Studies on the Resolution of Racemic 1,1'-Bi-2-naphthol and Applications of Chiral 1,1'-Bi-2-naphthyl Borate Complexes in Asymmetric Organic Transformations

A THESIS
SUBMITTED FOR THE DEGREE **OF**
DOCTOR OF PHILOSOPHY

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Dedicated to

My Father

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Statement

I hereby declare that the matter embodied in this thesis is the result of investigations carried out by me **in** the School of Chemistry, University of Hyderabad, under the supervision of Professor M. Periasamy.

In keeping with the general practice of reporting scientific observations, due acknowledgement has been made wherever the work described is based on the findings of other investigators.

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Certificate

Certified that the work embodied in this thesis entitled ' **Studies on the Resolution of Racemic l,l'-Bi-2-naphthol and Applications of Chiral l,l'-Bi-2-naphthyl Borate Complexes in Asymmetric Organic Transformations** ' has been carried out by Mr. L. Venkatraman, under my supervision and the same has not been submitted elsewhere for a Degree.

M. Periasamy
12/4/2000

PROFESSOR M. PERIASAMY
(THESIS SUPERVISOR)

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L.Venkatraman

ABBREVIATIONS

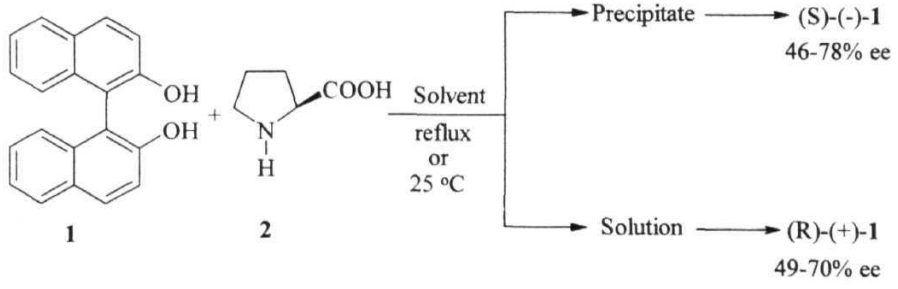
aq.	aqueous
Ar	aryl
Bu-	butyl
Bu^t	tertiarybutyl
DABCO	1,4-diazabicyclo[2.2.2]octane
DCM	dichloromethane
DIPT	di-isopropyl tartrate
DMAP	4-dimethylaminopyridine
ee	enantiomeric excess
Et	ethyl
EI	electron impact
eq.	equation
liq.	liquid
MeOH	methanol
Me	methyl
M	metal
n-	primary
OAc	acetyl
Ph	phenyl
Pr^i	isopropyl
THF	tetrahydrofuran
TMEDA	tetramethylethylene diamine
TMS	trimethylsilyl
PTSA	p-toluenesulphonic acid

Abstract

The thesis entitled, **"Studies on the Resolution of Racemic 1,1'-Bi-2-naphthol and Applications of Chiral l,l'-Bi-2-naphthyl Borate Complexes in Asymmetric Organic Transformations",** comprises of three chapters. Each chapter is subdivided into four parts namely, Introduction, Results and Discussion, Conclusion and Experimental Section along with references.

The first chapter describes the synthesis of chiral 1,1'-bi-2-naphthol (1) through new resolution procedures. The procedures reported for the resolution of 1,1'-bi-2-naphthol (1) are reviewed in the introductory section. Several of these procedures require expensive resolving agents and tedious experimental procedures. So, we have undertaken a systematic investigation to develop convenient resolution procedures. It has been observed that 1,1'-bi-2-naphthol (1) forms a 2:1 complex with (S)-proline 2 in various solvents (Scheme 1).

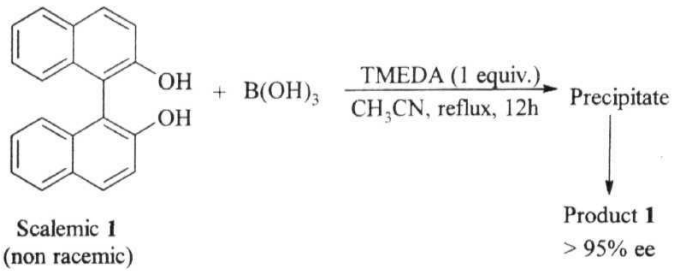
Scheme 1



The enantiomeric purity has been further enhanced by repeating this procedure (Scheme 1) successively. The nature of the complex formed between 1,1'-bi-2-naphthol (1) and (S)-proline (2) in methanol was characterised by X-ray diffraction analysis.

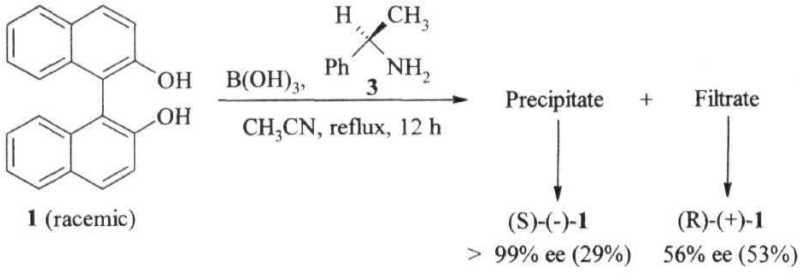
This method of resolution involves three successive operations in benzene, each requiring equimolar amounts of (S)-proline to obtain samples of >99% ee. Though, the resolving agent utilized can be readily recovered and recycled, we have undertaken efforts towards further purification of the scalemic (nonracemic, partially resolved) 1 without using (S)-proline again. It was anticipated that the preparation of complexes of the type B_2L_3 (L=1,1'-bi-2-naphthyloxy) using boric acid and partially resolved 1,1'-bi-2-naphthol (1) would lead to further purification. Indeed, this objective has been realised by refluxing the scalemic mixtures of 1 with boric acid and TMEDA (N,N,N',N'-tetramethylethylenediamine) in acetonitrile (Scheme 2). The concepts involved in this method of purification of partially resolved 1 are discussed.

Scheme 2

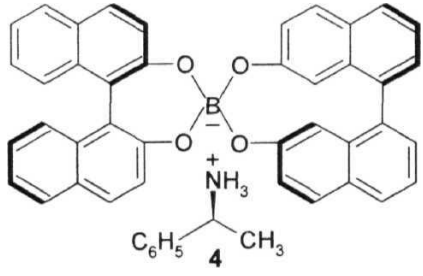


This resolution method using (S)-proline and further purification involving $B(OH)_3$/TMEDA still require two or three steps to obtain enantiomerically pure 1,1'-bi-2-naphthol (1). Also, recovery of the water soluble (S)-proline is somewhat difficult. Therefore, we have examined the resolution of l,l'-bi-2-naphthol (1) by forming diastereomeric borate complexes using a chiral amine. After extensive experimental work, it has been observed that the use of chiral (R)-(+)-α-methylbenzylamine (3) and $B(OH)_3$ leads to promising results (Scheme 3).

Scheme 3

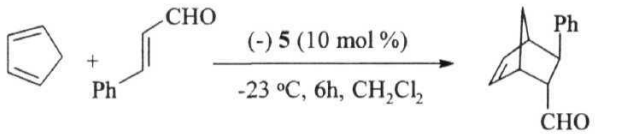


The X-ray structural analysis of crystals obtained from the mother liquor in the resolution method (Scheme 3) revealed that the complex obtained in this way is an ammonium borate complex 4.



Several Diels-Alder experiments were carried out using different dienophiles in the presence of 5. Initial experiments using dimethyl fumarate and methyl vinyl ketone with cyclopentadiene indicated that the borate 5 catalyses the Diels-Alder reaction of these substrates with cyclopentadiene. However, no asymmetric induction was observed in the resulting Diels-Alder adducts. The catalyst did effect the reaction of cyclopentadiene with several other dienophiles such as acrolein and methacrolein at 0 °C with poor asymmetric induction (up to 20% ee). It was found to induce optical activity into the adduct formed between cinnamaldehyde and cyclopentadiene to a significant extent (Scheme 5).

Scheme 5



6

50% ee (42%)

(endo:exo = 94:6)

Efforts towards estimation of the optical purity of the product 6 were carried out through preparation of several derivatives. It was observed that the diastereomeric acetals of 6, prepared using optically active (1R, 2R, 3S, 5R)-(-)-pinane-2,3-diol are useful in the assessment of the enantiomeric purity by ^{1}H NMR spectral analysis.

Also, efforts were made to examine the effect of molecular sieves and certain other additives on the Diels-Alder reaction catalysed by the chiral borate 5 (Scheme 5). The reagents $TiCl_4$, $Ti(OPr^i)_4$, $BF_3.OEt_2$, TMEDA, and NEt_3, were added in small amounts into the reaction mixture and their effect on the results of the reaction between cinnamaldehyde and cyclopentadiene were recorded.

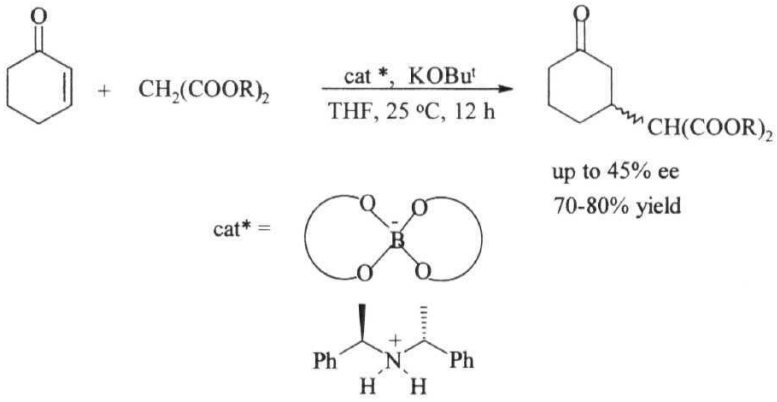
The effect of addition of chiral (S)-(-)-a-methylbenzylamine in the Diels-Alder reaction catalysed by racemic borate 5 was also examined. The Diels-Alder adduct was obtained in 25% ee (20% yield) in this case.

The Diels-Alder reaction catalysed by the borate 5 derived from l,l'-bi-2-naphthol (1) of different non-racemic compositions was also examined. The results indicate a positive nonlinear dependence of the ee of 1,1 '-bi-2-naphthol (1) with that of the product. The results are discussed comparing nonlinear effects reported for other systems.

In chapter 3, the results of a brief investigation on the asymmetric Michael reaction of various malonate esters with cyclohexenone are described. The reports on the asymmetric Michael reaction catalysed by the 'ate' complexes of lanthanides, aluminium and gallium derivatives inspired us to undertake the study on the ammonium borate complexes of the type 4 that are formed using 1,1'-bi-2-naphthol (1), $B(OH)_3$ and chiral amines. Asymmetric induction to a small extent was observed in the Michael reaction of dialkyl malonates with cyclohexenone using the

chiral ammonium borate complex 4 derived from chiral a-methylbenzylamine in the presence of $KOBu^t$.

Scheme 6



The C_2 chiral α,α'-dimethyldibenzylamine derived borate complexes gave modest selectivities (Scheme 6). The results are discussed.

Chapter 1

Studies on the resolution of racemic 1,1'-bi-2-naphthol

1.1 Introduction

Molecular chirality is an important element in nature. Life itself depends on chiral recognition, because living systems interact with enantiomers in different manner. A variety of biological functions occur because enzymes, receptors and other natural binding sites recognise substrates with specific chirality. Therefore, obtaining chiral molecule is an important problem in the synthesis of natural products and Pharmaceuticals.

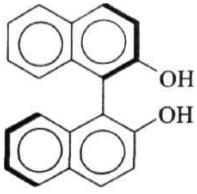
The methods of producing optically active compounds include *(i)* physical separation *via* enantiomeric crystal forms *(ii)* resolution based on physical separation of diastereomeric forms *(Hi)* kinetically controlled asymmetric transformations.[1,2] Asymmetric synthesis occurs because a reagent or substrate is chiral. It is important to use chiral reagents in an efficient manner and recover the same to use again. Also, the most effective way of using chiral reagents is to employ them in small quantities as catalysts.

Chemical synthesis of enantiomerically pure substances from prochiral substrates has been extremely difficult for a long time. However, recent dramatic advances in man made catalysts, particularly, homogeneous asymmetric catalysts provide numerous ways to get chiral molecules.[3,,6] Consequently, asymmetric

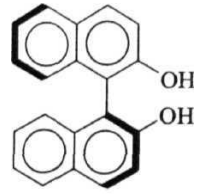
synthesis led to the production of large amounts of chiral molecules of either absolute configuration with a very small quantity of chiral source. Also, asymmetric syntheses is often the method of choice for obtaining chiral molecules and several spectacular successes have been achieved.[7]

Proper combination of selected central metals and well-designed chiral ligand is important for the efficiency of the chiral catalyst. The role played by the chiral ligand is to make the transition state diastereomeric leading to the two antipodes so that one of them is preferentially formed. A rational approach to the control of stereoselectivity revealed that C_2 symmetrical chiral auxiliaries are useful in obtaining optically active compounds in high enantiomeric excesses.

A large number of such chiral auxiliaries have been prepared and used in the last 20 years. Among them, the 2,2'-disubstituted-1-1'-binaphthyls have shown excellent chiral discriminating properties.[9-1] The rotation about the σ-bond of C_2 symmetric 1,1'-binaphthyl and its derivatives is so hindered that the optical isomers, *atropisomers*, may be isolated. Because of their highly stable chiral configuration, the 2,2'-disubstituted-1-1'-binaphthyls have been extensively used in many asymmetric processes.



(R)-1



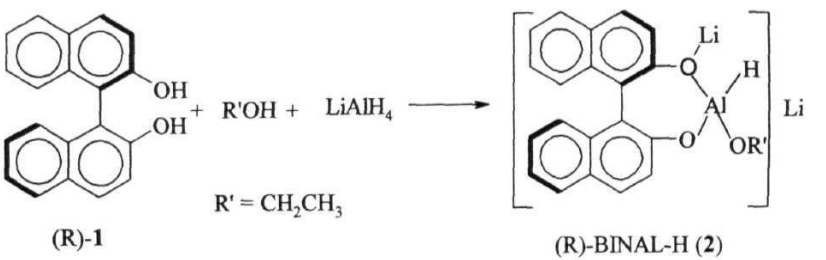
(S)-1

Among the binaphthyl derivatives, optically active l,l'-bi-2-naphthol (1) has emerged as the most widely used efficient chiral auxiliary in a number of asymmetric reactions in recent years. It has been successfully used as a ligand for both stoichiometric and catalytic asymmetric reactions. It will be helpful to briefly review the results reported on this subject.

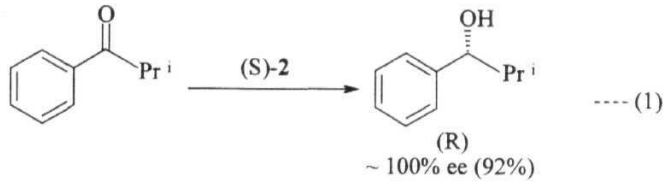
I. Asymmetric Reductions:

The enantioselective reduction of prochiral carbonyl compounds is one of the most extensively studied chiral transformations. In 1984, Noyori *et al* prepared the chiral hydride reagent BINAL-H (2) by modifying $LiAlH_4$ using equimolar amounts of (R) or (S)-1,1'-bi-2-naphthol (1) and a simple alcohol (Scheme 1).[11-12]

Scheme 1



This reducing agent 2 exhibits a high enantioface differentiating ability in the reduction of prochiral alkyl phenyl ketones in THF (eq. 1).

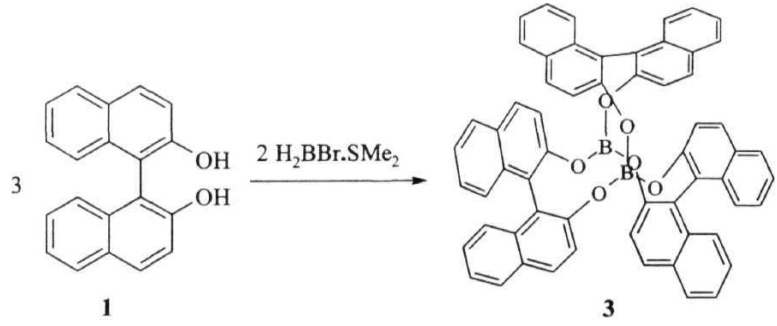


Recently, a chiral gallium complex prepared using monothio-l,l'-bi-2-naphthol has been used in the catalytic enantioselective reduction of ketones to obtain the corresponding alcohols in good ee.[13]

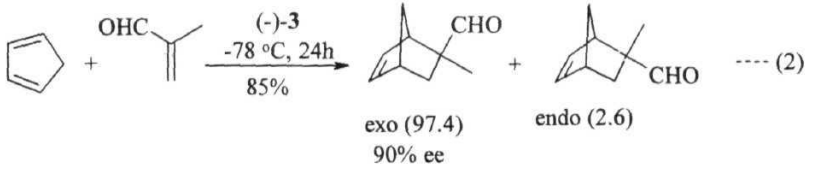
II. Asymmetric Diels-Alder reaction:

The Diels-Alder reaction is one of the most useful structural transformations in organic synthesis. Optically active 1 and its derivatives are important precursors for chiral Lewis acids that are used as chiral auxiliaries in Diels-Alder reactions.[14-17] For example, Kaufmann noticed that l,l'-bi-2-naphthol (1) and $H_2BBr.SMe_2$ reacts to form a C_3 symmetric diborate propeller 3 (Scheme **2).**[17]

Scheme 2



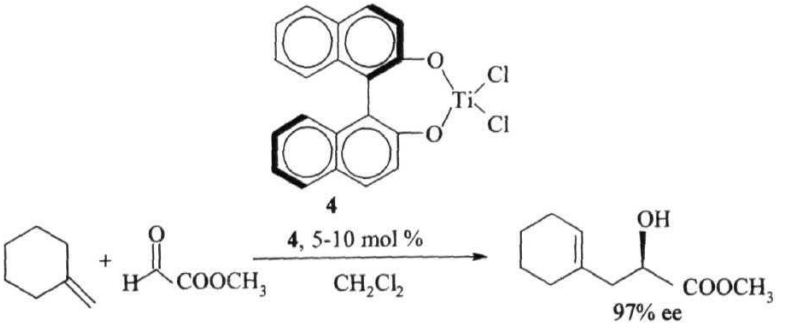
The (+)-3 or (-)-3 catalyses Diels-Alder reaction of methacrolein with cyclopentadiene to give the corresponding exo adduct in 85% yield with 90% ee (eq. 2). The combinations of 1 with several other Lewis acids were also used in catalytic asymmetric Diels-Alder reactions.[18]



III. Ene Reaction:

Mikami *et al* developed a family of enantioselective 'ene' reactions between glyoxylic aldehydes and a series of terminal olefins under the influence of chiral Lewis acids, especially of the type 4, derived from 1,1'-bi-2-naphthol (1) and $TiCl_2(OPr^i)_2$ (Scheme 3).[19] This ene reaction often proceeds with excellent enantioselectivity.

Scheme 3

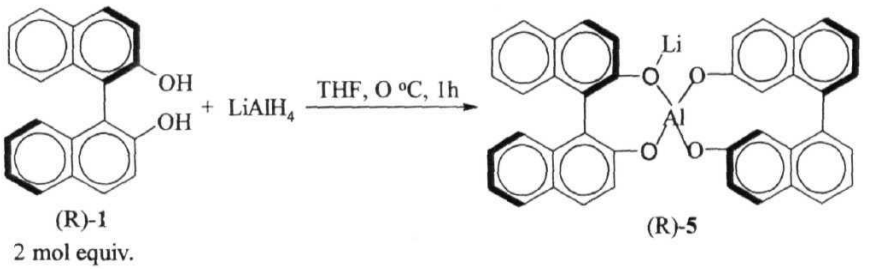


IV. Michael Addition :

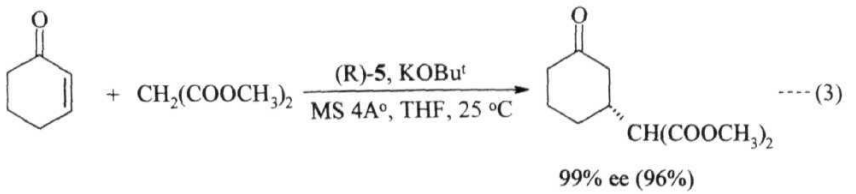
The Michael reaction is one of the most important methods for the construction of C-C bonds. Many chiral crown ethers and lanthanum complexes are prepared from optically active 1 and used as chiral auxiliaries in enantioselective Michael reactions.[20,22]

Shibasaki *et al* developed a variety of bimetallic chiral complexes from optically active 1 and used effectively in the catalysis of asymmetric Michael reactions (Scheme 4).

Scheme 4



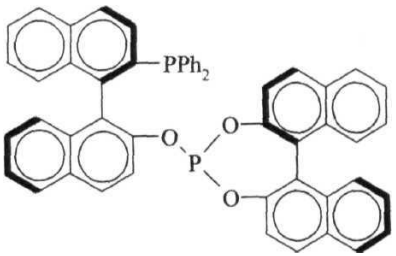
For example, the Al-Li-bis(l,l'-bi-2-binaphthylate) complex 5 catalyses the Michael reaction between cyclohexenone and dimethyl malonate, to give the corresponding adduct in 96% yield with 99% ee (eq. 3).



----(3)

V. Hydroformylation:

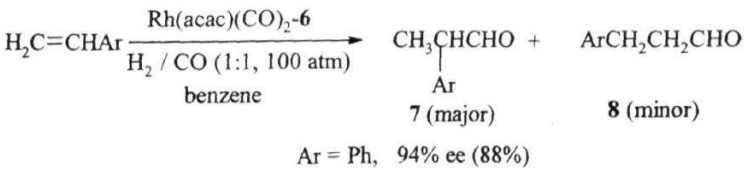
Hydroformylation is one of the most versatile methods for the functionalization of the C=C bonds. [3] Takaya *et al* synthesised a new class of unsymmetrical chiral bidendate ligands derived from l,l'-bi-2-naphthol (1), namely (R,S)-BINAPHOS (6).[24]



(R,S)-BINAPHOS (6)

The Rh(I) complexes of the ligand 6 are highly efficient catalysts for asymmetric hydroformylation of aryl ethenes and functionalised olefins such as vinyl acetate (Scheme 5).

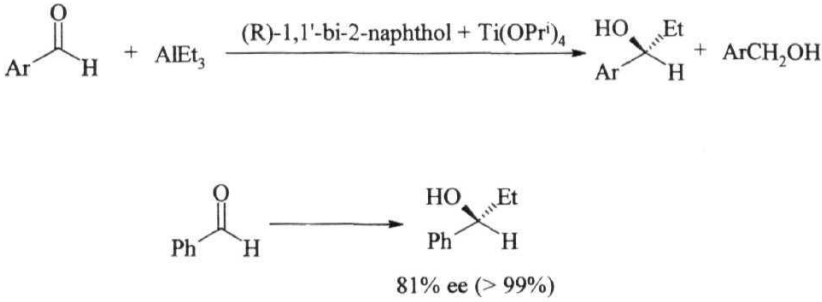
Scheme 5



VI. Alkylations:

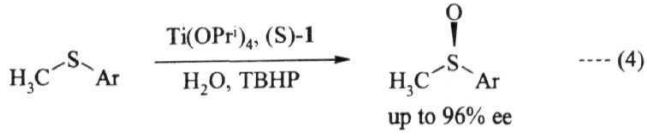
Catalytic asymmetric addition of trialkylaluminium compounds to aldehydes has high scientific and industrial interest. Chan *et al* reported the enantioselective alkylation of aldehydes with triethylaluminium using a catalyst derived from 1,1'-bi-2-naphthol (1) and $Ti(OPr^i)_4$ to obtain the corresponding secondary alcohol in high ee (Scheme **6).**[25]

Scheme 6



VII. Oxidation:

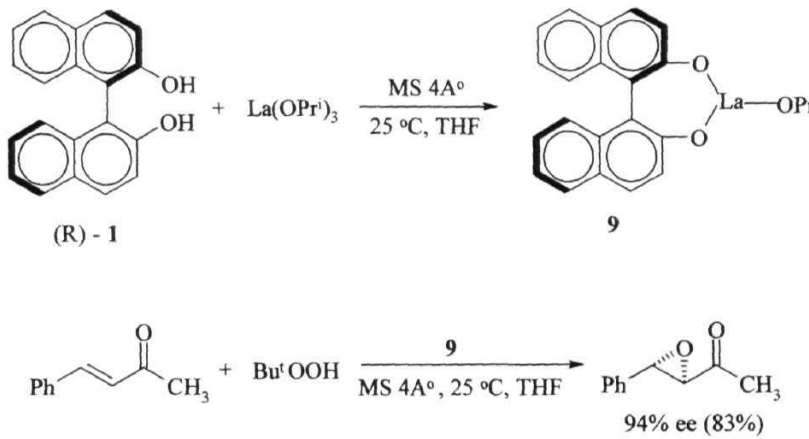
Chiral sulfoxides are useful synthons and their preparation has been studied for many years. Uemura and co-workers reported the asymmetric oxidation of sulfides to chiral sulfoxides in moderate yields with t-butyl hydroperoxide (TBHP) catalysed by a titanium complex produced ***in*** *situ* using titanium isopropoxide and (S)-1,1'-bi-2-naphthol **(1)** (eq. **4).**[26]



VIII. Epoxidation:

Catalytic asymmetric epoxidation is one of the most important asymmetric processes. Shibasaki *et al* communicated an efficient catalytic method for asymmetric epoxidation of enones using lanthanide complexes 9 derived from chiral 1,1'-bi-2-naphthol (1) and $La(OPr^i)_3$ (Scheme 7).[27]

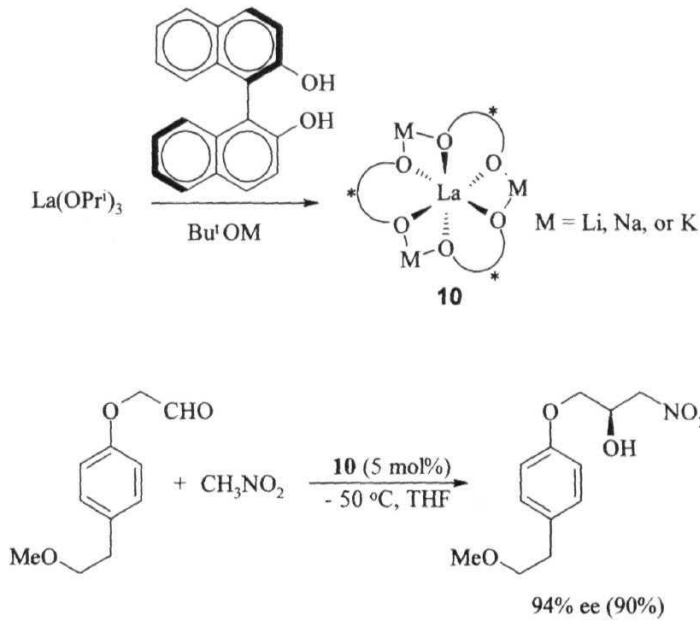
Scheme 7



IX. Nitro Aldol reaction:

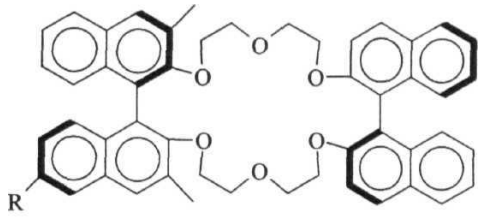
Shibasaki *et al* also reported a catalytic procedure for asymmetric nitro aldol reaction using rare earth l,l'-bi-2-naphthol complexes 10 (Scheme 8).[28]

Scheme 8



X. Host-Guest Complexation:

Optically active 1,1'-bi-2-naphthol (1) and its derivatives have been also applied in host-guest chemistry, molecular recognition and enantioselective chromatography separation.[29-32] For example, Cram *et al* synthesised a solid phase host 11 derived from optically active 1,1'-bi-2-naphthol (1) and used it as resin in the preparation of chromatographic columns.[31] Resolution of racemic amino acids and esters could be carried out efficiently using the columns containing 11.



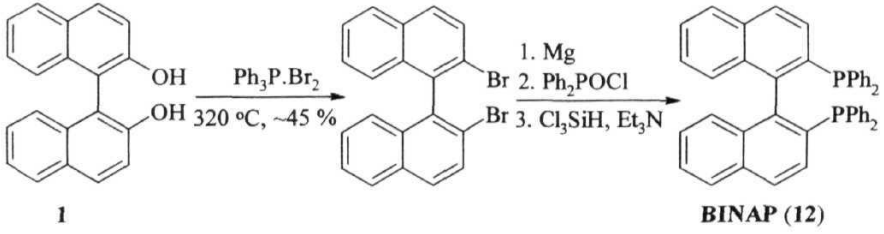
R = $CH_2CH_2OCH_2$-PS-CH_2OCH_3

(R,R) - **11**

XI. Other applications:

The chiral 1,1'-bi-2-naphthol is also useful as a source to prepare chiral reagents such as BINAP (12) (Scheme 9).[33]

Scheme 9

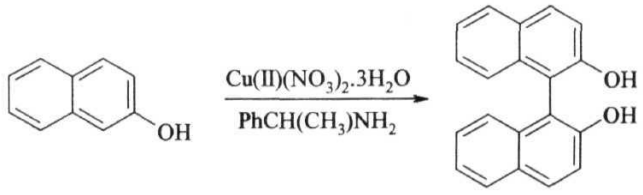


1 **BINAP (12)**

Also, derivatives of 1 have been used in the synthesis of chiral shift reagents[34] and in polymerisation processes to control the stereochemistry of polymers.[35,36]

The practical application of chiral l,l'-bi-2-naphthol (1) in large scale is hindered due to the cost of enantiomerically pure material. In recent years, significant advances have been made in the preparation of 1 in its enantiomerically pure form. Several methods such as asymmetric coupling from 2-naphthol and resolutions through formation of diastereomers, enzymatic resolution, resolution through inclusion complexes are available to obtain 1 in enantiopure form. A brief review of these methods will be helpful for the discussion.

The first example of asymmetric induction in the oxidative coupling of phenols using chiral oxidants was reported by Feringa and Wynberg.[37] The use of chiral Cu(II) amine complexes derived from $Cu(NO_3)_2.3H_2O$ and chiral a-methyl benzylamine or methylether of prolinol as oxidants gave low asymmetric induction in the coupling of 2-naphthol (eq. 5).

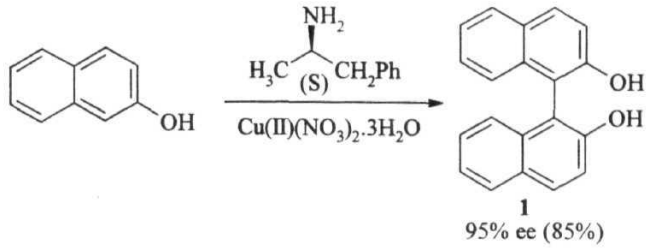


---- (5)

1

up to 7.9% ee (10 - 62%)

Brussee and Jansen reported a similar procedure with improved yield. A remarkable increase in asymmetric induction was realised using (S)-amphetamine (eq. 6).[38]

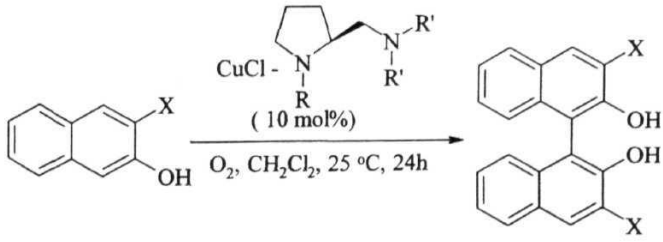


---- (6)

1
95% ee (85%)

Later, another procedure was reported by Kocovsky *et al* for the preparation of enantiomerically pure 1,1'-bi-2-naphthol (**1**).[39] In this procedure, enantiomerically enriched 1,1'-bi-2-naphthol (1) was obtained by oxidative coupling of 2-naphthol using a CuCl2-chiral amine complex. Deracemization of the partially enriched material employing second order asymmetric transformation *(i.e.* seeding a solution enriched in one enantiomer with crystals of pure enantiomer obtained from previous experiments) resulted in the crystallisation of pure or nearly pure enantiomers. Enantiomerically pure 1,1'-bi-2-naphthol (1) was obtained from the above mixture by a carefully controlled kinetic crystallisation. The $CuCl_2$-sparteine and $CuCl_2$-(R)-(+)-α-methylbenzylamine complexes were also used in the coupling process.[39]

Recently, Nakajima *et al* reported the enantioselective oxidative coupling of various 2-naphthol derivatives using (S)-prolinc derived diamines and CuCl to obtain the corresponding binaphthol derivatives in < 78% ee (eq. 7).[40]

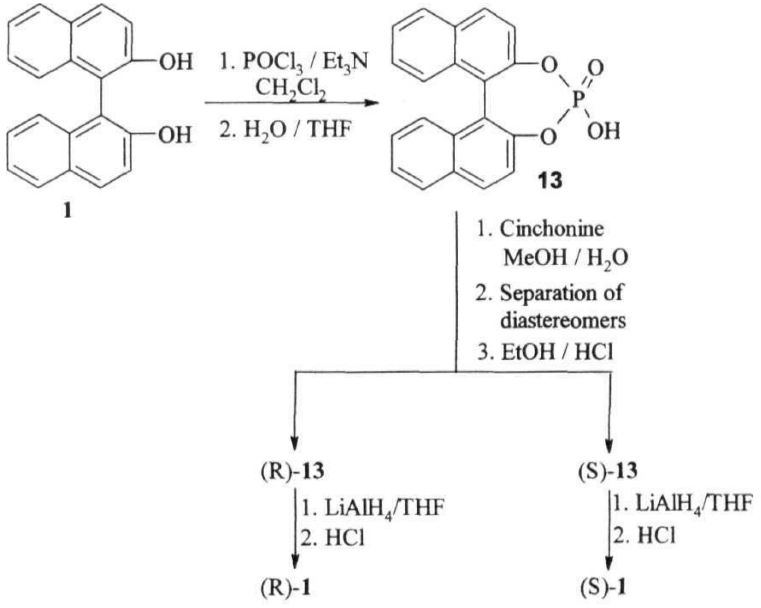


···· (7)

when X = H, 17% ee (89%)

Jacques *et al* reported a resolution procedure for obtaining optically pure l,l'-bi-2-naphthol (1) from the racemic mixture.[41] In this procedure, the cyclic phosphoric acid derivatives 13, prepared using racemic l,l'-bi-2-naphthol (1), were easily resolved into its enantiomers through formation of the diastereomeric cinchonine salts. The cyclic binaphthyl phosphoric acids (13) are strong acids and the enantiomers form well crystalline salts with a wide variety of organic bases (Scheme 10).

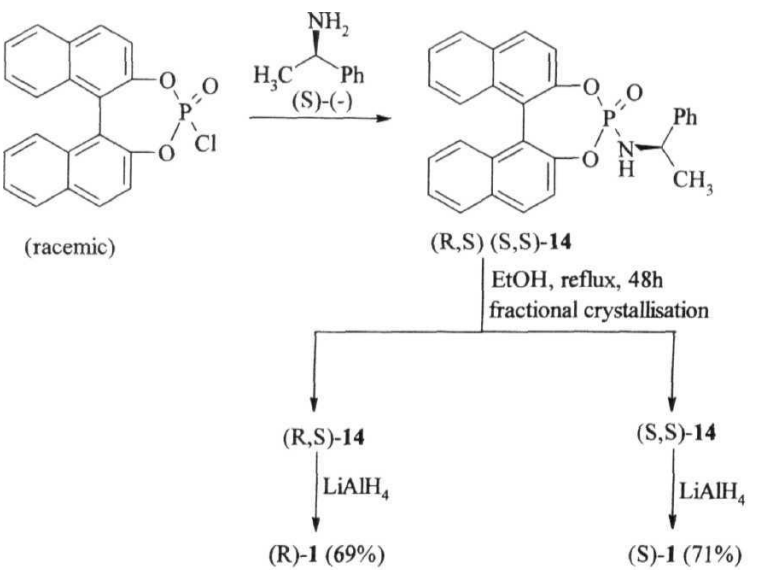
Scheme 10



Gong *et al* reported a method for the resolution of racemic 1 *via* the phosphoramidate 14 using optically active α-methylbenzylamine, a readily

accessible and widely used basic resolving agent.[42] A significant enhancement of over all yield [69% for (R) isomer and 71% for (S) isomer] and enantiomeric purity was achieved. Moreover, this procedure is also applicable in large-scale preparations (Scheme 11).

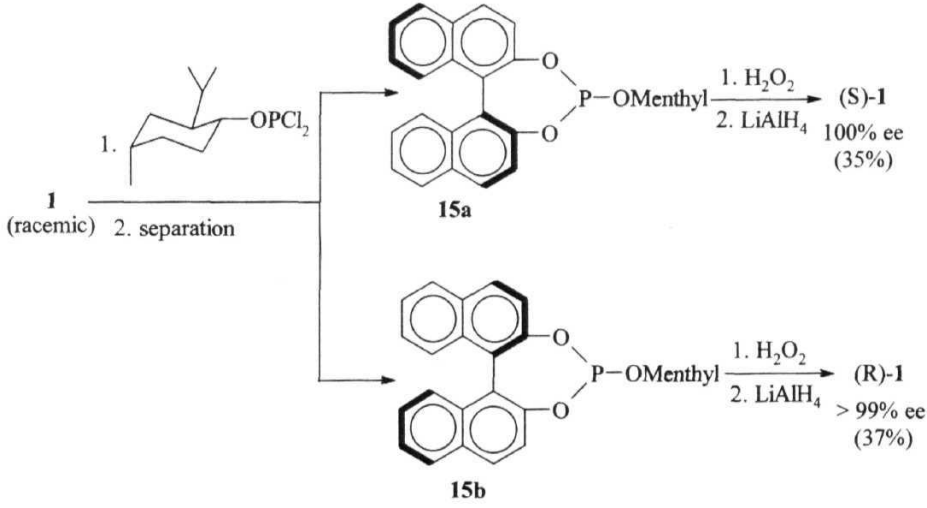
Scheme 11



Brunei and Buono reported a new method for the resolution of racemic 1,1'-bi-2-naphthol (1) using equimolar amounts of PCl_3 and L-menthol.[43] The reaction was carried out at 25 °C to prepare the menthyl phosphorodichloride that upon reaction with racemic 1 gave the mixture of diastereomers **15a** and **15b.**

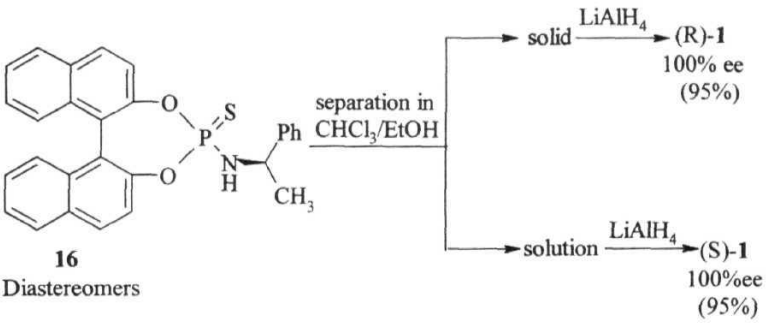
Enantiomerically pure 1 was obtained from these diastereomers through crystallisation and cleavage of the phosphite (Scheme **12).**

Scheme 12



Fabbri *et al* reported a resolution method employing condensation of thiophosphoryl chloride and (S)-(-)-<x-methylbenzylamine in pyridine. Reaction of the resulting phosphoramidate with racemic 1 gives a 1:1 mixture of diastereomers 16 that were clearly separated by single crystallisation from CHClrEtOH (Scheme 13).[44]

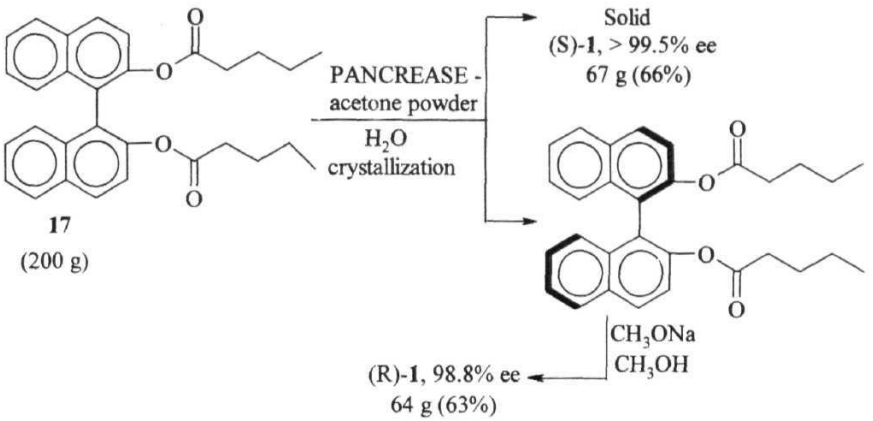
Scheme 13



Unfortunately, in all these cases, stoichiometric amounts of $LiAlH_4$ are required to cleave the cyclic phosphates to obtain the 1,1'-bi-2-naphthol (1).

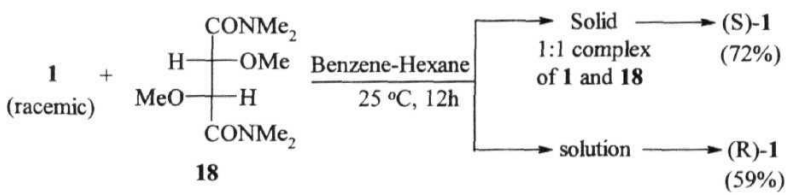
An enzymatic resolution method was reported by Kazlauskas.[45] Hydrolysis of l,l'-bi-2-naphthol (1) esters by cholesterol esterase is enantiospecific and this procedure was utilized for the enzymatic resolution of l,l'-bi-2-naphthol (1). When dipentanoate ester of l,l'-bi-2-naphthol (17) was hydrolysed by bovine or porcine pancreas acetone powder, each isomer was obtained in > 60% yield in enantiopure form (Scheme 14).

Scheme 14



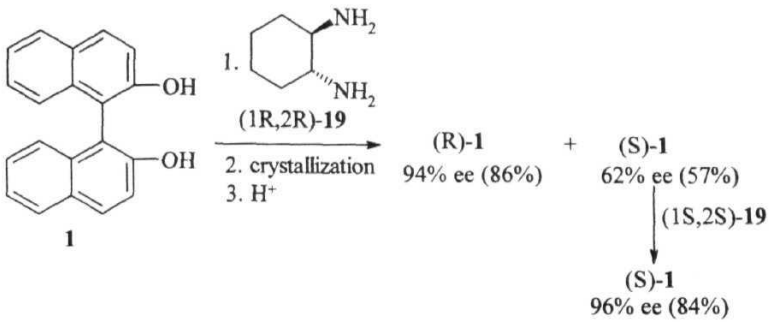
Toda and Tanaka reported a procedure for the resolution of 1,1'-bi-2-naphthol (1) and related compounds by complex formation with the chiral host compound 18 derived from tartaric acid (Scheme 15).[46]

Scheme 15



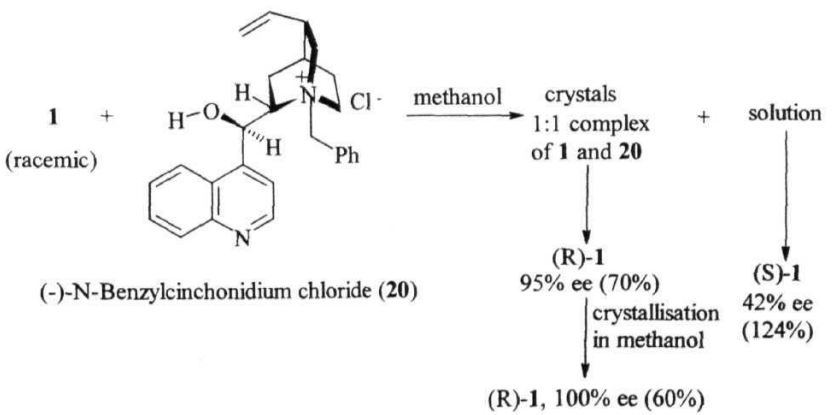
Kawashima and Hirayama reported a convenient method for the direct resolution of 1,1'-bi-2-naphthol (1) using chiral 1,2-diaminocyclohexane (19) (Scheme 16).[47] The (R)-(+)-l and (S)-(-)-l isomers were obtained in 94% and 96% ee, respectively.

Scheme 16



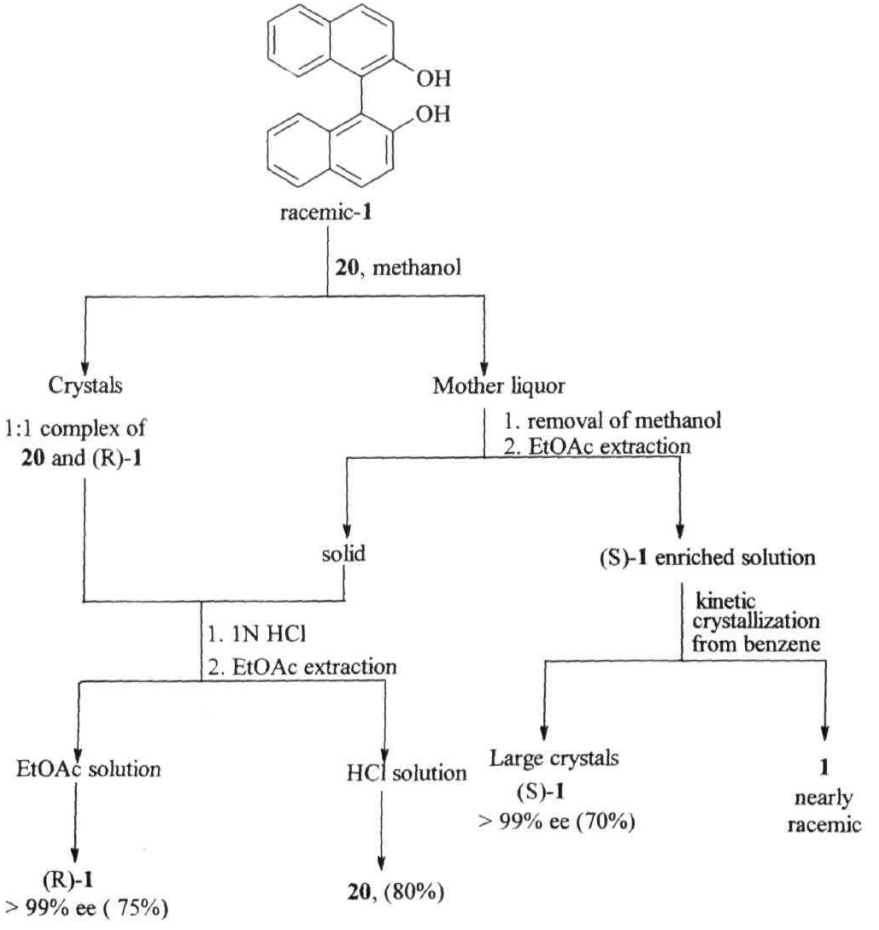
Toda *et al* observed that commercially available N-alkylcinchonidium halides are very effective for the resolution of **1**.[48] For example, when a solution of N-benzylcinchonidium chloride (20) and racemic 1 in methanol was kept at 25 °C for 6h, a 1:1 inclusion complex was precipitated as colourless prism which upon decomposition gave (R)-l in 95% ee (70% yield). The optical purity was enhanced to 100% by simple recrystallisation from methanol. From the filtrate fraction, the (S)-l isomer was obtained in 42% ee (Scheme **17).**

Scheme 17



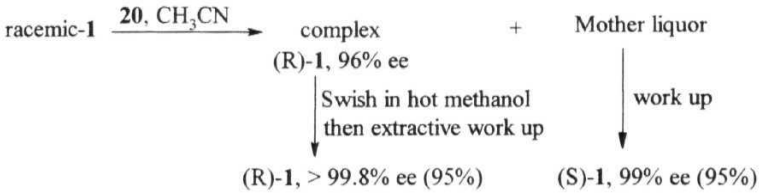
Hu *et al* reported a modified procedure using N-benzylcinchonidium chloride (20).[49] They demonstrated that both enantiomers of 1 could be obtained in optically pure form in this way (Scheme **18).**

Scheme 18



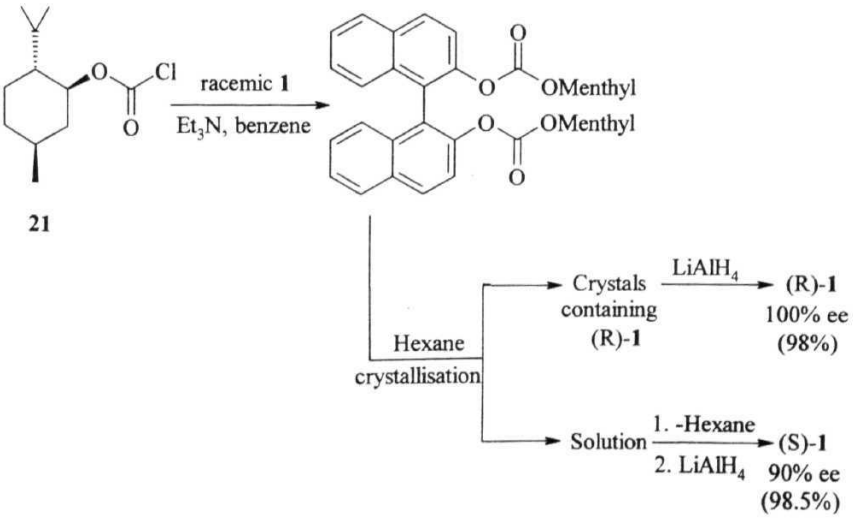
Cai *et al* developed a similar procedure using N-benzylcinchonidium chloride (20). When the resolution experiments were carried out in acetonitrile, both the enantiomers were obtained in > 99% ee (Scheme **19).**

Scheme 19



Fabbri *et al* reported a resolution procedure based on the facile separation of the pair of diastereomers through the reaction of 1 with (-)-menthyl chloroformate (**21**).[51] However, the ester has to be cleaved using $LiAlH_4$ to obtain the optically pure 1 (Scheme 20).

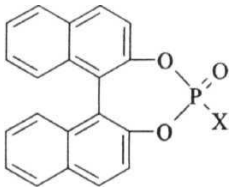
Scheme 20



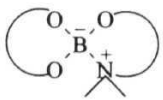
We have undertaken a systematic investigation to resolve 1,1 -bi-2-naphthol (1) through the preparation of the corresponding diastereomeric borate complexes. The results of this investigation are described in this chapter.

1.2 Results and Discussion

Although several new resolution procedures have been reported in recent years, the most widely used laboratory method involves the preparation of the cyclic phosphoric acid derivatives (Introduction, Scheme **10-13**).[41-44] Following this method, the resolution can be readily carried out on a large scale to get both enantiomers of high enantiomeric purity. However, there are some disadvantages. For instance, after resolution, the diastereomeric phosphate intermediates (22) require stoichiometric amounts of $LiAlH_4$ for cleavage to obtain the 1,1'-bi-2-naphthol (1) owing to the great stability of cyclic phosphate esters to hydrolysis.



22

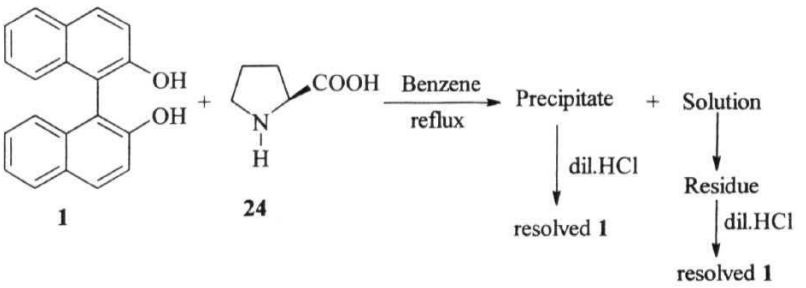


23

We have undertaken an exploratory research work for the resolution of 1,1'-bi-2-naphthol (1) through the preparation of diastereomeric borate complexes 23 using certain readily available, inexpensive chiral resolving agents such as amino acids. These borates are expected to be solid derivatives. Also, it is anticipated that such borate complexes (23) could be readily cleaved hydrolytically.

Initial experiments in this laboratory led to the discovery that the resolution of l,l'-bi-2-naphthol (1) could be effected even in the absence of $B(OH)_3$.[52] For example, when a mixture of racemic 1 and (S)-proline (24) were refluxed in benzene, an insoluble solid was obtained (Scheme 21). The solid and solution fractions, after dil.HCl treatment, afforded partially resolved 1. Repetition of the experiments successively three times resulted in essentially complete resolution.

Scheme 21



(R,S)-**1**, 0% ee ⟶ (S)-l, 65% ee (43%) **(R)-1,** 44% ee **(51%)**

(S)-l, 65% ee ⟶ (S)-l, 87% ee (66%) (S)-l, 06% ee (22%)

(S)-l, 87% ee - ⟶ (S)-l, >99% ee (77%) (S)-l, 35% ee **(11%)**

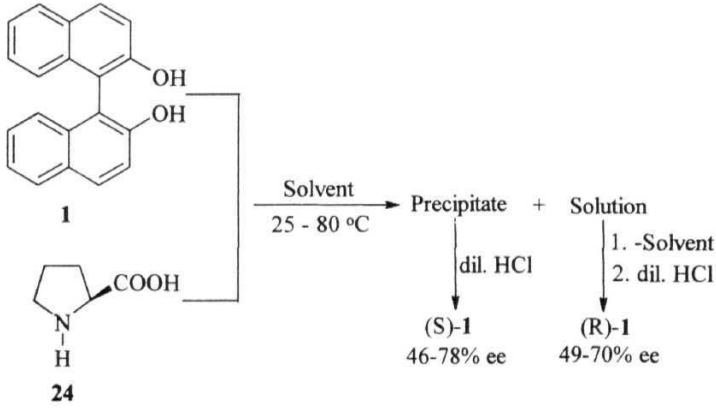
(R)-**1**, 44% ee • ⟶ (R)-**1**, 90% ee (45%) (R)-**1**, 06% ee **(41** %)

(R)-l,90%ee ⟶ (R)-l, 98% ee (70%) (R)-l, 28% ee (18%)

1.2.1 Partial resolution of racemic 1,1'-bi-2-naphthol using (S)-proline (24) in various solvents

Since benzene is carcinogenic, we were looking for an alternative solvent in which resolution using (S)-proline (24) can be carried out. We have observed that comparable results are obtained in solvents such as methanol, acetonitrile, chloroform, dichloromethane and methanol- dichloromethane mixtures (Scheme 22 and Table 1).[53]

Scheme 22



The results are summarised in Table 1. In most cases the reactions were carried out for 12 h. However, the complex formation is essentially complete in 0.5h in methanol (Table 1, entry 2).

Table 1. Partial resolution of racemic 1,1'-bi-2-naphthol using (S)-proline in various solvents[a]

S. No	Reaction Time	Solvent	1,l'-bi-2-naphthol from			
			Precipitate		Filtrate	
			% ee[b]	% Yield	% ee	% Yield
	12 h	CH_3OH	S 46	49	R 54	43
2.[c]	0.5 h	CH3OH	**S** 50	55	R 66	38
3.[d]	12 h	CH_2Cl_2	**S** 52	49	R 70	40
4.[d]	3h	CH_2Cl_2	**S** 46	56	R 73	35
5.[d]	36 h	CH_2Cl_2	**S** 66	52	R 63	38
6.[e]	12h	CH_3CN	**S** 52	43	R 52	40
7/	12 h	$CHCl_3$	**S** 49	48	R 58	39
8.[g]	12 h	$CH_3OH + CH_2Cl_2$	**S** 78	32	R 49	52

a) All experiments were performed using racemic 1,1'-bi-2-naphthol (5 mmol) and (S)-proline (5 mmol).

b) $[\alpha]_D^{25}$ = 34.5 for compound with 100% ee. Various authors report the values $[\alpha]_D^{25}$ of from 33.2 (ref. 48) to 35.2 (ref. 49) (C1, THF) for 1,1'-bi-2-naphthol of 100% ee. The Fluka catalogue (1995-96) reports the value of 34.5±1 for a sample of purity > 99% ee. We have calculated the ee values on the basis of the value of = 34.5 (C1, THF) for 100 %ee. This was also confirmed for few samples through chiral HPLC analysis on chiral pak OP columns.

c) The substrates were taken in methanol (15 ml) and heated at 60 °C for 10 minutes and left at 25 °C.

d) The substrates were taken in dichloromethane (20 ml) and refluxed

e) The substrates were taken in acetonitrile (15 ml) and heated at 60 °C for 10 minutes and left at 25 °C.

f) The substrates were taken in chloroform (30 ml) and heated at 60 °C for 10 minutes and left at 25 °C.

g) Dichloromethane (10 ml) and methanol (1 ml) were added to the substrates and the contents were refluxed.

Since allowing the reaction mixture at 25 °C for more time could result in excessive precipitation, which in turn is likely to reduce the enantiomeric purity, it was thought that filtering the reaction mixture at hot conditions would give better results. Unfortunately, the reaction mixtures after refluxing in methanol and filtering at hot yielded the S(-)-l in 59% ee but only in 7% yield.

It was noticed that the isomer present in the solution was obtained in better enantiomeric excess when the reactions were carried out in dichloromethane (entries 3-5, Table 1). We have also examined the effect of time to improve the enantiomeric excess of the products. However, the results of reaction after 3h and 12h are similar (entries 3-4, Table 1). Also, refluxing the mixture for 36h in dichloromethane resulted in only slight improvement in the ee of the S-(-)-l (entry 5, Table **1).**

1.2.2 Partial resolution of racemic l,l'-bi-2-naphthol: Effect of concentration of (S)-proline (24)

To determine the optimum amount of resolving agent required for the resolution process, the effect of concentration of the (S)-proline (24) was studied.

Table 2. Partial resolution of racemic l,l'-bi-2-naphthol: Effect of concentration of (S)-proline*

S. No	(S)-proline (24)	1,1'-bi-2-naphthol from			
		Precipitate		Filtrate	
		%ee	% Yield	%ee	ó Yield
1.	2.5 mmol	S 46	49	R 54	43
2.	5.0 mmol	S 52	49	R 70	40
3.	7.5 mmol	S 52	43	R 52	40
4.	10 mmol	S 49	48	R 58	39
5.[b]	5 mmol	S 60	25	R 21	69
6.[c]	5 mmol	-	-	R,S 00	100

a) All the experiments were carried out using racemic 1,1'-bi-2-naphthol 1 (5 mmol) in methanol. In entries 1 and 2, methanol (15 ml) and in other entries 25 ml methanol was used. The components were heated at 60 °C for 10 minutes and left at 25 °C for 12 h. The ee values are calculated on the basis of $[\alpha]_D^{25}$ = 34.5 for 100% ee.

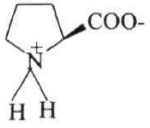
b) KOH (1.5 mmol) was added to the reaction mixture.

c) p-Toluenesulphonic acid (5 mmol) was added to the reaction mixture.

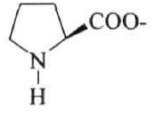
Though comparable results were obtained using (S)-proline (24) and 1,1'-bi-2-naphthol (1) in different ratios (Table 1, entries 1-4), they were used in 1:1 ratio for farther studies.

1.2.3 Partial resolution of racemic 1,1'-bi-2-naphthol (1) using (S)-proline (24): Effect of additives

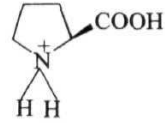
Since amino acids exist in the form of zwitter ion (i.e. **24a),** it was of interest to study the effect of deprotonated **(24b)** and protonated **(24c)** forms towards complexation with **1.** To examine this, experiments were carried out in the presence of KOH and p-toluenesulphonic acid (PTSA) in methanol (Table 2, entries 5-6). Addition of KOH, which is expected to favour the formation of **24b,** gave results without improvement. Interestingly, in the presence of PTSA, which is expected to promote the formation of the species **24c,** no precipitation occurred. This observation may indicate that the carboxylate form may be necessary for the resolution (Table 2, entries 5&6).



24a



24b



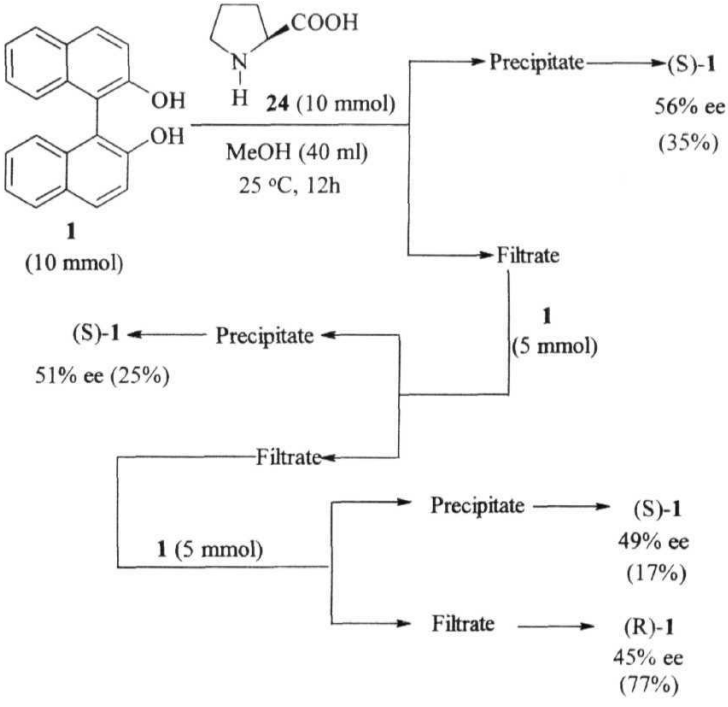
24c

1.2.4 Partial resolution of racemic l,l'-bi-2-naphthol (1): Sequential addition of racemic l,l'-bi-2-naphthol to (S)-proline (24) in methanol

An interesting observation was made when (S)-proline (24) (10 mmol) was taken in methanol and portions of 1 were added successively to obtain the

diastereomeric complex as precipitate (Scheme 23). In this way, mixtures of 1 enriched in (S) isomer were obtained in 49 - 56% ee and the sample enriched in (R) isomer (45% ee) was finally obtained from the filtrate fraction (Scheme **23).**

Scheme 23



1.2.5 Enrichment of enantiomeric excesses of partially resolved (scalemic) 1,1'-bi-2-naphthol using (S)-proline

Since the above resolution procedures did not result in complete resolution of racemic 1, we have attempted to recrystallize the diastereomeric complex obtained in methanol. After recrystallisation of the complex obtained from racemic 1 and (S)-proline in methanol, followed by dil.HCl treatment, the (S)-(-)-l was obtained in 81% ee (12% yield). The (S)-(-)-l sample of 37% ee (24% yield) was recovered from the solution.

Since this crystallisation method was not satisfactory, we decided to repeat the experiments starting from partially resolved 1 using equivalent amount of (S)-proline again. The results obtained in methanol solvent are summarised in Table 3. The ee of the (S)-l isomer could be further enhanced in this way (entries 1&2, 5&6). It may be of interest to note that better results were obtained previously using benzene as solvent (Scheme **21).**[50]

1.2.6. Structural characterisation of the 1,1'-bi-2-naphthol-(S)-proline complex 25

Elemental analysis of the complex formed between l,l'-bi-2-naphthol (1) and (S)-proline (24) revealed the presence of 1 and (S)-proline (24) in 2:1 ratio.

Table 3. Enrichment of enantiomeric excesses of partially resolved (scalemic) 1 using (S)-proline in methanol [a]

S. No	1,1'-bi-2-naphthol (1)	l,l'-bi-2-naphthol (1) from			
		Precipitate		Filtrate	
	(%ee)	%ee	% Yield	% ee	% Yield
1.[b]	S 47	S 70	62	R 03	27
2.[c]	S 57	S 83	69	R 40	14
3.[c]	R 47	S 43	12	R 71	73
4.[d]	R 73	--	00	R 73	100
5.[e]	S 69	S 85	70	S 18	17
6/	S 66	S 81	62	S 09	21

a) In all experiments, 1,1 '-bi-2-naphthol (5 mmol) and (S)-proline (5 mmol) were used. The ee values are calculated on the basis of $[\alpha]_D^{25}$ = 34.5 for 100% ee.

b) The components were dissolved in methanol (15 ml), heated at 60 °C for 10 minutes and left at 25 °C for 12h.

c) Refluxed in dichloromethane (25 ml) for 12h (in entry 3, 20 ml of dichloromethane was used).

d) Refluxed in dichloromethane (20 ml) for 12h.

e) Refluxed in acetonitrile (20 ml) for 12h.

f) Refluxed in methanol (1 ml) and dichloromethane (10 ml) mixture for 12h.

We have also examined the nature of the complex formed between l,l'-bi-2-naphthol and (S)-proline (24) through X-ray crystal structure analysis. The crystals obtained in the reaction of racemic 1 and (S)-proline in methanol were not suitable for X-ray crystal structure analysis. Fortunately, (S)-proline reacts with (S)-l to form a crystalline complex 25 in methanol suitable for X-ray diffraction analysis.[53] The intermolecular organization and association in the diastereomeric complex 25 are depicted in Figures **1** and **2.**

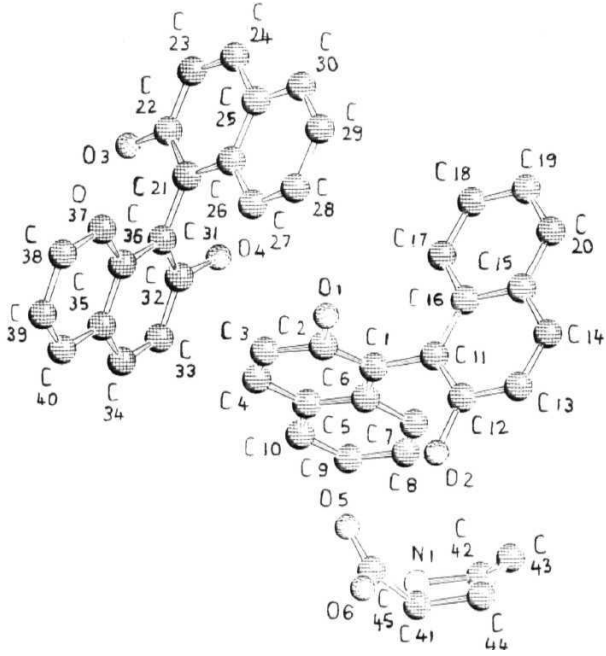


Figure 1 : Perspective view of the complex 25.

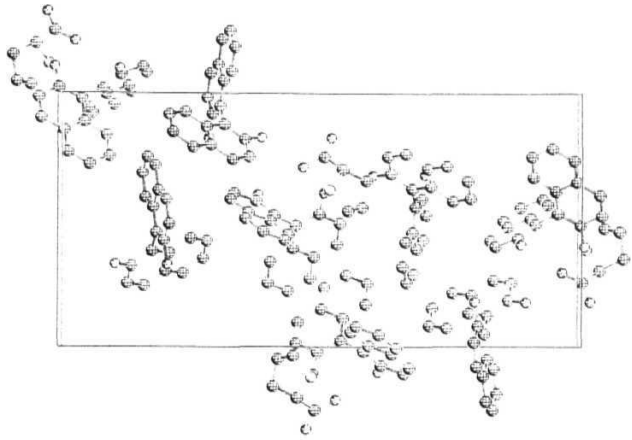


Figure 2: Packing diagram of the crystal structure of the complex 25.

The carboxylate and quaternary ammonium groups of the proline molecule make T-shaped hydrogen bonds with the hydroxyl group of the one bi-2-naphthol with the OH...N and O...HO distances of 2.088 and 2.109 A^0 respectively leading to the locally hydrogen bonded 1:1 host-to-guest complex. The host-guest interaction between one bi-2-naphthol and proline is complemented by a *n-n* stacking interaction between the bi-2-naphthols C21C22C23C24C25C26C27C28C29C30 and C11C12C13C14C15C16C17C18C19C20. Within the bi-2-naphthol that exhibits hydrogen bonding interaction with the proline molecule, the two naphthyl moieties are nearly perpendicular to each other with the dihedral angle between the mean planes 94.0°. However, in the other bi-2-naphthol the dihedral angle between

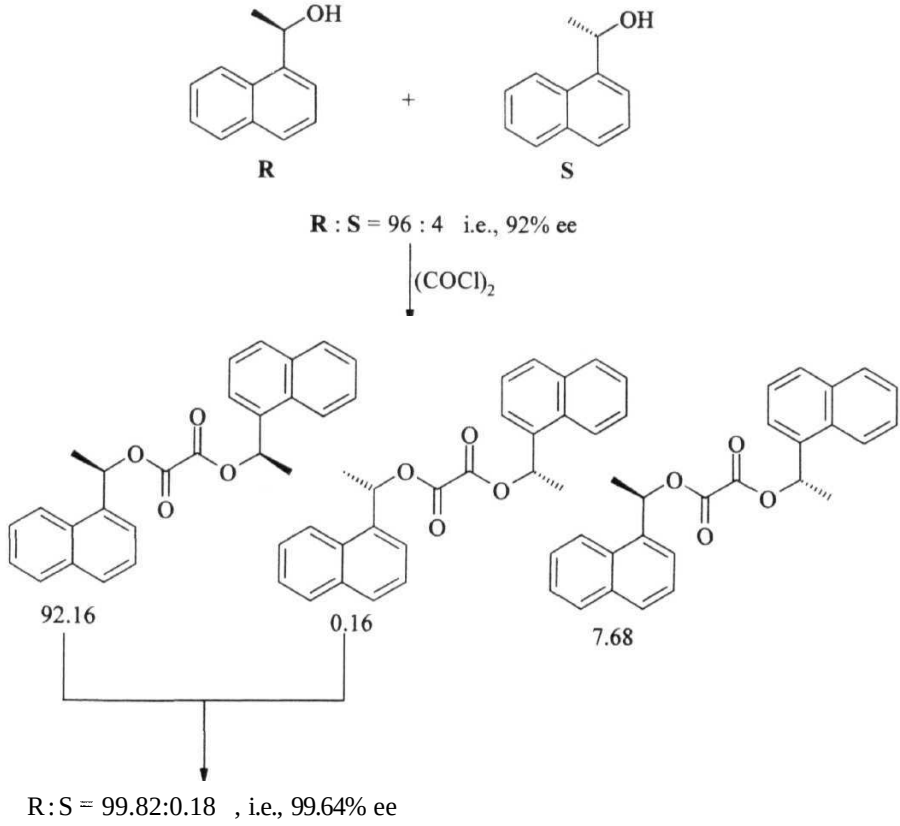
the mean planes of the naphthyl rings is 73.5°. Here, the larger bi-2-naphthyl groups probably prevent a simultaneous close approach of the two bi-2-naphthols near the proline molecule. There is also an another hydrogen bonding interaction between the two binaphthols where one CH group of the naphthyl ring acts as a proton donor and the oxygen site of the hydroxyl group acts as a proton acceptor at CH..0 distance of 2.715 A^0.[54]

1.2.7 Enhancement of enantiomeric excesses of scalemic l,l'-bi-2-naphthoI using $B(OH)_3$ and TMEDA

Although the (S)-proline used in the resolution and enrichment procedures (Scheme **21-23)** can be recovered easily, it would be advantageous if the partially resolved (scalemic, non-racemic) 1 could be enriched further without using another chiral source. In 1973, Horeau reported that chemical duplication of a non-racemic substrate, for example, through formation of two diastereomeric carbonate diesters from a scalemic alcohol, separation of the homochiral (RR, SS) chiral dimer and the achiral meso (RS) dimer and regeneration of the alcohol from the homochiral (RR, SS) dimer provided the scalemic alcohol with increased enantiomeric excess.[55]

Later, this idea was applied by Fleming and Ghosh to enrich the enantiomeric excess of a scalemic alcohol (R,S) (from 92.0% ee to 99.6% ee) using oxalyl chloride (Scheme 24).[56]

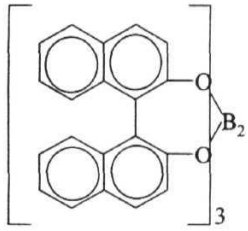
Scheme 24



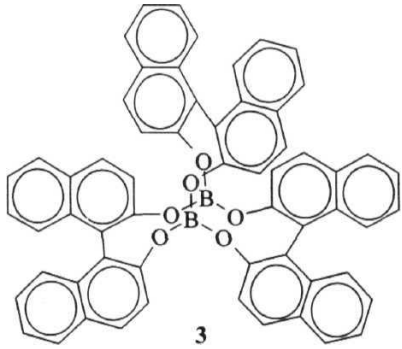
Also, Fleming and Ghosh showed that if there is no stereoselection, the derivative ML_2 would be formed following the algebraic expression, $X^2 : Y^2 : 2XY$. For example, if the starting enantiomeric excess is 80%, (i.e., X:Y = 90:10, X,Y are the concentrations of R and S, respectively) and since $(X^2 + Y^2)$ and 2XY are diastereomers, separation of the RR and SS diastereomers $(X^2 + Y^2)$ from the above

mixture and regeneration of R and S enantiomers should give R:S in the ratio (X^2 : Y^2) 8100:100 = 98.8:1.2, corresponding to an ee of 97.6%.

We were interested in adopting a similar idea for the enrichment of enantiomeric excess of scalemic 1. Since 1 is a bifunctional molecule, it can form a complex of the type (26).



26



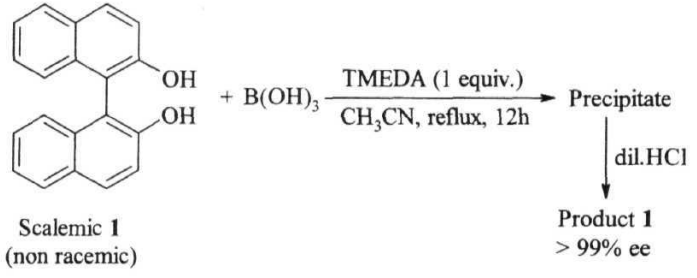
3

In such a situation, four isomers derived from RRR, SSS, RRS and RSS combinations of l,l'-bi-2-naphthol would be expected in the ratio of $X^3 : Y^3 : 3X^2Y : 3XY^2$. An initial ratio of R : S, 90 : 10 (X : Y = 90 : 10, i.e., 80% ee), would lead to the R:S ratio of $X^3 : Y^3$ (i.e. 99.86:0.14, 99.72% ee) after separation of RRR and SSS ($X + Y^3$) isomers and regeneration of R and S. However, it should be pointed out that this product distribution can be expected only if there is no stereoselectivity in the formation of RRR, SSS or RRS, SSR.

We have carried out a series of experiments to examine these possibilities. Initially, we have attempted to prepare the complex of the type 26 from $B(OH)_3$ and

1 in benzene using Dean-Stark apparatus. Unfortunately, the enriched enantiomer was obtained only in low yields (Table 4a, entry 1). Fortunately, better results were obtained (Scheme 25) when 1 and $B(OH)_3$ were taken in 3:2 ratio in acetonitrile and TMEDA was used to precipitate the complex (Table 4a, entries 2 and 3). However, the results are still poor. The results are better when the scalemic 1 and $B(OH)_3$ are taken in 5:2 ratio (Table 4a, entries 4-7).

Scheme 25



It is clear from the results that the precipitate fraction contains the enriched isomer, leaving behind the mixture with low ee in solution. So, it was decided to use $B(OH)_3$ equivalent to the enantiomer present in excess over the racemic 1 to form the complex 26. This led to very good results (Table 4b).

Table 4a. Enhancement of enantiomeric excesses of l,l'-bi-2-naphthol (1) using $B(OH)_3$ and TMEDA [a]

Entry No.	1 (% ee)	$B(OH)_3$ (mmol)	Product 1 obtainec from			
			Precipitate		Filtrate	
			%ee	Yield (%)[c]	%ee	Yield (%)[c]
1.	S 47	2.0	S 91	20	S 38	69
2.[b]	R 62	2.0	R 73	78	R 40	06
3.	R 34	2.0	R 51	47	S 03	33
4.[b]	R 16	2.0	R 41	28	R 01	56
5.[b]	S 28	2.0	S 58	38	R 03	52
6.	S 18	2.0	S 31	57	S 05	30
7.	R 34	2.0	R 88	38	R 12	48

a) All experiments were carried out using 5 mmol of 1 (in entries 1-3, only 3 mmol of 1 was used) and 1 mmol of TMEDA in acetonitrile (20 ml). The ee values are calculated on the basis of $[\alpha]_D^{25} = 34.5$ for 100% ee.

b) In these experiments, benzene (40 ml) was used as solvent and the contents were refluxed for 12h.

c) Yields are based on the amount of scalemic 1 used.

In the experiments using mixtures with high ee, the yields of enriched material were somewhat low and more amounts were left in solution (Table 4b, entries 4&5 and 9&10). This problem was rectified by using excess of TMEDA (5 equiv.) to precipitate the complex 26 (entries 11&12).

Table 4b. Enhancement of enantiomeric excesses of l,l'-bi-2-naphthol (1) using $B(OH)_3$ and TMEDA *

Entry No.	1 (% ee)	$B(OH)_3$ (mmol)	Product 1 obtained from			
			Precipitate		Filtrate	
			% ee	Yield (%)[c]	% ee	Yield (%)[c]
1.	R 17	0.57	R 88	11	R 03	76
2.	R 34	1.14	R 92	31	S 05	55
3.[b]	R 52	1.80	R 95	30	R 20	53
4.	R 68	2.30	R 94	41	R 52	45
5.	R 75	2.50	R 93	48	R 63	39
6.	S 18	0.60	S 89	13	S 05	75
7.	**S** 34	1.10	S 95	28	S 01	54
8.	**S** 52	1.80	**S** 95	38	**S** 16	47
9.	**S** 69	2.30	**S** 93	52	**S** 34	36
10.[b]	**S** 85	2.90	**S** 93	53	**S** 73	33
11.[b]	**R** 79	2.67	R 93	77	**S** 06	10
12.[b]	**S** 75	2.50	**S** 95	77	R,S 00	10

a) All experiments were carried out using 5 mmol of 1 in acetonitnle (20 ml). In entries 1-10, 1 mmol of TMEDA and in entries 11 and 12, 5 mmol of TMEDA was used. The ee values are calculated on the basis of $[\alpha]_D^{25}$ = 34.5 for 100% e

b) HPLC analysis on chiralpak OP using methanol as eluent did not detect the presence of the other enantiomer. Accordingly, the enantiomeric purity of these samples could be ≥ 99% ee.

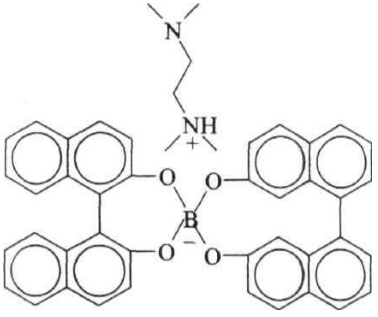
c) Yields are based on the amount of scalemic 1 used.

The results are in accordance with the selective formation of RRR or SSS complexes derived from the enantiomer present in excess over the racemic mixture. Poor results obtained when the scalemic 1 and $B(OH)_3$ were used in 3:2 ratio may indicate that the homochiral diastereomers RRR and SSS, and the heterochiral diastereomers RRS and SSR might not have formed as per the algebraic expression discussed above.

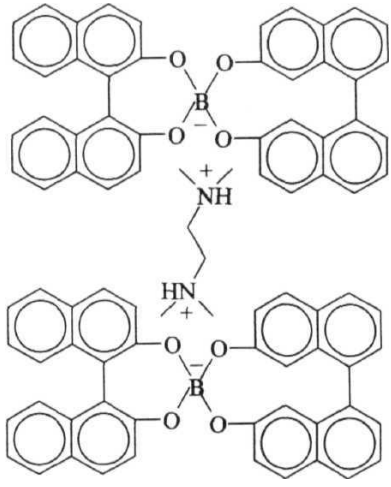
As outlined in the introoductory section, Kaufmann has previously noted that the reaction of racemic 1 with $BrBH_2.SMe_2$ results in the formation of enantiomers of the C_3 symmetric propeller compound 3 (Scheme 2).[17] It appears that the 1,1'-bi-2-naphthol tends to form the symmetric RRR and SSS compounds rather than the unsymmetrical SRR and RSS isomers. Unfortunately, the nature of the TMEDA complex of the borate complex obtained under the present conditions is not clearly understood. The complex is not crystalline enough for X-ray crystal structure analysis and we could not arrive at a molecular formula based on elemental analysis.

However, we have observed that the reaction of racemic 1 (3 equiv.) and boric acid (2 equiv.) in refluxing benzene (Dean-Stark apparatus) resulted in the formation of Kaufmann's C_3 symmetric RRR and SSS propeller 3 (see experimental

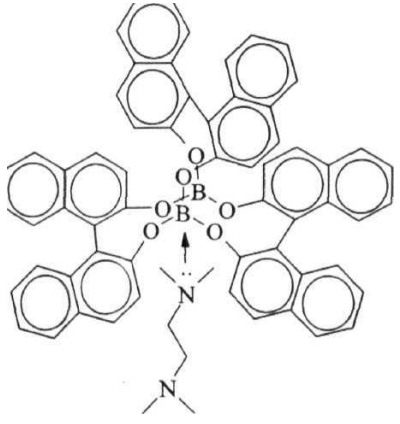
section). Presumably, the complication may be due to the formation of the ammonium borate complexes 27a and 27b in addition to the propeller complexes 27c to some extent.



27a



27b

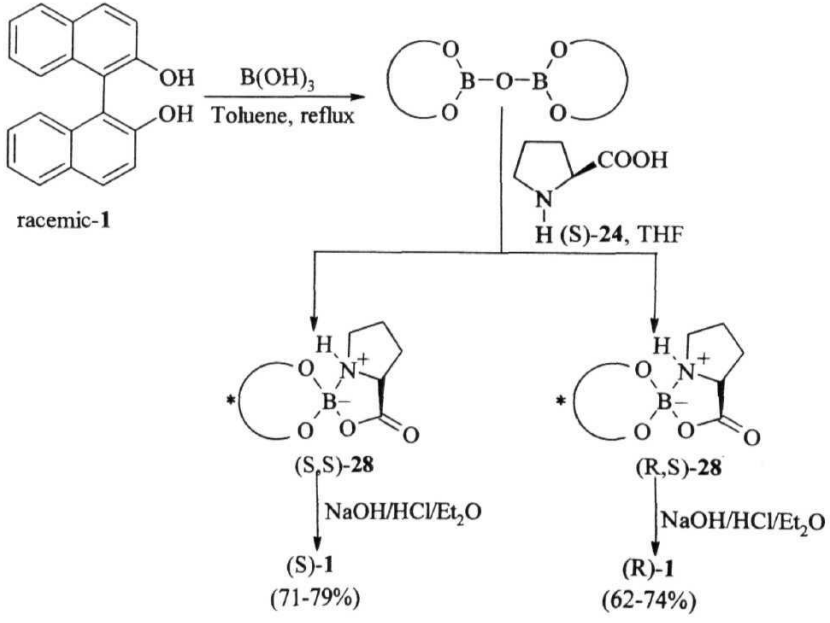


27c

1.2.8 One step procedure for resolution of racemic 1,1'-bi-2-naphthol (1) using $B(OH)_3$ and (R)-α-methylbenzylamine

After we have published our results on the resolution of racemic **l,l'-bi-2-**naphthol (1) using (S)-proline, Shan and co-workers **reported,** a modified procedure using (S)-proline and $B(OH)_3$ in THF solvent (Scheme 26)[58]. They prepared the l,l'-bi-2-naphthol boric anhydride through the reaction of racemic l,l'-bi-2-naphthol and $B(OH)_3$ (1:1 ratio) in toluene that on reaction with (S)-proline gave the diastereomeric derivative 28. The diastereomers were effectively separated to obtain optically active 1,1'-bi-2-naphthol after workup (Scheme 26).

Scheme 26



Although these procedures of resolution of racemic 1 involve the use of inexpensive (S)-proline, recovery of the water soluble amino acid is somewhat difficult. Therefore, we have undertaken studies to explore the development of a convenient resolution procedure using $B(OH)_3$ and a chiral amine which can be readily recovered.

In the enrichment experiments discussed above (Scheme 25), the l,l'-bi-2-naphthol (1) forms a borate complex with $B(OH)_3$ and TMEDA in CH_3CN. This prompted us to explore the development of a convenient resolution procedure using $B(OH)_3$ and a chiral amine. It was observed that the (R)-(+)-a-methylbenzylamine 29 (3 equiv.), $B(OH)_3$ (2 equiv.) and racemic 1 (3 equiv.) gave a precipitate on heating at reflux in CH_3CN (Scheme 27).

Scheme 27

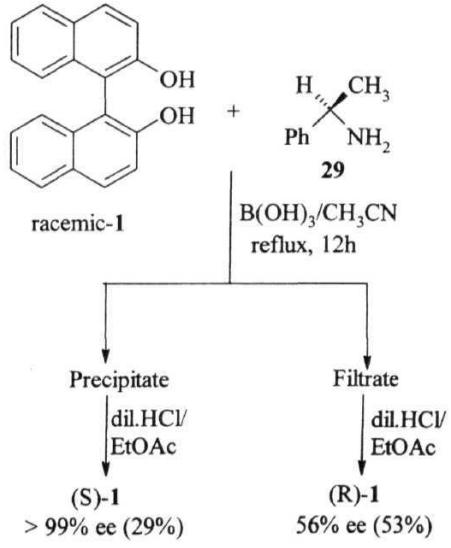


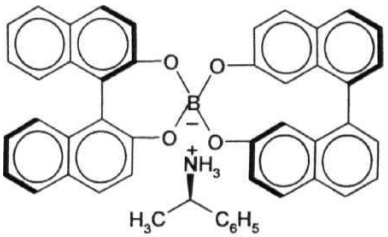
Table 5. One step resolution of racemic 1 using $B(OH)_3$ and (R)-(+)-α-methylbenzylamine (29)*:

S.No	1 (mmol)	$B(OH)_3$ (mmol)	29 (mmol)	Product 1 obtained from Precipitate %ee	Precipitate yield (%)	filtrate %ee	filtrate Yield (%)
1	3	2	3	(-)87	30	(+)27	56
2	6	6	6	(-)83	29	**(+)29**	64
3	6	12	12	(-)66	23	(+)23	67
4	12	12	12	(-)80	32	**(+)43**	55
5	12	6	6	(-)09	58	(+)21	35
6	12	6	12	(-)25	54	**(+)34**	33
7	6	2	6	(-)97	29	**(+)56**	52
8	6	2	6	(-)>99	29	(+)52	56
9	6	2	9	(-)>99	29	**(+)45**	58
10	6	3	9	(-) > 99	29	(+)53	58

a) All the experiments were carried out using amounts of 1, $B(OH)_3$ and (R)-(+)-α-methylbenzylamine indicated in the Table 5 in acetonitrile (in entries 1-3 20 ml, entries 4-6 30 ml, entries 7, 9 & 10 15 ml and 8 10 ml). The contents were refluxed for 12h. The ee values are calculated on the basis of the value of $[\alpha]_D^{25} = 34.5$ (C1, THF) for the sample of 100% ee.

Decomposition of the precipitate with dil.HCl gave the (S)-(-)-l in > 99% ee (29% yield, 58% of theoretical). The filtrate upon evaporation followed by dil.HCl treatment of the residue gave the (R)-(+)-l in 56% ee (53% yield). The use of (S)-(-)-α-methylbenzylamine gave the (R)-(+)-1 in > 99% ee and (S)-(-)-l in 52% ee in similar yields.[59]

We have used the 1 and boric acid in 3:2 ratio in these experiments, since it was anticipated that heating of the mixture of these substrates in benzene would lead to the formation of the C_3 symmetric propeller 3. Unfortunately, recrystallisation of the precipitate obtained in Scheme 27 using (±)-l, boric acid and 29 did not yield crystals suitable for X-ray crystal structure analysis. Very recently, it was observed in this laboratory that the filtrate obtained in this resolution experiments (Scheme 27) on standing yielded crystals suitable for X-ray crystal structure analysis.[59] The data revealed that the crystal obtained in this way is the ammonium borate complex **30**.[60]



30

Clearly, the l,l'-bi-2-naphthol and boric acid tend to form a complex of the type 30 in the presence of chiral α-methylbenzylamine. Therefore, we have carried out the resolution experiments using racemic 1 and boric acid in 2:1 ratio with different amounts of (R)-(+)-α-methylbenzylamine in CH_3CN (Table 6).

Table 6. Resolution of 1,1'-bi-2-naphthol using $B(OH)_3$ and (R)-(+)-a-metbylbenzylamine *

S. No	1 %ee	(+)-29 (mmol)	Solvent	Optically Active 1 from			
				Precipitate		Filtrate	
				%ee	Yield (%)	%ee	*Yield* (%)
1	0	15	CH_3CN	S, 91	40	R,61	50
2	0	10	CH_3CN	S, 81	45	R,40	50
3	S, 30	10	CH_3CN	S,97	55	R, 55	38
4	0	5	THF	R, 95	24	S,20	70
5	R, 20	5	THF	R, 97	25	S,20	68
6	R, 34	5	THF	R, >99	28	S,25	65

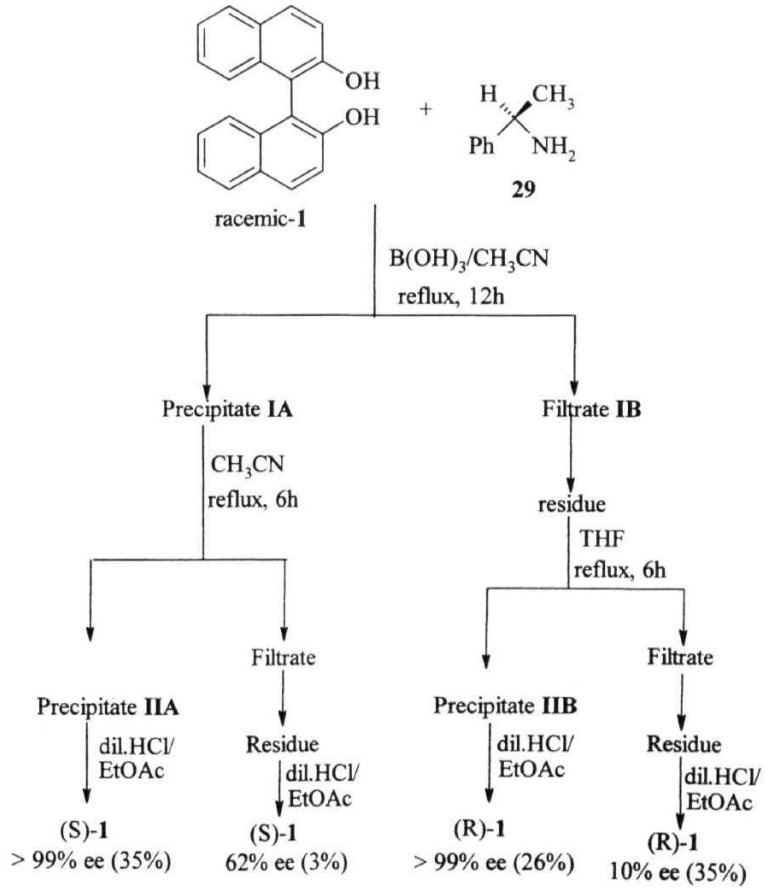
a) All experiments were performed using 1,1'-bi-2-naphthol (10 mmol), $B(OH)_3$ (5 mmol) and (R)-(+)-α-methylbenzylamine as mentioned in the Table 6. The substrates were taken in the solvent (20 ml) and the contents were refluxed for 12h

The partially enriched 1 gives better results (entry No. 3, Table 6). Moreover, it was observed that when THF was used as solvent, the opposite enantiomer was isolated from the precipitate in 95% ee (Table 6, entries 4-6). Again, the results are better when partially enriched 1 was used (Table 6, entries 5-

6). Obviously, one of the diastereomers is insoluble in CH_3CN and the other is insoluble in THF.

We have exploited this difference in solubility of the diastereomeric ammonium borate complexes in CH_3CN and THF to develop a convenient, practical method of resolution to obtain both (R)-l and (S)-l in > 99% ee using (R)-(+)-α-methylbenzylamine (Scheme 28).

Scheme 28

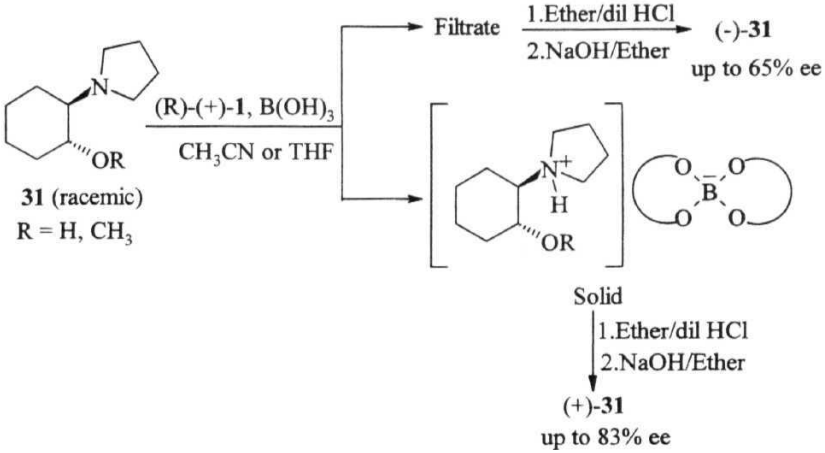


The recovered (S)-(-)-l (62% ee, 3% yield) and (R)-(+)-l (10% ee, 35% yield) have been recycled to obtain 1 with > 99% ee (Table 6 and Scheme 28). The experiment was also carried out using 50 mmol of racemic 1 and proportional amounts of other reagents to obtain chiral 1 with > 99% ee and there was no significant change in yields. The chiral amine and the solvents used can be readily recovered for use again. Therefore, the procedure described here for the resolution of l,l'-bi-2-naphthol (1) using inexpensive reagents should be highly economical.

1.2.9. Recent resolution studies using chiral l,l'-bi-2-naphthol

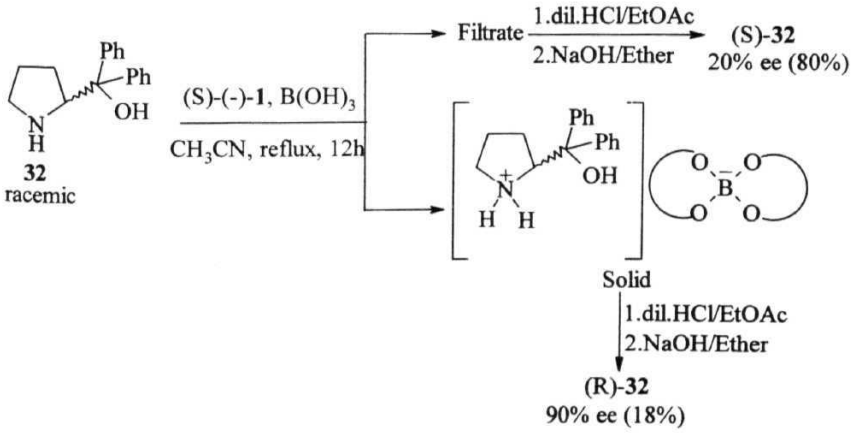
Recently, systematic investigations were carried out in this laboratory to use the chiral l,l'-bi-2-naphthol (1) for the resolution of several amino alcohols of interest. The trans-(±)-2-(pyrrolidinyl)cyclohexanol (31) and its methyl ether were resolved using chiral 1,1'-bi-2-naphthol (1) and $B(OH)_3$ in THF or CH_3CN (Scheme 29).[61]

Scheme **29**



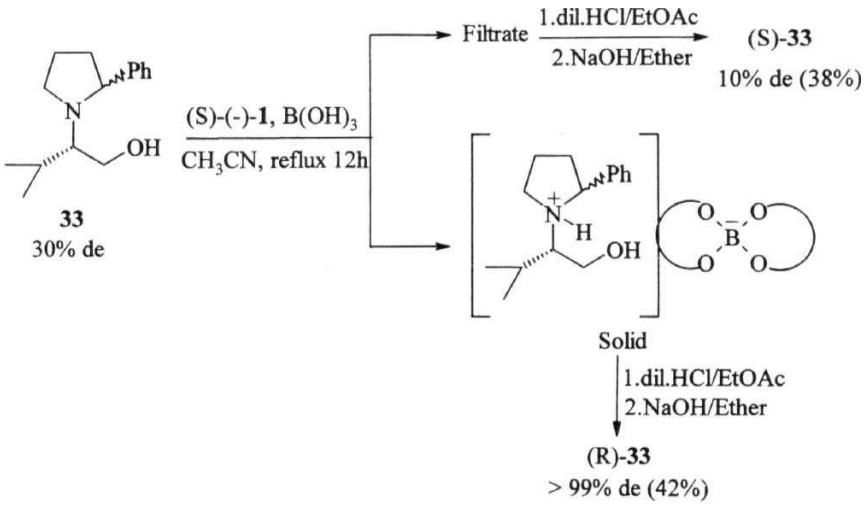
Also, resolution of the commercially important racemic α,α-diphenyl-2-pyrrolidinemethanol (32) could be effected through the preparation of the corresponding diastereomeric ammonium borate complexes using chiral bi-2-naphthol and $B(OH)_3$ (Scheme 30).[62]

Scheme 30



It was also discovered in this laboratory that the diastereomeric mixture of amino alcohol 33 can be readily purified using optically active l,l'-bi-2-naphthol (1) and B(0H)3 through preparation of the corresponding diastereomeric complexes as outlined in Scheme **31**.[62]

Scheme 31



In all cases, X-ray crystal structure analysis indicated that the complexes are ammonium borates of the type 30, containing 1,1'-bi-2-naphthol, $B(OH)_3$ and amine in 2:1:1 ratio.

1.3 Conclusion

Simple, convenient procedures for resolving racemic 1,1'-bi-2-naphthol (1) using (S)-proline were developed. The structure of the complex formed between 1,1'-bi-2-naphthol (1) and (S)-proline was characterised by X-ray diffraction method. Enantiomeric excesses of the incompletely resolved 1, 1'-bi-2-naphthol (1) samples were enriched to obtain essentially pure (R) and (S)-1 following a simple procedure using $B(OH)_3$ and TMEDA. A convenient, practical method of resolution to obtain both (R)-1 and (S)-1 in > 99% ee using (R)-(+)-α-methylbenzylamine and boric acid has been developed.

1.4 Experimental Section

1.4.1 General Information

Melting points reported in this thesis are uncorrected and were determined using a Buchi-510 capillary point apparatus. Infrared spectra were recorded on Perkin-Elmer IR Spectrometer Model-257 with polystyrene as reference. ^{1}H NMR and ^{13}C NMR spectra were recorded on BRUKER-AC-200 spectrometer with deuterated chloroform as solvent and TMS as reference (5=0 ppm). The chemical shifts values are expressed in ppm down field from the signal for internal TMS. Elemental analyses were performed on Perkin-Elmer elemental analyser model 240C. Mass spectral analysis was carried out on VG 7070H mass spectrometer using EI technique at 70 eV at the Indian Institute of Chemical Technology, Hyderabad, India.

Optical rotations were measured on AUTOPOL II automatic polarimeter (readability 0.01°) and JASCO polarimeter (readability 0.001°). The condition of the polarimeter was checked by measuring optical rotation of a standard solution of (R)-(+)-α-methylbenzylamine $[\alpha]_D^{25}$ (+) 30.2 (C1.0, EtOH) supplied by Fluka, Switzerland. Analytical thin layer chromatographic tests were carried out on glass plates (3x10 cm) coated with 250 mu Acme's silica gel G or GF containing 13%

calcium sulphate as binder. The spots were visualised by a short exposure to iodine vapour or UV light. Column chromatography was carried out using Acme's silica gel (100-200 mesh).

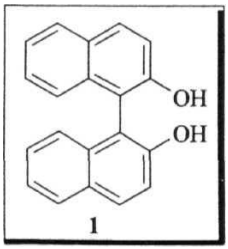
(R)-(+)-a-Methylbenzylamine supplied by Fluka, Switzerland and (S)-proline supplied by Aldrich, USA were used. Boric acid and TMEDA were supplied by Loba Chemicals, India. Methanol was distilled over calcium oxide. Benzene and THF were distilled from benzophenone-sodium. Amines were distilled over anhydrous KOH prior to use. Tetrahydrofuran supplied by E-Merck, India was kept over sodium-benzophenone ketyl and freshly distilled before use.

All the glassware were predried at 140 °C for at least 4h, assembled when hot and cooled under a stream dry nitrogen. Hexane refers to the fraction boiling between 60-80 °C. As a routine, all the organic extracts were washed with saturated sodium chloride solution (brine) and dried over anhydrous $MgSO_4$ and concentrated on a Buchi-EL rotary evaporator. All yields reported are isolated yields of material judged homogenous by TLC, IR and NMR spectroscopy.

1.4.2a Preparation of racemic 1,1'-bi-2-naphthol from 2-naphthol using FeCl3

In a two necked round bottom flask fitted with a reflux condenser, 2-naphthol (100 mmol, 14.4 g) and distilled water (600 ml) were taken and the contents were heated to reflux. A solution of $FeCl_3.3H_2O$ (100 mmol, 28 g) in 60 ml of distilled

water was added through an additional funnel during 1h. The oily drops of 2-naphthol disappeared and a solid separated out. The contents were boiled for 15-20 minutes and filtered at hot. The crude product was recrystallised from toluene (300 ml).



1

Data for 1

Yield	: 75% (10.7 g)
M.P.	: 217-218 °C (Lit.[63] 218 °C)
	: 3487, 3404, 1628, 1595, 1174 cm^{-1}
^{1}H NMR (200 MHz, $CDCl_3$)	: 6 ppm 5.1 (s, 2H), 7.1-7.30 (m, 8H) 7.8-7.9 (m, 4H) (Spectrum No. 1)
^{13}C NMR (50 MHz, $CDCl_3$)	: δ ppm 111.0, 117.8, 124.1, 124.3, 127.5, 128.4, 129.5, 131.4, 133.5, 152.8 (Spectrum No. 2)

The spectral data showed 1:1 correspondence with the reported data.[40]

1.4.2b Preparation of racemic 1,1'-bi-2-naphthol from 2-naphthol using Cu(OH)Cl.TMEDA[40]

a) Preparation of Cu(OH)Cl.TMEDA: A mixture of CuCl (10 g, 100 mmol) and TMEDA (23.2 g, 200 mmol) was taken in methanol (95%, 60 ml) in a 100 ml RB flask. The contents were stirred under oxygen atmosphere at 25 °C for 1h. The precipitate formed was filtered, washed with acetone (3X5 ml) and dried under vacuum to get a purple powder .

Yield: : 88% (20.3 g)

M.P. : : 136-137 °C

Lit[38] M.P. : 137-138 °C

b) Oxidative coupling of 2-naphthol using Cu(OH)Cl.TMEDA: A mixture of 2-naphthol (100 mmol, 14.4 g) and Cu(OH)Cl.TMEDA (1 mmol, 0.23 g) were taken in dichloromethane (200 ml) and the contents were stirred at 25 °C for lh in open air. The solvent was evaporated and the residue was recrystallised from toluene (300 ml).

Yield : 80% (11.4 g)

M.P. : 216-217 °C

Lit[63] M.P. :218°C

1.4.3 Resolution of racemic 1,1'-bi-2-naphthol using (S)-proline

Typical Procedure : Racemic 1,1'-bi-2-naphthol (5 mmol, 1.43g) and (S)-proline (5 mmol, 0.58 g) were taken in methanol (20 ml). The contents were heated at 60 °C for 12h. Then the reaction mixture was brought to 25 °C and filtered. Methanol was evaporated to obtain a residue. The precipitate and the residue were treated with a mixture of diethyl ether (100 ml) and dil.HCl (3N, 20 ml) in separate runs. The organic layer was separated, washed successively with water (2x 10 ml), brine (10 ml) and dried over anhydrous $MgSO_4$. The solvent was evaporated to obtain l,l'-bi-2-naphthol. The ee values are based on $[\alpha]_D^{25}$ = 34.5 (C1, THF) for compound with 100% ee.[53] The values were also confirmed for a few samples of 1,1'-bi-2-naphthol with > 90% ee by HPLC analysis with chiralpak OP column using methanol as solvent.

1,1'-Bi-2-naphthol obtained from the precipitate fraction:

Yield : 55% (0.79 g)

$[\alpha]_D^{25}$: (-) 17.24 (C1, THF)

Lit.[53] $[\alpha]_D^{25}$: (-) 34.5 (C1, THF)

1,1'-Bi-2-naphthol obtained from the filtrate fraction:

Yield : 38% (0.54 g)

$[\alpha]_D^{25}$: (+) 22.77 (C1, THF)

Lit.[53] $[\alpha]_D^{25}$: (+) 34.5 (C1, THF)

1.4.4 Enrichment of enantiomeric excesses of partially resolved l,l'-bi-2-naphthol using (S)-proline.

Typical Procedure : Partially enriched (-)-l,l'-bi-2-naphthol (1) (50% ee, 5 mmol, 1.43g) and (S)-proline (5 mmol, 0.58g) were taken in dichloromethane (20 ml) and the contents were refluxed for 12h. The reaction mixture was brought to 25 °C and filtered. The solvent was evaporated to obtain a residue. The precipitate and the residue were stirred in a mixture of diethyl ether (100 ml) and dil.HCl (3N, 20 ml) in separate runs. The organic layer was separated, washed successively with water (2x10 ml), brine (10 ml) and dried over anhydrous $MgSO_4$. The solvent was evaporated to isolate **1.**

1,1'-Bi-2-naphthol obtained from the precipitate fraction:

Yield : 62 % (0.89 g)

$[\alpha]_D^{25}$: (-) 24.15 (C1, THF)

Lit.[53] $[\alpha]_D^{25}$:(-)34.5(Cl,THF)

1,1'-Bi-2-naphthol obtained from the filtrate fraction

Yield : 27 % **(0.54** g)

$[\alpha]_D^{25}$: (+) 01.01 (C1, THF)

Lit.[53] $[\alpha]_D^{25}$: (+) 34.5 (C1, THF)

1.4.5 Enhancement of enantiomeric excesses of partially resolved (scalemic) 1,1'-bi-2-naphthol.

Typical Procedure : Scalemic l,l'-bi-2-naphthol (1) [(-)75% ee, 5 mmol)], $B(OH)_3$ (1.55 g, 2.5 mmol) and TMEDA were taken in acetonitrile (20 ml). The resulting suspension was refluxed for 12h. The reaction mixture was cooled to 25 °C and filtered. The filtrate was concentrated to obtain a residue. In separate runs, the precipitate and the residue were treated with diethyl ether (100 ml) and dil.HCl (3N, 20 ml) for 10 min., washed successively with water (2x10 ml), brine (10 ml) and dried over anhydrous $MgSO_4$. The solvent was removed to obtain **1.**

l,l'-Bi-2-naphthol obtained from the precipitate fraction:

Yield : 77 % (1.10 g)

M.P. : 208-210 °C (Lit.[51] 209-210 °C).

[a];,[5] : (-)32.60 (C1, THF)

Lit.[53] $[\alpha]_D^{25}$:(-)34.5(Cl,THF)

1,1'-Bi-2-naphthol obtained from the filtrate fraction

Yield : 10 % (0.14 g)

$[\alpha]_D^{25}$:(-)0.07(Cl,THF)

Lit.[53] $[\alpha]_D^{25}$:(-)34.5(Cl,THF)

1.4.6 Preparation of the diastereomeric complex of (S)-1,1'-bi-2-naphthol with (S)-proline in methanol

Suitable crystals of (S)-(-)-l,l'-bi-naphthol-(S)-proline complex were obtained by the following procedure: (S)-(-) 1 (5 mmol) was dissolved in methanol (20 ml). To the solution, (S)-proline (5 mmol) was added. The contents were heated at 60 °C gently for 10 minutes and left at 25 °C for 12h. The precipitated complex was re-dissolved in hot methanol (20 ml) and left at 25 °C for 12h to obtain the crystals of the complex 25.

Since the complex 25 formed in methanol was not soluble in most of the solvents, NMR spectra of the complex could not be recorded. However, elemental analysis of the complex revealed that 1 and (S)-proline are present in the ratio of 2:1 in the complex **25.**

Elemental analysis calculated for the complex 25

Calcd. for $C_{45}NO_6H_{37}$:	C% 78.58;	H% 5.42;	N% 2.46.
Found I	C % 78.36;	H % 5.50;	N % 2.04.

1.4.7 X-ray crystal structure analysis of the 1,1'-bi-2-naphthol-(S)-proline complex 25

The crystals obtained in the previous experiment was subjected to X-ray crystal structural analysis. A colourless prismatic crystal of dimension 0.35 x 0.25 x 0.52 mm suitable for X-ray diffraction was mounted on a glass capillary using glue and transferred to an automated Enraf-Nonius CAD4 diffractometer equipped with a graphite monochromator. Cell dimensions were obtained by the least-squares refinement of well centered 25 reflections in the 0 range 2.5 to 60.0 °. Intensity data were collected using Cu Ka (X =1.54184 A°) radiation by the ω-2θ scan mode with a constant scan speed of 4 deg/min. Decay of the crystal during the measurement

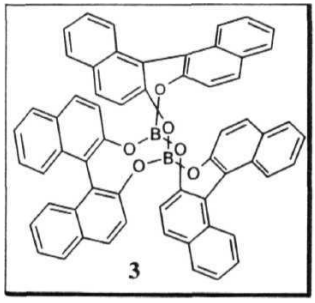
was monitored by measuring the intensity of two standard reflections at regular intervals and no appreciable deterioration of the crystal was noticed. 2933 unique data were collected out of which 2839 reflections had $I>2\sigma(I)$ and were flagged observed for subsequent calculations. The data were corrected for Lorentz and polarization effects.

The structure was solved by direct methods (SIR92) and refined on F^2 using Full-matrix least-squares technique (SHELXL92). All the hydrogens were located directly in different Fourier maps and refined isotropically. Convergence was achieved at R=0.0280 and wR=0.0756 for 2839 observed reflections. The final difference map revealed no chemically significant information and the residual density had maximum peak 0.314e $A^{\circ 3}$ and minimum trough at -0.245e $A^{\circ 3}$.

Crystal data for 25 (C45NO6H37): θ range 3.22 to 59 93°. Formula weight 687.76, Orthorhombic, Space group P 21 21 21, a = 9.0610(10) A°, b = 13.943(2) A°, c = 27.480(4) A°, V = 3471.8(8) $A^{\circ 3}$, Z = 4, $D_{calc.}$ = 1.316 g cm^{-3}, $\mu_{calc.}$ = 6.99 cm^{-1}, F(000) = 1448, index ranges $0<=h<=10$, $0<=k<=15$, $0<=l<=30$, S = 1.144.

1.4.8 Preparation of borate propeller 3 from l,l'-bi-2-naphthol and boric acid

A mixture of racemic 1,1'-bi-2-naphthol (3 mmol, 0.86 g) and $B(OH)_3$ (2.2 mmol, 0.136 g) were taken in benzene (30 ml) and the contents were refluxed for 12h using Dean-Stark apparatus. The solvent was evaporated to get a residue. It was dissolved in DCM (20 ml) and filtered. The solvent was removed from the filtrate under reduced pressure to obtain the borate propeller 3. It was kept under dry nitrogen as we find that this compound is highly sensitive to moisture.



3

Data for 3

Yield	: 80% (0.7 g)
M.P.	: > 350 °C
IR (KBr)	:3213 cm^{-1}
^1H NMR (400 MHz, $CDCl_3$)	: 5 ppm 6.5-6.7 (AB system, J = 8.8 Hz, 12H), 7.1 (d, J = 8.6 Hz, 6H), 7.2 (m, 6H), 7.5 (m, 6H), 7.8 (d, J = 8.4 Hz, 6H)

The spectral data correspond to the reported data for **3**.[17]

1.4.9 Resolution of racemic l,l'-bi-2-naphthol using B(OH)3 and (R)-(+)-a-methylbenzylamine

Racemic l,l'-bi-2-naphthol (1) (10 mmol, 2.86 g), $B(OH)_3$ (5 mmol, 0.31 g) and (R)-(+)-a-methylbenzylamine (15 mmol, 1.816 g) were refluxed in CH_3CN (20 ml) for 12h. The reaction mixture was cooled to 25 °C and filtered. To the precipitate **IA,** CH_3CN (10 ml) was added and refluxed for 6h. The contents were brought to 25 °C and filtered. The precipitate **I1A** was suspended in a mixture of EtOAc (25 ml) and dil.HCl (1N, 20 ml) and stirred until complete dissolution occurs. The organic layer was collected and the aqueous layer was extracted with EtOAc (2 x 10 ml). The organic extracts were combined and washed with saturated brine, dried over magnesium sulfate and evaporated under reduced pressure to obtain (S)-(-)-l.

The filtrate **IB** was concentrated. The residue was refluxed for 6h in THF (20 ml). The reaction mixture was brought to 25 °C and filtered. The precipitate **1IB** was digested in a mixture of EtOAc (25 ml) and dil.HCl (1N, 20 ml) followed by workup as outlined above to obtain the (R)-(+)-l.

1,1'-Bi-2-naphthol obtained from the precipitate fraction:

Yield : 35% (0.42 g)

M.P. : 208-210 °C (Lit.[51] 209-210 °C)

$[\alpha]_D^{25}$: (-) 34.37 (C1, THF)

Lit.[53] $[\alpha]_D^{25}$: (-) 34.5 (C1, THF)

HPLC analysis (chiralpak OP column using methanol as eluent) of the sample indicated that the optical purity is > 99% ee.

l,l'-Bi-2-naphthol obtained from the filtrate fraction

Yield : 26% (0.76 g)

M.P. : 208-210 °C (Lit.[51] 209-210 °C)

$[\alpha]_D^{25}$:(+) 34.23 (C1, THF)

Lit.[53] $[\alpha]_D^{25}$:(+)34.5(Cl,THF)

HPLC analysis (chiralpak OP column using methanoi as solvent) of the sample indicated that the optical purity is > 99% ee.

1.4.9 Isolation of the chiral amine used in the resolution experiments

The chiral resolving agent (R)-(+)-a-methylbenzylamine 4, used in the above experiment was recovered by aq.NaOH (1N, 30 ml) treatment of the combined dil.HCl fractions followed by extraction with diethyl ether (2 x 25 ml). After evaporation of the combined ether layers, the residue was distilled under reduced pressure to isolate 4 in 90% yield (99% ee).

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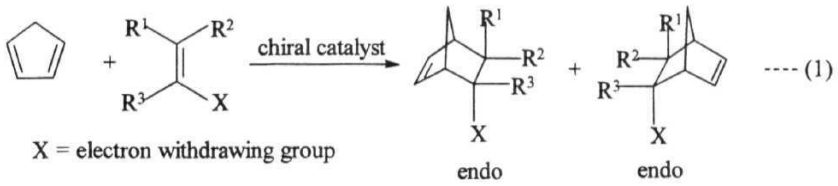
Chapter 2

Studies on the catalysis of Diels-Alder reaction by the chiral borate ester prepared using 1,1'-bi-2-naphthol and boric acid

2.1 Introduction

The Diels-Alder reaction is one of the most frequently employed methods for regio, diastereo and enantioselective construction of six membered and polycyclic ring systems in organic chemistry. Considering the importance of the preparation of natural products and physiologically active organic compounds, there has been immense interest in recent years on the development of catalytic methods.[1] Obviously, asymmetric catalysis of the Diels-Alder reaction for generating key building blocks is an important area of research. We describe in this chapter our research efforts on the use of the chiral borate ester prepared using boric acid and chiral 1,1'-bi-2-naphthol (1) for asymmetric Diels-Alder reaction. A brief review of the literature will be helpful for the discussion.

The Diels-Alder reaction allows, in principle, formation of four asymmetric centres. Relative stereochemistry is usually well defined because of the involvement of a cyclic transition state arising from *suprafacial-suprafacial* interaction with *endo* approach of the dienophile (eq. 1).



X = electron withdrawing group

New, powerful variants of Lewis acid catalysis of this classical reaction have been developed in recent years. Earlier methods use achiral catalysts and stoichiometric amounts of chiral auxiliaries that are incorporated into the substrate and subsequently removed from the product.[2-6] In this case, the enantioselectivity is dictated by the absolute stereochemistry of the substrate. Subsequently, an alternate method was developed in which achiral dienophiles can be reacted with dienes in the presence of a catalyst having the chiral moiety. This method has practical advantages: (i) a smaller amount of chiral auxiliary is required and (ii) the final product is obtained directly.

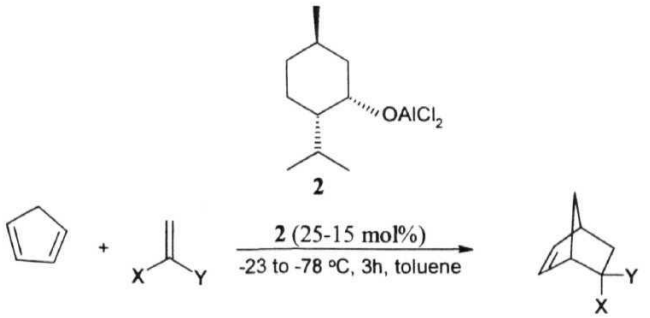
The discovery of Lewis acid catalysis of Diels-Alder reactions had a significant impact on synthetic organic chemistry.[7] These developments, which allow the reactions to be run under very mild conditions, often below 0 °C, are also responsible for high selectivity in these reactions.

The mechanism by which Lewis acids influence the rate and selectivity of the Diels-Alder reaction is readily explained in terms of frontier molecular orbital (FMO)

theory [8-10] The dienophiles that carry an electron withdrawing substituent lower the LUMO energy. Co-ordination of a Lewis acid to this moiety leads to further dramatic enhancement of its electron withdrawing capacity thereby increasing its rate as well as the selectivity. Several chiral Lewis acid catalysts developed for application in the Diels-Alder reaction are based on boron, aluminium and titanium reagents.

A few of the recent reports in this thrust area are discussed here. In 1979, Koga and co-workers reported that the cycloaddition of methacrolein to cyclopentadiene is catalysed by menthoxyaluminium dicholoride (2).[11,12] Unfortunately, only poor asymmetric induction was realised in this reaction (Scheme 1).

Scheme 1



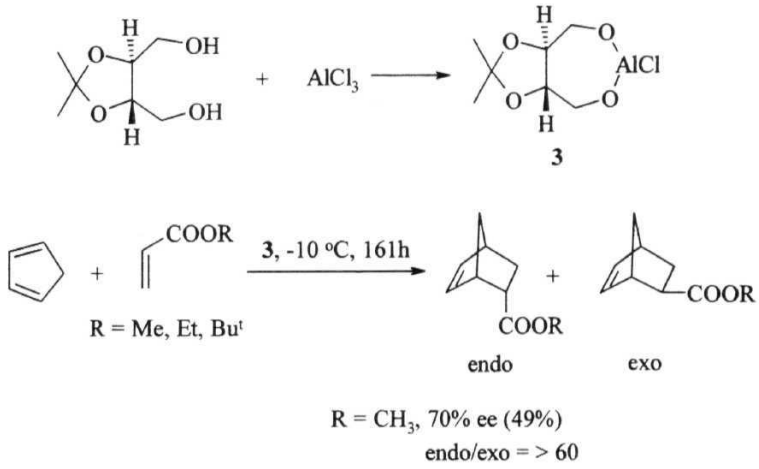
X = $COOCH_3$ Y = H, at -23°C, 6% ee (65%)

X = CHO Y = H, at -78 °C 27% ee (55%)

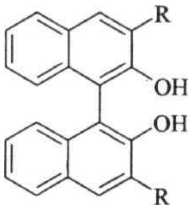
X = CH_3 Y= CHO, at -78 °C 72% ee (69%)

Hermann and co-workers carried out a systematic study on the Diels-Alder reactions of cyclopentadiene and methacrylate using chiral Lewis acids prepared using chiral diols and aluminium, titanium and tin as central metals.[13] Reasonable results were obtained when the catalyst 3 was used (Scheme 2).

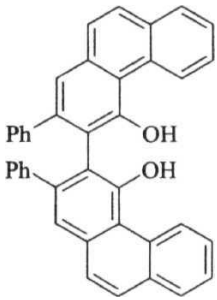
Scheme 2



Wulff and co-workers examined the catalysts prepared using vaulted biaryls 4a and 4b and diethylaluminium chloride for the Diels-Alder reactions of methacrolein and cyclopentadiene.



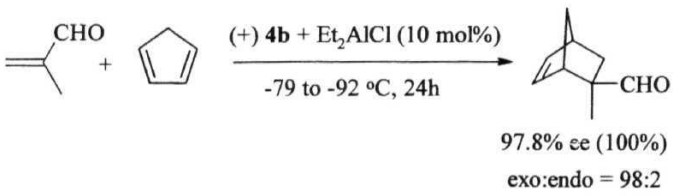
4a



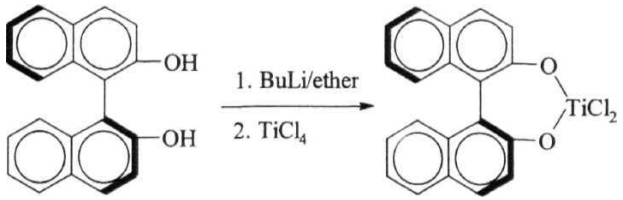
4b

The corresponding adduct was obtained in 97.8% ee with exo:endo ratio of 98:2 (Scheme 3). They pointed out that this is the highest induction ever reported for this reaction with a chiral catalyst and the lowest catalyst loading ever reported for any asymmetric reaction with any catalyst. Using the same catalyst in the reaction of methyl acrylate with cyclopentadiene, the corresponding Diels-Alder adduct was obtained in 93% yield in 86% ee, endo/exo selectivity of 243:1.

Scheme 3

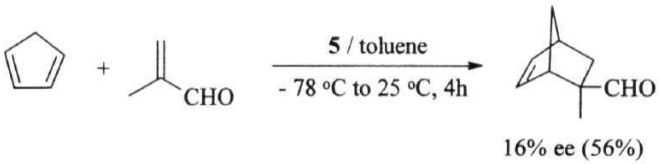


Reetz and co-workers performed the Diels-Alder reaction of cyclopentadiene with methacrolein in the presence of catalytic amounts of the chiral Lewis acid 5 derived from optically active l,l'-bi-2-naphthol (1) and $TiCl_4$.[15]

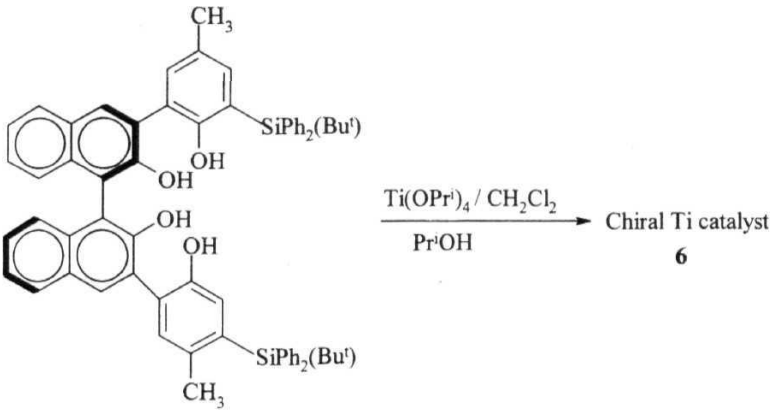


The corresponding adduct was obtained in 56% yield in 16% ee with an exo/endo selectivity of 90:10 (Scheme 4).

Scheme 4

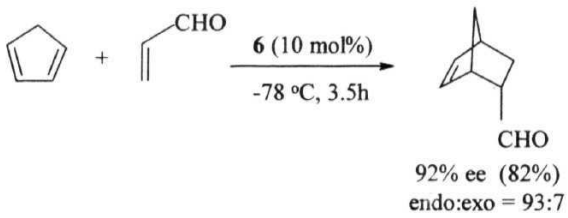


Yamamoto and co-workers synthesised a new member of chiral titanium complex 6 to achieve high enantioselectivity through the combination of intramolecular hydrogen bonding and attractive *n-n* donor-acceptor interaction in the transition state assembly.[16]



These chiral Lewis acid catalysts 6 were highly effective for the enantioselective Diels-Alder reactions. For example, high yield and selectivity were realised in the reaction of acrolein and cyclopentadiene (Scheme **5).**

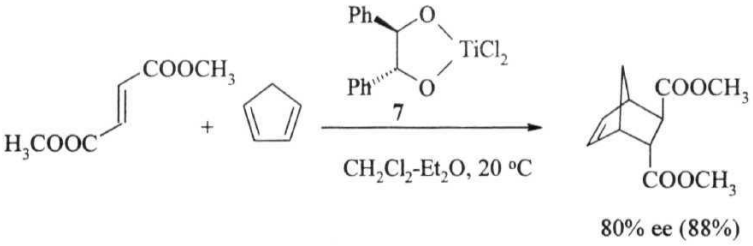
Scheme 5



Oh and co-workers developed a chiral titanium complex 7 which induces good enantioselectivity in the Diels-Alder reactions of ester dienophiles.[17] For example, an

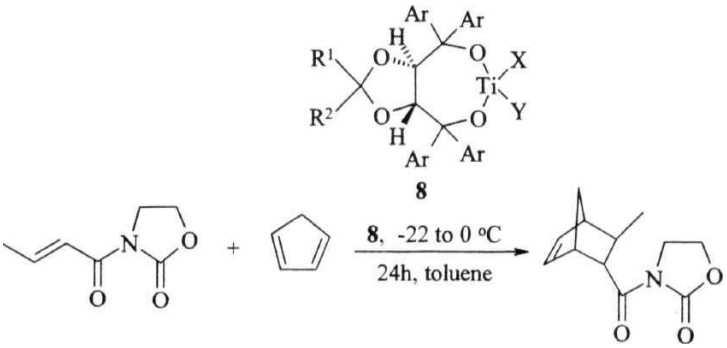
optical induction of 80% ee (88%) was realised in the reaction between dimethylfumarate and cyclopentadiene using the titanium catalyst 7 (Scheme **6).**

Scheme 6



Seebach and co-workers carried out a systematic investigation on the enantioselective Diels-Alder reactions of 3-butenoyl-1,3-oxazolidin-2-ones with cyclopentadiene under the influence of catalytic amounts of dichloro-Ti-complexes of TADDOLS 8 (Scheme **7**).[18]

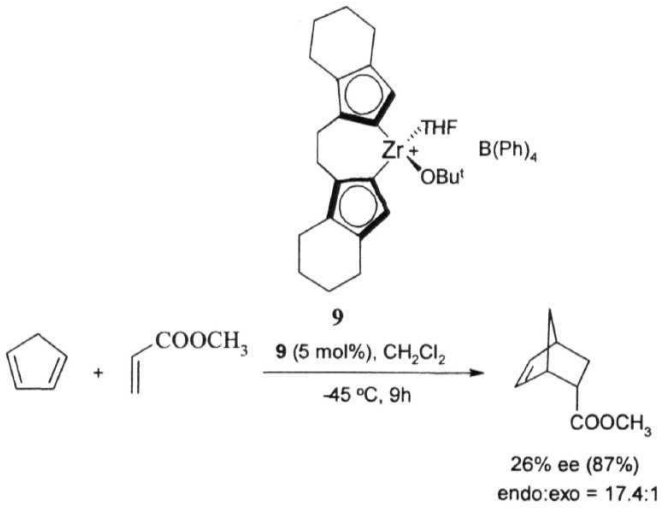
Scheme 7



$R^1 = R^2 = CH_3$, Ar = 2-naphthyl 92% ee (96%)
endo:exo = **90:10**

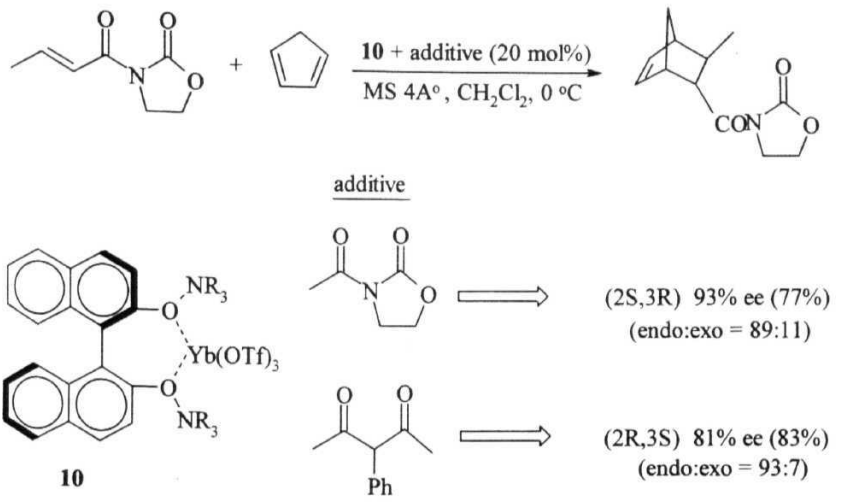
Collins and co-workers found that the cationic Zirconocene compound 9 is an efficient catalyst for the Diels-Alder reactions between cyclopentadiene and various dienophiles.[19] However, the products were obtained only in modest ee (Scheme 8).

Scheme 8



Kobayashi and co-workers prepared the chiral lanthanide trifluorosulfonate 10 using chiral l,l'-bi-2-naphthol that promotes the Diels-Alder reactions between acyl-l,3-oxazolidin-2-ones and cyclopentadiene to afford the corresponding adducts in high yields with high enantioselectivities (Scheme 9).[20]

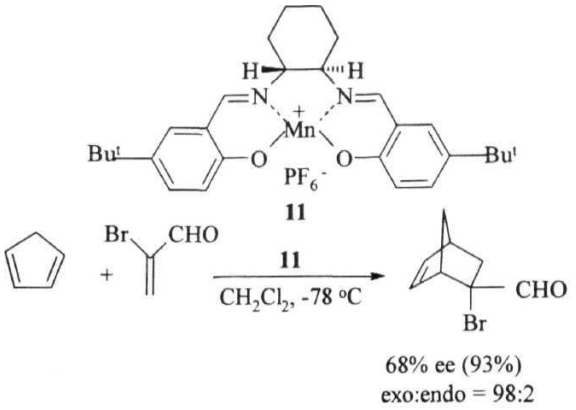
Scheme 9



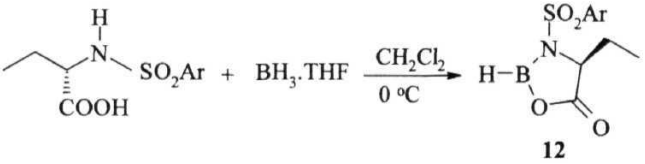
According to their procedure, both enantiomers of the Diels-Alder adducts were selectively prepared using a single chiral source, (R)-1,1'-bi-2-naphthol in the presence of certain achiral additives. These additives are effective not only in stabilising the catalyst, but also in controlling the enantiofacial selectivities in the Diels-Alder reactions.

Katsuki and co-workers prepared the optically active manganese complex **11** for the catalysis of asymmetric Diels-Alder reactions. This chiral complex 11 promotes the Diels-Alder reaction between cyclopentadiene and a-bromo acrolein to give the corresponding adduct in 68% ee with high exo selectivity (Scheme **10**).[21]

Scheme 10

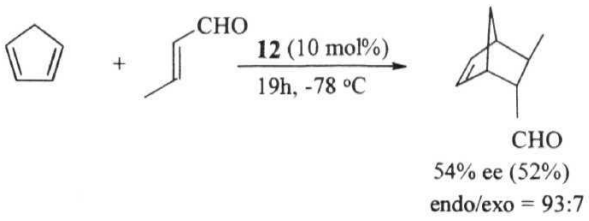


Yamamoto and co-workers prepared a boron catalyst from 2,4,6'-triisopropyl benzene sulfonamide of a-amino acids (12) for use in the enantioselective Diels-Alder reactions of various dienes and dienophiles.[22]



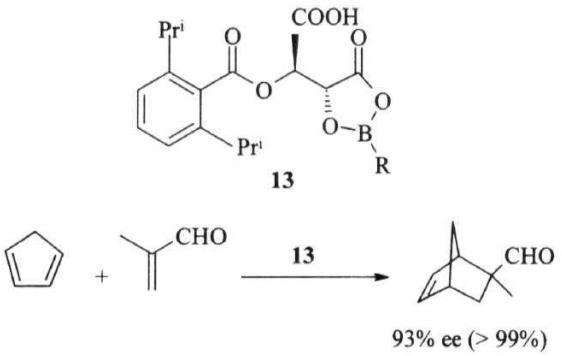
For example, the catalyst 12 gives the highest selectivity in the reaction between crotonaldehyde and cyclopentadiene (Scheme **11**).

Scheme 11



Later, chiral acyloxyborane (13) prepared using tartaric acid, were used for asymmetric Diels-Alder reactions (Scheme **12**).[23]

Scheme 12

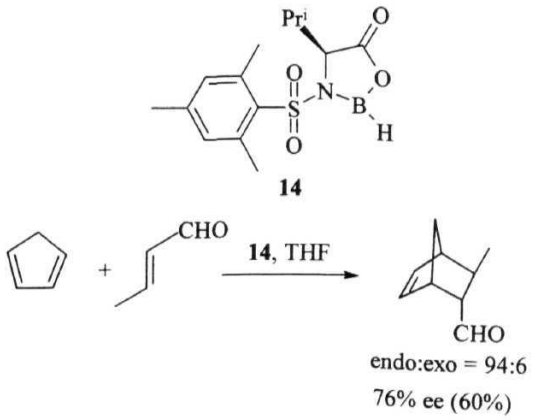


A new type of helical titanium reagent was prepared using $B(OMe)_3$ and a chiral ligand derived from optically active binaphthol derivatives.[24] Asymmetric Diels-Alder reaction between various dienes and dienophiles was effected in the presence of 10 mol % of this catalyst producing the major adduct in more than 92% ee and > 99% yield.

In most cases, asymmetric induction is controlled by steric interaction between the dienophile and a chiral ligand. This kind of interaction is insufficient to provide high level of enantioselectivity. On the other hand, there are many reports indicating that the attractive *n-n* donor-acceptor interaction between a dienophile and the chiral ligand is highly effective for realising higher selectivity.[24,27]

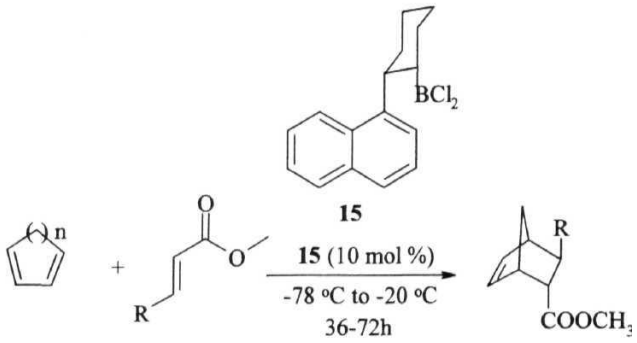
Helmchen and co-workers prepared a chiral Lewis acid (14), using N-sulphonylamino acids by reaction with BH_3.THF.[25] It was found that these catalysts are most useful for the promotion of Diels-Alder reactions between a,P-unsaturated aldehydes and cyclopentadiene. Reasonable enantioselectivity was realised in donor solvents such as THF (Scheme **13).**

Scheme 13



Hawkins and co-workers performed the Diels-Alder reactions of methyl acrylate, methyl crotonate and dimethyl fumarate with cyclopentadiene or cyclohexadiene using the catalyst 15 to obtain the corresponding adducts in 86-97% ee.[26] Later, it was found that the use of excess cyclopentadiene in the Diels-Alder reaction of methyl acrylate improves the ee from 97 to 99.5% (Scheme 14).[27]

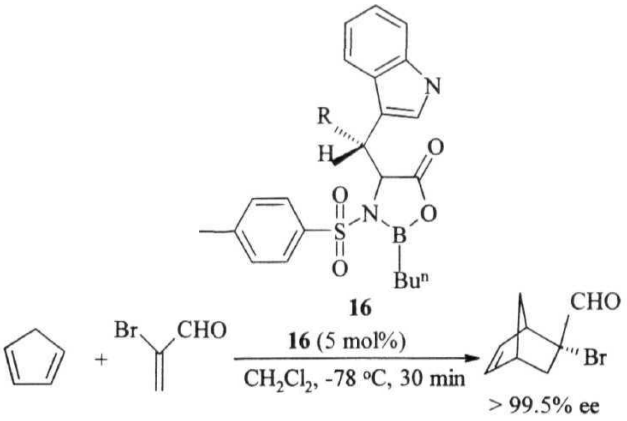
Scheme 14



n = 1, R = H	97% ee (97%)
n = 1, R = CH_3	93% ee (91%)
n = 1, R = $COOCH_3$	90% ee (92%)
n = 2, R = H	86% ee (83%)

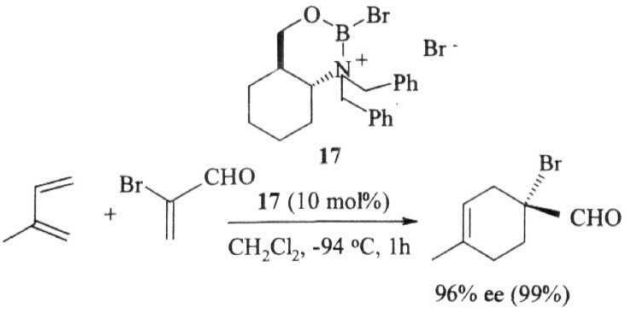
Corey and co-workers, reported that the (S)-tryptophan derived oxazaborolidine catalysts 16 are efficient for the catalysis of the Diels-Alder reaction of 2-bromo acrolein and cyclopentadiene.[28] The corresponding adduct was obtained with unprecedented enantioselectivity of 200:1 using the catalyst 16 (Scheme 15).

Scheme 15

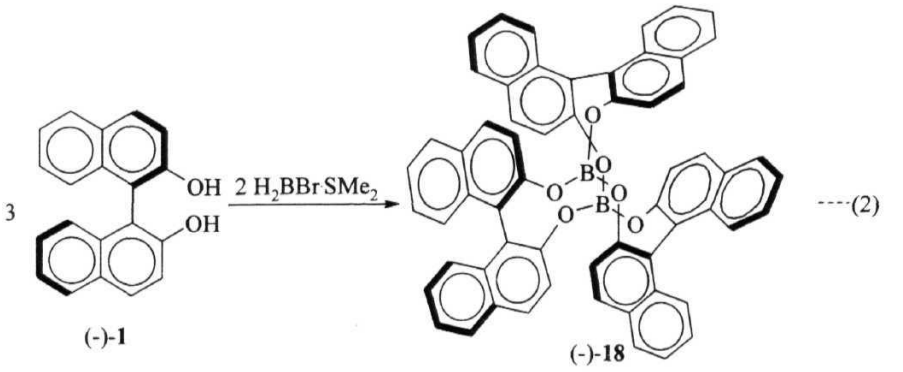


Most of the reported catalytic enantioselective Diels-Alder reactions involve reactive dienes such as cyclopentadiene and reactions involving less reactive diene such as 1,3-butadiene and 1,3-cyclohexadiene are not successful. So, in order to expand the scope and utility of the catalytic enantioselcetive Diels-Alder reactions, Corey and co-workers developed the new class of super reactive chiral Lewis acid catalyst system, oxazaborinane 17.[29] Less reactive dienes such as isoprene do react readily with 2-bromoacrolein using the catalyst 17 at -94 C with excellent yield (99%) and enantioselectivity (98% ee) (Scheme 16).

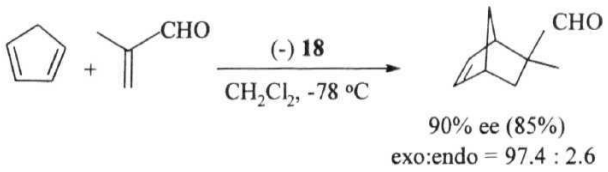
Scheme 16



Kaufmann and co-workers noticed the formation of a C_3 symmetric propeller compound (18) in the reaction of (S)-(-)-l,l'-bi-2-naphthol using monobromo borane.dimethylsulfide complex (eq. **2).**[30]



When they performed Diels-Alder reaction of methacrolein with cyclopentadiene using catalytic amount of (-)-18 in dichloromethane at -78 °C, the exo adduct was obtained in 97.4% endo selectivity with 90% ee and 85% yield (eq. 3).



90% ee (85%)
exo:endo = 97.4 : 2.6

---- (3)

We have observed that the Kaufmann chiral borate ester 18 can be readily prepared using l,l'-bi-2-naphthol and boric acid in benzene (Dean-Stark apparatus). Accordingly, we decided to investigate the applications of this chiral Lewis acid in the Diels-Alder reaction. Since this borate derivative is of the formula M_2L_3, it is expected to exhibit the Kagan's non-linear effect in the asymmetric catalysis. We have also examined this effect. The results are described in this chapter.

2.2 Results and Discussion

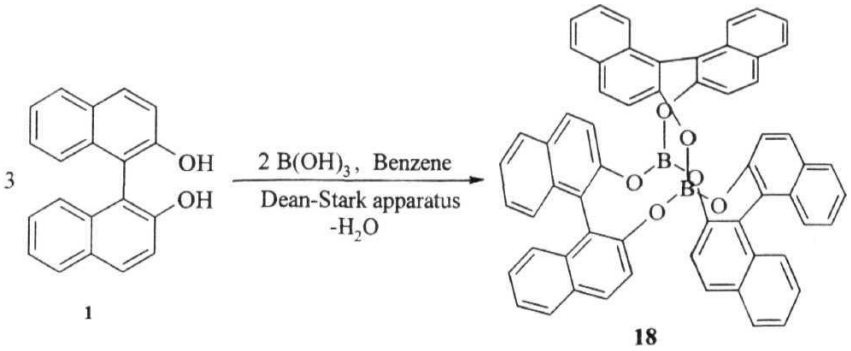
2.2.1 Preparation of borate ester 18 and its application in the Diels-Alder reaction

The influence of chiral Lewis acid catalysts, derived particularly from boron, on the rate of the reaction and stereoselectivity, prompted us to develop a catalytic system for the promotion of enantioselective Diels-Alder reaction.[22,30] As discussed in the introductory section, the reaction of l,l'-bi-2-naphthol (1) with $BrBH_2.SMe_2$ results in the formation of C_3 symmetric borate propeller compound **18**.[30]

We have undertaken efforts towards the preparation of this interesting chiral C_3 symmetric derivative 18 using inexpensive boric acid and readily accessible chiral 1,1'-bi-2-naphthol (1) through methods developed in this laboratory. Preliminary results indicated that the borate ester 18 is formed when 1,1'-bi-2-naphthol (1) and $B(OH)_3$ were refluxed in benzene with azeotropic removal of water using Dean-Stark apparatus (Scheme **17**) (see also page 63, Chapter I).

As outlined in the introductory section, it was briefly reported that the chiral borate 18 prepared using $BrBH_2.SMe_2$ and 1 catalyses asymmetric Diels-Alder reaction between cyclopentadiene and methacrolein.

Scheme 17



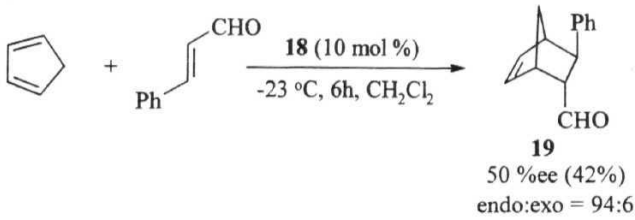
1 18

Since the catalyst 18 is readily available using inexpensive $B(OH)_3$ (Scheme 17), we have decided to examine the application of this chiral borate derivative 18 in detail. We have carried out several Diels-Alder experiments using different dienophiles in the presence of 18.

We have selected the reaction of trans-cinnamaldehyde with cyclopentadiene for a detailed study as the chiral borate ester 18 induces optical activity into the adduct 19 formed in the reaction of cinnamaldehyde and cyclopentadiene to a significant extent (Scheme 18).

An $[\alpha]_D^{25}$ value of -107.6 (C2, $CHCl_3$) has been reported for a 76:24 endo:exo mixture of the adduct 19.[31] The endo:exo ratio of the adduct obtained using the chiral borate ester 18 prepared using (-) 1,1'-bi-2-naphthol (1) was found to be 94:6. The $[\alpha]_D^{25}$ values of the product mixture at various temperatures are summarised in the Tables 1-4.

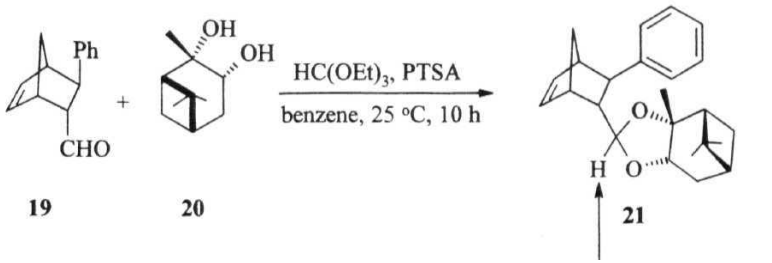
Scheme 18



Attempts to separate the endo/exo isomers of the adduct 19 by column chromatography were not successful. We have also made efforts to separate the endo/exo isomers of 19 and the corresponding enantiomers through HPLC analysis. These efforts were also not fruitful. The corresponding alcohol, and methyl ether derivatives were prepared and subjected to HPLC analysis. Unfortunately, these compounds did not separate in the HPLC columns (Chiral Cell OD and Chiral Pak OP) accessible for this work. The corresponding benzoate and anisoate ester derivatives also failed to separate in these HPLC columns using various eluents.

Then, we have undertaken efforts to estimate the enantiomeric excess through ^1H NMR analysis using chiral shift reagents $Eu(tfc)_3$. Again, these efforts were not successful. Finally, efforts were made to prepare the diastereomeric acetal derivatives using the chiral diols such as (S,S)-(-)-l,2-diphenyl-l,2-ethanediol and (1R, 2R, 3S, 5R)-(-)-pinane-2,3-diol 20. Fortunately, the diastereomeric acetal 21 prepared (Scheme 19) using the optically active (1R, 2R, 3S, 5R)-(-)-pinane-2,3-diol 20 was useful in the assessment of the enantiomeric ratios of the endo adduct 19 through ^1H NMR spectral analysis.

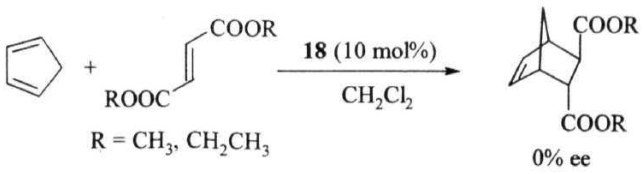
Scheme 19



Two doublets corresponding to the acetal CH proton (4.5 ppm, J = 7.1, 7.8 Hz) are obtained for the endo isomer. Comparison of this CH proton signals ratio of the acetal 21 obtained using racemic 19 and optically active 19, gave the ratio of these enantiomers and the ee. The ee values estimated in this way are given in Tables 1-4.

The chiral borate ester 18 also catalysed the reaction between dimethyl fumarate and diethyl fumarate (Scheme 20). However, no optical induction was observed for the resulting Diels-Alder adduct.

Scheme 20



The catalyst 18 did affect the reaction of cyclopentadiene with several other dienophiles such as acrolein and methacrolein at 0 °C, to give asymmetric induction only up to 20% ee. Reaction with methyl vinyl ketone also gave the corresponding racemic product. The reactions of other dienophiles such as methyl crotonate, methyl acrylate, methyl methacrylate, acrylic acid, cinnamic acid, and methyl cinnamate failed to proceed in the presence of 18 under ambient conditions. Accordingly, we have decided to examine the reaction of cinnamaldehyde for further studies.

2.2.2 Asymmetric Diels-Alder reaction between cinnamaldehyde and cyclopentadiene: Effect of solvents and temperature

It is always important to find a suitable solvent for the reaction to be carried out. The best solvents for the Lewis acid mediated Diels-Alder reactions are those with poor donor ability such as toluene, petroleum ether or dichloromethane (DCM). We have chosen DCM for use in all the experiments.

It has been reported that cinnamaldehyde did not give the Diels-Alder adduct with cyclopentadiene at 25 °C even after 20h.[32] Initially, we have examined the reaction at various temperatures. It was observed that the corresponding adduct was obtained in 24% yield (50% ee) at -23 °C (Table 1). We have decided to carry out other studies at this temperature.

Table 1. Asymmetric Diels-Alder reaction between cinnamaldehyde and cyclopentadiene using 18: Temperature effect [a]

S. No	18 (mmol)	Temperature °C	Yield	19	
				$[\alpha]_D^{25}$	%ee [b]
1.	0.5	-78	00	00	00
2.	0.5	-23	24	+ 31.96	50
3.	0.5	0	28	+ 29.05	45
4.	0.5	25	17	+ 25.82	**40**

a) All the reactions were carried out between cyclopentadiene (12 mmol, 0.66 g) and cinnamaldehyde (10 mmol, 1.32 g) in dichloromethane solvent in the presence of chiral propeller (0.5 mmol) prepared from (-) 1,1'-bi-2-naphthol and $B(OH)_3$.

b) The ee values of the endo isomer were estimated through ^1H NMR analysis of the corresponding diastereomeric acetal prepared using (1R, 2R, 3S, 5R)-(-)-pinane-2,3-diol.

2.2.3 Asymmetric Diels-Alder reaction between cinnamaldehyde and cyclopentadiene: Effect of concentrations of the borate ester 18

Initially, to find the optimum amount of catalyst required, reactions were carried out using different concentrations of the borate ester 18, prepared using racemic 1,1'-bi-2-naphthol (1). As expected, the chemical yields are better at higher catalyst loading (Table 2).

Table 2. Diels-Alder reaction between cinnamaldehyde and cyclopentadiene using 18: Effect of various concentration of 18 [a]

S. No	18 (mmol)	Temperature °C	19 Yield (%)
1.	0.5	-23	24
2.	1.0	-23	42
3.	1.5	-23	71

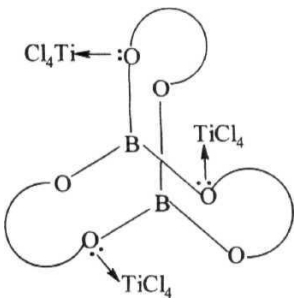
a) All the reactions were carried out between cyclopentadiene (12 mmol, 0.66 g) and cinnamaldehyde (10 mmol, 1.32 g) in dichloromethane solvent in the presence of the borate ester prepared from racemic 1,1'-bi-2-naphthol and $B(OH)_3$.

2.2.4 Asymmetric Diels-Alder reaction between cinnamaldehyde and cyclopentadiene: Effect of additives

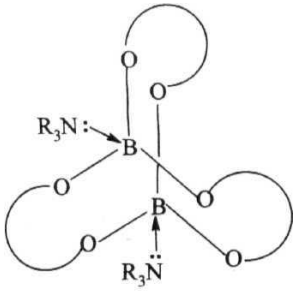
It is well known that addition of molecular sieves to the reaction mixture, to remove the traces of water, leads to better results. We have observed that the use of molecular sieves (4 A^0) under the present conditions did not have any significant effect.

The effect of the catalysis of the borate ester coordinated to another acidic moiety in the Diels-Alder reaction was also studied. It was anticipated that Lewis acids, such as $TiCl_4$ and $BF_3.OEt_2$, would co-ordinate to the oxygen site (22) of the

borate ester 18, and hence, would increase the acidic character of 18. To examine this possibility, we have performed the reaction between cinnamaldehyde and cyclopentadiene in the presence of chiral borate 18 and Lewis acids such as $TiCl_4$, $Ti(OPr^i)_4$ and $BF_3.OEt_2$. Whereas results obtained in the reactions using $Ti(OPr^i)_4$ and $BF_3.OEt_2$ are poor, slightly improved results are obtained in the presence of $TiCl_4$ (Table 3).



22



23

We have also studied the effect of basic amine additives. These amines are expected to coordinate to the acidic boron centers (23) present in the chiral borate ester 18 and would reduce the rate of reaction. When the Diels-Alder reaction was carried out in the presence of amines such as Et_3N and TMEDA only poor results were obtained (Table 3).

Table 3. Effect of some additives in the Diels-Alder reaction between cinnamaldehyde and cyclopentadiene catalysed by 18[a]

S. No	Additives	Yield	19	
			Wo	% **ee**
1.	$TiCl_4$	23	+ 35.62	55
2.	$Ti(OPr^i)_4$	08	+ 19.37	30
3.	$BF_3.OEt_2$	17	+ 24.75	39
4.	NEt_3	06	+ 08.61	13
5.	TMEDA	11	+ 11.84	18

a) All the experiments were carried out between cyclopentadiene (12 mmol, 0.66 g) and cinnamaldehyde (10 mmol, 1.32 g) in dichloromethane (45 ml) solvent at -23 °C for 6h using the chiral borate ester (1 mmol) derived from (-)-l,l'-bi-2-naphthol and $B(OH)_3$ and additives (0.10 mmol).

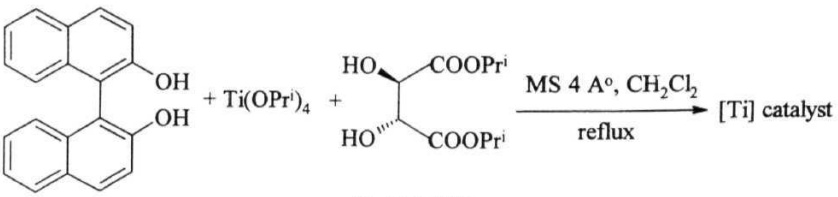
b) The ee values of the endo isomer were estimated through ^1H NMR analysis of the corresponding diastereomenc acetal prepared using (1R, 2R, 3S, 5R)-(-)-pinane-2,3-diol.

2.2.5 Diels-Alder reaction between cinnamaldehyde and cyclopentadiene: Chiral poisoning of borate ester (±)-18 using chiral α-methylbenzylamine

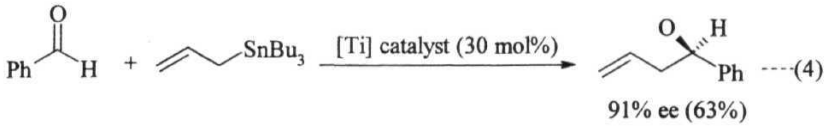
While non-racemic catalyst can generate non-racemic products, racemic catalysts inherently produce only a racemic mixture of chiral products. However, a strategy, known as *chiral poisoning,* whereby one of the antipodes of a racemic catalyst is selectively deactivated through reaction with a chiral compound is shown to yield non-racemic products.[33]

For example, Faller and co-workers, exploited this strategy in the reaction between benzaldehyde and allyltributyltin utilising a titanium catalyst derived from racemic 1, 1'-bi-2-naphthol, $Ti(OPr^i)_4$ and a chiral poison, di(isopropyl)-(S, S)-tartrate (DIPT) (Scheme **21**).[33]

Scheme 21



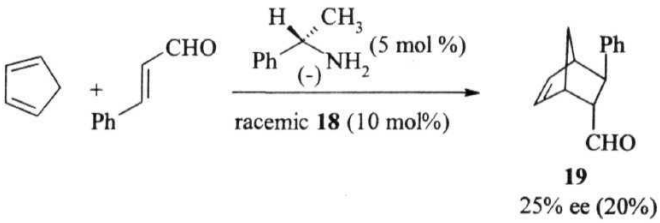
When they performed the reaction between benzaldehyde and allyltributyltin, the corresponding product was obtained in 91% ee (63% yield) (eq. 4).



Also, it was noted that a mixture of $Ti(OPr^i)_4$ and chiral (DIPT) failed to catalyse the reaction in the absence of 1,1'-bi-2-naphthol. In continuation of the efforts to understand the mechanism of the chiral poisoning, they performed the reaction using the catalyst derived from (R) and (S)-1,1'-bi-2-naphthol and (S,S)-tartrate. Whereas the reaction catalysed by (S)-l,l'-bi-2-naphthol yielded the alcohol in >95% ee (20% yield) the catalyst derived from (R)-1,1'-bi-2-naphthol failed to give the product. Therefore, the chiral poison, (S, S)-tartrate deactivates the (R)-1,1'-bi-2-naphthol catalyst more effectively.

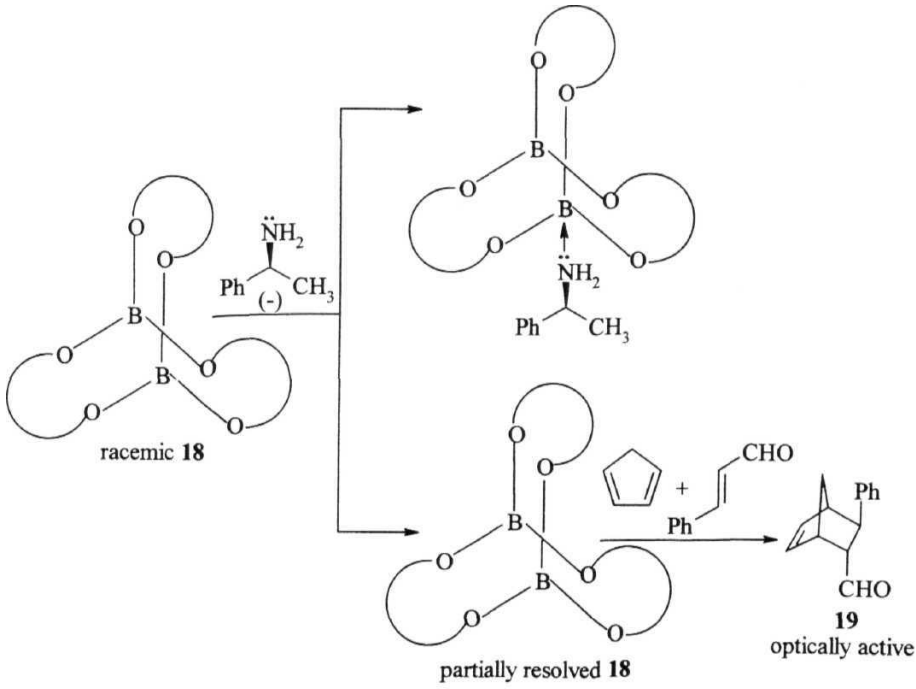
We have also examined this strategy using chiral (S)-a-methylbenzylamine in the Diels-Alder reaction between cinnamaldehyde and cyclopentadiene catalysed by racemic 18 (Scheme 22).

Scheme 22



It was observed that the Diels-Alder adduct 19 was obtained in 25% ee (20%). Presumably, the (-)-a-methylbenzylamine selectively removes one enantiomer from racemic 18 to some extent through complexation, leading to asymmetric catalysis by the other enantiomer of 18 (Scheme 23).

Scheme 23



2.2.6 Nonlinear effects in the catalysis of asymmetric Diels-Alder reaction by the borate ester 18 prepared using 1,1'-bi-2-naphthol and $B(OH)_3$

When the relation between the ee value of the chiral auxiliary or ligand and the ee value of the product deviates from linearity, *nonlinear effects* result.[34] Nonlinear effect (NLE) was discovered in 1986 by the groups of Agami and Kagan and are now frequently observed.[34,35] The case of asymmetric synthesis with a chiral catalyst, that is not enantiomerically pure, was considered. It is generally assumed that the ee value of the product (ee_{prod}) of any asymmetric synthesis is linearly correlated to the ee value of the chiral auxiliaries (ee_{aux}). However, this linearity is not always observed in systems subjected to other influences such as interaction between the catalytic species. In such a situation , as shown in Figure 1, one can expect a plain curve above (I, positive NLE), or below (III, negative NLE) or the straight line (II, linear relationship) in the plots of ee_{aux} against ee_{prod}.

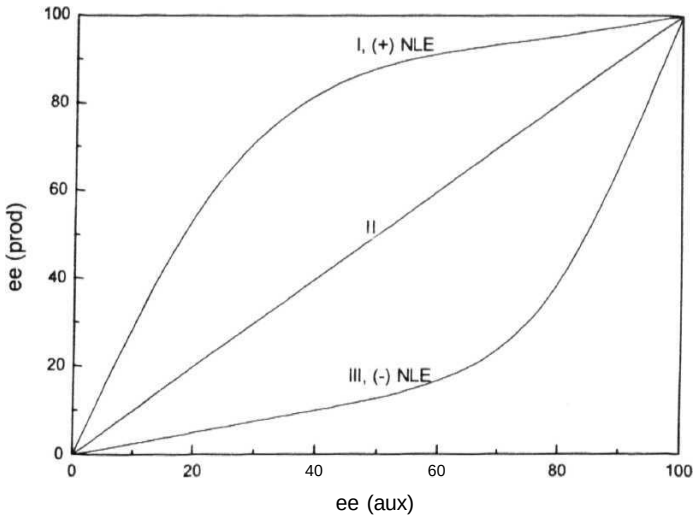


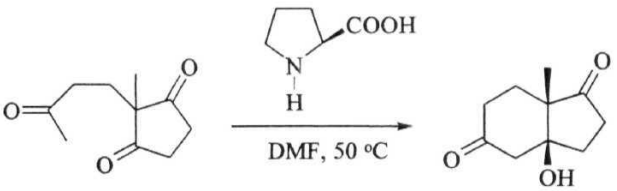
Figure 1. Relationship between the enantiomeric excess of the chiral auxiliary and that of the product in asymmetric synthesis.

The NLEs shown in the Figure 1 may, in principle, arise by auto association or association around a matrix of initial chiral species, which give diastereomeric perturbations. This perturbation is the reason for the diversion of relation between ee_{prod} and ee_{aux} from linearity. This phenomenon can be readily illustrated by the following examples.

Kagan and co-workers studied asymmetric Robinson annulation of the triketone using (S)-proline to test this hypothesis (Scheme **24**).[34,35,36] When the ee

value of the product 24 was plotted against various ee values of (S) proline, a slight (-) NLE was observed (Figure 1).

Scheme 24



(+) **24**

Mechanistic investigations by Agami, Kagan and co-workers suggested that the reaction proceeds through the formation of a chiral enamine followed by a complexation with a molecule of proline. This was confirmed by a kinetic model based on a second-order reaction in respect to proline (Figure 2).[36]

The (-) NLE was explained by considering the intermediates 25. Since the reactions involving heterochiral complexes proceed twice as fast as that of the homochiral complex, (-) NLE was observed.

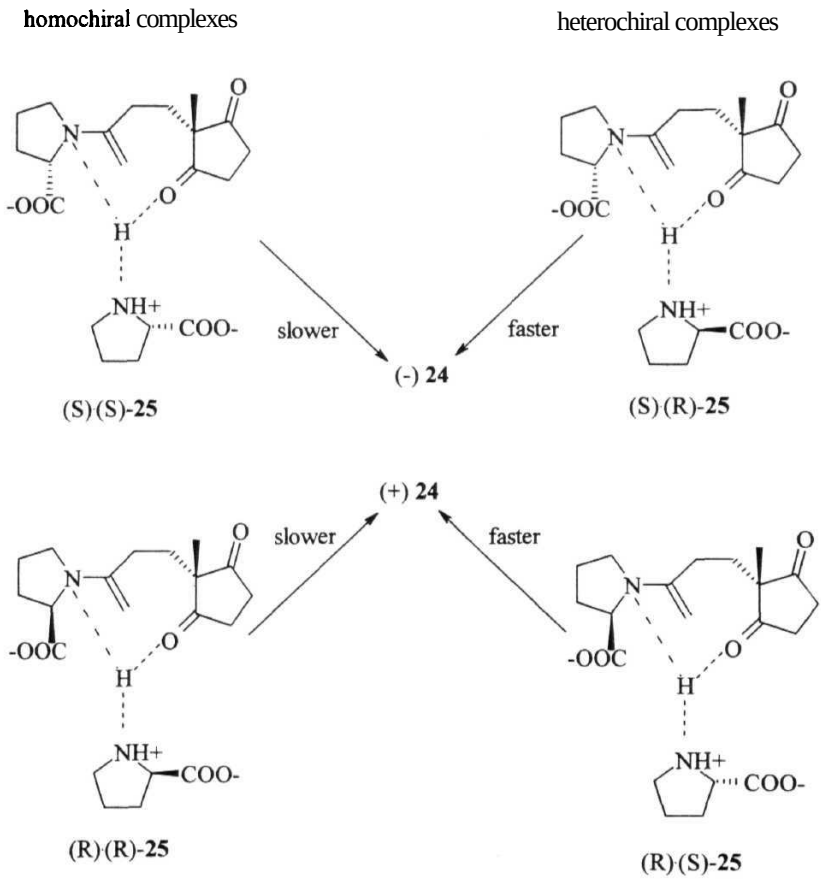
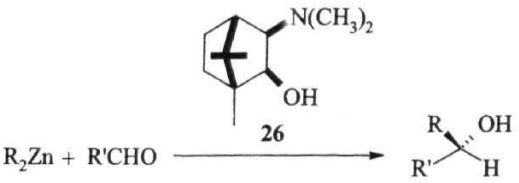


Figure 2. Intermediate complexes 25 in the Robinson annulation.

In 1989, Noyori and co-workers studied the enantioselective addition of dialkylzincs to aldehydes promoted by chiral amino alcohol, (-)-3-exo-(dimethylamino)isoborneol 26 (Scheme **25**).[37-

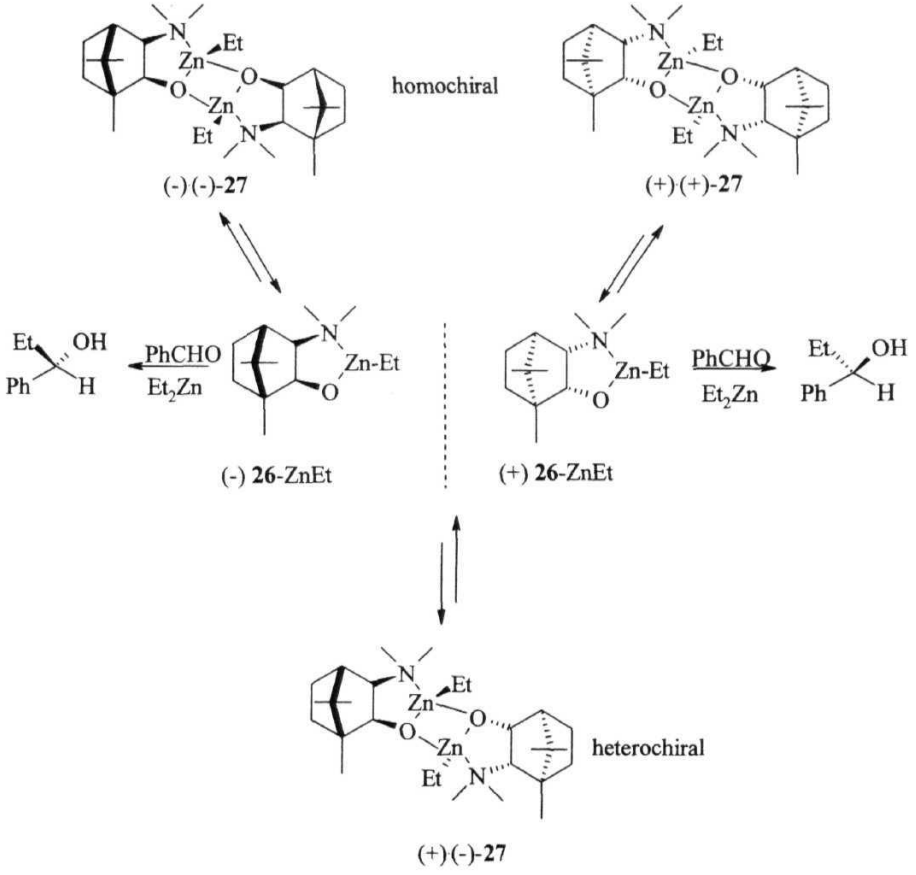
Scheme 25



They have observed a strong (+)-NLE (Figure 1) using chiral auxiliary with various ees. For example, in the reaction between benzaldehyde and diethylzinc, 1 -phenylpropanol is prepared in 95% ee with the catalyst of 15% ee. A mechanism in which auto association of the chiral reagent generated by the reaction between 26 and diethylzinc, as shown in Scheme 26 was proposed.

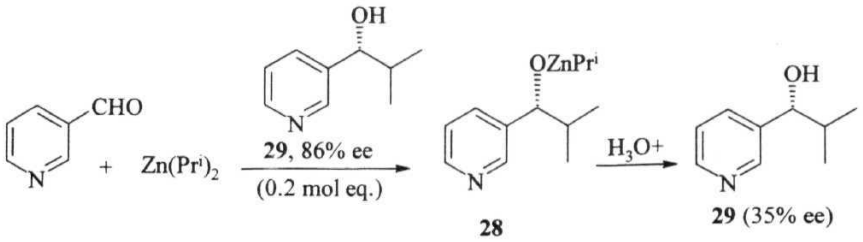
Under catalytic conditions, both homochiral and heterochiral complexes do promote alkylation (Scheme 26). However, the rate of the reaction involving homochiral complexes is very high compared to that involving heterochiral complexes and enantiomerically enriched products are obtained in high ee and hence (+)-NLE (Scheme 26).

Scheme 26



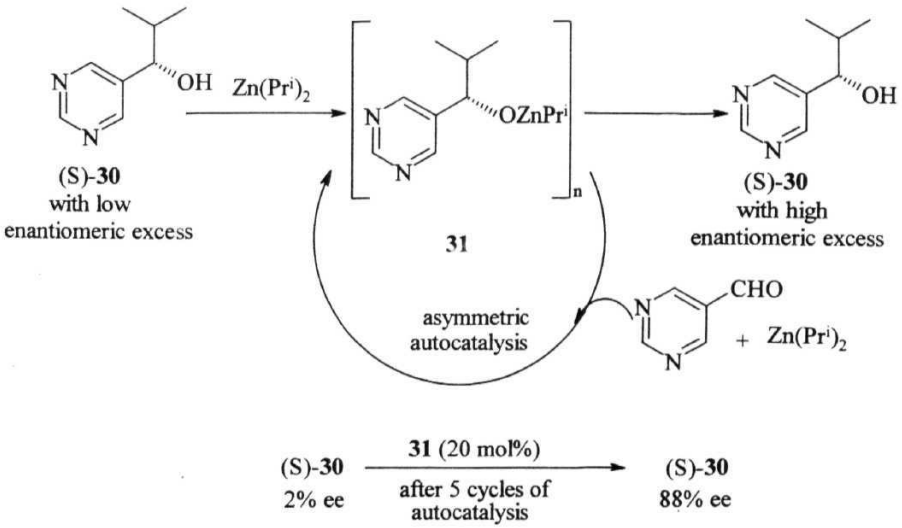
A dramatic chiral amplification through non-linear effect in an *autocatalytic process* was discovered by Soai and co-workers. It was reported that the chiral pyridyl alcohol 29 (of 86% ee) can catalyse its own formation in the reaction between aminoaldehyde and $Zn(Pr^i)_2$ in 35% ee (Scheme 27).[39]

Scheme 27



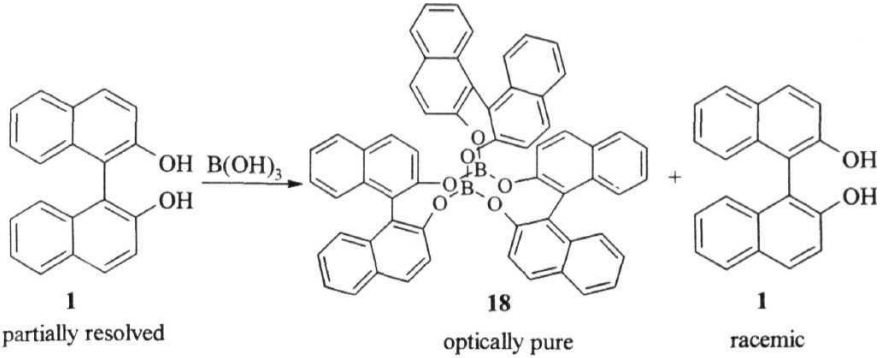
Further investigation of this concept using various types of aldehydes resulted in the discovery that 5-pyrimidyl alkanol with a small enantiomeric excess (2% ee) can autocatalyse the reaction between $Zn(Pr^i)_2$ and 5-pyrimidyl carboxaldehyde producing the corresponding alcohol 30 in highly amplified ee (Scheme 28).[40]

Scheme 28



It is clear that if a complex of the type ML_n (n > 2) is formed from non-racemic ligands L, non-linear effects in asymmetric reactions can be realised provided one of the diastereomeric complexes is more reactive. The borate ester 18 used in the Diels-Alder reaction of cyclopentadiene and cinnamaldehyde (Scheme 18) is derived from three moieties of l,l'-bi-2-naphthol (1). As discussed in chapter 1, we have observed that the racemic l,l'-bi-2-naphthol (1) gives only the C_3 symmetric (R,R,R) and (S,S,S) propeller and the (R,R,S) and (S,S,R) isomers are not formed. Also, as discussed in chapter 1, in the resolution experiments using calculated amounts of $B(OH)_3$ and amine, the excess enantiomer present in the partially resolved (scalemic) 1,1'-bi-2-naphthol can be precipitated leaving the racemic l,l'-bi-2-naphthol in solution. Accordingly, it was thought that using appropriate amounts of $B(OH)_3$ in the synthesis of 18, it may be possible to prepare the 18 derived mainly from the major enantiomer present in the scalemic mixture as outlined in the Scheme 29.

Scheme 29



1
partially resolved

18
optically pure

1
racemic

Typical ratios of **1** and $B(OH)_3$ and anticipated products

1	+	$B(OH)_3$	⟶	(-) **18**	+	**1**
(-) 46 %ee (6.5 mmol)		2 mmol		(1 mmol)		racemic (3.5 mmol)

If this happens, an interesting consequence would be the non-linear dependence of asymmetric induction on the % ee of the starting l,l'-bi-2-naphthol (1). We have examined this possibility in the Diels-Alder reaction of cyclopentadiene with cinnamaldehyde catalysed by the borate ester 18 that is derived from l,l'-bi-2-naphthol (1) of different non-racemic compositions. Partially resolved non-racemic l,l'-bi-2-naphthol (1) was taken such that 1 mmol of the catalyst 18 derived from the major enantiomer would be formed in all cases.

Table 4. Non-linear relationship in the catalysis of 18 in Diels-Alder reaction between cinnamaldehyde and cyclopentadiene[a]

S. No	(-) l,l'-bi-2-naphthol		$B(OH)_3$	19		
	(% ee)	(mmol)	(mmol)	Yield (%)	we	%ee
1.	24	12.50	2.0	14	(+) 18.57	29
2.	38	7.91	2.0	18	(+) 27.84	43
3.	46	6.50	2.0	23	(+) 30.12	47
4.	70	4.30	2.0	32	(+) 31.20	48
5.	82	3.67	2.0	35	(+) 31.50	49
5.	90	3.36	2.0	43	(+) 31.70	49
6.	98	3.00.	2.0	49	(+) 32.20	50

a) All the experiments were carried out at -23 °C for 6h using cyclopentadiene (12 mmol, 0.66 g) and cinnamaldehyde (10 mmol, 1.32g) in dichloromethane (45 ml) solvent.

b) The ee values of the endo isomer were estimated through ^1H NMR analysis of the corresponding diastereomeric acetal prepared using (1R, 2R, 3S, 5R)-(-)-pinane-2,3-diol 20.

For example, (S)-(-)-l,l'-bi-2-naphthol (1) (6.5 mmol, 46% ee) on reaction with boric acid (2 mmol) would give 18 (1 mmol) derived mainly from enantiomerically pure (S)-(-)-l leaving the racemic 1 in solution (Scheme 29). In this way, the borate ester 18 (1 mmol) and racemic 1 were prepared in benzene

(Dean-Stark apparatus). After removal of the benzene under reduced pressure, dichloromethane was added and the Diels-Alder reaction between cinnamaldehyde and cyclopentadiene was carried out. The results are summarised in Table 4.

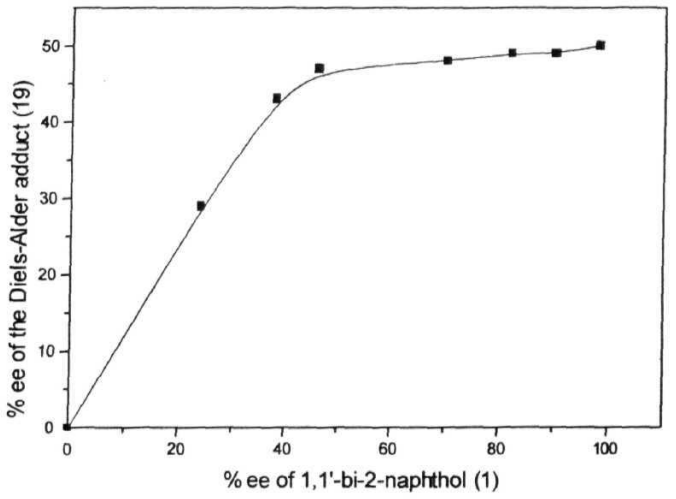


Figure 3. The relationship between enantiomeric excess of scalemic l,l'-bi-2-naphthol (1) and ee values of 19

In the Figure 3, the enantiomeric purity of the l,l'-bi-2-naphthol (1) used in these experiments (Table 4) and the ee values the Diels-Alder adduct 19 obtained are plotted. The most striking feature is the observation of positive nonlinear effect as anticipated. Thus, scalemic l,l'-bi-2-naphthol with relatively lower enantiomeric excesses can cause as much asymmetric induction as that observed using optically pure samples. Also, it should be pointed out that this is a new type of nonlinear

effect observed in asymmetric catalysis as mainly the homochiral C_3 symmetric catalyst 18 is selectively formed under the present conditions.

2.3 Conclusion

A simple, convenient method of preparation of the chiral borate ester derivative 18 from optically active l,l-bi-2-naphthol has been developed. This chiral borate is useful in the catalytic asymmetric Diels-Alder reactions of some dienophiles with cyclopentadiene to obtain the corresponding adducts in moderate ee. In the Diels-Alder reaction between cinnamaldehyde and cyclopentadiene catalysed by racemic borate ester 18 in the presence of (S)-(-)-a-methyl-benzylamine, the endo adduct was obtained in 20% ee. Positive nonlinear effect has been observed in the reaction between cinnamaldehyde and cyclopentadiene catalysed by the chiral borate ester 18 derived from scalemic l,l'-bi-2-naphthol. The nonlinear effect observed here is different since the homochiral C3 symmetric borate ester 18 is selectivey formed in the present case. Hence, the results would stimulate further investigations in this important area of research.

2.4 Experimental Section

General Information

Several of the general experimental details outlined in Chapter 1 are also applicable here. Methacrolein, crotonaldehyde, acrolein and methyl vinyl ketone were purchased from Fluka, Switzerland. trans-Cinnamaldehyde supplied by SD's India was utilised. Cyclopentadiene monomer was prepared from its dimer by cracking it over hot paraffin liquid (heavy). Sodium borohydride supplied by Lancaster, U.K. and (1R, 2R, 3S, 5R)-(-)-pinane-2,3-diol supplied by Aldrich, USA were used.

In all experiments, a round bottom flask of appropriate size with a side arm, a side septum, a magnetic stirring bar, a condenser and a connecting tube attached to a mercury bubbler were used. All dry solvents and reagents (liquids) used were distilled from appropriate drying agents just before use.

2.4.1 Preparation of chiral borate ester 18 using 1,1'-bi-2-naphthol and boric acid

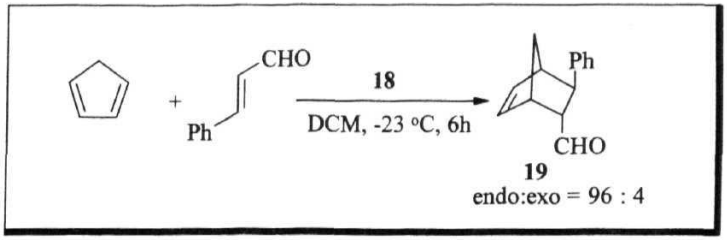
The borate ester 18 was prepared by taking l,l'-bi-2-naphthol (3 mmol, 0.86 g) and $B(OH)_3$ (2.2 mmol, 0.136 g) in benzene (30 ml) and refluxing the contents

for 12h using Dean-Stark apparatus. The solvent was evaporated under nitrogen atmosphere. The residue was dissolved in dichloromethane (25 ml) and filtered, and the filtrate was used in Diels-Alder reactions. The spectral data correspond to the reported data for 18.[30] (see also page 63, Chapter **1).**

2.4.2 Asymmetric Diels-Alder reaction between cyclopentadiene and various dienophiles.

Typical procedure: In a 100 ml two necked RB flask with side septum, cinnamaldehyde (10 mmol, 1.32 g) was taken in dichloromethane (25 ml). The chiral borate (-) 18 (1 mmol) prepared from (-)-1,1'-bi-2-naphthol (1), as above, was transferred to the reaction flask under nitrogen atmosphere and the contents were stirred at 25 °C for 30 minutes. The reaction temperature was brought to -23 °C and the contents were stirred for 10 minutes. Freshly prepared cyclopentadiene (12 mmol, 0.66 g) was added. After stirring for 6h at -23 °C, the contents were brought to 25 °C. It was quenched with aq.$NaHCO_3$ and extracted with dichloromethane. The organic layer was dried over anhydrous $MgSO_4$ and the solvent was evaporated. The Diels-Alder adduct 19 was isolated by chromatography on silica gel column using hexane/ethyl acetate (98:2) as eluent. The ratio of endo/exo

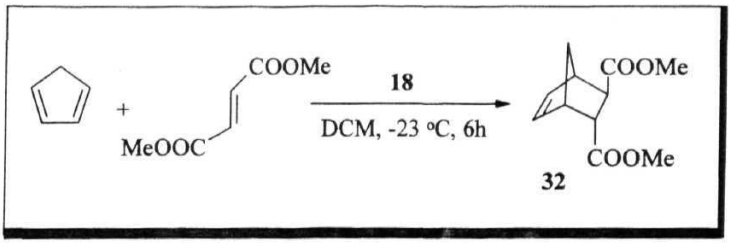
mixture was determined by ^1H NMR spectral analysis (ratio of the -CHO proton signals at 8 9.6 ppm and δ 9.9 ppm)



Data for **19**

Yield	: 0.83 g (42 %)
IR (neat)	:1716 cm^{-1}
^1H NMR (200 MHz, $CDCl_3$)	: δ ppm 1.50-1.70 (m, 1H), 1.80-1.90 (m, 1H), 2.98 (m, 1H), 3.08-3.14 (m, 2H), 3.34 (br, 1H), 6.17 (dd, J = 2.6, 3.5 Hz,lH), 6.42 (dd, J = 3.2, 3.5 Hz, 1H), 7.13-7.34 (m, 5H), 9.60 (d, J = 1.9 Hz,lH) **(Spectrum No. 3)**
13C NMR (50 MHz, $CDCl_3$)	: 8 ppm 45.2, 45.5, 45.8, 47.2, 48.4, 60.9, 126.2, 127.4, 127.9, 128.2, 128.6, 133.9, 203.3 **(Spectrum No. 4)**
$[\alpha]_D^{25}$	: (+) 31.96 (C1.2, $CHCl_3$)
Lit.[31] $[\alpha]_D^{25}$	: (+) 107.6 (C1.2, $CHCl_3$)

The spectral data of 19 show 1:1 correspondence with the reported data.[31] The above procedure was followed for the reaction of cyclopentadiene with several other dienophiles. The results are summarised below.



Data for 32:

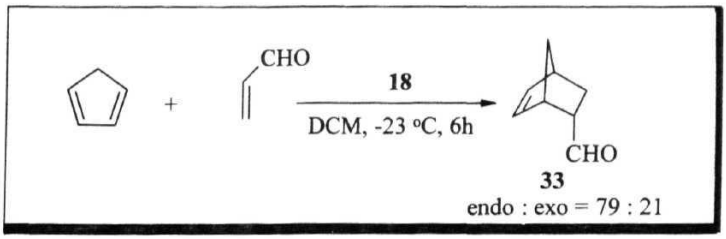
Yield : 1.52 g (72%)

IR (neat) : 1760 cm^{-1}

^1H NMR (200 MHz, $CDCl_3$) : 5 ppm 1.44-147 (m, 1H), 1.61 (d, J = 8.8 Hz, 1H), 2.66 (d, J = 2.7, 1H), 3.11 (m, 1H), 3.25 (m, 1H), 3.35 (m, 1H), 3.64 (s, 3H), 3.71 (s, 3H), 6.06 (dd, J = 3.6, 6.4 Hz, 1H), 6.26 (dd, J = 3.4, 6.6 Hz, 1H)

^{13}C NMR (50 MHz, $CDCl_3$) : 6 ppm 45.5, 47.0, 47.2, 47.5, 47.8, 51.6, 51.9, 135.1,137.4,173.5,174.7

The product was found to be racemic. The spectral data show 1.1 correspondence with the reported data.[17]



Date for **33**

Yield : 0.7 g (57 %)

IR (neat) : 1722 cm^{-1}

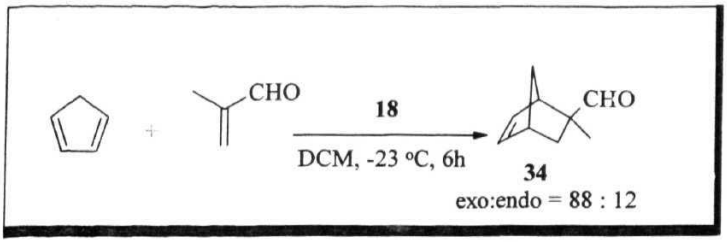
^1H NMR (200 MHz, $CDCl_3$) : δ ppm 1.20-1.60 (m, 3H), 1.90 (m, 1H), 2.94 (m, 1H), 3.05 (br, 1H), 3.26 (br, 1H), 6.03 (dd, J = 2.8, 6.0 Hz, 1H), 6.23 (dd, J =3.4, 6.2 Hz, 1H), 9.42 (d, J = 3.1 Hz, **1H) (Spectrum No. 10)**

^{13}C NMR (50 MHz, $CDCl_3$) : δ ppm **27.6, 42.1, 45.0, 49.6,** 52.2, **131.8,** 138.1, 204.9 **(Spectrum No. 11)**

$[\alpha]_D^{25}$:(+)18.8(Cl,EtOH)

Lit[27] $[\alpha]_D^{25}$: (+) 83.3 (C1, EtOH)

The spectral data show 1:1 correspondence with the data reported for the endo/exo mixture of **33**.[31]



Data for 34

Yield : 0.82 g (60%)

IR(neat) :1728 cm^{1}

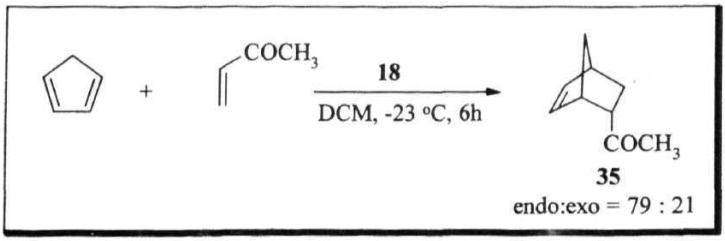
^{1}H NMR (200 MHz, $CDCl_3$) : 5 ppm 0.80 (d, J = 11.2 Hz, 1H), 1.02 (s, 3H), 1.30-1.40 (m, 2H), 2.30 (dd, J = 3.6, 11.6 Hz, 1H), 2.76 (br s, 1H), 2.83 (br s, 1H), 6.04 (dd, J = 2.8, 6.9 Hz, 1H), 6.28 (dd, J = 2.8, 7.0 Hz, 1H), 9.74 (s, 1H) **(Spectrum No. 12)**

^{13}C NMR (50 MHz, $CDCl_3$) : 5 ppm 20.0, 34.6, 43.2, 47.3, 47.5, 48.4, 133.0, 139.4, 205.8 **(Spectrum No. 13)**

$[\alpha]_D^{25}$: (+)14.01 (C1, EtOH)

Lit [11] $[\alpha]_D^{25}$: (+) 23.3 (C1, EtOH) for 2S isomer

The spectral data show 1:1 correspondence with the data reported for the exo/endo mixture of 34.[31]



Data for 35

Yield : 0.35 g (26%)

IR (neat) : 1708 cm^{-1}

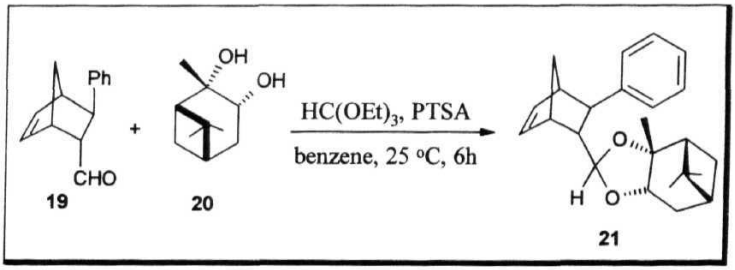
^1H NMR (200 MHz, $CDCl_3$) : 8 ppm 1.3 (m, 1H), 1.4-1.6 (m, 2H), 1.7 (m, 1H), 2.1 (s, 3H), 2.8 (br s, 1H), 2.9 (m, 1H), 3.2 (br s, 1H), 5.8 (dd, J = 2.8, 4.8 Hz, 1H), 6.2 (dd, J = 2.6, 4.7 Hz, 1H)

^{13}C NMR (50 MHz, $CDCl_3$) : δ ppm 27.4, 29.1, 42.6, 45.8, 49.9, 52.2, 131.2, 137.7,208.6

The product was found to be racemic. The spectral data show 1:1 correspondence with the data reported for the endo/exo mixture of 35.[32]

2.4.3 Preparation of the diastereomeric acetal 21

In a 50 ml two necked RB flask with side septum, the Diels-Alder adduct 19 (0.5 mmol, 0.99 g) was taken in dry benzene (30 ml). To this, (1R, 2R, 3S, 5R) (-) pinane-2,3-diol (20) (0.6 mmol, 0.102 g), triethyl orthoformate (0.75 mmol, 0.110 g) and p-toluenesulphonic acid (0.020 g) were added under nitrogen atmosphere and the contents were stirred at 25 °C for 6h. The reaction mixture was quenched with aq.$NaHCO_3$ and extracted with ether (2x20 ml). The organic layer was washed with water (2x10 ml) followed by brine, dried over anhydrous $MgSO_4$ and the solvent was evaporated. The endo/exo mixture 21 was isolated by chromatography on silica gel column using hexane and ethyl acetate (99:1) mixture.



Data for 21

Yield : 0.150 g (85 %)

IR (neat) :1450 cm"

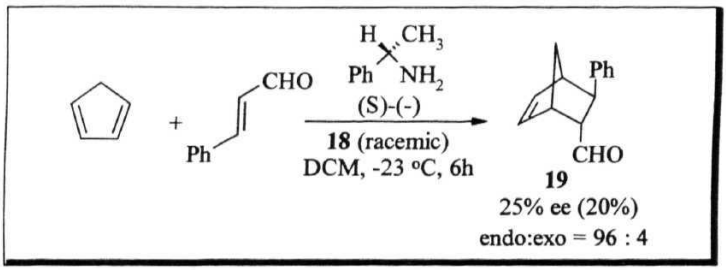
^1H NMR (200 MHz, $CDCl_3$) : 6 ppm 0.83 (s, 3H), 1.2-1.4 (m, 6H), 1.5-1.7 (m, 3H), 1.8-2.1 (m, 5H), 2.4 (m, 1H), 2.6 (t, J = 2.7 Hz, 1H) 3.0 (br s, 2H), 3.9 (t, J = 3.4 Hz, 1H), 4.5 (2d, J = 7.1, 7.8 Hz, 1H)), 6.2 (m, 1H), 6.4 (m, 1H), 7.27-7 .47(m, 5H) **(Spectrum** No. **5&6)**

^3C NMR (50 MHz, $CDCl_3$) : 6 ppm 24.2 (CH_3), 25.4 (CH_2), 25.8 (CH_3), 27.4 (CH), 33.2 (CH_2), 37.8 (quaternary), 40.3 (CH), 45.0 (CH), 46.5 (CH), 47.1 (CH_2), 48.4 (CH), 48.7 (CH_3), 51.0 (CH), 77.2 (HCO), 83.5 (CO, quaternary), 104.9 (HCO_2), 125.6 (CH), 128.0 (CH), 128.2 (CH), 135.5 (C=C), 137.7 (C=C), 145.2 (quaternary) **(Spectrum No. 7)** (Signal assignments are based on DEPT experiments), **(Spectrum No. 8)**

MS (EI) **:** m/z 350 (M^+, 2.5 **%), 93** (M^+- 257, 100 **%) (Spectrum No. 9)**

2.4.4 Diels-AIder reaction between cinnamaldehyde and cyclopentadiene using racemic borate 18 and (S)-(-)-α-methylbenzylamine - chiral poisoning

In a 100 ml two necked RB flask with side septum, racemic 18 (1 mmol) prepared from (±) l,l'-bi-2-naphthol, as above, and (S)-(-)-a-methylbenzylamine (0.5 mmol, 0.06 g) were taken and the contents were stirred at 25 °C under nitrogen atmosphere. Cinnamaldehyde (10 mmol, 1.32 g) was added and the reaction temperature was brought to -23 °C. The contents were stirred further for 10 minutes. Freshly prepared cyclopentadiene (12 mmol, 0.66 g) was added. After stirring for 6h at -23 °C, the contents were brought to 25 °C. The reaction mixture was quenched with aq.$NaHCO_3$ and extracted with dichloromethane. The organic layer was dried over anhydrous $MgSO_4$ and the solvent was evaporated. The Diels-AIder adduct 19 was isolated by chromatography on silica gel column using hexane/ethyl acetate (98:2) as eluent. The ratio of endo/exo mixture was determined by ^1H NMR spectral analysis.



Data for 19

Yield : 0.39 g (20 %)

$[\alpha]_D^{25}$: (+) 16.0 (C1.2, $CHCl_3$)

Lit.[31] [a]" : (+)107.6 (C1.2, $CHCl_3$)

The spectral data were identical to that obtained for 19 in previous experiments.

2.5 References

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Chapter 3

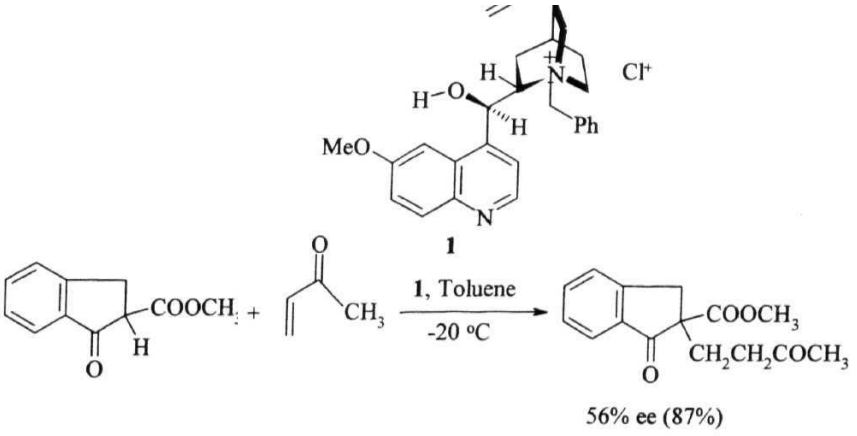
Studies on the Michael reaction catalysed by chiral ammonium 1,1'-bi-2-naphthyl borate complexes

3.1 Introduction

Enantioselective Michael addition to a substrate catalysed by a chiral catalyst is an attractive method for creating a chiral centre in an organic molecule.[1-6] Asymmetric inductions in these reactions depend on the recognition of the donor sites by the chiral catalysts. It may be of interest to briefly review the recent advances in the asymmetric Michael reactions promoted by various chiral auxiliaries.

In 1975, Wynberg and Helder[7] reported that Michael reactions using achiral donors and acceptors in the presence of catalytic amounts of (-)-quinine (1), gave optically active products. For example, the reaction between methyl indan-1-one-2-carboxylate and methyl vinyl ketone in the presence of 1 gave the corresponding adduct in 56% ee (Scheme **1).**

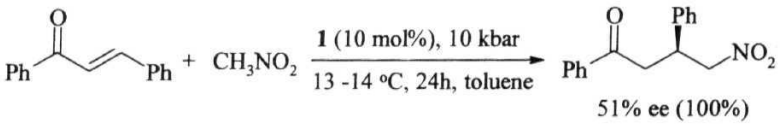
Scheme 1



There had been some previous reports on the asymmetric Michael reaction. However, optical purity of the products were not determined.[8-9]

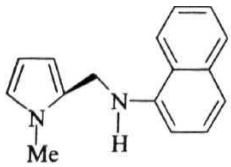
Some Michael type reactions, that are unsuccessful under conventional reaction conditions, proceeded smoothly on application of high pressure to give the adducts in good yields.[10-12] For example, the Michael reaction of nitromethane takes place under high pressure (at 10 kbar) in the presence of catalytic amount of chiral alkaloids such as quinine, cinchonidine, quinidine, cinchonine, brucine and strychinine.[13] Asymmetric induction of < 51% ee was realised using quinine (1) in toluene (Scheme 2).

Scheme 2



Later, studies on the pressure dependence on the degree of asymmetric inductions in the Michael addition of thiols, nitromethane and methyl indan-1-one-2-carboxylate to enones catalysed by alkaloid acrylonitrile copolymers were reported.[14]

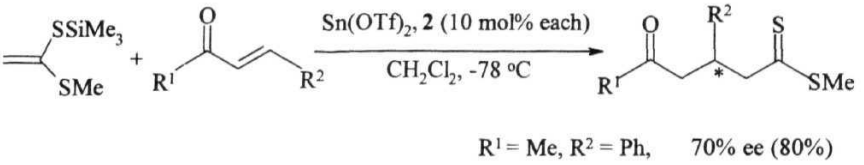
Mukaiyama and co-workers[15] reported the catalytic asymmetric Michael reaction of enethiolates employing catalytic amount of stannous triflate and the chiral diamine (2).



2

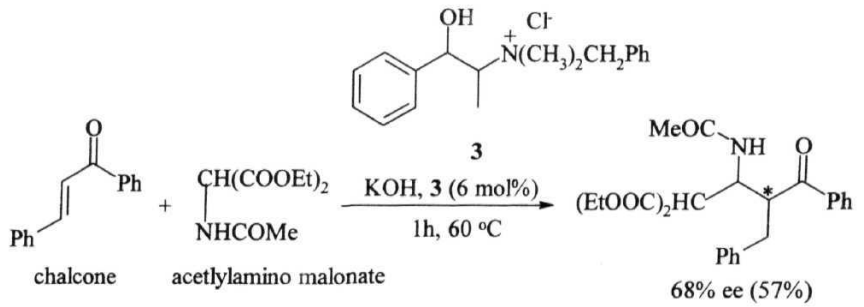
For example, in the reaction of benzalacetone with enethiolate in the presence of 10 mol% of $Sn(OTf)_2$-**2** complex, the Michael product was obtained in 70% ee (80% yield) (Scheme **3).**

Scheme 3

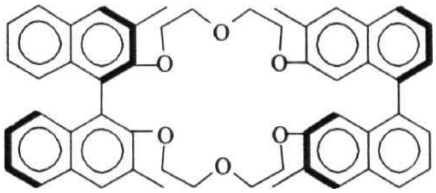


A solid-liquid phase transfer catalyst, without added solvent, efficiently promotes asymmetric Michael reaction.[1] For example, in the reaction of chalcone with acetylamino malonate in the presence of quaternary salt 3 derived from (+) or (-) N-methylephedrine, the corresponding adduct was obtained in 68% ee (57% yield) (Scheme **4).**

Scheme 4



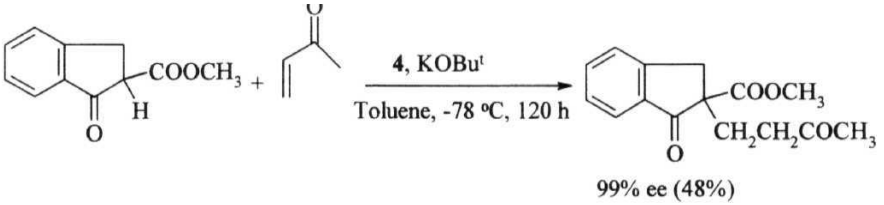
Cram and co-workers improved the enantioselectivity of certain Michael reactions using chiral crown ether 4 derived from optically active **l,l'-bi-2-**naphthol.[17]



4

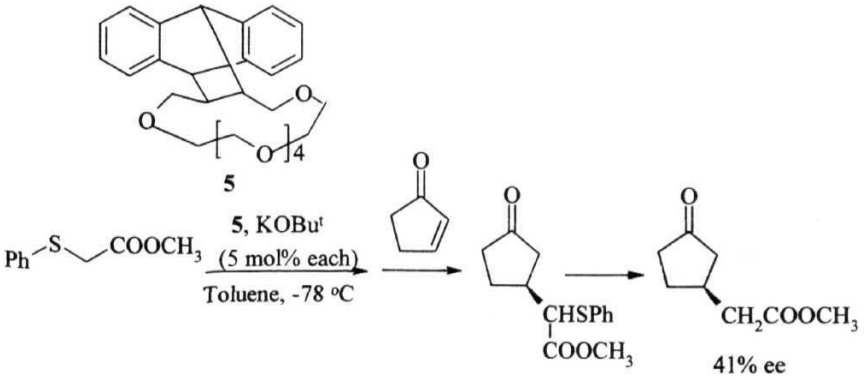
The crown ether complexes of potassium bases catalyse the Michael addition of P-ketoesters to methyl vinyl ketone and phenylacetic esters to methyl acrylate to give products up to 99% ee (Scheme **5)**

Scheme 5



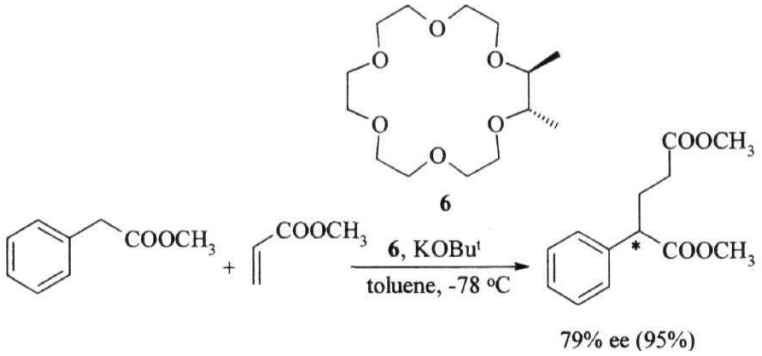
A chiral crown ether 5 derived from anthracene promotes the $KOBu^t$ induced Michael reaction between methyl phenylthioacetate and cyclopentenone.[18] However, the optical purity of the adduct was found to be only 41% ee (Scheme **6).**

Scheme 6



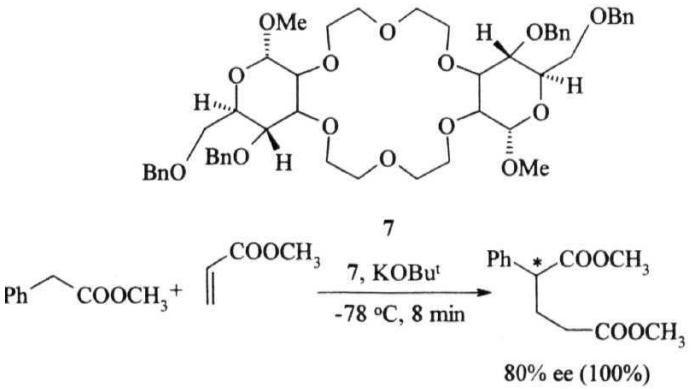
The simple chiral crown ether 6 complexed with $KOBu^t$ works as an efficient chiral catalyst in a Michael reaction.[19] Addition of phenylacetate derivatives to methyl acrylate at -78 °C, in the presence of 5 mol% of 6 $KOBu^t$ complexes, results in high asymmetric inductions (Scheme **7).**

Scheme 7



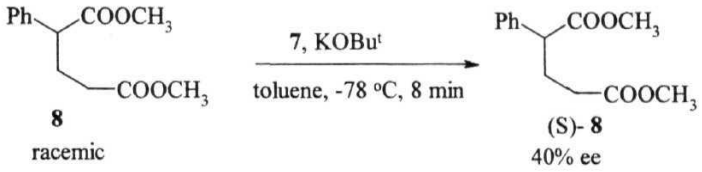
It was also reported that the use of chiral crown ether 7, anellated to sugar units catalyse enantioselective Michael reaction of methyl phenylacetate with methyl acry late to give the corresponding adducts in 80% ee (100% yield) (Scheme 8).[20]

Scheme 8



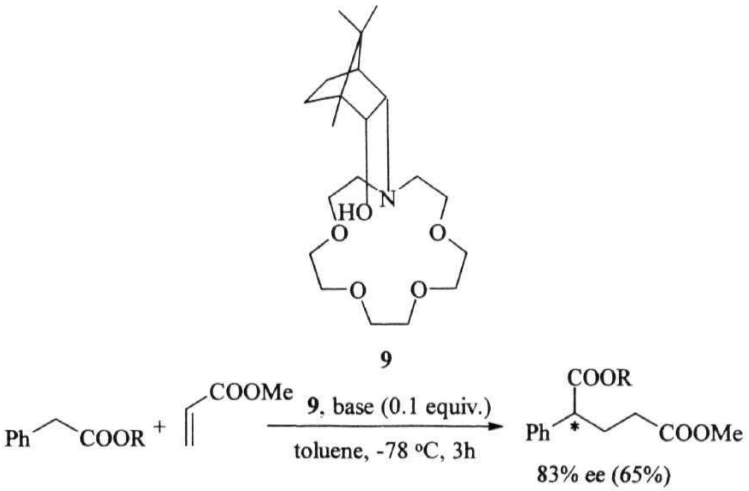
A novel CH-acid deracemization has also been discovered during this investigation. When experiments were carried out using the racemic 8 in the presence of $KOBu^t$ and 7 at -78 °C in toluene, 8 was obtained in 40% ee (Scheme 9).

Scheme 9

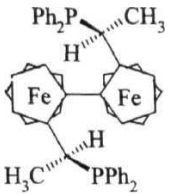


A novel optically active crown ether 9 derived from (+)-camphor was found to be effective in the enantioselective Michael reaction between phenylacetates and methyl acrylate (Scheme 10).[21]

Scheme 10



Ito and co-workers[22] synthesised a trans chelating chiral diphosphine ligand (10), 2,2"-bis[1-(diphenylphosphino)ethyl]1,1"-biferrocene (TRAP).

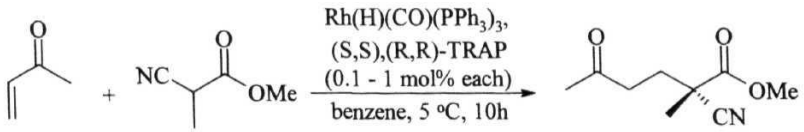


10

(S,S)-(R,R)- TRAP

It was observed that the rhodium complex of TRAP (10) prepared *in situ* using $RhH(CO)(PPh_3)_3$ and TRAP (0.1-mol%) was an effective catalyst for asymmetric Michael addition of α-cyanocarboxylate with vinyl ketones or acrolein (Scheme 11).

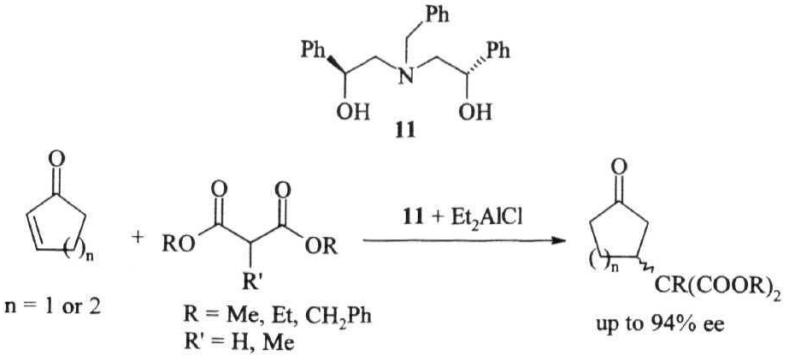
Scheme 11



72% ee (99%)

Sundararajan and Manickam[23] synthesised the C_2-symmetric chiral aminodiol, (1R,5R)-3-aza-3-benzyl-1,5-diphenylpenta-1,5-diol (11), which upon reaction with Et_2AlCl gave the corresponding aluminate. Michael reaction catalysed by this homochiral aluminate resulted in high asymmetric induction (Scheme 12).

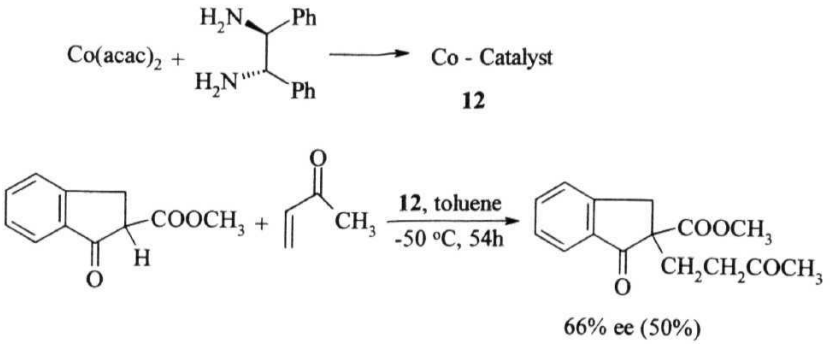
Scheme 12



R = Et, R' = H, n = 2, 94% ee (87 %)

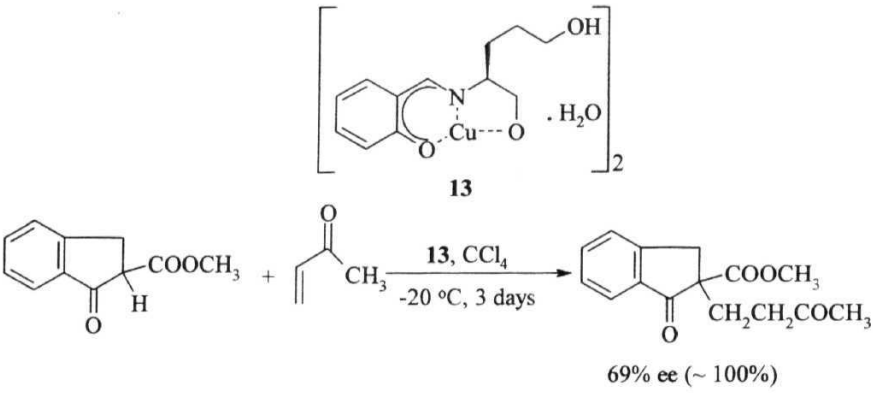
A cobalt catalyst 12 prepared using $Co(acac)_2$ and (+) or (-)-1,2-dipheny 1-1,2-ethanediamine is useful in the enantioselective addition to methyl vinyl ketone.[24] Asymmetric induction of < 66% ee was realised in the reaction of methyl indan-1-one-2-carboxylate (Scheme **13).**

Scheme 13



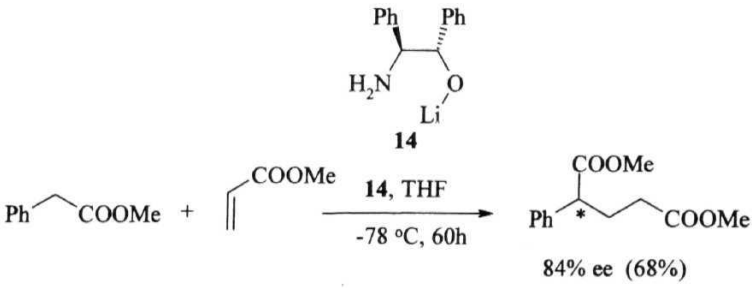
Enantioselective Michael addition of methyl indane-1-one-2-carboxylate with methyl vinyl ketone was also reported in the presence of various Cu(II) chiral complexes 13 (Scheme **14**).[25]

Scheme 14



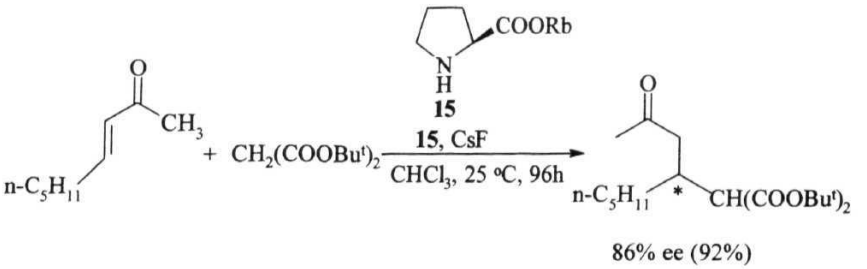
Koga *et al* prepared the simple chiral lithium alkoxides 14 for use in enantioselective Michael reaction of methyl phenylacetate and methyl acrylate.[26] The corresponding adduct was obtained in 84% ee (Scheme **15).**

Scheme 15



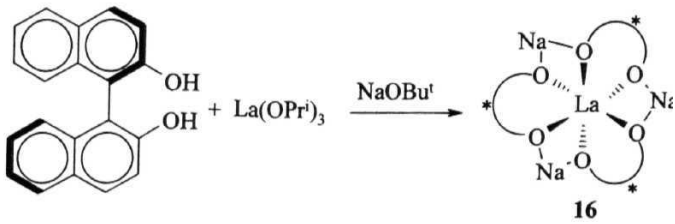
Yamaguchi *et al* found that the (S)-proline rubidium salt (15) catalyses the asymmetric Michael reaction of malonate anions. [7] High enantiomeric excesses were obtained when di(t-butyl) malonate was reacted with (E)-enones in the presence of CsF (Scheme **16).**

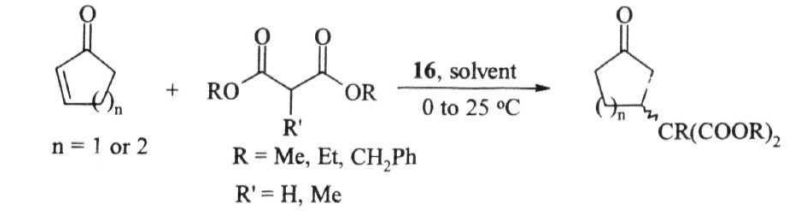
Scheme 16



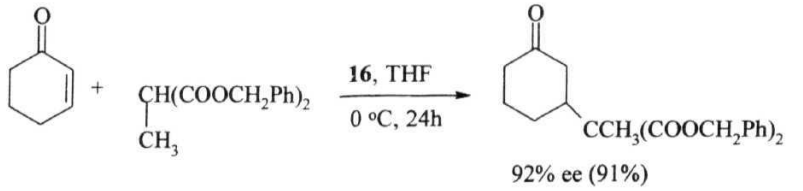
Shibasaki and co-workers reported that optically active lanthanum-sodium-l,l'-bi-2-naphthol complex (16),[28] prepared using $La(OPr^i)_3$, (R)-1,1'-bi-2-naphthol and $NaOBu^t$, is an effective catalyst for various Michael reactions to give adducts with < 92% ee (Scheme **17).**

Scheme 17



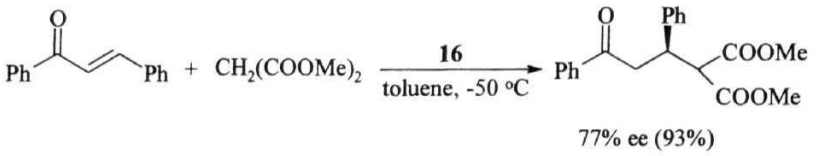


for example;



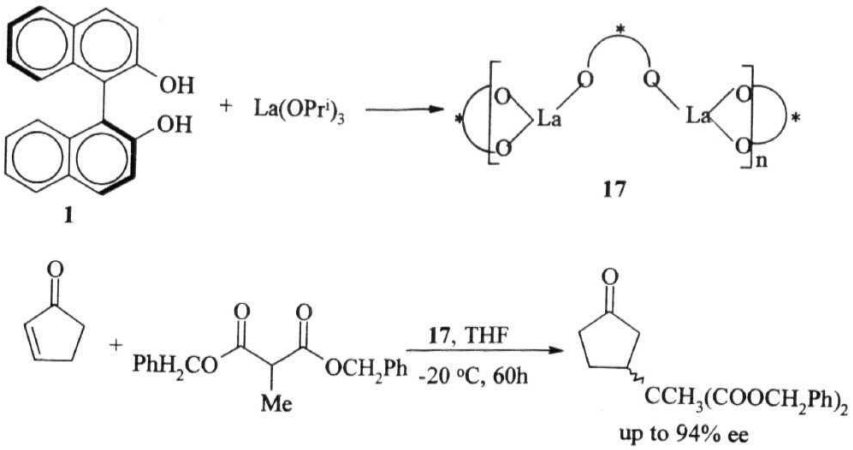
Similarly, in the reaction between chalcone and dimethyl malonate using 16, an asymmetric induction of 77% ee was realised (Scheme 18).

Scheme 18



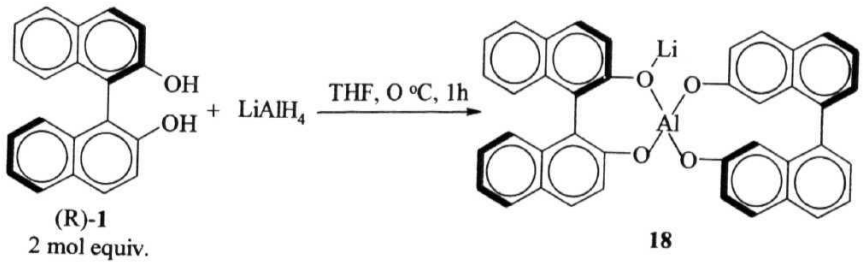
Later, Shibasaki *et al* prepared several chiral l,l'-bi-2-naphthol-rare earth metal-lithium bimetallic complexes which are also effective in catalytic nitro aldol reaction.[29] However, these bimetallic complexes were found to be ineffective towards the catalysis of Michael reaction. The corresponding lithium free 1,1'-bi-2-naphthol-Lanthanum complex 17 is effective in catalytic asymmetric Michael reaction to obtain the adduct in 95% ee in (97% yield) (Scheme 19).

Scheme 19

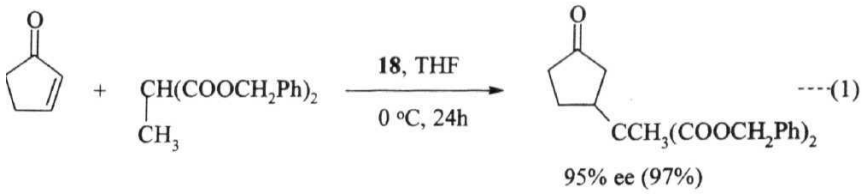


Most of these catalysts containing rare earth metals are heterobimetallic complexes which exhibit both Bronsted basicity and Lewis acidity. Shibasaki *et al* also extended this heterobimetallic concept to central metals other than rare earth metals (Scheme **20).**[30]

Scheme 20



The catalyst system 18 containing aluminium and lithium gave highest asymmetric induction (eq. **1**).[30]



---(1)

We have examined the use of the chiral ammonium l,l'-bi-2-naphthyl borate complexes, which are readily available through the reaction of B(0H)3, (R)-(+)-α-methylbenzylamine and chiral 1,1'-bi-2-naphthol for Michael reactions (Chapter 1, Scheme 27).[31] The results are discussed in this chapter.

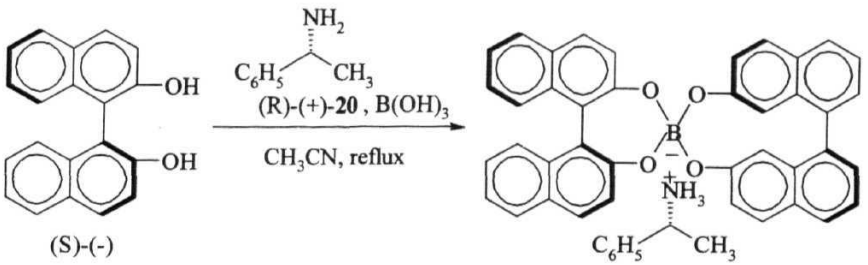
3.2 Results and Discussion

3.2.1 Michael reaction between diethyl mnlonate and cylohexenone using chiral ammonium l,l'-bi-2-naphthyl borate complex 19

Although base catalysis of the Michael reaction is a very efficient and high yielding process, applications are limited as strong basic conditions lead to a number of side and subsequent reactions. For instance, incompatibilities with base sensitive groups, ester solvolyses, aldol processes leading to cyclic products or retro Claisen type decompositions are the disadvantages associated with typical base catalysed Michael reactions. To avoid strongly alkaline conditions, several alternatives have been developed in recent years, which make use of weak Bronsted bases or employ mild reaction conditions.[32,,37]

The breakthrough in this field was the discovery of heterobimetallic alkali-lanthanide-1,1'-bi-2-naphtholate 16 catalysis which facilitate highly efficient catalytic asymmetric Michael reactions with excellent enantioselectivities (Scheme 17-19).[28,29] As discussed in the introductory section, Shibasaki *et al* also reported the application of the Li-Al-l,l'-bi-2-naphthol complexes (Scheme 20).[30] We have decided to investigate the application of the ammonium l,l'-bi-2-naphthyl borate complexes 19 readily accessible through the reaction of l,l'-bi-2-naphthol, boric acid and amines (Scheme 21).

Scheme 21



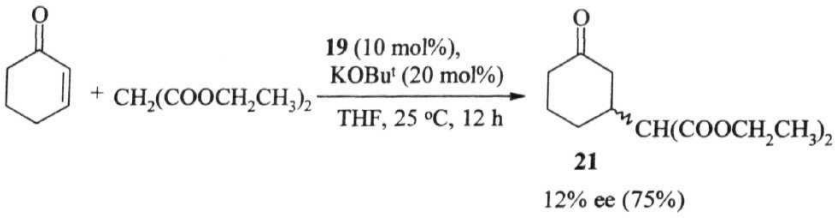
19

We have found that the Michael reaction of diethyl malonate and cyclohexenone using the complex 19 did not take place at 25 °C, even after 4 days. It was thought that the complex may not be basic enough to promote the Michael reaction. Hence, experiments were carried out using stoichiometric amounts of bases such as DMAP, DABCO, TMEDA, NEt_3, (R)-(+)-α-methylbenzylamine (20), in addition to the complex. However, these amine bases also failed to promote the Michael reaction.

Shibasaki *et al* used sodium or potassium alkoxides (NaOR or KOR) for the preparation of the bimetallic catalysts.[28] It appeared that the presence of Li, Na or K ion in the catalyst system may be necessary for the Michael reaction. Accordingly, we have examined the use of ammonium borate complexes in the presence of $KOBu^t$. Indeed, it was observed that the use of $KOBu^t$ in addition to complex 19 was effective in the catalysis of Michael reaction. For example, the reaction between diethyl malonate and cyclohexenone in THF solvent in the

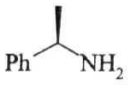
presence of the complex 19 (10 mol%) and $KOBu^t$ (20 mol%) gave the Michael product 21 in 75% yield and in 12% ee (Scheme 22).

Scheme 22

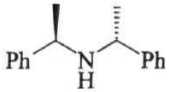


Since the complex 19 is capable of catalysing Michael reactions, we undertook efforts to modify the catalyst system, so as to achieve higher degree of asymmetric induction. It is well known that asymmetric induction of the reaction catalysed by a chiral auxiliary depends on the nature of the chiral elements present. The chiral components present in the complex 19 are optically active l,l'-bi-2-naphthol and (R)-(+)-α-methylbenzylamine. So, we decided to investigate the reaction using different chiral amines.

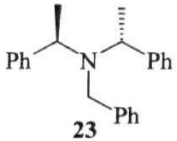
The chiral amines (R,R)-α,α'-dimethyldibenzylamine 22 and N-benzyl-(R,R)- α,α'-dimethyldibenzylamine 23 were synthesised following reported procedures.[41] Preparation of the corresponding ammonium 1,1'-bi-2-naphthyl borate complexes were studied (Scheme 23). Incidentally, the tertiary amine 23 failed to form the complex with chiral 1,1'-bi-2-naphthol and $B(OH)_3$ under the reaction conditions.



20



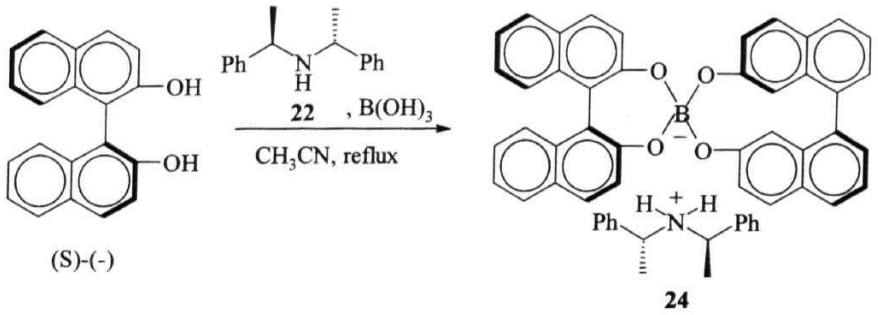
22



23

Fortunately, the complex 24, prepared using the amine 22 catalysed the Michael reaction between cyclohexenone and diethyl malonate. The results are better than that obtained with (R)-(+)-a-methylbenzylamine (Table 1).

Scheme 23



After extensive studies, we have decided to investigate the use of the complex 24 derived from amine 22, (-)-l,l'-bi-2-naphthol and $B(OH)_3$ for further studies. When the reaction between diethyl malonate and cyclohexenone were carried out at 25 °C in the presence of the complex 24 (10 mol%), the corresponding Michael product was obtained in 45% ee (80% yield) (Scheme 24).

Table 1 Catalytic asymmetric Michael reaction between cyclohexenone and diethyl malonate promoted by chiral ammonium borate complex 24: Amount of catalyst required *

S.No	**24** mmol	**KOBu^t** mmol	21 %ee (% yield)
1.	1.0	00	00
2.	1.0	1.0	00
3.[b]	0.5	1.0	04 (80)
4.[c]	0.5	1.0	23 (80)
5.	0.5	1.0	45 (80)

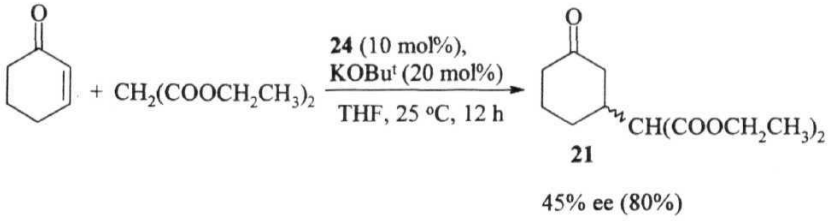
a) All the reactions were performed using complex 24 (0.5 mmol) diethyl malonate (5 mmol) and cyclohexenone (6 mmol) in THF at 25 °C (see experimental section for details). The ee values are calculated on the basis of reported $[\alpha]_D^{25}$ values.

b) The complex 24 (0.5 mmol) and **KOBu^t** (1.0 mmol) were stirred at 25 °C for 12h. The substrates were added and the reaction was carried out for **12h.**

c) Diethyl malonate (5 mmol) and **KOBu^t** (1.0 mmol) were stirred at 25 **°C** for 12h. **Thc** complex 24 (0.5 mmol) and cyclohexenone were added subsequently and the reaction was carried out for **12h.**

Control experiments indicated that both the chiral **1,1'-bi-2-naphthol** and the chiral **amine** moieties are required to obtain the asymmetric induction. For example, the ammonium borate complex prepared using **Et_3N** and chiral 1,1'-bi-2-naphthol did not give any **asymmetric** induction.

Scheme 24



3.2.2 Asymmetric Michael reaction between diethyl malonate and cyclohexenone using the ammonium l,I'-bi-2-naphthyl borate complex 24 at various temperatures and in different solvents

Generally, lowering of temperature leads to improvement in the enantioselectivity. To examine this, we carried out the reactions at lower temperatures. Unfortunately, there was not significant increase in the ee of the product when reactions were carried out at -23 °C and 0 °C. Also, the chemical yields are very poor under these conditions. Reactions were also carried out in various solvents such as dichloromethane, toluene and THF. The results are better in THF solvent (Table 2).

Table 2. Asymmetric Michael reaction between diethyl malonate and cyclohexenone in the presence of chiral ammonium l,l'-bi-2-naphthyl borate complex 24 in various solvents *

S.No[a]	Solvent and condition	21 %ee (% yield)
1.	Toluene	00
2.	Dichloromethane	00
3.	THF	45 (80)
4.[b]	THF	4(80)

a) All the reactions were performed using complex 24 (0.5 mmol) diethyl malonate (5 mmol) and cyclohexenone (6 mmol) in THF at 25 °C (see experimental section for details)

b) Molecular sieves 4A° (0.1 g) were added to the reaction mixture and then the contents were stirred at 25 °C for 12h.

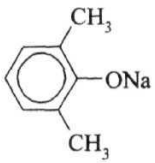
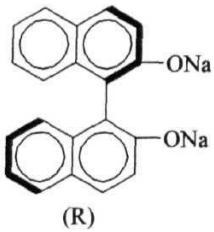
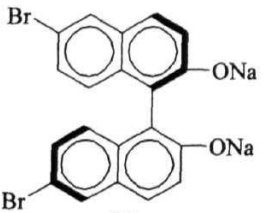
It is known that addition of molecular sieves to the reaction mixture, which would facilitate the removal of traces of water present, leads to better results in some reactions. To examine this effect, reactions were carried out in the presence of molecular sieves (MS 4 A°). Unfortunately, very poor asymmetric induction was obtained under these conditions (Table 2).

3.2.3 Asymmetric Michael reaction between diethyl malonate and cyclohexenone using chiral ammonium l,l'-bi-2-naphthyl borate complex 24 and various bases

Since carrying out reactions at lower temperature did not give fruitful results, we investigated further to examine the effect of the base used in the catalysis process. As outlined in the introductory section, Yamaguchi *et al* reported that (S)-proline salts of ions such as Li, Na, K, Rb and Cs were effective catalysts for Michael reaction.[27] They noted that the sodium and potassium ions were more effective than the lithium ions.

We have carried out the reactions using sodium. However, there was no significant change in the results. We have also examined the effect of alkyl groups present in the bases, such as NaOMe, $NaOPr^{i}$, $NaOBu^{t}$, sodium 2,6-dimethylphenoxide in the Michael reaction under the present conditions. The results obtained are summarised in Table 3. Unfortunately, these studies were not fruitful.

Table 3. Asymmetric Michael reaction between cyclohexenone and diethyl malonate in the presence of 24 using various bases

S. No	Base	21 (%ee)	Yield (%)
1.	$NaOBu^t$	09	70
2.	$KOBu^t$	45	80
3.		10	80
4.	 (R)	38	80
5.	 (R)	21	75

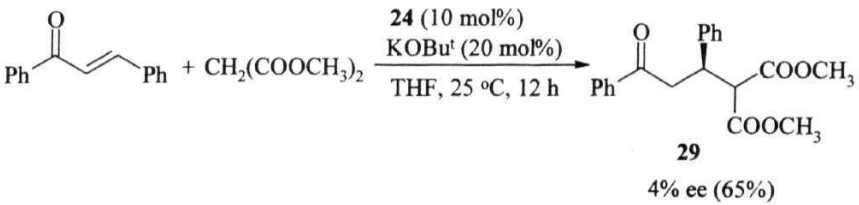
a) All the reactions were performed using complex 24 (0.5 mmol) diethyl malonate (5 mmol) and cyclohexenone (6 mmol) using 20 mol% of the base in 60 ml of THF at 25 °C (see experimental section for details).

3.2.4 Asymmetric Michael reaction using various malonate derivatives

It is obvious from these studies that only the borate complex prepared using (-)-l,l'-bi-2-naphthol, $B(OH)_3$ and α,α'-dimethyldibenzylamine (24) in combination with $KOBu^t$ gives good results. So, we have carried out further studies under these conditions using various malonate derivatives, such as dimethyl malonate, di(t-butyl) malonate, dibenzyl malonate and the corresponding methylmalonate derivative. The results are summarised in the Table 4.

The use of chalcone in the place of cyclohexenone was also carried out. However, the results are very poor (Scheme 26).

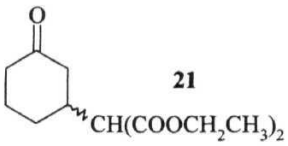
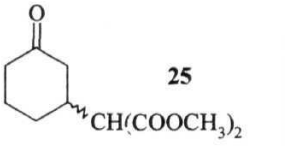
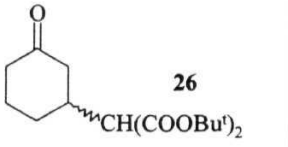
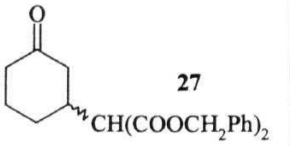
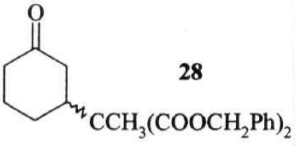
Scheme 26



29

4% ee (65%)

Table 4. Asymmetric Michael reaction between cyclohexenone and various malonate derivatives using 24 *

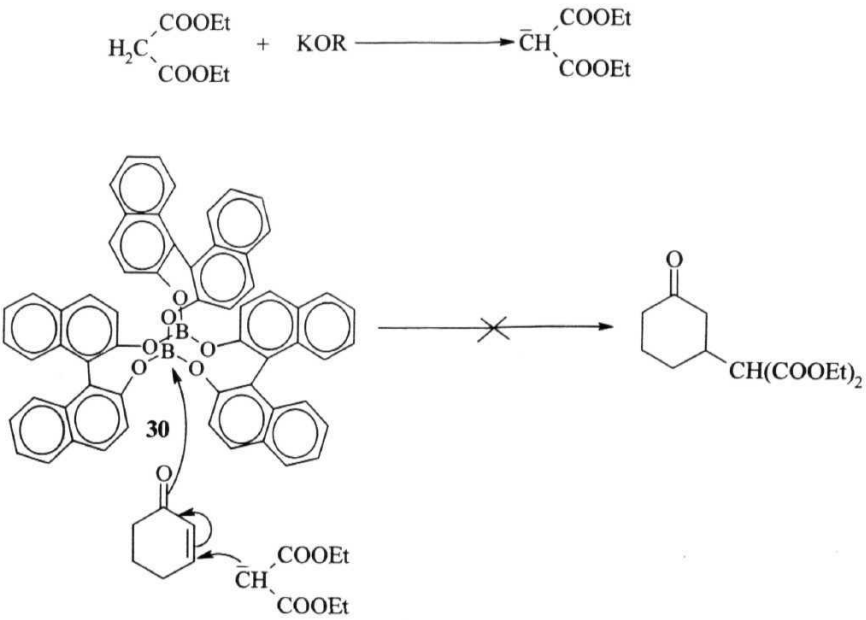
S.No	Substrate	Product	%ee (%yield)
1.	$CH_2(COOEt)_2$	 **21**	45 (80)
2.	$CH_2(COOCH_3)_2$	 **25**	40 (78)
3.	$CH_2(COOBu^t)_2$	 **26**	08 (70)
4.	$CH_2(COOCH_2Ph)_2$	 **27**	25 (75)
5.	$CHCH_3(COOCH_2Ph)_2$	 **28**	00 (65)

a) All the reactions were performed using malonate ester (6 mmol) and cyclohexenone (5 mmol) in the presence of the complex 24 (10 mol%) and **KOBu^t** (20 mol%) in THF (60 ml) 25 **°C** for 12h. The yields are of isolated products and the ee values were calculated on the basis of reported $[\alpha]_D^{rt}$ values.

3.2.5 Attempted Michael reaction between diethyl malonate and cylohexenone using chiral borate propeller 30

Since the chirai borate utilised in the Diels-Alder reaction is a Lewis acid (Chapter 2, Scheme 17), we thought that it may also be useful in promoting asymmetric Michael reactions under basic medium (Scheme 26). A series of experiments were carried out between the anion of diethyl malonate and cyclohexenone in the presence of the chirai propeller 30. Unfortunately, the corresponding Michael products were not obtained under these conditions.

Scheme 26

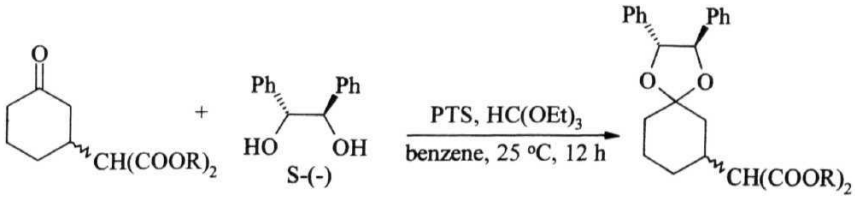


3.2.6 HPLC Analysis of the Michael adducts

The enantiomeric excesses of the Michael adducts formed in the Michael reactions using cyclohexenone by the chiral ammonium l,l'-bi-2-naphthyl borate complex 24 were calculated from the $[\alpha]_D^{25}$ values reported earlier by Shibasaki *et al*.[30] However, the $[\alpha]_D^{25}$ values exhibited by these derivatives are low and hence prone to have higher experimental errors. Therefore, we have carried out HPLC analysis of these samples. The adducts formed in the Michael reaction could not be analysed using the chiral columns (chiral cell OD and chiral pak OP) accessible for this work.

We have then made attempts to prepare the diastereomeric ketal derivatives for HPLC analysis. The ketal derivatives of (S,S)-(-)-l,2-diphenyl-l,2-ethanediol could be readily prepared (Scheme 27). The (±)-l,2-diphenyl-l,2-ethanediol has been resolved using (S)-proline to obtain (S,S)-(-)-1,2-diphenyl-1,2-ethanediol in > 99% ee following the procedure developed in this laboratory.[42]

Scheme 27



R = CH_3, CH_2CH_3, CH_2Ph

R = CH_2CH_3, **21a**
R = CH_3, **25a**
R = CH_2Ph, **27a**

The ^{1}H NMR and ^{13}C NMR data of the diastereomeric ketals were not helpful to estimate the ee of these isomers. HPLC analyses of the diastereomeric ketals of racemic adducts 25a and 27a and the optically active adducts 25a and 27a were carried out on Chiral cell OD column (hexane/2-propanol (96:4) mixture as eluent). Unfortunately, accurate values of the ee could not be estimated as the column efficiency was poor.

The chiral ammonium l,l-bi-2-naphthyl borate complex 24 contains an ML_2 unit derived from two 1,1'-bi-2-naphthol moieties. It would be of interest to look for nonlinear effects in the asymmetric Michael reactions observed here. However, the asymmetric inductions realised are poor and hence the values of ee could not be confirmed by ^{1}H NMR analysis or HPLC data. Therefore, we did not pursue further studies on this topic.

3.3 Conclusion

Catalytic asymmetric Michael reaction of various malonate derivatives with cyclohexenone using the chiral ammonium 1,1'-bi-2-naphthyl borate complexes prepared from chiral l,l'-bi-2-naphthol, $B(OH)_3$, and chiral amines was investigated. The chiral ammonium borate complex 24 derived from a,a'-dimethyldibenzylamine (22) in the presence $KOBu^{t}$ catalyses the Michael reaction of diethyl malonate to cyclohexenone to give the corresponding adducts in < 45% ee.

3.4 Experimental Section

General Information

Several of the general experimental details given in Chapter 1 and Chapter 2 are also applicable here. Cycohexenone, dibenzyl malonate, di(t-butyl) malonate, dimethyl malonate, and diethyl malonate were purchased from Lancaster, U.K. (S,S)-(-)-l,2-diphenyl-l,2-ethanediol was synthesised following the procedure reported from this laboratory.[42] Catalytic hydrogenations were carried out on a Parr hydrogenation apparatus in a 250 ml pressure bottle.

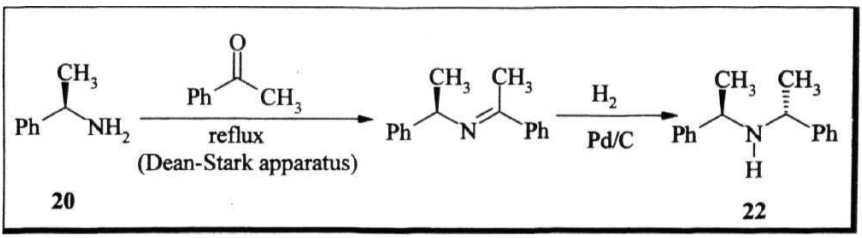
3.3.1 Preparation of (R,R)-α,α'-dimethyldibenzylamine (22)

A slightly modified reported procedure was followed.[41] A mixture of acetophenone (0.2 mol, 24.0 g), (R)-(+)-α-methylbenzylamine (0.2 mol, 24.2 g) and catalytic amount of p-toluenesulfonic acid (0.040 g) in 200 ml of benzene was refluxed under nitrogen atmosphere with continuos removal of water by means of a Dean-Stark apparatus during 36h. The reaction mixture was cooled in an ice bath and subsequently washed with ice cold saturated sodium bicarbonate solution, brine and dried over anhydrous $MgSO_4$. The solvent was evaporated and the corresponding imine was obtained in (40.3 g) 90% yield.

The imine obtained in the above experiment (50 mmol, 11.2 g) was dissolved in 40 ml ethyl acetate and 0.1 g of 5% Pd on activated charcoal was added. The mixture was shaken in a Parr apparatus during 16h under 3 atmosphere of hydrogen pressure. After removal of the catalyst by filtration, and evaporation of the solvent, the product obtained was treated with 3N HC1 (50 ml). The resulting white crystalline hydrochloride salt was isolated.

Yield	: 9.14 g (70%)
M.P.	: > 300 °C
$[\alpha]_D^{25}$	: + 82.7 (C3, EtOH)
Lit.[41] $[\alpha]_D^{25}$	: + 84.1 (C3, EtOH)

The amine hydrochloride was washed with ether (30 ml) and the amine was regenerated using 5N KOH. It was extracted into ether (3x50 ml), dried over anhydrous $MgSO_4$ and the solvent was evaporated. The residue was purified by distillation under reduced pressure to obtain the (R,R)-α,α'-dimethyldibenzylamine 22.



Data for 22

Yield	: 8.4 g (74 %)
B.P.	:150 °C / 0.4 mm Hg
Lit.[41] B.P.	:152 °C / 0.4 mm Hg
IR (neat) ν_{max}	: 1610,1400,1220,1025 cm^{-1}
r γ^{25}	:(+)153(C2.4,EtOH)
Lit.[41] $[\alpha]_D^{25}$	: (+) 157 (C2.4, EtOH)
^1H NMR (200 MHz, $CDCl_3$)	: 8 ppm 1.24 (d, J = 6.2 Hz, 6H), 1.58 (br, 1H), 3.47 (q, J = 4.6 Hz, 2H), 7.17 (m, 10 H)
^{13}C NMR (50 MHz, $CDCl_3$)	: δ ppm 24.8, 54.8, 126.3, 126.5, 128.1, 145.6

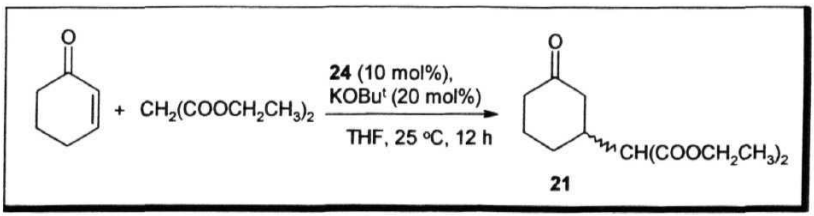
The spectral data showed 1:1 correspondence with the reported data.[41]

3.3.2 Preparation of the chiral l,l'-bi-2-naphthol ammonium borate complex (24):

(S) -(-) 1,1'-Bi-2-naphthol (10 mmol, 2.86 g), $B(OH)_3$ (5 mmol, 0.31 g) and (R,R)-α,α'-dimethyldibenzylamine (10 mmol, 2.25 g) were taken in CH_3CN (20 ml). The contents were refluxed for 12h. The reaction mixture was cooled to 25 °C and filtered. The precipitate was washed with CH3CN (2 x 5 ml) and dried under nitrogen atmosphere to get the complex 24. It was stored under nitrogen atmosphere for further use.

3.3.3 Michael reaction of cyclohexenone with various malonate derivatives

Typical procedure for the reaction between diethyl malonate and cyclohexenone: To a stirred solution of the complex 24 (0.5 mmol, 0.40 g) in THF (50 ml), $KOBu^t$ (1 mmol, 0.10 g) and diethyl malonate (5 mmol, 0.80 g) were successively added under nitrogen atmosphere at 25 °C. After stirring for 30 minutes, cyclohexenone (6 mmol, 0.58 g) dissolved in THF (10 ml) was added slowly and the contents were further stirred at 25 °C for 12h. The reaction mixture was treated with 1N HC1 (10 ml), and extracted with Et_2O (3x20 ml). The combined organic extracts were washed successively with water and brine, and dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel using hexane/EtOAc (93:7) as eluent to obtain the Michael adduct as a colourless oil.



Data for 21

Yield :1.03 g (80%)

IR(neat) : 1730, 1230, cm^{-1}

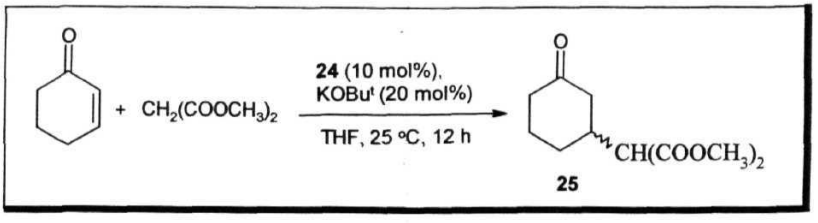
$[\alpha]_D^{25}$: (+) 1.59 (C 3, $CHCl_3$)

Lit.[29] $[\alpha]_D^{25}$: (+) 2.78 (C 2.56, $CHCl_3$) (78% ee)

^1H NMR (200 MHz, $CDCl_3$) : 8 ppm 1.20 (q, J - 6.8 Hz, 6H), 1.4-2.5 (m, 9H), 3.2 (d, J = 7.9 Hz, 1H), 4.1 (t, J = 7.1 Hz, 4H) **(Spectrum No. 14)**

^{13}C NMR (50 MHz, $CDCl_3$) : δ ppm 13.9, 24.4, 28.6, 37.9, 40.9, 45.0, 56.8, 61.3, 167.7, 209.4 **(Spectrum No. 15)**

The spectral data showed 1:1 correspondence with the reported data.[29] The above procedure was followed for the Michael reaction of various malonate esters with cyclohexenone and chalcone. The results are summarised in Table 4. The data are given here.



Data for 25

Yield : 0.89 g (78%)

IR (neat) : 1736, 1259, cm^{-1}

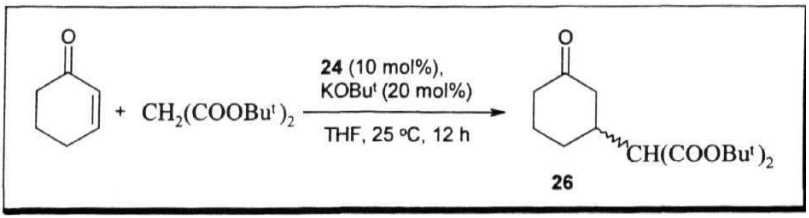
$[\alpha]_D^{25}$: (+) 1.60 (C 3, $CHCl_3$)

Lit.[29] $[\alpha]_D^{25}$: (+) 3.01 (C 2.1, $CHCl_3$) (75% ee)

^1H NMR (200 MHz, $CDCl_3$) : 6 ppm 1.4-2.6 (m, 9H), 3.30 (d, J = 7.9 Hz, 1H), 3.7 (s, 6H).

^{13}C NMR (50 MHz, $CDCl_3$) : 8 ppm 24.4, 28.7, 38.0, 40.9, 45.0, 52.4, 56.4, 168.1,209.4.

The spectral data showed 1:1 correspondence with the reported data.[29]



Data for 26

Yield : 1.18g(70%)

IR (KBr) : 1743, 1709 cm"

M.P. : 38-39 °C (Lit[27] 37-38 °C)

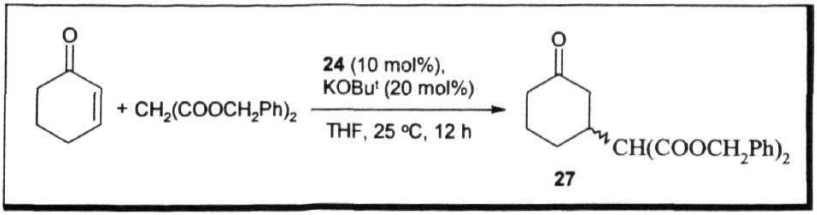
Mo : (+) 0.34 (C 2, $CHCl_3$)

: (+) 4.2 (C 1.02, $CHCl_3$) (100% ee)

^1H NMR (200 MHz, $CDCl_3$) : δ ppm 1.5 (s, 18H), 1.92-2.58 (m, 9H), 3.10 (d, J = 7.7 Hz, 1H)

^{13}C NMR (50 MHz, $CDCl_3$) : δ ppm 24.5, 27.8, 28.7, 37.7, 40.9, 45.0, 58.6, 81.6, 167.0,209.5

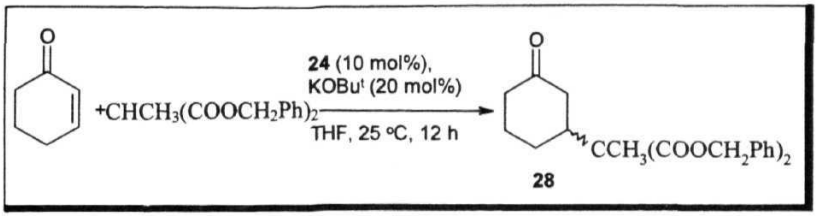
The spectral data showed 1:1 correspondence with the reported data.[27]



Data for 27

Yield	:1.42 g (75%)
IR (KBr)	: 1739, 1261 cm^{-1}
M.P.	: 43-44 °C (Lit[29] 43 °C)
$[\alpha]_D^{25}$	:(+)0.31 (C 3, $CHCl_3$)
Lit [29] $[\alpha]_D^{25}$	:(+) 1.15 (C 2.21, $CHCl_3$) (92 %ee)
^{1}H NMR (200 MHz, $CDCl_3$)	: 5 ppm 1.4-2.8 (m, 9H), 3.4 (d, J = 7.6 Hz, 1H), 5.2 (s, 4H), 7.2-7.4 (m, 10H) **(Spectrum No. 16)**
^{13}C NMR (50 MHz, $CDCl_3$)	: 5 ppm 24.5, 28.6, 38.1, 41.0, 45.0, 56.8, 67.2, 128.3, 128.5, 128.6, 135.3, 167.5, 167.5, 209.2 **(Spectrum No. 17)**

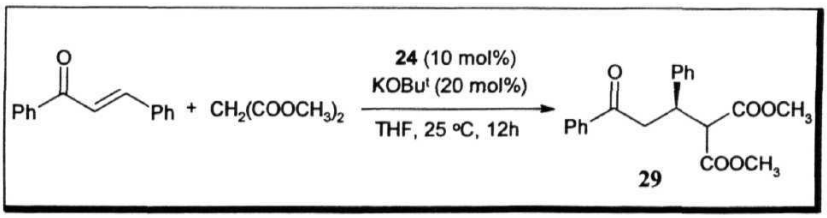
The spectral data showed 1:1 correspondence with the reported data.[29]



Data for 28

Yield	: 1.12 g (76%)
IR (neat)	: 1732, 1231 cm^{-1}
$[\alpha]_D^{25}$	: 0.0 (C 4, $CHCl_3$)
Lit.[29] $[\alpha]_D^{25}$	: (+) 0.32 (C 3.93, $CHCl_3$) (87% ee)
^1H NMR (200 MHz, $CDCl_3$)	: 6 ppm 1.2 (m, 1H), 1.4 (s, 3H), 1.50-2.7 (m, 8H), 5.1 (s,4H), 7.3 (m, 10H)
^{13}C NMR (50 MHz, $CDCl_3$)	: 6 ppm 16.8, 24.7, 26.6, 41.0, 42.6, 43.3, 57.0, 67.1, 128.1, 128.4, 128.6, 135.4, 170.5, 170.6, 209.7

The spectral data showed 1:1 correspondence with the reported data.[29]



Data for 29

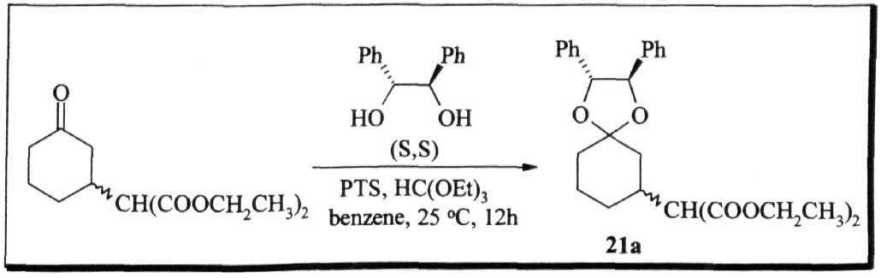
Yield	: 1.11 g (65%)
IR(KBr)	: 1732, 1680, 1235, cm^{-1}
M.P.	: 77-78 °C (Lit.[38] 78 °C)
$[\alpha]_D^{25}$	: (+) 1.18 (C 2, $CHCl_3$)
Lit.[38] $[\alpha]_D^{25}$	: (+) 25.64 (C 2, $CHCl_3$) (77% ee)
^1H NMR (200 MHz, $CDCl_3$)	: 6 3.5 (s, 3H), 3.6-3.7 (m, 2H), 3.8 (s, 3H), 3.9 (d, J = 8.3 Hz, 1H), 4.2 (m, 1H), 7.2-7.5 (m, 8H), 7.8-8.0 (m, 2H)
^{13}C NMR (50 MHz, $CDCl_3$)	: 5 ppm 40.8, 42.3, 52.3, 52.6, 57.3, 127.2, 128.1, 128.4, 128.5, 128.6, 133.0, 136.9, 140.5, 168.1, 168.7, 197.5 **(Spectrum No. 18)**

The spectral data showed 1:1 correspondence with the reported data.[38]

3.3.4 Preparation of the diastereomerir ketals of Michael adducts using chiral (S,S)-(-)-1,2-diphenyl-1,2-ethanediol

Typical procedure: In a 50 ml two necked RB flask with a side septum, the Michael adduct (0.5 mmol) was taken in dry benzene (30 ml). To this (S,S)-(-)l,2-diphenyl-l,2-ethanediol (0.6 mmol, 0.118 g), triethyl orthoformate (0.75 mmol, 0.110 g) and p-toluenesulphonic acid (0.020 g) were added under nitrogen

atmosphere and the contents were stirred at 25 °C for 6h. The reaction mixture was quenched with aq. $NaHCO_3$ and extracted with ether (2x20 ml). The organic layer was washed with water (2x10 ml) followed by brine, dried over anhydrous $MgSO_4$ and evaporated. The diastereomeric product mixture **21a** was isolated by chromatography on silica gel column using hexane / ethyl acetate (94:6) as eluent.



Data for **21a**

Yield : 0.2 g (89%)

IR (neat) : 1732 cm^{-1}

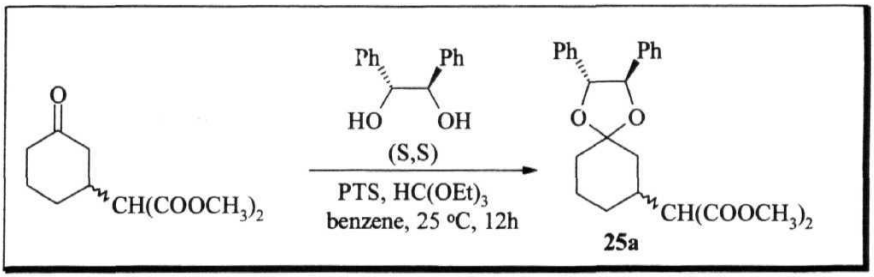
^1H NMR (200 MHz, $CDCl_3$) : δ ppm 1.1-1.3 (m, 6H), 1.4-2.5 (m, 9H), 3.4 (d, J = 7.9 Hz, 1H), 4.1 (m, 4H), 4.7 (d, J = 6.9 Hz, 2H), 7.1-7.5 (m, 10H) **(Spectrum** No. 19)

^{13}C NMR (50 MHz, $CDCl_3$) : 5 ppm 14.2, 22.5, 22.8, 29.2, 29.3, 35.2, 35.6, 35.9, 36.7, 39.9, 40.9, 57.3, 57.6, 61.2, 85.3, 85.5, 109.5, 127.8, 128.3, 128.4, 136.7, 136.9, 168.5 **(Spectrum No. 20)**

MS (EI) : m/z 452 (M^+, 2.5 %), 186 flvf-266, 100 %)

(Spectrum No. 21)

The above procedure was also followed for the preparation of other diastereomeric ketals. The results are summarised below.



Data for **25a**

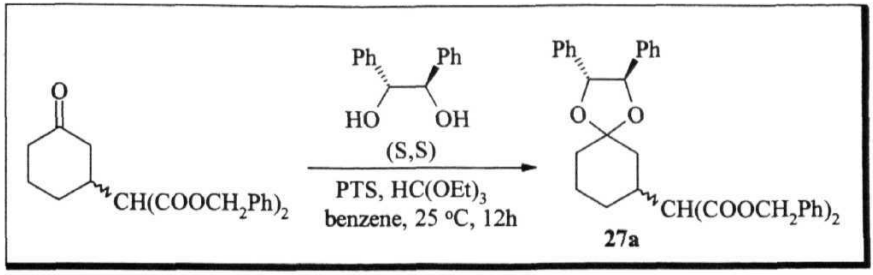
Yield : 0.19 g (90%)

IR (neat) : 1734 cm^{-1}

^1H NMR (200 MHz, $CDCl_3$) : 8 ppm 1.2-2.8 (m, 9H), 3.3-3.4 (d, J = 4.6 Hz, 1H), 3.7 (m, 6H), 4.8 (d, J = 7.1 Hz, 2H), 7.2-7.6 (m, 10H).

^{13}C NMR (50 MHz, $CDCl_3$) : 8 ppm 22.4, 22.9, 29.1, 29.3, 35.3, 35.8, 35.8, 36.6, 39.9, 40.8, 52.3, 56.9, 57.2, 85.3, 85.5, 109.5, 126.8, 128.4, 136.7, 137.0, 168.9

MS (EI) : m/z 424 (M^+, 3 %), 187 (M^+-237, 100 %)



Data for **27a**

Yield	**: 0.21 g (93%)**
IR(KBr)	: 1738 cm^{-1}
^{1}H NMR (200 MHz, $CDCl_3$)	: 8 ppm 1.2-2.8 (m, 9H), 3.4 (d, J = 7.6 Hz, 1H), 4.5 (m, 2H), 5.1-5.4 (m, 4H), 7.2-7.4 (m, 20H) **(Spectrum No. 22)**
^{3}C NMR (50 MHz, $CDCl_3$)	: δ ppm 22.6, 22.9, 29.5, 35.6, 36.0, 36.8, 40.0, 40.6, 57.6, 67.1, 85.3, 85.6, 109.5, 127.0, 128.5, 128.7, 135.7, 137.0, 137.1, 168.3 **(Spectrum No. 23)**

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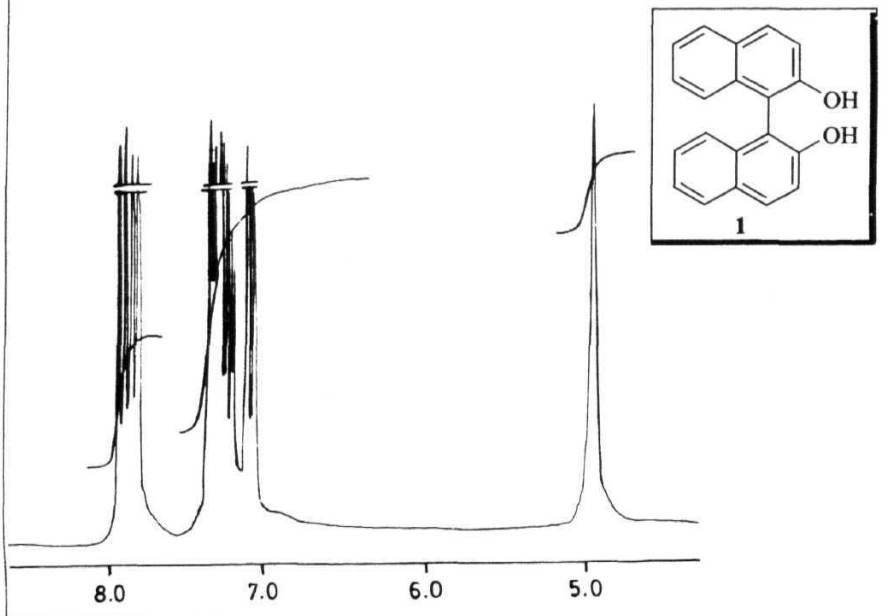
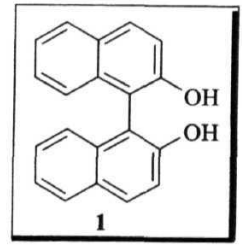
REPRESENTATIVE SPECTRA

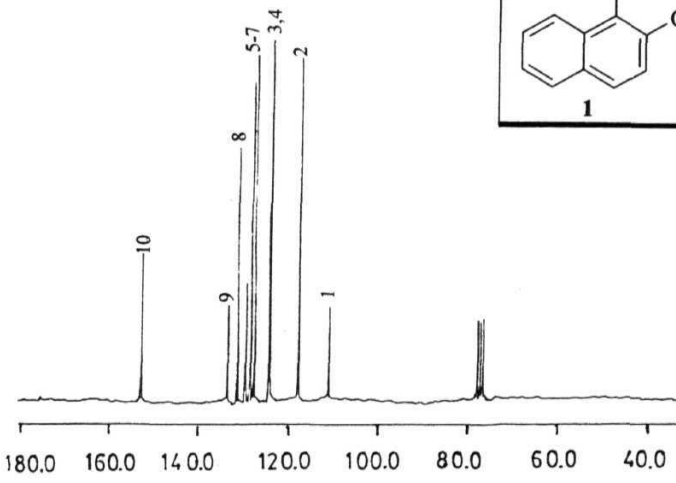
Spectrum No 1 (Chapter 1), ^{1}H NMR Spectrum (200 MHz, $CDCl_3$)



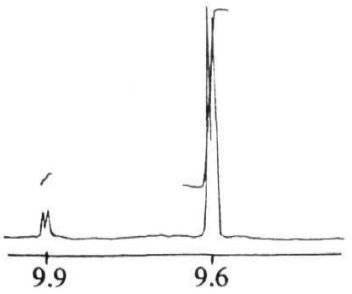
Spectrum No 2 (Chapter 1), ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)

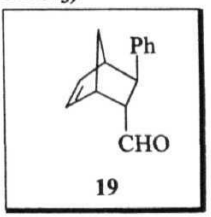
1. 111.0
2. 117.8
3. 124.1
4. 124.3
5. 127.5
6. 128.4
7. 129.5
8. 131.4
9. 133.5
10. 152.8

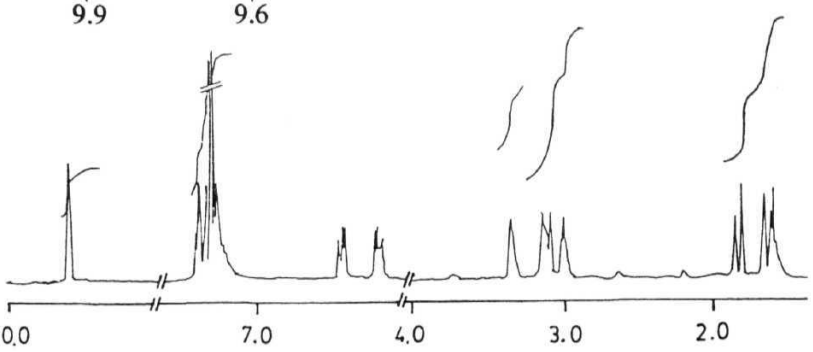




Spectrum No 3 (Chapter 2), ^{1}H NMR Spectrum (200 MHz, $CDCl_3$)

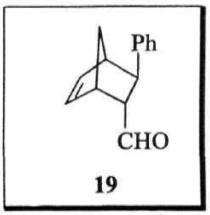


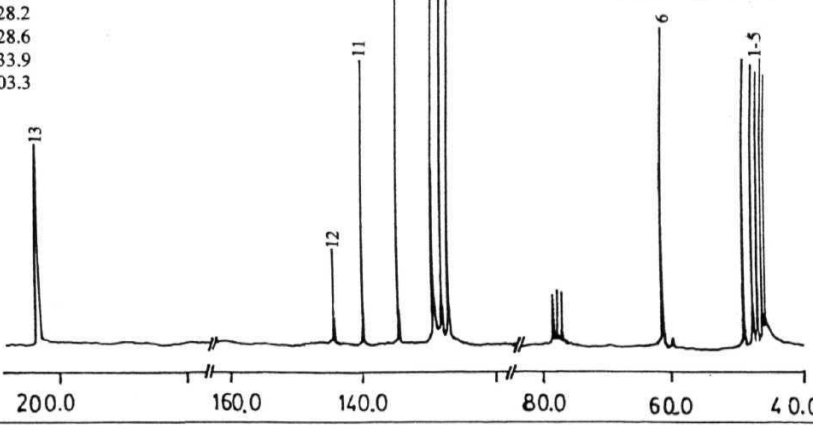




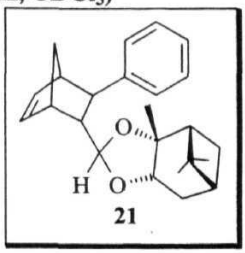
Spectrum No 4 (Chapter 2), ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)

1. 45.2
2. 45.5
3. 45.8
4. 47.2
5. 48.4
6. 60.9
7. 126.2
8. 127.4
9. 127.9
10. 128.2
11. 128.6
12. 133.9
13. 203.3





Spectrum No 5 (Chapter 2), ^{1}H NMR Spectrum (200 MHz, $CDCl_3$)



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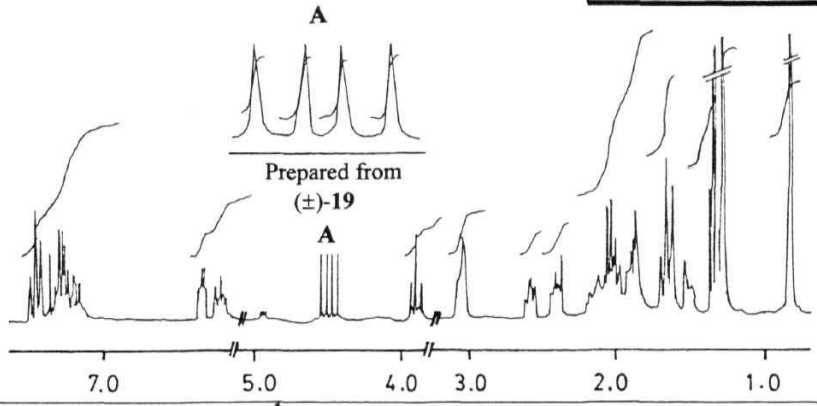
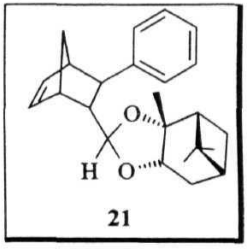
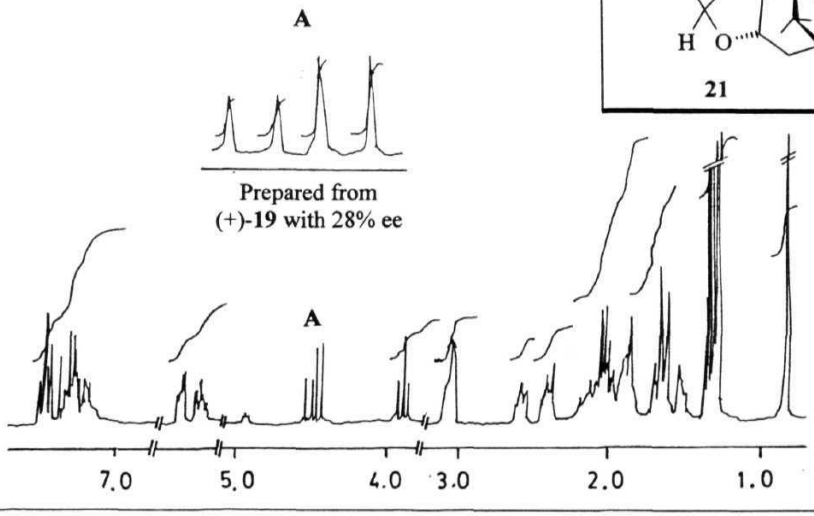


Spectrum No 6 (Chapter 2), ^{1}H NMR Spectrum (200 MHz, $CDCl_3$)

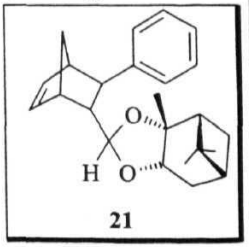


21

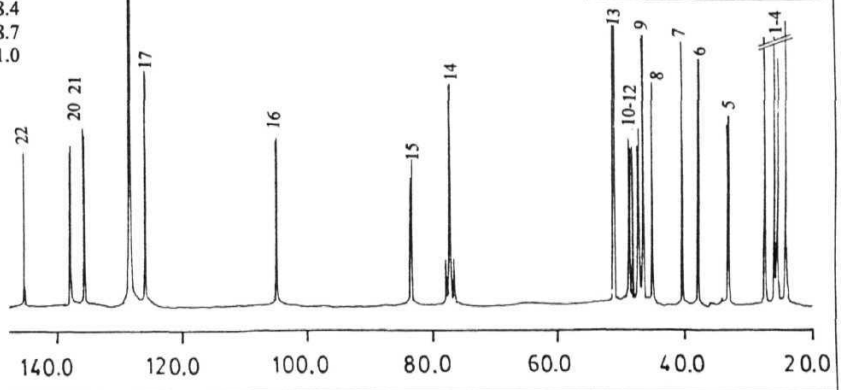


Spectrum No 7 (Chapter 2), ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)

1. 24.2 14. 77.2
2. 25.4 15. 83.5
3. 25.8 16. 104.9
4. 27.4 17. 125.6
5. 33.2 18. 128.0
6. 37.8 19. 128.2
7. 40.3 20. 135.5
8. 45.0 21. 137.7
9. 46.5 22. 145.2
10. 47.1
11. 48.4
12. 48.7
13. 51.0

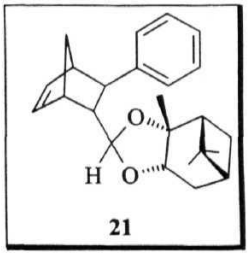


21

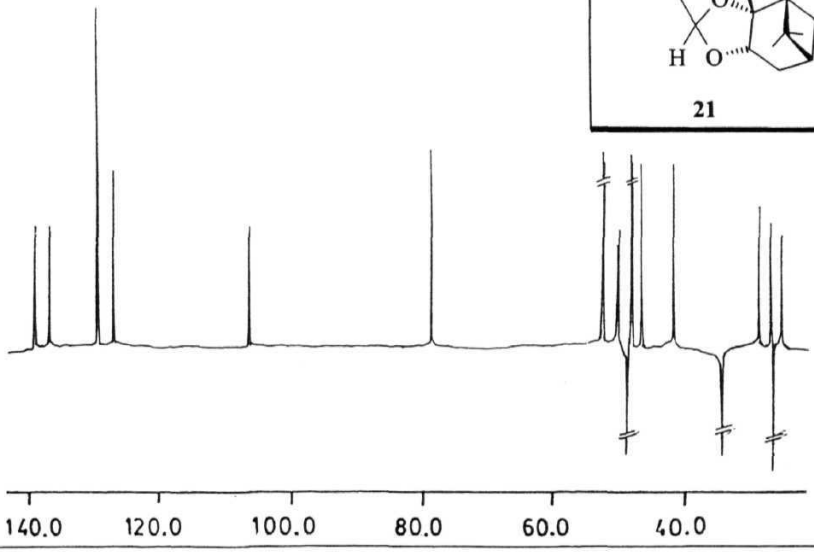


Spectrum No 8 (Chapter 2), DEPT Experiments

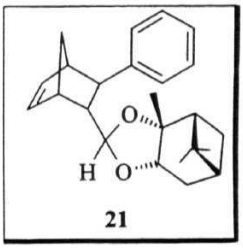
(CH_3 and CH up, CH_2 down)



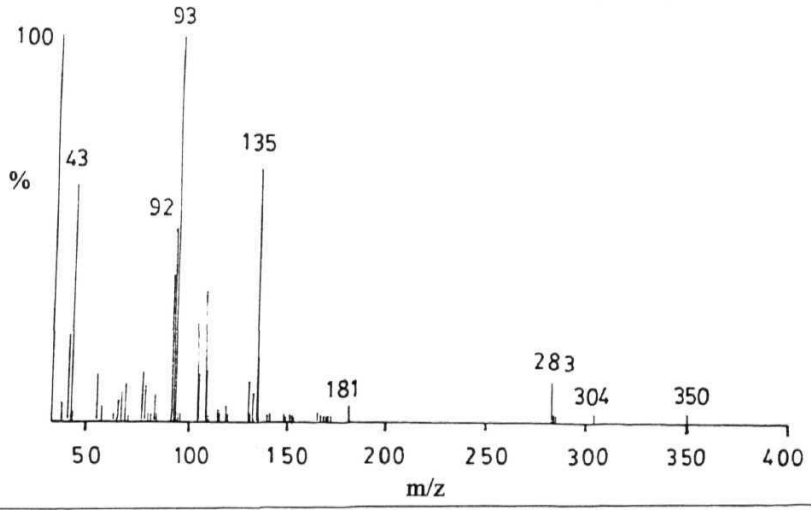
21



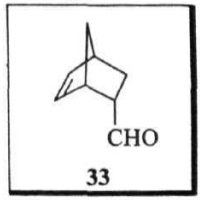
Spectrum No 9 (Chapter 2), Mass Spectrum (EI)



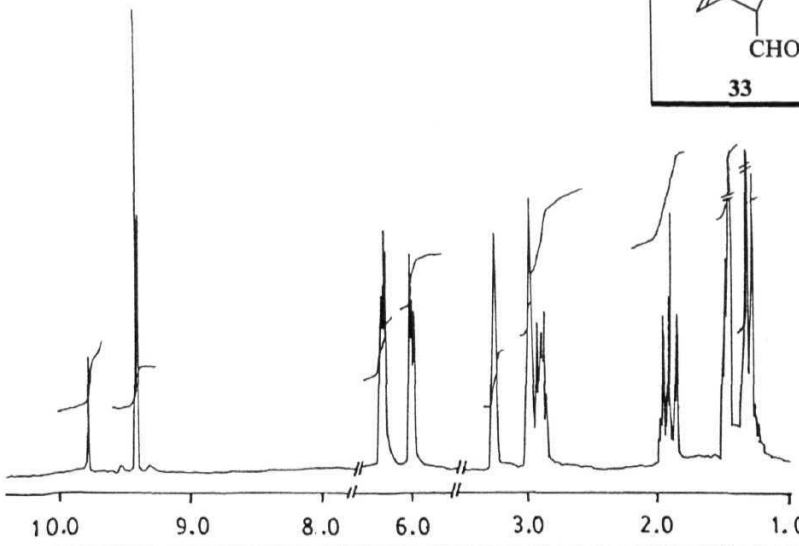
21



Spectrum No 10 (Chapter 2), ^{1}H NMR Spectrum (200 MHz, $CDCl_3$)

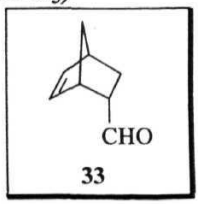


33



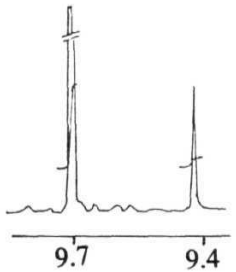
Spectrum No 11 (Chapter 2), ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)

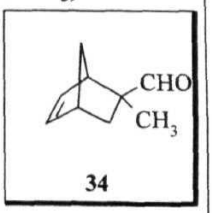
1. 27.6
2. 42.1
3. 45.0
4. 49.6
5. 52.2
6. 131.8
7. 138.1
8. 204.9

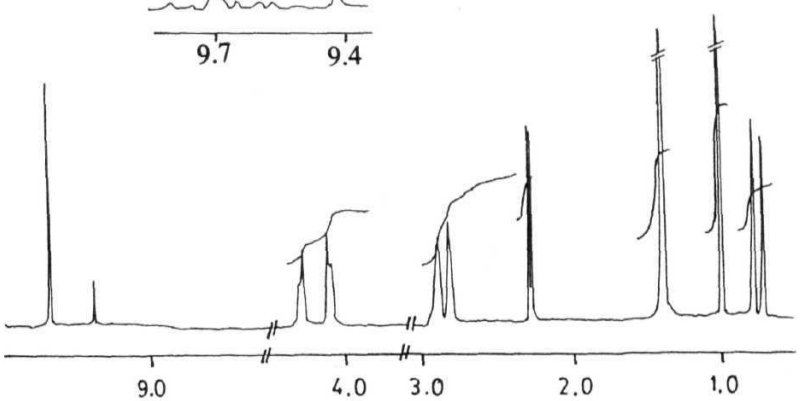


33

Spectrum No 12 (Chapter 2), ^{1}H NMR Spectrum (200 MHz, $CDCl_3$)

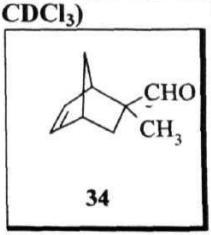




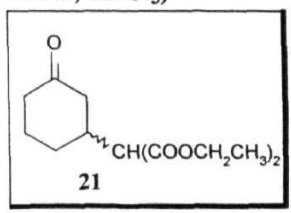


Spectrum No 13 (Chapter 2), ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)

1. 20.0
2. 34.6
3. 43.2
4. 47.3
5. 47.5
6. 48.4
7. 133.0
8. 139.4
9. 205.8



Spectrum No 14 (Chapter 3), ^{1}H NMR Spectrum (200 MHz, $CDCl_3$)



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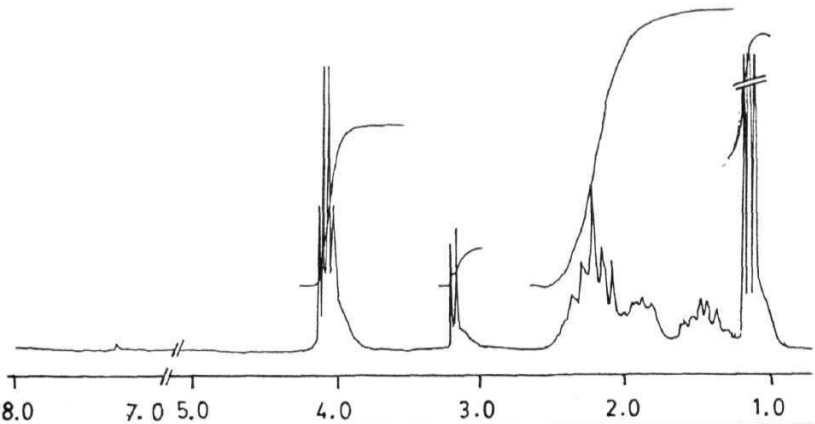
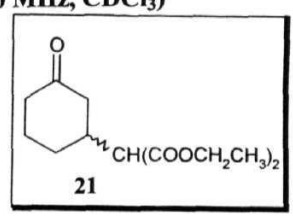


Spectrum No 15 (Chapter 3), ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)

1. 13.9
2. 24.4
3. 28.6
4. 37.9
5. 40.9
6. 45.0
7. 56.8
8. 61.3
9. 167.7
10. 209.4



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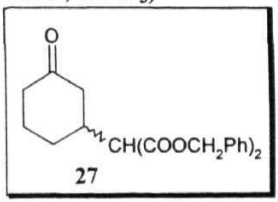
Spectrum No 16 (Chapter 3), ^{1}H NMR Spectrum (200 MHz, $CDCl_3$)



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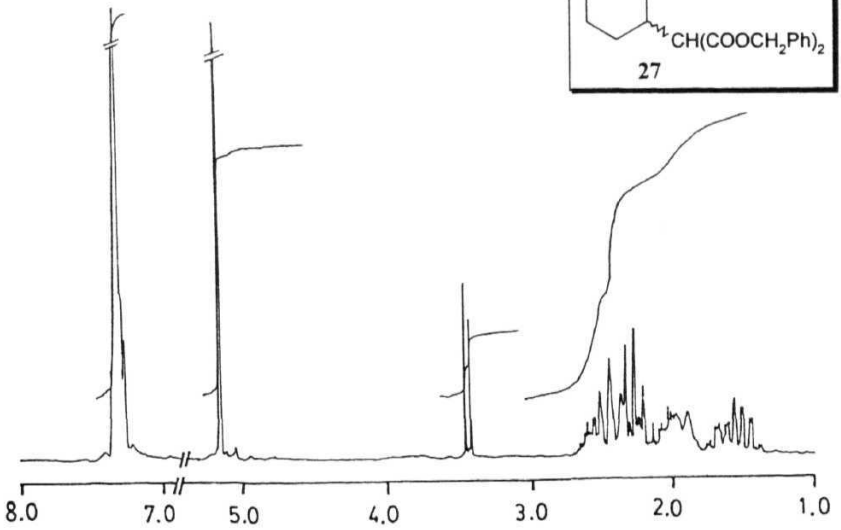
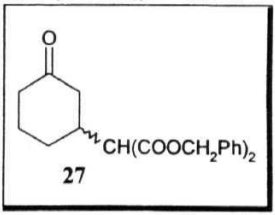


Spectrum No 17 (Chapter 3), ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)

1. 24.5
2. 28.6
3. 38.1
4. 41.0
5. 45.0
6. 56.8
7. 67.2
8. 128.3
9. 128.5
10. 128.6
11. 135.3
12. 167.5
13. 167.5
14. 209.2



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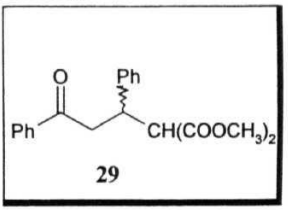
Spectrum No 18 (Chapter 3) ^{13}C Spectrum (50 MHz, $CDCl_3$)

1. 40.8
2. 42.3
3. 52.3
4. 52.6
5. 57.3
6. 127.2
7. 128.1
8. 128.4
9. 128.5
10. 128.6
11. 133.0
12. 136.9
13. 140.5
14. 168.1
15. 168.7
16. 197.5



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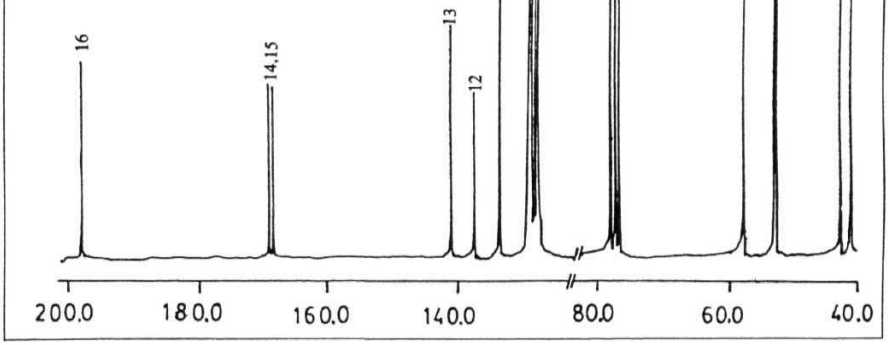
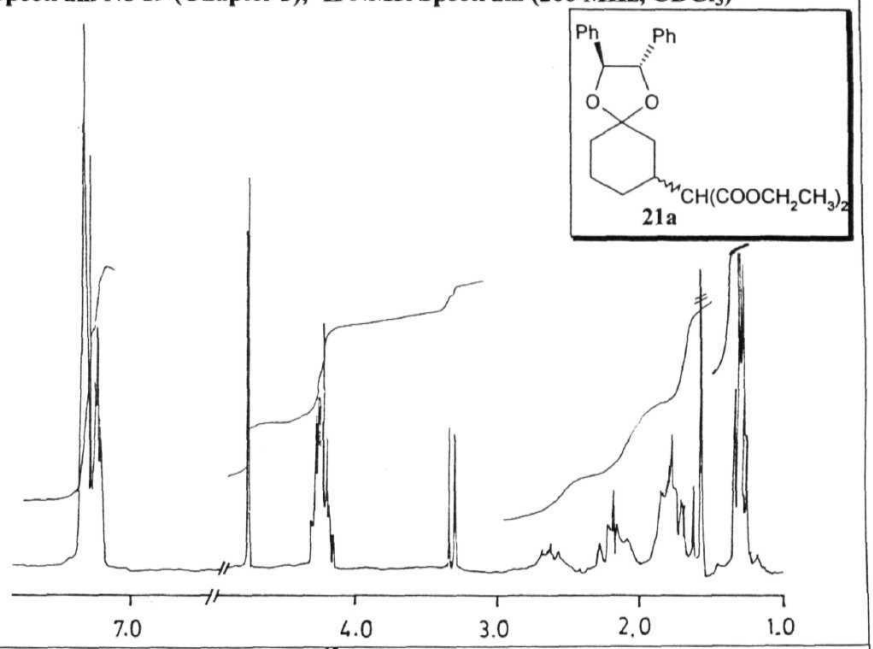
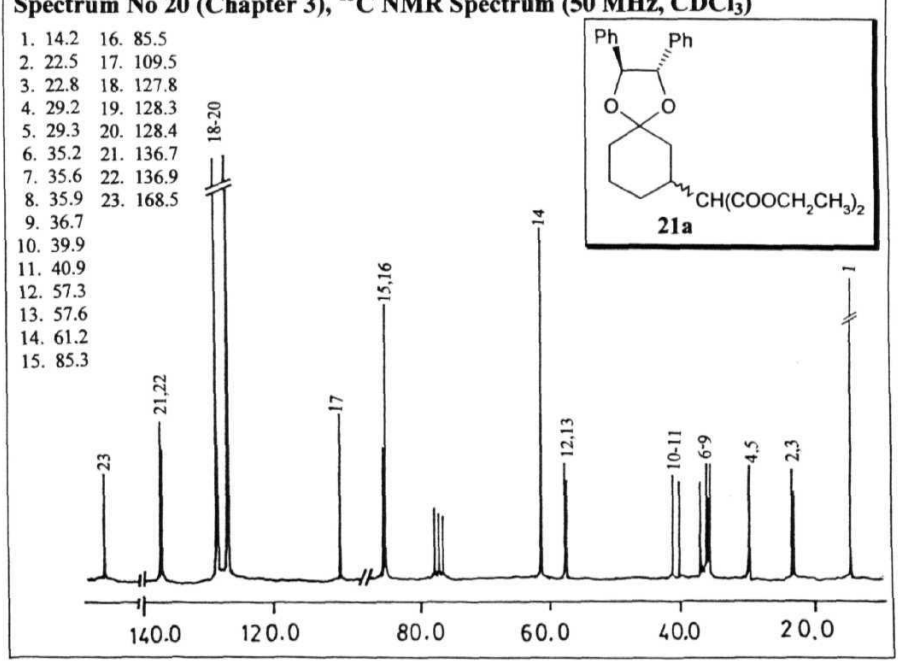


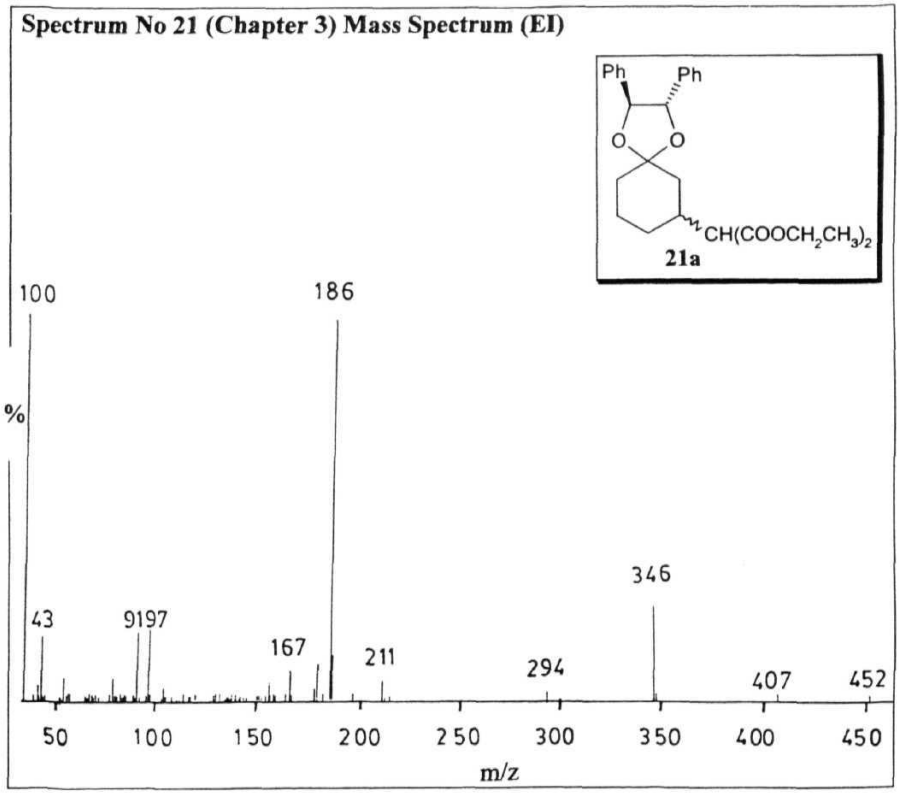
Spectrum No 19 (Chapter 3), ^{1}H NMR Spectrum (200 MHz, $CDCl_3$)



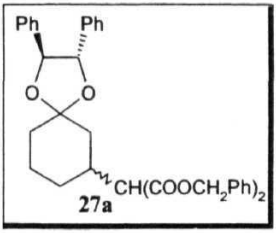
Spectrum No 20 (Chapter 3), ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)

1. 14.2
2. 22.5
3. 22.8
4. 29.2
5. 29.3
6. 35.2
7. 35.6
8. 35.9
9. 36.7
10. 39.9
11. 40.9
12. 57.3
13. 57.6
14. 61.2
15. 85.3
16. 85.5
17. 109.5
18. 127.8
19. 128.3
20. 128.4
21. 136.7
22. 136.9
23. 168.5




Spectrum No 21 (Chapter 3) Mass Spectrum (EI)
Ph
Ph
O
O
CH(COOCH2CH3)2
21a
100
186
%
346
43
9197
167
211
294
407
452
50
100
150
200
250
300
350
400
450
m/z

Spectrum No 22 (Chapter 3), ^{1}H NMR Spectrum (200 MHz, $CDCl_3$)



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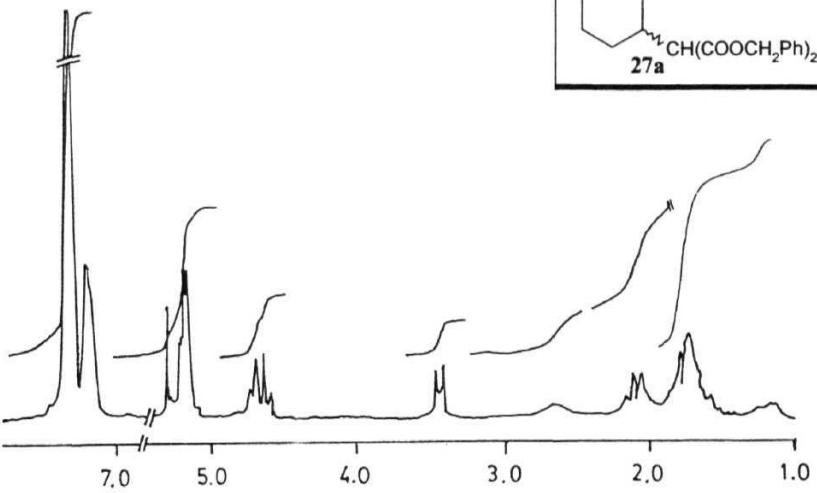
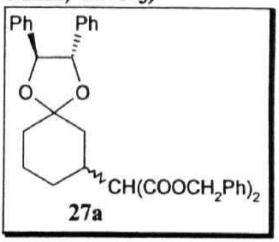


Spectrum No 23 (Chapter 3), ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)

1. 22.6
2. 22.9
3. 29.5
4. 35.6
5. 36.0
6. 36.8
7. 40.0
8. 40.6
9. 57.6
10. 67.1
11. 85.3
12. 85.6
13. 109.5
14. 127.0
15. 128.5
16. 128.7
17. 135.7
18. 137.0
19. 137.1
20. 168.3



27a

Research Publications

1. A Novel, Simple Method for Enrichment of Enantiomeric Excess of Scalemic 1,1'-bi-2-naphthol, **L. Venkatraman** and M. Periasamy, *Tetrahedron: Asymmetry,* 1996, 7, 2471.
2. New Methods of Resolution and Enrichment of Enantiomeric Excesses of 1,1'-bi-2-naphthol, M. Periasamy, L. **Venkatraman** and K.R.J. Thomas, *J. Org, Chem.*, 1997,62,4302.
3. A New, Convenient Method of Resolution of Racemic l,l'-bi-2-naphthol Using Boric Acid and R-(+)-a-Methylbenzylamine, M. Periasamy, **L. Venkatraman,** S. S. Kumar, N. S. Kumar and C. R. Ramanathan, *J. Org. Chem.*, 1999,64,7643.
4. Resolution of Racemic and Diastereomeric Amino Alcohols and Derivatives Through Preparation of Chiral ammonium 1,1'-bi-2-naphthyl Borate Complexes, M. Periasamy, C. R. Ramanathan, N. S. Kumar, V. Dhanna Rao, S. S. Kumar, and **L. Venkatraman,** *Communicated.*
5. Asymmetric Diels-Alder Reactions Catalysed by Chiral Lewis Borate Propeller Prepared Using l,l'-bi-2-naphthol and boric acid: Observation of a New Nonlinear effect, **L. Venkatraman** and M. Periasamy, *Manuscript under preparation.*

6. Asymmetric Michael Reactions using Chiral Ammonium 1,1'-Bi-2-naphthyl Borate Complexes Prepared Using l,l'-bi-2-naphthol, M. Periasamy, L. Venkatraman and S. S. Kumar, *Manuscript under preparation.*