Studies on the Synthesis, Resolution, Applications of Tröger Base Derivatives and Mechanism of the Osmium Catalyzed Asymmetric Dihydroxylation of Alkenes

A Thesis

Submitted for the Degree of

DOCTOR OF PHILOSOPHY

By

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September 2009

To my beloved Parents and Teachers

Contents

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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, 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 Synthesis, Resolution, Applications of Tröger Base Derivatives and Mechanism of the Osmium Catalyzed Asymmetric Dihydroxylation of Alkenes**" has been carried out by **Mr. Satishkumar Sakilam** under my supervision and the same has not been submitted elsewhere for a degree.

PROFESSOR M. PERIASAMY
(THESIS SUPERVISOR)

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Acknowledgements

I am glad to express my deep sense of gratitude with profound respect to my thesis supervisor **Prof. M. Periasamy** for his inspiring guidance, teaching, research support, constant encouragement and thought provoking discussions. It is always a pleasure for me to be his student.

I extend my heartfelt thanks to the former deans Prof. E. D. Jemmis, Prof. M. Periasamy and the present dean Prof. D. Basavaiah, School of Chemistry, for providing all necessary facilities to carry out my work. I thank all my teachers those who taught me since school education for their valuable teaching. I specially thank my B.Sc. lecturers Dr. B. Chandra Mouli and Dr. David Kumar for their help, encouragement and motivation towards higher studies. I would like to place on record my appreciation and gratitude to the Prof. D. Basavaiah, Prof. S. Pal and all the faculty members of the School of Chemistry for their valuable and inspiring teaching who have taught me during M.Sc. I also thank Prof. K. C. Kumara Swamy and Dr. Balamurugan and Dr. P. Ramu Sridhar for motivating talks.

I am thankful to my senior colleague Dr. G. V. Karunakar for his help during the initial stages of my research. I extend my sincere thanks to my past and present labmates Dr. A. Mukkanti, Dr. M. Seenivasaperumal, Dr. Narsi Reddy, Dr. S. Suresh, Dr. N. Kishore Babu, Dr. M. Padmaja, Dr. D. Shyam Raj, Mr. G. P. Muthukumara Gopal, Dr. Shaik Anwar, Mr. S. Selva Ganesan, Mr. M. Nagaraju, Mr. Mallesh Beesu, Mr. N. Sanjeeva Kumar, Mr. Guru Brahmam, Ms. Manasi Dalai, Mr. A. Laxman, Ms. Shravani, Dr. P. Vairaprakash, Mr. Yesu and Srinivas for creating a pleasant work atmosphere.

All the research scholars of the School of Chemistry have been extremely helpful, I thank them all. I specially thank Dr. Jagdadeesh babu for his help in many ways. Dr. Venu, Dr. Basavoju, Dr. L. S. R., Dr. Malla Reddy, Dr. Chandrasekar, Dr. Gupta, Dr. Pavan, Dr. Balaraman, Dr. Bhuvan, Dr. Raju, Dr. Devender, Dr. Veerender, Dr. K. V. Rao, Ramesh

Reddy, Das, Suparna, Satpal, Aravindu, Mallikarjun Reddy, Veera Ragavaiah, Ramsursh, Anji, K. Ramesh, Narahari, Pradeep, Thirupathi Reddy, Rajesh, G. V. Ramesh, Bipul, Ranjit, Naba, Tanmay, Srinu, Rambabu, G. D. P., Kishore(SKD), Sivaranjan Reddy, Karunakar, Ms. Saritha, Srinu, Kishore (DBR), Narayana, vijayender Reddy, Venky, D. K., Satish, Ravindhra, Ganesh, Sanjeev, Brijesh, Narender, Shekar Reddy, Hanesh, Kishore are few to mention. I also thank all my friends in this campus that made my stay memorable. Balu, Anji, Reddaiah, Vinil, Sathish are few to mention.

I extend my deepest gratitude to my B.Sc. friends Specially, Mrs. Shabana, Mrs. Arpitha and also Rajanikanth, Rajender, Ramakrishna, Ravi, Manoj, Kumar, Ms. Nagarani, Mrs. Srilatha for their encouragement, affection, and motivation.

I also thank my friends from Jammikunta, Pavan, Gopinath, Phani, Sridher, Praveen, Vidyasagar, Rambabu, Ch. Nagaraju, Vijay, A. Nagaraju, Santosh, Srikanth, late Chinna for making my stay at Jammikunta a memorable one since schooling days.

A special note of thanks to all my (M.Sc.) classmates for their help and cooperation. Among them Ramu, Phani Pavan, Venu, Sekara Reddy, Kurrella Srinu, Ramakumar, Vikram, Sridhar Reddy, Hariprasad are particular to mention.

I thank Mr. Raghavaiah for his help in X-ray data collection. All the non-teaching staff of the School has been helpful, I thank them all. Mr. Shetty, Mr. Deshbandhu, Mr. S. Satyanarayana, Mrs. Vijaya Lakshmi, Mr. V. Bhaskar Rao, Mrs. Asia Parwez, Mr. Vijaya Bhaskar, Mr. K. R. B. V. Prasad, Mr. Ramana, Mr. Joseph, Mr. Santosh and Mr. Sambasiva Rao are a few to mention.

It is beyond this book to acknowledge the contributions of my parents at each and every stage of my life. I am indebted to my father for his care and love. Although he is no longer with us, he is forever remembered. I am sure he shares our joy and happiness in the heaven. I thank the GOD for giving me such wonderful parents.

I cannot end without thanking my brothers Ravichander and Srinivas for unconditional support and encouragement to pursue my interests. whose constant encouragement and support I have relied throughout my educational career. I also thank my sister and brother-in-law for their affection.

Last but not least, I thank my fiancée Ms. Swathi for her love, caring and patience. I also thank her family members for their affection and support, Dr. B. Srinivasulu and Mrs. Shirisha are special to mention.

I wish to extend my sincere thanks to the University authorities for providing all the necessary facilities for my research work. The X-ray crystallographic data were collected in the National Single Crystal X-ray facility funded by DST, New Delhi.

Finally I would like to thank the CSIR New Delhi for the financial support during my tenure.

Satishkumar Sakilam

Abbreviations

$[\alpha]_D^{25}$	specific rotation at 25 °C, λ = 589 nm.
aq.	aqueous
Ac	acetyl
AD	asymmetric dihydroxylation
9-BBN	9-borabicyclononane
BINOL	1,1'-bi-2-naphthol
brs	broad singlet (spectral)
^{t}Bu	tertiarybutyl
cm^{-1}	wavenumber(s)
CSA	chiral solvating agent
DBTA	dibenzoyltartaric acid
DCC	dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
dd	doublet of doublet
$(DHQD)_2$-PHAL	phthalazine adduct with dihydroquinidine
DHQD	dihydroquinidine
DHQ	dihydroquinine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
$DPPONH_2$	*O*-(diphenylphosphinyl)hydroxylamine
dr	diastereomeric ratio
DTTA	ditoluoyltartaric acid
ee	enantiomeric excess
ESI-MS	electron-spray ionization mass spectrometry
Et	ethyl
h	hour(s)
HPLC	high-performance liquid chromatography
IR	infrared
J	coupling constant (in NMR spectroscopy)

K	equilibrium constant
LAH	lithium aluminium hydride
lit.	literature
m	multiplet (spectral)
M	moles/liter
Me	methyl
MHz	megahertz
mp	melting point
MSH	*O*-mesitylenesulfonylhydroxylamine
OPTEP	oak ridge thermal ellipsoid plot
Ph	phenyl
PPA	poly-phosphoric acid
ppm	parts per million (spectral)
^{i}Pr	isopropyl
q	quartet
rt	room temperature
s	singlet (spectral)
t	triplet
TB	Tröger base
THF	tetrahydrofuran
TFA	trifluoroacetic acid
TfOH	triflic acid
Tf_2NH	trifluoromethanesulfonimide
Ts	toluenesulfonyl
TS	transition state
y	yield

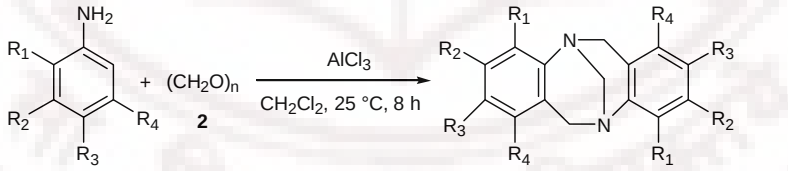
Abstract

This thesis describes, "**Studies on the Synthesis, Resolution, Applications of Tröger Base Derivatives and Mechanism of the Osmium Catalyzed Asymmetric Dihydroxylation of Alkenes**". It comprises of three chapters. 1) **Introduction**, 2) **Results and Discussion** and 3) **Experimental Section**. The work described in this thesis is exploratory in nature.

The first chapter describes a brief review of literature on the synthetic methods, resolution and various applications of Tröger base and its derivatives. The second chapter deals with the results and discussion on the studies undertaken on the synthesis, resolution of Tröger base derivatives and their applications in chiral recognition, asymmetric aziridination, osmium catalyzed dihydroxylation, reductions, and hydroboration studies.

A convenient method to readily access racemic Tröger base and its derivatives by Lewis acid catalysis was developed. Among all the Lewis acids screened, $AlCl_3$ gave the best yields (Scheme 1).

Scheme 1

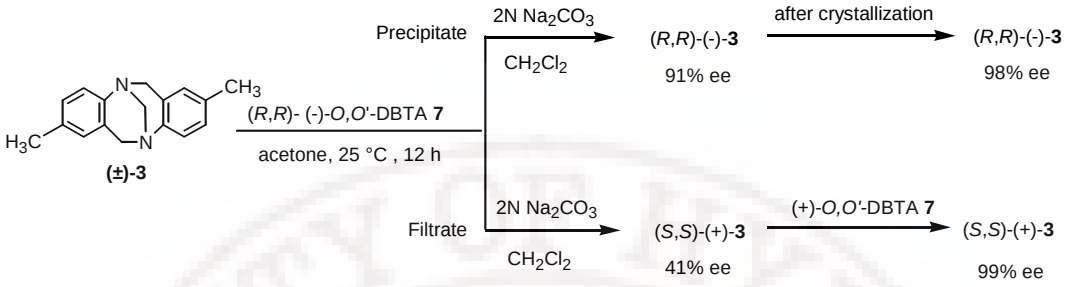


1

3:R_1 = H, R_2 = H, R_3 = CH_3, R_4 = H, 73% y
4:R_1 = H, R_2 = H, R_3 = OCH_3, R_4 = H, 76% y
5:R_1 = CH_3, R_2 = H, R_3 = CH_3, R_4 = H, 65% y
6:R_1 = H, R_2 = CH_3, R_3 = H, R_4 = CH_3, 50% y

A new method has been devised for the resolution of racemic Tröger base **3** by using readily available and recoverable dibenzoyl-L-tartaric acid **7** as resolving agent (Scheme 2). The configurations of the N-chiral centres of (-)-**3** were assigned as 5*R*,11*R* by the single crystal X-ray analysis of the precipitated diastereomeric complex.

Scheme 2



Similarly, the racemic methoxy Tröger base **4** was also resolved using dibenzoyl-L-tartaric acid **7** and the (**-**)-**4** enantiomer was obtained with >98% ee from the precipitate fraction.

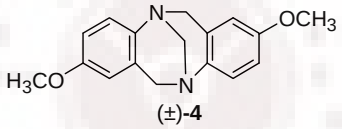
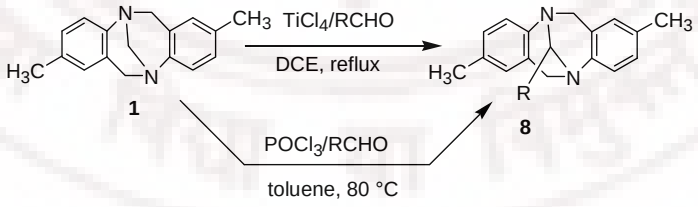


Figure 1

The 5,11-substituted Tröger base derivatives **8** were prepared in a single step by the reaction of Tröger base **3** with carbonyl compounds in the presence of $TiCl_4$ (Scheme 3). Further, these derivatives were also prepared by the reaction in the presence of $POCl_3$ (Scheme 3). The structure of the spiro compound obtained in the reaction with cyclopentanone was further confirmed by single crystal X-ray analysis.

Scheme 3



Attempts on the resolution of 5,11-endobenzylidine derivative of Tröger base **8a** (R = Ph) using different chiral acids were not successful. However, the enantiomers of 5,11-endosubstituted derivatives of Tröger base **8** were readily separated in analytical scale using HPLC on Chiralcel-OJ-H column using ethanol as mobile phase.

We have also examined the preparation of C_α-substituted chiral Tröger base analogs for applications in asymmetric transformations. The chiral amino alcohols **10** and **11** were prepared by the α-alkylation of the corresponding intermediate tertiary amine-BF_3 complexes **9**.

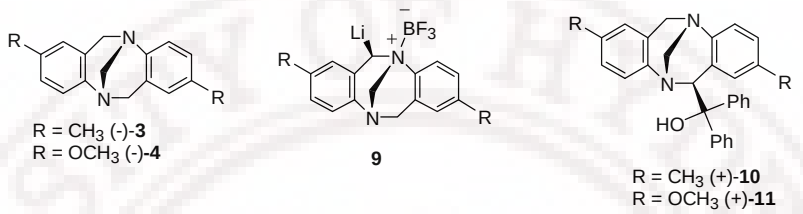


Figure 2

The configuration of the newly formed chiral centre was assigned as *S* by single crystal X-ray analysis of the oxazolidine derivative **12** prepared from the α,α'-diphenylcarbinol derivative **10** using *p*-TsCl/pyridine reagent system.

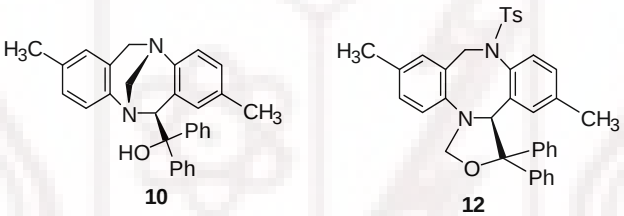


Figure 3

Similarly, we have also examined the preparation of the α-mono (**13**) and α,α'-dibenzyl (**14**) derivatives of Tröger base. During these studies, it was observed that the compound **15** is formed as major product through incorporation of the solvent THF under certain conditions.

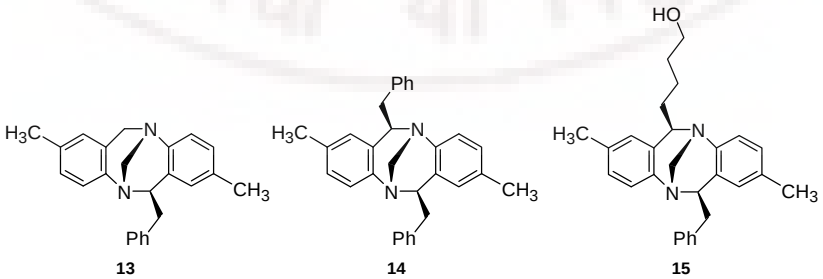
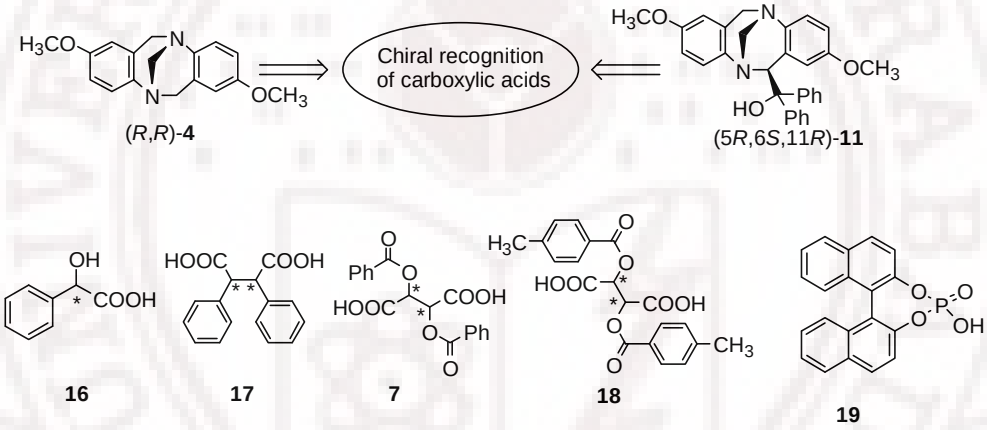


Figure 4

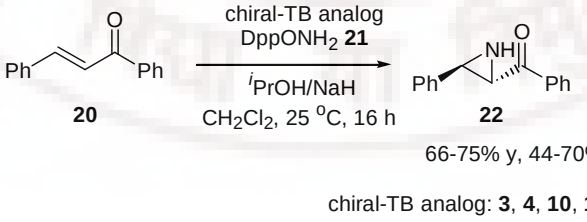
We have examined the application of some of these chiral Tröger base derivatives for chiral recognition of carboxylic acids and for some asymmetric transformations. Chiral recognition properties of the chiral methoxy Tröger base **4** and the α,α'-diphenylcarbinol derivative **11** towards the carboxylic acids **7**, **16**, **17**, **18** and **19** were probed by ^{1}H NMR spectroscopy (^{31}P NMR in the case of **19**) (Chart 1). Chemical shift nonequivalence (ΔΔδ) values in the range 4-42 Hz were realized upon addition of the chiral Tröger base derivatives **4** or **11**.

Chart 1



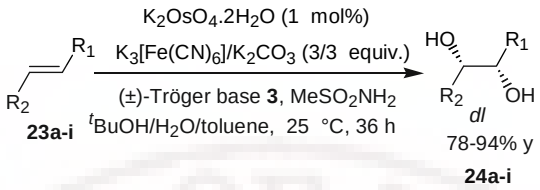
We have also examined the asymmetric NH-aziridination of chalcone using the chiral Tröger base **3** and its derivatives **10**, **11**, **13** as promoters. The product was obtained in 70% ee under optimized conditions (Scheme 4).

Scheme 4



The Tröger base facilitates the osmate catalyzed dihydroxylation reaction. Racemic *syn*-1,2-diarylethane-1,2-diols are formed in good yields (78-94%) under these conditions (Scheme 5).

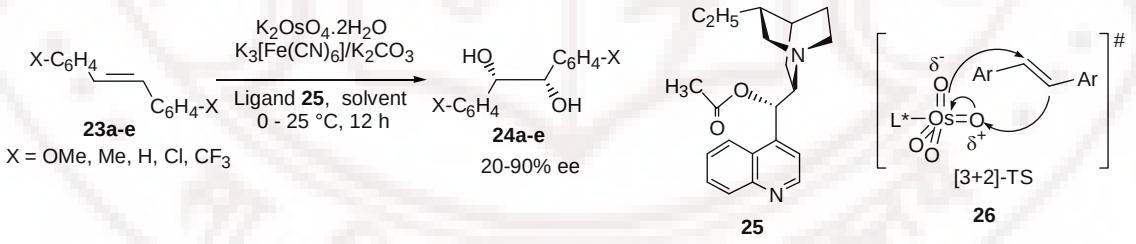
Scheme 5



However, use of the chiral Tröger base for the asymmetric dihydroxylation reaction of *trans*-stilbene, gave the corresponding 1,2-diphenylethane-1,2-diol only in 6% ee.

We have also undertaken studies to understand the mechanism of the catalytic asymmetric dihydroxylation of substituted *trans*-stilbenes using 9-*O*-acetyldihydrocinchonidine **25** as ligand in three different solvent systems (Scheme 6). The corresponding diols were obtained with lower enantioselectivity in the case of substrates containing electron donating and electron withdrawing substituents. The Hammett correlations of the enantiomeric ratios exhibit non-linear plots, in accordance with the conclusion that the reaction involves a 1,3-dipolar type [3+2] cycloaddition transition state **26**.

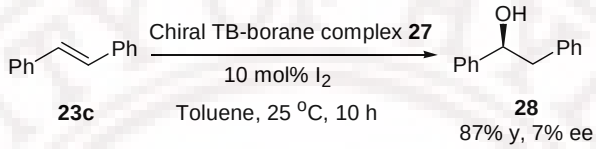
Scheme 6



We have also prepared the chiral Tröger base-BH_3 complex **27** by reaction with the diborane gas generated using $NaBH_4/I_2$. Efforts were made on the reduction of acetophenone with this chiral complex **27**, but no asymmetric induction was observed. Also, the hydroboration of α-methylstyrene with the chiral TB-borane complex **27** in toluene at 110 °C gave only the corresponding racemic alcohol in 75% yield after oxidation.

The hydroboration of prochiral olefins was also examined by the chiral TB-borane complex under I_2 activation, a newly introduced concept. In the case of *trans*-stilbene, the corresponding alcohol was obtained with up to 7% ee (Scheme 7).

Scheme 7



23c **28**

87% y, 7% ee

The reaction was also carried out in the presence of different additives and the results are discussed by considering the mechanistic aspects of the hydroboration reaction.

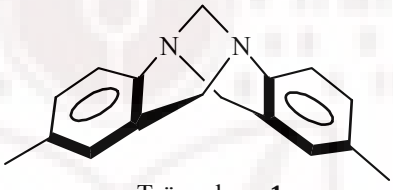
The experimental details are described in the third chapter. The physical constant data (mp), IR, ^{1}H NMR, ^{13}C NMR, mass spectral data, HPLC data and elemental analysis are presented.

Note: Scheme numbers and compound numbers given in this abstract are different from those given in the chapters.

1. Introduction

Molecules or phenomena that are known for many years offer new opportunities and renewed interest when employed with new concepts in mind.[1] Tröger base is one of such molecules known over a century that offers new avenues for explorations.

Tröger base was first discovered by Julius Tröger in 1887, while reinvestigating the condensation reactions of formaldehyde with aromatic amines.[2]



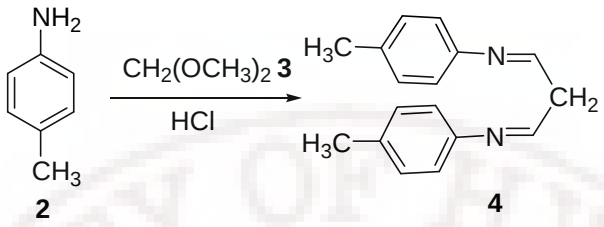
Tröger base **1**

We have developed a method for the synthesis of racemic Tröger base and its analogs by Lewis acid catalysis. We also developed a procedure for optical resolution of Tröger base and its derivatives. A brief review of the various methods reported in the literature for the synthesis, resolution and applications of Tröger base and its derivatives will be useful for the discussion.

1.1 Synthesis of racemic Tröger base and its derivatives

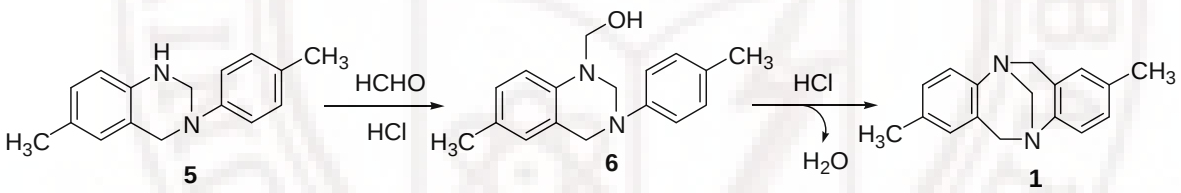
Tröger discovered that *p*-toluidine **2** upon condensation with methylal **3** in the presence of hydrochloric acid gave a product of the molecular formula $C_{17}H_{18}N_2$.[2] He proposed a structure of the type **4** (Scheme 1). The structure of this molecule remained controversial for decades.

Scheme 1



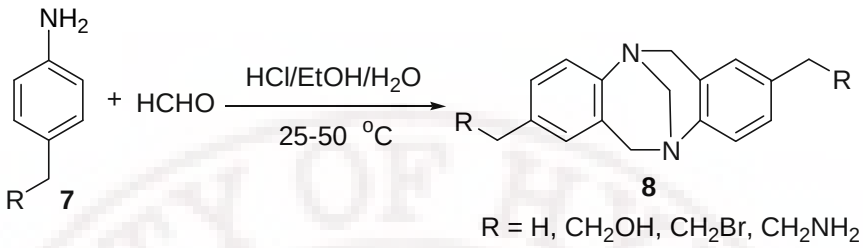
The correct connectivity was established by Spielman[3] in 1935. He confirmed the structure of Tröger base as **1** by synthesizing it from the cyclic precursor **5** by condensing with formaldehyde using HCl (Scheme 2). This particular compound **1** has become known as Tröger base, after the name of the discoverer of this compound.

Scheme 2



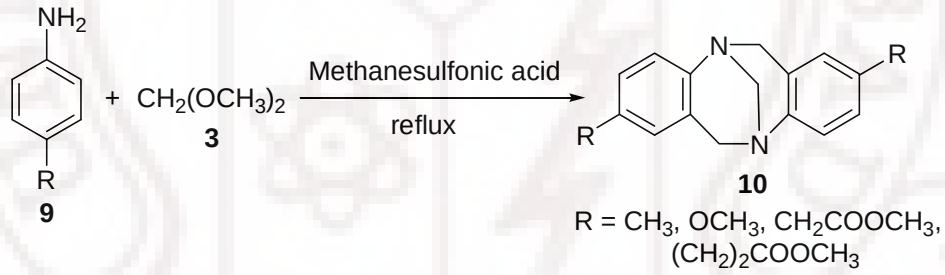
Later, the reaction conditions were modified by various other groups. Among all the methods reported, the most widely used general procedures developed for the synthesis of Tröger base and its derivatives are outlined here. A general method for the preparation of Tröger base derivatives involves acid-induced reaction of aromatic amine with formaldehyde or its equivalent. Wilcox *et al.*[4] reported that only anilines with electron-donating substituents afford Tröger base analogs in the reaction with HCHO in HCl/EtOH/H_2O (Scheme 3).

Scheme 3



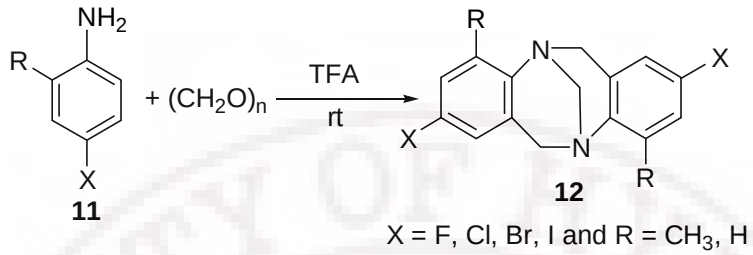
Maitra *et al*.[5] reported an alternative method for the preparation certain Tröger base derivatives, which involves the reaction of substituted anilines with dry methylal **3** (as formaldehyde equivalent) in the presence of methanesulfonic acid (Scheme 4).

Scheme 4



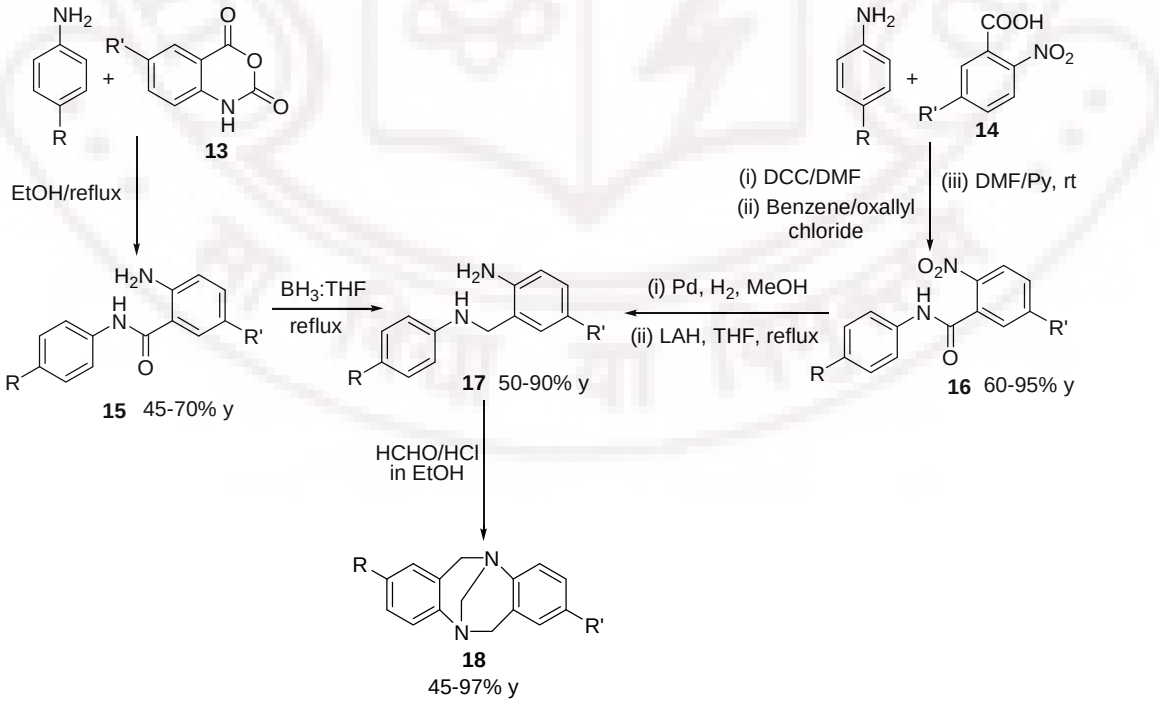
Wärnmark *et al.*[6] reported the synthesis of halogen substituted derivatives of Tröger base as the iodo and bromo substituents could provide handles for performing number of transition-metal catalyzed cross-coupling reactions for further functionalization of the Tröger base. This method involves the reaction of *p*-halogen substituted anilines with paraformaldehyde in the presence of TFA (Scheme 5).

Scheme 5



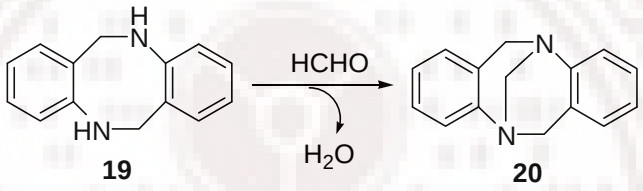
Wilcox *et al.*[7] developed a strategy for preparing the unsymmetrical Tröger base analogs. In this method, the starting aromatic amine was reacted with the derivative of isatoic anhydride, 3,1-benzoazine-2,4(1*H*)-dione **13** or with 2-nitrobenzoic acid **14** to afford the aminoamide **15** and nitroamide **16**, respectively. The reduction of **15** or **16** is followed by final cyclization of the bisamine **17** to yield the unsymmetrical Tröger base derivatives **18** (Scheme 6).

Scheme 6



The main complication in Tröger base formation from unsubstituted aniline is oligomerization through the unsubstituted *para* position. Cooper and Partridge[8] found a solution to this problem by using the intermediate 5,6,11,12-tetrahydrophenomazine **19**, which on condensation with formaldehyde gave the unsubstituted Tröger base **20** (Scheme 7).

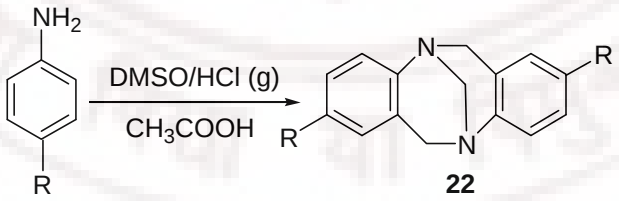
Scheme 7



19 **20**

Recently, Li *et al.*[9] reported a method that uses DMSO in AcOH/HCl as an equivalent of formaldehyde which tolerates a range of functional groups, including strongly electron-withdrawing substituents like -NO_2, -CN. However, the yields are often low and the tedious extraction procedure followed by these authors renders this method rather impractical (Scheme 8).

Scheme 8



21 **22**

R = CH_3, OCH_3, Cl, OC_2H_5, NO_2, CF_3, CN

The heterocyclic Tröger base derivatives were first prepared by Pardo *et al.*[10] by treating the C-amino heterocycles with formaldehyde (or its equivalent) in the presence of Brønsted acid in 6-52% yields (Fig. 1).

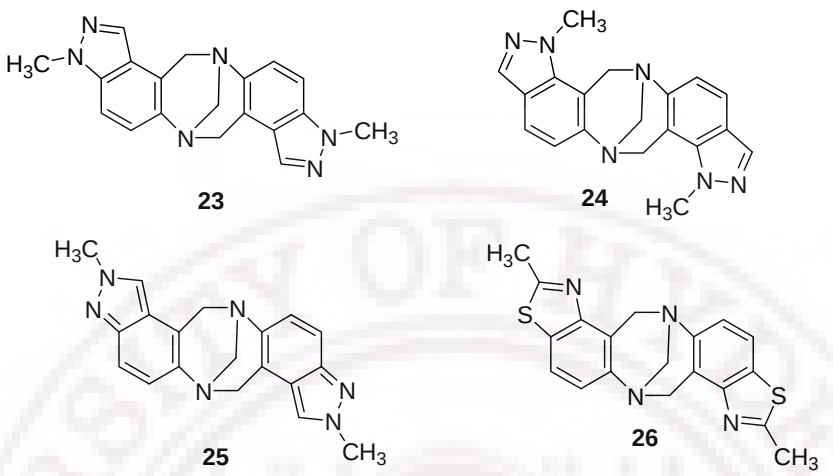
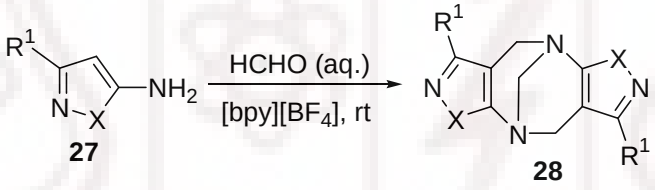


Figure 1

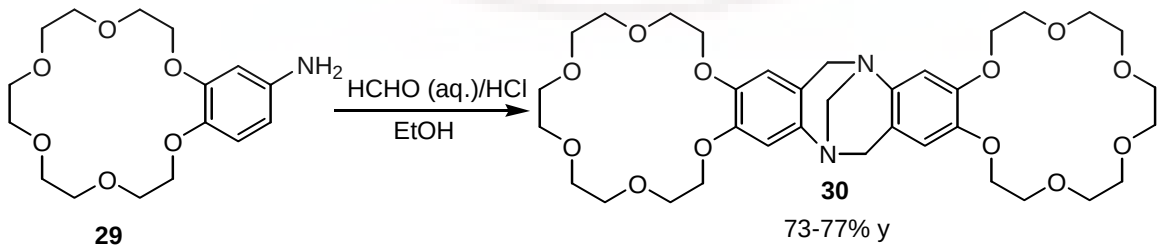
Recently, Wu *et al.*[11] prepared the heterocyclic Tröger bases in good to excellent yields (80-90%) by carrying out the reactions in ionic liquids (Scheme 9).

Scheme 9



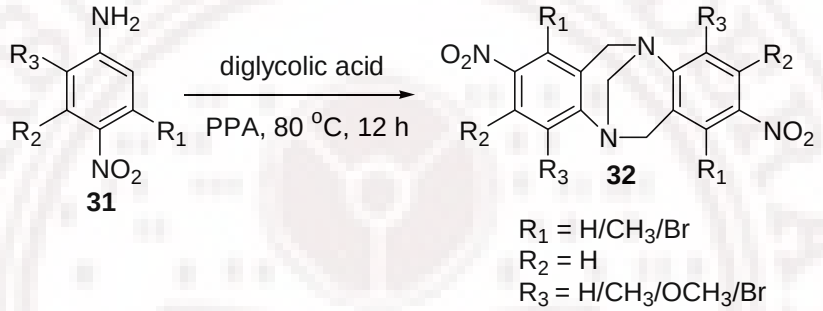
Wärnmark *et al.*[12] reported the preparation of a C_2-symmetric bis(18-crown-6) analog of Tröger base by following the protocol developed by Wilcox *et al.*[4] for the synthesis of **1** (Scheme 10).

Scheme 10



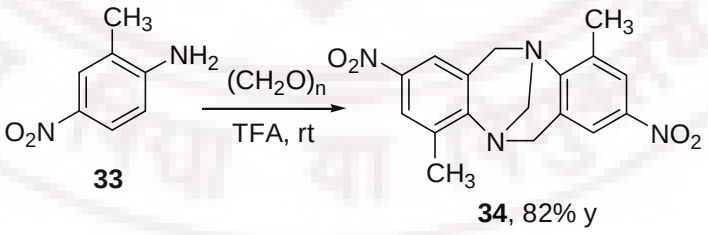
Very recently, Try *et al.*[13] reported a method for the synthesis of symmetrical dinitro-functionalized Tröger base analogs. This method involves the reaction of substituted nitroanilines with diglycolic acid in the presence of PPA, producing the desired products in 14-78% yields (Scheme 11).

Scheme 11



Synthesis of *ortho*-methyl substituted dinitro derivative of Tröger base by the reaction of 2-methyl-4-nitroaniline and paraformaldehyde in the presence of TFA was reported recently by Lützen and co-workers (Scheme 12).[14]

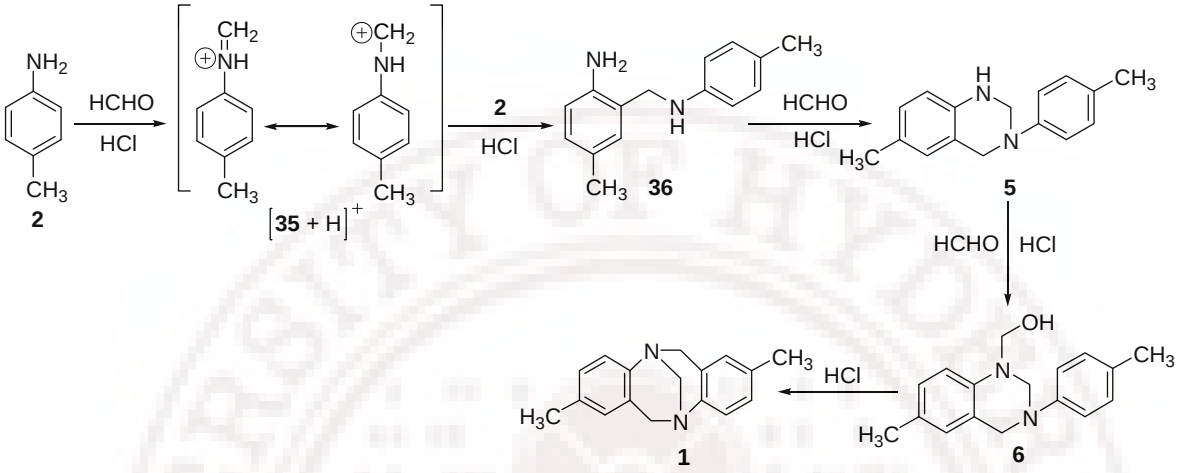
Scheme 12



1.1.1 Mechanism of the formation of Tröger base

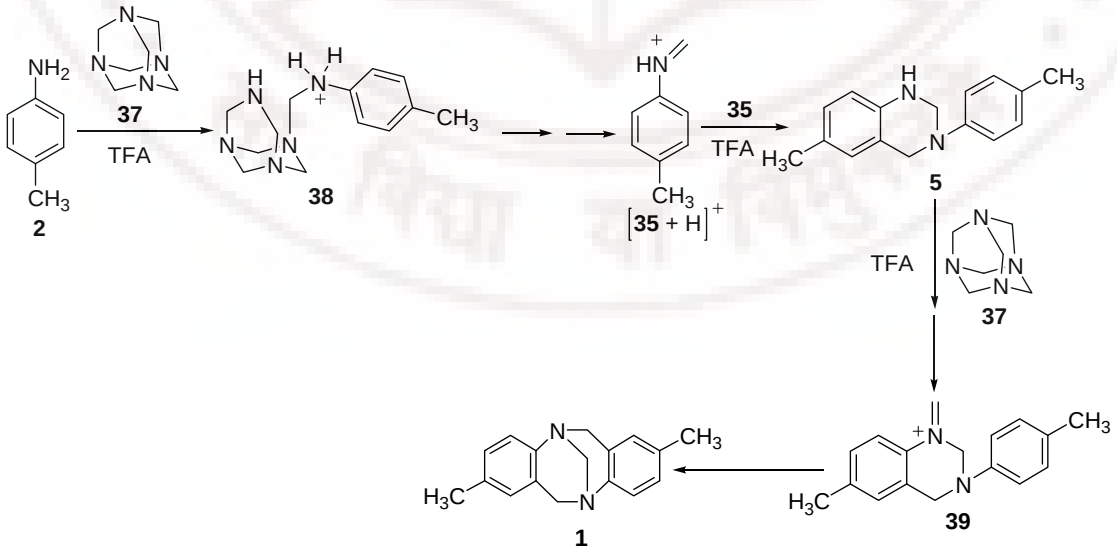
The mechanism of the Tröger base formation was extensively studied by Wagner[15] in 1930s (Scheme 13).

Scheme 13



Recently, Coelho and co-workers[16] probed the mechanism of the formation of Tröger base by using direct infusion electron-spray ionization mass and tandem mass spectrometric experiments [ESI-MS(/MS)]. They performed on-line monitoring of some of the reactions used to prepare Tröger bases and established a concise, experimentally probed mechanism for the formation of Tröger base (Scheme 14).[16]

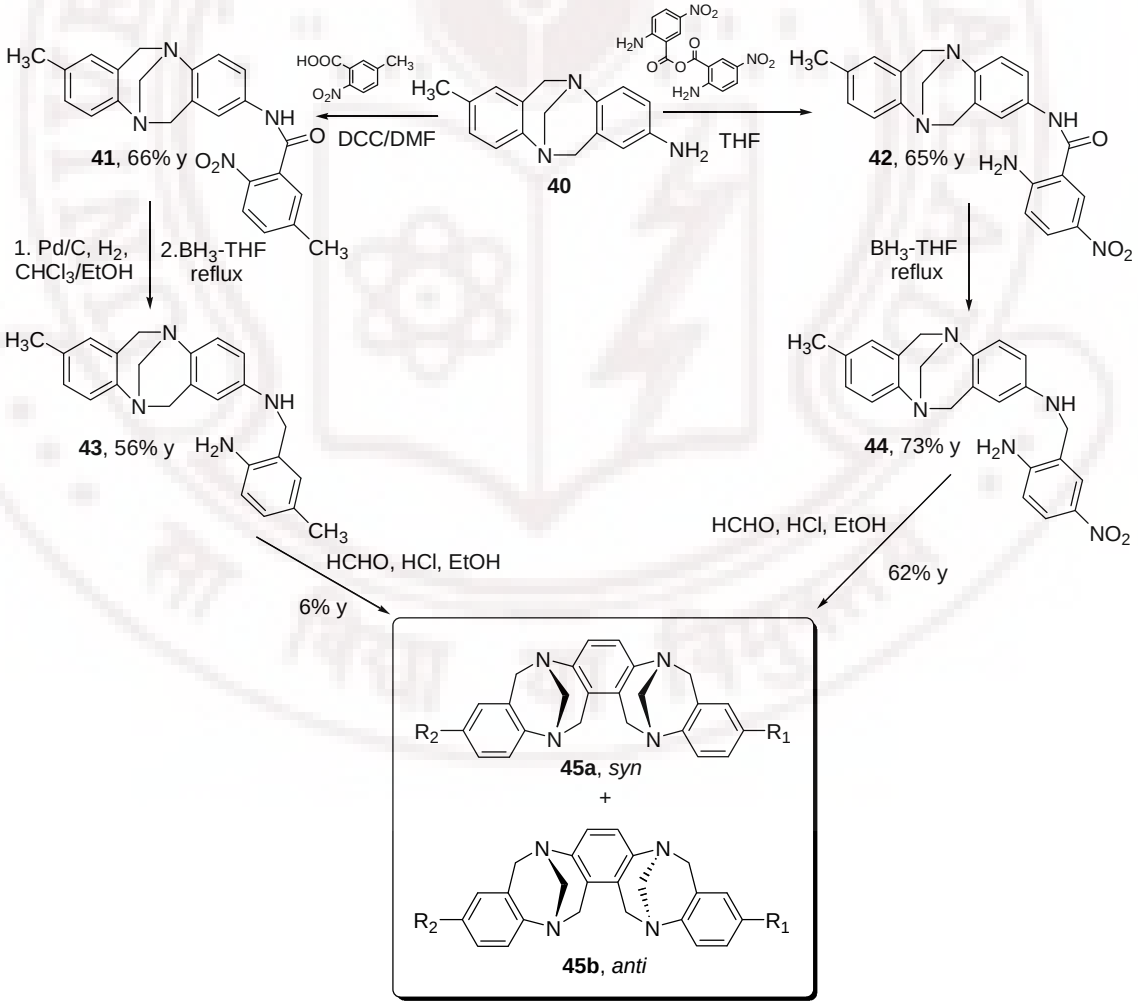
Scheme 14



1.1.2 Synthesis of oligo-Tröger base derivatives

Compounds containing two[17-19] and three[19] Tröger base units have also been reported recently. These bis- and tris-TB derivatives were prepared by a synthetic pathway similar to the Wilcox protocol for the synthesis of unsymmetrically substituted TB analogs.[7] Pardo and co-workers[17] developed a method based on the extension of the amino TB derivative **40** with an additional TB unit, in a so-called step-by-step methodology (Scheme 15).

Scheme 15

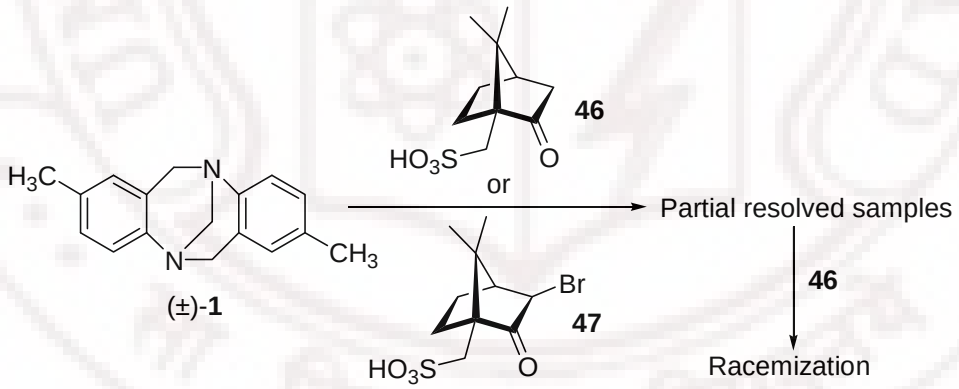


1.2 Resolution of racemic Tröger base and its derivatives

1.2.1 Chirality of Tröger base

In most cases, the enantiomers substituted asymmetrically at nitrogen are not completely resolved because of rapid pyramidal inversion under ambient conditions. Prelog and Wieland[20] postulated that the inversion of the Tröger base **1** through the nitrogen atoms would be sterically difficult because of ring strain. A rational approach for the resolution of Tröger base is *via* the diastereomeric salt formation with chiral acids, e.g., chiral camphor-10-sulfonic acid. However, the partially resolved salts were found to racemize in acidic media. Thus, attempts made by Prelog and Wieland[20] to separate the enantiomers by diastereomeric salt formation were not successful (Scheme 16).

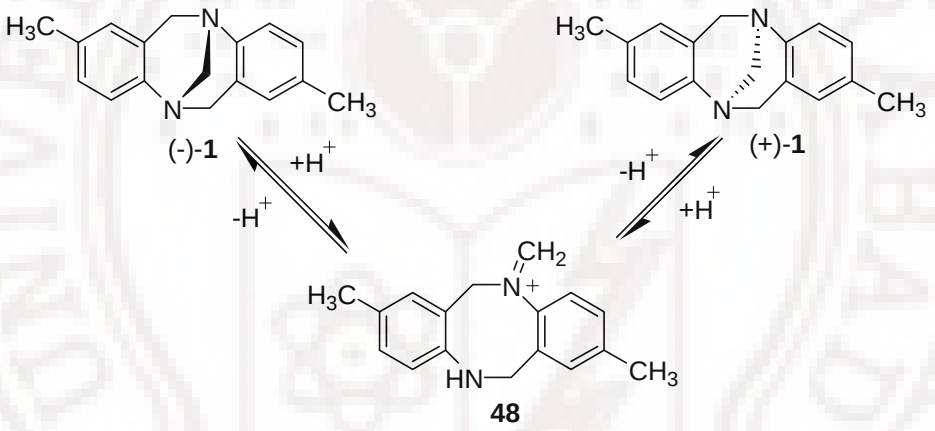
Scheme 16



However, Prelog and co-workers[20] were successful in the resolution of (±)-**1** by liquid chromatography using a *d*-lactose column. Incidentally, this was one of the first examples for chromatographic resolution of a chiral substance and it was the first example of the resolution of an amine, wherein the chirality is solely due to stereogenic N-atoms

with a very high inversion barrier. Although, the resolution of (±)-**1** resulted only in a 5.5% isolation of both enantiomers from the racemate, optically active **1** was made available in this way. The enantiomers (+)-**1** and (-)-**1** were found to be stable to the extent that they could be sublimed without any observable racemization. However, racemization takes place in the presence of strong acids. It was postulated that the racemization proceeds through the intermediacy of the iminium ion **48** (Scheme 17).

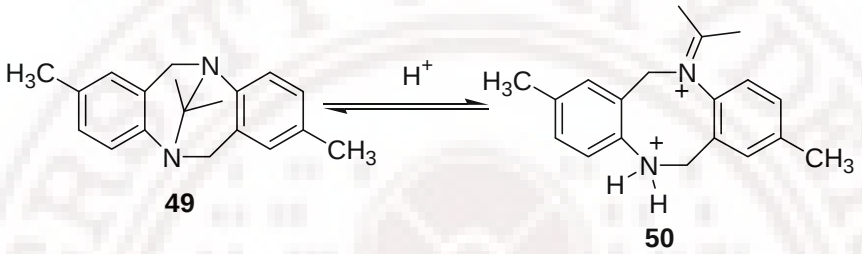
Scheme 17



Greenberg *et al.*[21] examined the mechanism of acid promoted racemization by NMR and UV spectroscopy at 25 °C. However, only protonated forms of **1**, instead of the expected iminium ion **48**, were detected in acidic solutions of **1**. The fact that the NMR spectrum of monoprotonated **1** reflects C_2-symmetry, indicates rapid proton exchange between the two bridgehead nitrogens on the NMR timescale. On the other hand, the 13,13-dimethyl derivative of TB, which easily loses acetone in dilute acid, was found to form an iminium ion in concentrated acid (Scheme 18). The authors invoked this observation to speculate that the iminium ion **48** might be present in undetectable amounts during the acid

promoted racemization process of **1**. The free energy of activation ($\Delta G^{\#}$) for acid induced racemization of Tröger base (Scheme 17) was estimated to be in the range 18.9–22.6 kcal/mol.

Scheme 18



49 **50**

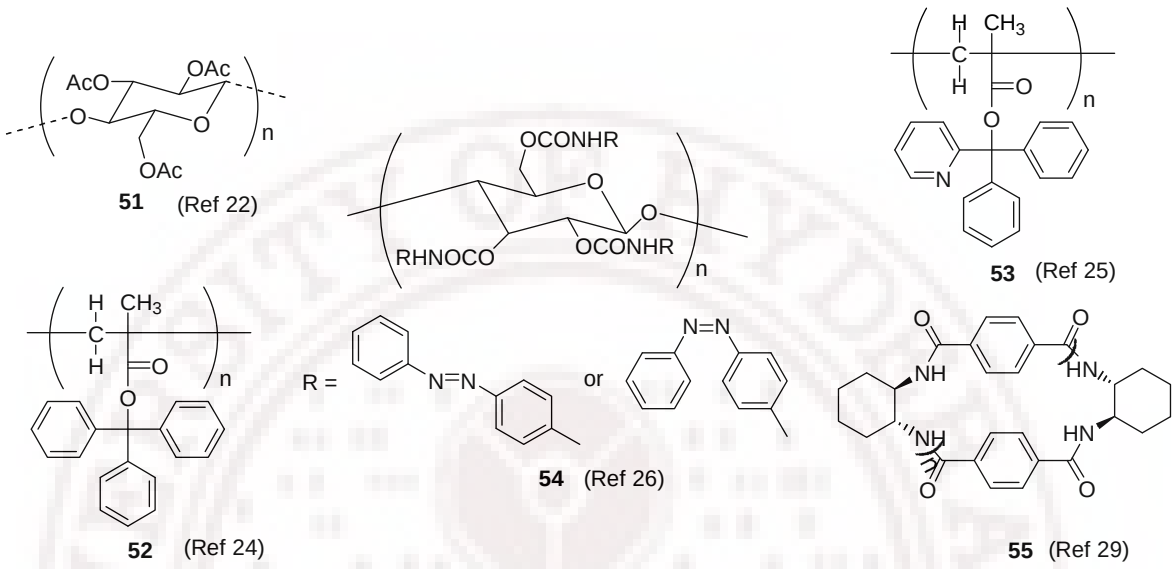
1.2.2 Various methods for the resolution of racemic Tröger base

As mentioned in the previous section, racemic Tröger base **1** was first resolved by using liquid chromatography on *d*-lactose stationary phase by Prelog and Wieland in 1944.[20] Later, several resolution procedures were developed based on chromatography using different chiral stationary phases (Chart 1).

A very good success was achieved in the resolution of (±)-**1** using cellulose triacetate (CTA) **51** based stationary phases.[22] Recently, Morbidelli and co-workers [23] considered the separation of (+)-**1** and (-)-**1** on CTA as a model system for simulated moving bed (SMB) chromatography.

Yuki and co-workers[24] reported the enatioseparation of (±)-**1** using high-performance liquid chromatography on helically chiral (+)-poly(triphenylmethyl methacrylate) **52** as stationary phase.

Chart 1



51 (Ref 22) **53** (Ref 25) **52** (Ref 24) **54** (Ref 26) **55** (Ref 29)

Blaschke *et al.*[25] resolved (±)-**1** using four different techniques, high-performance liquid chromatography (HPLC), capillary HPLC, pressure-assisted capillary electrochromatography (CEC) and CEC on wide-pore aminopropyl silica gel coated with helically chiral poly(diphenyl-2-pyridylmethyl methacrylate) (PDPM) **53** as chiral stationary phase (CSP).

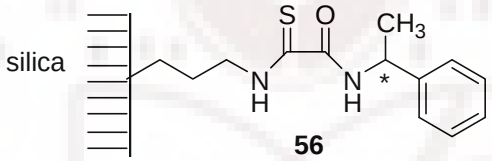
Use of *trans*- and *cis*-cellulose tris(4-phenylazophenylcarbamate) **54** and a steroidal glycoside as chiral selectors in high-performance liquid chromatography or capillary electrochromatography respectively, for the resolution of racemic Tröger base **1** was also reported.[26]

The application of supercritical fluid chromatography (SFC) and gas chromatography (GC) techniques using modified cyclodextrins (Chirasil-β-Dex)[27] and the

simulated moving bed (SMB) chromatography for the separation of (+)-**1** and (-)-**1** on amylase carbamate derivatives (Chiralpak-AS)[28] have also been reported.

The macrocycle **55** prepared from chiral 1,2-diaminocyclohexane and terephthalic acid was also used as chiral stationary phase for the resolution of (±)-**1** using high-performance liquid chromatography.[29]

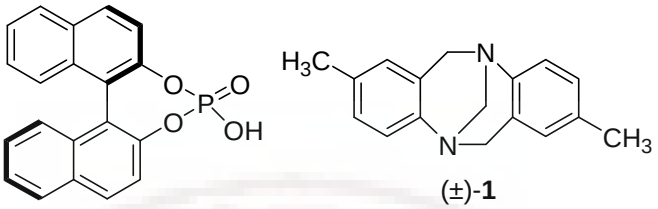
A new chiral selector *N*-(*O*)-propyl-*N*-(*S*)-(1-phenylethyl)thiooxamide (Fig. 2) was used as stationary phase for the high performance liquid-chromatographic (HPLC) separation of (±)-**1**.[30]



56

Figure 2

All the methods reported for the resolution of (±)-**1** until 1991 are chromatographic separations. For so many years, it was emphasized that the resolution of racemic Tröger base **1** *via* the formation of diastereomeric complexes or salts with the aid of chiral acids was not feasible because of the acid promoted racemization. The first and only successful resolution achieved for (±)-**1** was reported by Wilen *et al.*[31] in 1991. These authors used the (-)-1,1′-binaphthyl-2,2′-diylphosphoric acid **57** as resolving agent in EtOH (Fig. 3).



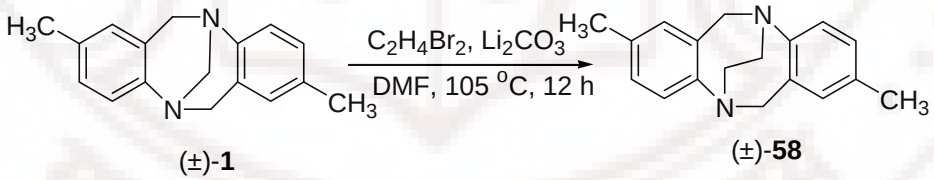
57 (±)-**1**

Figure 3

1.2.3 Resolution of Tröger base derivatives

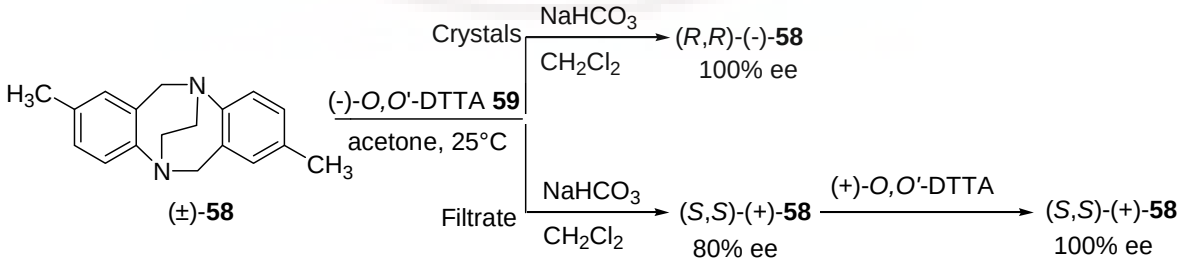
Although Tröger base derivatives are chiral, there are relatively few reports for their resolution. Hamada and Mukai[32] reported the synthesis of (±)-ethano-Tröger base **58** by the reaction of Tröger base with 1,2-dibromoethane in the presence of Li_2CO_3 in DMF (Scheme 19). They resolved this expanded derivative **58** into its enantiomers by diastereomeric salt formation using di-*p*-toluoyltartaric acid (DTTA) **59** in acetone (Scheme 20).

Scheme 19

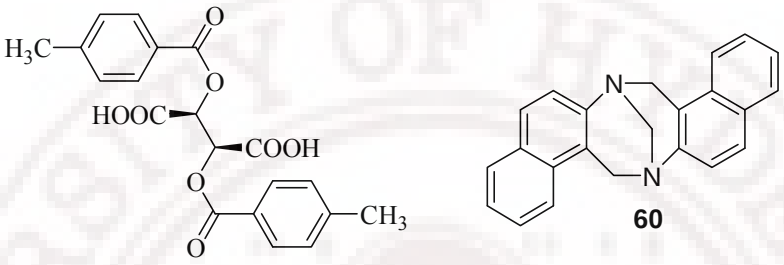


(±)-**1** (±)-**58**

Scheme 20



Margitfalvi *et al.*[33] reported the resolution of α-naphthyl analog of Tröger base using chiral di-*p*-toluoyltartaric acid **59** (Fig. 4) as resolving agent in dry acetone solvent. This resolution was successful only under anhydrous conditions.

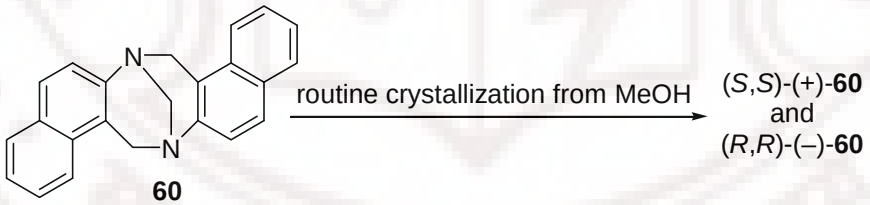


59 **60**

Figure 4

The spontaneous resolution of conglomerates of **60** as well as the second-order asymmetric transformation of (±)-**60** into a single enantiomer were also carried out by Kostyanovsky *et al.*[34] (Scheme 21).

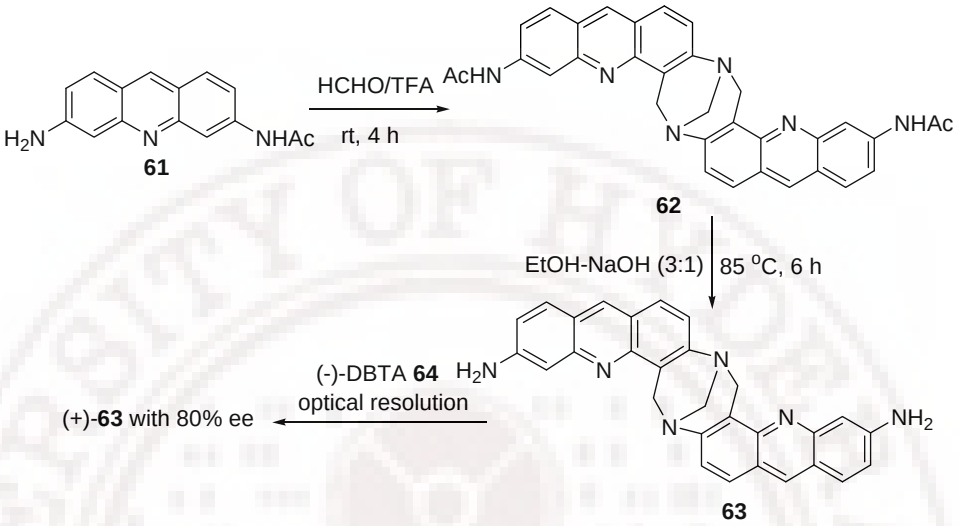
Scheme 21



60

Demeunynck and co-workers[35] resolved the proflavine TB analog **63** with the aid of chiral dibenzoyltartaric acid **64** as resolving agent (Scheme 22). The enantiomeric excess of the partially resolved sample was found to be 80%, determined by NMR.

Scheme 22



Crossley *et al.*[36] resolved the dizinc(II) bisporphyrin TB analog **65a** in a small scale by HPLC on commercial analytical chiral column (Pirkle Type 1A). Later, they reported the resolution of the same analog in moderate scale by chromatography over pre-adsorbed L-histidine benzyl ester on silica gel. This method is very specific to the dizinc(II) complex and the dicobalt(II), dipalladium(II), dicopper(II) complexes of bisporphyrin TB could not be resolved under the same conditions.[37]

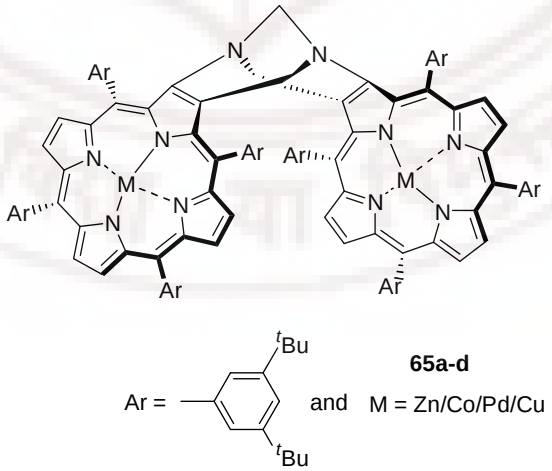
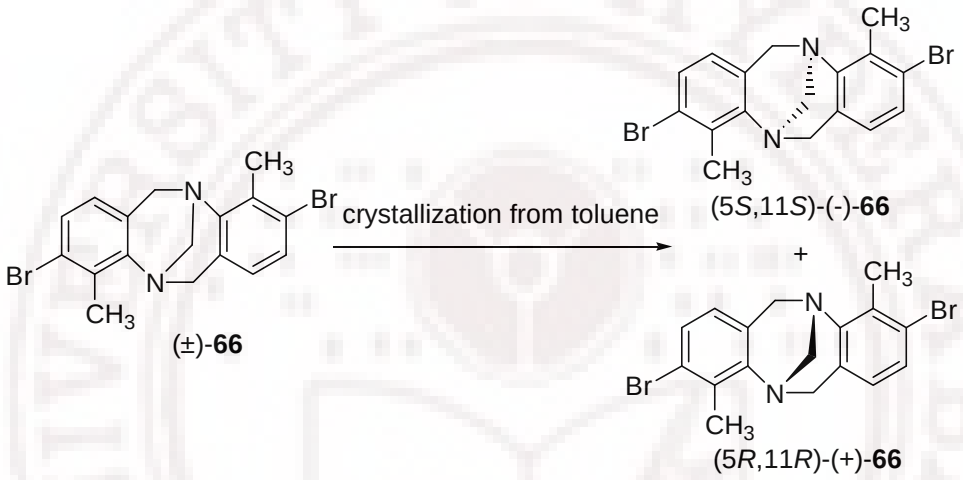


Figure 5

Recently, Lenev *et al.*[38] resolved the bis-*ortho*-methyl-bis-*meta*-bromo Tröger base **50** by conglomerate crystallization (spontaneous resolution) from toluene (Scheme 23). Manual separation these crystals gave the TB derivative **66** with 95% ee.

Scheme 23



Very recently, Lützen and co-workers[40] reported the synthesis of racemic 2,8-diboronic acid ester **67** (Fig. 6) and the 3,9-dibromo substituted derivative **66**. These derivatives were successfully resolved by HPLC on the commercially available chiral column Whelk-01.

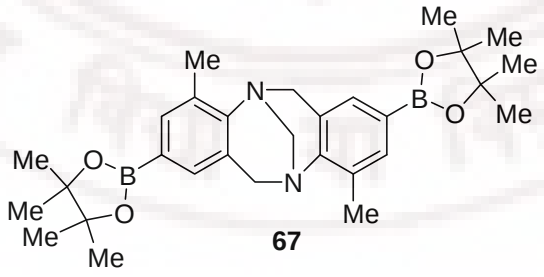
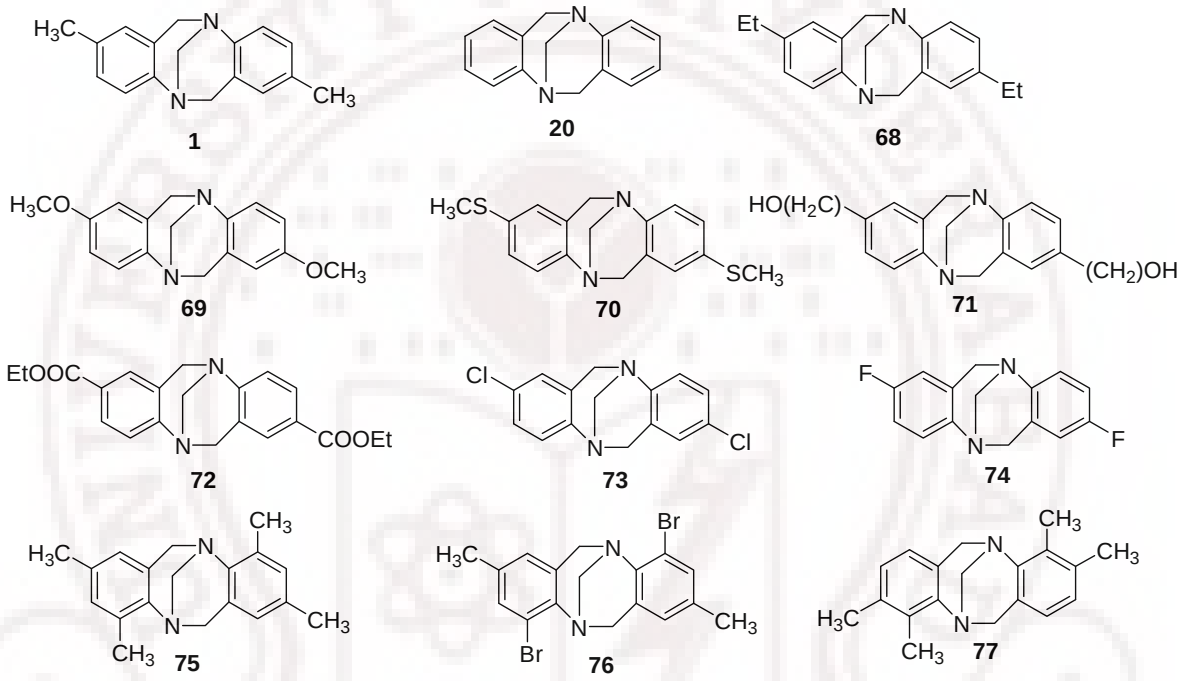


Figure 6

Sergeyev *et al.*[39] reported a method for the enantio-separation of a library of functionalized TB derivatives with various substitution pattern on the aromatic skeleton using a commercially available Whelk-01 chiral stationary phase (Chart 2).

Chart 2



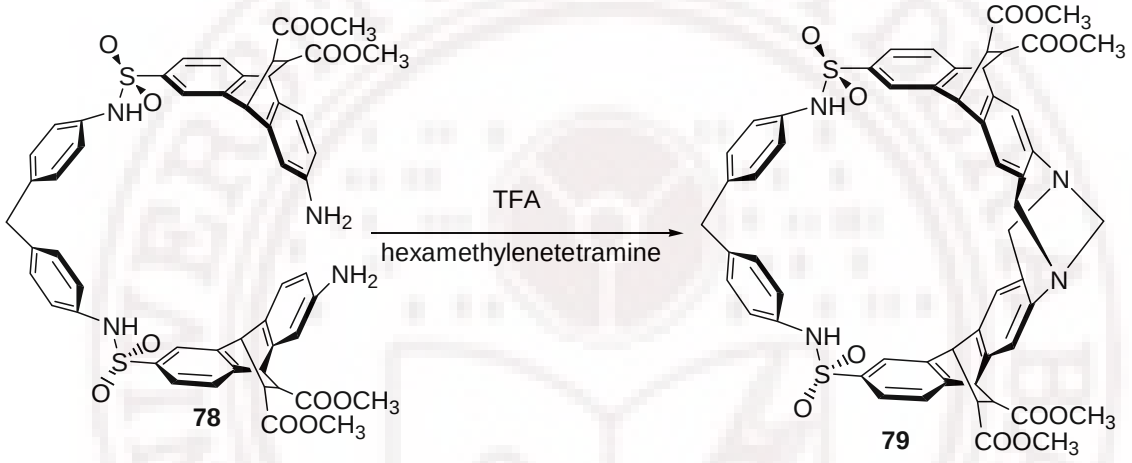
Clearly, the chromatographic resolution (mostly by HPLC) for obtaining enantopure Tröger base derivatives is still a significant method. This may be due to the fact that the methods for resolution of TB derivatives lack generality and require careful choice of resolving agents and experimental conditions on a case to case basis.

1.3 Approaches towards diastereoselective synthesis of Tröger base derivatives

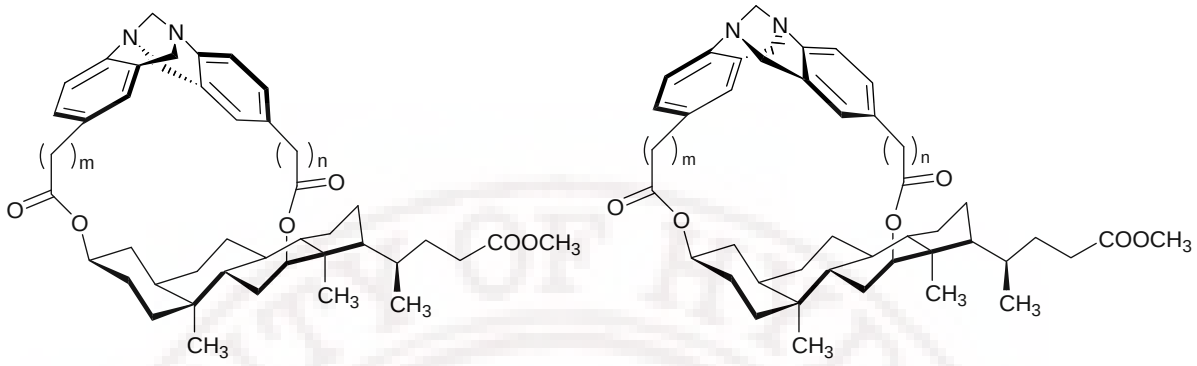
The first success in the synthesis of optically pure TB analogs by diastereoselective cyclization of a chiral precursor was achieved by Wilcox *et al.*[41] in 1991. Treatment of the

chiral diamine **78** with hexamethylenetetramine in the presence of trifluoroacetic acid provided the chiral macrocyclic tetraester **79** having the methanodiazocine bridge (Scheme 24).

Scheme 24



Maitra and co-workers[42] reported chiral induction of a 7-deoxycholic acid template in the preparation of diastereoisomers **80** and **81** (Fig. 7). As the two diastereoisomers have different orientations in space, the authors expected that the spacer lengths linking the two aniline fragments to the steroid would influence the stereoselectivity during the preparation of **80** and **81**. Systematic alteration of the spacer lengths provided the most affected isomer, (*S*,*S*)-**80c**, in 75% yield with 70% diastereoselectivity.[42a]



m,n: **a** (1,1), **b** (2,2), **c** (1,2), **d** (1,3), **e** (2,1), **f** (3,1)

Figure 7

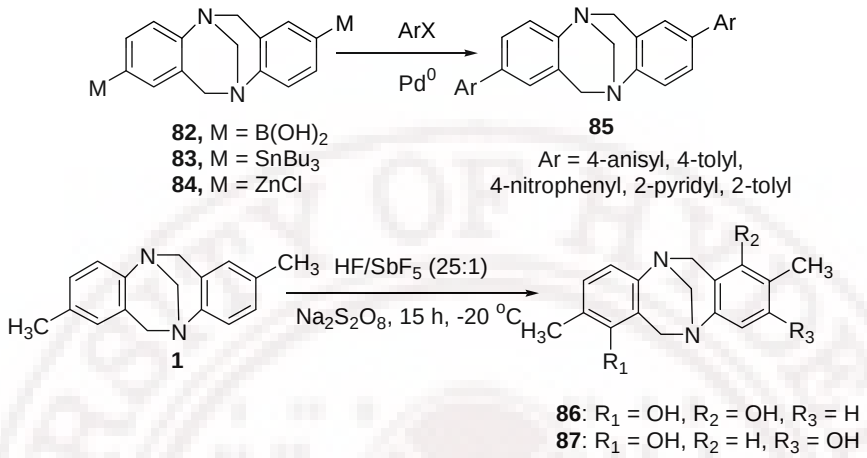
However, it was impossible to separate the diastereoisomeric mixture by chromatography, even using a C_{18}-HPLC column. Only slow crystallization of the mixture from EtOH afforded a very small amount of the pure diastereoisomer **81a**.[42b]

A diastereoselective synthesis of enantiomeric bis-adducts of C_{60} with chiral Tröger base analog was reported by Diederich *et al.*[42c] The high asymmetric induction in the addition of chiral Tröger base to fullerene C_{60} was attributed to the relatively large distance between the two reacting fullerene bonds spanned by the TB tether.

1.4 Functionalization of Tröger base

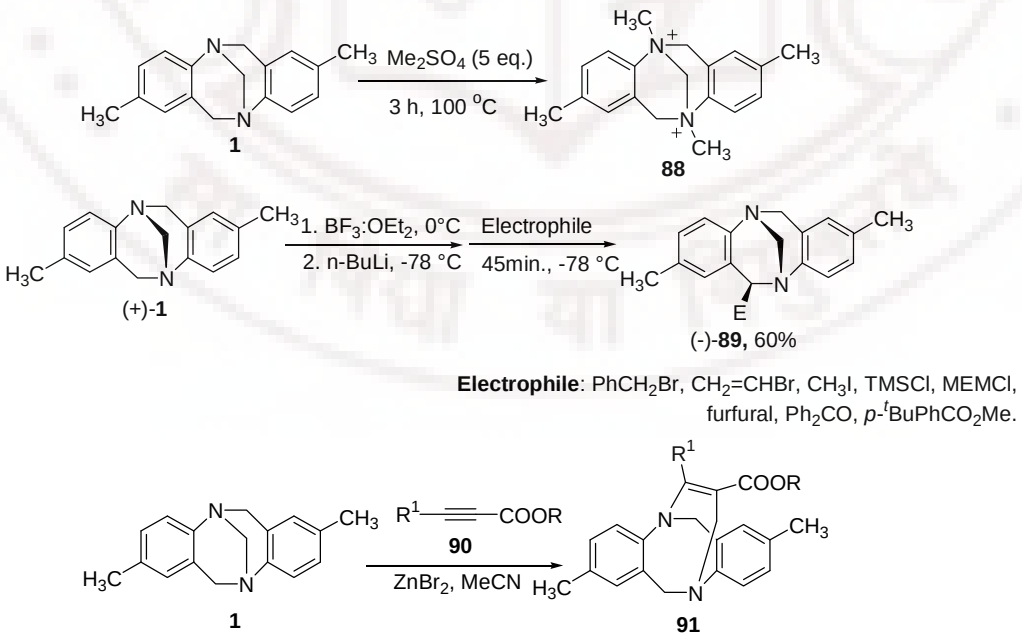
The chemical properties of Tröger base can be classified into two types (i) reactivity of the aromatic moieties (Chart 3) and (ii) reactivity of the saturated core (Chart 4 & 5). Reactions on aromatic moieties are non-specific and include, for example, Pd-catalyzed cross-coupling,[43] hydroxylation on aromatic moiety in the presence of super acid HF/SbF_5.[44]

Chart 3



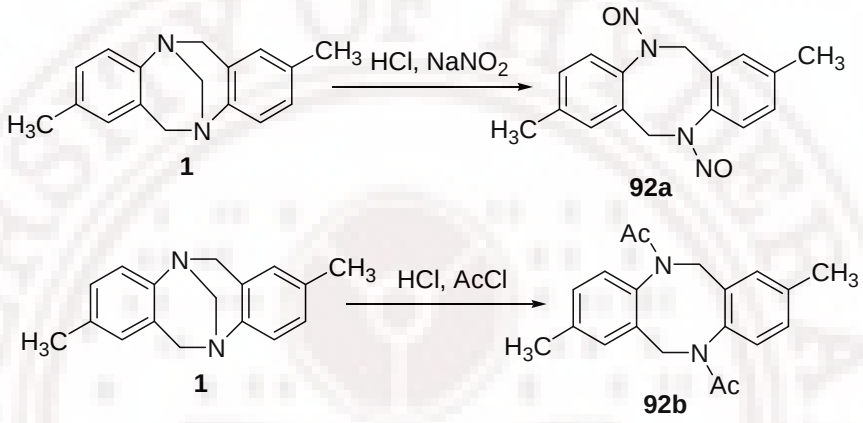
Reactions of the bicyclic core (bridging of the two N atoms) include racemization and diastereomerization[18,45] in acidic media, *N*-Mono and dialkylation reactions,[46] and benzylic C-lithiation in the presence of BF_3**:**OEt_2 using n-BuLi.[47] The reaction of Tröger base **1** with activated acetylenes **90** in the presence of $ZnBr_2$ in MeCN gives the [3.3.3]bicylic products **91** (Chart 4).[48]

Chart 4



Tröger base can be di-*N*-acylated, di-*N*-nitrosylated[8] (Chart 5) or converted into the corresponding ethano derivatives[32,49] with the loss of the methano-bridge (see Scheme 19).

Chart 5



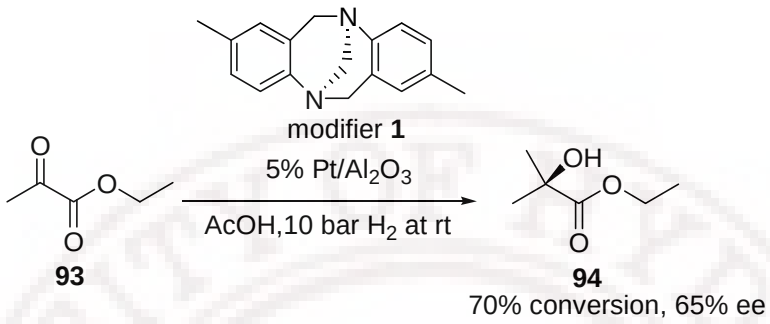
1.5 Applications of Tröger base and its derivatives

Apart from the synthesis and resolution of Tröger base and its derivatives, we have also undertaken studies on the use of these molecules in the chiral recognition of certain carboxylic acids, in asymmetric aziridination, in osmate catalyzed dihydroxylation of olefins, in the preparation and reactions of the Tröger base-borane complexes for hydroboration of prochiral olefins. Accordingly, it is of interest to briefly review the applications of Tröger base and its derivatives in various fields.

1.5.1 Catalytic activities of Tröger base and its metal complexes

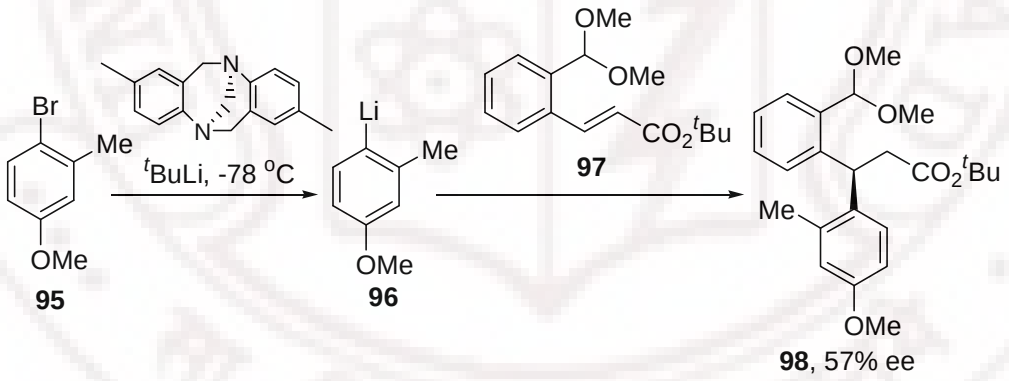
Baiker *et al.*[50] used the chiral Tröger base as modifier in the enantioselective hydrogenation of ethyl pyruvate **93** using alumina-supported Pt-metal catalyst (Scheme 25).

Scheme 25



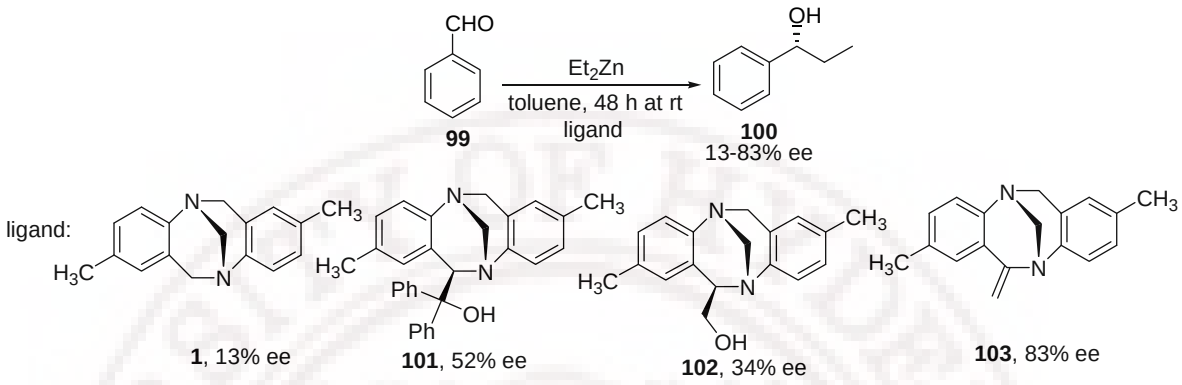
Xu *et al.*[51] used (-)-Tröger base as a chiral ligand in the 1,4-addition of aryllithium reagents to α,β-unsaturated *tert*-butyl esters. The corresponding 1,4-addition product was obtained with 57% ee (Scheme 26).

Scheme 26



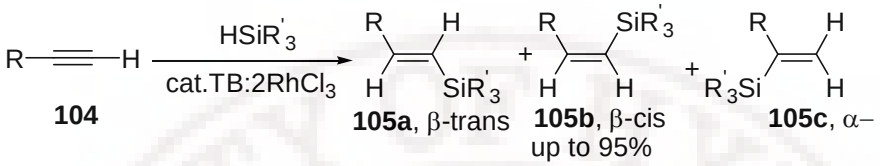
Harmata and Kahraman[52] reported the asymmetric addition of diethylzinc to aromatic aldehydes in the presence of chiral Tröger base but the enantioselectivity was poor (7-22% ee). Higher enantioselectivity was observed, when the reaction was carried out in the presence of modified chiral Tröger bases **101**, **102**, **103** (Scheme 27).

Scheme 27



Goldberg *et al.*[53] and Kostyanovsky *et al.*[54] reported that the nitrogen atom of TB is able to form a donor-acceptor bond with heavy metals such as rhodium, iridium and mercury *via* the nonbonding sp^3 orbital. Goldberg and Alper[53] described that addition of an ethanolic solution of **1** to a solution of rhodium(III) or iridium(III) chloride in EtOH at room temperature resulted in the formation of a pink solid and a dark violet powder, respectively. ^{1}H NMR spectra and elemental analysis showed that both nitrogen atoms are coordinated to metal atoms, resulting in the formation of complexes of the general formula **1**:2MCl_3. Both these complexes were air stable and non-hygroscopic. Catalytic activity of these complexes was tested for the hydrosilylation of terminal alkynes. The reaction afforded the normal *syn*-addition product (β-*trans*-alkenylsilane) and the thermodynamically less stable *anti*-addition product (β-*cis*-alkenylsilane), as well as the α-isomer (Scheme 28). The rhodium(III) complex readily catalyzed the addition of various silanes to terminal alkynes. The *anti*-addition product was formed in some cases with selectivities up to 95%.

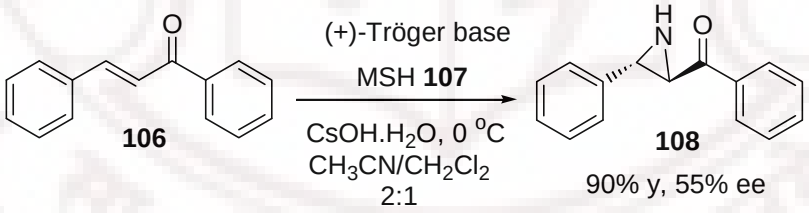
Scheme 28

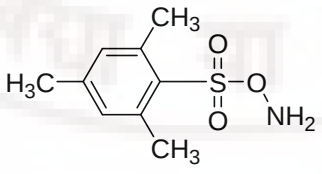


Herrmann *et al.*[55] prepared the (+)-TB-**1** adduct of methyltrioxorhenium and characterized it by crystal structure analysis and spectroscopic data. The catalytic properties of this complex were tested in the epoxidation of prochiral olefins and also in the oxidation of sulfides. However, no asymmetric induction was observed in both cases.

Shi and co-workers[56] reported the asymmetric aziridination of chalcones promoted by chiral Tröger base to obtain the product **108** in 90% yield and 55% ee (Scheme 29).

Scheme 29



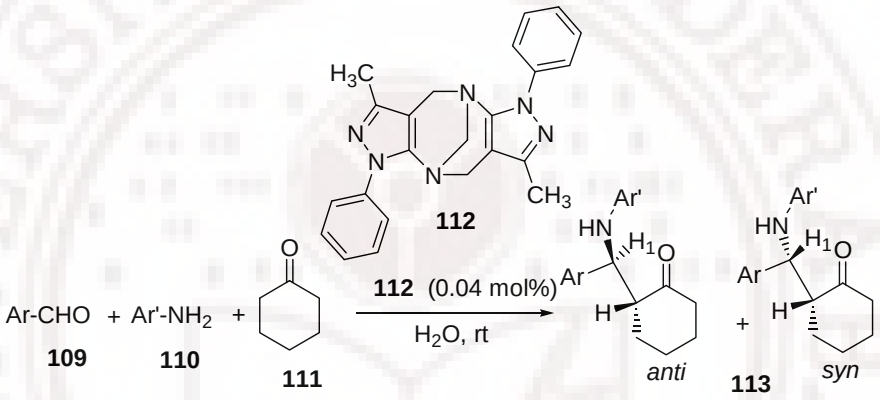


107

MSH: *O*-mesitylenesulfonylhydroxylamine

Very recently, Wu *et al.*[57] reported that the Tröger base analog **112** is an efficient catalyst for the three-component Mannich reactions of aromatic aldehydes and aromatic amines with ketones in water. The corresponding β-amino ketones were obtained in good yields (70-98%) with excellent stereoselectivity (up to 99:1; *anti*/*syn*) (Scheme 30).

Scheme 30



1.5.2 Applications of Tröger base analogs as synthetic receptors

The Tröger base scaffold has been used extensively for the construction of molecular receptors following the initial studies of Wilcox and co-workers.[58] The methanodiazocine bridge of Tröger base affords chirality and a rigid V-shaped geometry to the receptors.

1.5.2.1 Water-soluble cyclophane Tröger base analogs

The ability of water-soluble cyclophanes to form inclusion complexes with aromatic, aliphatic and alicyclic substrates inspired Wilcox and co-workers[41,58a,59] to develop macrocyclic analogs of Tröger base as rigid chiral receptors for small, neutral organic molecules (**114**, Fig. 8). Their binding properties were studied by NMR titrations carried out in DCl/KCl buffer (pD 1.9±0.1).[58a,60]

Optically pure, water-soluble macrocyclic TB tetra acid **115** has been examined as a receptor for terpenes. They observed that host **115** binds the isomeric menthols with reasonable selectivity.[59]

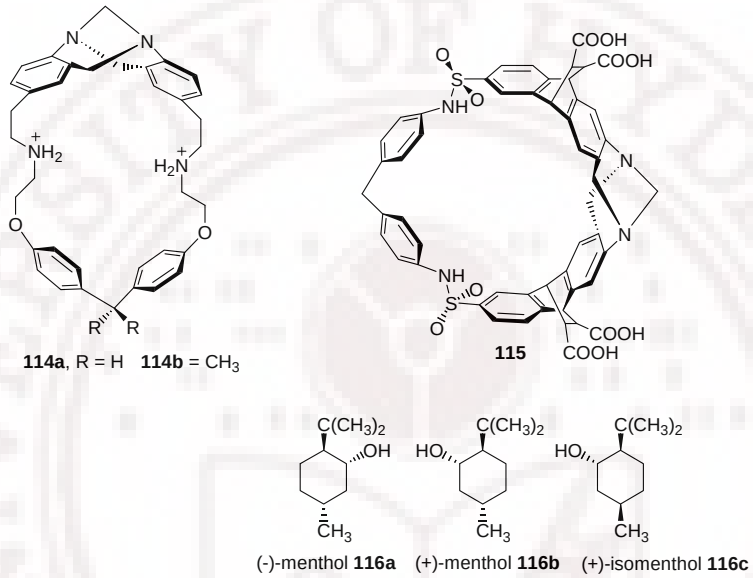


Figure 8

Recently, Wilcox and Miyake[61] reported the synthesis and binding studies of cyclophane bis-TB derivative **117** bearing mercaptoimidazole groups towards 4-nitrophenyl phosphate and 4-nitrophenol using NMR spectroscopy (Fig. 9).

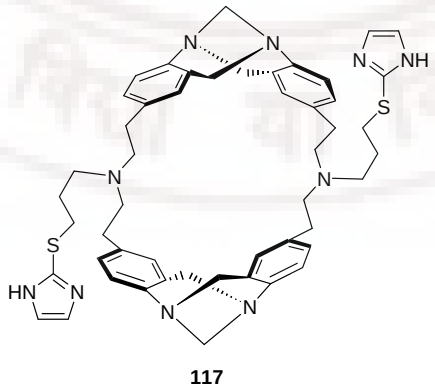
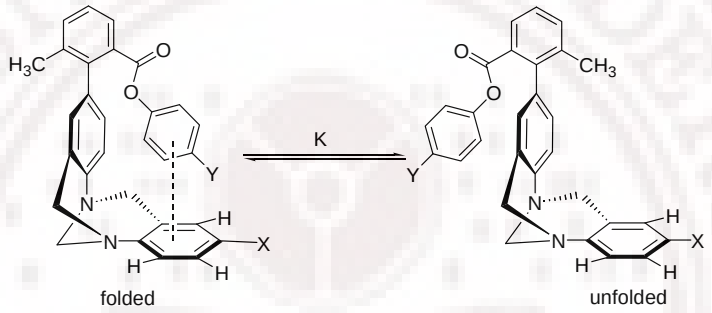


Figure 9

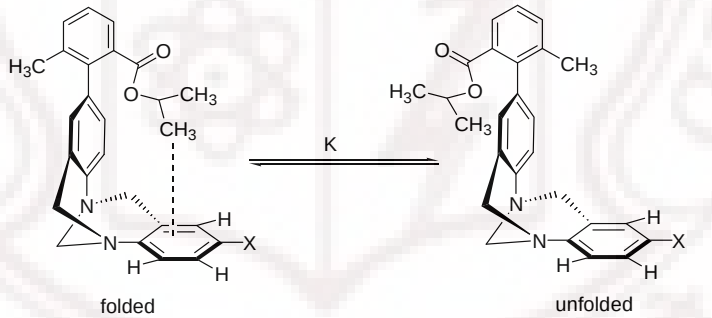
1.5.2.2 Tröger base scaffolds as molecular torsion balances

Wilcox and coworkers[62] also reported their design of molecular torsion balances **118-120** for the quantification of weak molecular forces such as edge-to-face aromatic interactions (**118**, Fig. 10) and CH-π interactions[63] (**119**, **120**, Fig. 10), properties that play key role in protein folding and molecular recognition.



118, X = CH_3; Y = H, OCH_3, NO_2, CN, I, CH_3

119, Y = H; X = NO_2, CN, Br, I, CH_3, OH, NH_2



120, X = NO_2, CN, Br, I, CH_3, OH, NH_2

Figure 10

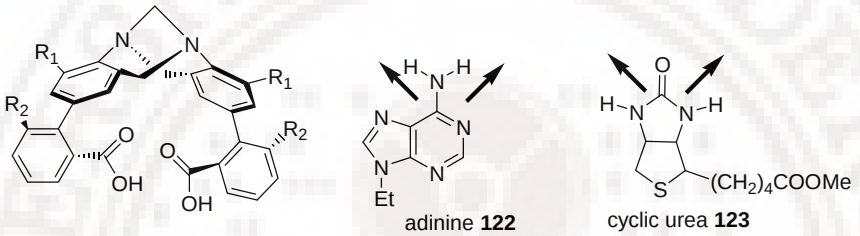
1.5.2.3 Applications of Tröger base scaffolds in molecular recognition

Crossley *et al.*[64] covalently linked two tetraarylporphyrins through the methanodiazocine bridge of TB and prepared well-defined chiral cleft-containing

molecules. Subsequently, these authors reported the binding properties of the corresponding Zn complex **65a** toward α,ω-diaminoalkane,[64] histidine and lysine esters.[36]

1.5.2.4 Tröger base scaffolds as hydrogen bonding receptors

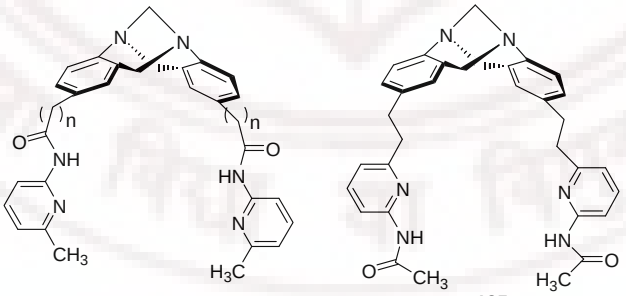
Wilcox *et al.*[65,58b] reported that the carboxylic acid TB derivatives **121** are good hosts for cyclic urea and adenine derivatives (Fig. 11).



121a R_1 = H, R_2 = COOH
121b R_1 = R_2 = H
121c R_1 = CH_3, R_2 = H
121d R_1 = H, R_2 = CH_3

Figure 11

Goswami and Ghosh[66,67] reported the design and synthesis of the amidopyridine TB receptors **124** and **125** (Fig. 11,12) to recognize dicarboxylic acids with precise chain lengths.

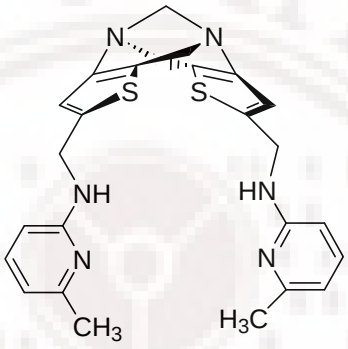


124a n = 0
124b n = 1

125

Figure 12

Kobayashi and Moriwaki[68] reported the thiophene TB derivative **126** (Fig. 13) bearing two pyridylamino groups, whose hydrogen-bonding mode is similar to receptors **124**. They reported binding properties of **126** toward the aliphatic and aromatic dicarboxylic acids.



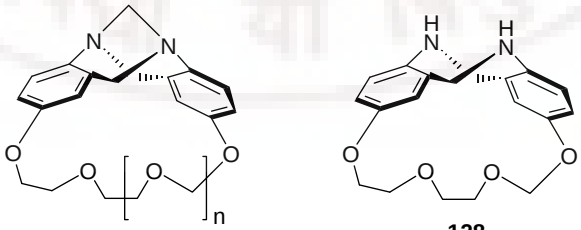
126

Figure 13

Wärnmark *et al.*[12] synthesized a TB scaffold **30** (see Scheme 10) bearing two benzo-18-crown-6 ethers, entities useful as being strong primary ammonium ion complexation partner.

1.5.2.5 Miscellaneous applications of Tröger base derivatives

Ibrahim *et al.*[69] and Nagarajan *et al.*[70] independently demonstrated TB macrocycles **127** for cation binding (Fig. 14).



127a, n = 1
127b n = 2-5

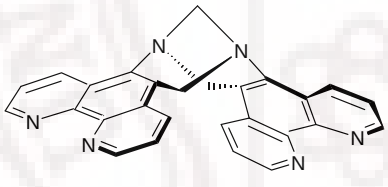
128

Figure 14

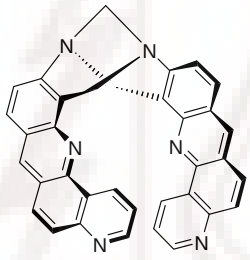
Miyahara *et al.*[71] prepared the dibenzodiazocine **128** by removing the endomethylene bridge in **127a**. It was resolved by HPLC separation using a cellulose based Chiralcel-OJ column. Preliminary complexation studies showed that diamine **128** is a good ligand for metal salts.

Yashima *et al.*[72] reported the synthesis of a Tröger base analog containing two 1,10-phenanthroline moieties **129** for DNA binding studies.

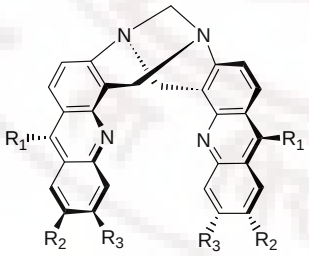
Demeunynck and co-workers[73,74,75] investigated the DNA binding aspect by synthesizing the heterocyclic TB analogs derived from benzophenathroline **130**, the asymmetric, symmetric acridine **131** and acridino-phenanthroline **132** (Fig. 15). They have also reported the sequence selectivity by DNase *I* footprinting.[76]



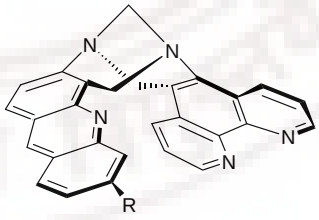
129



130



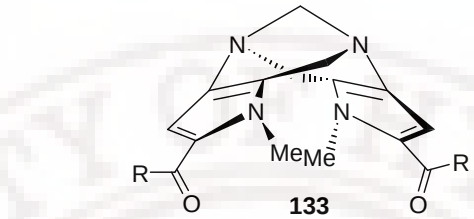
131a $R_1 = R_2 = R_3 = H$
131b $R_1 = R_2 = H$, $R_3 = NH_2$
131c $R_1 = NH_2$, $R_2 = OEt$, $R_3 = H$
131d $R_1 = NH(CH_2)_2OH$, $R_2 = OEt$, $R_3 = H$



132a = H
132b = NH_2

Figure 15

Valík and co-workers[77] reported that the TB analogs **133a**, **133b** (Fig. 16) derived from *N*-methylamidopyrrole also exhibited affinity for DNA.



133

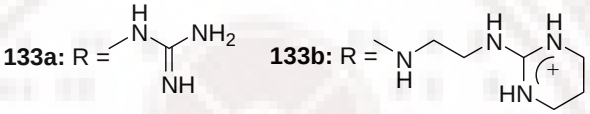


Figure 16

Clearly, considerable efforts are currently being made on exploiting the Tröger base and its derivatives for various applications. We have undertaken efforts to easily access Tröger base derivatives and explore their utility in chiral recognition and in asymmetric transformations. The results are discussed in the next section.

2. Results and Discussion

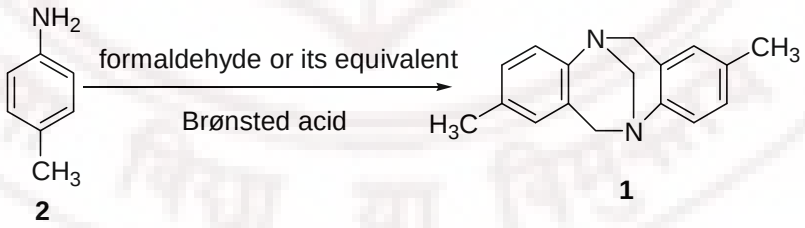
2.1 Synthesis and resolution of Tröger base and its derivatives

2.1.1 Synthesis of racemic Tröger base

As outlined in the introductory section, the 2,8-dimethyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine, the Tröger base **1**, was first prepared by Julius Tröger in 1887.[2] It was structurally characterized by Spielman in 1935.[3] Several procedures are available for the synthesis of Tröger base involving Brønsted acid catalysis. Still there have been increased interest on search for improved and alternative synthetic protocols.

Generally, the Tröger base is prepared by the condensation of 4-toluidine and formaldehyde in dilute acids (Scheme 31).[78]

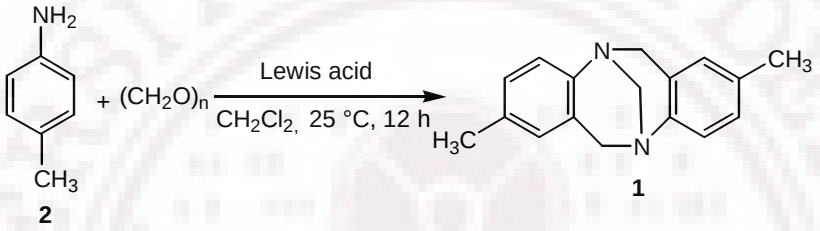
Scheme 31



Later, other synthetic methods were also developed but most of them are low yielding and involve tedious extraction procedures.[4,9] Since the formation of Tröger base goes through an electrophilic substitution reaction, it was thought that Lewis acids would

also promote the reaction. Accordingly, we examined the reaction of 4-toluidine and paraformaldehyde as methylene group equivalent in the presence of $TiCl_4$. The Tröger base was obtained in 63% yield in this reaction (Scheme 32).

Scheme 32



The reaction was optimized using various other Lewis acids. The results are summarized in Table 1.

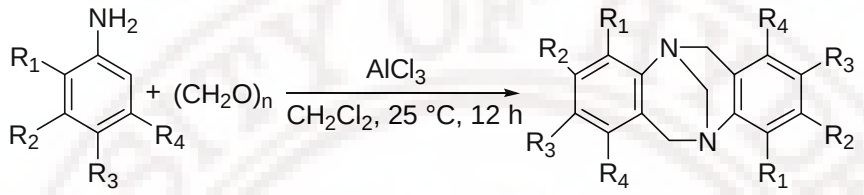
Table 1 Synthesis of **1** using various Lewis acids[a]

Entry	Lewis acid	Time	Yield[b] **1** (%)
1	$TiCl_4$	12 h	63
2	$AlCl_3$	8 h	73
3	$SnCl_4$	12 h	58
4	$ZnCl_2$	12 h	43
5	$ZrCl_4$	36 h	38

[a]All the reactions were carried out using 4-toluidine (10 mmol), paraformaldehyde (20 mmol) and Lewis acid (10 mmol) in CH_2Cl_2 (40 mL). [b]The product was identified by physical constant and spectral data (IR, ^{1}H-NMR, ^{13}C-NMR) and the yields are of isolated products.

The reaction was generalized with substituted anilines in the presence of $AlCl_3$ and the corresponding Tröger base derivatives are obtained in good yields (Scheme 33).

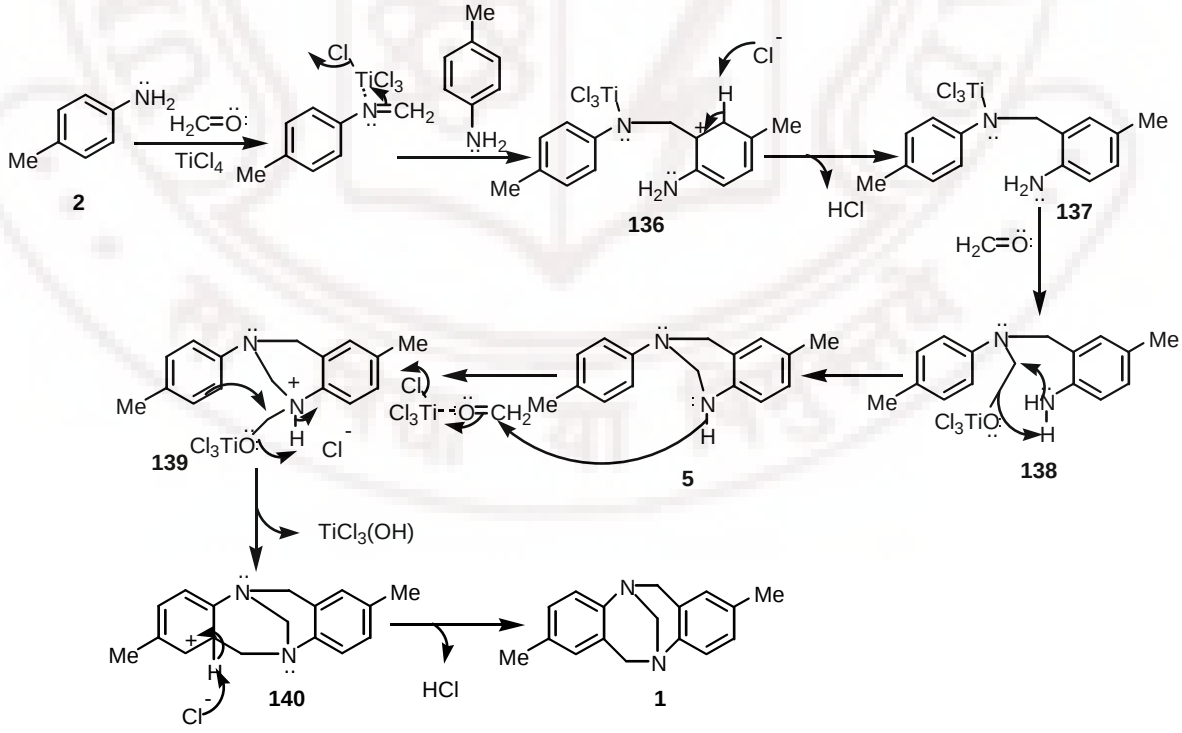
Scheme 33



69:R_1 = H, R_2 = H, R_3 = OCH_3, R_4 = H, 76% y
75:R_1 = CH_3, R_2 = H, R_3 = CH_3, R_4 = H, 65% y
135:R_1 = H, R_2 = CH_3, R_3 = H, R_4 = CH_3, 50% y

A plausible mechanism for the formation of Tröger base in the presence of Lewis acids is outlined in Scheme 34.

Scheme 34



2.1.2 New resolution methods for diamines, amino alcohols, dicarboxylic acids and diols

New resolution procedures to access important chiral diols,[79] amino alcohols,[80] diamines,[80,81] diacids[82] and BINOL[79] have been developed in this laboratory using a range of commercially available and inexpensive chiral resolving agents such as L-(+)-tartaric acid, chiral *O,O'*-dibenzoyltartaric acid, BINOL/boric acid, L-proline and chiral amine/boric acid (Chart 6 & Chart 7).

Chart 6

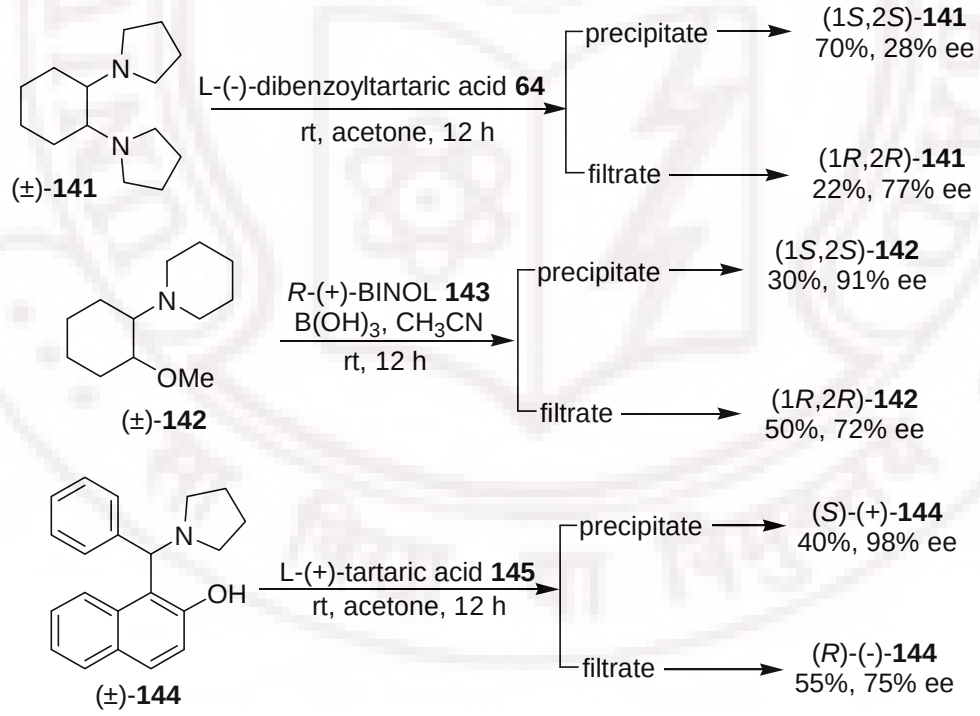


Chart 7

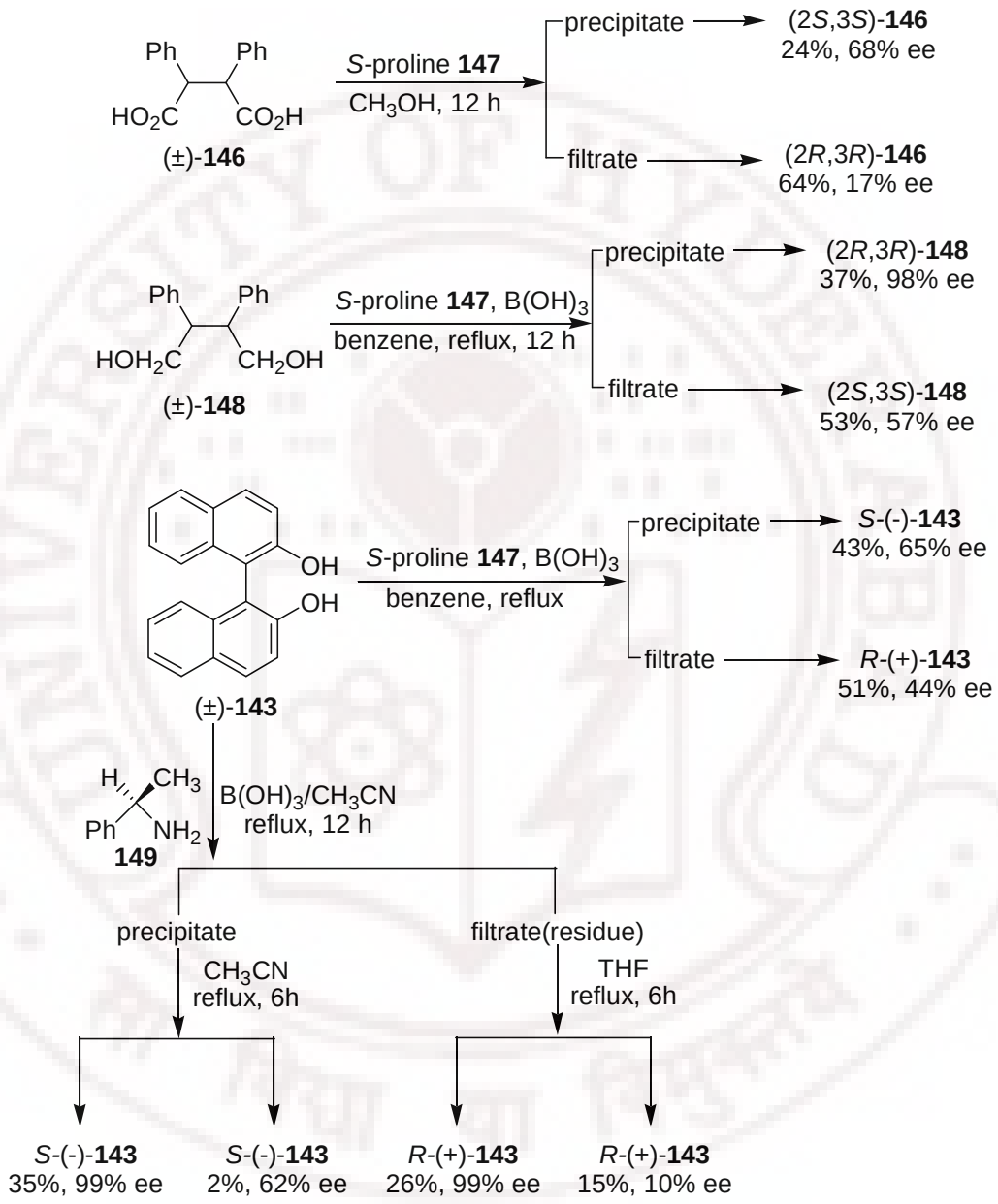
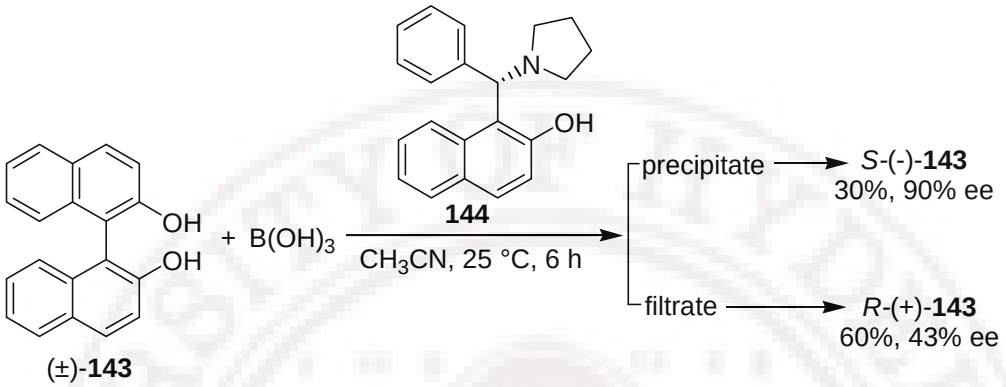

Ph
Ph
HO2C
CO2H
(±)-146
S-proline 147
CH3OH, 12 h
precipitate
(2S,3S)-146
24%, 68% ee
filtrate
(2R,3R)-146
64%, 17% ee
Ph
Ph
HOH2C
CH2OH
(±)-148
S-proline 147, B(OH)3
benzene, reflux, 12 h
precipitate
(2R,3R)-148
37%, 98% ee
filtrate
(2S,3S)-148
53%, 57% ee
OH
OH
(±)-143
S-proline 147, B(OH)3
benzene, reflux
precipitate
S-(-)-143
43%, 65% ee
filtrate
R-(+)-143
51%, 44% ee
H
CH3
Ph
NH2
149
B(OH)3/CH3CN
reflux, 12 h
precipitate
filtrate(residue)
CH3CN
reflux, 6h
THF
reflux, 6h
S-(-)-143
35%, 99% ee
S-(-)-143
2%, 62% ee
R-(+)-143
26%, 99% ee
R-(+)-143
15%, 10% ee

Chart 7 cont…



2.1.2.1 Resolution of racemic Tröger base

Tröger base **1**,[2] a molecule containing chiral nitrogen centers exists in two enantiomeric forms. Due to its rigid and concave shape, it has attracted an intense research in the last several decades.[83] It's chiral nature was first identified by Prelog and Wieland in 1944.[20] As mentioned in the introductory section, most of the hitherto reported methods for the resolution of **1** are based on chromatographic separation techniques. It was reported that the resolution of **1** *via* the formation of diastereomeric salt is not feasible by using chiral acids due to acid promoted racemization.[84] However, we have observed that the Tröger base can be readily resolved *via* preparation of hydrogen bonded aggregates by using dibenzoyl-L-tartaric acid (DBTA) **64**.

We examined the resolution in various solvents like acetone, CH_2Cl_2, ethyl acetate. In all cases, the partially resolved Tröger base was readily obtained (Table 2).

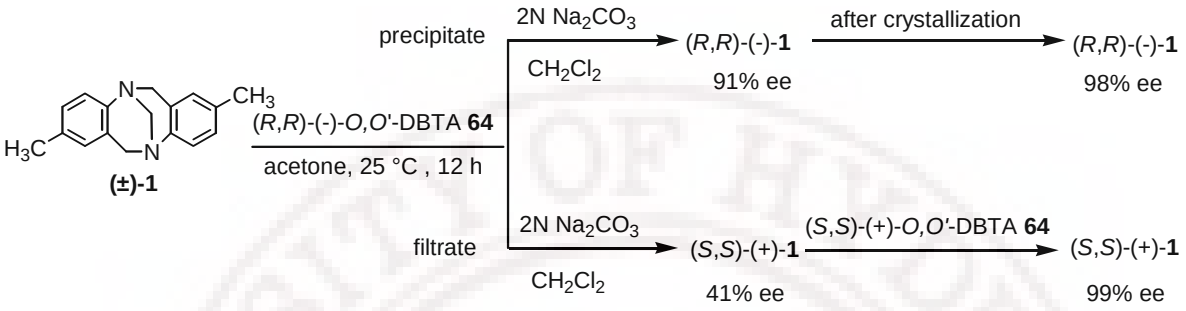
Table 2 Screening of solvents for the resolution of racemic Troger base **1** using dibenzoyl-L-tartaric acid **64**.

Entry	(±)-**1** mmol (% ee)	acid **64** mmol	Solvent	Tröger base **1** obtained from			
				Precipitate		Filtrate	
				% ee[a]/Conf.	% Yield[b]	% ee[a]/Conf.	% Yield[b]
1	2 (00)	4	Acetone (6 mL)	81 (*R,R*)	32	28 (*S,S*)	64
2	2 (00)	6	acetone (6 mL)	86 (*R,R*)	34	18 (*S,S*)	64
3	2 (00)	4	EtOAc (15 mL)	96 (*R,R*)	20	28 (*S,S*)	62
4	2 (00)	8	CH_2Cl_2 (15 mL)	71 (*R,R*)	38	30 (*S,S*)	56

[a]The enantiomeric purities are based on the HPLC analysis by using Chiralcel-OJ-H column. [b]The yields are of isolated products.

Optimum results were obtained in acetone when the racemic Tröger base **1** and dibenzoyl-L-tartaric acid **64** were used in 1:3 ratio (Scheme 35). After digestion of the precipitate fraction, the (*R,R*)-isomer of the Tröger base was obtained in 91% ee and from the filtrate fraction, the (*S,S*)-isomer was obtained in 41% ee. The resolution procedure was optimized in 20 mmol scale.

Scheme 35



The (*R,R*) isomer was obtained in 98% ee by crystallization of the sample of 91% ee from acetone and hexane mixture. The (*S,S*) isomer was easily enriched by repeating the experiment using dibenzoyl-D-tartaric acid. The results are summarized in Table 3.

The precipitated diastereomeric complex **150** [(-)-**1.** (-)-**64**] (entry 5, Table 3) was crystallized from methanol solvent and the X-ray structure analysis was carried out (Fig.17). The asymmetric unit of the crystal structure contains one molecule of Tröger base and one molecule of dibenzoyl-L-tartaric acid(1:1). The carboxylic acid moieties of the (-)-DBTA donate the protons to nitrogen acceptors of the Tröger base, making two separate strong O-H···N interactions. Bond lengths of the carboxylic acid groups in the (-)-DBTA - Tröger base complex **150** are: C26–O3 = 1.197 Å, C26–O4 = 1.312 Å; C28–O6 = 1.195 Å, and C28–O5 = 1.321 Å, indicating the presence of C=O and C-OH groups in the complex. Hence, it is clear from the X-ray data, that the diastereomeric complex formed is not a salt but a hydrogen bonded aggregate (Fig.18). Thus, the precipitation occurred because of aggregation due to strong O-H···N hydrogen bonding interactions (O4-H4···N1, 2.678(2) Å,

179˚; O5-H5···N2, 2.646(2) Å, 164˚) between the Tröger base and the resolving agent. The configuration of (-)-**1** was determined as 5*R*,11*R* relative to the chiral acid (*R,R*)-(-)-**64** used.[31]

Table 3 Resolution of racemic Tröger base **1** using (-)-dibenzoyl-L-tartaric acid **64**

Entry	(±)-**1** mmol (% ee)	acid **64** mmol	Acetone (mL)	Tröger base **1** obtained from			
				Precipitate		Filtrate	
				% ee[a]/Conf.	% Yield [b]	% ee[a]/Conf.	% Yield [b]
1	2 (00)	4	6	81 (*R,R*)	32	28 (*S,S*)	64
2	2 (00)	6	6	86 (*R,R*)	34	18 (*S,S*)	64
3	2 (00)	8	6	>98[c] (*R,R*)	31	39 (*S,S*)	62
4[d]	2 (39)	8	6	99[c] (*S,S*)	42	6 (*R,R*)	56
5	20 (00)	60	60	98[c] (*R,R*)	32	41 (*S,S*)	65
6[d]	20 (41)	60	60	99[c] (*S,S*)	62	12 (*R,R*)	35

[a]The enantiomeric purities are based on the HPLC analysis by using Chiralcel-OJ-H column. [b]The yields are of isolated products. [c]These ee's are after one recrystallization from acetone and hexane mixture. [d]In these experiments (+)-dibenzoyl-D-tartaric acid ((+)-*O*,*O*'-DBTA **64**) was used as resolving agent.

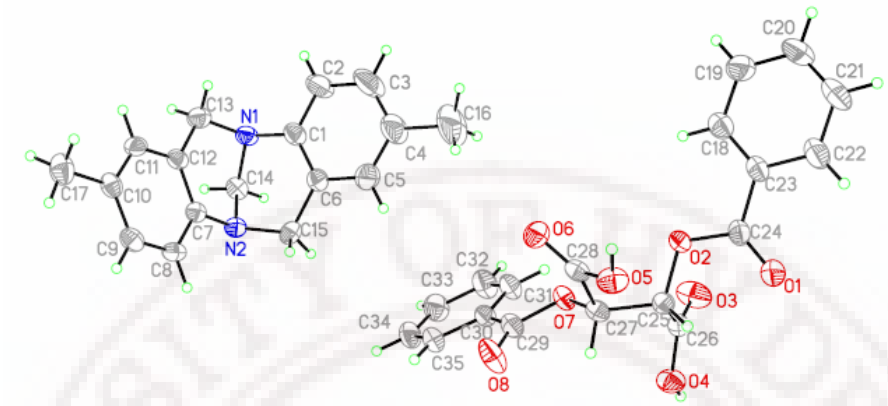


Figure 17 ORTEP representation of the crystal structure of the complex **150**[(-)-**1.** (-)-**64]** (Thermal ellipsoids are drawn at 35% probability and all the hydrogens are unlabelled for clarity)

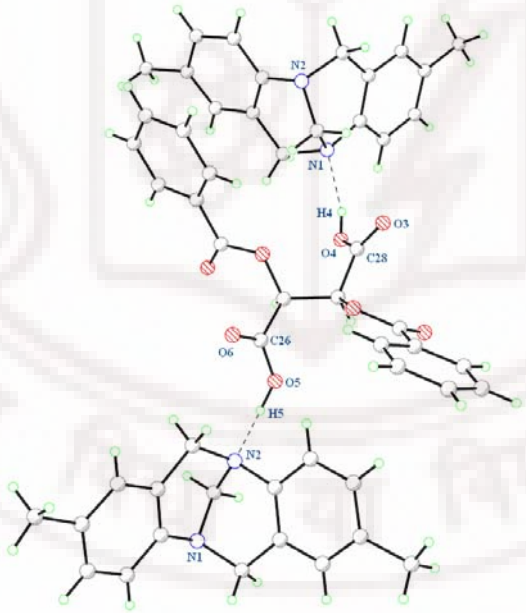


Figure 18 Packing diagram of the complex **150**[(-)-**1.** (-)-**64**] showing the strong O-H···N hydrogen bonding interactions

2.1.2.2 Resolution of racemic methoxy Tröger base

Although, Tröger base derivatives are also chiral, there are only a few reports on their resolution.[32,33,35] Hamada *et al.*[32] reported the resolution of (±)-ethano Tröger base **58** by the diastereomeric salt formation using the chiral *O,O'*-di-*p*-toluoyltartaric acid **59**. They attempted the resolution of its methoxy derivative but were not successful. To the best of our knowledge, there is no resolution procedure reported for obtaining the chiral methoxy Tröger base with the aid of chiral acids. Accordingly, we examined the resolution of methoxy Tröger base using different chiral acids. We have observed that the methoxy Tröger base could be readily resolved *via* the preparation of diastereomeric salt by using *O,O'*-dibenzoyl-L-tartaric acid **64** as resolving agent.

The resolution was carried out in various solvents like CH_2Cl_2, ethyl acetate, acetonitrile and in all cases, the partially resolved methoxy Tröger base was readily obtained. Then, we have also examined the effect of quantity of solvent (acetone) and chiral resolving agent (Table 4). Optimum results were obtained in acetone when the racemic methoxy Tröger base **69** and dibenzoyl-L-tartaric acid **64** were used in 1:1 ratio (Scheme 36). After digestion of the precipitate fraction, the (*R,R*)-enantiomer of the methoxy Tröger base was obtained in >98% ee and from the filtrate fraction, the (*S,S*)-isomer was obtained in 30% ee. The (*S,S*) enantiomer was easily enriched by repeating the experiment using *O,O'*-dibenzoyl-D-tartaric acid. The results are summarized in Table 4.

Scheme 36

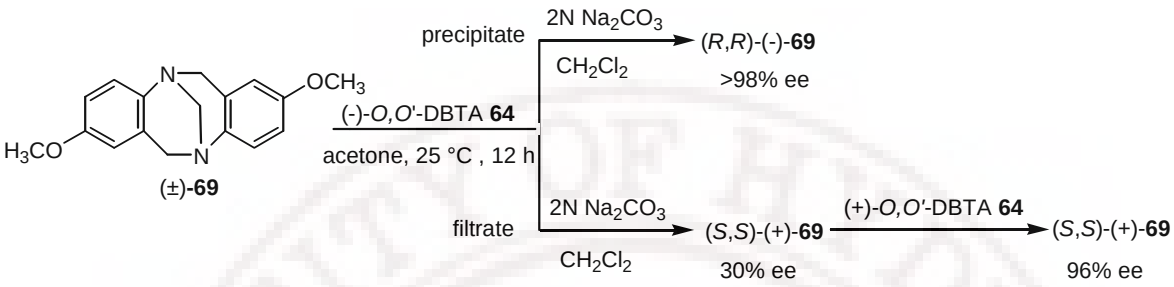


Table 4 Resolution of racemic methoxy Tröger base **69** using (-)-dibenzoyl-L-tartaric acid

Entry	(±)-**69** mmol (% ee)	acid **64** mmol	Acetone (mL)	methoxy Tröger base **69** obtained from Precipitate		Filtrate	
				% ee[a]/Conf.	% Yield[b]	% ee[a]/Conf.	% Yield[b]
1	2 (00)	1	20	79 (*R*,*R*)	24	19 (*S*,*S*)	73
2	2 (00)	2	20	83 (*R*,*R*)	34	43 (*S*,*S*)	60
3	2 (00)	2	25	86 (*R*,*R*)	35	28 (*S*,*S*)	60
4[c]	2 (28)	2	15	84 (*S*,*S*)	57	10 (*R*,*R*)	37
5	20 (00)	20	240	>98 (*R*,*R*)	30	30 (*S*,*S*)	66
6[c]	20 (30)	20	300	96 (*S*,*S*)	31	06 (*R*,*R*)	65

[a]The enantiomeric purities are based on the HPLC analysis by using Chiralcel-OD-H column. [b]The yields are of isolated products. [c]In these experiments (+)-dibenzoyl-D-tartaric acid ((+)-*O*,*O*'-DBTA **64**) was used as resolving agent.

The precipitated diastereomeric salt **151**[(-)-**69.** (-)-**64**] (entry 5, Table 4) was crystallized from methanol and the X-ray crystal structure analysis was carried out (Fig.

19). The asymmetric unit of the crystal structure contains one molecule of methoxy Tröger base and one molecule of dibenzoyl-L-tartaric acid(1:1). The ORTEP diagram clearly shows that only one proton from the two acid groups of (-) DBTA, transferred to nitrogen atom of methoxy Tröger base **69** and the other nitrogen atom is not involved in salt formation. It is of interest to note that, whereas the Tröger base itself gave a H-bonded aggregate, the methoxy derivative gives a salt. Presumably, the greater electron donating methoxy substituent makes this derivative more basic. This salt was packed in helical fashion and helix has formed because of the strong O-H···O & N-H···O hydrogen bonding interactions (Fig. 20). The configuration of (-)-**69** was determined relative to the chiral acid (*R,R*)-(-)-**64** used, as 5*R*,11*R*.

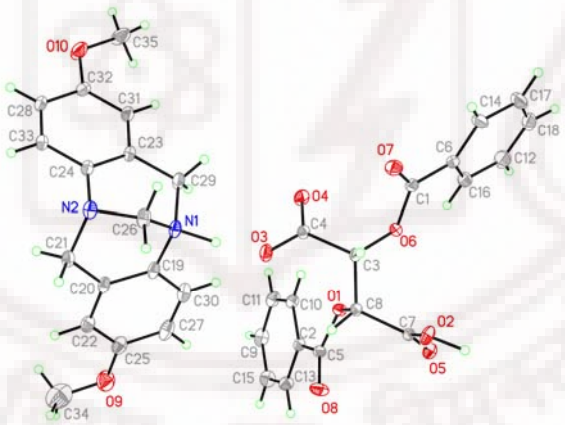


Figure 19 ORTEP representation of the crystal structure of the diastereomeric salt **151**[(-)-**69.** (-)-**64**] (Thermal ellipsoids are drawn at 15% probability and all the hydrogens atoms are unlabelled for clarity)

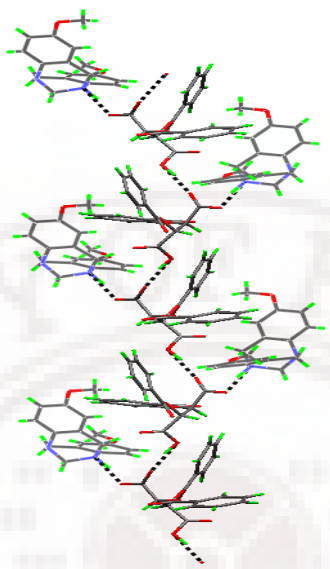
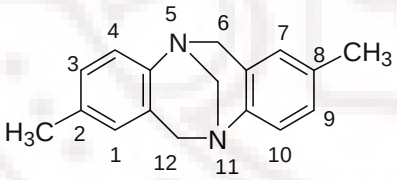


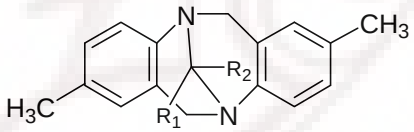
Figure 20 Packing diagram of the diastereomeric salt **151**[(-)-**69.** (-)-**64**] showing the helix formed due to Strong O-H···O & N-H···O hydrogen bonding interactions

2.2 Synthesis of Tröger base derivatives

2.2.1 Synthesis of 5,11-substituted derivatives of Tröger base



1



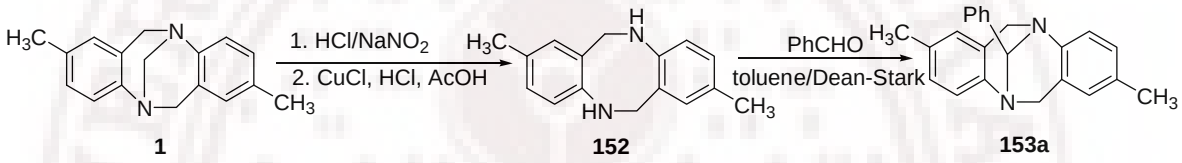
5,11-substituted TB

Figure 21

Johnson *et al.*[85a] reported that certain 5,11-substituted derivatives of Tröger base exhibited effective inhibition of the enzyme thromboxane A_2 synthase (TxA_2). Accordingly, methods for synthesis of a series of such derivatives have good potential for further exploitations.

Earlier, Cooper *et al*.[85b] prepared the 5,11-substituted derivatives of Tröger base. In this procedure, the Tröger base was first converted to 5,6,11,12-tetrahydro-2,8-dimethylphenomazine **152** and then condensed with benzaldehyde to get the analog **153a** (Scheme 37). It was reported that the Tröger base did not react with benzaldehyde to give these derivatives in single step.[85b]

Scheme 37

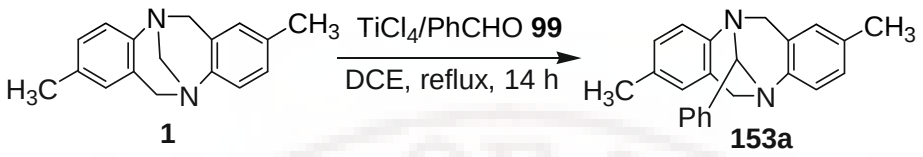


2.2.1.1 $TiCl_4$ promoted synthesis of 5,11-substituted Tröger base derivatives

As outlined in the introductory section, certain Lewis acids could activate the reactions at the endo methylene bridge in Tröger base. Since our objective was to prepare 5,11-substituted derivatives of Tröger base in single step, we examined the reaction of Tröger base with benzaldehyde in the presence of $ZnBr_2$ and also in the presence BF_3:OEt_2. In both reactions, only the starting material was recovered.

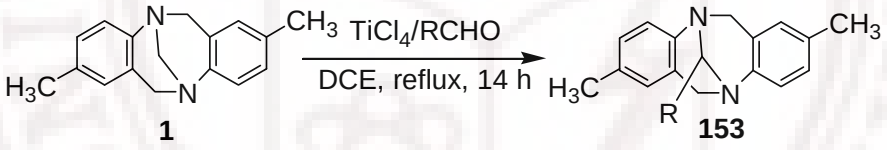
We have then examined the reaction of Tröger base with benzaldehyde in the presence of $TiCl_4$ under refluxing dichloroethane (Scheme 38). In this run, the 5,11-substituted derivative **153a** was obtained in 59% yield.

Scheme 38 Synthesis of 5,11-endo benzylidine derivative of Tröger base **153a**



The reaction was generalized for the other aldehydes and also for some aliphatic ketones (Scheme 39). The results are summarized in Table 5. The spiro compound **153n** was obtained in the reaction with cyclopentanone. The structure of this compound was further confirmed with X-ray crystal structure analysis. The ORTEP diagram is shown in Fig. 22.

Scheme 39: Reaction of Tröger base with carbonyl compounds in the presence of $TiCl_4$



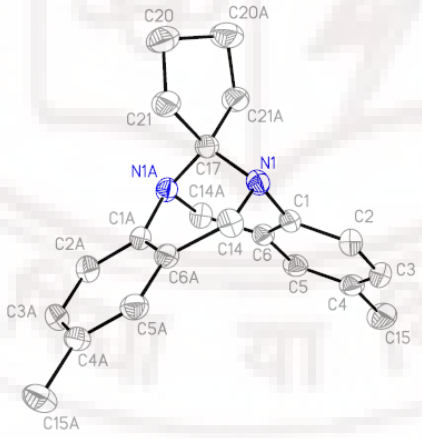


Figure 22 ORTEP representation of the 5,11-substituted spiro analog **153n** of Tröger base (Thermal ellipsoids are drawn at 35% probability and all the hydrogens atoms are removed for clarity)

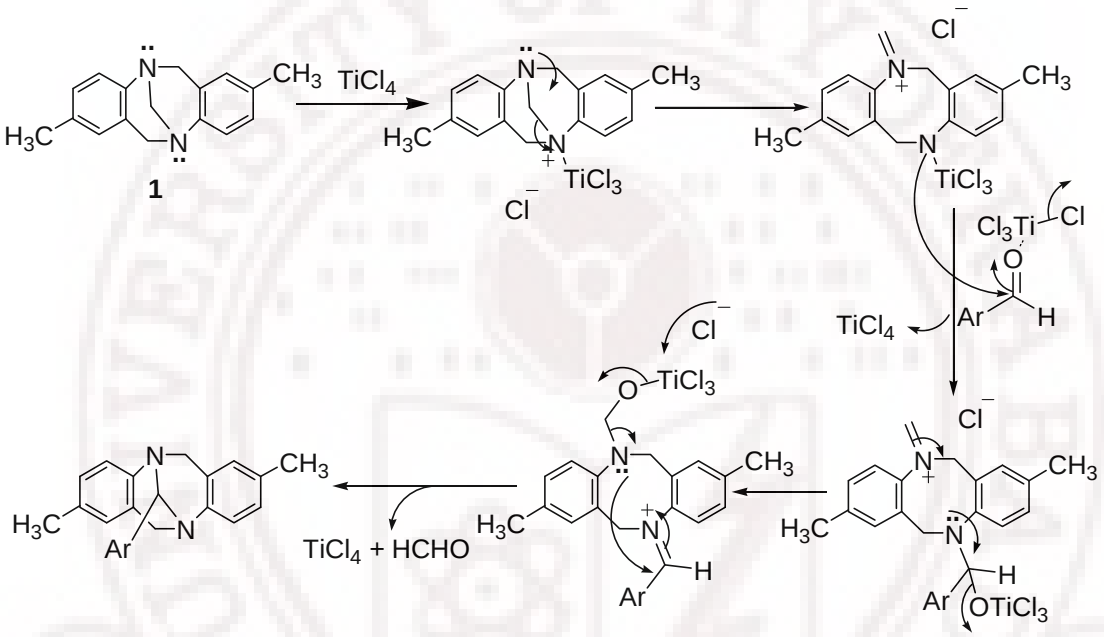
Table 5 Reaction of Tröger base with aldehydes and ketones in the presence of $TiCl_4$[a]

Entry	Carbonyl compound **R**	Product	% Yield[b,c]
1	Ph	**153a**	59
2	4- Tolyl	**153b**	61
3	4-Anisyl	**153c**	62
4	4-Chlorophenyl	**153d**	53
5	4-Nitrophenyl	**153e**	39
6	Terephthalyl	**153f**	52
7	1-Naphthyl	**153g**	57
8	2-Naphthyl	**153h**	60
9	Furfuryl	**153i**	61
10	n-Propyl	**153j**	45
11	Ethyl	**153k**	48
12	n-Hexyl	**153l**	43
13	Cyclohexanone	**153m**	50
14	Cyclopentanone	**153n**	41
15	(+)-2-Methyl-1-butanal	**153o**	40[d]

[a]All the reactions were carried out using Tröger base (2 mmol), carbonyl compound (2 mmol) and $TiCl_4$ (4 mmol) in DCE (15 mL). [b]The yields are of isolated products. [c] The products were characterized by spectral data (IR, ^{1}H-NMR, ^{13}C-NMR). All the unknown derivatives were further confirmed by mass spectral, elemental analysis. [d]The diastereomeric product obtained with 1:1 dr was analyzed by using HPLC.

A tentative mechanism for the formation of 5,11-substituted analogs of Tröger base is outlined in Scheme 40.

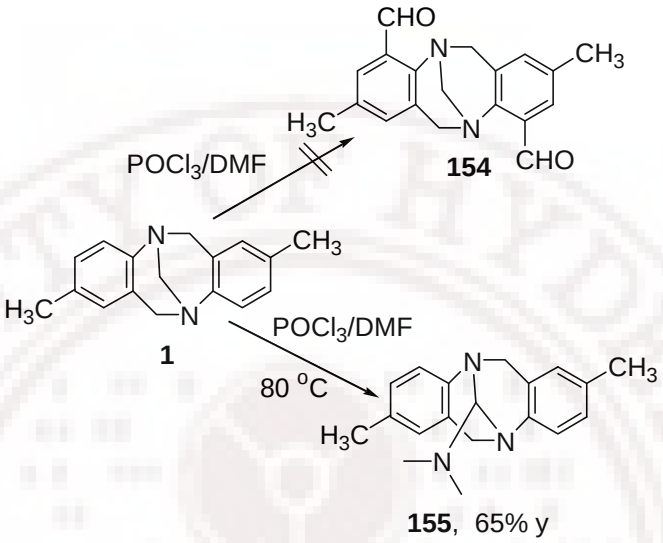
Scheme 40



2.2.1.2 $POCl_3$ promoted preparation of 5,11-substituted Tröger base derivatives

In another attempt, we have examined the Vilsmeier-Haack reaction of the Tröger base **1** to further explore the chemistry of this moiety. Surprisingly, instead of the formylated product **154**, the 5,11-substituted derivative of Tröger base **155** in 65% yield. Clearly, the DMF participated to exchange with the bridging methylene group in this case (Scheme 41).

Scheme 41



Then, we have also examined the reaction of benzaldehyde with Tröger base in the presence of $POCl_3$ in toluene solvent. In this case, the 5,11-endo benzylidine derivative of the Tröger base **153a** is obtained in moderate yield (Scheme 42). The reaction was also generalized with different aldehydes (Table 6).

Scheme 42

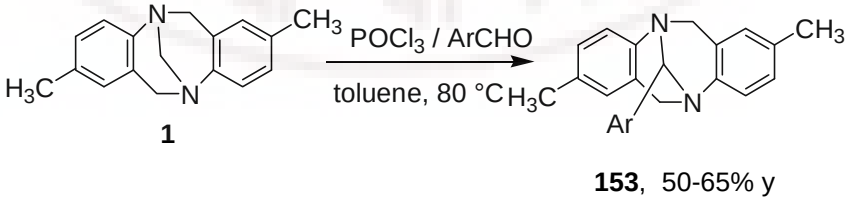


Table 6 Reaction of Tröger base with various aldehydes in the presence of $POCl_3$[a]

Aldehyde **Ar**	Product	% Yield[b]
Ph	**153a**	60
4-Tolyl	**153b**	65
4-Anisyl	**153c**	68
4-Chlorophenyl	**153d**	55
1-Naphthyl	**153g**	50
Furfuryl	**153i**	60

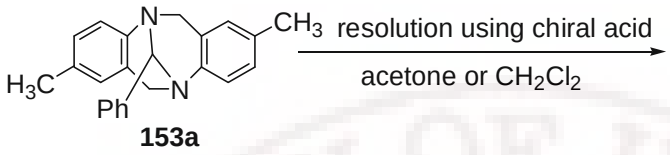
[a]All the reactions were carried out using Tröger base (2 mmol), aldehyde (2 mmol) and $POCl_3$ (4 mmol) in dry toluene (15 mL).[b]The product was identified by spectral data (IR, ^{1}H-NMR, ^{13}C-NMR). The yields are of isolated products.

In this case also, we have carried out the reaction using (+)-2-methyl-1-butanal. Unfortunately, the product **153o** (Table 5, entry 15) was obtained only as 1:1 diastereomeric mixture (confirmed by HPLC analysis).

2.2.1.3 Attempted resolution of 5,11-substituted Tröger base derivatives

We have also attempted the resolution of 5,11-endo benzylidine derivative of Tröger base **153a** using different chiral acids in various solvents, but in no case solid complex/salt was formed (Scheme 43).

Scheme 43



153a

Chiral acid: (-)-*O*,*O*'-DBTA **64**; (-)-*O*,*O*'-DTTA **59**; (-)-10-Camphorsulfonic acid **46**

We have then examined the chromatographic resolution. We have observed that the 5,11-substituted TB derivatives **153a**, **153b**, **153c**, **153m** are resolved on Chiralcel-OJ-H column using ethanol as mobile phase.

153a: Two enantiomers were separated with retention times 7.5 min. & 18.5 min.

153b: Two enantiomers were separated with retention times 9.2 min. & 22.5 min.

153c: Two enantiomers were separated with retention times 9.8 min. & 33.3 min.

153m: Two enantiomers were separated with retention times 6.2 min. & 33.4 min

These studies should be helpful in the isolation of pure enantiomers of these derivatives by carrying out the resolutions in preparative scale when required.

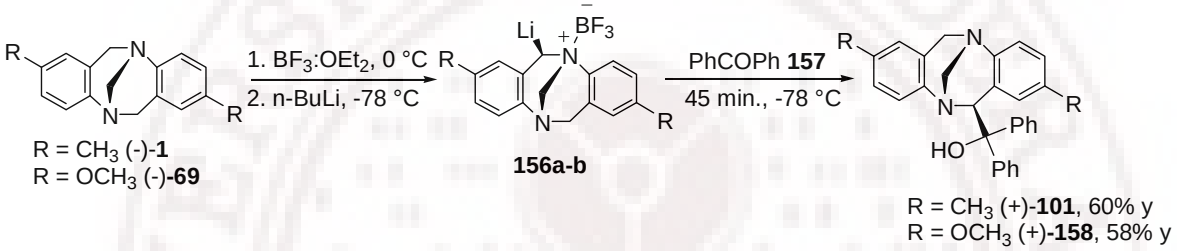
2.2.2 Synthesis of α-alkylated chiral Tröger base

2.2.2.1 Synthesis of α,α'-diphenylcarbinol derivative of chiral Tröger base

As outlined in the introductory section, C_α-alkylated chiral Tröger base derivatives can be readily accessed through α-lithiation by complexation of Tröger base with BF_3 followed by reaction with electrophiles (Chart 4).[47]

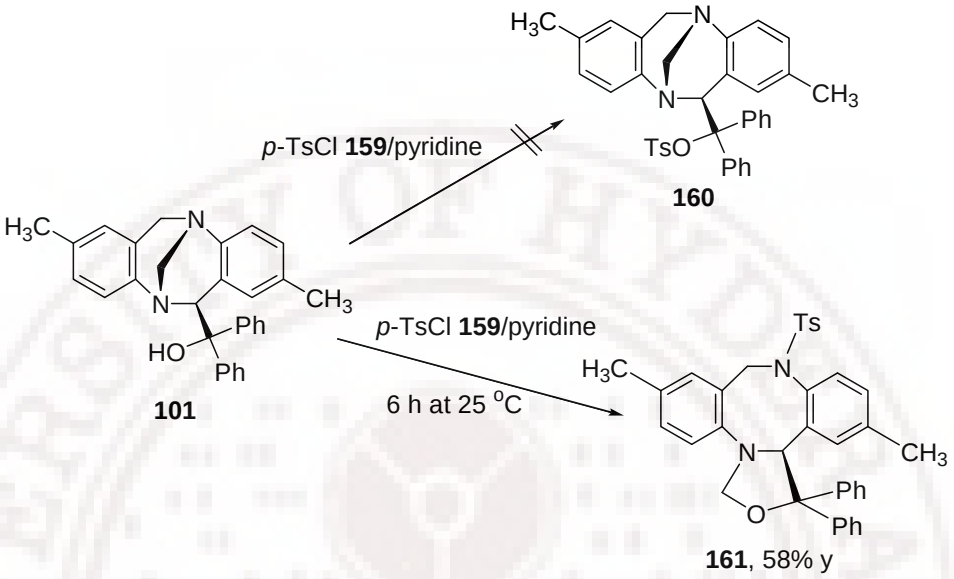
We have prepared the chiral amino alcohol derivatives **101** and **158** using this procedure *via* α-lithiation, followed by quenching with benzophenone to obtain the products **101** and **158** (Scheme 44).

Scheme 44



For determining the configuration of the newly formed chiral centre, we have attempted crystallization of the amino alcohol derivatives. Unfortunately, these attempts were not successful. We have then attempted the tosylation of the amino alcohol **101** by using *p*-toluenesufonyl chloride **158** in the presence of pyridine. Unexpectedly, instead of the *O*-tosylated derivative of the amino alcohol, a new chiral oxazolidine derivative **161** was formed *via* cleavage of methylene bridge of the Tröger base skeleton (Scheme 45). Fortunately, this compound gave suitable crystals in isopropanol/ethanol mixture for the X-ray analysis. Thus, the configuration of the newly formed chiral centre was found to be *S* from the X-ray crystal structure analysis of **161**. The ORTEP diagram is shown in Fig. 23.

Scheme 45



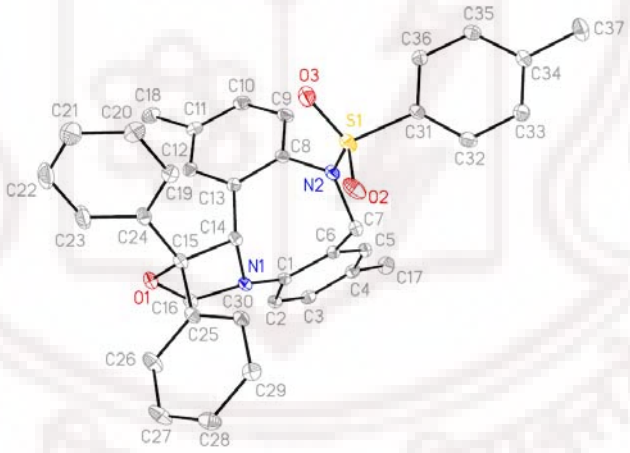
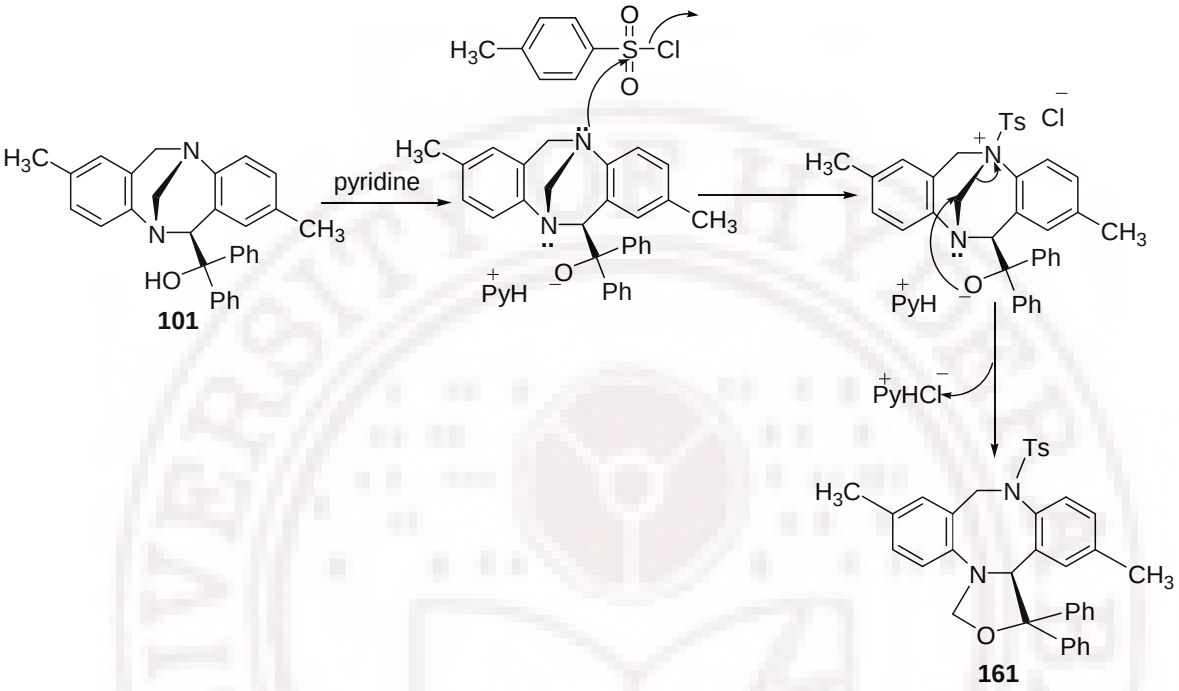


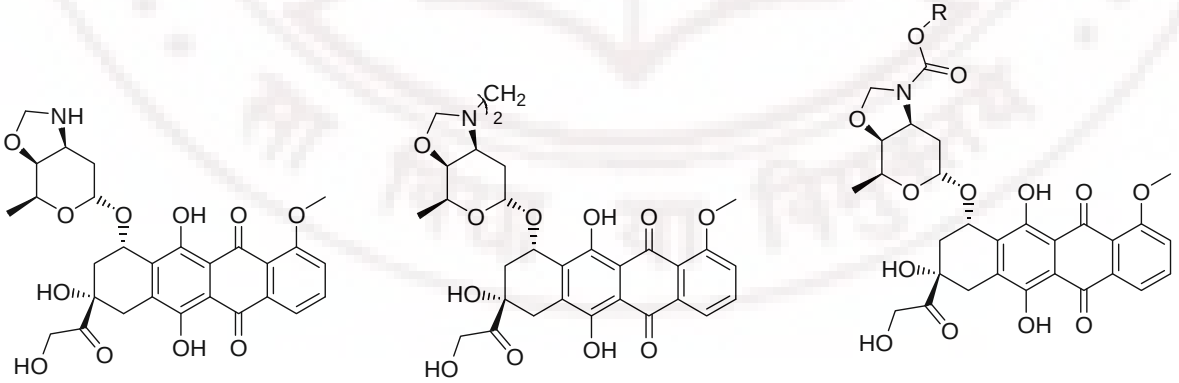
Figure 23 ORTEP representation of the compound **161** (Thermal ellipsoids are drawn at 10% probability and all the hydrogen atoms are removed for clarity)

A tentative mechanism for the formation of the oxazolidine **161** is outlined in Scheme 46.

Scheme 46



It is of interest to note that the oxazolidine ring systems are present in medicinally valuable compounds, such as the anticancer prodrugs doxazolidine **162**, doxoform **163**, and doxaz carbamate **164** (Fig. 24).[86a,86b]

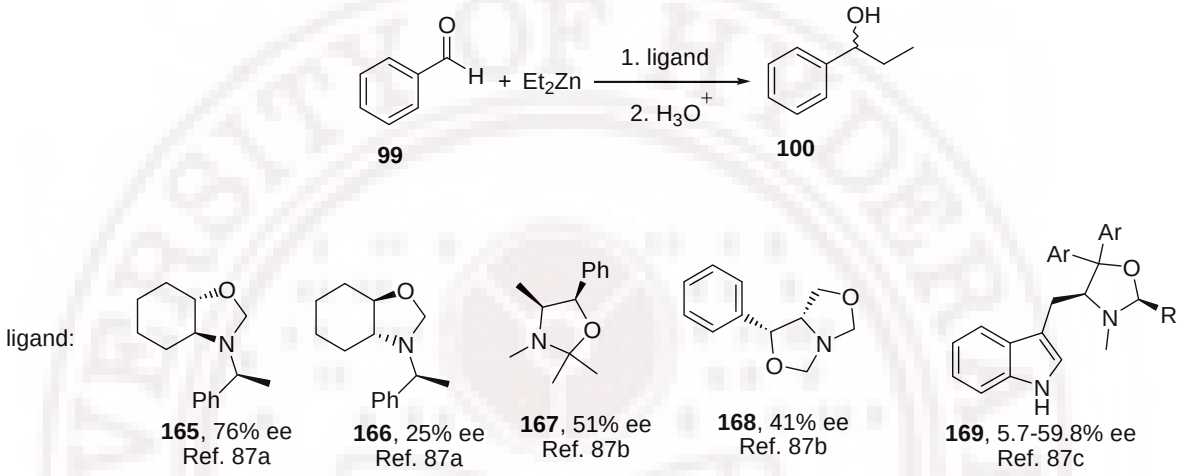


Doxazolidine **162** Doxoform **163** Doxaz carbamate **164**

Figure 24

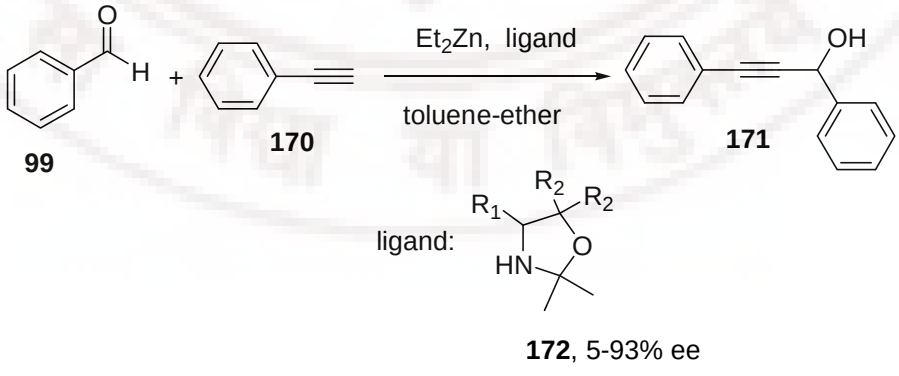
Chiral 1,3-oxazolidine ligands have been also useful in the asymmetric addition of diethyl zinc to aromatic aldehydes (Scheme 47).[87]

Scheme 47



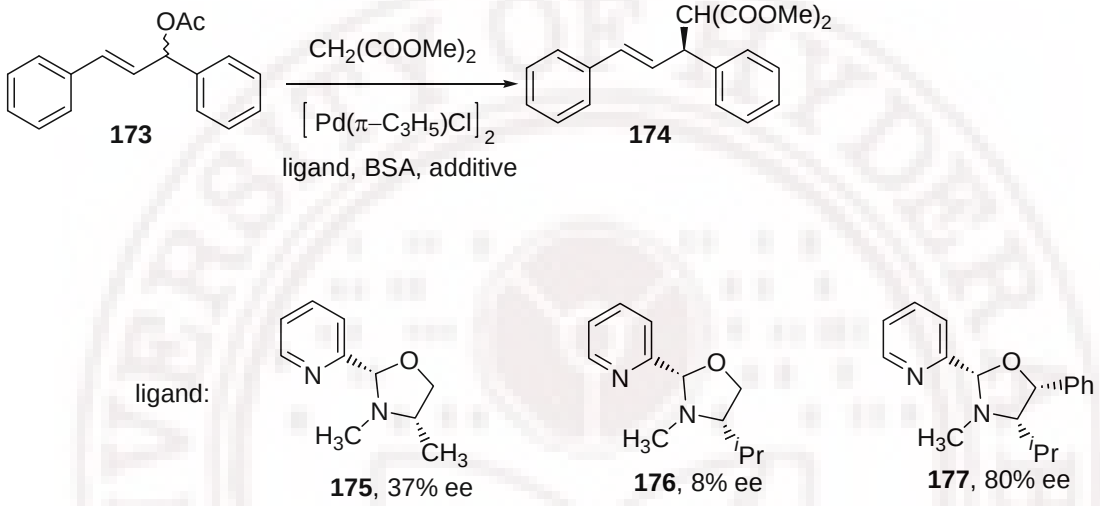
Chiral 1,3-oxazolidine ligands were also used for the enantioselective alkynylation of aldehydes to produce the chiral propargyl alcohols (Scheme 48).[88]

Scheme 48



It has been reported that the chiral pyridinyloxazolidine ligands promote the asymmetric allylic alkylation reaction (Scheme 49).[89]

Scheme 49



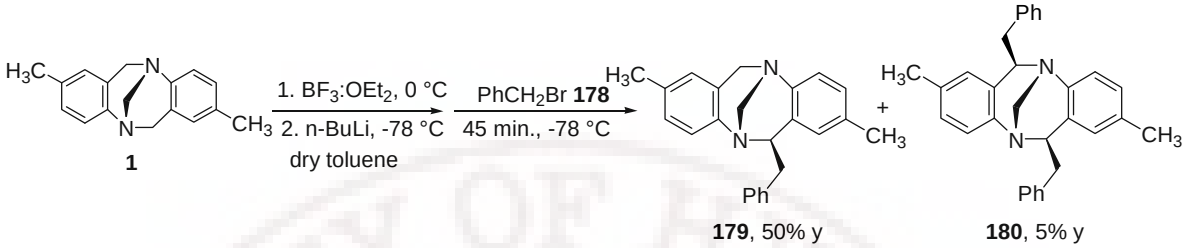
Hence, the chiral oxazolidine **161** obtained in Scheme 45 have potential for further exploitations in asymmetric transformations.

2.2.2.2 Synthesis of α-mono and α,α'-dibenzyl derivatives of chiral Tröger base

We have also examined the reaction of benzyl halides with α-lithiated chiral Tröger base to obtain derivatives for use in asymmetric transformations.

Initially, we have examined the reaction of the α-lithium intermediate of the Tröger base-BF_3 complex with benzyl bromide as electrophile in dry THF. In this reaction, along with the desired monobenzylated product **179**, the dibenzylated derivative **180** was also obtained in 20% yield. We have found that the use of dry toluene instead of THF, gave the monobenzylated Tröger base **179** in 50% yield and the dibenzylated Tröger base **180** in 5% yield (Scheme 50).

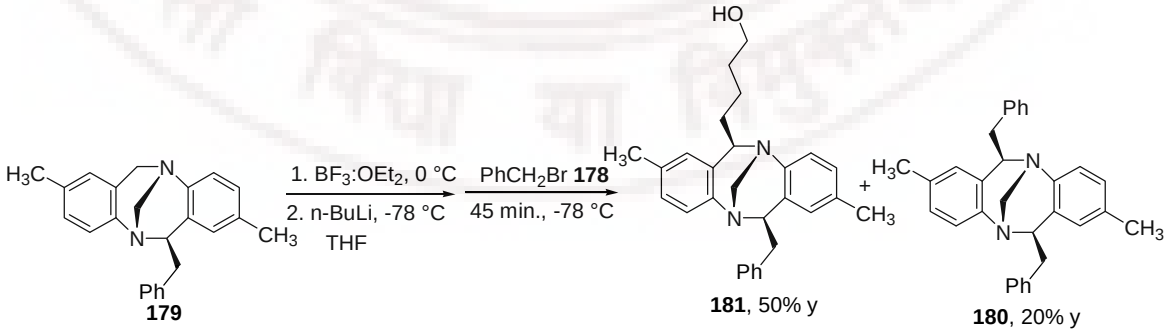
Scheme 50



The stereochemistry of the newly formed chiral centre would most probably be *R* as the electrophile would approach the intermediate anion from the less hindered convex face of the dibenzobicyclo[3.3.1] framework as in the case of formation of **101** (see Scheme 44).[47]

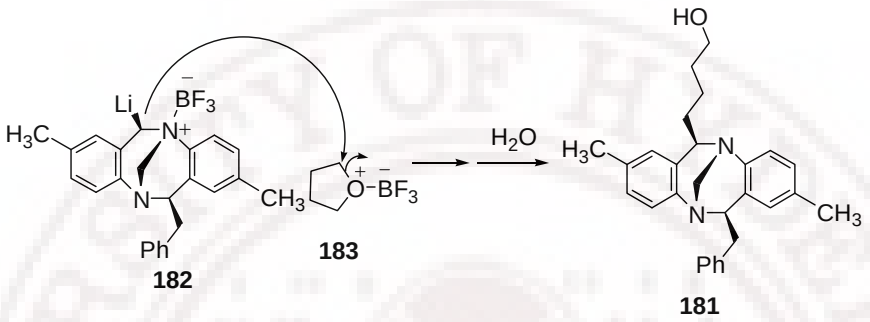
Subsequently, we carried out the reaction of monobenzylated Tröger base **179** with one more equivalent of BF_3:Et_2O, followed by lithiation of benzylic position using n-BuLi at -78 °C. The lithiated species was quenched with benzyl bromide to access the $C_{\alpha,\alpha'}$-dibenzylated Tröger base **180**. Surprisingly, in this reaction, the compound **181** derived from THF was obtained as major product along with the desired dibenzylated derivative **180** (Scheme 51). Fortunately, when the reaction was carried out in dry toluene, the desired dibenzylated **180** was obtained in 50% yield.

Scheme 51



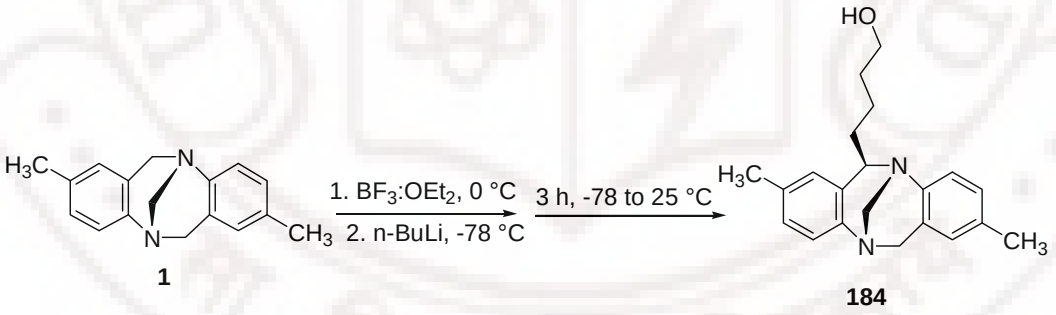
The formation of compound **181** may be due to participation of the THF activated by BF_3 coordination (Scheme 52).

Scheme 52



In order to examine this possibility, we have carried out the reaction of chiral TB **1** with BF_3:OEt_2, followed by treatment with n-BuLi in THF at -78 °C without using benzyl bromide. Indeed, in this reaction, the compound **184** was obtained in 40% yield (Scheme 53).

Scheme 53



2.3 Applications of Tröger base and its derivatives

As outlined in the introductory section, most of the reports on Tröger base derivatives deal with their applications as synthetic receptors. There have been also a few reports on the use of Tröger base as chiral ligand in asymmetric transformations. We have

decided to explore the application of Tröger base derivatives in chiral recognition and in asymmetric transformations. The results are described in the next sections.

2.3.1 Studies on the chiral recognition properties of methoxy Tröger base and its α,α'-diphenylcarbinol derivative towards chiral carboxylic acids

As discussed in the introductory section, the Tröger base scaffold has been used extensively for the construction of molecular receptors. We have undertaken studies on the chiral recognition properties of this unique chiral skeleton. We have observed that the enantiopure **69** and aminoalcohol **158** serve as chiral discriminating agents (CSA) towards certain chiral carboxylic acids.

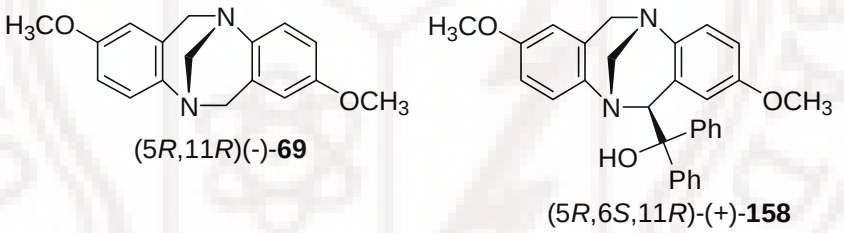


Figure 25

Chiral recognition phenomenon is essential for resolution of racemic mixtures, for the determination of enantiomeric purity of chiral compounds and for screening of chiral catalysts. Chiral carboxylic acids are the structural units of many natural products and drug molecules.[90] The growing use of enantiomerically pure carboxylic acids in synthetic operations has led to the development of fast and reliable methodologies for assessment of enantiomeric purity of chiral carboxylic acids.[91] Several approaches have been developed

for the evaluation of chiral recognition, including spectroscopic, chromatographic and electrochemical techniques. Among all, the NMR spectroscopy has the advantage of easy performance and requires no special equipment apart from the NMR spectrometer. Accordingly, NMR spectroscopy[92] is still widely used for examining the enantiomeric discrimination of amino acids, carboxylic acids, amines and amino alcohols by chiral synthetic receptors. The discrimination occurs when the addition of an optically pure chiral solvating agent reacts or associates with a pair of enantiomers to produce diastereomeric aggregates *via* rapidly reversible equilibria. These diastereomeric aggregates exhibit different shifts in the NMR spectrum. Another advantage of this method is that it also provides the structural and dynamic information of the complex.[93] However, only a few efficient chiral solvating agents are available for carboxylic acids.[94]

We have employed the ^{1}H and ^{31}P NMR spectroscopy methods to study the interaction of chiral ligands (5*R*,11*R)*-**69** and (5*R*,6*S*,11*R)*-**158** with the racemic acid guests **57**, **59**, **64**, **146** and **185**. We have observed that the methine proton signal of the carboxylic acids (except in the case of **57**), appears as a sharp singlet and does not overlap with the signals of any of the protons in the host molecule. Hence, it is an ideal probe for the present studies.

Initially, we recorded the ^{1}H NMR spectrum of (±)-2,3-diphenylsuccinic acid **146** in the presence of the chiral Tröger base **1** and **69**. In this case, the methine proton signal was split into doublet by 9.6 Hz & 12 Hz respectively (Fig. 26). Since the methoxy Tröger base **69** gave better resolution, we continued our study with this amine. The samples for analysis

were prepared by mixing equimolar amounts of the guests and chiral hosts **69** or **158**. The resulting chemical non-equivalences (ΔΔδ) are summarized in Table 7.

Table 7 Chemical shift changes (Δδ) and chemical shift nonequivalence (ΔΔδ)[a] observed in ^{1}H NMR spectra of guest acids in the presence of hosts **69** & **158**

Guests	Observed signal	Δδ (ppm)		ΔΔδ (Hz)	
		69	**158**	**69**	**158**
Mandelic acid, **185**	-CH	-0.13 -0.12 -0.205 -0.217	-0.122 -0.14 –	4 4.8[b]	7.2 –
2,3-Diphenylsuccinic acid, **146**	-CH	-0.08 -0.11	–	12	0
O,O′-Dibenzoyltartaric acid, **64**	*ortho*-CH of phenyl ring	+0.060 +0.008	-0.101 -0.137	21.2	14.4[c]
O,O′-Ditoluoyltartaric acid, **59**	*ortho*-CH of toluoyl ring	+0.001 -0.050	-0.05 0.102	20.8	20.4[c]

[a]All the ^{1}H NMR experiments were performed using 0.2M, 1:1 (host to guest ratio) solution in $CDCl_3$ at 25 °C and 400 MHz spectrometer. [b]In this case host to guest ratio was 2:1. [c]These ΔΔδ values correspond to the splitting observed in methine proton signal.

The methine proton signal of mandelic acid **185** was split into doublet by 4.8 Hz, 7.2 Hz in the presence of the chiral discriminating agents **69** and **158**, respectively with upfield chemical shift. The Δδ, chemical shift differences relative to the original signals in the absence of CSA, are in the range of 0.12-0.22. In the case of 2,3-diphenylsuccinic acid **146**, the methine proton signal was shifted upfield and split by 12 Hz in the presence of **69** (Fig. 26). The Δδ values are in the range of 0.08-0.11. The acid **146** did not show any splitting in the presence of **158**.

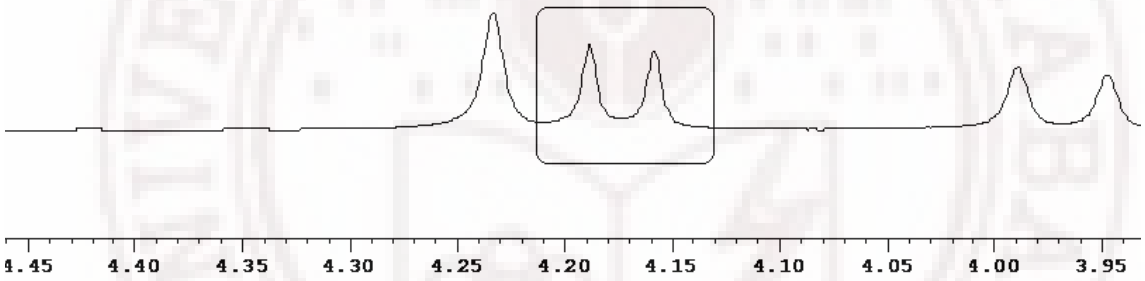


Figure 26 ^{1}H-NMR spectrum of (±)-2,3-diphenylsuccinic acid **146** in the presence of the chiral methoxy Tröger base **69** (1:1 ratio of 0.2 M solution in $CDCl_3$ at 25 °C)

The ee determined from the ^{1}H-NMR spectrum of the sample with 43% ee in the case of (*S*,*S*)-**146** in the presence of **69**, is in good agreement with the ee value estimated by optical rotation (Fig. 27).

The methine proton signal of (*S*)-mandelic acid appeared at lower field than the (*R*)-mandelic acid in the presence of **69** and **158**. In the case of 2,3-diphenylsuccinic acid, the (*R,R*)-enantiomer appeared at lower field than the corresponding (*S,S*)-enantiomer in the

presence of the chiral host **69**. It indicates that the (*S,S*)-enantiomer binds more strongly compared to its antipode with the host **69**. The results were confirmed by recording the ^{1}H NMR spectra of the samples containing non-racemic guest acids (Fig. 27).

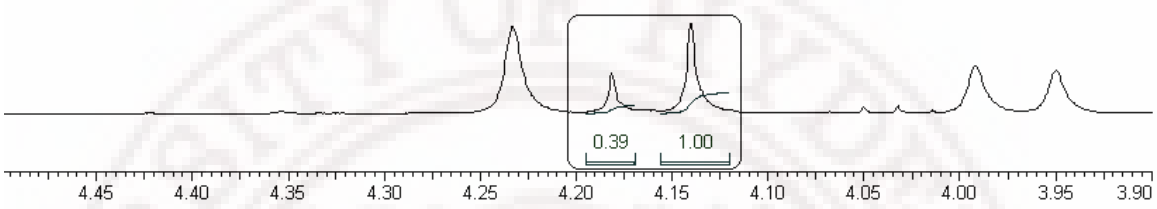


Figure 27 ^{1}H-NMR spectra of 43% ee of (*S*,*S*)-**146** in the presence of **69** (1:1 ratio of 0.2M solution in $CDCl_3$ at 25 °C)

In (±)-dibenzoyltartaric acid and (±)-ditoluoyltartaric acid, non-equivalence was observed for the *ortho*-C-H proton signal of the phenyl ring when **69** was used. The *ortho*-C-H proton appears as a doublet in the ^{1}H NMR spectrum of **64** or **59** in the absence of **69.** It was shifted downfield and split into two doublets by 21.2 Hz (Fig. 28c). The corresponding signal for (±)-ditoluoyltartaric acid was upfield shifted and split by 20.8 Hz in the presence of **69**. The Δδ values are in the range of 0.001-0.008. Whereas, in the presence of the amino alcohol **158**, splitting was observed in the *ortho*-C-H proton as well as the methine proton signal. The signals were shifted upfield and the chemical shift differences (Δδ) are in the range of 0.05-0.137. The methine proton signal of (±)-dibenzoyltartaric acid was split by 14.4 Hz (Fig. 28b) and the corresponding signal for (±)-ditoluoyltartaric acid was split by 20.4 Hz.

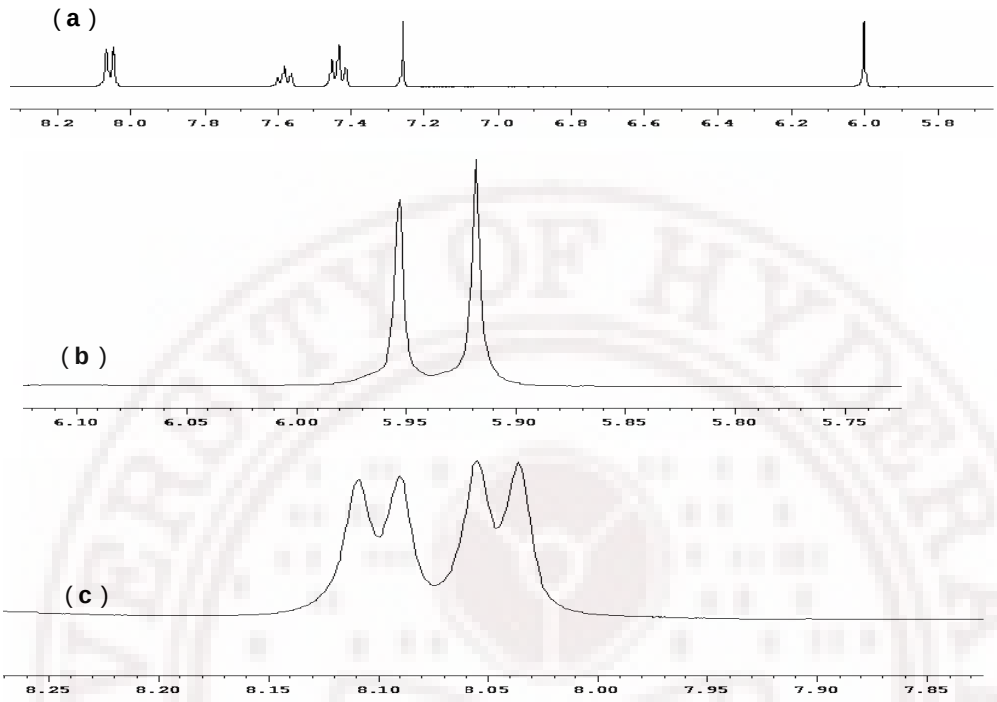


Figure 28 ^{1}H-NMR spectrum of (a) (±)-dibenzoyltartaric acid **64** in the absence of CSA (b) (±)-dibenzoyltartaric acid **64** in the presence of **158** (1:1 ratio of 0.2 M solution in $CDCl_3$ at 25 °C) (c) (±)-dibenzoyltartaric acid **64** in the presence of **69** (1:1 ratio of 0.2 M solution in $CDCl_3$ at 25 °C)

The *ortho*-C-H proton doublet of dibenzoyl-D-tartaric acid and ditoluoyl-L-tartaric acid appeared at lower field in the presence of **69**. The methine proton signal of the dibenzoyl-L-tartaric acid and ditoluoyl-L-tartaric acid appeared at lower field when **158** was used.

It is of interest to note that the chiral cyclic phosphoric acid derived from chiral BINOL were employed as chiral ligands and also catalysts in asymmetric organocatalysis.[95]

Therefore, a relatively inexpensive method for determining their optical purity would be useful. We have employed the chiral methoxy Tröger base **69** and the corresponding α,α'-diphenylcarbinol derivative **158** for ^{31}P NMR analysis of BINOL-phosphoric acid **57**. Generally, BINOL-derived phosphoric acids are sparingly soluble or insoluble in $CDCl_3$. The 1,1′-binaphthyl-2,2′-diylphosphoric acid **57** is insoluble in $CDCl_3$ but it is soluble in the presence of **69** or **158**. In the ^{31}P NMR spectrum of BINOL-phosphoric acid, a singlet appearing at 4.5 ppm (in DMSO-d_6), is split into a doublet in the presence of **69** or **158** (Fig. 29). The resulting chemical anisochronies (ΔΔδ) measured using ^{31}P NMR are summarized in Table 8.

Table 8 Chemical shift nonequivalence (ΔΔδ)[a] observed in ^{31}P NMR spectra of 1,1′-binaphthyl-2,2′-diylphosphoric acid **57** in the presence of hosts **69** & **158**

Ratio of amine/amino alcohol:acid	Observed signal	ΔΔδ (Hz)	
		69	**158**
1:1		39.2	42
1:2	Phosphorous	11.2	36.5
1:4		–	31.7

[a]All the ^{31}P NMR experiments were performed using 0.1 M solution of the host to guest mixture in $CDCl_3$ at 25 °C on 161 MHz spectrometer.

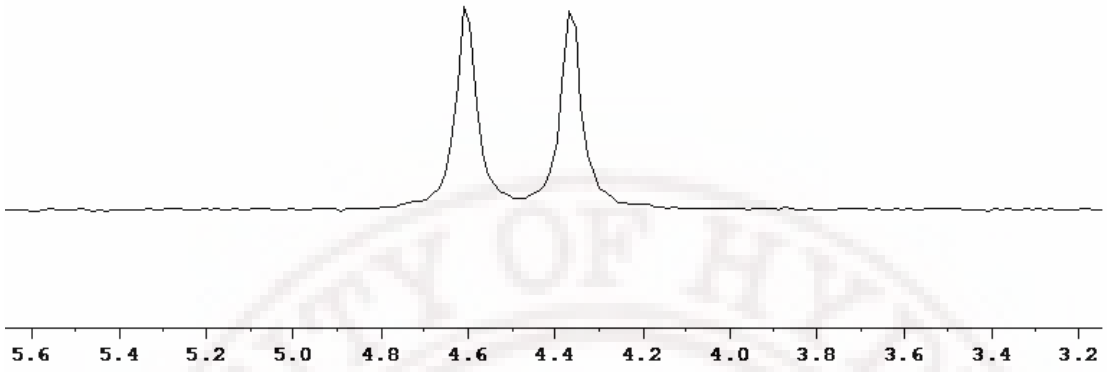
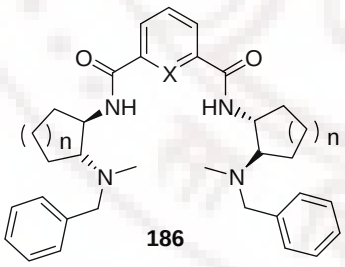


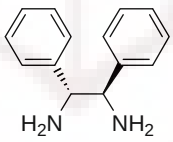
Figure 29 ^{31}P-NMR spectrum of 1,1′-binaphthyl-2,2′-diylphosphoric acid **57** in the presence of chiral methoxy Tröger base **69** (0.1M solution of the host to guest mixture in $CDCl_3$ at 25 °C)

Generally, amines, diamines and amino alcohol derivatives exhibit the chiral recognition towards carboxylic acids (chart 8).[93,96]

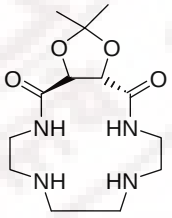
Chart 8



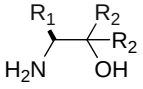
186
X = N or CH
n = 1 or 2
(Ref 97)



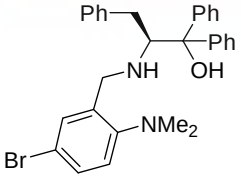
187
(Ref 92)



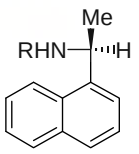
188
(Ref 98)



189
(Ref 96a)



190
(Ref 96a)



R = H **191** or Me **192**
(Ref 92)

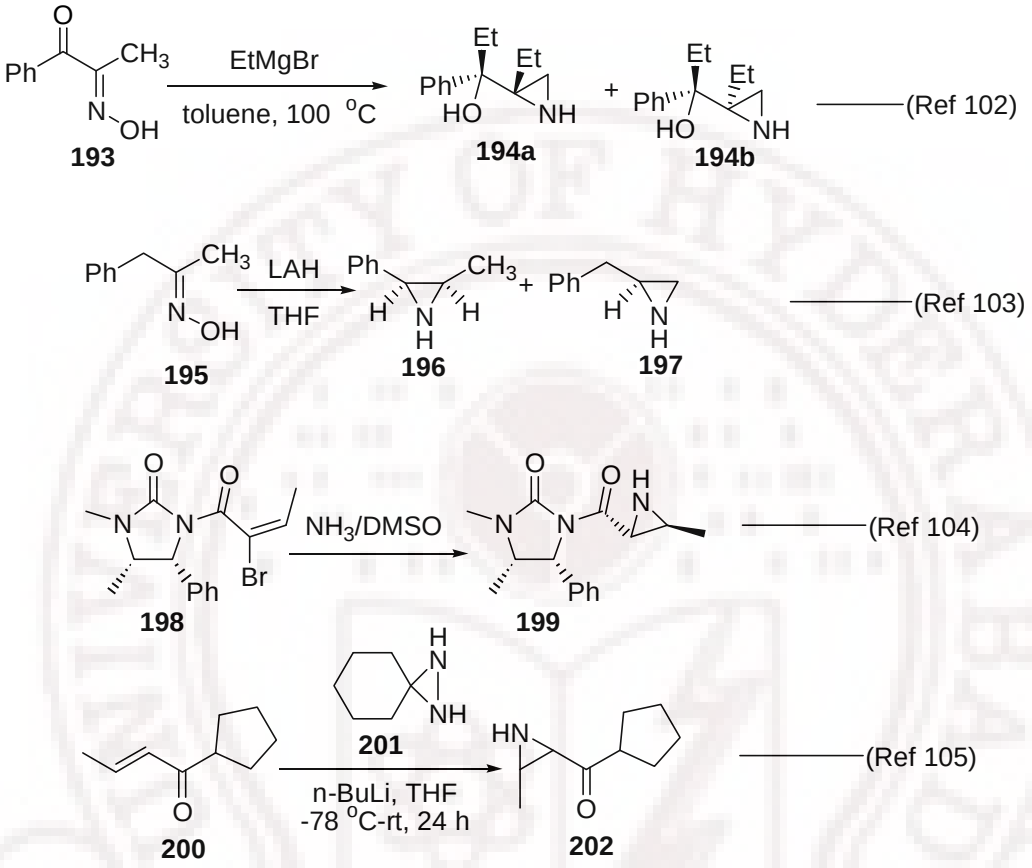
Several of the reported chiral discriminating agents for carboxylic acids are macrocyclic compounds and oligo/poly amine derivatives.[92,96,98] Whereas the readily accessible chiral Tröger base derivatives **69** and **158** are small molecule receptors and provide considerable discrimination. Therefore, these derivatives have significant potential for further exploitation.

2.3.2 Asymmetric aziridination of chalcones promoted by chiral Tröger base and its derivatives

In continuation of our studies on the applications of chiral Tröger base and its derivatives, we have examined the use of these compounds in asymmetric aziridination of chalcones. Aziridines are important building blocks of many biologically active molecules. A number of naturally occurring molecules possessing an aziridine ring have been shown to exhibit potent biological activity, which is intimately associated with the reactivity of the strained heterocycle.[99a]

A variety of methods for the asymmetric synthesis of aziridines have been developed.[100,101] However, most of the methods lead to *N*-substituted aziridines, such as *N*-arenesulfonyl, alkoxycarbonyl or aryl substituted aziridines. Removal of these substituents is carried out under harsh conditions in many cases. A few methods have been developed for the direct preparation of NH-aziridine derivatives (Chart 9).

Chart 9



Nitrogen ylides have potential for use as NH-transfer agents. Ikeda *et al.*[106] reported that the aminimide **203**, prepared *in situ* from *N*,*N*-dimethylhydrazine and oxirane, directly iminate chalcones to give aziridines.

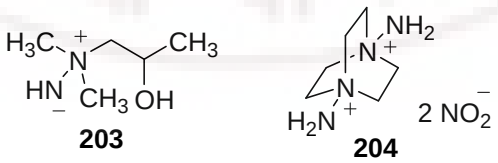
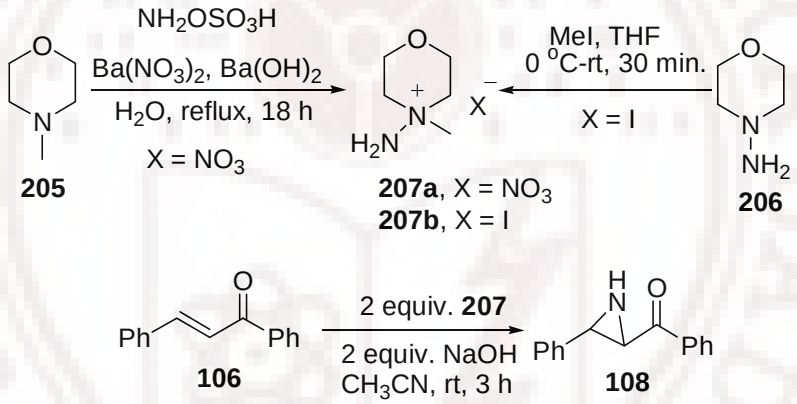


Figure 30

Later, Xu and co-workers[107] reported the direct NH-aziridination of the α,β-unsaturated ketones using the aminimide derived from the hydrazonium nitrate **204**, which in turn prepared from DABCO and hydroxylamine-*O*-sulfonic acid in the presence of barium oxide and barium nitrate.[108]

Recently, Armstrong *et al.*[109] reported a method for the NH-aziridination using aminimides derived from *N*-methylmorpholine **205** (Scheme 54).

Scheme 54

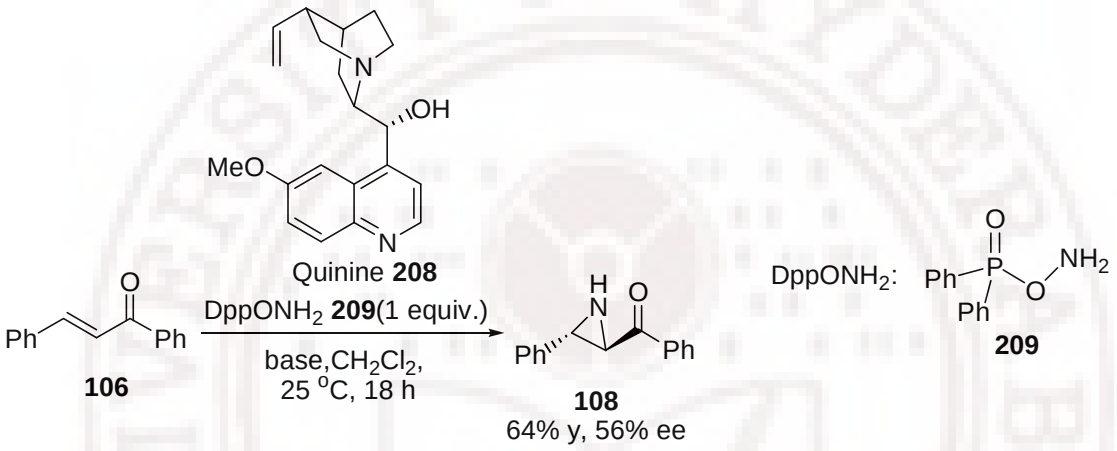


Later, they reported another methodology using *N*-*N* ylides prepared by *in situ* amination of tertiary amines like *N*-methylmorpholine (NMM) and *N*-methylpyrrolidine (NMP).[110]

Shi *et al.*[56] reported an alternative method for the NH-aziridination of chalcones promoted by the hydrazinium salt prepared *in situ* using NMM and *O*-mesitylsufonylhydroxylamine (MSH). Accordingly, these authors have developed the first amine-promoted asymmetric aziridination of chalcone using chiral Tröger base to obtain the corresponding aziridine in 55% ee (see Scheme 29).

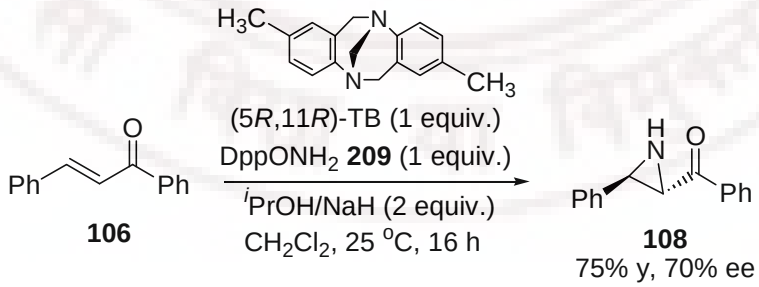
Later, Armstrong *et al.*[110] reported the asymmetric aziridination of chalcone by using the chiral hydrazinium salt derived from quinine **208**. In this case also the aziridine product was obtained with maximum of 56% ee.

Scheme 55



We have examined the reaction of chalcone using the chiral hydrazinium salt prepared from the chiral TB and *O*-(diphenylphosphinyl)hydroxylamine ($DppONH_2$) in the presence of ^{i}PrOH/NaH as base in CH_2Cl_2 solvent. The aziridine was obtained in 75% yield with 70% ee (Scheme 56).

Scheme 56



We have examined the reaction using different bases and various solvents for optimizing the conditions. The results are summarized in Table 9. We have observed that

the reactions using ^{i}PrOH/NaH as base in CH_2Cl_2 gave optimum results (Table 9, entries 1, 9, 10).

Table 9 Asymmetric aziridination of chalcone using different bases and various solvents[a]

Entry	Base	Solvent	% Yield[b]	% ee[c]
1	^{i}PrOH/NaH	CH_2Cl_2	75	70
2	NaOH	CH_2Cl_2	55	35
3	KO^{t}Bu	CH_2Cl_2	70	45
4	^{i}PrOH/NaH	toluene	61	50
5	^{i}PrOH/NaH	CH_3CN	53	38
6	^{i}PrOH/NaH	THF	62	60
7	^{i}PrOH/NaH	DCE	70	44
8[d]	^{i}PrOH/NaH	DCE	65	42
9[e]	^{i}PrOH/NaH	CH_2Cl_2	75	69
10[f]	^{i}PrOH/NaH	CH_2Cl_2	72	70
11[g]	^{i}PrOH/NaH	CH_2Cl_2	71	56

[a]All the reactions were performed using chalcone (0.12 mmol), $DppONH_2$ (0.13 mmol), chiral TB (0.12 mmol) and Base (0.12 mmol) in 2 mL of solvent. [b]Yields are of isolated products. [c]All the ee's reported here are based on HPLC analysis using Chiralpak-AD-H column. [d]In this case the reaction was carried out at 90 °C for 4 h. [e]In this case the 2 equiv. of chiral TB was used. [f]The reaction was carried out using 1 mL of solvent. [g]In this case 0.5 equiv. of chiral TB was used.

We have also examined the aziridination reaction of chalcone using various chiral Tröger base derivatives **101**, **69**, **158**, **179-181**, **184** using the ^{i}PrOH/NaH as base in CH_2Cl_2 solvent. In all cases, the aziridine was obtained in moderate to good enantioselectivity. The

results are presented in Table 10. We have observed that the α,α'-disubstituted TB derivatives did not promote the reaction. Presumably, more hindered N-atoms of the disubstituted TB derivatives have difficulty in giving the reactive hydrazinium salt intermediates.

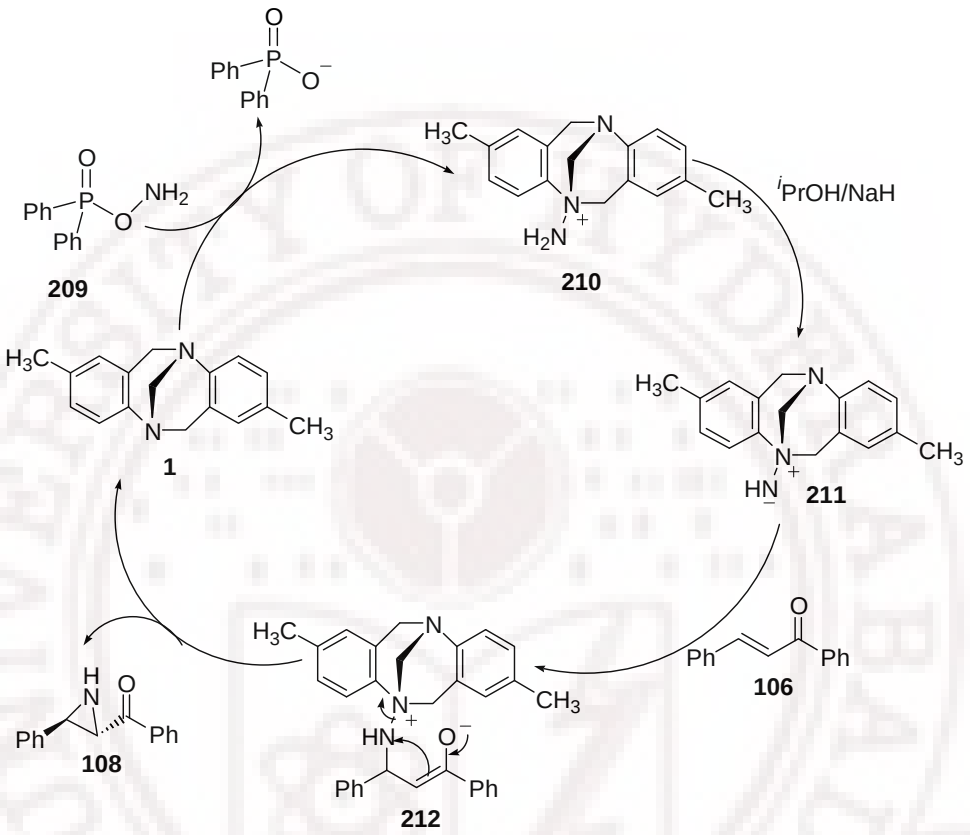
Table 10 Asymmetric aziridination of chalcone promoted by chiral TB derivatives[a]

Entry	Chiral TB derivative	% Yield[b]	% ee[c]
1	**101**	66	65
2	**179**	72	51
3	**180**	-	-
4	**184**	68	44
5	**181**	-	-
6	**69**	75	68
7	**158**	70	62

[a]All the reactions were performed using chalcone (0.12 mmol), $DppONH_2$ (0.13 mmol), chiral TB analog (0.13 mmol) and $^{i}PrOH$/NaOH (0.25 mmol) in CH_2Cl_2 (2 mL). [b]Yields are of isolated products. [c]All the ee's reported here are based on HPLC analysis using Chiralpak-AD-H column.

A plausible mechanistic cycle for the asymmetric aziridination of chalcone is depicted in Scheme 57.

Scheme 57



It is of interest to point out that the 70% enantioselectivity observed (entry 1, Table 9) is the maximum enantioselectivity reported so far for an amine-promoted NH-aziridination of chalcone. Systematic investigations on synthetic applications of the chiral hydrazinium salts generated *in situ* using Tröger base derivatives should lead to fruitful results.

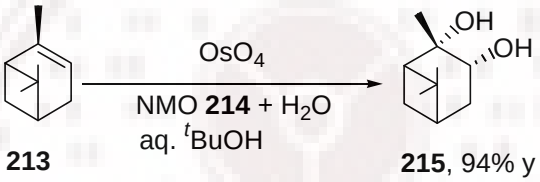
2.3.3 Ligand assisted osmium catalyzed dihydroxylation of *trans*-stilbenes using racemic Tröger base

We became interested in studying the ability of Tröger base to assist the osmate catalyzed dihydroxylation of alkenes with two objectives (i) to prepare racemic diols for

use in HPLC analysis of samples obtained in the mechanistic studies on the Sharpless asymmetric dihydroxylation reaction and (ii) to examine the efficacy of chiral Tröger base in osmate catalyzed asymmetric dihydroxylation reaction with alkenes.

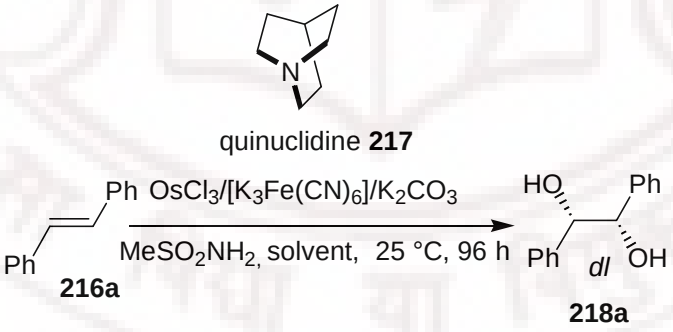
The racemic 1,2-diols can be readily prepared by osmate catalyzed dihydroxylation using NMO as stoichiometric oxidant (Scheme 58).[111]

Scheme 58



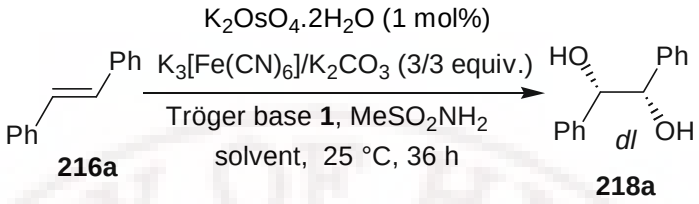
It has been reported that quinuclidine **217** assists in the osmium catalyzed dihydroxylation of *trans*-stilbene (Scheme 59).[112]

Scheme 59



We have observed that the racemic Tröger base promotes the osmium catalyzed dihydroxylation of *trans*-stilbenes (Scheme 60). The conditions were optimized to easily access the racemic *syn*-1,2-diols (Table 11).

Scheme 60



The reaction was also carried out using other solvent systems with different ligand molar ratios for optimization of the reaction conditions. The results are summarized in Table 11.

Table 11 Optimization of dihydroxylation of *trans*-stilbene **216a** using racemic Tröger base **1** as ligand at ambient conditions[a]

Entry	Solvent system[b]	Ligand **1** (mol %)	% Yield[c] **218a**
1	^{t}BuOH/H_2O	10	58
2	^{t}BuOH/H_2O/toluene	10	72
3	^{t}BuOH/H_2O/toluene	5	66
4	^{t}BuOH/H_2O/toluene	5	83
5	^{t}BuOH/H_2O/toluene	10	92
6	^{t}BuOH/H_2O/toluene	20	93

[a]All the reactions were carried out using *trans*-stilbene (2 mmol), K_2CO_3 (6 mmol), $K_3[Fe(CN)_6]$ (6 mmol), $K_2OsO_4.2H_2O$ (1 mol%) and methanesulfonamide (2 mmol). [b]In entry 1, ^{t}BuOH (20 mL)/H_2O (20 mL), in entries 2, 3 ^{t}BuOH (20 mL)/H_2O (20 mL)/toluene (20 mL) and in entries 4, 5, 6, ^{t}BuOH (10 mL)/H_2O (10 mL)/toluene (10 mL) used as solvent system. The reaction mixture was stirred at 25 °C for 36 h. [c]Yields are for isolated products.

The acceleration effect of Tröger base has been also studied under different conditions. The results are summarized in Table 12.

Table 12 Acceleration of dihydroxylation of *trans*-stilbene **216a** by Tröger base [a]

Entry	Additive	Time	% Yield[b] **218a**
1	None	24 h	10
2	Tröger base	24 h	55
3	Tröger base	36 h	66
4	Tröger base and methanesulfonamide	36 h	92

[a]All the reactions were carried out using *trans*-stilbene (1 mmol), K_2CO_3 (3 mmol), $K_3[Fe(CN)_6]$ (3 mmol), $K_2OsO_4.2H_2O$ (1 mol%), Tröger base (10 mol%) in ^tBuOH (5 mL)/H_2O (5 mL)/toluene (5 mL) solvent system. [b]Yields are for isolated products.

The reaction was also carried out with various stilbenes. The results are summarized in Table 13. The starting substituted stilbenes were prepared from the corresponding aldehydes by using McMurry coupling in good yields (67-80%).[113] The reaction was also carried out with 2-phenylpropene **216h** and styrene **218i**. The corresponding diols were obtained in good yields **(**Scheme 61, Table 13**)**.

Scheme 61 Racemic dihydroxylation of *trans*-olefins facilitated by Tröger base **1**

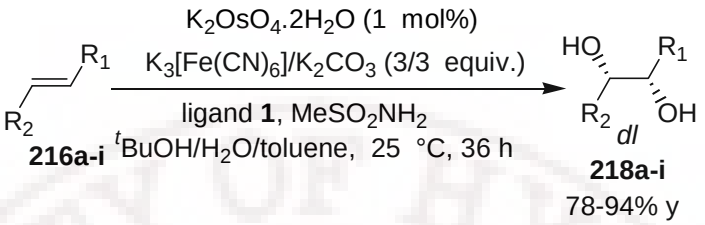


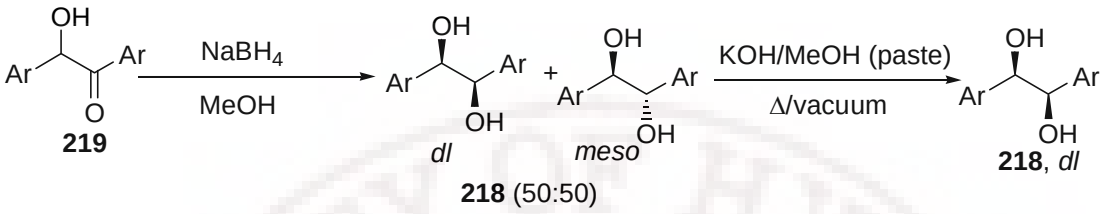
Table 13 Racemic dihydroxylation of various olefins[a]

Entry	Olefin	Diol yield (%)[b]
1	**216b**, R_1, R_2 = 4-MePh	**218b**, 90
2	**216c**, R_1, R_2 = 4-ClPh	**218c**, 94
3	**216d**, R_1, R_2 = 4-MeOPh	**218d**, 78
4	**216e**, R_1, R_2 = 4-CF_3Ph	**218e**, 90
5	**216f**, R_1, R_2 = 3-MeOPh	**218f**, 89
6	**216g**, R_1, R_2 = 2-BrPh	**218g**, 90
7	**216h**, R_1 = Ph, R_2 = Me	**218h**, 94
8	**216i**, R_1 = Ph, R_2 = H	**218i**, 80

[a]All the reactions were carried out using olefin (2 mmol), K_2CO_3 (6 mmol), $K_3[Fe(CN)_6]$ (6 mmol), $K_2OsO_4.2H_2O$ (1 mol%), Tröger base (10 mol%), methanesulfonamide (2 mmol) and ^{t}BuOH (10 mL)/H_2O (10 mL)/toluene (10 mL) was used as solvent system. [b]Yields are for isolated products.

The racemic 1,2-diarylethane-1,2-diols were previously prepared by a circuitous method (Scheme 62).[114]

Scheme 62



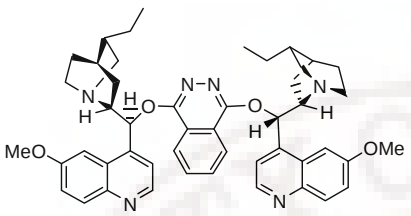
The method using the racemic Tröger base assisted osmate catalyzed dihydroxylation described here provides an alternative procedure for accessing such diols.

2.3.4 Efforts toward asymmetric dihydroxylation of *trans*-stilbene using chiral Tröger base

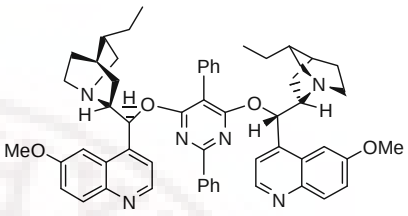
Since, the racemic Tröger base was found to assist the osmate catalyzed dihydroxylation of olefins, we have decided to examine the efficacy of chiral Tröger base in asymmetric version of this reaction. A brief review of reports on asymmetric dihydroxylation will be helpful for the discussion.

Since the pioneering studies on catalytic asymmetric dihydroxylation by Sharpless and co-workers,[115,116] most of the new ligands advanced for this catalytic asymmetric transformation are based on cinchona alkaloids. Several second generation ligands with C_2-symmetry were developed by connecting two dihydroquinine or dihydroquinidine units using different linkers (Chart 10).[115,116]

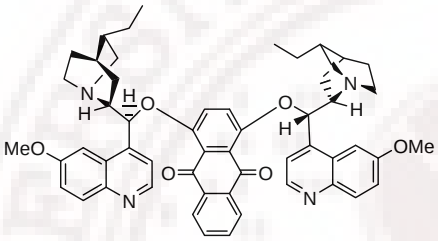
Chart 10



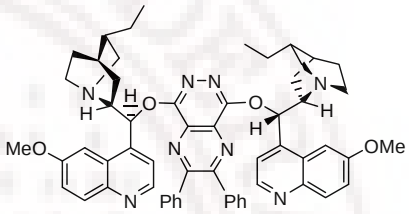
PHAL linker **220**



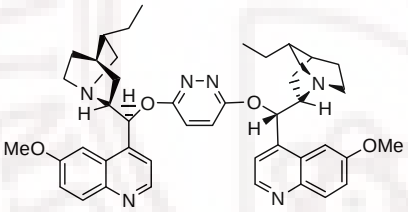
PYR linker **221**



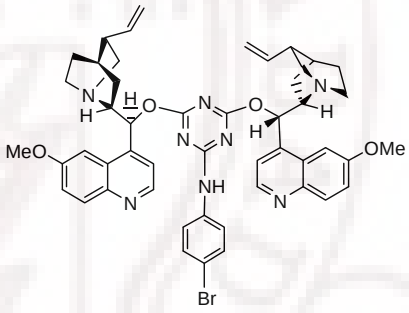
AQN linker **222**



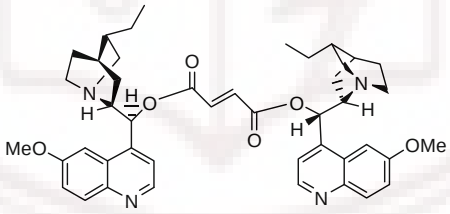
DPP linker **223**



Pyrazine linker **224**



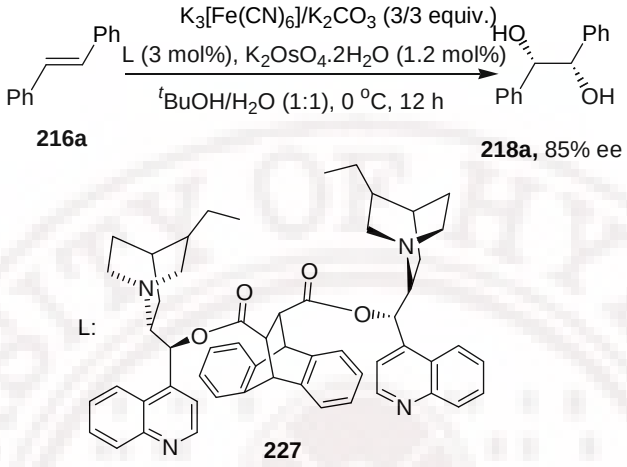
TRY linker **225**



Fumarate linker **226**

It has been reported from our laboratory that the ligand **227** derived from the dihydrocinchonine and the chiral C_2-symmetric linker 9,10-dihydro-9,10-ethanoanthracene-11,12-dicarboxylic acid also gives good enantioselctivity in the AD reaction (Scheme 63).[117]

Scheme 63

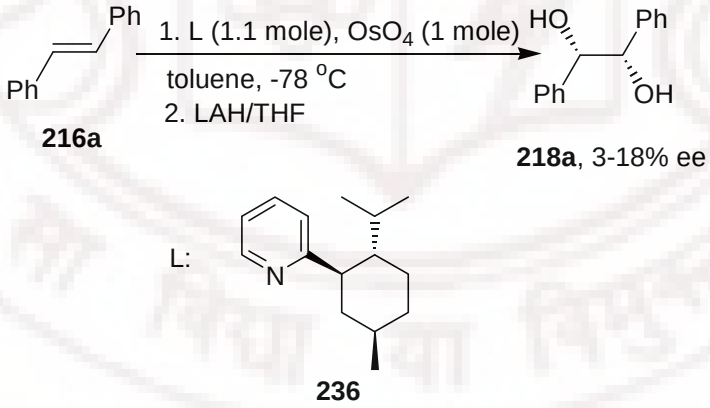


216a **218a,** 85% ee

227

Sharpless *et al.*[118] synthesized the chiral ligand **236** containing pyridine moiety and examined the AD reaction of olefins using OsO_4 under stoichiometric conditions. In this case, only poor enantioselectivity was observed (3-18% ee) (Scheme 64).

Scheme 64



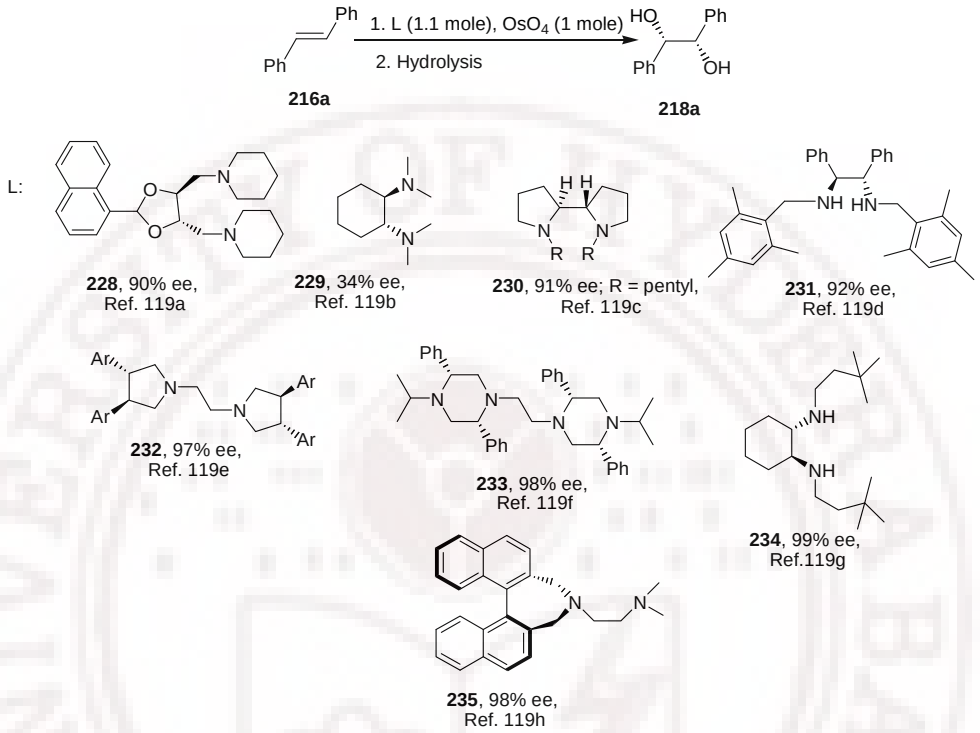
216a

218a, 3-18% ee

236

Subsequently, several amine ligands were used in stoichiometric quantities asymmetric dihydroxylation reaction (Scheme 65).[119] The diols were obtained with good to excellent enantioselectivities in these cases.

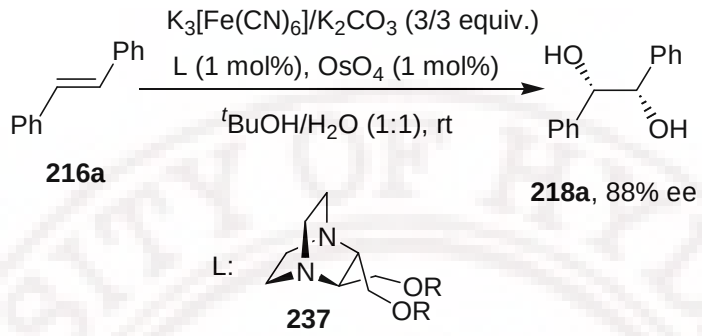
Scheme 65



Though, the cinchona alkaloid derivatives give excellent ee's in asymmetric dihydroxylation reactions, cost considerations and requirement of alkaloid derivatives led the scientists to look for other chiral ligands. Kokubo *et al.*[120] reported the use of bovine serum albumin (BSA)-2-phenylpropane-1,2-diolatodioxo-osmium(VI) complex. The AD reaction of α-methylstyrene using this reagent gave the corresponding diol in 68% ee employing the *tert*-butyl hydroperoxide as co-oxidant at 25 °C.

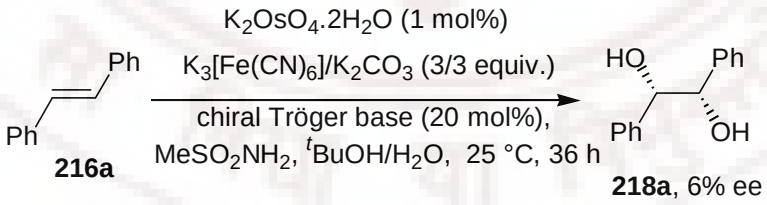
Later, it was reported that the chiral C_2-symmetric DABCO derivative **237** gives 88% ee in OsO_4 catalyzed AD reaction (Scheme 66).[121]

Scheme 66

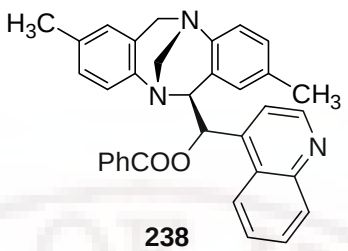


In continuation of the studies on the synthesis and applications of chiral Tröger base **1**, we carried out the dihydroxylation of *trans*-stilbene **216a** using $K_2OsO_4.2H_2O$ as catalytic oxidant, $K_3[Fe(CN)_6]$ as stochiometric oxidant and chiral Tröger base as accelerating ligand in the presence of K_2CO_3 and methanesulfonamide in $^tBuOH/H_2O$ solvent system. Indeed, the dihydroxylation of *trans*-stilbene was facilitated by Tröger base and the corresponding *syn*-1,2-diol **218a** was obtained in 92% yield but only with poor enantioselectivity (6% ee) (Scheme 67).

Scheme 67



It appears that in order to realize good enantioselectivity in catalytic asymmetric dihydroxylation, the ligand should be structurally similar to the cinchona derivative. Perhaps, the chiral skeleton **238** (Fig. 31) might give the better results.

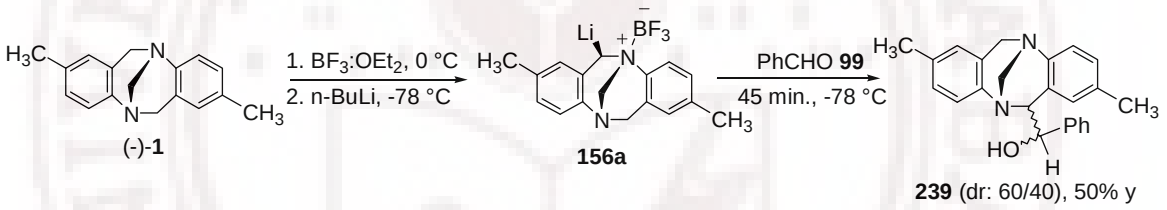


238

Figure 31

Accordingly, we have attempted the preparation of the model compound **239** by following the α-alkylation protocol (Scheme 68).

Scheme 68



Unfortunately, the corresponding α-phenylcarbinol was obtained only as a mixture of diastereomers (dr: 60/40). Further systematic efforts on the synthesis of enantiopure derivatives of the type **238** should give fruitful results.

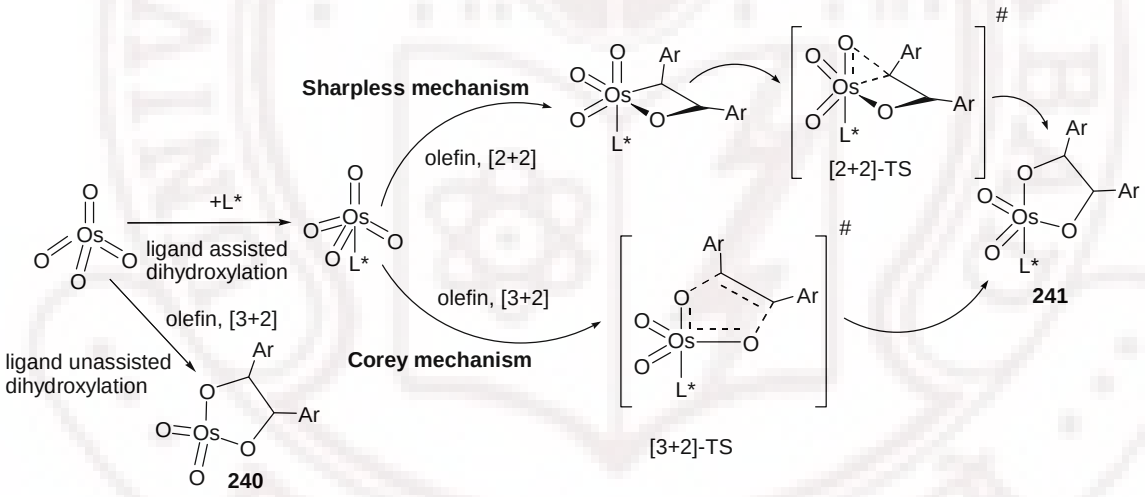
2.3.5 Studies on the mechanism of catalytic asymmetric dihydroxylation of substituted *trans*-stilbene derivatives

The Sharpless catalytic asymmetric dihydroxylation of olefins using OsO_4 and cinchona alkaloid derivatives is a very useful synthetic transformation.[115] Though, the stereochemical outcome of the AD reaction can be readily predicted,[115a] the mechanism of this useful reaction is not clearly understood.[122] The mechanism of the AD reaction has

been a subject of debate for a number of years. The controversy is mainly concerned with two aspects of the alkene addition step in the AD process. (i) The exact mechanism of the OsO_4 addition and (ii) the origin of the enantioselectivity in the chiral amine accelerated OsO_4 addition. A brief review of the mechanistic proposals and evidences will be helpful for the discussion.

Most of the mechanistic proposals advanced for this reaction are based on two basic themes: a concerted [3+2] cycloaddition and a stepwise process involving a [2+2]-like insertion with subsequent rearrangement (Scheme 69).

Scheme 69



The [3+2] mechanism was suggested for the addition of OsO_4 to an alkene by Boseken as early as in 1922,[123] and was further refined by Criegee[124] during his seminal investigation of the ligand accelerated OsO_4 addition. Their proposal is the concerted [3+2] mechanism involving direct oxygen attack at the unsaturation center leading to the cyclic Os(VI) ester intermediate. Later, this mechanism has been refined by Corey (Scheme 69).[125]

Sharpless *et al.*[126,127a] suggested a stepwise mechanism involving a [2+2]-like addition of the olefin to an Os-O bond, leading to a four membered osmaoxetane intermediate (Scheme 69). This intermediate is then considered to rearrange in a subsequent rate determining step to a five membered cyclic ester complex *i.e.* osmium(VI) glycolate complex. In this mechanism, the ligand acceleration effect which is so essential for the successful outcome of the AD, originates from ligand coordination to the osmaoxetane intermediate which is then more likely to rearrange to the osmium(VI) glycolate complex. Sharpless and co-workers[126] proposed this stepwise mechanism, which has its origin in their studies on general oxidation characteristics of oxo transition metal complexes of basic ligands (Scheme 69).

Evidence has been put forward in support of both the mechanisms. In 1982, Schroder and Constable[128] claimed the detection of the four membered ring intermediates **242a** and **242b** by NMR studies in support of the stepwise mechanism. However, Casey[129] showed that the structure detected by Schroder and Constable in NMR studies were not the intermediate **242a** or **242b** but the dimeric species **243a-d** (Fig. 32).

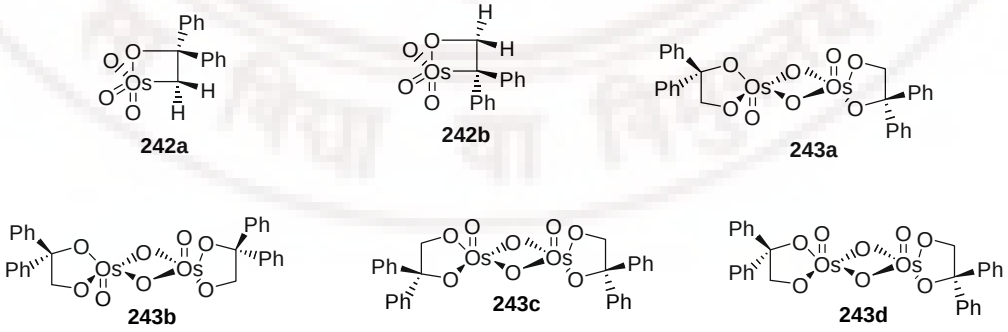


Figure 32

Corey *et al.*[119d] reported high stereoselectivity in the stoichiometric oxidation of alkenes by osmium tetroxide-diamine complexes. They rationalized their results invoking a transition state involving the [3+2] cycloaddition model, since the [2+2] cycloaddition pathway would involve prohibitive steric repulsions around a hexacoordinated octahedral osmium. According to their view, in the transition state for cycloaddition, geometry of the ligand approaches a C_2-symmetric structure. Also, they proposed that the coordination of the amine moiety with OsO_4 would make it behave like a 1,3-dipole with two different types of oxygen atoms, namely, electron rich axial (neucleophilic) oxygen (due to electron donation from N to σ* of the trans Os-O bond) and an equatorial (electrophilic) oxygen atom. This model, according to Corey *et al.*[119d] leads to an unambiguous prediction of absolute enantioselectivity.

Despite considerable efforts, it has been proven difficult to distinguish between these two mechanisms, partly because the [3+2] and [2+2] pathways are kinetically indistinguishable. The [2+2] mechanism has also received support from theoretical studies.[127b] However, later calculations on the different transition states using intrinsic coordinates (IRC) with DFT calculation favors the [3+2] mechanism. The [3+2] path way has a early transition state and a much smaller activation barrier. [120f,120g,130,131] Whereas in [2+2] cycloaddition reactions, both the base free and base assisted pathways involve large activation barriers (above 39 kcal/mol) and display similar energy profiles as per these recent calculations.

A classical method available for studying the organic reaction mechanisms is the determination of the linear free-energy relationships (LFER). The use of electronic perturbation as a probe to elucidate mechanistic details has resulted in the development of two empirical parameters, a substituent constant σ and the reaction constant ρ. These parameters developed by Hammett can be used to estimate the influence of different substituents (at *meta*- and *para*- positions of the substrate) on kinetic and thermodynamic phenamena.[132]

The plot of the Hammett equation is typically seen as being linear, with either a positive or negative slope correlating to the value of ρ. However, non-linear Hammett plots are normally seen when there is change in reaction mechanism or in the rate of the reaction or change in the rate-determining step due to change in substrate electronic properties. Failure to obey a LFER based on empirical substituent parameters σ has been reported for several different type of reactions. For example, the hydrolysis of phenyl substituted ethyl benzoate esters[133] and the solvolysis of 3-aryl-2-butylbrosylates[134] are well known examples of reactions that exhibit non-linear Hammett correlations caused by change in mechanism.

The concerted [3+2] pathway involving reaction of the amine-OsO_4 complex at the axial oxygen and one equatorial oxygen atoms should resemble a 1,3-dipolar cycloaddition.[135,136] The most unusual type of dipolar addition, occurs when HOMO and LUMOs of both dipole and dipolarophile are of roughly equal energy. Any type of

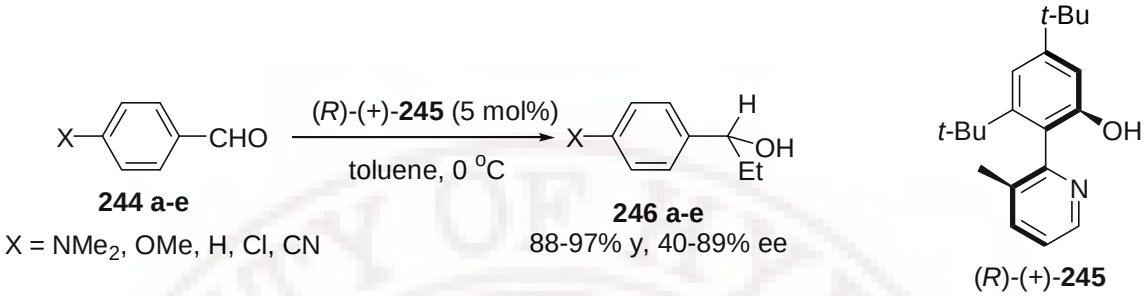
electron-donating or electron-withdrawing substituent on either reactant accelerates the reaction. Accordingly, 1,3-dipolar addition reaction exhibit non-linear Hammett plots.

In 1997, however, Sharpless *et al.*[137,138] reported somewhat ambiguous interpretation of their results. Whereas, the results on the Hammett correlation of the rates of reactions involving substituted amines and substituted olefins, non-linear Hammett plots were interpreted considering the changeover of the mechanisms,[137] the results of experimental and theoretical kinetic isotopic effect (^{13}C and ^{2}H) observed in the reaction with ^{t}butylethylene were interpreted to support a limiting [3+2] cycloaddition.[138]

More recently, AD reactions of a series of substituted styrenes were studied and a concave- type Hammett plot was interpreted on the basis of a change in the mechanism of the hydrolysis of the osmate ester intermediate going from electron-donating to electron-withdrawing substituents.[139] The effect of the size of substituents on the regioselectivity of Sharpless AD reactions has also been reported.[140]

Hammett correlation studies have been reported for the variation of enantioselectivity with the reactivity in certain other reactions. For example, in asymmetric diethylzinc addition to substituted aromatic aldehydes **244a**-**e**, higher enantioselectivity was realized for more electrophilic aldehydes containing electron withdrawing substituents and a linear Hammett plot [Log (e_r) vs σ] was obtained.[141]

Scheme 70



We decided to investigate the mechanism of the AD reaction by Hammett correlation studies of variation in enantioselectivities with substituted *trans*-stilbene derivatives.

Initially, we studied the substituent effects on the mechanism of the AD reaction with different *trans*-stilbenes (**216a-d**) using the excellent ligand[142] $(DHQD)_2$-PHAL **220** (Scheme 71). This ligand gives the diols (**218a-d**) with very high enantioselectivities in the case of electron donating as well as electron withdrawing substituents. The results are summarized in the Table 14.

Scheme 71 Asymmetric dihydroxylation of 4-substituted *trans*-stilbenes using ligand **220**

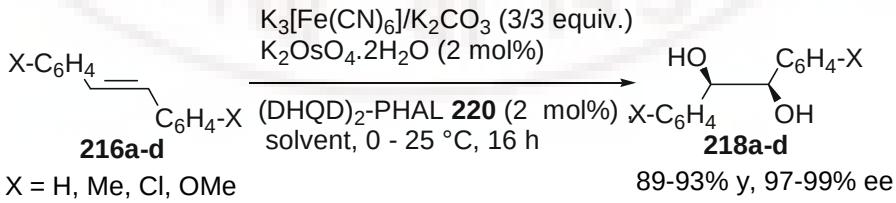


Table 14 Asymmetric dihydroxylation of *trans*-stilbenes using $(DHQD)_2$-PHAL **220** as ligand[a, b, c]

Entry	Product	% ee [d]	% Yield[e]
1	**218d**	97	93
2	**218b**	>98	95
3	**218a**	99	90
4	**218c**	99	89

[a]All the reactions were carried out using *trans*-stilbene (1 mmol). [b]In each case 2 mol% of potassium osmate and 2 mol% of ligand were used. [c]All the experiments were carried out using ^{t}BuOH (5 mL) /H_2O (5 mL) at 25 °C for 16 h. [d]All the enantiomeric purities were based on HPLC analysis. [e]Yields are of isolated products.

Clearly, the ligand $(DHQD)_2$-PHAL **220** leads to the saturation point (very high) of enantioselectivities. Previously, Sharpless *et al.*[119] reported that the corresponding cinchonine derivatives gave substantially lower enantioselectivities under stoichiometric conditions but these authors did not report the % ee of the products. Accordingly, we have chosen the 9-*O*-acetyldihydrocinchonidine **247** (Fig. 33) as the chiral ligand (Scheme 72, Table 15) for our studies.

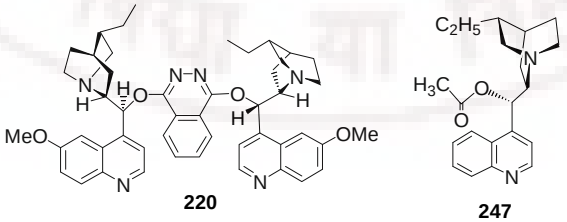


Figure 33

Scheme 72 Asymmetric dihydroxylation of *trans*-stilbene using ligand **247**

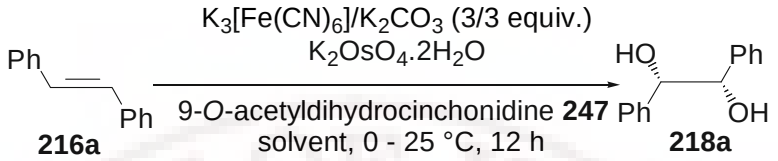


Table 15 Asymmetric dihydroxylation of *trans*-stilbene[a, b, c, d]

Entry	$K_2OsO_4.2H_2O$ mol%	Ligand **247** mol%	Diol-**218a** % ee[e]	% Yield[f]
1	1.2	3	(1*S*,2*S*),74	75
2	2.0	5	(1*S*,2*S*),82	82
3	2.8	7	(1*S*,2*S*),82	83
4	2.0	5	(1*S*,2*S*),91	91
5	2.0	5	(1*S*,2*S*),38	80

[a]In entries 1-5, *trans*-stilbene (1 mmol) was used. [b]In entries 1-3, the experiments were carried out at 0 °C for 12 h and in entries 4,5 the experiments were carried out at 25 °C for 12 h. [c]A mixture of ^{t}BuOH (15 mL) and H_2O (15 mL) was used as solvent in entries 1-4. [d]In entry 5, a mixture of ^{t}BuOH (70 mL) and H_2O (35 mL) was used as solvent. [e]ee based on $[\alpha]_D^{25}$ = - 94.5 (c 0.998, EtOH), (1*S*,2*S*)-(-)-diphenyl-1,2-ethane-1,2-diol[143] and HPLC analysis. [f]Yields are of isolated products.

We first examined the dihydroxylation of *trans*-stilbene under various conditions (Scheme 72). It was observed that by using 5 mol% of **247** along with 2 mol% of $K_2OsO_2(OH)_4$, the selectivity was better (91% ee, entry 4, Table 15) when the reaction was carried out at 25 °C. The use of more amounts of solvent led to lower selectivity (entry 5, Table 15), indicating that the ligand unassisted (direct dihydroxylation) addition of OsO_4 to the olefin may take place to a greater extent under these conditions. Previously, Sharpless *et al.*[137] noted that the solubility of substituted stilbenes in the

^{t}BuOH/H_2O solvent system is poor.[137] We have also encountered such difficulties during the present studies. To increase the solubility of the substituted stilbenes, we ran these reactions using toluene/^{t}BuOH/H_2O solvent system and increased the quantities of the solvent compared to those used in synthetic asymmetric dihydroxylation reactions. We have observed that the diols were obtained in 64-90% ee at 25 °C (Table 16).

Scheme 73 Asymmetric dihydroxylation of 4-substituted *trans*-stilbenes using ligand **247**

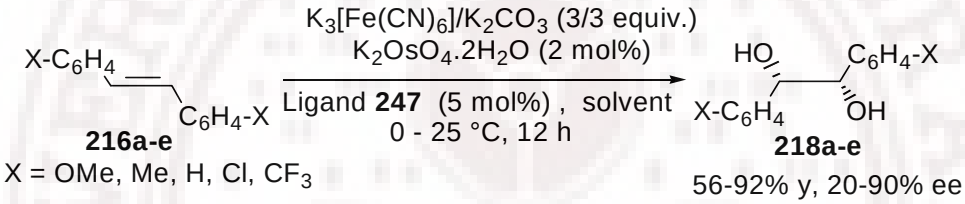


Table 16 Asymmetric dihydroxylation of 4-substituted *trans*-stilbenes using 9-*O*-acetyldihydrocinchonidine **247** as chiral ligand in toluene/^{t}BuOH/H_2O solvent system[a, b, c]

Entry	Olefin (X =)	Product	% Yield[e]	% ee[d]	e_r[f]
1	OMe, **216d**	**218d**	80	64	4.55
2	Me, **216b**	**218b**	76	66	4.88
3	H, **216a**	**218a**	92	90	19.0
4	Cl, **216c**	**218c**	85	76	7.33
5	CF_3, **216e**	**218e**	79	76	7.33

[a]In all the experiments olefin (1 mmol) was used. [b]In each case 2 mol% of potassium osmate and 5 mol% of ligand were used. [c]All the experiments were carried out at 25 °C for 12 h. [d]The enantiomeric excesses were based on HPLC analysis. [e]Yields are for isolated products. [f]e_r = enantiomeric ratio {(1*S*,2*S*)/(1*R*,2*R*)}.

The reactions were also carried out in acetone/^{t}BuOH/H_2O and THF/^{t}BuOH/H_2O solvent systems to examine the ee trends in different solvents. The corresponding diols were obtained in 26-56% ee using the reactions in acetone/^{t}BuOH/H_2O (Table 17).

Lower ee's (20-82%) were realized when the dihydroxylations were carried out using the THF/^{t}BuOH/H_2O solvent system (Table 18). It is of interest to note that use of the *tert*-butyl methyl ether/H_2O solvent system gave a lower ee in the asymmetric dihydroxylation of allyl bromide.[115]

Table 17 Asymmetric dihydroxylation of 4-substituted *trans*-stilbenes using 9-*O*-acetyldihydrocinchonidine **247** as chiral ligand in acetone/^{t}BuOH/H_2O solvent system[a, b, c]

Entry	Olefin (X =)	Product	% Yield[e]	% ee[d]	e_r[f]
1	OMe, **216d**	**218d**	65	40	2.33
2	Me, **216b**	**218b**	60	40	2.33
3	H, **216a**	**218a**	85	56	3.54
4	Cl, **216c**	**218c**	62	52	3.17
5	CF_3, **216e**	**218e**	56	26	1.70

[a]In all the experiments olefin (1 mmol) was used. [b]In each case 2 mol% of potassium osmate and 5 mol% of ligand were used. [c]All the experiments were carried out at 25 °C for 12 h. [d]The enantiomeric excesses were based on HPLC analysis. [e]Yields are for isolated products. [f]e_r = enantiomeric ratio {(1*S*,2*S*)/(1*R*,2*R*)}.

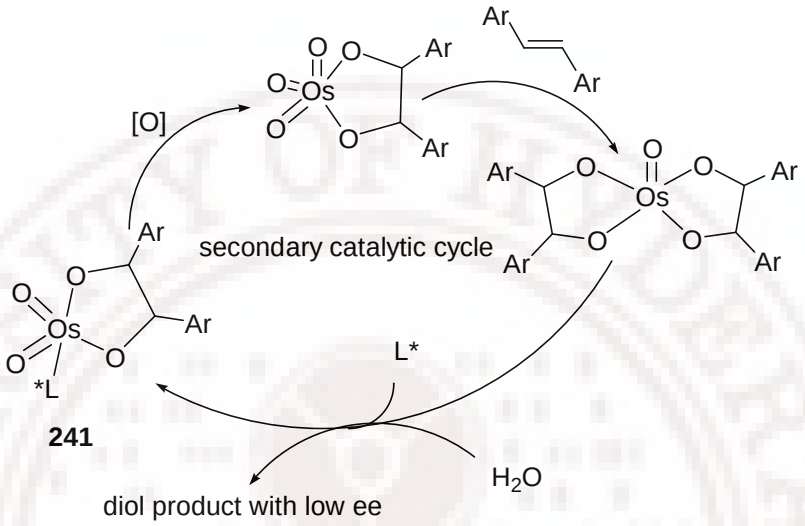
Table 18 Asymmetric dihydroxylation of 4-substituted *trans*-stilbenes using 9-*O*-acetyldihydrocinchonidine **247** as chiral ligand in THF/^{t}BuOH/H_2O solvent system[a, b, c]

Entry	Olefin (X =)	Product	% Yield[e]	% ee[d]	e_r[f]
1	OMe, **216d**	**218d**	68	34	2.03
2	Me, **216b**	**218b**	70	30	1.86
3	H, **216a**	**218a**	92	82	10.1
4	Cl, **216c**	**218c**	72	36	2.12
5	CF_3, **216e**	**218e**	65	20	1.5

[a]In all the experiments olefin (1 mmol) was used. [b]In each case 2 mol% of potassium osmate and 5 mol% of ligand were used. [c]All the experiments were carried out at 25 °C for 12 h. [d]The enantiomeric excesses were based on HPLC analysis. [e]Yields are for isolated products. [f]e_r = enantiomeric ratio {(1*S*,2*S*)/(1*R*,2*R*)}.

Though, the diols were obtained in reasonable chemical yields, substantially lower enantioselectivities were realized with electron donating and electron withdrawing derivatives in all the solvent systems (Tables 16, 17 & 18). A possible explanation is that in these cases, direct dihydroxylation of the olefin by OsO_4 could have taken place to a greater extent compared to unsubstituted olefins, leading to lower selectivity.[115] Another possibility is that the secondary catalytic cycle (proposed by Sharpless *et al*.[115a]) involving the corresponding osmate ester intermediate **241** (Scheme 74) could have taken place to a greater extent in these cases, leading to lower enantioselectivity.[115] These parallel processes would take place to a greater extent, if the ligand accelerated AD reaction path becomes difficult.

Scheme 74



A 1,3-dipole would find it difficult to react with the stilbene derivatives containing electron withdrawing substituents as transfer of electrons from the olefin to the dipole is difficult in these cases (TS **248**, Fig. 34).

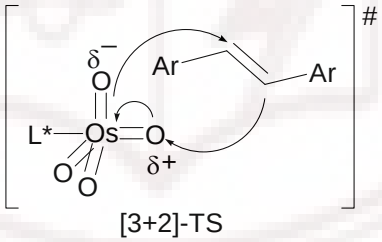


Figure 34

In the case of stilbene derivatives containing electron donating substituents, the transfer of electrons from the dipole to the olefin would become difficult. Therefore, the ligand unassisted dihydroxylation or reaction through the secondary catalytic cycle would take place to a greater extent in these cases, resulting in lower

enantioselectivities.

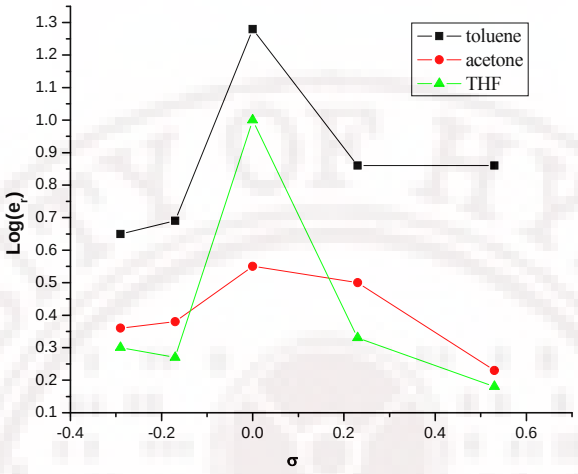


Figure 35 Plots of Log(enantiomeric ratio) vs Hammett σ values

The enantioselectivities realized in these cases would also lead to non-linearity in the correlation of Log(enantiomeric ratio) vs σ (Fig. 35).[144] Clearly, the results indicate a change in mechanism for the unsubstituted and substituted *trans*-stilbenes.[145] This would be expected if the diols are produced through the L-OsO_4 1,3-dipole (TS **248**) to a greater extent in the case of unsubstituted stilbene and to a lesser extent in the case of stilbenes substituted with electron donating and electron withdrawing substituents. Thus, the results obtained in the present studies are in accordance with the conclusion that the ligand acceleration effect on the catalytic asymmetric dihydroxylation of olefins is due to the ability of the ligand to convert OsO_4 into an efficient 1,3-dipole upon complexation for reaction with olefins.[130,145] Obviously, one has to look for chiral ligands that would lead to optimum chiral descrimination by

providing a binding pocket for this 1,3-dipole as good as the cinchona alkaloid derivatives seem to provide.

2.3.6 Asymmetric reduction studies using chiral Tröger base-borane complex

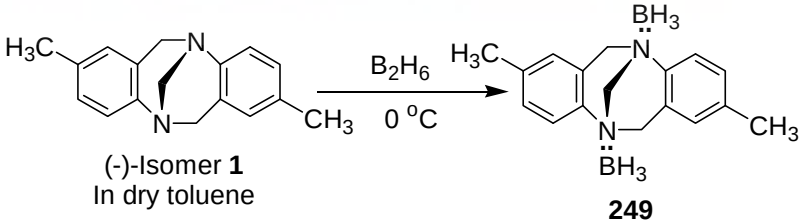
Amine-borane complexes have practical advantages as reducing agents in organic synthesis owing to their stability and solubility in a wide variety of solvents. The application of chiral amine-boranes for asymmetric reduction of ketones has not been extensively investigated. A very few reports are available on the use of borane complexes of chiral α-methylbenzyl amine,[146a] *N*,*N*-dimethyl-α-methylbenzyl amine,[146b] *N*,*N*-di-α-methylbenzyl amine[146c] for enantioselective reductions of prochiral ketones. Accordingly, it was of interest to us to examine the asymmetric reduction of acetophenone using the chiral Tröger base-borane complex.

2.3.6.1 Preparation of chiral Tröger base-borane complex

The chiral Tröger base-borane complex **249** can be readily prepared by passing the B_2H_6, generated by adding I_2 in diglyme to $NaBH_4$ in diglyme at 25 °C (eqn. 1) through the solution of the chiral TB **1** in toluene at 0 °C (Scheme 75).

$$2NaBH_4 + I_2 \xrightarrow[25\ ^oC]{\text{Diglyme}} B_2H_6\uparrow + 2NaI + H_2\uparrow \quad \text{----------(eqn. 1)}$$

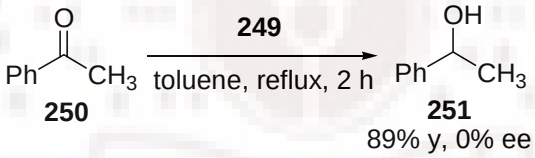
Scheme 75



2.3.6.2 Reduction of acetophenone by chiral Tröger base-borane complex

The Tröger base-borane complex is somewhat strong and it does not reduce ketones under ambient conditions. It may be of interest to note that the borane complex of relatively weak amine, *N*,*N*-diethyl aniline reduces ketones at 25 °C. The chiral Tröger base-borane complex **249** does reduce the acetophenone under refluxing conditions and gives the racemic alcohol product **251** (Scheme 76).

Scheme 76



Previously, it was reported from this laboratory that the chiral amine-borane complexes **252**-**255** reduce the acetophenone with 10-57% ee in the presence of BF_3:OEt_2 at 25 °C. This reduction would probably go through a transition state **256** (Fig. 36).[146d,e]

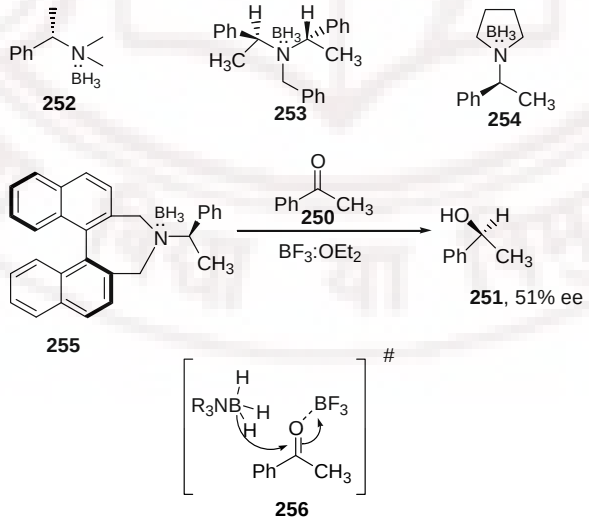
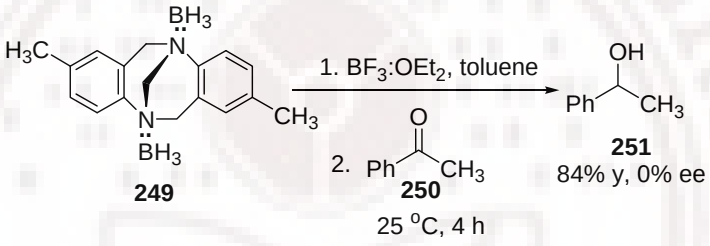


Figure 36

Hence, we have carried out the reduction of acetophenone **250** using the chiral Tröger base-borane complex **249**, in the presence of BF_3:OEt_2 at 25 °C. The product 1-phenylethanol **251** was obtained in 84% yield but there was no enantioselectivity (Scheme 77). The same reaction was also carried out at 0 °C but only the racemic product was obtained.

Scheme 77



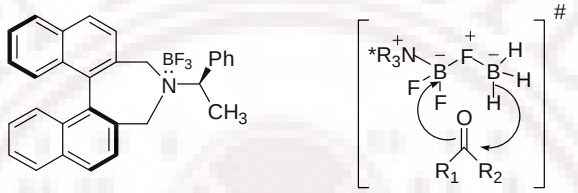
It is well-known that addition of BF_3:OEt_2 to amine-boranes could also liberate diborane (eqn. 2).

$$R_3N{:}BH_3 + BF_3{:}OEt_2 \rightleftharpoons R_3N{:}BF_3 + BH_3{:}OEt_2 \longrightarrow B_2H_6 + OEt_2 \quad \text{(eqn.2)}$$

Accordingly, if such exchange reaction occurs in this case and the resulting ether borane complex reduces the ketone directly, then there would not be any asymmetric induction.

It has been reported that the BF_3 complex of chiral amine **252** (Fig. 237) promotes the asymmetric reduction of acetophenone by Et_3N:BH_3 with 48.9 % ee. The transition state **253** has been proposed for this reaction.[146d] In order to examine this possibility with Tröger base, we prepared the chiral TB-BF_3 complex *in situ* by adding the BF_3:OEt_2 to

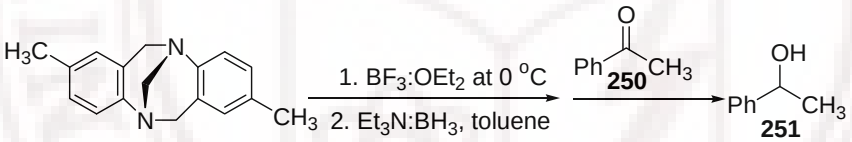
chiral TB in toluene at 0 °C (formation of BF_3 complex was confirmed by ^{11}B NMR). Unfortunately, in this case also no enantioselectivity was observed in the reduction of acetophenone using $Et_3N{:}BH_3$ (Scheme 78). The reduction was also carried out at 0 °C but again no enantioselectivity was observed.



252 **253**

Figure 37

Scheme 78



1

The reaction using the chiral BF_3 complex **252** and $Et_3N{:}BH_3$ combination requires equilibrium outlined in eqn. 3.

$$R_3N{:}BF_3 + Et_3N{:}BH_3 \rightleftharpoons R_3N{:}BF_2\text{-}F\text{-}BH_3 + Et_3N \quad \text{(eqn. 3)}$$

Presumably, the Tröger base-BF_3 complex does not give reactive species like **253** and hence there is no asymmetric induction.

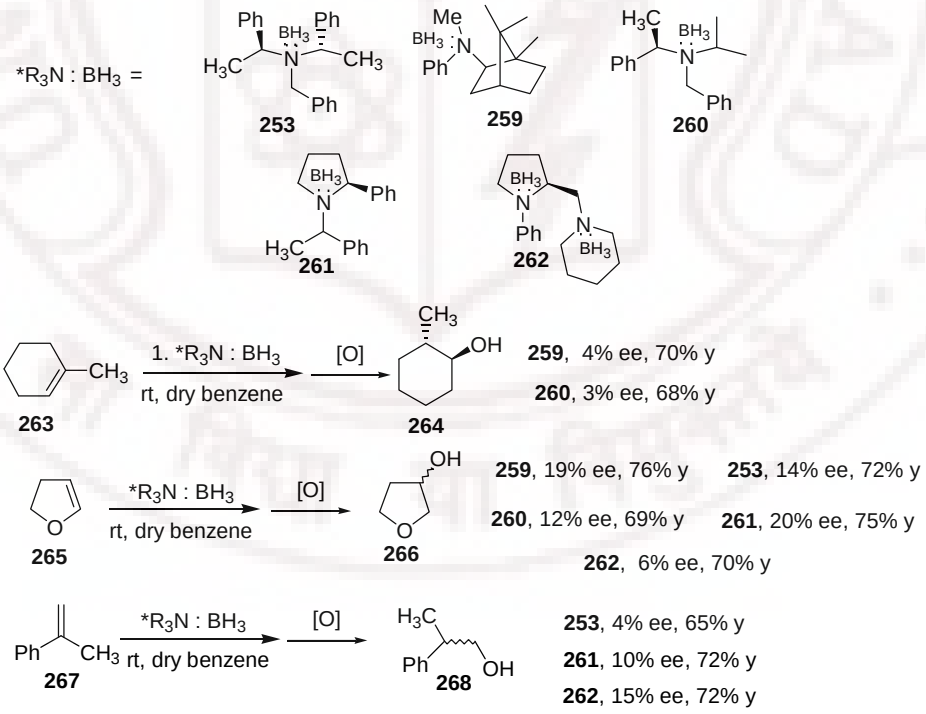
2.3.7 Hydroboration of prochiral olefins using chiral amine-borane complexes

Since H. C. Brown's discovery that ether complexes of borane hydroborate olefins, diverse hydroborating agents like $BH_3{:}SMe_2$, $BH_3{:}N(C_2H_5)_2Ph$ and 9-BBN became

commercially available.[147] The amine-borane complexes are relatively stable and therefore are 'easy to handle' carriers of borane. Due to strong complexation, most of the amine-boranes hydroborate olefins only at elevated temperatures. For example, the pyridine-borane hydroborates alkenes in diglyme at 100 °C.[148] However, the *N*,*N*-diethyl aniline-borane hydroborates olefins at ambient conditions due to decrease in strength of the N-B bond.

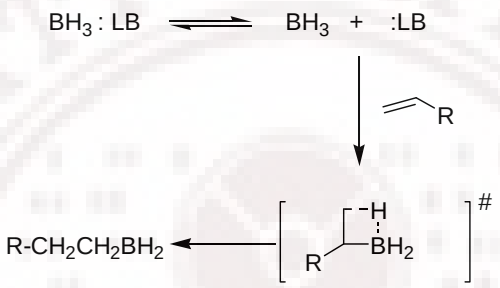
Previously, it was reported in this laboratory that hydroboration of representative prochiral olefins **263**, **265** and **267** with chiral tertiary amine-borane complexes **253**, **259**-**262** produce alcohols with up to 20% ee after $NaOH/H_2O_2$ oxidation (Chart 11).[149]

Chart 11

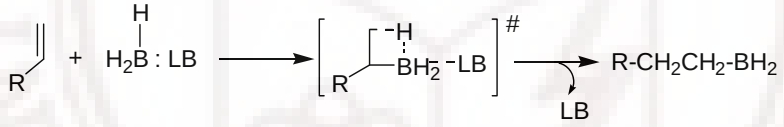


These results indicate that the hydroboration reaction may go through a spectrum of mechanisms, S_N1 or S_N2 or S_N2 with π-complex intermediate depending on the nature of the olefin and amine-borane complex.[149b,149c]

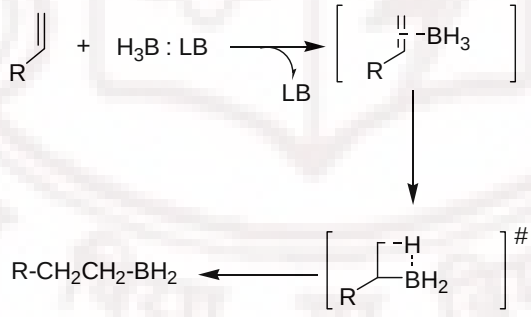
S_N1-Type mechanism



S_N2-Type mechanism



S_N2-Type mechanism with π-complex intermediate

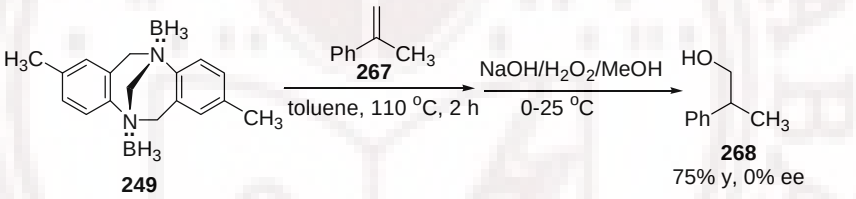


Whereas the reaction with electron rich olefins may take the S_N2 mechanistic pathway, the reaction involving sterically crowded borane complex or olefin may go through S_N2 reaction with a π-complex intermediate or the S_N1 reaction in which the borane complex dissociates in to free BH_3 species before hydroboration.

2.3.7.1 Efforts toward hydroboration of α-methylstyrene using chiral Tröger base-borane complex

We have examined the hydroboration of α-methylstyrene **267** using chiral Tröger base-borane complex **249** at 25 °C. However, this borane complex was found to be stable and there was no reaction with olefin under these conditions. The hydroboration did take place at 110 °C. However, after oxidation with $NaOH/H_2O_2$, only the racemic alcohol product **268** was isolated in 75% yield (Scheme 79).

Scheme 79

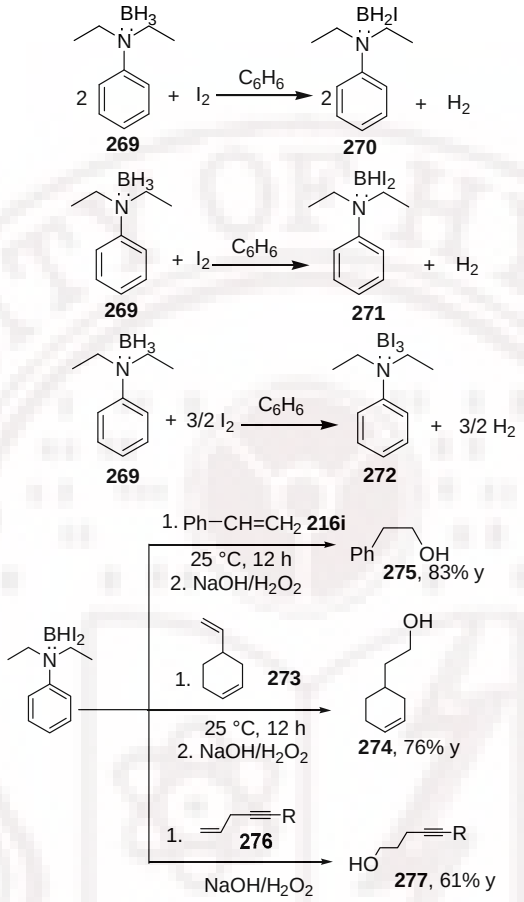


Accordingly, we were looking for a means, which would permit us to carry out this reaction under mild conditions.

2.3.7.2 Efforts toward hydroboration of prochiral olefins using chiral Tröger base-borane complex under iodine activation

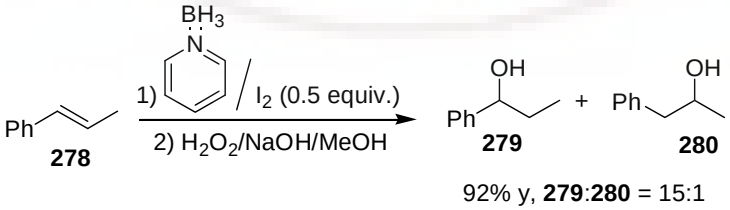
Previously, hydroboration studies using *N*,*N*-diethylaniline iodoborane complexes have been reported from this laboratory.[150] It was found that appropriate amounts of I_2 give the corresponding BH_2I, BHI_2 and BI_3 complexes (Chart 12). Among these, the BHI_2 complex has been used for hydroborations of alkenes, including some selective hydroborations.

Chart 12



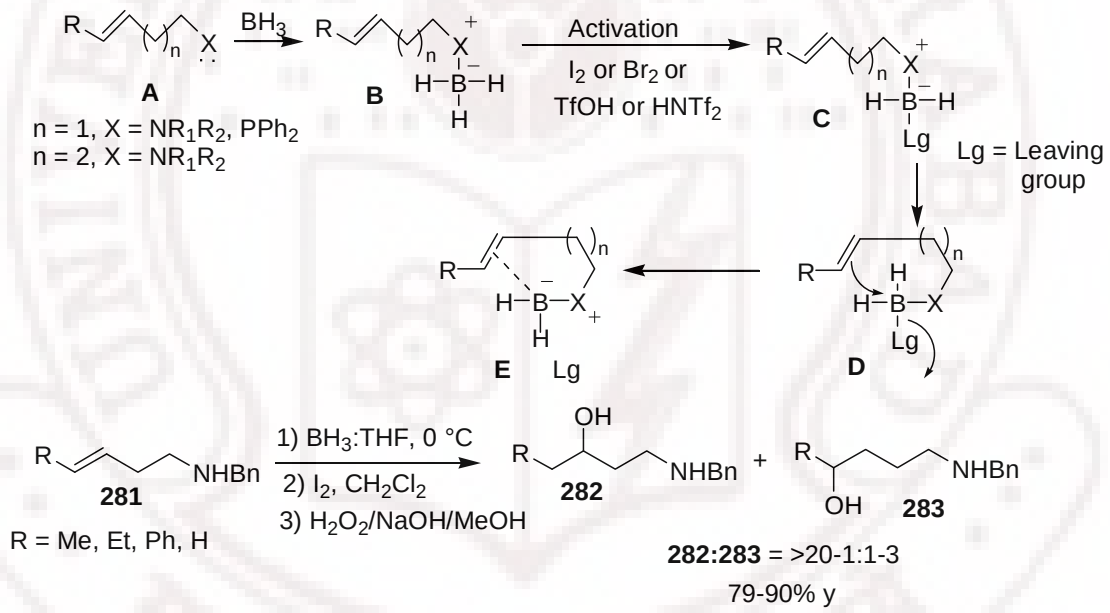
As mentioned earlier, stable amine-borane complexes such as pyridine-borane hydroborates alkenes only at 100 °C. Recently, Vedejs *et al*.[151a] reported that pyridine-borane hydroborates β-methylstyrene at 25 °C under iodine activation (Scheme 80).

Scheme 80



Vedejs *et al.*[151b,c,d] also reported that intramolecular hydroboration of homoallylic amine-boranes, phosphine-boranes and bis-homoallylic amine-boranes takes place at 25 °C through activation by electrophiles like I_2, Br_2, TfOH, $HNTf_2$. This process involves activation *via* incorporation of exocyclic leaving group (I, Br, OTf or NTf_2) at the boron by replacing one of the hydrides, resulting in a new mechanistic pathway for intramolecular hydroboration (Scheme 81).

Scheme 81

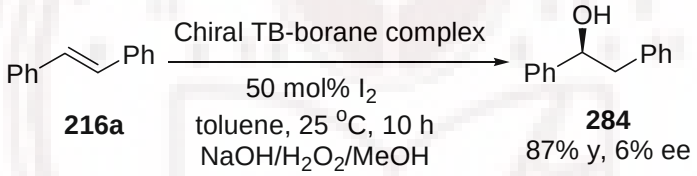


Vedejs *et al.*[151b,c,d] also observed that iodine activation method dramatically improves the regioselectivity from the amine directed hydroboration *via* intermediates having N-B bond intact throughout the reaction (Scheme 81).

We became interested in the preparation of appropriate chiral amine-BH_2X complex in which the "X" group would leave upon attack by a prochiral olefin keeping the chiral amine moiety intact in transition state of the hydroboration reaction.

As discussed earlier, Tröger base-borane complex **249** does not hydroborate olefins at 25 °C. We have examined the asymmetric hydroboration of prochiral olefins using chiral Tröger base-borane complex **249** activated with molecular iodine. Accordingly, we have carried out the hydroboration reaction of *trans*-stilbene **216a** with chiral Tröger base-BH_3 complex **249** (prepared as discussed in the previous section) in toluene activated with 50 mol% of I_2. After the standard oxidative workup using NaOH and H_2O_2, the alcohol product was obtained with 6% ee (Scheme 82).

Scheme 82



We have then examined various conditions to optimize the reaction (see Table 19). When the hydroboration was carried out using catalytic amount (10 mol% relative to TB equivalents) of I_2, the alcohol product was obtained in 7% ee after oxidation. We have also carried out the hydroboration reaction in the presence of additives like THF, *N*,*N*-diethylaniline **285** to examine whether this could lead to better selectivities through formation of complex like $R_3N^*BH_2$:THF I^- complex (Scheme 83). Surprisingly, in these cases the alcohol product obtained was found to be racemic. This could be explained if the hindered chiral Tröger base-BH_2I complex reacts with the external Lewis base before the hydroboration reaction resulting in hydroboration by the achiral additive-BH_2I species (Scheme 83).

Scheme 83

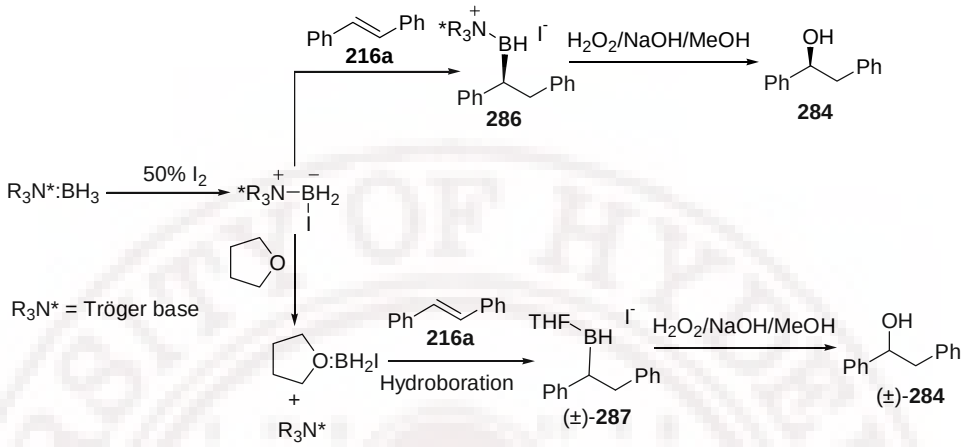


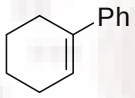
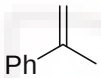
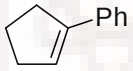
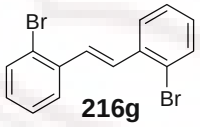
Table 19 Hydroboration *trans*-stilbene **216a** using I_2 activated chiral Tröger base-borane complex.[a]

Entry	I_2 (mol%.)	Additive	% Yield[d] **284**	% ee[e] (Conf.)
1	50	—	87	6 (*S*)
2	10	—	85	7 (*S*)
3[b]	10	—	45	4 (*S*)
4[c]	50	$PhNEt_2$	80	0
5[c]	50	THF	82	0

[a]All the reactions were carried out using *trans*-stilbene (1 mmol) and chiral Tröger base-borane complex (4 mL, 1 mmol (0.25 M solution in toluene)) in dry toluene (5 mL) solvent at 25 °C for 10 h. then it was oxidized using $NaOH/H_2O_2$. [b]In this case the reaction was carried out at –20 °C. [c]In this case, after the addition of I_2 (0.1 mmol) in dry toluene (5 mL) to chiral Tröger base-borane complex **249**, to the reaction mixture was added *N*,*N*-diethyl aniline (weaker than Tröger base) (1 mmol) and allowed to stir for 20 min. Then *trans*-stilbene (1 mmol) was added and stirred for 10 h. [d]The yields are for isolated products. [e]ee's were based on the HPLC analysis using Chiralcel-OD-H column with IPA/Hexane (10/90) mixture and flow rate: 0.5 mL/min.

We have also examined the hydroboration of a other prochiral olefins using the chiral TB-borane complex activated by I_2 (10 mol%). The results are summarized in Table 20.

Table 20 Hydroboration of different olefins using iodine activated chiral Tröger base-borane complex[a]

Entry	Substrate	% Yield[b]	% ee[c]
1	 **288**	**289**, 83	4 (1*R*,2*S*)
2	 **262**	**263**, 85	0
3	 **290**	**291**, 80	0
4	 **216g**	**292**, 70	5

[a]All the reactions were carried out using olefin (1 mmol) and I_2 (0.1 mmol) in dry toluene (5 mL) chiral Tröger base-borane complex (4 mL, 1 mmol (0.25 M solution in toluene)) in dry toluene (5 mL) solvent at 25 °C. [b]All the yields reported here are of isolated products. [c]ee's were based on HPLC analysis.

The hydroboration of *trans*-stilbene **216a** was also carried out using the chiral TB-borane complex in the presence of TfOH as activator but in this case only the racemic alcohol was obtained after the usual oxidative workup.

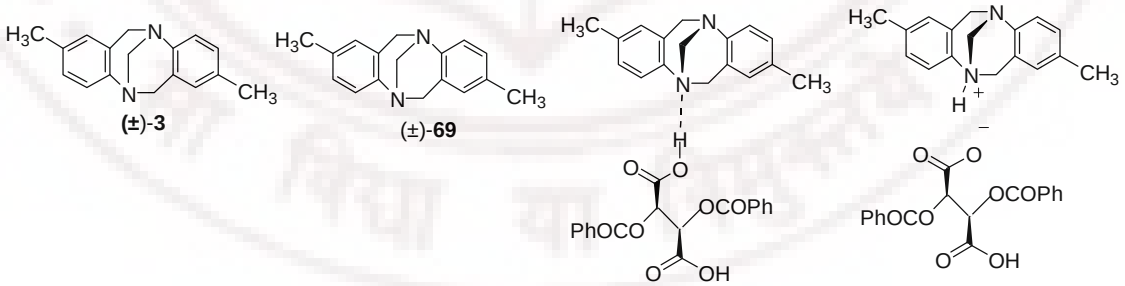
We have also attempted to probe the sequence of events using ^{11}B-NMR experiments for understanding the nature of boron species formed during the course of the reaction. The Tröger base-borane complex **249** exhibits a signal at δ = -9.1 ppm in ^{11}B NMR (toluene+$CDCl_3$). After addition of iodine (0.5 equiv.) to the TB-borane complex, a new signal appeared at δ = -12.1 (toluene) in addition to the signal at δ = -9.0 ppm (corresponds to the parent TB-borane complex), presumably, due to the formation of the BH_2I complex.

We have also examined conversion of the presumed Tröger base-BH_2I complex formed *in situ* to the corresponding PPh_3:BH_2I complex. one equivalent of triphenyl phosphine was added with an objective to form the BH_2I species as a stable PPh_3:BH_2I complex. In this case, the ^{11}B NMR spectrum showed two signals, one at δ = -37.1 ppm (corresponding to the PPh_3:BH_3 complex) and a second one at δ = -11.2 ppm, may be corresponding to a BH_2I complex. Attempts to crystallize the PPh_3:BH_2I complex from this mixture were not successful.

A systematic investigation on the hydroboration reaction using chiral Tröger base-borane complexes containing more electron donating substituents in the aromatic ring and chiral pendent groups at the saturated core should give more fruitful results.

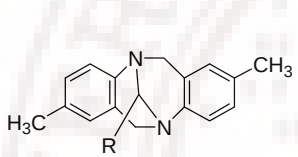
2.4 Conclusions

We have developed a convenient method to readily access the racemic Tröger base **1** and its derivatives. These racemic Tröger base derivatives were prepared by the reaction of the corresponding substituted aniline with paraformaldehyde in the presence of a Lewis acid. A new method has been devised for the resolution of racemic Tröger base through the preparation of hydrogen bonded aggregates **150** using the readily available and recoverable dibenzoyl-L-tartaric acid. The methoxy Tröger base analog **69** was also successfully resolved by diastereomeric salt **151** formation with dibenzoyl-L-tartaric acid to obtain samples with >98% ee. The configurations of the 'N' chiral centers were found to be 5*R*,11*R* as determined by the X-ray crystal structure analysis of the diastereomeric complexes **150** and **151**.

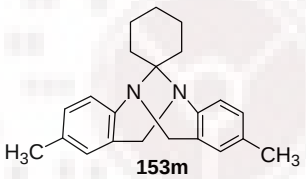


A general method for the synthesis of 5,11-substituted Tröger base derivatives was developed involving the reaction of racemic Tröger base and a carbonyl compound in the

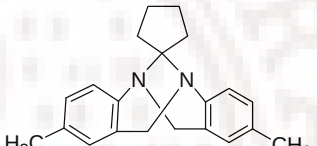
presence of $TiCl_4$ in DCE under reflux conditions. The reaction was also generalized with various carbonyl compounds. The 5,11-substituted spiro compound **153n** obtained in the reaction with cyclopentanone was further confirmed by X-ray crystal structure analysis. These 5,11-substituted derivatives were also prepared by the reaction using $POCl_3$ in toluene at 80 °C. The compounds **153a**, **153b**, **153c** and **153m** were successfully resolved by HPLC on Chiralcel-OJ-H column using ethanol as mobile phase.



153a: R = Ph
153b: R = 4-tolyl
153c: R = 4-anisyl

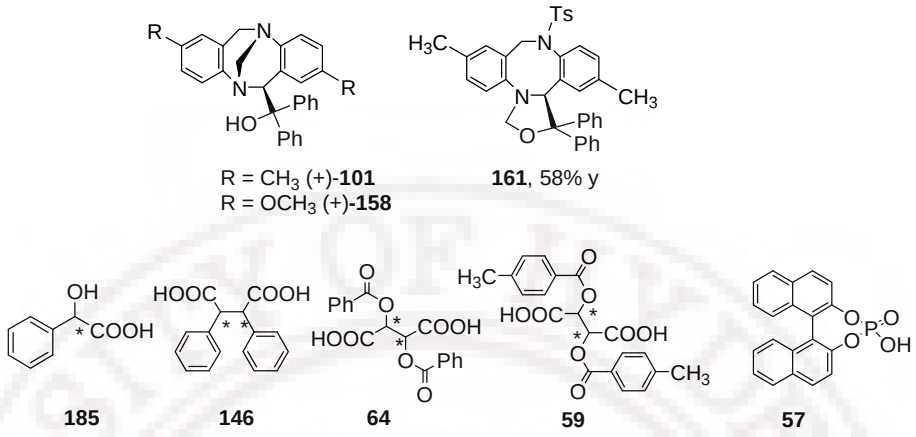


153m

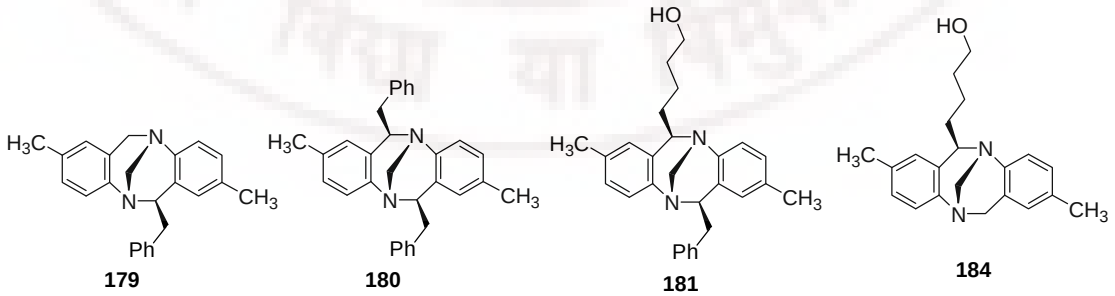


153n

The chiral amino alcohols **101** and **158** derivatives of Tröger base **1** and its methoxy derivative **69** were prepared by following the α-alkylation of tertiary amine-BF_3 complex protocol. The configuration of the newly formed chiral center was determined by the X-ray crystal structure analysis of the compound **161** formed in the reaction of the Tröger base derivative **101** with TsCl in pyridine. The chiral recognition properties of the Tröger base derivatives **1**, **96** and **158** towards the acid guests **57**, **59**, **64**, **146** and **185** were studied using ^{1}H & ^{31}P NMR spectroscopy. It was observed that the methoxy Tröger base **69** is more effective as chiral solvating agent compared to Tröger base **1**. In particular, the chiral methoxy Tröger base **69** exhibits a better enantio discrimination towards the C_2-symmetric acids **59**, **64** and **146**, whereas the Tröger base derivative **158** exhibited better discrimination towards unsymmetrical acids **57** and **185**.

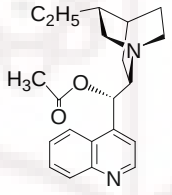


Asymmetric NH-aziridination of chalcone promoted by chiral Tröger base was developed using the *O*-(diphenylphosphinyl)hydroxylamine ($DppONH_2$) as NH source. The corresponding aziridine was obtained in 75% yield with up to 70% ee. The reaction was also carried out using various chiral Tröger base analogs **69**, **101**, **158**, **179**, **180**, **181**, **184**. With the exception of **180** and **181**, all other chiral Tröger base derivatives promoted the asymmetric aziridination and the corresponding NH-aziridine was obtained in good yields (66-75%) with moderate enantioselectivities (44-70%). Presumably, due to more hindered N-atoms, the disubstituted Tröger base derivatives **180** and **181** would have difficulty in giving the reactive amine-amide intermediates.



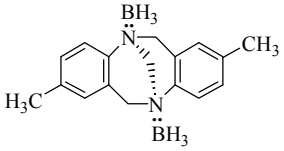
A new protocol for osmium catalyzed dihydroxylation of olefins facilitated by racemic Tröger base **1** was developed. The corresponding *dl*-diols were obtained in good yields (78-94%). Asymmetric dihydroxylation of *trans*-stilbene was also attempted using the chiral Tröger base for ligand acceleration, but the corresponding 1,2-diphenylethane-1,2-diol was obtained only with 6% enantioselectivity.

Studies on the mechanism of the catalytic asymmetric dihydroxylation of substituted *trans*-stilbene derivatives was carried out using the 9-*O*-acetyldihydrocinchonidine **247** as chiral ligand. The concave shaped plots in the Hammett correlations and the lower enantioselectivites in the case of *trans*-stilbenes containing electron donating as well as electron withdrawing substituents are in accordance with 1,3-dipolar type [3+2] cycloaddition pathway.



247

The chiral Tröger base-BH_3 complex **249** was prepared by passing the diborane gas generated using $NaBH_4/I_2$. Efforts were made toward studies on reduction of acetophenone using the chiral TB-borane complex **249**.



249

Efforts were also undertaken toward the hydroboration of prochiral olefins with **249** activated by I_2. Indeed, iodine activation phenomenon was confirmed and in the case of *trans*-stilbene, the corresponding alcohol was obtained with up to 7% ee. A more rational design of chiral Tröger base derivatives should lead to more fruitful results.

3. Experimental Section

3.1 General information

Melting points reported in this thesis are uncorrected and were determined using a Superfit capillary point apparatus. IR (KBr) spectra and the neat IR spectra were recorded on JASCO FT-IR spectrophotometer model-5300. ^{1}H NMR (200 MHz), ^{13}C NMR (50 MHz) and ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz) spectra were recorded on Bruker-AC-200 and Bruker-Avance-400 spectrometers, respectively with chloroform-d as solvent and tetramethylsilane as reference (δ = 0 ppm). The chemical shifts are expressed in δ downfield from the signal of internal tetramethylsilane. Gas chromatography and Mass spectral analyses (GC-MS) for the compounds were carried out on VG 7070H mass spectrometer using EI technique at 70 eV. Elemental analyses were carried out using a Perkin-Elmer elemental analyzer model-240C and Thermo finnigan analyzer series Flash EA 1112. Optical rotations were measured on Rudolph Research Analytical AUTOPOL-IV (readability ±0.001^{o}) automatic polarimeters. The condition of the polarimeter was checked by measuring the optical rotation of a standard solution of (*R)*-(+)-α-methylbenzylamine {$[\alpha]_D^{25}$ = +30.2° (*c* 10, EtOH)} supplied by Fluka.

Analytical thin layer chromatographic tests were carried out on glass plates (3 x 10 cm) coated with 250 mμ acme's silica gel-GF_{254} containing 13% calcium sulfate as binder. The spots were visualized by short exposure to iodine vapor or UV light. Column

chromatography was carried out using acme's silica gel (100-200 mesh), neutral alumina and basic alumina.

All the glassware were pre-dried at 140 ^{o}C in an air-oven for 4 h, assembled in hot condition and cooled under a stream of dry nitrogen. Unless otherwise mentioned, all the operations and transfer of reagents were carried out using standard syringe-septum technique recommended for handling air sensitive reagents and organometallic compounds. Reagents prepared *in situ* in solvents were transferred using a double-ended stainless steel needle under a pressure of nitrogen whenever required.

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 was used. The outlet of the mercury bubbler was connected to the atmosphere by a long tube. All dry solvents and reagents (liquids) used were distilled from appropriate drying agents. As a routine practice, all organic extracts were washed with saturated sodium chloride solution (brine) and dried over anhydrous Na_2SO_4 or K_2CO_3 and concentrated on Heidolph-EL-rotary evaporator. All the yields reported are of isolated materials judged homogeneous by TLC, IR and NMR spectroscopy.

Racemic binaphthylphosphoric acid was prepared following the reported procedure in organic syntheses collective volumes.[152]

Dichloromethane, 1,2-dichloroethane and chloroform were distilled over CaH_2 and dried over molecular sieves. THF supplied by E-Merck, India were kept over sodium-benzophenone ketyl and freshly distilled before use. Toluene and diglyme were also kept

over sodium-benzophenone ketyl, distilled and stored over sodium wire. Triethylamine was distilled over CaH_2 and stored over KOH pellets. *p*-Toludine, *p*-anisidine, zinc powder, anhydrous zinc chloride, 2,4-dimethylaniline, 3,5-dimethylaniline, anhydrous aluminium chloride, ammonium chloride, anhydrous sodium sulfate, hydroxylammmonium chloride, sodium borohydride, Iodine (resublimed), potassium carbonate anhydrous were supplied by E-Merck (India) and potassium osmate(IV) dihydrate was supplied by E-Merck (Germany). Titanium tetrachloride, acetyl chloride, zirconium tetrachloride, tin tetrachloride, furfural and n-heptanaldehyde were supplied by Loba chemie (P) Ltd, India were used as purchased. Benzaldehyde, 4-tolualdehyde, 4-methoxybenzaldehyde, 4-chlorobanzaldehyde, and terepthaladehyde were supplied by Sisco Research Laboratories (P) Ltd. Phosphorus oxychloride, benzophenone, benzyl bromide, *p*-toluene sulfonylchloride, acetophenone and ^tBuOH were supplied by Sdfine chemicals (P) Ltd. Racemic 1,1'-bi-2-napthol was supplied by Gerchem Labs (P) Ltd.

Magnesium turnings were purchased from Rankem (P) Ltd, India. Methane sulfonamide used was obtained from Lancaster (P) Ltd, India. Dibenzoyl-L-tartaric acid, cyclohexanone, cyclopentanone, 4-nitrobenzaldehyde, 2-napthaldehyde, BF_3:OEt_2, styrene, 4-(trifluoromethyl)benzaldehyde, triphenylphosphine, 2-bromobenzaldehyde, sodium hydride (60% dispersion in mineral oil), diphenylphosphinyl chloride, α-methylstyrene, *trans*-stilbene, trifluoromethanesulfonic acid, monoethanolamine, cinchonidine, $(DHQD)_2$-PHAL and the Pd/C catalyst were supplied by Aldrich, USA. Pyridine and diglyme (diethylene glycol dimethyl ether) were supplied by spetrochem, India.

X-ray diffraction measurements for the compounds **150**, **151**, **153n**, **161** were carried out at 298 K on Bruker-Nonius SMART APEX CCD area detector system. The data were reduced using XTAL 3.4 or SAINT program,[153] without applying absorption correction. The refinement for structure was made by full-matrix least squares on F^2 (SHELX 97 or SHELXTL)[154]

3.2 Synthesis of racemic Tröger base and its analogs

3.2.1 General procedure for the synthesis of racemic Tröger base and its derivatives:

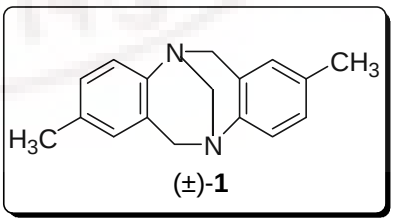
To a solution of substituted anilines (10 mmol) and paraformaldehyde (0.60g, 20 mmol) in CH_2Cl_2 (40 mL) was added the Lewis acid (10 mmol) under N_2 atmosphere. The reaction mixture was allowed to stir for 12 h at 25 °C and quenched with cold water (10 mL). The reaction mixture was extracted with CH_2Cl_2 (50 mL) and the combined organic extracts were successively washed with water, brine and dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was subjected to chromatography on basic alumina column using ethyl acetate in hexane to elute the desired Tröger base derivatives.

2,8-Dimethyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine

Yield 0.79 g (63%, $TiCl_4$ was used as Lewis acid)

mp 135-137 °C (lit.[3] mp 135-136 °C)

IR (KBr) (cm^{-1}) 3150, 1493, 1431, 1325, 1207, 1095, 960, 896, 829



(±)-**1**

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm)

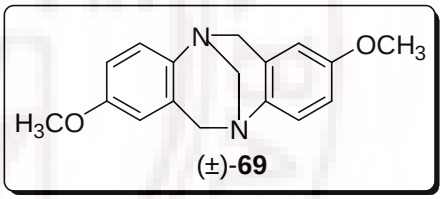
2.21 (s, 6H), 4.10 (d, 2H, *J* = 16.6 Hz), 4.30 (s, 2H), 4.64 (d, 2H, *J* = 16.6 Hz), 6.70 (s, 2H), 6.95 (d, 2H, *J* = 8.1 Hz), 7.02 (d, 2H, *J* = 8.2 Hz) **(Spectrum No. 1)**

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm)

20.9, 58.7, 67.1, 124.8, 127.3, 127.5, 128.1, 133.4, 145.4 **(Spectrum No. 2)**

2,8-Dimethoxy-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine

Yield 1.08 g (76% $AlCl_3$ was used as Lewis acid)



(±)-**69**

mp 168-170 °C (lit.[84a] mp 172-174 °C)

IR (KBr) (cm^{-1}) 3150, 1493, 1431, 1325, 1207, 1095, 960, 896, 829

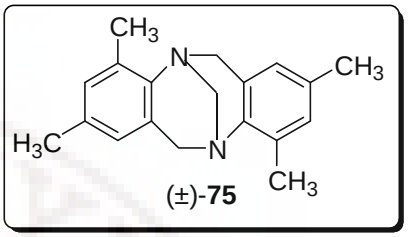
^{1}H NMR (400 MHz, $CDCl_3$, δ ppm)

3.70 (s, 6H), 4.08 (d, 2H, *J* = 16.6 Hz), 4.29 (s, 2H), 4.64 (d, 2H, *J* = 16.4 Hz), 6.42 (s, 2H), 6.74 (d, 2H, *J* = 8.8 Hz), 7.05 (d, 2H, *J* = 8.8 Hz) **(Spectrum No. 3)**

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm)

55.4, 58.9, 67.3, 110.9, 114.0, 126.0, 128.7, 141.0, 156.1 **(Spectrum No. 4)**

2,4,8,10-Tetramethyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine



(±)-**75**

Yield 0.90 g (65% $AlCl_3$ was used as Lewis acid)

mp 112-113 °C (lit.[46a] mp 114-115 °C)

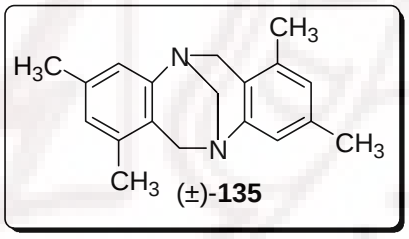
IR (KBr) (cm^{-1}) 2949, 2878, 2833, 1429, 1323, 1213, 1033,916, 852, 752, 650

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm)

2.18 (s, 6H), 2.35 (s, 6H), 3.92 (d, 2H, *J* = 16.8 Hz), 4.30 (s, 2H), 4.53 (d, 2H, *J* = 16.8 Hz), 6.56 (s, 2H), 6.85 (s, 2H) **(Spectrum No. 5)**

^{13}C NMR (400 MHz, $CDCl_3$, δ ppm) 17.0, 20.8, 55.1, 67.7, 124.8, 127.7, 129.7, 132.5, 132. 9, 143.5 **(Spectrum No. 6)**

1,3,7,9-Tetramethyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine



(±)-**135**

Yield 0.53 g (50% $AlCl_3$ was used as Lewis acid)

mp 184-186 °C

IR (KBr) (cm^{-1}) 3049, 2918, 1714, 1614, 1572, 1444, 1344, 1176, 1093, 976

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 2.00 (s, 6H), 2.24 (s, 6H), 4.09 (d, 2H, *J* = 15.6 Hz), 4.23 (s, 2H), 4.48 (d, 2H, *J* = 15.6 Hz), 6.64 (s, 2H), 6.82 (s, 2H)

^{13}C NMR (400 MHz, $CDCl_3$, δ ppm) 18.0, 21.1, 55.2, 66.1, 123.3, 126.5, 135.4, 136.6, 148.4

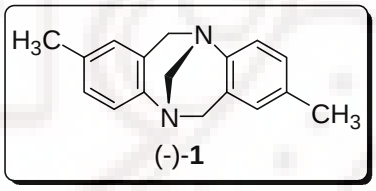
3.3 Optical resolution of racemic Tröger base and its derivatives

3.3.1 Resolution of racemic Tröger base:

The dibenzoyl-L-tartaric acid (5.37 g, 15 mmol) and the racemic Tröger base **1** (1.25 g, 5 mmol) were taken in acetone (15 mL) and the contents were stirred at 25 °C for 12 h. The precipitate was collected and suspended in a mixture of CH_2Cl_2 (20 mL) and 2 N Na_2CO_3 and stirred until the dissolution occurred. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 15 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and evaporated to obtain the product (*R,R*)-**1** enantiomer with 91% ee. The filtrate was concentrated and the residue was treated as outlined above to obtain the (*S,S*)-**1**enantiomer with 41% ee.

The (*R,R*)-**1** isomer (91% ee) was recrystallized from acetone and hexane mixture to obtain the sample of 98% ee $[\alpha]_D^{25}$ = -301° (*c* 0.22, Hexane), lit.[12] $[\alpha]_D^{25}$ = -307° (*c* 0.31, Hexane).

After decomposition:



(-)-**1**

From precipitate:

Yield 0.485 g (39%)

$[\alpha]_D^{25}$ -279° (*c* 0.22, Hexane), {lit.[31] $[\alpha]_D^{25}$ = -307° (*c* 0.31, Hexane)}

From filtrate:

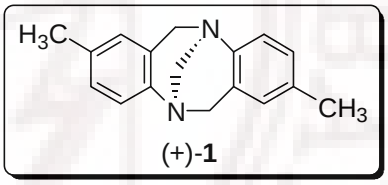
Yield 0.725 g (58%)

$[\alpha]_D^{25}$ +121° (*c* 0.22, Hexane), {lit.[31] $[\alpha]_D^{25}$ = +287 ± 7° (*c* 0.281, Hexane)}

3.3.2 Enrichment of enantiomeric purity of nonracemic Tröger base:

To a solution of nonracemic Tröger base (41% ee, 1.25 g, 5 mmol) in acetone (15 mL) was added dibenzoyl-D-tartaric acid (5.37 g, 15 mmol) and the contents were stirred at 25 °C for 12 h. The precipitate was collected and suspended in a mixture of CH_2Cl_2 (20 mL) and 2 N Na_2CO_3 and stirred until the dissolution occurred. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 15 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and evaporated to obtain (*S*,*S*)-enantiomer with 99% ee. The filtrate was concentrated and the residue was treated as outlined above to obtain the (*R*,*R*)-enantiomer with 12% ee.

After decomposition:



(+)-**1**

From precipitate:

Yield 0.775 g (62%)

$[\alpha]_D^{25}$ +279° (*c* 0.22, Hexane), {lit.[31] $[\alpha]_D^{25}$ = +287 ± 7° (*c* 0.281, Hexane)}

From filtrate:

Yield 0.437 g (35%)

$[\alpha]_D^{25}$ -37° (*c* 0.22, Hexane), {lit.[31] $[\alpha]_D^{25}$ = -307° (*c* 0.31, Hexane)}

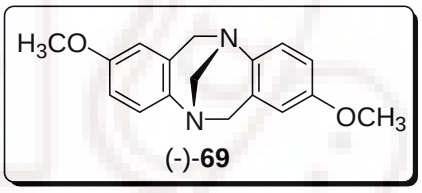
The samples were also analyzed by HPLC on Chiralcel-OJ-H column using ethanol as mobile phase, flow rate: 1.0 mL/min.

3.3.3 Resolution of racemic methoxy Tröger base:

The dibenzoyl-L-tartaric acid (7.2 g, 20 mmol) and the racemic methoxy Tröger base **69** (5.64 g, 20 mmol) were taken in acetone (240 mL) and the contents were stirred at 25 °C for 12 h. The precipitate was collected and crystallized by dissolving in hot acetone. The crystals were suspended in a mixture of CH_2Cl_2 (50 mL) and 2 N Na_2CO_3 and stirred until the dissolution occurred. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 25 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and evaporated to obtain the product (*R*,*R*)-**69** enantiomer >98% ee. The filtrate was concentrated and the residue was treated as outlined above to obtain the (*S*,*S*)-**69** enantiomer 30% ee.

After decomposition:

From precipitate:



(-)-**69**

Yield 1.7 g (30%)

$[\alpha]_D^{25}$ -242±5° (*c* 0.22, $CHCl_3$)

From filtrate:

Yield 3.7 g (66%)

$[\alpha]_D^{25}$ +74° (*c* 0.22, $CHCl_3$)

3.3.4 Enrichment of enantiomeric purity of nonracemic methoxy Tröger base:

To a solution of nonracemic Tröger base (30% ee, 5.64 g, 20 mmol) in acetone (300 mL) was added dibenzoyl-D-tartaric acid (7.2 g, 20 mmol) and the contents were stirred at

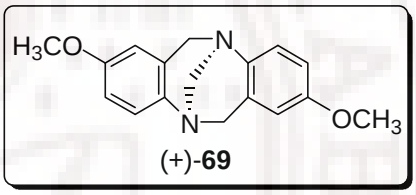
25 °C for 12 h. The precipitate was collected and suspended in a mixture of CH_2Cl_2 (30 mL) and 2 N Na_2CO_3 and stirred until the dissolution occurred. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 15 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and evaporated to obtain (*S,S*)-**69**enantiomer with 96% ee. The filtrate was concentrated and the residue was treated as outlined above to obtain the (*R,R*)-**69**enantiomer with 6% ee.

After decomposition:

From precipitate:

Yield 1.74 g (31%)

$[\alpha]_D^{25}$ +236±5° (*c* 0.22, $CHCl_3$)



(+)-**69**

From filtrate:

Yield 3.65 g (65%)

$[\alpha]_D^{25}$ -14° (*c* 0.22, $CHCl_3$)

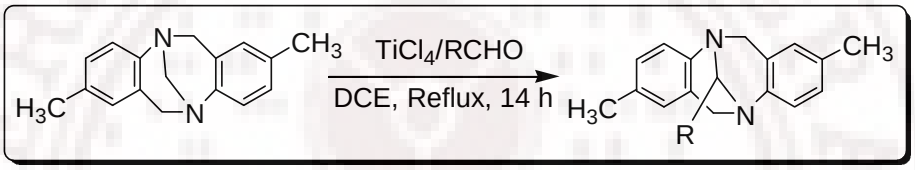
The samples were also analyzed by HPLC on Chiralcel-OJ-H column using ethanol as mobile phase, flow rate: 1.0 mL/min.

3.4 Preparation of new Tröger base derivatives

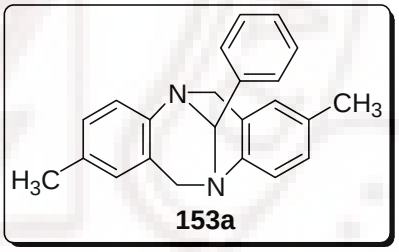
3.4.1 General procedure for the preparation of 5,11-substituted derivatives of Tröger base using $TiCl_4$:

To a reaction flask cooled under N_2, was added Tröger base (1.25 g, 5 mmol) in DCE (20 mL) and $TiCl_4$ (1.9 g, 1.1 mL, 10 mmol). Then the carbonyl compound (5.1 mmol) was

added at 25 °C and the reaction mixture was refluxed for 14 h. It was then cooled to 0 °C and quenched with saturated K_2CO_3 solution. The aqueous layer was extracted with CH_2Cl_2 (2 x 15 mL) and the combined organic extracts were successively washed with water, brine and dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was subjected to chromatography on silicagel using 2% ethyl acetate in hexane to elute the desired 5,11-substituted derivative of Tröger base (appears as dark spot in TLC under I_2 vapor).



2,8-Dimethyl-13-phenyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine(5,11-endo benzylidine analog of Tröger base)



153a

Yield 0.96 g (59%)

mp 180-182 °C (lit.[85b] mp 182-183 °C)

IR (KBr) (cm^{-1}) 3012, 2908, 2856, 1493, 1346, 1197, 837, 746, 696

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm)

2.17 (s, 3H), 2.27 (s, 3H), 3.91 (d, 1H, *J* = 20.0 Hz), 4.15 (d, 1H, *J* = 17.2 Hz), 4.35 (d, 1H, *J* = 16.0 Hz), 4.83 (d, 1H, *J* = 16.0 Hz), 5.35 (s, 1H), 6.49 (s, 1H), 6.81 (s, 1H), 6.99-7.33 (m, 8H), 7.61 (d, 1H, *J* = 7.6 Hz) **(Spectrum No. 7)**

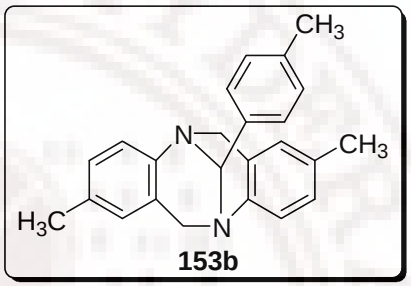
^{13}C NMR (100 MHz, $CDCl_3$, δ ppm)

21.0, 52.8, 61.0, 74.7, 125.5, 127.0, 127.4, 127.7, 128.1, 128.3, 128.4, 133.0, 133.4, 138.6, 143.9, 147.8 **(Spectrum No. 8)**

MS *m/z* 326.2 (GCMS)

2,8-Dimethyl-13-(4-methylphenyl)-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine

Yield 1.03 g (61%)



153b

mp 168-170 °C

IR (KBr) (cm^{-1}) 3011, 2993, 2910, 2845, 1491, 1199, 816

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm)

2.13 (s, 3H), 2.23 (s, 3H), 2.29 (s, 3H), 3.87 (d, 1H, *J* = 16.8 Hz), 4.13 (d, 1H, *J* = 16.8 Hz), 4.31 (d, 1H, *J* = 16.4 Hz), 4.79 (d, 1H, *J* = 16.4 Hz), 5.31 (s, 1H), 6.45 (s, 1H), 6.77 (s, 1H), 6.97-7.17 (m, 7H), 7.45 (d, 1H, *J* = 8.0 Hz)

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm)

20.9, 21.1, 52.6, 60.8, 74.5, 125.1, 125.4, 127.0, 127.3, 127.5, 127.8, 128.0, 128.2, 128.9, 132.9, 133.2,135.6, 136.7, 143.9, 147.8

MS *m/z* 340.2 (GCMS)

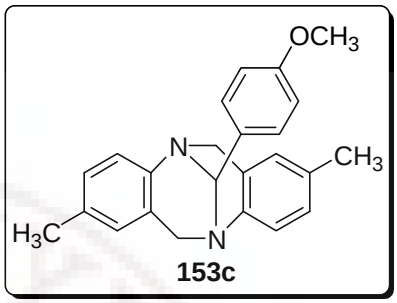
Analysis Calculated for $C_{24}H_{24}N_2$: C, 84.67%; H, 7.11%; N, 8.23%

Found: C, 84.69%; H, 7.11%; N, 8.37%

2,8-Dimethyl-13-(4-methoxyphenyl)-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine

Yield 1.1 g (62%)

mp 152-154 °C (lit.[85b] mp 155-156 °C)



153c

IR (KBr) (cm^{-1}) 3015, 2908, 2856, 1491, 1344, 1199, 825

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm)

2.26 (s, 3H), 2.37 (s, 3H), 3.83 (s, 3H), 4.03 (d, 1H, *J* = 16.8 Hz), 4.30 (d, 1H, *J* = 16.4 Hz), 4.45 (d, 1H, *J* = 16.4 Hz), 4.92 (d, 1H, *J* = 16.0 Hz), 5.43 (s, 1H), 6.59 (s, 1H), 6.89-7.34 (m, 8H), 7.67 (d, 1H, *J* = 8.4 Hz) **(Spectrum No. 9)**

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm)

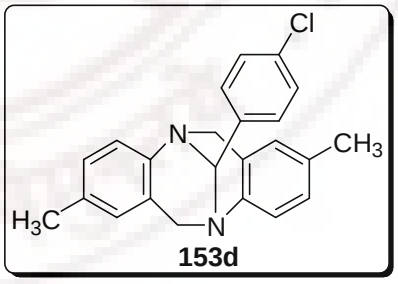
20.8, 52.5, 55.1, 60.8, 74.3, 113.6, 125.1, 125.4, 127.0, 127.3, 128.0, 128.2, 128.7, 130.6, 132.9, 133.2, 143.8, 147.6, 158.8 **(Spectrum No. 10)**

MS *m/z* 356.3 (GCMS)

2,8-Dimethyl-13-(4-chlorophenyl)-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine

Yield 0.954 g (53%)

mp 156-158 °C



153d

IR (KBr) (cm^{-1}) 3015, 2995, 2899, 2853, 1491, 1087, 821

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm)

2.13 (s, 3H), 2.23 (s, 3H), 3.87 (d, 1H, *J* = 17.2 Hz), 4.08 (d, 1H, *J* = 17.2 Hz), 4.30 (d, 1H, *J* = 16.8 Hz), 4.77 (d, 1H, *J* = 16.8 Hz), 5.28 (s, 1H), 6.45 (s, 1H), 6.76 (s, 1H), 6.95-7.53 (m, 7H), 7.81 (d, 1H, *J* = 8.0 Hz)

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm)

21.8, 53.4, 61.6, 75.0, 126.0, 126.3, 127.9, 128.1, 128.4, 128.6, 129.0, 129.3, 130.0, 134.1, 134.4, 137.9, 144.3, 148.3

MS *m/z* 360.2 (GCMS)

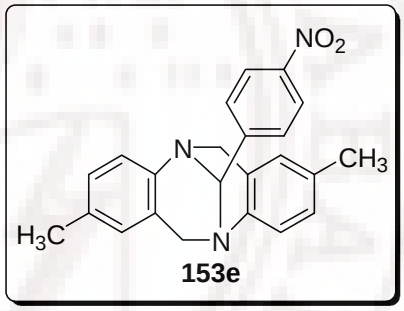
Analysis Calculated for $C_{23}H_{21}ClN_2$: C, 76.55%; H, 5.87%; N, 7.76%; Cl, 9.82%

Found: C, 76.45%; H, 5.90%; N, 7.81%

2,8-Dimethyl-13-(4-nitrophenyl)-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine

Yield 0.65 g (35%)

mp 159-161 °C (lit.[85b] mp 160.5-161 °C)



153e

IR (KBr) (cm^{-1}) 2920, 2852, 1601, 1521, 1493, 1344, 1084, 833

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm)

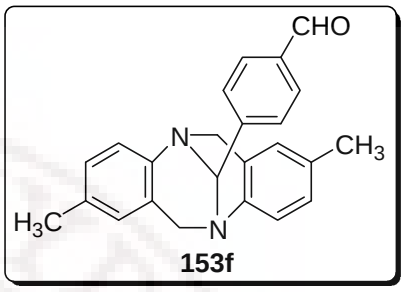
2.14 (s, 3H), 2.28 (s, 3H), 3.95 (d, 1H, *J* = 17.2 Hz), 4.06 (d, 1H, *J* = 16.8 Hz), 4.33 (d, 1H, *J* = 16.4 Hz), 4.84 (d, 1H, *J* = 16.4 Hz), 5.32 (s, 1H), 6.46 (s, 1H), 6.79 (s, 1H), 6.98-7.19 (m, 4H), 7.80 (d, 2H, *J* = 8.4 Hz), 8.12 (d, 2H, *J* = 8.4 Hz)

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm)

21.8, 53.6, 61.5, 75.2, 124.4, 126.0, 126.5, 127.9, 128.0, 128.3, 128.9, 129.2, 129.6, 129.7, 134.7, 146.8, 148.2

MS *m/z* 371.2 (GCMS)

2,8-Dimethyl-13-(4-formylphenyl)-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine



153f

Yield 0.92 g (52%)

mp 180-182 °C

IR (KBr) (cm^{-1}) 3012, 2918, 2845, 2727, 1701, 1606, 1493, 1201, 1084, 825

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm)

2.13 (s, 3H), 2.24 (s, 3H), 3.91 (d, 1H, *J* = 20.0 Hz), 4.07 (d, 1H, *J* = 20.0 Hz), 4.33 (d, 1H, *J* = 16.8 Hz), 4.81 (d, 1H, *J* = 16.4 Hz), 5.33 (s, 1H), 6.45 (s, 1H), 6.78 (s, 1H), 6.99-7.43 (m, 4H), 7.79 (s, 4H), 9.96 (s, 1H)

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm)

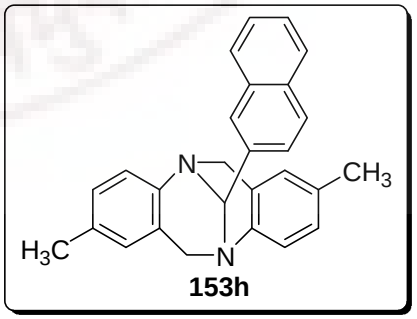
20.9, 52.7, 60.7, 74.6, 125.0, 125.4, 126.9, 127.0, 127.3, 127.4, 128.0, 128.2, 128.3, 128.5, 129.7, 133.4, 133.7, 135.5, 137.4, 143.3, 145.4, 147.4, 192.1

MS *m/z* 354.2 (GCMS)

Analysis Calculated for $C_{24}H_{22}N_2O$: C, 81.33%; H, 6.26%; N, 7.90%; O, 4.51%

Found: C, 81.34%; H, 6.28%; N, 7.88%

2,8-Dimethyl-13-(2-napthyl)-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine



153h

Yield 1.12 g (60%)

mp 167-169 °C

IR (KBr) (cm^{-1}) 3040, 3018, 2903, 2856, 1493, 1344, 1201, 825, 746

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm)

2.20 (s, 3H), 2.42 (s, 3H), 4.02 (d, 1 H, *J* = 16.8 Hz), 4.25 (d, 1H, *J* = 16.8 Hz), 4.48 (d, 1H, *J* = 16.4 Hz), 4.95 (d, 1H, *J* = 16.4 Hz), 5.57 (s, 1H), 6.50 (s, 1H), 6.57 (s, 1H), 6.89-8.0 (m, 11H)

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm)

20.9, 52.9, 60.9, 74.9, 125.2, 125.5, 125.6, 125.8, 125.9, 127.0, 127.4, 127.6, 127.8, 128.0, 128.2, 128.4, 132.9, 133.1, 133.4, 133.5, 136.1, 143.8, 147.8

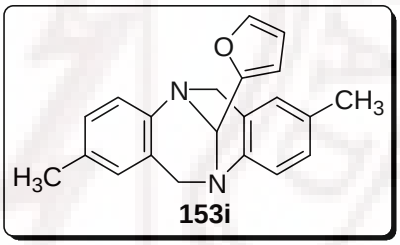
MS *m/z* 376.2 (GCMS)

Analysis Calculated for $C_{27}H_{24}N_2$: C, 86.13%; H, 6.43%; N, 7.44%;

Found: C, 86.16%; H, 6.46%; N, 7.85%

2,8-Dimethyl-13-furfuryl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine

Yield 0.96 g (61%)



153i

mp 133-135 °C (lit.[85b] mp 135-135.5 °C)

IR (KBr) (cm^{-1}) 3014, 2916, 2854, 1493, 1197, 831, 596

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm)

2.21 (s, 3H), 2.27 (s, 3H), 4.01 (d, 1H, *J* = 16.8 Hz), 4.19 (d, 1H, *J* = 16.8 Hz), 4.27 (d, 1H, *J* = 16.4 Hz), 4.82 (d, 1H, *J* = 16.8 Hz), 5.40 (s, 1H), 6.13 (s, 1H), 6.28 (s, 1H), 6.59 (s, 1H), 6.78 (s, 1H), 7.0-7.21 (m, 4H), 7.44 (s, 1H) **(Spectrum No. 11)**

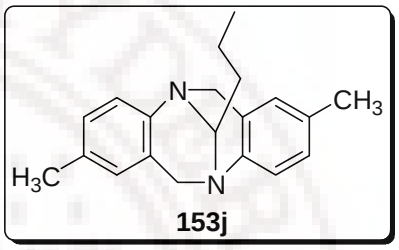
^{13}C NMR (100 MHz, $CDCl_3$, δ ppm)

20.9, 53.5, 60.6, 71.3, 109.1, 110.3, 125.1, 125.4, 126.9, 127.2, 127.4, 127.5, 128.2, 133.4, 133.8, 142.3, 143.5, 146.2, 151.6 **(Spectrum No. 12)**

MS *m/z* 316.2 (GCMS)

2,8-Dimethyl-13-propyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine

Yield 0.66 g (45%)



153j

IR (neat) (cm^{-1}) 2993, 2920, 2856, 1493, 832, 648

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm)

0.83 (t, 3H, *J* = 7.08 Hz), 1.59-1.73 (m, 4H), 2.15 (s, 6H), 3.92 (d, 1H, *J* = 17.2 Hz), 4.12 (t, 1H, *J* = 5.88 Hz), 4.19 (d, 1H, *J* = 16.4 Hz), 4.55 (d, 1H, *J* = 16.8 Hz), 4.70 (d, 1H, *J* = 16.4 Hz), 6.73 (d, 2H, *J* = 12 Hz), 6.9-7.06 (m, 4H) **(Spectrum No. 13)**

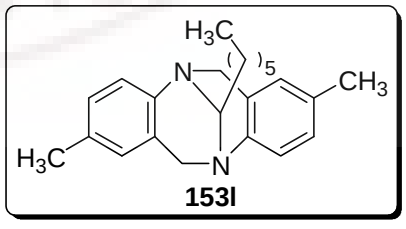
^{13}C NMR (100 MHz, $CDCl_3$, δ ppm)

14.0, 19.2, 20.8, 33.5, 52.3, 60.7, 73.3, 124.9, 125.9, 126.9, 127.3, 128.0, 128.3, 133.0, 133.2, 143.5, 148.0 **(Spectrum No. 14)**

MS *m/z* 292.1 (GCMS)

2,8-Dimethyl-13-hexyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine

Yield 0.71 g (43%)



153l

IR (neat) (cm^{-1}) 2994, 2922, 2856, 1493, 1203, 831, 648

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm)

0.90-1.7 (m, 12H), 2.25 (s, 6H), 4.01-4.11 (m, 3H), 4.20 (d, 1H, *J* = 16.8 Hz), 4.55 (d, 1H, *J* = 17.2 Hz), 4.70 (d, 1H, *J* = 16.4 Hz), 6.73 (d, 2H, 11.6 Hz), 7.0-7.07 (m, 4H)

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm)

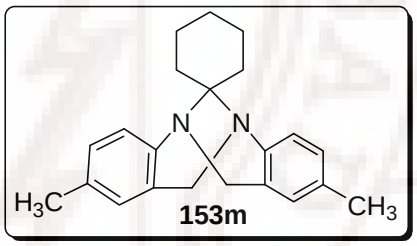
14.1, 20.9, 22.6, 26.0, 29.2, 31.4, 31.8, 52.3, 60.7, 73.5, 124.9, 125.9, 126.9, 127.2, 127.9, 128.2, 133.0, 133.2, 143.4, 147.9

MS *m/z* 334.3 (GCMS)

2,8-Dimethyl-13-spiro[cyclohexane-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine]

Yield 0.79 g (50%)

mp 192-194 °C (lit.[85b] mp 195-196 °C)



153m

IR (KBr) (cm^{-1}) 2920, 2854, 1493, 1199, 1103, 833

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm)

1.52-1.84 (m, 10H), 2.25 (s, 6H), 4.07 (d, 2H, *J* = 16.8 Hz), 4.61 (d, 2H, *J* = 17.2 Hz), 6.99 (s, 2H), 6.99-7.08 (m, 4H) **(Spectrum No. 15)**

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm)

20.9, 22.1, 26.0, 33.3, 54.6, 70.2, 126.1, 126.6, 128.1, 128.4, 133.0, 146.0 **(Spectrum No. 16)**

MS *m/z* 318.3 (GCMS)

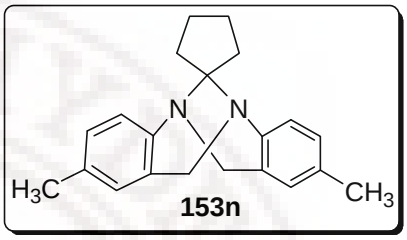
Analysis Calculated for $C_{22}H_{26}N_2$: C, 82.97%; H, 8.23%; N, 8.80%

Found: C, 82.94%; H, 8.22%; N, 8.72%

2,8-Dimethyl-13-spiro[cyclopentane-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine]

Yield 0.62 g (41%)

mp 182-184 °C



153n

IR (KBr) (cm^{-1}) 2922, 2854, 1493, 1332, 1186, 837

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm)

1.73-2.07 (m, 8H), 2.25 (s, 6H), 4.13 (d, 2H, *J* = 17.2 Hz), 4.74 (d, 2H, *J* = 17.2 Hz), 6.72 (s, 2H), 6.98-7.07 (m, 4H)

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm)

20.9, 23.9, 35.9, 55.6, 80.7, 125.8, 126.8, 127.8, 127.9, 133.1, 146.7

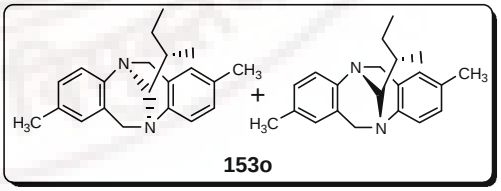
MS *m/z* 304.2 (GCMS)

Analysis Calculated for $C_{21}H_{24}N_2$: C, 82.85%; H, 7.95%; N, 9.20%

Found: C, 82.21%; H, 8.61%; N, 9.25%

2,8-Dimethyl-13-(2-butyl)-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine

Yield 0.61 g (40%)



153o

IR (neat) (cm^{-1}) 2990, 2925, 2860, 1493, 840, 647

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm)

0.83 (t, 3H, *J* = 7.6 Hz), 0.87-0.93 (m, 2H), 0.98 (d, 3H, *J* = 6.4 Hz), 1.19-1.22 (m, 1H), 2.2 (s, 6H), 3.58 (t, 1H, *J* = 10.4 Hz), 3.95 (d, 1H, *J* = 16.8

Hz), 4.13 (dd, 1H, J_1 = 13.2 Hz, J_2 = 3.6 Hz), 4.41 (dd, 1H, J_1 = 10.4 Hz, J_2 = 6.8 Hz), 4.56 (dd, 1H, J_1 = 12.4 Hz, J_2 = 4.0 Hz), 6.67 (d, 2H, J = 15.2 Hz), 6.92-7.0 (m, 4H) **(Spectrum No. 17)**

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm)

10.6, 11.1, 15.3, 15.6, 20.8, 25.2, 25.7, 33.8, 34.2, 52.1, 52.4, 60.9, 77.6, 77.8, 125.0, 125.8, 126.8, 127.1, 127.7, 128.0, 128.3, 132.7, 132.9, 143.6 (dr = 1:1, signals of both diastereomers are included) **(Spectrum No. 18)**

$[\alpha]_D^{25}$ 19° (*c* 0.4, $CHCl_3$) (dr was estimated by chiral HPLC analysis on Chiralcel-OD-H column, hexane/2-propanol = 95:5, flow rate: 1 mL/min.)

MS *m/z* 306.2 (GCMS)

Analysis Calculated for $C_{21}H_{26}N_2$: C, 82.31%; H, 8.55%; N, 9.14%

Found: C, 82.76%; H, 7.91%; N, 9.32%

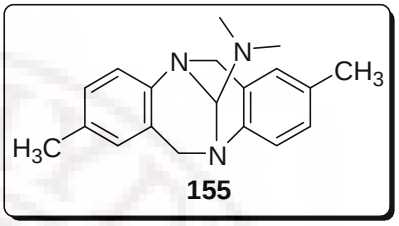
3.4.2 Procedure for the exchange of DMF with the endo methylene group of Tröger base in the presence of $POCl_3$:

To a solution of Tröger base (1.25 g, 5 mmol) in DMF (5 mL) was added $POCl_3$ (0.8 mL, 8.75 mmol) slowly at 0 °C. The reaction mixture was brought to 25 °C and allowed to stir for 3 h at 80 °C. Then it was diluted with ethyl acetate and neutralized with aq. NaOH solution. The aqueous layer was extracted with ethyl acetate and the combined organic extracts were successively washed with water, brine and dried over anhydrous Na_2SO_4. After removal of the solvent the residue was subjected to chromatography on silicagel using 5% ethyl acetate in hexane to elute the 5,11-substituted derivative **155**.

2,8-dimethyl-13-yl(dimethylamine)-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine

Yield 0.95 g (63%)

IR (neat) (cm^{-1}) 2995, 2947, 2856, 2773, 1493, 1433, 1354, 1105, 821, 736



155

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 2.09 (d, 6H, *J* = 7.08 Hz), 2.31 (s, 6H), 3.74 (d, 2H, *J* = 19.6 Hz), 4.06 (d, 1H, *J* = 16.8 Hz), 4.49 (d, 2H, *J* = 16.8 Hz), 6.58 (d, 2H, 16.4 Hz), 6.80-7.92 (m, 4H) **(Spectrum No. 19)**

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 20.9, 41.6, 51.7, 59.5, 90.4, 125.2, 125.4, 127.0, 127.8, 128.0, 128.3, 133.0, 133.2, 142.2, 146.4 **(Spectrum No. 20)**

MS *m/z* 293.1 (GCMS)

3.4.3 General procedure for the preparation of 5,11-substituted derivatives of Tröger base using $POCl_3$:

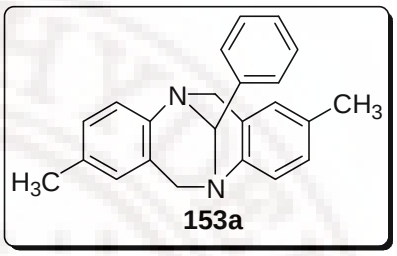
To a solution of Tröger base (1.25 g, 5 mmol) in toluene (15 mL) was added $POCl_3$ (0.8 mL, 8.75 mmol) slowly at 0 °C under N_2. Then carbonyl compound (5.1 mmol) was added at 0 °C. The reaction mixture was brought to 25 °C and allowed to stir for 3 h at 80 °C. Then it was diluted with ethyl acetate and neutralized with 10% aq. NaOH solution. The aqueous layer was extracted with ethyl acetate and the combined organic extracts were successively washed with water, brine and dried over anhydrous Na_2SO_4. After removal of

the solvent the residue was subjected to chromatography on silicagel using 2% ethyl acetate in hexane to elute the desired 5,11-substituted derivatives of Tröger base.

2,8-Dimethyl-13-phenyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine(5,11-endo benzylidine analog of Tröger base)

Yield 0.98 g (60%)

mp 180-182 °C (lit.[85b] mp 182-183 °C)

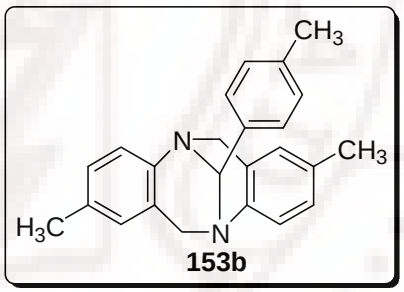


153a

2,8-Dimethyl-13-(4-methylphenyl)-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine

Yield 1.1 g (65%)

mp 168-170 °C

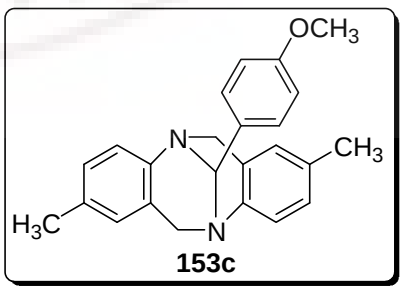


153b

2,8-Dimethyl-13-(4-methoxyphenyl)-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine

Yield 1.2 g (68%)

mp 152-154 °C (lit.[85b] mp 155-156 °C)

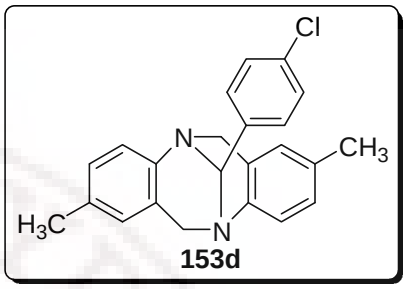


153c

2,8-Dimethyl-13-(4-chlorophenyl)-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine

Yield 0.99 g (60%)

mp 156-158 °C

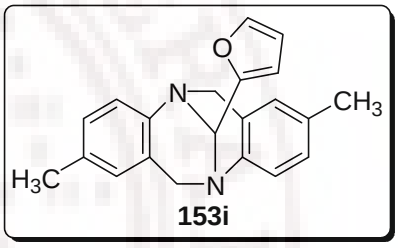


153d

2,8-Dimethyl-13-furfuryl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine

Yield 0.95 g (60%)

mp 133-135 °C (lit.[85b] mp 135-135.5 °C)



153i

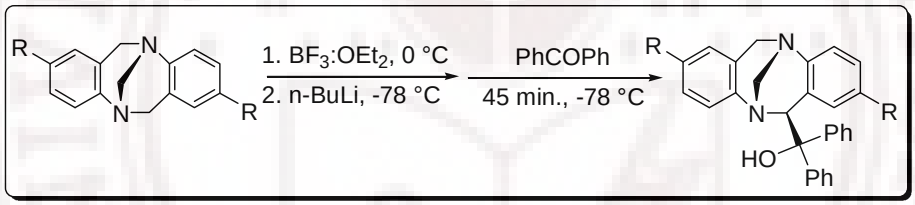
3.4.4 Resolution of 5,11-endo substituted Tröger base analogs:

Separation (analytical) of **153a**, **153b**, **153c** and **153m** was carried out using high performance liquid chromatography (HPLC) on chiralcel-OJ-H column and ethanol was used as mobile phase with flow rate 1 mL/min.

3.4.5 General procedure for the preparation of aminoalcohols 101 and 158:

To an oven dried round bottom flask equipped with a stir bar, septum, cooled under nitrogen, was added chiral Tröger base (for **101**) or chiral methoxy Tröger base (for **158**) (4 mmol) and 30 mL of dry THF. The solution was cooled to 0 °C, BF_3:OEt_2 (0.58 mL, 4.1 mmol) was added and allowed to stir for 15 min. The solution was cooled to -78 °C and allowed to stir for 10 min. Then, n-BuLi (2.7 mL of 1.6 M solution in hexanes, 4.1 mmol)

was added and the resulting orange-red solution was stirred for 10 min. Benzophenone (0.75 g, 4.1 mmol, in dry THF) was added slowly through syringe. The orange-red colour disappeared at the end of addition and the solution was allowed to stir for 45 min. at -78 °C. The reaction was quenched by the careful addition of cold water (5 mL). The reaction mixture was extracted with diethyl ether (2 x 15 mL) and the combined organic extracts were successively washed with water, brine and dried over anhydrous Na_2SO_4. After the removal of solvent, the residue was subjected to chromatography on silicagel to elute the desired amino alcohol.

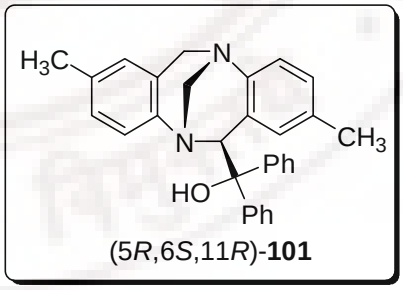


(5*R*,6*S*,11*R*)-2,8-Dimethyl-6-yl(diphenylcarbinol)-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine

Yield 1.04 g (60%)

mp 100-102 °C (lit.[52] mp 100-105 °C)

IR (KBr) (cm^{-1}) 3360, 3024, 2920, 1491, 1217, 958, 700



(5*R*,6*S*,11*R*)-**101**

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm)

1.93 (s, 3H), 2.22 (s, 3H), 3.44 (dd, 1H, J_1 = 11.2 Hz, J_2 = 1.6 Hz), 3.64 (d, 1H, J = 13.2 Hz), 3.94 (d, 1H, J = 16.8 Hz), 4.48 (d, 1H, J = 16.8 Hz), 4.77

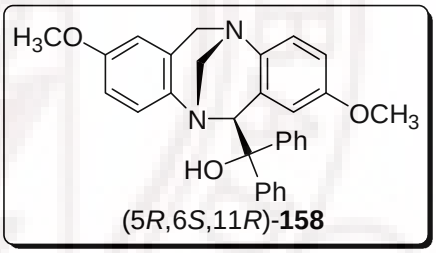
(s, 1H), 4.88 (brs, 1H), 5.83 (d, 2H, 11.2 Hz), 6.65 (s, 1H), 6.93-7.33 (m, 11H), 7.40-7.50 (m, 2H)

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm)

20.8, 20.9, 58.3, 61.5, 77.3, 78.8, 124.3, 124.9, 125.8, 126.4, 127.3, 127.4, 127.7, 128.1, 128.2, 128.3, 128.5, 128.6, 129.0, 132.7, 134.0, 142.0, 144.4, 145.4, 146.6

$[\alpha]_D^{25}$ +37° (*c* 1, $CHCl_3$) (dr was estimated by chiral HPLC analysis on Chiralcel-OD-H column, hexane/2-propanol = 95:5, flow rate: 1 mL/min.)

(5*R*,6*S*,11*R*)-2,8-Dimethoxy-6-yl(diphenylcarbinol)-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine



(5*R*,6*S*,11*R*)-**158**

Yield 1.07 g (58%)

mp 148-150 °C

IR (KBr) (cm^{-1}) 3416, 3057, 3003, 2924, 2852, 1493, 1344, 1238, 702

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm)

3.14 (s, 3H), 3.30 (d, 1H, *J* = 13.2 Hz), 3.54 (d, 1H, *J* = 13.2 Hz), 3.61 (s, 3H), 3.84 (d, 1H, *J* = 16.8 Hz), 4.38 (d, 1H, *J* = 16.8 Hz), 4.67 (s, 1H), 5.58 (d, 1H, *J* = 2.8 Hz), 5.75 (s, 1H), 6.28 (d, 1H, *J* = 2.8 Hz), 6.65 (dd, 1H, J_1 = 2.8 Hz, J_2 = 6 Hz), 6.72 (dd, 1H, J_1 = 2.8 Hz, J_2 = 6 Hz), 6.91 (d, 1H, *J* = 8.8 Hz), 7.33-7.13 (m, 9H), 7.54 (d, 2H, *J* = 8.0 Hz) **(Spectrum No. 21)**

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm)

54.7, 55.4, 58.4, 61.9, 77.6, 78.9, 110.5, 111.1, 114.0, 116.5, 125.5, 126.3, 127.2, 127.4, 127.9, 128.2, 128.3, 128.7, 129.7, 140.9, 141.8, 142.1, 144.5, 155.3, 156.4 **(Spectrum No. 22)**

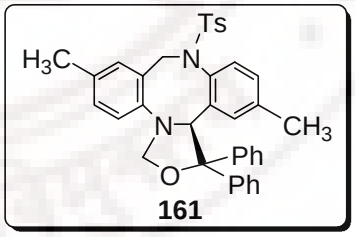
$[\alpha]_D^{25}$ +27±1° (*c* 1, $CHCl_3$) (dr was estimated by chiral HPLC analysis on Chiralcel-OD-H column, hexane/2-propanol = 95:5, flow rate: 1 mL/min.)

3.4.6 Procedure for the preparation of compound 161:

To a solution of aminoalcohol **101** (1.27 g, 3 mmol) in pyridine (5 mL) was added *p*-toluenesulfonyl chloride (0.69 g, 3.6 mmol) at 0 °C under N_2. The contents were stirred for 6 h at 25 °C, then diluted with diethyl ether (10 mL). The organic phase was washed with aq. $NaHCO_3$ (5 mL) and brine. The organic phase was dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was subjected to chromatography on silicagel (100-200 mesh) column using 10% ethyl acetate in hexane to obtain compound **161**.

Yield 1.39 g (58%)

mp 188-190 °C



161

IR (KBr) (cm^{-1}) 3024, 2932, 1510, 1236, 1039

^1H NMR (400 MHz, $CDCl_3$, δ ppm)

1.91 (s, 3H), 2.13 (s, 3H), 2.44 (s, 3H), 4.60 (d, 1H, *J* = 12.6 Hz), 4.98 (s, 1H), 5.14 (d, 1H, *J* = 12.6 Hz), 5.2 (s, 1H), 5.9 (s, 1H), 5.94 (d, 1H, *J* = 8.4 Hz), 6.69 (s, 1H), 6.74 (d, 2H, *J* = 8.0 Hz), 6.97-7.40 (m, 14H), 7.86 (d, 2H, *J* = 8.4 Hz) **(Spectrum No. 23)**

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm)

20.2, 21.1, 21.7, 56.0, 67.4, 81.0, 90.4, 115.9, 122.4, 123.8, 124.4, 125.9, 126.5, 127.1, 127.8, 127.9, 128.0, 128.2, 128.6, 129.1, 129.5, 129.9, 130.0, 130.3, 134.2, 134.3, 136.1, 136.8, 137.4, 137.5, 142.6, 143.9, 144.7, 146.0

(Spectrum No. 24)

$[\alpha]_D^{25}$ -24±1° (*c* 0.5, $CHCl_3$)

Analysis Calculated for $C_{37}H_{34}N_2O_3S$: C, 75.74%; H, 5.84%; N, 4.77%; O, 8.18%; S, 5.47%

Found: C, 75.81%; H, 5.81%; N, 4.85%

3.4.7 Procedure for the preparation of α-monobenzylated Tröger base:

To an oven dried round bottom flask equipped with a stir bar, septum, cooled under nitrogen, was added chiral Tröger base (1.0 g, 4 mmol) and 30 mL of dry toluene. The solution was cooled to 0 °C, BF_3:OEt_2 (0.58 mL, 4.1 mmol) was added and allowed to stir for 15 min. The solution was cooled to -78 °C and allowed to stir for 10 min. n-BuLi (2.7 mL of 1.6 M solution in hexanes, 4.1 mmol) was added and the resulting solution was stirred for 10 min. Then, benzyl bromide (0.48 mL, 4.1 mmol, in dry toluene) was added slowly through syringe. The mixture was allowed to stir for 1 h at -78 °C. The reaction was quenched by the careful addition of cold water (5 mL). The reaction mixture was extracted in ethyl acetate (2 x 15 mL) and the combined organic extracts were successively washed with water, brine and dried over anhydrous Na_2SO_4. After removal of the solvent, the

residue was subjected to chromatography on silicagel using 10% ethyl acetate in hexane to elute the desired monobenzylated Tröger base **179**.

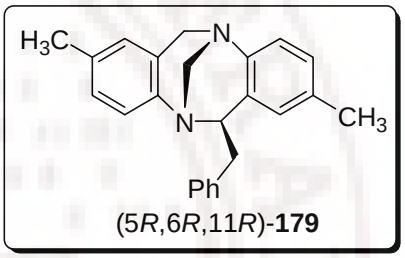
(5*R*,6*R*,11*R*)-2,8-Dimethoxy-6-benzyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine

Yield 0.68 g (50%)

IR (neat) (cm^{-1}) 3028, 2922, 2855, 1493, 1221, 827

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm)

2.16 (s, 3H), 2.24 (s, 3H), 3.0-3.19 (m, 2H), 4.0-4.20 (m, 3H), 4.49 (dd, 1H, J_1 = 11.6 Hz, J_2 =1.6 Hz), 4.65 (d, 1H, J = 16.8 Hz), 6.41 (d, 1H, J = 8.4 Hz), 6.64 (s, 1H), 6.77-6.84 (m, 2H), 6.97-7.0 (m, 2H), 7.23-7.45 (m, 5H) **(Spectrum No. 25)**



(5*R*,6*R*,11*R*)-**179**

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm)

21.0, 43.1, 58.5, 61.5, 69.2, 115.5, 124.5, 125.0, 126.4, 127.4, 128.1, 128.4, 129.6, 130.9, 133.3, 140.1, 145.6, 146.5 **(Spectrum No. 26)**

$[\alpha]_D^{25}$ -262±2° (*c* 0.5, $CHCl_3$) (dr was estimated by chiral HPLC analysis on Chiralcel-OD-H column, hexane/2-propanol = 98:2, flow rate: 1 mL/min.)

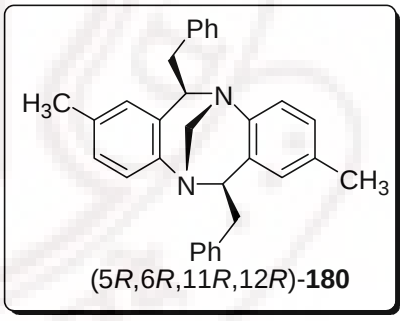
Note: We carried out the same reaction in dry THF and obtained the monobenzylated product **179** in 40% yield and dibenzylated Tröger base **180** in 20% yield.

3.4.8 Procedure for the preparation of α,α'-dibenzylated Tröger base:

To an oven dried round bottom flask equipped with a stir bar, septum, cooled under nitrogen, was added chiral monobenzylated Tröger base (1.36 g, 4 mmol) and 30 mL of dry

toluene. The solution was cooled to 0 °C, BF_3:OEt_2 (0.58 mL, 4.1 mmol) was added and allowed to stir for 15 min. The solution was cooled to -78 °C and allowed to stir for 10 min. n-BuLi (2.7 mL of 1.6 M solution in hexanes, 4.1 mmol) was added and the resulting solution was stirred for 10 min. Then, benzyl bromide (0.48 mL, 4.1 mmol, in 2 mL of dry toluene) was added slowly through syringe. The mixture was stirred for 1 h at -78 °C. The reaction was quenched by the careful addition of cold water (5 mL). The reaction mixture was extracted in ethyl acetate (2 x 15 mL) and the combined organic extracts were successively washed with water, brine and dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was subjected to chromatography on silicagel using 6% ethyl acetate in hexane to elute the desired dibenzylated Tröger base **180**.

(5*R*,6*R*,11*R*,12*R*)-2,8-Dimethoxy-6,12-dibenzyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5] diazocine



(5*R*,6*R*,11*R*,12*R*)-**180**

Yield 0.86 g (50%)

mp 206-208 °C (lit.[155] mp 206-208 °C)

IR (KBr) (cm^{-1}) 3077, 3030, 3003, 2924, 2852, 1493, 1034, 694

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm)

2.19 (s, 6H), 3.07-3.19 (m, 4H), 4.16-4.19 (m, 2H), 4.39 (s, 2H), 6.42 (d, 2H, *J* = 8.0 Hz), 6.78 (s, 2H), 6.81 (d, 2H, *J* = 8 Hz), 7.30-7.46 (m, 10H) **(Spectrum No. 27)**

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm)

20.9, 43.0, 56.0, 68.9, 124.5, 126.3, 128.1, 128.2, 128.3, 129.6, 130.6, 132.7, 140.1, 146.5 **(Spectrum No. 28)**

$[\alpha]_D^{25}$ -255±2° (*c* 0.46, $CHCl_3$) (dr was estimated by chiral HPLC analysis on Chiralcel-OD-H column, hexane/2-propanol = 95:5, flow rate: 1 mL/min.)

Note: We carried out the same reaction in dry THF and obtained the dibenzylated product **180** in 20% yield, compound **181** in 50% yield.

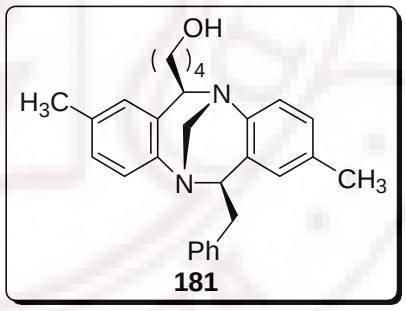
(5*R*,6*R*,11*R*)-2,8-Dimethoxy-6-benzyl-12-yl(n-butanol)-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine

Yield 0.82 g (50%)

mp 148-150 °C

IR (KBr) (cm^{-1}) 3300, 3022, 2928, 2856, 1491, 1238, 825

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm)



181

1.72-1.86 (m, 6H), 2.06 (brs, 1H), 2.19 (s, 3H), 2.25 (s, 3H), 3.09-3.22 (m, 2H), 3.79 (t, 2H, *J* = 6 Hz), 3.92-3.98 (m, 1H), 4.18-4.34 (m, 3H), 6.41 (d, 1H, *J* = 5.2 Hz), 6.72 (s, 1H), 6.79 (d, 1H, *J* = 8.4 Hz), 6.84 (s, 1H), 6.98 (s, 2H), 7.30-7.43 (m, 5H) **(Spectrum No. 29)**

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm)

20.9, 23.5, 32.7, 36.2, 43.1, 56.0, 62.8, 67.3, 68.9, 124.3, 124.8, 126.3, 128.0, 128.3, 129.6, 130.9, 131.5, 132.7, 132.8, 140.1, 146.2, 146.7 **(Spectrum No. 30)**

$[\alpha]_D^{25}$ +230±1° (*c* 0.35, $CHCl_3$) (dr was estimated by chiral HPLC analysis on Chiralcel-OD-H column, hexane/2-propanol = 95:5, flow rate: 1 mL/min.)

MS m/z 412.2 (GCMS)

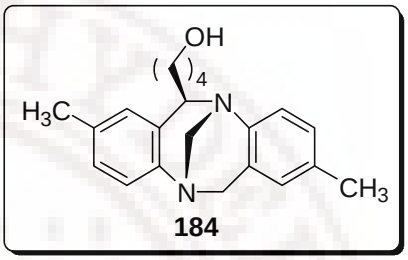
Analysis Calculated for $C_{28}H_{32}N_2O$: C, 81.51%; H, 7.82%; N, 6.79%; O, 3.88%

Found: C, 81.20%; H, 7.38%; N, 6.75%

3.4.9 Procedure for the preparation of compound 184:

To an oven dried round bottom flask equipped with a stir bar, septum, cooled under nitrogen, was added chiral Tröger base (1.0 g, 4 mmol) and 30 mL of dry THF. The solution was cooled to 0 °C, BF_3:OEt_2 (1.2 mL, 8.2 mmol) was added and allowed to stir for 15 min. It was then cooled to -78 °C and allowed to stir for 10 min. n-BuLi (2.7 mL of 1.6 M solution in hexanes, 4.1 mmol) was added and the resulting orange-red solution was stirred for 10 min. Then, the reaction mixture was allowed to warm to 25 °C during 3 h and quenched by the careful addition of cold water (5 mL). The reaction mixture was extracted with ethyl acetate (2 x 15 mL) and the combined organic extracts were successively washed with water, brine and dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was subjected to chromatography on silicagel using 25% ethyl acetate in hexane to elute compound **184**.

(5*R*,6*R*,11*R*)-2,8-Dimethoxy-6-yl(n-butanol)-dibenzyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine



184

Yield 0.51 g (40%)

IR (neat) (cm^{-1}) 3375, 2926, 2854, 1493, 1035, 829

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm)

1.68-1.73 (m, 6H), 1.82 (brs, 1H), 2.20 (s, 3H), 2.22 (s, 3H), 3.77 (t, 2H, *J* = 6 Hz), 3.92-3.98 (m, 1H), 4.06-4.13 (m, 2H), 4.34 (d, 1H, *J* = 12.8 Hz), 4.65 (d, 1H, *J* = 16.8 Hz), 6.68 (s, 1H), 6.77 (s, 1H), 6.92-7.02 (m, 4H) **(Spectrum No. 31)**

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm)

20.9, 23.7, 32.7, 36.3, 58.4, 61.4, 62.6, 67.5, 124.8, 127.3, 127.5, 128.1, 128.2, 128.3, 131.8, 133.1, 133.3, 145.0, 146.6 **(Spectrum No. 32)**

$[\alpha]_D^{25}$ -25.4° (*c* 0.4, $CHCl_3$) (dr was estimated by chiral HPLC analysis on Chiralcel-OD-H column, hexane/2-propanol = 95:5, flow rate: 1 mL/min.)

MS *m/z* 322.2 (GCMS)

Analysis Calculated for $C_{21}H_{26}N_2O$: C, 78.22%; H, 8.13%; N, 8.69%; O, 4.96%

Found: C, 78.10%; H, 8.18%; N, 8.75%

3.5 Asymmetric aziridination of chalcones promoted by chiral Tröger base and derivatives

3.5.1 Preparation of *O*-diphenylphosphinyl hydroxylamine ($DppONH_2$):

Aqueous NaOH (1.94 g, 48.6 mmol, 7.0 mL (H_2O), 7.1M) was added to a stirred solution of hydroxylamine hydrochloride (3.96 g, 57.0 mmol) in H_2O (8.5 mL). Dioxane (30 mL) was added and the solution was cooled to -5 °C using an ice/salt bath. Diphenylphosphinyl chloride (4.0 mL, 21.1 mmol) in dioxane (25 mL) was added in one portion with vigorous stirring. Stirring continued for 15 min as copious precipitation ensued. Water (30 mL) was added and the slurry was filtered, washed with cold water (30 mL). The white solid was dried under vacuum (2 h), then purified by stirring with aqueous NaOH (0.5 g in 50 mL, 0.25M) at 0 °C for 30 min. The product was filtered, washed with cold water (30 mL), then dried under vacuum at 100 °C (1 h) to give *O*-diphenylphosphinyl hydroxylamine as a white powdery solid.

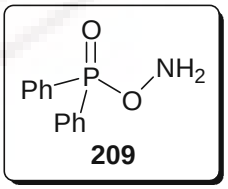
Yield 2.1 g (43 %)

mp >132 °C gradual decomp. (lit.[156] >130 °C gradual decomp.)

IR (KBr) (cm^{-1}) 3273, 3167, 3074, 1440, 1205, 893, 526

^1H NMR (400 MHz, $CDCl_3$, δ ppm) **(Spectrum No. 33)**

5.89 (brs, 2H), 7.31-7.50 (m, 4 H), 7.60-7.70 (m, 2H), 7.86-7.97 (m, 4H)

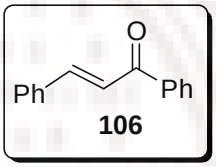


209

^{31}P NMR (162 MHz, $CDCl_3$, δ ppm) 37.5 **(Spectrum No. 34)**

3.5.2 Procedure for the prepation of chalcone:

Acetophenone (1.44 mL, 12.5 mmol), benzaldehyde (1.25mL, 12.5 mmol) and NaOH (0.5 g, 12.5 mmol) were mixed and grounded in pestle and mortar for 10 min. Then, the mixture was extracted with ethyl acetate and the organic layer was successively washed with water, brine and dried over anhydrous Na_2SO_4. The solvent was evaporated to get the chalcone **106**.



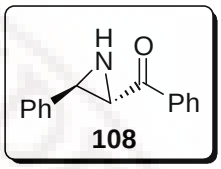
106

Yield	quantitative
mp	56-58 °C. (lit.[157] 56-58 °C)
IR (KBr)	(cm^{-1}) 3061, 1662, 1604, 746
^{1}H NMR	(400 MHz, $CDCl_3$, δ ppm)
	7.36-8.04 (m, 12 H)

3.5.3 General procedure for the chiral Tröger base promoted asymmetric aziridination of chalcones:

Chiral Tröger base (33 mg, 0.13 mmol) was added in one portion to a suspension of $DppONH_2$ **209** (29 mg, 0.13 mmol) in CH_2Cl_2 (2 mL) at 25 °C. The white mixture was allowed to stir for 30 min (It becomes clear solution), then 2-propanol (20 μL, 0.25 mmol), NaH (60% dispersion in mineral oil, 10 mg, 0.25 mmol) and chalcone (25 mg, 0.12 mmol) were added sequentially. The mixture was stirred for 16 h at 25 °C, then quenched by the addition of saturated NH_4Cl solution (2 mL). The aqueous layer was extracted with CH_2Cl_2

(3 x 10 mL). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. Purification by column chromatography on silicagel using ethyl acetate/hexane (8:92) to elute the aziridine **108**.



108

Yield 15 mg (58%)

mp 98-100 °C. (lit.[107] 100-101 °C)

IR (KBr) (cm^{-1}) 3217, 3057, 2920, 1660, 698

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm)

2.67 (brs, 1H), 3.18 (dd, 1H, J_1 = 7.2 Hz, J_2 = 2.0 Hz), 3.51 (dd, 1H, J_1 = 6.0 Hz, J_2 = 2.0 Hz), 7.31-7.37 (m, 5H), 7.47-7.51 (m, 2H), 7.60-7.63 (m, 1H) 8.0 (d, 2H, J = 8.4 Hz) **(Spectrum No. 35)**

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm)

43.5, 44.0, 126.2, 127.9, 128.1, 128.3, 128.6, 128.8, 133.8, 135.9, 138.3, 195.7 **(Spectrum No. 36)**

$[\alpha]_D^{25}$ +186° (*c* 0.2, $CHCl_3$)

ee 70% ee {determined by HPLC analysis on Chiralcel-OD-H, hexane/2-propanol = 90:10, Flow rate: 1.0 mL/min, 254 nm.

Note: Same experimental procedure was followed for the asymmetric aziridination reaction using different chiral Tröger base as ligands.

3.6 Racemic dihydroxylation of *trans*-stilbenes using Tröger base 1 as ligand

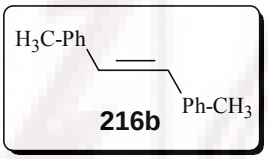
3.6.1 General procedure for the preparation of substituted *trans*-stilbenes:

To a stirred suspension of activated Zn (2.6 g, 40 mmol) in dry THF (40 mL), was added $TiCl_4$ (2.2 mL, 20 mmol) slowly under N_2 atmosphere at 0 °C. The reaction mixture was stirred for 1 h and the aldehyde (10 mmol) in 5 mL of THF was added at 0 °C. Then the contents were refluxed for 5 h. and quenched with saturated NH_4Cl solution (10 mL). The organic layer was separated and the aqueous layer was extracted with ether (2 x 15 mL). The combined organic extracts were washed with brine and dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was subjected to chromatography on silicagel using hexane and ethyl acetate mixture to isolate the stilbene derivative.

4,4'-Dimethyl *trans*-stilbene

Yield 1.45 g (70%)

mp 178-179 °C (lit.[158] mp 180 °C)

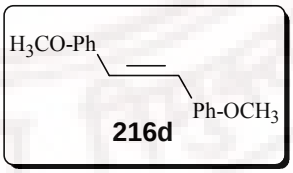


216b

4,4'-Dimethoxy *trans*-stilbene

Yield 1.75 g (73%)

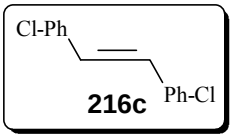
mp 210-211 °C



216d

4,4'-Dichloro *trans*-stilbene

Yield 1.89 g (75%)



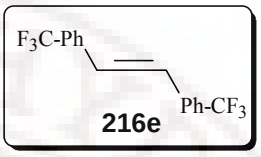
216c

mp 170-172 °C (lit.[159] mp 168-170 °C)

4,4'-Bis(trifluoromethyl) *trans*-stilbene

Yield 2.50 g (80%)

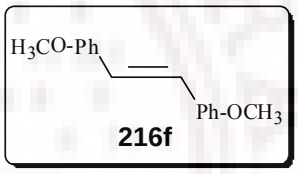
mp 132-134 °C (lit.[160] mp 134-135 °C)



3,3'-Dimethoxy *trans*-stilbene

Yield 1.67 g (70%)

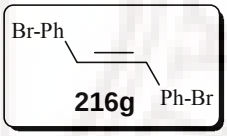
mp 99-101 °C (lit.[161] mp 99-100 °C)



2,2'-Dibromo *trans*-stilbene

Yield 2.25 g (67%)

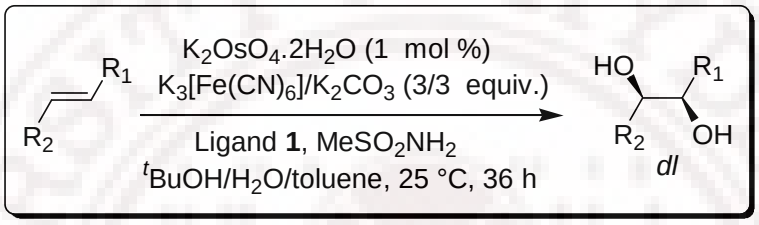
mp 105-107 °C (lit.[162] mp 108-108.5 °C)



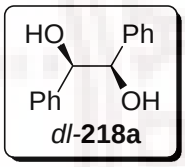
3.6.2 General procedure for dihydroxylation of *trans*-stilbenes in the presence of racemic Tröger base 1 as ligand using toluene/^{t}BuOH/H_2O solvent system:

To a mixture of potassium ferricyanide (1.98 g, 6 mmol), potassium carbonate (0.84 g, 6 mmol), ligand **1** (0.05 g, 10 mol %) and potassium osmate dihydrate (0.007 g, 1 mol %) was added toluene (10 mL)/^{t}BuOH (10 mL)/H_2O (10 mL) and stirred vigorously at 25 °C for 10 min and then the reaction mixture was cooled to 0 °C. To this solution were added methanesulfonamide (0.19 g, 2 mmol), substituted *trans*-olefin (2 mmol) at once and the mixture was stirred for 36 h at 25 °C. It was quenched with sodium sulfite (3.0 g). After stirring for 1.5 h, the organic layer was separated and the aqueous layer was extracted with

ether (2 x 10 mL). The combined organic layer was successively washed with 8 N hydrochloric acid, brine and dried over anhydrous Na_2SO_4. The solvent was evaporated and the crude diol was purified by chromatography on silca gel column using ethyl acetate/hexane (3:7) as eluent.



_dl_-1,2-Diphenylethane-1,2-diol



Yield 0.39 g (92%)

mp 145-148 °C (lit.[144] 148-150 °C)

IR (KBr) (cm^{-1}) 3499, 3400, 2893, 1452, 1197, 1043, 777, 696

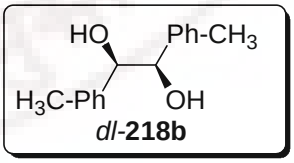
^1H NMR (400 MHz, $CDCl_3$, δ ppm)

3.03 (brs, 2H), 4.67 (s, 2H), 7.08-7.19 (m, 10H)

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm)

79.1, 126.9, 127.9, 128.1, 139.8

_dl_-1,2-Bis(4-methylphenyl) ethane-1,2-diol



Yield 0.43 g (90%)

mp 108-110 °C (lit.[163] 110 °C)

IR (KBr) (cm^{-1}) 3490, 3400, 2892, 1450, 1197,1043, 776, 694

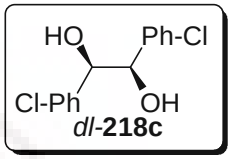
^1H NMR (400 MHz, $CDCl_3$, δ ppm)

2.29 (s, 6H), 2.82 (brs, 2H), 4.65 (s, 2H), 7.02 (brs, 8H)

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm)

21.1, 78.8, 126.8, 128.8, 137.0, 137.5

_dl_-1,2-Bis(4-chlorophenyl) ethane-1,2-diol



_dl_-**218c**

Yield 0.53 g (94%)

mp 126-128 °C (lit.[164] 127 °C)

IR (KBr) (cm^{-1}) 3486, 3399, 2890, 1448, 1198,1042, 692

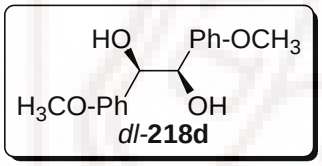
^{1}H NMR (400 MHz, $CDCl_3$, δ ppm)

3.16 (brs, 2H), 4.56 (s, 2H), 6.98 (d, 4H, *J* = 8.36 Hz), 7.19 (d, 4H, *J* = 8.36 Hz)

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm)

78.5, 128.4, 133.8, 137.9

_dl_-1,2-Bis(4-methoxyphenyl) ethane-1,2-diol



_dl_-**218d**

Yield 0.42 g (78%)

mp 118-119 °C (lit.[165] 118-119 °C)

IR (KBr) (cm^{-1}) 3489, 3398, 2890, 1448, 1193, 1043, 774

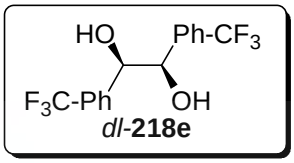
^{1}H NMR (400 MHz, $CDCl_3$, δ ppm)

2.80 (brs, 2H), 3.76 (s, 6H), 4.63 (s, 2H), 6.75 (d, 4H, *J* = 8.64 Hz), 7.03 (d, 4H, *J* = 8.64 Hz)

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm)

55.2, 78.8, 113.5, 128.2, 132.2, 159.2

_dl_-1,2-Bis(4-trifluoromethylphenyl) ethane-1,2-diol



_dl_-**218e**

Yield 0.63 g (90%)

mp 128-130 °C

IR (KBr) (cm^{-1}) 3400, 3344, 2928, 1928, 1622, 1331, 1122, 1070, 839, 763, 609, 524

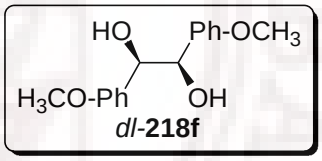
^{1}H NMR (400 MHz, $CDCl_3$, δ ppm)

3.18 (br s, 2H), 4.74 (s, 2H), 7.20 (d, 4H, *J* = 8.08 Hz), 7.50 (d, 4H, *J* = 8.08 Hz)

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm)

78.3, 122.5, 125.2, 127.3, 130.3, 143.3

_dl_-1,2-Bis(3-methoxyphenyl) ethane-1,2-diol



_dl_-**218f**

Yield 0.48 g (89%)

mp 128-130 °C

IR (neat) (cm^{-1}) 3419, 2950, 2840, 1590, 1448, 1163, 1043, 883, 724, 710

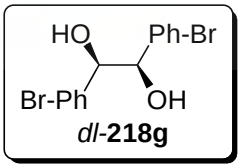
^{1}H NMR (400 MHz, $CDCl_3$, δ ppm)

3.10 (brs, 2H), 3.69 (s, 6H), 4.63 (s, 2H), 6.70-6.77 (m, 6H), 7.13 (t, 2H, *J* = 8. Hz)

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm)

55.1, 78.8, 112.2, 113.5, 119.2, 129.1, 141.5, 159.4

_dl_-1,2-Bis(2-bromophenyl) ethane-1,2-diol



_dl_-**218g**

Yield 0.66 g (90%)

mp 122-124 ˚C (lit.[162] 118.5-119 °C)

IR (KBr) (cm^{-1}) 3327, 3065, 2930, 2858, 1591, 1568, 1195, 1006, 844, 754, 453

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm)

2.83 (s, 2H), 5.32 (s, 2H), 7.13-7.15 (m, 2H), 7.34 (t, 2H, J = 8.0 Hz), 7.45 (d, 2H, J = 8.0 Hz), 7.69 (dd, 2H, J_1 = 8.0 Hz and J_2 = 1.8 Hz) **(Spectrum No. 37)**

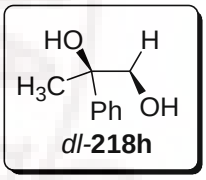
^{13}C NMR (100 MHz, $CDCl_3$, δ ppm)

75.2, 123.0, 127.5, 129.6, 129.8, 132.8, 138.8 **(Spectrum No. 38)**

***dl*-1-Phenyl-1-methylethane-1,2-diol**

Yield 0.28 g (94%)

IR (neat) (cm^{-1}) 3387, 3059, 2978, 1602, 1494, 1446, 1039, 954, 866, 702



***dl*-218h**

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm)

1.54 (s, 3H), 1.78 (brs, 1H), 2.56 (brs, 1H), 3.64 (d, 1H, J = 12 Hz), 3.81 (d, 1H, J = 8 Hz), 7.28-7.30 (m, 1H), 7.39-7.36(m, 2H), 7.48-7.45 (m, 2H)

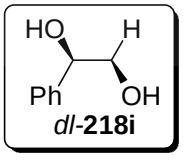
^{13}C NMR (100 MHz, $CDCl_3$, δ ppm)

26.0, 70.9, 74.9, 125.1, 127.1, 128.4, 145.0

***dl*-1-Phenylethane-1,2-diol**

Yield 0.22 g (80%)

IR (neat) (cm^{-1}) 3375, 3040, 2988, 1596, 1494, 1440, 1039, 958, 860, 702



***dl*-218i**

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm)

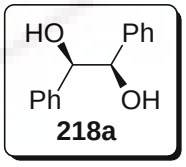
2.56 (brs, 2H), 3.56-3.60. (m, 1H), 3.72 (d, 1H, J = 12 Hz), 4.75 (dd, 1H, J_1 = 2.8 Hz and J_2 = 2.4 Hz), 7.19-7.29 (m, 5H)

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm)

68.0, 74.7, 126.1, 127.8, 128.4, 136.6, 140.5

3.6.3 Catalytic asymmetric dihydroxylation of *trans*-stilbene using chiral TB as ligand:

To a mixture of potassium ferricyanide (1.98 g, 6 mmol), potassium carbonate (0.84 g, 6 mmol), chiral TB **1** (0.1 g, 20 mol %) and potassium osmate dihydrate (0.007 g, 1 mol %) was added ^{t}BuOH (10 mL)/H_2O (10 mL) and stirred vigorously at 25 °C for 10 min and then the reaction mixture was cooled to 0 °C. To this solution was added methanesulfonamide (0.19 g, 2 mmol), substituted *trans*-stilbene (0.36 g, 2 mmol) at once and the mixture was stirred for 36 h at 25 °C. It was quenched with sodium sulfite (3.0 g). After stirring for 1.5 h, the organic layer was separated and the aqueous layer was extracted with ether (2 x 10 mL). The combined organic layer was successively washed with 8 N hydrochloric acid, brine and dried over anhydrous Na_2SO_4. The solvent was evaporated and the crude diol was purified by chromatography on silca gel column using ethyl acetate/hexane (3:7) as eluent to isolate **218a**.



218a

Yield 0.39 g (92%)

mp 145-148 °C (lit.[144] 148-150 °C)

IR (KBr) (cm^{-1}) 3499, 3400, 2893, 1452, 1197, 1043, 777, 696

ee 6% (Estimated using HPLC on Chiralcel-OJ-H, hexane/2-propanol = 90:10, flow rate: 1 mL/min.)

3.6.4 Preparation of chiral α-phenylcarbinol derivative of Tröger base 239:

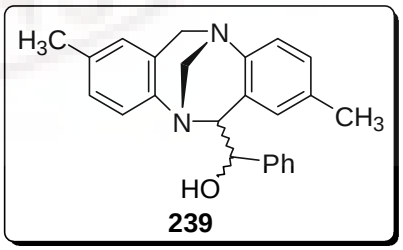
To an oven dried round bottom flask equipped with a stir bar, septum, cooled under nitrogen, was added chiral Tröger base (1.0 g, 4 mmol) and 30 mL of dry THF. The solution was cooled to 0 °C, BF_3:OEt_2 (0.58 mL, 4.1 mmol) was added and allowed to stir for 15 min. The solution was cooled to -78 °C and allowed to stir for 10 min. n-BuLi (2.7 mL of 1.6 M solution in hexanes, 4.1 mmol) was added and the resulting orange-red solution was stirred for 10 min. Benzaldehyde (0.42 mL, 4.1 mmol, in 4 mL of dry THF) was added slowly through syringe. The orange-red colour disappeared at the end of addition and the solution was allowed to stir for 1 h at -78 °C. The reaction was quenched by the careful addition of cold water (5 mL). The reaction mixture was extracted in diethyl ether (2 x 15 mL) and the combined organic extracts were successively washed with water, brine and dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was subjected to chromatography on silicagel column using ethyl acetate/hexane (1:9) to elute the desired amino alcohol **239**.

Yield 1.44 g (50%)

mp 202-204 °C

IR (KBr) (cm^{-1}) 3412, 3034, 2912, 1494, 700, 540

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm)



239

1.88 (s, 3H), 2.24 (s, 3H), 4.03 (d, 1H, *J* = 9.6 Hz), 4.11 (d, 1H, *J* = 16.8 Hz), 4.28 (d, 1H, *J* = 13.2 Hz), 4.58 (d, 1H, *J* = 12.8 Hz), 4.69-4.73 (m, 2H), 5.41 (s, 1H), 6.74-7.13 (m, 6H), 7.40-7.44 (m, 5H)

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm)

20.7, 20.9, 58.6, 61.5, 73.5, 75.3, 124.4, 124.6, 125.5, 127.5, 128.3, 128.4, 128.5, 128.6, 128.8, 130.2, 134.1, 140.4, 145.3, 145.5

dr 60:40 (Estimated by chiral HPLC analysis of the crude reaction mixture on Chiralcel-OD-H column, hexane/2-propanol = 95:5, flow rate: 1 mL/min.)

MS(ESI) m/z 357.2 (M^+)

Analysis Calculated for $C_{24}H_{24}N_2O$: C, 80.87%; H, 6.79%; N, 7.86%; O, 4.49

Found: C, 80.75%; H, 6.72%; N, 7.95%

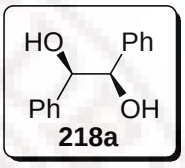
3.7 Studies on the mechanism of the catalytic asymmetric dihydroxylation of substituted *trans*-stilbene derivatives

3.7.1 General procedure for the asymmetric dihydroxylation of *trans*-stilbenes in the presence of $(DHQD)_2$-PHAL 220 ligand using ^{t}BuOH/H_2O solvent system:

To a mixture of potassium ferricyanide (0.99 g, 3 mmol), potassium carbonate (0.42 g, 3 mmol), $(DHQD)_2$-PHAL **220** (0.015 g, 2 mol%) and potassium osmate dihydrate (0.007 g, 2 mol%) was added ^{t}BuOH (5 mL)/H_2O (5 mL) and the reaction mixture was stirred vigorously at 0 °C for 0.5 h. To this solution was added *trans*-stilbenes (1 mmol) and the mixture stirred for 16 h at 25 °C. The reaction mixture was quenched with sodium sulphite (1.5 g). After stirring for 3 h, the organic layer was separated and the aqueous layer

was extracted with ether (3 x 20 mL). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated and the crude stilbene/substituted stilbene diol was purified by column chromatography on silcagel using ethyl acetate/hexane (3:7) as eluent.

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



218a

Yield 0.195 g (90%)

mp 145-148 °C (lit.[119] 148-150 °C)

IR (KBr) (cm^{-1}) 3499, 3400, 2893, 1452, 1197, 1043, 777, 696

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm)

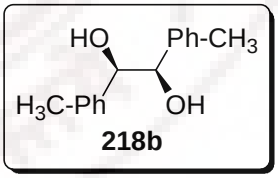
3.05 (brs, 2H), 4.68 (s, 2H), 7.11-7.22 (m, 10H) **(Spectrum No. 39)**

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm)

79.1, 127.0, 127.9, 128.1, 139.9 **(Spectrum No. 40)**

ee 99% (Estimated using HPLC on Chiralcel-OJ-H, hexane/2-propanol = 90:10, flow rate: 1 mL/min.)

(1*R*,2*R*)-1,2-Bis(4-methylphenyl) ethane-1,2-diol



218b

Yield 0.23 g (95 %)

mp 108-110 °C (lit.[163] 110 °C)

IR (KBr) (cm^{-1}) 3490, 3400, 2892, 1450, 1197,1043, 776, 694

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm)

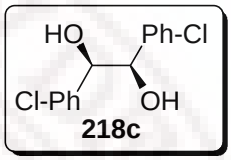
2.29 (s, 6H), 2.82 (brs, 2H), 4.65 (s, 2H), 7.02 (brs, 8H) **(Spectrum No. 41)**

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm)

21.1, 78.8, 126.9, 128.8, 137.0, 137.5 **(Spectrum No. 42)**

ee >98% (Estimated using HPLC on Chiralpak-AS-H, hexane/2-propanol = 90:10, flow rate: 1 mL/min.)

(1*R*,2*R*)-1,2-Bis(4-chlorophenyl) ethane-1,2-diol



218c

Yield 0.25 g (89 %)

mp 126-128 ˚C (lit.[164] 127 °C)

IR (KBr) (cm^{-1}) 3486, 3399, 2890, 1448, 1198,1042, 692

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm)

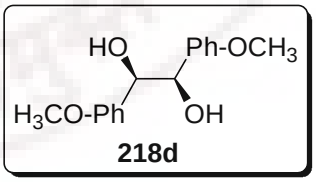
3.16 (brs, 2H), 4.56 (s, 2H), 6.98 (d, 4H, *J* = 8.4 Hz), 7.19 (d, 4H, *J* = 8.4 Hz) **(Spectrum No. 43)**

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm)

78.5, 128.4, 133.9, 138.0 **(Spectrum No. 44)**

ee 99% (Estimated using HPLC on Chiralpak-AS-H, hexane/2-propanol = 70:30, flow rate: 1 mL/min.)

(1*R*,2*R*)-1,2-Bis(4-methoxyphenyl) ethane-1,2-diol



218d

Yield 0.25 g (93 %)

mp 118-119 °C (lit.[165] 118-119 °C)

IR (KBr) (cm^{-1}) 3489, 3398, 2890, 1448, 1193, 1043, 774

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm)

2.83 (brs, 2H), 3.76 (s, 6H), 4.63 (s, 2H), 6.75 (d, 4H, J = 8.4 Hz), 7.03 (d, 4H, J = 8.8 Hz) **(Spectrum No. 45)**

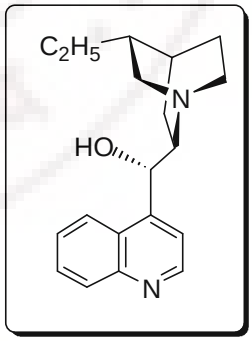
^{13}C NMR (100 MHz, $CDCl_3$, δ ppm)

55.2, 78.8, 113.5, 128.2, 132.2, 159.2 **(Spectrum No. 46)**

ee 97% (Estimated using HPLC on Chiralcel-OJ-H, hexane/2-propanol = 70:30, flow rate: 1 mL/min.)

3.7.2 Preperation of dihydrocinchonidine:

Cinchonidine (11.76 g, 40 mmol) dissolved in 50 mL of 0.5 M H_2SO_4 was taken in a hydrogenation flask. To this clear solution was added 5% Pd/C (1 g) and the contents were flushed with stream of hydrogen and shaken in a parr hydrogenation apparatus at 0.1 bar, at 25 °C. After 2 h the solution was filtered using celite bed. The filtrate was neutralized with 25 mL of 2 N NaOH. The white precipitate was collected and washed with water. The precipitate was suspended twice in cold EtOH, filtered and dried under vacuum at 100 °C.



Yield 10.02 g (85%)

mp 234-236 °C (lit.[166] 237 °C)

IR (KBr) (cm^{-1}) 3065, 2932, 2876, 1591, 1508, 1462, 1120, 760

^{1}H NMR (200 MHz, $CDCl_3$, δ ppm)

0.80 (t, 3H, J = 7.2 Hz), 1.23 (q, 2H, J_1 = 8.4 Hz, J_2 = 7.3 Hz), 1.3-1.64 (m, 3H), 1.8-2.0 (m, 2H), 2.45-2.60 (m, 1H), 2.66-2.92 (m, 2H), 3.08-3.28 (m,

2H), 3.62-3.90 (m, 1H), 5.92 (d, 1H, *J* = 3.2 Hz), 7.32 (d, 1H, *J* = 7.4 Hz), 7.52-7.63 (m, 2H), 8.00 (t, 2H, *J* = 7.6 Hz), 8.85 (d, 1H, *J* = 4.6 Hz)

^{13}C NMR (50 MHz, $CDCl_3$, δ ppm)

11.9, 20.0, 27.4, 37.0, 43.5, 58.1, 60.5, 70.3, 118.3, 122.9, 125.2, 126.8, 129.0, 130.2, 148.3, 150.1

$[\alpha]_D^{25}$ -94.4° (*c* 0.3, EtOH) {lit.[166] $[\alpha]_D^{25}$ = -98.4° (EtOH)}

3.7.3 Preparation of 9-*O*-acetyldihydrocinchonidine:

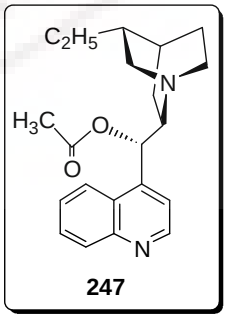
Dihydrocinchonidine (1.24 g, 4.2 mmol) was dissolved in CH_2Cl_2 (20 mL). Acetyl chloride (0.36 mL, 5 mmol) was added dropwise over a period of 0.5 h with stirring at 0 °C. The reaction mixture was brought to 25 °C and stirring was continued for 12 h followed by reflux for 2 h. The contents were cooled to 25 °C, solid K_2CO_3 was added and the mixture was stirred for 0.5 h. Water was added and the organic layer was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated and the crude product was purified by column chromatography on silica gel (100-200 mesh) using methanol/chloroform/hexane (0.15/3/6.85) to elute viscous sample of 9-*O*-acetyldihydrocinchonidine **247**.

Yield 0.88 g (62%)

IR (neat) (cm^{-1}) 2935, 2862, 1745, 1593, 1230, 761

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm)

0.85 (t, 3H, *J* = 7.2 Hz), 1.18-1.38 (m, 3H), 1.40-1.65 (m, 3H), 1.66-1.94 (m, 2H), 2.11 (s, 3H), 2.23-2.30 (m,



247

1H), 2.59-2.78 (m, 1H), 2.98-3.25 (m, 2H), 3.28-3.46 (m, 1H), 6.60 (d, 1H, *J* = 4.2 Hz), 7.36-7.39 (m, 1H), 7.55-7.79 (m, 2H), 8.12 (d, 1H, *J* = 8.6 Hz), 8.28 (d, 1H, *J* = 8.6 Hz), 8.86 (d, 1H, *J* = 4.2 Hz)

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm)

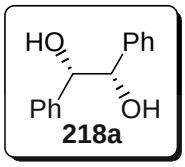
12.0, 21.0, 23.7, 25.3, 27.6, 28.1, 37.2, 42.6, 58.2, 59.4, 73.8, 118.5, 123.5, 125.9, 129.2, 130.4, 145.1, 148.7, 149.9, 169.7

$[\alpha]_D^{25}$ -28.2° (*c* 0.5, EtOH)

3.7.4 Asymmetric dihydroxylation of *trans*-stilbene in the presence of 9-*O*-acetyldihydrocinchonidine as ligand:

To a mixture of potassium ferricyanide (0.99 g, 3 mmol), potassium carbonate (0.42 g, 3 mmol), ligand **247** (0.017 g, 5 mol%) and potassium osmate dihydrate (0.007 g, 2 mol%) was added ^{t}BuOH (15 mL)/H_2O (15 mL). The reaction stirred vigorously at 0 °C for 0.5 h. *trans*-Stilbene (0.18 g, 1 mmol) was added and the mixture was stirred for 12 h at 25 °C. The reaction mixture was quenched with sodium sulphite (1.5 g). After stirring for 3 h, the organic layer was separated and the aqueous layer was extracted with ether (3 x 20 mL). The combined organic layer was washed successively with 3 N hydrochloric acid, brine and dried over anhydrous Na_2SO_4. The solvent was evaporated and the crude diol was purified by column chromatography on silca gel using ethyl acetate/hexane (3:7) as eluent.

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



218a

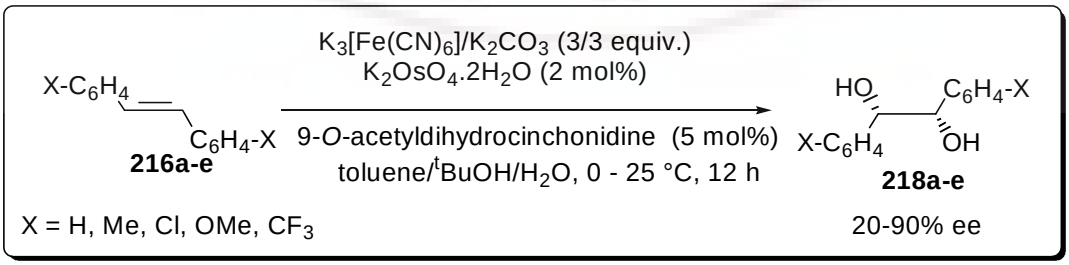
Yield 0.194 g (91%)

mp 145-148 °C (lit.[144] 148-150 °C)

ee 91% (Estimated using HPLC on Chiralcel-OJ-H, hexane/2-propanol = 90:10, flow rate: 1 mL/min.)

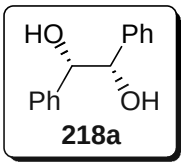
3.7.5 General procedure for the asymmetric dihydroxylation of *trans*-stilbenes 180a-e in the presence of 9-*O*-acetyldihydrocinchonidine ligand using toluene/^{t}BuOH/H_2O solvent system:

To a mixture of potassium ferricyanide (0.99 g, 3 mmol), potassium carbonate (0.42 g, 3 mmol), ligand **247** (0.17 g, 5 mol%) and potassium osmate dihydrate (0.007 g, 2 mol%) was added toluene (20 mL)/^{t}BuOH (20 mL)/H_2O (20 mL). The mixture was stirred vigorously at 0 °C for 0.5 h. To this solution was added *trans*-stilbenes (1 mmol) and the mixture was stirred for 12 h at 25 °C. The reaction mixture was quenched with sodium sulphite (1.5 g). After stirring for 3 h, the organic layer was separated and the aqueous layer was extracted with ether (3 x 20 mL). The combined organic layer was washed successively with 3 N hydrochloric acid, brine and dried over anhydrous Na_2SO_4. The solvent was evaporated and the crude diol was purified by column chromatography on silca gel using ethyl acetate/hexane (3:7) as eluent.



216a-e **218a-e**

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



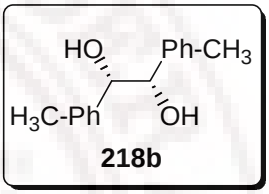
218a

Yield 0.196 g (92%)

mp 145-148 °C (lit.[144] 148-150 °C)

ee 90% (Estimated using HPLC on Chiralcel-OJ-H, hexane/2-propanol = 90:10, flow rate: 1 mL/min.)

(1*S*,2*S*)-1,2-Bis(4-methylphenyl) ethane-1,2-diol



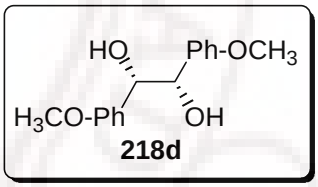
218b

Yield 0.186 g (76%)

mp 108-110 °C (lit.[163] 110 °C)

ee 66% (Estimated using HPLC on Chiralpak-AS-H, hexane/2-propanol = 90:10, flow rate: 1 mL/min.)

(1*S*,2*S*)-1,2-Bis(4-methoxyphenyl) ethane-1,2-diol



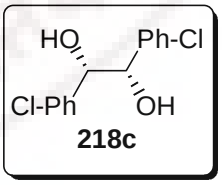
218d

Yield 0.22 g (80%)

mp 118-119 °C (lit.[165] 118-119 °C)

ee 64% (Estimated using HPLC on Chiralcel-OJ-H (hexane/2-propanol = 70:30, flow rate: 1 mL/min.)

(1*S*,2*S*)-1,2-Bis(4-chlorophenyl) ethane-1,2-diol



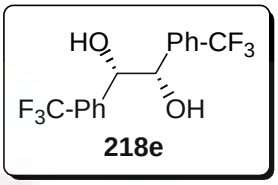
218c

Yield 0.25 g (89%)

mp 126-128 ˚C (lit.[164] 127 °C)

ee 99% (Estimated using HPLC on Chiralpak-AS-H (hexane/2-propanol = 70:30, flow rate: 1 mL/min.)

(1*S*,2*S*)-1,2-Bis(4-trifluoromethylphenyl) ethane-1,2-diol



218e

Yield 0.228 g (79%)

mp 128-130 °C

IR (KBr) (cm^{-1}) 3400, 3344, 2928, 1928, 1622, 1331, 1122, 1070, 839, 763, 609, 524

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm)

3.18 (brs, 2H), 4.74 (s, 2H), 7.22 (d, 4H, *J* = 8.0 Hz), 7.51 (d, 4H, *J* = 8.4 Hz) **(Spectrum No. 47)**

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm)

78.4, 122.6, 125.2, 127.3, 130.3, 143.3 **(Spectrum No. 48)**

ee 76% (Estimated using HPLC on Chiralcel-OD-H, hexane/2-propanol = 85:15, flow rate: 1 mL/min.)

Note: The same experimental procedure as above was followed for the asymmetric dihydroxylation of *trans*-stilbenes in acetone/^{t}BuOH/H_2O and THF/^{t}BuOH/H_2O solvent systems.

3.8 Studies using the borane complexe of chiral Tröger base

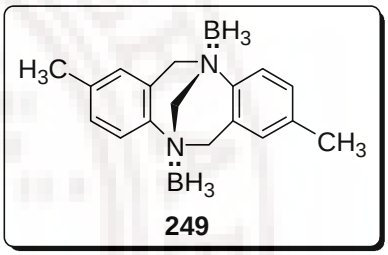
3.8.1 Preparation of stock solution of chiral Tröger base-borane complex:

To a two neck reaction flask containing $NaBH_4$ (1.6 g, 40 mmol) in diglyme (20 mL), was added a solution of I_2 (5.2 g, 20 mmol) in diglyme (10 mL) dropwise thorough addition funnel for 1 h. The diborane gas generated in this way was bubbled through a side arm using a bubbler into another reaction flask containing chiral Tröger base (2.5 g, 10

mmol) in dry toluene (40 mL) at 0 °C. The outlet from the latter flask was vented through a mercury bubbler and a trap containing adequate amount of acetone to destroy excess diborane. When the bubbling of the gases in the reaction flask had ceased, the bubbler was removed and replaced by a glass stopper under nitrogen atmosphere. The stock solution flask was again flushed with a stream of nitrogen to get rid of the dissolved borane in toluene. The stock solution of borane complex prepared in this way (approx. 0.25 M) concentration and it was stored in refrigerator.

^{11}B NMR (128.3 MHz, toluene + $CDCl_3$, δ ppm) -9.4

{δ = 0, BF_3:Et_2O (external reference)}



249

3.8.2 Typical procedure for the estimation of the no. of coordinated 'N' atoms of the chiral Tröger base:

To a reaction flask, containing Tröger base-borane stock solution (4 mL, 1 mmol) in toluene, was added excess triphenylphosphine (0.78 g, 3.0 mmol) at 25 °C under N_2 atmosphere. The reaction mixture was allowed to stir for 3 h at 25 °C. The solvent was evaporated and residue was subjected to chromatography on silica gel column using hexane/ethyl acetate (97:3) as eluent to obtain triphenylphosphene-borane complex.

Yield 0.48 g (1.75 mmol)

mp 186-188 ^{o}C (lit.[167] mp 188 ^{o}C)

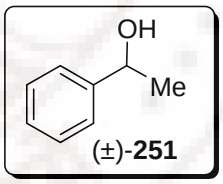
IR (KBr) (cm^{-1}) 2378, 2343, 2253, 740, 710

^{11}B NMR (128.3 MHz, $CDCl_3$, δ ppm) -36.7 (d, J = 48.1 Hz) {δ = 0, BF_3:Et_2O (external reference)}

^{31}P NMR (162 MHz, $CDCl_3$, δ ppm) 20.56 {δ = 0, H_3PO_4 (external reference)}

3.8.3 Reduction of acetophenone with chiral Tröger base-borane complex:

To an oven dried round bottom flask equipped with a stir bar, septum, cooled under nitrogen, was added chiral Tröger base-borane complex (2 mmol, 8 mL in toluene) and acetophenone (0.23 mL, 2 mmol) was added at 25 °C. The contents were refluxed for 2 h. Then, the reaction mixture was quenched with water (5 mL) and monoethanolamine (3 mL). The aqueous layer was extracted with ether (2 x 10 mL). The combined organic layer was successively washed with 1 M hydrochloric acid, water, brine and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the crude product was purified by chromatography on silicagel column using hexane/ethyl acetate (95:5) as eluent to isolate the 1-phenylethanol **251**.



(±)-**251**

1-Phenylethanol

Yield 0.22 g (89%)

IR (neat) (cm^{-1}) 3383, 3063, 2972, 1602, 1493, 1076, 900

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm)

1.46 (d, 3H, J = 7 Hz), 2.65 (brs, 1H), 4.88 (q, 1H, J_1 = 6.48 Hz, J_2 = 2.44 Hz), 7.34 (m, 5H)

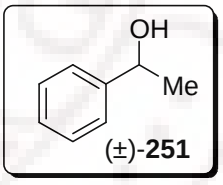
^{13}C NMR (50 MHz, $CDCl_3$, δ ppm)

25.1, 70.3, 125.5, 127.4, 128.5, 146.0

3.8.4 Reduction of acetophenone with chiral Tröger base-borane complex in the presence of BF_3:OEt_2:

To a reaction flask cooled under N_2, containing acetophenone (0.23 mL, 2 mmol), was added BF_3:OEt_2 (0.25 mL, 2 mmol) at 0 °C and allowed to stir for 10 min. at the same temperature. Then chiral Tröger base-borane complex (2 mmol) was added and the contents were stirred for 4 h at 25 °C. The reaction mixture was quenched with water (5 mL), monoethanolamine (3 mL) and the aqueous layer was extracted with ether (2 x 10 mL). The combined organic layer was successively washed with 1 M hydrochloric acid, water, brine and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the crude product was purified by chromatography on silicagel column using hexane/ethyl acetate (95:5) as eluent to isolate the 1-phenylethanol **251**.

1-Phenylethanol



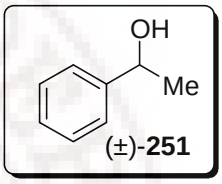
Yield 0.20 g (84%)

IR (neat) (cm^{-1}) 3383, 3063, 2972, 1602, 1493, 1076, 900

3.8.5 Reduction of acetophenone with chiral Tröger base-BF_3 complex in the presence of BH_3:NEt_3:

To a reaction flask cooled under N_2, containing chiral Tröger base (0.5 g, 2 mmol) in toluene (10 mL), was added BF_3:OEt_2 (0.52 mL, 4 mmol) at 0 °C and allowed to stir for 15 min. at the same temperature. Then, BH_3:NEt_3 (2 mmol) and acetophenone (0.23 mL, 2 mmol) were added. The contents were stirred for 36 h at 25 °C. The reaction mixture was

quenched with water (5 mL), monoethanolamine (3 mL) and the aqueous layer was extracted with ether (2 x 10 mL). The combined organic layer was successively washed with 1 M hydrochloric acid, water, brine and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the crude product was purified by chromatography on silicagel column using hexane/ethyl acetate (95:5) as eluent to isolate the 1-phenylethanol **251**.



1-Phenylethanol

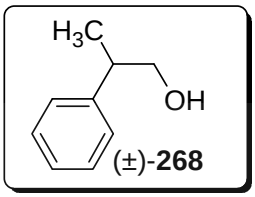
Yield 0.13 g (55%)

IR (neat) (cm^{-1}) 3383, 3063, 2972, 1602, 1493, 1076, 900

3.8.6 Hydroboration/oxidation of α-methylstyrene using chiral Tröger base-borane complex:

To a reaction flask cooled under N_2, containing chiral Tröger base-borane complex (2 mmol, 8 mL in toluene), was added α-methylstyrene (0.26 mL, 2 mmol) at 25 °C. The reaction mixture was refluxed for 2 h. It was brought to 25 °C quenched with MeOH (5 mL). The organoborane was oxidized using 3 N NaOH (4 mL), H_2O_2 (30%, 4 mL) and stirred for about 4 h. The organic layer was separated and the aqueous layer was extracted with ether (2 x 10 mL). The combined organic layer was successively washed with water, brine and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the crude product was purified by chromatography on silicagel column using hexane/ethyl acetate (95:5) as eluent to isolate the 2-phenylpropanol **268**.

2-Phenylpropanol



Yield 0.20 g (75%)

IR (neat) (cm^{-1}) 3375, 3050, 2950, 1603, 1057

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm)

1.12-1.32 (m, 3H), 1.88 (s, 1H), 2.76-3.12 (m, 1H), 3.52-3.72 (m, 2H), 7.20-7.46 (m, 5H)

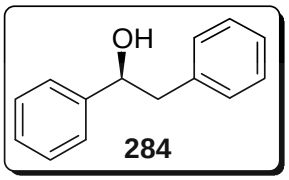
^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm)

17.4, 42.1, 68.1, 126.3, 127.3, 128.3, 143.9

3.8.7 Hydroboration/oxidation of *trans*-stilbene using chiral Tröger base-borane complex system activated by iodine:

To a reaction flask cooled under N_2, containing chiral Tröger base-borane complex (1 mmol, 4 mL in toluene), was added *trans*-stilbene (0.18 g, 1 mmol) at 25 °C. Then, I_2 (0.125 g, 0.5 mmol) in toluene (6 mL) was added dropwise through an addition funnel and the contents stirred for 10 h at 25 °C. The reaction mixture was quenched with MeOH (5 mL) and the organoborane was oxidized using 3 N NaOH (4 mL), H_2O_2 (30%, 4 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The combined organic layer was successively washed with water, brine and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the crude product was purified by chromatography on silicagel column using hexane/ethyl acetate (92:8) as eluent to isolate the alcohol product **284**.

1,2-Diphenylethanol



284

Yield 0.17 g (87%)

mp 65-67 °C

IR (KBr) (cm^{-1}) 3329, 3078, 3026, 2922, 1039, 696

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm)

1.95 (s, 1H), 2.96-3.1 (m, 2H), 4.90-4.91 (m, 1H), 7.20-7.36 (m, 10H) **(Spectrum No. 49)**

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm)

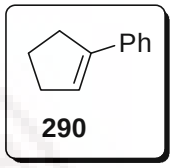
46.1, 75.3, 125.9, 126.6, 127.6, 128.4, 128.5, 129.5, 138.1, 143.9 **(Spectrum No. 50)**

$[\alpha]_D^{25}$ +3.2° (*c* 1, EtOH), {lit.[168] for 100% ee, $[\alpha]_D^{25}$ = +52.8° (*c* 1.40, EtOH)} (6% ee, confirmed by HPLC using chiral column, chiralcel OD-H, hexane/2-propanol = 90:10, flow rate: 0.5 mL/min.)

3.8.8 Preparation of 1-phenylcyclopentene:[169]

To a solution of cyclopentanone (2.7 mL, 30 mmol) was added PhMgBr (30 mmol) dropwise at 25 °C under N_2 atmosphere. The mixture was allowed to stir for 2 h at the same temperature and then poured into with ice-cold 1 N HCl solution (50-60 mL). The aqueous layer was extracted with ether and the combined organic layer was washed with brine solution. After evaporation of the solvent, the crude alcohol product obtained was dissolved in toluene and *p*-TsOH was added. The reaction mixture was refluxed for 8 h while the

generated water was removed *via* Dean-Stark apparatus. Then, it was concentrated and the residue was purified by chromatography on silicagel column using hexane as eluent to isolate the 1-phenylcyclopentene **290**.



290

Yield 3.6 g (85%)

IR (neat) (cm^{-1}) 3096, 3400, 2953, 2840, 1505, 756, 703

^1H NMR (400 MHz, $CDCl_3$, δ ppm)

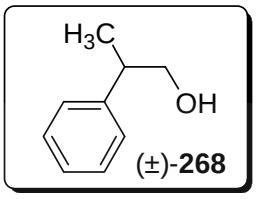
1.99-2.07 (m, 2H), 2.51-2.57 (m, 2H), 2.70-2.75 (m, 2H), 6.19-6.21 (m, 1H), 7.20-7.24 (m, 1H), 7.30-7.35 (m, 2H), 7.46 (d, 2H, *J* = 7.6 Hz)

Note: 1-Phenylcyclohexene was also prepared using the same procedure.[169]

3.8.9 General procedure for hydroboration/oxidation of prochiral olefins using chiral Tröger base-BH_3 complex system activated by iodine:

To a reaction flask cooled under N_2, containing chiral Tröger base-borane complex (1 mmol, 4 mL in toluene), was added olefin (1 mmol) at 25 °C. Then, I_2 (0.025 g, 0.1 mmol) in toluene (6 mL) was added dropwise through an addition funnel and the contents stirred for 10 h at 25 °C. The reaction mixture was quenched with MeOH (5 mL) and the organoborane was oxidized using 3 N NaOH (4 mL), H_2O_2 (30%, 4 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The combined organic layer was successively washed with water, brine and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the crude product was purified by chromatography on silicagel using hexane/ethyl acetate mixture.

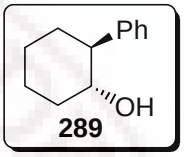
2-Phenylpropanol



Yield 0.23 g (85%)

IR (neat) (cm^{-1}) 3375, 3050, 2950, 1603, 1057

2-Phenylcyclohexanol



Yield 0.147 g (83%)

mp 62-64 °C (lit.[170a] 64-65 °C)

IR (KBr) (cm^{-1}) 3308, 3026, 2932, 2854, 1446, 1059, 696

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm)

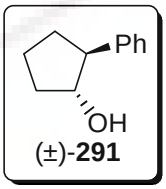
1.32-1.58 (m, 4H), 1.62 (s, 1H), 1.75-1.88 (m, 3H), 2.11-2.14 (m, 1H), 2.40-2.47 (m, 1H), 3.63-3.69 (m, 1H), 7.22-7.27 (m, 3H), 7.34 (t, 2H, J = 7.6 Hz)

^{13}C NMR (100 MHz, $CDCl_3$, δ ppm)

25.2, 26.2, 33.4, 34.5, 53.3, 74.5, 126.9, 128.0, 128.8, 143.4

$[\alpha]_D^{25}$ -2.3° (c 1.0, EtOH), {lit.[170b] for 100% ee, $[\alpha]_D^{25}$ = +56.9° (c 1.0, EtOH)} (4% ee, confirmed by HPLC using chiral column, chiralcel OD-H, hexane/2-propanol = 98:2, flow rate: 1.0 mL/min.)

2-Phenylcyclopentanol



Yield 0.13 g (80%)

IR (neat) (cm^{-1}) 3366, 3061, 3026, 2957, 2872, 1601, 1087, 754

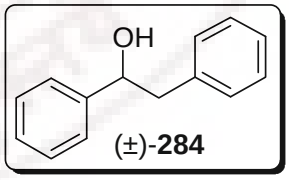
^{1}H NMR (400 MHz, $CDCl_3$, δ ppm)

1.58 (s, 1H), 1.68-1.84 (m, 4H), 2.04-2.23 (m, 2H), 2.87 (d, 1H, *J* = 7.6 Hz), 4.16 (d, 1H, *J* = 5.6 Hz), 7.22-7.31 (m, 5H)

3.8.10 Hydroboration/oxidation of *trans*-stilbene using chiral Tröger base-BH_3 complex system activated by triflic acid:

To a reaction flask cooled under N_2, containing chiral Tröger base-borane complex (1 mmol, 4 mL in toluene), was added *trans*-stilbene (0.18 g, 1 mmol) at 25 °C. Then, triflic acid (0.09 mL, 1.0 mmol) in toluene (5 mL) was added dropwise through addition funnel and the contents were allowed to stir for 10 h at 25 °C. The reaction mixture was quenched with MeOH (5 mL) and the organoborane was oxidized using 3 N NaOH (4 mL), H_2O_2 (30%, 4 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The combined organic layer was successively washed with water, brine and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the crude product was purified by chromatography on silicagel using hexane/ethyl acetate (92:8) as eluent to isolate the alcohol product **284**.

1,2-Diphenylethanol



(±)-**284**

Yield 0.14 g (70%)

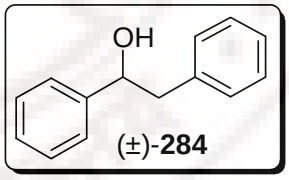
mp 65-67 °C

IR (KBr) (cm^{-1}) 3329, 3078, 3026, 2922, 1039, 696

3.8.11 Hydroboration/oxidation of *trans*-stilbene using chiral Tröger base-BH_3 complex system activated by iodine in the presence of an additive:

To a reaction flask cooled under N_2, containing chiral Tröger base-borane complex (1 mmol, 4 mL in toluene), was added I_2 (0.125 g, 0.5 mmol) in toluene (6 mL) was added dropwise through addition funnel and allowed to stir for 1 h at 25 °C. Then, the additive *N*,*N*-diethyl aniline (or THF) (0.1 mL, 1 mmol) was added and it was stirred for 0.5 h. *trans*-Stilbene (0.18 g, 1 mmol) was added at 25 °C and allowed to stir for 10 h. The reaction mixture was quenched with MeOH (5 mL) and the resulting organoborane was oxidized using 3 N NaOH (2 mL), H_2O_2 (30%, 2 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The combined organic layer was successively washed with water, brine and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the crude product was purified by chromatography on silicagel using hexane/ethyl acetate (92:8) as eluent to isolate the alcohol product **284**.

1,2-Diphenylethanol



(±)-**284**

Yield 0.16 g (80%)

mp 65-67 °C

IR (KBr) (cm^{-1}) 3329, 3078, 3026, 2922, 1039, 696

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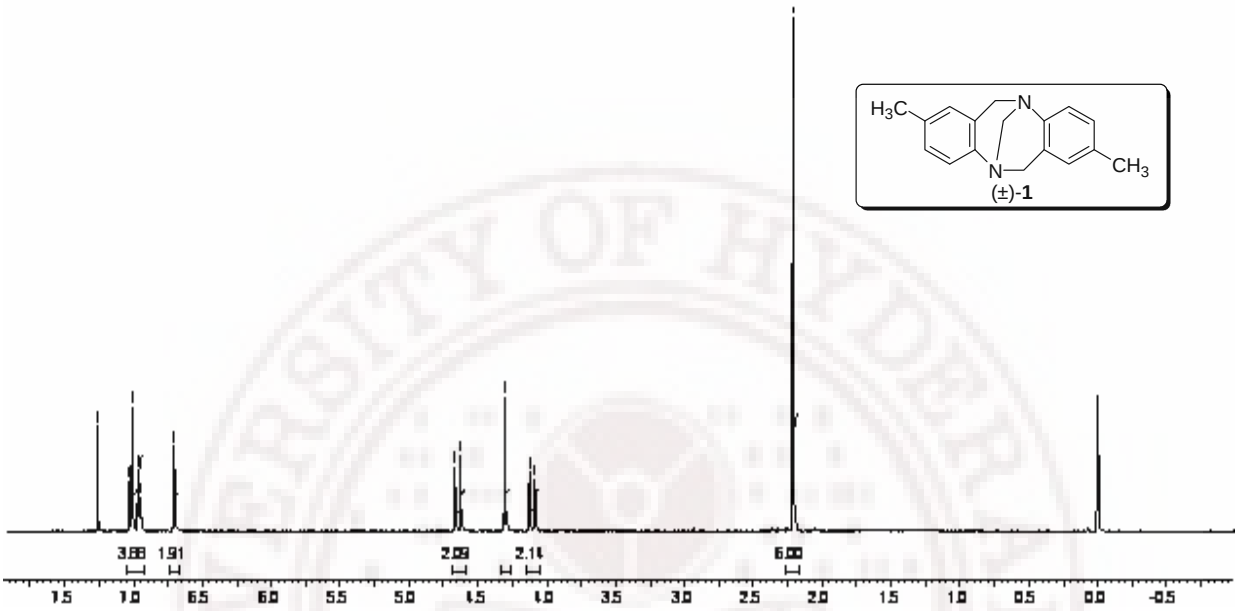
Appendix I

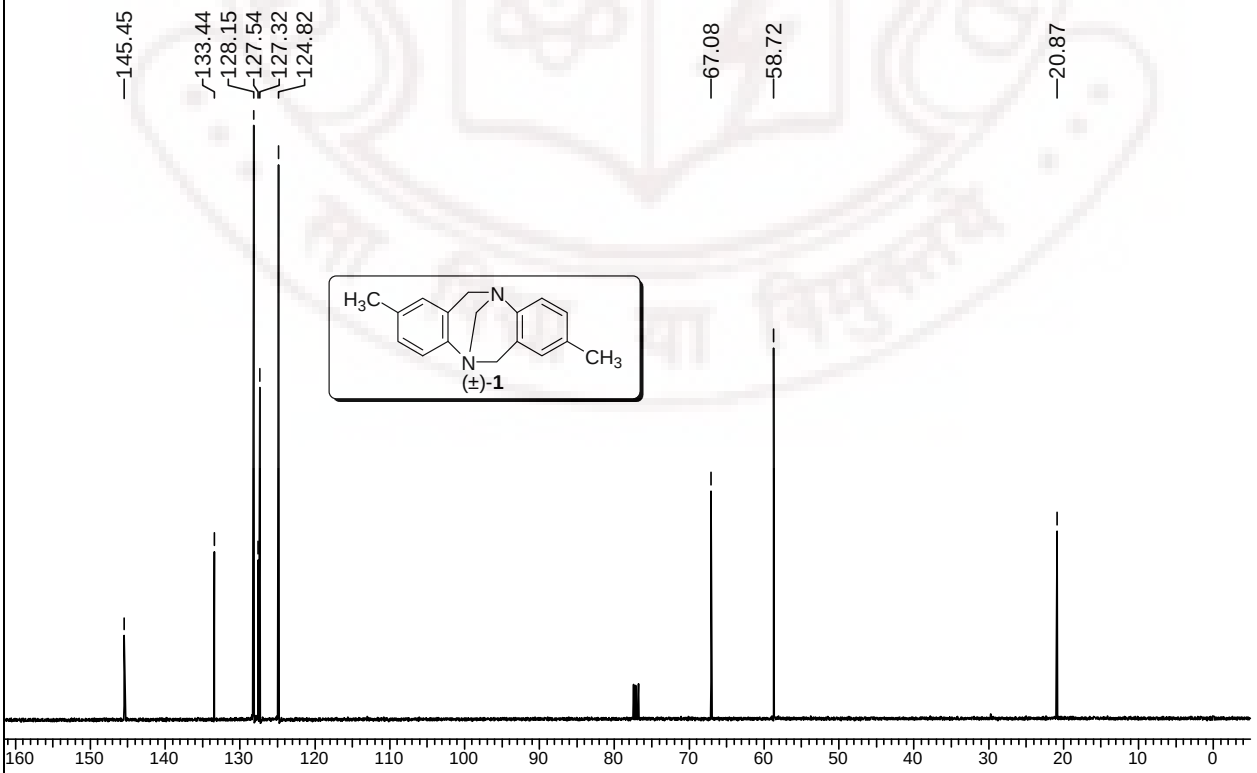
(Representative Spectra)

Spectrum No. 1 (Chapter 3, Section 3.2.1) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



ppm

Spectrum No. 2 (Chapter 3, Section 3.2.1) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



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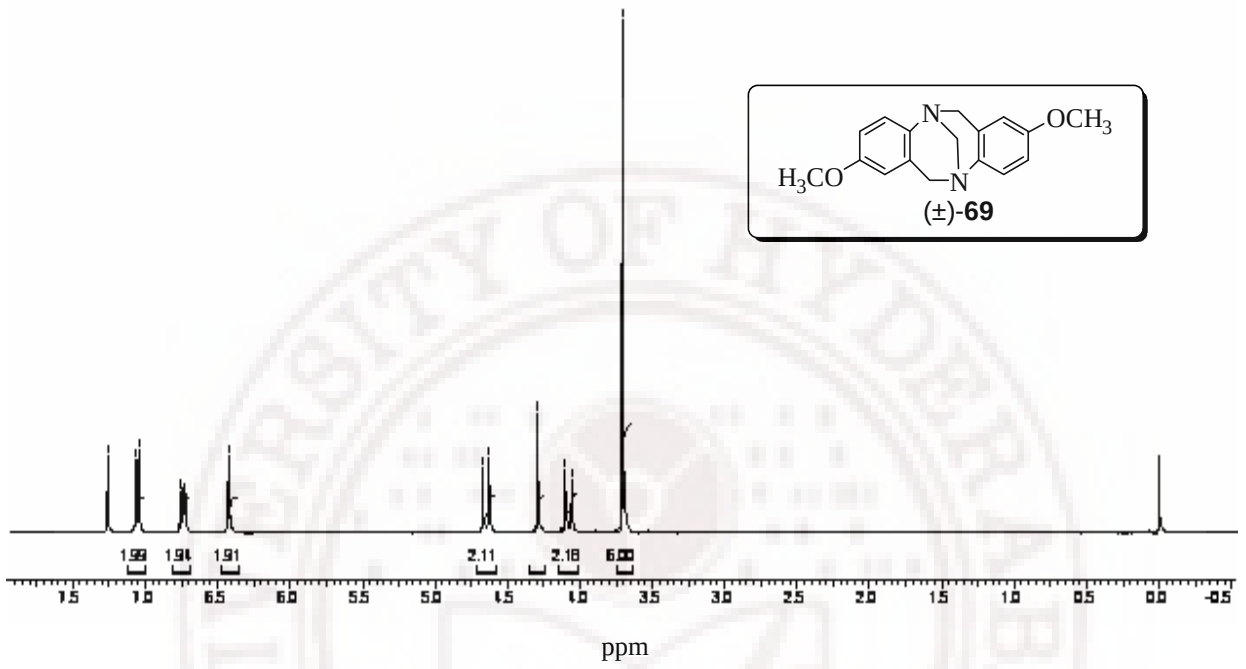
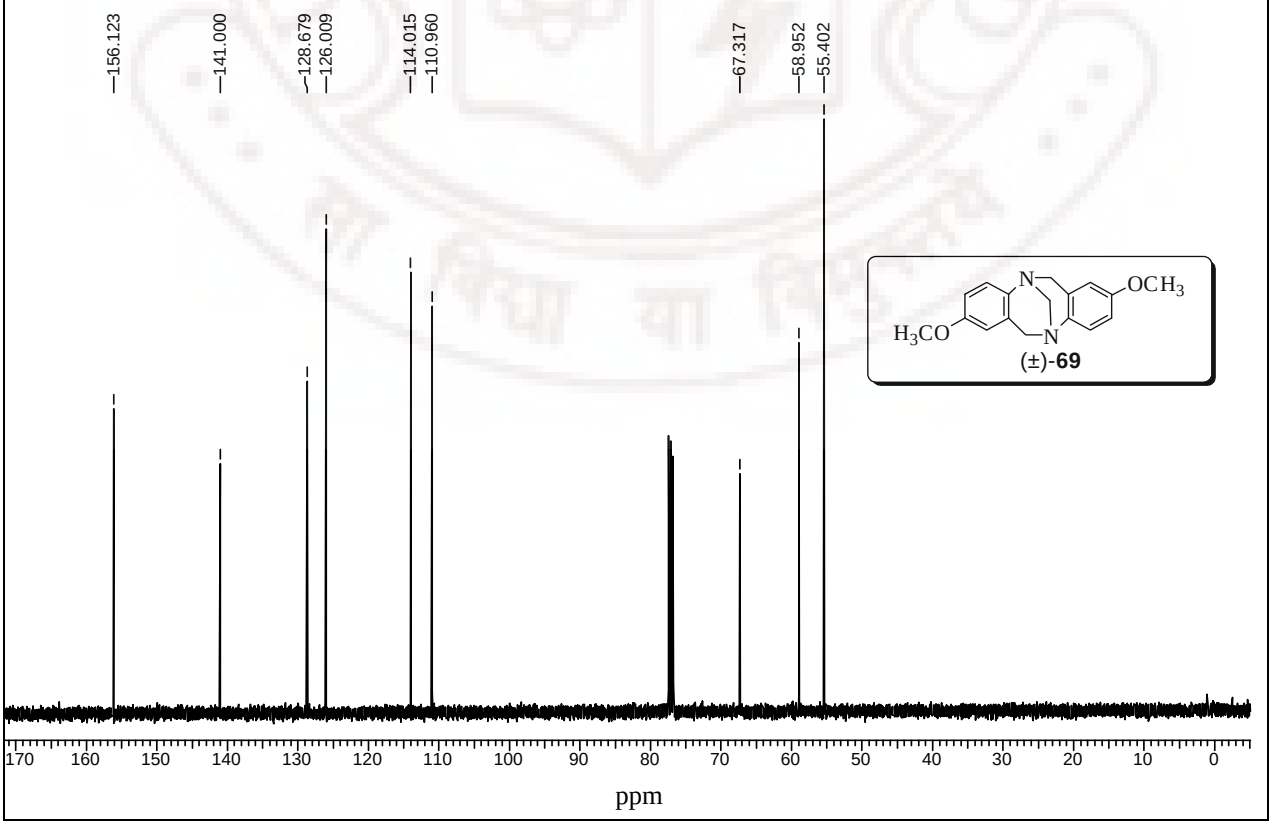
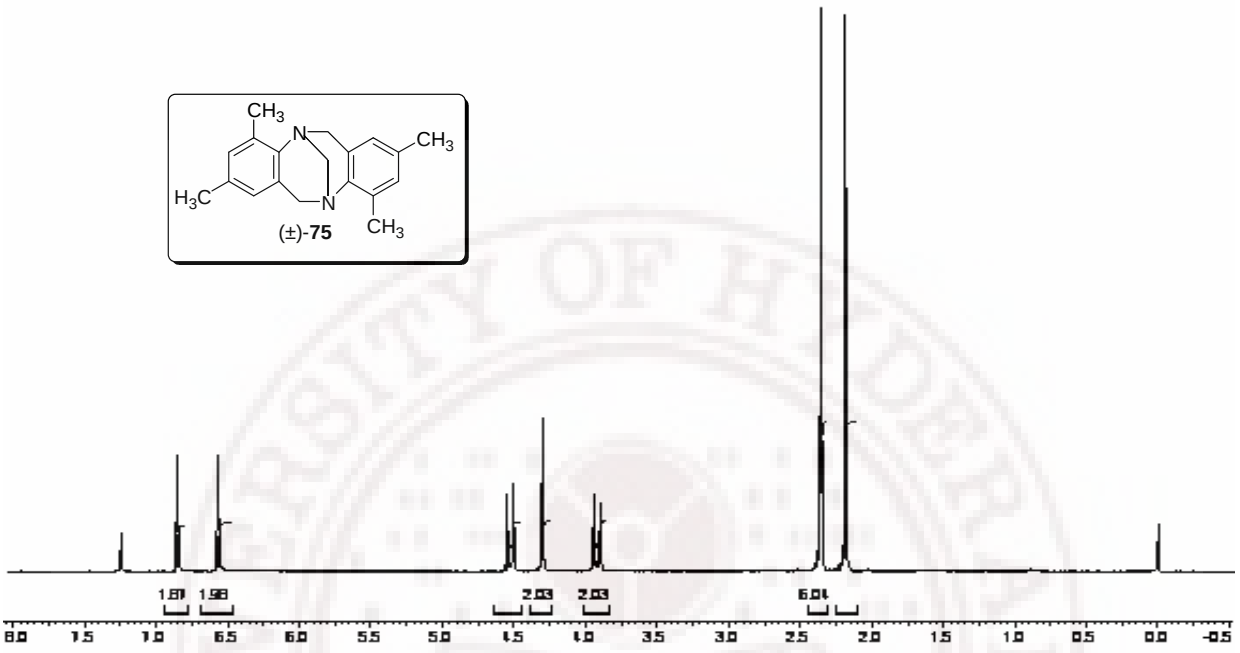
Spectrum No. 3 (Chapter 3, Section 3.2.1) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



Spectrum No. 4(Chapter 3, Section 3.2.1) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



Spectrum No. 5 (Chapter 3, Section 3.2.1) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



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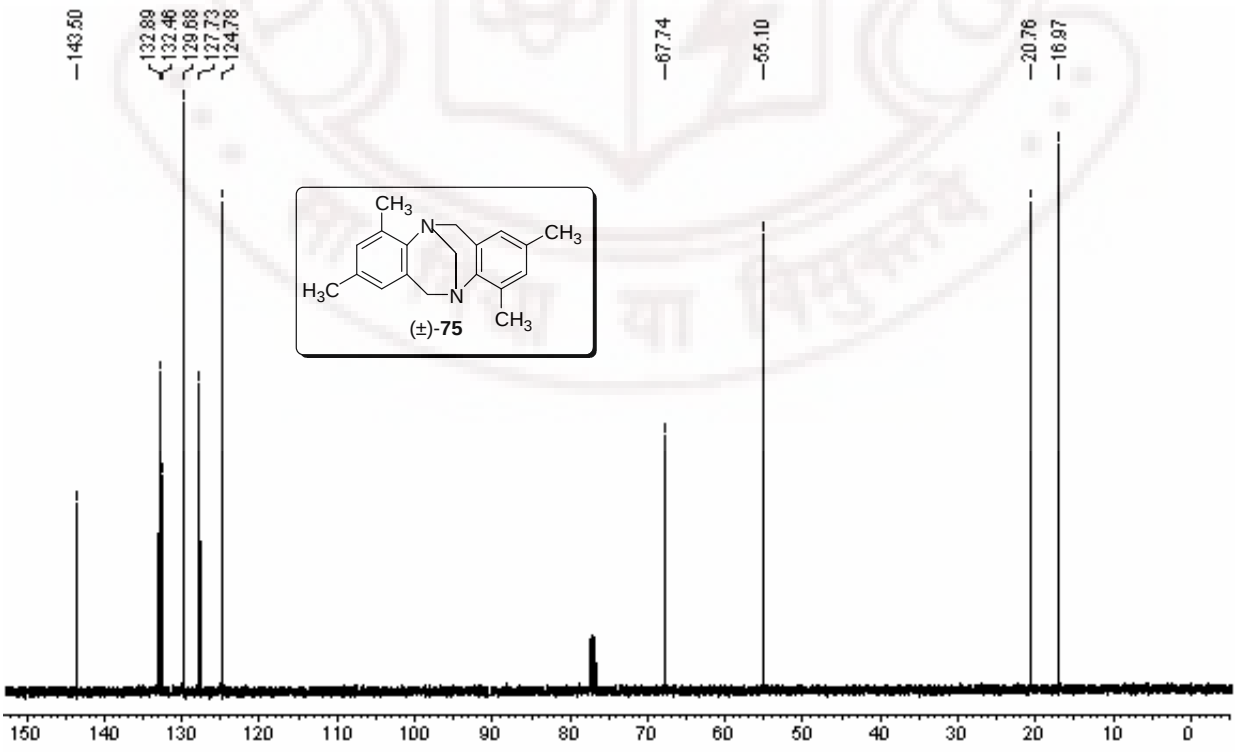
Spectrum No. 6 (Chapter 3, Section 3.2.1) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



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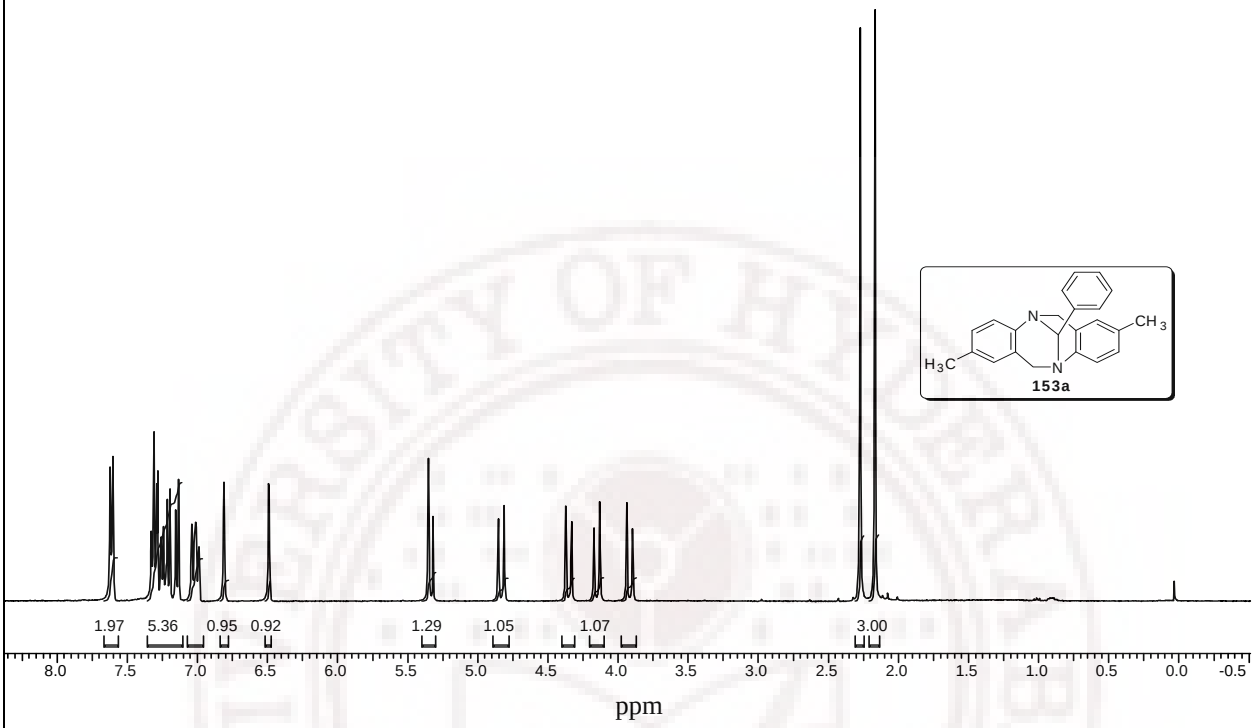
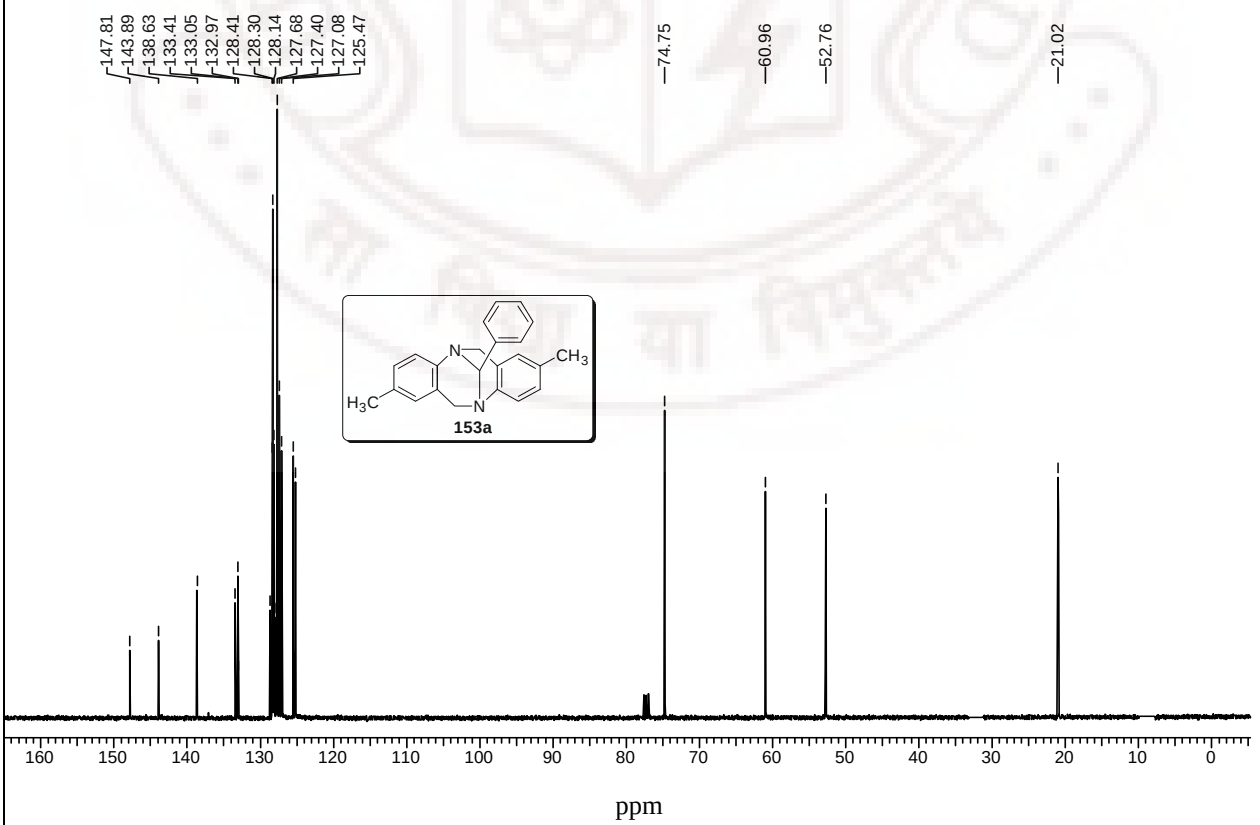
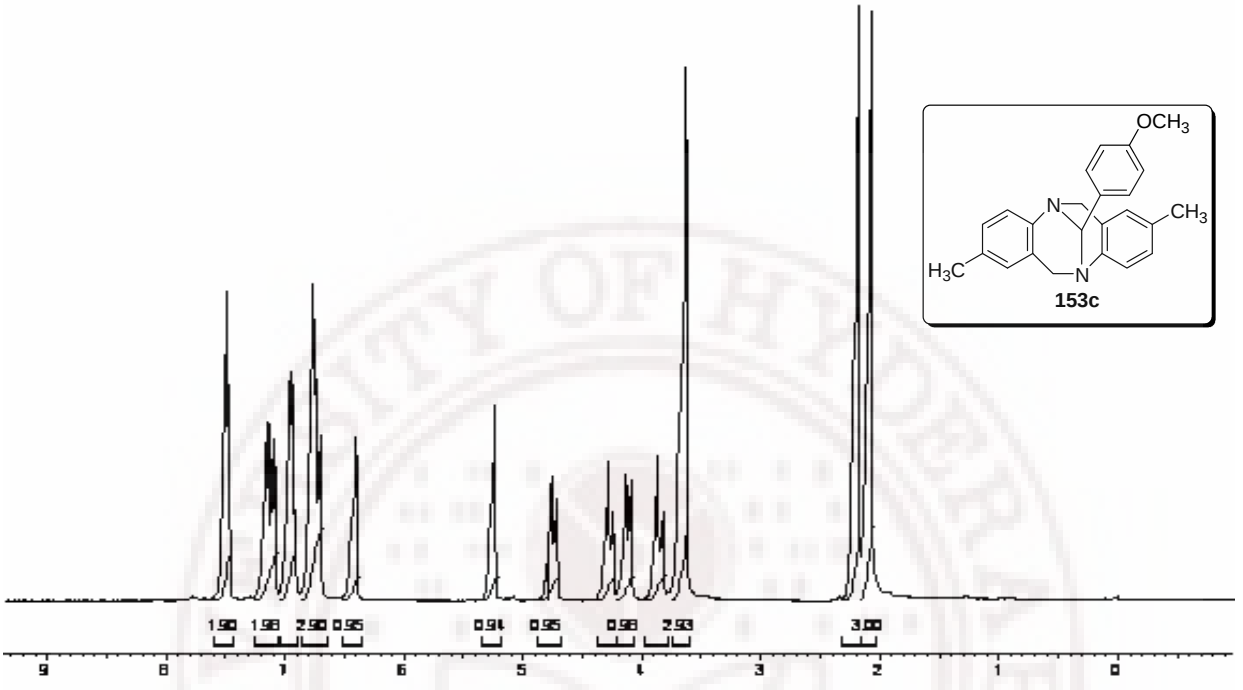
Spectrum No. 7 (Chapter 3, Section 3.4.1) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



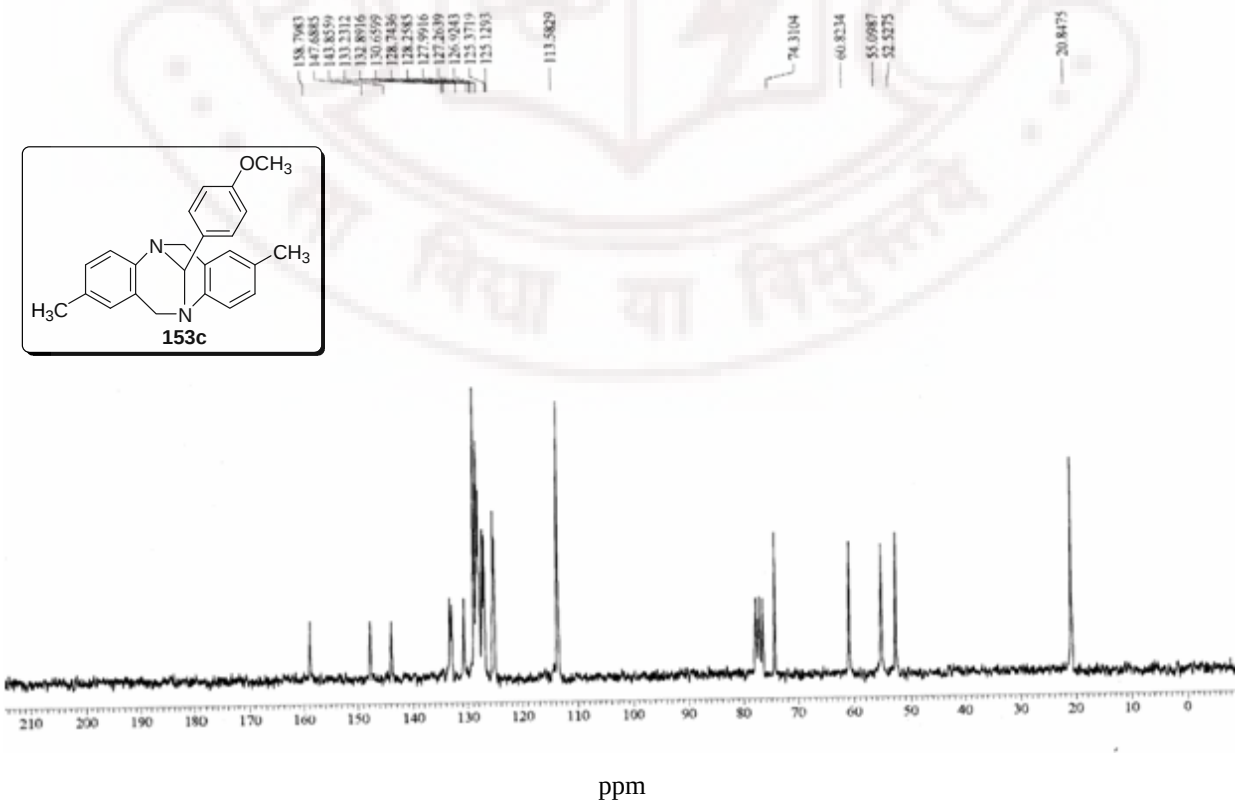
Spectrum No. 8 (Chapter 3, Section 3.4.1) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



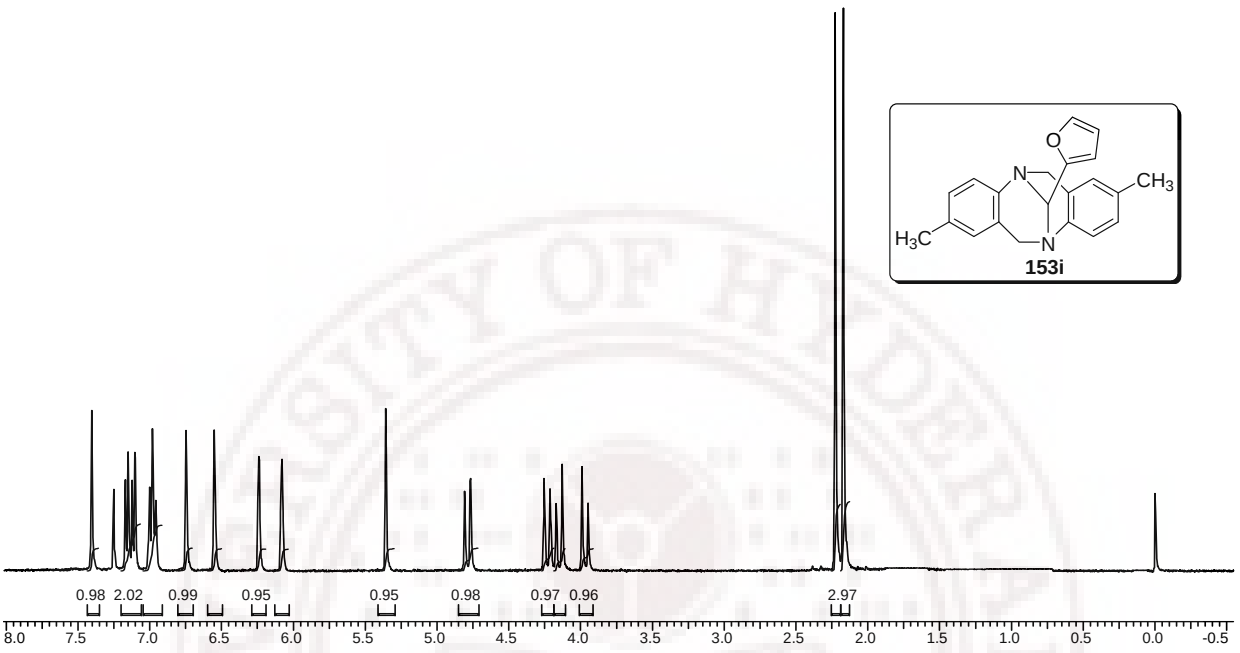
Spectrum No. 9 (Chapter 3, Section 3.4.1) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



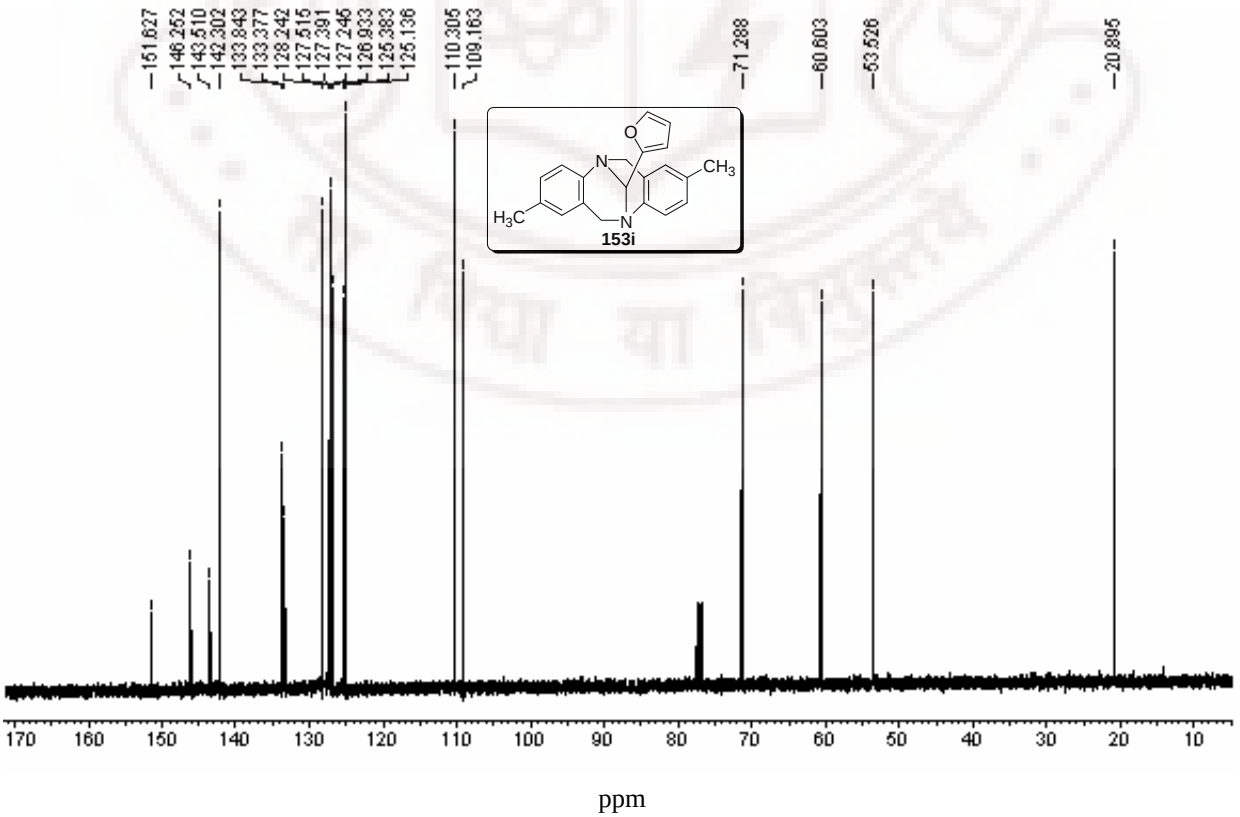
Spectrum No. 10 (Chapter 3, Section 3.4.1) ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)



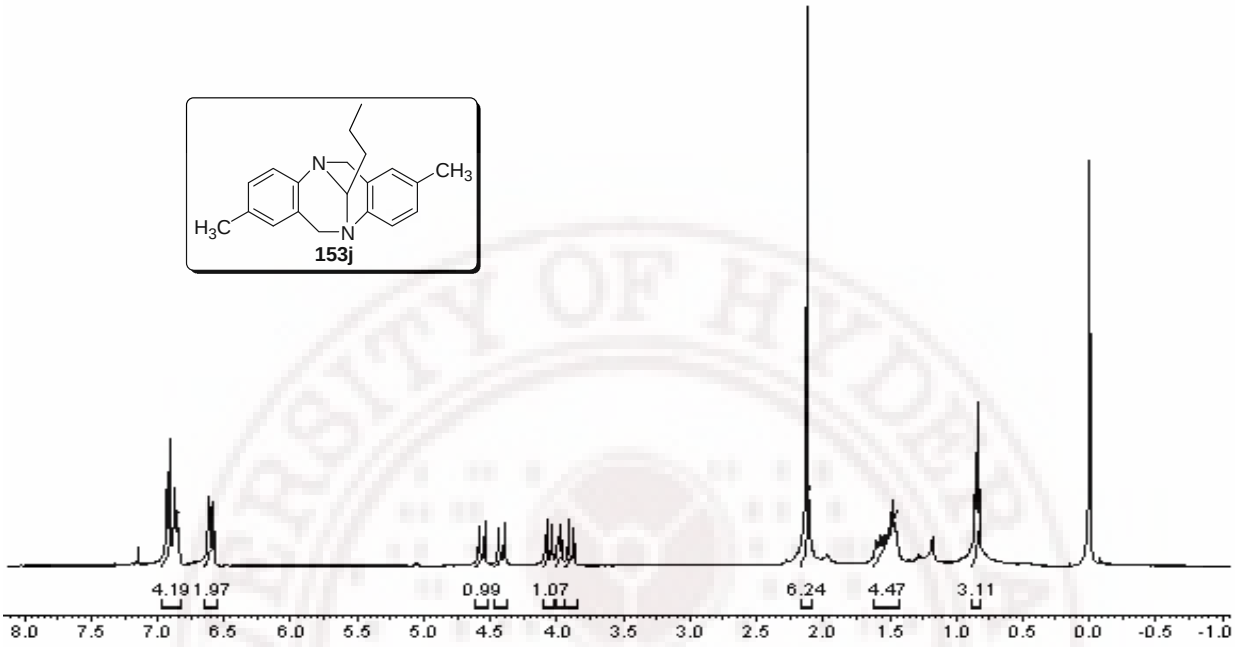
Spectrum No. 11 (Chapter 3, Section 3.4.1) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



Spectrum No. 12 (Chapter 3, Section 3.4.1) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



Spectrum No. 13 (Chapter 3, Section 3.4.1) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



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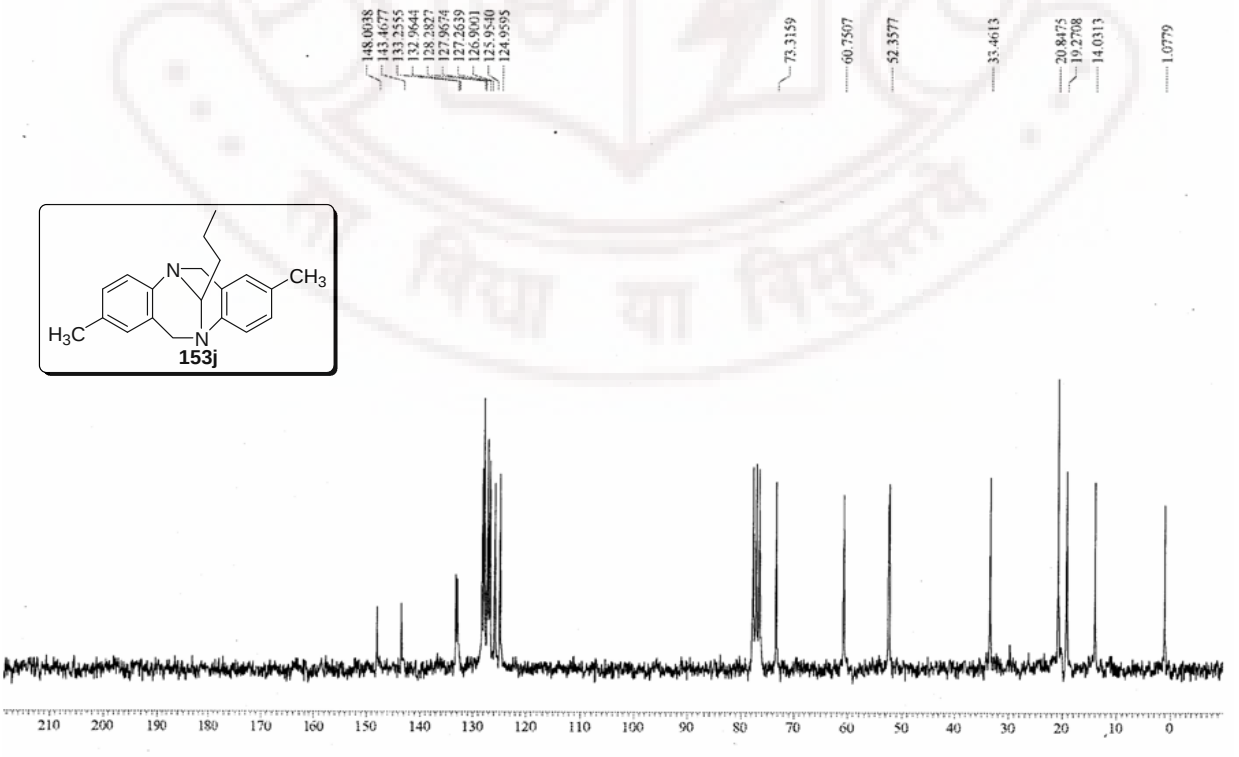
Spectrum No. 14 (Chapter 3, Section 3.4.1) ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)



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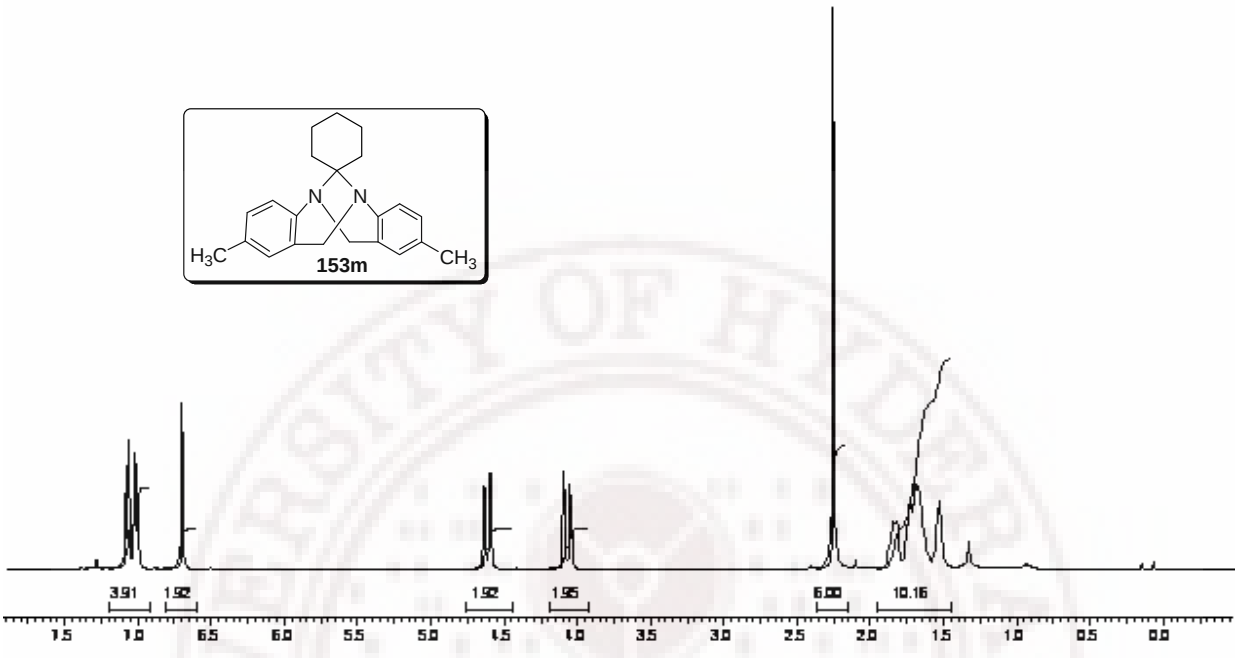
Spectrum No. 15 (Chapter 3, Section 3.4.1) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



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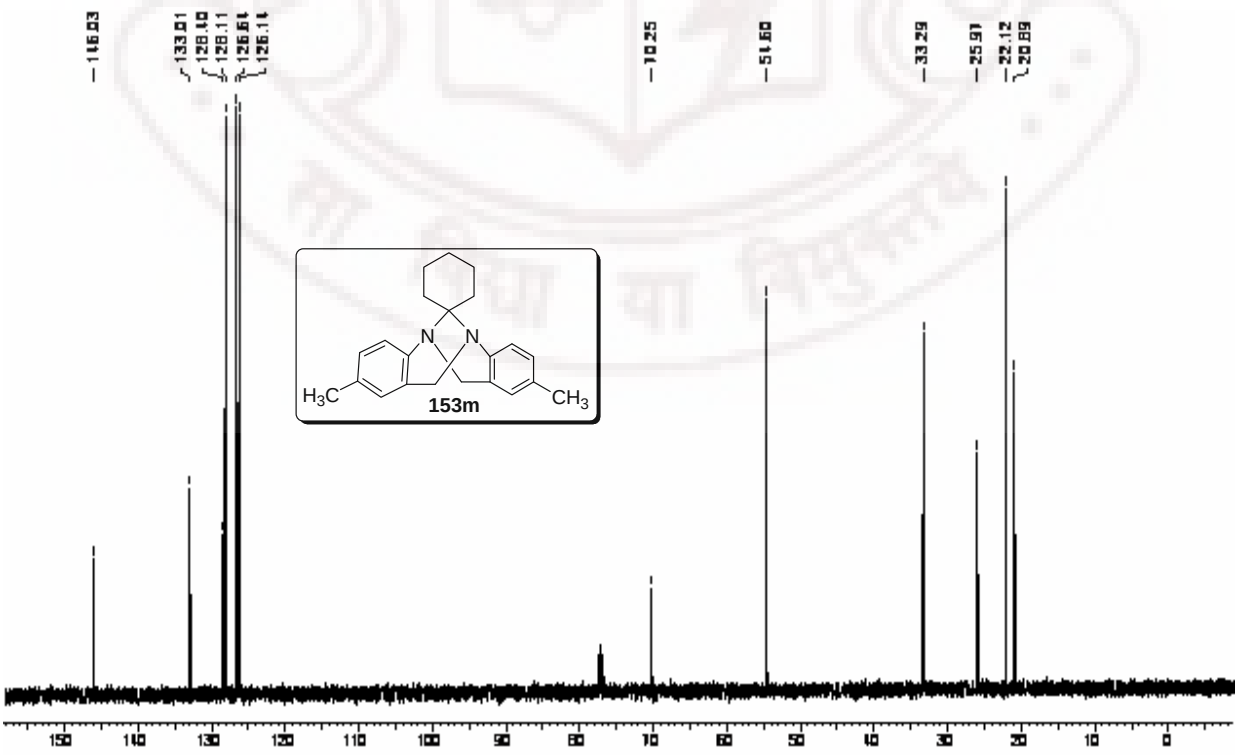
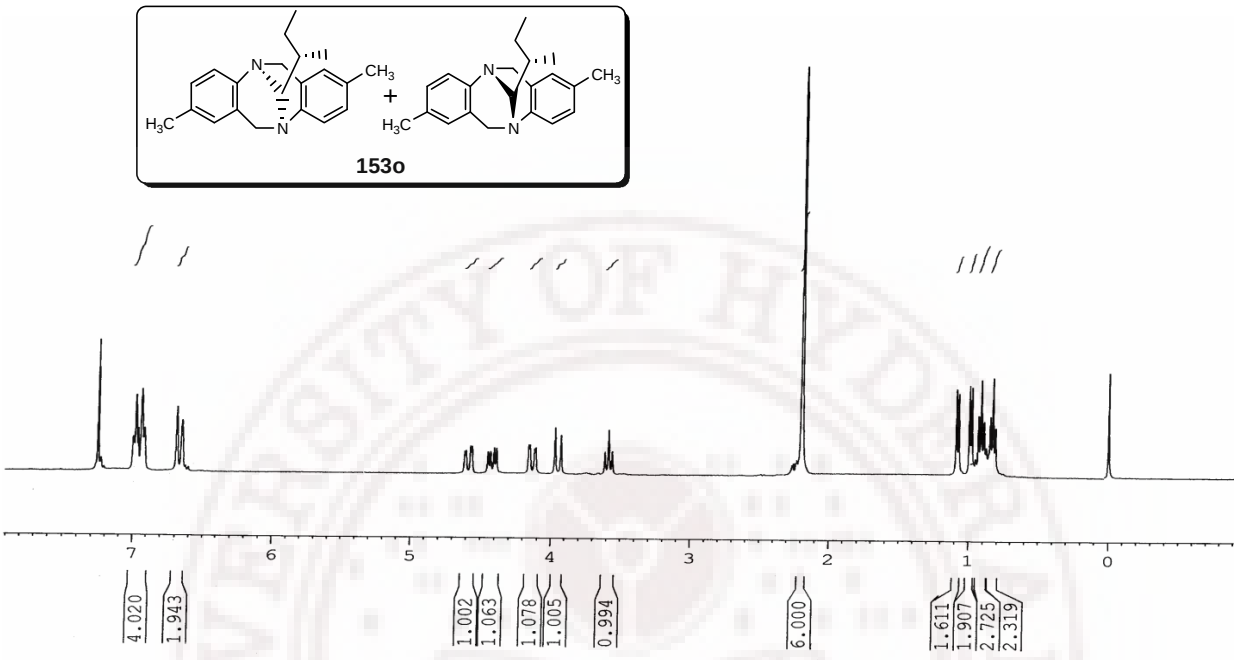
Spectrum No. 16 (Chapter 3, Section 3.4.1) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)

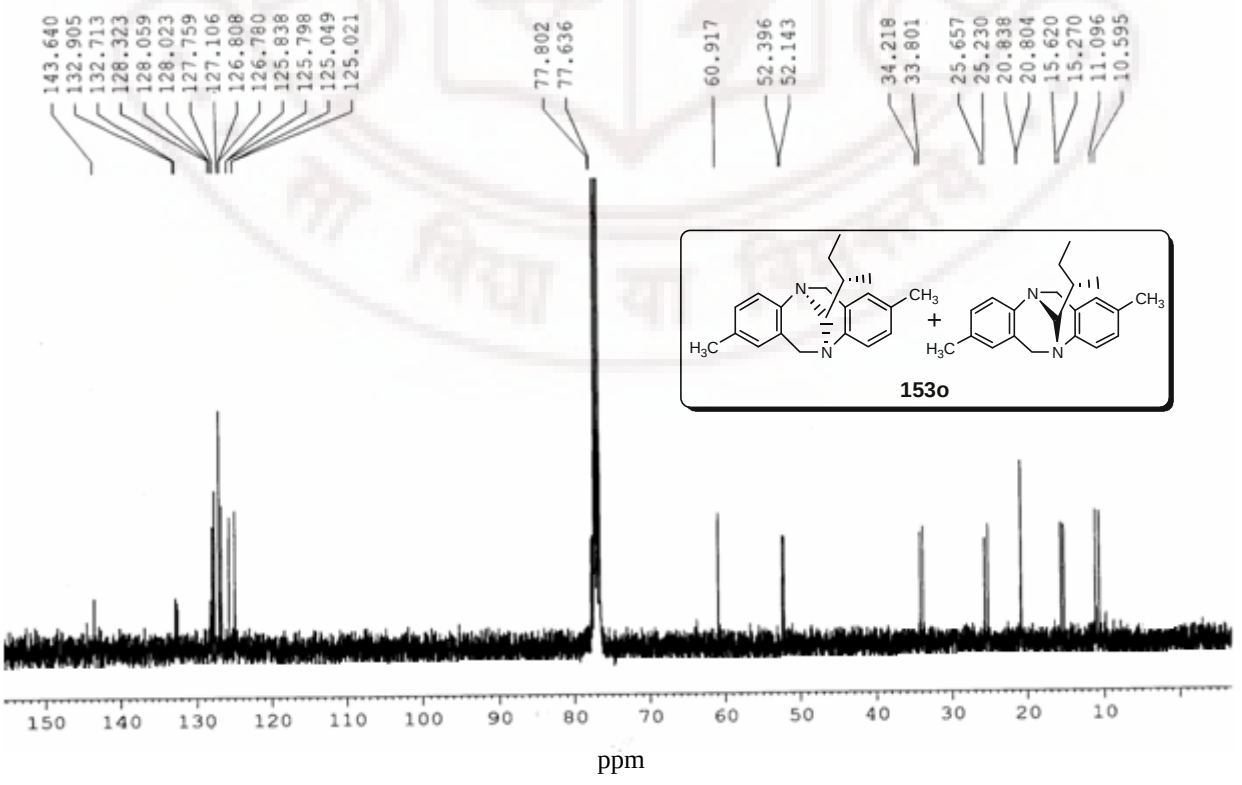


ppm

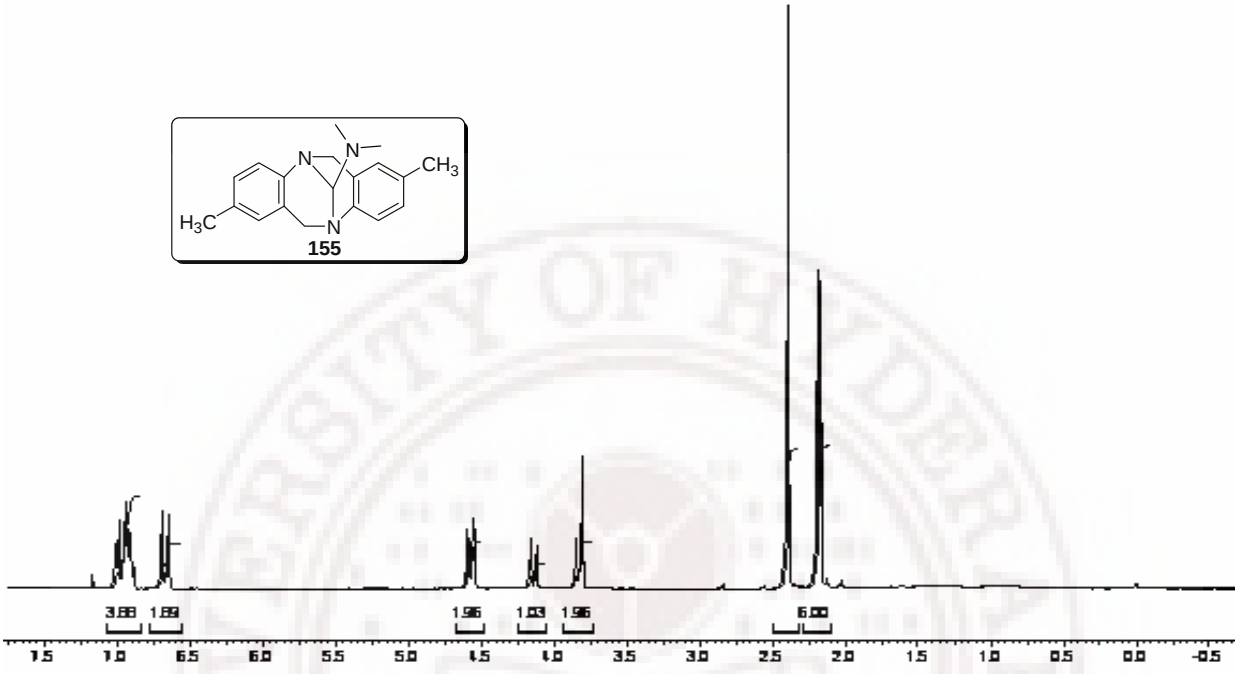
Spectrum No. 17 (Chapter 3, Section 3.4.1) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



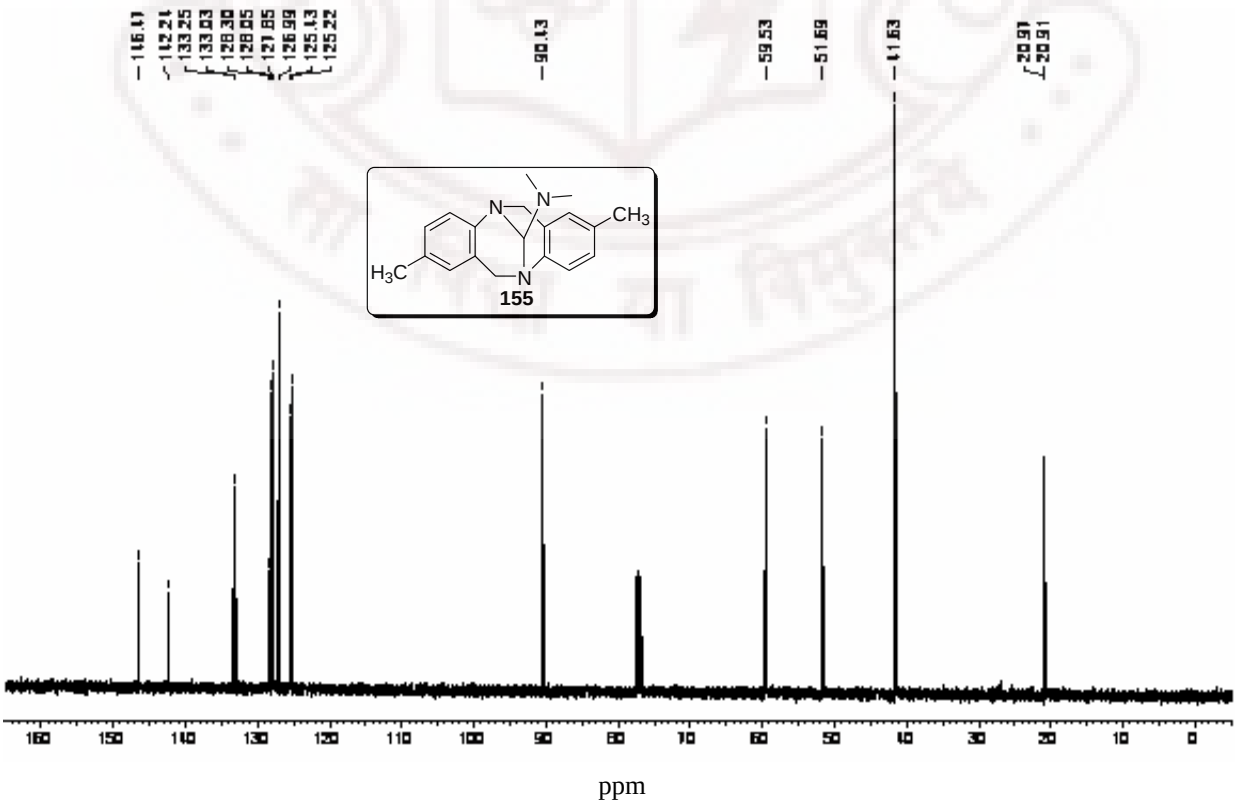
Spectrum No. 18 (Chapter 3, Section 3.4.1) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



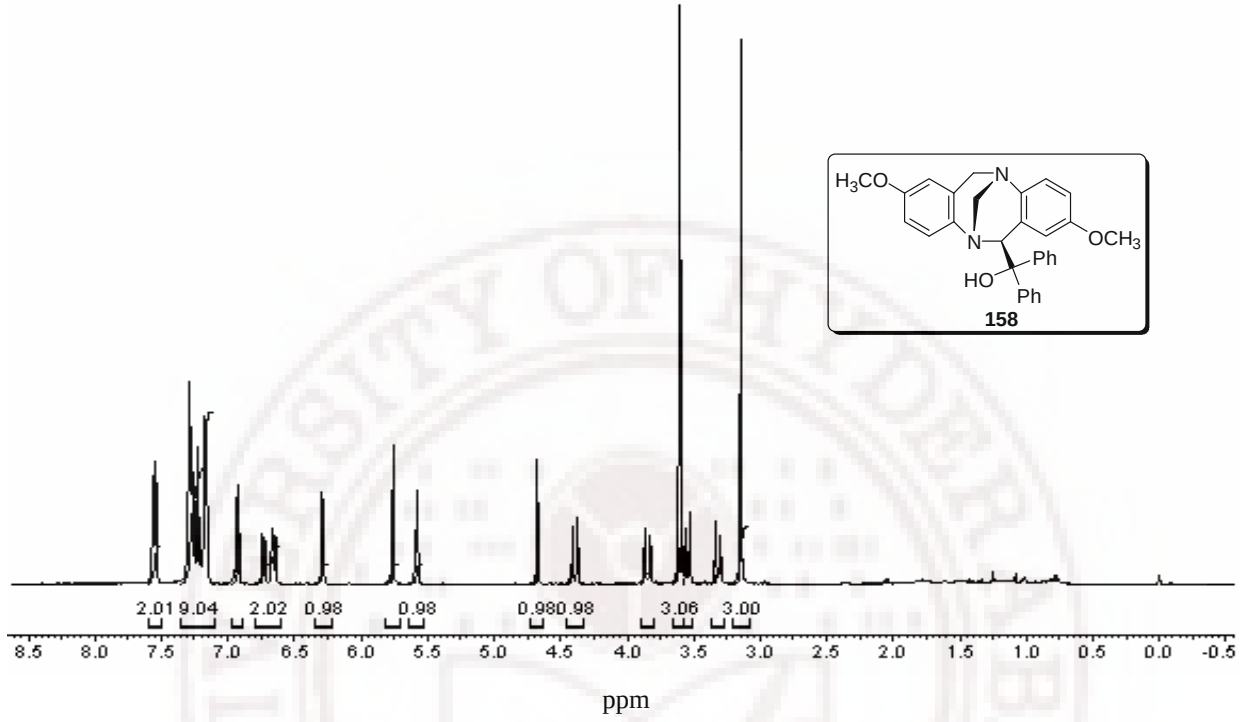
Spectrum No. 19 (Chapter 3, Section 3.4.2) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



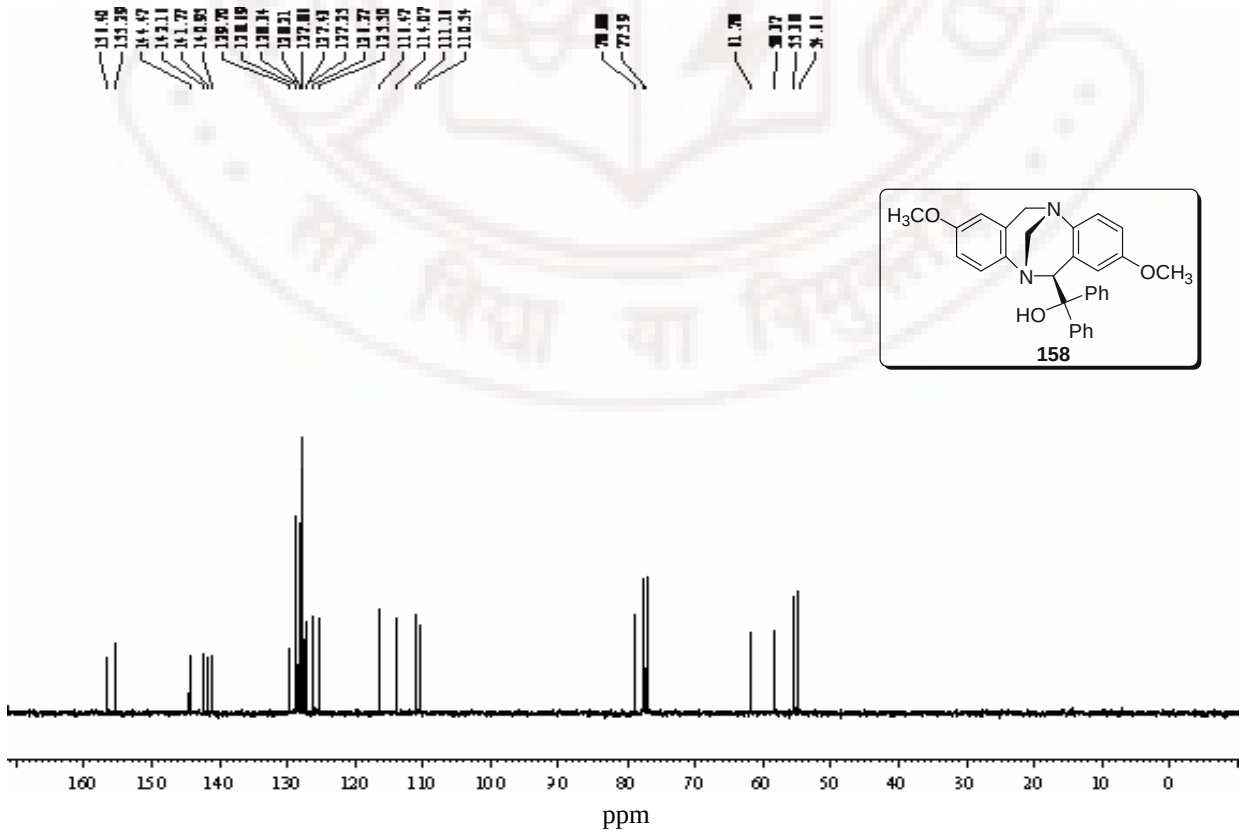
Spectrum No. 20 (Chapter 3, Section 3.4.2) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



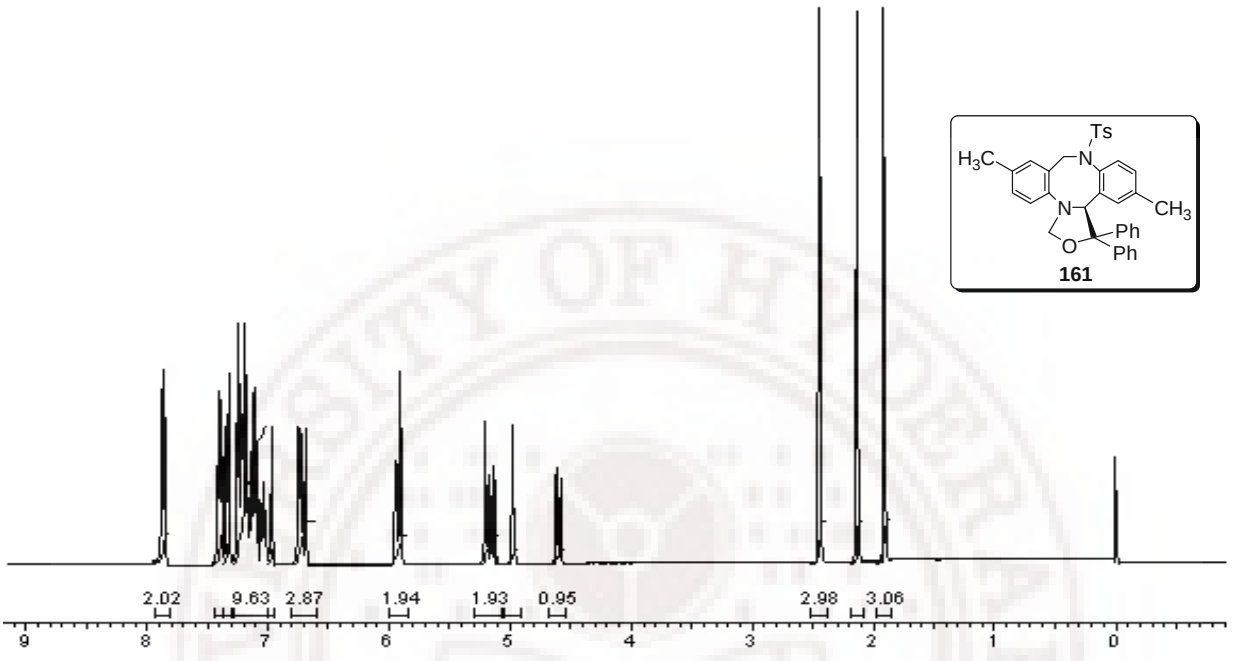
Spectrum No. 21 (Chapter 3, Section 3.4.5) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



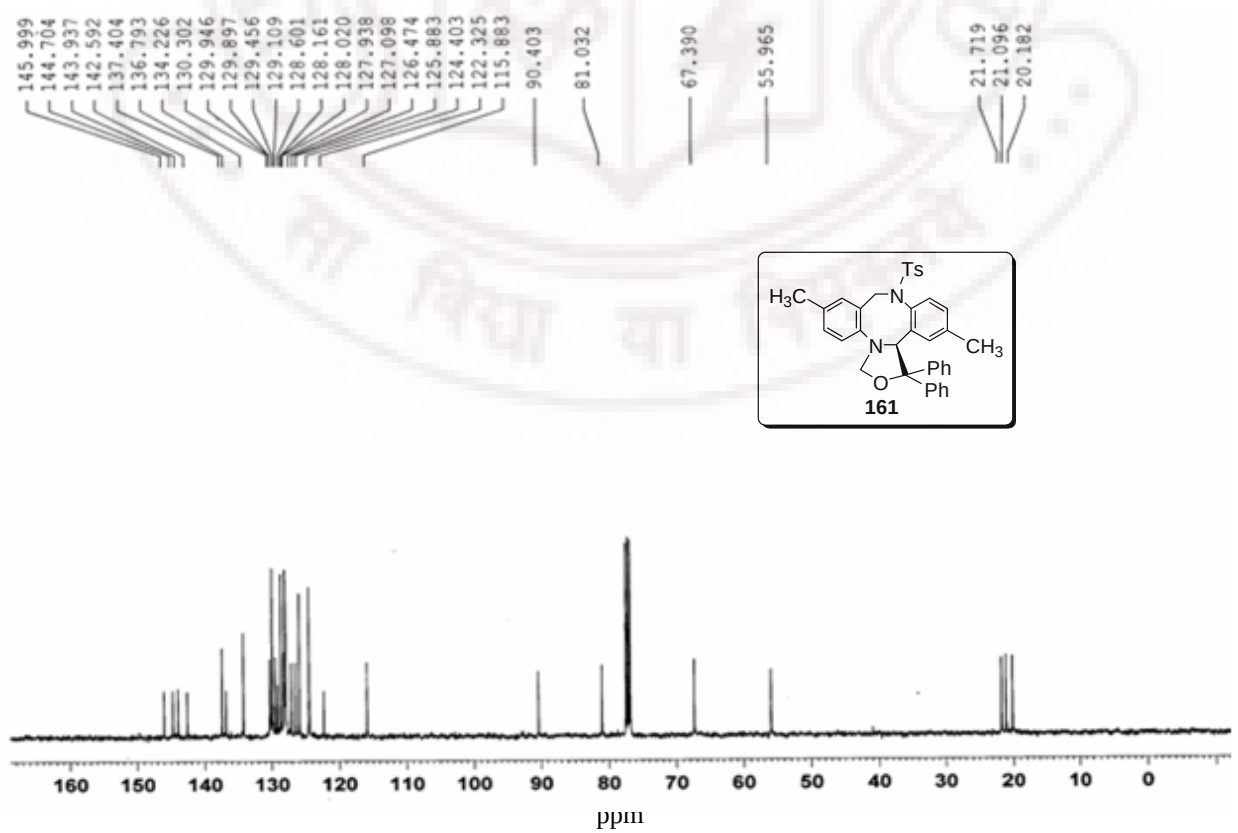
Spectrum No. 22 (Chapter 3, Section 3.4.5) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



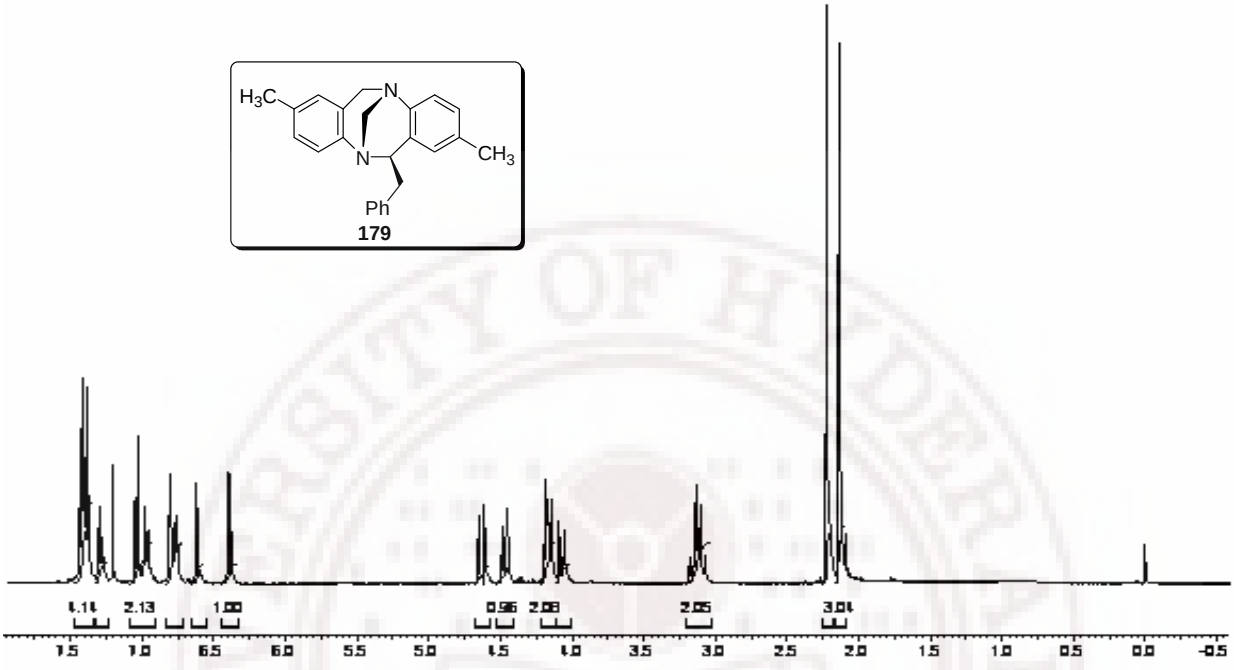
Spectrum No. 23 (Chapter 3, Section 3.4.6) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



Spectrum No. 24 (Chapter 3, Section 3.4.6) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)

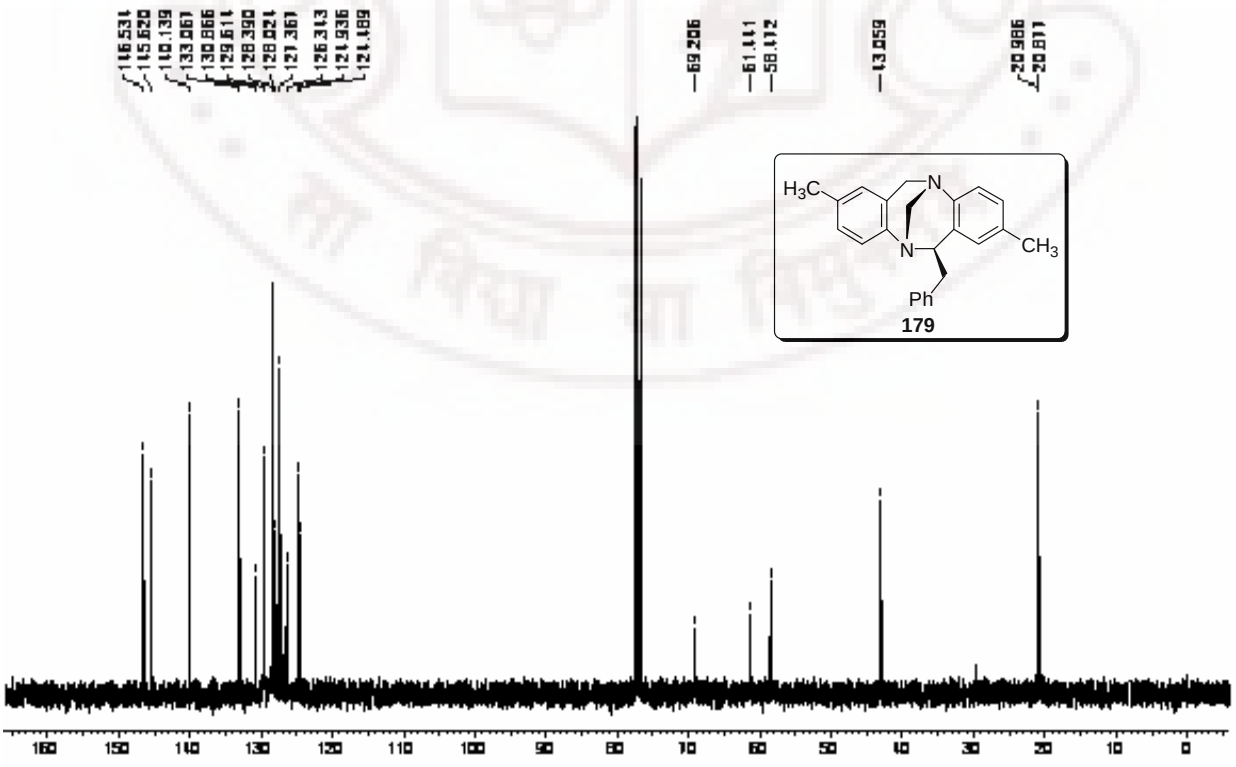


Spectrum No. 25 (Chapter 3, Section 3.4.7) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



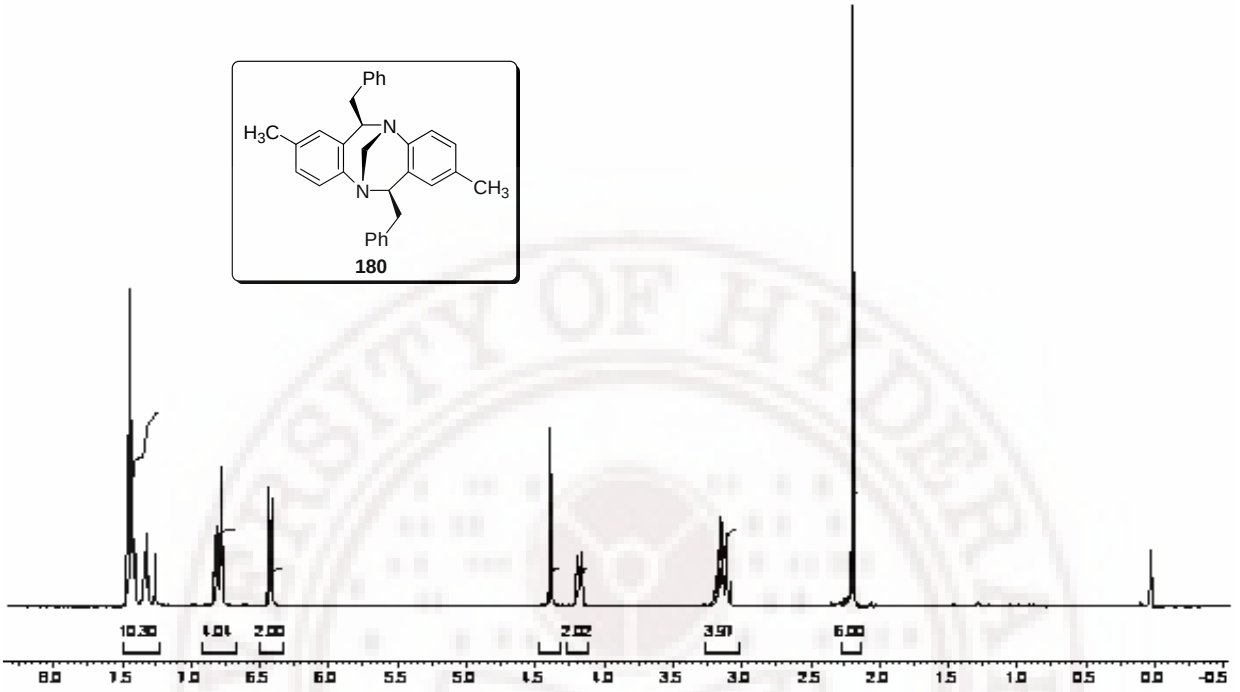
ppm

Spectrum No. 26 (Chapter 3, Section 3.4.7) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



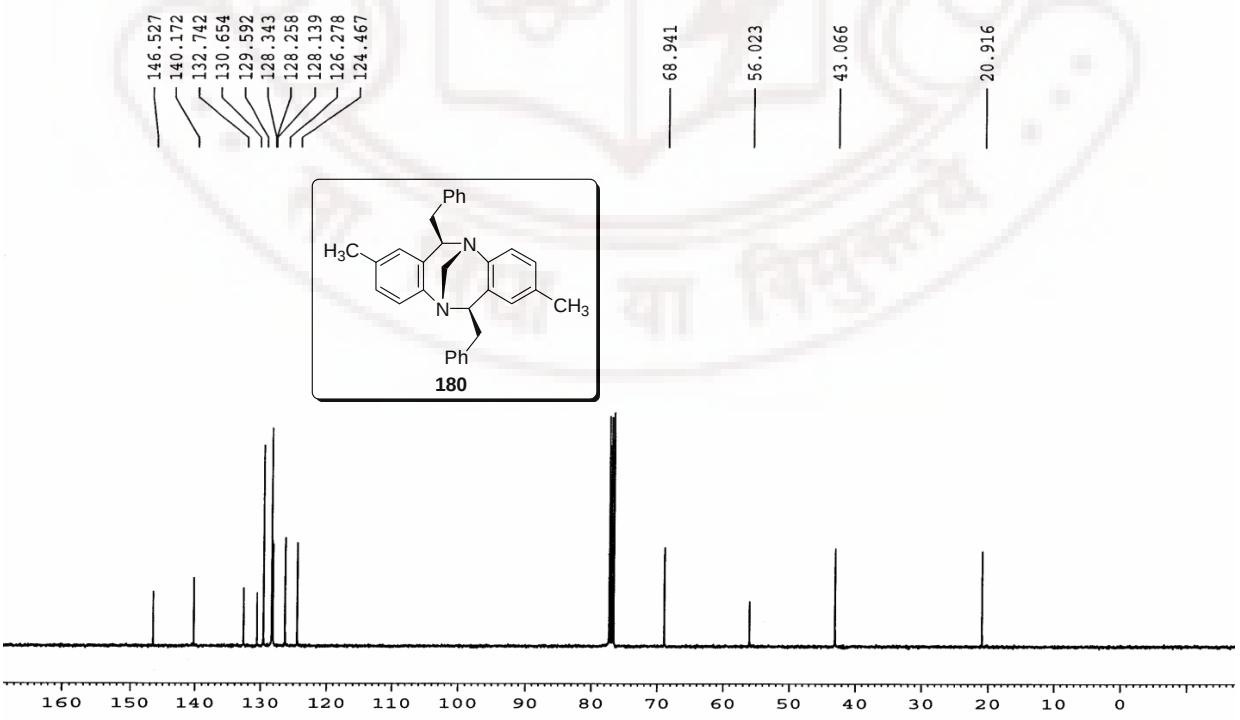
ppm

Spectrum No. 27 (Chapter 3, Section 3.4.8) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



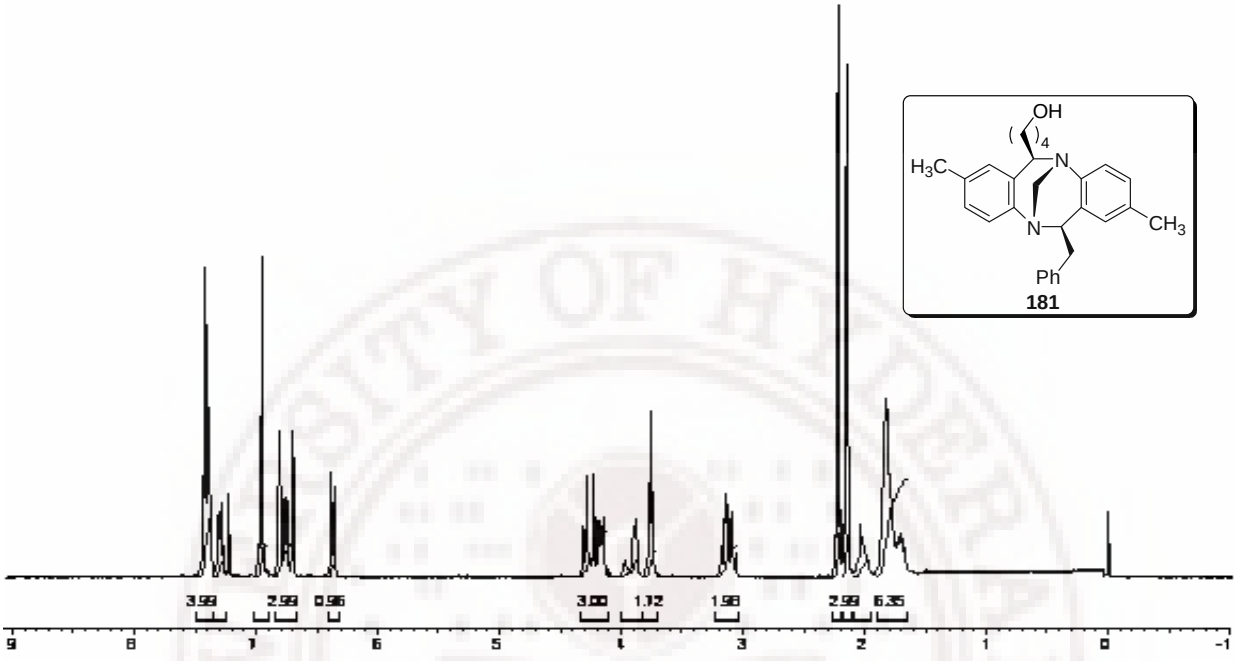
ppm

Spectrum No. 28 (Chapter 3, Section 3.4.8) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



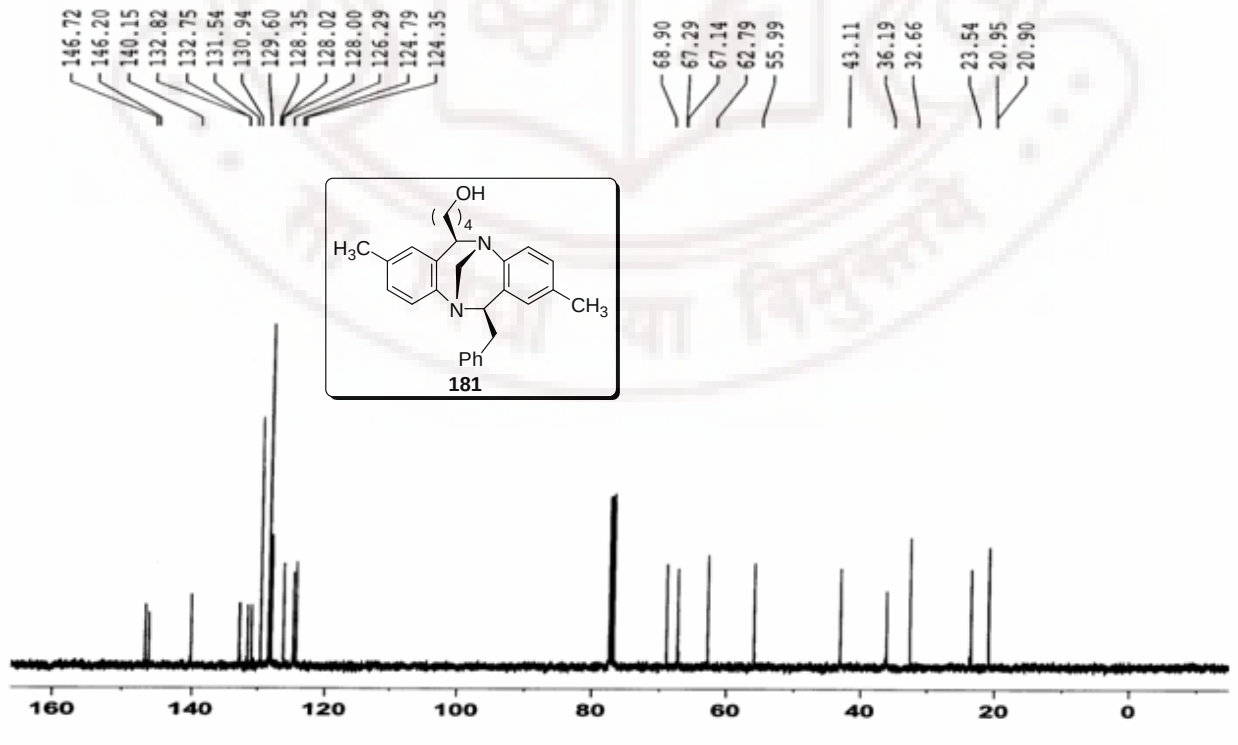
ppm

Spectrum No. 29 (Chapter 3, Section 3.4.8) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



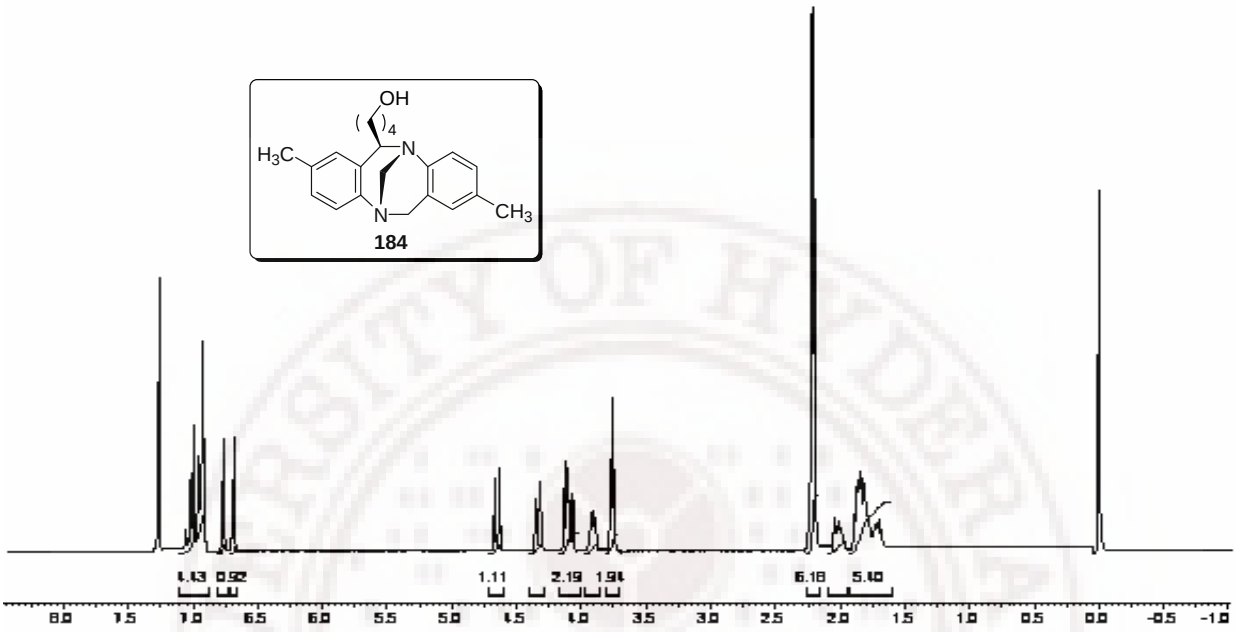
ppm

Spectrum No. 30 (Chapter 3, Section 3.4.8) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



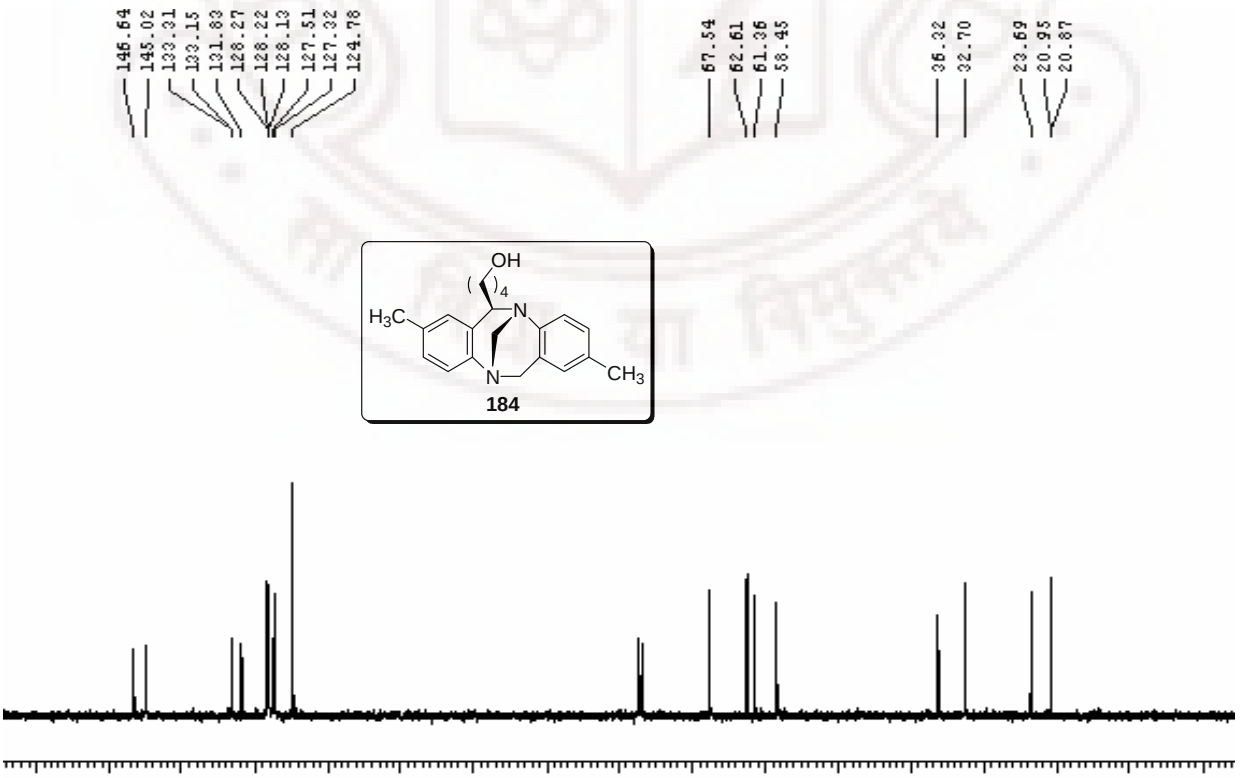
ppm

Spectrum No. 31 (Chapter 3, Section 3.4.9) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



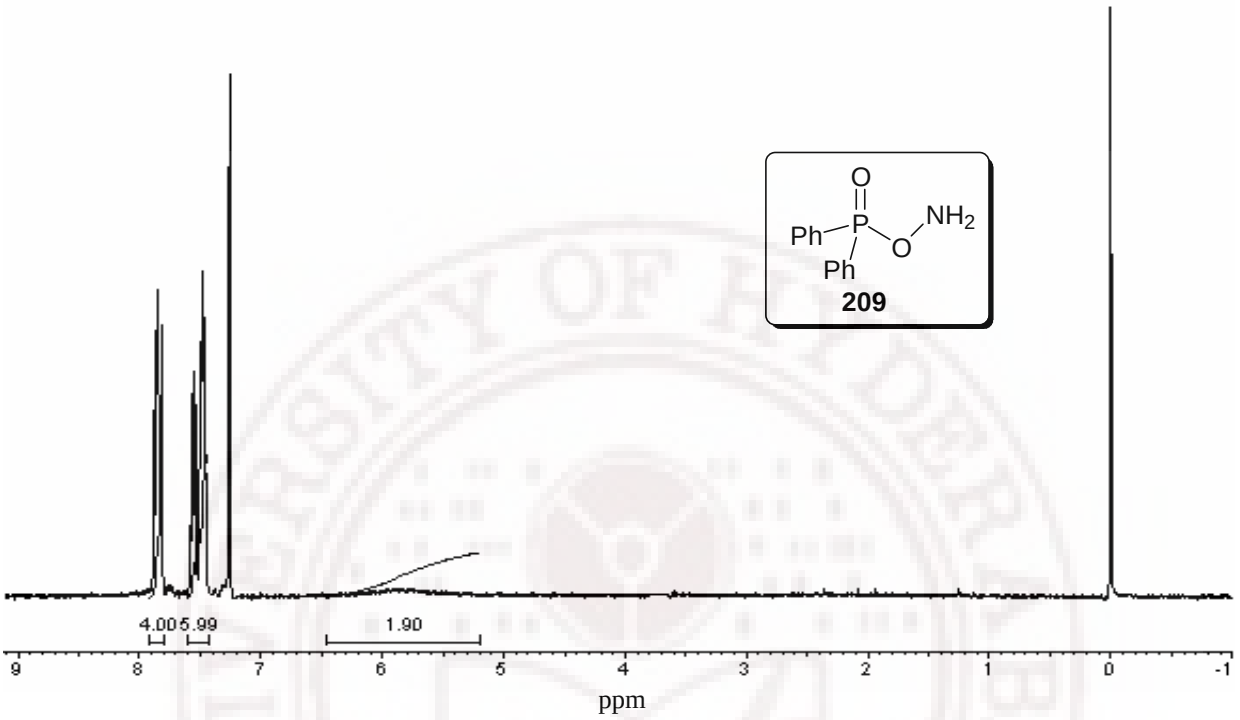
ppm

Spectrum No. 32 (Chapter 3, Section 3.4.9) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)

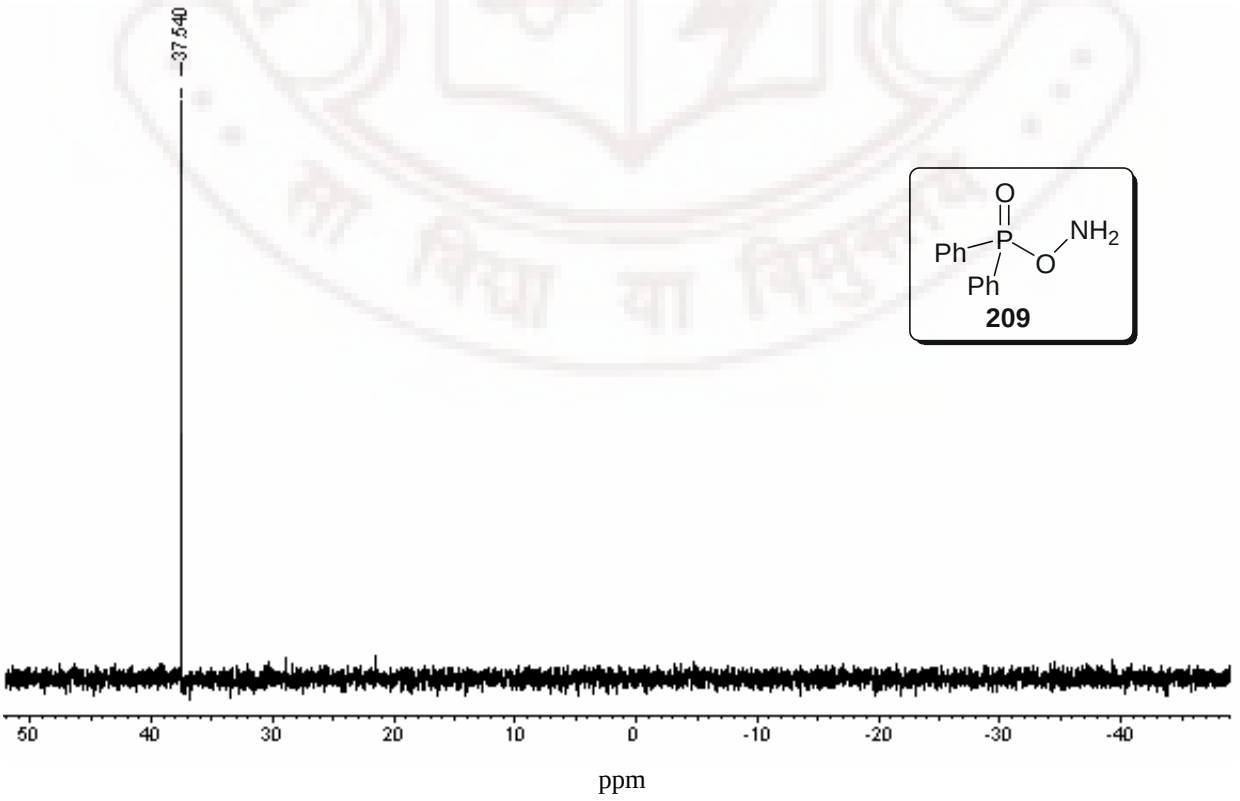


ppm

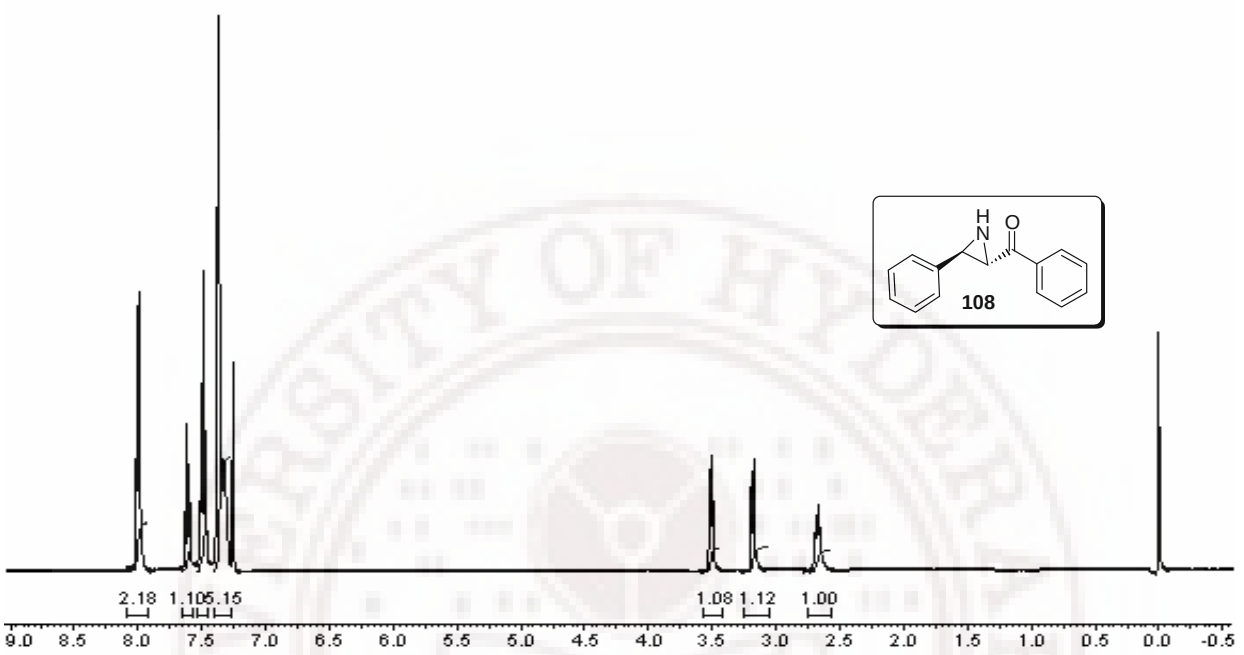
Spectrum No. 33 (Chapter 3, Section 3.5.1) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



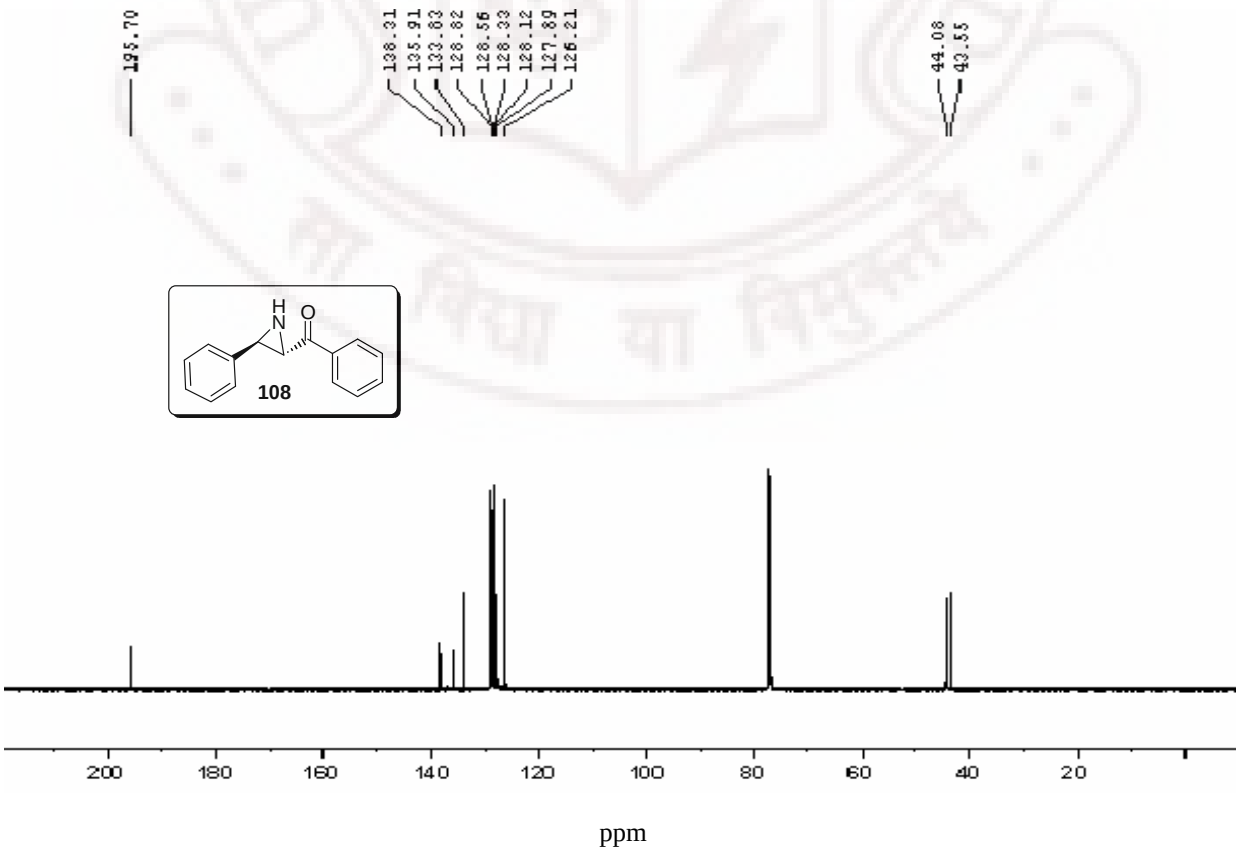
Spectrum No. 34 (Chapter 3, Section 3.5.1) ^{31}P NMR Spectrum (162 MHz, $CDCl_3$)



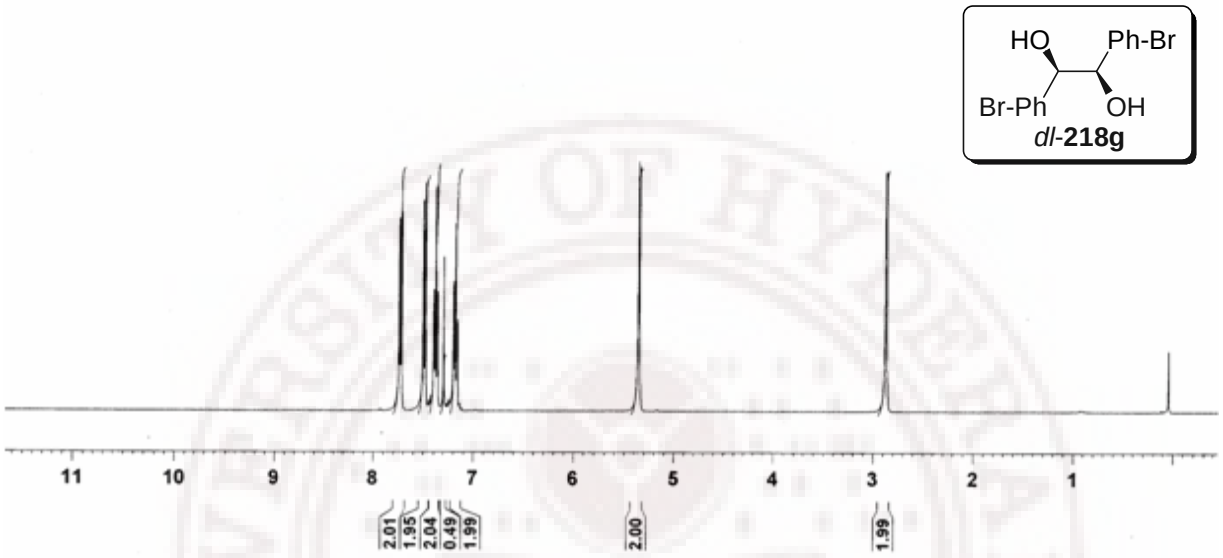
Spectrum No. 35 (Chapter 3, Section 3.5.3) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



Spectrum No. 36 (Chapter 3, Section 3.5.3) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)

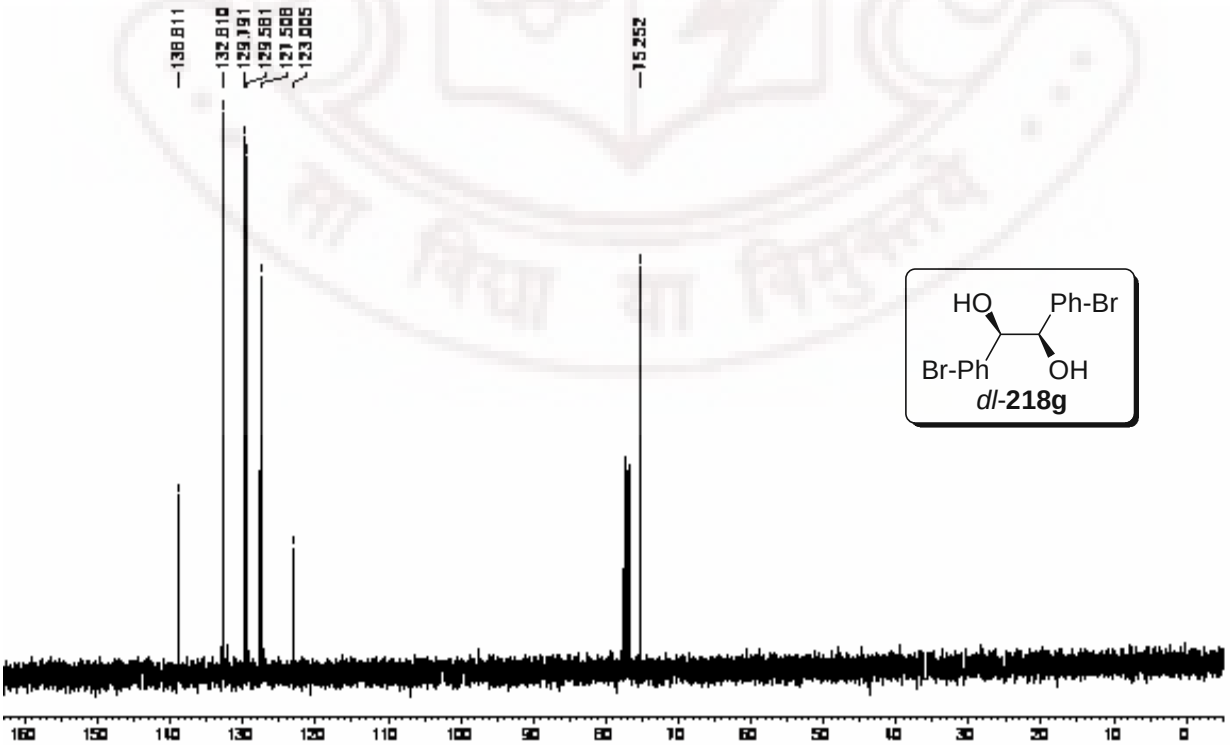


Spectrum No. 37 (Chapter 3, Section 3.6.2) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



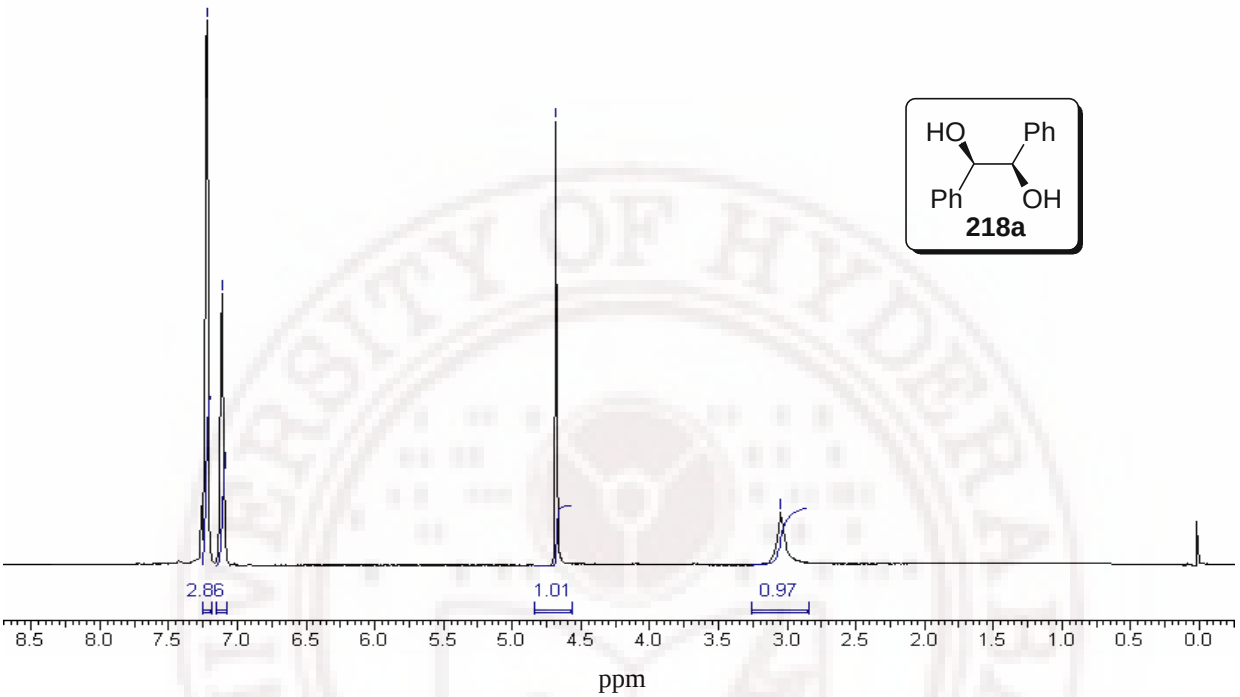
ppm

Spectrum No. 38 (Chapter 3, Section 3.6.2) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)

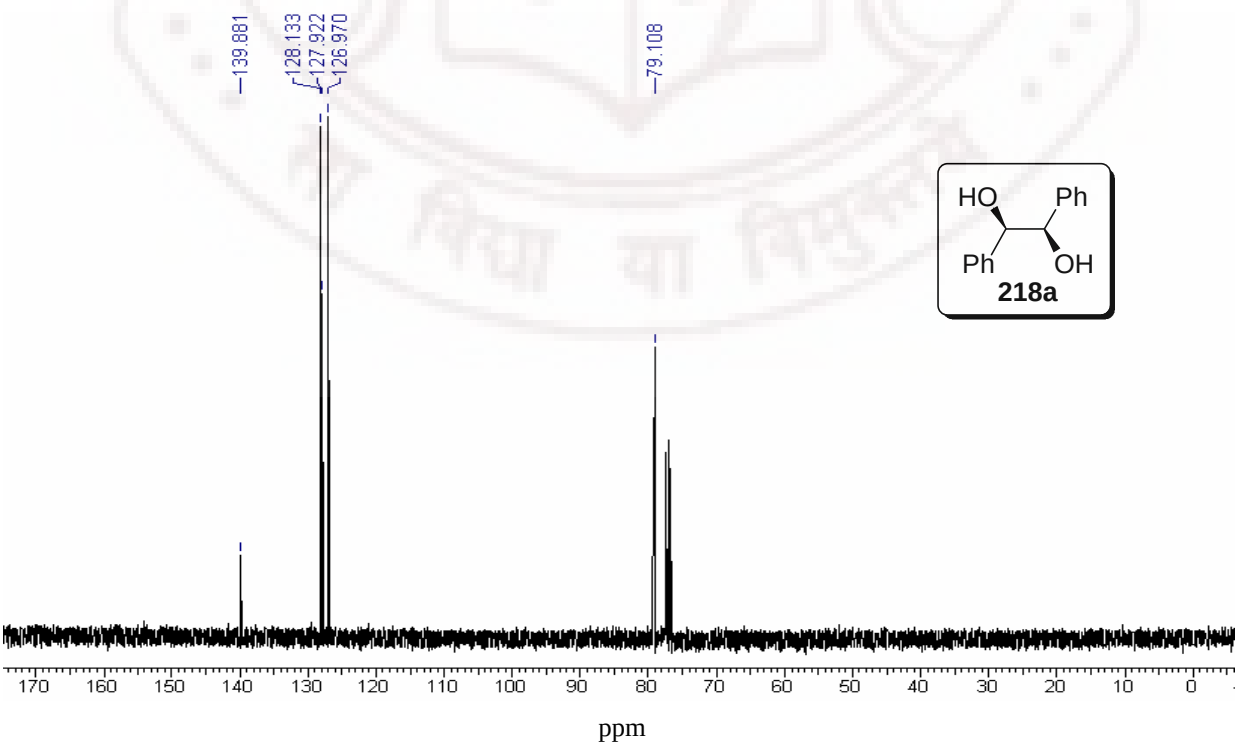


ppm

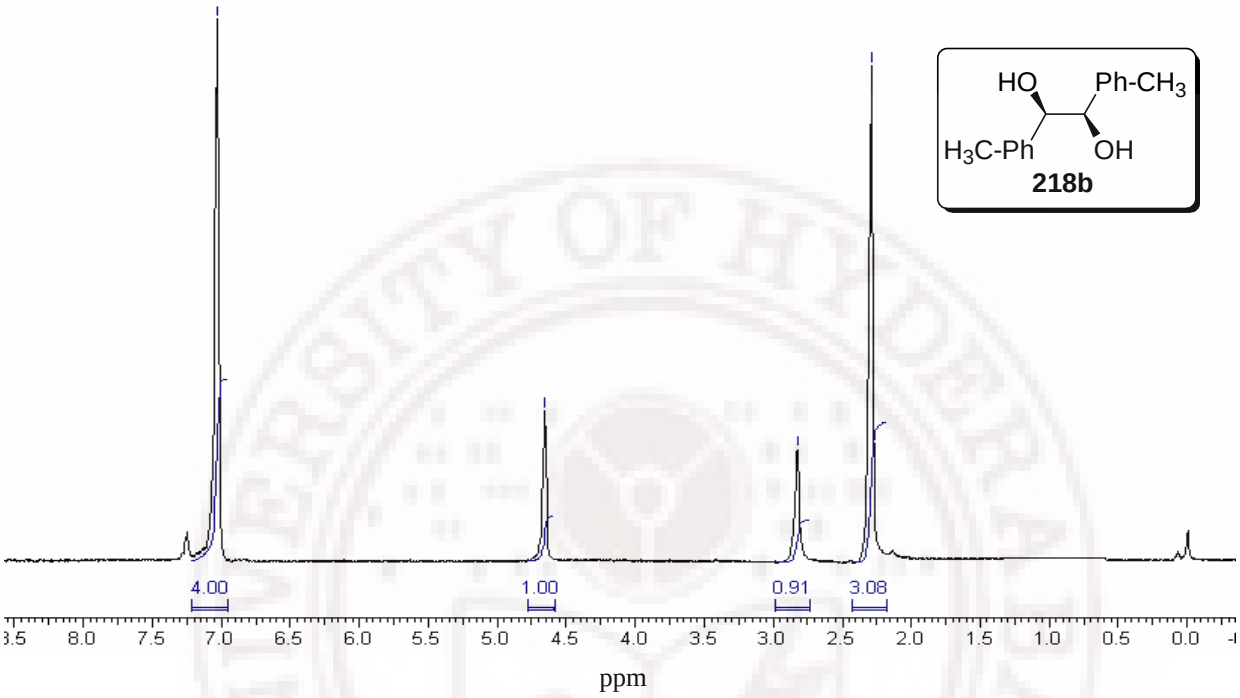
Spectrum No. 39 (Chapter 3, Section 3.7.1) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



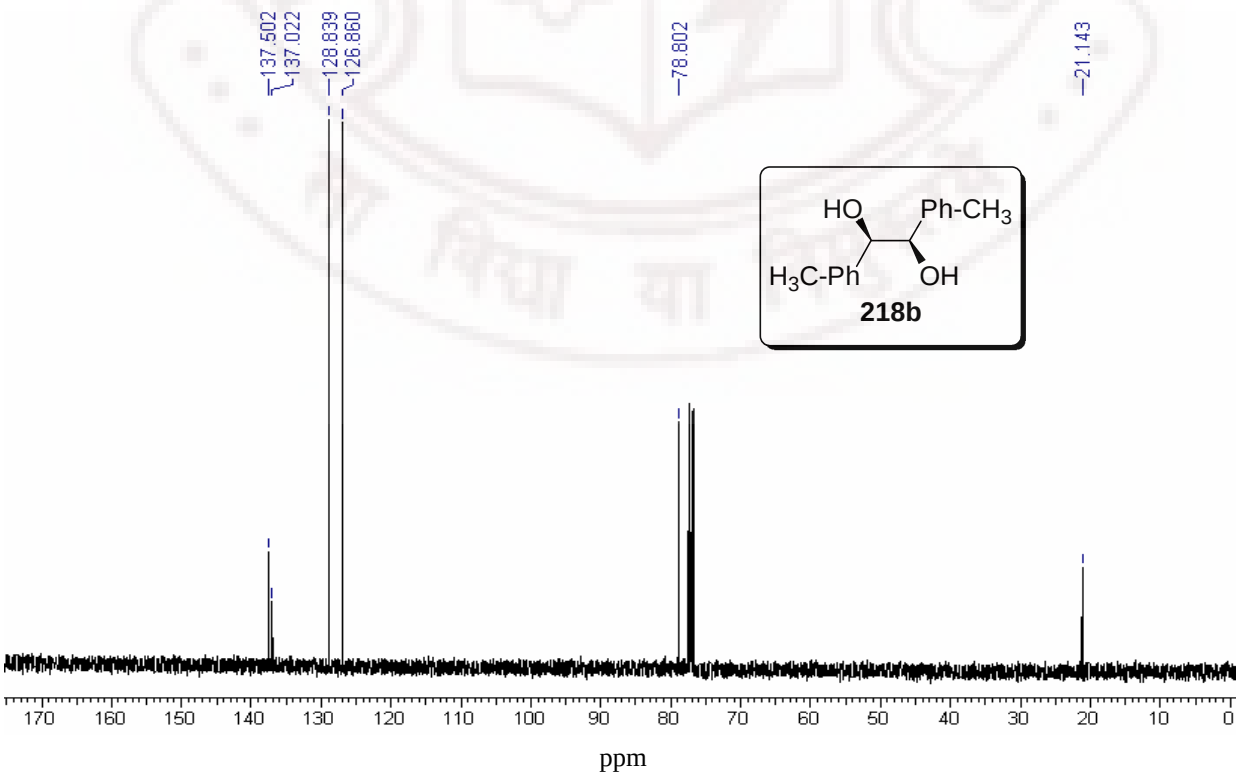
Spectrum No. 40 (Chapter 3, Section 3.7.1) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



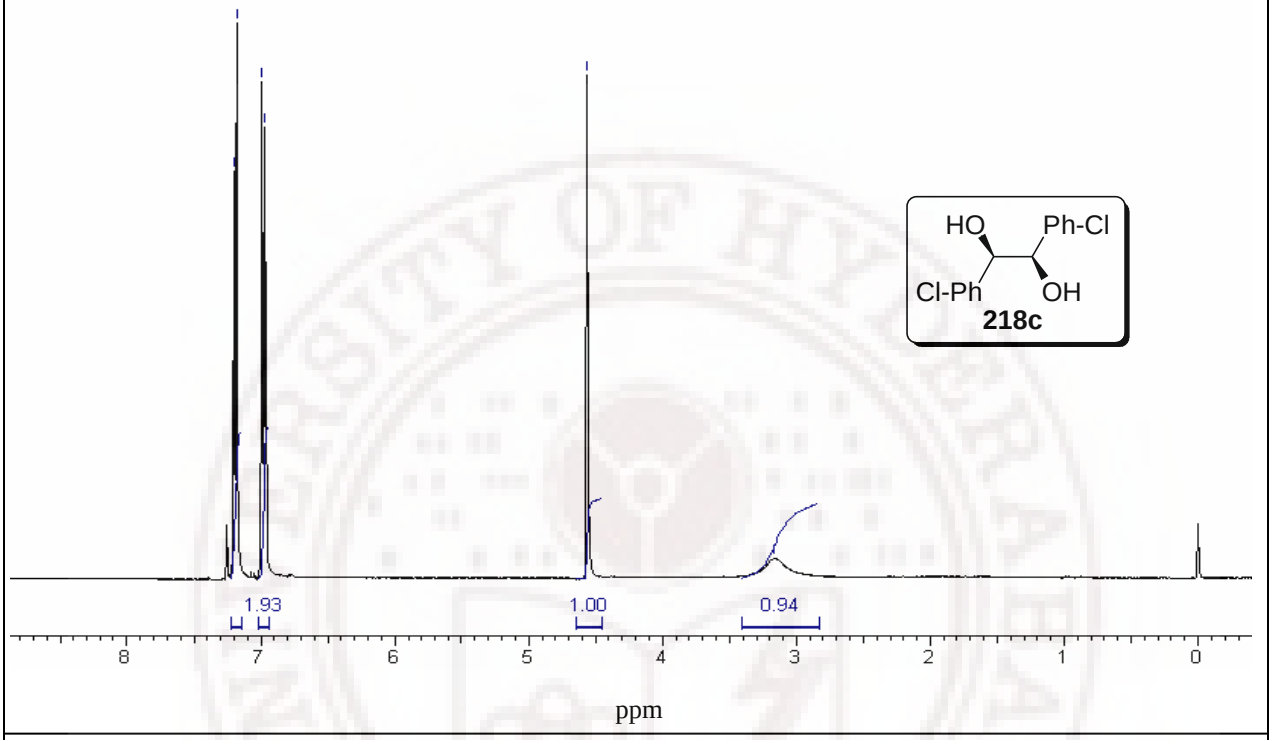
Spectrum No. 41 (Chapter 3, Section 3.7.1) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



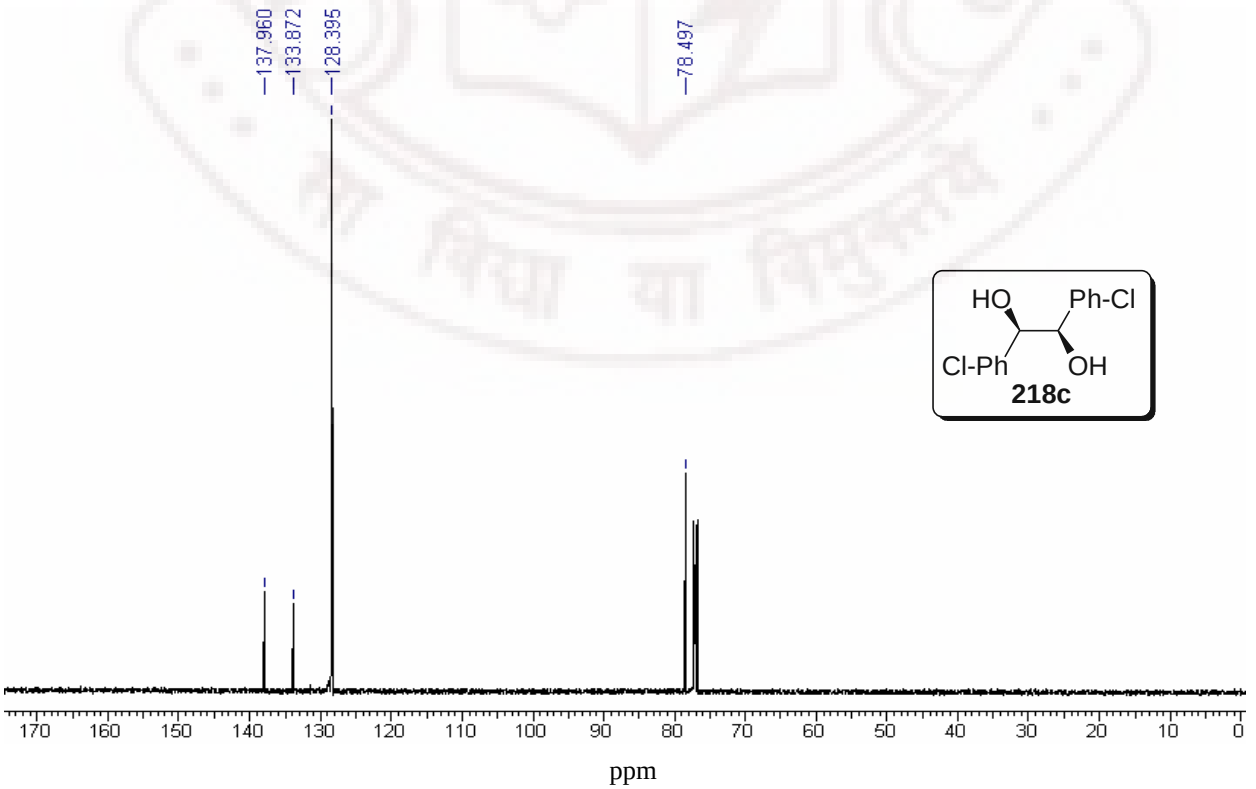
Spectrum No. 42 (Chapter 3, Section 3.7.1) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



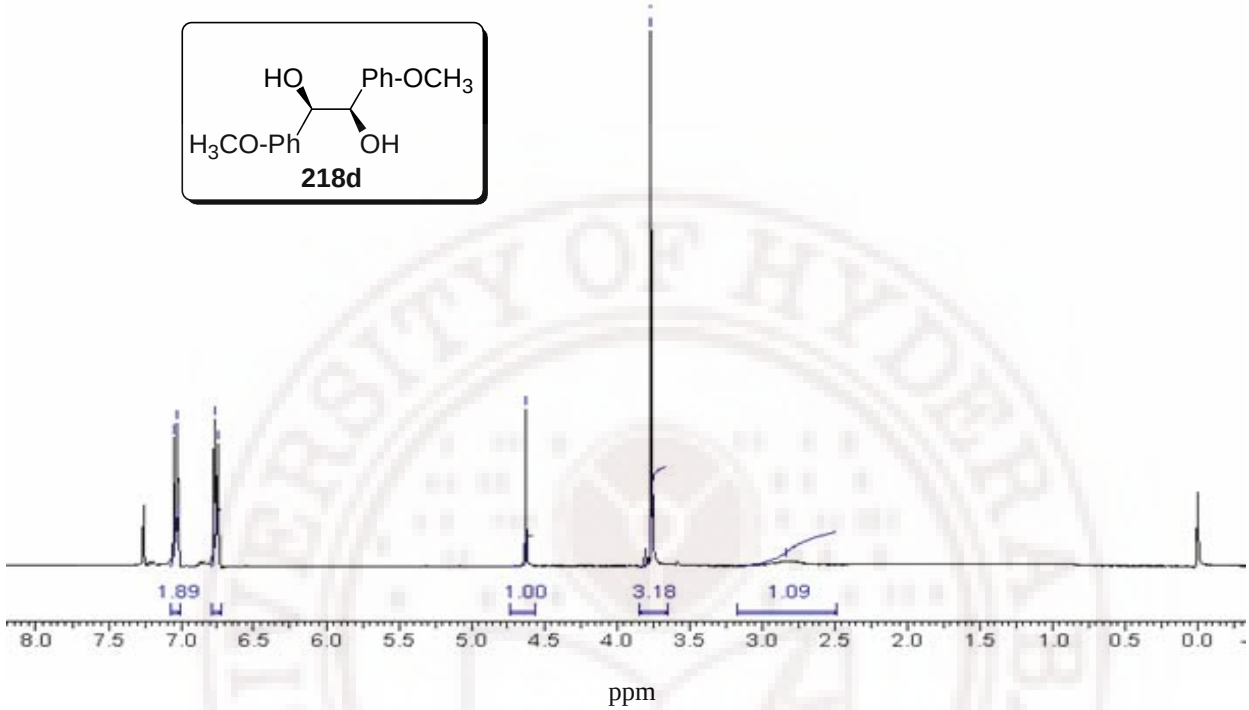
Spectrum No. 43 (Chapter 3, Section 3.7.1) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



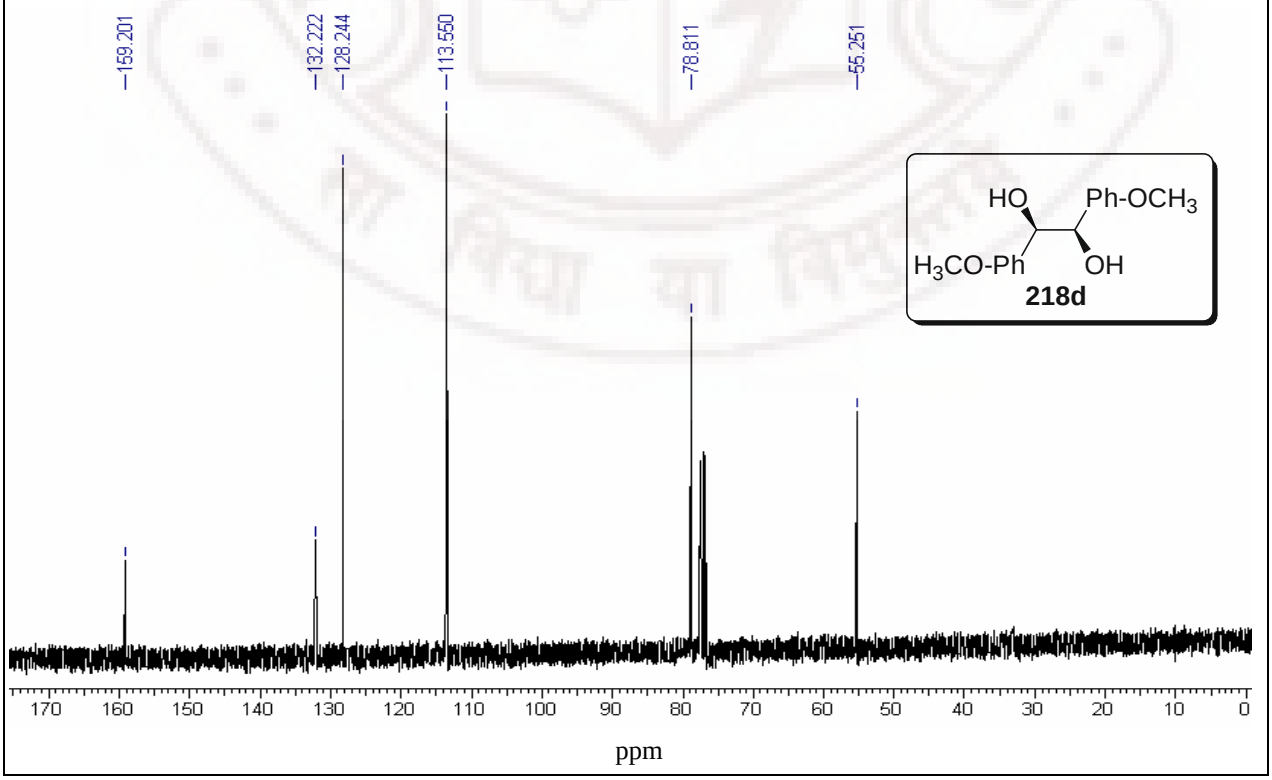
Spectrum No. 44 (Chapter 3, Section 3.7.1) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



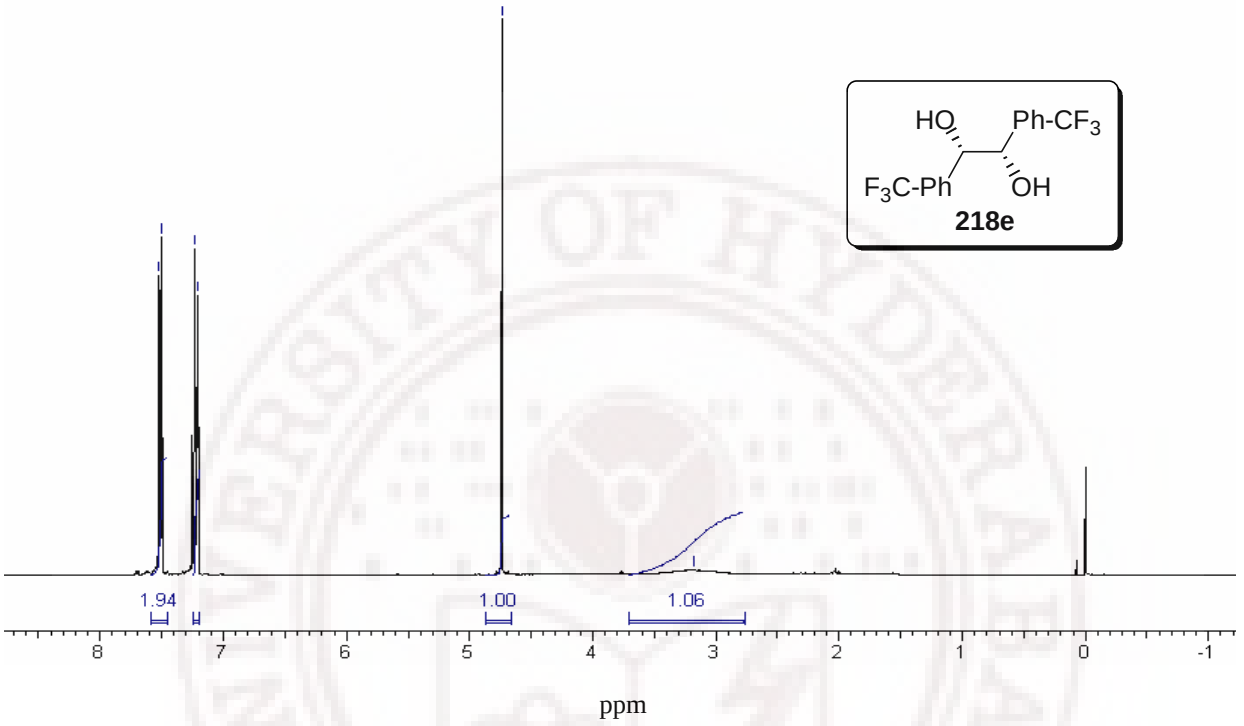
Spectrum No. 45 (Chapter 3, Section 3.7.1) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



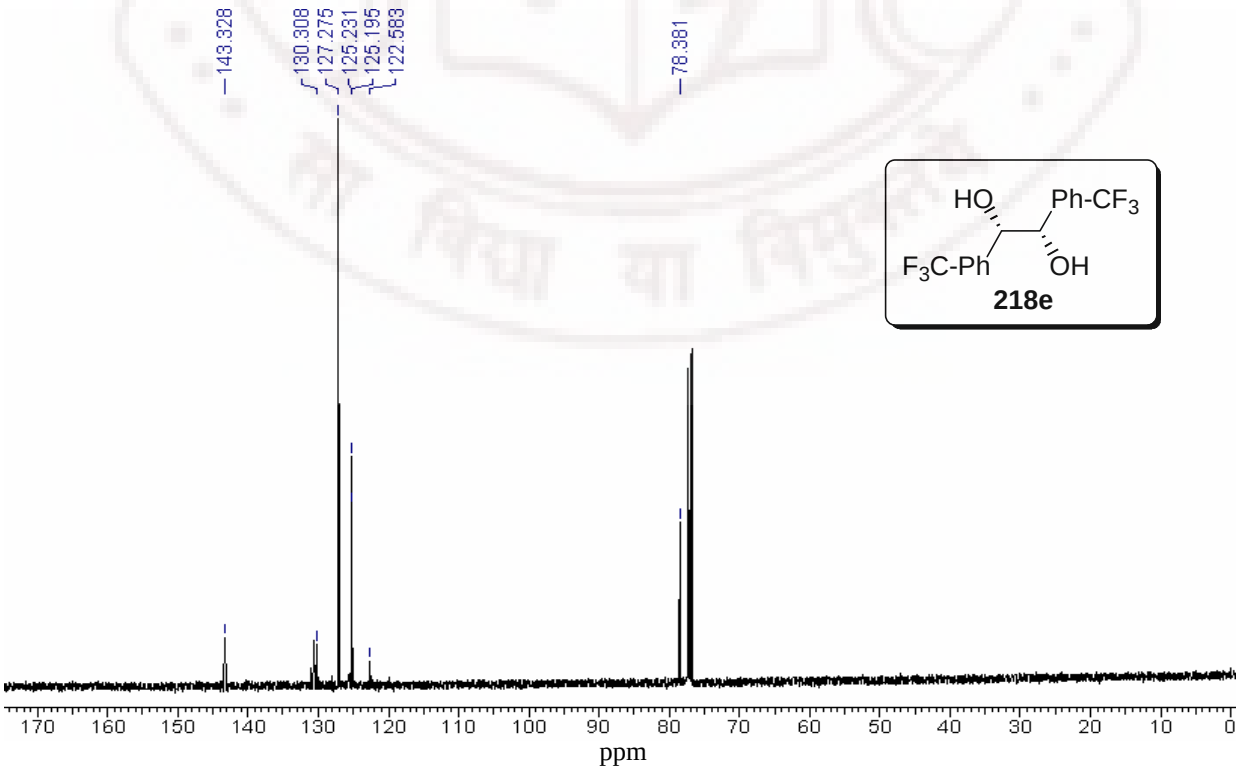
Spectrum No. 46 (Chapter 3, Section 3.7.1) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



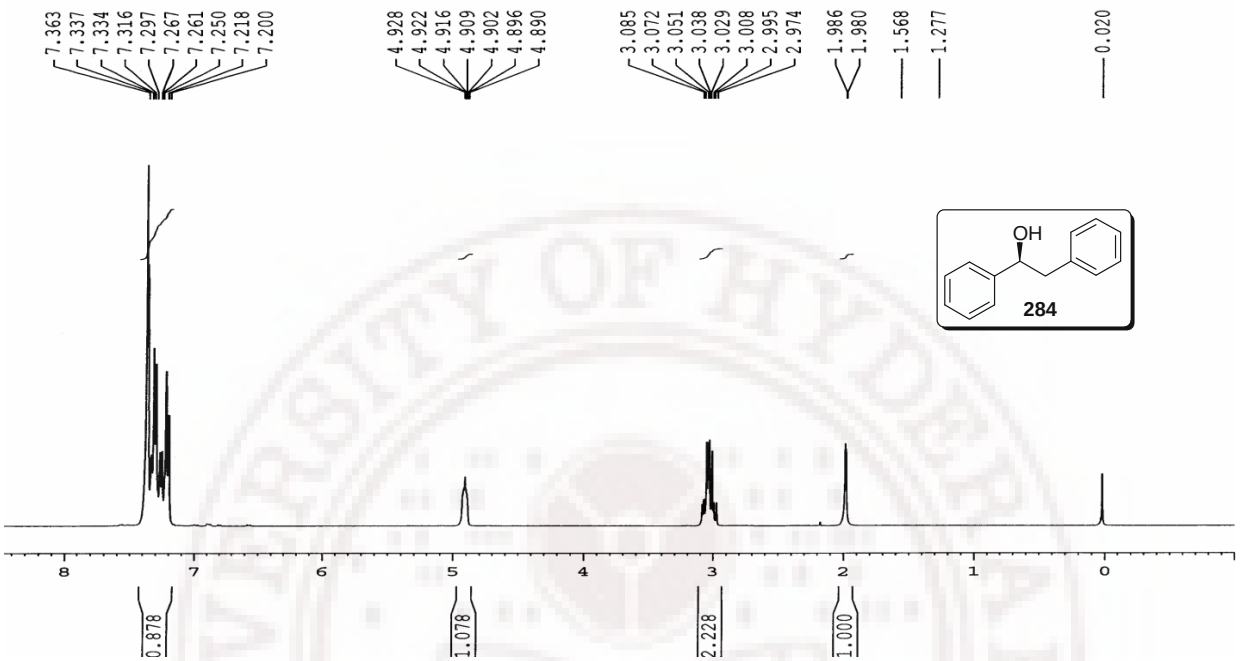
Spectrum No. 47 (Chapter 3, Section 3.7.5) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



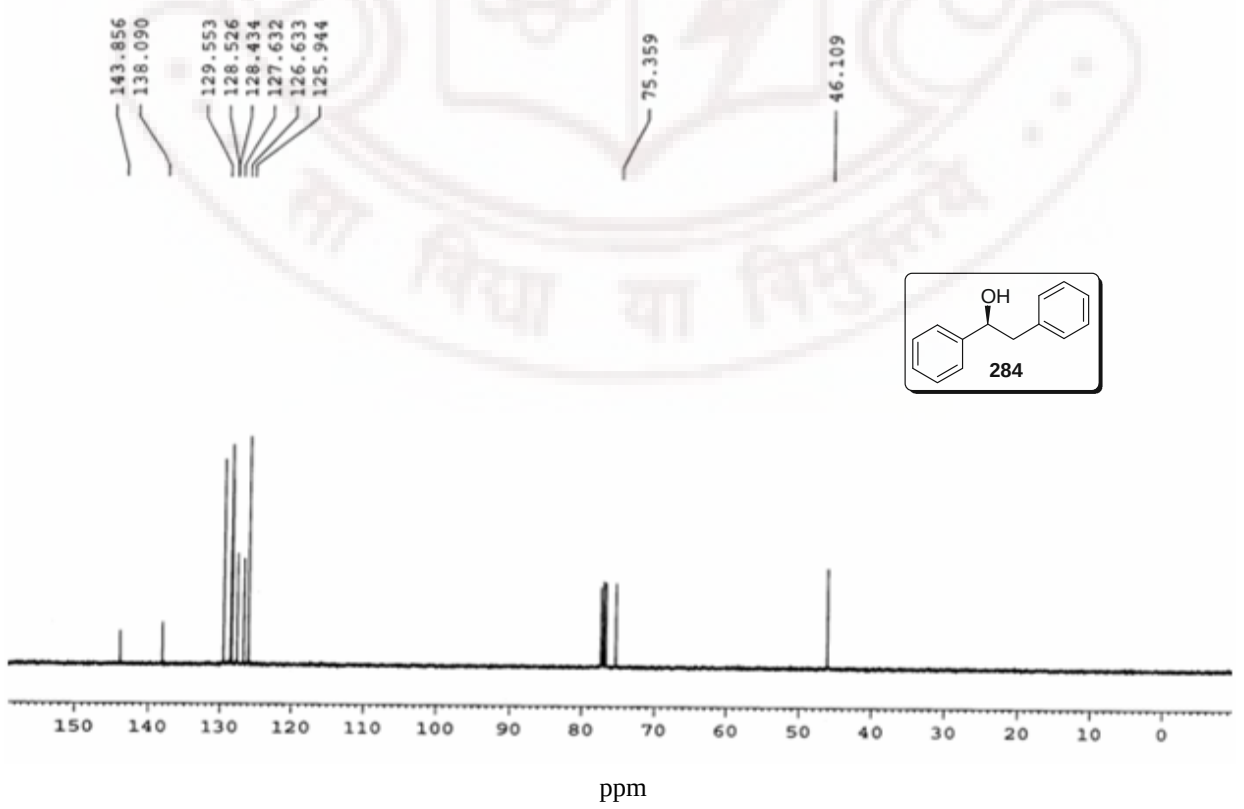
Spectrum No. 48 (Chapter 3, Section 3.7.5) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



Spectrum No. 49 (Chapter 3, Section 3.8.7) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



Spectrum No. 50 (Chapter 3, Section 3.8.7) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



Appendix II

(X-Ray Crystallographic Data)

Table 1. Crystal data and structure refinement of diastereomeric complex **150 (Chapter 2, Section 2.1.2.1)**

Empirical formula	C35 H32 N2 O8
Formula weight	608.63
Temperature	273(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)
Unit cell dimensions	a = 8.1272(6) Å, α = 90°
	b = 18.1103(14) Å, β = 90.5680(10)
	c = 10.4433(8) Å, γ = 90°
Volume	1537.0(2) $Å^3$
Z	2
Density (calculated)	1.315 Mg/m^3
Absorption coefficient	0.094 mm^{-1}
F(000)	640
θ range for data collection	1.95 to 28.30°.
Index ranges	-10≤h≤10, -24≤k≤23, -13≤l≤13
Reflections collected	17971
Independent reflections	7210 [R(int) = 0.0452]
Completeness to θ = 28.30°	96.9 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	7210 / 1 / 416
Goodness-of-fit on F^2	0.832
Final *R* indices [I>2σ(I)]	*R1* = 0.0438, *wR2* = 0.0667
R indices (all data)	*R1* = 0.0795, *wR2* = 0.0749
Absolute structure parameter	0.0(7)
Largest diff. peak and hole	0.135 and -0.165 e.$Å^{-3}$

Table A1. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for diastereomeric complex **150 (Chapter 2, Section 2.1.2.1)**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

atom	x	y	z	U(eq)
C(23)	4571(3)	7770(1)	-2238(2)	44(1)
O(2)	4625(2)	7087(1)	-299(1)	41(1)
O(7)	5448(2)	6641(1)	2468(1)	41(1)
C(12)	8846(3)	9395(1)	10956(2)	39(1)
O(6)	2920(2)	7633(1)	2550(2)	51(1)
O(5)	1448(2)	6987(1)	1116(2)	51(1)
N(1)	11390(2)	9464(1)	9659(2)	45(1)
C(7)	8906(2)	8630(1)	10837(2)	37(1)
C(11)	7510(3)	9708(1)	11566(2)	44(1)
O(1)	3727(2)	6524(1)	-2084(2)	72(1)
N(2)	10303(2)	8263(1)	10264(2)	40(1)
O(4)	5883(2)	5279(1)	598(1)	55(1)
C(27)	4001(2)	6492(1)	1720(2)	39(1)
C(24)	4271(3)	7063(1)	-1573(2)	44(1)
C(8)	7634(3)	8207(1)	11303(2)	43(1)
C(29)	5353(3)	6437(1)	3724(2)	46(1)
C(6)	10129(3)	8665(1)	7991(2)	46(1)
C(14)	11738(2)	8755(1)	10277(2)	45(1)
C(10)	6234(3)	9293(1)	12049(2)	45(1)
O(8)	4116(2)	6199(1)	4168(1)	71(1)
C(28)	2738(2)	7109(1)	1866(2)	39(1)
C(25)	4466(2)	6384(1)	332(2)	40(1)
C(30)	6939(3)	6529(1)	4432(2)	41(1)
C(1)	10745(3)	9345(1)	8373(2)	49(1)
O(3)	7278(2)	6213(1)	-273(2)	73(1)
C(26)	6056(3)	5956(1)	177(2)	44(1)
C(13)	10224(3)	9870(1)	10485(2)	51(1)
C(9)	6317(3)	8531(1)	11900(2)	47(1)
C(18)	5364(3)	8359(1)	-1671(2)	51(1)
C(15)	9990(3)	8035(1)	8913(2)	48(1)

C(34)	8395(3)	6390(1)	6418(2)	60(1)
C(35)	6948(3)	6359(1)	5719(2)	53(1)
C(31)	8380(3)	6750(1)	3860(2)	53(1)
C(17)	4830(3)	9659(1)	12727(2)	65(1)
C(5)	9637(3)	8573(2)	6725(2)	64(1)
C(2)	10808(3)	9919(2)	7509(2)	74(1)
C(22)	4059(3)	7823(2)	-3508(2)	67(1)
C(21)	4309(4)	8466(2)	-4169(3)	91(1)
C(32)	9814(3)	6776(2)	4574(2)	65(1)
C(33)	9822(3)	6594(1)	5847(2)	65(1)
C(19)	5636(3)	9001(1)	-2351(3)	68(1)
C(20)	5095(4)	9052(2)	-3596(3)	87(1)
C(3)	10314(4)	9812(2)	6259(3)	96(1)
C(4)	9744(4)	9131(2)	5849(3)	84(1)
C(16)	9265(5)	9013(2)	4437(3)	145(2)

Table 2. Crystal data and structure refinement for diastereomeric salt **151 (Chapter 2, Section 2.1.2.2)**

Empirical formula	C35 H32 N2 O10
Formula weight	640.63
Temperature	298(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)
Unit cell dimensions	a = 10.640(2) Å, α = 90°
	b = 14.726(3) Å, β = 114.366(2)
	c = 11.347(2) Å, γ = 90°
Volume	1619.6(6) $Å^3$
Z	2
Density (calculated)	1.314 Mg/m^3
Absorption coefficient	0.097 mm^{-1}
F(000)	672
θ range for data collection	1.97 to 26.06°.
Index ranges	-12≤h≤13, -17≤k≤17, -13≤l≤13
Reflections collected	14906
Independent reflections	6356 [R(int) = 0.0288]
Completeness to θ = 26.06°	99.3 %
Absorption correction	Semi-empirical from equivalents
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6356 / 1 / 434
Goodness-of-fit on F^2	1.020
Final *R* indices [I>2σ(I)]	*R1* = 0.0489, *wR2* = 0.1180
R indices (all data)	*R1* = 0.0767, *wR2* = 0.1328
Absolute structure parameter	-0.9(11)
Largest diff. peak and hole	0.436 and -0.165 $e.Å^{-3}$

Table A2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for diastereomeric salt **151 (Chapter 2, Section 2.1.2.2)**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

atom	x	y	z	U(eq)
O(6)	5476(2)	1495(1)	4502(2)	51(1)
O(1)	3384(2)	1837(1)	5437(2)	51(1)
O(4)	6120(2)	3046(1)	5911(2)	71(1)
C(1)	6636(3)	1473(2)	4301(3)	56(1)
O(2)	4653(2)	-409(1)	5418(2)	72(1)
O(3)	6306(2)	2310(1)	7684(2)	73(1)
O(7)	7759(2)	1391(2)	5175(2)	77(1)
C(2)	1549(3)	2675(2)	5542(3)	51(1)
C(3)	5679(3)	1447(2)	5818(2)	44(1)
O(8)	2219(3)	1206(2)	6467(3)	81(1)
C(4)	6067(3)	2363(2)	6506(3)	50(1)
O(5)	2648(2)	230(2)	4174(2)	65(1)
C(5)	2378(3)	1833(2)	5871(3)	54(1)
C(6)	6372(4)	1531(2)	2925(3)	67(1)
C(7)	3759(3)	272(2)	5028(3)	49(1)
C(8)	4356(3)	1111(2)	5863(3)	47(1)
C(9)	-10(4)	4222(3)	5072(4)	86(1)
C(10)	1972(3)	3444(2)	5107(3)	58(1)
C(11)	1177(4)	4225(2)	4872(3)	76(1)
C(12)	4845(6)	1753(3)	687(4)	112(2)
C(13)	359(3)	2699(2)	5737(3)	69(1)
C(14)	7445(5)	1346(3)	2576(5)	96(1)
C(15)	-425(4)	3466(3)	5498(4)	86(1)
C(16)	5086(5)	1740(3)	1988(3)	87(1)
C(17)	7214(9)	1360(4)	1283(7)	135(2)
C(18)	5909(9)	1553(4)	354(6)	125(2)
C(19)	5613(4)	3934(2)	9419(3)	65(1)
N(2)	8317(3)	4273(2)	11191(2)	65(1)
N(1)	6770(3)	3755(2)	9083(2)	65(1)

C(20)	5835(4)	4179(2)	10670(3)	61(1)
C(21)	7258(3)	4282(2)	11705(3)	65(1)
C(22)	4674(4)	4314(2)	10934(4)	76(1)
C(23)	7976(3)	5227(2)	9317(3)	60(1)
C(24)	8492(3)	5118(2)	10644(3)	59(1)
O(10)	9353(3)	7476(2)	9175(3)	121(1)
C(25)	3381(4)	4214(3)	9980(4)	85(1)
C(26)	8053(4)	3544(2)	10277(3)	73(1)
C(27)	3198(5)	3968(3)	8744(4)	97(1)
C(28)	9464(4)	6601(3)	10924(3)	82(1)
C(29)	7111(4)	4512(2)	8388(3)	72(1)
C(30)	4310(4)	3836(3)	8462(4)	83(1)
C(31)	8256(3)	6008(2)	8784(3)	70(1)
O(9)	2210(4)	4358(3)	10172(4)	131(1)
C(32)	9017(4)	6696(3)	9611(4)	80(1)
C(33)	9215(3)	5817(2)	11437(3)	69(1)
C(35)	8902(6)	7583(4)	7808(4)	136(2)
C(34)	2295(8)	4658(7)	11345(10)	211(4)

Table 3. Crystal data and structure refinement for **153n (Chapter 2, Section 2.2.1.1)**

Empirical formula	C21 H24 N2
Formula weight	304.42
Temperature	298(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	C2/c
Unit cell dimensions	a = 14.7341(11) Å, α = 90°
	b = 8.3650(6) Å, β = 91.7610(10)
	c = 13.5544(10) Å, γ = 90°
Volume	1669.8(2) $Å^3$
Z	4
Density (calculated)	1.211 Mg/m^3
Absorption coefficient	0.071 mm^{-1}
F(000)	672
θ range for data collection	2.77 to 25.95°.
Index ranges	-18≤h≤17, -10≤k≤10, -16≤l≤16
Reflections collected	8334
Independent reflections	1639 [R(int) = 0.0238]
Completeness to θ = 25.95°	99.9 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1639 / 0 / 153
Goodness-of-fit on F^2	1.032
Final *R* indices [I>2σ(I)]	*R1* = 0.0509, *wR2* = 0.1323
R indices (all data)	*R1* = 0.0607, *wR2* = 0.1398
Largest diff. peak and hole	0.312 and -0.168 $e.Å^{-3}$

Table A3. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for **153n (Chapter 2, Section 2.2.1.1)**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

atom	x	y	z	U(eq)
N(1)	4279(1)	769(2)	2896(1)	38(1)
C(6)	4434(1)	2278(2)	1335(1)	38(1)
C(1)	3940(1)	1882(2)	2160(1)	37(1)
C(2)	3088(1)	2558(2)	2271(1)	48(1)
C(5)	4044(1)	3298(2)	630(1)	45(1)
C(4)	3192(1)	3961(2)	731(1)	50(1)
C(14)	4624(1)	1612(2)	3782(1)	43(1)
C(3)	2726(1)	3587(2)	1574(2)	53(1)
C(17)	5000	-249(3)	2500	40(1)
C(21)	5401(2)	-1394(2)	3297(2)	54(1)
C(15)	2789(2)	5072(3)	-43(2)	75(1)
C(20)	5421(2)	-3019(3)	2836(2)	72(1)

Table 4. Crystal data and structure refinement for **161 (Chapter 2, Section 2.2.2.1)**

Empirical formula	C37 H34 N2 O3 S
Formula weight	586.72
Temperature	298(2) K
Wavelength	0.71073 Å
Crystal system	Tetragonal
Space group	P4(1)2(1)2
Unit cell dimensions	a = 12.1034(17) Å, α = 90°
	b = 12.1034(17) Å, β = 90°
	c = 42.250(8) Å, γ = 90°
Volume	6189.3(17) $Å^3$
Z	8
Density (calculated)	1.259 Mg/m^3
Absorption coefficient	0.144 mm^{-1}
F(000)	2480
θ range for data collection	1.75 to 26.02°.
Index ranges	-14≤h≤14, -14≤k≤14, -52≤l≤52
Reflections collected	64707
Independent reflections	6088 [R(int) = 0.0499]
Completeness to θ = 26.02°	100.0 %
Absorption correction	Semi-empirical from equivalents
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6088 / 0 / 395
Final *R* indices [I>2σ(I)]	*R1* = 0.0516, *wR2* = 0.1132
R indices (all data)	*R1* = 0.0641, *wR2* = 0.1193
Absolute structure parameter	-0.06(9)
Largest diff. peak and hole	0.231 and -0.126 $e.Å^{-3}$

Table A4. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for **161 (Chapter 2, Section 2.2.2.1)**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

atom	x	y	z	U(eq)
S(1)	5506(1)	10001(1)	635(1)	63(1)
N(1)	4514(2)	6597(2)	1066(1)	46(1)
C(1)	5595(2)	6241(2)	999(1)	45(1)
O(1)	2633(1)	6294(1)	1000(1)	57(1)
O(2)	5240(2)	10309(2)	953(1)	85(1)
N(2)	5818(2)	8675(2)	630(1)	54(1)
C(2)	4020(2)	7545(2)	898(1)	45(1)
C(3)	5858(2)	5121(2)	1022(1)	54(1)
C(4)	6361(2)	8219(2)	918(1)	54(1)
C(5)	2833(2)	7459(2)	1022(1)	52(1)
C(6)	7739(2)	5422(2)	862(1)	59(1)
C(7)	4242(2)	7441(2)	547(1)	46(1)
C(8)	5176(2)	7962(2)	429(1)	50(1)
C(9)	3286(2)	8718(2)	1495(1)	53(1)
C(10)	6456(2)	6972(2)	916(1)	47(1)
C(11)	6898(2)	4724(2)	956(1)	59(1)
C(12)	6740(2)	10688(2)	534(1)	54(1)
C(13)	2748(2)	7815(2)	1373(1)	52(1)
C(14)	3685(2)	6704(2)	350(1)	55(1)
C(15)	5538(3)	7753(2)	125(1)	65(1)
C(16)	4040(2)	6485(2)	44(1)	62(1)
C(17)	7486(2)	6534(2)	850(1)	56(1)
C(18)	3642(2)	5747(2)	1071(1)	59(1)
C(19)	1971(2)	8088(2)	833(1)	58(1)
C(20)	3174(2)	9004(2)	1810(1)	61(1)
C(21)	8362(3)	11680(2)	670(1)	72(1)
C(22)	8616(2)	11857(2)	359(1)	62(1)
C(23)	2182(2)	9133(2)	723(1)	59(1)
O(3)	4724(2)	10182(2)	390(1)	82(1)
C(24)	7908(3)	11431(3)	136(1)	70(1)
C(25)	4976(3)	7018(3)	-63(1)	71(1)

C(26)	2497(3)	8395(3)	2004(1)	74(1)
C(27)	3453(3)	5667(3)	-164(1)	85(1)
C(28)	2063(3)	7212(2)	1572(1)	76(1)
C(29)	6983(2)	10842(3)	218(1)	67(1)
C(30)	1367(3)	9748(3)	578(1)	76(1)
C(31)	8881(3)	5010(3)	778(1)	85(1)
C(32)	1945(3)	7506(3)	1885(1)	87(1)
C(33)	939(3)	7658(4)	784(1)	112(2)
C(34)	7425(3)	11110(2)	761(1)	66(1)
C(35)	9632(3)	12486(3)	259(1)	95(1)
C(36)	343(3)	9326(4)	535(1)	104(1)
C(37)	133(3)	8288(5)	631(1)	142(2)

List of publications

1. A convenient method for the synthesis and resolution of Tröger base; **Satishkumar, S.**; Periasamy, M. *Tetrahedron: Asymmetry* **2006**, *17*, 1116.

2. Catalytic asymmetric dihydroxylation of substituted *trans*-stilbene derivatives: Implications of the variation of enantioselectivities on the mechanism of OsO_4 addition to olefins; Periasamy, M.; **Satishkumar, S**.; Sampath Kumar, N. *Tetrahedron Lett*. **2008**, *49*, 4416.

3. A convenient procedure for the synthesis of racemic *syn*-1,2-diarylethane-1,2-diols by osmate catalyzed dihydroxylation of *trans*-stilbenes facilitated by Tröger base; **Satishkumar, S**.; Periasamy, M. *Indian J. Chem*. **2008**, *47B*, 1080.

4. Chiral recognition of carboxylic acids by Tröger base derivatives; **Satishkumar, S**.; Periasamy, M. *Tetrahedron*: *Asymmetry* **2009**, *20*, 0000.

5. Asymmetric NH-aziridination of chalcones using chiral Tröger base and its derivatives as promoters; **Satishkumar, S**.; Periasamy, M. *To be communicated*.

6. A one pot synthesis and resolution of 5,11-endosubstituted analogs of Tröger base; **Satishkumar, S**.; Periasamy, M. *To be communicated*.

Posters/Papers presented in symposia

1. A convenient method for the synthesis and resolution of Tröger base; **Satishkumar, S**.; Periasamy, M. Presented a poster in the "9th *CRSI*" national symposium held at University of Delhi, Delhi, Feb'**2007. Adjudged as best poster** (Award instituted by Prof. G. Mehta)

2. Synthesis, resolution of Tröger base and its analogs and application in chiral recognition of carboxylic acids; **Satishkumar, S**.; Periasamy, M. Oral presentation in the "4th *J-NOST*" national symposium held at Madurai Kamaraj University, Madurai, Dec'**2008**.

3. Synthesis, resolution and applications of Tröger base and its analogs; **Satishkumar, S**.; Periasamy, M. Presented a poster in the "*5th Indo-Singapore collaborative and cooperative chemistry international symposium*" held at University of Hyderabad, Hyderabad, Feb'**2009**.

4. Synthesis, resolution, applications of Tröger Base derivatives and mechanism of the osmium catalyzed asymmetric dihydroxylation; **Satishkumar, S**.; Periasamy, M. Oral presentation in the *"6th Chemfest"* in house symposium held at University of Hyderabad, Hyderabad, March'**2009**.