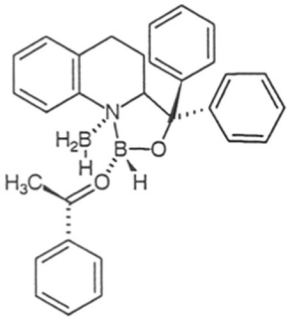
Kim *et. al.* utilized[86] oxazaborolidines **109-111** derived from (*S*)-indoline 2-carboxylic acid in the enantioselective reduction of prochiral ketones. Acetophenone was reduced in the presence of catalyst **109** to afford the (*R*)- 1-phenethanol in 96% *ee*. Surprisingly the reduction in presence of **110** & **111** (obtained by hydrogenation of **109**) afforded the antipode of the product alcohol in 49% and 90% *ee* respectively. It was interesting that diphenyl substitution in **109** was essential for high *%ee* whereas least substitution is required in the reduction with amino alcohols obtained from the hydrogenolysis of **109.** (scheme 23).



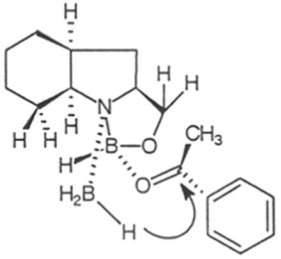
scheme 23

The remarkable reversal of enantioselection with a change in the catalyst structure was explained by steric factor in **109** due to gem diphenyl group leading to the formation of favorable intermediate **112** whereas in **113** the steric effect

of cyclohexyl group appears to enforce the approach of the chiral auxiliary to the opposite face of the ketone leading to alcohols of opposite stereochemistry.

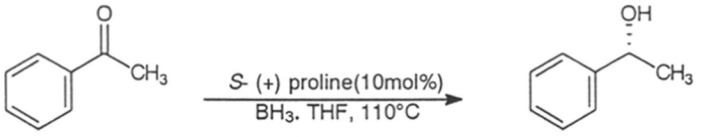


112



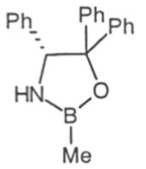
113

Brunel *et. al.*[87] found an intersting temperature effect on the enantioselectivity in the enantioselective reduction of prochiral ketones with oxazaborolidine from prolinol formed *in situ*. Acetophenone was reduced with BH_3.THF in the presence of proline at 25°C affording product alcohol with 8% *ee* while runing the reaction in refluxing toluene (110°C) provided 95% *ee* (scheme 24).

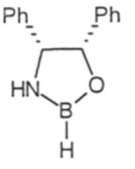


scheme 24

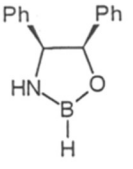
Berenguer *et. al.*[88] investigated several oxazaborolidines derived from ephedrine and found that the substitution on nitrogen other than methyl with CH_2Ph, $CH_2{}^tBu$ or SO_2Ph decreased the enantioselectivity of the product alcohols whereas oxazaborolidine from ephedrine gave alcohol up to 72% *ee* in acetophenone reduction.The same group[89] has found that oxazaborolidine **114** derived from phenyl glycine catalyzed the reduction of prochiral ketones with borane to afford the corresponding secondary alcohols in good chemical yields and with moderate to high enantiomeric excesses (61- 96%).



114



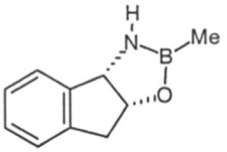
115



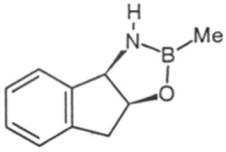
116

Quallich and Woodall reported[90] an *in situ* preparation of oxazaborolidines from *erythro*-2-amino-1,2-diphenylethanol **115** and used them as the catalysts for the enantioselective reduction of ketones. Very high selectivities were realized for the product alcohols (up to 96% *ee*).

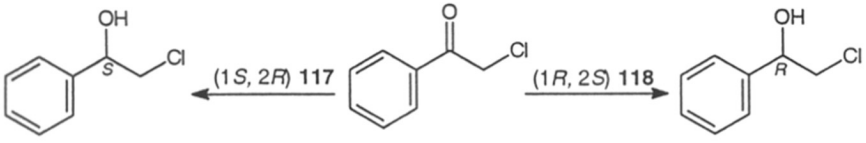
Yaozhong *et. al.*[91] have shown that the oxazaborolidine prepared from (1*R*,2*S*)-1,2 diphenyl-2-aminoethanol with borane **116** catalyzes the enantioselective reduction of prochiral ketones in excellent enantioselectivities (up to 99% for acetophenone). However this catalyst provided low *ees* for aliphatic ketones. A new class of oxazaborolidines from *cis*-1-amino 2-indanol **117** by Sepracor group was utilized[92] in the reduction of prochiral ketones. Enantioselectivity up to 96% was observed in the reduction of phenacyl chloride with both the catalysts (scheme 25).



(1*S*,2*R*)
117

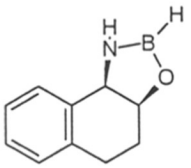


(1*R*,2*S*)
118

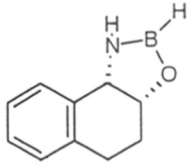


scheme 25

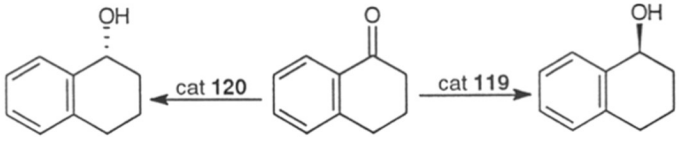
Simone *et. al.*[93] found that the oxazaborolidines **119, 120** derived from same indanol derivatives were efficient catalysts in the reduction of tetralones (scheme 26).



119

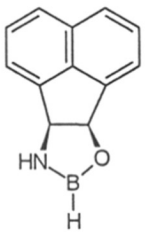


120



scheme 26

Sudo *et. al.*[94] utilized *cis*- 2- amino 1- acenaphthol oxazaborolidines **121, 122** and acheived a maximum of 95% *ee* in the reduction of prochiral ketones (scheme 27).



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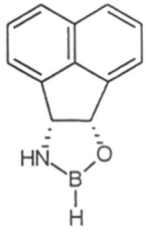

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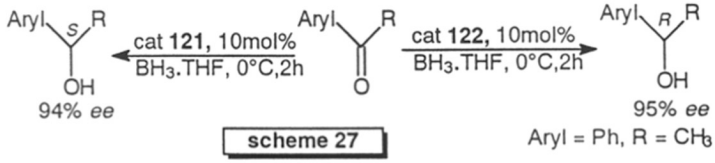
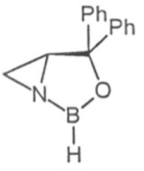
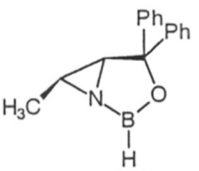


scheme 27

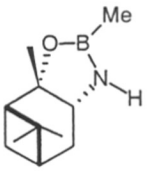
Willems *et. al.*[95] used oxazaborolidines **123** and **124** derived from aziridine carboxylic acids in the enantioselective reduction of prochiral ketones. The use of 10 mol% of **123** and **124** reduced acetophenone in 94% *ee* with *R* configuration.



123



124



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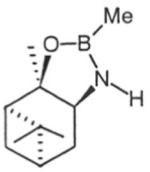

126

Recently Masui and Shiori used[96] the oxazaborolidines **125** and **126** prepared from the corresponding aminoalcohols derived from (+)-α-pinene and acheived high enantioselectivities (up to 95%) in the reduction of prochiral ketones.

Conclusions:

The discovery of the ligand accelerated catalysis for the alkylation of aldehydes and reduction of prochiral ketones has provided new avenues in asymmetric synthesis. In fact, the mechanism for the enantioselective addition of diethylzinc reagents to aldehydes and that for the oxazaborolidine catalyzed reduction of ketones, has an elegant common feature involving simultaneous activation of the reagent and substrate. Both the areas obviously have been rich seams of investigations and many more aspects still await to be explored.

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CHAPTER - 2

Enantioselective Addition of Diethylzinc to Aldehydes

The enantioselective version of the reaction between organometallic reagents and carbonyl compounds leading to optically active alcohols, is desirable because of its general synthetic importance. In this context, the addition of diethylzinc to aldehydes in the presence of suitable ligands has emerged as a valuable synthetic operation[1].

A vareity of catalysts have been utilized for this reaction, to achieve maximum enantioselectivity. As already reviewed in Chapter 1, the discovery that β- amino alcohols catalyze the addition of dietylzinc to aldehydes led to vigorous investigation of the reaction with a number of auxiliaries.

Our interest in this area led us to investigate this reaction with chiral diols, amino alcohols and oxazolidines as the auxiliaries.

The Chapter is divided into the following sections.

a. Catalysts based on C_2- Symmetric diols.

b. Catalysts based on Amino alcohols.

c. Catalysts based on Oxazolidines.

SECTION - 2a

Catalysts Based on C_2- Symmetric Diols

Ligand accelarated enantioselective addition of diethylzinc to aldehydes has emerged as a prominent reaction in recent times. After the discovery that certain additives catalyzes the addition of dialkylzincs to aldehydes, majority of the catalysts utilized for this transformation were based on β- amino alcohols[2]. The pioneering work by Noyori and Soai led to the elucidation of the mechanism which in its simplest form is shown below. The mechanism involves an assembly of the tri coordinated zinc alkoxide formed by the reaction of amino alcohol with dialkylzinc, the aldehyde and the dialkylzinc as shown in fig. 1.

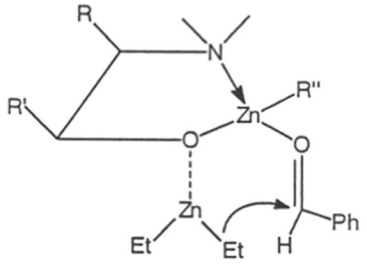
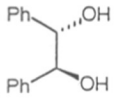


fig. 1

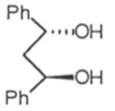
It is presumed that diethylzinc coordinates to the oxygen atom of the catalyst. We reasoned that if this is true then the catalyst need not be based on an amino alcohol. In fact a C_2- symmetric dialkoxide should function as an effective catalyst. Also, it would be of interest to know the effect of other metals as Lewis acid centre in the catalyst. We examined some structurally well defined alkoxides of zinc, magnesium, boron, aluminum and lithium derived from certain C_2-symmetric diols. This section deals with these results.

Results and Discussion

The chiral auxiliaries selected for the present study are representative 1,2-, 1,3- and 1,4- diols which can be easily synthesized by known methods[3]. Some of these diols (**1 - 4**) have served as ligands for the transition metal based catalysts for asymmetric transformations[4].



1



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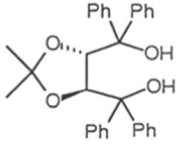

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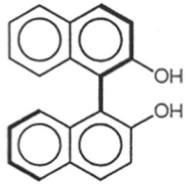
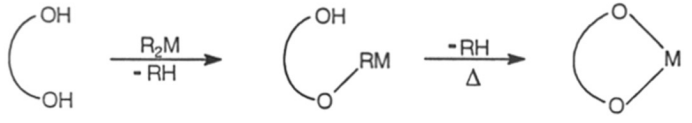


4

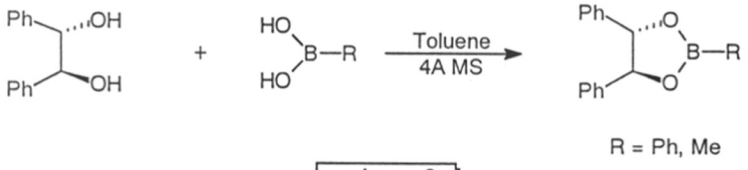
It is known that diethylzinc reacts rapidly with primary, secondary and tertiary alcohols to give the corresponding monoalkoxide. Further reaction of monoalkoxide with alcohols is very slow[5]. We envisioned that equimolar quantities of diethylzinc or dibutyl magnesium would produce first the monoalkoxide which on heating can be forced to form the well defined dialkoxide (scheme 1).



scheme 1

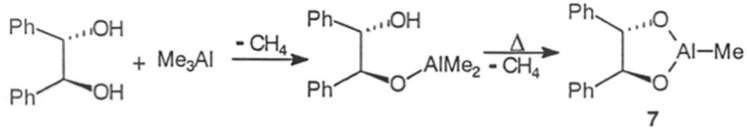
Indeed, the reaction of the diol with equimolar quantity diethylzinc/ dibutyl magnesium proceeded very smoothly at room temperature to form the monoalkoxide which upon heating (80°C, 30min) formed the desired dialkoxide.

The boron analogue of the diol **1** was prepared[6] by stirring the diol with butyl/ phenyl boronic acid in the presence of molecular seives using toluene as solvent (scheme 2).



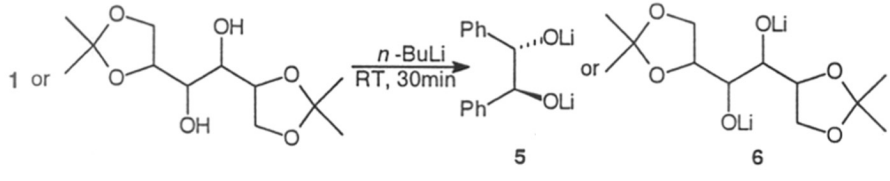
scheme 2

The alumino alkoxide derivative was prepared by the reaction of the diol **1** with trimethyl aluminum as described for diethylzinc (scheme 3).



scheme 3

The lithium dialkoxide (**5**) of 1,2-diphenylethanediol and mannitol diacetonide(**6**) was prepared by treating the diol with *n*-BuLi at room temperature for 30min (scheme 4).



scheme 4

We next turned our attention to utilize these alkoxides as catalysts in the addition of diethylzinc to aldehydes. Rosini *et. al.*[7] have shown that 1,2-diphenylethanediol (**1**) catalyzes the addition of diethylzinc to benzaldehyde in 77% *ee*. But the reported procedure involves long reaction times and a large excess of diethylzinc. We found that the reaction after 24h at room temperature gives a mixture of benzyl alcohol (19%), unreacted benzaldehyde (36%) and product alcohol (45%) as estimated by GC.

We beleive that the reaction proceeded through the monoalkoxide which is not likely to be a good catalyst. The dialkoxide prepared in the present study using **1** as auxiliary smoothly catalyzed the reaction yielding 98% of the product alcohol after 24h with 89% *ee*. It was surprising that the corresponding magnesium alkoxides does not catalyze the reaction and no appreciable reaction occured even after 24h. The corresponding boron analogue did provide the product alcohol in 67% yield but the enantiomeric excess of the product was considerably low(15%). We also examined the 1,3-diol (**2**) for this reaction. The dialkoxides of zinc and magnesium from the diol **2** do not catalyze the addition of diethylzinc to benzaldehyde. Equally intriguing was the fact that the dialkoxide of magnesium from the diol **3** does not catalyze the reaction whereas the zinc analogue yielded the product alcohol in 65%yield and 45% *ee*. The zinc dialkoxide derived from BINOL (**4**) is a polymeric material and does not catalyze the reaction at all.

Aluminum dilakoxide **7** failed to catalyze the reaction whereas the dialkoxides **5** and **6** did catalyze the addition of diethylzinc to benzaldehyde within 8h at 0°C, however the enantiomeric excess of the product was below 10%. All these observations are summarized in table 1.

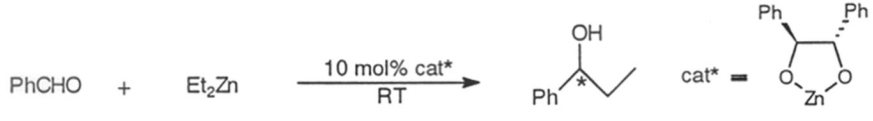
Table 1: Addition of Diethylzinc to Benzaldehyde Catalyzed by C_2-Symmetric Metal Dialkoxides.

Entry	Diol	M	Time , h[a]	%yield	%*ee*[b]
1	**1**	B	48	67	15
2	**1**	Al	48	c	-
3	**1**	Mg	24	c	-
4	**1**	Li	8	95	8
5	**1**	Zn	18	98	89
6	**2**	Mg	48	c	-
7	**2**	Zn	48	c	-
8	**3**	Mg	48	c	-
9	**3**	Zn	48	65	44
10	**4**	Zn	48	c	-
11	**5**	Li	8	95	5

[a]All the reactions were conducted at room temperature except entry 4 and 11. [b]By comparision with literature rotation. [c]No appreciable reaction.

We finally utilized the dilakoxide derived from diol **1** and diethylzinc as the catalyst for the addition of diethylzinc to a vareity of aryl aldehydes. The addition proceeded very smoothly for all aromatic aldehydes. The substituent at *orhto* position on aryl aldehyde rendered the reaction sluggish. Infact, *ortho* tolualdehyde and *orhto* anisaldehyde gave <50% yield of the product even after 48h. Aldehydes with substitution at *para* position (e.g. fluoro, chloro and methyl) were alkylated smoothly. β- Naphthaldehyde was alkyalated efficiently whereas α- naphthaldehyde was sluggish. These results are summarized in table2.

Table 2: Enantioselective Addition of Diehtylzinc to Arylaldehydes Catalyzed by Zinc Dilakoxide from **1.**



Entry	Aldehyde	Time, h[a]	%Yield[b]	% *ee*[c]	Config[d]
1	benzaldehyde[e]	24	89	87	*R*
2	benzaldehyde	18	98	89	*R*
3	β- naphthaldehyde	20	94	84	*R*
4	*p*- tolualdehyde	14	98	82	*R*
5	*p*- chlorobenzaldehyde	24	85	69	*R*
6	*p*- fluorobenzaldehyde	9	95	70	*R*

[a]All the reactions were performed using 1:2:0.1 molar equivalents of aldehyde:Et_2Zn:catalyst. [b]Yields refer to GC yields, the remainder being benzyl alcohol and unreacted benzaldehyde. [c]Estimated by comparing with the reported maximum rotations (see experimental section). [d]Based on the sign of rotation for the known compound. [e]1.2 Equivalent of Et_2Zn was used.

Conclusions

1. Amongst various 1,2-, 1,3- and 1,4-diols examined, only 1,2-diphenylethanediol proved to be an efficient ligand. Zinc dialkoxide derived from this diol catalyzes the addition of diethylzinc to arylaldehydes. We believe that other zinc alkoxides are sterically less hindered and hence form nonactive oligomers.
2. Dialkoxide derived from other metals such as boron, magnesium and aluminum do not catalyze the reaction.
3. Dilithium dialkoxide catalyzes the raction with low enantioselectivity.

Experimental

General :

Diethylzinc was purchased form Aldrich Chemical Company and diluted to 2M solution in toluene. Chiral 1,2-diphenylethanediol **1** was prepared by asymmetric reduction of benzil[3b] and the other chiral auxiliaries were synthesized by known procedures[3]. All the aldehydes were purified prior to use by standarad procedures. GC analysis was carried out on HP 5890 Series II chromatograph using 10m x 0.5 mm PhMe silicon column.

Preparation of dialkoxide of Zinc from 1,2-diphenylethanediol (1):

(*S,S*)-(-)-1,2-Diphenylethanediol (0.107g, 0.5mM) in 2 ml toluene was heated to 80°C to dissolve the diol completely. Diethylzinc (0.25 ml of 2M solution in toluene, 0.5mM) was added dropwise to the solution at the same temperature. Immediate evolution of ethane was observed. The reaction mixture was kept at 80°C for 0.5 h during which it turned to a gel indicating the formation of the dialkoxide. The resulting suspension formed a clear solution upon the addition of aldehyde and diethylzinc.

Preparation of the dialkoxides of Magnesium and Aluminum:

These dialkoxides were prepared in a similar fashion as described above, utilizing dibutyl magnesium (0.5 ml of 1M solution in heptane 0.5mM)/ and trimethyl aluminum (0.5ml of 1M solution in toluene, 0.5 mM). The reaction mixture was kept at 80°C for 0.5h during which it turns to gel in the case of aluminum alkoxide or remains clear solution in the case of magnesium.

Preparation of Zinc dialkoxide from 1,3-diphenylpropane-1,3- diol(2) and TADDOL (3)

The diol (0.5 mM) in 2 ml toluene was warmed (~50°C) to dissolve the diol completely and diethylzinc was introduced dropwise at the same temperature. Immediate evolution of ethane was observed. The reaction mixture was kept at 80°C for 0.5 h. A clear solution of the catalyst was obtained which was utilized as it is for alkylation step.

Preparation of boronate esters from 1,2-diphenylethane diol (1) :

(*S,S*)-(-)-1,2-Diphenylethane diol (0.107g, 5mM) in toluene (~10ml) was warmed to dissolve the diol completely. To this was added equimolar amount of phenyl/ butyl boronic

acid and stirred at ~50°C for 3h in the presence of 4A molecular seives. Decantation of the resulting solution gave the boronate ester which was used as such in the next step.

Addition of diethylzinc to arylaldhydes catalyzed by Zinc dialkoxide derived from (1):

The following procedure for benzaldehyde is representative:

The zinc dialkoxide prepared as described above, was cooled to 0°C and treated with diethylzinc (5 ml of 2M solution in toluene, 10mM) and benzaldehyde (0.53g, 5mM). The reaction mixture was gradually allowed to come to room temperature and stirred at ambient temperature till TLC indicated the disappearance of benzaldehyde. Thereafter it was quenched with MeOH (0.5ml) followed by 1N HCl. The reaction mixture was extracted with ether. The ether extract was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by "flash chromatography" followed by kugelrohr distillation to obtain pure 1-phenyl-1-propanol. Yield : 0.47g (69%).

(*R*)- (+)-1-Phenyl-1-propanol

^{1}HNMR ($CDCl_3$)	1.00 (t, J 6.9Hz, 3H), 1.85 (m, 2H), 2.9 (bs, OH), 4.6 (t , J 6.9Hz, 1H), 7.2- 7.5 (Ar, 5H).
$[\alpha]_D$	+ 40. 46 (c 5.2, $CHCl_3$)
	lit[8]. -45.45 (c 5.15, $CHCl_3$) for the *S* enantiomer
ee	89%

(*R*)-(+)-1-(*p*-Tolyl)-1-propanol

Yield	0.50g, (66%)
^{1}HNMR ($CDCl_3$)	0.9 (t, J 6.8Hz, 3H), 1.75 (m, 2H), 2.25 (bs, OH), 2.35 (s, 3H), 4.55 (t, J 6.8Hz, 1H), 7.1 - 7.3 (Ar, 4H).
$[\alpha]_D$	+ 35.65 (c 5.06, benzene)
	lit[9]. +39.3 (c 5, benzene)
ee	82%

(*R*)-(+)-1-(*p*- Fluorophenyl)-1-propanol

Yield	0.54g, (70%)
^{1}HNMR ($CDCl_3$)	0.9 (t, J 7.1Hz, 3H), 1.75 (m, 2H), 2.2 (bs, OH), 4.55 (t, J 7.1Hz, 1H), 6.95- 7.1 (Ar, 2H), 7.2- 7.4 (Ar, 2H).
$[\alpha]_D$	+ 35.78 (c 2.44, $CHCl_3$)
	lit[10]. +51.2 (c 2.5, $CHCl_3$)
ee	70%

(*R*)-(+)-1-(*p*- Chlorophenyl)-1- propanol

Yield	0.59g, (69%)
^{1}HNMR ($CDCl_3$)	0.9 (t, J 6.8Hz, 3H), 1.75 (m, 2H), 2.25 (bs, OH), 4.55 (t, J 6.8Hz, 1H) 7.2- 7.3 (Ar, 4H).
$[\alpha]_D$	+19.32 (c 5, benzene)
	lit[10]. +28 (c 5, benzene)
ee	69%

(*R*)-(+)-1-(β - Naphthyl)-1-propanol

Yield	0.63g, (67%)
^{1}HNMR ($CDCl_3$)	0.9 (t, J 7.3Hz, 3H), 1.85 (m, 2H), 2.2 (bs, OH), 4.75 (t, J 6.6Hz, 1H) 7.4- 7.6 (Ar, 3H), 7.7 - 8.0 (Ar, 2H).
$[\alpha]_D$	+25.31 (c 4.64, benzene)
	lit[10]. +29.8 (c 4.7, benzene)
ee	84%

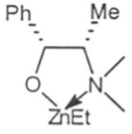
SECTION - 2b

Catalysts Based on Amino Alcohols

As discussed in Chapter 1, most studies during the addition of diethylzinc to aldehydes, are directed at the structural modifications of β- amino alcohol ligands. Eventhough there is a plethora of publications on the variety of aminoalcohols, as a ligand for the enantioselective addition of diethylzinc to aldehydes, there is no study dealing with the structural modification around the metal centre. We anticipated that if the bulk can be tuned around the metal centre of the catalyst in such away that the attack of the nucleophile can be directed exclusively through only one face. It was also of interest to evaluate some amino alcohols which are close in structure to the most succesful DBNE ligand developed by Soai *et. al.*[11] We also wanted to investigate some tridentate ligands as catalysts for the addition of diethylzinc to aldehydes. In this section we present our results dealing with these aspects.

Results and Discussion

Several catalysts (**8 - 12**) were prepared so as to obtain a gradual increase in the bulk around the metal center. Also, a change in the metal centers (zinc/ magnesium/ lithium) provided a variation of Lewis acidities.



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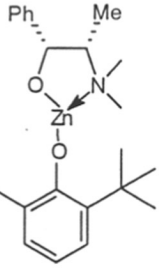

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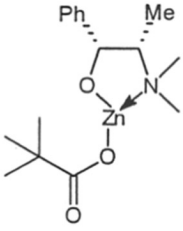

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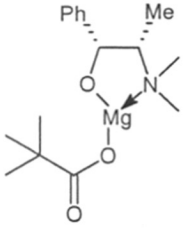

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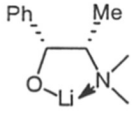


12

We chose N-Me ephedrine as the parent structure for the reason that it is cheaply available, the structural modification around nitrogen is known to increase the *ee* considerably[11] and the recycling of the catalyst is possible easily.

At the outset, we studied the reaction of the zinc alkoxide **8** as the catalyst in the ethylation of benzaldehyde. The product obtained was of 83% *ee,* comparable to the known value. We then utilized the lithio derivative **12** as the catalyst, anticipating that the harder Lewis acidity of lithuim will increase the rate of the reaction thereby leading to enhanced *ee*. The reaction did proceed faster but without much improvement in *ee* (80%). The increase of bulk around the zinc atom of the catalyst with a 2,6-di *tert* butyl phenol moiety (**9**) resulted in slight decrease in the enantioselectivity (80%). Surprising was the

fact that the change in substituent from ethyl to pivaloyl moiety around the zinc atom of the catalyst (**10**) yielded the product alcohol with considerably low *ee* (20%). The presence of magnesium instead of zinc atom in the catalyst resulted in very low enantiomeric excess of the product. These results are summarized in table 3.

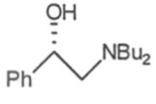
Table 3: Metal Alkoxide (**8 - 12**) Catalyzed Enantioselective Addition of Diethylzinc to Benzaldehyde[a].

Entry	Catalyst	Time (h)	Temp(°C)	% *ee*[b]
1	**8**	4	0	83
2	**9**	4	0	80
3	**10**	10	RT	20
4	**11**	10	RT	-
5	**12**	4	0	80

[a]All the reactions were performed with 10mol% of the catalyst and 2eq of diethylzinc. [b]By comparision with the literature rotation.

The low enantioselectivity observed in the addition of diethylzinc to arylaldehydes with increasing the bulk at metal center can be attributed to the retarded coordination of the incoming diethylzinc. Furthermore, it is possible that a competitive coordination also takes place at the sidechain oxygen atom.

We further synthesized a variety of bi- and tridentate ligands which are structurally close to the most successful ephedrine catalysts developed by Soai. *et. al.*[11]



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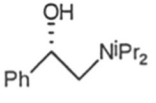

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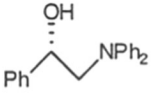

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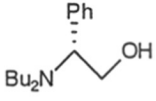
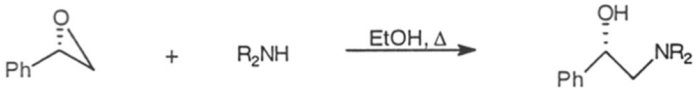


16

The alcohols **13-15** were prepared by the regioselective ring opening of optically pure styrene oxide by corresponding secondary amines[12] (scheme 5).



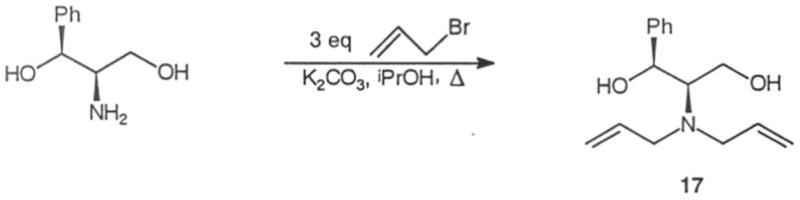
scheme 5

Catalyst **16** was derived from phenyl glycinol. These ligands were tested as catalysts in the addition of diethylzinc to benzaldehyde. It was observed that the ligands **13** and **14** catalyzed the addition in 77% *ee* and 63% *ee* respectively. The lithio derivative of **13** gave slightly low *ee* (70%). The catalyst derived from styrene oxide and diphenyl amine (**15**) did not catalyze the reaction owing to the fact that the nitrogen atom in (**15**) is too weak a base to form the cyclic chelate. It was surprising that the amino alcohol **16** which is close in structure to DBNE catalyzed the reaction at lower rate with low *ee* (15%). These results were summarized in table 4.

Table 4 : Amino Alcohol **13-16** Catalyzed Enantioselective Addition of Diethylzinc to Benzaldehyde.

Entry	Ligand	Time (h)	% *ee*	Config
1	**13**	8	77	*S*
2	**14**	20	63	*S*
3	**15**	36	-	-
4	**16**	24	17	*S*
5	**13**-lithio	8	70	*S*

We also synthesized and examined some tridentate ligands for the ethylation of benzaldehyde. The amino diol **17** was prepared by the alkylation of the corresponding amino alcohol, (1*S*,2*S*)-2-amino,1-phenyl-1,3-propanediol with allyl bromide (scheme 6).

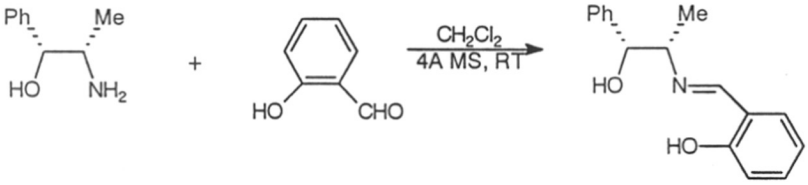


17

scheme 6

The ligand **17** failed to catalyze the addition of diethylzinc to benzaldehyde.

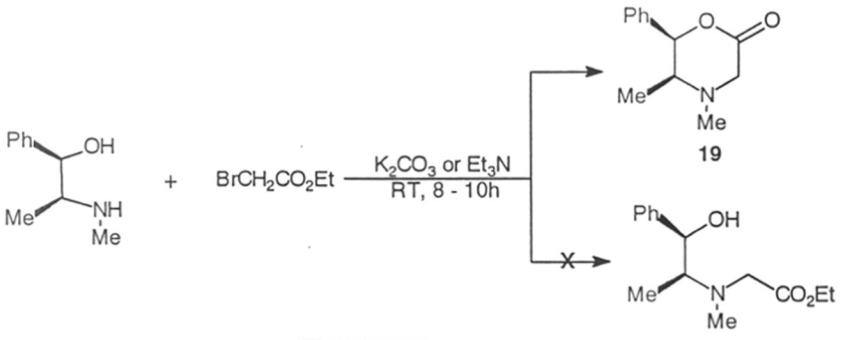
The Schiff base **18** prepared by stirring (1*R*,2*S*)-norephedrine and salicylaldehyde in CH_2Cl_2 in the presence of 4A molecular sieves[13] did catalyze the addition, but the enantiomeric excess of the product alcohol was only 30% (scheme7).



scheme 7

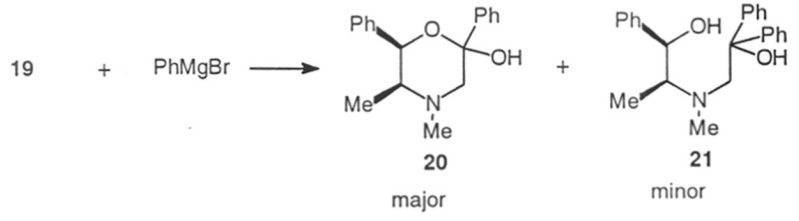
18

During our search for tridentate ligands, we encountered an unusual formation of lactol. The reaction of ephedrine with ethyl bromoacetate in presence of K_2CO_3, $LiCO_3$ or Et_3N led directly to the formation of the lactone (**19**) rather than the corresponding amino ester (scheme 8).



scheme 8

We anticipated that the addition of Grignard reagent (PhMgBr) to the lactone **19** should lead to the desired tridentate ligand **21**. However, the lactone (**19**) reacted with PhMgBr to yield unexpectedly the lactol **20** as the major product while the desired compound **21** was isolated as the minor product (Scheme 9).



scheme 9

It was surprising to note that the lactol **20** was intact even after treatment with 8 fold excess of PhMgBr. The structure of the lactol **20** was unequivocally proved by ^{1}H, ^{13}C NMR and by 2D-NMR. The ^{1}H-NMR spectrum of lactol exhibited a doublet corresponding to C_3-CH_3, a singlet for N-CH_3, a doublet of doublet for C_2-H. Interestingly, a multiplet at δ 2.45 was observed for 2H whereas a doublet at δ 3.00 was obtained for 1H. A geminal coupling of J= 3.0 Hz was observed for the C_5 protons . The C_5 protons are not equivalent. They are well separated and exhibited a large coupling of J

= 11.7 Hz with the C_3 protons and a very little NOE with the C_2-proton. These observations were confirmed by decoupling experiments and by 2D NMR.

We did not attempt to determine the absolute configuration at the quaternary carbon center. For the sake simplicity the conformation is shown as fig. 2.

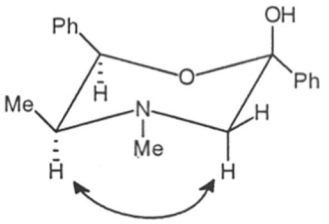


fig. 2

The addition of Et_2Zn to benzaldehyde in the presence of **21** was sluggish and the product obtained showed poor *ee* 21%.

Conclusions

1. The increase of steric bulk around the metal center leads to decreased enantioselectivity.
2. The amino alcohols derived from styrene oxide catalyzed the addition of diethylzinc to benzaldehyde in moderate *ee*'s (up to 77%) whereas tridentate ligands are found to be ineffective. The failure of all the tridentate ligands can be attributed to poor Lewis acidity of the resulting tri coordinated zinc dialkoxides.

Experimental

Preparation of zinc alkoxide(8) derived from N- methyl ephedrine:

To a solution of N-methyl ephedrine (0.179g, 1mM) in 2ml of toluene was added Et_2Zn (0.5 ml of 2M solution in toluene, 1mM) at 0°C and slowly allowed to come to room temperature.

Preparation of zinc alkoxide (9):

To the zinc alkoxide (**8**) prepared from N-methyl ephedrine, was added 2,6-di *tert* butyl phenol (0.206g, 1mM) dissolved in minimum amount of toluene at room temperature. The resulting mixture was heated to 80°C and kept at that temperature for 1h and then cooled to room temperature.

Preparation of zinc alkoxide (10):

To the zinc alkoxide **8** prepared as above, was added pivalic acid (2ml of 0.5M solution in toluene, 1mM). The resultant mixture was heated to 80°C and kept at that temperature for 1h and then cooled to room temperature.

Preparation of magnesium alkoxide (11):

To N-methyl ephedrine (0.179g, 1mM) in 2ml toluene, dibutyl magnesium was added at room temperature. The resulting solution was treated with pivalic acid (2ml of 0.5M solution in toluene, 1mM) and mixture was heated to 80°C for 1h.

Addition of diethylzinc to benzaldehyde catalyzed by alkoxides (8-11) prepared in situ from N- methyl ephedrine:

The alkoxide solutions in toluene prepared as described above were cooled to 0°C and treated with diethylzinc (6 ml of 2M solution in toluene) followed by benzaldehyde (0.53g, 5mM). The yellow reaction mixture was slowly allowed to come to room temperature, and then stirred for the specified period (table 3). Disappearance of benzaldehyde was monitored by TLC. The reaction mixture was then cooled to 0°C,

quenched with MeOH (1ml), and then with 1N HCl (10ml). Organic phase was separated and the aqueous phase was extracted with ether (2 x 20ml). The combined extract was washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure and then "flash chromatography" of the residue followed by kugelrohr distillation provided pure 1-phenyl-1-propanol.

preparation of ligands (13-17)

(*S*)- Styrene oxide was prepared through the enantioselective reduction of 1-chloro acetophenone followed by cyclization[14]. Aminolysis of styrene oxide to obtain the amino alcohols **13-15** was carried out as described in the literature[12]. **16** was obtained by dibutylation of (*R*)-(+)-phenyl glycinol according to the procedure outlined for the dibutylation of norephedrine[11].

Preparation of 2-phenyl- 3-methyl- 6-phenyl- 6- hydroxy- N- methyl morpholine (20):

To the lactone **19**[15] (1.03g, 5mM) was added phenyl magnesium bromide (25mM) in THF and stirred at room temperature overnight followed by 1h reflux. The reaction mixture was then cooled to 0°C and quenched cautiously with sat. NH_4Cl. The organic layer was dried over anhydrous Na_2SO_4. The residue after evaporation of solvent was chromatographed using 30% ethylacetate in pet- ether as the eluent to obtain the lactol **20** as the pure compound. The tridentate ligand (**21**) was also isolated as the minor product .

(2R,3S)-2-Phenyl-3-methyl-6-phenyl-6-hydroxy-N-methyl morpholine (20):

Yield	0.824g, (58%)
m. p.	126-129°C
IR $CHCl_3$ (cm^{-1})	3300, 1590 , 1498, 1284.
^1H NMR($CDCl_3$)	δ 0.95 (d, J 6.6Hz, 3H), 2.35 (S, 3H), 2.45 (m, 2H), 3.00 (dd, J_{AA} 3.0Hz, J_{AB} 11.7Hz), 4.5 (bs, OH), 7.2- 7.7 (Ar, 10H).
^{13}CNMR($CDCl_3$)	13.6, 42.79, 63.6, 66.57, 71.2, 98.27, 126.37, 126.54, 127.66, 127.87, 128.12, 128.26, 140.07, 141.83.
Mass	284 (M^++1), 178, 104 (100%)
$[\alpha]_D$	-17.75 (c 1 $CHCl_3$)

(2*R*,3*S*)-N-(2',2'-Diphenylhydroxyethyl)-ephedrine (21)

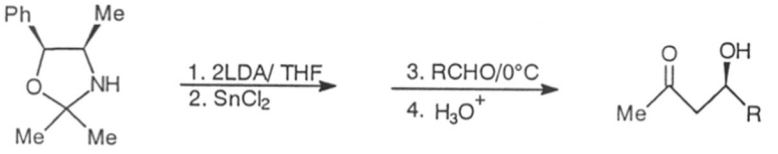
Yield	0.126g, (7%)
m. p.	123-126°C
IR $CHCl_3$ (cm^{-1})	3401 , 1599, 1493, 1271.
^1H NMR	δ 0.95 (d, J 6.8Hz, 3H), 2.35 (dd, J_{AA} 3.0Hz, J_{AB} 13.5Hz, 1H), 2.5 (S, 3H), 3.1 (m, 2H), 3.8 (q, J 6.8Hz), 4.55 (dd, J_{AA} 3.0Hz, J_{AB} 10.8Hz, 1H), 7.1- 7.7 (Ar, 15H).
^{13}C NMR	8.11, 42.51, 60.88, 63.53, 70.92, 76.64, 77.27, 77.90, 81.64, 125.91, 126.33, 126.69, 127.15, 127.44, 127.62, 127.92, 128.28, 141.92, 145.64, 147.17.
$[\alpha]_D$	-15.38 (c 1.3 $CHCl_3$)

SECTION - 2c

Catalysts Based on Oxazolidines

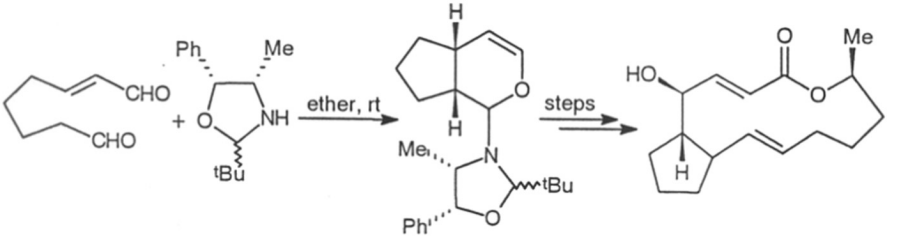
Oxazolidines in general can be easily prepared by ketalization of amino alcohols with aldehydes/ ketones. The chemistry of oxazolidines was mainly explored in the synthesis of *tertiary* amines by the addition of organometallic reagents. Eventhough these auxiliaries were readily available, they were used only in a few specific reactions.

Narasaka *et. al.*[16] utilized the oxazolidine derived from norephedrine and acetone in the asymmetric aldolization reaction yielding aldol products with up to 99%*ee* (scheme10).



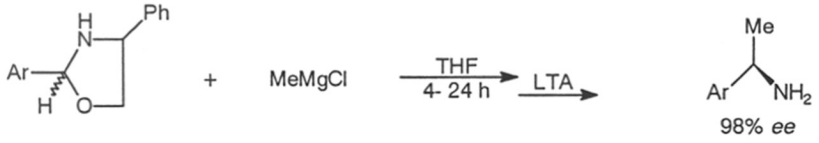
scheme 10

Schreiber and Meyers utilized[17] the oxazolidine derived from norephedrine and pivalaldehyde in their synthesis of brefeldin involving the cyclization of a key intermediate (scheme 11).



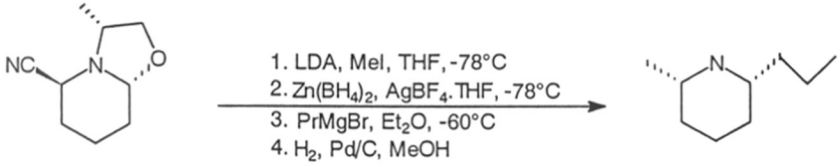
scheme 11

Wu and Pridgen utilized[18] oxazolidines derived from phenyl glycinol for the synthesis of amines in high enantiomeric purities by the reaction of Grignard reagents followed by lead tetra acetate treatment (scheme 12).



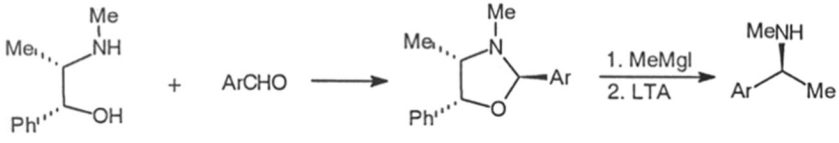
scheme 12

Husson *et. al.*[19] used the oxazolidines as imine equivalent in the synthesis of 2,5- dialkyl piperidines and picolinic acid (scheme 13).



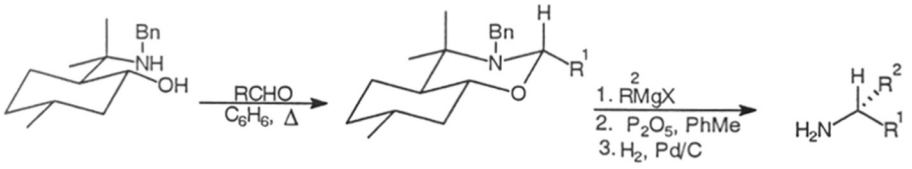
scheme 13

Neelakantan showed[20] that the oxazolidine derived from ephedrine can be cleaved by Grignard reagents to form a *tertiary* amino alcohol which was then cleaved with LTA to form the *tertiary* amine (scheme 14).



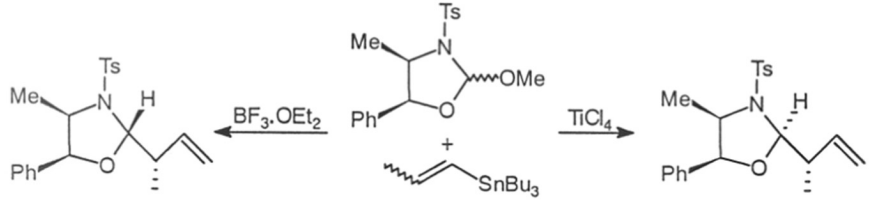
scheme 14

An alternative methodology using the oxazolidine as auxiliary was employed by Alberola *et. al.*[21] in the synthesis of *tertiary* amines (scheme 15).



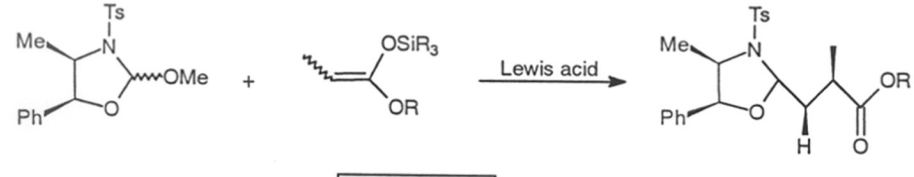
scheme 15

Pasquarello *et. al.*[22] showed that 2- methoxy oxazolidines with crotyl-*n*-butyl stannanes can be used for the C-C bond formation selectively. It was observed that the Lewis acid employed can control the stereochemical outcome of the product (scheme 16).



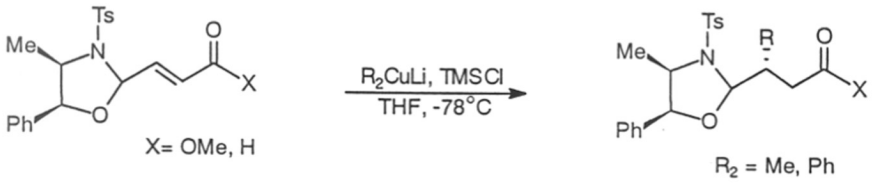
scheme 16

These oxazolidines were also utilized[23] as an alternative to acetals in the aldol type reactions (scehme 17).



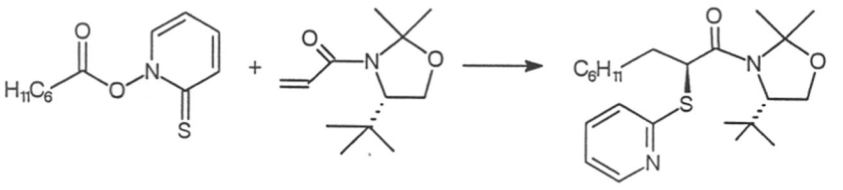
scheme 17

Bernardi *et. al.* utilized[24] the oxazolidines derived from ephedrine in the 1,4-cuprate addition to an α,β-unsaturated carbonyl system (scheme 18).



scheme 18

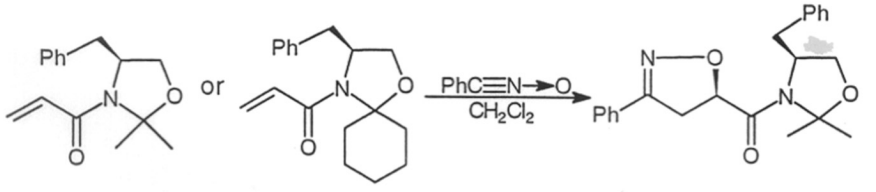
Porter *et. al.*[25] have shown that α,β-unsaturated amides derived from oxazolidine underwent facile radical addition reaction with very high control of stereoselectivity (scheme 19).



scheme 19

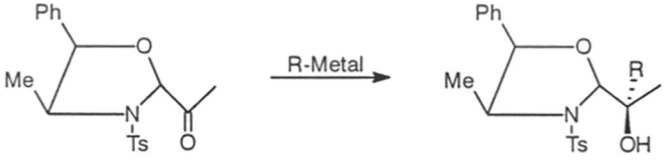
de = 70 : 1

Kanemasa and Onimura utilized[26] oxazolidines derived from acryloyl amides in the diastereoselective nitrile oxide cycloadditions to yield 2-isoxazoline-5-methanols (scheme 20).



scheme 20

Recently Poli *et. al.*[27] showed that 2-acyl-N-tosyl oxazolidines derived from ephedrine undergo highly diastereoselective addition reactions with organometallic reagents such as RMgX and RLi (scheme 21).



scheme 21

As evident from the foregoing account, oxazolidines are easily accessible and efficient chiral auxiliaries. To the best of our knowledge, there has never been an attempt to utilize these as ligands for a catalytic process.

As outlined in Chapter 1, the prime requirement for achieving maximum stereoselection in the addition of dialkylzinc reagents to aldehydes is considered to be the presence of a di- or tri-coordinated zinc that chelates to the carbonyl oxygen and a tri or tetra coordinated zinc that transfers the alkyl group. We postulated that the oxazolidines will satisfy these conditions and hence can serve as efficient ligands as shown below (fig. 3).

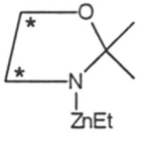
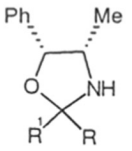


fig. 3

We therefore prepared and examined the zinc amides of various structurally diverse oxazolidines for the addition of diethylzinc to aldehydes.

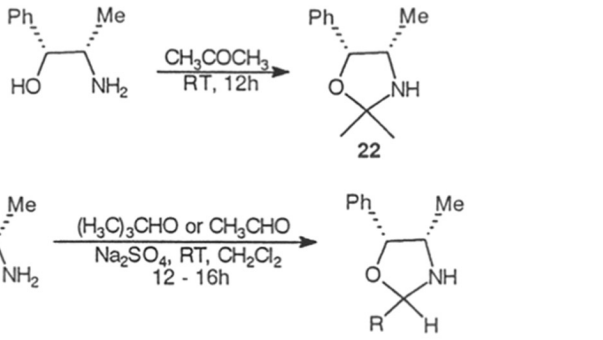
Results and Discussion

At the outset, we took commercially available (1*R*,2*S*)-(-)-norephedrine as the auxiliary for the reasons that it is cheaply available and the recovery of the auxiliary is easy. Various oxazolidines **22-24** were prepared by reacting it with aldehydes/ ketones using known methods.[16,17] All of them except **24** were stable at room temperature for several months. The oxazolidine **24** deteriorates at room temperature within a few days.



R = R' = Me = **22**
R = $(CH_3)_3$, R' = H = **23**
R = CH_3, R' = H = **24**

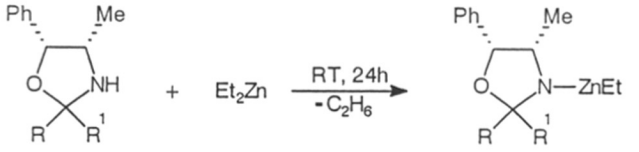
The oxazolidine **22** was prepared by stirring an acetone solution of norephedrine overnight, whereas the oxazolidines **23** and **24** were prepared by stirring norephedrine with pivalaldehyde and acetaldehyde respectively in presence of anhydrous Na_2SO_4 in CH_2Cl_2 (scheme 22).



R = $(CH_3)_3$ = **23**, R = CH_3 = **24**

scheme22

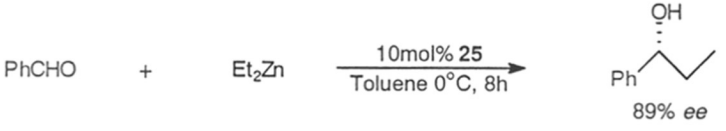
The preparation of the corresponding zinc amide from these oxazolidines was achieved by stirring the oxazolidine with equimolar amount of diethylzinc at room temperature for 24h (scheme 23).



R = R^1 = Me = **25**

scheme 23

We then utilized the oxazolidine zinc amide **25** (10mol%) as the catalyst in the addition of diethylzinc to benzaldehyde. The reaction proceeded very smoothly at 0°C and after 8h the reaction was complete with no trace of benzyl alcohol which is normally obtained as side product *via* reduction. Eventhough the reaction is fast, the enantiomeric excess of the product was only moderate (82%) (scheme 24).



scheme 24

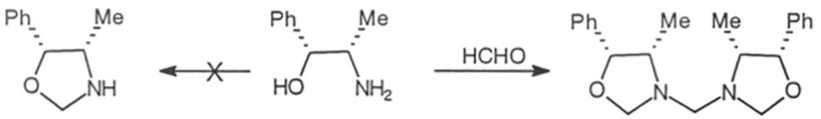
We then turned our attention to the oxazolidine **24** which was less bulky than the oxazolidine **22** as the ligand. The oxazolidine zinc amide catalyzed the reaction fast, albeit with lower *ee* (72%). We then examined oxazolidine derivative which was bulkier with a *tertiary* butyl substituent at the C_2- position. The reaction was catalyzed by this ligand but the enantiomeric excess was even lower (50%). These results are summarized in table 5.

Table 5: Oxazolidines (**22 -24**) mediated Enantioselective Addition of Diethylzinc to Benzaldehyde[a]

Ligand	Time (h)	Temp (°C)	% *ee*[b]
22	8	0	82
22	6	RT	81
24	5	RT	72
25	4	RT	50

[a]All the reactions were performed with 10mol% of the ligand and 2 eq of diethylzinc. [b]By comparision with literature rotation.

It thus appeared that we needed an oxazolidine with least steric hindrance at C_2- position. Our efforts to prepare the oxazolidine of norephedrine and formaldehyde always led to the dimer **26** (scheme 25).

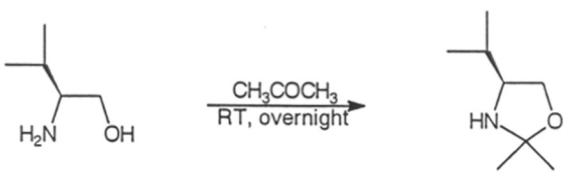


26

scheme 25

The decrease in enantioselctivity observed in the product with the oxazolidines **23** and **24** can be attributed to the presence of a diastereotopic center at the C_2-position. The diastereomers which were found to be in a ratio of 67:23 in oxazolidine from pivalaldehyde and in 75:25 for oxazolidine from acetaldehyde, increases the number of transition states in the course of the reaction thereby decreasing the enantioselectivity.

To overcome this difficulty, we utilized the oxazolidine **27** derived from (S)-valinol and acetone. The acetonide was prepared easily by stirring an acetone solution of valinol at room temperature overnight (scheme 26).



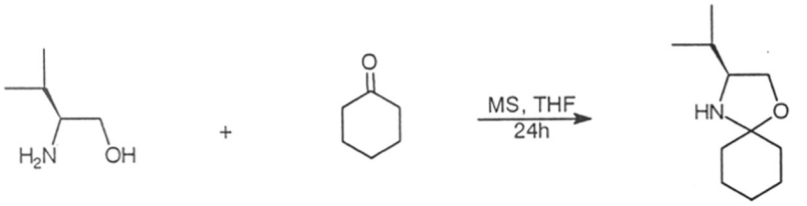
scheme 26

27

The addition of diethylzinc to benzaldehyde with 10mol% of zinc amide of oxazolidine **27** was slow, requiring overnight stirirng at room temperature to yield (*R*)-(+)-1-phenyl-1-propanol in 38% *ee*. The use of corresponding lithium salt provideed the product in 40% *ee*.

We next prepared the oxazolidine from (S)- valinol and cyclohexanone which is bulkier than the oxazolidine **27**. It was conveniently obtained by stirring a mixture of

valinol and cyclohexanone in the presence of molecular sieves in THF for 24h (scheme 27).



scheme 27 **28**

The oxazolidine did catalyze the reaction albeit with very low enantioselectivity (18%). The preferential formation of (*R*)- product can be explained by preferential chelation of incoming diethylzinc to the oxygen of the oxazolidine rather than the nitrogen atom, as shown below (fig. 4). The steric around the oxygen atom is very less as compared to that around nitrogen atom thereby fecilitating the chelation of diethylzinc to the oxygen atom.

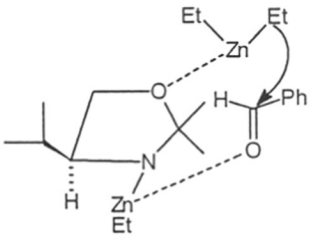


fig. 4

The low enantioselectivity observed in the case of oxazolidine derived from cyclohexanone may be due to the sterics at C-2 position. This leads to a random coordination of the incoming diethylzinc to either O or N atom providing the attack from either side and poor enantioselection (fig. 5).

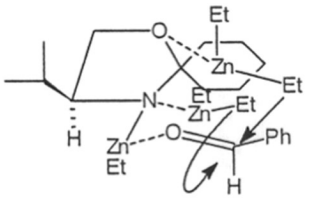
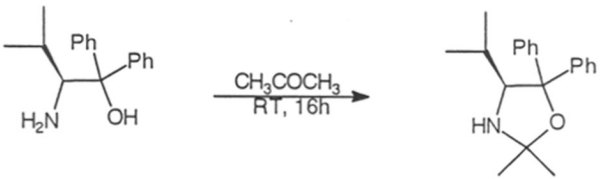


fig. 5

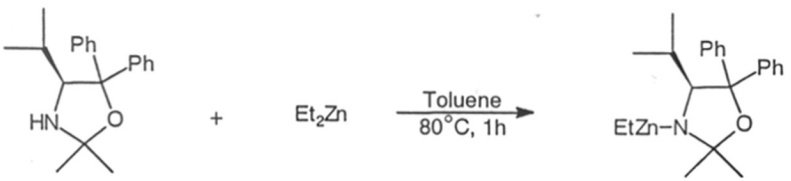
α,α-Diphenyl valinol which has proved to be a very good catalyst for the enantioselective reduction of prochiral ketones was not very good ligand for the enantioselective addition of diethylzinc to aldehyde. The reaction was reported[28] to be sluggish and provided almost racemic product.

We envisaged that the oxazolidine of the amino alcohol which has sufficient bulk around both the hetero atoms *viz.* N and O, should serve as efficient catalyst as its amide. The acetonide of diphenyl valinol (2,2- dimethyl-5,5-diphenyl-4-isopropyl)-1,3-oxazolidine **29** was easily prepared by stirring an acetone solution of diphenyl valinol for 16h at room temperature (scheme 28).



scheme 28 **29**

The corresponding zinc amide **30** of the oxazolidine was conveniently prepared by heating a toluene solution of the oxazolidine with equimolar quantity of diethylzinc at 80°C for 30-35 min. However on storage at ambient temperature, the catalyst solution deteriorates and therefore the catalyst prepared *in situ* was used as such for the next step (scheme 29).



scheme 29 **30**

The addition of diethylzinc to benzaldehyde using **30** as the catalyst proceeded smoothly within 4h at 0°C and no trace of benzaldehyde was seen (confirmed by GC). The product alcohol was of 99% *ee* and had surprisingly (*S*)- configuration contrary to

the (*R*)- configuration obtained in the case of oxazolidine derived from valinol. The reaction at room temperature was very fast, and was over in 45 min. yielding (*S*)-1-phenyl-1-propanol in very high *ee* >99%. Utilization of 5 mol% of oxazolidine did not change the rate of the reaction considerably but the enantiomeric excess of the product decreased to 96%. The use of ether as a co- solvent with toluene decreased both the rate as well as the enantioselectivity (93%). The use of THF and toluene as solvent system provided very sluggish reaction. These results are summarized in table 6.

Table 6 : Addition of Diethylzinc to Benzaldehyde with Oxazolidine Zincamide (**30**) as Catalyst.

Entry	Catalyst (mol%)	Temp, °C	Solvent	% *ee*[a]
1[b]	10	0	Toluene	>99
2	10	0	Toluene	>99
3	10	RT	Toluene	>99
4	5	0	Toluene	96
5	10	0	Ether-Toluene	93
6	10	0	Toluene- THF	-

[a]determined by chiral HPLC analysis. [b]1.2 equivalent of diethylzinc was used.

To simplify the reaction procedure, diehtylzinc that is required for the entire reaction, was added to the oxazolidine in one lot and the mixture was kept at 80°C for 1h forming the catalyst *in situ.*

The reaction was then extended to a variety of substituted aldehydes which were smoothly alkylated in high enantiomeric excess (up to 100% *ee*). Both the α- and β- naphthaldehydes were alkyalted in 96% and 100% *ee* respectively. *Ortho* tolualdehyde was alkylated faster than *para* tolualdehyde. *Para* chloro benzaldehyde was alkylated in >99% *ee* whereas *para* fluoro benzaldehyde in 78% *ee*. Alipahtic aldehydes were alkylated in much less *ee* (43%, entry 8, table 7).

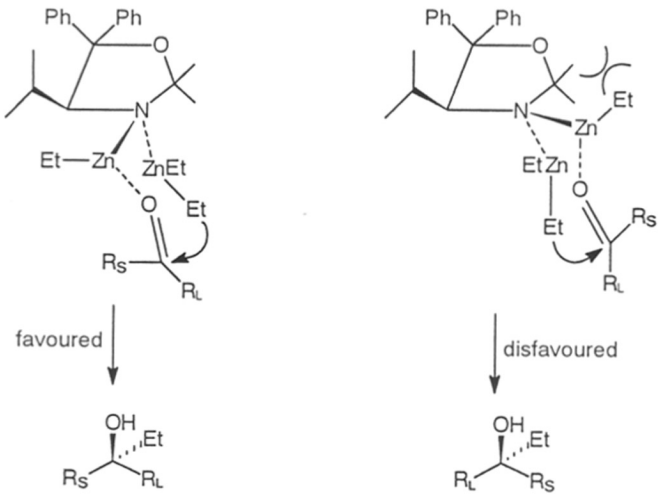
Table 7: Enantioselctive Addition of Diethylzinc to Aldehydes Catalyzed by Zincamide (**30**).

Entry	Aldehyde[a]	Time , h	Yield[b]	%ee[c]
1	benzaldehyde	4	85	100
2	α- naphthaldehyde	8	70	96
3	β- naphthaldehyde	8	75	100
4	*para*- fluoro benzaldehyde	3	80	78[d]
5	*para*- chloro benzaldehyde	4	90	100
6	*ortho*- tolualdehyde	8	75	98[d]
7	*para*- tolualdehyde	8	75	95[d]
8	cyclohexane carboxaldehyde	8	43	49[d]

[a]all reactions were done in toluene at 0°C except entry 3 & 8 which were performed at RT. [b]yields refer to isolated yields. [c]estimated on a chiracel OD HPLC column. [d]estimated by comparing with literature rotation.

Mechanism:

We propose that with ligand **27**, the incoming diethtylzinc being a softer Lewis acid coordinates to the oxygen atom of the oxazolidine. However, in the case of **29**, the sterics around the oxygen atom due to diphenyl substitution forces diethylzinc molecule to chelate exclusively to the nitrogen atom. The stereochemical outcome of the reaction is determined by the disposition of the substituents at the nitrogen atom which in turn is governed by the steric interaction between diethylzinc and the geminal dimethyl substituents of oxazolidine ring (fig. 6).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Zn
EtZn
O
Et
RS
RL
disfavoured
OH
Et
RL
RS

fig. 6

Conclusions

1. The oxazolidines prepared from (1*R*,2*S*)-(-)-norephedrine catalyzed the addition of diethylzinc to benzaldehyde with up to 82% ee.

2. Oxazolidines derived from (S)-valinol were found to be ineffective providing only 40% *ee* of the product.

3. Oxazolidines derived from (*S*)-(-)-α,α-diphenyl valinol catalyzed the addition of diethylzinc to arylaldehydes with very high yields and enantioselectivities.

4. Increase of steric bulk around oxygen atom switches the stereochemical outcome of the reaction.

Experimental

Oxazolidines **22-24** were prepared by reacting (1*R*,2*S*)-(-)-norephedrine and acetone/pivalaldehyde/acetaldehyde respectively following the reported procedures.[16,17] 2,2-Dimethyl-4-*iso*propyl-1,3-oxazolidine (**27**) was prepared by stirring overnight an acetone solution of (*S*)- valinol and evaporating the excess acetone. The compound thus obtained showed the spectral data and $[\alpha]_D$ same as the reported one.[26]

2, 2- Dimethyl-4-isopropyl-5,5-diphenyl-1,3-oxazolidine (29):

(*S*)-(-)-Diphenyl valinol was prepared as reported.[29] An acetone solution of (*S*)-(-)-diphenyl valinol was stirred for 16h at room temperature. Acetone was then evoparated and the obtained oxazolidine residue (quantitative yield) was used as such. A part of the sample was purified by column chromatograpghy on alumina for microanalysis. The compound was a thick viscous liquid.

IR (neat), cm^{-1}	3100, 2900, 1600, 1390.
^1H NMR ($CDCl_3$)	δ 0.45 (d, J 6.7Hz, 3H), 1.05 (d, J 6.7Hz, 3H), 1.2 (s, 3H), 1.75 (s, 3H), 1.85 (m, 1H), 2.1 (1H, NH), 4.00 (d, J 4.8Hz, 1H), 7.1 - 7.6 (Ar, 10 H).
^{13}C NMR ($CDCl_3$)	17.68, 23.09, 26.73, 27.73, 28.43, 71.91, 88.22, 94.14, 126.97, 127.40, 127.55, 127.91, 144.02, 147.98.
Mass (*m/z*)	296 (M+1), 113 (100%)
Analysis for	$C_{20}H_{25}ON$
Calculated	C: 81.30 H: 8.53 N: 4.74
Found	C: 81.28 H: 8.51 N: 4.79
$[\alpha]_D$	-118 (c 1.1 $CHCl_3$)

*Preparation of zinc amides from oxazolidines **22-24**:*

To a solution of 2,2-dimethyl-4-methyl-5-phenyl-1,3-oxazolidine **22** (1ml of 0.5M solution in toluene, 5mM) was added diethylzinc (0.25 ml of 2M solution in toluene, 5mM) and stirred at room temperature for 24h during which the amide was formed by evolution of 1 equivalent ethane. The amide thus formed *in situ* was used as it is for the next step.

Being a sterically hindered oxazolildine, the reaction of **29** with diethylzinc was slow at room temperature. It was conveniently obtained *in situ* by heating at 80°C for 1h during the course of the reaction as described below.

Enantioselective addition of diehtylzinc to arylaldehydes mediated by 2,2-dimethyl-4-isopropyl-5,5-diphenyl oxazolidine (29):

The following procedure for benzaldehyde is representative.

To the oxazolidine **29** (1 ml of 0.5 M solution in toluene, 0.5mM) was added diethtylzinc (5ml of 2M solution in toluene, 10mM) at room temperature and the reaction mixture was heated to 80°C for 1h. The resulting solution was then cooled to 0°C and treated with benzaldehyde (0.53g, 5mM) and stirred at 0°C. After 4h (GC showed no trace of benzaldehyde) the reaction mixture was quenched with MeOH (2ml), followed by 3N HCl (5ml). The reaction mixture was diluted with ether (50ml) and stirred vigorously for 15min. The precipitated hydrochloride of oxazolidine was filtered off and the solid was washed with ether. The ethereal layer was washed with brine and dried over Na_2SO_4. Residue after evaporation of solvent was purified by "flash chromatography" followed by kugelrohr distillation to obtain pure (*S*)-(-)-1-phenyl-1-propanol in 85% isolated yield (0.58g). The enantiomeric excess of the product was >99% as estimated by HPLC using a chiracel OD column.

All the products obtained showed the spectral data that is already described in Section **2a** page 57.

(S)-(-)-1-Phenyl-1-propanol

Yield	(0.58g), 85%
$[\alpha]_D$	-46.7 (c 5.14 $CHCl_3$)
ee	100% (estimated by HPLC on a chiracel OD column)

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

Yield	(0.60g), 80%
$[\alpha]_D$	-37.31 (c 4.98 benzene)
	lit.[30] -34.87 (c 4 benzene) for 92% *ee*
ee	95%

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

Yield	(0.563g), 75%
$[\alpha]_D$	-56.18 (c 4 benzene)
	lit.[30] -57.51 (c 4 benzene)
ee	98%

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

Yield	(0.767g), 90%
$[\alpha]_D$	-28.3 (c 5.18 benzene)
ee	100% (estimated by HPLC on a chiracel OD column)

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

Yield	(0.62g), 80%
$[\alpha]_D$	-38.62 (c 2.6 $CHCl_3$)
	lit.[10] +51.2 (c 2.5 $CHCl_3$) for the *R* enantiomer
ee	75%

(S)-(-)-1-(β-Naphthyl)-1-propanol

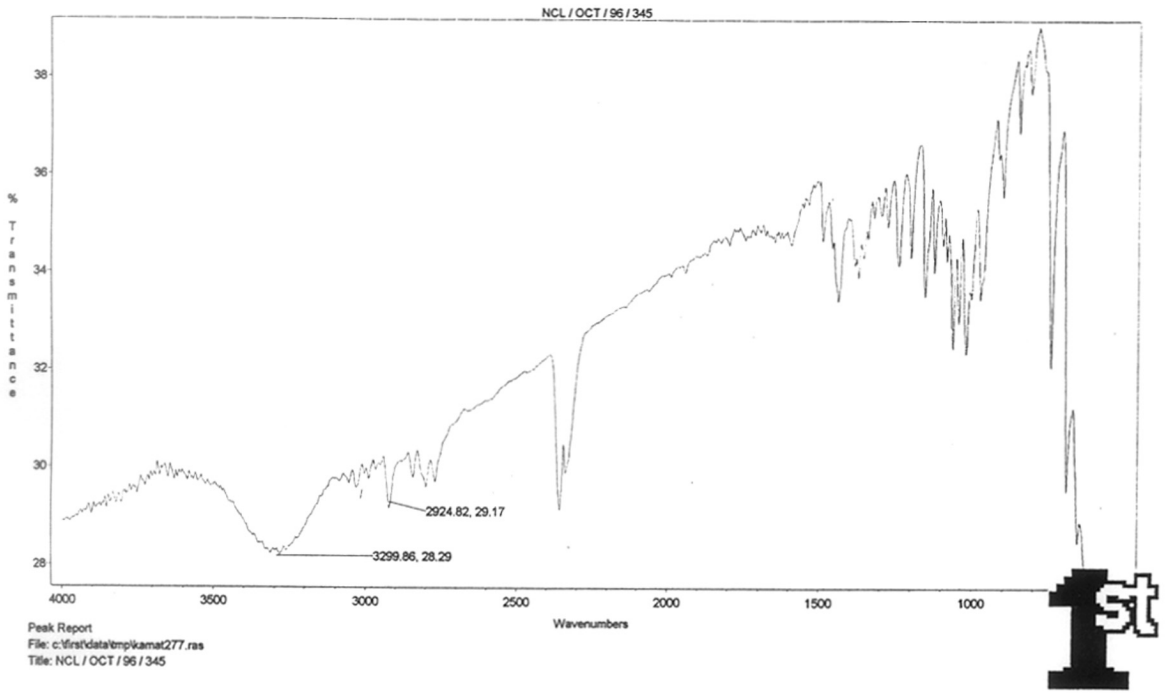
Yield	(0.70g), 75%
$[\alpha]_D$	-28.24 (c 3.4 benzene)
ee	100% (estimated by HPLC on a chiracel OD column)

(S)-(-)-1-(α-Naphthyl)-1-propanol

Yield	(0.65g), 70%
$[\alpha]_D$	-50.53 (c 2.46 $CHCl_3$)
ee	96% (estimated by HPLC on a chiracel OD column)

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

Yield	(0.35g), 49%
$[\alpha]_D$	-3.5 (c, neat)
	lit.[31] -8.1 (c, neat)
ee	43%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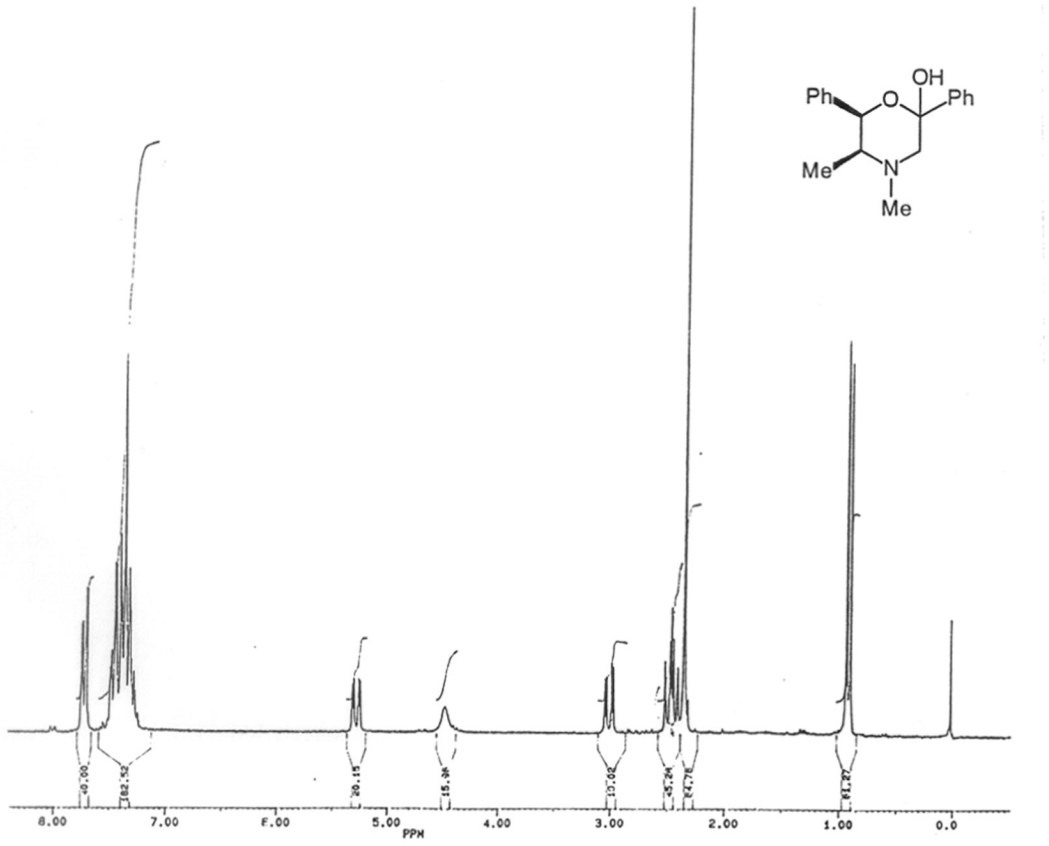
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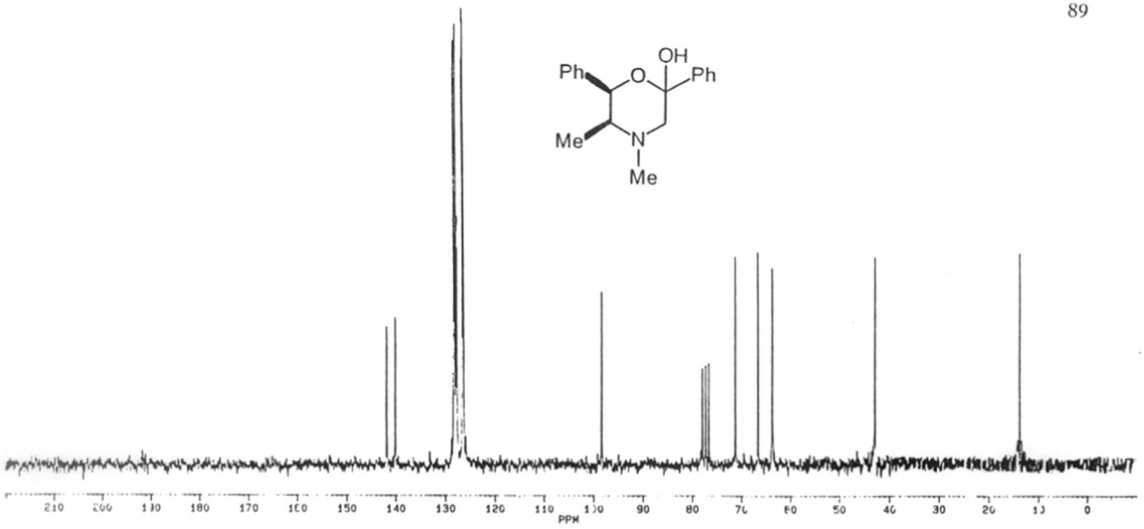
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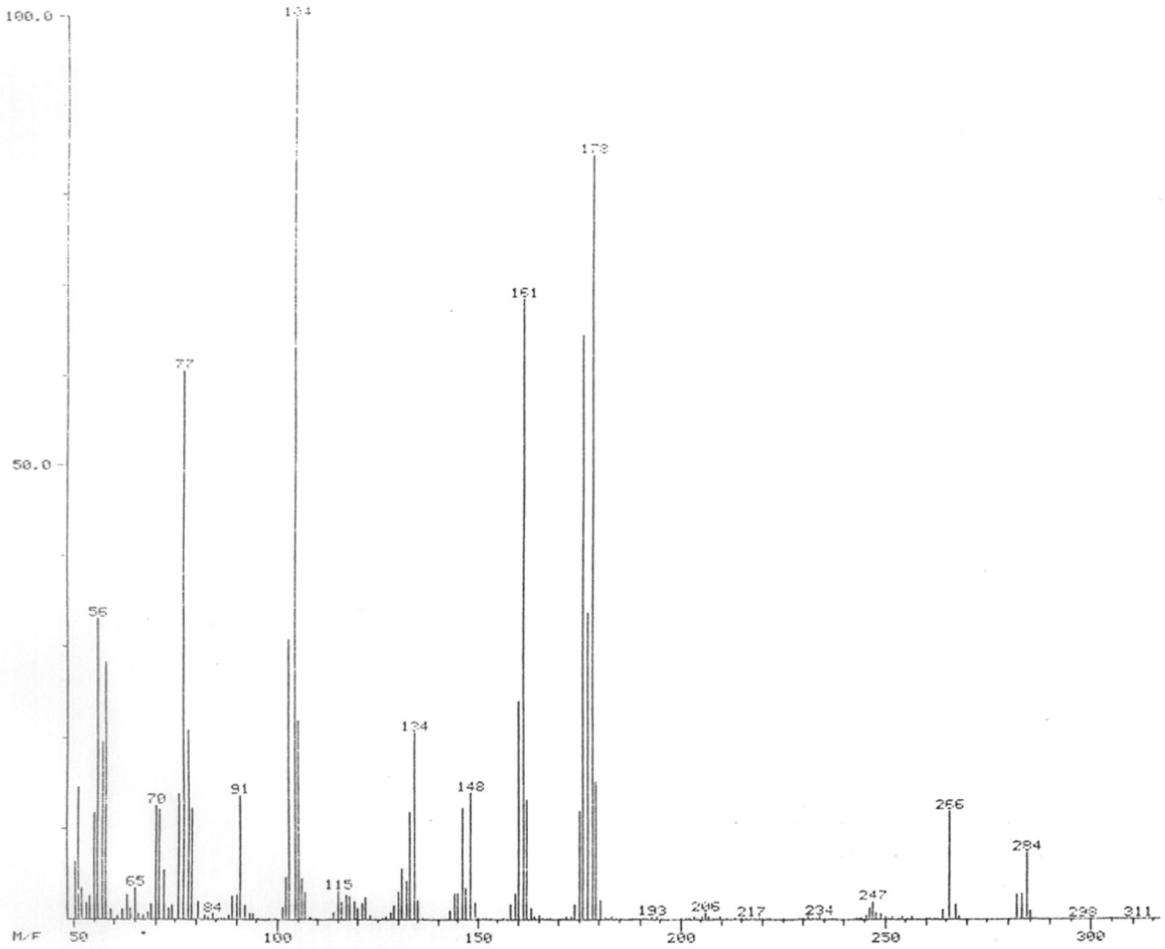
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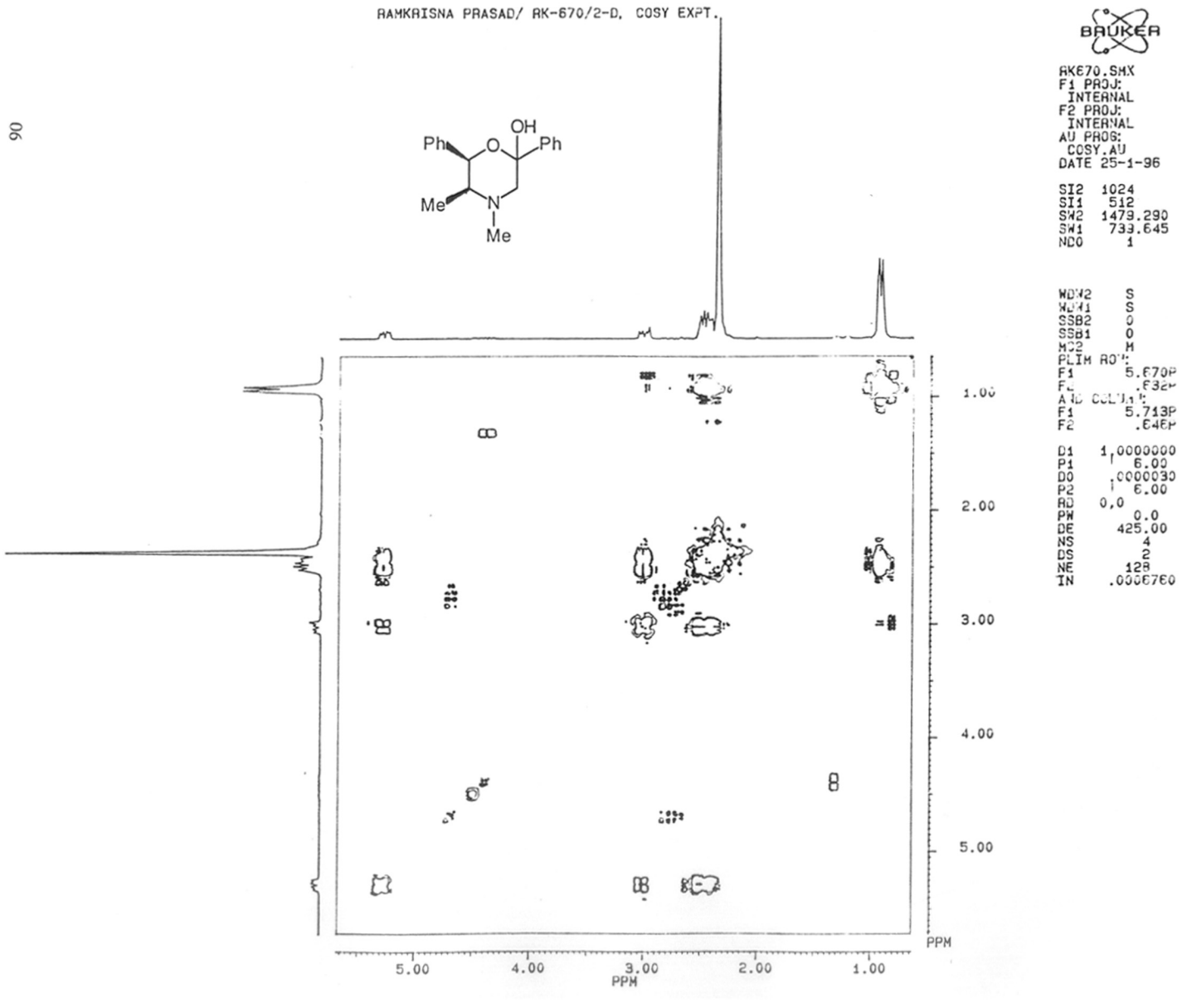

BRUKER

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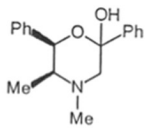

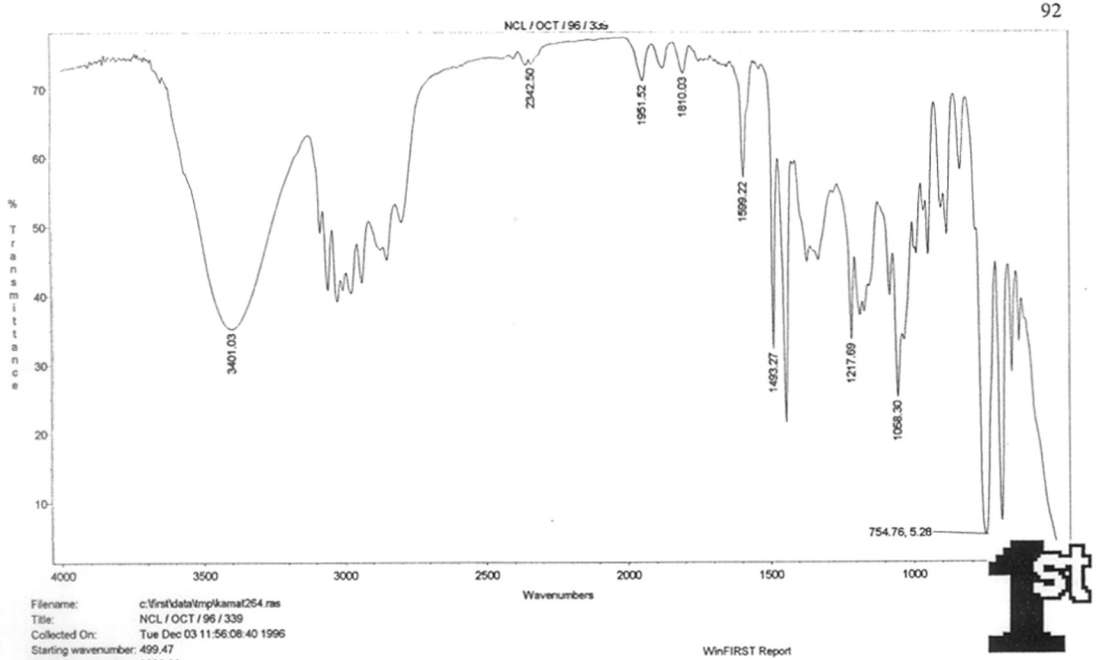

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WinFIRST Report

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Date: 03 / 12 / 96
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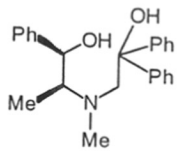

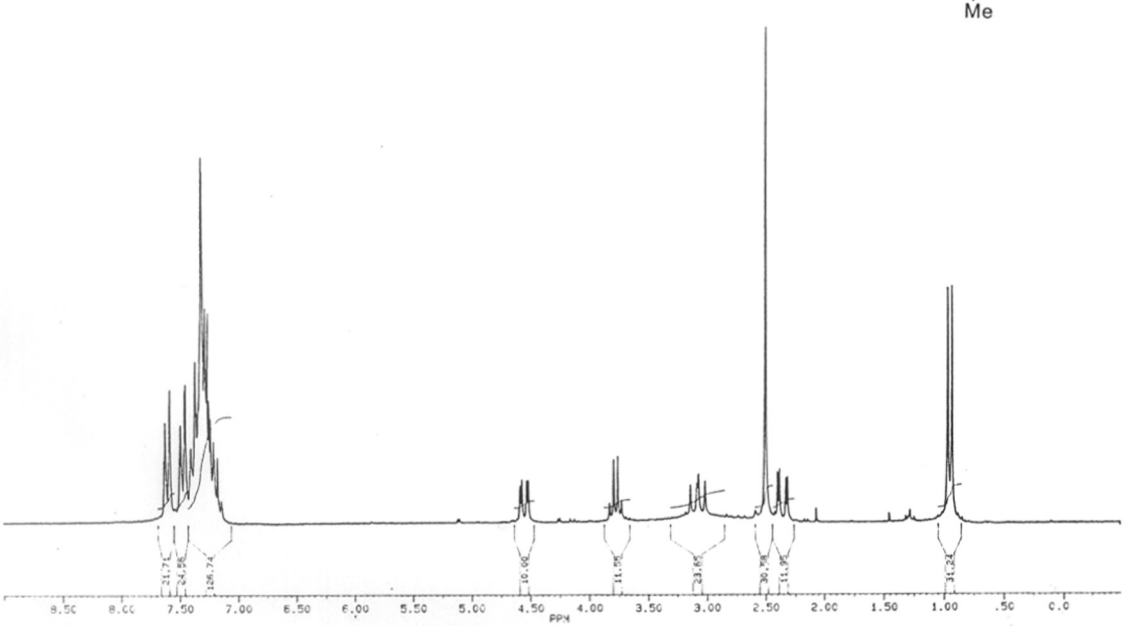

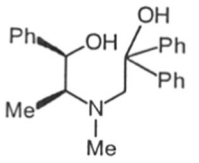
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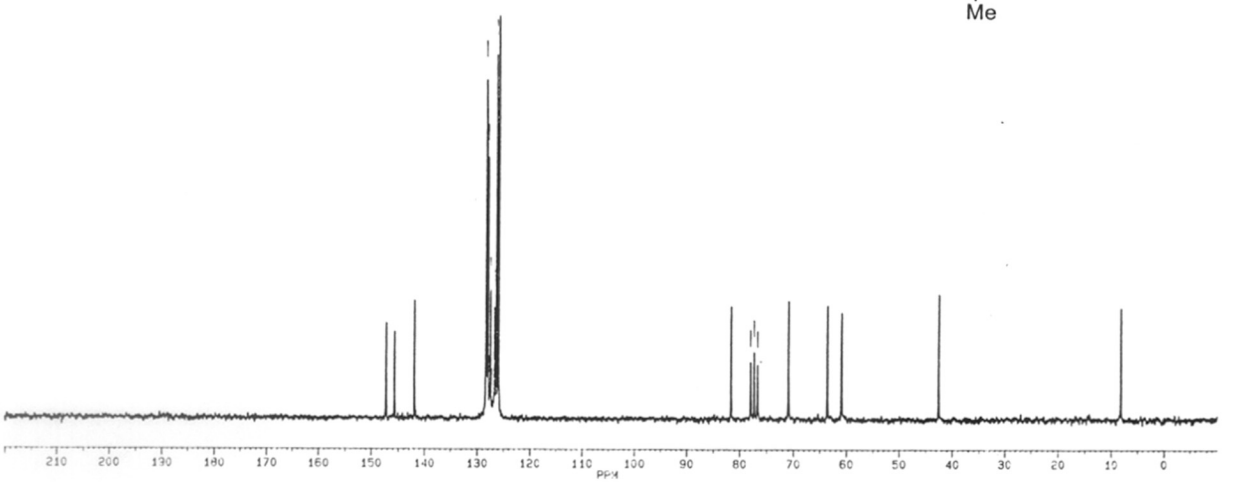
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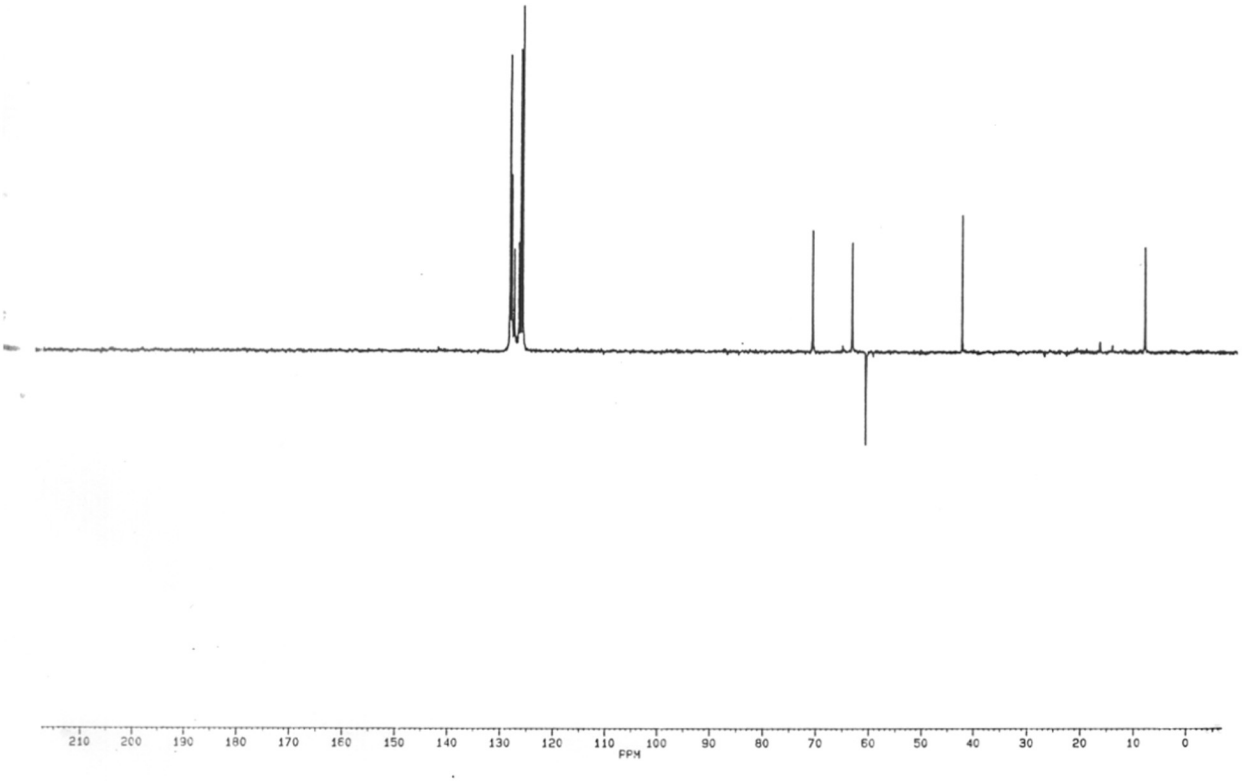
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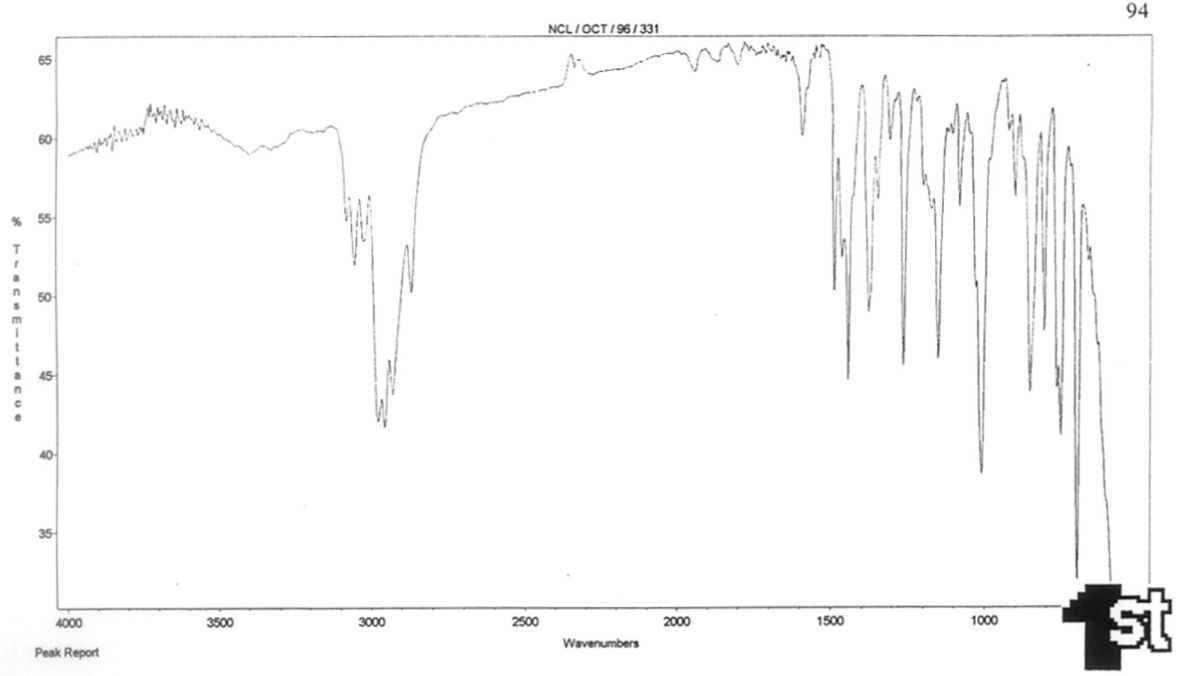
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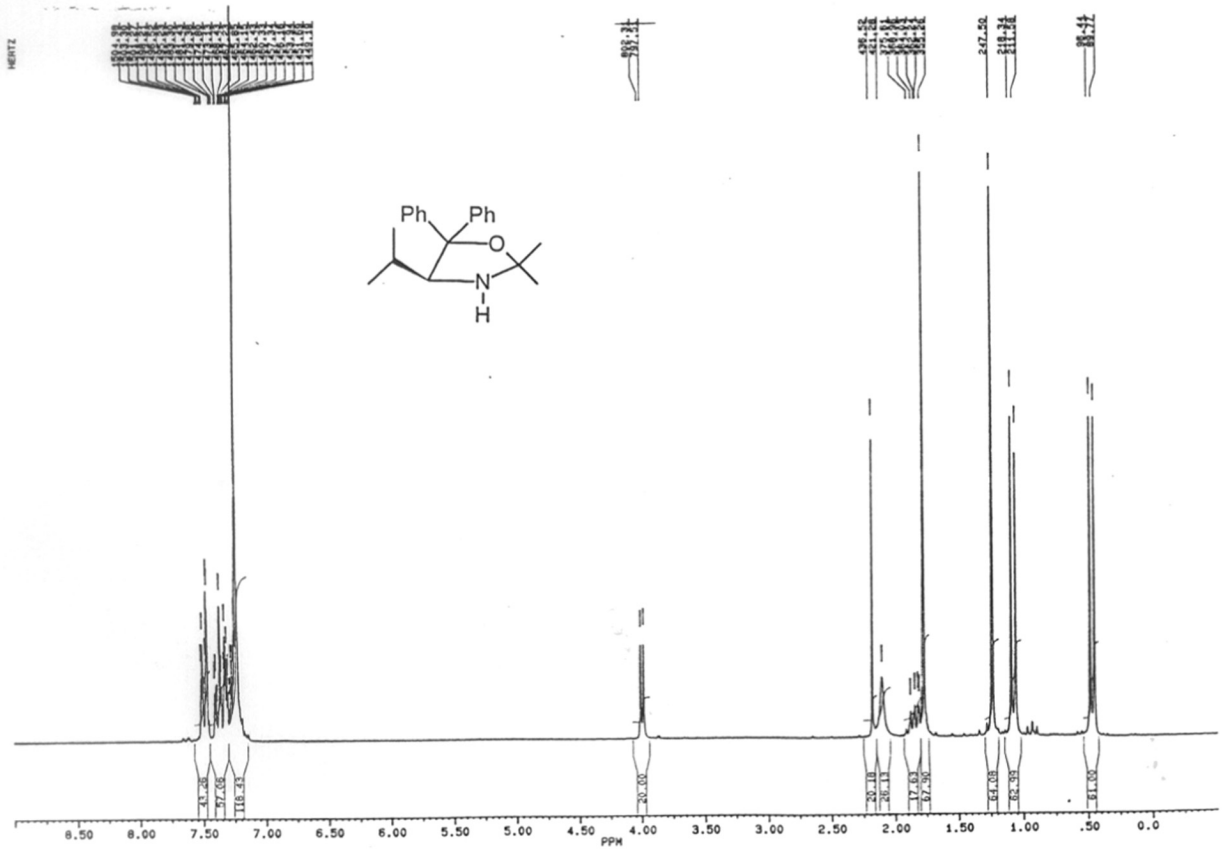
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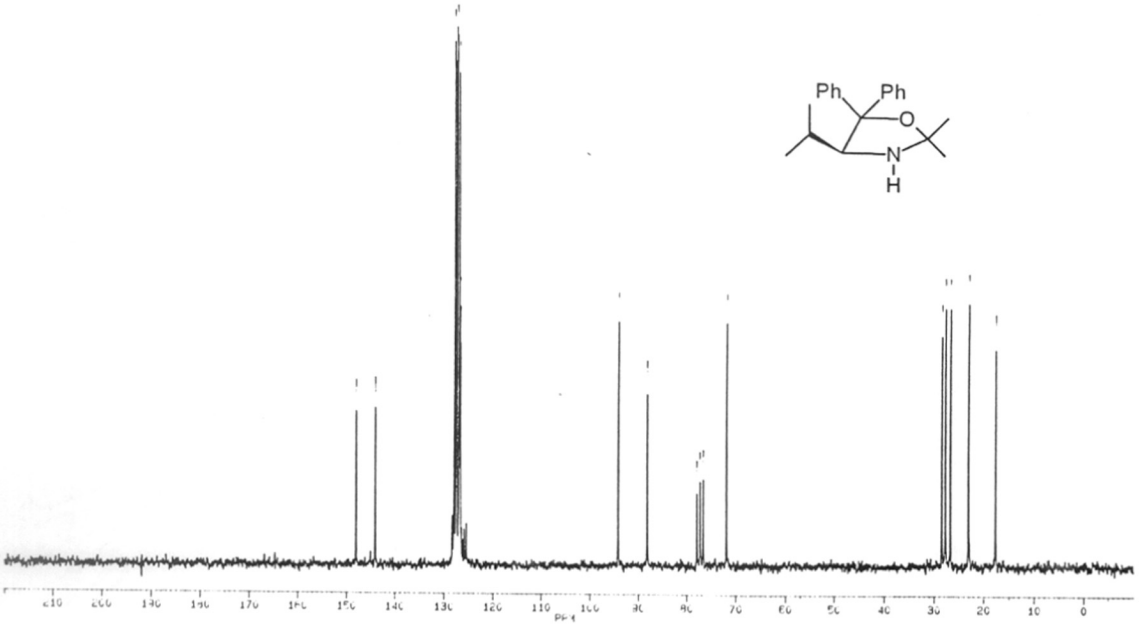
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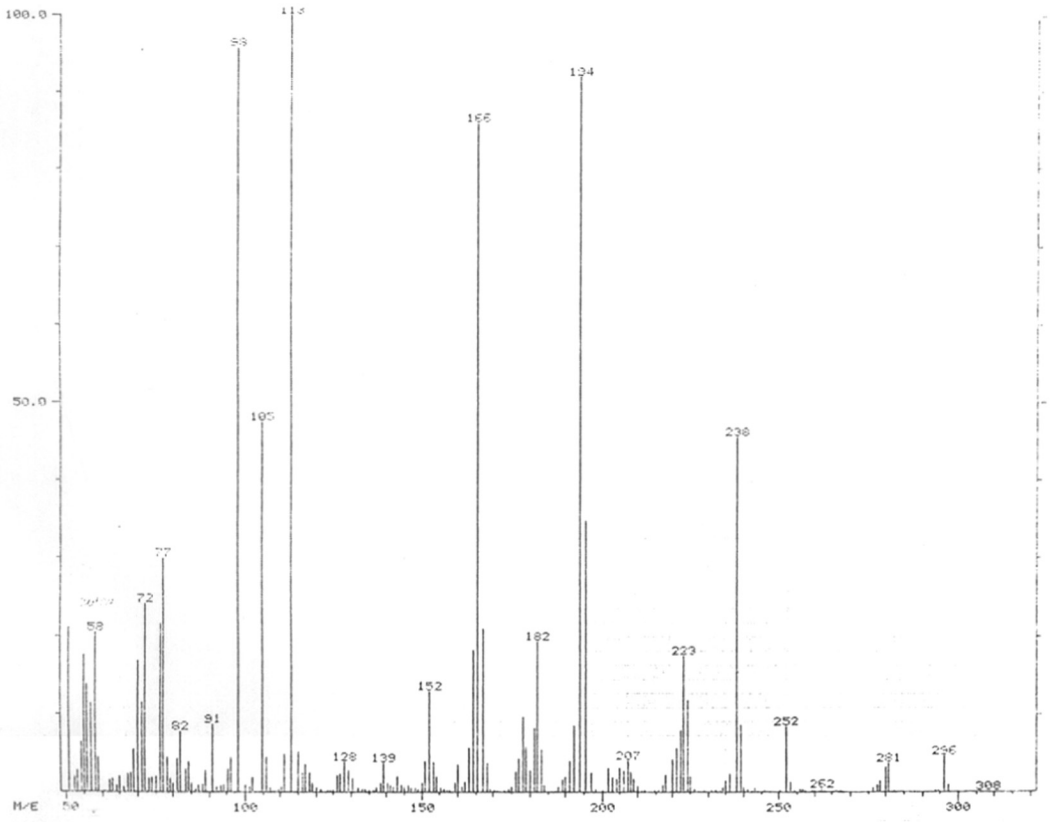
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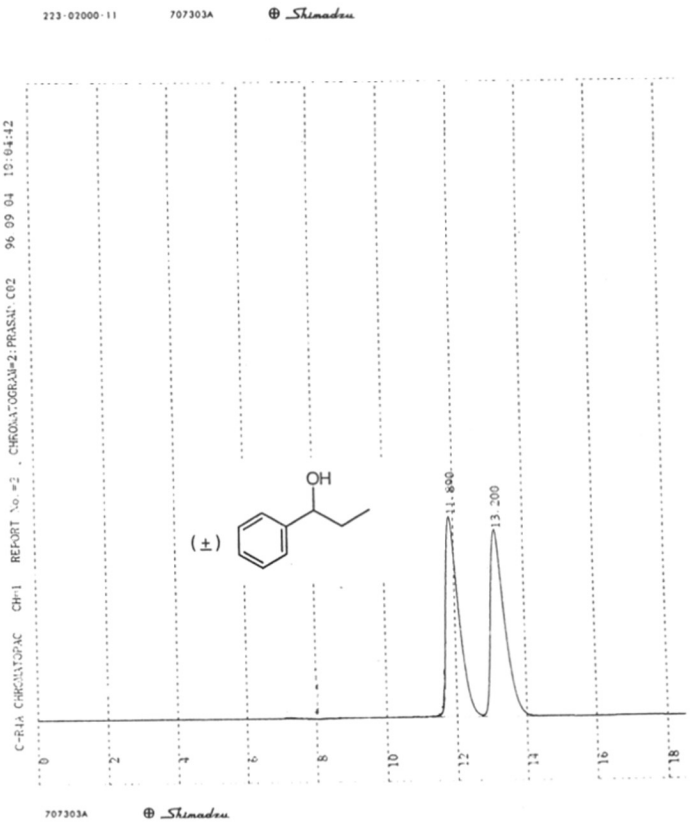
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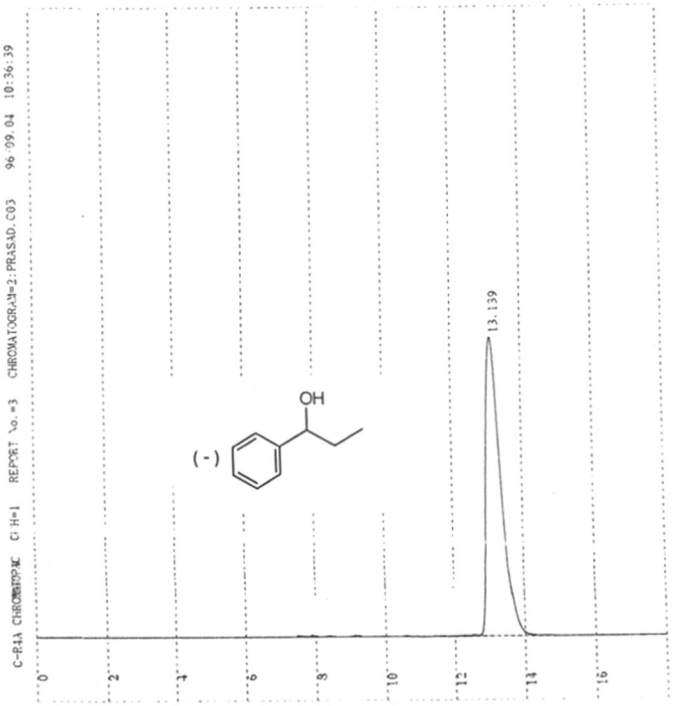
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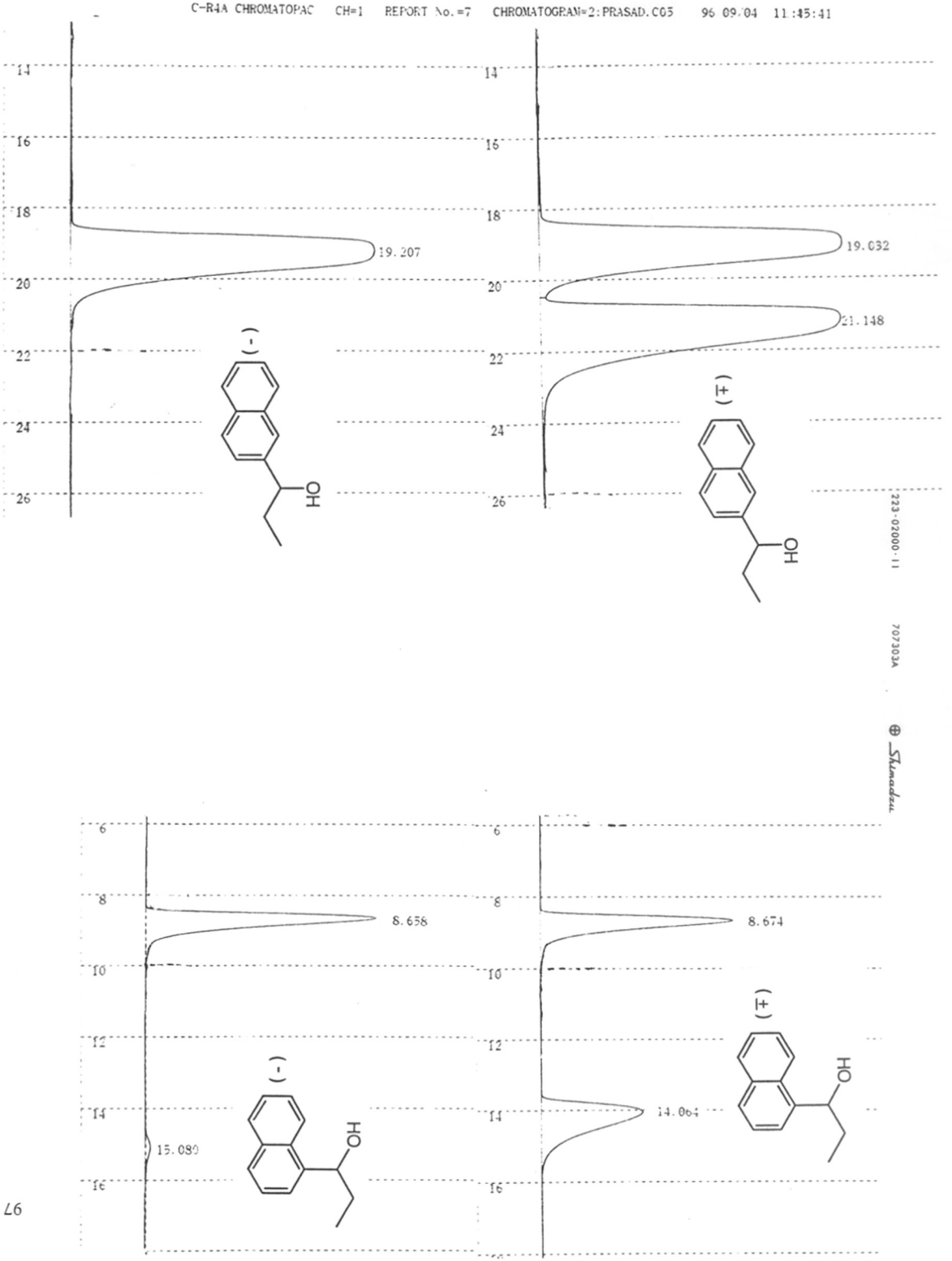
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CHAPTER - 3

Stereoselective Reduction of Ketones

Stereoselective reduction of prochiral ketones is a simple synthetic operation of pivotal importance in asymmetric synthesis. The overall addition of the Hydrogen (hydride ion) to one of the prochiral carbonyl face to yield optically pure secondary alcohols is highly desirable. Various reagents were developed over the years for the reduction to achieve high asymmetric inductions. As reviewed in Chapter 1, stoichiometric reagents *viz.* BINAL-H, DIP-Cl, Alpine borane, etc. have emerged as successful reagents for the reduction of ketones. With the advent of oxazaborolidine catalysts, the enantioselective reduction of ketones in a catalytic manner has been perfected. The past decade has seen tremendous growth of interest in the structural modifications of the oxazaborolidine catalysts to achieve maximum stereoselection and to further simplify the process. Eventhough there are several reports on the reduction of simple prochiral ketones, the stereoselective reduction of functionalized ketones was scantily addressed in the literature. In this chapter, we present our investigations in this area.

This chapter is divided into the following two sections.

a. An optimised *in situ* procedure for the oxazoborolidine catalyzed enantioselective reduction of prochiral ketones.

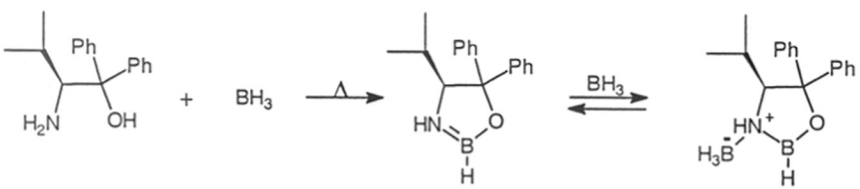
b. Stereoselective reduction of 1,2- diketones.

SECTION - 3a

An Optimized in situ Procedure for the Oxazaborolidine Catalyzed Enantioselective Reduction of Ketones.

Itsuno *et. al.*[1] first utilized the amine- borane complex derived from diphenylvalinol in the reduction of prochiral ketones. They found that 1:2 complex of amino alcohol and borane reduces efficiently the prochiral ketones in very high enantioselectivities. They also found that reaction of diphenylvalinol with excess borane in THF evolved hydrogen. After evaporation of unreacted borane and THF under reduced pressure, a complex was obtained as a white powder which was of "unknown composition".

Later Corey *et. al.*[2] investigated this reaction and found that a fast reaction occurs between diphenylvalinol and 2 eq of BH_3 in THF to give 2 equivalents of hydrogen gas and the corresponding oxazaborolidine. They were able to isolate the oxazaborolidine and its structure proved based on Electron-Impact-Mass spectrum and B^{11} NMR (scheme 1).

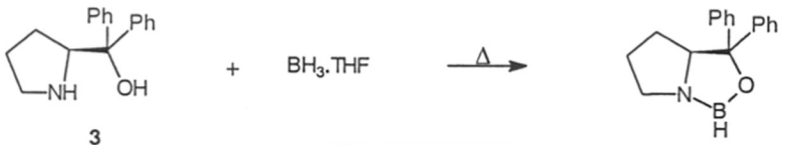


1 2

scheme 1

An even better catalyst for the reduction of ketones, the oxazaborolidine **4** derived from (*S*) (-)-2-(diphenylhydroxymethyl) pyrrolidine was obtained by heating diphenyl prolinol **3** with BH_3.THF (3 eq) under a closed Argon-BH_3 atmosphere (total

pressure 117 bar). Removal of the solvent, sublimation at 150-160° (0.1 Torr) and resublimation at 145-160°C (0.05 Torr) provided **4** as a white solid (scheme 2).

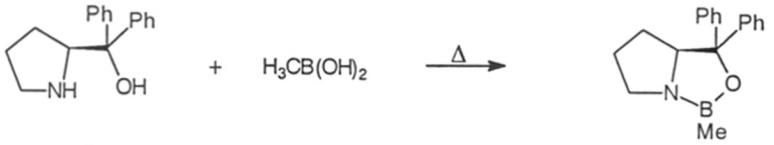


3 **4**

scheme 2

They also found that **4** is a mixture of monomer and dimer in THF solution. The proportion of dimer decreases with higher temperature and lower concentration. The authors reported that the optimum temperature for the reduction is 25°C and the enantioselectivity decreases with a decrease in temperature.

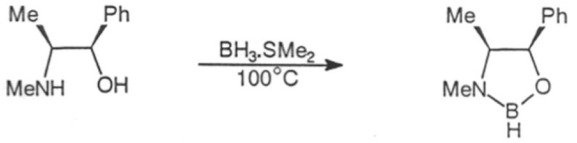
B-Me substituted oxazaborolidine **5** was prepared[3] by refluxing diphenyl prolinol and methylboronic acid (1.1 eq) in toluene in the presence of molecular seives for 1.5 hr (scheme 3).



3 **5**

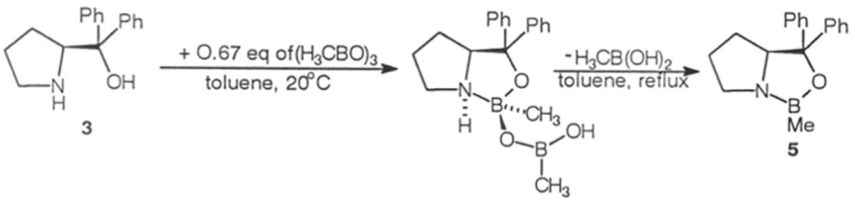
scheme 3

Joshi *et. al.*[4] prepared the oxazaborolidine from ephedrine by heating ephedrine with 1 eq of BMS at 100°C (scheme 4).



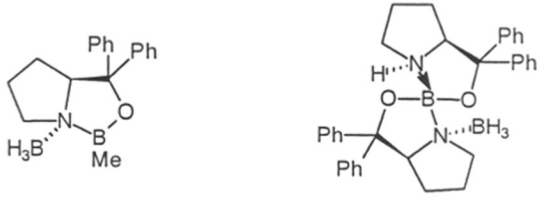
scheme 4 **6**

Due to the air and moisture sensitive nature of the parent oxazaborolidine, the corresponding B-Me derivative is preferred. Merck chemists found[5] that oxazaborolidines prepared by Corey's procedure gave erratic results. They claimed that oxazaborolidine (**5**) prepared by Corey's method contains 2-13% unreacted amino alcohol. The presence of 1 mol % of either (**3**) or methyl boronic acid was found to significantly decreased the enantioselection. Also traces of water were deleterous. They altered the procedure for the formation of the oxazaborolidine (**5**) by adding 0.67 equivalents of trimethylboroxine to a toluene solution of (**3**) and then removing toluene and methyl boronic acid by distillation (scheme 5).



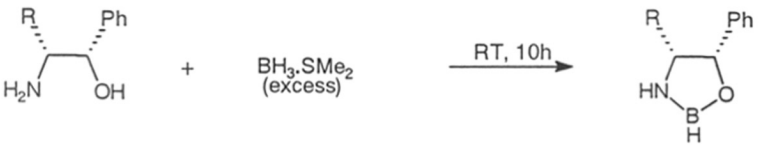
scheme 5

Mathare *et. al.*[6] isolated the oxazaborolidine **5**-BH_3 complex as a stable, free flowing crystalline solid. They found that BH_3 complexes of a variety of oxazaborolidines can be isolated as crystalline solids. However, they were unable to prepare the corresponding borane complex of the parent B-H oxazaborolidine (**4**) obtaining instead a dimer.



The authors realized high levels of induction > 99% utilising a stoichiometric as well as catalytic amount of the borane complex of oxazaborolidine (**5**). They found that the level of enantioselection increases by decreasing the temperature and the enantioselectivity was slightly higher when 1.0 eq. of BMS was used. The increase of the substituent size on boron in the oxazaborolidine decreased the enantioselectivity.

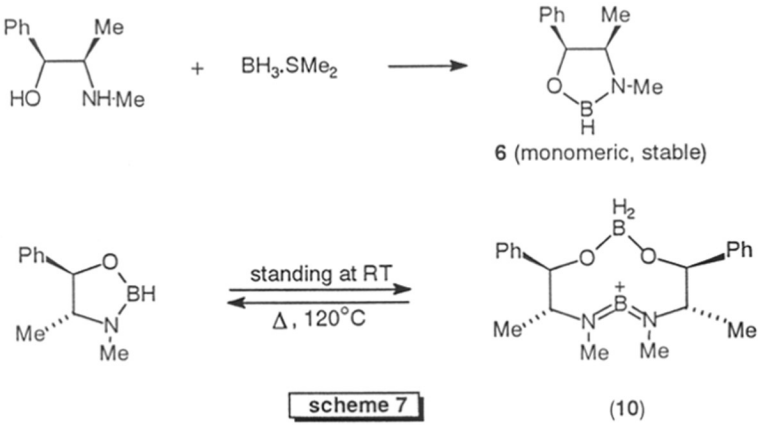
An *in situ* preparation of oxazaborolidines from 2-amino-1,2-diphenylethanol, norephedrine and diphenylprolinol was reported by Quallich and Woodall.[7]. They found that in the presence of excess borane at ambient temperatures, the amino alcohols generated the oxazaborolidine within 8-10 hr. The reduction of prochiral ketones with 10 mol % of these catalysts yielded alcohols in >90% *ee* (scheme 6).



scheme 6

7 = R= C_6H_5
8 = R= CH_3

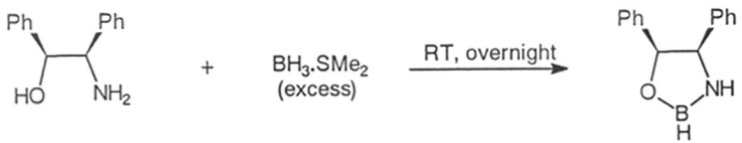
J. M. Brown *et. al.*[8] has shown that the oxazaborolidine **6** prepared from (1*R*,2*S*)-ephedrine was a monomeric compound while the oxazaborolidine **9** prepared from (1*R*,2*R*)-ephedrine gradually gets converted to the dimeric species **10**, similar to that in oxazaborolidine **7** observed by Mathare *et. al.*[6] (scheme 7).



scheme 7

(10)

Yaozhong *et. al.*[9] prepared oxazaborolidine (**11**) from (1*R*,2*S*)-1,2-diphenyl-2-aminoethanol and excess borane by stirring it overnight at room temperature (scheme 8).



scheme 8

Quallich *et. al.*[10] investigated the relationship of oxazaborolidine structure to the enantioselectivity obtained in the reduction of ketones. Enantiomeric excess was demonstrated to be dependent on the extent to which one oxazaborolidine face was precluded from attaining two point binding and on non-bonded interactions that developed during the formation of the borane-oxazaborolidine complex. *Erythro* substituted oxazaborolidines were found to be useful catalysts for the reduction of prochiral ketones. Alkyl substitution on nitrogen resulted in decrease in enantioselectivity. They also found that *in situ* prepared B-H oxazaborolidines gave higher *ee*.

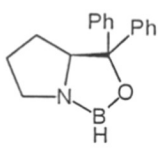
Recently Periasamy *et. al.*[11] have shown that oxazaborolidine **4** can be generated by reaction of α,α-diphenylpyrrolidine methanol and diborane in benzene followed by heating with N,N-diethylanilline. This in combination with BH_3.THF reduced acetophenone in 94.7% *ee*.

Eventhough there are a number of reports concerning the preparation of oxazaborolidines from variety of amino alcohols, there is a dearth of information regarding the optimum parameters which include the structural requirement of the catalyst, the stiochiometry of reactants, the solvent and the temperature for reduction. In fact there are some conflicting reports, for example, Mathare *et. al.*[6] described that they are unable to prepare the corresponding borane complex of parent BH oxazaborolidine **4** whereas Quallich *et. al.*[7] observed that excess borane-dimethylsulfide and amino alcohol at ambient temperature generated the oxazaborolidine. Also, Mathare *et. al.*[6] state that "the level of enantioselection increased by decreasing the temperature" whereas Corey *et. al.*[2] found that "reduction loses stereoselectivity at lower temperature".

We decided to study the optimum conditions that are required for the *in situ* generated oxazaborolidines and their application in selective reduction of prochiral ketones.

Results and Discussion

At the outset, we studied the reduction of acetophenone with three representative oxazaborolidines *viz.* **4, 12, 13** derived from commonly available L-amino acids.



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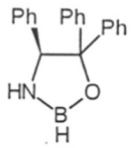

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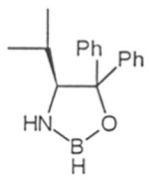


13

The study of Quallich *et. al.*[10] reveals that geminal diphenyl substituents are optimum for high enantioselectivity. We therefore excluded other structural modifications. As for the substitution on boron atom, we opted for simple B-H derivatives for the following reasons.

1. It has been shown that increased steric bulk on boron atom leads to slightly decreased reaction rate whereas the enantioselectivity remains practically unchanged.

2. Considering the mechanistic study by Corey *et. al.*[2] and Mathare *et. al.*[6] if the substitution at boron and R_S of the carbonyl compound is indeed responsible for the selectivity, the smallest substituent B-H should be preferred.

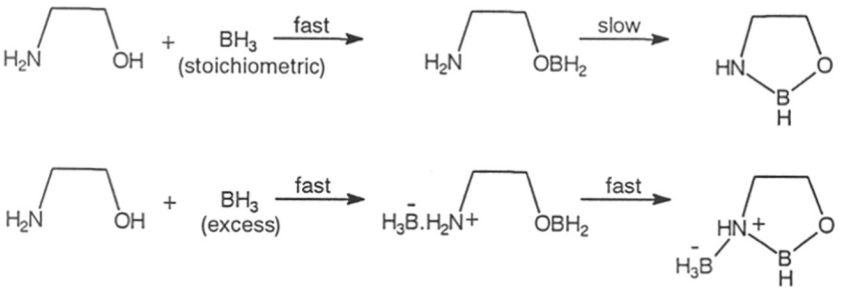
3. The other two commonly used derivatives *viz.* B-Me and B-Ph are not easy to prepare. Also, traces of water was found to be highly deleterious with these catalysts[5].

4. As for the substituent on nitrogen atom, it was shown by Quallich *et. al.*[10] that an alkyl substituent on nitrogen atom will create unfavourable interaction with the adjacent substituent leading to weaker coordination of borane to nitrogen atom and hence slower catalysis.

Preparation of the catalyst : Having selected the catalyst structures to be investigated, we turned our attention to the preparation of the catalyst. As discussed in the introduction, a variety of conditions have been recommended for the preparation of oxazaborolidines with -BH substituent.

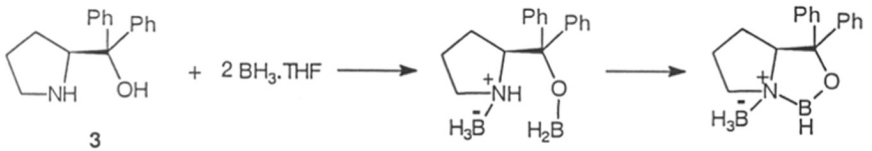
The formation of B-H oxazaborolidines involves the formation of B-N bond which is slow. More recently, Quallich and Woodall reported[7] the formation of oxazaborolidine **4** *in situ* by stirring a mixture of amino alcohol and excess $BH_3.SMe_2$ at room temperature for 10h. We found that this procedure works well for the preparation of **12** and **13**, but not for **4**. We believe that formation of **4** which involves a strained [3.3.0] fused ring system, was incomplete under the conditions described.

We therefore examined the preparation of oxazaborolidine **4**. The reaction of amino alcohol in the presence of excess BH_3 is likely to proceed as in scheme 9.



scheme 9

Excess borane renders the nitrogen atom more acidic and facilitates the easy cyclization to form the B-N bond. Such a mode of cyclization explains why the intermediate "ate" complex obtained by using 1 eq. of borane requires prolong heating at 100°C to cyclize in the case of oxazaborolidine from ephedrine (scheme 4). We anticipated that heating the ate complex to elevated temperature should hasten the formation of N-B bond than stirring at room temperature for long time. It was indeed the case when diphenyl prolinol (**3**) was treated with 2 eq. BH_3 at room temperature to form the ate complex which on heating at 80°C for 1h. evolved the second equivalent of hydrogen to form the oxazaborolidine (scheme 10).



scheme 10

Oxazaborolidine (5-10 mol %) thus formed, catalyzed the enantioselective reduction of acetophenone in very good isolated yield and 97% *ee*. However, this procedure does not work well when the concentration of the catalyst was decreased to 1 mol %. The same was the case observed with oxazaborolidine prepared by Quallich and Woodall procedure which does work well for acetophenone reduction when the catalyst concentration is > 10 mol %, yielding phenethanol in 93% *ee*. However, when the catalyst concentration is < 5 mol %, the enantiomeric excess of the product is <10%.

We therefore stirred the (*S*)-diphenyl prolinol with a large excess of $BH_3.SMe_2$ (the entire amount required for the reduction) at 45°C for 12-16h. Increasing the temperature beyond 50°C leads to the loss of borane. The catalyst thus obtained reduced acetophenone with very high enantioselectivity (97% *ee*). The catalyst prepared in this way successfully reduced acetophenone even at 1 mol % concentration within 15min. providing the product alcohol in 88% *ee*. Thus, the results obtained with the catalyst prepared *in situ* were almost similar to those obtained with the isolated and sublimed catalyst of Corey *et. al.*[2]

The Reaction Temperature : We used a convenient 2M solution of $BH_3.SMe_2$ in toluene for the reduction. The choice of toluene as a solvent is based on the consideration that since it's less volatile and non-hygroscopic, the reagent deterioration will be considerably minimized than in other solvents *viz.* THF, Et_2O or CH_2Cl_2.

As it was mentioned earlier, the temperature at which the reaction should be conducted remained controversial. For example, Corey *et. al.*[2] observed a decrease in enantiomeric excess with the decrease in temperature whereas Mathare *et. al.*[6] have reported that decrease in the temperature increased the enantioselectivity. There has

been a definite study concerning the B-Me and B-Ph derivatives of oxazaborolidines[12], the parent B-H oxazaborolidine reduction however remained unexamined.

We have carried out several studies with varying temperatures using the oxazaborolidine catalysts prepared *in situ*. The reduction was conducted at 0°C, 25°C and 45°C and surprisingly, the best results were obtained at 45°C. The reduction at 0°C did not go to completion at all, with 1 mol % of catalyst. Reduction at 25°C gave phenethanol in 40% *ee* and at 45°C, the reduction was over in 15min yielding the alcohol in 88% *ee*.

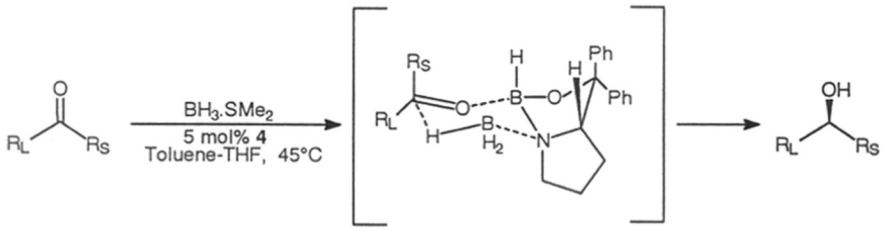
We attribute the enhancement of enantioselectivity with temperature to the increase in catalytically active monomeric oxazaborolidine, as compared to the dimeric structure which should be more stable at lower temperatures. The effect of temperature on the reduction was more dramatic with catalyst **4** which has more basic nitrogen atom than **12** and **13**. These results were summarized in table 1.

Table 1 : Oxazaborolidine Catalyzed Reduction of Acetophenone[a]

Entry	Catalyst	Temp, 0°C	Time, min	% *ee*
1	**4**, 1mol%	25[b]	c	-
2	**4**, 1mol%	25[d]	60	40
3	**4**, 1mol%	45	15	88
4	**4**, 5mol%	45	<5	**97**
5	**4**, 5mol%	45[e]	<5	96
6	**12**, 5mol%	25	c	-
7	**12**, 5mol%	45	<5	47
8	**13**, 5mol%	25	15	89
9	**13**, 5mol%	45	<5	71

[a]All the reactions, except entry 5 were carried out using 0.6 equivalent of $BH_3.SMe_2$ in toluene - THF (~1:1). [b]Catalyst made at 25°C, 10h. [c] Incomplete reaction even after 2h. [d]Catalyst made at 45°C, 16h. [e]Using 1.0 equivalent of $BH_3.SMe_2$.

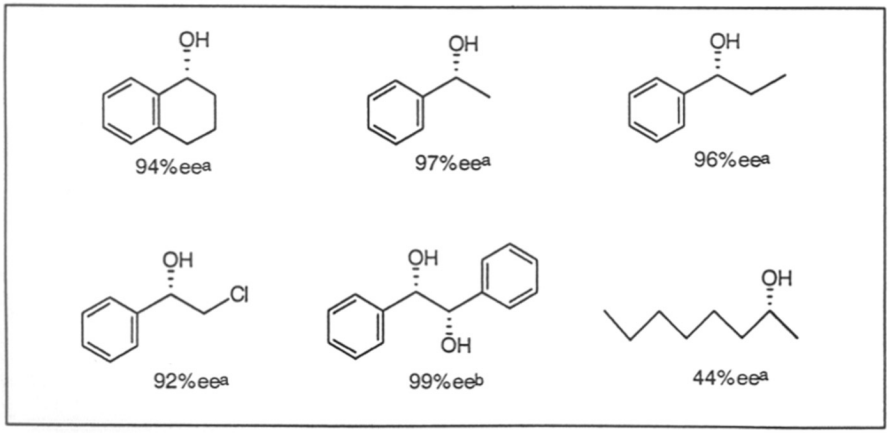
No significant change in the reaction outcome was observed by increasing the quantity of $BH_3.SMe_2$ from 0.6 eq. to 1 equivalent (scheme 11).



scheme 11

We reduced six representative ketones using the best conditions *i.e.* 5 mol % catalyst and at a reduction temperature of 45°C in toluene solution. All the ketones gave product alcohols in *ee*'s ranging from 92-99% (table-2). It is noteworthy to mention here that the diketone reduction which strictly requires catalyst > 5 mol % does not proceed with the catalyst prepared by the method of Quallich and Woodall.

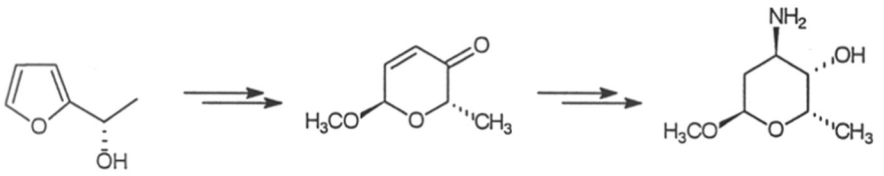
Table 2: Enantioselective Reduction of representative Ketones.



[a]determined by comparing with maximum known rotation.[b]% *de* 88:12, ref 13.

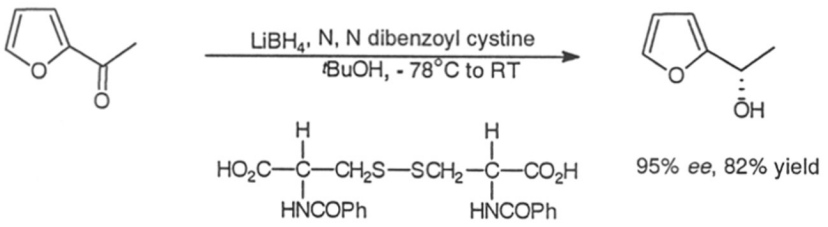
Enantioselective reduction of 2- thienyl and 2- furyl ketones.

Optically active furyl carbinols and thienyl carbinols form an important class of compounds because the heterocyclic group can be used for a variety of manipulations. For example, one can synthesize a series of dihydropyranoses which would serve subsequently as suitable substrates for the facile introduction of various other functionalities[14] (scheme 12).



scheme 12

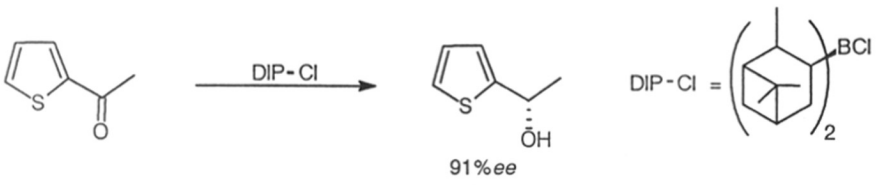
Sammes and Thetfort reported[15] the reduction of 2-acetyl furan with lithium borohydride in THF and *tert*-butyl alcohol in presence of (*R,R*)-N,N-dibenzoyl cystine (**14**) in 82% yield and 95% *ee* (scheme 13).



(14)

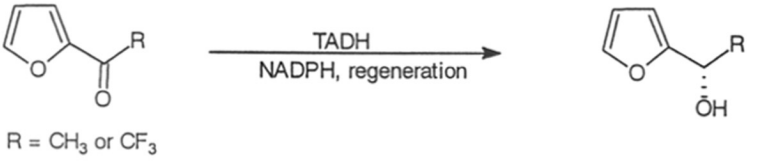
scheme 13

Brown *et. al.*[16] reduced 2-acetyl thiophene with DIP-Cl in 87% *ee*. They observed a marked influence of the amount of reducing agent used to the substrate. With 1 equivalent of the reagent, the *ee* of the product alcohol was 85% whereas using 2 equivalents of the reagent yielded alcohol of 91% *ee* (scheme 14).



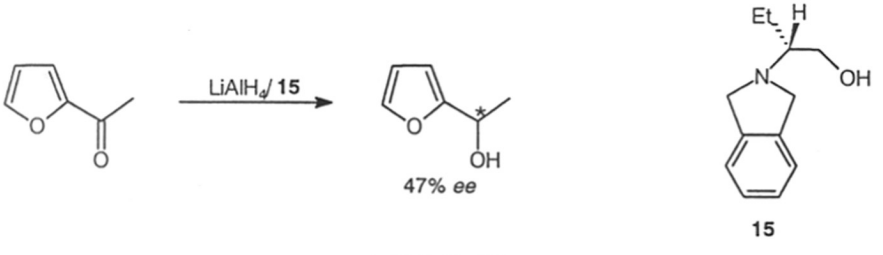
scheme 14

Drueckhammer *et. al*[17] utilized *Thermoanaerobium brockii* alcohol dehydrogenase coupled with an NADPH regeneration in the reduction of 2-acetyl and 2-trifluoroacetyl furan to yield the alcohols (scheme 15).



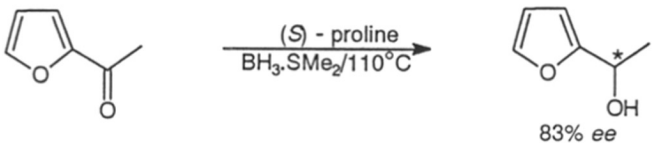
scheme 15

Brown *et. al.*[18] utilized a LAH- modified by amino alcohol (**15**) as a reducing agent in the reduction of 2-acetylfuran to yield the product alcohol in 47% *ee* (scheme 16).



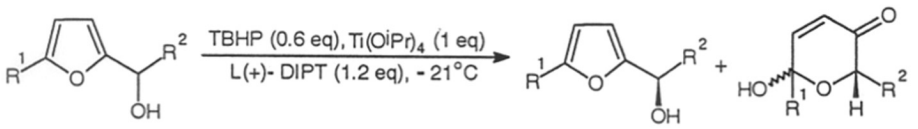
scheme 16

Brunel *et. al.*[19] reduced 2-acetylfuran with $BH_3.Me_2S$ catalyzed by (*S*)-proline in toluene at 110°C to yield the alcohol in 83% *ee* (scheme 17).



scheme 17

Kobayashi *et. al.*[20] prepared optically active furyl carbinols by Sharpless kinetic resolution conditions (utilising TBHP, Ti(O^iPr)$_4$ and L(+)- diisopropyl tartrate) on 4-substituted-2-acyl furans (Scheme 18).

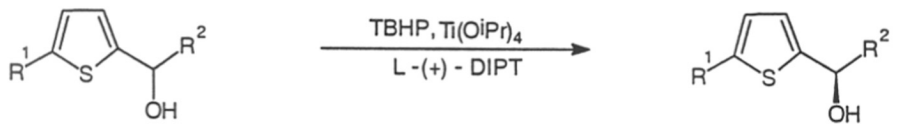


R^1 = H R^2 = Me 95% *ee*

R^1 = H R^2 = Ph 99% *ee*

scheme 18

The same group[21] later extended the methodology for the synthesis of 2-thienyl carbinols (scheme 19).



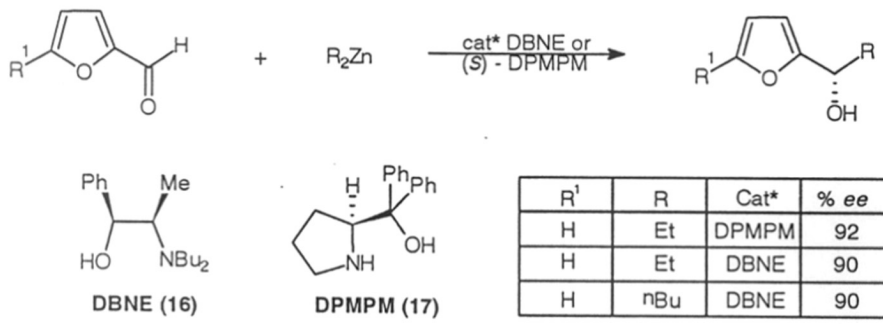
R^1 = H R^2 = ^{n}Bu 95% *ee*

R^1 = H R^2 = ^{n}Am 95% *ee*

scheme 19

Soai *et. al.*[22] demonstrated that optically active 2- furyl carbinols of good *ee*'s (upto 94% *ee*) can be obtained by the enantioselective addition of dialkylzincs to

furylaldehydes in the presence of N, N- dibutylnorephedrine and (*S*)-(-)-diphenyl (1-methyl pyrrolidin-2-yl) methanol as chiral catalysts (scheme 20).

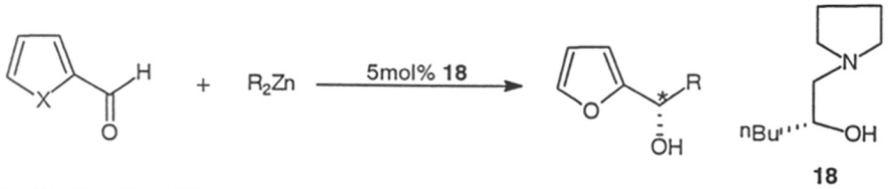


DBNE (16) **DPMPM (17)**

R^1	R	Cat*	% *ee*
H	Et	DPMPM	92
H	Et	DBNE	90
H	nBu	DBNE	90

scheme 20

Hayashi *et. al.*[23] synthesized optically active 2-furyl and 2-thienyl alcohols by the enantioselective addition of dialkylzincs to furyl and thienyl aldehydes in presence of chiral amino alcohol (**18**) in very high *ee*'s in upto 95% (scheme 21).

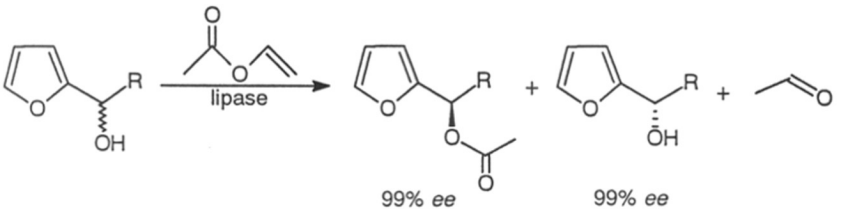


18

X = O, R = Et 92% *ee*
X = S, R = Et 95% *ee*

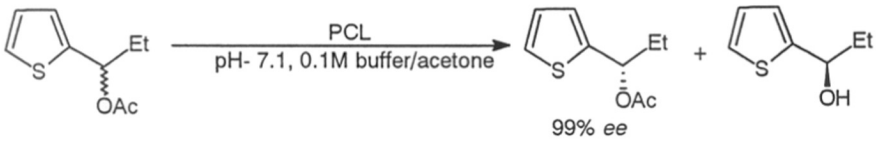
scheme 21

Recently the thienyl and furyl carbinols were prepared by enzymatic hydrolysis of the corresponding acetates in very high enantioselectivities. Kaminska *et. al.*[24] shown that 1-(2- furyl)ethanol was resolved by irreversible trans-esterification with vinyl acetate using lipozome IM or Porcine Pancreas Lipase in an organic solvent (scheme 22).



scheme 22

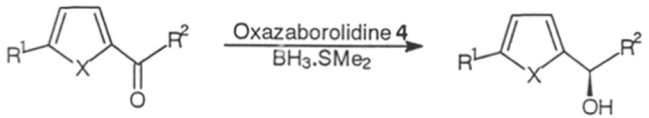
Kang *et. al.*[25] resolved (±)-1- (2-thienyl) propylacetate by PCL (Pseudomonas Cepacia Lipase) catalyzed hydrolysis to afford (S)-(-)-1-(2-thienyl) propylacetate in >99% *ee*. (scheme 23).



scheme 23

Present Work:

As evident from the above discussion, thienyl and furyl carbinols were prepared either by enantioselective alkylation or by resolution. The kinetic resolution which is widely utilized for the preparation of these compounds, suffers with the inherent disadvantage that the maximum yield can be 50%. The enantioselective alkylation can be limited to only a few dialkylzinc derivatives. There is no systematic study on the reduction of the 2-furyl and 2-thienyl ketones. There are only scattered examples of the reduction of these compounds. Since we had established[26] an optimized protocol for enantioselective reduction of ketones, we applied the same for the reduction of 2-acyl and thienyl ketones (scheme 24).



X = O, S

scheme 24

We studied the reduction of six representative furyl and thienyl ketones, an array which is easily available through standard transformations from furan and thiophene. The reduction of these ketones was studied with $BH_3.Me_2S$ in the presence of *in* situ generated oxazaborolidine **4**. The reduction proceeded smoothly at 45°C (the temperature optimized for normal ketone reduction) with 1eq of $BH_3.SMe_2$ and 10 mol% of catalyst to give the product alcohols in good *ee* and yields. Significantly, the reduction proceeded with 1 eq of $BH_3.SMe_2$ in spite of the fact that hetero atom chelates to BH_3. Variation of the amount of catalyst from 10 mol % to 20 mol % did enhance the % *ee* in the case of thienyl carbinols, but has very little or no effect in the case of furyl carbinols. The change in the amount of $BH_3.Me_2S$ used for the reduction from 1 eq to 2 eq has no effect on the enantiomeric excess of the product. These results are summarized in table 3.

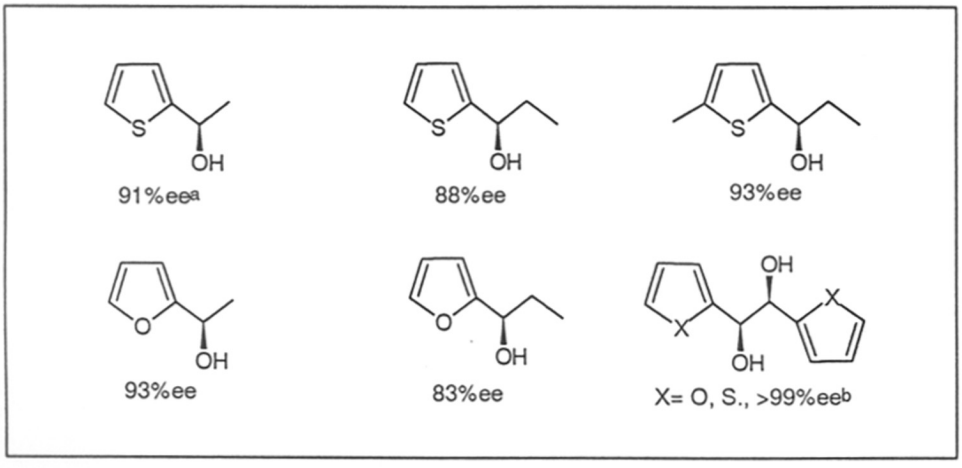
Table 3 : Effect of catalyst and $BH_3.SMe_2$ on the enantioselectivity in the reduction of 2-thienyl and 2-furyl ketones.

Entry	Compound	Catalyst, mol%	BMS (eq)	%Yield[a]	%*ee*[b]
1	2-acetylthiophene	5	0.6	c	c
2	2-acetylthiophene	5	1	60	53
3	2-acetylthiophene	10	1	70	60
4	2-acetylthiophene	10	2	75	82
5	2-acetylthiophene	20	2	75	91[d]
6	2-acetylfuran	20	1	50	90
7	2-acetylfuran	20	2	50	93

[a]Isolated yields. [b]Estimated by comparision with the reported maximum specific rotations. [c]Incomplete reduction. [d]Estimated by capillary GC analysis of MTPA-ester.

Moderate to high enantioselectivities were realized in these reductions, with consistant *R* configuration of the products (table 4).

Table 4 : Enantioselective reduction of 2-furyl and 2-thienyl ketones.



[a]Estimated by capillary GC of MTPA-ester. [b] Diastereomeric ratio (75 : 25 for X = O, 92 : 8 for X= S) and *% ee* estimated by NMR using shift reagent, see ref.13.

Conclusions

1. An optimized procedure for *in situ* generation of oxazaborolidines in the enantioselective reduction of ketones was developed.
2. Aryl alkyl ketones were reduced in high enantioselectivities by this *in situ* procedure.
3. 2-Furyl and thienyl ketones were reduced to corresponding alcohols in moderate to high % *ee*'s which are hitherto obtained by other routes.

Experimental

General:

Borane-Dimethyl sulfide complex ($BH_3.Me_2S$) was purchased from Aldrich Chemical Company, USA, diluted to 2M solution in toluene and estimated by gassimetry. Toluene was distilled over P_2O_5, degassed and stored over molecular seives. THF was freshly distilled over sodium benzophenone ketyl . (*S*)-(-)-diphenyl valinol[1], (*R*)-(+)-diphenyl phenylglycinol[27] and (*S*)-(-)-diphenyl prolinol[28], were prepared according to the literature procedures.

Preparation of oxazaborolidine catalysts and reduction of prochiral ketones

The following procedure for the preparation of (**4**) and reduction of acetophenone is representative.

Procedure A: To a solution of $BH_3.Me_2S$ (3.25 ml of 2M in toluene 6.5 mM), a solution of (*S*)-(-)-diphenyl prolinol (0.126g, 0.5 mM) in THF (2 ml) was added and the reaction mixture was stirred at 45°C (bath temperature 50°C) for 12-16h under a static atmosphere of argon. To the resulting turbid solution of **4**, a solution of acetophenone (1.2g, 10mM) dissolved in anhydrous THF (5 ml) was added dropwise (using a syringe pump) over a period of 35-40 min. After the addition was over, the reaction mixture was continued to stir at the same temperature for 15 min. It was then cooled to room temperature and cautiously quenched with excess MeOH (4 ml). Solvent was evaporated and the residue was dissolved in ether. The ether phase was washed with 2N HCl followed by brine and dried over anhydrous Na_2SO_4. The residue obtained after the removal of ether was purified by "flash chromatography" followed by Kugelrohr distillation, to obtain pure alcohol.

Procedure B: To a toluene solution of (*S*)-(-)-diphenyl prolinol (**3**) (1mM, 1 ml of 1M solution) was added BH_3SMe_2 (2mM, 1 ml of 2M solution in toluene) at room temperature. Immediate formation of a white solid was observed which was heated to 80°C and kept at the temperature for 1h. The reaction mixture first turned to clear solution and then to a white suspension during the course.

To the resulting suspension of the catalyst was added $BH_3.SMe_2$ (6mM, 3 ml of 2M in toluene), the solution heated to 45°C (bath temperature 50°C) and treated with

acetophenone (10mM, 1.2g. in 6 ml THF) over about 35-40 min through a syringe pump. The remaining procedure is the same as described for procedure A.

Reduction of thienyl ketones: To the catalyst prepared by Procedure **A** was added 2-acyl thiophene (6mM) through a syringe pump over 35-40 min. The progress of the reaction was monitored by TLC. After 10 min. the reaction mixture was cooled to room temperature and quenched cautiously with excess MeOH (4 ml). The solvents were evaporated under reduced pressure. The residue was dissolved in ether and extracted with 2N HCl. The ethereal layer was washed with water, brine and dried over anhydrous Na_2SO_4. The residue after evaporation of ether, was purified by "flash chromatography" followed by Kugelrohr distillation to obtain the pure 2-thienyl carbinol.

Reduction of 2-furyl ketones: The procedure for the reduction of furyl ketones is almost same as above except after quenching with MeOH and evaporation of solvents, the residue was directly purified by chromatography, followed by kugelrohr distillation. The modified work-up was necessary since 2-furyl carbinols have significant solubility in water and deteriorates on treatment with acid.

(*R*)-(+)-1-Phenyl ethanol

Yield	1.02g, (84%)
b.p.	120°-125° (bath temp)/20mm Hg
^{1}HNMR ($CDCl_3$)	δ 1.5 (d, J=7.2Hz, 3H), 2.25 (bs, 1H), 4.85 (q, J=7.2Hz, 1H), 7.2-7.4 (m, 5H).
$[\alpha]_D$	+ 44.12 (c 3 MeOH)
	+41.85 (neat)
	lit.[6] +43.6 (neat)
ee	97%

(*R*)-(-)-1,2,3, 4-Tetrahydro-1-naphthol

Yield	1.36g, (85%)
m.p.	39-40°C
^{1}HNMR ($CDCl_3$)	δ 1.7- 2.1 (m, 5H), 2.65- 2.95 (m, 2H), 4.25- 4.35 (m, 2H), 7.1-7.5 (m, 4H).
$[\alpha]_D$	- 23.14 (c 1.3 MeOH)
	lit.[6] -24.6 (c 1.29 MeOH)
ee	94%

(*R*)-(+)-1-Phenyl-1-proanol

Yield	1.16g, (85%)
b.p.	130°(bath temp)/20mm Hg
^{1}HNMR ($CDCl_3$)	δ 1.0 (d, J= 6.9Hz, 3H), 1.85 (m, 2H), 2.9 (bs, 1H), 4.6 (t, J= 6.9Hz, 3H), 7.2-7.5 (m, 5H).
$[\alpha]_D$	+ 43.03 (c 5.15 $CHCl_3$)
	lit.[29] +45.45 (c 5.15 $CHCl_3$)
ee	96%

(*S*)-(+)-2-Chloro-1-phenyl ethanol

Yield	1.25g, (80%)
b.p.	150° (bath temp)/20mm Hg
^{1}HNMR ($CDCl_3$)	δ 2.85 (bs, 1H), 3.62 (d, J=7.5Hz, 2H), 4.82 (t, J= 7.5Hz,1H) 7.3-7.4 (m, 5H).
$[\alpha]_D$	+ 48.93 (c 2.8 cyclohexane)
	lit.[30] +53.3 (c 2 cyclohexane)
ee	92%

(*S*,*S*)-(-)-1,2-Diphenylethane-1,2-diol

Yield	0.91g, (85%) (88:12 of *dl:meso*)
m.p.	148- 150°C
^{1}HNMR Pure *dl* compound($CDCl_3$)	δ 2.90 (bs, 1H), 4.60 (S, 2H), 7.05 (m, 4H), 7.15 (m, 6H).
$[\alpha]_D$	-94.1 (c 1 EtOH)
	Lit.[31] - 94.5 (c 0.95 EtOH)
ee	>99%

(*R*)-(+) 1-(2-Thienyl) ethanol

Yield	0.94g, (75%)
b.p.	130° (bath temp)/20mm Hg
^{1}HNMR ($CDCl_3$)	δ 1.6 (d, J=6.37Hz, 3H), 2.7 (bs, 1H), 5.1 (q, J=6.37Hz, 1H), 6.95-7.05 (m, 2H), 7.2-7.3 (m, 1H).
$[\alpha]_D$	+ 21.9 (neat)
ee	91% as estimated by GC analysis of the corresponding MTPA ester

(*R*)-(+) 1-(2-Thienyl) propanol

Yield	1.11g, (80%)
b.p.	150°C (bath temp) /20mm Hg
^{1}HNMR ($CDCl_3$)	δ 0.95 (t J=6.4Hz, 3H), 1.9 (m, 2H), 2.5 (bs 1H), 4.85 (t J=6.4Hz, 1H), 6.95- 7.05 (m, 2H), 7.2- 7.3 (m, 1H).
$[\alpha]_D$	+ 25.45 (c 2.01 $CHCl_3$)
	lit.[23] +25.9 (c 2.02 $CHCl_3$) for 95% *ee*.
ee	93%

(*R*)-(+)-1- (5-Methyl- 2-thienyl) propanol

Yield	1.22g, (80%)
b.p.	150°C (bath temp)/10mm Hg
^{1}HNMR ($CDCl_3$)	0.95 (t, J=6.5Hz, 3H), 1.9 (m, 2H), 2.4 (s, 3H), 2.6 (bs, 1H), 4.7 (t, J=6.5Hz, 1H), 6.5- 6.6 (m, 1H), 6.7- 6.8 (m, 1H).
$[\alpha]_D$	+25.68 (c 1.24 $CHCl_3$)
	lit.[25] -29.1 (c 1.2 $CHCl_3$) for *S* enantiomer
ee	88%

(*R*)-(+)-1-(2-Furyl) ethanol

Yield	0.545g, (50%)
b.p.	130°C (bath temp)/10mm Hg
^{1}HNMR	δ 1.45 (d, J=6.5Hz, 3H), 3.5 (bs, 1H), 4.55 (m, 1H), 6.15- 6.35 (m,2H), 7.3 (m, 1H).
$[\alpha]_D$	+22.82 (neat)
	lit.[24] -24.4 (neat) for the *S* isomer
ee	93%

(*R*)-(+)- 1-(2-Furyl) propanol

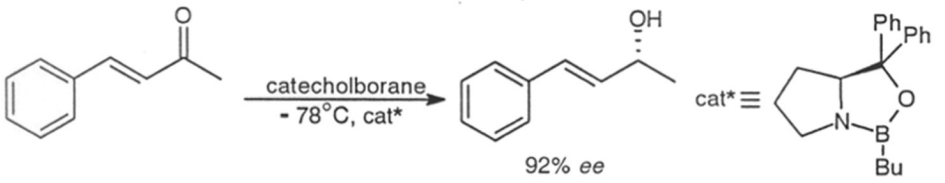
Yield	0.615g, (62%)
b.p.	150°C (bath temp)/10mm Hg
^{1}H-NMR ($CDCl_3$)	0.95 (t, J= 6.4Hz; 3H), (1.85m, 2H), 2.3 (bs, 1H), 4.6 (t, J= 6.4Hz; 1H), 6.15-6.25 (m, 1H), 6.3-6.4 (m, 1H), 7.35-7.45 (m, 1H).
$[\alpha]_D$	+16.04 (c 2.04 $CHCl_3$)
	lit.[32] -17.9 (c 1.75 $CHCl_3$) for 93% *ee* for the *S* isomer
ee	84%

SECTION - 3b

Stereoselective Reduction of 1, 2- Diketones

With the advent of oxazaborolidine catalysts, the reduction of simple prochiral ketones has been perfected. The reduction of functionalized ketones however has received very little attention.

Corey *et. al.*[33] have shown that the reduction of α,β-unsaturated ketones with catecholborane catalyzed by oxazaborolidine yields allylic alcohols in very high enantiomeric excesses (scheme 25).

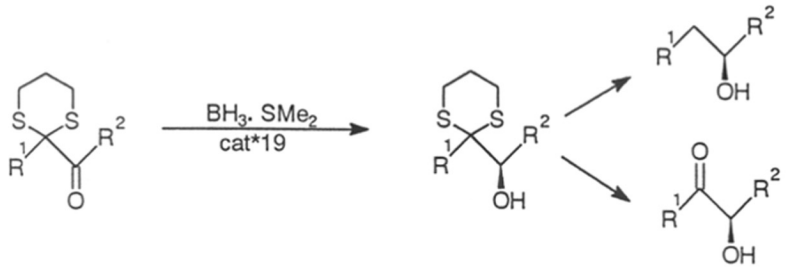


19

scheme 25

The methodology was elegantly applied for the synthesis of α,α-hydroxy acids, prostaglandin intermediates and in the synthesis of Forskolin[34], Ginkolide B, etc.

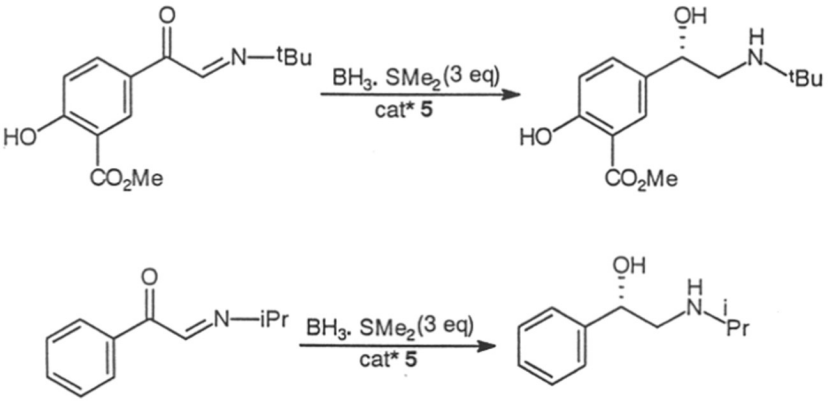
Deninno *et. al.*[35] has shown that the oxazaborolidine catalyzed enantioselective reduction of acyl dithianes provided the corresponding alcohols in very high enantioselectivities. The dithiane group can be hydrolyzed back to ketone or removed reductively (scheme 26).



scheme 26

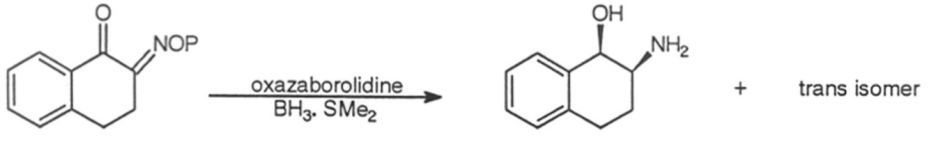
94-96% ee

Hong *et. al.*[36] have shown that oxazaborolidine catalyzed reduction of α-ketoximes yielded the corresponding amino alcohols in upto 93% *ee* (scheme 27).



scheme 27

Merck chemists[37] found that oxazaborolidine catalyzed enantioselective reduction of ketoximes provided amino alcohols in very high diastereo and enantioselectivities. The ketoxime **20** derived from α-tetralone yielded the *cis*-amino alcohol in 95% yield and in 96% *ee* whereas the *trans*- isomer showed 90% *ee* (scheme 28).



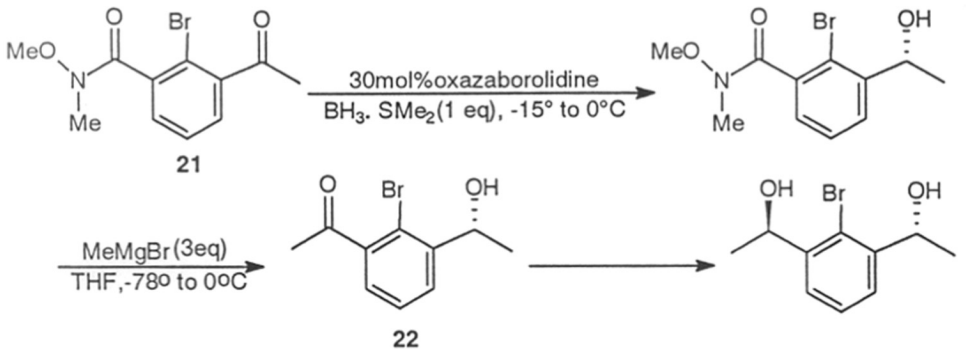
20

96% *ee*

P = TBS *cis : trans* 6:1
P = TBDPS *cis : trans* 10:1

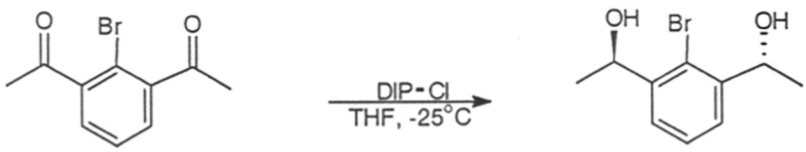
scheme 28

Deziel *et. al.*[38] reduced the ketone **21** with $BH_3.Me_2S$ catalyzed by the oxazaborolidine in 84% *ee*, which was then converted to the ketone **22** and reduced again to form the C_2- symmetric (*R,R*) alcohol in 53% yield and >98% *ee* (scheme 29).



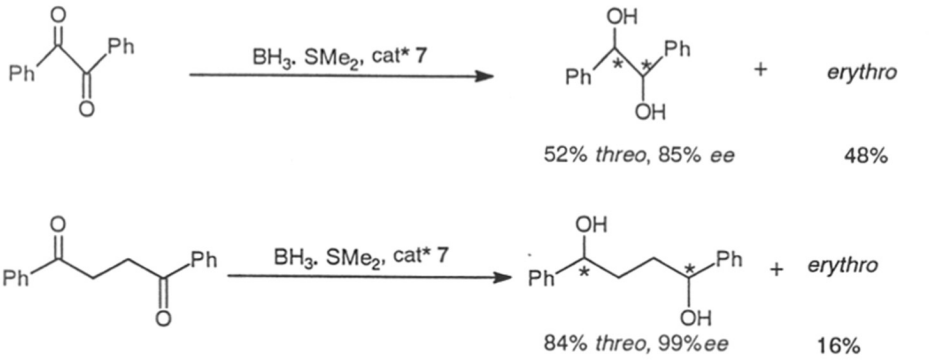
scheme 29

Recently, the same group found that irreproducible yields and enantioselectivities were obtained with CBS reagent[39]. The reduction of the diketone **23** with (+) or (-) DIP-Cl gave the corresponding (*R,R*) or (*S,S*)- diol in very high *ee*'s (99%) and good yields (82%) (scheme 30).



scheme 30

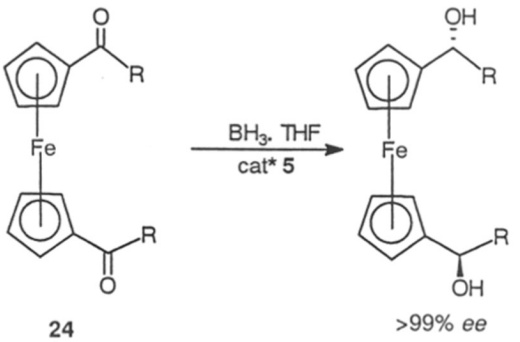
Quallich *et. al.*[40] investigated the oxazaborolidine **7** catalyzed $BH_3.Me_2S$ reduction of 1,2-diketones. It was found that the reduction of benzil using 10 mol % of catalyst **7** afforded the corresponding diol in 48:52 ratio of *erythro:threo* with 85% *ee*, while the reduction of 1,4-diketone afforded the alcohol in 16:84 ratio *erythro:threo* in 99% *ee* with employment of 100 mol % of the catalyst (scheme 31).



scheme 31

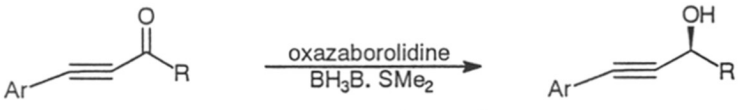
Chong *et. al.*[41] found that the reduction of 1,4-diphenyl-1,4-butanedione with DIP-Cl in THF gave the corresponding *threo* diol in >98% *ee* with only a trace (<2%) of *erythro (meso)* isomer.

Very recently Schwink and Knochel have shown[42] that oxazaborolidine catalyzed $BH_3.SMe_2$ reduction of 1,1-ferrocenyl diketones (**24**) provided C_2-symmetrical ferrocenyl diols >98% *ee* accompanied by small amounts of *erythro* (*meso*) diols (scheme 32).



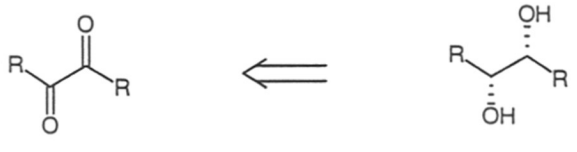
scheme 32

Parker and Ledeborer reported[43] that the reduction of acetylinic ketones with $BH_3.SMe_2$ in the presence of oxazaborolidine proceeds smoothly to yield propargyl alcohols in high enantiomeric excesses (scheme 33).



scheme 33

In recent years there has been an emphasis placed on C_2-symmetric auxiliaries during the design of enantioselective catalysts[44]. Among these, hydrobenzoin[45] and other derivatives received particular attention owing to their diverse applications. Although several enantioselective routes to the parent compound itself are available, including the most useful asymmetric dihydroxylation reaction (ADH), there is no general procedure for the synthesis of 1,2-diarylethanediols. We envisaged that the asymmetric reduction of benzils should provide a convenient route to these diols.



Eventhough the reduction of simple prochiral ketones has been one of the extensively studied reaction during the past decade, the reduction of functionalized ketones and the problem of diastereoselectivity have been scantly addressed. Our interest in the synthesis of C_2- symmetric diols prompted us to examine these aspects.

Results and Discussion

At the outset, we studied the reduction of benzil as a representative dione for the following reasons:

1. It's cheaply available.
2. The reduction gives a valuable chiral auxiliary *viz.* 1,2-diphenylethanediol which has wide applicability in asymmetric synthesis.

Simple diastereoselective reduction of benzil with various hydride agents *viz.* $NaBH_4$, $LiAlH_4$ is known to provide predominant *erythro* diastereomer[46]. We attempted to modify these reagents as well as the reaction conditions to alter the diastereoselectivity. The use of reagents like LiAlH $(O^tBu)_3$ or $LiAl(O^tBu)_2H_2$ did not change the stereochemical outcome of the reaction.

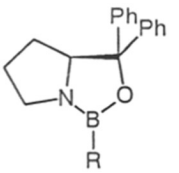
The reduction of benzil with $BH_3.Me_2S$ did not proceed even after 72h at room temperature. We were surprised to discover that oxazaborolidine catalyzed reduction of benzil with borane-dimethylsulfide proceeded very smoothly within 1h at room temperature and provided predominantly *threo* isomer (table 4). Equally intriguing was the fact that higher diastereoselectivity was observed when the reduction temperature was 45°- 50°C.

Table 4: Reduction of benzil to hydrobenzoin

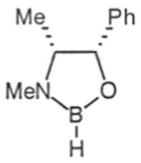
Reagent	Solvent	Catalyst[a]	Temp, °C	Time, min	*threo: erythro*[b]
$NaBH_4$	MeOH	-	25	120	0:100
LAH	THF	-	0	30	4:96
$LiAl(O^tBu)_4$	THF	-	0	120	20:80
BMS	THF	-	25		-
BMS	THF	**5**	25	120	66:34
BMS	THF	**5**	45	15	87:13
BMS	THF	**4**	45	<5	88:12

[a]20mol% catalyst was employed. [b]Estimated by ^1H NMR

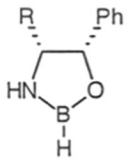
We undertook a systematic examination of the catalyst structure, the temperature and the reducing agent on the outcome of the diastereoselectivity in the reduction of benzil.



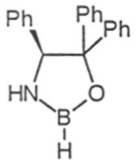
(4) R = H
(5) R = Me



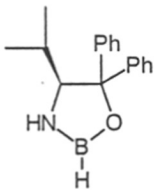
(6)



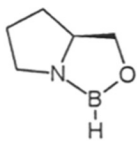
(7) R = Ph
(8) R = Me



(12)



(13)



25

Amongst the oxazaborolidines examined, oxazaborolidines derived from diphenyl prolinol gave good diastereoselectivity. Salient observations as a function of catalyst structure and the reaction conditions were as follows:

(i) An *in situ* prepared catalyst is as efficient as the conventionally pre-formed one. (ii) Optimum reaction temperature, the most crucial parameter for the reduction is in the range of 45°- 50°C. (iii) At the specified temperature, the solvent and the substituent on the boron atom do not significantly influence either the rate or the diastereoselectivity of the reduction (table 5).

Significantly the oxazaborolidines derived from diphenyl phenylglycinol and diphenyl valinol (**12** & **13**) which proved to be successful in the reduction of simple prochiral ketones, failed to provide good diastereoselectivity. No appreciable reduction was observed in the reduction of benzil with catecholborane at 45°C even after 24h. The reduction at 110°C with **4** as catalyst decreased the ratio to 79:21. The reduction with mono *tert* butoxy borane yielded almost exclusive *meso* isomer. These observations are summarized in table 6. By all considerations, oxazaborolidine **4** proved to be the most efficient catalyst.

Table 5: Reduction of Benzil to Hydrobenzoin with $BH_3.SMe_2$ Catalyzed by Various Oxazaborolidines.[a,b]

Catalyst	mol%	Temp, °C	Time, min	*threo:erythro*[c]
6	20	45	15	26:74
6	100	45	<5	26:74
7	20	25	180	27:73
8	20	25	60	42:58
13	20	45	180	33:67
12	20	45	180	36:64
25	20	45	180	10:90
5	20	25	120	66:34
5	20	45	15	87:13
4	20	45	<5	88:12
4	10	45	<5	88:12

[a]All oxazaborolidines except **5** were prepared according to procedure described in Chapter 3a, ref. 26. [b]All the reductions were carried in THF-toluene (1:1) as solvent. [c]Estimated by ^{1}H-NMR

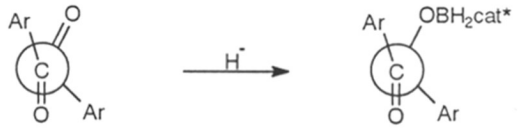
Table 6: Stereoselective Reduction of Benzil catalyzed by **4**[a]

S.No.	Temperature,°C	Reducing Agent	Time/min.	*threo/erythro*
1	45	$BH_3.SMe_2$	<5	88:12
2	45	$BH_2(O^tBu)$	180	5:95
3	45	Catecholborane	b	b
4	45	$^iPrOBH_2$	180	5:95

[a]All the reductions were performed in ~ toluene:THF (1:1) as solvent. [b]No appreciable reduction even after 24 hrs.

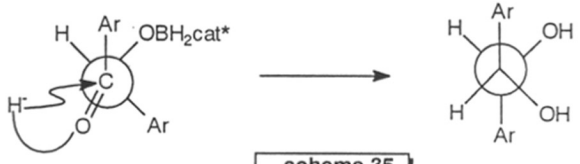
Mechanism:

As for the mechanism, we believe that the reduction of benzil involves fast and consecutive attack on both the keto groups placed in antiperiplanar conformation (scheme 34).



scheme 34

The chiral reagent first attacks almost exclusively the *Re* face of the carbonyl groups to produce the *S* configuration at the stereogenic centre. This is then followed by diastereoselective reduction of second carbonyl group leading to the formation of *threo* isomer (scheme 35).



scheme 35

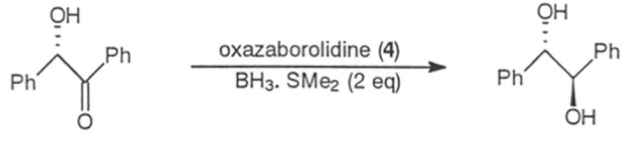
The realization of very high enantioselectivity was not surprising considering the fact that all the catalysts selected in the present study are known to provide >90% *ee* for the reduction of acetophenone. We were however puzzled by the origin of the *erythro* isomer and its dependance on the catalyst structure.

The possible origin for the formation of *erythro* isomer may be

(i) The intermolecular reduction of the second carbonyl group is not stereospecific or

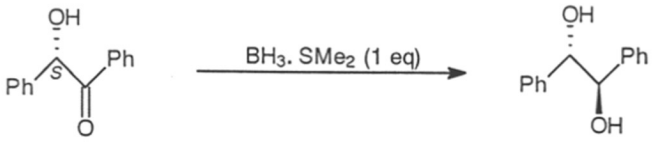
(ii) The reduction takes place *via* an intramolecular process involving the initially formed OBH_2 group.

To investigate this question convincingly, we undertook the reduction of chiral benzoin. The reduction of (*S*)-(-)-benzoin with 2 equivalents of BMS in the presence of 10 mol% oxazaborolidine (**4**) produced exclusively *erythro* hydrobenzoin (scheme 36).



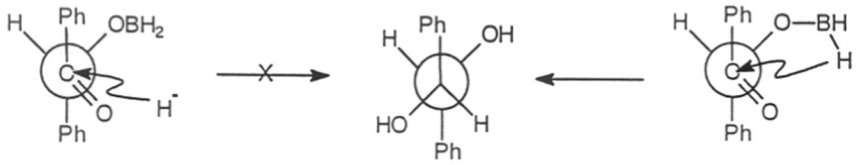
scheme 36

Secondly, reduction of (*S*)-(-)-benzoin with 1 equivalent of BMS without the presence of oxazaborolidine (**4**) again gave exclusively the *erythro* isomer (scheme 37).



scheme 37

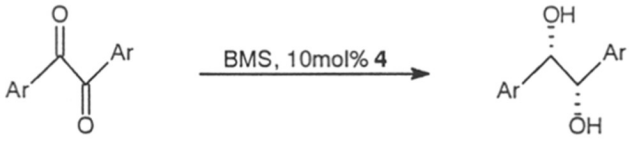
We thus unequivocally could ascertain that the formation of *erythro* isomer is indeed due to the intramolecular hydride transfer. Thus it can be rationalized that the faster the rate of the catalyzed reduction the better will be the diastereoselectivity (scheme 38).



scheme 38

Finally we applied the optimized protocol to the reduction of six representative symmetrical 1, 2-diaryl ketones, an array of which is easily accessible. As evident from the table, very good yields and diastereoselectivity were realized for all the compounds. The diastereomeric purity of the products could be easily upgraded by crystallization from MeOH. More gratifying was the fact that the desired stereoisomers (even before crystallization) were of almost 100% *ee*. Additionally, in all the cases examined, (*S*)- **4** consistently provided (*S,S*)-(-)- enantiomers.

Table 7: Stereoselective Reduction of Diaryl-1,2-Diones



Ar	*threo:erythro*[a]	config[b]	*% ee*[c]
phenyl	88:12	*S, S*	>99
4- anisyl	89:11	*S, S*	>99
4- tolyl	85:15	*S, S*	>99
3- tolyl	84:16	*S, S*	>99
2- furyl	89:11	*S, S*	>99
2- thienyl	92:8	*S, S*	>99

[a]By integration of the benzylic protons in ^{1}H NMR. [b]By analogy to the known 1,2-diphenylethanediol, ref.31. [c]By ^{1}H NMR (300mhz) of the diacetate with Eu(hfc)$_3$.

We also examined the methodology for the reduction of aliphatic diketones, only to obtain erythro diols exclusively.

Conclusions

1. The reduction of benzil with common reducing agents *viz.* H_2/Ni, $LiAlH_4$, $NaBH_4$ leads to predominantly *erythro* isomer whereas oxazaborolidine-catalyzed BH_3 reduction yields *threo* as the major isomer.
2. The product ratio of *erythro:threo* isomers depends on the catalyst structure and reduction temperature. Highest ratio of 88:12 was obtained using diphenylprolinol as the catalyst and carrying out the reduction at 45°C.
3. The enantioselectivity for the reduction of all 1,2-diarylketones was >99%.
4. Unlike 1,2-diarylketones, the aliphatic 1,2-diketones gave exclusively *erythro* isomer.

Experimental

General:

All the reactions were conducted under dry N_2 or Ar atmosphere. THF was freshly distilled over sodium benzophenone. Other anhydrous solvents were obtained following the standard procedure[47] and stored over 4A molecular seives. Neat BMS was purchased from Aldrich, diluted with toluene to 2M and estimated by gasimmetry. All the starting diones were synthesized following known procedure.[48,49]

Preparation of optically pure (S ,S)- (-)- 1, 2- diaryl 1, 2- diones

The following procedure for hydrobenzoin is representative:

To a stirred solution of (*S*)-(-)-diphenyl prolinol[28] (0.127g, 5mM) in anhydrous THF (5 ml) was added BMS (5 ml of 2M solution in toluene, 10 mM) and the mixture was stirred while the temperature was maintained at 45°C (bath temperature 50°C) for 16h to obtain a solution of catalyst **4**. It was treated (over a period of 30 min) with a solution of benzil (1.05g, 5mM) dissolved in a minimum volume of anhydrous THF (6 ml) at 45°C. After the addition, the reaction mixture was stirred for 5 min, cooled to room temperature, quenched cautiously with MeOH (1 ml), and stirred for an additional 15 min. Most of the solvent was evaporated and the residue directly chromatographed using EtOAc-Hexane (1:9) to obtain chemically pure hydrobenzoin (0.910g, 85%).

^{1}H NMR analysis of the above product revealed it to be a 88:12 mixture of *threo:erythro* isomers. Furthermore, examination of the corresponding diacetate at 300 MHz using shift reagent Eu(hfc)$_3$ (20 mol %) showed no (*R,R*)-enantiomer within detectable limits. Single crystallisation from MeOH provided pure (*S,S*)-(-)-hydrobenzoin .

(*S, S*)-(-)-1,2-Diphenylethane-1,2-diol

m.p.	148-150°C
$[\alpha]_D$	-94.1 (c 1, EtOH)
^{1}HNMR($CDCl_3$)	δ 2.90 (br, 2H)), 4.60 (s, 2H), 7.05 (m, 4H), 7.15 (m, 6H).

(*S*, *S*)-(-)-1, 2-(4-Anisyl) ethane-1,2-diol

Yield	1.096g, (80%)
m.p.	132-134°C
$[\alpha]_D$	-118.3 (c 1, EtOH)
IR (cm^{-1}) $CHCl_3$	3382, 1612, 1514.
^{1}HNMR($CDCl_3$)	δ 2.90 (s, 2H), 3.80 (s, 6H), 4.65 (s, 2H), 6.80 (m, 4H), 7.10 (m, 4H).
^{13}CNMR($CDCl_3$)	δ 55.4, 78.9, 113.9, 128.4, 132.4, 159.3.
Mass (m/z)	274(M^+), 137 (base)
Analalysis for	$C_{16}H_{18}O_4$
Calculated	C: 70.06 H, 6.61
Found	C: 69.76 H, 6.91

(*S*,*S*)-(-)-1, 2- Di(4-tolyl)ethane-1,2-diol

Yield	1.096g, (80%)
m.p.	105-107°C
$[\alpha]_D$	-102.5 (c 1, EtOH)
IR (cm^{-1}) $CHCl_3$	3383, 1654, 1614, 1560, 1025, 836.
^{1}HNMR($CDCl_3$)	δ 2.35 (s, 6H), 2.95 (br, 2H), 4.70 (s, 2H), 7.10-7.20 (m, 8H).
^{13}CNMR($CDCl_3$)	δ 21.3, 78.9, 127.1, 128.8, 137.3, 137.4
Mass (m/z)	242(M^+), 121(base)
Analalysis for	$C_{16}H_{18}O_2$
Calculated	C: 79.30 H, 7.49
Found	C: 79.05 H, 7.59

(*S*, *S*)-(-)-1, 2-Di(3-tolyl) ethane-1,2-diol

Yield	0.99g, (82%)
m.p.	54-56°C
$[\alpha]_D$	-77.81 (c 1, EtOH)
IR (cm^{-1}) $CHCl_3$	3400, 1657, 1500.
^{1}HNMR($CDCl_3$)	δ 2.30 (s, 6H), 3.25 (br, 2H), 4.65 (s, 2H), 6.90-7.40 (m, 8H).
^{13}CNMR($CDCl_3$)	δ 21.5, 79.0, 124.2, 128.1, 128.7, 137.8, 140.3.
Mass (m/z)	242(M^+), 122(base)
Analysis for	$C_{16}H_{18}O_2$
Calculated	C: 79.30 H, 7.49
Found	C: 78.05 H, 7.58

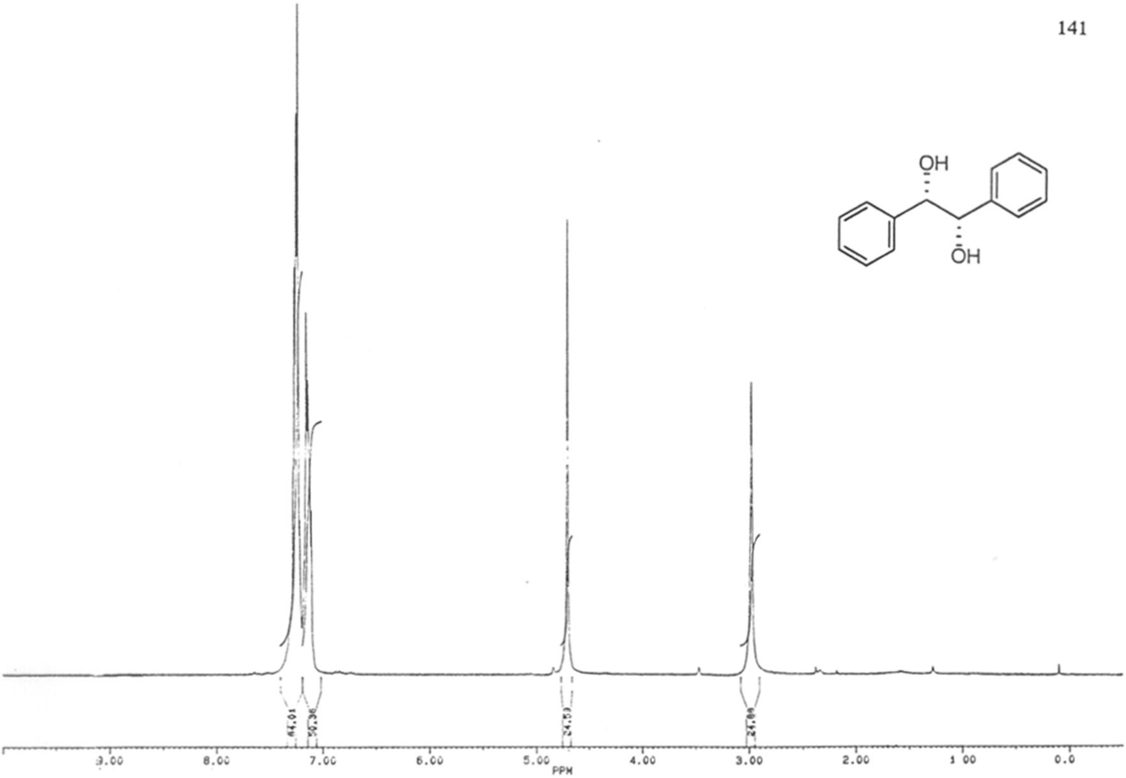
(*S*, *S*)-(-)-1,2-Di(2-furyl)ethane-1,2-diol

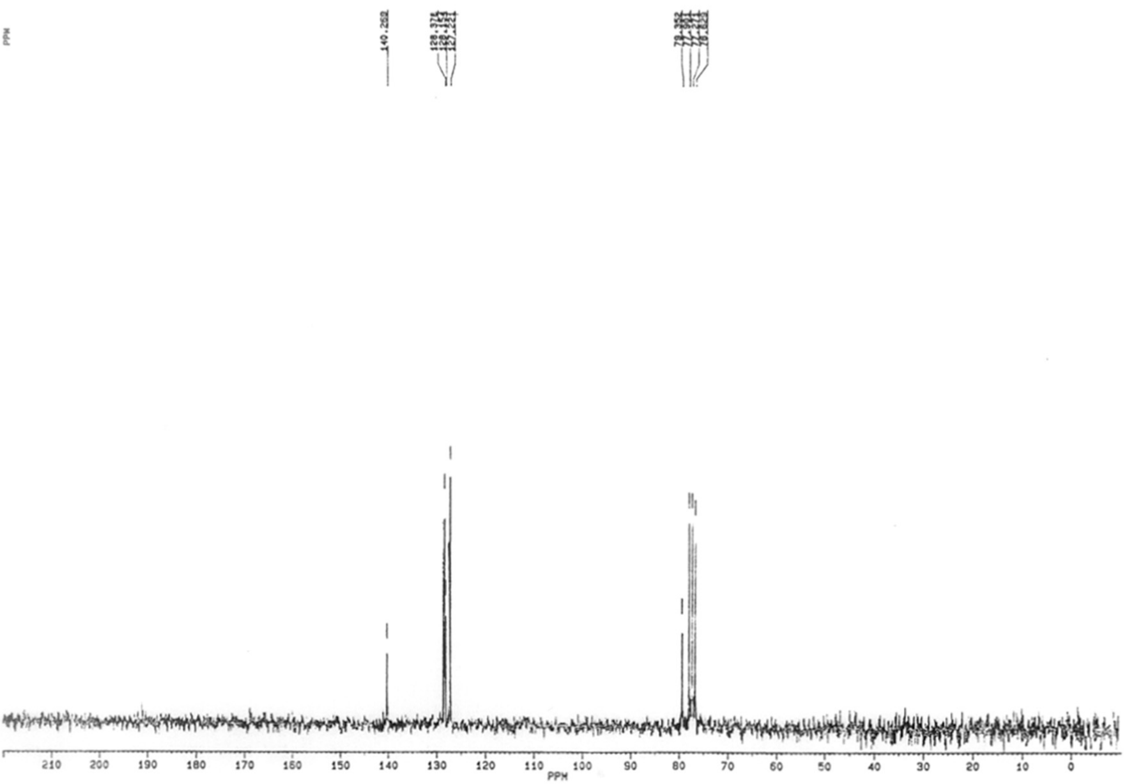
This compound is a viscous liquid and deteriorates rapidly at ambient temperatures. Therefore it was difficult to crystallize and upgrade the *de* or obtain accurate elemental analysis of this compound. However, the chemical and optical purity was established beyond doubt with the help of LC and spectral data.

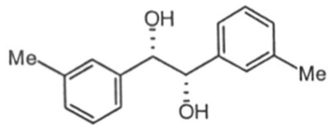
Yield	0.68g, (70%)
^{1}HNMR($CDCl_3$)	δ 4.00 (br, 2H), 4.95 (s, 2H), 6.15-6.35 (m, 4H), 7.30 (s, 2H).
^{13}CNMR($CDCl_3$)	δ 69.9, 108.8, 110.4, 142.4, 152.9, 169.4.
Mass (m/z)	176($M-H_2O$), 57(base)
$[\alpha]_D$	-31.0 (c1 EtOH)

(*S*,*S*)-(-)-1,2-Di(2-thienyl)-1,2-ethanediol

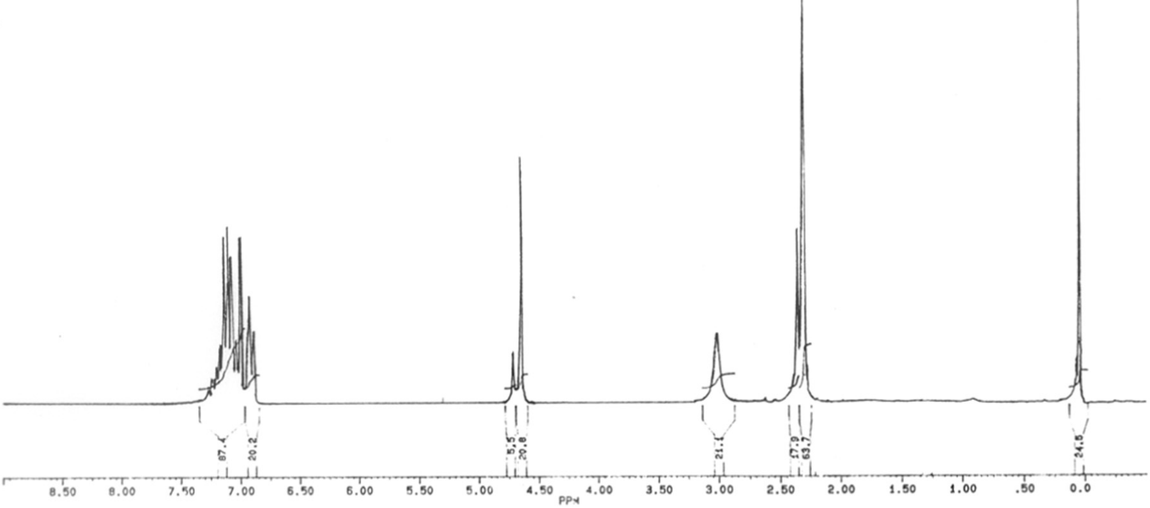
Yield	0.904g, (80%)
m.p.	99-100°C
$[\alpha]_D$	-49.3 (C1 EtOH)
IR (cm^{-1})$CHCl_3$	3487, 3383, 1490.
^{1}H-NMR	δ 5.05 (s, 2H), 6.80 (m, 2H), 6.95 (m, 2H), 7.30 (m, 2H)
^{13}C-NMR	δ 75.0, 125.5, 125.9, 126.8, 143.1
Mass (m/z)	226(M^+), 113(base)
Analysis for	$C_{10}H_{10}O_2S_2$
Calculated	C: 53.07 H: 4.45 S: 28.32
Found	C: 53.23 H: 4.49 S: 27.69

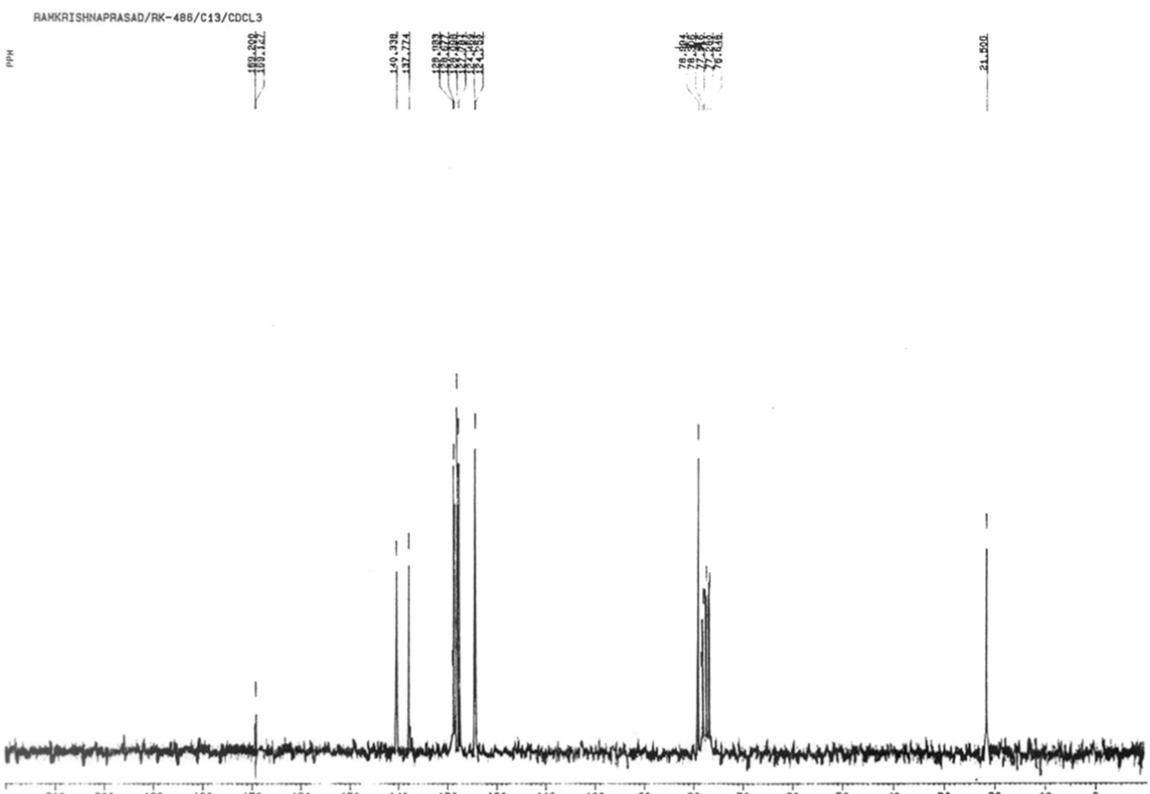

OH
OH
64.01
50.36
24.53
24.88
9.00
8.00
7.00
6.00
5.00
4.00
3.00
2.00
1.00
0.0
PPM

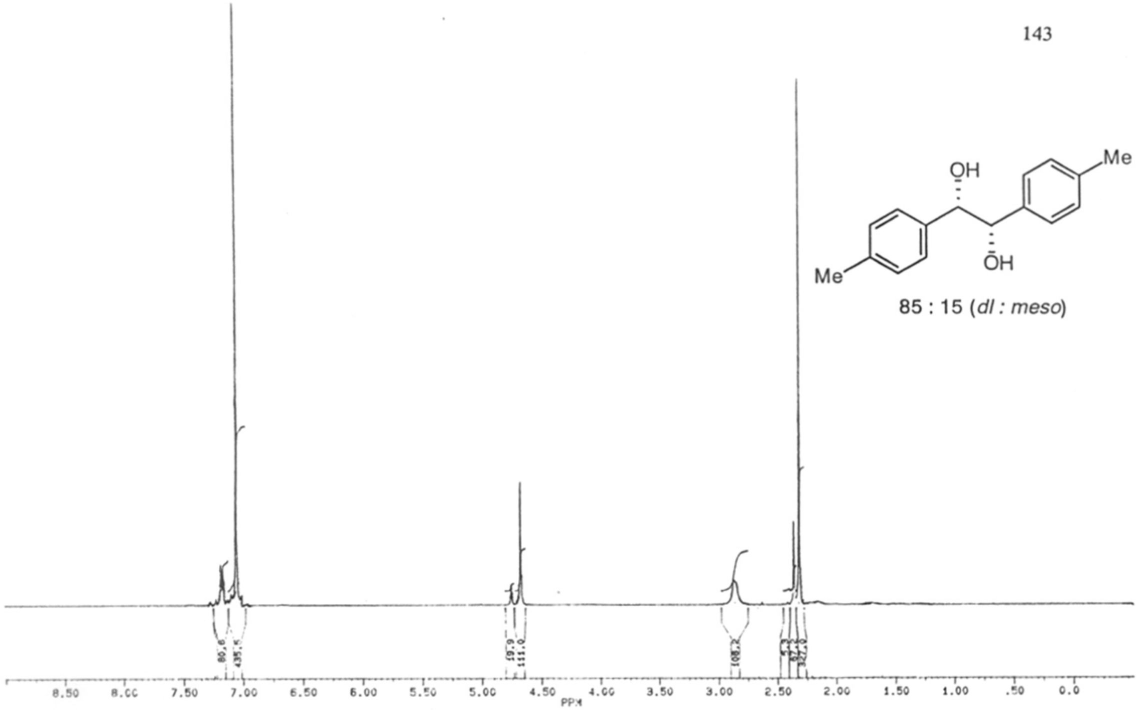

PPM
140.262
128.374
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
PPM


OH
Me
Me
OH

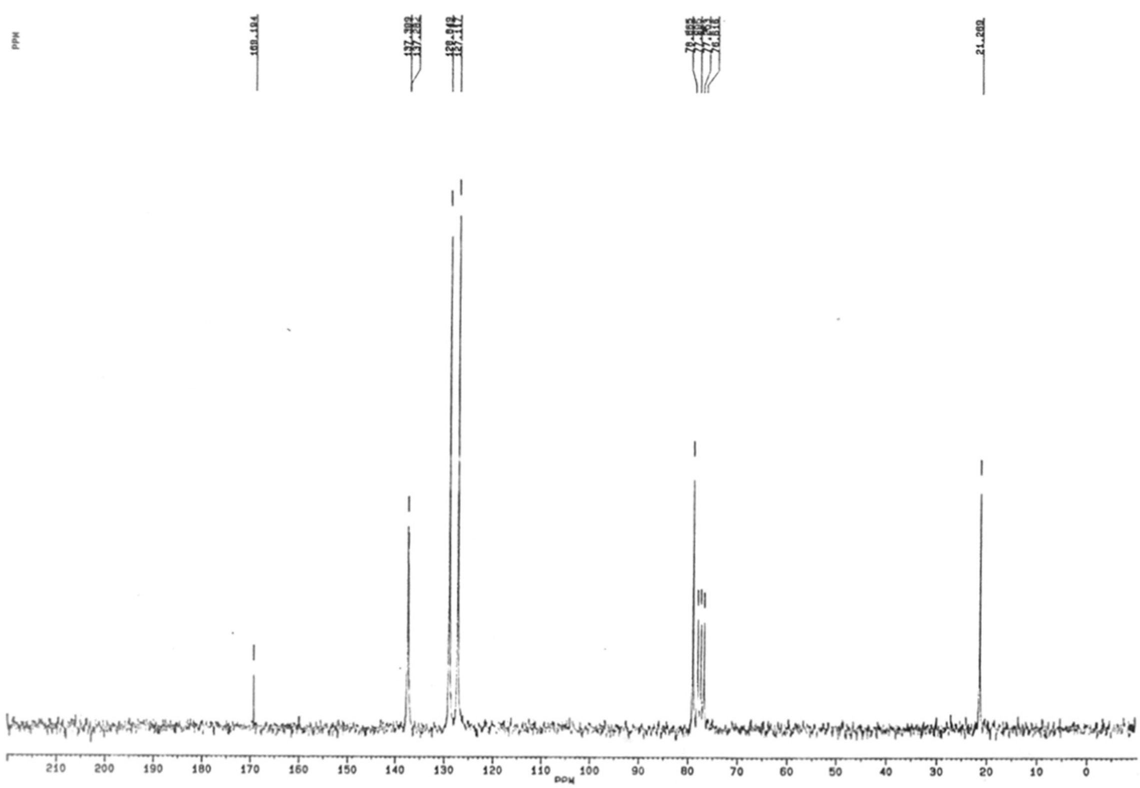
84 : 16 (*dl* : *meso*)

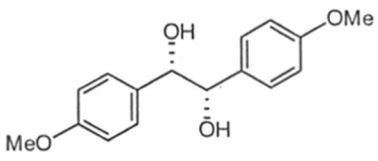

87.4
20.2
5.5
20.8
21.1
17.9
63.7
24.6
8.50
8.00
7.50
7.00
6.50
6.00
5.50
5.00
4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00
.50
0.0
PPM


RAMKRISHNAPRASAD/RK-486/C13/CDCL3
PPM
140.338
137.774
21.500
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
PPM


OH
Me
Me
OH
8.50
8.00
7.50
7.00
6.50
6.00
5.50
5.00
4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00
.50
0.0
PPM

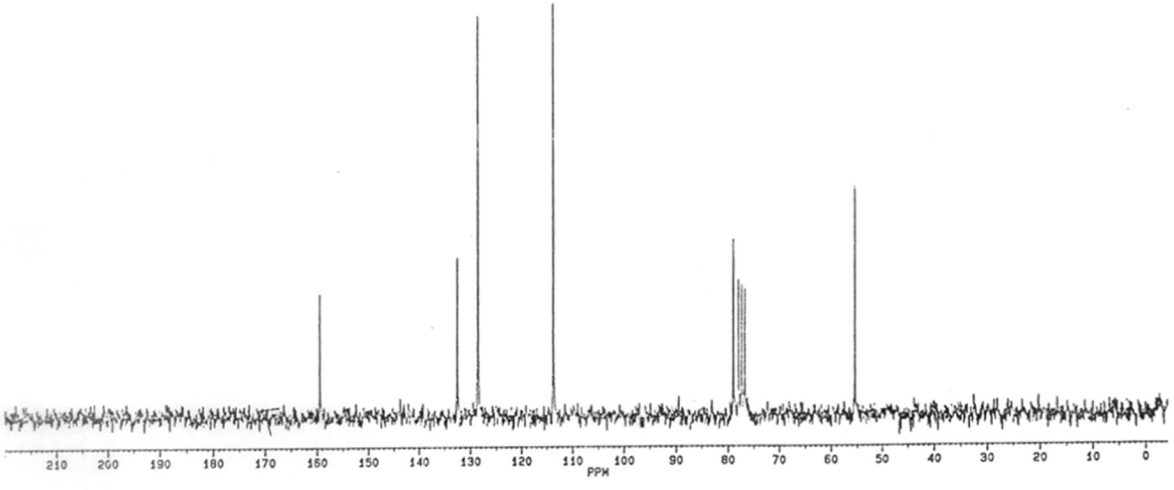
85 : 15 (*dl* : *meso*)

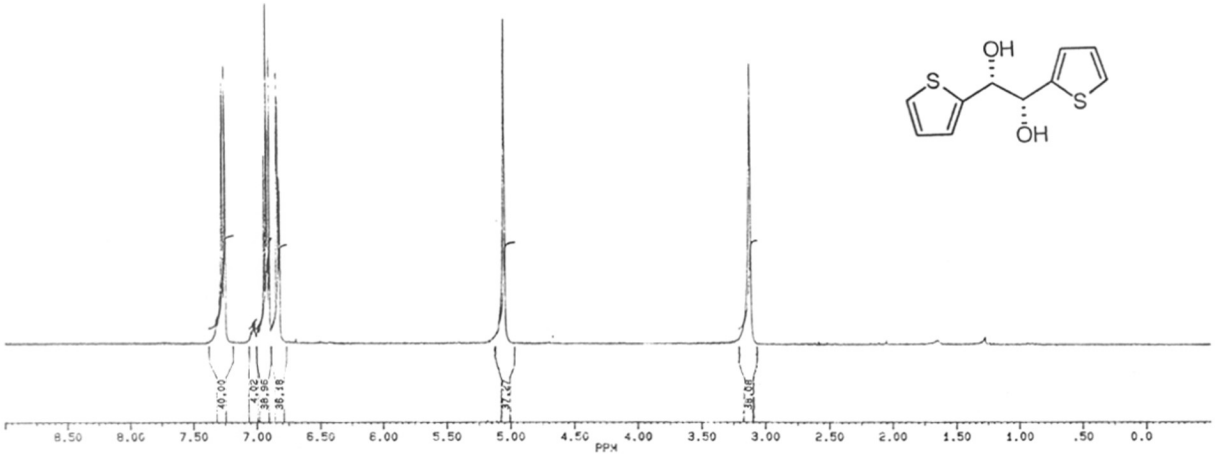

PPM
169.194
21.269
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
PPM

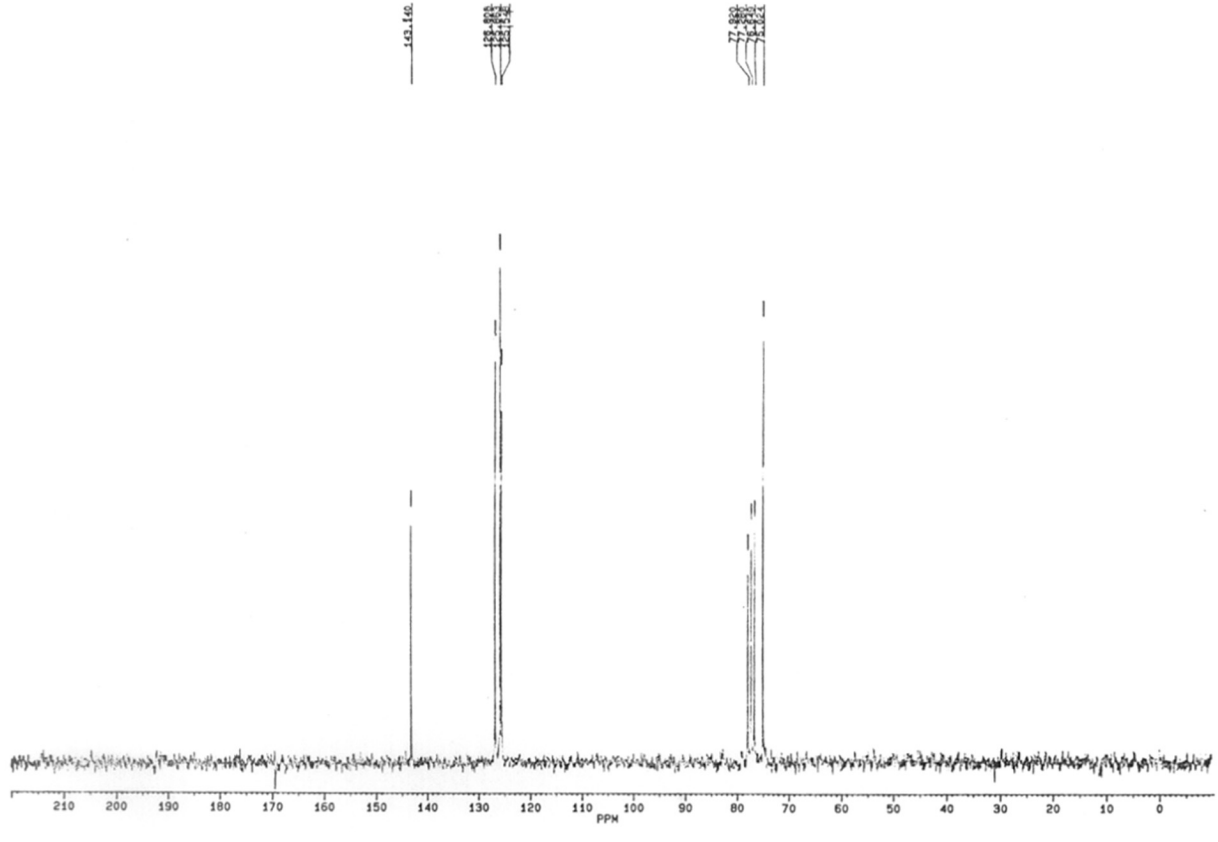

OH
OMe
MeO
OH

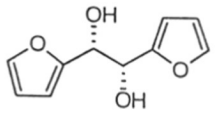
89 : 11 (*dl : meso*)

9.00
8.00
7.00
6.00
5.00
4.00
3.00
2.00
1.00
0.0
PPM


210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
PPM


OH
S
S
OH
40.00
4.02
38.96
36.18
37.07
18.08
8.50
8.00
7.50
7.00
6.50
6.00
5.50
5.00
4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00
.50
0.0
PPM

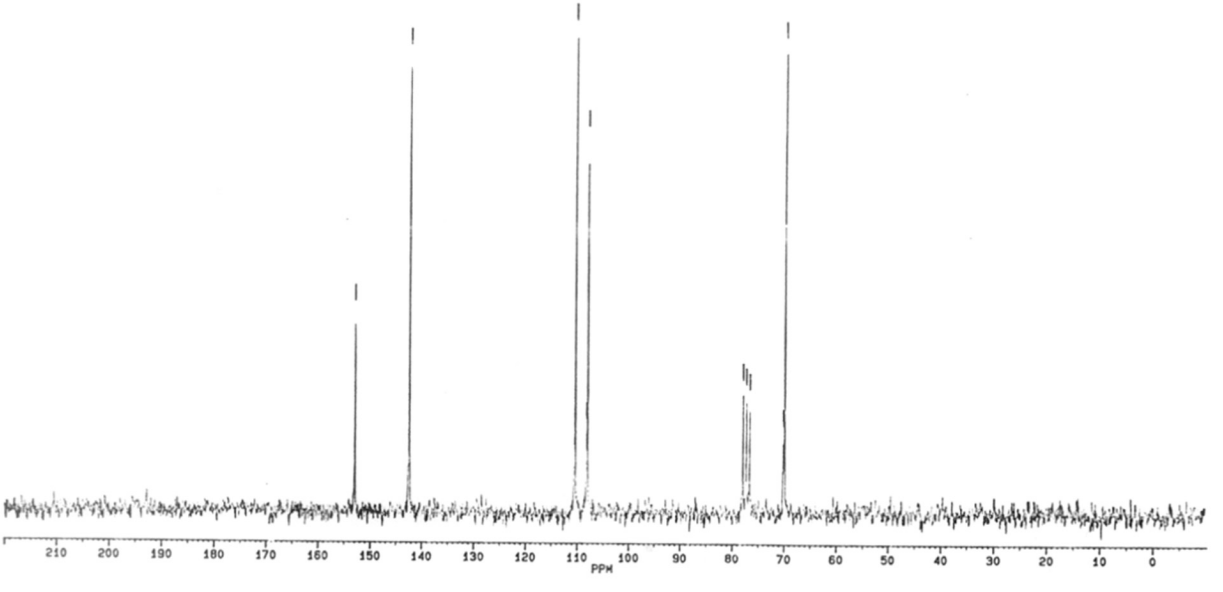

143.140
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
PPM

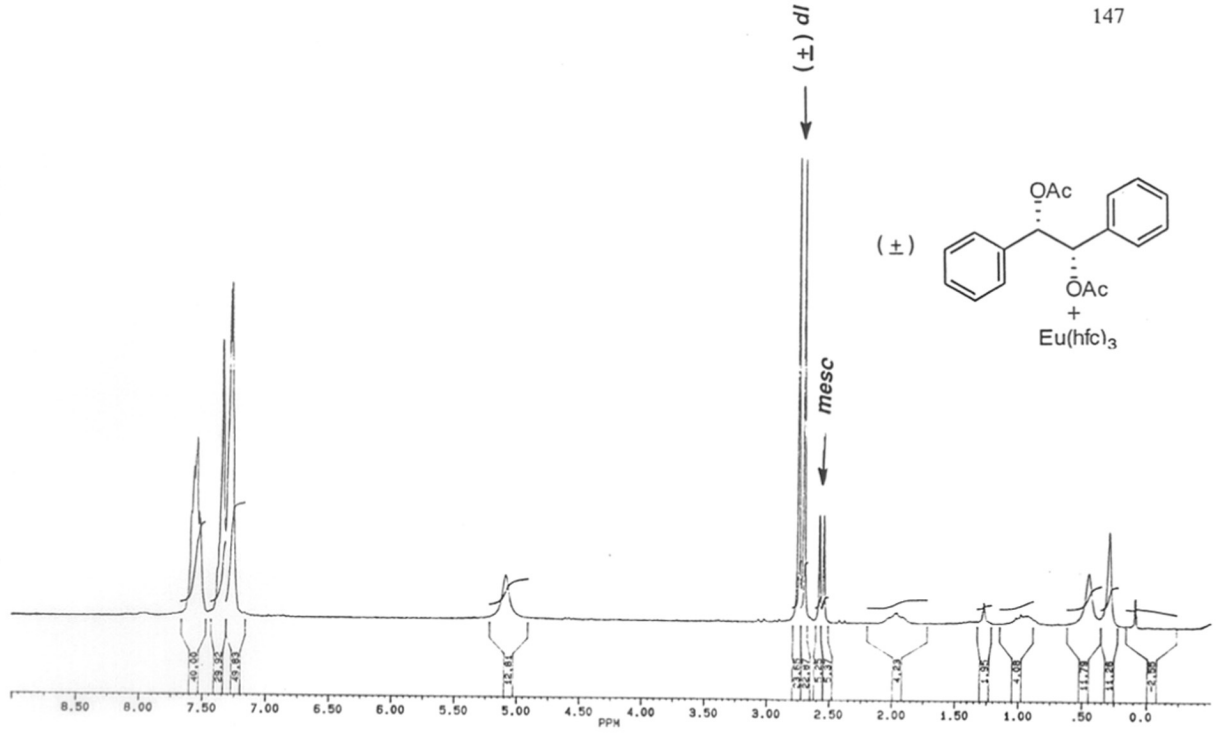

OH
O
O
OH

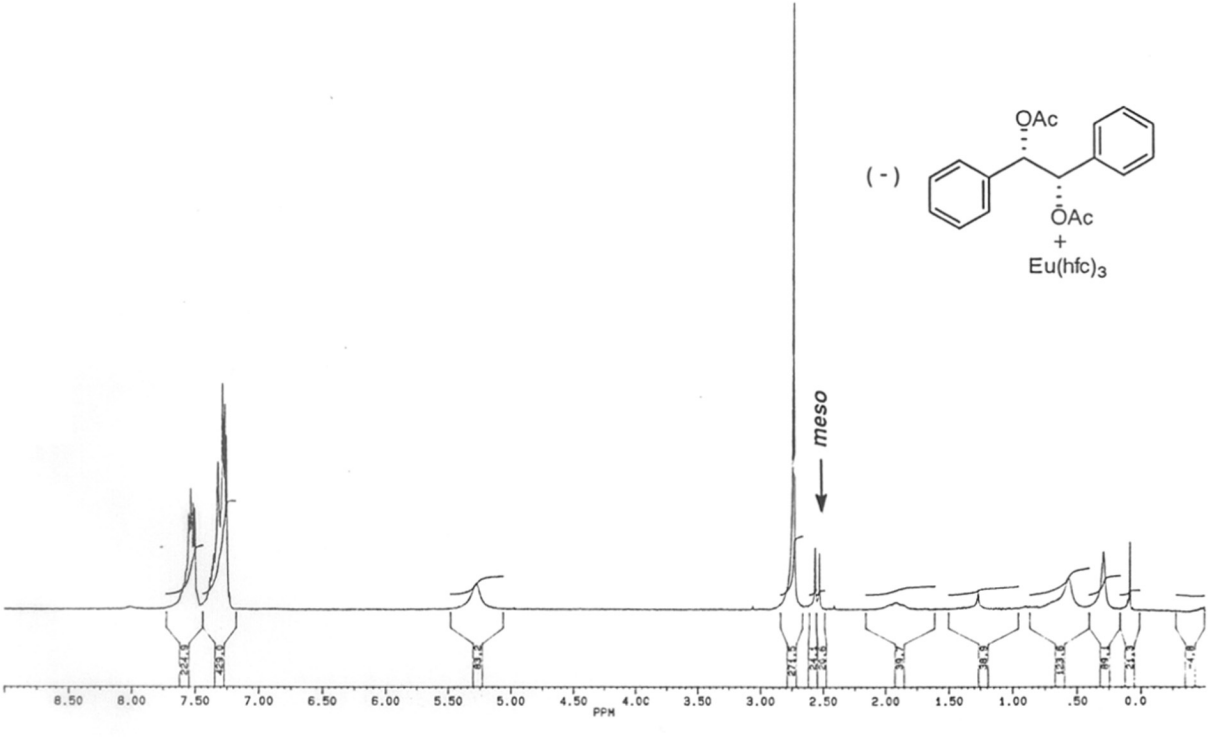
89 : 11 (*dl : meso*)

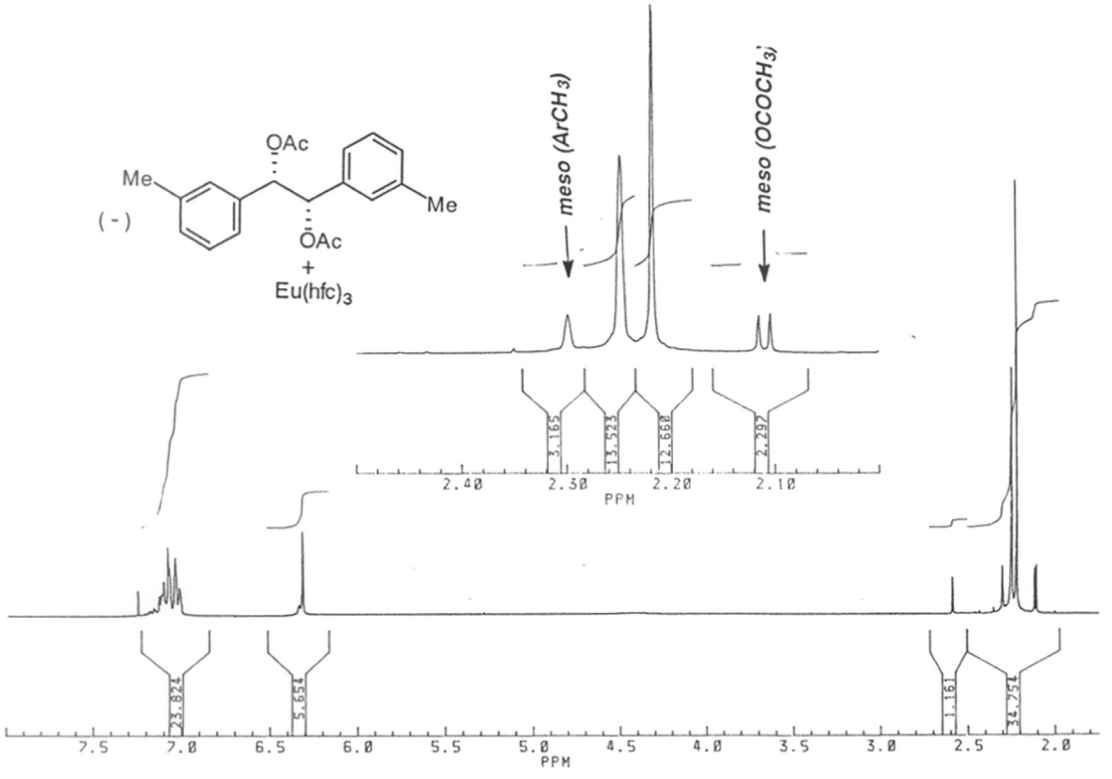
19.0
51.0
86.1
65.8
15.6
60.8
71.3
12.5
8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 .50 0.0
PPM

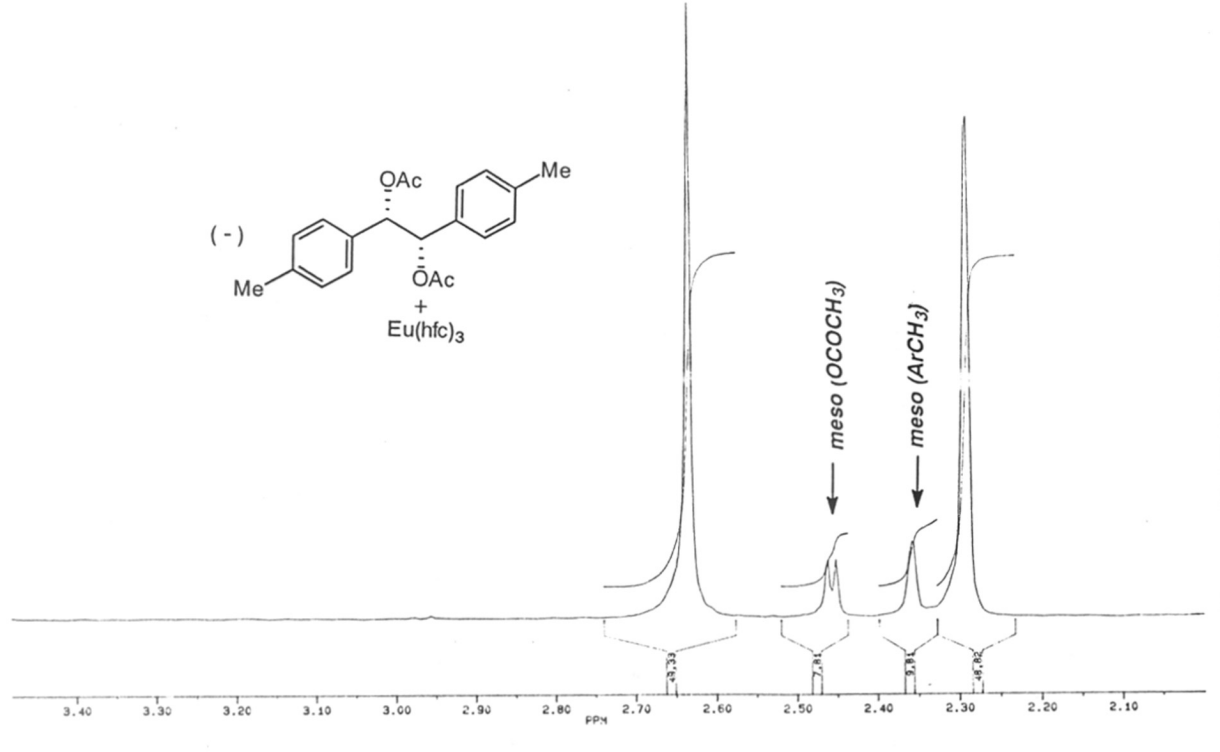

152.698
142.406
110.
108.
77.
76.
70.
69.

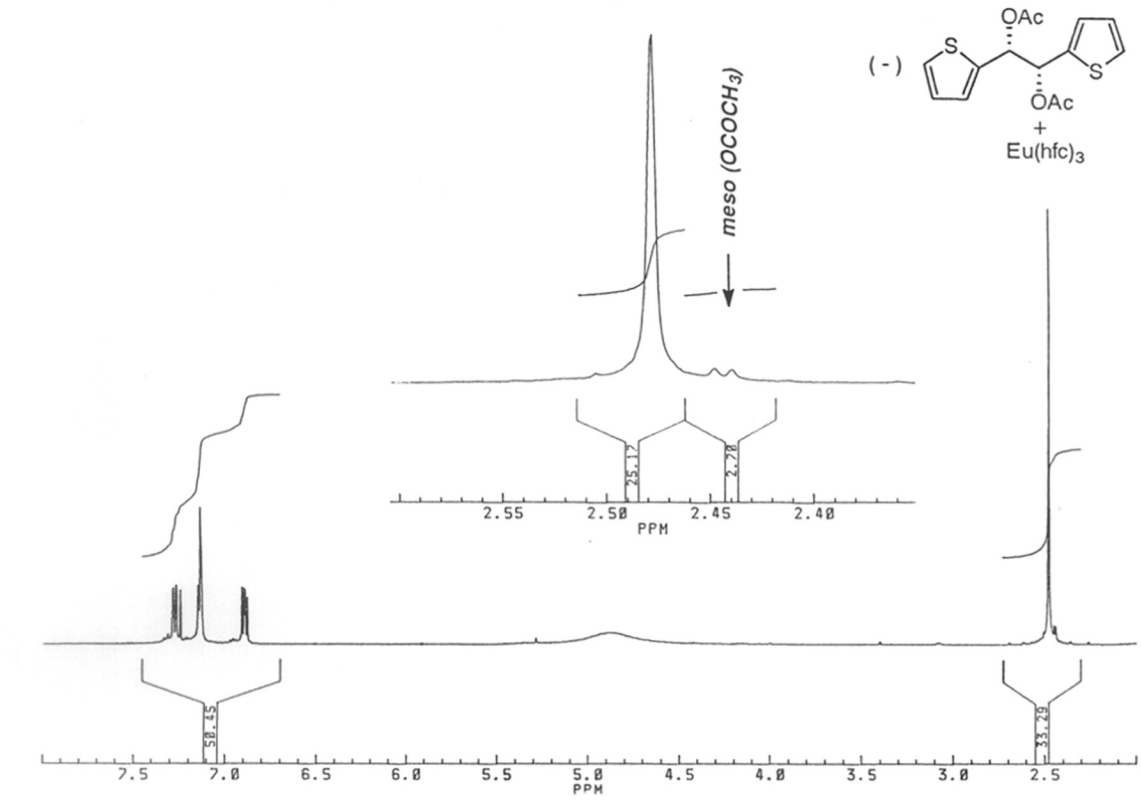

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
PPM

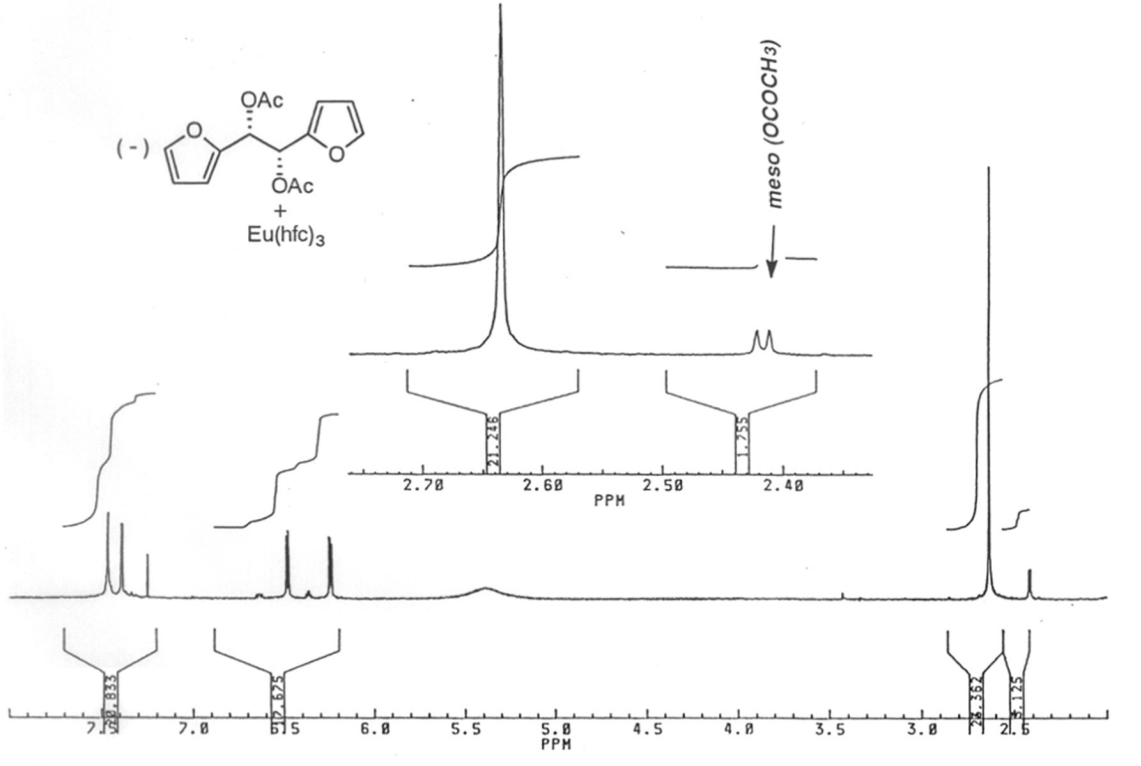

(±) dl
mesc
(±)
OAc
OAc
+
Eu(hfc)3
PPM


meso
(-)
OAc
OAc
+
Eu(hfc)3
PPM


OAc
Me
Me
(-)
OAc
+
Eu(hfc)3
meso (ArCH3)
meso (OCOCH3)
3.165
15.523
12.668
2.297
2.40
2.30
2.20
2.10
PPM
23.824
5.654
1.161
34.751
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
PPM


OAc
Me
(-)
Me
OAc
+
Eu(hfc)3
meso (OCOCH3)
meso (ArCH3)
3.40
3.30
3.20
3.10
3.00
2.90
2.80
2.70
2.60
2.50
2.40
2.30
2.20
2.10
PPM


(-)
OAc
OAc
+
Eu(hfc)3
meso (OCOCH3)
25.17
2.78
2.55
2.50
2.45
2.40
PPM
50.45
35.29
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
PPM


(-)
OAc
OAc
+
Eu(hfc)3
meso (OCOCH3)
21.248
1.755
2.70
2.60
2.50
2.40
PPM
20.833
17.625
26.362
3.125
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
PPM


meso (ArOCH3)
meso (OCOCH3)
25.0
188.0
7.9
187.2
19.7
PPM
3.90
3.80
3.70
3.60
3.50
3.40
3.30
3.20
3.10
3.00
2.90
2.80
2.70
2.60
2.50
2.40
2.30
(-)
MeO
OAc
OAc
+
Eu(hfc)3
OMe

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List of Publications

1. Stereoselective Reduction of Benzils: A New Convenient route to Enantiomerically Pure 1,2-Diarylethanediols
   K. R. K. Prasad and N. N. Joshi, *J. Org. Chem.*, 1996, *61*, 3888.
2. C_2-Symmetric Zinc Dialkoxides as Catalysts for the Enantioselective Addition of Diethylzinc to Arylaldehydes
   K. R. K. Prasad and N. N. Joshi, *Tetrahedron Asymm.*, 1996, *7*, 1957.
3. An Optimised *in situ* procedure for the Enantioselective Reduction of Prochiral Ketones
   K. R. K. Prasad and N. N. Joshi, *Tetrahedron Asymm.*, 1996, *7*, 3147.
4. Oxazaborolidine Catalysed Enantioselective Reduction of 2-Acyl Thiophenes and 2-Acyl Furans
   K. R. K. Prasad and N. N. Joshi, *Tetrahedron Asymm (in Press).*
5. Chiral Zinc Amides as the Catalysts for the Enantioselective Addition of Diethylzinc to Aldehdyes
   K. R. K. Prasad and N. N. Joshi, *J. Org. Chem. (in press).*
6. 1, 3- Oxazolidine Zinc Amides as the Catalysts in the Enantioselective Addition of Diethylzinc to Aldehydes
   K. R. K. Prasad and N. N. Joshi *(Manuscript Under Preparation).*
7. Unusual Formation of Lactols in the Addition of Grignard reagents to Lactone Derived from Ephedrine
   K. R. K. Prasad and N. N. Joshi *(Manuscript Under Preparation).*