Synthesis and Applications of Chiral Amines and Quaternary Ammonium Salts Containing *trans*-1,2-Cyclohexyl Moiety

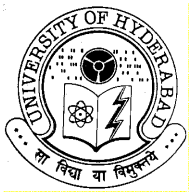
A Thesis

Submitted for the Degree of

DOCTOR OF PHILOSOPHY

by

MEDURI PADMAJA



SCHOOL OF CHEMISTRY
UNIVERSITY OF HYDERABAD
HYDERABAD-500 046
INDIA

November 2005

to

amma and daddy

School of Chemistry
University of Hyderabad
Central University P. O.
Hyderabad 500 046
India

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.

MEDURI PADMAJA

School of Chemistry
University of Hyderabad
Central University P. O.
Hyderabad 500 046
India

Certificate

Certified that the work embodied in this thesis entitled '**Synthesis and Applications of Chiral Amines and Quaternary Ammonium Salts Containing *trans*-1,2-Cyclohexyl Moiety**' has been carried out by Ms. **Meduri Padmaja** under my supervision and the same has not been submitted elsewhere for a Degree.

PROFESSOR M. PERIASAMY
(THESIS SUPERVISOR)

DEAN
SCHOOL OF CHEMISTRY

ACKNOWLEDGEMENTS

I thank my supervisor ***Prof. M. Periasamy*** *for his constant encouragement and guidance throughout my stay here. It is always a pleasure for me to be his student. His courage and commitment to the society are inspiring.*

I thank all the former and present Deans of the School of Chemistry for providing facilities to carry out my research. I thank Prof. Basavaiah and all the faculty members of the School of Chemistry for their valuable teaching. I thank one of my high school teachers Mrs. Yashoda Rangaswamy for her affection and encouragement.

I thank the Director, IICT, Hyderabad and Dr. M. Vairamani, Mass Spectroscopy Division, IICT for providing the mass spectra for some of the compounds. I also thank Prof. G. Sunderarajan, IIT Madras, for the GPC analysis.

I thank my senior colleague Dr. N. Sampath Kumar for his help during the initial stages of my research. I thank all my past and present colleagues in the lab Dr. V. Dharma Rao, Dr. G. Srinivas, Dr. S. Sivakumar, Dr. K. N. Jayakumar, Mr. G. V. Karunakar, Dr. A. Mukkanti, Dr. M. Seenivasaperumal, Mr. M. Narsi Reddy, Mr. S. Suresh, Mr. N. Kishorebabu, Mr. D. Shyamraj, Mr. P. Vairaprakash, Mr. G. P. Muthukumaragopal, Mr. S. Selvaganesan, Mr. S. Satish Kumar, Mr. M. Nagaraju, Mr. B. Mallesh, Mr. N. Sanjeev Kumar and Mr. Yesu for creating an amenable work atmosphere.

I thank all the research scholars of the School of Chemistry for their cooperation and concern.

I thank Mr. S. Satyanarayana, Mrs. B. Vijaya Lakshmi, Mr. V. Bhaskar Rao, Mrs. Asia Parvez, Mr. Raghavaiah, Mr. K. R. B. V. Prasad, Mr. Shetty and the rest of the non-teaching staff of the school for their cooperation.

I thank CSIR, New Delhi, for fellowship, DST for NMR and X-ray facilities and the University authorities for research facilities.

My stay in the hostel was a very edifying experience. I thank Dr. SubbaLakshmi, Ms. Aparna, Ms. Saritha, Dr. Sailaja and all my friends in the hostel for making my stay memorable.

It is beyond this book to acknowledge the contributions of my parents at each and every stage of my life. They have always been my strength and inspiration. I thank them for their affection and support and I thank GOD for giving me such wonderful parents.

I thank my paternal grand parents who are my mentors, for all the support, guidance, encouragement and love they have showered upon me. I also thank my maternal grand parents for their affection.

I thank my aunts Mrs. Kamala, Mrs. Lakshmi, Mrs. Yasoda, Mrs. Satya, Mrs. Hemalatha, Mrs. Sandhya and my uncles Mr. Subba Rao, Mr. Subramanyam, Mr. Sadasivam and Mr. Murthy for always being there for me. I also thank all the members of the Meduri and the Sankaramanchi families.

I thank my parents-in-law for their encouragement and affection. I thank Babbu for creating a pleasant and jovial atmosphere at home. The time I spent with Namish, Aparna and Naveen is memorable. I thank Sri Koride Hanumanlu for his blessings.

I thank my friends Vasulu, Prathima, Sabitha, Sheena, Phani, Banala, Desigan, Nagesh, Santosh and all my M.Sc classmates for the memorable time I had on the campus. Special thanks to Harsha for his friendship and support.

I admire all the women who have inspired me with their unique abilities.

I thank my long time friend, philosopher and critic, my husband Sharath for his unconditional love and support. Thanks to him for always spreading positive energy and optimism. But for his cooperation and encouragement it would not have been possible for me to complete my research on time.

padmaja

Abbreviations

[α]	specific rotation [expressed without units; the actual units, deg.mL/g. dm, are understood]
Ac	acetyl
AIBN	2,2′-azobis(2-methylpropionitrile)
All	allyl
aq.	aqueous
Ar	aryl
9-BBN	9-borabicyclo[3.3.1]nonane
Bn	benzyl
Boc	*tertiary*-butoxycarbonyl
BOX	bis(oxazoline)
bp	boiling point
br	broad (spectral)
Bu	butyl
Bz	benzoyl
*c*hex	cyclohexyl
cat.	catalytic
CNS	central nervous system
CSA	camphorsulphonic acid
Cp	cyclopentadiene
δ	chemical shift in parts per million downfield from tetramethyl silane
d	doublet (spectral)
DCM	dichloromethane
de	diastereomeric excess
DCC	1,3-dicyclohexylcarbodiimide
DCE	dichloroethane
DHQ-CLB	dihydroquinine-(4-chlorobenzoylether)
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminum hydride
DMF	dimethylformamide
DMAP	4-(dimethylamino)pyridine
DPPE	1,2-bis(diphenylphosphino)ethane
EDC	*N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide
ee	enantiomeric excess
Et	ethyl
EtOH	ethyl alcohol
equiv.	equivalent
FAB	fast atom bombardment (in mass spectrometry)
hex	hexane

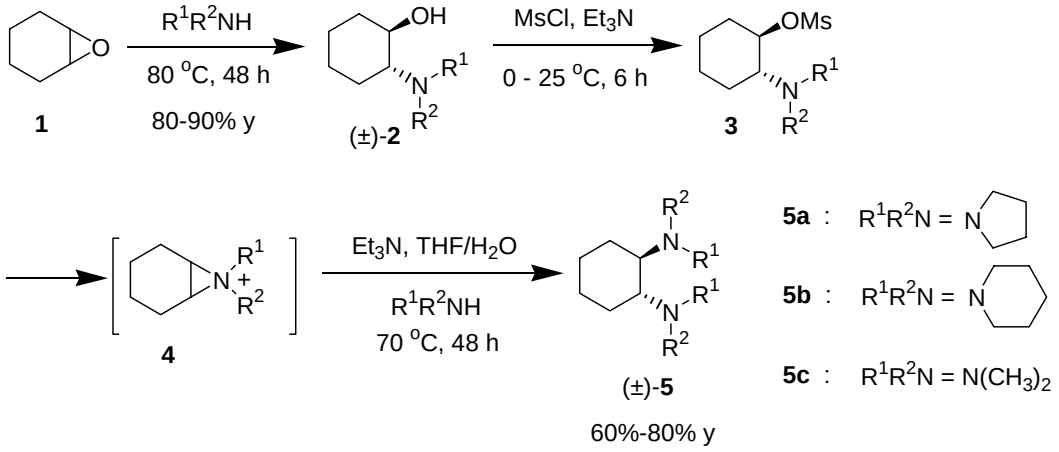
HOBT	1-hydroxybenzotriazole
HPLC	high-performance liquid chromatography
Hz	hertz
*i*Pr	isopropyl
IR	infrared
J	coupling constant (in NMR Spectroscopy)
KHMDS	potassium hexamethyl disilazide
LAH	lithium aluminium hydride
lit.	literature
m	multiplet (spectral)
MALDI-TOF	matrix assisted laser desorption ionization-time of flight
Me	methyl
MeCN	acetonitrile
MHz	megahertz
mmol	millimolar
mp	melting point
MS	molecular sieves
Ms	methanesulphonyl
n-	primary
nbd	7-nitrobenzo-2-oxa-1,3-diazole
NMO	4-methylmorpholine *N*-oxide
Np	naphthyl
Ns	*para*-nitrobenzenesulphonyl
ORTEP	oak ridge thermal ellipsoid plot
p	para
Ph	phenyl
Phth	phthalyl
PMB	*para*-methoxybenzyl
PMP	*para*-methoxyphenyl
ppm	parts per million
q	quartet (spectral)
rt	room temperature
s	singlet (spectral)
t	triplet (spectral)
t	tertiary
TBDMS	*tertiary*-butyldimethylsilyl
TFA	triflouroacetic acid
THF	tetrahydrofuran
TMEDA	*N*,*N*,*N*′,*N*′-tetramethylethylenediamine
TMS	trimethylsilyl
Ts	toluenesulfonyl

Abstract

This thesis describes studies on the "**Synthesis and Applications of Chiral Amines and Quaternary Ammonium Salts Containing *trans*-1,2-Cyclohexyl Moiety**". It comprises of three chapters. Each chapter is subdivided into four parts namely, **Introduction**, **Results and Discussion**, **Conclusions** and **Experimental Section** along with **References**.

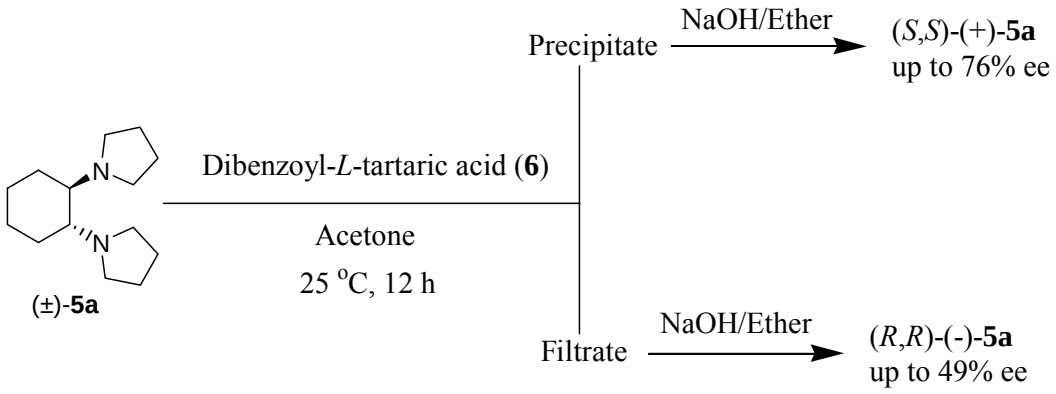
The first chapter describes the synthesis of *trans*-(±)-1,2-diamines via the sequential opening of cyclohexene oxide and aziridinium ion intermediates. *trans*-(±)-1,2-Diaminocyclohexane derivatives **5** were synthesized by the opening of cyclohexene oxide **1** with secondary amines followed by the opening of the corresponding aziridinium ions **4**, prepared *in situ* from the mesylate **3** of the *trans*-(±)-2-(*N*,*N*-dialkyl-amino)cyclohexanol **2** by achiral secondary amines (Scheme 1).

Scheme 1



The *trans*-(±)-1,2-bis(pyrrolidino)cyclohexane derivative **5a** prepared in this way was partially resolved using dibenzoyl-*L*-tartaric acid **6** (Scheme 2).

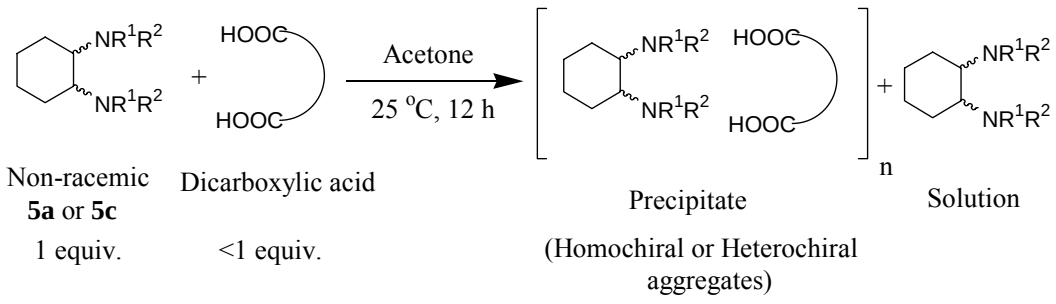
Scheme 2



The racemic diamine **5c** was partially resolved using (*S*)-(-)-1,1′-bi-2-naphthol **7**.

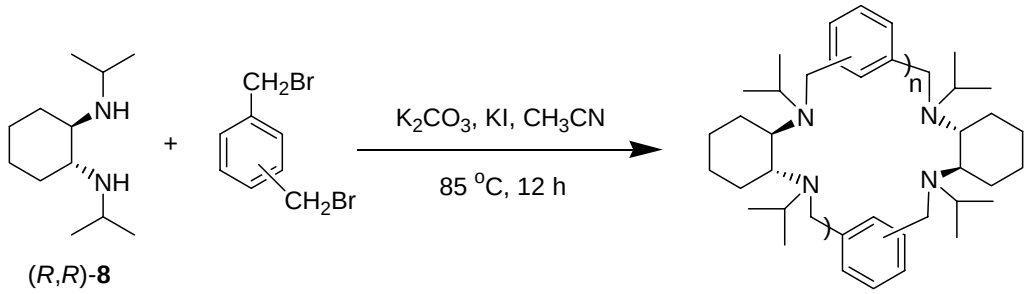
A conceptually new method was developed for the purification of the non-racemic 1,2-diamines **5a** and **5c** using achiral dicarboxylic acids like oxalic, fumaric and terephthalic acids by the preparation of the corresponding hydrogen-bonded homochiral and heterochiral aggregates (Scheme 3).

Scheme 3

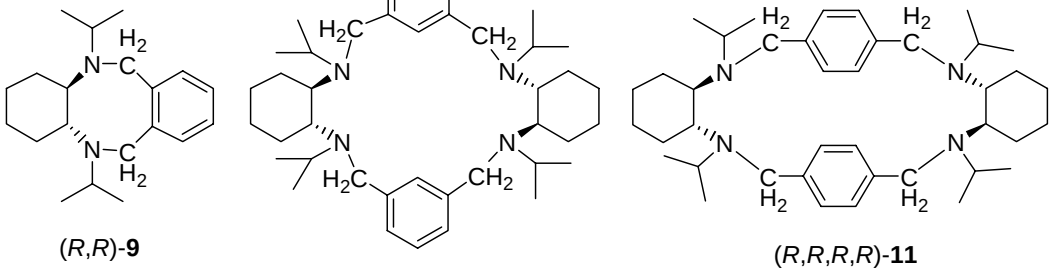


Chapter 2 describes the synthesis of chiral macrocyclic, oligomeric and polymeric amines and quaternary ammonium salts derived from (*R*,*R*)-1,2-diaminocyclohexane. The reaction of (*R*,*R*)-*N*,*N*′-diisopropyl-1,2-diaminocyclohexane **8** with the isomeric 1,2- 1,3- and 1,4-benzylic bromides gave the heterocyclic and macrocyclic amines (Scheme 4).

Scheme 4



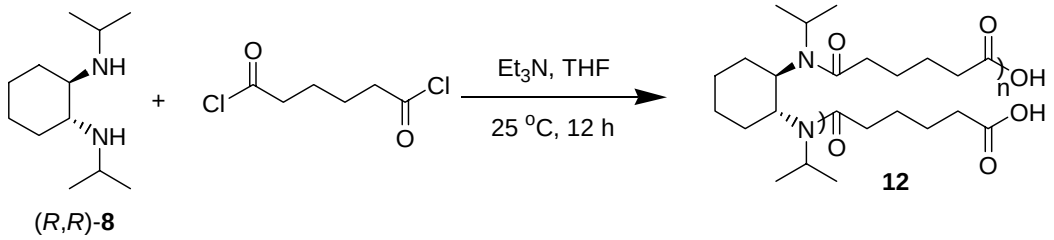
The reaction of the diamine **8** with the 1,2-bis(bromomethyl)benzene gave the heterocyclic amine **9**. The macrocyclic amines **10** and **11** were isolated from the reaction of the diamine **8** with the 1,3- and 1,4-bis(bromomethyl)benzenes, respectively.



Variable temperature ^{1}H-NMR spectral studies of the macrocyclic amines **10** and **11** were carried out.

The reaction of the diamine **8** with adipoyl chloride gave the polyamide **12** which could be readily reduced using the $NaBH_4/I_2$ reagent system to the corresponding polyamine (Scheme 5).

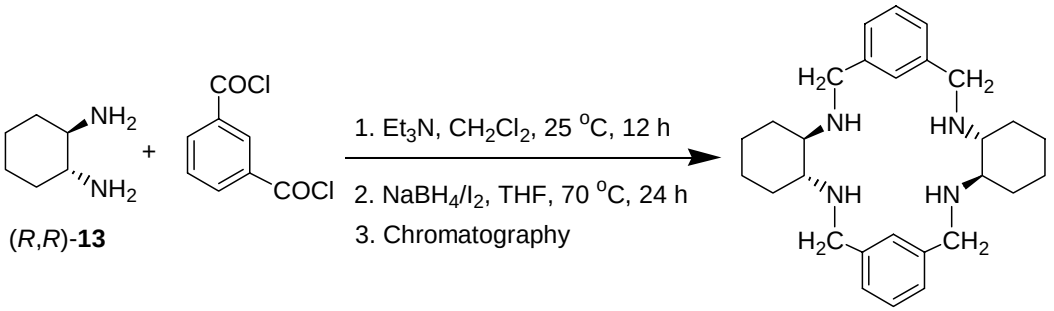
Scheme 5



(*R*,*R*)-**8**

The reaction of (*R*,*R*)-1,2-diaminocyclohexane **13** with phthaloyl, isophthaloyl and terephthaloyl chlorides gave insoluble amides which on reduction using the $NaBH_4/I_2$ reagent system yielded soluble amines. For example, the macrocyclic secondary amine **14** was isolated in the reduction of the amides obtained by the reaction of the diamine **13** with isophthaloyl chloride (Scheme 6).

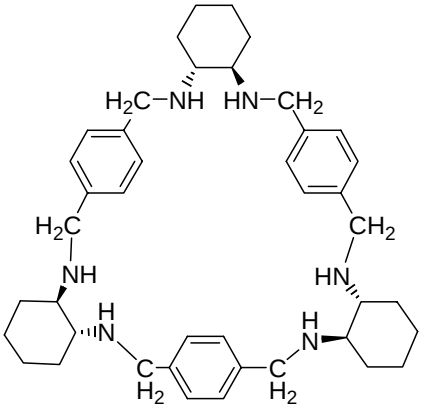
Scheme 6



(*R*,*R*)-**13**

(*R*,*R*,*R*,*R*)-**14**

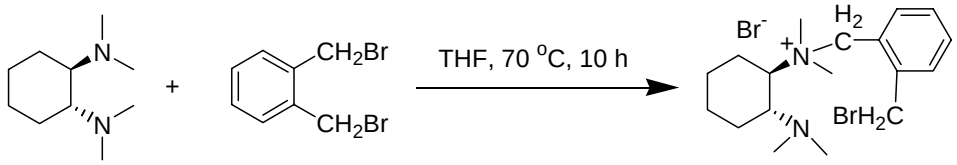
The macrocylic amine **15** was synthesized from (*R*,*R*)-1,2-diaminocyclohexane **13** and terephthalaldehyde following a reported procedure. Synthesis of oligomeric and polymeric macrocyclic amides was carried out by the reaction of **15** with adipoyl chloride and sebacoyl chloride. The amides were characterized by MALDI-TOF technique.



(*R*,*R*,*R*,*R*,*R*,*R*)-**15**

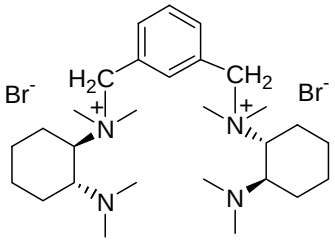
Chiral quaternary ammonium salts were synthesized from the (*R*,*R*)-*N*,*N*,*N*′,*N*′-tetramethyl-1,2-diaminocyclohexane **5c** using the 1,2-, 1,3- and 1,4-isomeric benzylic bromides. The reaction of the diamine **5c** with the 1,2-bis(bromomethyl)benzene afforded the monoammonium salt **16** (Scheme 7).

Scheme 7

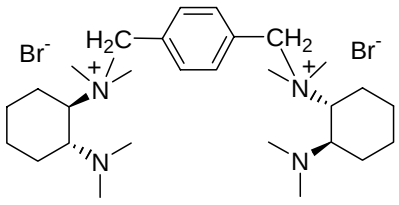


(*R*,*R*)-**5c** (*R*,*R*)-**16**

The reaction of the 1,3- and 1,4-dibromides afforded the dicationic salts **17** and **18** respectively.



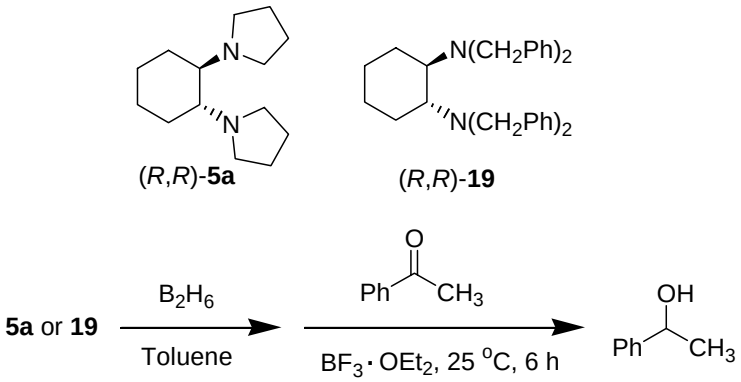
(*R*,*R*,*R*,*R*)-**17**



(*R*,*R*,*R*,*R*)-**18**

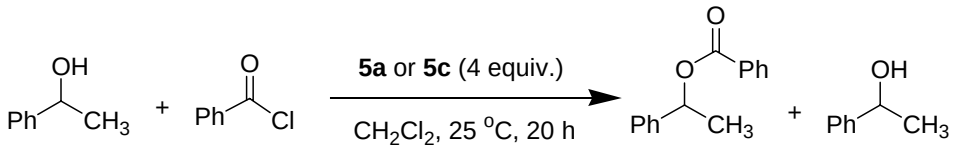
Results of the efforts undertaken towards the application of the chiral diamines, quaternary ammonium salts and macrocyclic amines are described in Chapter 3. Efforts were made towards the asymmetric reduction of acetophenone in the presence of $BF_3{\cdot}OEt_2$ using the chiral amine-borane complexes prepared *in situ* from the chiral 1,2-diamines **5a** and **19** (Scheme 8).

Scheme 8



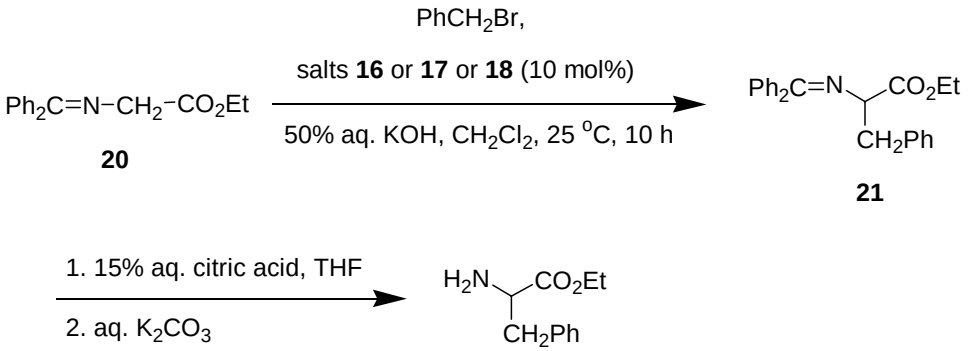
Efforts were also undertaken towards the kinetic resolution of racemic 1-phenylethanol using the diamines (*R*,*R*)-**5a** and (*R*,*R*)-**5c**. The ester was obtained in up to 18% ee (Scheme 9).

Scheme 9

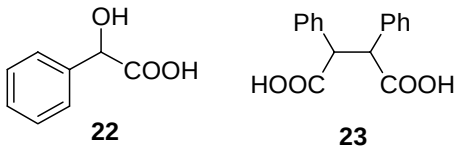


Attempts towards the development on enantioselective alkylation of the benzophenone Schiff base **20** catalyzed by the chiral quaternary ammonium salts **16**, **17** and **18** are described (Scheme 10).

Scheme 10



Application of the chiral macrocyclic amines **14** and **15** for the enantiomeric recognition of mandelic acid **22** and 2,3-diphenylsuccinic acid **23** by ^{1}H-NMR spectroscopy was carried out. It was observed that the macrocyclic amine **15** is an effective chiral solvating agent for mandelic acid **22**. Whereas **14** showed better enantiomeric recognition towards 2,3-diphenylsuccinic acid **23**. The ^{1}H-NMR titrations between the amine **15** and mandelic acid were also carried out. The enantiomeric excess of the non-racemic samples of the diacid **23** obtained by resolution with (*S*)-proline, was established using the macrocyclic amine **14**.



Note: Scheme numbers and compound numbers given in this abstract are different from those given in the chapters. Also, different set of numbers for Schemes, Tables, compounds, Figures and references etc. are given in different chapters.

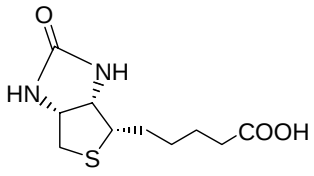
Contents

Chapter 1

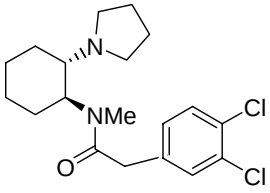
Synthesis, resolution and enhancement of enantiomeric purity of non-racemic 1,2-diamines

1.1 Introduction

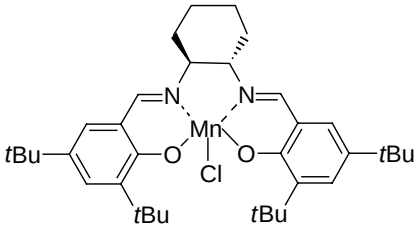
Chiral compounds incorporating the 1,2-diamine moiety are of current research interest as they find applications in various fields. Many natural products that exhibit biological properties like Biotin **1** contain the 1,2-diamine moiety.[1] In the recent years, several synthetic diamine derivatives like the compound **2** have been found to show analgesic properties.[2] The 1,2-diamine containing compounds are also valuable synthetic intermediates for the preparation of heterocycles[3] and nitrogen containing macrocycles[4] with potential for applications in host-guest chemistry. Apart from these, enantiomerically pure 1,2-diamines and their derivatives (e.g. **3**) are particularly useful as chiral auxiliaries or ligands that have proven applications in enantioselective organic synthesis.[5]



1



2



3

We have envisaged the synthesis of a series of C_2-symmetric 1,2-diamines starting from 1,2-amino alcohols via opening of the aziridinium ion intermediates. A brief review of the various methods available for the synthesis of chiral 1,2-diamines should be useful for the discussion.

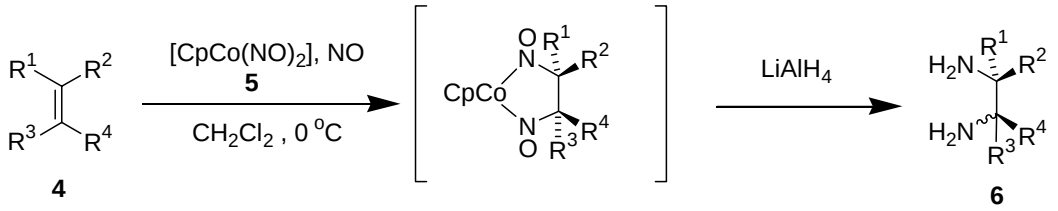
1.1.1 Synthesis of 1,2-diamines

Although chiral 1,2-diamines can be obtained by resolution of the racemates,[6] several diastereo and enantioselective methods have been reported.

1.1.1.1 Synthesis of chiral 1,2-diamines from olefins

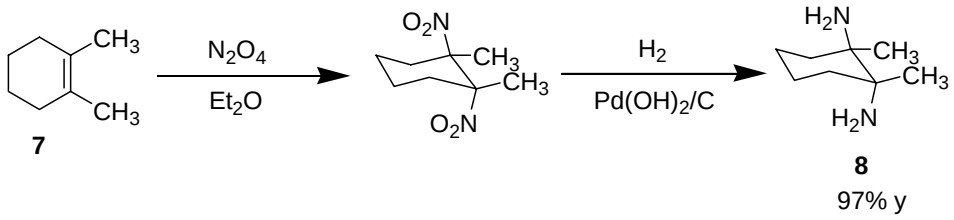
In 1980 Bergman *et al.*[7] reported a general method of 1,2-diamination of alkenes **4** with nitric oxide and a cobalt complex **5** (Scheme 1). This procedure works satisfactorily for terminal *E*, *Z*, di, tri, and tetrasubstituted alkenes and leads to various aliphatic primary 1,2-diamines.

Scheme 1



Jacobsen *et al.*[8] reported the preparation of *trans*-1,2-diamino-1,2-dimethylcyclohexane **8** by the highly diastereoselective oxidation of the olefin **7** by dinitrogen tetroxide (Scheme 2). This methodology is mainly suited for the synthesis of vicinal diamines adjacent to tertiary centres because primary and secondary dinitro intermediates would be prone to epimerization.

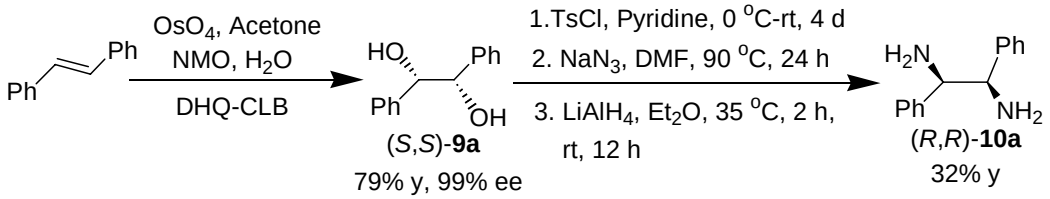
Scheme 2



1.1.1.2 Synthesis of chiral 1,2-diamines from 1,2-diols

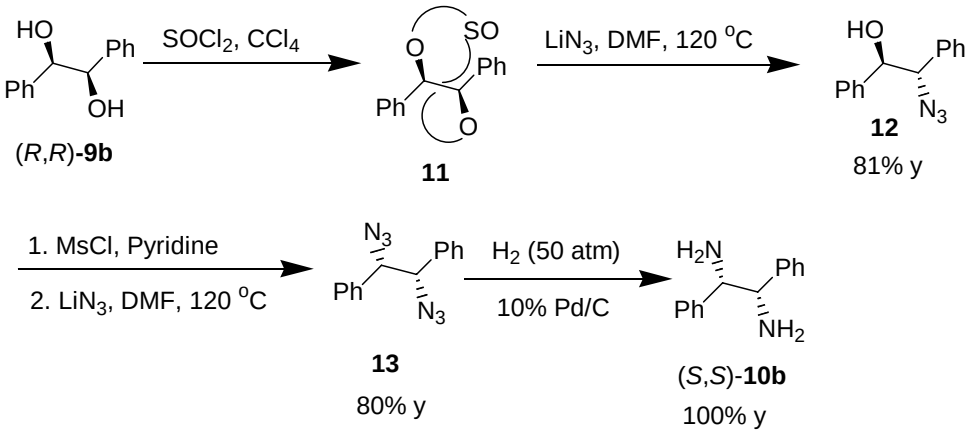
The efficiency of osmium catalyzed asymmetric dihydroxylation[9] allows access to various enantiomerically pure 1,2-diols that can be converted by several methods into enantiopure vicinal diamines. For example, the synthesis of the vicinal diamine (*R,R*)-**10a** from enantiomerically pure diol (*S,S*)-**9a** is readily accomplished through double displacement by azide nucleophile[10] (Scheme 3).

Scheme 3



Sharpless *et al.*[11] synthesized the chiral diamine (*S,S*)-**10b** from the optically pure 1,2-diol (*R,R*)-**9b** through the cyclic sulphate intermediate **11** (Scheme 4).

Scheme 4

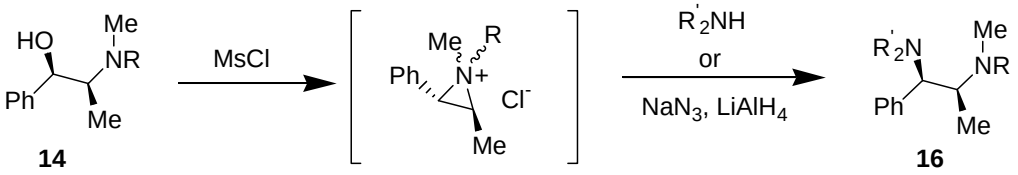


1.1.1.3 Synthesis of chiral 1,2-diamines from 1,2-amino alcohols

A stereo- and regioselective route to chiral diamines from (-)-ephedrine and (-)-pseudoephedrine was developed by Dieter *et al.*[12] (Scheme 5). Their strategy relied on

the transformation of the chiral 1,2-amino alcohol **14** into aziridinium ion **15**, which was then treated with various nitrogen nucleophiles to afford the corresponding diamines **16**.

Scheme 5



14 **15** **16**

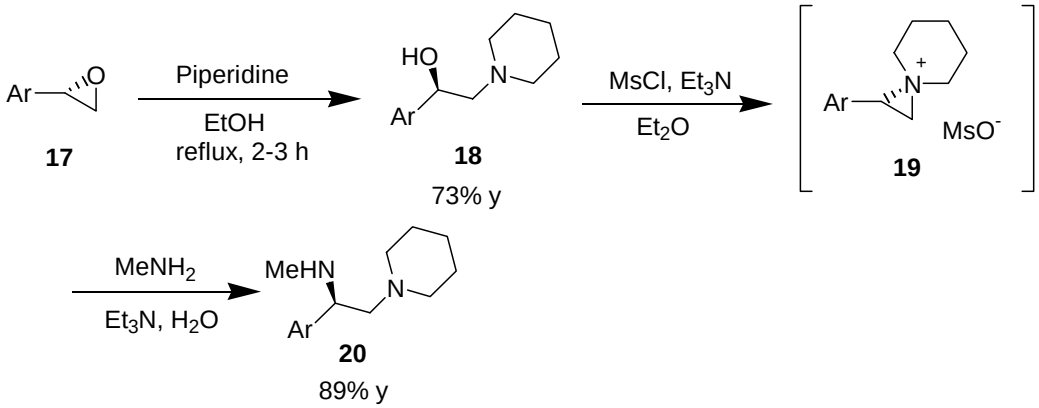
50-96% y

R = Me, NR'_2 = *n*BuNH, phthalimido

R = Et, NR'_2 = NH, *c*hexNH

Rossiter and co-workers[13] described a method of synthesis of the 1,2-diamine **20** by the opening of the aziridinium ion **19** generated from the amino alcohol **18** with methylamine as the nucleophile (Scheme 6). The starting amino alcohol **18** was synthesized from the ring opening of the chiral epoxide **17**.

Scheme 6



17 **18** **19** **20**

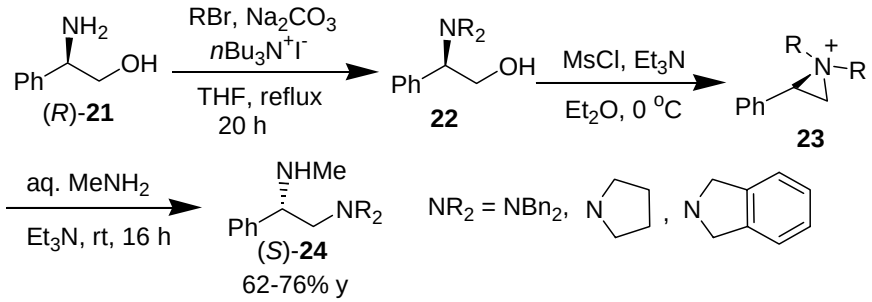
73% y

89% y

O′Brien *et al.*[14] showed that phenylglycinol **21**, which is commercially available in both enantiomeric forms, can be used as a precursor for the synthesis of the diamines **24** (Scheme 7). The opening of the aziridinium ion **23**, generated from *N* - alkylated

amino alcohol **22** by aqueous methylamine, yielded the chiral diamines **24**.

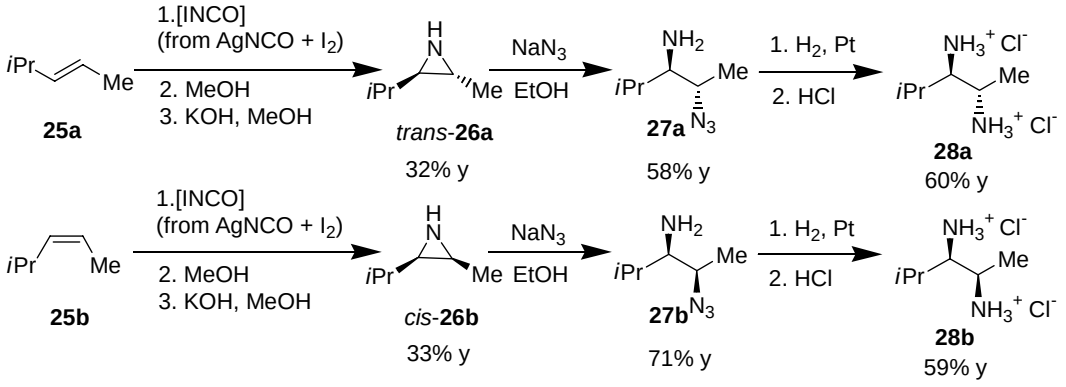
Scheme 7



1.1.1.4 Synthesis of chiral 1,2-diamines from aziridines

A method of synthesis of *syn*- or *anti*-1,2-diamines involving aziridines, which are readily accessible from olefins, was devised by Swift and Swern[15] in 1967 (Scheme 8). In this transformation, iodine isocyanate, generated *in situ* from silver isocyanate and iodine, is added stereospecifically to *E*-methyl-2-pentene **25a** or *Z*-methyl-2-pentene **25b**, to yield *trans*-aziridine **26a** and *cis*-aziridine **26b** respectively, after treatment with base. These aziridines were then converted to the corresponding diamine hydrochloride salts **28a** and **28b** by ring opening with the azide ion, followed by catalytic hydrogenation.

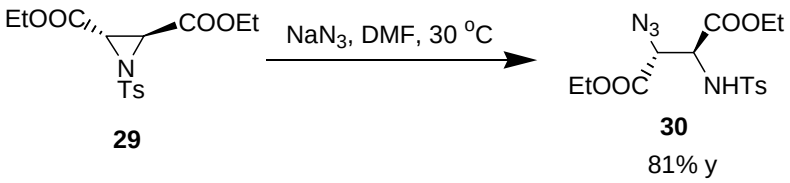
Scheme 8



In 1990, Tanner *et al.*[16] performed the ring opening of the non-racemic aziridine

29 derived from tartaric acid with sodium azide (Scheme 9). In this way, the precursor **30** of the vicinal diamine was obtained as a single adduct.

Scheme 9

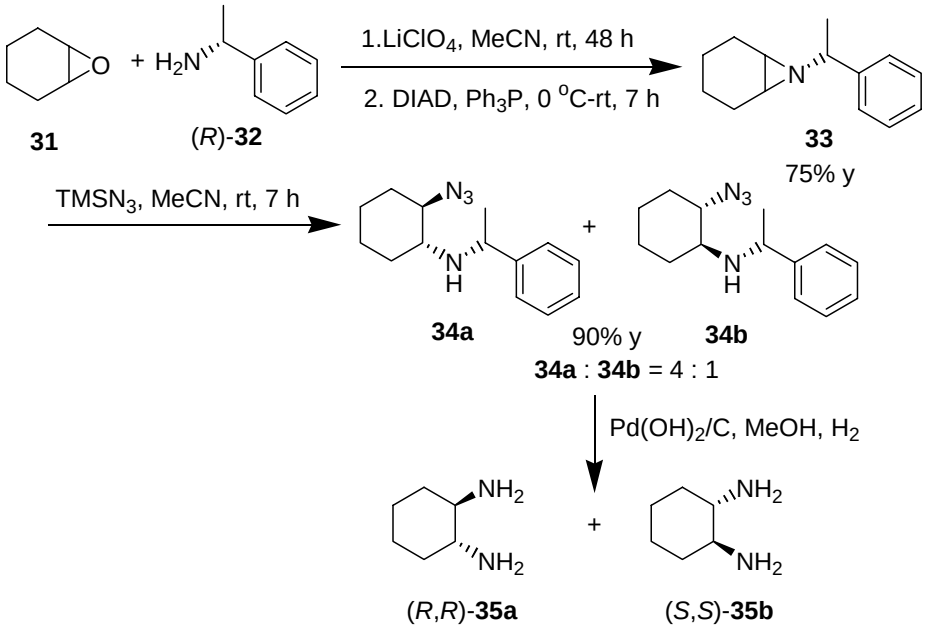


29 **30**

81% y

Recently, Singh *et al.*[17] reported the synthesis of chiral 1,2-diaminocyclohexanes starting from the chiral aziridine **33** (Scheme 10). The chiral aziridine **33** synthesized from cyclohexene oxide **31** and (*R*)-1-phenylethylamine **32**, was opened with TMS azide in acetonitrile to give two distinctly separable diastereomers **34a** and **34b** in 4:1 ratio respectively. Hydrogenation of the diastereomers yielded the corresponding (*R*,*R*)-1,2-diaminocyclohexane **35a** and (*S*,*S*)-1,2-diaminocyclohexane **35b**.

Scheme 10



31 (*R*)-**32** **33**

75% y

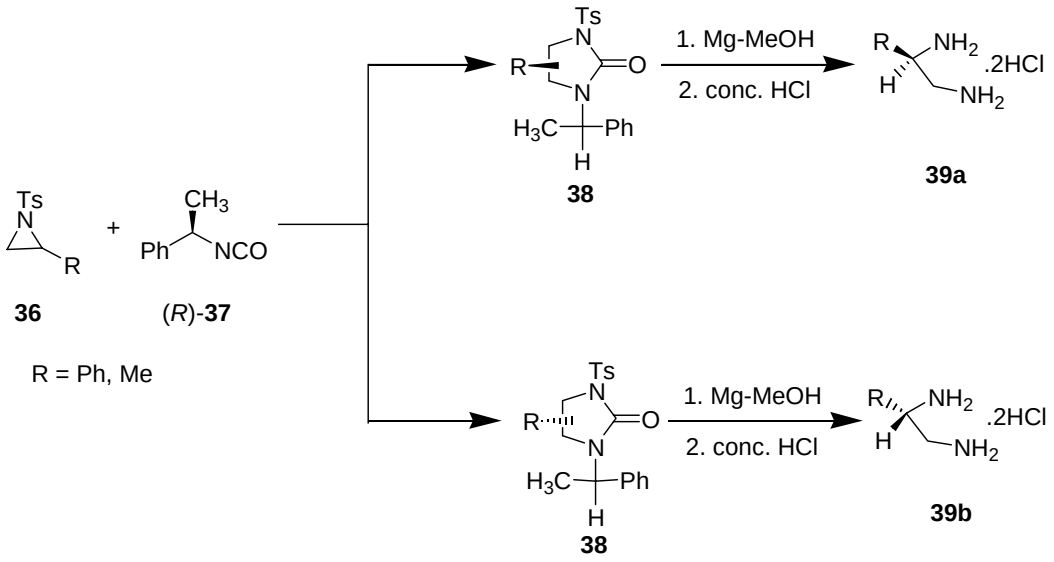
34a 90% y **34b**

34a : **34b** = 4 : 1

(*R*,*R*)-**35a** (*S*,*S*)-**35b**

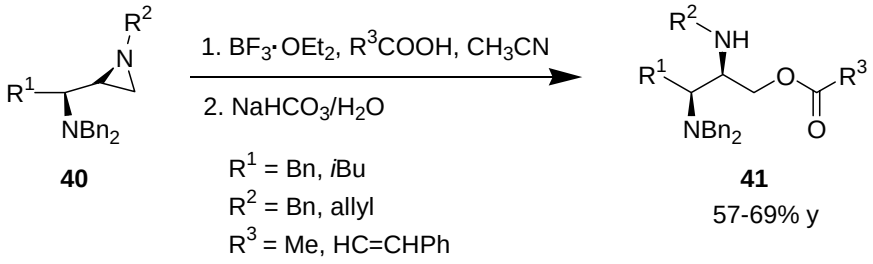
In 2005, Nadir *et al*.[18] reported the synthesis of the chiral 1,2-diamine salts **39a** and **39b** by the ring opening of *N*-tosylsulfonyl aziridine **36** with the (*R*)-(+)-α-methylbenzyl isocyanate **37** to obtain the diastereomeric mixture of the 2-imidazolidinone **38** (Scheme 11). The diastereomers were separated by crystallization and hydrolyzed to obtain the chiral diamine salts **39a** and **39b**.

Scheme 11



Concellon and co-workers[19] synthesized the *O*-acylated 2,3-diaminoalkanol **41** by the ring opening of the unactivated aziridine **40** using carboxylic acid in the presence of $BF_3{\cdot}OEt_2$ (Scheme 12).

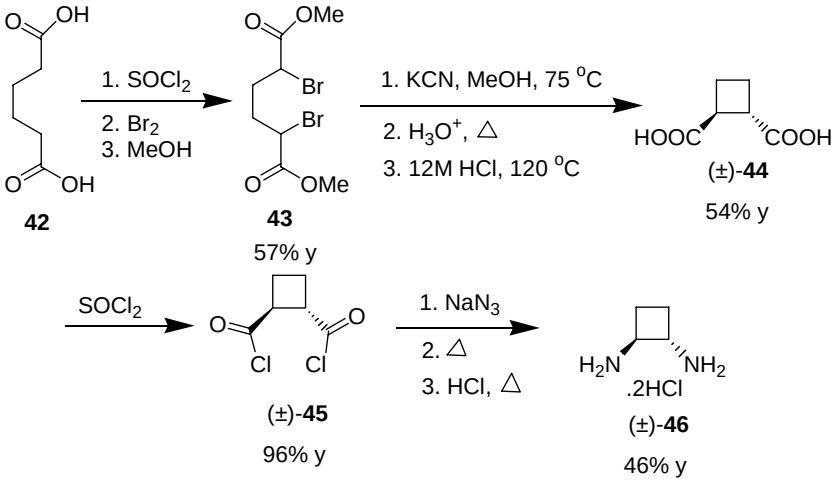
Scheme 12



1.1.1.5 Synthesis of chiral 1,2-diamines from carboxylic acids

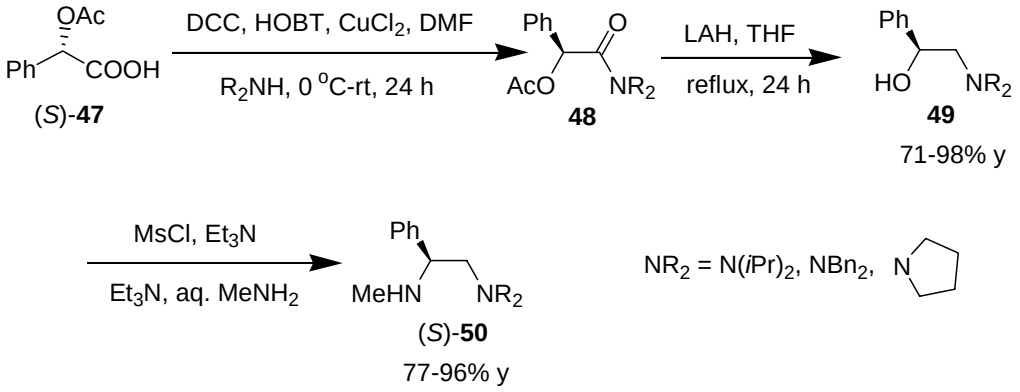
Recently, Gilheany *et al*.[20] reported the synthesis of the *trans*-1,2-diaminocyclobutane **46** starting from adipic acid **42** (Scheme 13). In this synthesis, the dibromo-dimethyl ester **43** prepared from adipic acid was cyclized to the nitrile diester, which on subsequent hydrolysis and decarboxylation yielded the diacid **44**. Curtius rearrangement of the diacyl azide derivative obtained from the acid chloride **45** of the diacid leads to the formation of the racemic *trans*-1,2-diamine **46**. Finally, resolution of the diamine **46** using *L*-tartaric acid yielded the enantiopure (+)-1,2-diaminocyclobutane.

Scheme 13



Singh and co-workers[21] reacted (*S*)-*O*-acetylmandelic acid **47** with various amines to obtain the desired amides **48**, which on reduction gave the corresponding 1,2-amino alcohols **49** (Scheme 14). Subsequent opening of the aziridinium ion obtained by the mesylation of the amino alcohols with various amine nucleophiles gave the corresponding 1,2-diamines **50**.

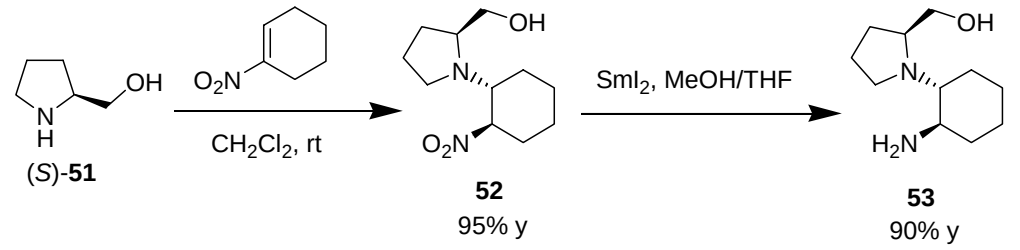
Scheme 14



1.1.1.6 Synthesis of chiral 1,2-diamines from nitroalkenes

Conjugate addition of a nitrogen nucleophile onto a nitroalkene affords a compound that could serve as a precursor of a vicinal diamine, since the nitro group can be reduced by a variety of reagents. Thus, Strugess *et al*.[22] found that the reaction of (*S*)-2-pyrrolidinylmethanol **51** with 1-nitro-1-cyclohexene afforded a single adduct **52** in excellent yield and stereoselectivity (Scheme 15). The reduction of the nitro group with samarium diiodide in methanol-THF mixture yielded the diamine **53**.[22]

Scheme 15

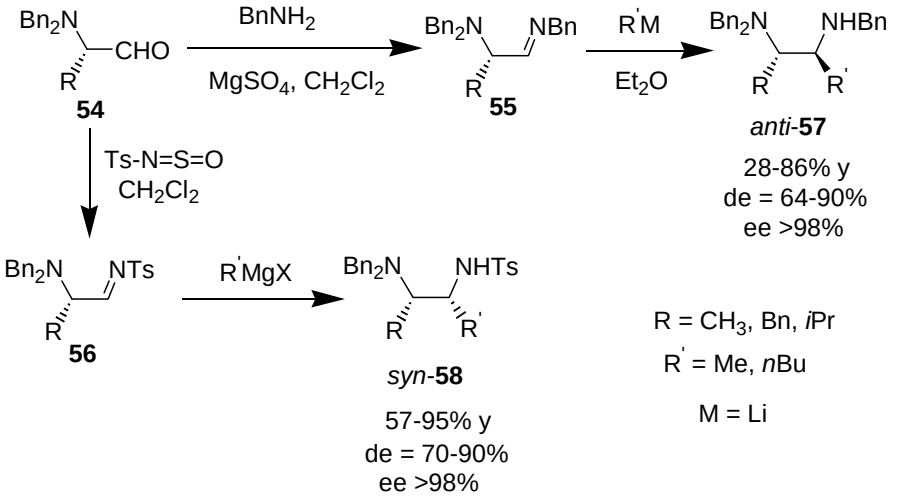


1.1.1.7 Synthesis of chiral 1,2-diamines from amino acids and their derivatives

Reetz *et al*.[23] reported an approach to the synthesis of *anti*- and *syn*-1,2-diamines **57** and **58** respectively, involving the stereoselective alkylation of the α-

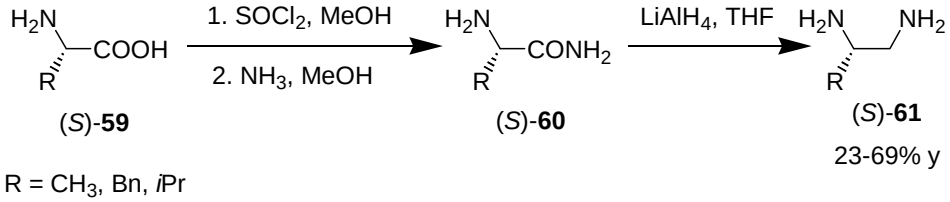
amino imines **55** and **56** prepared from *N*,*N*′-dibenzylamino aldehydes **54** which in turn can be readily accessed from the corresponding α-amino acids (Scheme 16).

Scheme 16



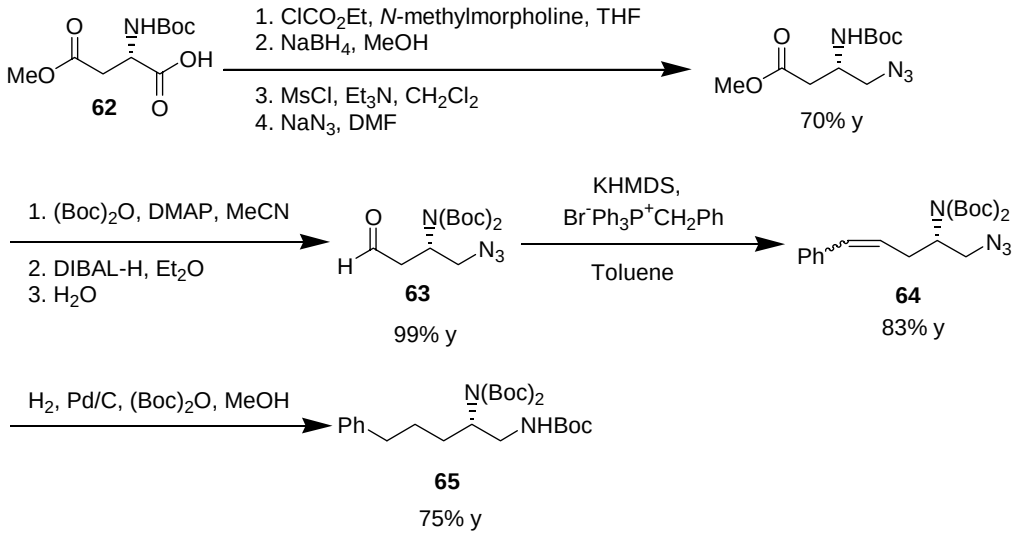
Brunner and co-workers[24] synthesized the monosubstituted chiral vicinal diamine **61** by the reduction of amides **60** prepared from natural α-amino acids **59** with high enantiomeric purity (Scheme 17).

Scheme 17



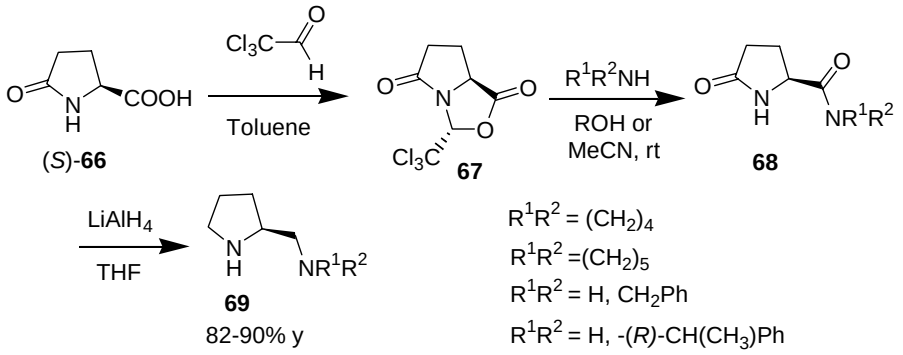
Kokotos and co-workers[25] devised a strategy to synthesize 1,2-diamines from the Wittig olefination of the aldehyde **63** prepared from glutamic acid to produce the unsaturated azide **64** (Scheme 18). Finally, catalytic hydrogenation in the presence of $(Boc)_2O$ results in the *N*-protected 1,2-diamine **65** (Scheme 18).

Scheme 18



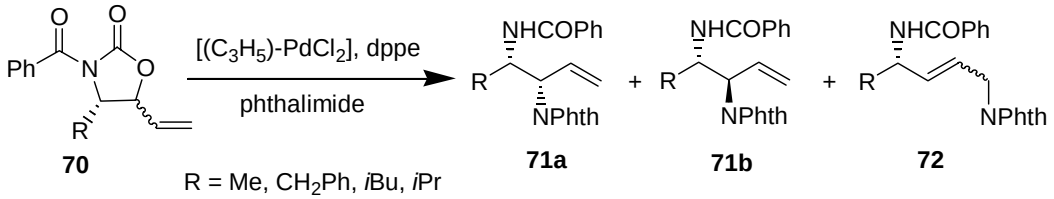
Amedjkouh and co-workers[26] synthesized the oxazolidindione **67** starting from (*S*)-2-pyrrolidinone-5-carboxylic acid **66** which was readily transformed into the amide **68** by nucleophilic ring opening with amines. Subsequent reduction of the amides resulted in the 1,2-diamine **69** (Scheme 19).

Scheme 19



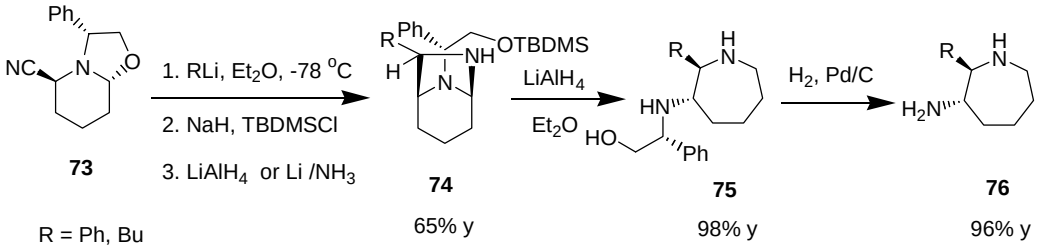
Cook *et al*.[27] reported a palladium mediated dynamic kinetic resolution for the stereoselective synthesis of the vicinal diamine derivative **71** by the reaction of the oxazolidinone **70** with phthalimide to obtain the *syn*-**71a** as major product besides the *anti*-**71b**, and the regioisomer **72** (Scheme 20).

Scheme 20



3-Aminoazepane **76** was prepared by Bonin and co-workers[28] starting from 2-cyano 6-oxazolopiperidine **73** through conversion to a diastereomeric mixture of the bicyclic aminal **74** and subsequent reduction with $LiAlH_4$ and cleavage using Pd-C/H_2 (Scheme 21). The 3-aminoazepane moiety is found in antitumor chiral *cis*-platin analogues[29] and in various CNS receptor ligands.[30]

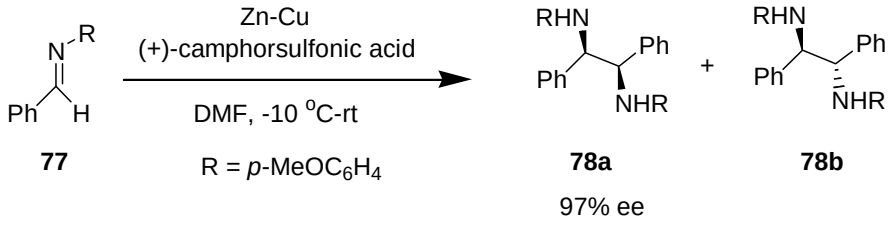
Scheme 21



1.1.1.8 Synthesis of chiral 1,2-diamines from imines

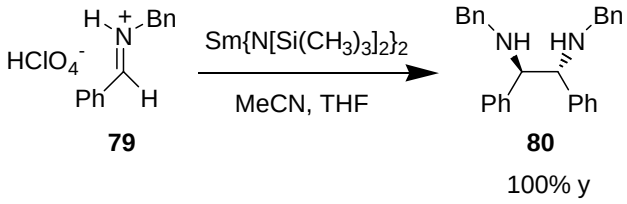
In principle, the reductive coupling of imines with the help of a metal or a metallic complex is a simple way to prepare 1,2-diamines. In 1995, Fujisawa *et al.*[31] reported the enantioselective coupling of *N*-*para*-methoxyphenylbenzaldimine **77** by the use of a zinc-copper couple, in the presence of three equivalents of (+)-camphorsulphonic acid (Scheme 22). The *syn* and *anti* adducts **78a** and **78b** were formed with good diastereoselectivity and the *syn*-**78a** was obtained with 97% enantioselectivity.

Scheme 22



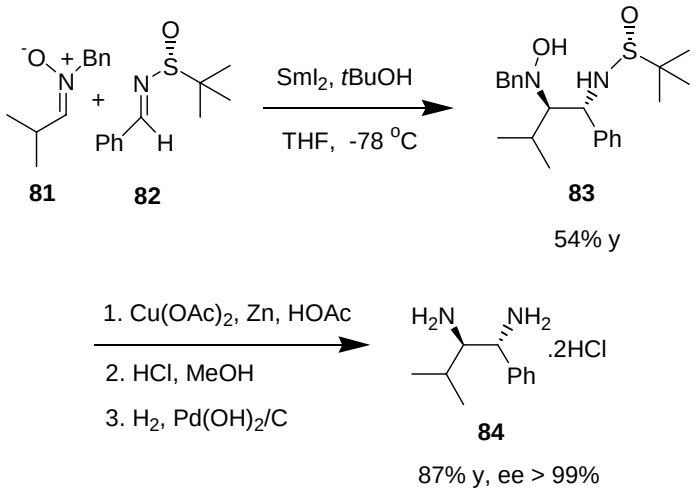
Recently, Flowers and co-workers[32] reported that the reductive coupling of the iminium perchlorate **79** in the presence of $Sm\{N[Si(CH_3)_3]_2\}_2$ reagent system yielded the *syn*-diamine **80** in 100% yield (Scheme 23).

Scheme 23



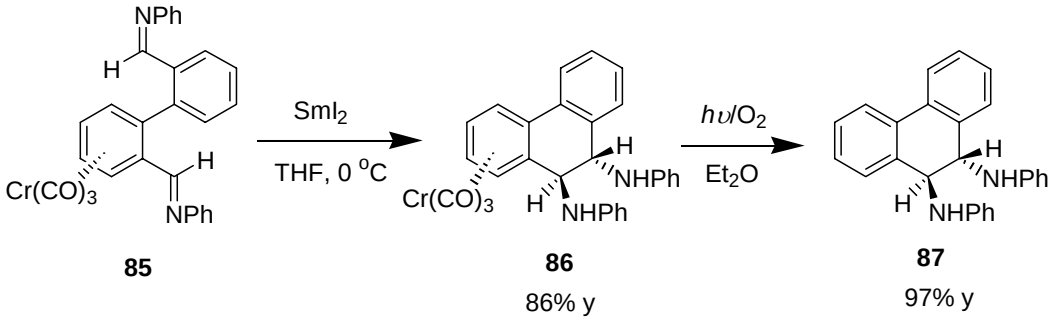
Xu *et al*.[33] reported an efficient method for the diastereoselective and enantioselective reductive cross-coupling of the nitrone **81** with the chiral *N*-*tert*-butanesulfinyl imine **82** induced by SmI_2, to yield the diastereomerically pure coupled product **83** (Scheme 24). The conversion of the cross-coupling product **83** to the corresponding unsymmetrical diamine **84** was accomplished following the procedure outlined in Scheme 24. Later, the same group reported the synthesis of enantiopure C_2-symmetrical 1,2-diamines following this synthetic strategy.[34]

Scheme 24



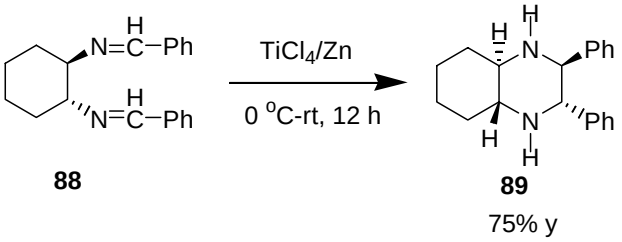
In 1999, Uemura *et al*.[35] reported the stereoselective synthesis of the cyclic *trans*-1,2-diamine **87** via the SmI_2 mediated intramolecular coupling of the mono-$Cr(CO)_3$ complex of the diiminobiphenyl **85** (Scheme 25). Subsequently, the diamino complex **86** was exposed to sunlight to give the corresponding chromium-free *trans*-1,2-diamine.

Scheme 25



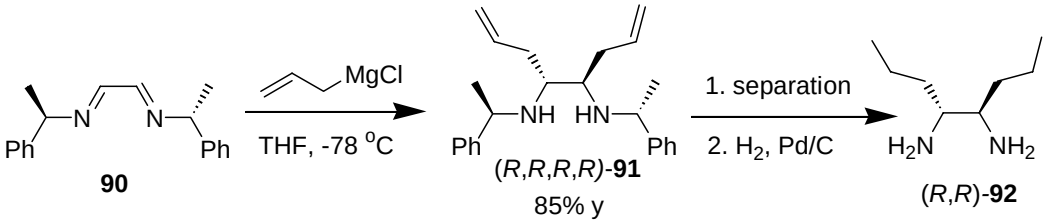
It has been reported from this laboratory that the chiral 3,4-disubstituted 2,5-diazabicyclo[4.4.0]decane **89** can be readily prepared by the intramolecular coupling of the bisimine **88** using low-valent titanium species (Scheme 26).[36]

Scheme 26



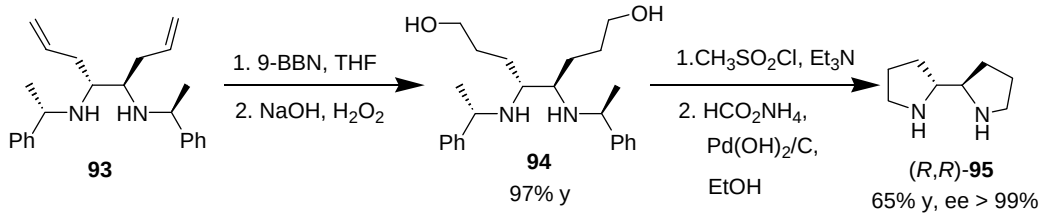
In 1991 Neumannn *et al*.[37] showed that the nucleophilic addition of allylmagnesium chloride to the chiral bis-imine **90** prepared from glyoxal and (*R*)-α-methylbenzylamine afforded a mixture of the two *syn* diastereomers (Scheme 27). The major (*R*,*R*)-isomer **91** was then converted to the enantiomerically pure C_2-symmetric diamine **92**.

Scheme 27



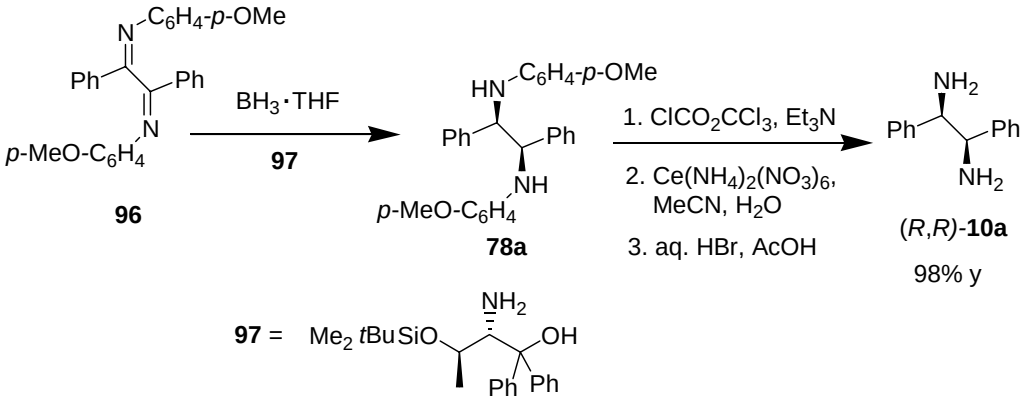
Alexakis and co-workers[38] reported the synthesis of (*R*,*R*)-2,2′-bipyrrolidine **95** from the chiral diamine **93** prepared from (*S*)-α-methylbenzylamine (Scheme 28) via hydroboration-oxidation of the diamine to the diaminodiol **94** followed by the cyclisation and de-α-methylbenzylation.

Scheme 28



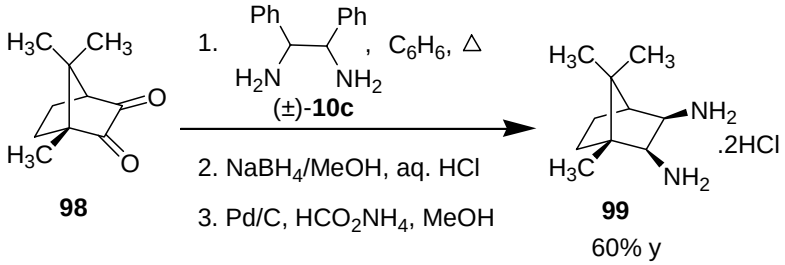
The catalytic asymmetric reduction of 1,2-bis(*para*-methoxy-phenylimino)-1,2-diphenylethane **96** was reported by Fujisawa *et al*.[39] (Scheme 29). In this procedure, an oxazaborolidine, obtained from *L*-threonine derivative **97** served as the catalyst that afforded selectively the *syn*-diamine **10a** in high yield and enantiomeric purity.[39]

Scheme 29



A convenient stereoselective synthesis of (*R*)-camphordiamine dihydrochloride **99** by the reduction of the bisimine prepared from (*R*)-camphorquinone **98** and racemic 1,2-diphenylethylenediamine **10c** followed by hydrogenolysis was reported by Busacca and co-workers[40] (Scheme 30).

Scheme 30

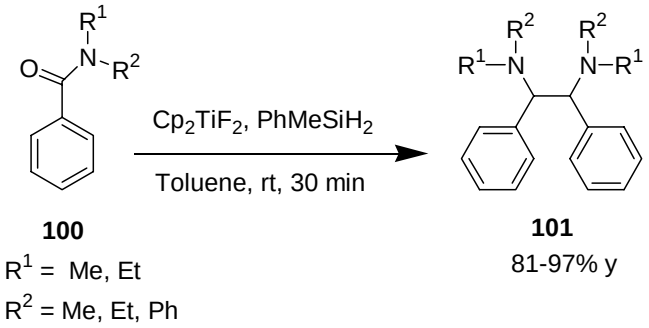


1.1.1.9 Synthesis of chiral 1,2-diamines from amides

Recently, Harrod *et al*.[41] reported that the titanocene catalyzed coupling of the

amide **100** in the presence of organosilanes gives a *meso*/racemic mixture of 1,2-diamines **101** (Scheme 31).

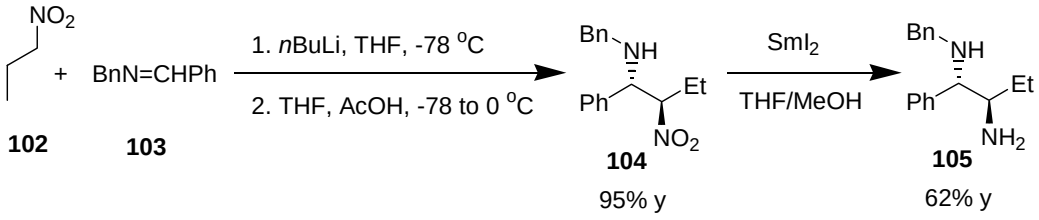
Scheme 31



1.1.1.10 Synthesis of chiral 1,2-diamines from nitroalkanes

Anderson and co-workers[42] reported the addition of the nitropropane **102** to the imine **103** (nitro-Mannich reaction) to provide the β-nitroamines **104** which on reduction with SmI_2 gave the 1,2-diamine **105** in high yield and good diastereoselectivity (Scheme 32).

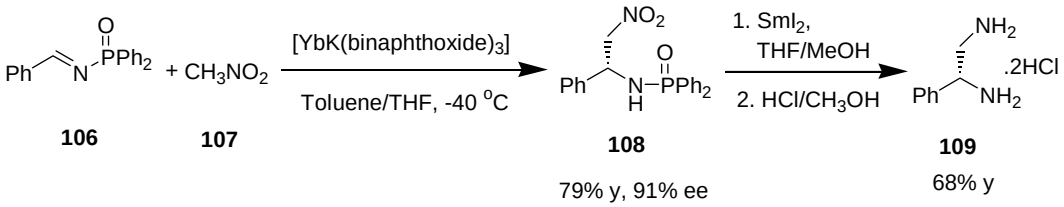
Scheme 32



Later, Shibasaki *et al*.[43] investigated the catalytic asymmetric nitro-Mannich reaction of the *N*-phoshinoylimine **106** with nitromethane **107**, catalyzed by the heterobimetallic complex [YbK(binaphthoxide)$_3$] (Scheme 33). The *N*-phosphinoyl

nitroamine **108** obtained in this way was subsequently transformed into the 1,2-diamine salt **109** using SmI_2.

Scheme 33

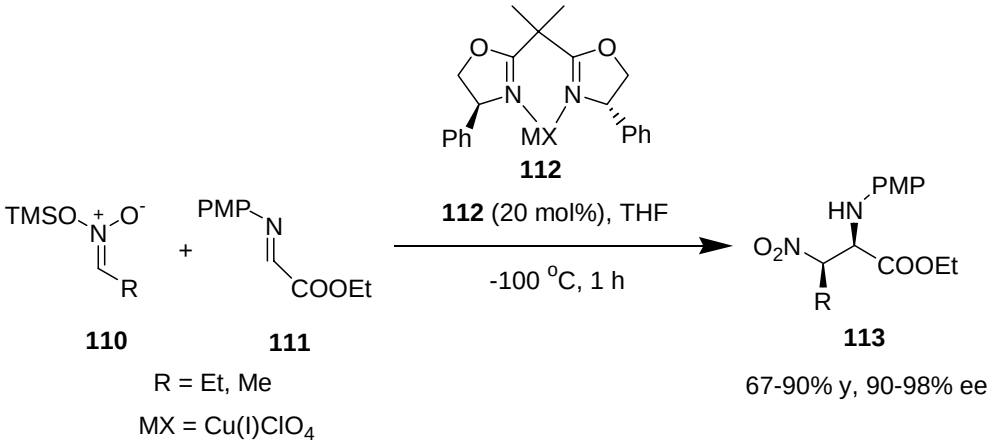


106 **107** **108** **109**

79% y, 91% ee 68% y

Recently, JØrgenson and co-workers[44] reported the addition of the trimethylsilyl nitronate **110** to *N*-protected α-imino esters **111** catalyzed by the (*S*)-Ph-BOX-copper catalyst **112**, to afford the β-nitro-α-amino esters **113** (Scheme 34). The amino esters **113** can be converted to the synthetically useful α,β-diamino esters.

Scheme 34



110 **111** **113**

R = Et, Me

MX = $Cu(I)ClO_4$

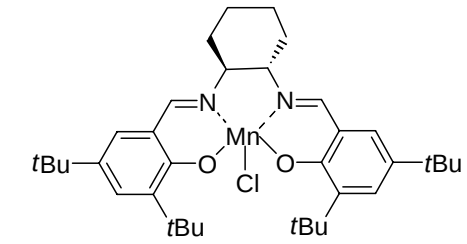
67-90% y, 90-98% ee

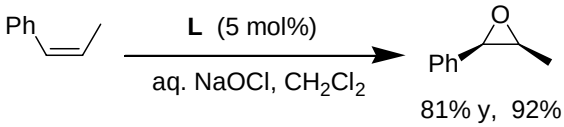
1.1.2 Synthetic applications of chiral 1,2-diamine derivatives

Several C_2-symmetric chiral diamine derivatives containing 1,2-cyclohexyl moiety are known to give good enantioselectivities in a variety of asymmetric organic transformations (Chart 1).

Chart 1

Epoxidation of Olefins

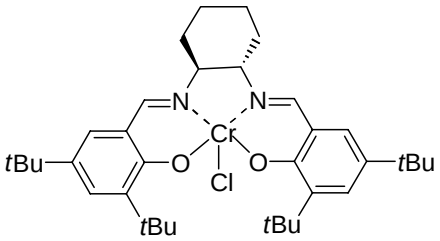


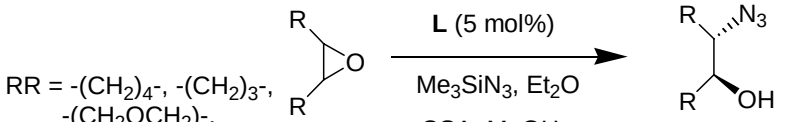


81% y, 92% ee

Ref. 45

Asymmetric Epoxide Opening

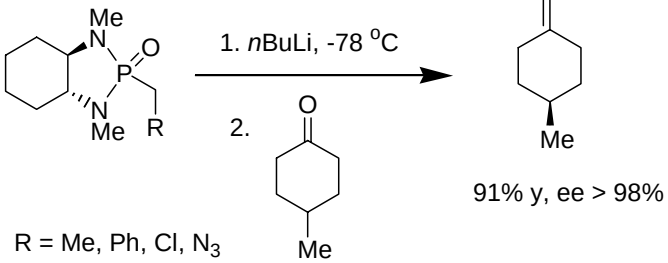




72-80% y, 81-98% ee

Ref. 46

Asymmetric Olefination

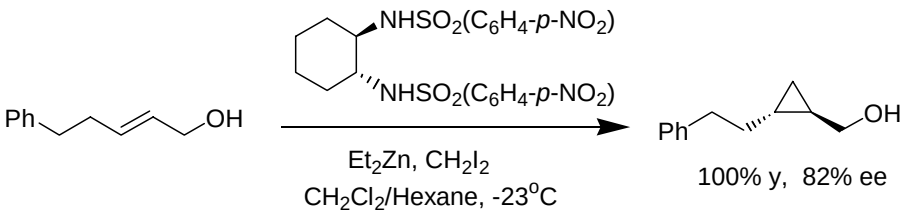


R = Me, Ph, Cl, N_3

91% y, ee > 98%

Ref. 47

Enantioselective Cyclopropanation

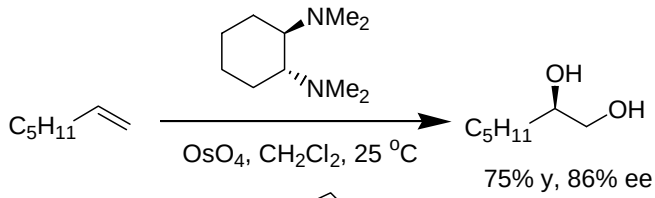


100% y, 82% ee

Ref. 48

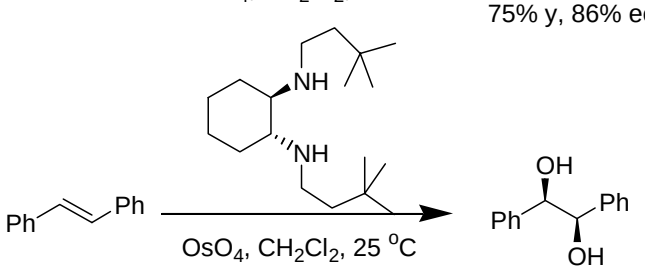
Chart 1 (continued)

Asymmetric Dihydroxylation



75% y, 86% ee

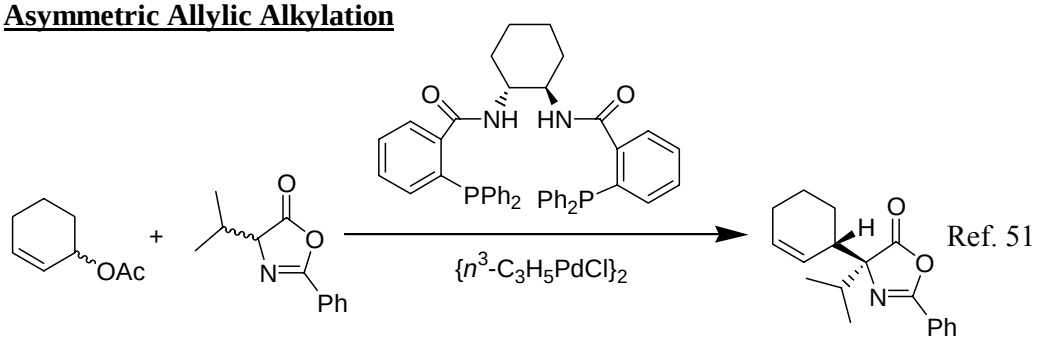
Ref. 49



80% y, 99% ee

Ref. 50

Asymmetric Allylic Alkylation

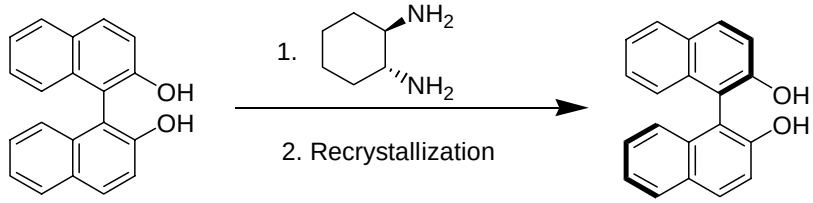


91% y

de > 99%, ee = 95%

Ref. 51

Resolution of Racemates



(±)

94% ee

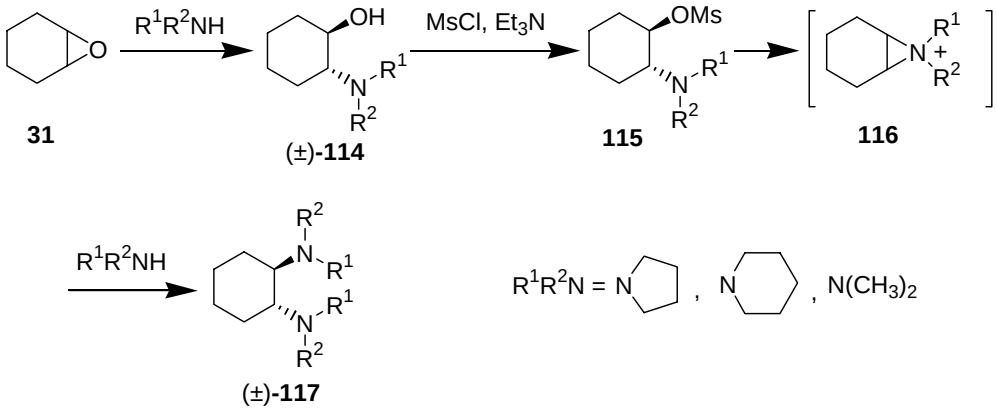
Ref. 52

Accordingly, we have undertaken efforts towards the synthesis, resolution and enhancement of the enantiomeric excess of C_2-symmetric derivatives of 1,2-diaminocyclohexane. The results are discussed in the next section.

1.2 Results and Discussion

We have developed a method of synthesis of C_2-symmetric 1,2-diaminocyclohexane derivatives **117** by the nucleophilic ring opening of the aziridinium ion intermediates **116** with various amines. The aziridinium ions were prepared *in situ* from the mesylates **115** of the 1,2-amino alcohols **114**. The amino alcohols were obtained by the ring opening of cyclohexene oxide **31** with various amine nucleophiles (Scheme 35). The results are discussed in this section.

Scheme 35



1.2.1 Synthesis of *trans*-(±)-1,2-amino alcohols from cyclohexene oxide

There are several methods available for the synthesis of *trans*-(±)-1,2-amino alcohols by the ring opening of cyclohexene oxide with amine nucleophiles.[53] We have observed that the *trans*-(±)-1,2-amino alcohols **114** can be readily prepared by refluxing cyclohexene oxide **31** with the corresponding amines (Scheme 36). The results are summarized in Table 1.

Scheme 36

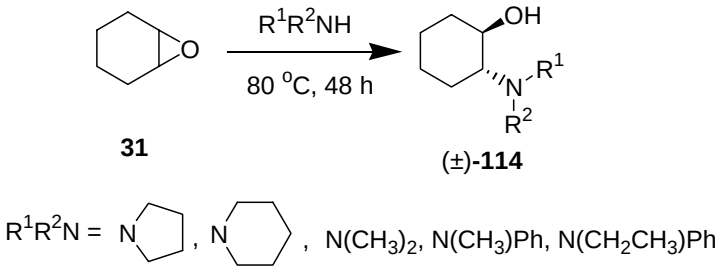
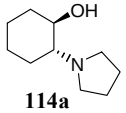
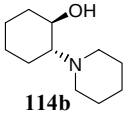
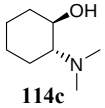
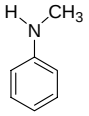
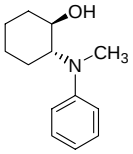
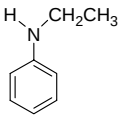
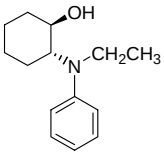


Table 1. Synthesis of *trans*-(±)-1,2-amino alcohols 114 from cyclohexene oxide 31

S.No.	Nucleophile	(±)-1,2-amino alcohol[a]	Yield (%)[b]
1.[c]		 **114a**	90
2.[c]		 **114b**	85
3.[d]		 **114c**	80
4.[e]		 **114d**	15
5.[e]		 **114e**	10

a. The products were identified by the spectral data (IR, ^{1}H-NMR, ^{13}C-NMR).

b. The yields are of the isolated products.

c. The reaction was carried out using amine (200 mmol) and cyclohexene oxide **31** (200 mmol).

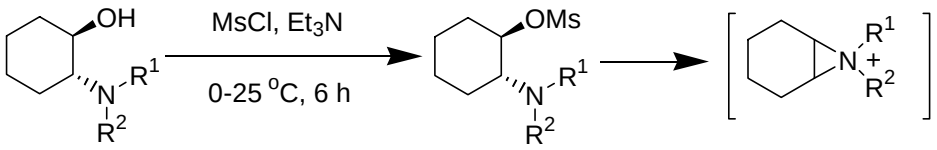
d. The reaction was carried out using amine (400 mmol) and cyclohexene oxide **31** (50 mmol).

e. The reaction was carried out using amine (25 mmol) and cyclohexene oxide **31** (25 mmol).

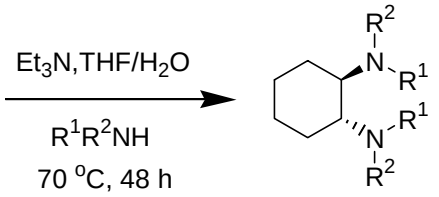
1.2.2 Synthesis of *trans*-(±)-1,2-diaminocyclohexane derivatives by the opening of the aziridinium ion intermediates with achiral amines

We have carried out the synthesis of the *trans*-(±)-1,2-diamines **117** starting from the corresponding *trans*-(±)-2-(*N*,*N*-dialkylamino)cyclohexanol derivatives **114**.[54] The synthesis of the mesylates **115** of the amino alcohols was accomplished by the reaction with MsCl in the presence of triethylamine. Solvolysis of the mesylates produced the aziridinium ions **116** *in situ* which are readily trapped with the secondary amine nucleophiles like dimethylamine, pyrrolidine and piperidine to obtain the corresponding C_2-symmetric *trans*-(±)-1,2-diamines **117** in good yields (Scheme 37). The results are summarized in Table 2.

Scheme 37



(±)-**114** **115** **116**



(±)-**117**

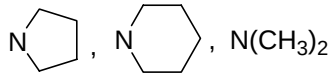
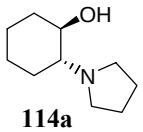
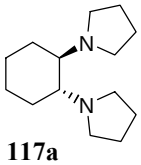
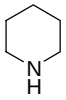
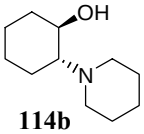
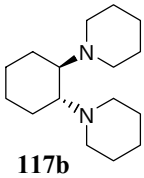
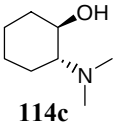
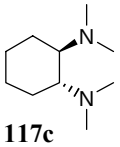
R^1R^2N =  , $N(CH_3)_2$

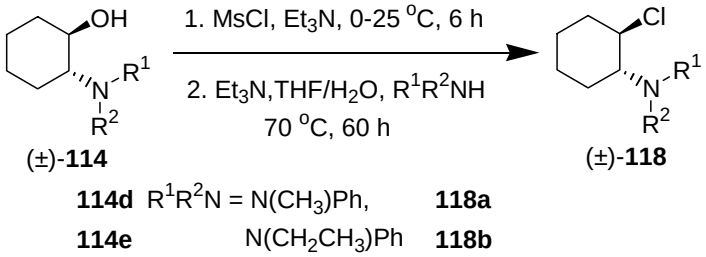
Table 2. Synthesis of *trans*-(±)-1,2-diaminocyclohexane derivatives 117[a]

S. No.	Nucleophile	trans-(±)-1,2-amino alcohol	trans-(±)-1,2-diamine	Yield (%)[b]
1.[c]		 **114a**	 **117a**	80
2.[d]		 **114b**	 **117b**	75
3.[e]		 **114c**	 **117c**	60

a. The products were identified by the spectral data (IR, ^{1}H-NMR, ^{13}C-NMR).
b. The yields are of the isolated products.
c. The reaction was carried out using amino alcohol (30 mmol) and amine (7.5 mL).
d. The reaction was carried out using amino alcohol (30 mmol) and amine (12 mL).
e. The reaction was carried out using amino alcohol (30 mmol) and aq. amine (50 mL).

However, the amino alcohols **114d-e** and MsCl did not react with the aromatic amines to yield the corresponding *trans*-1,2-diamines. Instead, the hydroxyl group of the amino alcohol was substituted with chlorine to give the β-chloro amine **118** (Scheme 38). Previously, it was reported that the formation of the aziridinium ion proceeds through the β-chloro amine intermediate.[55] Presumably, in this case, due to the steric bulk offered by the phenyl group, the reaction might not have proceeded further.

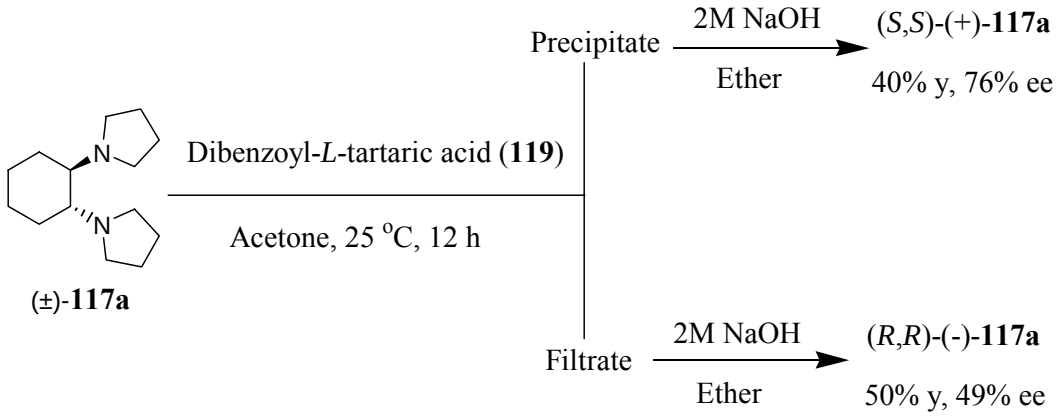
Scheme 38



1.2.3 Resolution of the *trans*-(±)-1,2-diamines

We have undertaken efforts towards the resolution of the *trans*-(±)-1,2-diamines **117a** and **117c** through preparation of diastereomeric complexes using readily available chiral resolving agents. Initially, we examined the resolution of *trans*-(±)-1,2-bis(pyrrolidino)cyclohexane **117a**. It was observed that the diamine **117a** formed diastereomeric complexes with dibenzoyl-*L*-tartaric acid **119** (Scheme 39). These diastereomeric complexes are solid derivatives and are readily cleaved hydrolytically.

Scheme 39



The resolutions were carried out using various solvents like acetone, acetonitrile, THF and methanol. In acetone and acetonitrile, the diamine gave precipitate leading to partial resolution. The effect of the amount of solvent, reaction

time and the concentration of dibenzoyl-*L*-tartaric acid were studied in order to optimize the reaction conditions. The results are summarized in Table 3.

Table 3. Resolution of *trans*-(±)-1,2-bis(pyrrolidino)cyclohexane 117a using dibenzoyl-*L*-tartaric acid 119[a]

S. No	Ratio of **117a** : **119**	Solvent	Diamine **117a** obtained from			
			Precipitate		Filtrate	
			%ee[b]/Conf.	Yield (%)[c]	%ee[b]/Conf.	Yield (%)[c]
1.[d]	1:1	Acetone (15 mL)	29 (*SS*)	54	74 (*RR*)	33
2.	1:1	Acetone (15 mL)	28 (*SS*)	70	77 (*RR*)	27
3.	1:1	Acetone (30 mL)	37 (*SS*)	65	66 (*RR*)	22
4.	2:1	Acetone (15 mL)	76 (*SS*)	40	49 (*RR*)	50
5.	2:1	Acetone (30 mL)	65 (*SS*)	16	46 (*RR*)	53
6.	1:1	Acetonitrile(15 mL)	28 (*SS*)	59	49 (*RR*)	40
7.	1:1	Acetonitrile(30 mL)	58 (*SS*)	37	52 (*RR*)	46
8.[e]	2:1	Acetone(15 mL)	96 (*SS*)	50	40 (*SS*)	30

a. The reactions were performed using racemic diamine **117a** (2 mmol) and dibenzoyl-*L*-tartaric acid **119**, in solvent and stirred at 25 ^{o}C for 12 h.

b. All ee values reported are based on the maximum $[\alpha]_D^{25}$ = -31.85 (*c* 0.5, 1N HCl) obtained from the sample of (*R*,*R*)-**117a** with >99% ee, prepared following a reported procedure.[56a]

c. The yields are of the isolated products, based on the total amount of the starting racemic **117a** used.

d. The reaction was performed in acetone at 25 ^{o}C for 6 h.

e. The reaction was carried out using 76% ee of (*S*,*S*)-**117a**.

It is evident from the results in Table 3 that acetone is a better solvent for resolution compared to acetonitrile. It was observed that increasing the reaction time from 6 to 12 hours resulted in a slight increase in the yield of the diamine (Table 3, entries 1-2). As the volume of the solvent increased, the ee of the product decreased (Table 3, entries 3 and 5). To determine the optimum amount of chiral resolving agent required for the resolution, we have studied the effect of concentration of dibenzoyl-*L*-

tartaric acid (Table 3, entries 1-5). It was observed that always non-racemic (*S*,*S*)-**117a** was obtained from the precipitate and non-racemic (*R*,*R*)-**117a** was obtained from the filtrate. Interestingly, when the diamine **117a** and the acid **119** were used in 1:1 ratio, the (*R*,*R*)-**117a** was obtained with higher ee (Table 3, entries 1-3) and when the ratio was 2:1, the (*S*,*S*)-**117a** was obtained with higher ee (Table 3, entries 4-5). The non-racemic (*S*,*S*)-**117a** with 76% ee obtained by partial resolution was further enriched using dibenzoyl-*L*-tartaric acid to obtain a sample with 96% ee (Table 3, entry 8).

We then examined the resolution of the diamine **117c**. This diamine could not be resolved using dibenzoyl-*L*-tartaric acid in various solvents like acetone, THF, acetonitrile and DCM. The resolution of various amino alcohols and amino ethers using chiral 1,1′-bi-2-naphthol has been well-studied in this laboratory previously.[57] Accordingly, the resolution of the diamine **117c** was examined using both (*S*)-(-)-1,1′-bi-2-naphthol **120a** and (*R*)-(+)-1,1′-bi-2-naphthol **120b** in acetonitrile (Scheme 40). The results are summarized in Table 4. It is of interest to note that previously the (*R*,*R*)-1,2-diaminocyclohexane was used to resolve racemic 1,1′-bi-2-naphthol and its derivatives (Section 1.1, Chart 1).[52]

Scheme 40

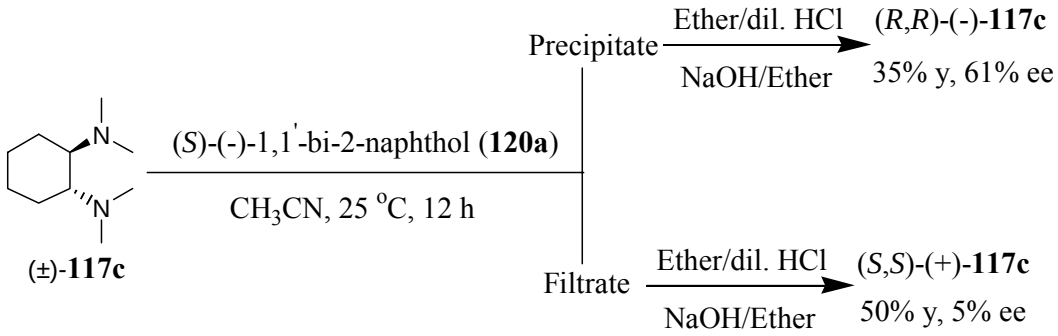


Table 4. Resolution of *trans*-(±)-1,2-bis(*N*,*N*-dimethylamino)cyclohexane 117c using chiral 1,1′-bi-2-naphthol 120[a]

S. No.	Starting ee of **117c**/ Conf.	Resolving agent, Ratio of **117c** : **120**	Diamine **117c** obtained from			
			Precipitate		Filtrate	
			%ee[b]/Conf.	Yield (%)[c]	%ee[b]/Conf.	Yield (%)[c]
1.[d]	0	**120a**, 1:1	36 (*RR*)	43	23 (*SS*)	46
2.	0	**120a**, 1:1	43 (*RR*)	45	36 (*SS*)	40
3.[e]	0	**120a**, 1:1	44 (*RR*)	40	32 (*SS*)	36
4.	0	**120a**, 2:1	61 (*RR*)	35	5 (*SS*)	50
5.	61, (*RR*)	**120a**, 2:1	92 (*RR*)	30	55 (*RR*)	46
6.	92, (*RR*)	**120a**, 2:1	98 (*RR*)	22	70 (*RR*)	63
7.	0	**120b**, 2:1	57 (*SS*)	25	16 (*RR*)	60
8.	57, (*SS*)	**120b**, 2:1	90 (*SS*)	30	7 (*SS*)	50

a. The reactions were performed using racemic diamine **117c** (3 mmol) and chiral 1,1′-bi-2-naphthol **120**, in acetonitrile (15 mL) and stirred at 25 ^{o}C for 12 h.

b. All ee values reported are based on the maximum $[\alpha]_D^{25}$ = -60.6 (*c* 1, $CHCl_3$) obtained for the sample of (*R*,*R*)-**117c** with >99% ee, prepared following a reported procedure.[56b]

c. The yields are of the isolated products, based on the total amount of the starting racemic **117c** used.

d. The reaction was performed in acetonitrile (15 mL) at 25 ^{o}C for 6 h.

e. The reaction was performed in acetonitrile (30 mL) at 25 ^{o}C for 12 h.

When the reaction time was changed from 6 h to 12 h there was an improvement in the ee of the diamine **117c** using (*S*)-(-)-1,1′-bi-2-naphthol **120a** as the resolving agent (Table 4, entries 1-2). However, the increase in the volume of the solvent did not improve the ee or the yield of the diamine (Table 4, entry 3). The concentration of the resolving agent **120** had an effect on the resolution of the diamine **117c**. Optimum resolution resulted when the ratio of the diamine and binaphthol was 2:1 than when compared to 1:1 (Table 4, entries 1-6). The partially resolved diamine **117c** was enriched to obtain samples with 98% ee by repeating the resolution procedure

(Table 4, entries 5-6). Similar results were obtained when (*R*)-(+)-1,1′-bi-2-naphthol **120b** was employed as the resolving agent (Table 4, entries 7-8).

The precipitate obtained in the reaction of (*R*,*R*)-**117c** and (*S*)-**120a** was crystallized from methanol. The X-ray crystal structure of the complex revealed that two molecules of binaphthol are involved in complex formation with one molecule of the diamine (Figure 1).

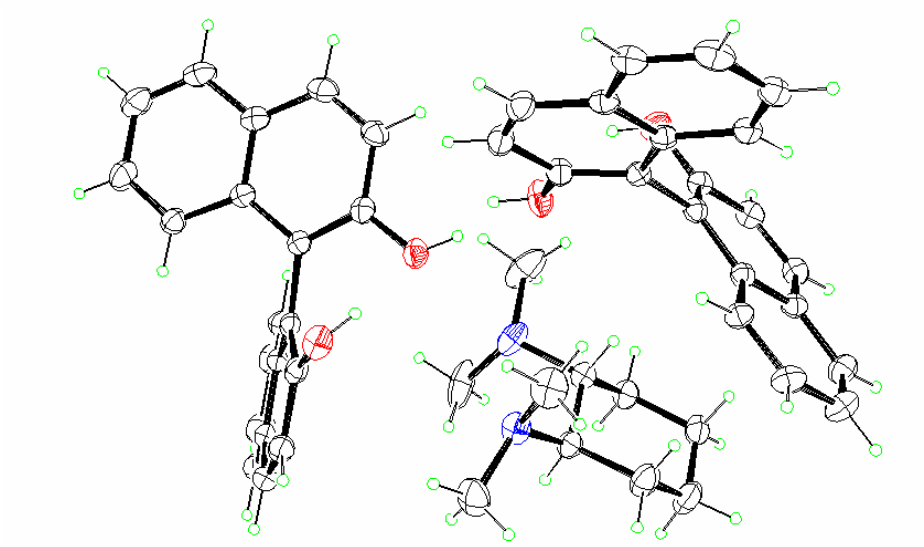


Figure 1. ORTEP diagram of the complex of (*R*,*R*)-117c with (*S*)-binaphthol 120a

In the packing diagram, intramolecular hydrogen bonding (O-H···O) with bond distance of 1.843 Å and 1.963 Å between the two hydroxyl groups in each of the binaphthol moiety was observed. In addition, the two binaphthol moieties were intermolecularly hydrogen bonded with each other with bond distances of 1.722 Å and 1.77 Å. One of the nitrogen atoms of the diamine is involved in hydrogen bonding with the hydroxyl group of the binaphthol with the O-H···N hydrogen bond distance of 2.611 Å (Figure 2). The crystal structure data of the complex of the (*R*,*R*)-**117c** with (*S*)-1,1′-bi-2-naphthol **120a** are summarized in Table 5 and Table A1 (Appendix II).

Table 5. X-ray data and structure refinement for the complex of the diamine (*R*,*R*)-117c with (*S*)-1,1′-bi-2-naphthol 120a

Empirical formula	$C_{50}\ H_{50}\ N_2\ O_4$
Formula weight	742.92
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	*P* 21
Unit cell dimensions	a = 11.3598(17) Å, $\alpha = 90^o$
	b = 17.864(3) Å, $\beta = 116.987(2)^o$
	c = 11.4084(17) Å, $\gamma = 90^o$
Volume	2063.1(5) $Å^3$
Z	2
Calculated density	1.196 Mg/m^3
Absorption coefficient	0.075 mm^{-1}
F(000)	792
θ range for data collection	2.00 to 26.13^o
Limiting indices	$-13 \le h \le 3$, $-22 \le k \le 22$, $-14 \le l \le 14$
Reflections collected / unique	21529 / 8132 [R(int) = 0.0502]
Refinement method	full-matrix least-squares on F^2
Data / restraints / parameters	8132 / 1 / 513
Goodness-of-fit on F^2	0.894
Final R indices [$I>2\sigma(I)$]	$R_1 = 0.0448$, $wR_2 = 0.0986$
R indices (all data)	$R_1 = 0.0677$, $wR_2 = 0.1063$
Largest diff. peak and hole	0.309 and -0.146 $eÅ^{-3}$

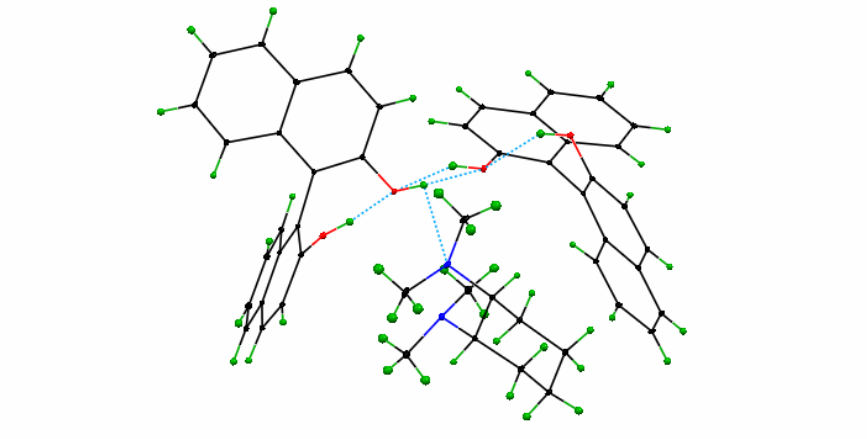


Figure 2. Packing diagram of the complex of (*R*,*R*)-117c with (*S*)-binaphthol 120a

1.2.4 Enhancement of enantiomeric purity of the non-racemic diamines using achiral dicarboxylic acids

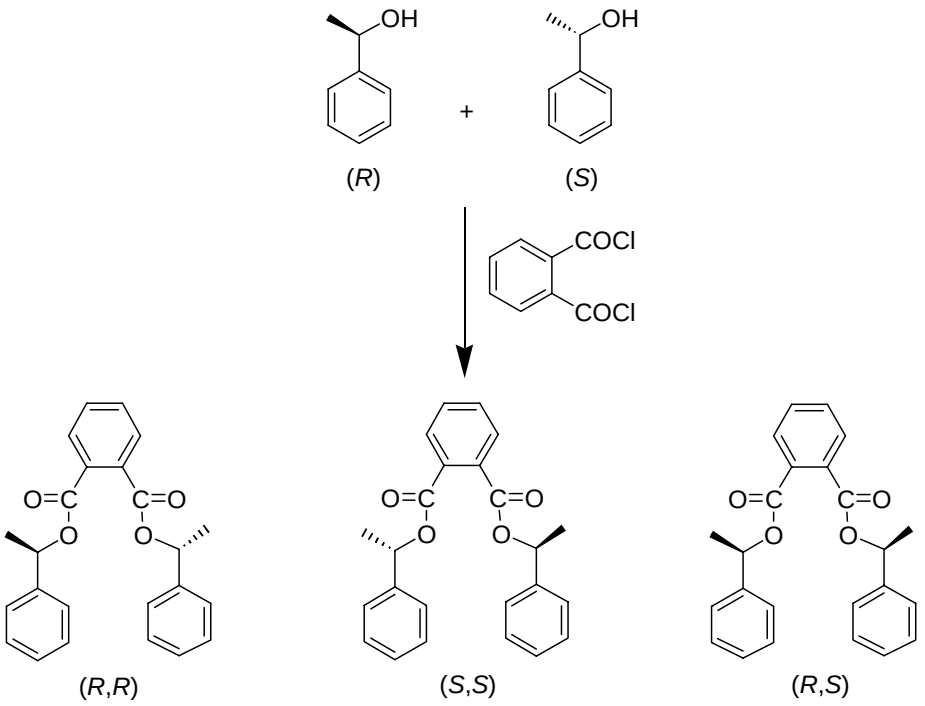
Although the dibenzoyl-*L*-tartaric acid **119** and the chiral binaphthol **120** used in the resolution and enrichment can be readily recovered (Schemes 39 and 40, Tables 3 and 4), it would be advantageous if the partially resolved (scalemic, non-racemic) 1,2-diamines can be enriched further without using any other chiral source. Such enhancement of enantiomeric purity of samples with small enantiomeric excesses to obtain samples of high levels of enantiomeric purity has relevance not only to the evolution of chiral homogeneity in Nature,[58-60] but also to the spectacular successes realized in recent years in Kagan's non-linear effects in asymmetric catalysis,[61] Mikami's asymmetric activation of racemic catalysts[62] and Soai's asymmetric autocatalysis in dialkyl zinc additions.[63]

Various processes developed so far for amplification of small enantiomeric excesses of non-racemic (partially resolved) compounds include, amplification during (i) evaporation and precipitation,[64,65] (ii) incomplete reaction,[66] (iii) stereoselective

autocatalysis-crystallization[67-69] and (iv) polymerization.[70] Whereas the method of amplification by evaporation requires differential solubility of enantiomers and the racemate, most of the other methods involve formation of diastereomers through covalent bonds.

In 1973, Horeau *et al.*[66] reported the chemical duplication of non-racemic alcohol samples via preparation of the corresponding carbonates, phthalates, malonates and oxalates (Scheme 41).

Scheme 41

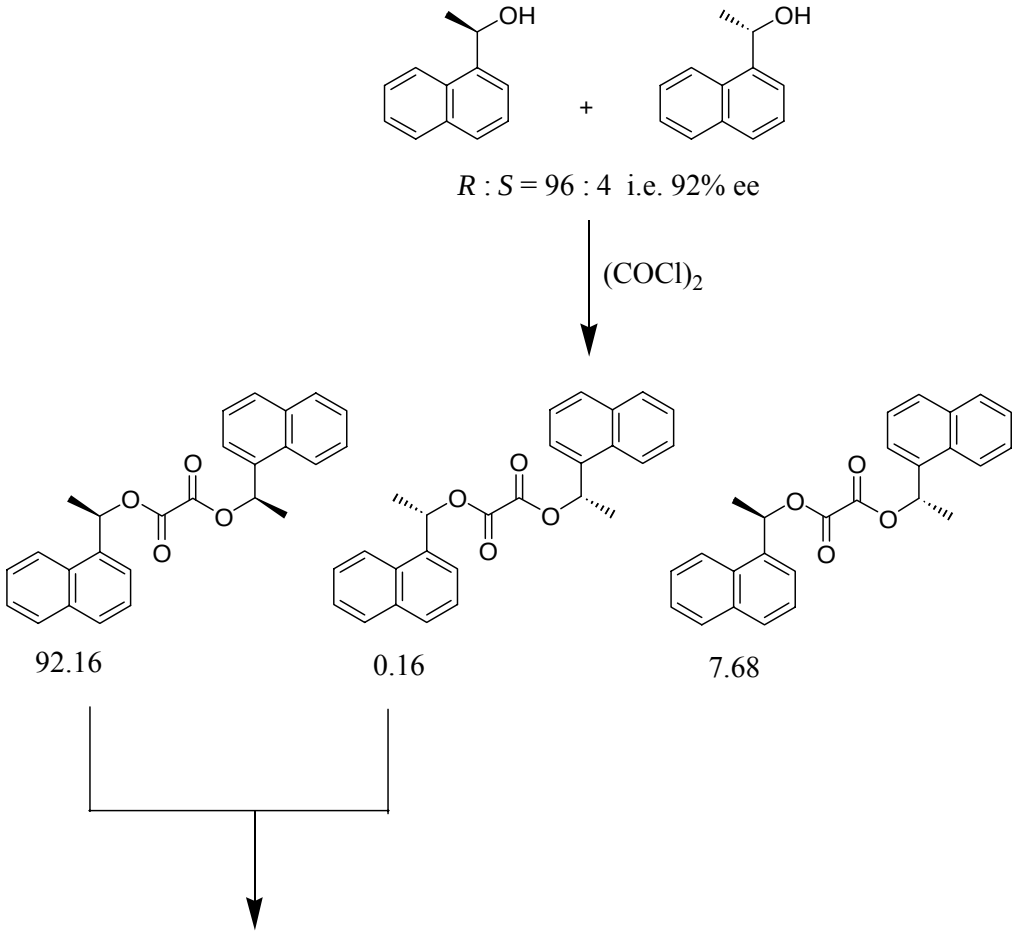


The enhancement of enantiomeric excess realized here is due to the formation of (*R*,*R*) diester derived from the enantiomer (*R*) present in excess in higher amounts compared to that of the (*S*,*S*) diester and the (*R*,*S*) diester. Since the (*R*,*R*) and (*S*,*S*) enantiomers obtained in this way could be readily separated from the (*R*,*S*)

diastereomer, the (*R*,*R*) and (*S*,*S*) diester mixture upon decomposition yielded the non-racemic alcohol sample in higher enantiomeric excess.

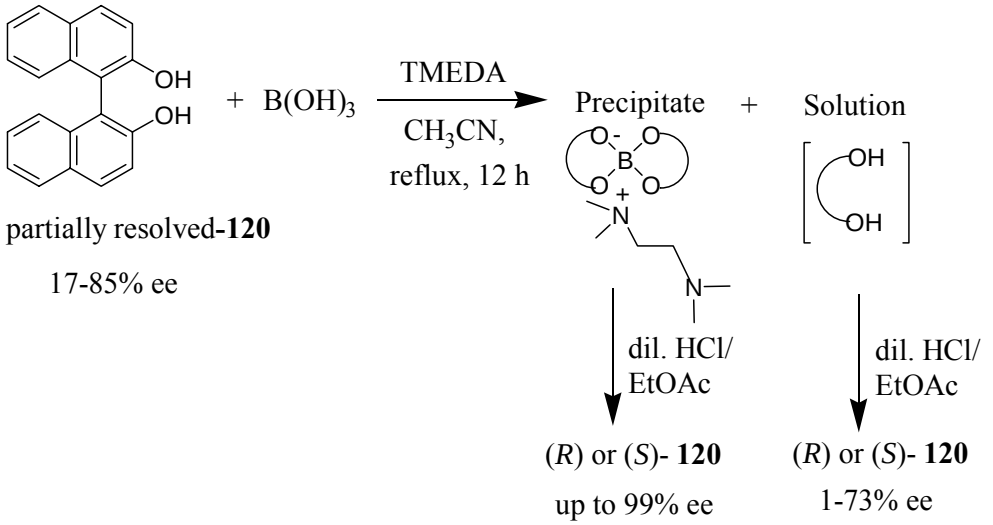
Later, Fleming and Ghosh[71] applied this idea to enrich the enantiomeric excess of a scalemic alcohol (from 92% ee to 99.6% ee) using oxalyl chloride (Scheme 42).

Scheme 42



It has been previously reported from this laboratory that the non-racemic samples of 1,1′-bi-2-naphthol **120** can be enriched using smaller amounts of the $B(OH)_3$ and TMEDA to obtain samples of 99% enantiomeric purity from the precipitate fraction leaving behind samples of lower ee in the solution (Scheme 43).[72]

Scheme 43



In all these cases, the enhancement of enantiomeric purity is due to formation of covalently bonded diastereomeric complexes. It was of interest to examine whether the enrichment of the enantiomeric purity of the partially resolved (non-racemic) 1,2-diamines can be achieved by the formation of hydrogen bonded aggregates (Figure 3).

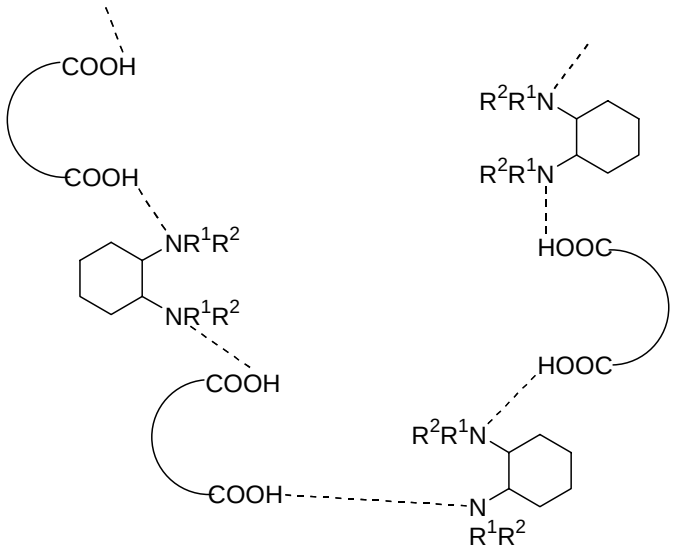


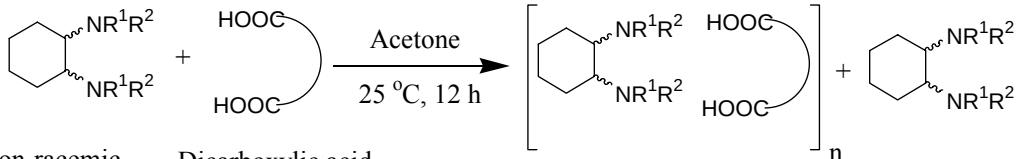
Figure 3

The results are described in the next section.

1.2.4.1 Enhancement of enantiomeric purity of the non-racemic 1,2-diamine 117a using oxalic, fumaric and terephthalic acids

We have devised a conceptually new method of purification of non-racemic 1,2-diamines[73] using achiral dicarboxylic acids by the preparation of the corresponding hydrogen-bonded homochiral or heterochiral aggregates **121** (Scheme 44).

Scheme 44



Non-racemic **117a** or **117c** 1 equiv. | Dicarboxylic acid <1 equiv. | **121** Precipitate (Homochiral or Heterochiral aggregates) | Solution

We have envisaged that if the formation of the diastereomeric aggregates **121** could be induced using achiral spacers through hydrogen bonds (Figure 3), it would result in the enhancement of enantiomeric excess, especially if the achiral spacers are used in lesser amounts than that required for interaction with all of the non-racemic material present in the mixture.

Initially, we examined the purification of the non-racemic 1,2-diamine **117a** using oxalic, fumaric and terephthalic acids. A precipitate was formed when the non-racemic **117a** was stirred with oxalic acid in acetone solvent at 25 °C for 12 h. Upon workup of the precipitate and filtrate fractions, a sample of higher enantiomeric excess was obtained from the filtrate fraction (Scheme 45). The results are summarized in Table 6.

Scheme 45

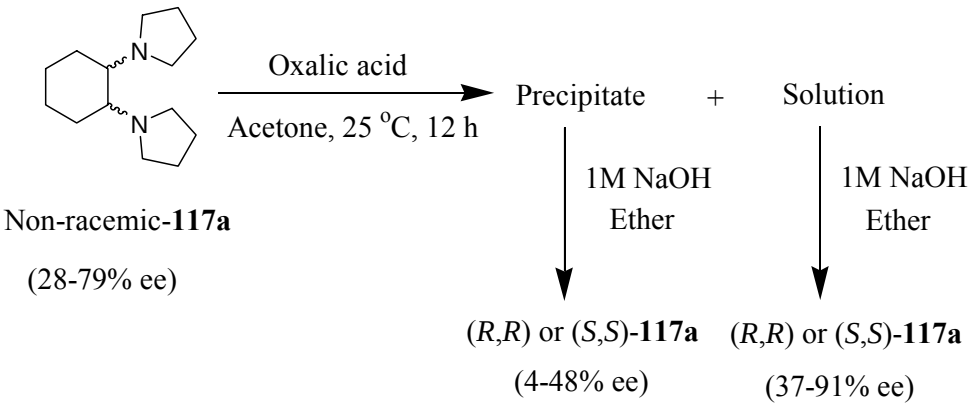


Table 6. Enhancement of enantiomeric excess of the non-racemic diamine 117a using oxalic acid[a]

S. No.	Substrate **117a** (% ee)	Oxalic acid	Diamine **117a** obtained from			
			Precipitate		Filtrate	
	(2 mmol)	(mmol)	%ee[b]/Conf.	Yield (%)[c]	%ee[b]/Conf.	Yield (%)[c]
1.	(*SS*) 28	0.56	11 (*SS*)	17	37 (*SS*)	60
2.	(*SS*) 37	0.74	13 (*SS*)	27	45 (*SS*)	46
3.	(*SS*) 45	0.90	4 (*SS*)	38	65 (*SS*)	47
4.	(*SS*) 65	1.30	15 (*SS*)	14	79 (*SS*)	60
5.	(*SS*) 79	1.58	18 (*SS*)	14	91 (*SS*)	60
6.	(*RR*) 30	0.60	8 (*RR*)	41	50 (*RR*)	41
7.	(*RR*) 50	1.00	7 (*RR*)	13	64 (*RR*)	60
8.	(*RR*) 64	1.28	8 (*RR*)	13	78 (*RR*)	68
9.	(*RR*) 78	1.56	48 (*RR*)	28	91 (*RR*)	57

a. The reactions were carried out using non-racemic diamine **117a** (2 mmol) and oxalic acid in acetone (5 mL) and the contents were stirred at 25 °C for 12 h.

b. All ee values reported are based on the maximum $[\alpha]_D^{25}$ = -31.85 (*c* 0.5, 1N HCl) obtained for the sample of (*R*,*R*)-**117a** with >99% ee, prepared following a reported procedure.[56a]

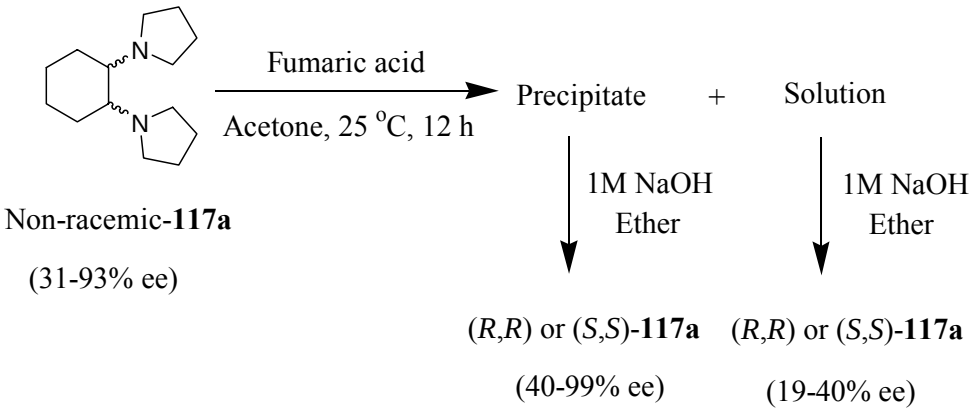
c. The yields are of the isolated products, based on the total amount of the starting non-racemic **117a** used.

Optimum results were obtained when oxalic acid was used in 1:1 molar amounts equivalent to the enantiomer present in excess in the starting non-racemic

samples; that is, when 2 mmol of 79% ee of the diamine **117a** was treated with 1.58 mmol of oxalic acid in acetone at 25 ^{o}C for 12 h, an enriched sample of the diamine with 91% ee was obtained from the filtrate fraction and a sample of 18% ee was obtained from the precipitate fraction (Table 6, entry 5).

We then examined the purification of the non-racemic 1,2-diamine **117a** using fumaric acid in acetone solvent (Scheme 46).

Scheme 46



Interestingly, in this case, it was observed that the enrichment of **117a** was observed in the precipitate fraction and samples of lower enantiomeric purity were obtained from the filtrate fraction. This is in contrast to the results obtained in the case of oxalic acid. The results are summarized in Table 7.

These results are in accordance with the precipitation of predominantly heterochiral aggregates (*RR*, *SS*, *RR*, *SS*…..) in the case of oxalic acid and homochiral aggregates (*RR*, *RR*….. or *SS*, *SS*…..) in the case of fumaric acid. As a result, enrichment is observed in the filtrate fraction in the case of oxalic acid, whereas in the case of fumaric acid enrichment is observed in the precipitate fraction.

Table 7. Enhancement of enantiomeric excess of the non-racemic diamine 117a using fumaric acid[a]

S. No	Substrate **117a** (% ee)	Fumaric acid	Diamine **117a** obtained from			
			Precipitate		Filtrate	
	(2 mmol)	(mmol)	%ee[b]/Conf.	Yield (%)[c]	%ee[b]/Conf.	Yield (%)[c]
1.	(*SS*) 31	0.62	40 (*SS*)	30	21 (*SS*)	51
2.	(*SS*) 40	0.80	60 (*SS*)	30	25 (*SS*)	51
3.	(*SS*) 60	1.20	74 (*SS*)	68	19 (*SS*)	27
4.	(*SS*) 74	1.48	91 (*SS*)	71	19 (*SS*)	15
5.	(*RR*) 42	0.84	59 (*RR*)	47	23 (*RR*)	52
6.	(*RR*) 59	1.18	78 (*RR*)	47	27 (*RR*)	40
7.	(*RR*) 78	1.56	93 (*RR*)	60	33 (*RR*)	20
8.	(*RR*) 93	1.86	99 (*RR*)	75	40 (*RR*)	10

a. The reactions were carried out using non-racemic diamine **117a** (2 mmol) and fumaric acid in acetone (5 mL) and the contents were stirred at 25 ^{o}C for 12 h.

b. All ee values reported are based on the maximum $[\alpha]_D^{25}$ = -31.85 (*c* 0.5, 1N HCl) obtained for the sample of (*R*,*R*)-**117a** with >99% ee, prepared following a reported procedure.[56a]

c. The yields are of the isolated products, based on the total amount of the starting non-racemic **117a** used.

This method is different from the previously reported co-crystallization techniques for the purification of certain non-racemic carboxylic acids,[74] because in these reported methods, the enantiomer present in excess invariably crystallizes out. In contrast, in the method described here, the purification is due to selective formation of predominantly homo- or heterochiral aggregates in the precipitate fractions (Schemes 45 and 46, Tables 6 and 7). This method is also different from the Horeau duplication[66] (Scheme 41) in which enhancement of ees of the crystallized samples is due to the statistical distribution of dimers derived from the enantiomers present in the mixture without any selectivity.

The non-racemic (*S*,*S*)-**117a** and fumaric acid complex (Table 7, entry 4) gave

single crystals suitable for X-ray analysis from the mixture of acetonitrile and methanol solvents (4:1) (Figure 4). The crystal structure data of the complex of the non-racemic (*S*,*S*)-**117a** and fumaric acid are summarized in Table 8 and Table A2 (Appendix II). The crystal structure revealed that the diamine and diacid formed a 1:1 complex and it is not a salt. The packing diagram shows that the diamine moieties are placed in between layers of the intermolecularly hydrogen bonded fumaric acid (1.66 Å) through three types of C-H···O interactions of the hydrogens of the pyrrolidine ring with the fumaric acid, the shortest (2.48 Å) being the hydrogen bond between the C-H α to the nitrogen and the oxygen atom of the carbonyl group of the fumaric acid moiety (Figure 5). The other two hydrogen bonds involve the C-H α' to the nitrogen and the oxygen of the hydroxyl group of the acid (2.55 Å); whereas the hydrogen on the carbon β to the nitrogen is hydrogen bonded to the carbonyl oxygen of the fumaric acid (2.56 Å).

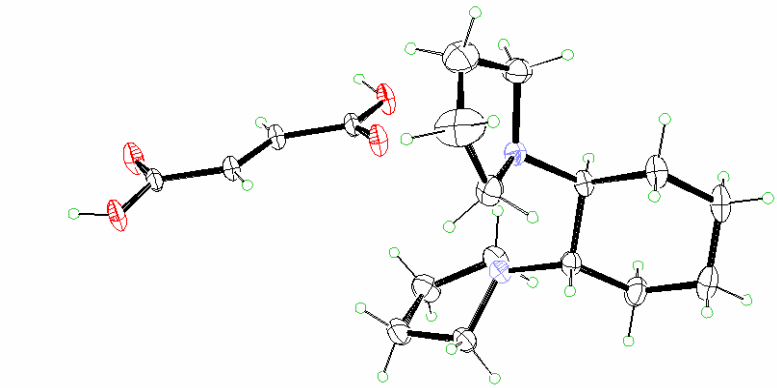


Figure 4. ORTEP diagram of the complex of non-racemic (*S*,*S*)-117a and fumaric acid

Presumably, the enantiomer present in excess in these cases forms hydrogen-bonded complexes with the achiral dicarboxylic acid spacer, and the selective packing

to obtain homochiral aggregates or heterochiral aggregates dictates the precipitation of homochiral or heterochiral aggregates from the solution.

Table 8. X-ray data and structure refinement for the non-racemic (*S*,*S*)-117a with fumaric acid

Empirical formula	$C_{18}\ H_{30}\ N_2\ O_4$
Formula weight	338.44
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	*P* 21
Unit cell dimensions	a = 7.792(4) Å, $\alpha = 90^o$
	b = 15.115(13) Å, $\beta = 98.12(6)^o$
	c = 8.009(9) Å, $\gamma = 90^o$
Volume	933.9(14) $Å^3$
Z	2
Calculated density	1.204 Mg/m^3
Absorption coefficient	0.085 mm^{-1}
F(000)	368
θ range for data collection	2.57 to 29.96^o
Limiting indices	$0 \leq h \leq 10$, $0 \leq k \leq 21$, $-11 \leq l \leq 11$
Reflections collected / unique	2801 / 2801 [R(int) = 0.0000]
Refinement method	full-matrix least-squares on F^2
Data / restraints / parameters	2801 / 1 / 219
Goodness-of-fit on F^2	1.025
Final R indices [$I>2\sigma(I)$]	$R_1 = 0.0549$, $wR_2 = 0.1323$
R indices (all data)	$R_1 = 0.0835$, $wR_2 = 0.1516$
Largest diff. peak and hole	0.284 and -0.264 $eÅ^{-3}$

Unfortunately, the crystals suitable for X-ray analysis could not be obtained with the complex of oxalic acid and the racemic or chiral diamine **117a**.

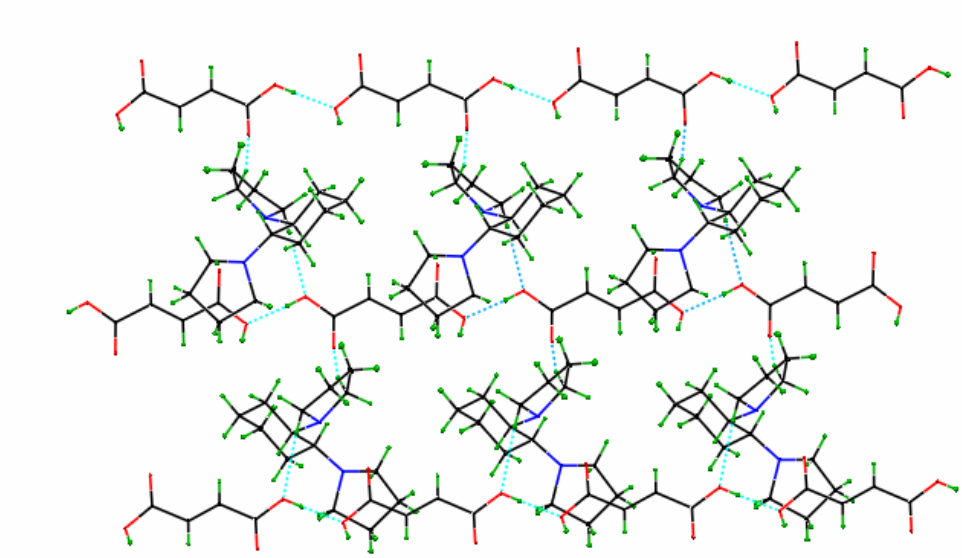


Figure 5. Packing diagram of the complex of the non-racemic (*S*,*S*)-117a and fumaric acid

We have also examined the purification of the non-racemic diamine **117a** using terephthalic acid. Here also, the samples of higher enantiomeric purity were obtained from the precipitate fraction, leaving behind the sample with lower ee in the solution (Scheme 47). The results are summarized in Table 9.

Scheme 47

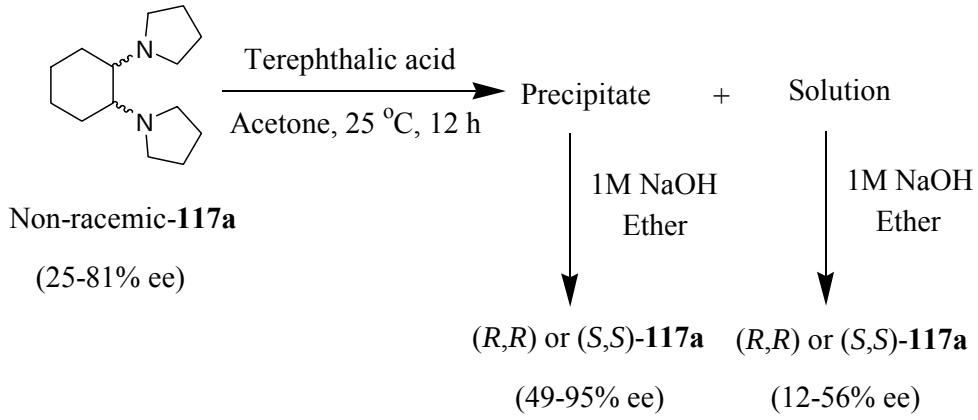


Table 9. Enhancement of enantiomeric excess of the non-racemic diamine 117a using terephthalic acid[a]

S. No	Substrate **117a** (% ee)	Terephtha -lic acid	Diamine **117a** obtained from			
			Precipitate		Filtrate	
	(2 mmol)	(mmol)	%ee[b]/Conf.	Yield (%)[c]	%ee[b]/Conf.	Yield (%)[c]
1.	(*SS*) 38	0.76	53 (*SS*)	21	21 (*SS*)	62
2.	(*SS*) 53	1.06	75 (*SS*)	30	25 (*SS*)	55
3.	(*SS*) 75	1.50	88 (*SS*)	63	50 (*SS*)	21
4.	(*RR*) 25	0.50	49 (*RR*)	25	12 (*RR*)	60
5.	(*RR*) 49	0.98	81 (*RR*)	30	31 (*RR*)	50
6.	(*RR*) 81	1.62	95 (*RR*)	48	56 (*RR*)	36

a. The reactions were carried out using non-racemic diamine **117a** (2 mmol) and terephthalic acid in acetone (5 mL) and the contents were stirred at 25 ^{o}C for 12 h.

b. All ee values reported are based on the maximum $[\alpha]_D^{25}$ = -31.85 (*c* 0.5, 1N HCl) obtained for the sample of (*R*,*R*)-**117a** with >99% ee, prepared following a reported procedure.[56a]

c. The yields are of the isolated products, based on the total amount of the starting non-racemic **117a** used.

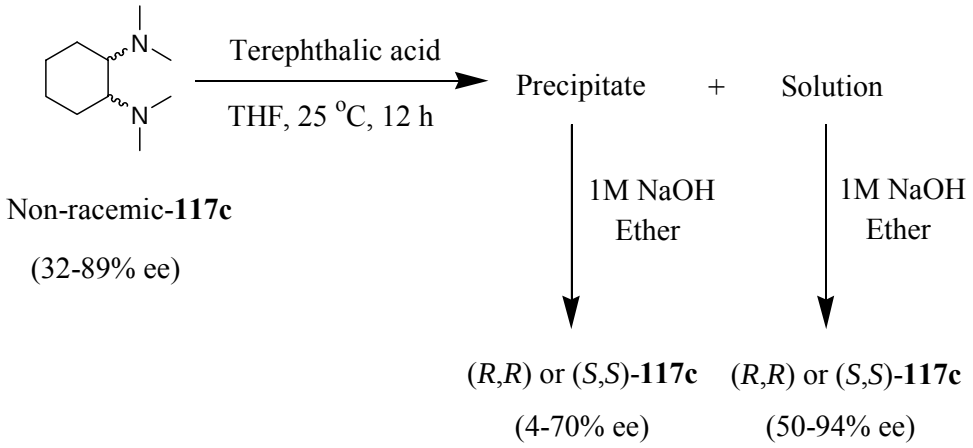
The complex of the diamine **117a** with terephthalic acid could not be crystallized from the solvents acetonitrile, ethanol, methanol and THF.

1.2.4.2 Enhancement of enantiomeric purity of the non-racemic 1,2-diamine 117c using terephthalic acid

We have also undertaken efforts for the purification of the non-racemic diamine **117c** using oxalic, fumaric and terephthalic acids. The results are summarized in Table 10. It was observed that with oxalic and fumaric acids, there was no enrichment either in the precipitate fraction or in the filtrate fraction, instead only a distribution was observed (Table 10 entries 1-4). However, when the diamine **117c** was treated with terephthalic acid in THF solvent, the samples with higher enantiomeric purity were

obtained from the filtrate fraction (Scheme 48). This observation is in contrast to the results obtained for the diamine **117a** with terephthalic acid.

Scheme 48



When the non-racemic **117c** and terephthalic acid were used in 1:1 ratio, there was no enrichment in the ee of the diamine (Table 10, entry 5). Enrichment was observed when terephthalic acid was used in equivalent amount to the enantiomer present in excess. As the enrichment is observed in the filtrate fraction indicating the precipitation of heterochiral aggregates, we attempted to precipitate out the racemic sample from the mixture by using terephthalic acid equivalent to the amount of the racemic diamine present in the starting non-racemic sample (Table 10, entries 11-12). It was observed that for lower ee of the diamine there was only a slight improvement in the enhancement (Table 10, entry 11). However, for higher ee samples enrichment was not observed at all (Table 10, entry 12). Further systematic study of this concept using various diamine derivatives should throw light on the phenomenon involved in the enrichment of non-racemic samples.

Table 10. Reaction of the non-racemic diamine 117c with oxalic, fumaric and terephthalic acids[a]

S. No.	Substrate **117c** (% ee)	Diacid[b]	Diamine **117c** obtained from			
			Precipitate		Filtrate	
	(3 mmol)	(mmol)	%ee[c]/Conf.	Yield (%)[d]	%ee[c]/Conf.	Yield (%)[d]
1.	(*RR*) 60	OA, 1.80	56 (*RR*)	37	69 (*RR*)	47
2.	(*RR*) 69	OA, 2.07	68 (*RR*)	24	74 (*RR*)	50
3.	(*RR*) 58	FA, 1.74	59 (*RR*)	34	65 (*RR*)	42
4.	(*RR*) 65	FA, 1.95	65 (*RR*)	47	68 (*RR*)	29
5.	(*RR*) 40	TA, 3.00	38 (*RR*)	78	19 (*RR*)	10
6.	(*SS*) 32	TA, 0.96	4 (*SS*)	17	50 (*SS*)	65
7.	(*SS*) 50	TA, 1.50	17 (*SS*)	36	67 (*SS*)	50
8.	(*SS*) 67	TA, 2.00	53 (*SS*)	29	84 (*SS*)	52
9.	(*RR*) 41	TA, 1.23	8 (*RR*)	24	57 (*RR*)	74
10.	(*RR*) 57	TA, 1.71	38 (*RR*)	45	76 (*RR*)	36
11.	(*RR*) 35	TA, 1.95	7 (*RR*)	40	56 (*RR*)	32
12.	(*RR*) 76	TA, 0.72	67 (*RR*)	9	74 (*RR*)	70
13.	(*RR*) 76	TA, 2.28	70 (*RR*)	54	89 (*RR*)	20
14.	(*RR*) 89	TA, 2.67	58 (*RR*)	10	94 (*RR*)	70

a. The reactions were carried out using non-racemic diamine **117c** (3 mmol) and diacid in THF (15 mL) and the contents were stirred at 25 ^{o}C for 12 h.

b. OA = oxalic acid; FA = fumaric acid; TA = terephthalic acid.

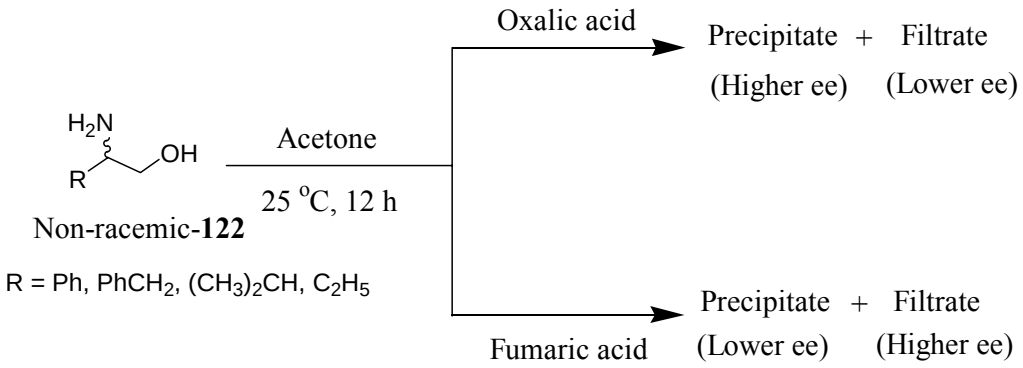
c. All ee values reported are based on the maximum $[\alpha]_D^{25}$ = -60.6 (*c* 1, $CHCl_3$) obtained for the sample of (*R*,*R*)-**117c** with >99% ee, prepared following a reported procedure.[56b]

d. The yields are of the isolated products, based on the total amount of the starting non-racemic **117c** used.

This concept was also applied in this laboratory for the enrichment of non-racemic 1,2-amino alcohols **122** using oxalic and fumaric acids.[73] The results obtained with the amino alcohols are different from those obtained with the diamine **117a**. Whereas the use of oxalic acid resulted in samples of higher ees in the precipitate

fraction, samples of higher ees were obtained in the filtrate fraction using fumaric acid (Scheme 49).

Scheme 49



The results discussed here may have relevance to the concept of chemical evolution of homogeneity of chirality in Nature through amplification of small amounts of non-racemic materials that could have formed by chance.[58,75] Furthermore, the methods of purification of the non-racemic diamines using inexpensive achiral reagents described here should find applications in large-scale synthetic operations to purify partially resolved chiral compounds.

1.3 Conclusions

Racemic C_2-symmetric derivatives of 1,2-diaminocyclohexane **117a-c** were synthesized by the sequential opening of cyclohexene oxide and the corresponding aziridinium ions using various amine nucleophiles. The diamines **117a** and **117c** were partially resolved using dibenzoyl-*L*-tartaric acid and chiral 1,1′-bi-2-naphthol, respectively. A conceptual methodology was developed for the enhancement of enantiomeric purity of the non-racemic samples of 1,2-diamines **117a** and **117c** using achiral dicarboxylic acids like oxalic, fumaric and terephthalic acids by the formation of hydrogen bonded homochiral and heterochiral aggregates.

1.4 Experimental Section

1. 4. 1 General Information

Melting points reported in this thesis are uncorrected and were determined using a Superfit capillary point apparatus. IR (KBr) spectra were recorded on JASCO FT-IR spectrophotometer Model 5300 and the neat IR spectra were recorded on SHIMADZU FT-IR spectrophotometer Model 8300 with polystyrene as reference. ^{1}H-NMR (200 MHz), ^{13}C-NMR (50 MHz) and ^{1}H-NMR (400 MHz), ^{13}C-NMR (100 MHz) were recorded on Bruker-AC-200 and Bruker-Avance-400 spectrometers respectively with chloroform-d, methanol-d_4 and water-d_2 as solvents. Tetramethylsilane was used as a reference (δ = 0 ppm) for chloroform-d and methanol-d_4 and sodium-3-(trimethylsilyl)propionate-2,2,3,3-d_4 (TSP) was used as reference (δ = 0 ppm) for water-d_2. The chemical shifts are expressed in δ downfield from the signal of internal tetramethyl silane. Elemental analyses were carried out using a Perkin-Elmer elemental analyzer model-240 C and Thermo Finnigan analyzer series Flash EA 1112. Analytical thin layer chromatographic tests were carried out on glass plates (3 x 10 cm) coated with 250 mμ acme's silica gel-G, GF_{254} and HF_{254} containing 13% calcium sulfate as binder. The spots were visualized by short exposure to iodine vapour or UV light. Column chromatography was carried out using Acme's silica gel (100-200 mesh and 60-120 mesh) and Acme's neutral alumina.

All the glassware were pre-dried at 140 ^{o}C in an air-oven for 6 h, assembled hot and cooled under a stream of dry nitrogen. Unless, otherwise mentioned, all the

operations and transformations of reagents were carried out using standard syringe, septum technique recommended for handling air sensitive organometallic compounds. Reagents prepared *in situ* in solvents were transformed using a double-ended stainless steel (Aldrich) needle under a stream 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 were used. The outlet of the mercury bubbler was connected by a long tube to the atmosphere. All dry solvents and reagents (liquids) used were distilled from appropriate drying agents. As a routine practice, all organic extracts were concentrated on Heidolph-EL-rotary evaporator. All yields reported are isolated yields of materials judged homogeneous by TLC, IR and NMR spectroscopy. Optical rotations were measured in a Rudolph Research AUTOPOL-II automatic polarimeter (readability $\pm 0.01^{o}$) or Rudolph Research Analytical AUTOPOL-IV automatic polarimeter (readability $\pm 0.001^{o}$). 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).

Benzene and toluene were distilled over sodium-benzophenone ketyl. THF supplied by E Merck (India), was kept over sodium-benzophenone ketyl and freshly distilled before use. Methanol and ethanol supplied by Ranbaxy were distilled over CaO before use. Dichloromethane and chloroform were distilled over CaH_2 and dried over molecular sieves (4 Å). $NaBH_4$ was purchased from Lancaster Synthesis Ltd., UK. Iodine supplied by E Merck, India was used. Dibenzoyl-*L*-tartaric acid was

supplied by Fluka, Switzerland. Oxalic, fumaric and terephthalic acids were supplied by E Merck (India).

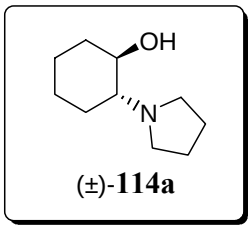
The X-ray diffraction measurements for the complex of **117a** with fumaric acid were carried out at 293 K on an automated Enraf-Nonius MACH 3 diffractometer using graphite monochromated, Mo-Kα (λ = 0.71073 Å) radiation with CAD4 software. The single crystal was fixed to a capillary head by an appropriate fixing material. Primary unit cell constants were determined with a set of 25 narrow frame scans. Intensity data were collected by the ω scan mode. Stability of the crystal during the measurement was monitored by measuring the intensity of the three standard reflections after every one and half hour intervals. No appreciable variation of the crystal was detected. X-ray diffraction measurements for the complex of the compound **117c** with (*S*)-binaphthol **120a** were carried out at 293 K on Bruker-Nonius SMART APEX CCD area detector system. The data were reduced using XTAL or SAINT programme[76] without applying absorption correction. The structure was solved by direct methods and refined by full-matrix least-squares procedure using the SHELXS-86[77] and SHELXL-93[78] program packages respectively.

1.4.2 General procedure for the ring opening of cyclohexene oxide 31 with secondary amines

A mixture of cyclohexene oxide and the secondary amine was refluxed for 48 h and the product was distilled under reduced pressure to obtain the *trans*-(±)-2-(*N*,*N*-dialkylamino)cyclohexanol. In the case of the aromatic secondary amine nucleophile, the amino alcohol was chromatographed on a silica gel column using hexanes:ethyl acetate as eluent.

***trans*-(±)-2-(Pyrrolidinyl)cyclohexanol 114a**

Cyclohexene oxide (19.6 g, 20.0 mL, 200 mmol) and pyrrolidine (14.2 g, 16.6 mL, 200 mmol) were used.



(±)-**114a**

Yield	30.4 g (90%)
bp	76 ^{o}C/0.25 mm Hg; [lit.[53a] bp: 130 ^{o}C/5 mm Hg]
IR (neat)	(cm^{-1}) 3454, 2932, 2858, 1450, 1078
^{1}H-NMR	(200 MHz, $CDCl_3$, δ ppm) 1.16-1.25 (m, 4H), 1.60-1.78 (m, 7H), 2.04-2.10 (m, 1H), 2.35-2.70 (m, 5H), 3.20-3.40 (m, 1H), 3.83 (br s, 1H)
^{13}C-NMR	(50 MHz, $CDCl_3$, δ ppm) 21.2, 23.6, 24.2, 25.3, 33.3, 47.2, 65.0, 70.7

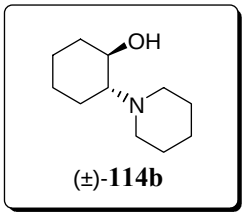
***trans*-(±)-2-(Piperidinyl)cyclohexanol 114b**

Cyclohexene oxide (19.6 g, 20.0 mL, 200 mmol) and piperidine (17.0 g, 19.7 mL, 200 mmol) were used.

Yield	31.0 g (85%)

bp 72-74 °C/0.2 mm Hg; [lit.[53b] bp: 70-72 °C /0.2 mm Hg]

IR (neat) (cm^{-1}) 3447, 2932, 2856, 1452, 1082



(±)-**114b**

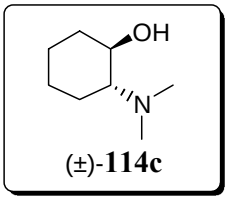
^{1}H-NMR (200 MHz, $CDCl_3$, δ ppm)
0.80-0.92 (m, 4H), 1.10-1.47 (m, 9H), 1.80-1.84 (m, 2H), 2.30-2.45 (m, 2H), 2.30-2.39 (m, 2H), 2.95-3.15 (m, 1H), 3.62 (s, 1H)

^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm) 21.9, 23.9, 24.6, 25.4, 26.5, 33.1, 49.4, 68.2, 70.8

***trans*-(±)-2-(*N*,*N*-dimethylamino)cyclohexanol 114c**

Cyclohexene oxide (4.9 g, 5.0 mL, 50 mmol) and aqueous dimethylamine (40%, 44 mL, 400 mmol) were used.

Yield 5.7 g (80%)



(±)-**114c**

bp 64 °C/0.25 mm Hg

IR (neat) (cm^{-1}) 3460, 2934, 1452, 1082

^{1}H-NMR (200 MHz, $CDCl_3$, δ ppm) 1.05-1.20 (m, 4H), 1.66-1.74 (m, 3H), 2.06-2.16 (m, 2H), 2.22 (s, 6H), 3.26-3.31 (m, 1H), 3.90 (brs,1H)

^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm) 20.4, 24.1, 25.3, 33.2, 40.2, 69.3, 69.6

***trans*-(±)-2-(*N*-methyl-*N*-phenyl)cyclohexanol 114d**

Cyclohexene oxide (2.4 g, 2.5 mL, 25 mmol) and *N*-methylaniline (2.6 g, 2.7 mL, 25 mmol) were used.

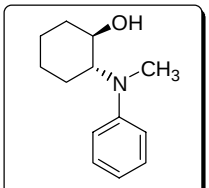
Yield 0.76 g (15%)

IR (neat) (cm^{-1}) 3419, 3058, 2929, 1596, 1504, 1033, 748

^{1}H-NMR (200 MHz, $CDCl_3$, δ ppm) 1.20-1.50 (m, 5H), 1.70-1.88 (m, 4H),

2.78 (s, 3H), 3.40-3.50 (m, 1H), 3.65-3.80 (m, 1H), 6.80-7.00 (m, 3H), 7.30 (t, *J* = 8 Hz, 2H)

^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm) 24.4, 25.5, 26.1, 31.1, 33.5, 66.9, 70.1, 115.6, 118.5, 129.0, 151.4



(±)-**114d**

***trans*-(±)-2-(*N*-ethyl-*N*-phenyl)cyclohexanol 114e**

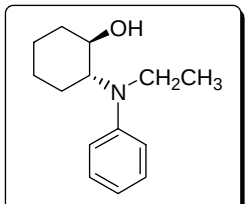
Cyclohexene oxide (2.4 g, 2.5 mL, 25 mmol) and *N*-ethylaniline (3.0 g, 3.1 mL, 25 mmol) were used.

Yield 0.54 g (10%)

IR (neat) (cm^{-1}) 3440, 3058, 2931, 1596, 1500, 746

^{1}H-NMR (200 MHz, $CDCl_3$, δ ppm)

1.19 (t, *J* = 8 Hz, 2H), 1.27-1.42 (m, 5H), 1.74-1.80 (m, 5H), 3.00 (s, 1H), 3.26 (q, *J* = 8 Hz, 2H), 3.60-3.70 (m, 1H), 6.84-6.99 (m, 3H), 7.24-7.31 (m, 2H)



(±)-**114e**

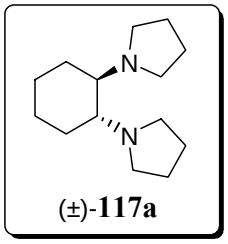
^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm) 14.5, 24.3, 25.6, 26.8, 33.5, 38.7, 67.5, 70.4, 117.2, 118.9, 129.0, 149.3

1.4.3 Reaction of *trans*-(±)-1,2-amino alcohols with amine nucleophiles

1.4.3.1 Synthesis of *trans*-(±)-1,2-bis-(pyrrolidino)cyclohexane 117a

trans-(±)-2-(Pyrrolidinyl)cyclohexanol **114a** (5.0 g, 30 mmol) was taken in dry THF (100 mL) and triethylamine (12.6 mL, 90 mmol) was added and the solution was cooled to 0 ^{o}C. To this, methanesulfonyl chloride (2.8 mL, 36 mmol) was added. The reaction mixture was stirred at 25 ^{o}C for 6 h and triethylamine (8.3 mL, 60 mmol) was added. After stirring at 25 ^{o}C for further 2 h, pyrrolidine (7.5 mL) and water (20 mL) were added and the resulting two-phase reaction mixture was refluxed for 48 h. The

contents were brought to 25 ^{o}C and the layers were separated and the aqueous layer was extracted with ether (2 X 25 mL). The combined organic extract was washed with 5% aqueous $NaHCO_3$ (25 mL), water (25 mL), brine (15 mL) and dried over anhydrous sodium sulfate. The solvent was removed and the crude product was purified on a silica gel column using hexanes as eluent.



(±)-**117a**

Yield 5.3 g (80%)

IR (neat) (cm^{-1}) 2962, 2935, 1446,

^{1}H-NMR (200 MHz, $CDCl_3$, δ ppm)

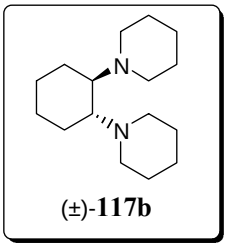
1.29-1.85 (m, 16H), 2.27 (m, 2H),

2.51-2.52 (m, 8H) (**Spectrum No. 1**)

^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm) 21.7, 23.4, 25.2, 51.0, 62.8 (**Spectrum No. 2**)

1.4.3.2 Synthesis of *trans*-(±)-1,2-bis-(piperidino)cyclohexane 117b

The compound **117b** was prepared using *trans*-(±)-2-(piperidinyl)cyclohexanol **114b** (5.6 g, 30 mmol), triethylamine (12.6 mL, 90 mmol), methanesulfonyl chloride (2.8 mL, 36 mmol) and piperidine (12.0 mL) following the procedure described in experiment 1.4.3.1. After workup, the crude product was purified on a silica gel column using hexanes:ethyl acetate (99:1) as eluent.



(±)-**117b**

Yield 5.6 g (75%)

IR (neat) (cm^{-1}) 2924, 1442, 1107

^{1}H-NMR (200 MHz, $CDCl_3$, δ ppm)

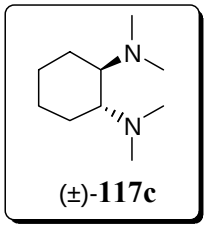
1.09-1.15 (m, 4H), 1.40-1.50 (m, 12H),

1.63-1.75 (m, 4H), 2.32-2.37 (m, 2H), 2.56-2.65 (m, 8H) (**Spectrum No. 3**)

^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm) 25.3, 26.0, 27.1, 27.8, 49.9, 65.1 (**Spectrum No. 4**)

1.4.3.3 Synthesis of *trans*-(±)-1,2-bis-(*N*,*N*-dimethylamino)cyclohexane 117c

The compound **117c** was prepared using *trans*-(±)-2-(*N*,*N*-dimethylamino)cyclohexanol **114c** (4.4 g, 30 mmol), triethylamine (12.6 mL, 90 mmol), methanesulfonyl chloride (2.8 mL, 36 mmol) and aqueous dimethylamine (40%, 50 mL) following the procedure described in experiment 1.4.3.1. After workup, the residue was distilled under reduced pressure to obtain pure **117c**.



(±)-**117c**

Yield 3.0 g (60%)

bp 65 ^{o}C/2 mm Hg

IR (neat) (cm^{-1}) 2939, 1458, 1361

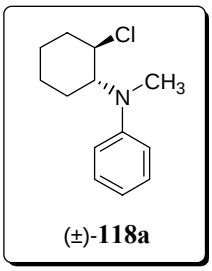
^{1}H-NMR (200 MHz, $CDCl_3$, δ ppm) 1.07-1.15 (m, 4H), 1.72-1.80 (m, 2H), 1.90-2.00 (m, 2H), 2.26 (s, 12H), 2.37-2.40 (m, 2H) (**Spectrum No.5**)

^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm) 22.9, 25.5, 40.1, 63.8 (**Spectrum No.6**)

1.4.3.4 Synthesis of *trans*-(±)-1-chloro-2-(*N*-methyl-*N*-phenyl)cyclohexane 118a

The compound **118a** was prepared using *trans*-(±)-2-(*N*-methyl-*N*-phenyl)cyclohexanol **114d** (2.0 g, 10 mmol), triethylamine (4.2 mL, 30 mmol), methanesulfonyl chloride (0.90 mL, 12 mmol) and *N*-methylaniline (1.3 mL) following

the procedure described in experiment 1.4.3.1. After workup, the crude product was chromatographed on a silica gel column using hexanes:ethyl acetate (95:5) as eluent.



(±)-**118a**

Yield 0.22 g (10%)

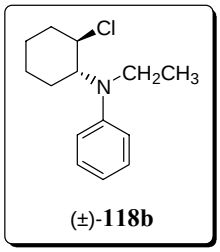
IR (neat) (cm^{-1}) 3025, 2930, 1590, 746

^{1}H-NMR (200 MHz, $CDCl_3$, δ ppm) 1.37-1.56 (m, 3H), 1.87-2.00 (m, 4H), 2.40-2.49 (m, 1H), 2.88 (s, 3H), 3.70-3.83 (m, 1H), 4.00-4.14 (m, 1H), 6.77-6.90 (m, 3H), 7.33 (t, *J* = 4 Hz, 2H)

^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm) 25.2, 26.2, 29.6, 30.6, 37.5, 61.5, 65.0, 113.6, 117.0, 129.1, 150.6

1.4.3.5 Synthesis of *trans*-(±)-1-chloro-2-(*N*-ethyl-*N*-phenyl)cyclohexane 118b

The compound **118b** was prepared using *trans*-(±)-2-(*N*-ethyl-*N*-phenyl)cyclohexanol **114e** (2.2 g, 10 mmol), triethylamine (4.2 mL, 30 mmol), methanesulfonyl chloride (0.90 mL, 12 mmol) and *N*-ethylaniline (1.4 mL) following the procedure described in experiment 1.4.3.1. After workup, the crude product was chromatographed on a silica gel column using hexanes:ethyl acetate (95:5) as eluent.



(±)-**118b**

Yield 0.19 g (8%)

IR (neat) (cm^{-1}) 3022, 2935, 1596, 1500, 746

^{1}H-NMR (200 MHz, $CDCl_3$, δ ppm) 1.30 (t, *J* = 8 Hz, 2H), 1.35-2.05 (m, 6H), 2.34-2.50 (m, 1H), 3.25-3.45 (m, 3H), 3.60-3.80 (m, 2H), 3.95-4.10 (m, 1H), 6.70-6.90 (m, 3H), 7.20-7.30 (m, 2H)

^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm) 14.0, 25.4, 26.1, 30.6, 37.6, 38.2, 61.8, 65.3, 114.5, 116.9, 129.0, 148.6

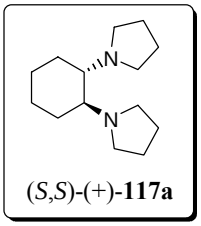
1.4.4 Resolution of *trans*-(±)-1,2-diamines

1.4.4.1 Resolution of *trans*-(±)-1,2-bis-(pyrrolidino)cyclohexane 117a using dibenzoyl-*L*-tartaric acid 119

The dibenzoyl-*L*-tartaric acid **119** (0.35 g, 1 mmol) and the racemic 1,2-bis-(pyrrolidino)cyclohexane **117a** (0.44 g, 2 mmol) were taken in acetone (15 mL) and the contents were stirred at 25 ^{o}C for 12 h and filtered. The precipitate was suspended in a mixture of ether (20 mL) and 2M NaOH (10 mL) and stirred until dissolution occurred. The organic layer was separated and the aqueous layer was extracted with ether (2 X 10 mL). The combined organic extract was washed with brine (10 mL), dried over anhydrous sodium sulfate and the solvent was evaporated to dryness to obtain the enriched (*S*,*S*)-(+)-**117a**. The filtrate was concentrated and the residue was digested with ether (20 mL) and 2M NaOH (10 mL). The organic layer was separated and the aqueous layer was extracted with ether (2 X 10 mL). The combined organic extract was washed with brine (10 mL), dried over anhydrous sodium sulfate and the solvent was evaporated to obtain the enriched (*R*,*R*)-(-)-**117a**.

After decomposition

From precipitate



(*S*,*S*)-(+)-**117a**

Yield 0.17 g (40%)

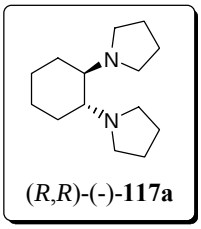
$[\alpha]_D^{25}$ +24.2 (*c* 1, 1N HCl), based on $[\alpha]_D^{25}$ = -31.85 (*c* 0.5, 1N HCl) for a sample of (*R*, *R*)-**117a** obtained

from the sample of (*R*,*R*)-**35** with >99% ee, following a reported procedure[56a]

From filtrate

Yield 0.22 g (50%)

$[\alpha]_D^{25}$ -15.6 (*c* 1, 1N HCl), based on $[\alpha]_D^{25}$ = -31.85 (*c* 0.5, 1N HCl) for a sample of (*R*,*R*)-**117a** obtained from the sample of (*R*,*R*)-**35** with >99% ee, following a reported procedure[56a]



(*R*,*R*)-(-)-**117a**

1.4.4.2 Purification of partially resolved 1,2-bis-(pyrrolidino)cyclohexane 117a using dibenzoyl-*L*-tartaric acid 119

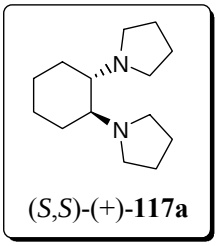
The procedure outlined in experiment 1.4.4.1 was followed for the purification of partially resolved (*S*,*S*)-1,2-bis-(pyrrolidino)cyclohexane **117a** (76% ee, 0.44 g, 2 mmol) using dibenzoyl-*L*-tartaric acid **119** (0.35 g, 1 mmol) in acetone (15 mL). The enriched (*S*,*S*)-(+)-**117a** was obtained from the precipitate and the (*S*,*S*)-(+)-**117a** with lower ee was obtained from the filtrate.

After decomposition

From precipitate

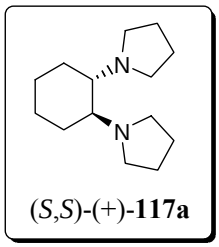
Yield 0.22 g (50%)

$[\alpha]_D^{25}$ +30.5 (*c* 1, 1N HCl), based on $[\alpha]_D^{25}$ = -31.85 (*c* 0.5, 1N HCl) for a sample of (*R*,*R*)-**117a** obtained from the sample of (*R*,*R*)-**35** with >99% ee, following a reported procedure[56a]



(*S*,*S*)-(+)-**117a**

From filtrate


(*S*,*S*)-(+)-**117a**

Yield 0.13 g (30%)

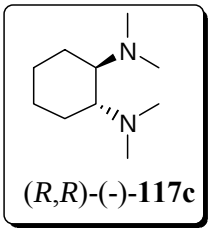
$[\alpha]_D^{25}$ +12.7 (*c* 1, 1N HCl), based on $[\alpha]_D^{25}$ = -31.85 (*c* 0.5, 1N HCl) for a sample of (*R*,*R*)-**117a** obtained from the sample of (*R*,*R*)-**35** with >99% ee, following a reported procedure[56a]

1.4.4.3 Resolution of *trans*-(±)-1,2-bis-(*N*,*N*-dimethylamino)cyclohexane 117c using (*S*)-(-)-1,1′-bi-2-naphthol 120a

The (*S*)-(-)-1,1′-bi-2-naphthol **120a** (0.42 g, 1.5 mmol) and the racemic 1,2-bis-(*N*,*N*-dimethylamino)cyclohexane **117c** (0.51 g, 3 mmol) were taken in acetonitrile (15 mL) and the contents were stirred at 25 ^oC for 12 h and filtered. The precipitate was suspended in a mixture of ether (20 mL) and 2M HCl (10 mL) and stirred until dissolution occurred. The (*S*)-(-)-1,1′-bi-2-naphthol **120a** (90%) was recovered from the ether layer. The aqueous layer was treated with 2M NaOH (10 mL) and the free diamine was extracted with ether (2 X 10 mL). The combined organic extract was washed with brine (10 mL), dried over anhydrous sodium sulfate and the solvent was evaporated to obtain the enriched (*R*,*R*)-(-)-**117c**. The filtrate was concentrated and the residue was digested with a mixture of ether (20 mL) and 2M HCl (10 mL). After workup as outlined above, the (*S*,*S*)-(+)-**117c** was obtained.

After decomposition

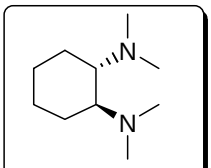
From precipitate


(*R*,*R*)-(-)-**117c**

Yield 0.18 g (35%)

$[\alpha]_D^{25}$ -36.9 (*c* 1, $CHCl_3$), based on $[\alpha]_D^{25}$ = -60.6 (*c* 1, $CHCl_3$) for a sample of (*R*,*R*)-**117c** obtained from the sample of (*R*,*R*)-**35** with >99% ee, following a reported procedure[56b]

From filtrate


(*S*,*S*)-(+)-**117c**

Yield 0.25 g (50%)

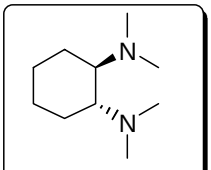
$[\alpha]_D^{25}$ +3.0 (*c* 1, $CHCl_3$), based on $[\alpha]_D^{25}$ = -60.6 (*c* 1, $CHCl_3$) for a sample of (*R*,*R*)-**117c** obtained from the sample of (*R*,*R*)-**35** with >99% ee, following a reported procedure[56b]

1.4.4.4 Purification of partially resolved 1,2-bis-(*N*,*N*-dimethylamino)cyclohexane 117c using (*S*)-(-)-1,1′-bi-2-naphthol 120a

The procedure outlined in experiment 1.4.4.3 was followed for the purification of partially resolved (*R*,*R*)-(-)-1,2-bis-(*N*,*N*-dimethylamino)cyclohexane **117c** (61% ee, 0.51 g, 3 mmol) using (*S*)-(-)-1,1′-bi-2-naphthol **120a** (0.42 g, 1.5 mmol) in acetonitrile (15 mL). The enriched (*R*,*R*)-(-)-**117c** was obtained from the precipitate and the (*R*,*R*)-(-)-**117c** with lower ee was obtained from the filtrate.

After decomposition

From precipitate

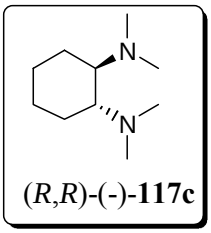

(*R*,*R*)-(-)-**117c**

Yield 0.15 g (30%)

$[\alpha]_D^{25}$ -55.7 (*c* 1, $CHCl_3$), based on $[\alpha]_D^{25}$ = -60.6 (*c* 1, $CHCl_3$) for a sample of (*R*,*R*)-**117c** obtained from the sample of (*R*,*R*)-**35** with >99% ee, following a reported procedure[56b]

From filtrate

Yield 0.23 g (46%)


(*R*,*R*)-(-)-**117c**

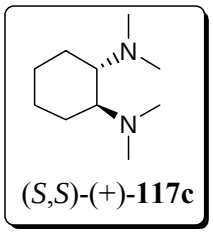
$[\alpha]_D^{25}$ -33.3 (*c* 1, $CHCl_3$), based on $[\alpha]_D^{25}$ = -60.6 (*c* 1, $CHCl_3$) for a sample of (*R*,*R*)-**117c** obtained from the sample of (*R*,*R*)-**35** with >99% ee, following a reported procedure[56b]

1.4.4.5 Resolution of *trans*-(±)-1,2-bis-(*N*,*N*-dimethylamino)cyclohexane 117c using (*R*)-(+)-1,1′-bi-2-naphthol 120b

The procedure outlined in experiment 1.4.4.3 was followed for the resolution of the racemic 1,2-bis-(*N*,*N*-dimethylamino)cyclohexane **117c** (0.51 g, 3 mmol) using (*R*)-(+)-1,1′-bi-2-naphthol **120b** (0.42 g, 1.5 mmol) in acetonitrile (15 mL). The enriched (*S*,*S*)-(+)-**117c** was obtained from the precipitate and the (*R*,*R*)-(-)-**117c** was obtained from the filtrate.

After decomposition

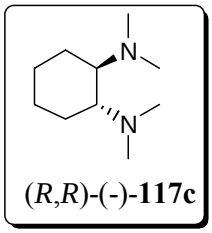
From precipitate


(*S*,*S*)-(+)-**117c**

Yield 0.12 g (25%)

$[\alpha]_D^{25}$ +34.5 (*c* 1, $CHCl_3$), based on $[\alpha]_D^{25}$ = -60.6 (*c* 1, $CHCl_3$) for a sample of (*R*,*R*)-**117c** obtained from the sample of (*R*,*R*)-**35** with >99% ee, following a reported procedure[56b]

From filtrate


(*R*,*R*)-(-)-**117c**

Yield 0.30 g (60%)

$[\alpha]_D^{25}$ -9.6 (*c* 1, $CHCl_3$), based on

$[\alpha]_D^{25}$ = -60.6 (*c* 1, $CHCl_3$) for a sample of (*R*,*R*)-**117c** obtained from the sample of (*R*,*R*)-**35** with >99% ee, following a reported procedure[56b]

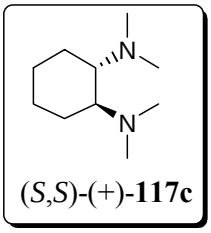
1.4.4.6 Purification of partially resolved 1,2-bis-(*N*,*N*-dimethylamino)cyclohexane 117c using (*R*)-(+)-1,1′-bi-2-naphthol 120b

The procedure outlined in experiment 1.4.4.3 was followed for the purification of the partially resolved (*S*,*S*)-(+)-1,2-bis-(*N*,*N*-dimethylamino)cyclohexane **117c** (57% ee, 0.51 g, 3 mmol) using (*R*)-(+)-1,1′-bi-2-naphthol **120b** (0.42 g, 1.5 mmol) in acetonitrile (15 mL). The enriched (*S*,*S*)-(+)-**117c** was obtained from the precipitate and the (*S*,*S*)-(+)-**117c** with lower ee was obtained from the filtrate.

After decomposition

From precipitate

Yield 0.15 g (30%)

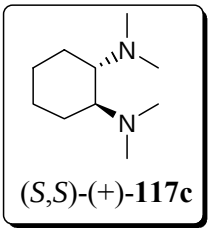


(*S*,*S*)-(+)-**117c**

$[\alpha]_D^{25}$ +54.5 (*c* 1, $CHCl_3$), based on $[\alpha]_D^{25}$ = -60.6 (*c* 1, $CHCl_3$) for a sample of (*R*,*R*)-**117c** obtained from the sample of (*R*,*R*)-**35** with >99% ee, following a reported procedure[56b]

From filtrate

Yield 0.25 g (50%)



(*S*,*S*)-(+)-**117c**

$[\alpha]_D^{25}$ +4.2 (*c* 1, $CHCl_3$), based on $[\alpha]_D^{25}$ = -60.6 (*c* 1, $CHCl_3$) for a sample of (*R*,*R*)-**117c** obtained from the sample of (*R*,*R*)-**35** with >99% ee, following a reported procedure[56b]

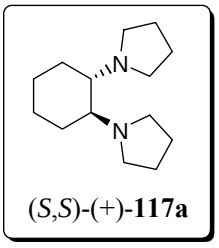
1.4.5 Enhancement of enantiomeric purity of non-racemic 1,2-bis-(pyrrolidino) cyclohexane 117a and 1,2-bis-(*N*,*N*-dimethylamino)cyclohexane 117c using achiral dicarboxylic acids

1.4.5.1 Purificaton of non-racemic 1,2-bis-(pyrrolidino)cyclohexane 117a using oxalic acid

The partially resolved (*S*,*S*)-(+)-1,2-bis-(pyrrolidino)cyclohexane **117a** (79% ee, 0.44 g, 2 mmol) was taken in acetone (5 mL), to this oxalic acid (0.14 g, 1.58 mmol) was added and the contents were stirred at 25 ^{o}C for 12 h and filtered. The filtrate was concentrated and the residue was suspended in a mixture of diethyl ether (20 mL) and 1M NaOH (10 mL) and stirred until dissolution occurred. The organic layer was separated and the aqueous layer was extracted with diethyl ether (2 X 10 mL). The combined organic extract was washed with brine (10 mL), dried over anhydrous sodium sulfate and the solvent was evaporated to obtain the enriched sample of (*S*,*S*)-(+)-**117a**. The precipitate was taken in diethyl ether (20 mL) and digested with 1M NaOH (10 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (2 X 10 mL). The combined organic extract was washed with brine (10 mL), dried over anhydrous sodium sulfate and the solvent was evaporated to obtain the sample of (*S*,*S*)-(+)-**117a** with lower ee.

<u>After decomposition</u>

<u>From precipitate</u>



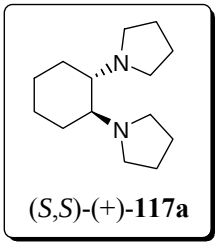
(*S*,*S*)-(+)-**117a**

Yield 0.06 g (14%)

$[\alpha]_D^{25}$ +5.7 (*c* 0.4, 1N HCl), based on $[\alpha]_D^{25}$ = -31.85 (*c* 0.5, 1N HCl) for a sample of (*R*, *R*)-**117a** obtained

from the sample of (*R*,*R*)-**35** with >99% ee, following a reported procedure[56a]

From filtrate


(*S*,*S*)-(+)-**117a**

Yield 0.26 g (60%)

$[\alpha]_D^{25}$ +28.9 (*c* 1, 1N HCl), based on $[\alpha]_D^{25}$ = -31.85 (*c* 0.5, 1N HCl) for a sample of (*R*,*R*)-**117a** obtained from the sample of (*R*,*R*)-**35** with >99% ee, following a reported procedure[56a]

1.4.5.2 Purificaton of non-racemic 1,2-bis-(pyrrolidino)cyclohexane 117a using fumaric acid

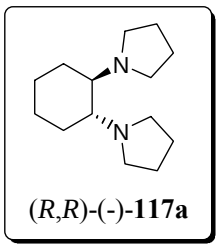
The partially resolved (*R*,*R*)-(-)-1,2-bis-(pyrrolidino)cyclohexane **117a** (93% ee, 0.44 g, 2 mmol) was taken in acetone (5 mL), to this fumaric acid (0.21 g, 1.86 mmol) was added and the contents were stirred at 25 ^oC for 12 h and filtered. The precipitate was suspended in a mixture of diethyl ether (20 mL) and 1M NaOH (10 mL) and stirred until dissolution occurred. The organic layer was separated and the aqueous layer was extracted with diethyl ether (2 X 10 mL). The combined organic extract was washed with brine (10 mL), dried over anhydrous sodium sulfate and the solvent was evaporated to obtain the enriched sample of (*R*,*R*)-(-)-**117a**. The filtrate was concentrated and the residue taken in diethyl ether (20 mL) and digested with 1M NaOH (10 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (2 X 10 mL). The combined organic extract was washed with brine (10 mL), dried over anhydrous sodium sulfate and the solvent was evaporated to obtain the sample of (*R*,*R*)-(-)-**117a** with lower ee.

After decomposition

From precipitate

Yield 0.33 g (75%)

$[\alpha]_D^{25}$ -31.5 (*c* 1, 1N HCl), based on $[\alpha]_D^{25}$ = -31.85 (*c* 0.5, 1N HCl) for a sample of (*R*,*R*)-**117a** obtained from the sample of (*R*,*R*)-**35** with >99% ee, following a reported procedure[56a]

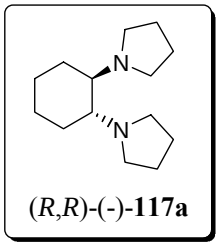


(*R*,*R*)-(-)-**117a**

From filtrate

Yield 0.04 g (10%)

$[\alpha]_D^{25}$ -12.7 (*c* 0.4, 1N HCl), based on $[\alpha]_D^{25}$= -31.85 (*c* 0.5, 1N HCl) for a sample of (*R*,*R*)-**117a** obtained from the sample of (*R*,*R*)-**35** with >99% ee, following a reported procedure[56a]



(*R*,*R*)-(-)-**117a**

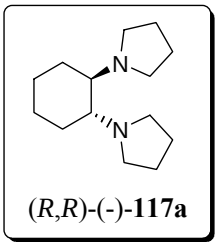
1.4.5.3 Purificaton of non-racemic 1,2-bis-(pyrrolidino)cyclohexane 117a using terephthalic acid

The partially resolved (*R*,*R*)-(-)-1,2-bis-(pyrrolidino)cyclohexane **117a** (81% ee, 0.44 g, 2 mmol) was taken in acetone (5 mL), to this terephthalic acid (0.26 g, 1.60 mmol) was added and the contents were stirred at 25 ^oC for 12 h and filtered. The precipitate was suspended in a mixture of diethyl ether (20 mL) and 1M NaOH (10 mL) and stirred until dissolution occurred. The organic layer was separated and the aqueous layer was extracted with diethyl ether (2 X 10 mL). The combined organic extract was washed with brine (10 mL), dried over anhydrous sodium sulfate and the solvent was evaporated to obtain the enriched sample of (*R*,*R*)-(-)-**117a**. The filtrate was

concentrated and the residue taken in diethyl ether (20 mL) and digested with 1M NaOH (10 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (2 X 10 mL). The combined organic extract was washed with brine (10 mL), dried over anhydrous sodium sulfate and the solvent was evaporated to obtain the sample of (*R*,*R*)-(-)-**117a** with lower ee.

After decomposition

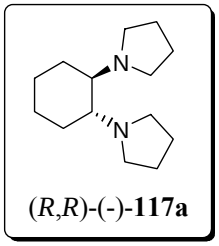
From precipitate


(*R*,*R*)-(-)-**117a**

Yield 0.21 g (48%)

$[\alpha]_D^{25}$ -30.2 (*c* 1, 1N HCl), based on $[\alpha]_D^{25}$= -31.85 (*c* 0.5, 1N HCl) for a sample of (*R*,*R*)-**117a** obtained from the sample of (*R*,*R*)-**35** with >99% ee, following a reported procedure[56a]

From filtrate


(*R*,*R*)-(-)-**117a**

Yield 0.16 g (36%)

$[\alpha]_D^{25}$ -17.8 (*c* 1, 1N HCl), based on $[\alpha]_D^{25}$ = -31.85 (*c* 0.5, 1N HCl for a sample of (*R*,*R*)-**117a** obtained from the sample of (*R*,*R*)-**35** with >99% ee, following a reported procedure[56a]

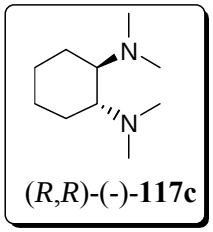
1.4.5.4 Purificaton of non-racemic 1,2-bis-(*N*,*N*-dimethylamino)cyclohexane 117c using terephthalic acid

The partially resolved (*R*,*R*)-(-)-1,2-bis-(*N*,*N*-dimethylamino)cyclohexane **117c** (89% ee, 0.51 g, 3 mmol) was taken in THF (15 mL), to this terephthalic acid (0.43 g, 2.67 mmol) was added and the contents were stirred at 25 ^oC for 12 h and filtered. The

filtrate was concentrated and the residue was suspended in a mixture of diethyl ether (20 mL) and 1M NaOH (10 mL) and stirred until dissolution occurred. The organic layer was separated and the aqueous layer was extracted with diethyl ether (2 X 10 mL). The combined organic extract was washed with brine (10 mL), dried over anhydrous sodium sulfate and the solvent was evaporated to obtain the enriched sample of (*R*,*R*)-(-)-**117c**. The precipitate was taken in diethyl ether (20 mL) and digested with 1M NaOH (10 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (2 X 10 mL). The combined organic extract was washed with brine (10 mL), dried over anhydrous sodium sulfate and the solvent was evaporated to obtain the sample of (*R*,*R*)-(-)-**117c** with lower ee.

After decomposition

From precipitate


(*R*,*R*)-(-)-**117c**

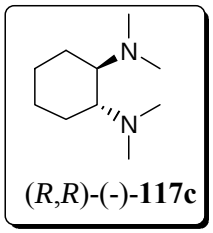
Yield 0.05 g (10%)

$[\alpha]_D^{25}$ -35.1 (*c* 0.4, $CHCl_3$), based on $[\alpha]_D^{25}$ = -60.6 (*c* 1, $CHCl_3$) for a sample of (*R*,*R*)-**117c** obtained from the sample of (*R*,*R*)-**35** with >99% ee, following a reported procedure[56b]

From filtrate

Yield 0.35 g (70%)

$[\alpha]_D^{25}$ -56.9 (*c* 1, $CHCl_3$), based on $[\alpha]_D^{25}$ = -60.6 (*c* 1, $CHCl_3$) for a sample of (*R*,*R*)-(-)-**117c** obtained from the sample of (*R*,*R*)-**35** with >99% ee, following a reported procedure[56b]


(*R*,*R*)-(-)-**117c**

1.5 References

1. (a) Eisenberg, M. A. In *Escherichia coli and Salmonella typhimurium*; F. C. Neidhardt, Ed.; American Society for Microbiology: Washington DC, 1987, 1, 544. (b) Marquet, A. *Pure Appl. Chem*. **1993**, *65*, 1249.

2. (a) Lord, J. A.; Waterfield, A. A.; Hughes, J.; Kosterlitz, H. W. *Nature* **1977**, *267*, 495. (b) Paterson, S. J.; Robson, L. E.; Kosterlitz, H. W. *Br. Med. Bull.* **1983**, *39*, 31. (c) Szmuszkovicz, J.; Von Voigtlander, P. F. *J. Med. Chem*. **1982**, *25*, 1125. (d) Costello, G. F.; James, R.; Shaw, J. S.; Slater, A. M.; Stutchbury, N. C. J. *J. Med. Chem.* **1991**, *34*, 181. (e) Cowan, A.; Gmerek, D. E. *Trends Pharmacol. Sci.* **1986**, *7*, 69. (f) Millan, M. J. *Trends Pharmacol. Sci.* **1990**, *11*, 70. (g) Cheney, B. V.; Szmuszkovicz, J.; Lahti, R. A.; Zichi, D. A. *J. Med. Chem*. **1985**, *28*, 1853. (h) de Costa, B. R.; Bowen, W. D.; Hellewell, S. B.; George, C.; Rothman, R. B.; Reid, A. A.; Walker, J. M.; Jacobsen, A. E.; Rice, K. C. *J. Med. Chem*. **1989**, 3*2*, 1996. (i) de Costa, B. R.; Rice, K. C.; Bowen, W. D.; Thurkauf, A.; Rothman, R. B.; Band, L.; Jacobsen, A. E.; Radesca, L.; Contreras, P. C.; Gray, N. M.; Daly, I.; Iyengar, S.; Finn, D. T.; Vazirani, S.; Walker, J. M. *J. Med. Chem*. **1990**, *33*, 3100. (j) Radesca, L.; Bowen, W. D.; Di Paolo, L.; de Costa, B. R. *J. Med. Chem*. **1991**, *34*, 3058. (k) Schlichter, W. H.; Frahm, A. W. *Tetrahedron: Asymmetry* **1992**, *3*, 329. (l) Chang, A. C.; Takemori, A. E.; Ojala, W. H.; Gleason, W. B.; Portoghese, P. S. *J. Med. Chem*. **1994**, *37*, 4490.

3. Popter, A. E. A. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1984, 3, 179.

4. Lehn, J.-M. *Acc. Chem. Res*. **1978**, *11*, 49.

5. (a) Bennani, Y.; Hanessian, S. *Chem. Rev*. **1997**, *97*, 3161. (b) Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem. Int. Ed.* **1998**, *37*, 2580.

6. (a) Dwyer, F. P.; Garvan, F. L.; Shulman, A. *J. Am. Chem. Soc*. **1959**, *81*, 290. (b) Asperger, R. G.; Liu, C. F. *Inorg. Chem*. **1965**, *4*, 1492. (c) Pikul, S.; Corey, E. J. *Org. Synth*. **1992**, *71*, 22. (d) Saigo, K.; Kubota, N.; Takebayashi, S.; Hasegawa, M. *Bull. Chem. Soc. Jpn*. **1986**, *59*, 931. (e) Corey, E. J.; Lee, D.-H.; Sarshar, S. *Tetrahedron: Asymmetry* **1995**, *6*, 3.

7. (a) Becker, P. N.; White, M. A.; Bergman, R. G. *J. Am. Chem. Soc*. **1980**, *102*, 5676. (b) Becker, P. N.; Bergman, R. G. *Organometallics* **1983**, *2*, 787.

8. Zhang, W.; Jacobsen, E. N. *Tetrahedron Lett*. **1991**, *32*, 1711.

9. Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev*. **1994**, *94*, 2483.

10. Pini, D.; Iuliano, A.; Rosini, C.; Salvadori, P. *Synthesis* **1990**, 1023.

11. (a) Oi, R.; Sharpless, K. B. *Tetrahedron Lett*. **1991**, *32*, 999. (b) Richardson, P. F.; Nelson, L. T. J.; Sharpless, K. B. *Tetrahedron Lett*. **1995**, *36*, 9241.

12. Dieter, R. K.; Deo, N.; Lagu, B.; Dieter, J. W. *J. Org. Chem.* **1992**, *57*, 1663.

13. Miao, G.; Rossiter, B. E. *J. Org. Chem.* **1995**, *60*, 8424.

14. (a) O'Brien, P.; Poumellec, P. *Tetrahedron Lett*. **1996**, *37*, 5619. (b) de Sousa, S. E.; O'Brien, P. *Tetrahedron Lett*. **1997**, *38*, 4885. (c) de Sousa, S. E.;

O'Brien, P. *Tetrahedron: Asymmetry* **1997**, *8*, 2613. (d) de Sousa, S. E.; O'Brien, P. *J. Chem. Soc., Perkin Trans. 1*, **1998**, 1483.

15. Swift, G.; Swern, D. *J. Org. Chem.* **1967**, *32*, 511.
16. Tanner, D.; Birgersson, C.; Dhaliwal, H. K. *Tetrahedron Lett*. **1990**, *31*, 1903.
17. Chandrasekhar, M.; Sekar, G.; Singh, V. K. *Tetrahedron Lett*. **2000**, 4*1*, 10079.
18. Nadir, U. K.; Krishna, R. V.; Singh, A. *Tetrahedron Lett*. **2005**, *46*, 479.
19. Concellon, J. M.; Riego, E.; Suarez, J. R. *J. Org. Chem.* **2003**, *68*, 9242.
20. Daly, A. M.; Gilheany, D. G. *Tetrahedron: Asymmetry* **2003**, *14*, 127.
21. Saravanan, O.; Bisai, A.; Baktharaman, S.; Chandrasekhar, M.; Singh, V. K. *Tetrahedron* **2002**, *58*, 4693.
22. Sturgess, M. A.; Yarberry, D. J. *Tetrahedron Lett*. **1993**, *34*, 4743.
23. Reetz, M. T.; Jaeger, R.; Drewlies, R.; Hubel, M. *Angew. Chem. Int. Ed. Engl*. **1991**, *30*, 103.
24. Brunner, H.; Schmidt, M.; Unger, G.; Schonenberger, H. *Eur. J. Med. Chem. Chim. Ther*. **1985**, *20*, 509.
25. Markidis, T.; Kokotos, G. *J. Org. Chem.* **2001**, *66*, 1919.
26. Amedjkouh, M.; Ahlberg, P. *Tetrahedron: Asymmetry* **2002**, *13*, 2229.
27. Cook, G. R.; Shanker, P. S.; Pararajasingham, K. *Angew. Chem. Int. Ed.* **1999**, *38*, 110.
28. Cutri, S.; Bonin, M.; Micouin, L.; Husson, H.-P. *J. Org. Chem.* **2003**, *68*, 2645.
29. Rezler, E. M.; Fenton, R. R.; Esdale, W. J.; McKeage, M. J.; Russel, P. J.; Hambley, T. W. *J. Med. Chem.* **1997**, *40*, 3508.

30. Matecka, D.; Rothman, R. B.; Radesca, L.; de Costa, B. R.; Dersch, C. M.; Partilla, J. S.; Pert, A.; Glowa, J. R.; Wojnicki, H. E.; Rice, K. C. *J. Med. Chem.* **1996**, *39*, 4704.

31. Shimizu, M.; Iida, T.; Fujisawa, T. *Chem. Lett.* **1995**, 609.

32. Kim, M.; Knettle, B. W.; Dahlen, A.; Hilmersson, G.; Flowers II, R. A. *Tetrahedron* **2003**, *59*, 10397.

33. Zhong, Y.-W.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* **2004**, *6*, 3953.

34. Zhong, Y.-W.; Izumi, K.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* **2004**, *6*, 4747.

35. Taniguchi, N.; Hata, T.; Uemura, M. *Angew. Chem. Int. Ed.* **1999**, *38*, 1232.

36. Periasamy, M.; Srinivas, G.; Suresh, S. *Tetrahedron Lett*. **2001**, *42*, 7123.

37. Neumann, W. L.; Rogic, M. M.; Dunn, T. J. *Tetrahedron Lett*. **1991**, *32*, 5865.

38. Alexakis, A.; Tomassini, A.; Chouillet, C.; Roland, S.; Mangeney, P.; Bernardinelli, G. *Angew. Chem. Int. Ed.* **2000**, *39*, 4093.

39. Shimizu, M.; Kamei, M.; Fujisawa, T. *Tetrahedron Lett*. **1995**, *36*, 8607.

40. Busacca, C. A.; Campbell, S.; Dong, Y.; Grossbach, D.; Ridges, M.; Smith, L.; Spinelli, E. *J. Org. Chem.* **2000**, *65*, 4753.

41. Selvakumar, K.; Harrod, J. F. *Angew. Chem. Int. Ed.* **2001**, *40*, 2129.

42. Adams, H.; Anderson, J. C.; Peace, S.; Pennell, A. M. K. *J. Org. Chem.* **1998**, *63*, 9932.

43. Yamada, K.; Harwood, S. J.; Groger, H.; Shibasaki, M. *Angew. Chem. Int. Ed.* **1999**, *38*, 3504.

44. Knudsen, K. R.; Risgaard, T.; Nishiwaki, N.; Gothelf, K. V.; JØrgensen, K. A. *J. Am. Chem. Soc.* **2001**, *123*, 5843.

45. (a) Zhang, W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1990**, *112*, 2801. (b) Jacobsen, E. N.; Zhang, W.; Muci, A. R.; Ecker, J. R.; Deng, L. *J. Am. Chem. Soc.* **1991**, *113*, 7063. (c) Deng, L.; Jacobsen, E. N. *J. Org. Chem.* **1992**, *57*, 4320.

46. (a) Martinez, L. E.; Leighton, J. L.; Carsten, D. H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, *117*, 5897. (b) Jacobsen, E. N.; Kakiuchi, F.; Konsler, R. G.; Larrow, J. F.; Tokunaga, M. *Tetrahedron Lett.* **1997**, *38*, 773. (c) Larrow, J. F.; Schaus, S. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1996**, *118*, 7420.

47. (a) Hanessian, S.; Delorme, D.; Beaudoin, S.; Leblanc, Y. *J. Org. Chem.* **1984**, *49*, 5754. (b) Bennani, Y. L.; Hanessian, S. *Tetrahedron* **1996**, *52*, 13837. (c) Hanessian, S.; Bennani, Y. L.; Delorme, D. *Tetrahedron Lett.* **1990**, *31*, 6461. (d) Hanessian, S.; Bennani, Y. L. *Tetrahedron Lett.* **1990**, *31*, 6465.

48. (a) Takahashi, H.; Yoshioka, M.; Ohno, M.; Kobayashi, S. *Tetrahedron Lett.* **1992**, *33*, 2575. (b) Takahashi, H.; Yoshioka, M.; Shibasaki, M.; Ohno, M.; Imai, N.; Kobayashi, S. *Tetrahedron* **1995**, *51*, 12013. (c) Imai, N.; Sakamoto, K.; Takahashi, H.; Kobayashi, S. *Tetrahedron Lett.* **1994**, *35*, 7045.

49. Tokles, M.; Snyder, J. K. *Tetrahedron Lett.* **1986**, *27*, 3951.

50. Hanessian, S.; Meffre, P.; Girard, M.; Beaudoin, S.; Sanceau, J. Y.; Bennani, Y. L. *J. Org. Chem.* **1993**, *58*, 1991.

51. Trost, B. M.; Ariza, X. *J. Am. Chem. Soc.* **1999**, *121*, 10727.

52. (a) Kawashima, M.; Hirayama, A. *Chem. Lett.* **1990**, 2299. (b) Tanaka, K.; Moriyama, A.; Toda, F. *J. Org. Chem.* **1997**, *62*, 1192.

53. (a) Meguro, M.; Naoki, A.; Yamamoto, Y. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2597. (b) Fiorenza, M.; Ricci, A.; Taddei, M.; Tassi, D. *Synthesis* **1983**, 640. (c) Sekar, G.; Singh, V. K. *J. Org. Chem.* **1999**, *64*, 287. (d) Bisai, A.; Pandey, G.; Pandey, M. K.; Singh, V. K. *Tetrahedron Lett*. **2003**, *44*, 5839. (e) Barbaro, P.; Bianchini, C.; Sernau, V. *Tetrahedron: Asymmetry* **1996**, *7*, 843. (f) Chini, M.; Crotti, P.; Favero, L.; Macchia, F.; Pineschi, M. *Tetrahedron Lett*. **1993**, 3*4*, 433. (g) Kato, K.; Furuta, K.; Yamamoto, H. *Synlett* **1992**, 565.

54. Periasamy, M.; Seenivasaperumal, M.; Padmaja, M.; Rao, V. D. *Arkivoc* **2004**, *viii*, 4.

55. Anderson, S. R.; Ayers, J. T.; Devries, K. M.; Ito, F.; Mendenhall, D.; Vanderplas, B. C. *Tetrahedron: Asymmetry* **1999**, *10*, 2655.

56. (a) Larock, R. C. In *Comprehensive Organic Transformations: A Guide to Functional Group Preparations*; VCH: 1989. (b) Pine, S. H.; Sanchez, B. L. *J. Org. Chem*. **1971**, *36*, 829.

57. Periasamy, M.; Kumar, N. S.; Kumar, S. S.; Rao, V. D.; Ramanathan, C. R.; Raman, L. V. *J. Org. Chem.* **2001**, *66*, 3828.

58. Bonner, W. A. In *Topics in Stereochemistry*; Wiley: New York, 1988, 18, 1.

59. Bada, J. L. *Nature* **1995**, *374*, 594.

60. Feringa, B. L.; van Delden, R. A. *Angew. Chem. Int. Ed.* **1999**, *38*, 3418.

61. Girard, C.; Kagan, H. B. *Angew. Chem. Int. Ed.* **1998**, *37*, 2923.

62. (a) Mikami, K.; Matsukawa, S. *Nature* **1997**, *385*, 613. (b) Mikami, K.; Terada, M.; Korenaga, T.; Matsumoto,Y.; Matsukawa, S. *Acc. Chem. Res*. **2000**, *33*, 391.

63. (a) Soai, K.; Shibata, T.; Marioka, H.; Choji, K. *Nature* **1995**, *378*, 767. (b) Soai, K.; Shibata, T.; Sato, I. *Acc. Chem. Res*. **2000**, *33*, 382.

64. Morowitz, H. J. *J. Theor. Biol*. **1969,** *25*, 491.

65. Thiemann, W. *J. Mol. Evol*. **1974**, *4*, 85.

66. Vigneron, J. P.; Dhaenens, M.; Horeau, A. *Tetrahedron* **1973**, *29*, 1055.

67. Kondepudi, D. K.; Nelson, G. W. *Physica* **1984**, *125A*, 465.

68. Kondepudi, D. K.; Kaufman, R. J.; Singh, N. *Science* **1990**, *250*, 975.

69. van Mil, J.; Addadi, L.; Gati, E.; Lahav, M. *J. Am. Chem. Soc*. **1982**, *104*, 3429.

70. Tsuruta, T.; Matsuura, K.; Inoue, S. *Biopolymers* **1967**, *5*, 313.

71. Fleming, I.; Ghosh, S. K. *J. Chem. Soc., Chem. Commun*. **1994**, 99.

72. Venkataraman, L.; Periasamy, M. *Tetrahedron: Asymmetry* **1996**, *7*, 2471.

73. Periasamy, M.; Sivakumar, S. K.; Reddy, M. N.; Padmaja, M. *Org. Lett.* **2004**, *6*, 265.

74. (a) Gabard, A.; Collet, A.; *New J. Chem.* **1986**, *10*, 685. (b) Potter, G. A.; Garcia, C.; McCague, R.; Adger, B.; Collet, A. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1666.

75. Elias, W. E. *J. Chem. Ed*. **1972**, *49*, 448.

76. Hall, S. R.; King, G. S. D.; Stewart, J. M., Eds, *Xtal*, 3.4 *User's Manual*, Xtal System, University of Western Australia, **1995**.

77. Sheldrick, G. M. SHELXS-86, in *Crystallographic Computing 3*, Sheldrick, G. M.; Kurger, G.; Goddard, R. Eds. Oxford University Press; Oxford, **1985**.

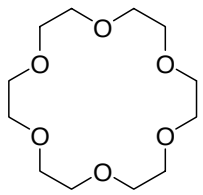
78. Sheldrick, G. M. SHELXL-93, *Crystal Structure Refinement Programme*, University of Gottingen, Gottingen, Germany, **1993**.

Chapter 2

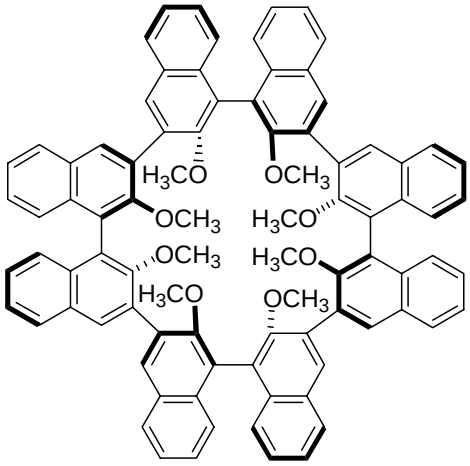
Synthesis of chiral macrocyclic, oligomeric, polymeric amines and quaternary ammonium salts containing trans-1,2-cyclohexyl moiety

2.1 Introduction

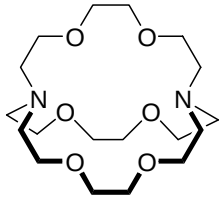
Chiral macrocycles attracted considerable attention since the initial studies carried out by Pederson[1] on the synthesis and molecular recognition studies of crown ethers **1**. Subsequent work by Cram[2] on the spherands **2** and Lehn[3] on the cryptands **3** led to the explosive growth of knowledge in this area of investigation that resulted in the award of the Nobel prize for their pioneering work in this field.[4]



1

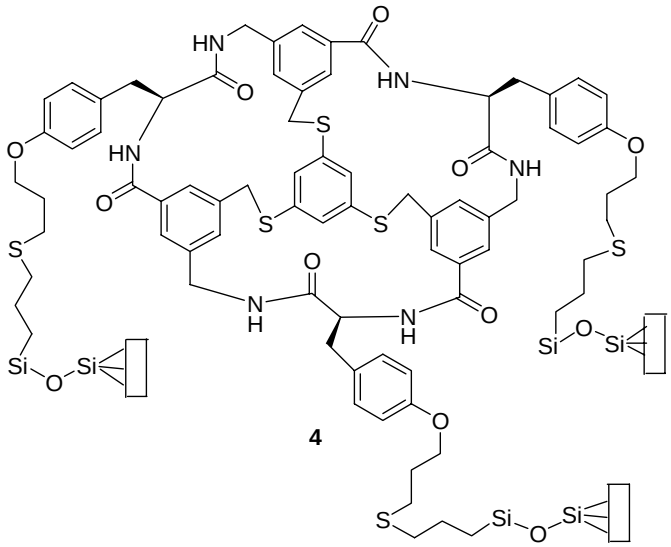


2

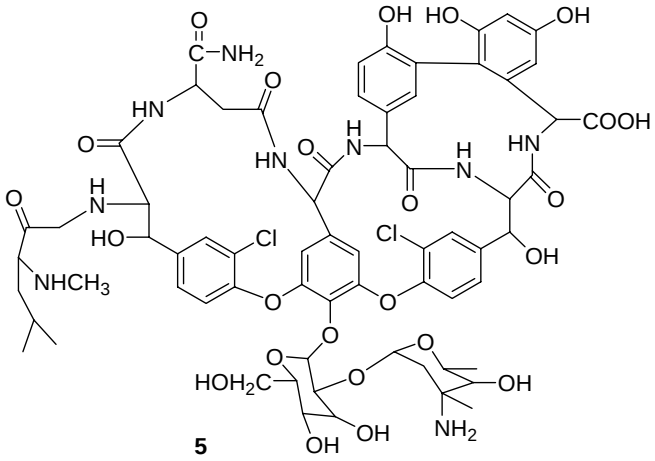


3

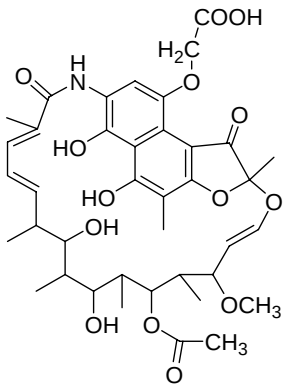
It is well recognized that the architecture of macrocyclic compounds naturally provides them with cavities suitable for a range of functions such as the formation of inclusion complexes,[5] chiral molecular recognition,[6] asymmetric catalysis[7] and mimicry of natural enzymes.[8] Chiral macrocycles are also used in the preparation of chiral stationary phases **4**[9] for chromatographic applications and as chiral resolving agents for racemic and non-racemic mixtures.[10] Biological activity of certain classes of macrocycles has also given them a role in drug development.[11] For example, the antibiotics such as Vancomycin **5**, Rifamycin-B **6** and Thiostrepton **7** are macrocyclic



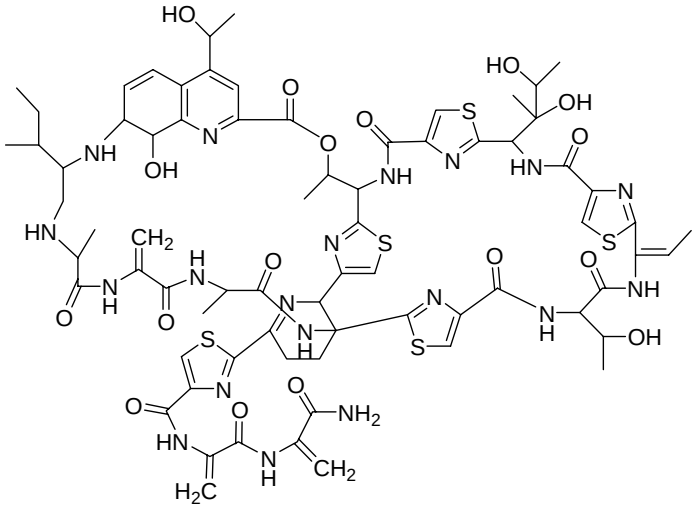
4



5



6



7

compounds and were also used as chiral stationary phases for the separation of various amino acids.[12]

We have undertaken efforts to synthesize chiral macrocycles containing (*R*,*R*)-1,2-diaminocyclohexane moiety. Accordingly, a brief survey of the reports on the synthesis of chiral macrocycles will facilitate the discussion.

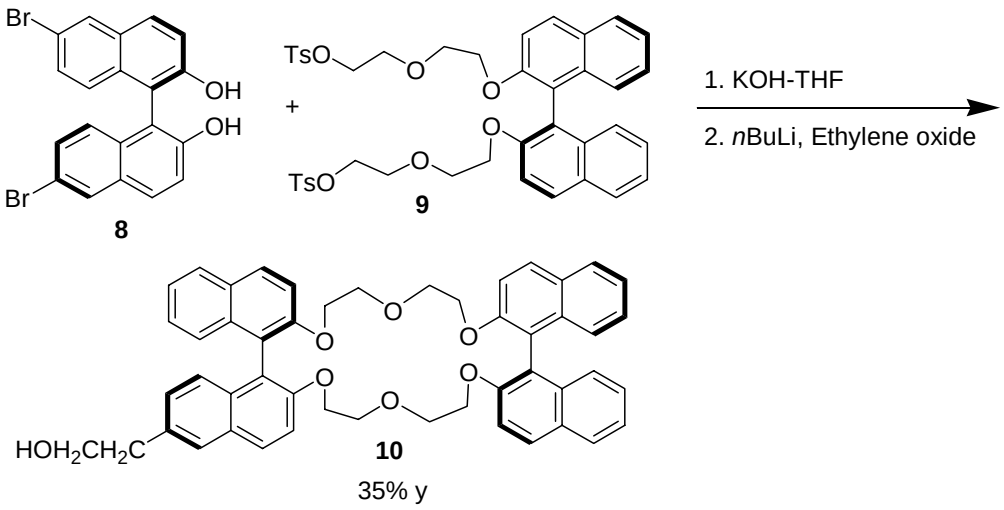
2.1.1 Synthesis of chiral macrocycles

Chiral macrocycles were synthesized starting from chiral compounds containing various functional groups like alcohols, amino acids, amino alcohols and diamines.

2.1.1.1 Oxygen containing macrocycles

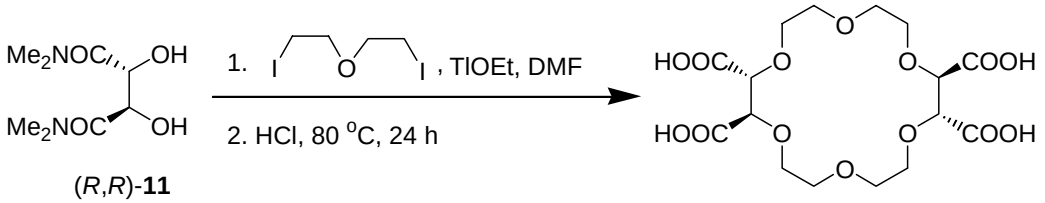
Cram and Sogah[13] reported the synthesis of the macrocycle **10** starting from (*R*)-6,6′-dibromo-2,2′-dihydroxy-1,1′-binaphthyl **8** in 35% yield (Scheme 1). The polystyrene-divinylbenzene copolymer resin containing this macrocyclic moiety was used for the chromatographic resolution of enantiomers of amino acid and ester salts.[13]

Scheme 1



Lehn and co-workers[14a] synthesized the chiral tetracarboxylic 18-crown-6 ether **12** starting from the (*R*,*R*)-(+)-*N*,*N*,*N*′,*N*′-tetramethyltartaramide **11** (Scheme 2). The tetracarboxylic acid and its derivatives are reported to show chiral recognition towards amino acids, amino acid esters and amino alcohols.[14b-c]

Scheme 2



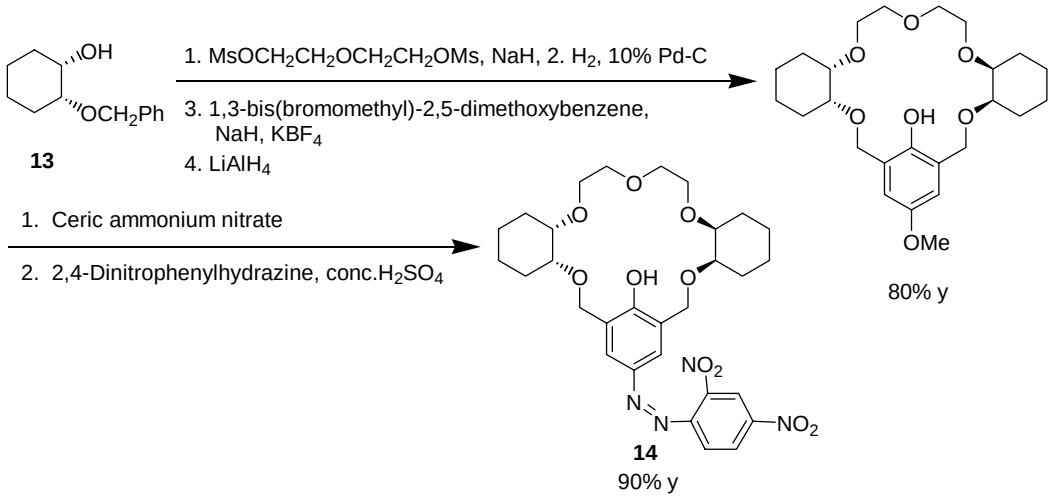
(*R*,*R*)-**11**

12

19% y

Naemura *et al.*[15] synthesized the azophenolic crown ether **14** incorporating the *cis*-cyclohexane-1,2-diol residue **13** and studied the chiral recognition behaviour of **14** towards chiral 2-aminoethanols (Scheme 3).

Scheme 3



13

80% y

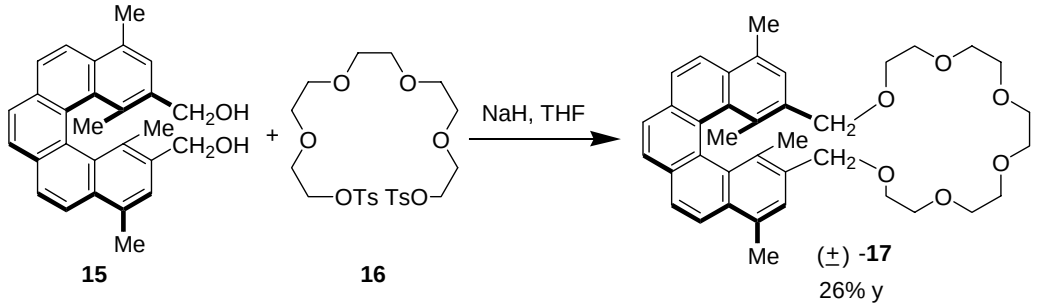
14

90% y

Yamamoto and co-workers[16] synthesized the optically active crown ether **17** incorporating a pentahelicene chiral centre (Scheme 4). The condensation of 2,13-

bis(hydroxymethyl)-1,4,11,14-tetramethylpentahelicene **15** with 3,6,9,12-tetraoxa decane-1,14-diyl bis(*p*-toluenesulfonate) **16** gave the pentahelicino-crown **17** which was resolved into its enantiomers by HPLC.

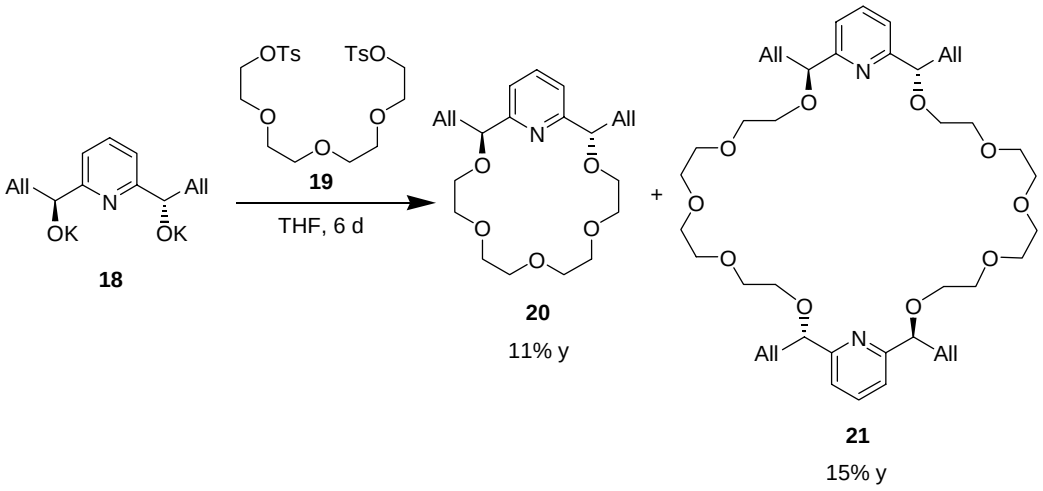
Scheme 4



2.1.1.2 Azaoxa macrocycles

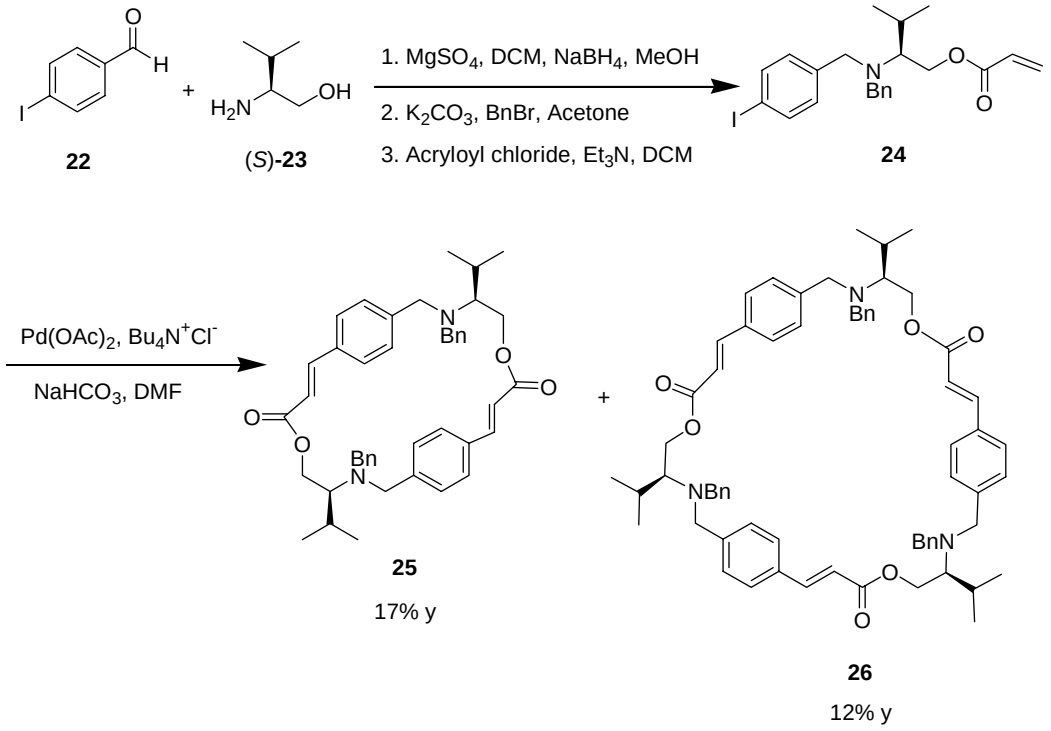
Brown *et al.*[17] synthesized the chiral pyridino-18-crown-6 ligands **20** and **21** by the reaction of the dipotassium salt of the chiral diol **18** with tetraethylene glycol di(*p*-toluenesulfonate) **19** (Scheme 5). The starting optically active diol was prepared by the asymmetric reduction of 2,6-diacylpyridines with B-chlorodiisopinocampheylborane.

Scheme 5



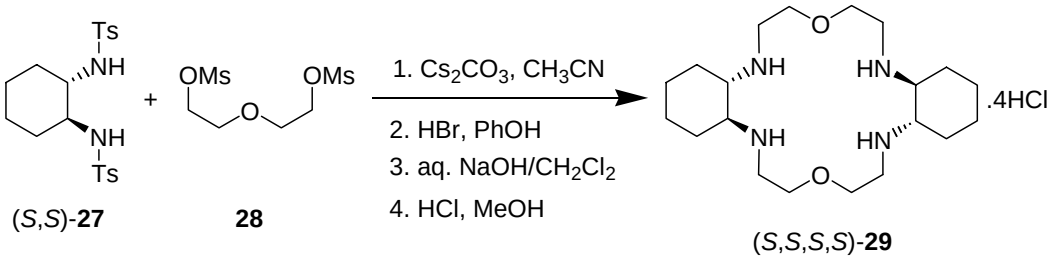
Gibson and co-workers[18] reported the head-to-tail Heck coupling of the iodo derivatives of amino alcohols. Reductive amination of the iodoaryl aldehyde **22** with (*S*)-valinol **23** resulted in the iodo derivative of the amino alcohol which was reacted with acryloyl chloride to give the prop-2-enoyl derivative **24** (Scheme 6).[18] Subjecting the derivative **24** to Heck coupling generated the macrocycles **25** and **26**.

Scheme 6



Gotor and co-workers[19] synthesized the D_2-symmetric dioxatetraaza macrocyle (*S*,*S*,*S*,*S*)-**29** from the tosyl derivative **27** of (*S*,*S*)-1,2-diaminocyclohexane (Scheme 7). The chiral anion recognition studies of the triprotonated macrocycle showed moderate enantioselectivity towards malate and tartrate anions.[19]

Scheme 7

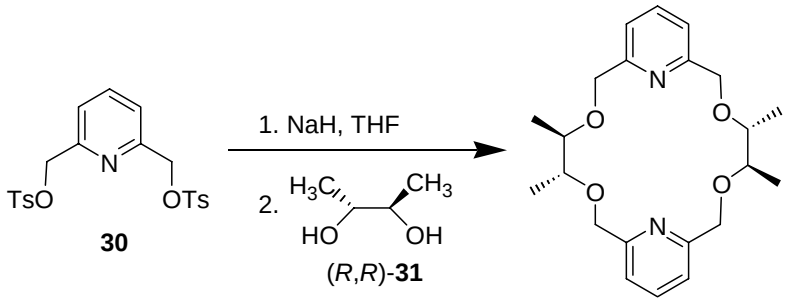


(*S*,*S*)-**27** **28** (*S*,*S*,*S*,*S*)-**29**

80% y

The bis-pyridino-18-crown-6 ligand **32** was synthesized by the cyclisation of (*R*,*R*)-2,3-butanediol **31** with 2,6-bis[(tosyloxy)methyl]pyridine **30** by Izatt and co-workers[20] (Scheme 8). This ligand **32** was later on used by Kobayashi *et al*.[21] to catalyze the asymmetric aldol reaction of various aldehydes with 68-82% enantioselectivity.

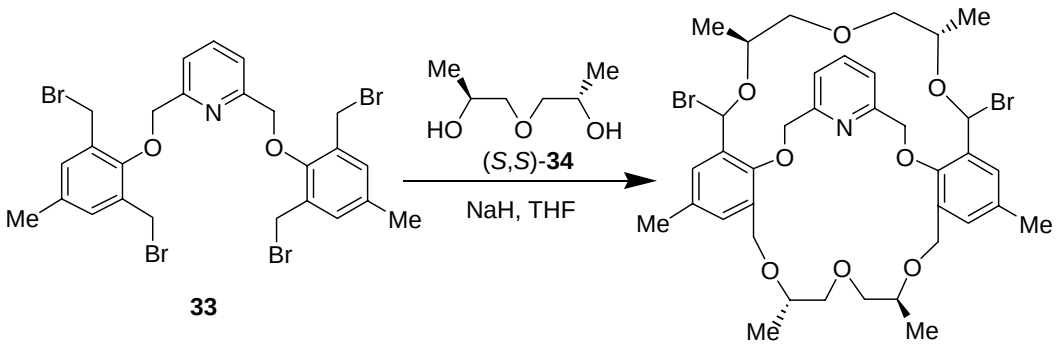
Scheme 8



30 (*R*,*R*)-**31** (*R*,*R*,*R*,*R*)-**32**

Bradshaw *et al*.[22] synthesized the chiral macrobicyclic compound **35** by the reaction of 2,6-bis[[2′,6′-bis(bromomethyl)-4′-methylphenoxy]methyl]pyridine **33** with (1*S*,5*S*)-3-oxapentane-1,5-diol **34** (Scheme 9). The compound (*S*,*S*,*S*,*S*)-**35** exhibited a high degree of enantiomeric recognition for the (*S*)-enantiomer of α-(1-naphthyl)-ethylammonium perchlorate over its (*R*) form.

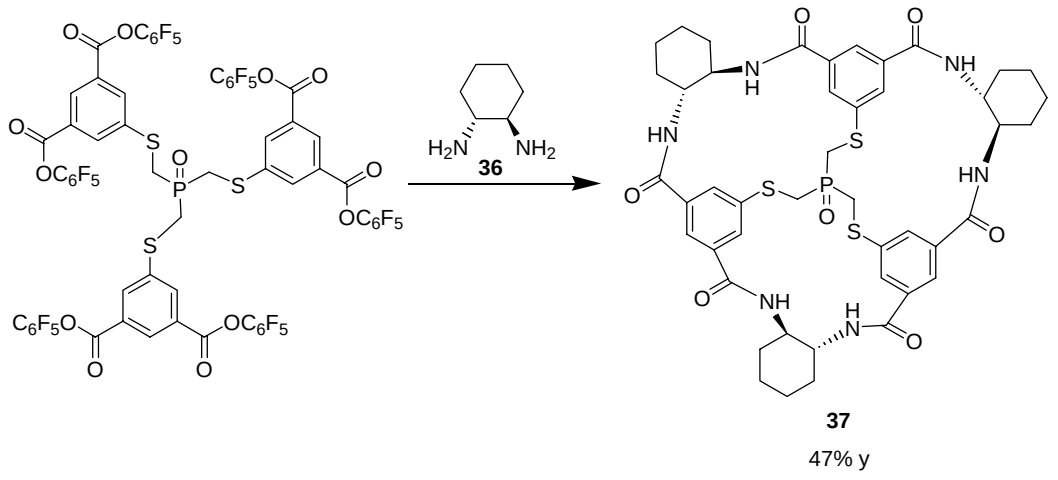
Scheme 9



2.1.1.3 Polyamide macrocycles

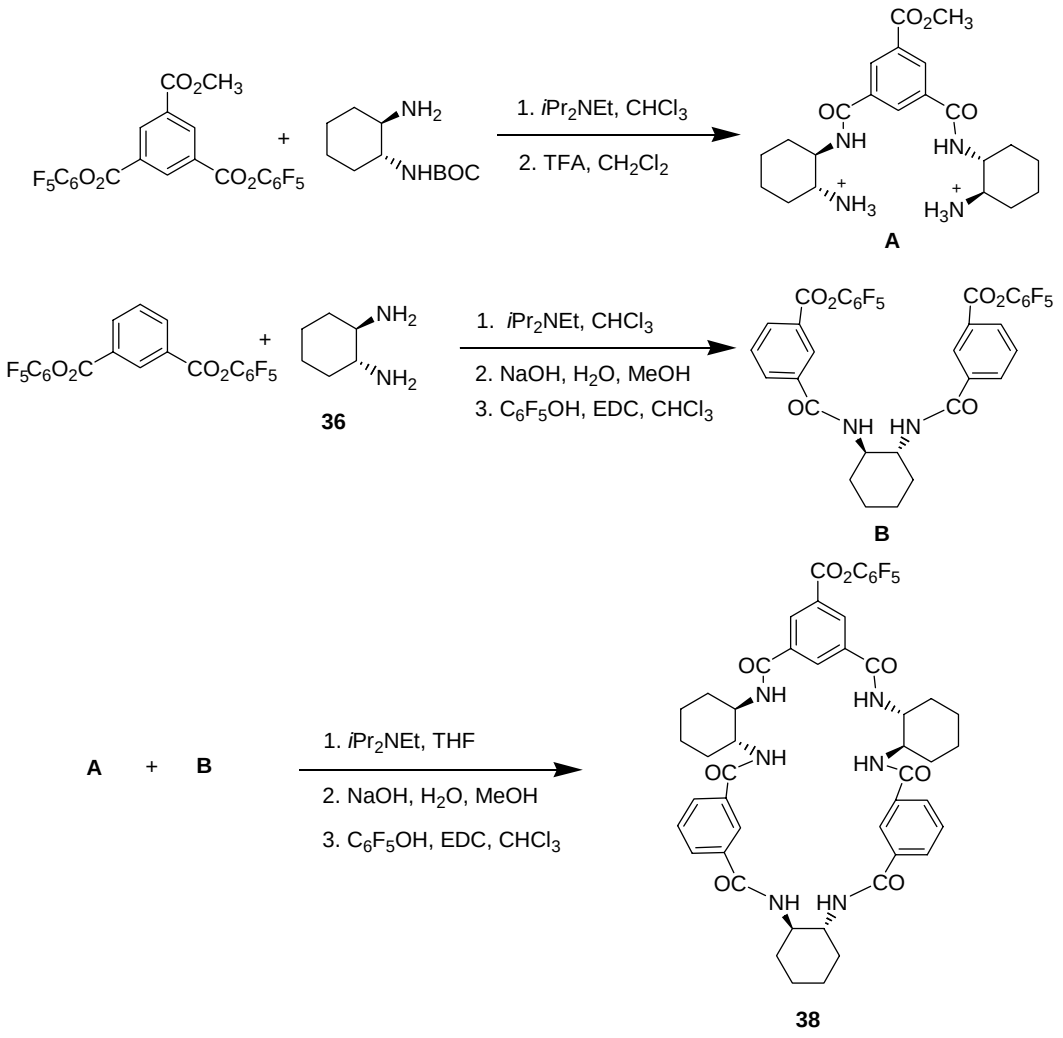
Recently, a bowl shaped C_3-symmetric receptor **37**, with concave phosphine oxide functionality was synthesized by Hong and co-workers[23] (Scheme 10). The receptor **37** showed a remarkable selectivity for asparagine derivatives.

Scheme 10



Still *et al.*[24a] synthesized the macrocyclic oligomer **38** of isophthalic acid and (*R*,*R*)-1,2-diaminocyclohexane **36** as outlined in Scheme 11. The oligomer was used in the synthesis of new, sequence-selective receptors for peptide binding.[24b-c]

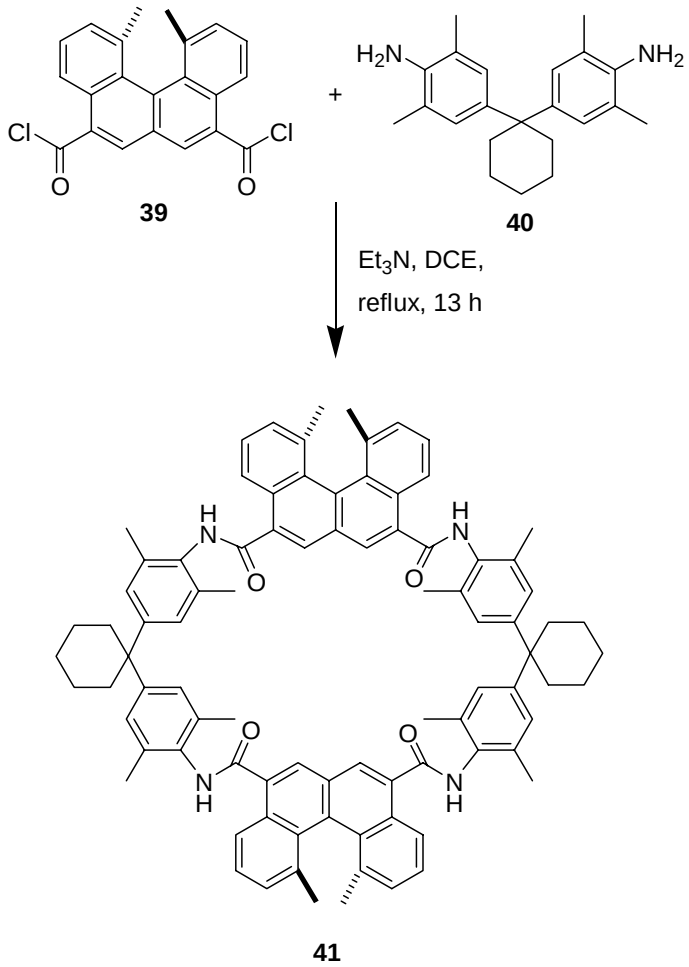
Scheme 11



Yamaguchi and co-workers[25] reported the synthesis of the macrocycle **41** by the reaction of the acid chloride **39** of the chiral 1,12-dimethylbenzo[c]phenanthrene-5,8-dicarboxylic acid with the dianiline spacer **40** (Scheme 12). The [1+1], [3+3] and [4+4] condensation products were also obtained in the reaction along with the [2+2]

condensation product **41**. The macrocycle **41** catalyzed the asymmetric addition of diethylzinc to aromatic aldehydes with 50% selectivity.[25]

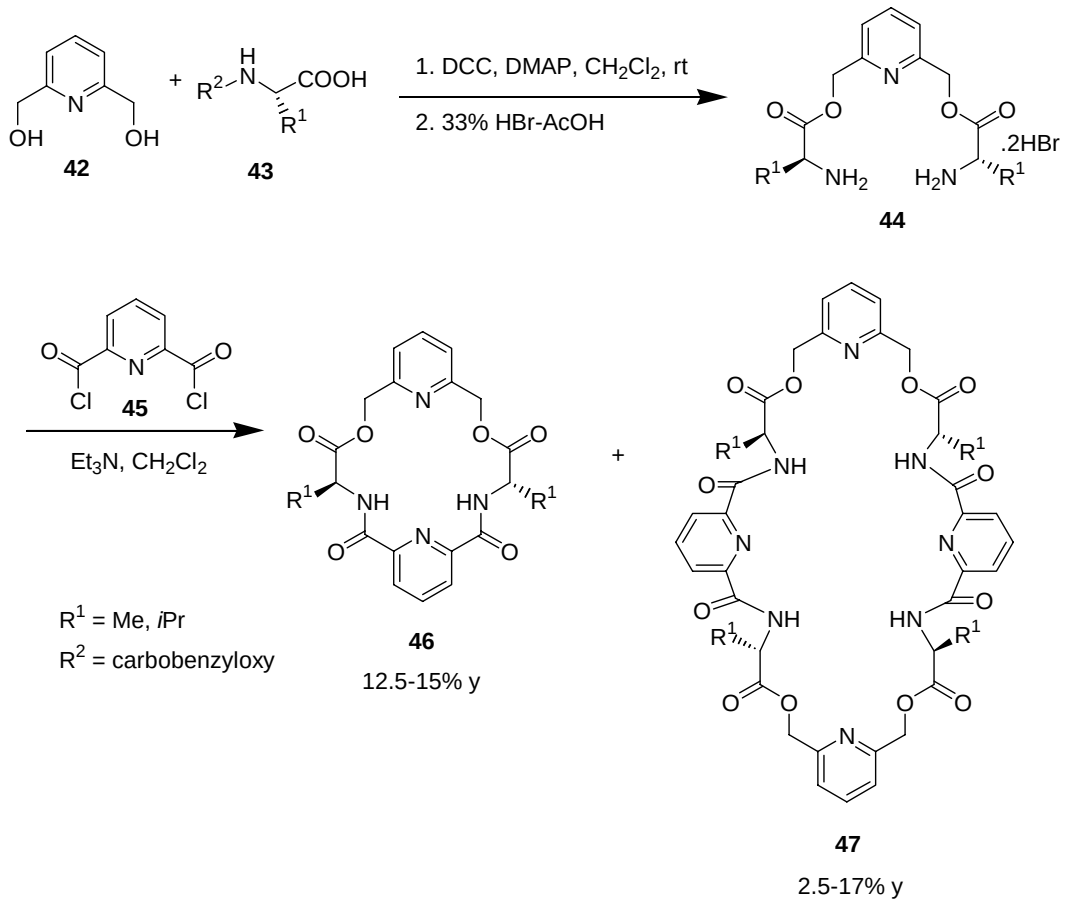
Scheme 12



Hua and Zhao[26] prepared the macrocycles **46** and **47** by the acylation-cyclization of the chiral diamine dihydrobromide intermediates **44** with 2,6-pyridinedicarbonyl dichloride **45** (Scheme 13). The chiral diester intermediates **44**, needed for the preparation of the macrocycles, were obtained by the condensation of *L*-amino acids **43** and 2,6-bis(hydroxymethyl)pyridine **42**. These macrocycles exhibit

chiral recognition for the enantiomers of *D*- and *L*-amino acid methyl ester hydrochlorides.[26]

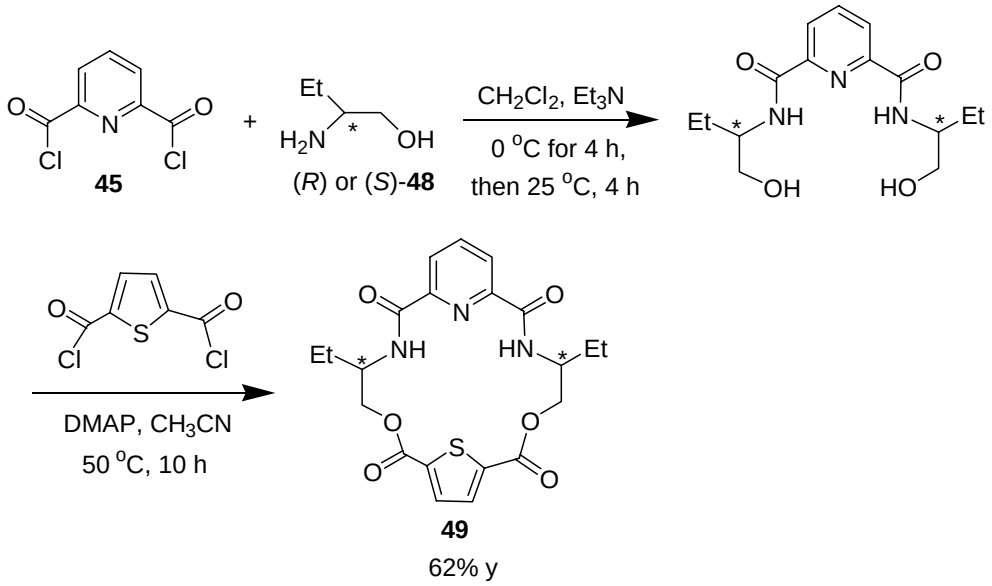
Scheme 13



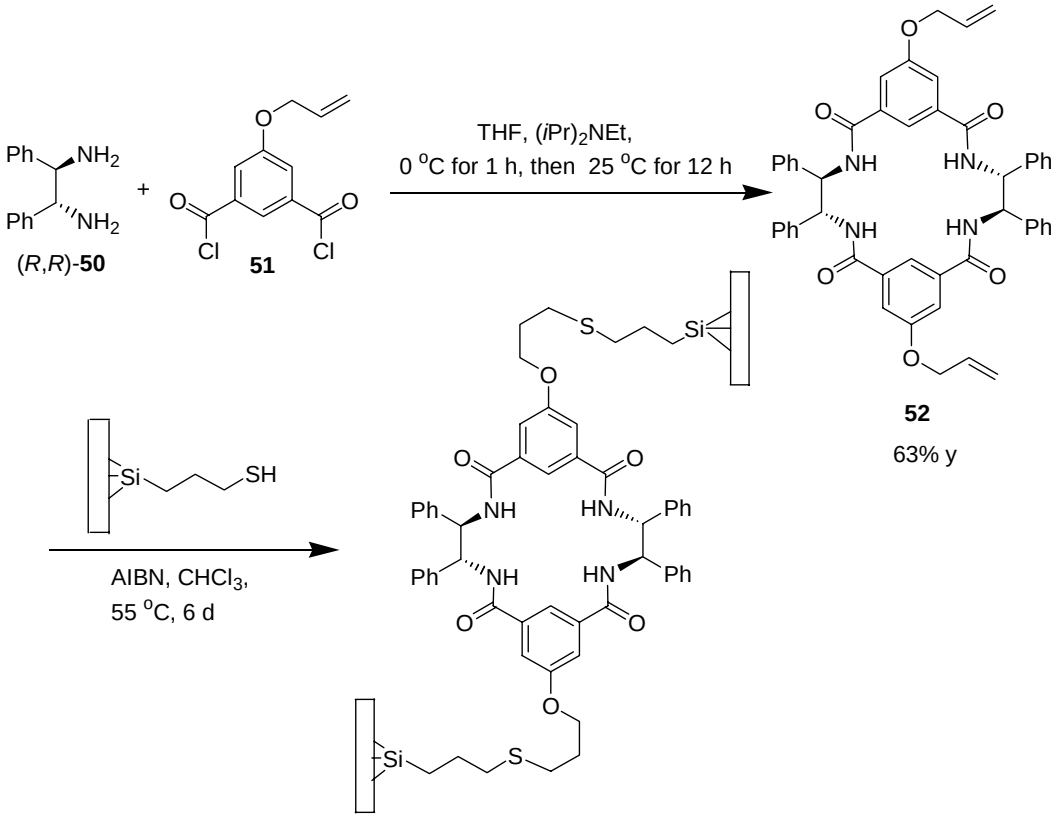
Zingaro and co-workers[27] synthesized the macrocycle **49** by the condensation of 2,6-pyridinedicarbonyl dichloride **45** with chiral 2-amino-1-butanol **48** (Scheme 14). The macrocycle **49** was found to display antifungal activity.[27]

Villani and co-workers[28] reported the synthesis of the minireceptor **52** from (*R*,*R*)-1,2-diamino-1,2-diphenylethane **50** and 5-allyloxyisophthaloyl chloride **51** (Scheme 15). It has been reported that after immobilization on HPLC silica, the chiral macrocycle preferentially binds the *L*-enantiomers of simple amino acid derivatives.

Scheme 14



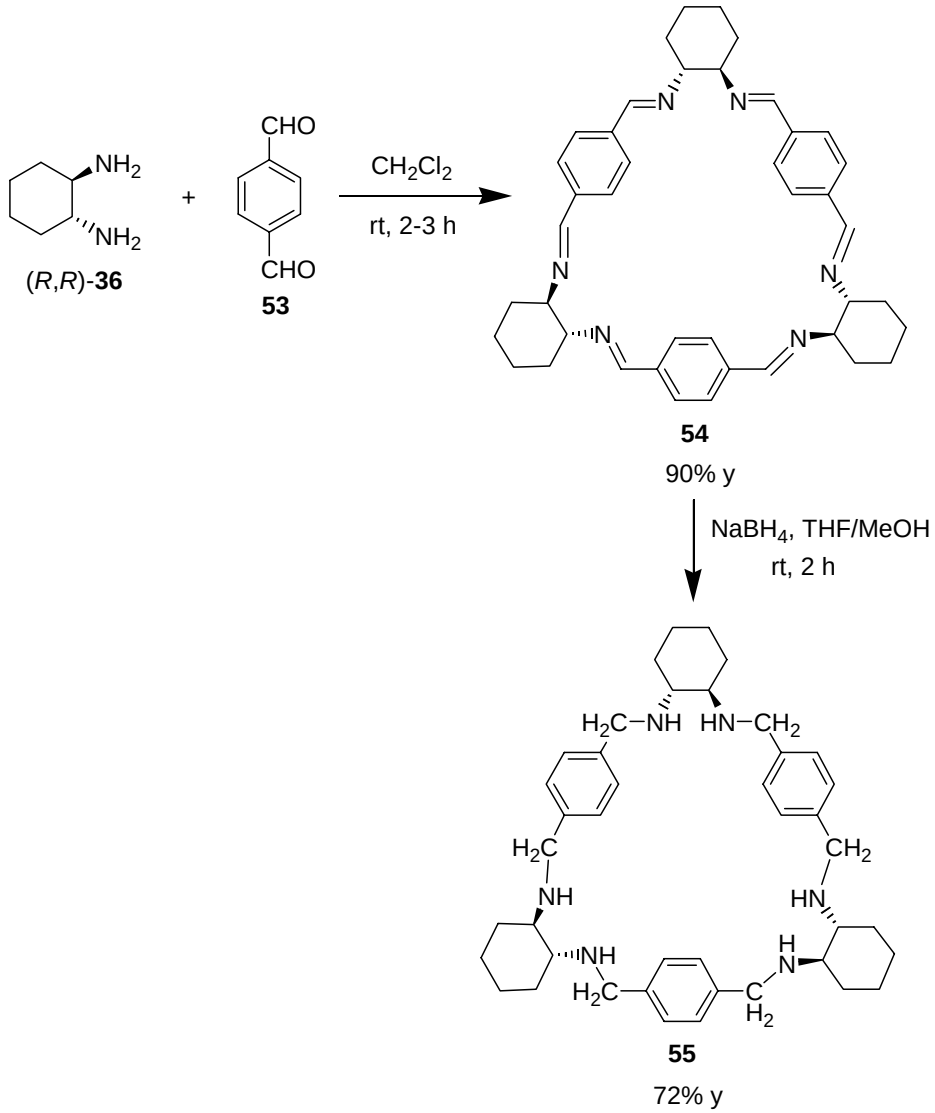
Scheme 15



2.1.1.4 Polyaza macrocycles

Gawronski *et al.*[29] synthesized the hexaimino macrocycle **54** by the [3+3] condensation of (*R*,*R*)-1,2-diaminocyclohexane **36** with terephthalaldehyde **53**. The reduction of the imine by $NaBH_4$ yielded the cyclic hexaamine **55** (Scheme 16). A similar [3+3] condensation product was also obtained using isophthalaldehyde.

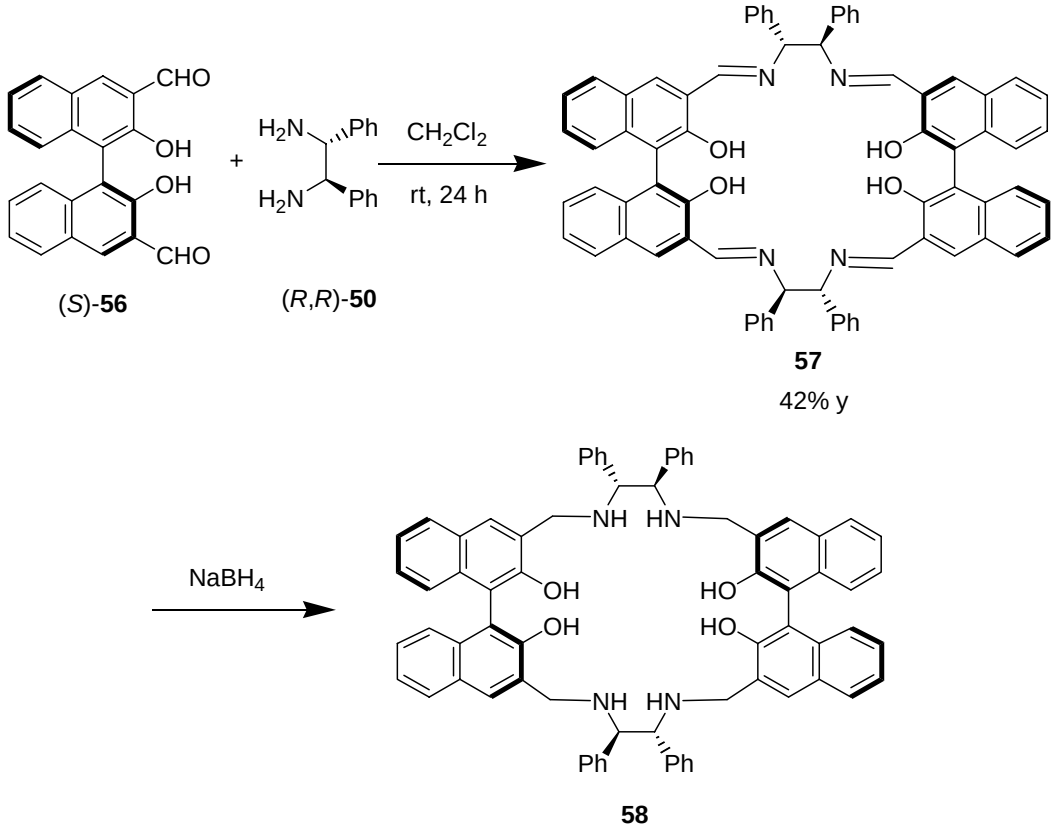
Scheme 16



Following this report, several groups synthesized the cyclic hexaamines from (*R*,*R*)-1,2-diaminocyclohexane with various substituted aldehyde and ketone spacers.[30]

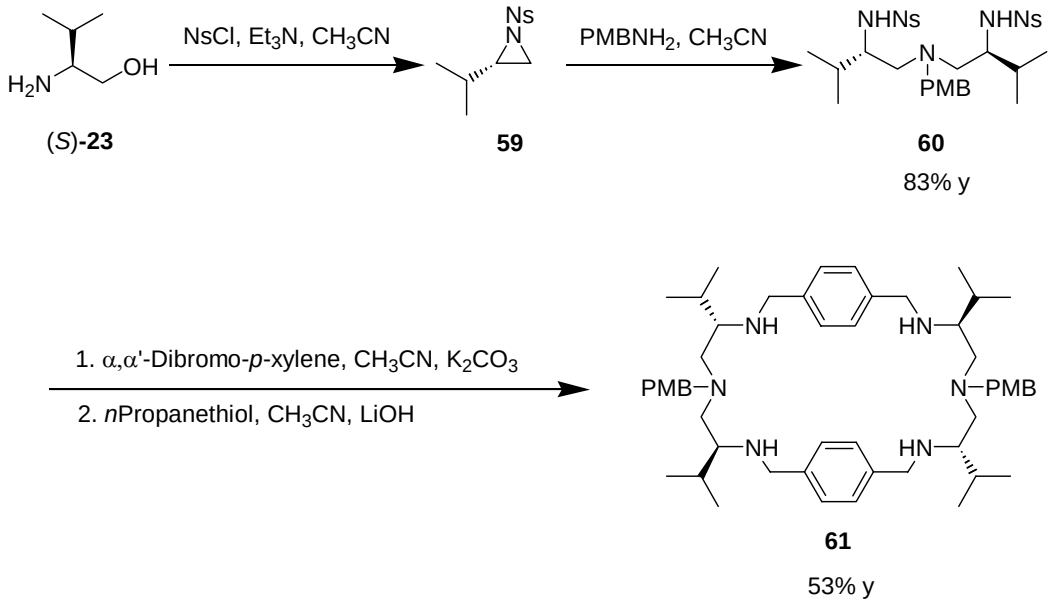
In 1994, Brunner and Schiessling[31] reported the synthesis of the chiral bis(binaphthyl) macrocycle **58** by the condensation of the (*S*)-2,2′-dihydroxy-1,1′-binaphthyl-3,3′-dialdehyde **56** with (*R*,*R*)-1,2-diamino-1,2-diphenylethane **50** followed by the reduction of the macrocyclic imine **57** to yield **58** (Scheme 17). Interestingly, it was reported that the (*R*)-enantiomer of **56** yielded a polyimine. The macrocycle **58** was later on used by Pu and co-workers[32] for the fluorescence recognition of various α-amino acids.

Scheme 17



Kim and co-workers[33] reported the synthesis of chiral peraza-macrocycle **61** from the chiral aziridine **59** prepared using (*S*)-valinol **23**. The ring opening of the chiral aziridine followed by the Richman-Atkins coupling of the resultant triamine **60** with α,α′-dibromo-*p*-xylene yielded the macrocycle **61** (Scheme 18).[33]

Scheme 18

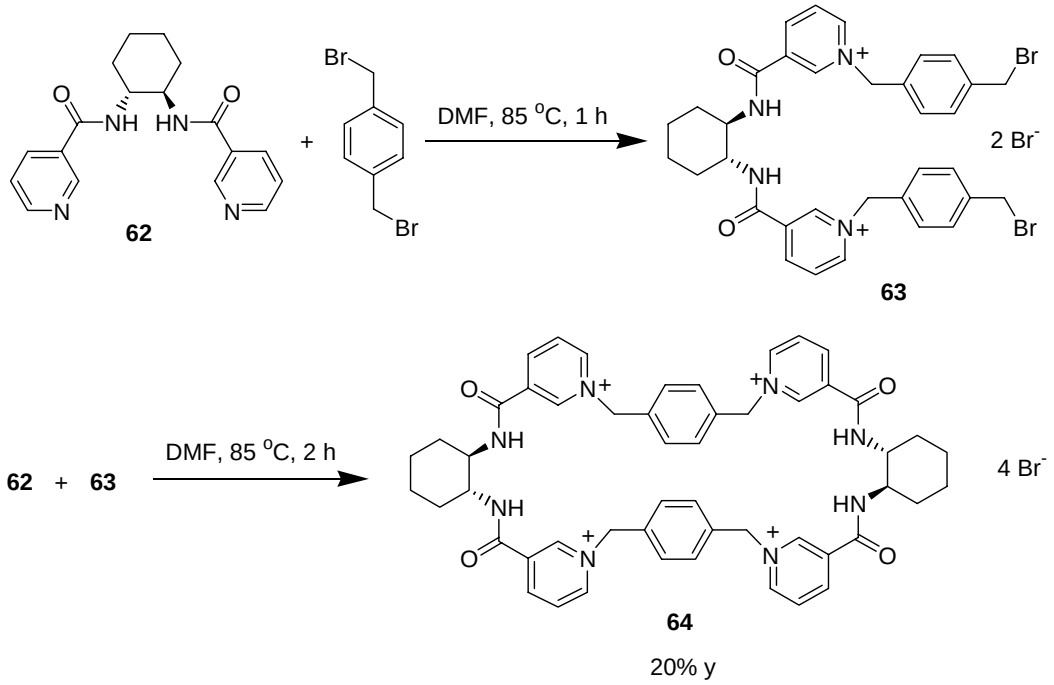


(*S*)-**23** **59** **60** 83% y

61 53% y

Wennerström *et al.*[34] synthesized a positively charged, tetravalent, D_2-symmetric, water soluble macrocycle **64** from the nicotinamide **62** of (*R*,*R*)-1,2-diaminocyclohexane and the dicationic intermediate **63** following a two step procedure outlined in Scheme 19. The macrocycle **64** formed a complex with *N*-benzyldihydronicotinamide in water in which a hydride ion is transferred from the guest to the host.[34]

Scheme 19

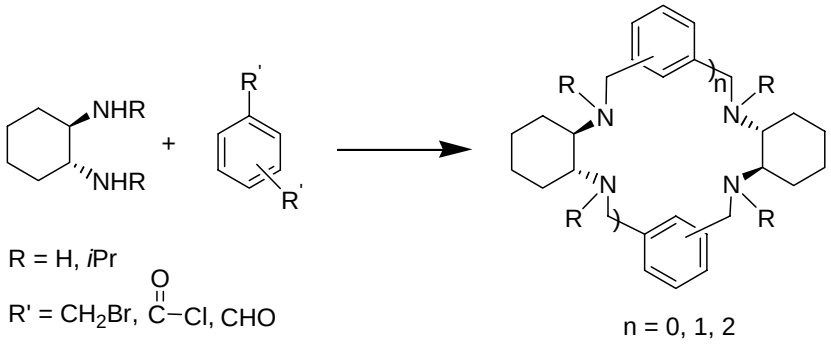


We have explored the methods of synthesis of chiral macrocycles and quaternary ammonium salts containing the (*R*,*R*)-1,2-diaminocyclohexane moiety. The results are discussed in the next section.

2.2 Results and Discussion

We have developed methods of synthesis of chiral secondary and tertiary macrocyclic amines from (*R*,*R*)-1,2-diaminocyclohexane **36** (Scheme 20). The results are discussed in this section.

Scheme 20

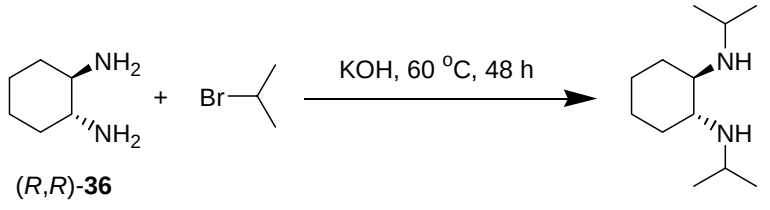


2.2.1 Synthesis of chiral tertiary macrocyclic amines and polymer

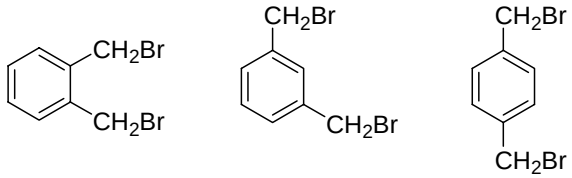
We have studied the synthesis of chiral tertiary macrocyclic and polymeric amines by the reaction of (*R*,*R*)-*N*,*N*′-diisopropyl-1,2-diaminocyclohexane **65** with isomeric benzylic bromides and adipoyl chloride.[35] Previous reports on the synthesis of the diisopropyl derivative **65** involved a two step procedure of the synthesis and reduction of the acetone-imine.[36] However, we synthesized the secondary amine **65** in a single step by direct *N*-alkylation of (*R*,*R*)-1,2-diaminocyclohexane **36** using a large excess of isopropyl bromide (Scheme 21).

We have then examined the reaction of the secondary amine **65** with the benzylic dibromide derivatives **66**, **67** and **68** to obtain the corresponding chiral heterocyclic and macrocyclic amines.

Scheme 21



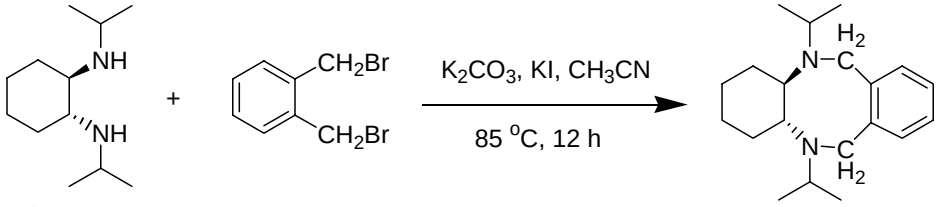
(*R*,*R*)-**36** (*R*,*R*)-**65**
65% y



66 **67** **68**

The [1+1] heterocyclic product **69** was obtained by the reaction of the diamine **65** with **66** in 80% yield (Scheme 22). The formation of macrocycles, if any, in this reaction could not be detected by ^{1}H-NMR, ^{13}C-NMR and mass spectral analysis of the crude product.

Scheme 22

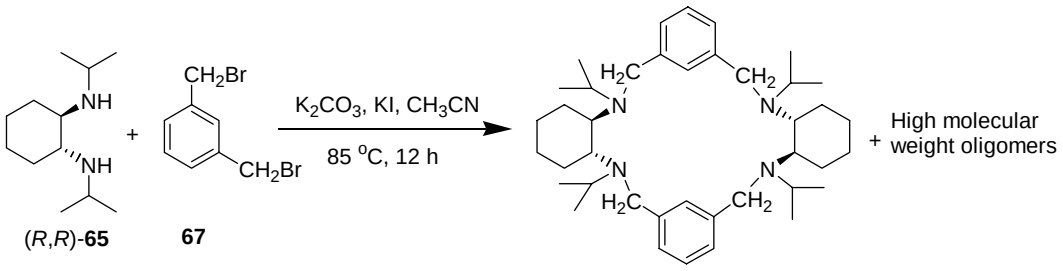


(*R*,*R*)-**65** **66** (*R*,*R*)-**69**
80% y

The reaction of the diamine **65** with the 1,3-dibromide derivative **67** gave the [2+2] condensation product **70**, in addition to high molecular weight macrocyclic and oligomeric products (Scheme 23). Separation of the products was achieved by treating

the mixture of products with oxalic acid in DCM. The diacid complex of the high molecular weight oligomers precipitated from the solution. The macrocycle **70** obtained from the filtrate, was purified further by chromatography on a silica gel column.

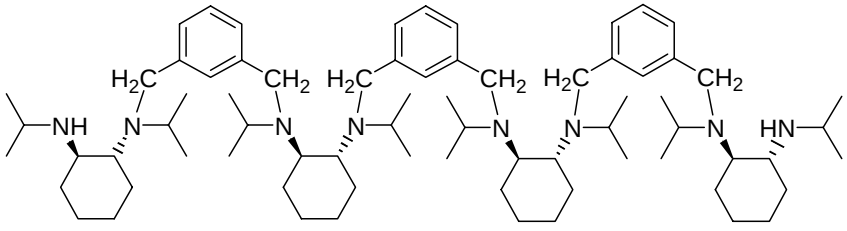
Scheme 23



(*R*,*R*)-**65** **67** (*R*,*R*,*R*,*R*)-**70**

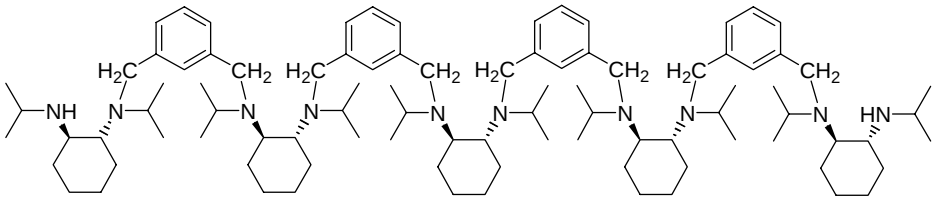
60% y

The mass spectral analysis of the precipitate fraction indicated the presence of [1+1], [2+2], [3+3], [4+4] and [5+5] cyclic condensation products along with the linear oligomeric products **71**, **72** and **73**. The molecular weights of each of these oligomers from the mass spectrum corresponded to the [M+2+Na^+] peak (Figure 1). However, the precipitated mixture of oligomers showed eleven carbon signals (19.9, 23.8, 26.6, 28.5, 46.4, 48.3, 59.8, 126.9, 127.5, 130.0, 140.9 δ ppm; 50 MHz) in the ^{13}C-NMR spectrum indicating the predominant formation of macrocyclic amines.



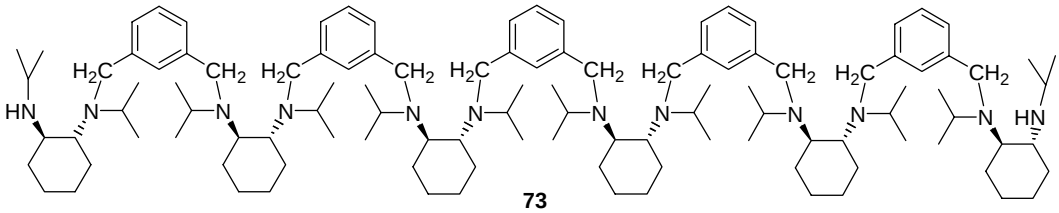
71

M = 1098



72

M = 1398



73

M = 1698

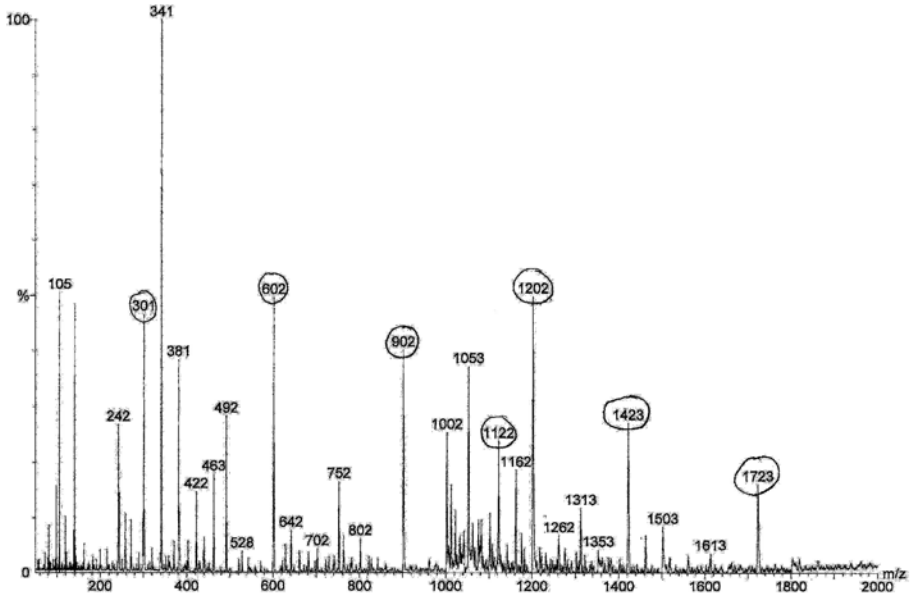


Figure 1. CI Mass spectrum of the mixture of oligomers from the reaction of 65 with 67

The ^{1}H-NMR spectrum (400 MHz) of the compound **70** exhibited broad signals at 20 ^{o}C, with two sets of signals for the benzylic as well as for the isopropyl groups. However, the signals were more resolved at 0 ^{o}C (Figure 2).

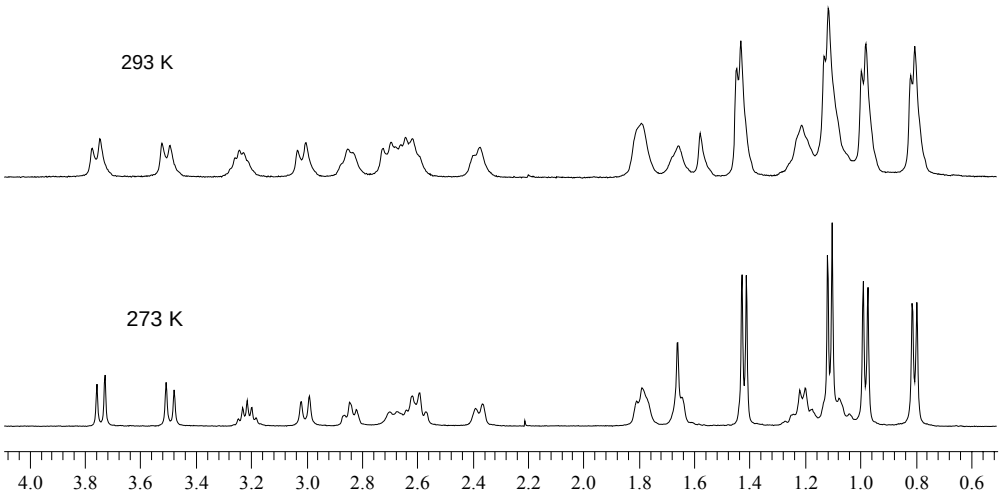


Figure 2. Low temperature ^{1}H-NMR spectra of compound 70

The X-ray structure analysis of the crystals of **70**, crystallized from hexane was carried out. The data revealed the presence of one molecule of water and there are two types of isopropyl groups (Figure 3).

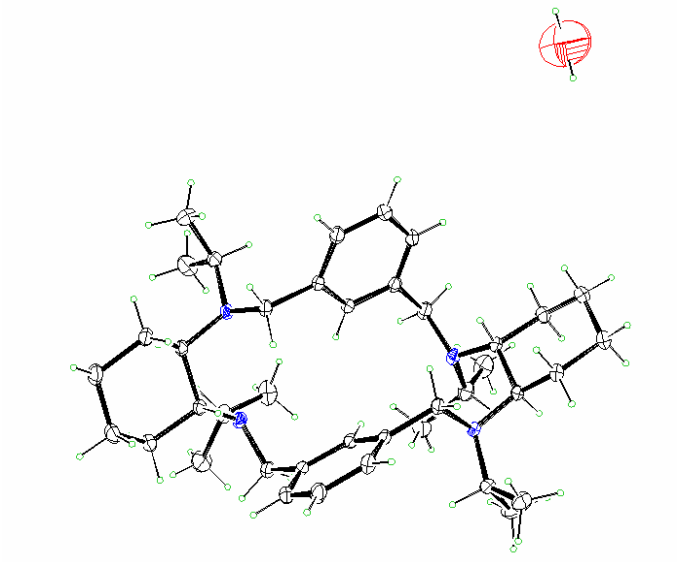


Figure 3. ORTEP diagram of the macrocyclic amine 70

Furthermore, the aryl rings are equivalent but in each ring the benzylic CH_2, the quaternary carbon atoms and the 2,4-carbon atoms are not equivalent. Although, the

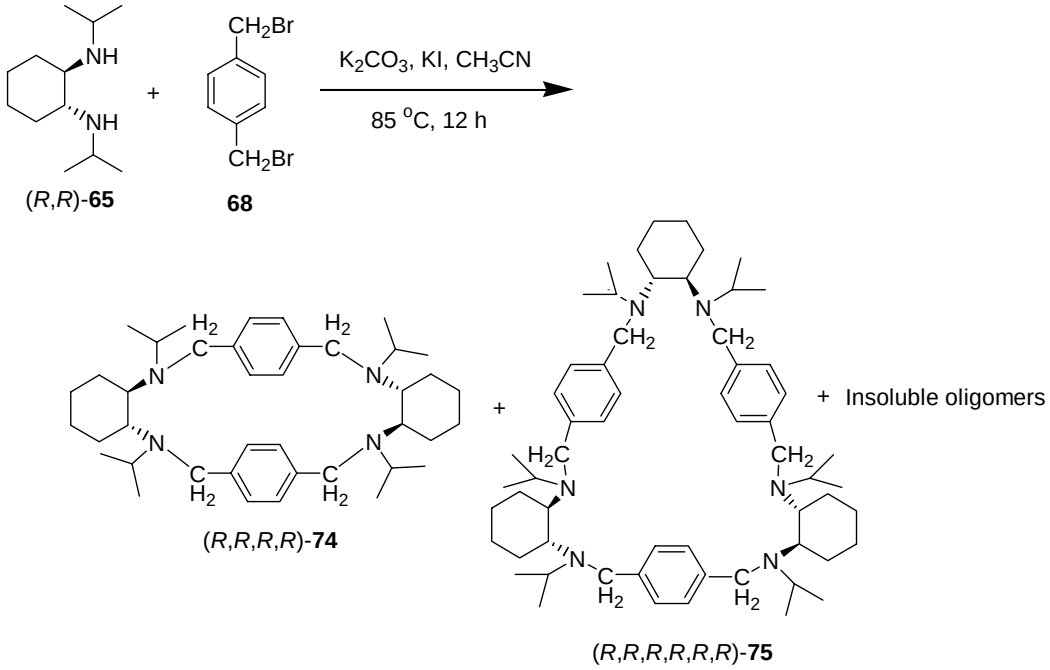
conformations of the molecule in the crystal and in the solution need not be the same, the six aromatic signals in the ^{13}C-NMR spectrum indicate that the conformations of the compound in the crystal and in the solution at 0 ^{o}C are similar. The crystal structure data of **70** are summarized in Table 1 and Table A3 (Appendix II).

Table 1. X-ray data and structure refinement for the macrocyclic amine 70

Empirical formula	C_{40} H_{64} N_4
Formula weight	600.96
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	*I* 222
Unit cell dimensions	a = 14.204(3) Å, α = 90^{o}
	b = 16.717(3) Å, β = 90^{o}
	c = 17.267(4) Å, γ = 90^{o}
Volume	4100(14) Å^3
Z	120
Calculated density	1.030 Mg/m^3
Absorption coefficient	0.063 mm^{-1}
F(000)	1404
θ range for data collection	1.70 to 31.95^{o}
Limiting indices	$0 \le h \le 21$, $0 \le k \le 24$, $0 \le l \le 25$
Reflections collected / unique	3890 / 3890 [R(int) = 0.0000]
Refinement method	full-matrix least-squares on F^2
Data / restraints / parameters	3890 / 0 / 220
Goodness-of-fit on F^2	0.989
Final R indices [I>2σ (I)]	R_1 = 0.0579, wR_2 = 0.1457
R indices (all data)	R_1 = 0.1772, wR_2 = 0.1991
Largest diff. peak and hole	0.251 and -0.106 eÅ^{-3}

A mixture of products soluble and insoluble in the DCM/THF solvents was obtained in the condensation of the diamine **65** with the 1,4-dibromide **68**. The mass spectral analysis (CI) of the soluble fraction indicated the presence of the macrocyclic amines **74** and **75**, in 81% and 4% yield, respectively (Scheme 24). The macrocyclic amine **74** could be isolated in pure form from the mixture by precipitation using oxalic acid in dichloromethane. Attempts to obtain the macrocycle **75** in pure form from the mother liquor were unsuccessful.

Scheme 24



The macrocyclic amine **74** was analyzed by single crystal X-ray analysis of the crystals obtained by crystallization from toluene (Figure 4). The crystal structure revealed that there are two types of isopropyl groups and the diagonal isopropyl groups are equivalent. The crystal data of the macrocycle **74** are summarized in Table 2 and Table A4 (Appendix II).

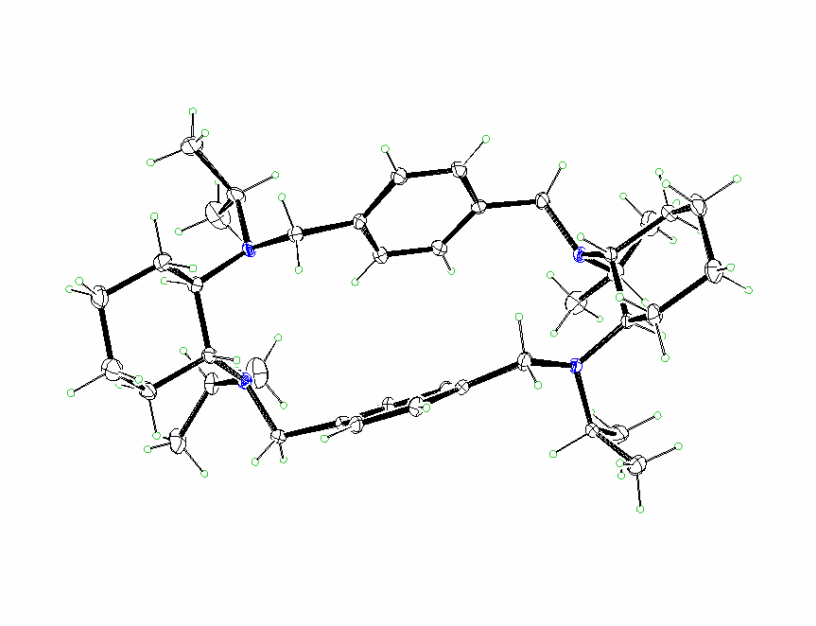


Figure 4. ORTEP diagram of the macrocyclic amine 74

The macrocyclic amine **74** also displayed broad ^{1}H-NMR (400 MHz) signals at 20 ^{o}C. However, the signals were resolved better at lower temperatures and indicate the presence of two types of isopropyl groups (Figure 5). Furthermore, the benzene rings are equivalent, but in each ring, the quaternary carbon atoms and the 2,6-carbon atoms are not equivalent. Although, the conformation in solution and crystal need not be the same, the four aromatic signals in the ^{13}C-NMR spectrum instead of the two signals expected for a symmetrical 1,4-substitution, indicate that the conformations in the crystal and in the solution at low temperatures are similar. However, at higher temperatures, the signals due to the isopropyl groups in the aliphatic region began to coalesce (Figure 5). In addition, the doublets due to the benzylic protons began to coalesce at 323 K. Presumably, the rotation about the isopropyl group which was slower at low temperatures is accelerated at higher temperatures as a result of which all the isopropyl groups and benzylic protons tend to become equivalent.

In addition, the ^{13}C-NMR spectrum (50 MHz) of the compound showed broad signals at room temperature. However the signals were resolved better in the 100 MHz ^{13}C-NMR spectrum of the compound.

Table 2. X-ray data and structure refinement for the macrocyclic amine 74

Empirical formula	$C_{40}\ H_{64}\ N_4$
Formula weight	600.96
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	*P* 212121
Unit cell dimensions	a = 15.051(3) Å, α = 90°
	b = 16.556(3) Å, β = 90°
	c = 29.858(6) Å, γ = 90°
Volume	7440(3) Å^3
Z	18
Calculated density	1.207 Mg/m^3
Absorption coefficient	0.070 mm^{-1}
F(000)	2988
θ range for data collection	1.36 to 27.48°
Limiting indices	$0 \le h \le 19$, $0 \le k \le 21$, $0 \le l \le 38$
Reflections collected / unique	9308 / 9308 [R(int) = 0.0000]
Refinement method	full-matrix least-squares on F^2
Data / restraints / parameters	9308 / 0 / 793
Goodness-of-fit on F^2	1.037
Final R indices [I>2σ (I)]	R_1 = 0.0549, wR_2 = 0.1239
R indices (all data)	R_1 = 0.1539, wR_2 = 0.1739
Largest diff. peak and hole	0.132 and -0.167 eÅ^{-3}

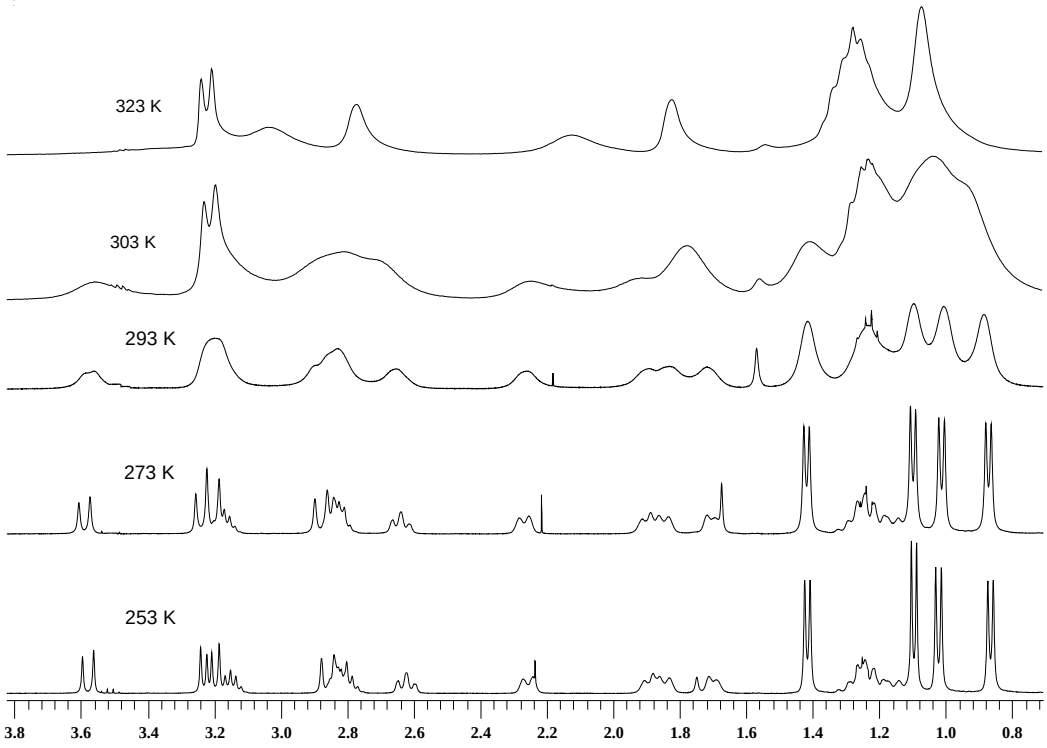
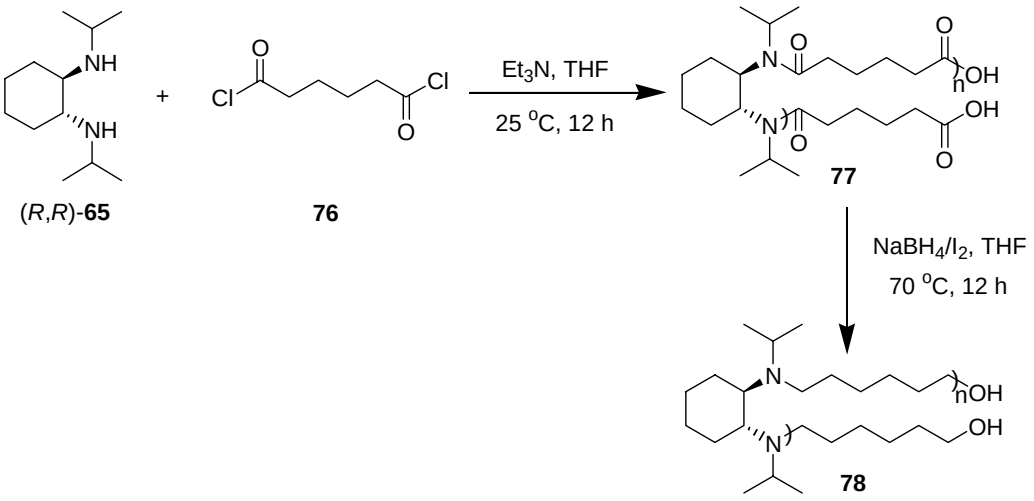


Figure 5. Variable temperature ^{1}H-NMR spectra of compound 74

Interestingly, the complex of the macrocyclic amine **74** with oxalic acid also showed a well resolved ^{1}H-NMR spectrum at 25 ^{o}C. The ^{13}C-NMR spectrum of the complex was similar to the spectrum of **74** with four signals in the aromatic region and twelve signals in the aliphatic region. The ^{1}H-NMR spectrum of the complex showed two doublets in the aromatic region indicating that the protons on the 2,6-carbon atoms are not equivalent. Presumably, the complex formation with the acid arrests the rapid rotation about the isopropyl groups resulting in a well resolved spectrum. In addition, the oxalic acid complex of the macrocyclic amine **74** did not show any optical rotation at 589 nm. However, the CD spectrum of the complex showed a negative cotton effect at 225 nm at a concentration of 0.001M in dichloromethane.

We have then examined the possibility of the preparation of macrocyclic amines containing aliphatic spacer groups. The diamine **65** failed to react with 1,6-dibromohexane under various conditions. Therefore, we carried out the condensation of the diamine **65** with adipoyl chloride **76** (Scheme 25).

Scheme 25



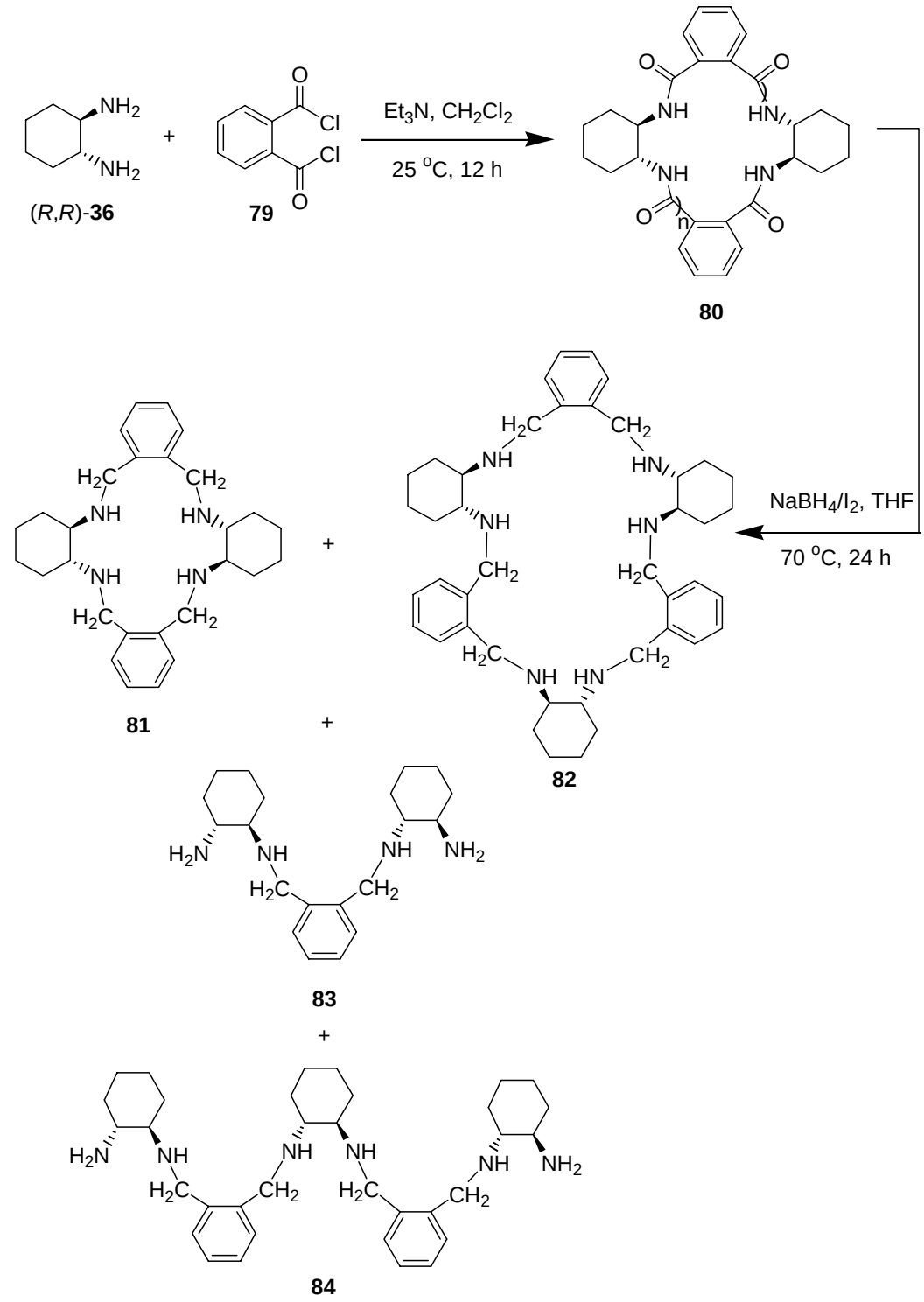
In contrast to the macrocyclic products formed using aromatic benzylic bromides, in this case, macrocyclic products were not obtained. The IR spectrum of the product exhibited absorptions at 1741 cm^{-1} and 1631 cm^{-1}. The signals observed at 172 ppm and 171 ppm in the ^{13}C-NMR spectrum of the product **77** clearly confirmed that this product is an amide with carboxylic acid end group. The gel permeation chromatography analysis showed that the number average molecular weight of this polyamide-carboxylic acid is 27499. The polymeric amide **77** was readily reduced by the $NaBH_4/I_2$ reagent system developed from this laboratory[37] to obtain the corresponding polyamino alcohol **78**.

2.2.2 Synthesis of chiral secondary macrocyclic amides and amines

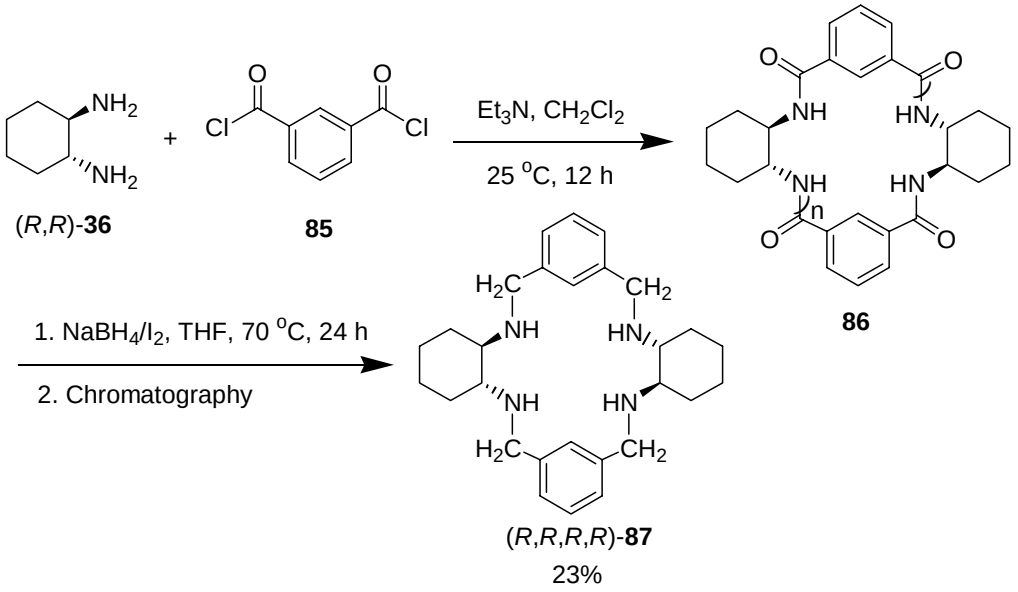
We have made attempts to synthesize chiral macrocyclic amides from (*R*,*R*)-1,2-diaminocyclohexane **36** using the 1,2-, 1,3- and 1,4-phthaloyl chlorides. The reduction of the amides yielded the corresponding polyamines. The reaction of the diamine **36** with phthaloyl chloride **79** in dichloromethane resulted in an insoluble polyamide material **80**. The reduction of the polyamide yielded a mixture of soluble polyamines **81**-**84** (Scheme 26). Unfortunately, the soluble polyamines could not be purified. The 50 MHz ^{13}C-NMR spectrum of the mixture of the products showed peaks at 25.0, 31.0, 31.5, 35.7, 48.2, 61.5, 64.4, 126.9, 129.4, 139.1 δ ppm, in addition to some auxiliary peaks. The LCMS spectrum of the crude polyamine product showed peaks with molecular weights corresponding to the [2+2] product **81** (M+1 = 433) and the [3+3] product **82** (M = 649.5). In addition, peaks corresponding to the linear products **83** and **84** formed due to condensation of one molecule of **79** with two molecules of **36** (M+1 = 331, **83**) and two molecules of **79** with three molecules of **36** (M+3 = 549, **84**), respectively were also observed.

The reaction of the diamine **36** with isophthaloyl chloride **85** also gave an insoluble mixture of amides **86**. Reduction of the crude product mixture using the $NaBH_4/I_2$ reagent system followed by chromatography of the polyamine mixture gave the [2+2] condensation product **87** in 23 % yield (Scheme 27). The application of **87** as a chiral solvating agent for carboxylic acids will be discussed in Chapter 3.

Scheme 26

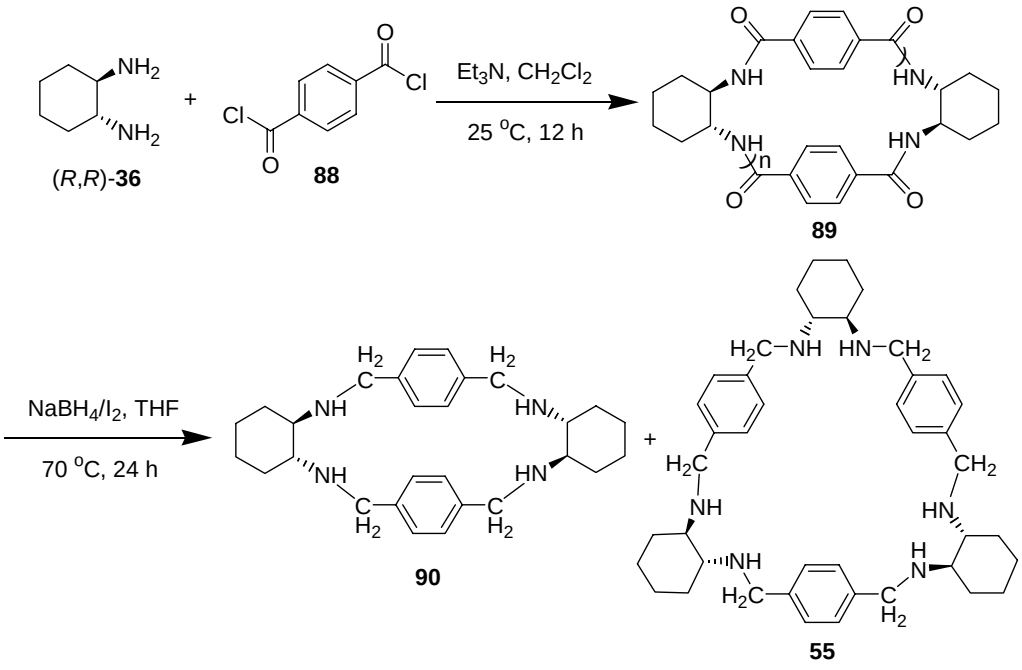


Scheme 27

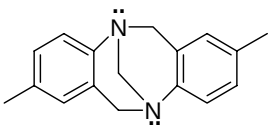


The condensation of the diamine **36** with terephthaloyl chloride **88** yielded an insoluble mixture of polyamides **89**. The polyamine mixture obtained after reduction of the amides could not be purified (Scheme 28).

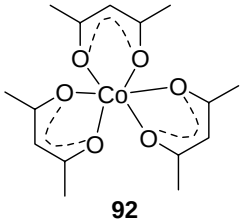
Scheme 28



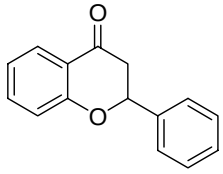
The ^{13}C-NMR spectrum of the mixture of amines showed signals corresponding to only cyclic structure (25.0, 31.5, 50.6, 60.8, 128.1, 139.4 δppm; 50 MHz). The signals in the ^{1}H-NMR spectrum also supported the cyclic structure. The LCMS spectrum of the mixture of reduced products showed peaks corresponding to the [2+2] condensation product **90** (M-1 = 431) and the [3+3] condensation product **55** (M-2 = 647.5). The polyamide **89** was previously used as packing material for the preparation of chiral stationary phase and it was found that this gave better resolution in the HPLC analysis of several racemic compounds like Tröger's base **91**, cobalt(III)-tris(acetylacetonate) **92**, flavone **93** and the dianilide **94** of *trans*-cyclopropanedicarboxylic acid.[38]



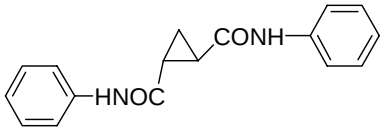
91



92



93



94

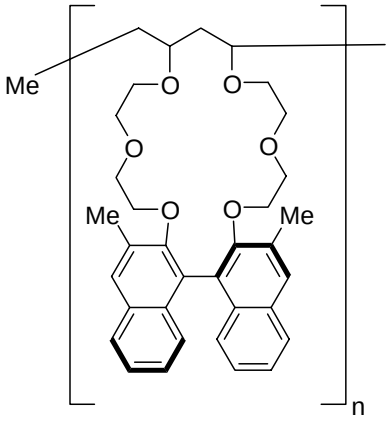
2.2.3 Synthesis of chiral oligomeric macrocycles

Chiral polymeric macrocycles have potential for synthetic exploitations because of their metal and molecular recognition properties and for use as chiral stationary phases for the enantiomeric recognition of various racemates.

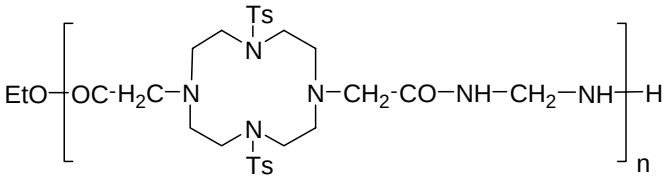
Yokota and co-workers[39] synthesized the chiral polymeric macrocycle **95** containing chiral binaphthyl moiety and studied the molecular recognition properties.

It was found that the macrocycle **95** exhibited high enantiomeric recognition towards amino esters and alcohols.[39]

Mouaziz *et al*.[40] synthesized the macrocyclic oligomers **96** of the tetraazacyclododecane, which has applications in medicine[41] and in extraction and separation of cationic mixtures of Ni^{+2}, Co^{+2}, Cu^{+2}, Zn^{+2} and Pb^{+2} ions.[42]



95

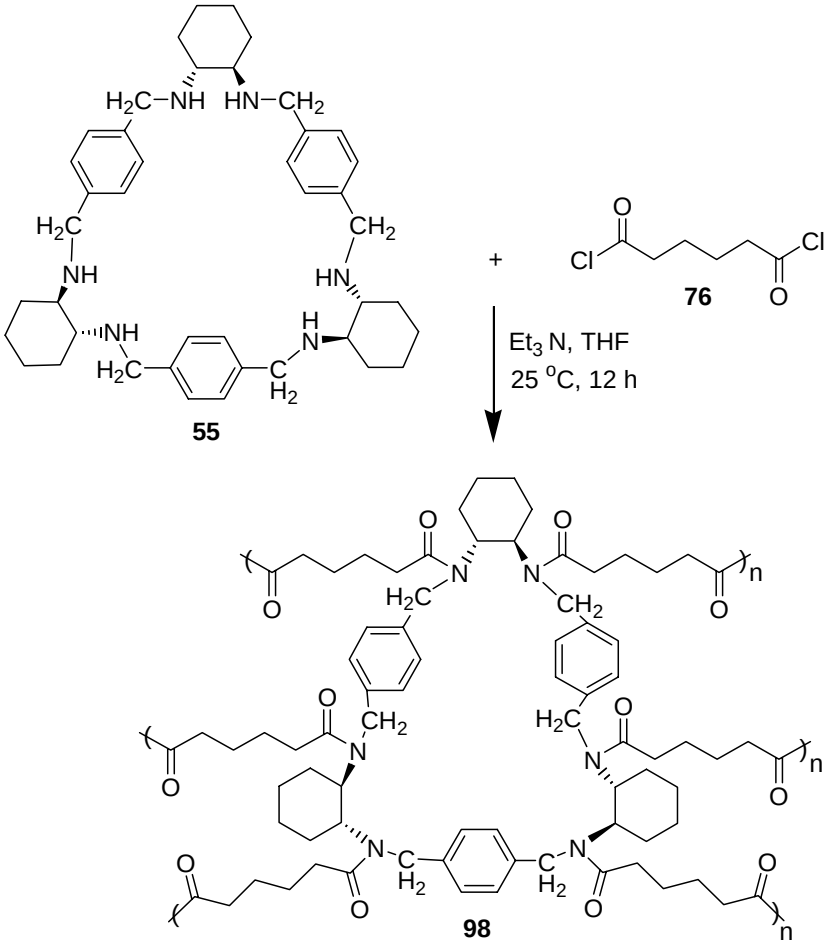


96

n = 2-7

Accordingly, we have envisaged the synthesis of chiral oligomeric macrocyclic amides and amines for applications in chromatographic resolutions and also to assess their material properties. For this purpose, we synthesized the macrocyclic amine **55** described in the introductory section (Scheme 16). We examined the reaction of the amine **55** with spacers like adipoyl chloride **76** and sebacoyl chloride **97**. When the macrocyclic amine **55** was reacted with adipoyl chloride, under dilute conditions, an insoluble polyamide **98** was obtained (Scheme 29). This could possibly be due to the formation of polymeric macrocycles.

Scheme 29

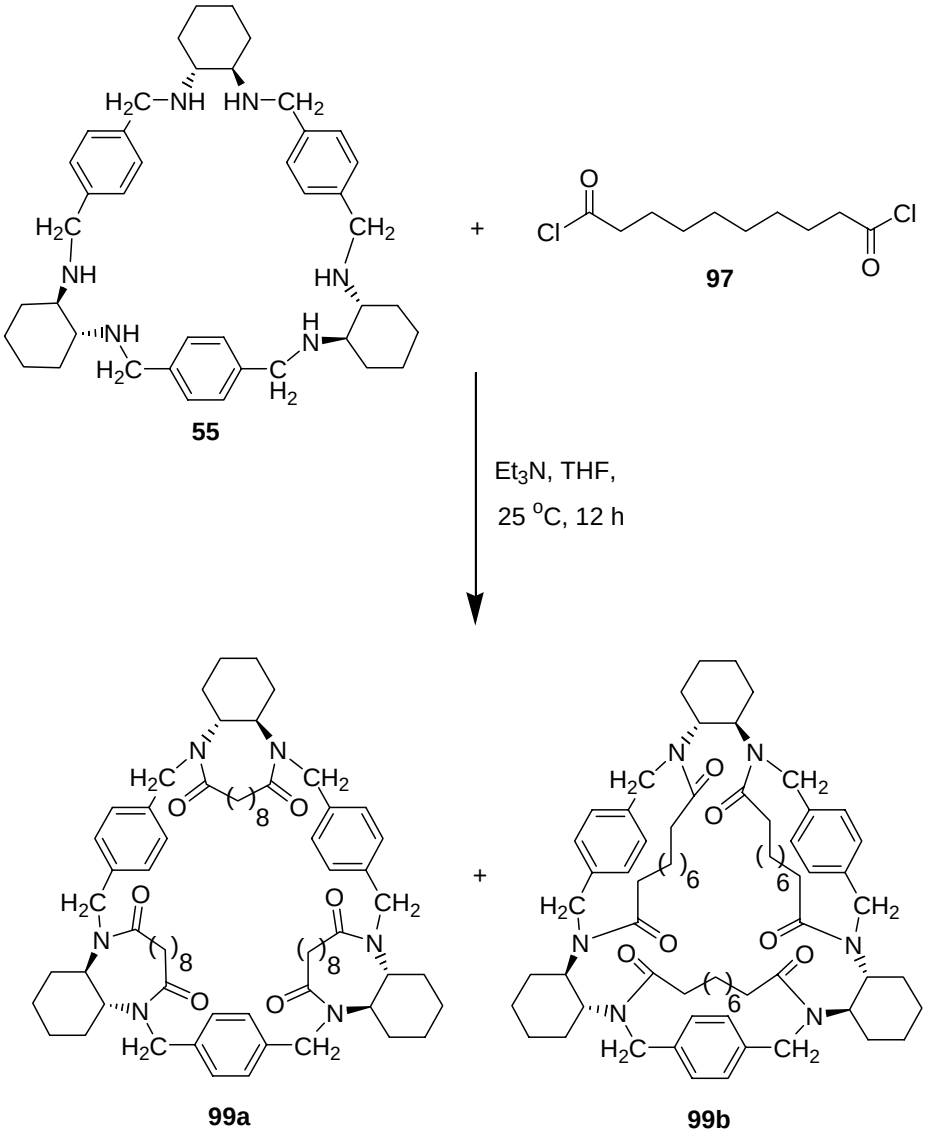


However, the reaction of the amine **55** with sebacoyl chloride **97** gave soluble polyamides (Scheme 30).

The MALDI-TOF mass spectral analysis showed the formation of a series of oligomers in this reaction (Figure 6). The intramolecular condensation of the macrocyclic amine **55** with three molecules of sebacoyl chloride gave the macrotetracyclic molecule **99** with molecular weight of 1148 as the major product. There are two structures possible with molecular weight of 1148 - **99a** and **99b**.

Although the formation of the structure **99a** is less probable, the cross linked structure **99b** could be more possible.

Scheme 30



M = 1148

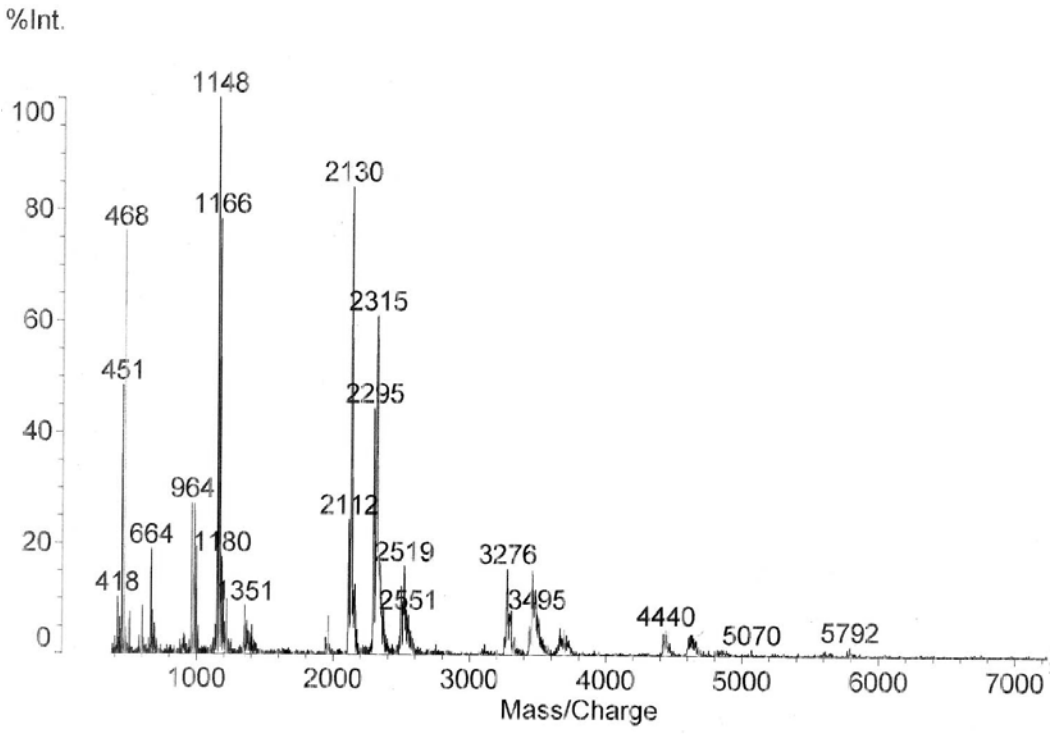


Figure 6. MALDI-TOF mass spectrum of the oligomers obtained from the reaction of 55 with 97

In addition, the condensation of two molecules of **55** with six molecules of **97** would have given the cyclized product **100** (M = 2130) and the incomplete reaction of the amine and the diacid chloride should have resulted in the products **101** (M = 2295) and **102** (M = 3276) (Figure 7).

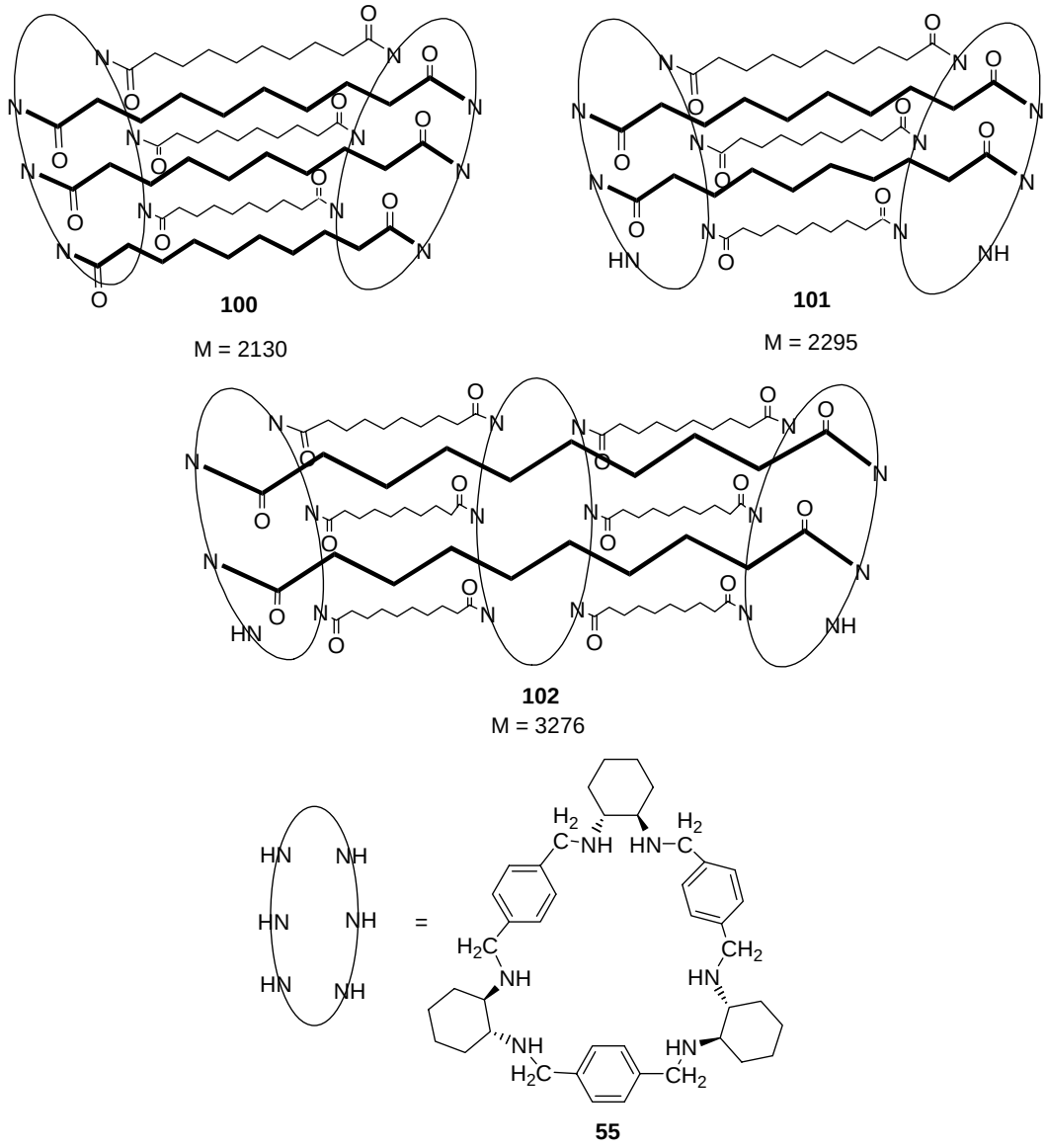
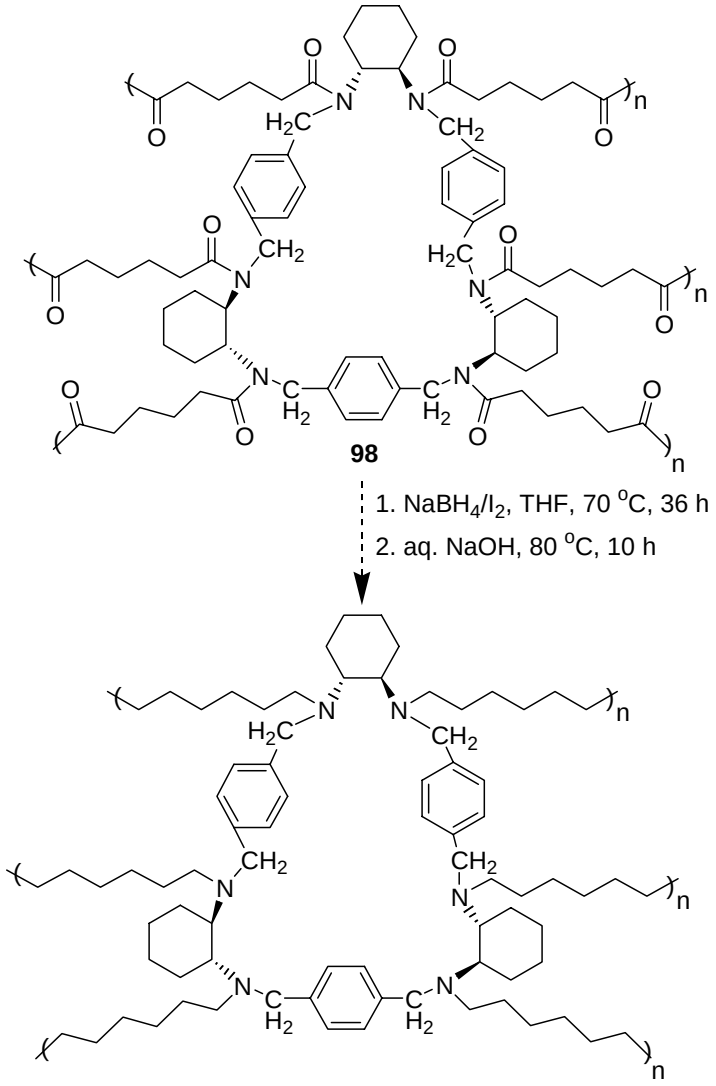


Figure 7. Graphical representation of the structures of 100, 101 and 102

However, the MALDI-TOF mass spectrum of the products obtained in the reduction of the polyamides of both adipoyl and sebacoyl chloride did not show any high molecular weight peaks corresponding to the reduced polyamides. Presumably, cleavage of the polyamides could have occurred during the course of the reaction (Scheme 31).

Scheme 31



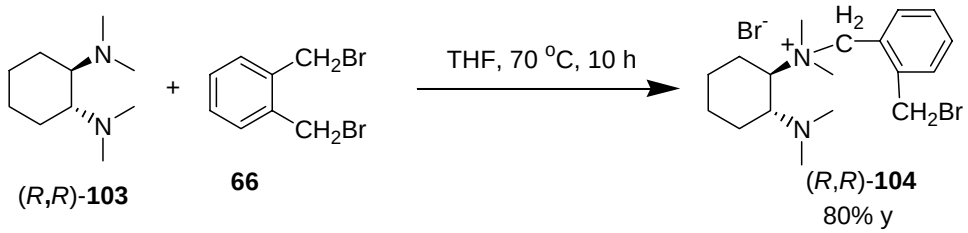
2.2.4 Synthesis of chiral quaternary ammonium salts

Chiral quaternary ammonium salts have been widely studied because of their potential synthetic applications as phase transfer catalysts for the synthesis of various natural and unnatural chiral derivatives[43-45] like amino acids, epoxy ketones and for use as anionic receptors.[46] In addition, polyammonium salts have been reported to exhibit certain biological properties, such as bacteriocidal and anti-heparin agents.[47]

We have envisaged the synthesis of chiral polyammonium salts from the (*R*,*R*)-*N*,*N*,*N*′,*N*′-tetramethyl-1,2-diaminocyclohexane **103** using the benzylic bromides **66**, **67** and **68**. The tetramethyl derivative **103** was prepared from *trans*-(±)-2-(*N*,*N*-dimethylamino)cyclohexanol through aziridinium ion intermediate and resolved using chiral 1,1′-bi-2-naphthol as outlined in Chapter 1. Alternately, the diamine **103** was also prepared from (*R*,*R*)-1,2-diaminocyclohexane **36** following a reported procedure.[48]

The monoammonium salt **104** was obtained from the reaction of the diamine **103** with the dibromide **66** in 80% yield (Scheme 32).

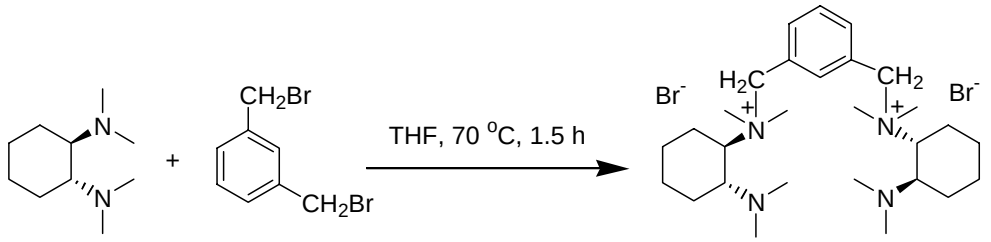
Scheme 32



(*R*,*R*)-**103** **66** (*R*,*R*)-**104** 80% y

The reaction of the diamine **103** with the 1,3-dibromide **67** in THF solvent gave the diammonium salt **105** along with other oligomeric products (Scheme 33). The mixture of the polyammonium salts, which precipitated from the reaction was fractionated between dichloromethane and water. The unreacted starting materials along with the low molecular weight salts were soluble in dichloromethane. The residue obtained by evaporation of the water was purified by chromatography on a silica gel column using a mixture of methanol and 10% aqueous ammonium bromide (98:2) as eluent to obtain the salt **105** in pure form.

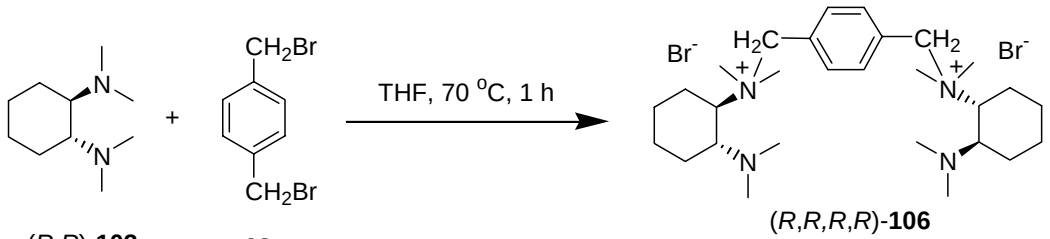
Scheme 33



(*R*,*R*)-**103** **67** (*R*,*R*,*R*,*R*)-**105**
35% y

The reaction of the diamine **103** with the 1,4-dibromide **68** also gave a mixture of polyammonium salts. The precipitated mixture of the salts was fractionated between dichloromethane and water. The mixture of salts obtained after evaporation of the water was chromatographed on a silica gel column using a mixture of methanol and 10% aqueous ammonium bromide (99:1) as eluent to obtain the diammonium salt **106** in 20 % yield (Scheme 34).

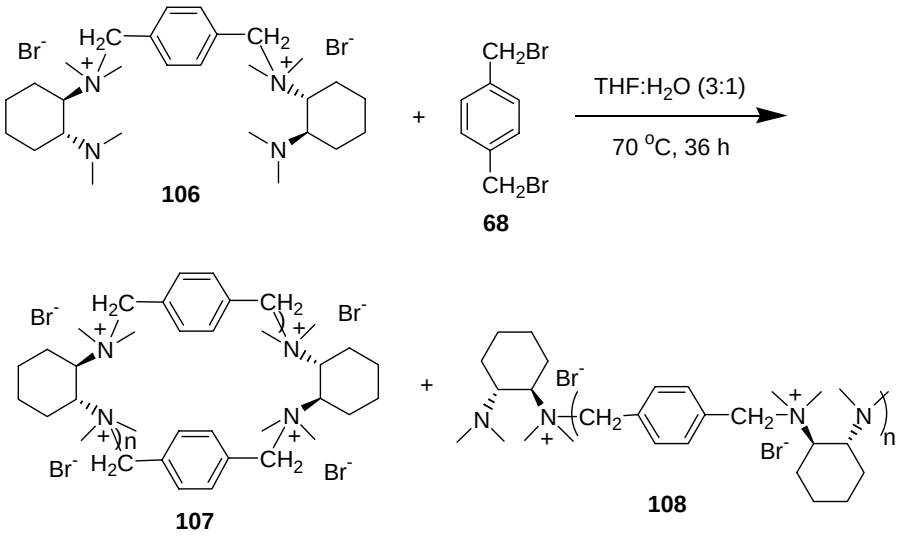
Scheme 34



(*R*,*R*)-**103** **68** (*R*,*R*,*R*,*R*)-**106**
20% y

We have then made attempts to synthesize chiral macrocyclic and polymeric ammonium salts by the reaction of the dicationic salt **106** with the 1,4-dibromide **68** in aqueous THF (Scheme 35).

Scheme 35



A mixture of products insoluble in DCM and soluble in methanol was obtained in the reaction. The ^{13}C-NMR spectrum of the products in CD_3OD showed thirteen peaks in the aliphatic region (17.0, 18.5, 22.1, 22.5, 23.9, 43.1, 44.5, 55.2, 61.4, 64.5, 64.9, 71.8, 73.1 δ ppm, 50 MHz) and four peaks in the aromatic region (128.2, 129.2, 131.1, 135.7 δ ppm, 50 MHz). Presumably, the macrocyclic products of the type **107** and the linear oligomeric products of the type **108** were obtained in the reaction. Further studies on the synthesis of these polycationic salts would lead to fruitful results.

2.3 Conclusions

A simple method of synthesis of chiral tertiary heterocyclic amine **69** and macrocyclic amines **70** and **74** from the (*R*,*R*)-*N*,*N*′-diisopropyl-1,2-diaminocyclohexane **65** was developed. The polyamidocarboxylic acid **77** with number average molecular weight of 27499 was prepared from the diamine **65** and adipoyl chloride **76**. The polyamide **77** was readily reduced using the $NaBH_2/I_2$ reagent system to obtain the polyamino alcohol **78**. The reaction of the (*R*,*R*)-1,2-diaminocyclohexane **36** with the acid chlorides **79**, **85** and **88** was carried out to obtain the polyamides **80**, **86** and **89** which could be readily reduced to the corresponding polyamines. The macrocyclic amine **87** could be isolated from the reduction products of the amide **86**. The oligomeric macrocyclic amides were prepared by the reaction of the macrocyclic amine **55** with sebacoyl chloride **97** and adipoyl chloride **76** and were characterized by MALDI-TOF. The chiral quaternary ammonium salts **104**, **105** and **106** were synthesized from the (*R*,*R*)-*N*,*N*,*N*′,*N*′-tetramethyl-1,2-diaminocyclohexane **103**.

2.4 Experimental Section

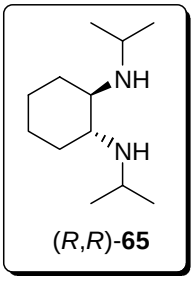
2.4.1 General information

Most of the information given in the experimental section of Chapter 1 is also applicable to the experiments described here. The mixture of *cis* and *trans*-1,2-diaminocyclohexane supplied by Lancaster was resolved using *L*-tartaric acid following a reported procedure to obtain (*R*,*R*)-1,2-diaminocyclohexane.[49] The dibromides were prepared from the corresponding diacids by reduction[37] followed by reaction with HBr. The acid chlorides were prepared from the corresponding acids by refluxing with thionyl chloride and purified by distillation under reduced pressure. Mass spectral analyses were carried out on a VG Autospec M Mass Spectrometer using EI technique and LSIMS technique (FAB Mass). MALDI-TOF mass spectral analyses were carried out using Kratos Kompact MALDI SEQ instrument. LCMS and CI mass spectra were recorded on a LCMS-2010A and Quattro LC, Micromass instruments. GPC was recorded on a Waters instrument with Styragel® columns (10^6, 10^5, 10^3 Å columns connected in series) equipped with a RI detector using THF as solvent at a flow rate of 1.0 mL/min. The X-ray diffraction measurements for the compounds **70** and **74** were carried out at 293 K on an automated Enraf-Nonius MACH3 diffractometer using graphite monochromated, Mo-Kα (λ = 0.71073 Å) radiation with CAD4 software.

2.4.2 Synthesis of (*R*,*R*)-*N*,*N*′-diisopropyl-1,2-diaminocyclohexane 65

(*R*,*R*)-1,2-Diaminocyclohexane **36** (11.4 g, 100 mmol) and KOH (25 g) were taken in isopropylbromide (100 mL) and refluxed for 48 h. The isopropyl bromide was

distilled out and to the residue water (40 mL) and dichloromethane (60 mL) were added and stirred for 10 minutes. The organic layer was separated and the aqueous layer was extracted with dichloromethane (20 mL). The combined organic extract was washed with brine (30 mL), dried over anhydrous sodium sulfate and the solvent was evaporated. The crude product was chromatographed on a silica gel column using hexanes:ethyl acetate (90:10) as eluent.



(*R*,*R*)-**65**

Yield 12.9 g (65%)

IR (neat) (cm^{-1}) 3296, 2958, 2927, 1471, 1170

^{1}H-NMR (200 MHz, $CDCl_3$, δ ppm) 0.96 (d, *J* = 6.5 Hz, 6H), 1.02 (d, *J* = 6.5 Hz, 6H), 1.15-1.24 (m, 2H), 1.64-1.68 (m, 5H), 2.00-2.14 (m, 5H), 2.84 (septet, *J* = 6 Hz, 2H) (**Spectrum No. 7**)

^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm) 22.5, 24.7, 25.0, 32.4, 45.3, 58.9 (**Spectrum No. 8**)

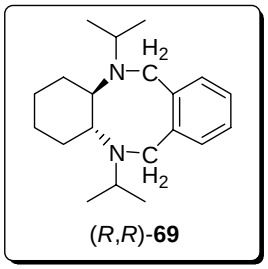
$[\alpha]_D^{25}$ -124.5 (*c* 0.5, CH_2Cl_2) [lit.[36a] $[\alpha]_D^{25}$ = -125.2 (*c* 9.6, CH_2Cl_2)]

2.4.3 Synthesis of chiral macrocyclic, oligomeric and polymeric amines

2.4.3.1 Reaction of (*R*,*R*)-*N*,*N'*-diisopropyl-1,2-diaminocyclohexane 65 with 1,2-bis(bromomethyl)benzene 66

To a solution of (*R*,*R*)-*N*,*N'*-diisopropyl-1,2-diaminocyclohexane **65** (0.50 g, 2.5 mmol) in acetonitrile (40 mL) was added the dibromide **66** (0.65 g, 2.5 mmol), K_2CO_3 (2 g), KI (20 mg) and the mixture was stirred under reflux for 12 h. The solids were filtered off and the filtrate was evaporated. The residue obtained after evaporation was extracted with dichloromethane (2 X 20 mL) and water (30 mL). The combined

organic extract was washed with brine (15 mL), dried over anhydrous sodium sulfate and the solvent was evaporated. The crude product was purified by column chromatography on a neutral alumina column using hexanes:ethyl acetate (96:4) as eluent to isolate the heterocyclic amine **69**.



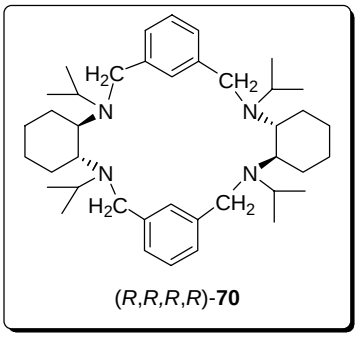
(*R*,*R*)-**69**

Yield	0.60 g (80%)
IR (neat)	(cm^{-1}) 3058, 2927, 1448, 1170
^{1}H-NMR	(200 MHz, $CDCl_3$, δ ppm) 1.10 (d, *J* = 6.4 Hz, 12H), 1.31-1.36 (m, 3H), 1.56-1.77 (m, 5H), 2.70-2.66 (m, 2H), 3.17 (septet, *J* = 6.4 Hz, 2H), 3.78 (d, *J* = 13.5 Hz, 2H), 4.46 (d, *J* = 13.4 Hz, 2H), 7.09 (br s, 4H) (**Spectrum No. 9**)
^{13}C-NMR	(50 MHz, $CDCl_3$, δ ppm) 20.6, 22.6, 26.3, 31.7, 49.0, 50.3, 64.5, 126.4, 129.5, 140.8 (**Spectrum No. 10**)
$[\alpha]_D^{25}$	+63.0 (*c* 0.4, 1N HCl)
MS (EI)	m/z 300 (M^+) (**Spectrum No. 35**)

2.4.3.2 Reaction of (*R*,*R*)-*N*,*N'*-diisopropyl-1,2-diaminocyclohexane 65 with 1,3-bis(bromomethyl)benzene 67

To a solution of (*R*,*R*)-*N*,*N'*-diisopropyl-1,2-diaminocyclohexane **65** (0.50 g, 2.5 mmol) in acetonitrile (40 mL) was added the dibromide **67** (0.65 g, 2.5 mmol), K_2CO_3 (2 g), KI (20 mg) and the mixture was stirred under reflux for 12 h. The solids were filtered off and extracted with dichloromethane (2 X 20 mL) and water (30 mL). The combined organic extract was dried over anhydrous sodium sulfate and the solvent was evaporated. The crude product (0.65 g) was stirred with oxalic acid (0.25 g, 2 mmol) in

dichloromethane (40 mL) for 8 h and was filtered. The precipitate was suspended in a mixture of dichloromethane (10 mL) and 1M NaOH (5 mL) until dissolution occurred. The organic layer was separated, washed with brine (10 mL), dried over anhydrous sodium sulfate and evaporated to obtain the high molecular weight oligomers (0.16 g). The filtrate was concentrated and the residue obtained was stirred with dichloromethane (10 mL) and 1M NaOH (5 mL) until dissolution occurred. The organic layer was separated and the aqueous layer was extracted with dichloromethane (2 X 10 mL). The combined organic extract was washed with brine (10 mL), dried over anhydrous sodium sulfate and the solvent was evaporated. The crude product was purified by chromatography on a neutral alumina column using hexanes:ethyl acetate (90:10) as eluent to isolate the macrocyclic amine **70** in pure form.



(*R*,*R*,*R*,*R*)-**70**

Yield 0.45 g (60%)

mp 244-248 ^{o}C (with decomposition)

IR (KBr) (cm^{-1}) 2962, 2932, 1464, 1167

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm; 0 ^{o}C)

0.80 (d, *J* = 6.8 Hz, 6H), 0.98 (d, *J* = 6.8 Hz, 6H), 1.11 (d, *J* = 6 Hz, 6H), 1.19-1.21 (m, 6H), 1.42 (d, *J* = 6 Hz, 6H), 1.64-1.66 (m, 2H), 1.78-1.80 (m, 6H), 2.37 (d, *J* = 10.8 Hz, 2H), 2.56-2.69 (m, 6H), 2.84 (t, *J* = 8 Hz, 2H), 3.00 (d, *J* = 11.6 Hz, 2H), 3.21 (septet, *J* = 6.0 Hz, 2H), 3.49 (d, *J* = 12 Hz, 2H), 3.74 (d, *J* = 12 Hz, 2H), 6.88-6.89 (m, 2H), 6.98 (d, *J* = 6.8 Hz, 2H), 7.04-7.06 (m, 2H), 8.03 (s, 2H) (**Spectrum No. 11**)

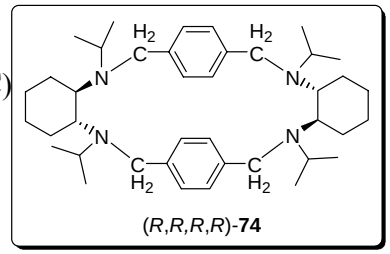
^{13}C-NMR	(50 MHz, $CDCl_3$, δ ppm) 19.1, 19.8, 21.4, 23.9, 26.5, 26.9, 31.1, 45.5, 47.5, 48.4, 58.0, 125.8, 127.7, 128.8, 133.3, 139.6, 142.0 (**Spectrum No. 12**)
$[\alpha]_D^{25}$	-95.0 (*c* 0.4, 1N HCl)
MS (FAB)	m/z 601 (M+1) (**Spectrum No. 36**)
Analysis	Calculated for $C_{40}H_{64}N_4$: C, 80.0%; H, 10.6%; N, 9.3%
	Found : C, 79.9%; H, 10.9%; N, 8.9%

2.4.3.3 Reaction of (*R*,*R*)-*N*,*N*′-diisopropyl-1,2-diaminocyclohexane 65 with 1,4-bis(bromomethyl)benzene 68

To a solution of (*R*,*R*)-*N*,*N*′-diisopropyl-1,2-diaminocyclohexane **65** (0.50 g, 2.5 mmol) in acetonitrile (40 mL) was added the dibromide **68** (0.65 g, 2.5 mmol), K_2CO_3 (2 g), KI (20 mg) and the mixture was stirred under reflux for 12 h. The solids were filtered off and extracted with dichloromethane (2 X 20 mL) and water (30 mL). The combined organic extract was dried over anhydrous sodium sulfate and the solvent was evaporated. The crude product (0.32 g) was stirred with oxalic acid (0.12 g, 1 mmol) in dichloromethane (30 mL) for 6 h and was filtered. The precipitate was suspended in a mixture of dichloromethane (10 mL) and 1M NaOH (5 mL) until dissolution occurred. The organic layer was separated and the aqueous layer was extracted with dichloromethane (2 X 10 mL). The combined organic extract was washed with brine (10 mL), dried over anhydrous sodium sulfate and the solvent was evaporated to obtain the macrocyclic amine **74** in pure form.

Yield	0.25 g (34%)
mp	252 ^{o}C (with decomposition)

IR (KBr) (cm^{-1}) 2961, 2922, 1167


(*R*,*R*,*R*,*R*)-**74**

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm; -20 ^oC) 0.86 (d, *J* = 6.8 Hz, 6H), 1.02 (d, *J* = 6.8 Hz, 6H), 1.10 (d, *J* = 6.4 Hz, 6H), 1.14-1. 28 (m, 6H), 1.42 (d, *J* = 6.4 Hz, 6H), 1.68-1.74 (m, 2H), 1.83-1.90 (m, 6H), 2.26 (d, *J* = 12 Hz, 2H), 2.62 (t, *J* = 9.6 Hz, 2H), 2.80 (septet, *J* = 6.8 Hz, 2H), 2.84 (t, *J* = 8.8 Hz, 2H), 2.85 (d, *J* = 14.8 Hz, 2H), 3.15 (septet, *J* = 6.4 Hz, 2H), 3.20 (d, *J* = 14.8 Hz, 2H), 3.22 (d, *J* = 13.2 Hz, 2H), 3.58 (d, *J* = 13.6 Hz, 2H), 6.98 (s, 8H) (**Spectrum No. 13**)

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm) 18.9, 20.3, 21.8, 25.5, 26.6, 27.2, 28.2, 30.6, 45.5, 47.5, 49.0, 56.7, 60.1, 127.6, 129.0, 138.7, 139.7 (**Spectrum No. 14**)

$[\alpha]_D^{25}$ -20.5 (*c* 0.3, CH_2Cl_2)

MS (FAB/LCMS) m/z 601 (M+1) (**Spectrum No. 37**)

Analysis Calculated for $C_{40}H_{64}N_4$: C, 80.0%; H, 10.6%; N, 9.3%

Found : C, 79.9%; H, 10.8%; N, 9.0%

Oxalic acid complex of the macrocyclic amine 74

mp > 300 ^oC

IR (KBr) (cm^{-1}) 3412, 2937, 1728, 1637, 1460, 1388

^{1}H-NMR (400 MHz, CD_3OD, δ ppm) 1.00 (d, *J* = 6.4 Hz, 6H), 1.22 (d, *J* = 6.8 Hz, 6H), 1.52 (d, *J* = 7.2 Hz, 6H), 1.56-1.61 (m, 8H), 1.83 (d, *J* = 5.6 Hz, 6H), 1.85-1.91 (m, 4H), 2.00-2.04 (m, 2H), 2.16 (d, *J*

= 12 Hz, 2H), 2.56 (d, *J* = 12 Hz, 2H), 3.01-3.05 (m, 4H), 3.48 (t, *J* = 11.4 Hz, 2H), 3.64 (d, *J* = 16.8 Hz, 2H), 4.02-4.07 (m, 2H), 4.11 (d, *J* = 12.8 Hz, 2H), 4.50 (d, *J* = 14 Hz, 2H), 6.87 (d, *J* = 7.6 Hz, 4H), 7.46 (d, *J* = 7.6 Hz, 4H)

^{13}C-NMR (50 MHz, CD_3OD, δ ppm) 16.2, 20.0, 21.7, 24.1, 24.7, 25.5, 28.6, 49.0, 49.8, 52.1, 54.3, 63.8, 127.7, 129.8, 130.9, 138.6, 164.2

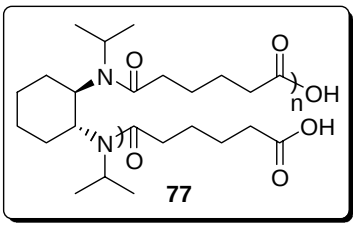
2.4.3.4 Reaction of (*R*,*R*)-*N*,*N*′-diisopropyl-1,2-diaminocyclohexane 65 with adipoyl chloride 76

To a stirred solution of (*R*,*R*)-*N*,*N*′-diisopropyl-1,2-diaminocyclohexane **65** (0.50 g, 2.5 mmol) and triethylamine (2 mL, 14 mmol) in tetrahydrofuran (40 mL) was added adipoyl chloride **76** (0.36 mL, 2.5 mmol) at 0 ^{o}C and the reaction mixture was stirred at 25 ^{o}C for 12 h. The solids were filtered off and the solution was extracted with ether (2 X 30 mL) and water (25 mL). The organic extract was washed with 10% aq. NaOH (2 X 10 mL) and brine (20 mL). The combined organic extract was dried over anhydrous sodium sulfate and the solvent was evaporated to obtain the polyamide **77**.

Yield 0.60 g

IR (neat) (cm^{-1}) 3476, 2964, 2934, 1741, 1631

^{1}H-NMR (200 MHz, $CDCl_3$, δ ppm) 2.64 (t, *J* = 7.4 Hz), 2.79 (d, *J* = 7.0 Hz), 2.88-2.92 (m),



77

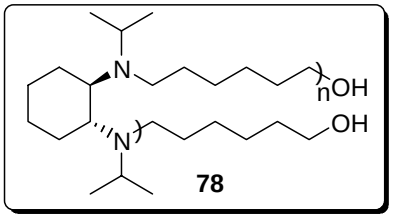
2.99 (d, *J* = 6.0 Hz), 3.10 (d, *J* = 6.8 Hz), 3.21-3.24 (br), 3.73-4.13 (br), 4.89-5.09 (br), 5.55-5.67 (br), 5.83-5.95 (br) **Spectrum No. 15**)

$[\alpha]_D^{25}$ -42.0 (*c* 0.8, CH_2Cl_2)

MS (GPC) M_n = 27499; M_w = 30720; PDI = 1.11 (**Spectrum No. 38**)

2.4.3.5 Reduction of the polyamide 77

To a suspension of $NaBH_4$ (0.42 g, 12 mmol) in tetrahydrofuran (75 mL) was added a solution of I_2 (1.40 g, 6 mmol) in THF (30 mL) at 0 ^oC under nitrogen atmosphere over 30 minutes. The polyamide **77** (0.60 g) dissolved in THF (30 mL) was added to the generated diborane and refluxed for 12 h. The reaction was quenched with 1M HCl (10 mL). The mixture was neutralized with 1M NaOH (15 mL) and the resultant amino alcohol was extracted with ether (2 X 15 mL). The organic extract was washed with brine (30 mL), dried over anhydrous sodium sulfate and the solvent was evaporated to obtain the polyamino alcohol **78**.



78

Yield 0.30 g

IR (neat) (cm^{-1}) 3292, 2961, 2930

^{1}H-NMR (200 MHz, $CDCl_3$, δ ppm) 0.86-1.02 (m), 1.14-1.27 (m), 1.58-1.71 (m), 1.93-1.98 (m), 2.27-2.34 (m), 2.69-2.79 (m), 2.87-2.94 (m), 3.50 (t, *J* = 6.4 Hz) (**Spectrum No. 17**)

$[\alpha]_D^{25}$ -80.0 (*c* 0.4, CH_2Cl_2)

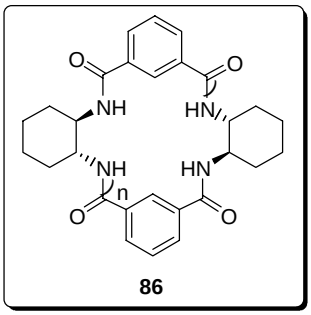
2.4.3.6 Synthesis of the chiral macrocyclic amine 87

2.4.3.6.1 Reaction of (*R*,*R*)-1,2-diaminocyclohexane 36 with isophthaloyl chloride

To a stirred solution of (*R*,*R*)-1,2-diaminocyclohexane **36** (1.14 g, 10 mmol) and triethylamine (5.6 mL, 40 mmol) in dichloromethane (40 mL) was added isophthaloyl chloride **85** (2.0 g, 10 mmol) at 0^{o}C and the reaction mixture was stirred at 25 ^{o}C for 12 h. The reaction was quenched with water (15 mL). The solids were filtered off and washed with dichloromethane (20 mL) to obtain the insoluble polyamide **86**.

Yield 2.0 g

IR (KBr) (cm^{-1}) 3290, 2932, 1635, 1543, 866

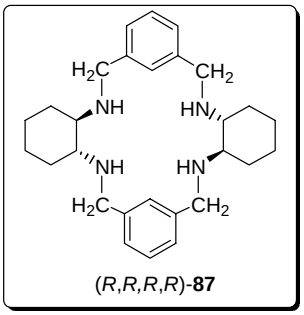


86

2.4.3.6.2 Reduction of the polyamide 86

To a suspension of $NaBH_4$ (1.43 g, 40 mmol) in tetrahydrofuran (100 mL) was added a solution of I_2 (4.8 g, 20 mmol) in THF (30 mL) at 0 ^{o}C under nitrogen atmosphere over 30 minutes. The polyamide **86** (1.0 g) was added to the generated diborane and refluxed for 24 h. The reaction was quenched with methanol and the solvents were evaporated. The residue obtained after evaporation was refluxed with 10N KOH for 6 h and the resultant polyamine was extracted with dichloromethane (2 X 30 mL). The combined organic extract was washed with brine (30 mL), dried over anhydrous sodium sulfate and the solvent was evaporated to obtain the polyamine. The crude amine was chromatographed on a silica gel column using chloroform:methanol (95:5) as eluent to isolate the macrocyclic amine **87** in pure form.

Yield 0.20 g (23%)



(*R*,*R*,*R*,*R*)-**87**

mp	108-110 ^{o}C
IR (KBr)	(cm^{-1}) 3296, 3024, 2928, 1452, 1114, 787
^{1}H-NMR	(400 MHz, $CDCl_3$, δ ppm) 1.05-1.07 (m, 4H), 1.26-1.31 (m, 4H), 1.77-1.88 (m, 9H), 2.26-2.31 (m, 7H), 3.66 (d, *J* = 12.8 Hz, 4H), 3.96 (d, *J* = 13.2 Hz, 4H), 7.07 (d, *J* = 7.6 Hz, 4H), 7.20 (t, *J* = 7.6 Hz, 2H), 7.64 (s, 2H) (**Spectrum No. 19**)
^{13}C-NMR	(50 MHz, $CDCl_3$, δ ppm) 25.1, 31.4, 50.8, 60.9, 126.4, 126.9, 127.7, 141.1 (**Spectrum No. 20**)
$[\alpha]_D^{25}$	-101 (*c* 0.4, $CHCl_3$)
LCMS	m/z 433 (M+1) (**Spectrum No. 39**)
Analysis	Calculated for $C_{28}H_{40}N_4$: C, 77.7%; H, 9.2%; N, 12.9%
	Found : C, 77.7%; H, 9.3%; N, 12.8%

2.4.3.7 Synthesis of the chiral macrocyclic amine 55[29]

2.4.3.7.1 Synthesis of the chiral macrocyclic imine 54

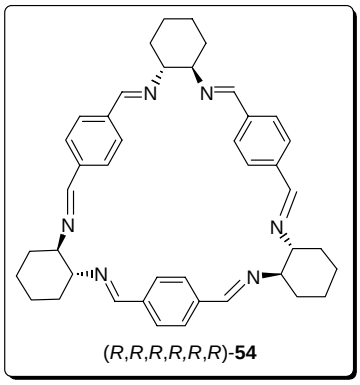
To a solution of (*R*,*R*)-1,2-diaminocyclohexane **36** (1.14 g, 10 mmol) in dichloromethane (10 mL) was added at 0 ^{o}C a solution of terephthalaldehyde **53** (1.34 g, 10 mmol) in dichloromethane (15 mL). The mixture was stirred at 25 ^{o}C for 2-3 h, the solvent was evaporated and the crude product was crystallized from ethyl acetate to obtain **54**.

Yield 2.0 g (90%)

mp > 300 °C [lit.[29] mp: >360 °C]

IR (KBr) (cm^{-1}) 3026, 2926, 1641, 933, 821

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 1.39-1.49 (m, 6H), 1.82-1.86 (m, 18H), 3.37-3.40 (m, 6H), 7.54 (s, 12H), 8.16 (s, 6H)


(*R*,*R*,*R*,*R*,*R*,*R*)-**54**

^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm) 24.4, 32.7, 74.4, 127.9, 137.8, 160.1

$[\alpha]_D^{25}$ -354 (*c* 0.4, $CHCl_3$); [lit.[29] $[\alpha]_D^{25}$ = -356.2 (*c* 0.5, $CHCl_3$)]

2.4.3.7.2 Synthesis of the chiral macrocyclic amine 55

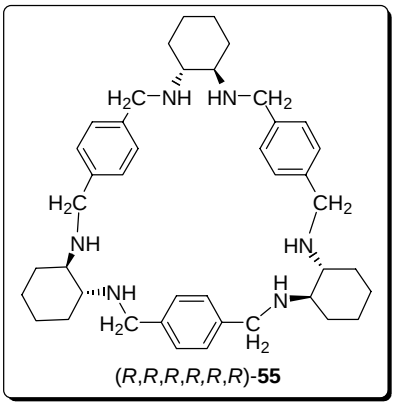
To a stirred solution of **54** (1.0 g, 1.55 mmol) in tetrahydrofuran-methanol (1:1, 60 mL) $NaBH_4$ (0.58 g, 16 mmol) was added gradually and the solution was stirred at 25 °C for 2 h. After removal of solvents the residue was extracted with dichloromethane (2 X 20 mL) and water (2 X 20 mL). The combined organic extract was washed with brine (20 mL), dried over anhydrous sodium sulfate and the solvent was evaporated to obtain the amine **55** in pure form.

Yield 0.72 g (72%)

mp 148-151 °C [lit.[29] mp : 153-155 °C]

IR (KBr) (cm^{-1}) 3294, 3015, 2924, 1452, 798

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 1.16-1.22 (m, 6H), 1.25-1.30 (m, 6H), 1.78-1.79 (m, 6H), 2.22-2.26 (m, 6H),


(*R*,*R*,*R*,*R*,*R*,*R*)-**55**

	2.38-2.40 (m, 6H), 3.03 (br s, 6H), 3.67 (d, J = 12.8 Hz, 6H), 3.98 (d, J = 12.8 Hz, 6H), 7.30 (s, 12H)
^{13}C-NMR	(50 MHz, $CDCl_3$, δ ppm) 25.1, 31.4, 50.5, 60.7, 127.9, 139.3
$[\alpha]_D^{25}$	-80.0 (c 0.5, $CHCl_3$) [lit.[29] $[\alpha]_D^{25}$ = -81 (c 0.5, $CHCl_3$)]

2.4.3.8 Reaction of the chiral macrocyclic amine 55 with adipoyl chloride 76

To a stirred solution of the macrocyclic amine **55** (0.50 g, 0.77 mmol) and triethylamine (3 mL, 21 mmol) in tetrahydrofuran (150 mL), adipoyl chloride **76** (0.33 mL, 2.3 mmol) dissolved in tetrahydrofuran (50 mL) was added at 0 ^oC and the reaction mixture was stirred at 25 ^oC for 12 h. The reaction was quenched with water (40 mL), the solids were filtered off and washed with tetrahydrofuran to obtain the mixture of insoluble polyamides **98**.

Yield	0.70 g
IR (KBr)	(cm^{-1}) 3485, 2934, 1637

2.4.3.9 Reaction of the chiral macrocyclic amine 55 with sebacoyl chloride 97

To a stirred solution of the macrocyclic amine **55** (0.50 g, 0.77 mmol) and triethylamine (3 mL, 21 mmol) in tetrahydrofuran (150 mL), sebacoyl chloride **97** (0.49 mL, 2.3 mmol) dissolved in tetrahydrofuran (50 mL) was added at 0 ^oC and the reaction mixture was stirred at 25 ^oC for 12 h. The solids were filtered off and the filtrate was extracted with ether (2 X 30 mL) and water (40 mL). The combined organic extract was washed with brine (30 mL), dried over anhydrous sodium sulfate and the solvent was evaporated to obtain the mixture of polyamides.

Yield	0.87 g

IR (KBr) (cm^{-1}) 2928, 1734, 1643, 804

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 0.811-1.54 (br), 2.19-2.29 (br, s), 2.97 (q, *J* = 7.6 Hz), 7.03-7.20 (br)

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm) 8.5, 25.0, 27.7, 29.0, 29.6, 45.2, 53.4, 125.9 (br), 139.0 (br), 176.9 (br)

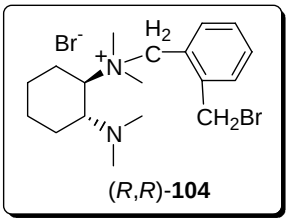
$[\alpha]_D^{25}$ -28.8 (*c* 0.5, $CHCl_3$)

2.4.4 Synthesis of the chiral quaternary ammonium salts

2.4.4.1 Reaction of (*R*,*R*)-*N*,*N*,*N*′,*N*′-tetramethyl-1,2-diaminocyclohexane 103 with 1,2-bis(bromomethyl)benzene 66

(*R*,*R*)-*N*,*N*,*N*′,*N*′-Tetramethyl-1,2-diaminocyclohexane **103** (0.34 g, 2 mmol) and the dibromide **66** (0.26 g, 1 mmol) were refluxed in tetrahydrofuran (25 mL). After 10 h, the solvent was decanted and the precipitated monoammonium salt **104** was purified by crystallization from methanol.

Yield 0.48 g (80%)



(*R*,*R*)-**104**

mp 172-174 °C

IR (KBr) (cm^{-1}) 3398, 3007, 2955, 1485, 1458, 869, 746

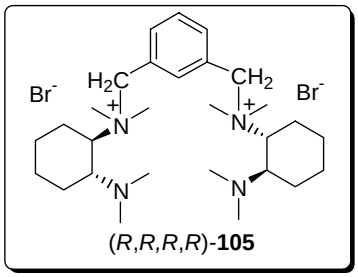
^{1}H-NMR (400 MHz, D_2O, δ ppm) 1.39-1.48 (m, 1H), 1.70-1.98 (m, 6H), 2.15-2.23 (m, 1H), 2.36-2.44 (m, 1H), 3.16 (d, *J* = 7.2 Hz, 6H), 3.34 (s, 3H), 3.50 (s, 3H), 3.69-3.71 (m, 1H), 4.67 (d, *J* = 14.4 Hz, 1H), 4.71 (d, *J* = 14.4 Hz, 1H), 5.08 (d, *J* = 5.2 Hz, 1H), 5.12 (d, *J* = 5.2 Hz, 1H), 7.73-7.76 (m, 4H) (**Spectrum No. 21**)

^{13}C-NMR	(50 MHz, D_2O, δ ppm) 14.3, 14.8, 19.1, 21.9, 45.0, 47.3, 50.6, 55.3, 62.7, 65.6, 68.6, 70.7, 127.9, 130.1, 132.1, 134.1, 135.5 (**Spectrum No. 22**)
$[\alpha]_D^{25}$	+25.8 (*c* 0.4, MeOH)
LCMS	m/z 353 (M-Br)
Analysis	Calculated for $C_{18}H_{30}N_2Br_2$: C, 49.8%; H, 6.9%; N, 6.4%; Br, 36.9%
	Found : C, 49.7%; H, 6.9%; N, 6.4% Br, 36.8%

2.4.4.2 Reaction of (*R*,*R*)-*N*,*N*,*N*′,*N*′-tetramethyl-1,2-diaminocyclohexane 103 with 1,3-bis(bromomethyl)benzene 67

(*R*,*R*)-*N*,*N*,*N*′,*N*′-Tetramethyl-1,2-diaminocyclohexane **103** (0.34 g, 2 mmol) and the dibromide **67** (0.26 g, 1 mmol) were refluxed in tetrahydrofuran (15 mL) for 1.5 h. The precipitate obtained was dissolved in dichloromethane (5 mL) and water (5 mL). The organic layer was separated and the aqueous layer was washed with dichloromethane (2 X 5 mL). The water was evaporated to obtain the mixture of salts, which was chromatographed on a silica gel column (60-120 mesh) using methanol:10 % aqueous NH_4Br (98:2) as eluent to isolate the diammonium salt **105** in pure form.

Yield	0.21 g (35%)
mp	132-134 °C
IR (KBr)	(cm^{-1}) 3416, 3018, 2935, 1479, 1456



(*R*,*R*,*R*,*R*)-**105**

^{1}H-NMR	(400 MHz, $CDCl_3$, δ ppm) 1.22-1.25 (m, 2H), 1.36-1.49 (m, 4H), 1.72-1.82 (m, 3H), 1.93-2.09 (m, 6H), 2.34 (s, 12H), 2.49 (br ,

1H), 2.84-2.89 (m, 2H), 3.24 (d, *J* = 5.6 Hz, 12H), 4.14-4.19 (m, 2H), 4.90 (d, *J* = 12 Hz, 2H), 5.40 (d, *J* = 12 Hz, 2H), 7.49 (t, *J* = 7.6 Hz, 1H), 7.77 (d, *J* = 7.2 Hz, 2H), 8.70 (s, 1H) (**Spectrum No. 23**)

^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm) 23.0, 24.2, 25.4, 27.4, 40.2, 48.5, 48.7, 64.1, 64.9, 74.0, 129.3, 135.2, 139.3 (**Spectrum No. 24**)

$[\alpha]_D^{25}$ -40.7 (*c* 0.4, $CHCl_3$)

LCMS m/z 524 (M-Br)

Analysis Calculated for $C_{28}H_{52}N_4Br_2$: C, 55.6%; H, 8.6%; N, 9.2%; Br, 26.4%

Found : C, 55.5%; H, 8.7%; N, 9.3%; Br, 26.5%

2.4.4.3 Reaction of (*R*,*R*)-*N*,*N*,*N*′,*N*′-tetramethyl-1,2-diaminocyclohexane 103 with 1,4-bis(bromomethyl)benzene 68

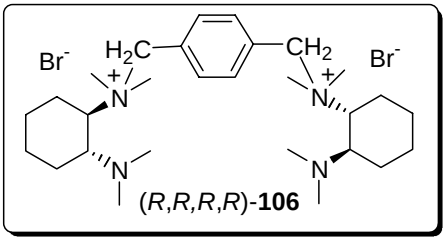
(*R*,*R*)-*N*,*N*,*N*′,*N*′-Tetramethyl-1,2-diaminocyclohexane **103** (0.34 g, 2 mmol) and the dibromide **68** (0.26 g, 1 mmol) were refluxed in tetrahydrofuran (15 mL) for 1 h. The precipitate obtained was dissolved in dichloromethane (5 mL) and water (5 mL). The organic layer was separated and the aqueous layer was washed with dichloromethane (2 X 5 mL). The water was evaporated to obtain the mixture of salts which was chromatographed on a silica gel column (100-200 mesh) using methanol:10% aqueous NH_4Br (99:1) as eluent to isolate the diammonium salt **106**.

Yield 0.12 g (20%)

mp 182-184 ^oC

IR (KBr) (cm^{-1}) 3425, 2932, 1458, 860

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm)



(*R*,*R*,*R*,*R*)-**106**

1.23-1.29 (m, 2H), 1.35-1.56 (m, 4H), 1.68-1.74 (m, 2H), 1.79-1.83 (m, 2H), 1.93-2.04 (m, 5H), 2.34 (s, 12H), 2.55-2.60 (m, 1H), 2.83-2.88 (m, 2H), 3.20 (s, 6H), 3.25 (s, 6H), 4.24-4.29 (m, 2H), 4.99 (d, *J* = 12 Hz, 2H), 5.42 (d, *J* = 12 Hz, 2H), 7.81 (s, 4H) (**Spectrum No. 25**)

^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm) 23.0, 24.2, 25.4, 27.5, 40.2, 47.9, 48.7, 64.3, 64.9, 73.7, 130.6, 134.2 (**Spectrum No. 26**)

$[\alpha]_D^{25}$ -53.4 (*c* 0.4, $CHCl_3$)

LCMS m/z 523 ($M-Br^-$)

Analysis Calculated for $C_{28}H_{52}N_4Br_2$: C, 55.6%; H, 8.6%; N, 9.2%; Br, 26.4%

Found : C, 55.7%; H, 8.6%; N, 9.2%; Br, 26.5%

2.5 References

1. Pederson, C. J. *J. Am. Chem. Soc.* **1967**, *89*, 2945.
2. (a) Helgeson, R. C.; Mazaleyrat, J.-P.; Cram, D. J. *J. Am. Chem. Soc.* **1981**, *103*, 3929. (b) Cram, D. J. *Science* **1983**, *219*, 1177. (c) Cram, D. J. *Science* **1988**, *240*, 760.
3. Lehn, J.-M. *Science* **1985**, *227*, 849.
4. (a) Cram, D. J. *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1009. (b) Lehn, J.-M. *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 90. (c) Pederson, C. J. *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1021.
5. Cram, D. J.; Cram, J. M. *Acc. Chem. Res.* **1978**, *11*, 8.
6. Zhang, X. X.; Bradshaw, J. S.; Izatt, R. M. *Chem. Rev.* **1997**, *97*, 3313.
7. (a) Aspinall, H. C. *Chem. Rev.* **2002**, *102*, 1807. (b) Groves, J. T.; Viski, P. *J. Org. Chem.* **1990**, *55*, 3628. (c) O'Malley, S.; Kodadek, T. *Organometallics* **1992**, *11*, 2299.
8. (a) Breslow, R.; Czanic, A. W.; Lauer, M.; Leppkes, R.; Winkler, J.; Zimmerman, S. *J. Am. Chem. Soc.* **1986**, *108*, 1969. (b) Diederich, F. In *Cyclophanes*; RSC: Cambridge, 1991, 276.
9. Gasparrini, F.; Misiti, D.; Villani, C. *J. Org. Chem.* **1995**, *60*, 4314.
10. (a) Wenzel, T. J.; Thurston, J. E. *J. Org. Chem.* **2000**, *65*, 1243. (b) Yuan, Q.; Fu, E.; Wu, X.; Fang, M.; Xue, P.; Wu, C.; Chen, J. *Tetrahedron Lett.* **2002**, *43*, 3935.

11. (a) Shu, Y. Z. *J. Nat. Prod*. **1998**, *61*, 1053. (b) Newman, D. J.; Gragg, G. M.; Snader, K. M. *Nat. Prod. Rep*. **2000**, *17*, 215.

12. Armstrong, D. W.; Tang, Y.; Chen, S.; Zhou, Y.; Bagwill, C.; Chen, J.-R. *Anal. Chem*. **1994**, *66*, 1473.

13. Sogah, G. D. Y.; Cram, D. J. *J. Am. Chem. Soc*. **1979**, *108*, 3035.

14. (a) Behr, J. P.; Girodeau, J. M.; Hayward, R. C.; Lehn, J.-M.; Sauvage, J.-P. *Helvitica Chimica Acta* **1980**, *63*, 2096. (b) Lehn, J.-M.; Sirlin, C. *J. Chem. Soc., Chem. Commun*. **1978**, 949.

15. Naemura, K.; Takeuchi, S.; Hirose, K.; Tobe, Y.; Kaneda, T.; Sakata, Y. *J. Chem. Soc., Perkin Trans. 1* **1995**, 213.

16. Yamamoto, K.; Ikeda, T.; Kitsuki, T.; Okamoto, Y.; Chikamatsu, H.; Nakazaki, M. *J. Chem. Soc., Perkin Trans. 1* **1990**, 271.

17. Chen, G.-M.; Brown, H. C.; Ramachandran, P. V. *J. Org. Chem.* **1999**, *64*, 721.

18. (a) Gibson, S. E.; Mainolfi, N.; Kalindjian, S. B.; Wright, P. T. *Chem. Commun*. **2003**, 1568. (b) Gibson, S. E.; Mainolfi, N.; Kalindjian, S. B.; Wright, P. T.; White, A. J. P. *Chem. Eur. J*. **2005**, *11*, 69.

19. Alfonso, I.; Rebolledo, F.; Gotor, V. *Chem. Eur. J*. **2000**, *6*, 3331.

20. Bradshaw, J. S.; Huszthy, P.; McDaniel, C. W.; Zhu, C. Y.; Dalley, N. K.; Izatt, R. M. *J. Org. Chem.* **1990**, *55*, 3129.

21. Kobayashi, S.; Hamada, T.; Nagayama, S.; Manabe, K. *Org. Lett*. **2001**, *3*, 165.

22. Hellier, P. C.; Bradshaw, J. S.; Young, J. J.; Zhang, X. X.; Izatt, R. M. *J. Org. Chem.* **1996**, *61*, 7270.

23. Lee, K. H.; Lee, D. H.; Hwang, S.; Lee, O. S.; Chung, D. S.; Hong, J. I. *Org. Lett*. **2003**, *5*, 1431.

24. (a) Pan, Z.; Still, W. C. *Tetrahedron Lett.* **1996**, *37*, 8699. (b) Still, W. C. *Acc. Chem. Res*. **1996**, *29*, 155. (c) Yoon, S. S.; Still, W. C. *Tetrahedron* **1995**, *51*, 567.

25. Okubo, H.; Yamaguchi, M.; Kabuto, C. *J. Org. Chem.* **1998**, *63*, 9500.

26. Zhao, H.; Hua, W. *J. Org. Chem.* **2000**, *65*, 2933.

27. Gao, M. Z.; Gao, J.; Xu, Z. L.; Zingaro, R. A. *Tetrahedron Lett.* **2002**, *43*, 5001.

28. Gasparrini, F.; Misiti, D.; Pierini, M.; Villani, C. *Org. Lett*. **2002**, *4*, 3993.

29. Gawronski, J.; Kolbon, H.; Kwit, M.; Katrusiak, A. *J. Org. Chem.* **2000**, *65*, 5768.

30. (a) Kuhnert, N.; Lopez-Periago, A. M. *Tetrahedron Lett.* **2002**, *43*, 3329. (b) Chadim, M.; Budesinsky, M.; Hodacova, J.; Zavada, J.; Junk, P. *Tetrahedron: Asymmetry* **2001**, *12*, 127. (c) Kuhnert, N.; Rossignolo, G. M.; Lopez-Periago, A. M. *Org. Biomol. Chem*. **2003**, *1*, 1157. (d) Kuhnert, N.; Burzlaff, N.; Patel, C.; Lopez-Periago, A. M. *Org. Biomol. Chem*. **2005**, *3*, 1911. (e) Kuhnert, N.; Lopez-Periago, A. M.; Rossignolo, G. M. *Org. Biomol. Chem*. **2005**, *3*, 524. (f) Kuhnert, N.; Patel, C.; Jami, F. *Tetrahedron Lett.* **2005**, *49*, 7575.

31. Brunner, H.; Schiessling, H. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 125.

32. (a) Lin, J.; Zhang, H. C.; Pu, L. *Org. Lett*. **2002**, *4*, 3297. (b) Lin, J.; Li, Z.-B.; Zhang, H. C.; Pu, L. *Tetrahedron Lett.* **2004**, *45*, 103.

33. Kim, M. B.; So, S. M.; Choi, H. J. *Org. Lett*. **2002**, *4*, 949.

34. Wennerstrom, O.; Skog, K. *Tetrahedron Lett*. **1995**, *36*, 4629.

35. Padmaja, M.; Periasamy, M. *Tetrahedron: Asymmetry* **2004**, *15*, 2437.

36. (a) Alexakis, A.; Mutti, S.; Mangeney, P. *J. Org. Chem.* **1992**, *57*, 1224. (b) Tye, H.; Eldred, C.; Wills, M. *Tetrahedron Lett.* **2002**, *43*, 155.

37. Prasad, A. S. B.; Kanth, J. V. B.; Periasamy, M. *Tetrahedron* **1992**, *48*, 4623.

38. Okamoto, Y.; Nagamura, Y.; Fukumoto, T.; Hatada, K. *Polymer Journal* **1991**, *23*, 1197.

39. (a) Yokota, K.; Kakuchi, T.; Sasaki, H.; Ohmori, H. *Makromol. Chem*. **1989**, *190*, 1269. (b) Yokota, K.; Matsumura, M.; Yamaguchi, K.; Takada, Y. *Makromol. Chem., Rapid Commun*. **1983**, *4*, 721. (c) Yokota, K.; Haba, O.; Satoh, T. *Macromol. Chem. Phys*. **1995**, *196*, 2383. (d) Kakuchi, T.; Takaoka, T.; Yokota, K. *Makromol. Chem*. **1988**, *189*, 2007.

40. Mouaziz, H.; Soutif, J.-C.; Montembault, V. *Eur. Polym. J.* **2003**, *39*, 1773.

41. (a) Aime, S.; Botta, M.; Crich, S. G.; Giovenzanna, G.; Palmisano, G.; Sisti, M. *Bioconjugate Chem*. **1999**, *10*, 192. (b) Lewis, M. R.; Raubitschek, A.; Shively, J. E. *Bioconjugate Chem*. **1994**, *5*, 565.

42. Louvet, V.; Handel, H.; Appriou, P.; Guglielmetti, R. *Eur. Polym. J.* **1987**, *23*, 585.

43. (a) Dehmlow, E. D.; Dehmlow, S. S. In *Phase-transfer Catalysis*; 3rd ed.; VCH: Weinheim, 1993. (b) Starks, C. M.; Liotta, C. L. Halpern, M. In *Phase-transfer Catalysis*; Chapman & Hall: New York, 1994.

44. Shiori, T. In *Handbook of Phase-Transfer Catalysis*; Sasson, Y.; Neumann, R. Eds.; Blackie: London, 1997, chap.14. (b) O'Donnell, M. J. In *Phases*: (Sachem's Phase-Transfer Catalysis Newsletter) 1999, 5, 5.

45. (a) O'Donnell, M. J. *Aldrichimica Acta* **2001**, *34*, 3. (b) O'Donnell, M. J. *Acc. Chem. Res.* **2004**, *37*, 506. (c) Lygo, B.; Andrews, B. I. *Acc. Chem. Res.* **2004**, *37*, 518.

46. Schmidtchen, F. P.; Berger, M. *Chem. Rev.* **1997**, *97*, 1609.

47. Rembaum, A.; Baumgartner, W.; Eisenberg, A. *J. Polym. Sci. B*, **1968**, *6*, 159.

48. Pine, S. H.; Sanchez, B. L. *J. Org. Chem*. **1971**, *36*, 829.

49. Larrow, J. F.; Jacobsen, E. N. *J. Org. Chem*. **1994**, *59*, 1969.

Chapter 3

Studies on the applications of chiral 1,2-diamines, macrocyclic amines and quaternary ammonium salts

3.1 Introduction

Asymmetric organic transformations mediated by chiral ligands and catalysts that provide enantiomerically enriched products are of central importance in modern synthetic and pharmaceutical chemistry.[1] Accordingly, the development of stereoselective reactions using a stoichiometric or catalytic quantity of a chiral reagent has reached unprecedented levels of diversity, efficiency and applicability.[2]

We have made efforts to explore the application of various chiral 1,2-diamine derivatives prepared via the methods described in Chapters 1 and 2 for various synthetic applications: asymmetric reduction of prochiral ketones by chiral amine-borane complexes, kinetic resolution of racemic alcohols by chiral amines and use of chiral ammonium salts for asymmetric alkylation reaction. In addition, we have also studied the application of various chiral macrocyclic amines towards enantiomeric recognition of racemic carboxylic acids. A brief review of the reports on these topics will be helpful for the discussion.

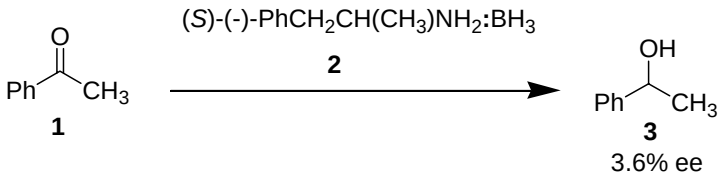
3.1.1 Asymmetric reductions by chiral amine-boranes

Chiral amine-borane complexes are promising reagents for the asymmetric reduction of prochiral carbonyl compounds since the amine can be readily recovered and recycled.[3]

In 1969, Fiaud and Kagan[4] reported that acetophenone **1** can be reduced to 1-phenylethanol **3** with the amine-borane complex prepared from (*S*)-(-)-1-methyl-2-

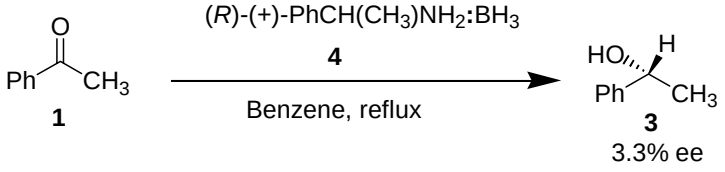
phenylethylamine **2** and its derivatives with asymmetric induction of 3.6-5% ee (Scheme 1).

Scheme 1



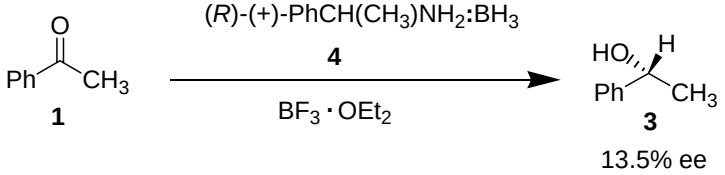
The asymmetric reduction of acetophenone **1** with (*R*)-(+)-1-phenylethylamine-borane **4** was studied by Borch and Levitan.[5] It was found that the optical yield of the resultant alcohol was only 1.5-3.3% and the reduction was incomplete (Scheme 2).

Scheme 2



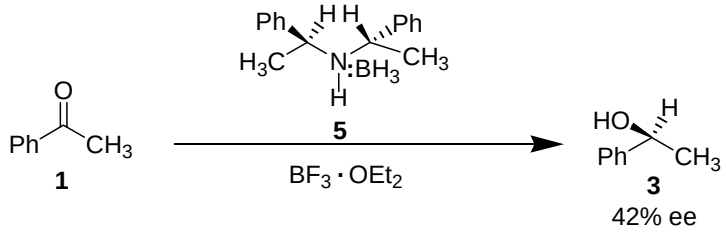
Grundon *et al*.[6] reported that the asymmetric reduction of acetophenone **1** with equimolar quantities of (*R*)-(+)-1-phenylethylamine-borane **4** in the presence of $BF_3{\cdot}OEt_2$ resulted in complete reduction to give (*R*)-(+)-1-phenylethanol in 13.5% ee (Scheme 3).

Scheme 3

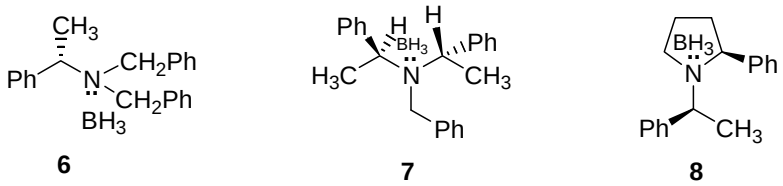


Eleveld and Hogeveen[7] found that the asymmetric reduction of acetophenone using stoichiometric quantities of the (*S*,*S*)-α,α′-dimethyldibenzylamine-borane **5** and $BF_3{\cdot}OEt_2$ in THF gave 1-phenylethanol in 78% yield and 42% ee (Scheme 4).

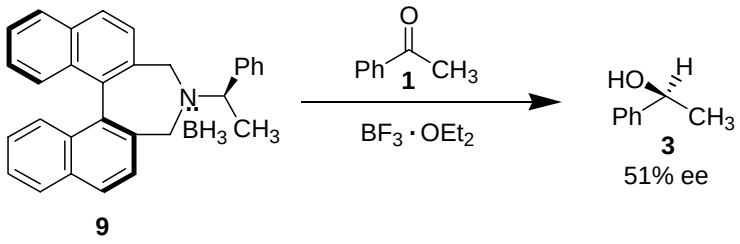
Scheme 4



It has been previously reported from this laboratory that the chiral amine-borane complexes **6**, **7**, **8** and **9** reduce prochiral aromatic ketones to alcohols in 10-57% ee in the presence of $BF_3{\cdot}OEt_2$.[8] The amine-borane complex **9** containing binaphthyl moiety reduced acetophenone in the presence of $BF_3{\cdot}OEt_2$ in 51% ee (Scheme 5).[8a]



Scheme 5



We decided to examine the synthesis of amine-borane complexes of the C_2-chiral diamines and study their application in the asymmetric reduction of prochiral ketones. The results are discussed in the Section 3.2.1.

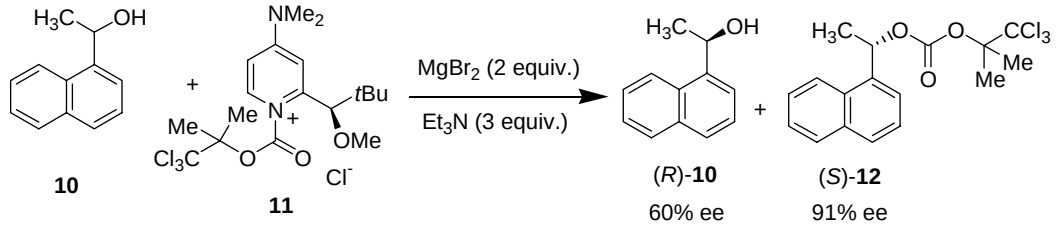
3.1.2 Kinetic resolution via acylation promoted by chiral amine derivatives

Kinetic resolution is a general efficient synthetic method to obtain optically active compounds. It has been widely used for the synthesis of complex natural products and their derivatives.[9] Despite the development of some effective methods for enzymatic kinetic resolution,[10] racemate resolution through nonenzymatic, enantioselective acylation pathway has become the focus of research attention over the past few years and it remains as a valuable alternative method for the preparation of optically active compounds.[11] Major advances have been made in the development of chiral catalysts for the kinetic resolution of various functional groups like alcohols, amines, amino alcohols, alkenes and epoxides.

We have examined the use of chiral C_2-symmetric diamines for kinetic acylation studies. Accordingly, it is of interest to briefly review the recent reports on this topic.

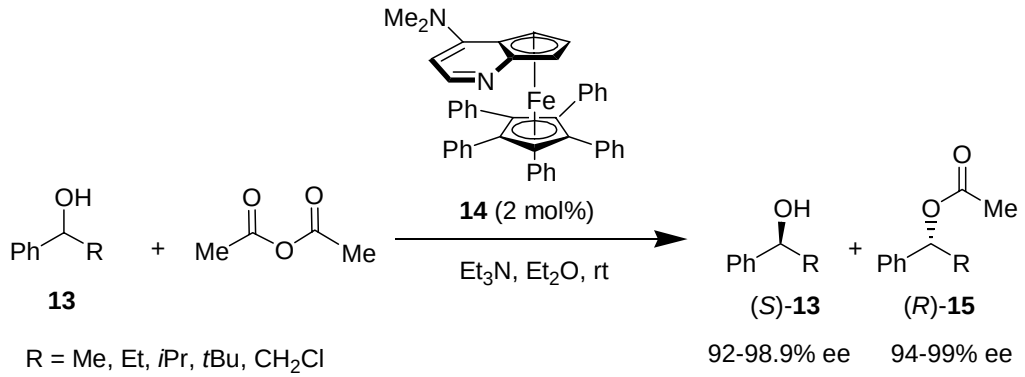
In 1996, Vedejs and Chen[12] reported the synthesis of a chiral reagent **11** based on the 4-(dimethylamino)pyridine nucleus for the enantioselective acylation of the secondary alcohol **10** to obtain **12** in 91% ee. The unreacted alcohol **10** was also isolated with 60% ee (Scheme 6).

Scheme 6



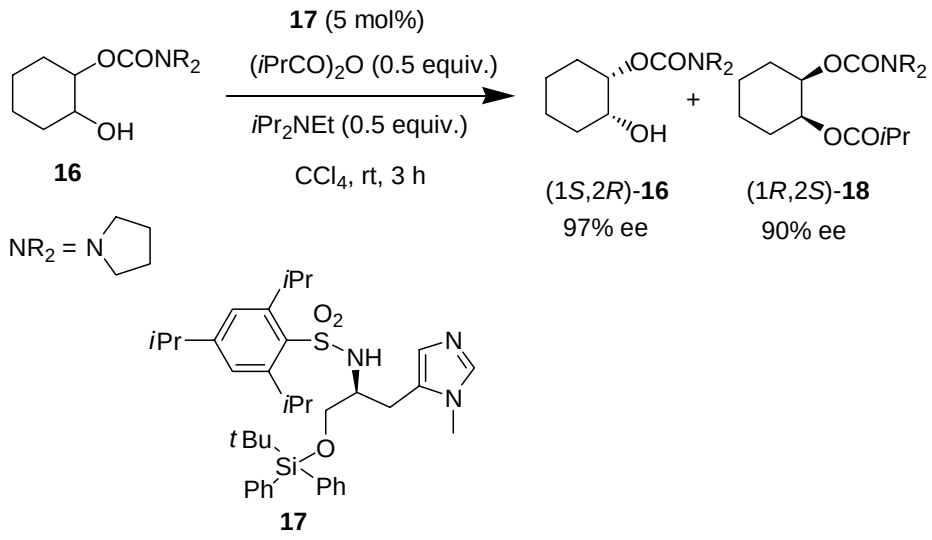
Fu *et al.*[13] utilized the iron complex **14** of the planar-chiral analogue of the 4-(dimethylamino)pyridine for the kinetic resolution of the racemic alcohols **13** (Scheme 7).

Scheme 7



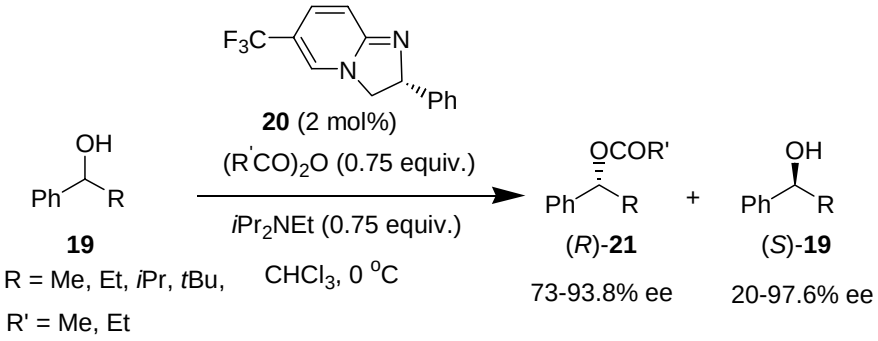
Recently, Ishihara and co-workers[14] developed a new artificial acylase **17** synthesized from *L*-histidine which catalyzes the kinetic resolution of the alcohol **16** (Scheme 8).

Scheme 8



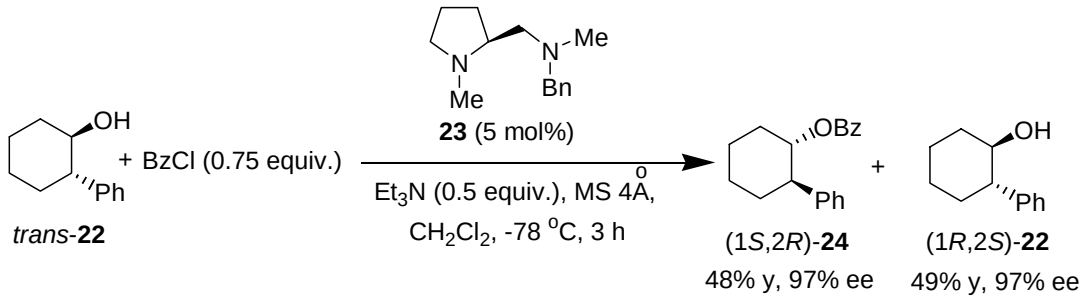
Birman *et al.*[15] reported the use of chiral (*R*)-2-phenyl-2,3-dihydroimidazo[1,2-a]pyridine **20** synthesized from (*R*)-phenylglycinol for the kinetic resolution of the alcohols **19** to obtain the esters **21** with 30-93% ee (Scheme 9).

Scheme 9



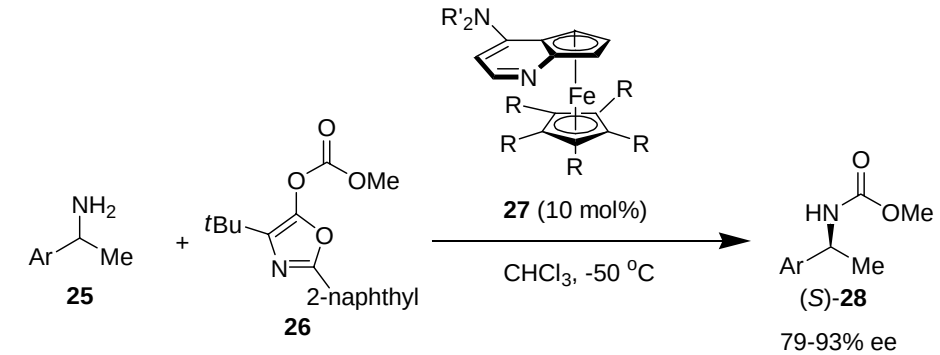
The organocatalyst **23** prepared from (*S*)-proline was used by Oriyama *et al.*[16] for the catalytic asymmetric acylation of the racemic alcohol **22** to obtain both the alcohol and the ester **24** in 97% ee (Scheme 10).

Scheme 10



Fu and co-workers[17] reported the kinetic resolution of 1-arylethylamine **25** catalyzed by the planar chiral DMAP derivative **27** using the *O*-acylated azlactone **26** as an acylating agent (Scheme 11).

Scheme 11



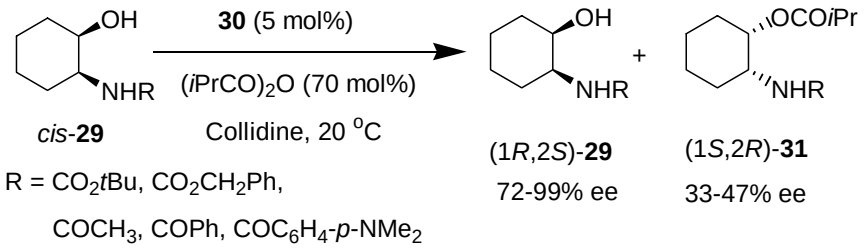
Ar = Ph, 2-naphthyl, *o*-Me-C_6H_4, *p*-MeO-C_6H_4, *m*-MeO-C_6H_4, *p*-CF_3-C_6H_4

NR_2' = pyrrolidino

R = Me

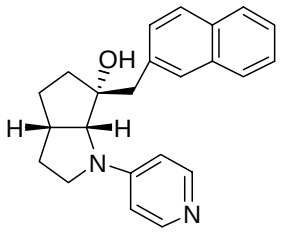
Recently, Kawabata *et al.*[18] reported the acylative kinetic resolution of racemic cyclic *cis*-amino alcohol **29** using the chiral nucleophilic catalyst **30** (Scheme 12).

Scheme 12



R = CO_2tBu, CO_2CH_2Ph, $COCH_3$, COPh, COC_6H_4-*p*-NMe_2

30 =

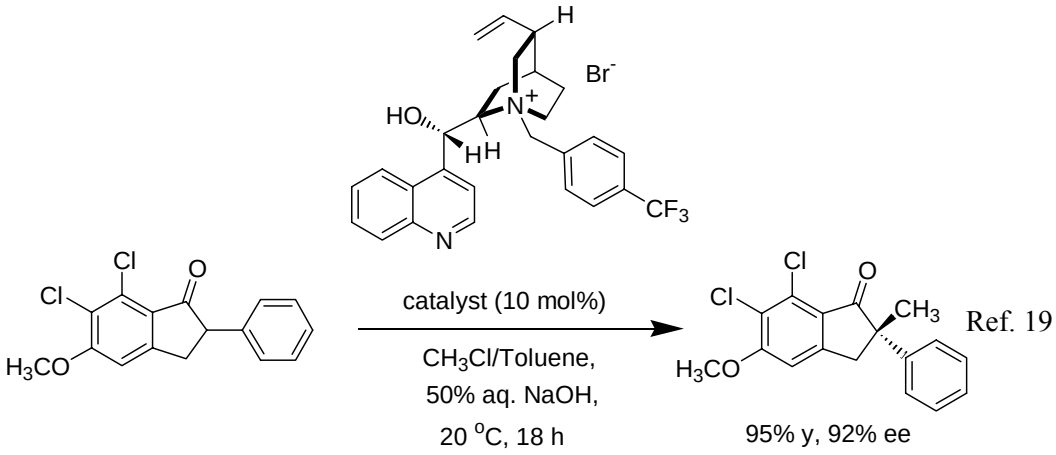


We have made attempts towards the kinetic resolution of racemic 1-phenylethanol using chiral 1,2-diamines. The results are discussed in the Section 3.2.2.

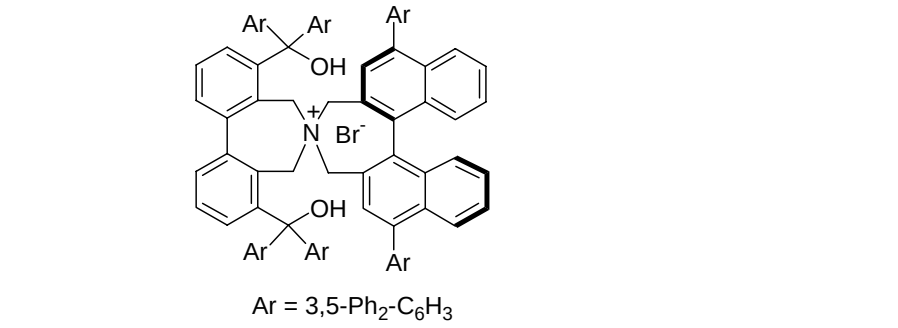
3.1.3 Synthetic applications of chiral quaternary ammonium salts : Asymmetric α-alkylation of Schiff bases of amino esters

In recent years, chiral quaternary ammonium salts have been used for several useful asymmetric transformations (Chart 1).

Chart 1



Ref. 19

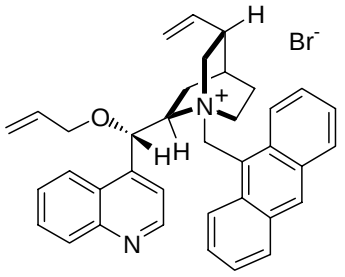


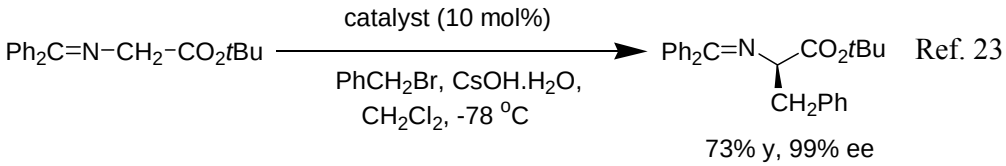
Ref. 20

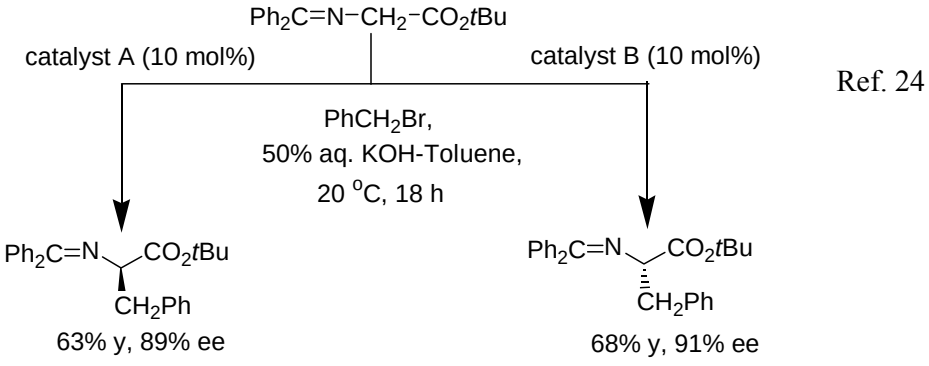
Although a variety of methods are available for the synthesis of α-amino acids[21] like the widely practiced Strecker synthesis, the alkylation of the Schiff bases of amino

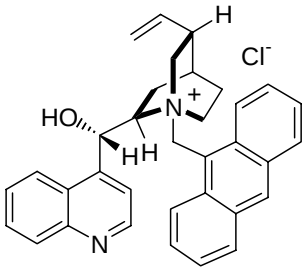
esters by using chiral phase transfer catalysts has been recognized as a convenient and efficient method of synthesis of chiral natural and unnatural α-alkyl and α,α-dialkyl-α-amino acids. Accordingly, several phase transfer catalysts have been developed that produce amino acid derivatives.[22] Some recent reports on this transformation are summarized in Chart 2.

Chart 2

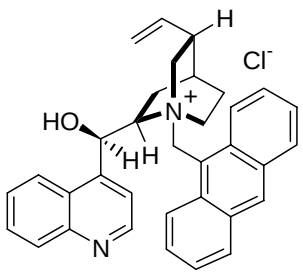






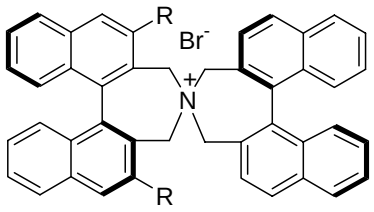


catalyst A

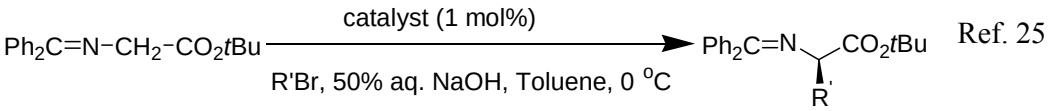


catalyst B

Chart 2 (continued)



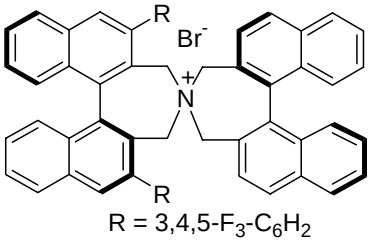
R = 2-naphthyl



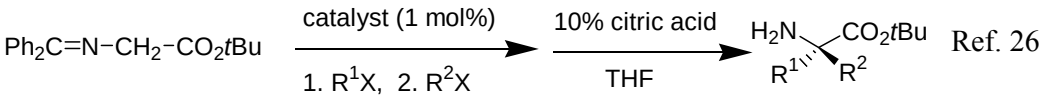
Ref. 25

R' = allyl, $PhCH_2$, *p*-Me-C_6H_4-CH_2-
p-F-C_6H_4-CH_2-, 2-naphthyl

60-95% y, 94-96% ee



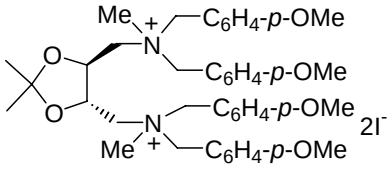
R = 3,4,5-F_3-C_6H_2



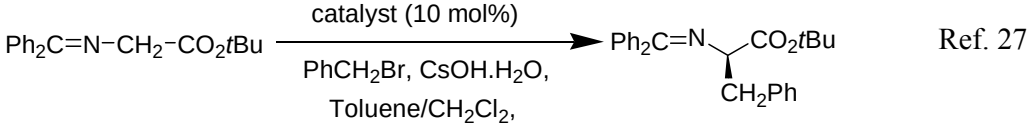
Ref. 26

R^1 = $PhCH_2$, allyl
R^2 = 2-methylallyl, propargyl, $PhCH_2$

58-80% y, 96-98% ee



$2I^-$



Ref. 27

87% y, 93% ee

We have made efforts towards the application of chiral quaternary ammonium salts for the asymmetric benzylation of the benzophenone Schiff base of ethyl glycinate. The results are discussed in the Section 3.2.3.

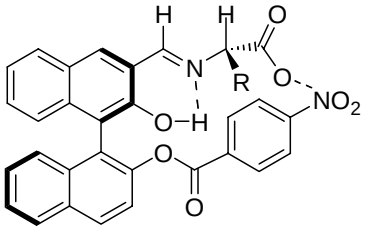
3.1.4 Enantiomeric recognition of chiral compounds by synthetic receptors

The study of enantiomeric recognition phenomenon is of great value in many fields, such as the resolution of racemic mixtures of technically and biologically relevant compounds; the determination of enantiomeric composition of chiral compounds; the screening of chiral catalysts etc. Optically active amines, carboxylic acids, alcohols, amino acids and amino alcohols are important building blocks for the synthesis of several natural products and drug molecules. The growing use of such chiral molecules has therefore given rise to the need for the development of fast and accurate methodologies for the determination of their enantiomeric composition.[28] There are several methods used for the enantiomeric recognition of various functional groups by chiral synthetic receptors like enantioselective coloration,[29a] mass spectrometry,[29b] fluorescence spectroscopy[29c-d] and NMR spectroscopy.[29e-f] However, the NMR and fluorescence spectroscopy are the most widely used methods. The chiral receptors generally used for enantiomeric recognition are acyclic compounds or macrocyclic compounds. A brief review of the available reports will be helpful for the discussion.

3.1.4.1 Enantiomeric recognition by chiral acyclic synthetic receptors

The enantiomeric recognition by chiral acyclic receptors has been extensively studied by the ^{1}H-NMR spectroscopy. Recently, Kim *et al*.[30] synthesized the (*R*)-binol

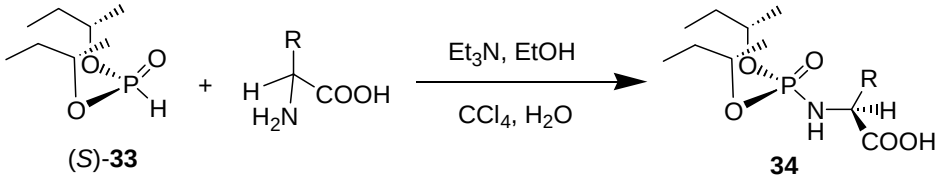
based chiral aldehyde that forms resonance assisted hydrogen bonded imine **32** with amino acids. The ^{1}H-NMR signals of the hydrogen bonded protons in the diastereomeric imine complexes are well resolved and highly shifted to downfield. As a result, this compound is used for evaluating the enantiomeric excess and absolute stereochemistry of amino acids like alanine, valine, phenylalanine, tyrosine, tryptophan, threonine and asparagines.



(*S*)-**32**

Feringa and co-workers[31] reported ^{31}P-NMR method for the determination of the enantiomeric excess of unprotected amino acids based on the use of the phosphonate **33** synthesized from (*S*)-2-butanol and PCl_3. The reaction of the phosphonate **33** with racemic amino acids provided the diastereomeric phosphonic amides **34** which were analyzed by NMR to evaluate the enantiomeric composition of the amino acids (Scheme 13).

Scheme 13



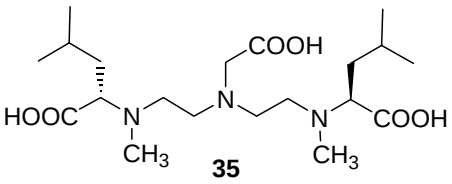
(*S*)-**33**

R = CH_3, CH_2Ph, Ph, *i*Pr

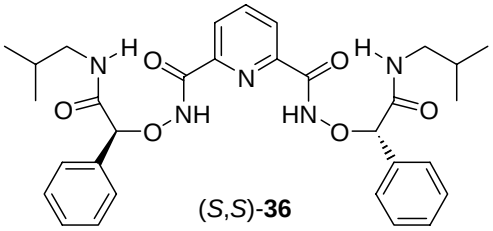
34

A water soluble europium(III) complex of *N*,*N*-bis[2-{*N*-methyl((1*S*)-1-carboxy-3-methyl}butylamino)ethyl]glycine **35** was reported by Kojima and co-

workers[32] as a chiral NMR shift reagent for the α-amino acids alanine, methionine, valine and *N*-acyl-oligopeptides.



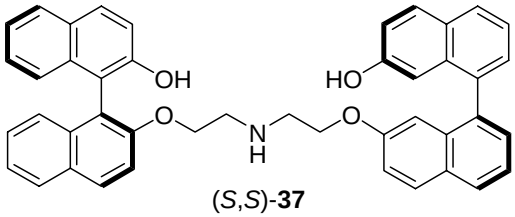
35



(*S*,*S*)-**36**

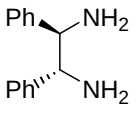
Very recently, the C_2-symmetric receptor **36** was designed by Yang *et al*.[33] for the enantioselective recognition of a series of substituted mandelic acids and carboxylic acids. The receptor was synthesized from (*R*)-mandelic acid in four steps.

Pu and co-workers[34] reported the use of the bis(binaphthyl) molecule **37** for the fluorescence recognition of chiral mandelic acid. It was observed that the (*R*) enantiomer of **37** showed fluorescence enhancement for (*R*)-mandelic acid, whereas the (*S*) enantiomer of **37** showed fluorescence enhancement for (*S*)-mandelic acid.

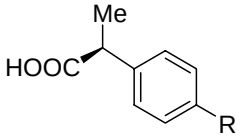


(*S*,*S*)-**37**

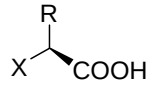
Parker and co-workers[35] reported that the (*R*,*R*)-1,2-diamino-1,2-diphenylethane **38** acts as an effective chiral solvating agent in the ^{1}H-NMR analysis of the enantiomeric purity of chiral α-arylpropanoic acids like ibuprofen **39**, ketoprofen **40**, α-halo carboxylic acids **41** and carboxylic acids **42**.



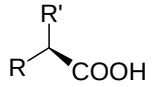
38



39 R = CH_2*i*Pr
40 R = COPh

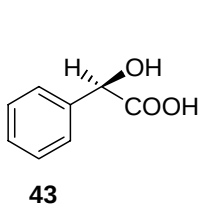


R = Me, Ph, Et
X = Br, Cl
41

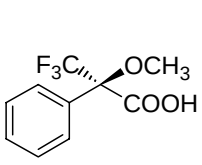


R = OH, Me, Et, OAc
R' = Me, Ph
42

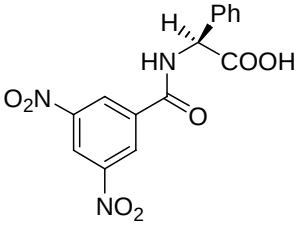
Snyder *et al.*[36] reported the use of mandelic acid **43**, Mosher's acid **44** and *N*-(3,5-dinitrobenzoyl)phenylglycine **45** as chiral solvating agents to induce non-equivalence in the ^{1}H-NMR spectra of substituted 1,1′-binaphthyl-2,2′-diamine **46**, 1,2-diaminocyclohexane **47**, 1,2-diphenylethanediamine **48** and amino alcohols **49**.



43

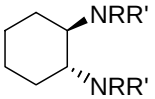


44

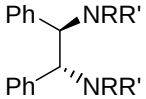


45

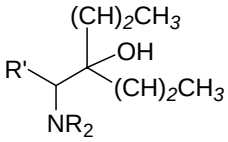
46



47



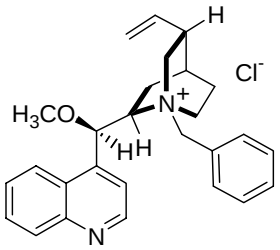
48



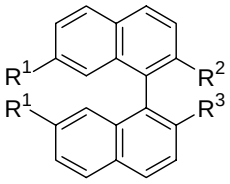
49

R = CH_3 R' = H, CH_3, Ph, CH_2Ph, *i*Pr

Salvadori *et al.*[37] reported the use of quinine **50** as a chiral solvating agent for the enantiomeric determination of binaphthyl derivatives **51** and alkylarylcarbinols **52** by ^{1}H and ^{19}F-NMR spectroscopy.



50

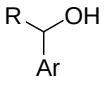


51

R^1 = H, OMe

R^2 = OH, OMe, O*i*Pr, OCOMe, OCO*t*Bu

R^3 = OH, NH_2, NHMe



52

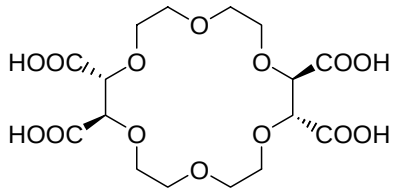
R = Me, *t*Bu, CF_3, *i*Pr, CH_2OH

Ar = Ph, *p*-MeO-C_6H_4, 9-anthryl, 1-naphthyl, *m*-Me-C_6H_4

3.1.4.2 Enantiomeric recognition by chiral macrocyclic synthetic receptors

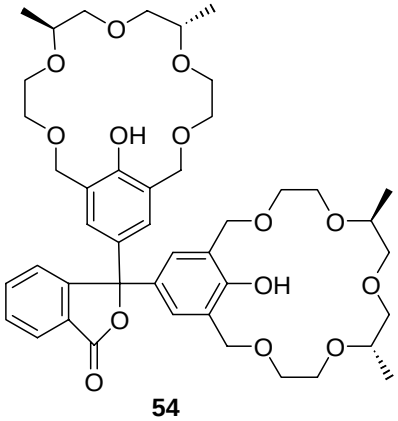
Chiral macrocyclic compounds have been demonstrated to be very effective in enantiomeric recognitions[28] since the pioneering work by Cram, Lehn and Pederson.

The (+)-(18-crown-6)-2,3,11,12-tetracarboxylic acid **53** was evaluated as a useful chiral NMR discriminating agent for protonated amino acid esters, amines and amino alcohols by Wenzel and Thurston.[38] The ytterbium(III) complex of the crown ether enhanced the enantiomeric discrimination ability of the crown ether.

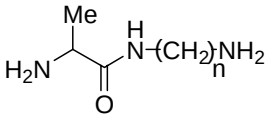


53

Fuji and co-workers[39a] developed the optically active host molecule **54** based on a phenolphthalein skeleton for the visual enantiomeric recognition of the alanine derivatives **55** and **56**. This receptor discriminates the (*R*)-**55** and (*R*)-**56** from the (*S*)-**55** and (*S*)-**56** respectively to develop a purple colour. The same group also reported the visual enantiomeric discrimation of amino alcohols using the receptor **54**.[39b]



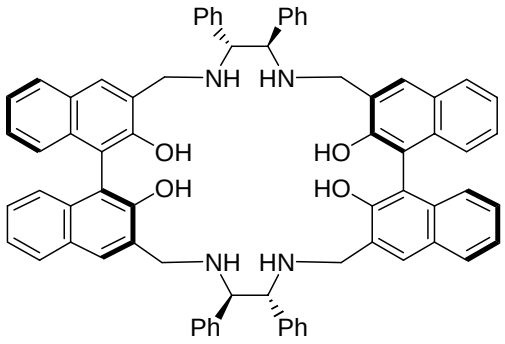
54



n = 5 **55**

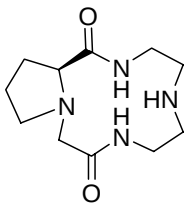
n = 6 **56**

Pu *et al.*[40] used the bis(binaphthyl) based macrocycles (*R*)-**57** and (*S*)-**57** synthesized from (*R*)- and (*S*)-1,1′-bi-2-naphthol respectively, to carry out enantioselective fluorescence recognition of α-amino acid derivatives. It was observed that the *D*-enantiomer of *N*-benzyloxycarbonyl phenylglycine increases the fluorescence intensity of the binaphthyl fluorophore (*S*)-**57** by over 4-fold but the *L* enantiomer does not cause much fluorescence enhancement.[40]

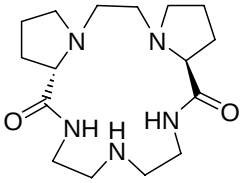


(*S*)-**57**

Recently, Fu *et al.*[41] synthesized the *L*-proline derived chiral macrocyclic dioxopolyamines **58** and **59**, which exhibited chiral recognition towards the enantiomers of racemic carboxylic acids like substituted mandelic acids and dibenzoyltartaric acid.



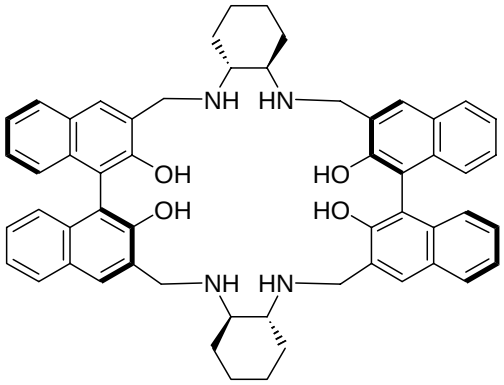
58



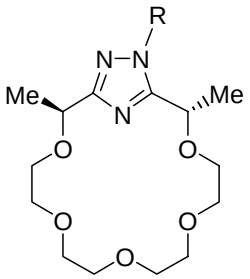
59

Very recently, Pu *et al.*[42] reported the synthesis of the chiral 1,2-diaminocyclohexane based bis(binaphthyl) macrocycle (*S*)-**60** similar to **57** starting from the derivative of (*S*)-1,1′-bi-2-naphthol and (*R*,*R*)-1,2-diaminocyclohexane, for the

enantioselective fluorescence recognition of mandelic acid. The corresponding (*R*)-**60** was prepared from the (*R*)-1,1′-bi-2-naphthol and (*S*,*S*)-1,2-diaminocyclohexane. While the (*S*)-mandelic acid caused an increase in the fluorescence intensity of the (*S*)-**60**, (*R*)-mandelic acid had almost no effect on the fluorescence of (*S*)-**60**. Converse results were obtained when the (*R*)-**60** was used as the host molecule.[42]



(*S*)-**60**



R = CH_2COOcholesteryl **61**

R = *n*dodecyl **62**

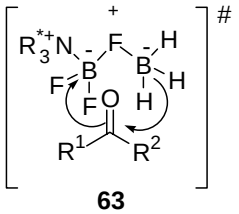
Echegoyen and Li[43] reported the use of the chiral triazole-18-crown-6-ligands **61** and **62** with lipophilic side arms, for the chiral recognition of the enantiomers of [1-(1-naphthyl)ethyl]ammonium cation and [1-phenylethyl]ammonium cation. The (*S*,*S*) chiral host recognizes preferentially the (*R*) enantiomer of the ammonium salt over the (*S*) enantiomer.

We have made efforts towards the application of the various chiral macrocyclic amines synthesized, for the enantiomeric recognition of racemic carboxylic acids. The results are discussed in the Section 3.2.4.

3.2 Results and Discussion

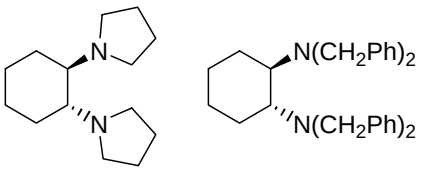
3.2.1 Asymmetric reduction studies using chiral amine-borane complexes

It has been previously observed in this laboratory that some chiral amine-borane complexes reduce prochiral ketones with 10-57% enantioselectivity in the presence of $BF_3 \cdot OEt_2$.[8] The reduction is proposed to go through the transition state **63**.



63

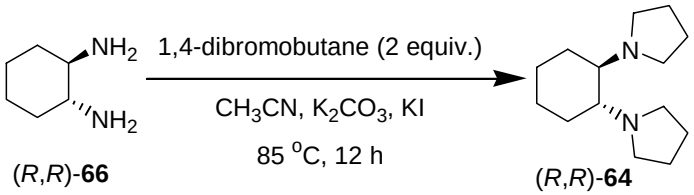
Accordingly, it was of interest to us to examine the asymmetric reduction of acetophenone using the chiral amine-borane complexes of the diamines **64** and **65**.



(*R*,*R*)-**64** (*R*,*R*)-**65**

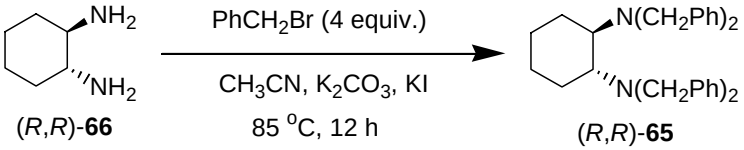
The diamine **64** was synthesized from the sequential opening of cyclohexene oxide and the corresponding aziridinium ion intermediate using pyrrolidine and resolved using dibenzoyl-*L*-tartaric acid (Chapter 1).[44] Alternately, the diamine **64** was also synthesized by the alkylation of (*R*,*R*)-1,2-diaminocyclohexane **66** using 1,4-dibromobutane (Scheme 14).[45]

Scheme 14



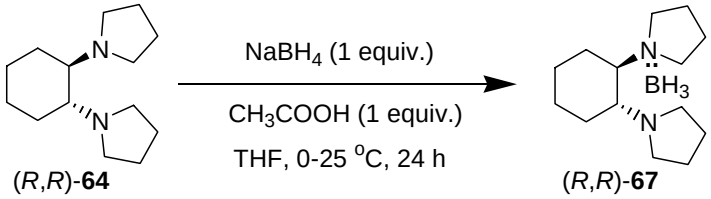
The diamine **65** was synthesized by the benzylation of the (*R*,*R*)-1,2-diaminocyclohexane **66** using benzyl bromide (Scheme 15).

Scheme 15



When acetophenone **1** was added to the amine-borane complex of the diamine **64**, prepared by the passing of B_2H_6 through the solution of the diamine in toluene, the reduction did not take place and the starting material was recovered. It has been previously reported from this laboratory that the diamine **64** forms the monoborane-diamine complex **67** on reacting with one equivalent of $NaBH_4$ and acetic acid in THF (Scheme 16).[46]

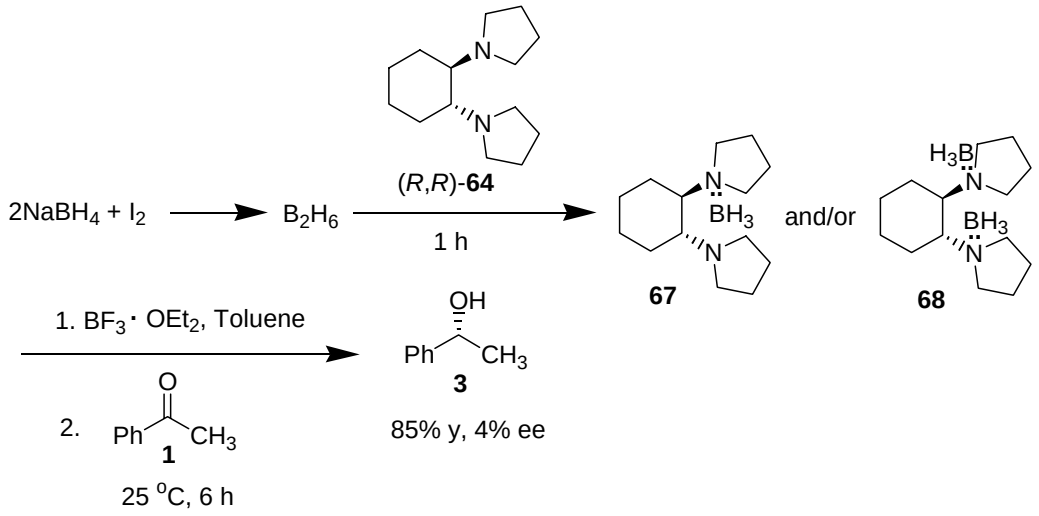
Scheme 16



Hence, the reduction of acetophenone was carried out in the presence of $BF_3{\cdot}OEt_2$. In this run, the product 1-phenylethanol **3** was obtained in quantitative yield but with low induction of 4% ee (Scheme 17). To study the effect of temperature on

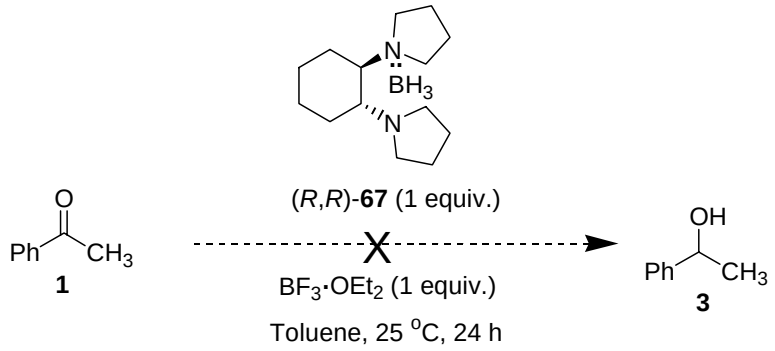
the enantioselectivity of the reaction, the reduction was carried out at 0 °C. It was observed that in this run the yield of the 1-phenylethanol obtained was 80%, but there was no improvement in the ee of the alcohol (4% ee).

Scheme 17



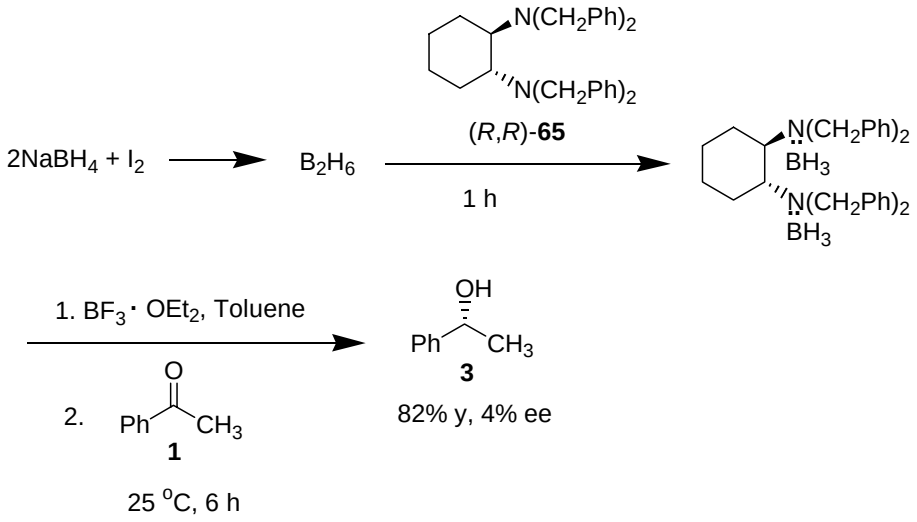
To examine the reactivity of the pre-formed diamine-monoborane complex **67**, we have carried out the reduction of acetophenone using this complex (1 equiv.) in the presence of $BF_3{\cdot}OEt_2$ (1 equiv.) (Scheme 18). In this run, the 1-phenylethanol was not obtained.

Scheme 18



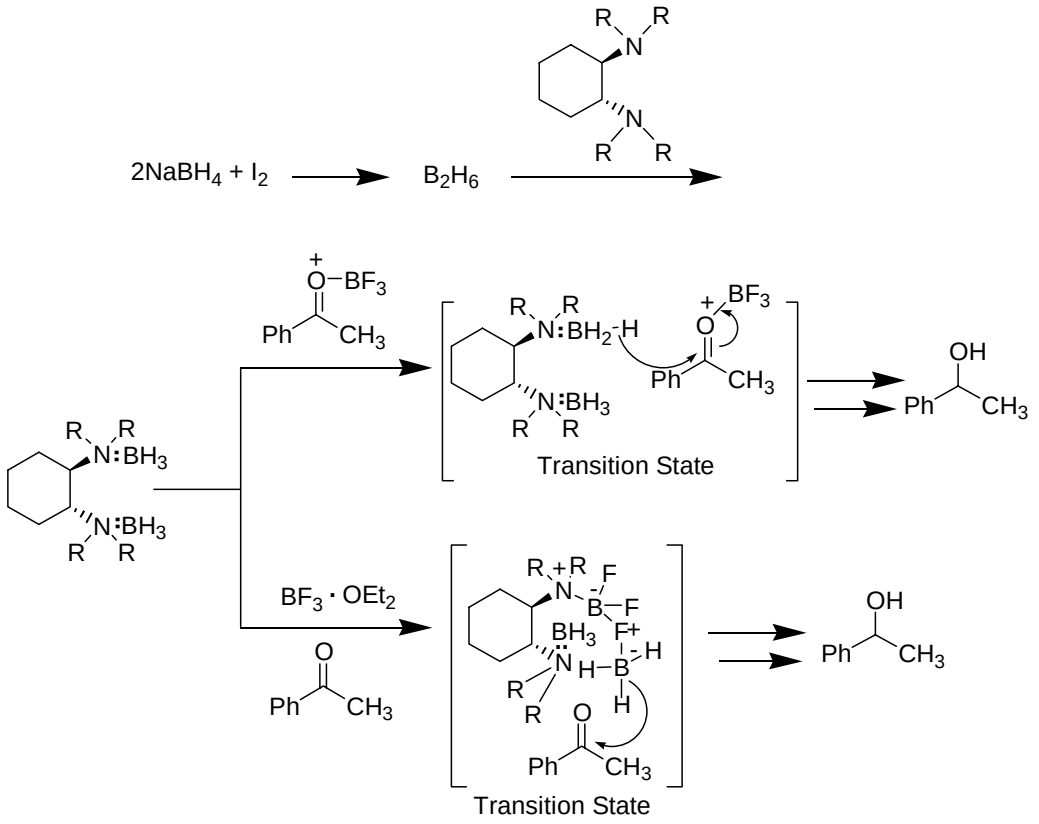
Presumably, only the amine-borane complex **68** (Scheme 17) may be the reactive species involved in the reduction of acetophenone. Similar results were also obtained when the borane complex of the diamine **65** was used for the reduction of acetophenone in the presence of $BF_3{\cdot}OEt_2$. The 1-phenylethanol obtained was formed in very low ee (4%) (Scheme 19).

Scheme 19



Presumably, the reaction may go through the intermediate and the transition state[6-8,47] as outlined in Scheme 20 which may be too crowded to give good enantioselection.

Scheme 20



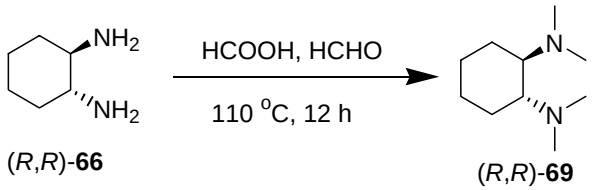
Since the enantioselectivity realized was very poor, we did not pursue further research efforts in these lines.

3.2.2 Kinetic resolution studies of racemic 1-phenylethanol using chiral diamines

As outlined in the introductory section, chiral amines have been used for the kinetic acylation of racemic alcohols. We have made attempts to use the chiral diamines **64** and **69** for the enantioselective acylation of racemic 1-phenylethanol **3**. The chiral diamine **69** was prepared from the sequential opening of cyclohexene oxide and the corresponding aziridinium ion intermediate using aqueous dimethylamine and resolved using chiral 1,1′-bi-2-naphthol (Chapter 1).[44] Alternately, the diamine **69** was

also synthesized from (*R*,*R*)-1,2-diaminocyclohexane **66** by reaction with formic acid and formaldehyde mixture (Scheme 21).[48]

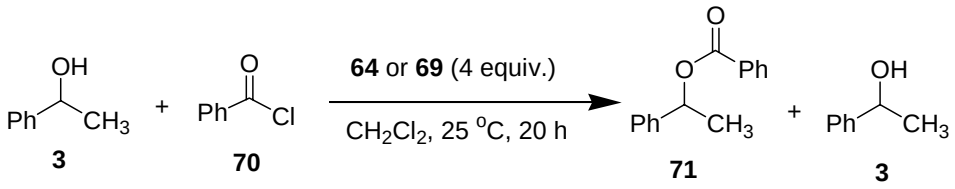
Scheme 21



(*R*,*R*)-**66** (*R*,*R*)-**69**

We have made efforts to achieve kinetic resolution of racemic 1-phenylethanol **3** in the presence of stoichiometric amounts of the chiral diamines **64** and **69** using benzoyl chloride **70** (Scheme 22).

Scheme 22



3 **70** **71** **3**

The two nitrogen atoms of the chiral diamine are expected to coordinate to the carbonyl carbon of the benzoyl chloride so as to facilitate the benzoylation process (Scheme 23). The results are summarized in Table 1.

Scheme 23

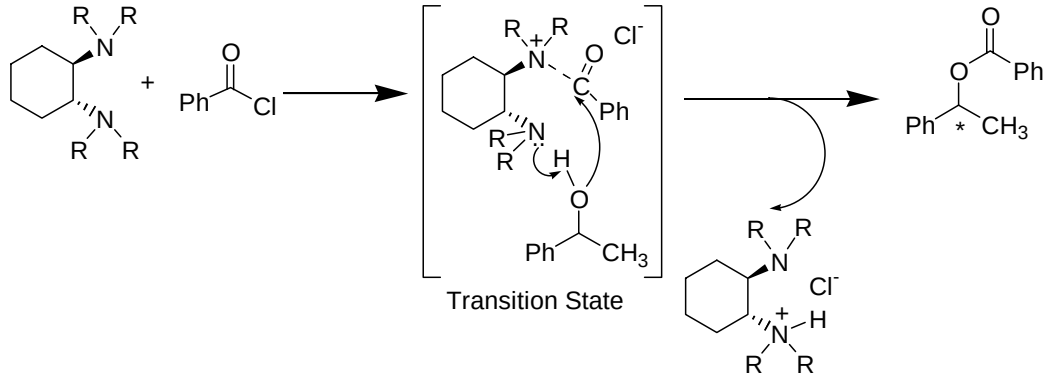


Table 1. Kinetic resolution of 1-phenylethanol 3 in the presence of the chiral diamines 64 and 69[a]

S. No.	Diamine	Solvent	Temp.	Time /h	Ester **71**		Alcohol **3**	
					%ee/ conf[b]	Yield[c] (%)	%ee/ conf[b]	Yield[c] (%)
1.	**64**(4 equiv.)	DCM	25 ^{o}C	20	4 (*S*)	44	3 (*R*)	46
2.	**69**(4 equiv.)	DCM	25 ^{o}C	20	9 (*S*)	46	8 (*R*)	45
3.	**69**(4 equiv.)	DCM	-20 ^{o}C	36	18 (*S*)	32	5 (*R*)	61
4.	**69**(4 equiv.)	DCM	-70 ^{o}C	40	16 (*S*)	30	5 (*R*)	60
5.	**69**(4 equiv.)	THF	25 ^{o}C	20	16 (*S*)	37	6 (*R*)	50
6.	**69**(4 equiv.)	THF	-78 ^{o}C	48	16 (*S*)	29	3 (*R*)	61
7.[d]	**69**(2 equiv.)	DCM	25 ^{o}C	24	13 (*S*)	55	5 (*R*)	37
8.[d]	**69**(2 equiv.)	DCM	-78 ^{o}C	48	12 (*S*)	31	3 (*R*)	60
9.[e]	**69**(0.2 eq.)	DCM	25 ^{o}C	20	5 (*S*)	47	0	44

a. The reactions were carried out using **3** (4 mmol), benzoyl chloride **70** (2 mmol) and the chiral diamine in solvent (30 mL).

b. The ee values reported are based on the maximum $[\alpha]_D^{25}$ = +27.3 (*c* 1, EtOH), reported for (*S*)-**71**[49]and maximum $[\alpha]_D^{25}$ = +45.9 (*c* 3.3, MeOH) reported for (*R*)-**3**.[50]

c. The yields are of the isolated products based on the amount of alcohol and acid chloride used.

d. The reactions were carried out using the chiral diamine (2 mmol) and triethylamine (2 mmol).

e. The reaction was carried out using the chiral diamine (0.2 mmol) and triethylamine (4 mmol).

When the reaction was carried out using stoichiometric amount of the diamine **64** at 25 ^{o}C, in dichloromethane, the ester and the alcohol were obtained with very low enantioselectivity (Table 1, entry 1). It was observed that there was improvement in the enantioselectivity of the ester and the alcohol in dichloromethane using the diamine **69** (Table 1, entry 2). Encouraged by this result, we carried out the reaction using the diamine **69** under various conditions (Table 1, entries 2-9).

It was observed that at -20 ^{o}C, there was an increase in the ee of the ester, although there was no improvement in the ee of the alcohol (Table 1, entry 3). When

the reaction was carried at still lower temperatures (i.e., -70 ^{o}C), there was no further improvement in the ee of the ester and alcohol (Table 1, entry 4).

To study the effect of the solvent on the reaction, the reaction was performed in THF at 25 ^{o}C. The ee was better in THF than in dichloromethane (Table 1, entry 5). Also, lowering the temperature to -78 ^{o}C did not improve the enantioselectivity of the reaction (Table 1, entry 6).

We next examined the effect of the stoichiometry of the chiral diamine **69** on the reaction. Use of two equivalents of **69** and two equivalents of triethylamine in dichloromethane at 25 ^{o}C and -78 ^{o}C did not increase the enantioselectivity (Table 1, entries 7-8). The use of catalytic amount of the chiral diamine **69** in the presence of triethylamine gave the ester with very low ee and the racemic alcohol (Table 1, entry 9). In all these reactions, always the (*S*)-isomer of the ester **71** was obtained.

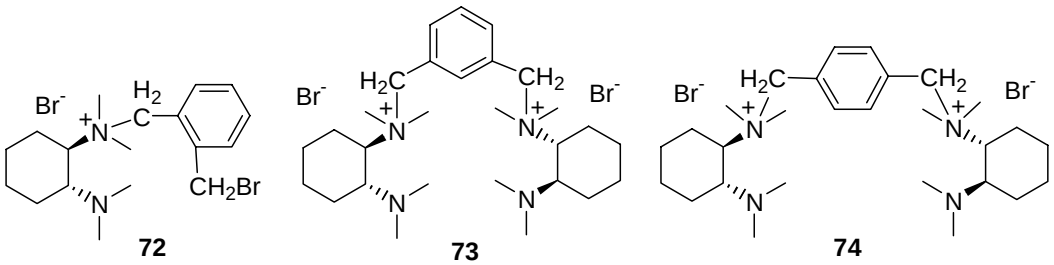
Presumably, the envisaged transition state (Scheme 23) is too crowded to be lower in energy and the reaction may go through an alternate, intermolecular pathway. Careful further investigation of the structural effects of the ligand on the enantioselectivity of the reaction should lead to more fruitful results.

3.2.3 Efforts towards the application of the chiral quaternary ammonium salts as phase transfer catalysts

3.2.3.1 Attempted enantioselective alkylation of the Schiff base 75 using the chiral quaternary ammonium salts 72, 73 and 74

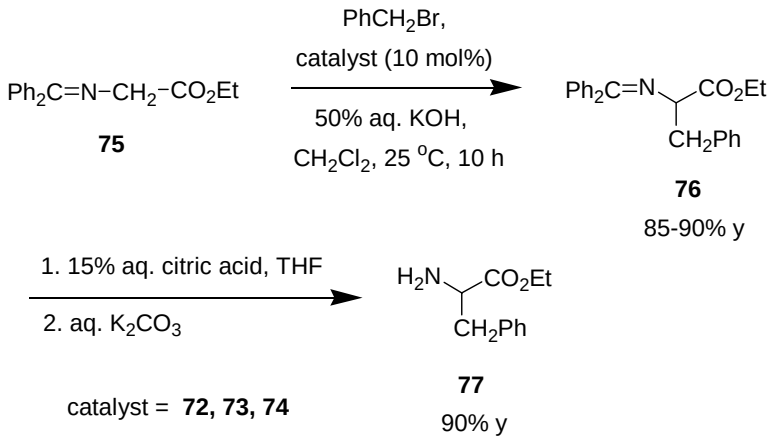
We have examined the application of the chiral quaternary ammonium salts **72**, **73** and **74** prepared by the methods described in Chapter 2, as phase transfer catalysts

for the enantioselective alkylation of the benzophenone Schiff base **75** of ethyl glycinate (Scheme 24).



72 **73** **74**

Scheme 24



It was observed that the salts **72**, **73** and **74** catalyzed the alkylation of the Schiff base **75** with benzyl bromide. However, there was no asymmetric induction. The imino ester **76** obtained could be readily hydrolyzed to the corresponding amino ester **77** using aqueous citric acid.

We have studied the reaction catalyzed by the salt **74** under various conditions (Table 2). It was observed that even 1 mol% of the salt **74** could catalyze the reaction. However, enantioselective induction was not observed even at low temperatures. Clearly, this diamine skeleton is not suitable to such applications.

Table 2. Alkylation of the Schiff base 75 of ethyl glycinate catalyzed by 74[a]

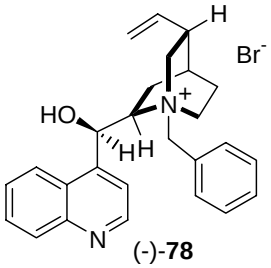
S.No.	Catalyst **74** (mol%)	Temperature	Yield of **76** (%)[b]
1.	1	25 °C	90
2.[c]	1	0 °C	80
3.	5	25 °C	92
4.	10	25 °C	89

a. The reactions were carried out using **75** (2 mmol), benzyl bromide (2 mmol), catalyst **74**, 50% aq. KOH (5 mL) in dichloromethane (30 mL) for 10 h.
b. The yields are of the isolated products based on the total amount of **75** used.
c. The reaction was carried out for 60 h.

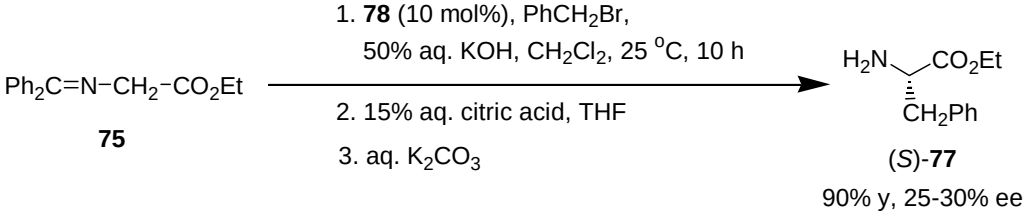
3.2.3.2 Enantioselective alkylation of the Schiff base 75 using chiral *N*-benzylcinchonidinium bromide 78

In connection with our efforts on the studies on the enhancement of enantiomeric purity via preparation of hydrogen bonded aggregates (Chapter 1), it was of interest to prepare the non-racemic amino ester **77**. We have observed that the amino ester **77** was formed in 25-30% ee by the enantioselective alkylation of the Schiff base **75** using *N*-benzylcinchonidinium bromide **78** as phase transfer catalyst (Scheme 25).[51]

Scheme 25



(-)-**78**



(*S*)-**77**

90% y, 25-30% ee

We have also examined the reaction of the non-racemic amino ester **77** with oxalic acid and fumaric acid. The results are summarized in Table 3.

Table 3. Reaction of the non-racemic amino ester 77 with oxalic and fumaric acids[a]

S. No.	Substrate **77** (% ee)	Diacid[b]	Amino ester **77** obtained from			
			Precipitate		Filtrate	
	(3 mmol)	(mmol)	%ee[c]/Conf.	Yield (%)[d]	%ee[c]/Conf.	Yield (%)[d]
1.[e]	(*S*) 28	OA, 0.84	0	22	23 (*S*)	62
2.[e]	(*S*) 29	FA, 0.87	3 (*S*)	25	5 (*S*)	76
3.	(*S*) 25	OA, 0.75	12 (*S*)	41	41 (*S*)	40
4.	(*S*) 41	OA, 1.23	31 (*S*)	56	44 (*S*)	36
5.	(*S*) 44	OA, 1.32	39 (*S*)	48	45 (*S*)	37
6.	(*S*) 25	FA, 0.75	18 (*S*)	10	27 (*S*)	75

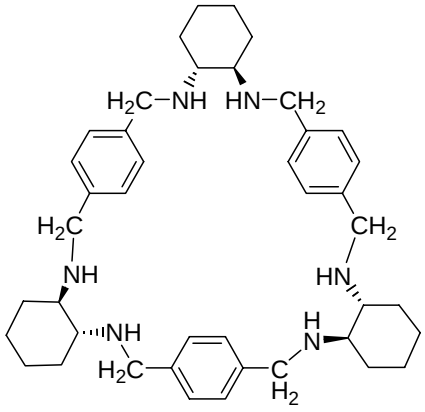
a. The reactions were carried out using non-racemic **77** (3 mmol) and diacid in dichloromethane (15 mL) and stirred at 25 ^{o}C for 12 h.
b. OA = oxalic acid, FA = fumaric acid.
c. All ee values are based on the maximum $[\alpha]_D^{25}$ = +22.8 (*c* 0.5, EtOH) reported for (*S*)-**77**.[52]
d. The yields are of the isolated products, based on the total amount of the starting non-racemic **77** used.
e. The reactions were carried out in acetone solvent.

When the non-racemic amino ester **77** was treated with oxalic and fumaric acids in acetone, racemization of the amino ester was observed (Table 3, entries 1-2). Previously it was reported that the reaction of chiral amino acids with acetic acid in the presence of catalytic amount of salicylaldehyde in acetone solvent results in the racemization of the amino acids.[53] Hence, we carried out the reaction of the non-racemic amino ester **77** with oxalic and fumaric acids in dichloromethane (Table 3, entries 3-6). In these runs, the samples with higher ees were obtained from the filtrate fraction but there was very little enrichment. Presumably, the amino ester behaves like

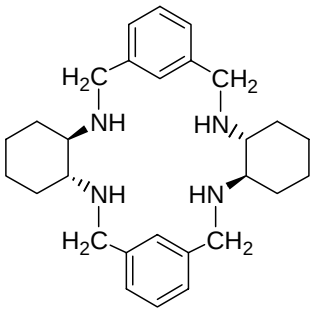
a simple amine due to the protection of the acid group and hence the formation of hydrogen bonded network (Chapter 1) for selective precipitation of homochiral or heterochiral aggregates does not take place in this case.

3.2.4 Application of chiral macrocyclic amines as chiral solvating agents for carboxylic acids

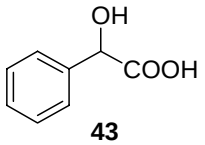
As discussed in the introductory section, chiral macrocycles are useful in the molecular recognition studies. Accordingly, we have made efforts towards the application of chiral macrocyclic amines described in Chapter 2 for the enantiomeric recognition of carboxylic acids. The chiral recognition ability of the secondary macrocyclic amines **79** and **80** towards mandelic acid **43** and 2,3-diphenylsuccinic acid **81** was evaluated.



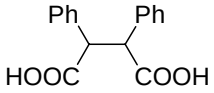
79



80



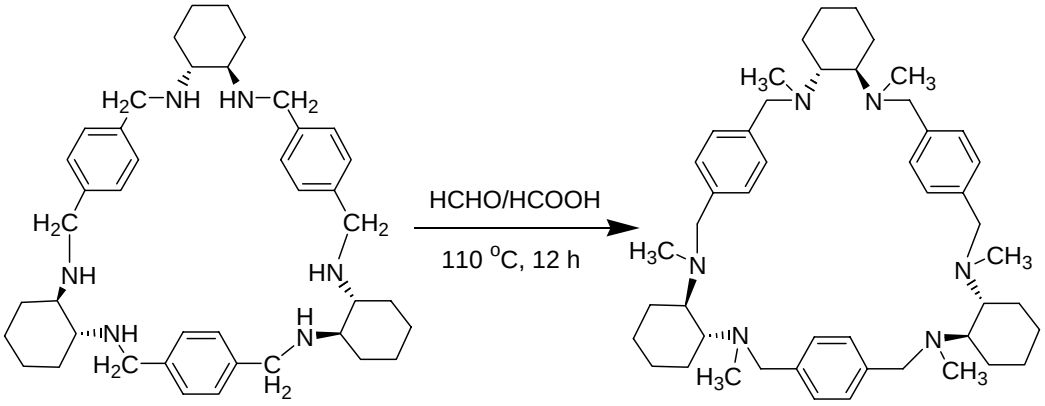
43



81

In addition, the application of the tertiary macrocyclic amine **82** as a chiral solvating agent was also studied. The macrocyclic amine **82** was synthesized by the methylation of **79** using formic acid and formaldehyde mixture (Scheme 26).

Scheme 26



79 **82**
90% y

Due to the difference in the interaction of the enantiomers of the carboxylic acids with the macrocyclic amines, the methine CH proton signals of mandelic acid **43** and 2,3-diphenylsuccinic acid **81** were split into two singlets. The nonequivalence in the interaction is given by the Δδ which is the difference in the chemical shifts of the two methine singlets. The results are summarized in Table 4.

Table 4. Nonequivalences of the methine CH proton signals in the ^{1}H-NMR spectra (400 MHz) of the acids 43 and 81 in the presence of the macrocyclic amines 79, 80 and 82 in $CDCl_3$ at 25 °C

S. No.	Macrocyclic amine	**43**			**81**		
		Ratio of amine:acid	Δδ		Ratio of amine:acid	Δδ	
			ppm	Hz		ppm	Hz
1.	**79**	1:3	0.044	17.6	6:1	0.029	11.6
2.	**80**	1:4	0.034	13.6	2:1	0.100	40.0
3.	**82**	1:6	0.011	4.4	1:2	0.009	3.6

The difference in the chemical shift of the methine signals of racemic mandelic acid **43** was found to be maximum (17.6 Hz) in the presence of the macrocyclic amine **79** when the ratio of the amine and acid was 1:3 (Figure 1).

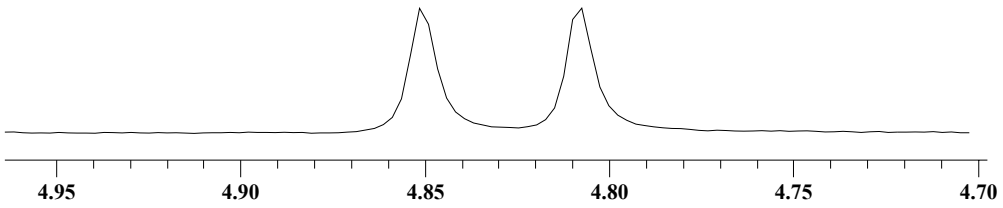


Figure 1. ^{1}H-NMR spectrum of racemic mandelic acid 43 in the presence of 79

However, when the 2,3-diphenylsuccinic acid **81** was used as the guest, a chemical shift difference of 11.6 Hz was observed at 6:1 ratio of the amine and acid (Figure 2).

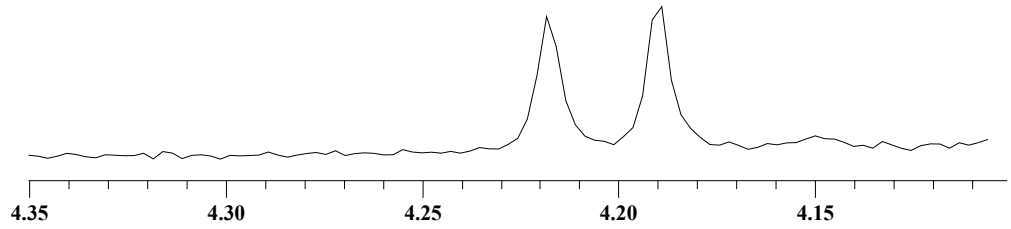


Figure 2. ^{1}H-NMR spectrum of racemic 2,3-diphenylsuccinic acid 81 in the presence of 79

The stoichiometry of the complex formed between the macrocyclic amine **79** and mandelic acid **43** was evaluated by carrying out the Job's titration between the macrocyclic amine **79** and both (*R*)-and (*S*)-mandelic acids in different ratios. The product ($\Delta\delta X$) of the difference in chemical shift ($\Delta\delta$) and the mole fraction of the acid (X) was plotted against the mole fraction of the acid to obtain the Job's plot (Table 5, Figure 3).

Table 5. Job's plot of 79 with (*R*)- and (*S*)-mandelic acids 43

S. No.	Mole fraction of the acid **43** (X)	(*S*)-Mandelic acid **43**		(*R*)-Mandelic acid **43**	
		$\Delta\delta^a$	$\Delta\delta X$	$\Delta\delta^a$	$\Delta\delta X$
1.	0.10	0.36	0.03	0.36	0.03
2.	0.20	0.37	0.07	0.37	0.07
3.	0.30	0.38	0.11	0.38	0.11
4.	0.40	0.39	0.15	0.39	0.15
5.	0.50	0.40	0.20	0.40	0.20
6.	0.60	0.42	0.25	0.42	0.25
7.	0.70	0.43	0.30	0.42	0.29
8.	0.75	0.43	0.32	0.40	0.30
9.	0.80	0.38	0.30	0.35	0.28
10.	0.90	0.25	0.22	0.22	0.20

a. The change in the chemical shift (Δδ) of the acid in the presence of **79** was calculated with reference to the methine CH proton signal of the acid at 5.26 δ ppm in the absence of **79**.

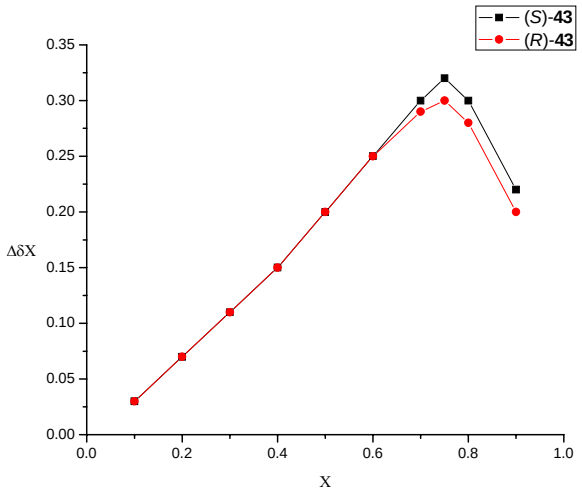


Figure 3. Job's plot of 79 with (*R*)- and (*S*)-mandelic acids 43 [X = mole fraction of the acid; Δδ = change in the chemical shift of the methine proton signal of (*R*)- and (*S*)- mandelic acids]

A maximum was observed when the mole fraction of the (*R*)- or (*S*)-mandelic acid was 0.75 indicating that the macrocyclic amine **79** forms a 1:3 complex with (*R*)- or (*S*)-mandelic acid.

From the plot (Figure 3) it is evident that the chemical shift changes of the (*S*)-mandelic acid are greater when compared to the (*R*)-mandelic acid. To further assess the discriminating ability of the amine **79**, the titration of the macrocyclic amine **79** with the (*R*)- and (*S*)-mandelic acids was carried out by varying the relative ratio of the acid and amine as: 0.25, 0.5, 0.75, 1.00, 1.25, 1.5, 2.00, 2.5 and 3.00. The change in the chemical shift of the methine CH signal of the (*R*)- or (*S*)-mandelic acid was recorded. The relative concentration of the acid (C) was plotted against the change in the chemical shift of the methine signal of the acid (Δδ) (Table 6, Figure 4).

Table 6. ^{1}H-NMR titration of 79 with (*R*)- and (*S*)-mandelic acids 43

S. No	Relative concentration of **43**:**79** (C)	(*S*)-Mandelic acid Δδ[a]	(*R*)-Mandelic acid Δδ[a]
1.	0.25	0.44	0.42
2.	0.50	0.42	0.41
3.	0.75	0.41	0.40
4.	1.00	0.40	0.39
5.	1.25	0.39	0.38
6.	1.50	0.39	0.38
7.	2.00	0.39	0.38
8.	2.50	0.38	0.37
9.	3.00	0.38	0.37

a. The change in the chemical shift (Δδ) of the acid in the presence of **79** was calculated with reference to the methine CH proton signal of the acid at 5.26 δ ppm in the absence of **79**.

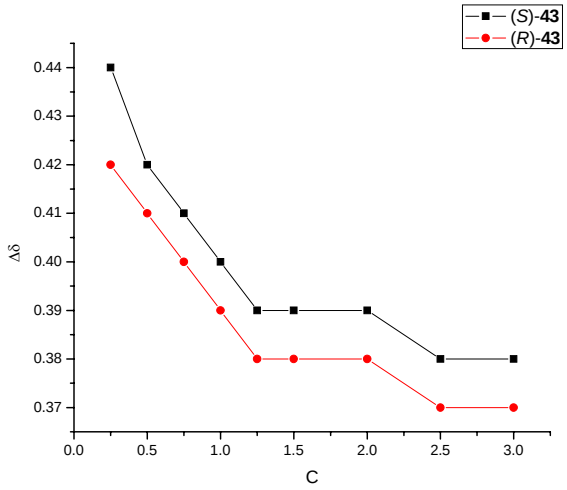


Figure 4. ^{1}H-NMR titration curves of 79 with (*R*)- and (*S*)-mandelic acids 43 [C = relative concentration of the acid with respect to the amine; Δδ = change in the chemical shift of the methine proton signal of (*R*)- and (*S*)-mandelic acids]

However, the association constant of **79** with (*R*)- and (*S*)-mandelic acids could not be calculated by the nonlinear least-square fitting method.[54]

It was observed that in the presence of both (*R*)- and (*S*)-mandelic acids, there was a downfield chemical shift of the signals due to the benzylic protons of the macrocyclic amine **79**.

The methine proton signals of the mandelic acid **43** showed a chemical shift difference of 13.6 Hz, in the presence of the macrocyclic amine **80**, with the amine and acid ratio of 1:4. It was observed that the methine signal of the (*S*)-mandelic acid was shifted more downfield when compared to the (*R*)-mandelic acid (Figure 5).

Some changes in the ^{1}H-NMR chemical shift values of the macrocyclic amine **80** were observed in the presence of the (*R*)- and (*S*)-mandelic acids. The doublets due to the benzylic protons of the macrocyclic amine **80** shifted downfield by about 72 Hz and the signals due to the cyclohexane ring shifted upfield in the presence of the (*R*)-

mandelic acid. However, in the presence of the (*S*)-mandelic acid, there was no significant change in the chemical shift values of the benzylic protons of the amine **80**, but the signals due to the cyclohexane ring shifted downfield.

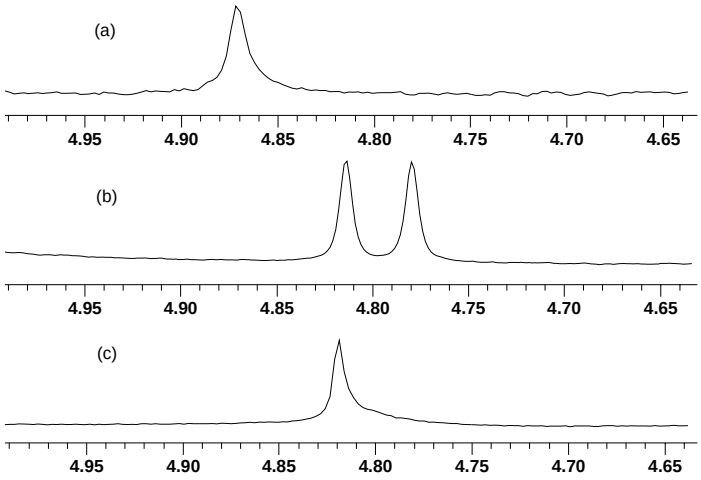
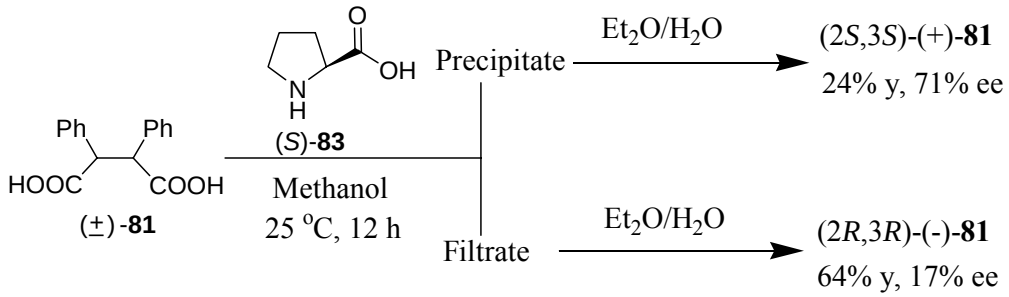


Figure 5. ^{1}H-NMR spectra of : (a) (*S*)-mandelic acid 43 in the presence of 80 (b) racemic mandelic acid 43 in the presence of 80 (c) (*R*)-mandelic acid 43 in the presence of 80

The splitting of the methine proton signal of the 2,3-diphenylsuccinic acid **81** was found to be very large (40 Hz) when the ratio of the macrocyclic amine **80** and the diacid was 2:1. To evaluate the efficiency of the amine **80** in the determination of the enantiomeric excess of the diacid **81**, the enantiomeric composition of the non-racemic samples of the diacid was determined in the presence of the macrocyclic amine. The non-racemic samples of the diacid **81** were obtained by partial resolution using (*S*)-proline **83** following a procedure developed in this laboratory (Scheme 27).[55]

Scheme 27



The enantiomeric excess of the non-racemic diacid **81** with 71% ee and 17% ee determined by ^{1}H-NMR in the presence of the amine **80** was in correspondence with the ee values determined by optical rotation (Figure 6). It was observed that the methine signal of the (*S*,*S*)-**81** was shifted more downfield when compared to the (*R*,*R*)-**81**.

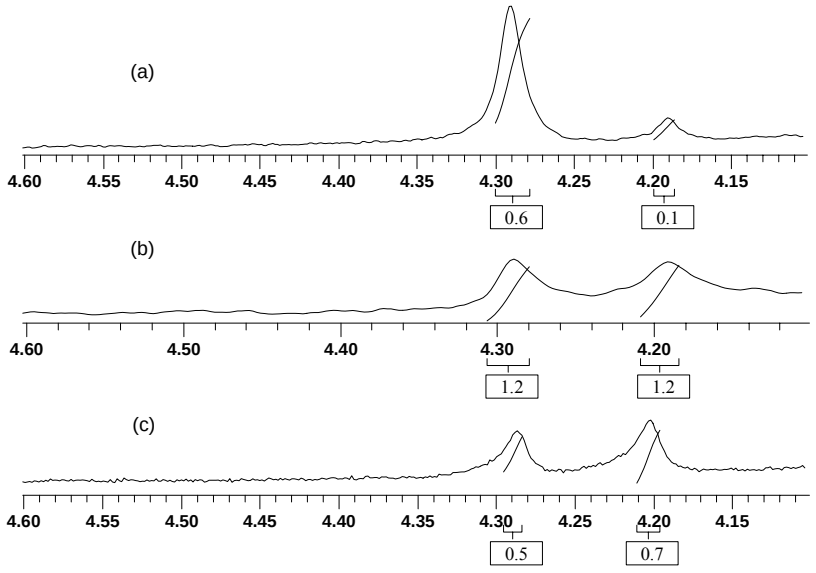


Figure 6. ^{1}H-NMR spectra of : (a) 71% ee of (*S*,*S*)-81 in the presence of 80 (b) racemic 81 in the presence of 80 (c) 17% ee of (*R*,*R*)-81 in the presence of 80

In the presence of the racemic 2,3-diphenylsuccinic acid **81**, there was a broadening of the doublets due to the benzylic protons of the macrocyclic amine **80**. The signals due to the cyclohexane were also broadened but there was no significant change in the chemical shifts of the amine.

In the presence of the macrocyclic amine **82**, the splitting of the mandelic acid **43** was 4.4 Hz and that of the 2,3-diphenylsuccinic acid **81** was 3.6 Hz. It was observed that the methine signal of the (*S*)-**43** was shifted more downfield when compared to the (*R*)-**43** (Figure 7).

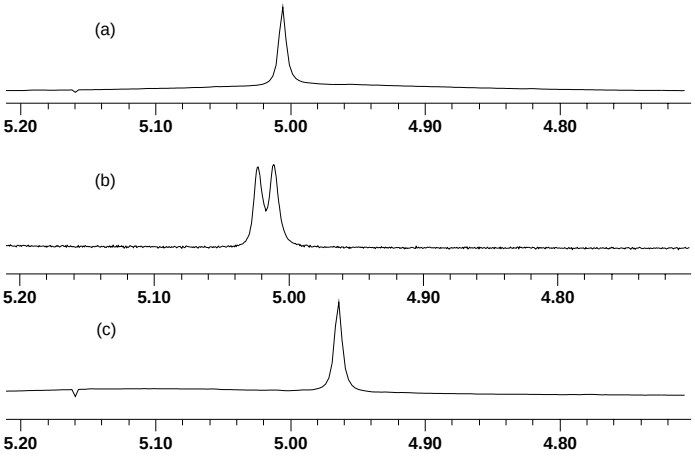


Figure 7. ^{1}H-NMR spectra of : (a) (*S*)-mandelic acid 43 in the presence of 82 (b) racemic mandelic acid 43 in the presence of 82 (c) (*R*)-mandelic acid 43 in the presence of 82

From these results, it is evident that the macrocyclic amine **79** is an effective chiral solvating agent for the mandelic acid and the macrocyclic amine **80** is effective for 2,3-diphenylsuccinic acid. The macrocyclic amine **82** splits the methine signals of both mandelic acid and 2,3-diphenylsuccinic acid to a lesser extent indicating that the presence of the N-H proton plays a significant role in the formation of hydrogen bonding with the guest molecule, thus leading to better enantiomeric recognition.

3.3 Conclusions

Efforts were made to achieve asymmetric reduction of acetophenone using the amine-borane complexes prepared from the chiral diamines **64** and **65**. Though, the asymmetric induction realized was very poor, the results would help in further studies on the design of ligands for this application.

Efforts were also made to achieve the kinetic resolution of 1-phenylethanol using benzoyl chloride in the presence of stoichiometric amounts of the chiral diamines **64** and **69**. Although it was observed that the diamine **69** showed better results when compared to **64**, the enantioselectivity of the ester obtained was poor.

The application of chiral quaternary ammonium salts **72**, **73** and **74** towards the enantioselective alkylation of the benzophenone Schiff base **75** of ethyl glycinate was studied. It was observed that although the chiral quaternary salts catalyze the alkylation of the Schiff base of ethyl glycinate, the imino ester product obtained was found to be racemic.

The chiral secondary macrocyclic amines **79** and **80** proved to be effective chiral NMR solvating agents for mandelic acid **43** and 2,3-diphenylsuccinic acid **81**. The macrocyclic amine **79** showed better enantiomeric recognition towards the mandelic acid. Whereas the amine **80** was a better solvating agent for the 2,3-diphenylsuccinic acid.

3.4 Experimental Section

3.4.1 General Information

Most of the information given in the experimental section of Chapter 1 and Chapter 2 is also applicable to the experiments described here. The racemic 1-phenylethanol was synthesized by the reduction of acetophenone using $NaBH_4$ in methanol under refluxing conditions.[56] The racemic 2,3-diphenylsuccinic acid was synthesized following a reported procedure.[57] The benzophenone Schiff base of ethyl glycinate was synthesized following a reported procedure.[58] The *N*-benzylcinchonidinium bromide was synthesized from cinchonidine following a reported procedure.[51] The racemic mandelic acid supplied by Aldrich, USA; (*R*)-(-)-mandelic acid supplied by Acros Organics, USA; and the (*S*)-(+)-mandelic acid supplied by Merck (Germany) were used. The sodium borohydride and (*S*)-proline supplied by Lancaster Synthesis Ltd., UK were used.

3.4.2 Synthesis of (*R*,*R*)-1,2-bis-(pyrrolidino)cyclohexane 64[45]

The (*R*,*R*)-1,2-diaminocyclohexane **66** (5.7 g, 50 mmol), 1,4-dibromobutane (12.5 mL, 102.5 mmol), anhydrous K_2CO_3 (23 g) and KI (50 mg) were taken in acetonitrile (100 mL) and refluxed for 12 h. The solution was filtered, dried over anhydrous sodium sulfate and then concentrated. The residue obtained was purified by column chromatography on a silica gel column using hexanes:ethyl acetate (98:2) as eluent to isolate the (*R*,*R*)-1,2-bis-(pyrrolidino)cyclohexane **64**.

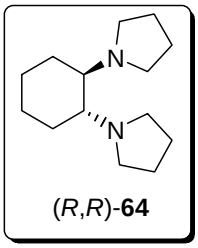
Yield 8.3 g (75%)

IR (neat) (cm^{-1}) 2962, 2935, 1446,

^{1}H-NMR (200 MHz, $CDCl_3$, δ ppm)

1.20-1.80 (m, 16H), 2.20-2.30 (m, 2H),

2.50-2.60 (m, 8H)



(*R*,*R*)-**64**

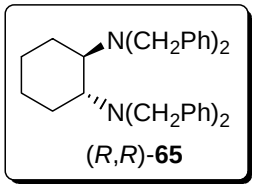
^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm) 21.8, 23.4, 25.3, 51.1, 62.9

$[\alpha]_D^{25}$ -31.85 (*c* 0.5, 1N HCl)

3.4.3 Synthesis of (*R*,*R*)-*N*,*N*,*N′*,*N′*-tetrabenzyl-1,2-diaminocyclohexane 65

The (*R*,*R*)-1,2-diaminocyclohexane **66** (5.0 g, 44 mmol), benzyl bromide (18.8 mL, 180 mmol), anhydrous K_2CO_3 (22 g) and KI (50 mg) were taken in acetonitrile (100 mL) and refluxed for 12 h. The solution was filtered, dried over anhydrous sodium sulfate and then concentrated. The residue obtained was purified by chromatography on a silica gel column using hexanes as eluent to isolate the (*R*,*R*)-*N*,*N*,*N′*,*N′*-tetrabenzyl-1,2-diaminocyclohexane **65**.

Yield 14.5 g (70%)



(*R*,*R*)-**65**

mp 103-104 °C

IR (KBr) (cm^{-1}) 3024, 2930, 1493, 740

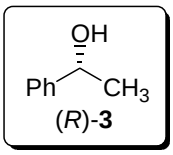
^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 1.01-1.10 (m, 4H), 1.69-1.70 (m, 2H), 2.07-2.09 (m, 2H), 2.68-2.70 (m, 2H), 3.35 (d, *J* = 13.6 Hz, 4H), 3.76 (d, *J* = 13.6 Hz, 4H), 7.19-7.26 (m, 8H), 7.40-7.42 (m, 12H)

^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm) 25.0, 26.0, 53.3, 58.3, 126.6, 128.0, 129.0, 140.6

$[\alpha]_D^{25}$ + 50.9 (*c* 0.8, CH_2Cl_2)

3.4.4 Reduction of acetophenone with (*R*,*R*)-1,2-bis-(pyrrolidino)cyclohexane 64-BH_3 complex in the presence of $BF_3.OEt_2$

The (*R*,*R*)-1,2-bis-(pyrrolidino)cyclohexane-borane complex (5 mmol) was prepared *in situ* by bubbling diborane gas [generated by dropwise addition of I_2 (1.9 g, 7.5 mmol) in diglyme (15 mL) to $NaBH_4$ (0.60 g, 15 mmol) in diglyme (10 mL) at 25 ^oC] into the solution of (*R*,*R*)-1,2-bis-(pyrrolidino)cyclohexane **64** (1.10 g, 5 mmol) in dry toluene (30 mL) for 1 h. $BF_3 \cdot OEt_2$ (0.63 mL, 5 mmol) and acetophenone (0.58 mL, 5 mmol) were added to the reaction mixture at 0 ^oC and stirred for 6 h at 25 ^oC. The reaction mixture was quenched with water (5 mL). The organic layer was separated, and the aqueous layer was extracted with ether (2 X 15 mL). The combined organic extract was washed with 1M HCl (10 mL), water (15 mL), brine (15 mL) and dried over anhydrous sodium sulfate. After evaporation of the solvent, the crude product was purified by chromatography on a silica gel column using hexanes:ethyl acetate (97:3) as eluent to isolate the 1-phenylethanol.



(*R*)-**3**

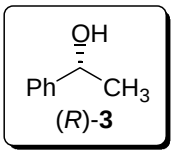
Yield	0.51 g (85%)
IR (neat)	(cm^{-1}) 3352, 3063, 3030, 2974, 898, 761
^{1}H-NMR	(400 MHz, $CDCl_3$, δ ppm)
	1.52 (d, *J* = 6.4 Hz, 3H), 4.91 (q, *J* = 6.4 Hz, 1H), 7.30-7.31 (m, 1H), 7.37-7.39 (m, 4H)
^{13}C-NMR	(50 MHz, $CDCl_3$, δ ppm) 25.0, 70.2, 125.3, 127.3, 128.4, 145.8
$[\alpha]_D^{25}$	+1.8 (*c* 2, MeOH), {lit.[50] for 100% ee, of (*R*)-**3** $[\alpha]_D^{25}$ = +45.9 (*c* 3.3, MeOH)}

3.4.5 Reduction of acetophenone with (*R*,*R*)-*N*,*N*,*N′*,*N′*-tetrabenzyl-1,2-diaminocyclohexane 65-BH_3 complex in the presence of $BF_3.OEt_2$

The procedure outlined in the experiment 3.4.4 was followed using (*R*,*R*)-*N*,*N*,*N′*,*N′*-tetrabenzyl-1,2-diaminocyclohexane **65** (2.28 g, 5 mmol).

Yield 0.5 g (82%)

$[\alpha]_D^{25}$ +1.8 (*c* 2, MeOH), {lit.[50] for 100% ee, for (*R*)-**3** $[\alpha]_D^{25}$ = +45.9 (*c* 3.3, MeOH)}



(*R*)-**3**

3.4.6 Synthesis of (*R*,*R*)-*N*,*N*,*N′*,*N′*-tetramethyl-1,2-diaminocyclohexane 69[48]

The (*R*,*R*)-1,2-diaminocyclohexane **66** (5.0 g, 44 mmol), formic acid (36 mL) and formaldehyde (18 mL) were heated at 110 ^oC for 12 h. The formic acid and formaldehyde mixture was distilled out and the residue was neutralized with 2M NaOH (15 mL) and extracted with dichloromethane (2 X 30 mL). The combined organic extract was washed with brine (20 mL), dried over anhydrous sodium sulfate and the solvent was evaporated to give the crude product which was distilled under reduced pressure to give the (*R*,*R*)-*N*,*N*,*N′*,*N′*-tetramethyl-1,2-diaminocyclohexane **69**.

Yield 4.5 g (60%)

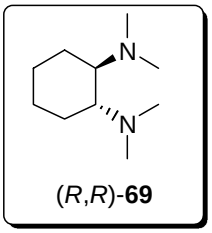
bp 65 ^oC/2 mm Hg

IR (neat) (cm^{-1}) 2939, 1458, 1361

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 1.07-1.15 (m, 4H), 1.70-1.80 (m, 2H), 1.90-2.00 (m, 2H), 2.40 (s, 12H), 2.37-2.40 (m, 2H)

^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm) 23.0, 25.6, 40.1, 63.9

$[\alpha]_D^{25}$ -60.6 (*c* 1, $CHCl_3$)

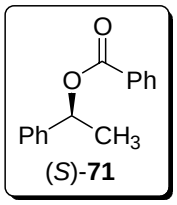


(*R*,*R*)-**69**

3.4.7 Representative procedure for the kinetic resolution of racemic 1-phenylethanol 3 using the chiral diamine 69

To a stirred solution of 1-phenylethanol **3** (0.68 g, 4 mmol) in dichloromethane (30 mL), the chiral diamine **69** (0.48 g, 4 mmol) and benzoyl chloride **70** (0.20 mL, 2 mmol) were added at -20 ^{o}C and stirred for 36 h. The reaction was quenched with water (10 mL) and extracted with dichloromethane (2 X 10 mL). The combined organic extract was washed with brine (10 mL), dried over anhydrous sodium sulfate and the solvent was evaporated. The crude product was chromatographed on a silica gel column using hexanes:ethyl acetate (98:2) as eluent to isolate 1-phenylethyl benzoate **71** and hexanes:ethyl acetate (97:3) as eluent to isolate 1-phenylethanol **3**.

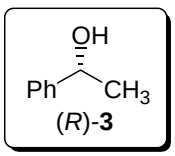
1-Phenylethyl benzoate **71**:



(*S*)-**71**

Yield	0.28 g (32%)
IR (neat)	(cm^{-1}) 3065, 3034, 2982, 1716, 1271, 873
^{1}H-NMR	(400 MHz, $CDCl_3$, δ ppm) 1.68 (d, *J* = 7.2 Hz, 3H), 6.14 (q, *J* = 6.4 Hz, 1H), 7.32-7.26 (m, 2H), 7.35-7.39 (m, 2H), 7.42-7.46 (m, 2H), 7.54-7.55 (m, 2H), 8.07-8.10 (m, 2H) (**Spectrum No. 27**)
^{13}C-NMR	(50 MHz, $CDCl_3$, δ ppm) 22.4, 72.9, 126.1, 127.9, 128.3, 128.5, 129.6, 130.6, 141.8, 165.8 (**Spectrum No. 28**)
$[\alpha]_D^{25}$	+5.1 (*c* 2, EtOH), {lit.[49] for 100% ee, of (*S*)-**71** $[\alpha]_D^{25}$ = +27.3 (*c* 1, EtOH)

1-Phenylethanol **3**:



(*R*)-**3**

Yield	0.30 g (61%)
IR (neat)	(cm^{-1}) 3352, 3063, 3030, 2974, 898, 761

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 1.52 (d, *J* = 6.4 Hz, 3H), 4.91 (q, *J* = 6.4 Hz, 1H), 7.30-7.31 (m, 1H), 7.37-7.39 (m, 4H)

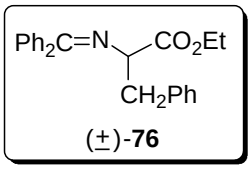
^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm) 25.0, 70.2, 125.3, 127.3, 128.4, 145.8

$[\alpha]_D^{25}$ +2.2 (*c* 2, MeOH), {lit.[50] for 100% ee, for (*R*)-**3** $[\alpha]_D^{25}$ = +45.9 (*c* 3.3, MeOH)

3.4.8 Alkylation of the benzophenone Schiff base 75 of ethyl glycinate catalyzed by the chiral quaternary ammonium salt 74

To a stirred solution of **75** (0.50 g, 1.8 mmol) in dichloromethane (30 mL), the chiral salt **74** (0.11 g, 0.018 mmol), benzyl bromide (0.22 mL, 2.1 mmol), 50% aq. NaOH (5 mL) were added and stirred at 25 ^oC. After 10 h the organic layer was separated and the aqueous layer was extracted with dichloromethane (2 X 15 mL). The combined organic extract was washed with brine (10 mL), dried over anhydrous sodium sulfate and the solvent was evaporated. The residue was purified by chromatography on a silica gel column using hexanes:ethyl acetate (97:3) as eluent to isolate the product **76** which was found to be racemic.

Yield 0.57 g (90%)



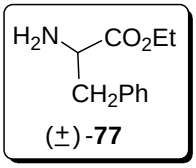
(±)-**76**

IR (KBr) (cm^{-1}) 3061, 3028, 2982, 1736, 1660, 1446, 781

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm) 1.26 (t, *J* = 6.8 Hz, 3H), 3.15-3.30 (m, 2H), 4.14-4.25 (m, 3H), 7.03-7.05 (m, 3H), 7.26-7.57 (m, 9H), 7.58 (d, *J* = 8 Hz, 3H) (**Spectrum No. 29**)

^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm) 14.2, 39.7, 61.0, 67.3, 126.2, 127.7, 128.0, 128.1, 128.3, 128.7, 129.8, 130.2, 136.2, 138.0, 139.4, 170.7, 171.7 (**Spectrum No. 30**)

The imino ester **76** (0.57 g, 1.59 mmol) obtained by the above procedure was dissolved in tetrahydrofuran (10 mL) and hydrolyzed by stirring with 15% aqueous citric acid (4.5 mL) for 3 h. The reaction mixture was then diluted with water (15 mL) and extracted with diethyl ether (2 X 15 mL) to remove any excess alkylating agent and benzophenone. The aqueous layer was then basified with 10% aq. K_2CO_3 (20 mL), extracted with ethyl acetate (3 X 15 mL) and the combined organic extract was washed with brine (15 mL). The concentration of the ethyl acetate afforded the racemic ethyl phenylalaninate **77**.



(±)-**77**

Yield 0.27 g (90%)

IR (KBr) (cm^{-1}) 3373, 1734, 1599, 1032, 748

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm)

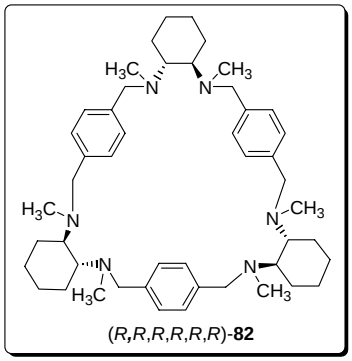
1.26 (t, *J* = 7.8 Hz, 3H), 1.57 (s, 2H), 2.87 (dd, *J* = 7.8 Hz, 1H), 3.09 (dd, *J* = 4.6 Hz, 1H), 3.72 (t, *J* = 5.8 Hz, 1H), 4.17 (q, *J* = 7.2 Hz, 2H), 7.22 (d, *J* = 8 Hz, 2H), 7.26 (d, *J* = 7.2 Hz, 1H), 7.32 (t, *J* = 6.8 Hz, 2H) (**Spectrum No. 31**)

^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm) 14.1, 41.2, 55.8, 60.8, 126.7, 128.4, 129.3, 137.3, 174.9 (**Spectrum No. 32**)

3.4.9 Synthesis of the chiral macrocyclic amine 82

The secondary macrocyclic amine **79** (1.50 g, 2.4 mmol), formic acid (2 mL) and formaldehyde (1 mL) were heated at 110 ^oC for 12 h. The reaction mixture was

neutralized with 2M NaOH (15 mL) and extracted with dichloromethane (2 X 15 mL). The combined organic extract was washed with brine (15 mL), dried over anhydrous sodium sulfate and the solvent was evaporated to give the product **82**.



(*R*,*R*,*R*,*R*,*R*)-**82**

Yield	1.58 g (90%)
mp	178-180 ^{o}C
IR (KBr)	(cm^{-1}) 3028, 2926, 1450, 763
^{1}H-NMR	(400 MHz, $CDCl_3$, δ ppm) 1.15-1.23 (m, 6H), 1.30-1.40 (m, 6H), 1.80-1.85 (m, 6H), 2.00-2.05 (m, 6H), 2.21 (s, 18H), 2.72-2.74 (m, 6H), 3.76 (AB q, *J* = 12.8 Hz, 12H), 7.40 (s, 12H) (**Spectrum No. 33**)
^{13}C-NMR	(50 MHz, $CDCl_3$, δ ppm) 25.9, 26.3, 35.8, 58.6, 64.9, 128.6, 139.3 (**Spectrum No. 34**)
$[\alpha]_D^{25}$	-16.9 (*c* 0.9, CH_2Cl_2)
LCMS	m/z 734 (M+1)
Analysis	Calculated for $C_{48}H_{72}N_6$: C, 78.5%; H, 9.8%; N, 11.4%
	Found : C, 78.5%; H, 9.9%; N, 11.4%

3.4.10 ^{1}H-NMR experiments

^{1}H-NMR experiments were performed by mixing molar amounts of the compounds **79**, **80** and **82** with the acids **43** and **81** in varying ratios in $CDCl_3$, until the maximum splitting of the methine peaks was observed.

3.4.11 Evaluation of the stoichiometry of the complex formed between 79 and (*R*)- and (*S*)-mandelic acids 43 by Job's method

The stoichiometry of the complex formed between **79** and **43** was determined according to Job's method of continuous variations. Equimolar amounts of **79** (0.0025M) and (*R*)- or (*S*)-**43** (0.0025M) were dissolved in $CDCl_3$. These solutions were distributed among ten NMR tubes in such a way that the molar fractions of **43** and **79** in the resulting solutions increased from 0.1 to 0.9. The complexation induced shifts of the methine signal ($\Delta\delta$) were multiplied by the molar fraction of the acid **43** (X) (Table 5, Section 3.2.4) and plotted against X to obtain the Job's plot (Figure 3, Section 3.2.4).

3.4.12 NMR host-guest titrations

The mandelic acid **43** [(*R*) or (*S*)] (0.0031M [2.4 mg in 5 mL]) was dissolved in $CDCl_3$ and evenly distributed (0.5 mL) among ten NMR tubes. The first NMR tube was sealed without any amine. The macrocyclic amine **79** was dissolved in $CDCl_3$ (0.039M [51.5 mg in 2 mL]) and added in increasing amounts to the NMR tubes so that the solutions with the relative concentrations of the acid versus amine of 0.25, 0.5, 0.75, 1.00, 1.25, 1.50, 2.00, 2.50 and 3.00 are obtained. The change in the chemical shift values of the methine signal (Table 6, Section 3.2.4) are plotted against the relative concentration of the acid versus amine (Figure 4, Section 3.2.4).

3.5 References

1. (a) Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. In *Comprehensive Asymmetric Catalysis*; Springer: Berlin, 1999, 1-3. (b) Gawley, R. E.; Aube, J. In *Principles of Asymmetric Synthesis*; Pergamon: London, 1996. (c) Kagan, H. B. In *Comprehensive Organic Chemistry*; Pergamon: Oxford, 1992, 8. (d) Brunner, H.; Zettlmeier, W. In *Handbook of Enantioselective catalysis*; VCH: Weinheim, 1993.
2. (a) Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*, Ojima, J. Ed.; VCH: New York, 1993, 103. (b) Noyori, R. In *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994.
3. (a) Andrews, G. C.; Crawford, T. C. *Tetrahedron Lett.* **1980**, *21*, 693. (b) Andrews, G. C. *Tetrahedron Lett.* **1980**, *21*, 687. (c) Pelter, A.; Smith, K. In *Comprehensive Organic Chemistry*, Jones, D. Ed.; Pergamon: Oxford, 1979, 3, 687.
4. Fiaud, J. C.; Kagan, H. B. *Bull. Soc. Chim. France* **1969**, 2742.
5. Borch, R. F.; Levitan, S. R. *J. Org. Chem.* **1972**, *37*, 2347.
6. Grundon, M. F.; McCleery, D. G.; Wilson, J. W. *J. Chem. Soc., Perkin Trans. 1* **1981**, 231.
7. Eleveld, H. B.; Hogeveen, H. *Tetrahedron Lett.* **1986**, *27*, 635.
8. (a) Kanth, J. V. B.; Periasamy, M. *J. Chem. Soc., Chem. Commun*. **1990**, 1145. (b) Periasamy, M.; Kanth, J. V. B.; Reddy, Ch. K. *J. Chem. Soc., Perkin Trans. 1* **1995**, 427.

9. (a) Belan, A.; Bolte, J.; Fauve, A.; Gourcy, J. G.; Veschambre, H. *J. Org. Chem.* **1987**, *52*, 256. (b) Stokes, T. M.; Oehlschlager, A. C. *Tetrahedron Lett.* **1987**, *28*, 2091. (c) Morgan, B.; Oehlschlager, A. C.; Stokes, T. M. *Tetrahedron* **1991**, *47*, 1611.

10. (a) Chen, C.-S.; Sih, C. J. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 695. (b) Klibanov, A. M. *Acc. Chem. Res.* **1990**, *23*, 114. (c) Andersch, P.; Berger, M.; Hermann, J.; Laumen, K.; Lobell, M.; Seemayer, R.; Waldinger, C.; Schneider, M. P. *Methods Enzymol.* **1997**, *286*, 406. (d) Schmid, R. D.; Verger, R. *Angew. Chem. Int. Ed.* **1998**, *37*, 1609. (e) Roberts, S. M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1. (f) Stecher, H.; Faber, K. *Synthesis* **1997**, 1. (g) Reetz, M. T.; Jaeger, K. E. *Chem. Eur. J.* **2000**, *6*, 407.

11. Vedejs, E.; Jure, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 3974.

12. Vedejs, E.; Chen, X. *J. Am. Chem. Soc*. **1996**, *118*, 1809.

13. Ruble, J. C.; Latham, H. A.; Fu, G. C. *J. Am. Chem. Soc*. **1997**, *119*, 1492.

14. Ishihara, K.; Kosugi, Y.; Akakura, M. *J. Am. Chem. Soc*. **2004**, *126*, 12212.

15. Birman, V. B.; Uffman, E. W.; Jiang, H.; Li, X.; Kilbane, C. J. *J. Am. Chem. Soc*. **2004**, *126*, 12226.

16. Sano, T.; Imai, K.; Ohashi, K.; Oriyama, T. *Chem. Lett.* **1999**, 265.

17. Arai, S.; Bellemin-Laponnaz, S.; Fu, G. C. *Angew. Chem. Int. Ed.* **2001**, *40*, 234.

18. Kawabata, T.; Yamamoto, K.; Momose, Y.; Yoshida, H.; Nagaoka, Y.; Fuji, K. *Chem. Commun*. **2001**, 2700.

19. Dolling, U.-H.; Davis, P.; Grabowski, E. J. *J. Am. Chem. Soc.* **1984**, *106*, 446.

20. Ooi, T.; Ohara, D.; Tamura, M.; Maruoka, K. *J. Am. Chem. Soc.* **2004**, *126*, 6844.

21. (a) Williams, R. M. In *Synthesis of Optically Active α-Amino Acids*; Baldwin, J. E. Ed.; Organic Chemistry Series, Pergamon: Oxford, 1989. (b) Williams, R. M.; Hendrix, J. A. *Chem. Rev*. **1992**, *92*, 889.

22. (a) Dehmlow, E. D.; Dehmlow, S. S. In *Phase-transfer Catalysis*, 3rd ed.; VCH: Weinheim, 1993. (b) Starks, C. M.; Liotta, C. L. Halpern, M. In *Phase-transfer Catalysis*; Chapman & Hall: New York, 1994.

23. Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414.

24. Lygo, B.; Wainwright, P. G. *Tetrahedron Lett*. **1997**, *38*, 8595.

25. Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **1999**, *121*, 6519.

26. Ooi, T.; Takeuchi, M.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2000**, *122*, 5228.

27. Shibuguchi, T.; Fukuta, Y.; Akachi, Y.; Sekine, A.; Ohshima, T.; Shibasaki, M. *Tetrahedron Lett*. **2002**, *43*, 9539.

28. Eliel, E. L.; Wilen, S. In *Stereochemistry of Organic Compounds*; John Wiley & Sons: New York, 1994.

29. (a) Kaneda, T. In *Crown Ethers and Analogous Compounds*; Hiraoka, M. Ed.; Elsevier: Amsterdam, 1992, Chapter 6. (b) Sawada, M. *J. Mass Spectrom. Soc. Jpn*. **1997**, *45*, 439. (c) Pu, L.; *Chem. Rev*. **2004**, *104*, 1687. (d) Matsushita, M.; Yoshida, K.; Yamamoto, N.; Wirsching, P.; Lerner, R. A.; Janda, K. D. *Angew. Chem. Int. Ed.* **2003**, *42*, 5984. (e) Parker, D. *Chem. Rev*. **1991**, *91*,

1441. (f) Juliano, A.; Uccello-Barretta, G.; Salvadori, P. *Tetrahedron: Asymmetry* **2000**, *11*, 1555.

30. Chin, J.; Kim, D. C.; Kim, H.-J.; Panosyan, F. B.; Kim, K. M. *Org. Lett*. **2004**, *6*, 2591.

31. Hulst, R.; de Vries, N. K.; Feringa, B. L. *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1092.

32. Watanabe, M.; Hasegawa, T.; Miyake, H.; Kojima, Y. *Chem. Lett*. **2001**, 4.

33. Yang, D.; Li, X.; Fan, Y.-F.; Zhang, D.-W. *J. Am. Chem. Soc*. **2005**, *127*, 7996.

34. (a) Lin, J.; Hu, Q.-S.; Xu, M.-H.; Pu, L. *J. Am. Chem. Soc*. **2002**, *124*, 2088. (b) Xu, M.-H.; Lin, J.; Hu, Q.-S.; Pu, L. *J. Am. Chem. Soc*. **2002**, *124*, 14239.

35. Fulwood, R.; Parker, D. *J. Chem. Soc., Perkin Trans. 2* **1994**, 57.

36. Benson, S. C.; Cai, P.; Colon, M.; Haiza, M. A.; Tokles, M.; Snyder, J. K. *J. Org. Chem*. **1988**, *53*, 5335.

37. Rosini, C.; Uccello-Barretta, G.; Pini, D.; Abete, C.; Salvadori, P. *J. Org. Chem*. **1988**, *53*, 4579.

38. Wenzel, T. J.; Thurston, J. E. *J. Org. Chem*. **2000**, *65*, 1243.

39. (a) Tsubaki, K.; Nuruzzaman, M.; Kusumoto, T.; Hayashi, N.; Bin-Gui, W.; Fuji, K. *Org. Lett*. **2001**, *3*, 4071. (b) Tsubaki, K.; Tanima, D.; Nuruzzaman, M.; Kusumoto, T.; Fuji, K.; Kawabata, T. *J. Org. Chem*. **2005**, *70*, 4609.

40. Lin, J.; Li, Z.-B.; Zhang, H.-C.; Pu, L. *Tetrahedron Lett*. **2004**, *45*, 103.

41. Yang, X.; Wu, X.; Fang, M.; Yuan, Q.; Fu, E. *Tetrahedron: Asymmetry* **2004**, *15*, 2491.

42. Li, Z.-B.; Lin, J.; Pu, L. *Angew. Chem. Int. Ed.* **2005**, *44*, 1690.

43. Li, Y.; Echegoyen, L. *J. Org. Chem*. **1991**, *56*, 4193.

44. Periasamy, M.; Seenivasaperumal, M.; Padmaja, M.; Rao, V. D. *Arkivoc* **2004**, *viii*, 4.

45. Larock, R. C. In *Comprehensive Organic Transformations: A Guide to Functional Group Preparations*; VCH: 1989.

46. Ramanathan, C. R. Ph. D Thesis, School of Chemistry, University of Hyderabad.

47. Brown, H. C.; Choi, Y. M.; Narasimhan, S. *J. Org. Chem*. **1982**, *47*, 3153.

48. Pine, S. H.; Sanchez, B. L. *J. Org. Chem*. **1971**, *36*, 829.

49. Mukaiyama, T.; Kikuchi, W.; Shintou, T. *Chem. Lett*. **2003**, *32*, 300.

50. Anders, M. W.; Cooper, M. J. *Anal. Chem*. **1971**, *43*, 1093.

51. O'Donnell, M. J.; Bennett, W.; Wu, S. *J. Am. Chem. Soc.* **1989**, *111*, 2353.

52. Liu, W.; Ray, P.; Benezra, S. A. *J. Chem. Soc., Perkin Trans. 1* **1995**, *5*, 553.

53. Yamada, S.; Hongo, C.; Yoshioka, R.; Chibata, I. *J. Org. Chem*. **1983**, *48*, 843.

54. (a) Wilcox, C. S. In *Frontiers in Supramolecular Organic Chemistry and Photochemistry*; Schneider, H. J., Durr, H., Eds.; VCH: Weinheim, 1991, 123. (b) Macomber, R. S. *J. Chem. Ed*. **1992**, *69*, 375.

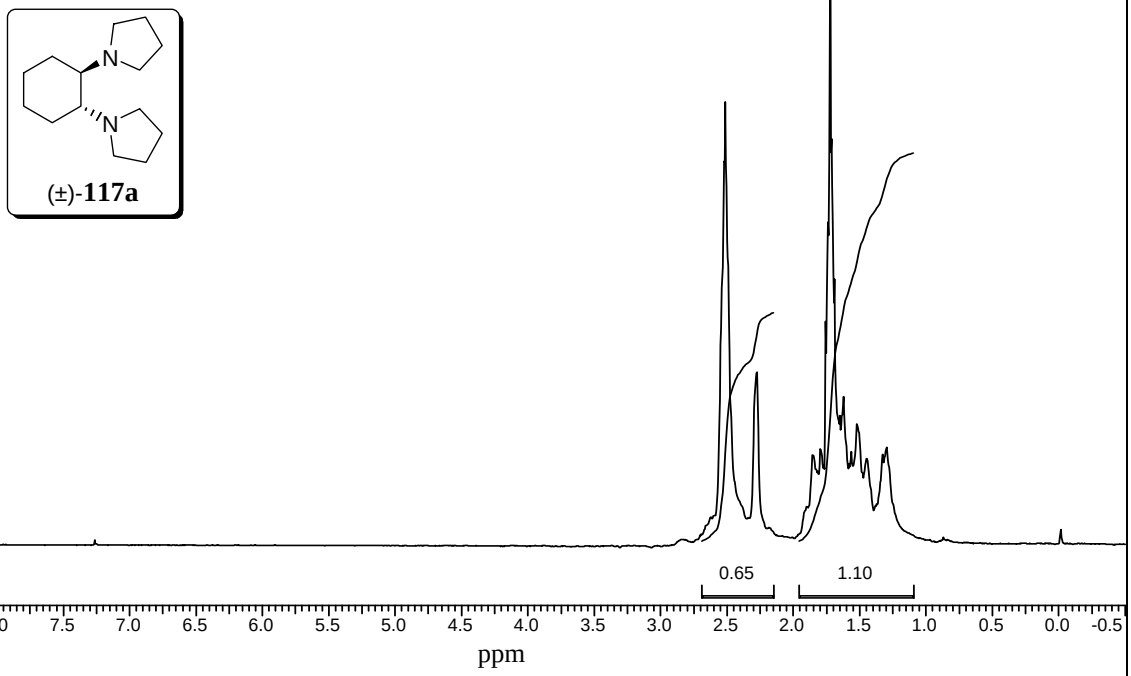
55. Ramanathan, C. R.; Periasamy, M. *Tetrahedron: Asymmetry* **1998**, *9*, 2651.

56. Vogel, A. I. In *Text Book of Practical Organic Chemistry*; Longman: London, 1978.

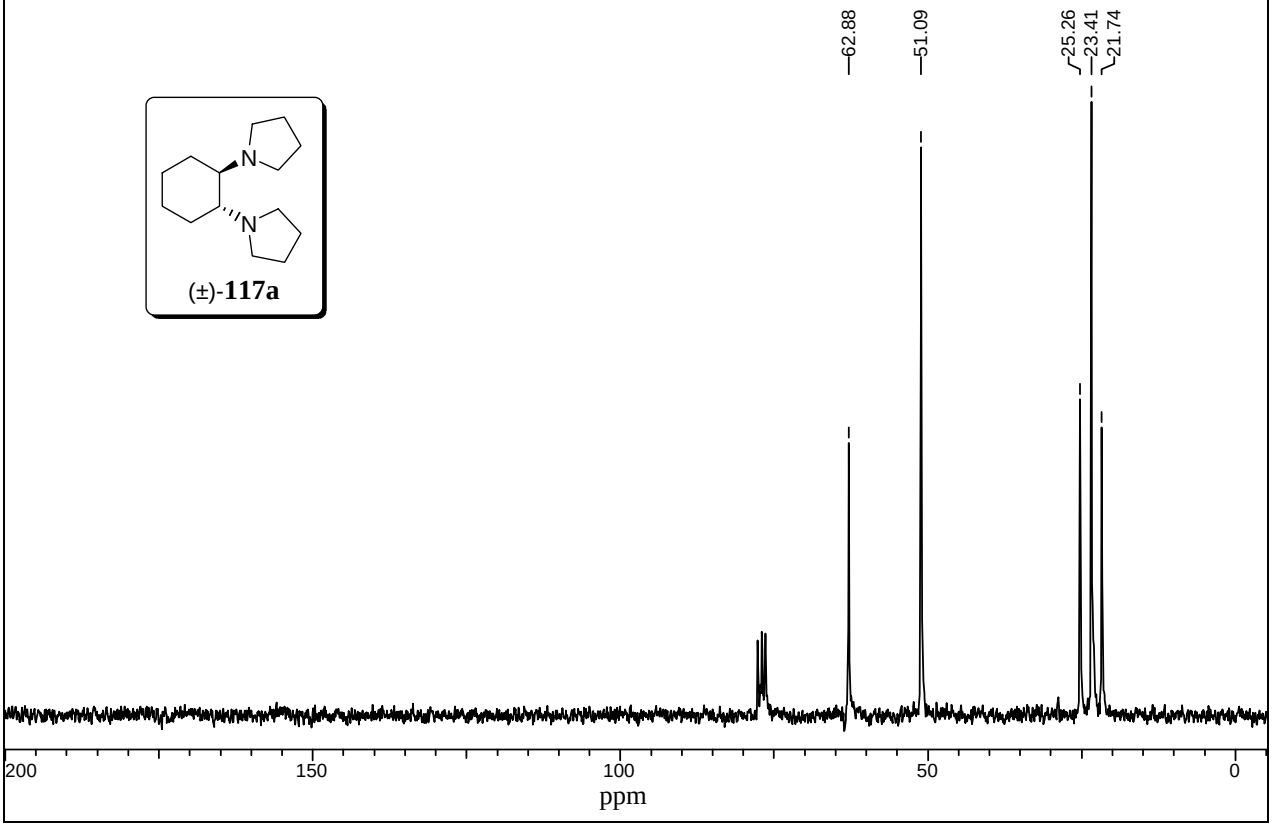
57. Matsumura, Y.; Nishimura, M.; Hiu, H.; Watanabe, M.; Kise, N. *J. Org. Chem*. **1996**, *61*, 2809.

58. O'Donnell, M. J.; Polt, R. L. *J. Org. Chem*. **1982**, *47*, 2663.

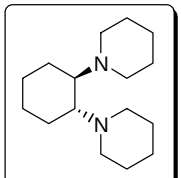
Spectrum No. 1 (Chapter 1, Section 1.4.3.1) ^{1}H NMR Spectrum (200 MHz, $CDCl_3$)



Spectrum No. 2 (Chapter 1, Section 1.4.3.1) ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)

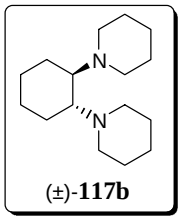


Spectrum No. 3 (Chapter 1, Section 1.4.3.2) ^{1}H NMR Spectrum (200 MHz, $CDCl_3$)



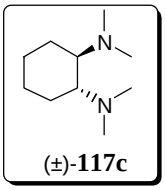
(±)-**117b**

Spectrum No. 4 (Chapter 1, Section 1.4.3.2) ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)



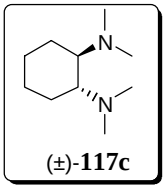
(±)-**117b**

Spectrum No. 5 (Chapter 1, Section 1.4.3.3) ^{1}H NMR Spectrum (200 MHz, $CDCl_3$)



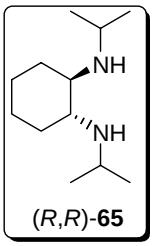
(±)-**117c**

Spectrum No. 6 (Chapter 1, Section 1.4.3.3) ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)



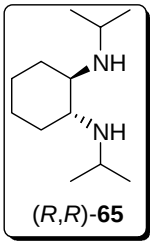
(±)-**117c**

Spectrum No. 7 (Chapter 2, Section 2.4.2) ^{1}H NMR Spectrum (200 MHz, $CDCl_3$)



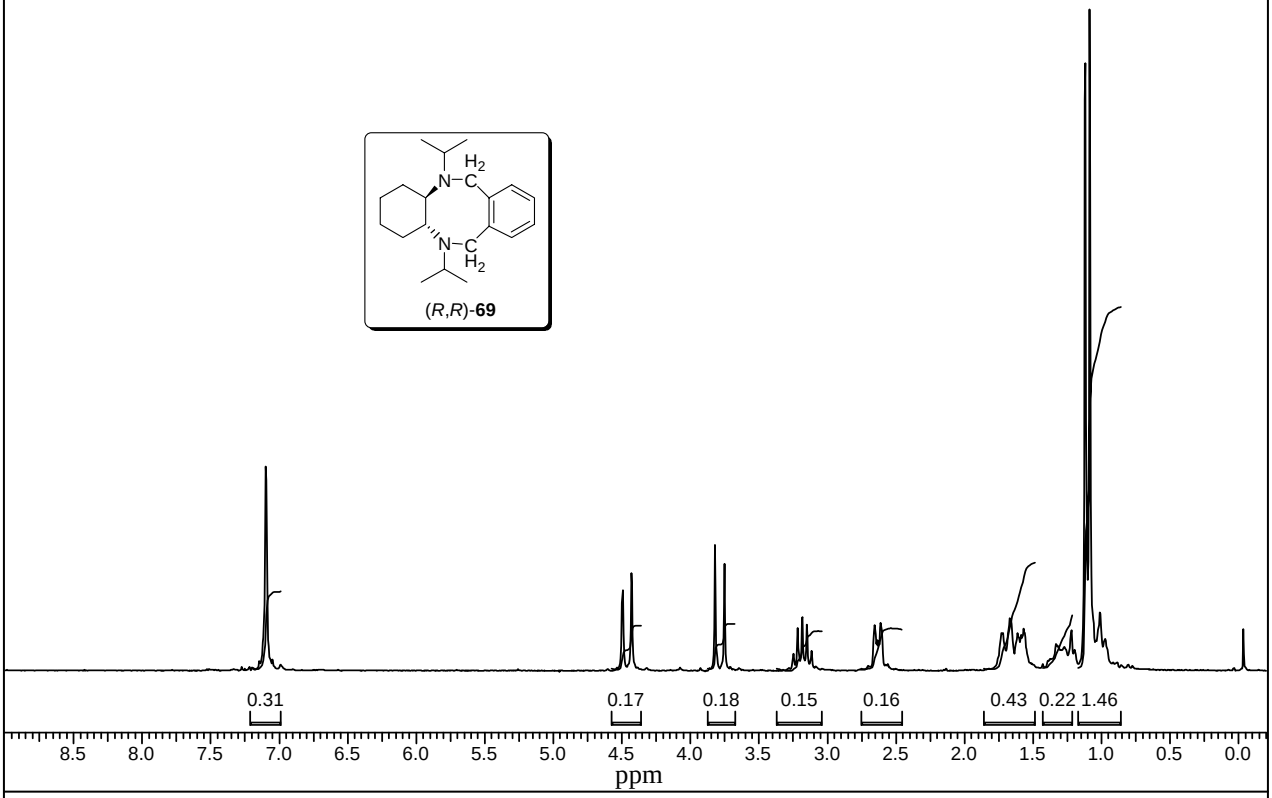
(*R*,*R*)-**65**

Spectrum No. 8 (Chapter 2, Section 2.4.2) ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)

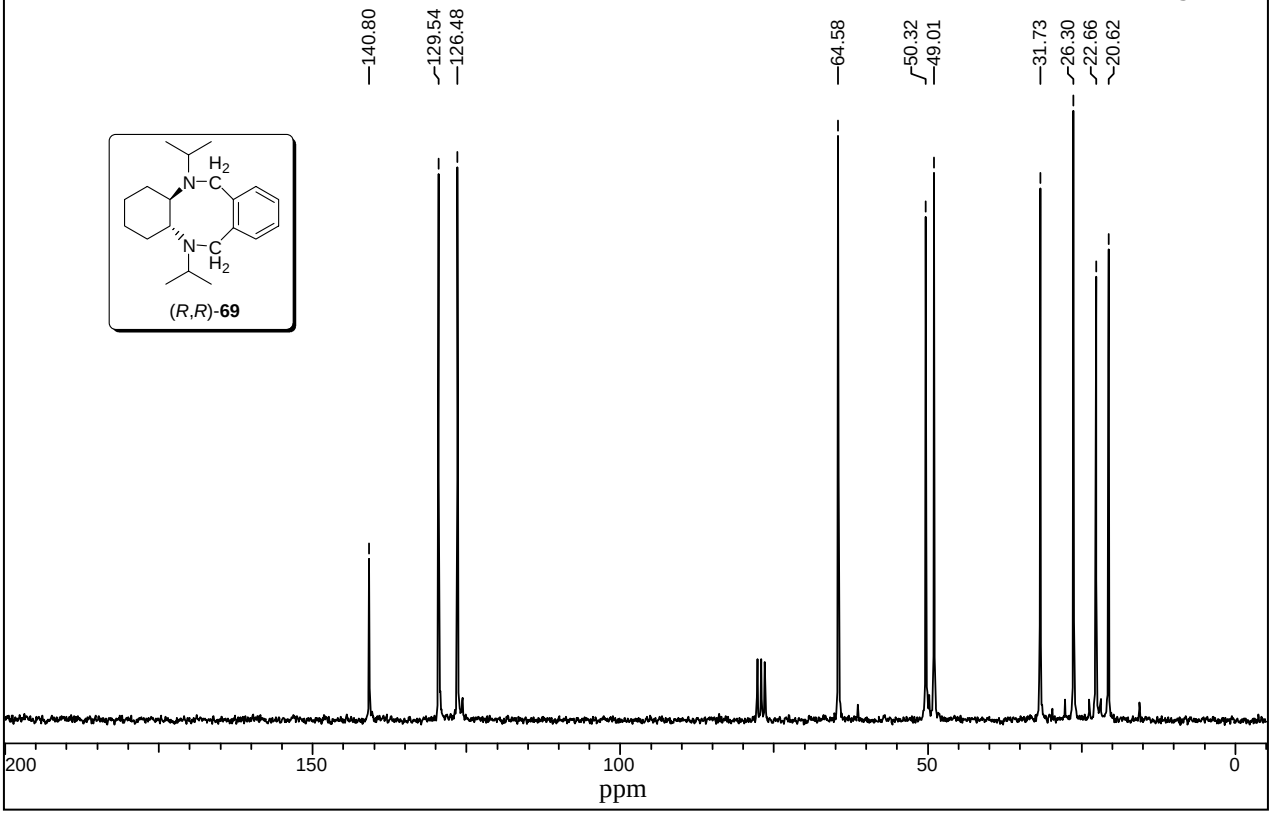


(*R*,*R*)-**65**

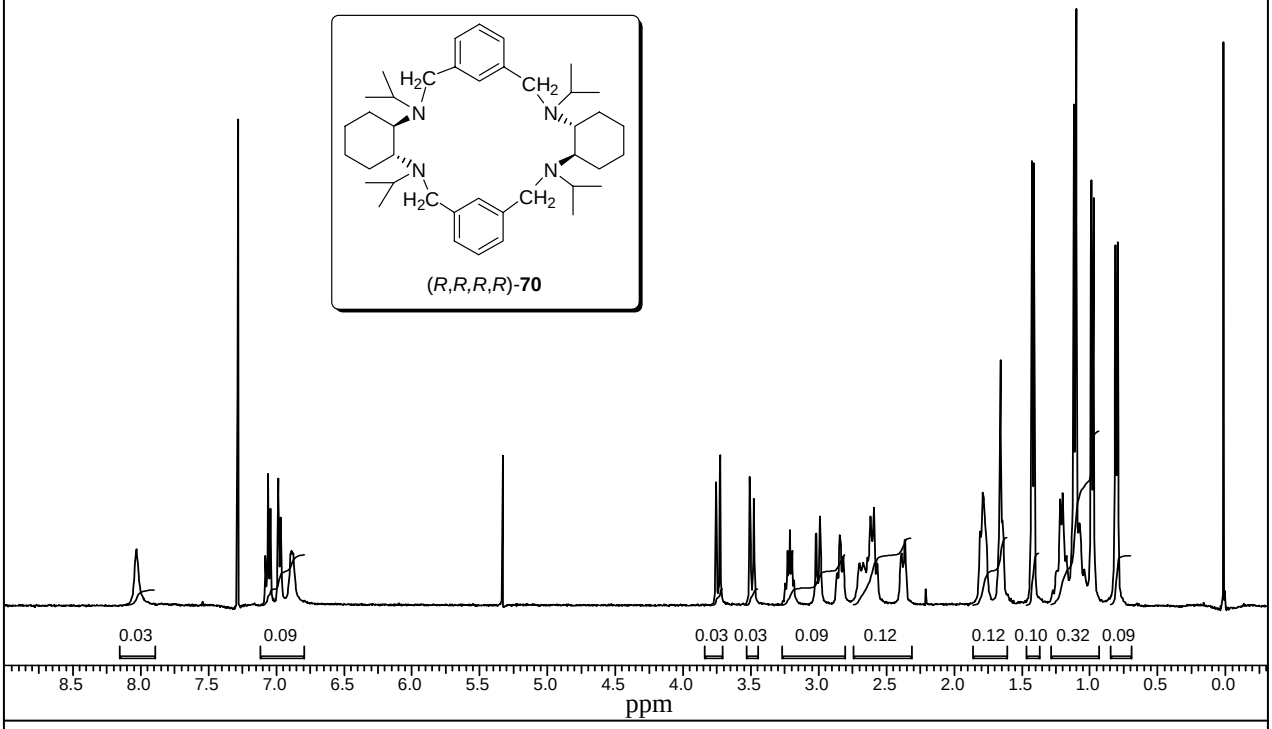
Spectrum No. 9 (Chapter 2, Section 2.4.3.1) ^{1}H NMR Spectrum (200 MHz, $CDCl_3$)



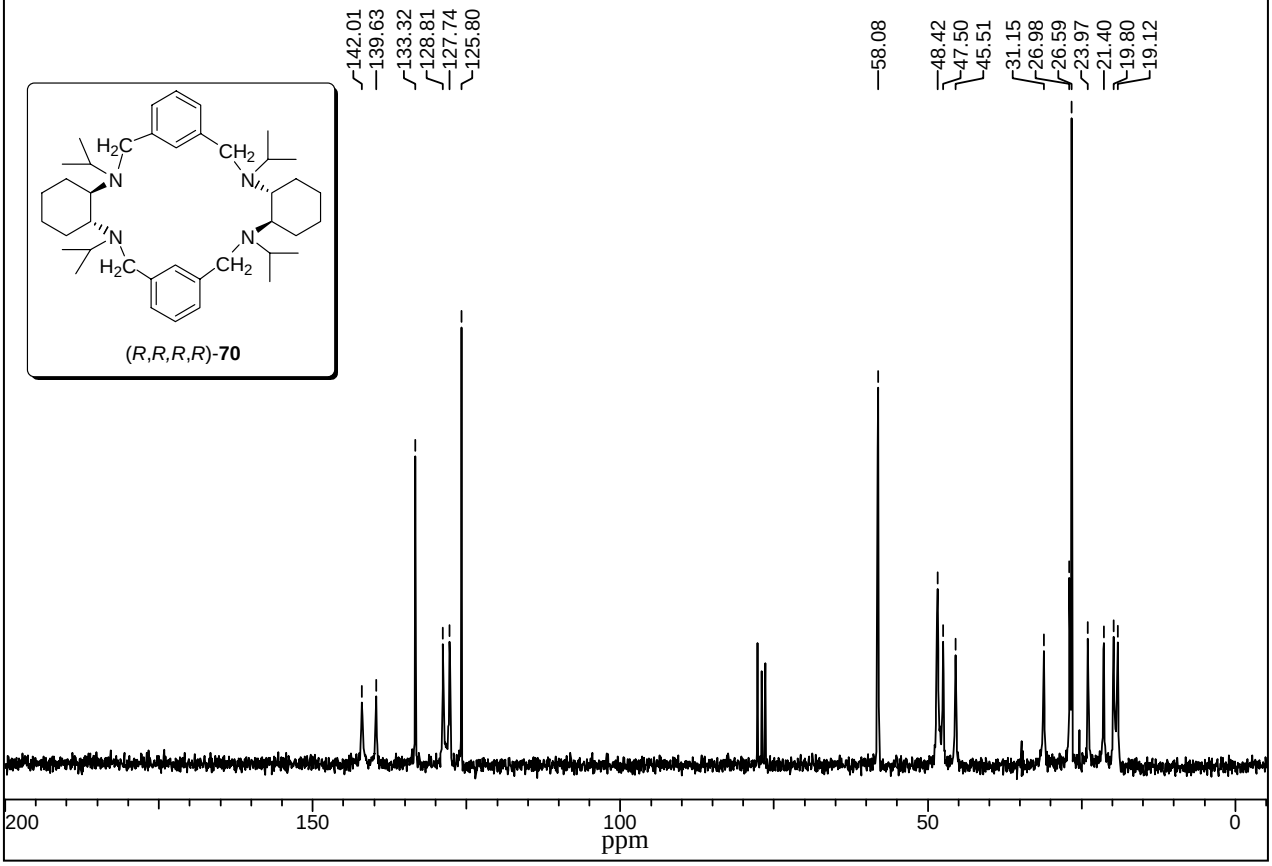
Spectrum No. 10 (Chapter 2, Section 2.4.3.1) ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)



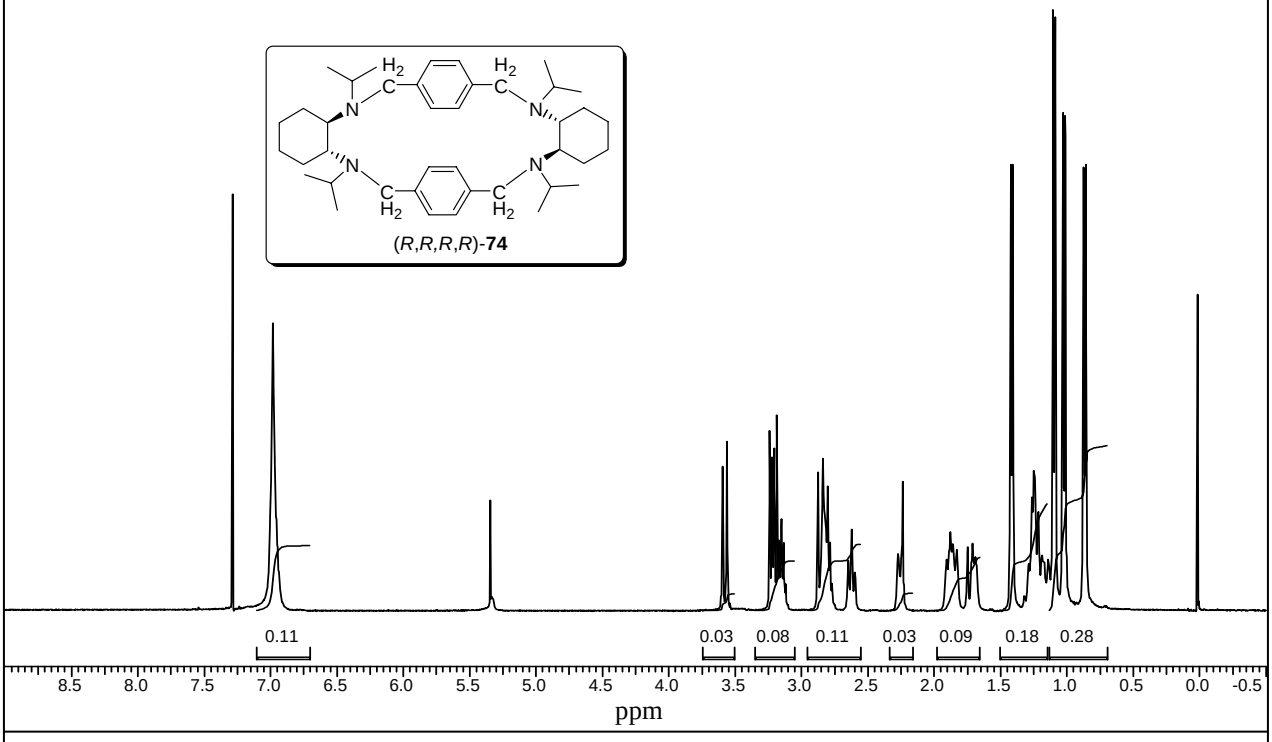
Spectrum No. 11 (Chapter 2, Section 2.4.3.2) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$, 0 °C)



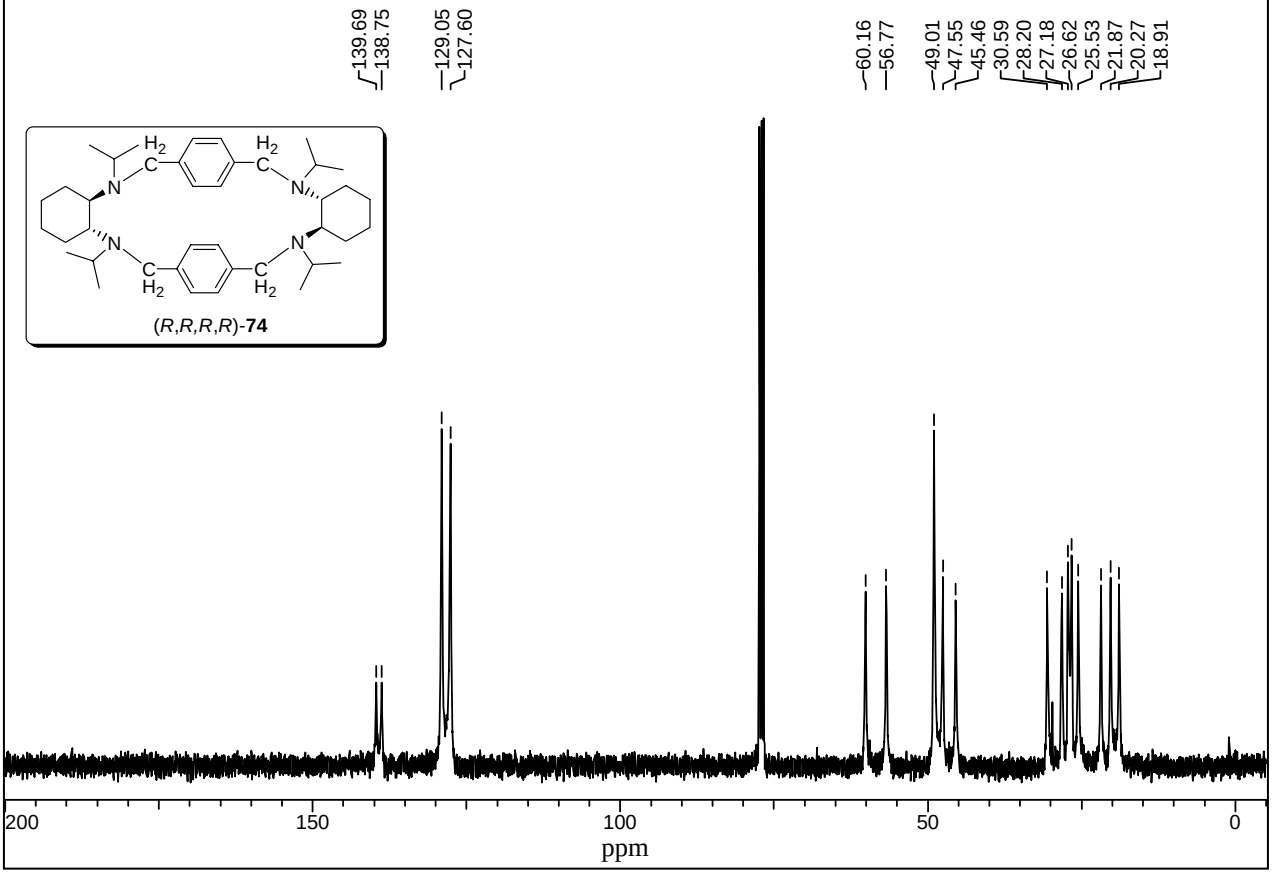
Spectrum No. 12 (Chapter 2, Section 2.4.3.2) ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)



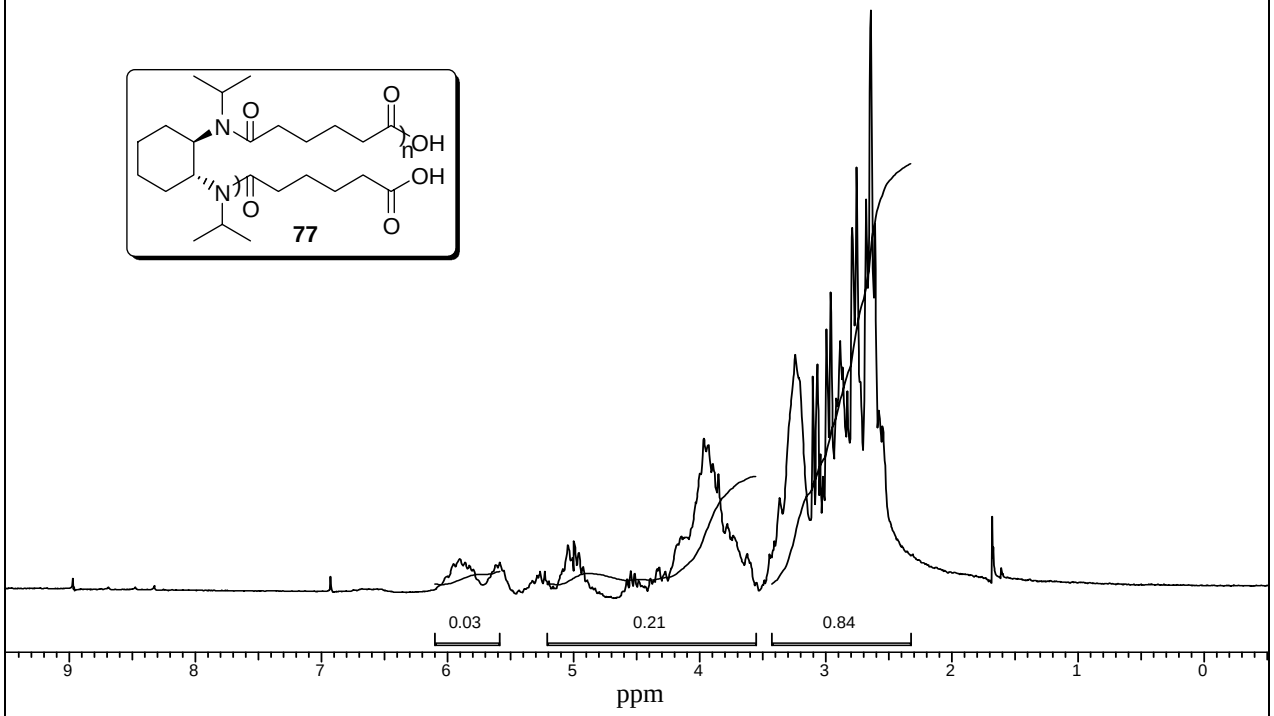
Spectrum No. 13 (Chapter 2, Section 2.4.3.3) ^{1}H NMR Spectrum (400 MHz,$CDCl_3$,-20 ºC)



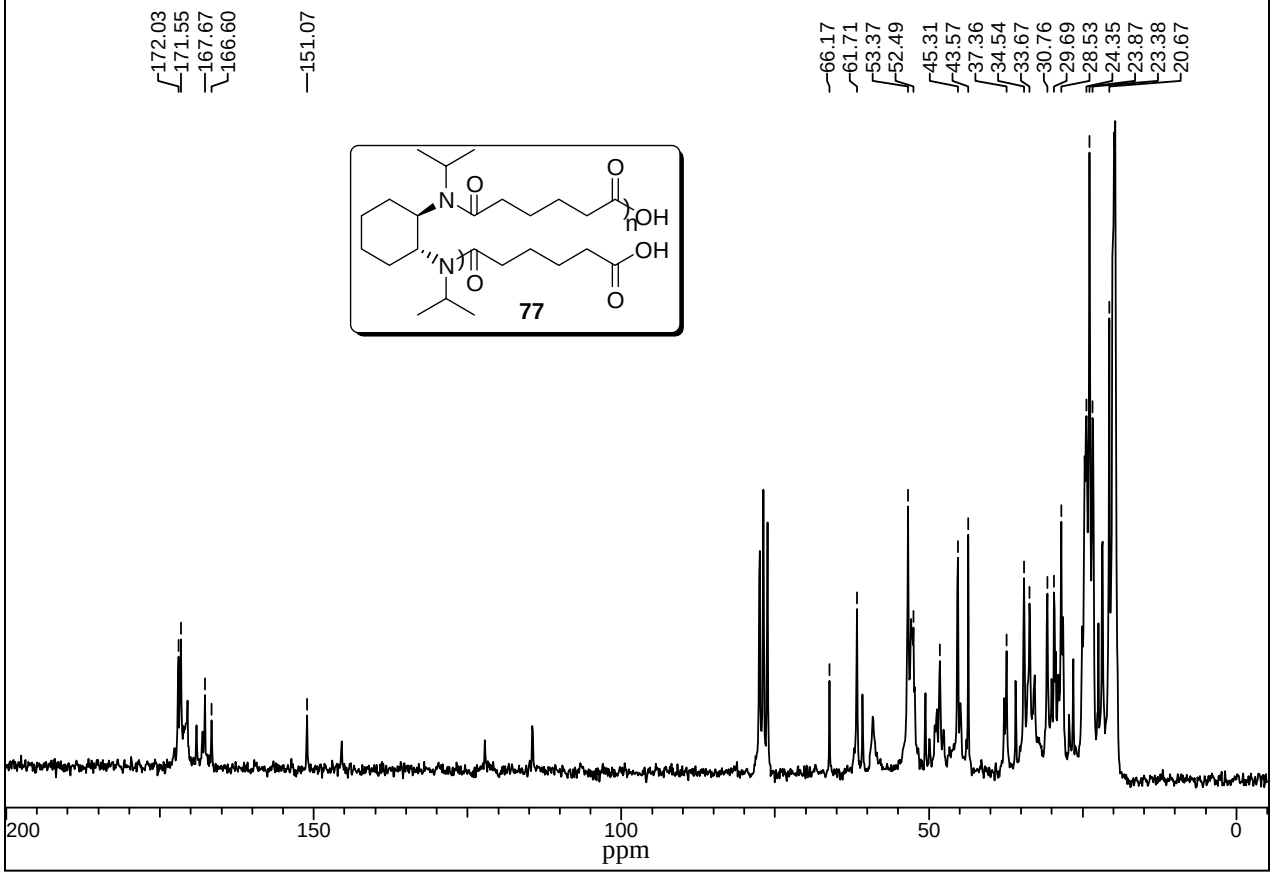
Spectrum No. 14 (Chapter 2, Section 2.4.3.3) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



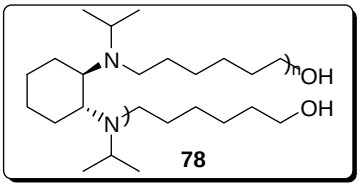
Spectrum No. 15 (Chapter 2, Section 2.4.3.4) ^{1}H NMR Spectrum (200 MHz, $CDCl_3$)



Spectrum No. 16 (Chapter 2, Section 2.4.3.4) ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)



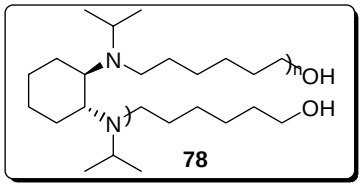
Spectrum No. 17 (Chapter 2, Section 2.4.3.5) ^{1}H NMR Spectrum (200 MHz, $CDCl_3$)



78

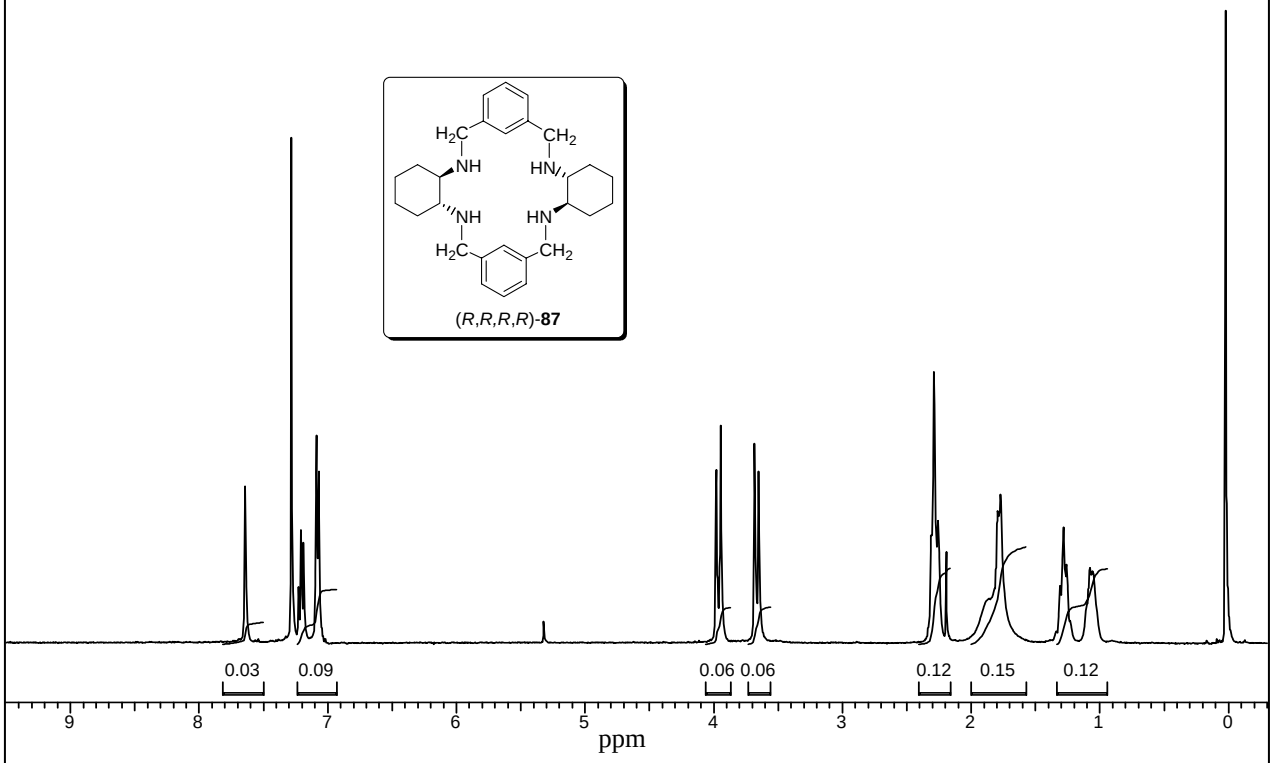
Spectrum No. 18 (Chapter 2, Section 2.4.3.5) ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)

61.42
58.02
55.50
45.31
43.37
32.21
29.30
26.59
25.23
23.87
23.67
22.22
21.35
18.34

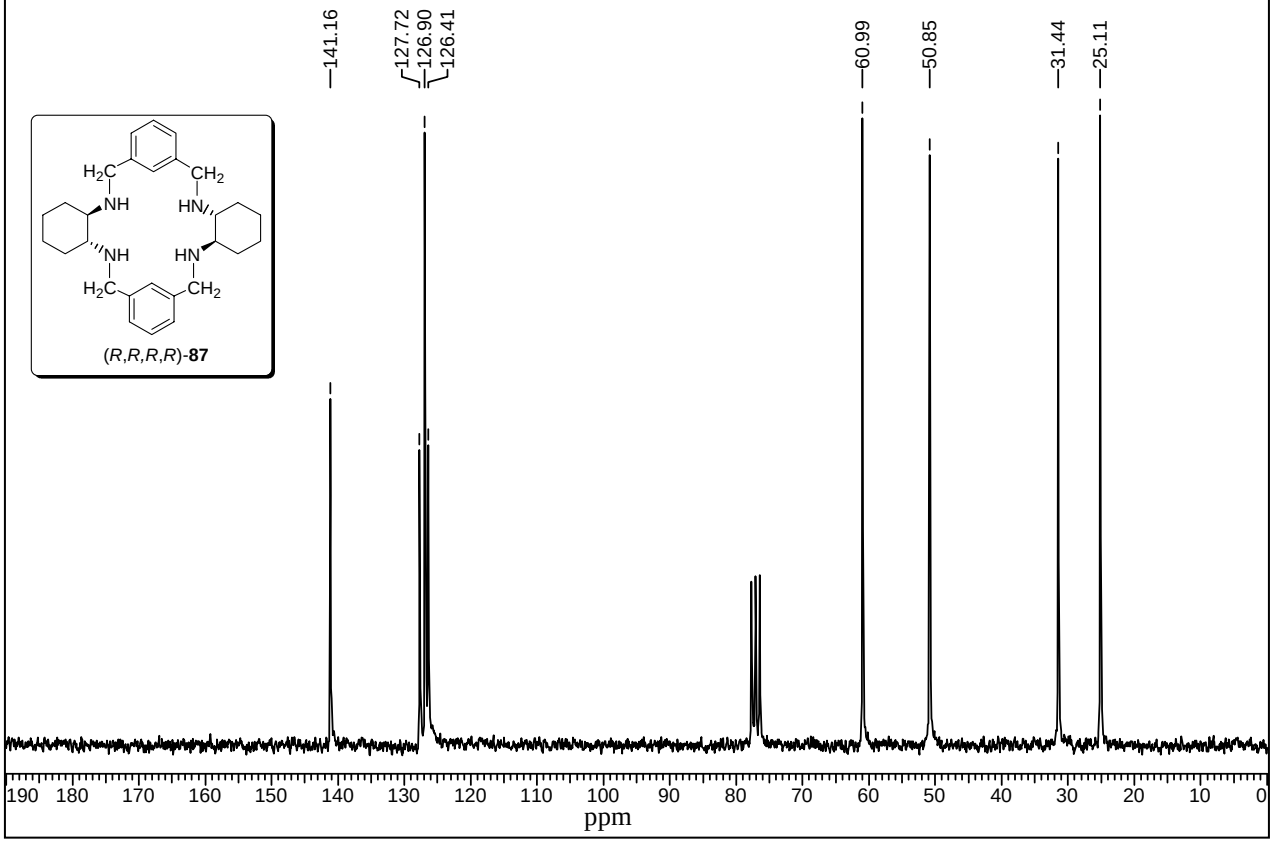


78

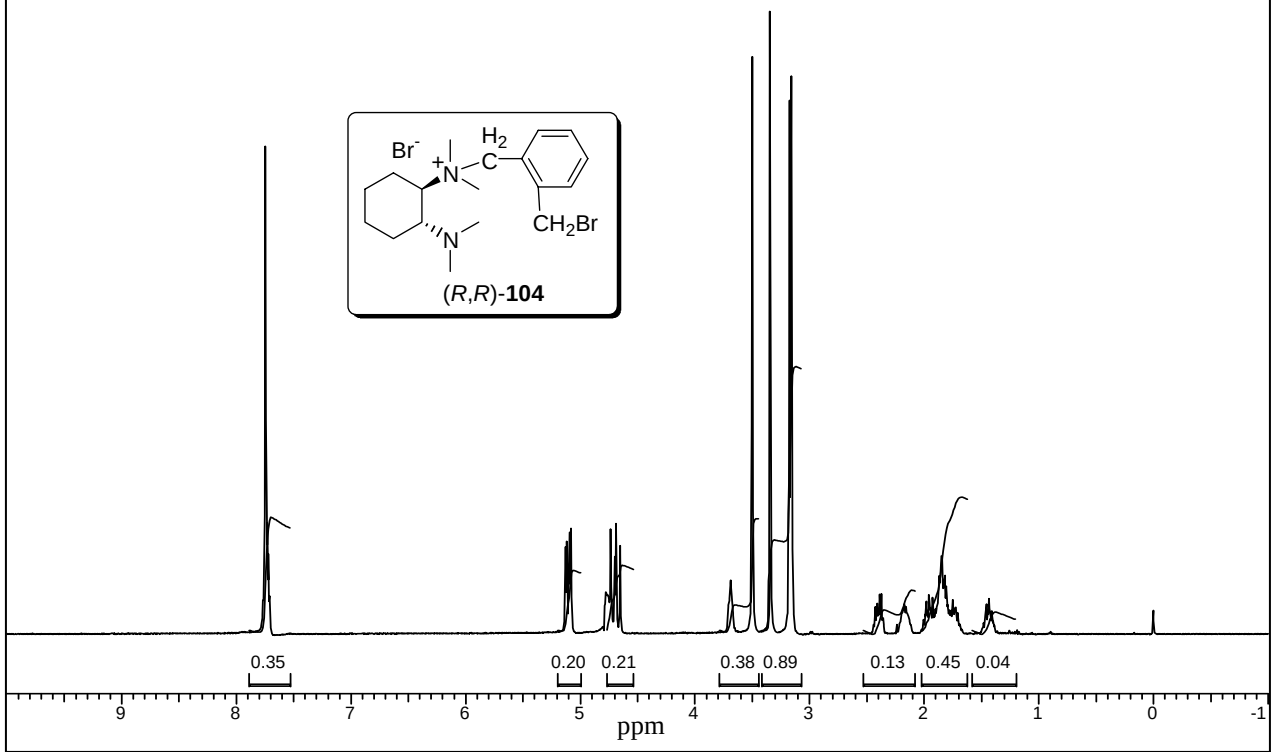
Spectrum No. 19 (Chapter 2, Section 2.4.3.6.2) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



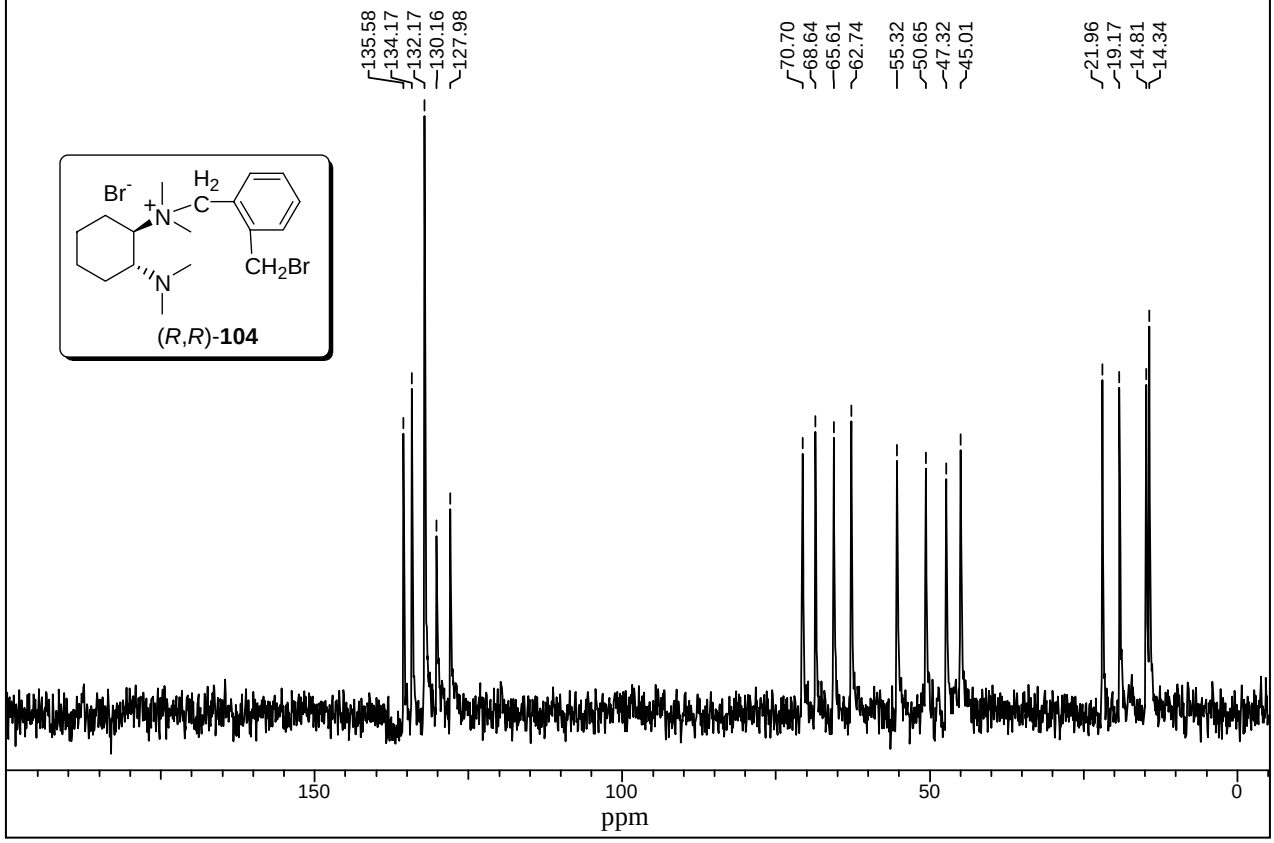
Spectrum No. 20 (Chapter 2, Section 2.4.3.6.2) ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)



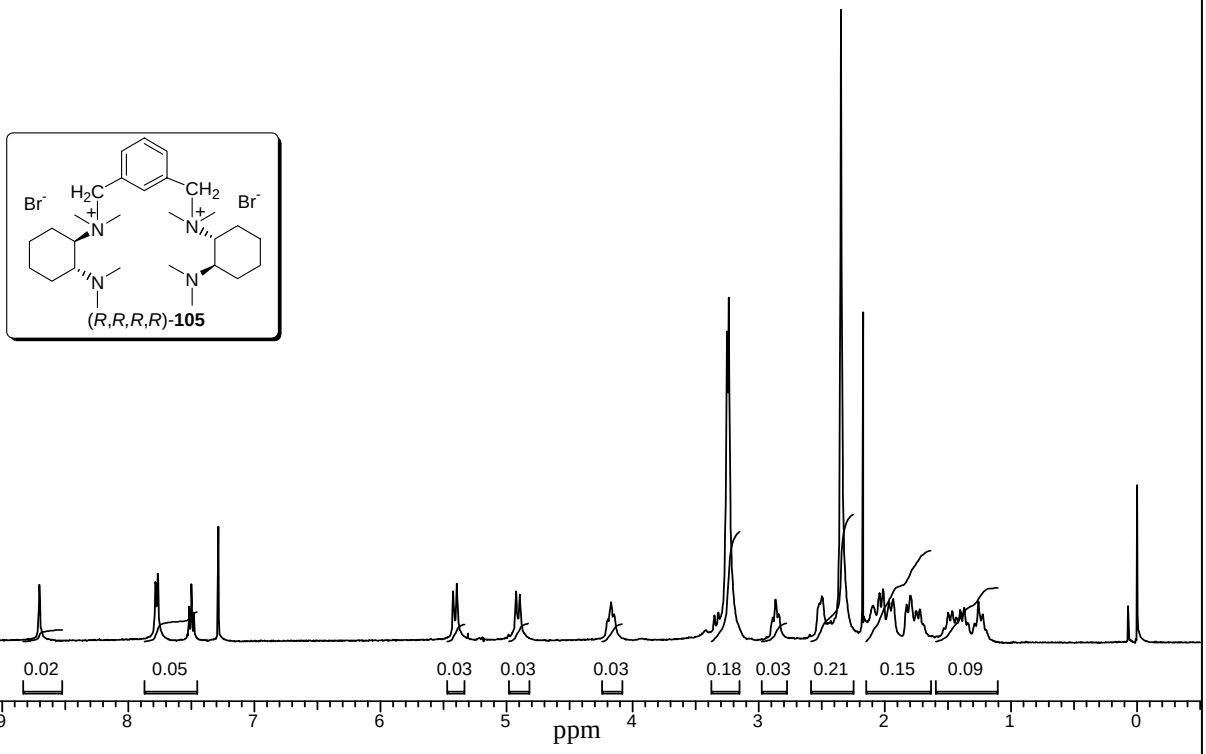
Spectrum No. 21 (Chapter 2, Section 2.4.4.1) ^{1}H NMR Spectrum (400 MHz, D_2O)



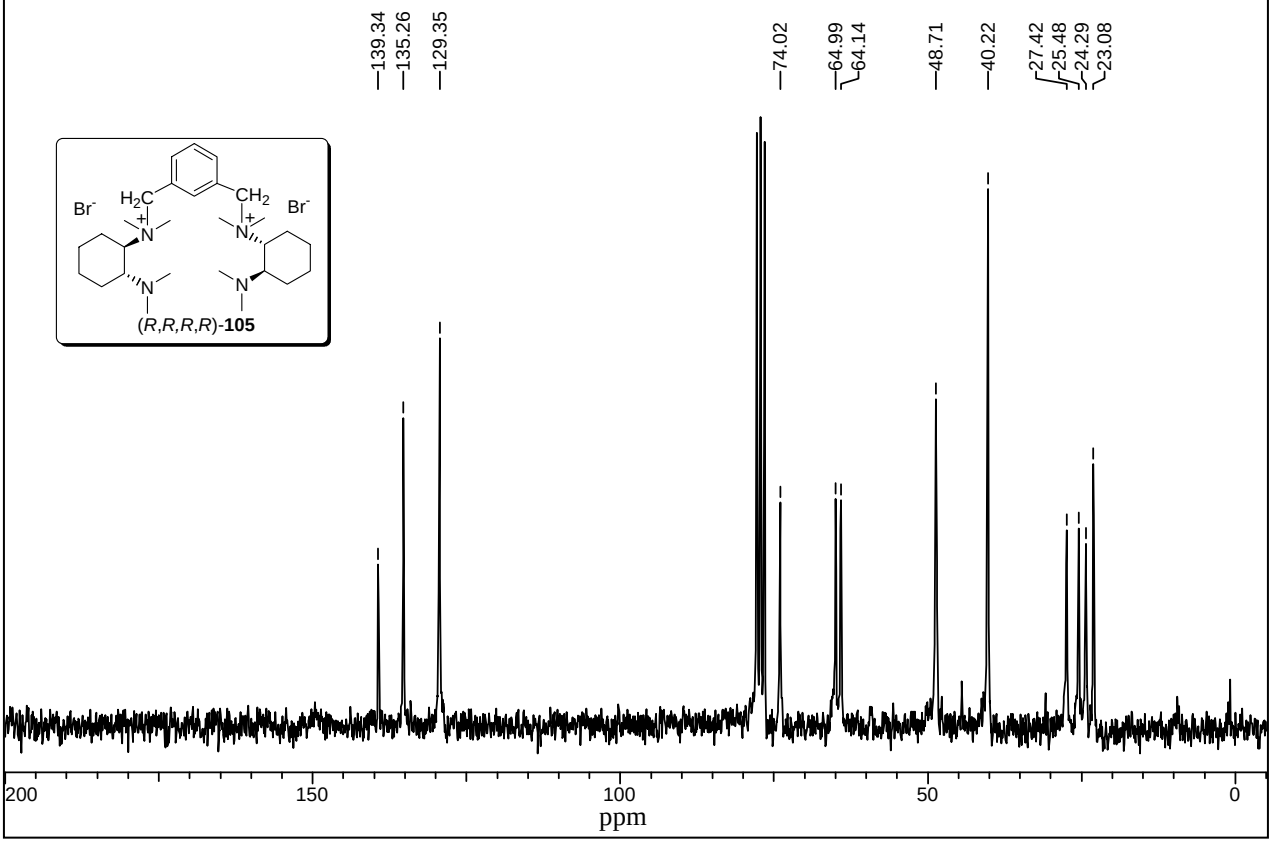
Spectrum No. 22 (Chapter 2, Section 2.4.4.1) ^{13}C NMR Spectrum (50 MHz, D_2O)



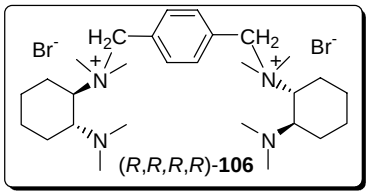
Spectrum No. 23 (Chapter 2, Section 2.4.4.2) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



Spectrum No. 24 (Chapter 2, Section 2.4.4.2) ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)

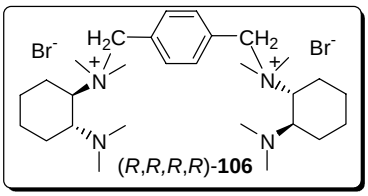


Spectrum No. 25 (Chapter 2, Section 2.4.4.3) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



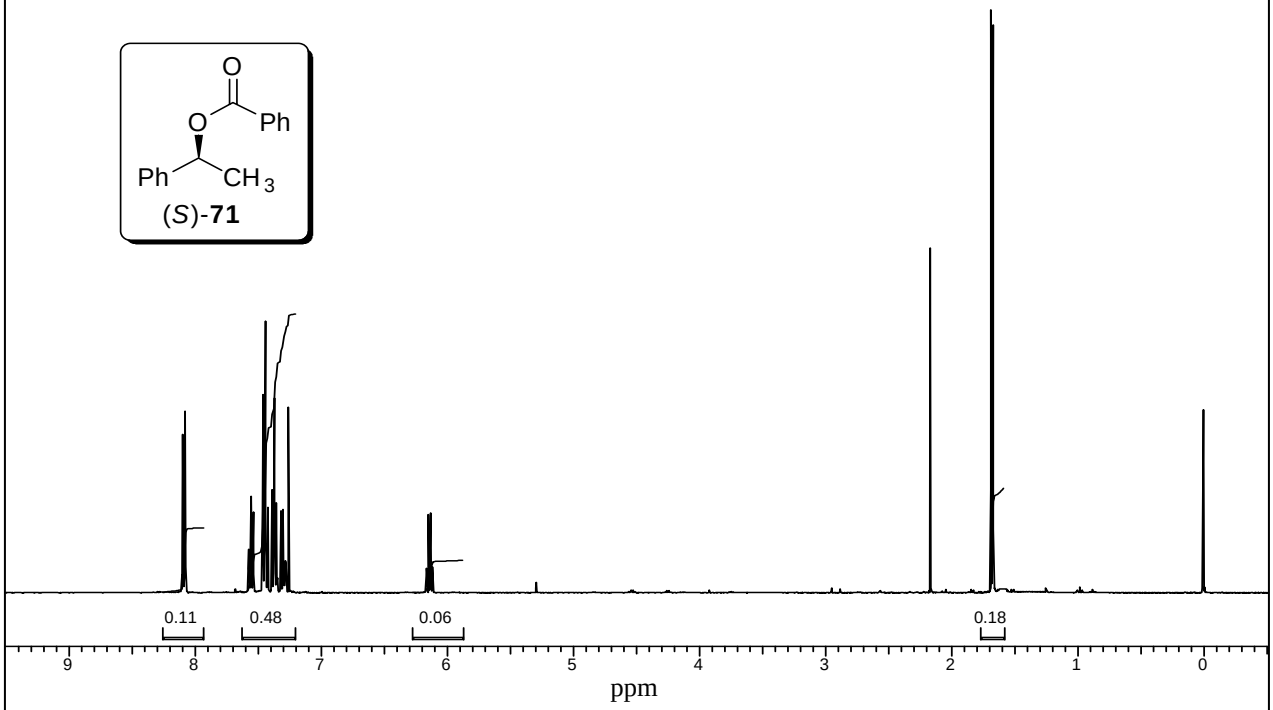
(*R*,*R*,*R*,*R*)-**106**

Spectrum No. 26 (Chapter 2, Section 2.4.4.3) ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)

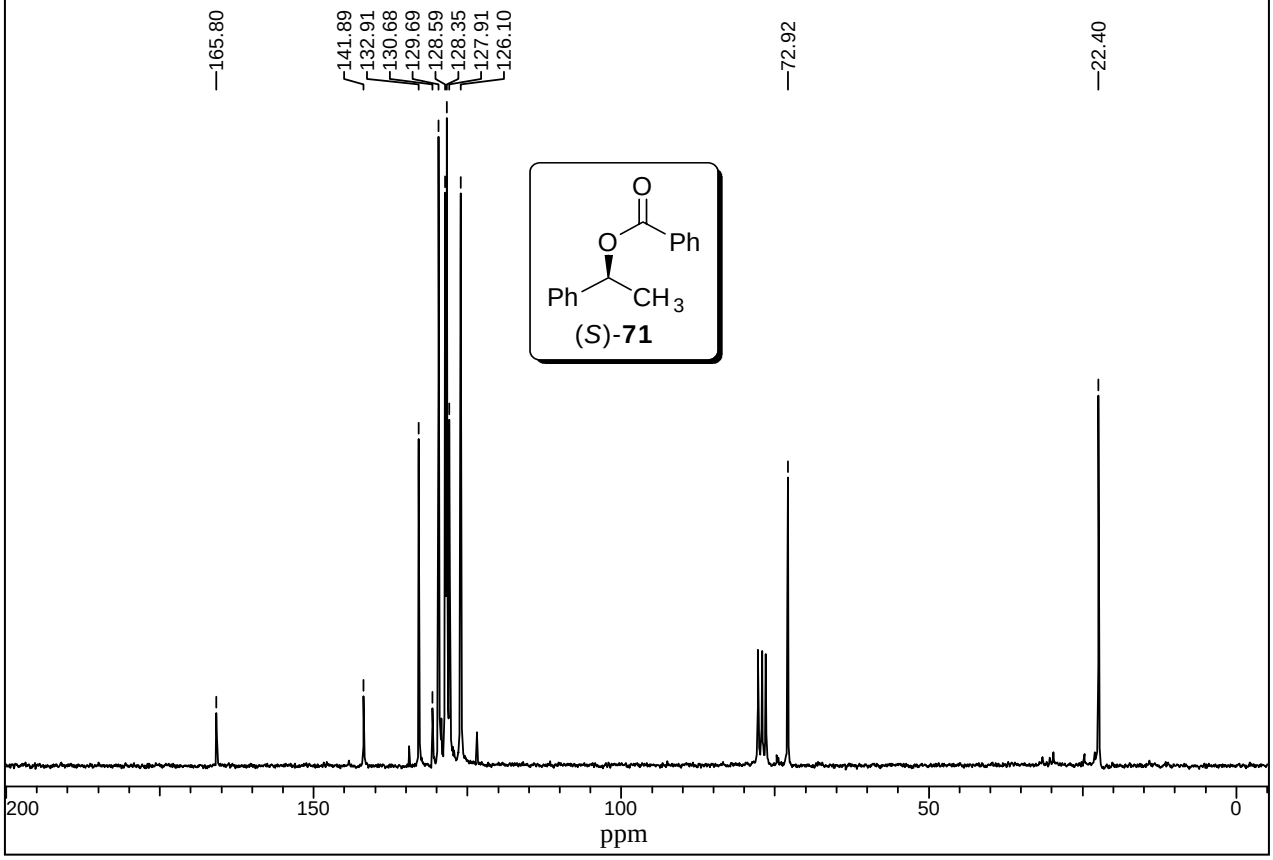


(*R*,*R*,*R*,*R*)-**106**

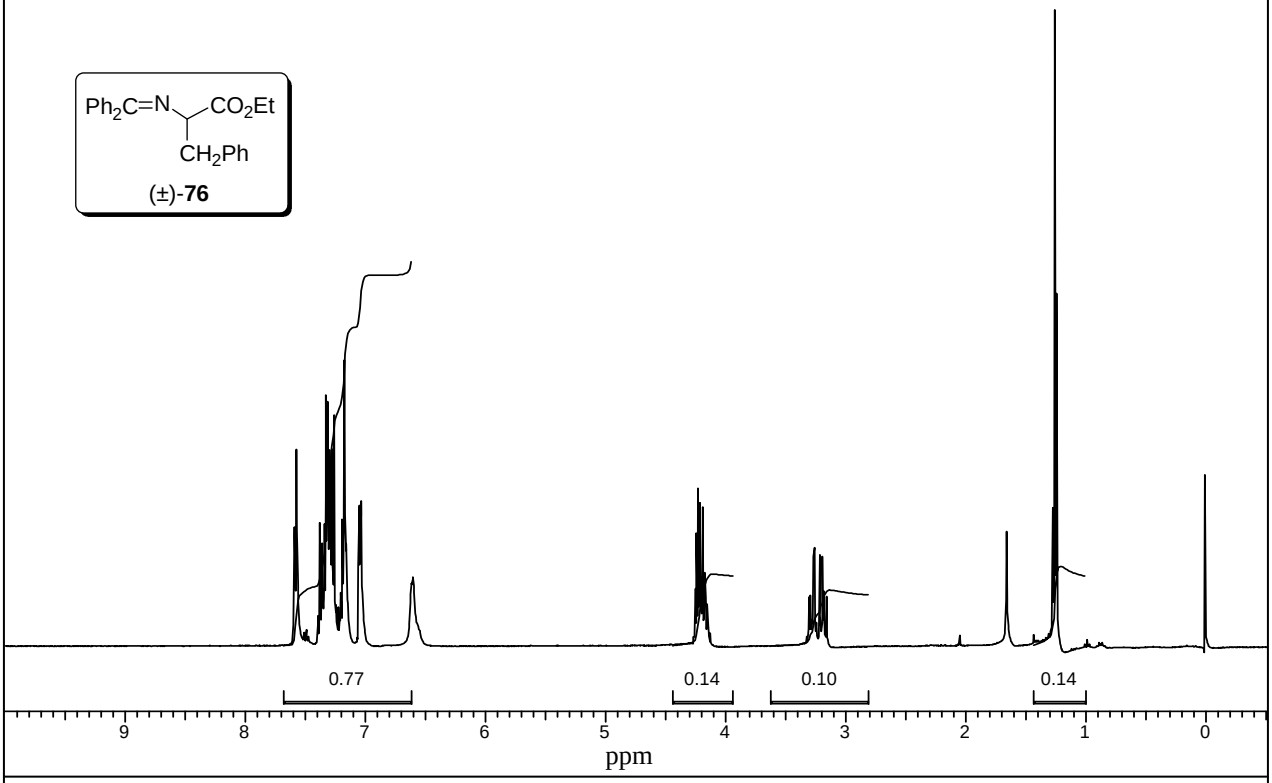
Spectrum No. 27 (Chapter 3, Section 3.4.7) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



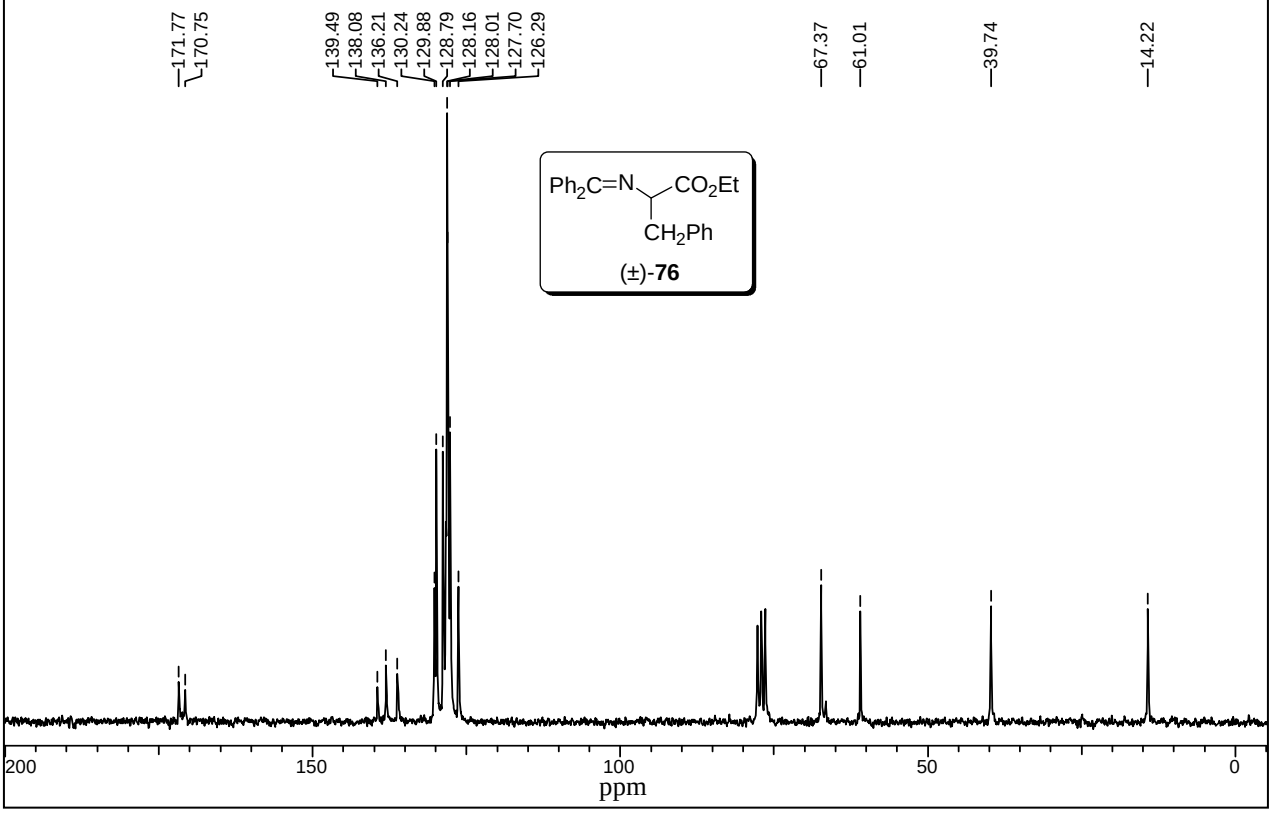
Spectrum No. 28 (Chapter 3, Section 3.4.7) ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)



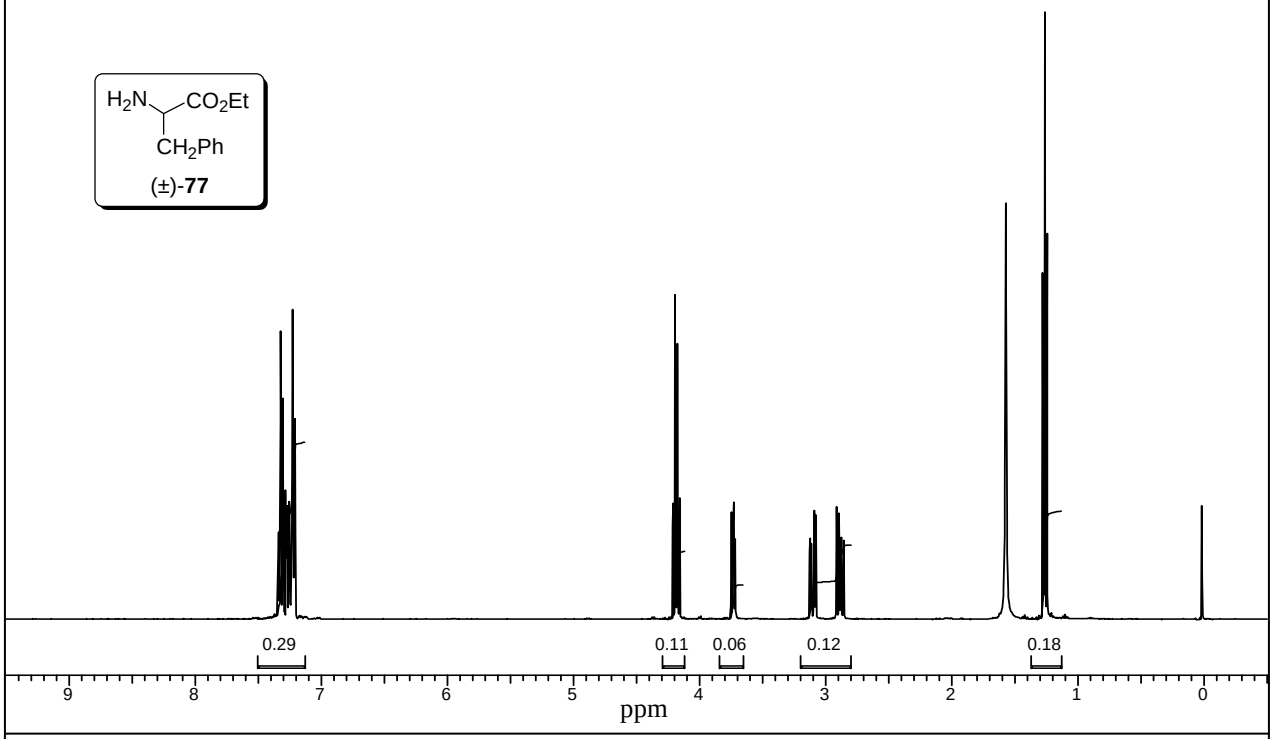
Spectrum No. 29 (Chapter 3, Section 3.4.8) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



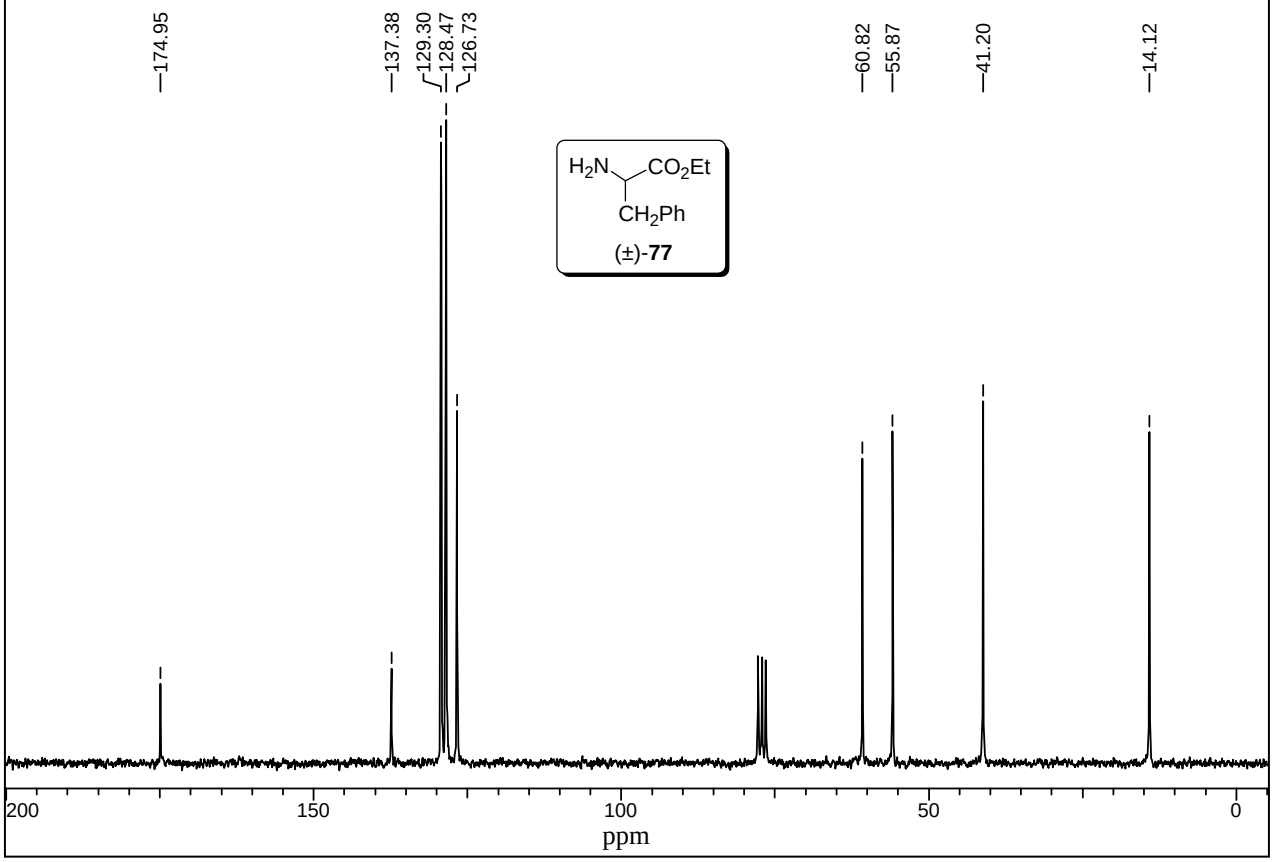
Spectrum No. 30 (Chapter 3, Section 3.4.8) ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)



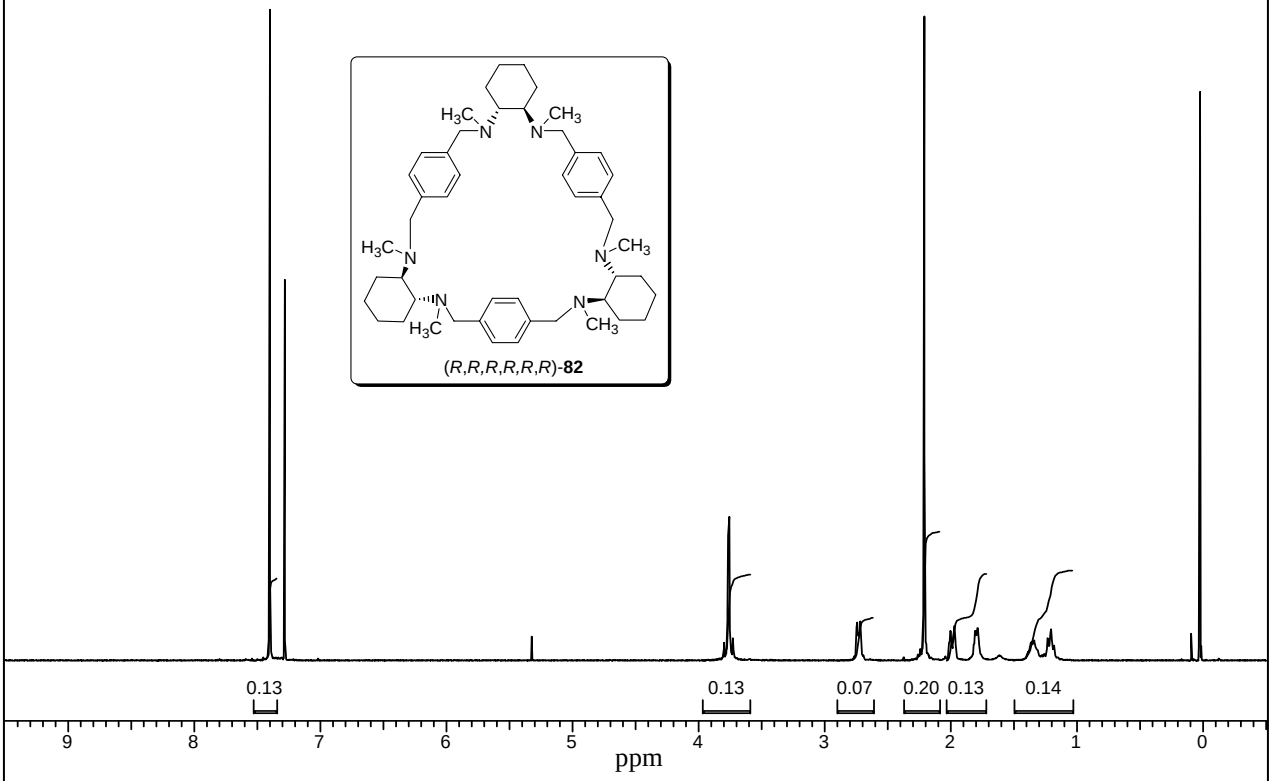
Spectrum No. 31 (Chapter 3, Section 3.4.8) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



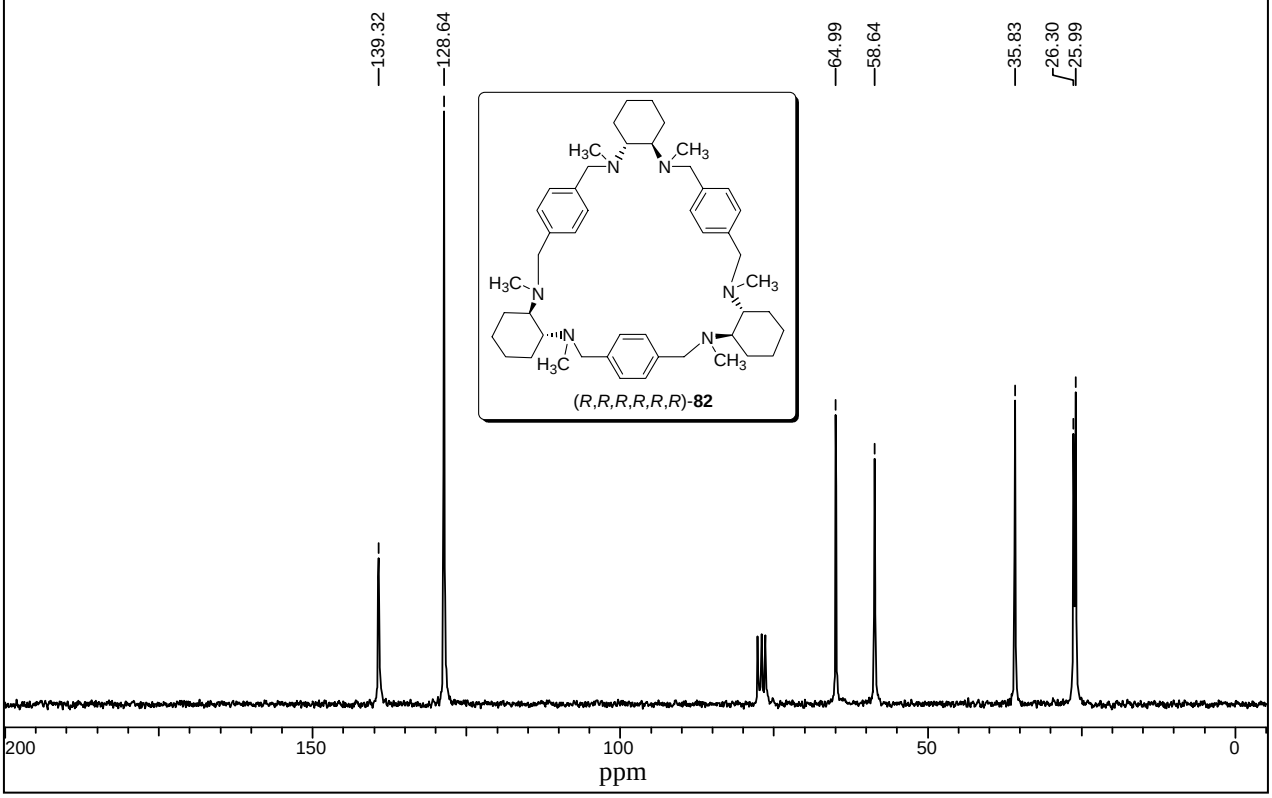
Spectrum No. 32 (Chapter 3, Section 3.4.8) ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)



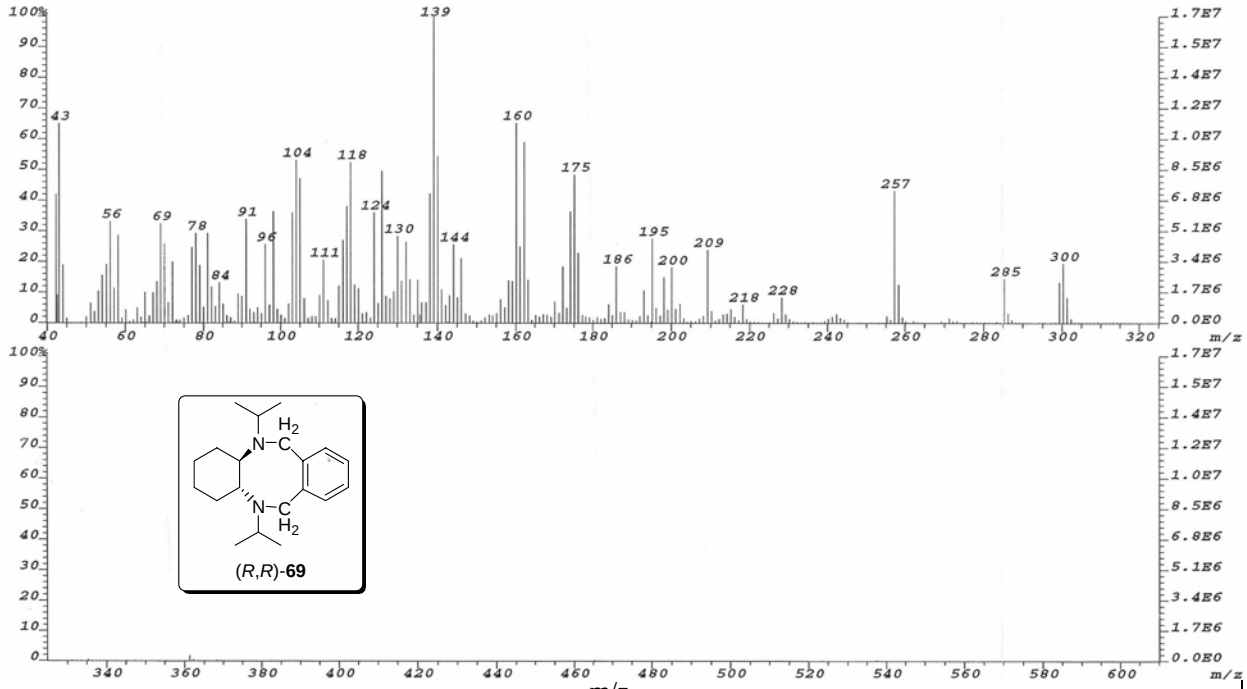
Spectrum No. 33 (Chapter 3, Section 3.4.9) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



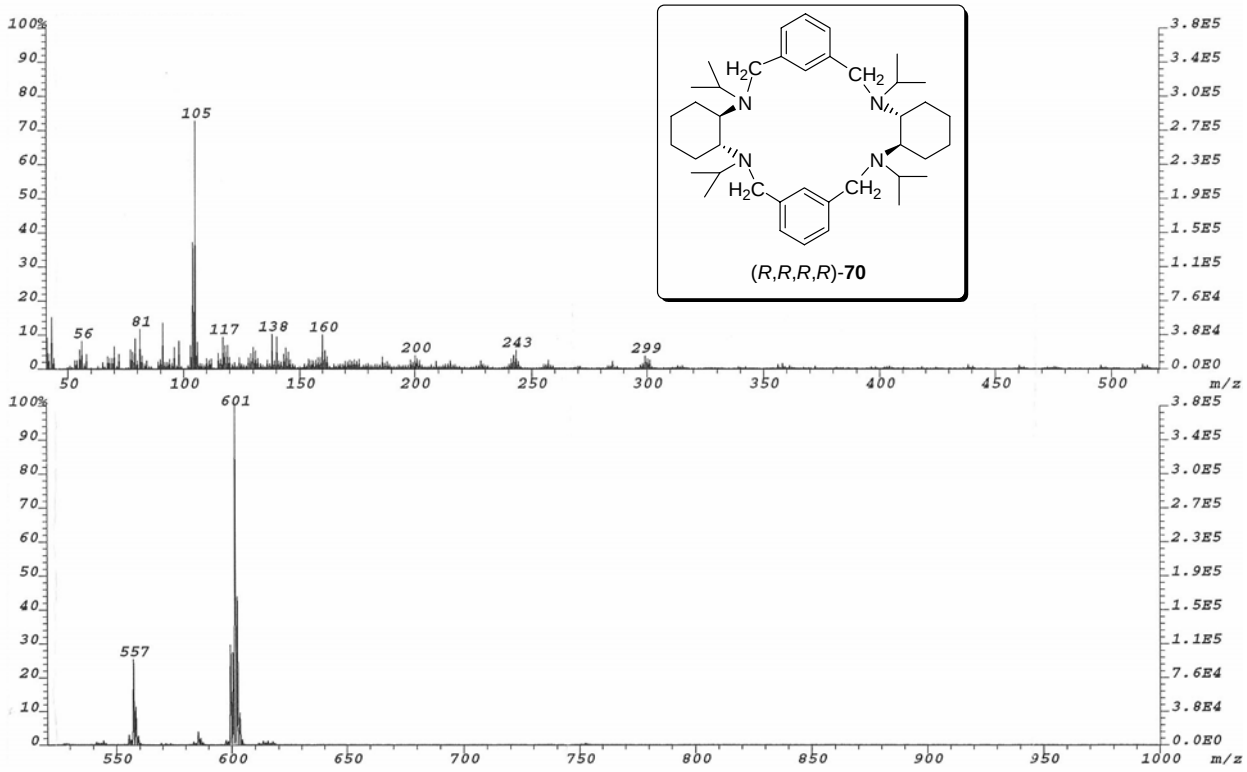
Spectrum No. 34 (Chapter 3, Section 3.4.9) ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)



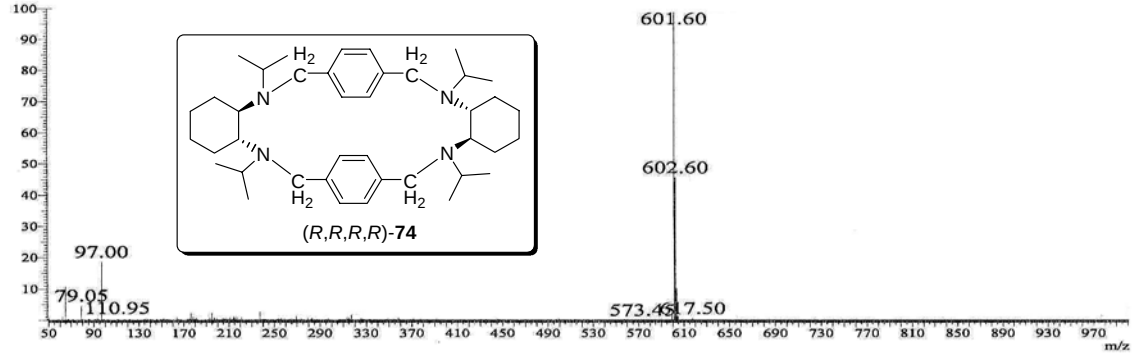
Spectrum No. 35 (Chapter 2, Section 2.4.3.1) EI Mass Spectrum



Spectrum No. 36 (Chapter 2, Section 2.4.3.2) FAB Mass Spectrum

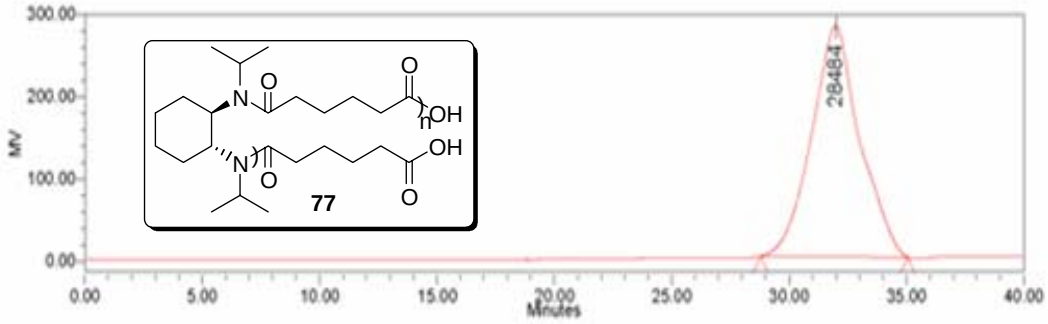


Spectrum No. 37 (Chapter 2, Section 2.4.3.3) LCMS (CI)



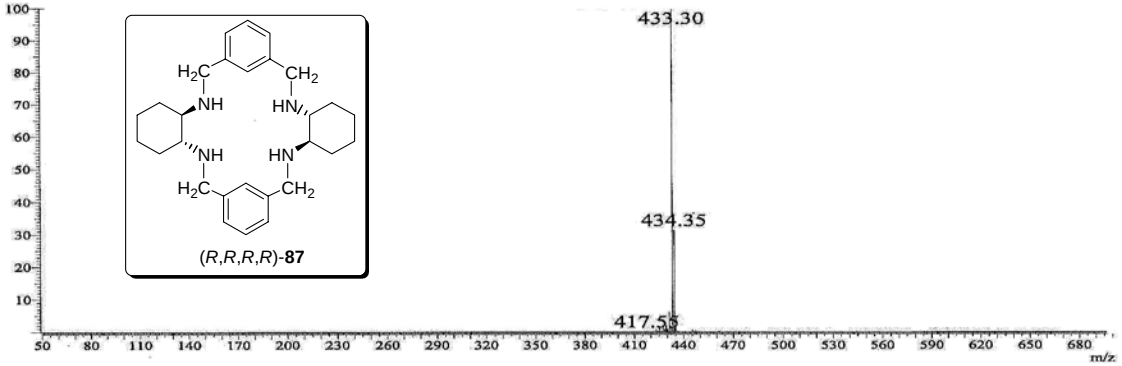
m/z

Spectrum No. 38 (Chapter 2, Section 2.4.3.4) GPC Chromatogram



Retention time = 31.98 min; Mn = 27499; Mw = 30720; MP = 28484; PDI = 1.117

Spectrum No. 39 (Chapter 2, Section 2.4.3.6.2) LCMS (CI)



m/z

Table A1. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) **for the complex of (*R*,*R*)-117c with (S)-1,1′-bi-2-naphthol 120a (Chapter 1, Section 1.2.3).** U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

atom	x	y	z	U(eq)
O(1)	2141(2)	7123(1)	5046(2)	59(1)
C(49)	1390(2)	8818(1)	6868(2)	46(1)
O(2)	-41(2)	7847(1)	3680(2)	66(1)
C(42)	307(2)	8382(1)	4634(2)	52(1)
C(32)	1814(2)	6917(1)	002(2)	50(1)
C(41)	930(2)	8204(1)	5959(2)	44(1)
C(39)	686(2)	7143(1)	7320(2)	47(1)
C(44)	364(3)	9697(2)	5060(3)	66(1)
C(31)	1155(2)	7413(1)	6418(2)	44(1)
C(43)	-3(3)	9128(2)	4196(3)	64(1)
C(48)	2194(2)	8710(2)	8222(2)	55(1)
C(40)	1017(2)	6413(1)	7853(2)	56(1)
C(50)	1104(2)	9564(1)	6418(3)	53(1)
C(33)	2158(3)	6200(2)	6552(3)	60(1)
C(34)	1797(3)	5960(2)	7463(3)	64(1)
C(47)	2685(3)	9312(2)	9055(3)	74(1)
C(37)	-562(3)	7300(2)	8563(3)	75(1)
C(45)	1593(3)	10159(2)	7303(3)	72(1)
C(35)	553(3)	6161(2)	8751(3)	73(1)
C(38)	-138(2)	7578(2)	7708(2)	57(1)
C(46)	2379(4)	10035(2)	8603(4)	84(1)
C(36)	-192(3)	6593(2)	9111(3)	84(1)
C(11)	5065(2)	6023(1)	3178(2)	44(1)
O(4)	5869(2)	5608(1)	5423(2)	69(1)
O(3)	3526(2)	6305(1)	4443(2)	72(1)
C(12)	6045(2)	5981(1)	4463(2)	49(1)
C(21)	3763(2)	5648(1)	2782(2)	45(1)
C(30)	2012(2)	4766(1)	1411(2)	49(1)
C(19)	5322(2)	6455(1)	2275(2)	44(1)
C(22)	3007(2)	5829(1)	3411(2)	52(1)
C(20)	6584(2)	6795(1)	2688(2)	48(1)

C(28)	3985(2)	4832(1)	1119(2)	52(1)
C(25)	1536(3)	4207(1)	431(3)	60(1)
C(29)	3267(2)	5094(1)	1773(2)	43(1)
C(14)	7547(2)	6705(1)	3984(2)	54(1)
C(24)	1274(2)	5000(2)	2058(3)	60(1)
C(13)	7282(2)	6319(1)	4856(2)	56(1)
C(26)	2248(3)	3980(2)	-189(3)	69(1)
C(15)	6838(3)	7209(2)	1777(3)	61(1)
C(18)	4360(2)	6586(1)	972(2)	51(1)
C(27)	3490(3)	4295(1)	162(2)	60(1)
C(16)	5886(3)	7299(2)	513(3)	72(1)
C(23)	1750(3)	5512(2)	3025(3)	61(1)
C(17)	4637(3)	6987(1)	112(3)	64(1)
N(1)	4411(2)	8079(2)	5693(2)	70(1)
N(2)	2881(2)	8428(1)	3088(2)	65(1)
C(1)	5107(2)	8227(1)	4868(2)	52(1)
C(7)	7124(3)	8701(2)	4756(3)	67(1)
C(2)	4234(2)	8709(2)	3689(2)	55(1)
C(8)	6468(2)	8575(2)	5639(2)	62(1)
C(5)	4912(3)	8809(2)	2821(3)	81(1)
C(6)	6269(3)	9160(2)	3576(3)	86(1)
C(10)	4077(3)	8760(3)	6212(3)	114(2)
C(4)	2654(3)	7774(2)	2243(3)	92(1)
C(9)	5179(3)	7523(3)	6776(3)	117(2)
C(3)	1930(3)	9019(2)	2399(3)	95(1)

Table A2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) **for the complex of the non-racemic 117a with fumaric acid (Chapter 1, section 1.2.4.1).** U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

atom	**x**	**y**	**z**	**U(eq)**
O(4)	2317(3)	7743(2)	10002(2)	59(1)
O(1)	2802(4)	8358(2)	2871(2)	58(1)
O(2)	1951(3)	7071(2)	3836(2)	58(1)

O(3)	3484(4)	8955(2)	9076(3)	62(1)
N(2)	642(3)	5864(2)	1305(3)	43(1)
N(1)	-2072(3)	6993(2)	1626(3)	45(1)
C(1)	-2360(4)	6344(2)	255(3)	44(1)
C(2)	-3622(5)	6613(3)	-1321(4)	65(1)
C(3)	-3845(6)	5851(3)	-2583(5)	77(1)
C(4)	-2115(6)	5585(3)	-3094(4)	70(1)
C(5)	-834(5)	5317(2)	-1549(4)	59(1)
C(6)	-610(4)	6068(2)	-275(3)	43(1)
C(7)	-3322(4)	6978(3)	2814(4)	56(1)
C(8)	-2736(5)	7744(3)	3987(4)	65(1)
C(9)	-2092(6)	8426(3)	2819(5)	70(1)
C(10)	-1922(5)	931(2)	1186(4)	59(1)
C(11)	2465(5)	5630(3)	1002(5)	63(1)
C(12)	3196(6)	5112(4)	2499(7)	93(2)
C(13)	1731(8)	4660(5)	3071(9)	126(2)
C(14)	119(5)	5156(3)	2442(4)	59(1)
C(15)	2487(4)	7831(2)	4046(3)	42(1)
C(16)	2814(4)	8228(2)	5771(3)	45(1)
C(17)	2466(4)	7826(2)	7126(3)	43(1)
C(18)	2812(4)	8231(2)	8858(3)	40(1)

Table A3. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) **for the macrocyclic amine 70 (Chapter 2, section 2.2.1).** U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

atom	**x**	**y**	**z**	**U(eq)**
N(2)	2407(2)	79(2)	3177(1)	59(1)
C(16)	612(2)	-924(2)	3036(2)	59(1)
C(1)	2008(2)	1511(2)	2901(2)	62(1)
C(6)	2768(2)	902(2)	3150(2)	59(1)
C(14)	1717(2)	-55(2)	3788(2)	63(1)
C(15)	1168(2)	-817(2)	3675(2)	57(1)
N(1)	1396(2)	1238(2)	2271(2)	66(1)
C(7)	3087(2)	-577(2)	3103(2)	77(1)

C(5)	3234(2)	1210(2)	3889(2)	75(1)
C(17)	92(2)	-1615(2)	2918(2)	62(1)
C(2)	2487(3)	2327(2)	2777(3)	82(1)
C(13)	522(2)	1702(2)	2216(2)	76(1)
C(20)	1202(2)	-1426(2)	4219(2)	75(1)
C(10)	1841(3)	1078(2)	1527(2)	85(1)
C(18)	161(2)	-2211(2)	3461(2)	79(1)
C(3)	2960(3)	2627(2)	3500(3)	99(1)
C(19)	705(3)	-2123(3)	4111(3)	90(1)
C(8)	3638(4)	-528(3)	2354(3)	121(2)
C(4)	3675(3)	2036(3)	3791(3)	93(1)
C(9)	3746(3)	-743(3)	3790(3)	118(2)
C(11)	1859(4)	1773(3)	945(3)	121(2)
C(12)	1403(4)	345(3)	1155(3)	119(2)
O(2)	681(17)	5529(8)	4823(18)	630(20)

Table A4. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) **for the macrocyclic amine 74 (Chapter 2, section 2.2.1).** U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

atom	**x**	**y**	**z**	**U(eq)**
N(8)	1991(2)	5938(2)	335(1)	54(1)
N(7)	842(2)	7186(2)	-44(1)	47(1)
N(6)	-2525(2)	4076(2)	184(1)	44(1)
C(80)	-2645(3)	3223(3)	311(2)	44(1)
C(79)	-1644(3)	5318(3)	352(2)	45(1)
C(78)	-1791(3)	2715(3)	251(2)	46(1)
C(77)	-1360(3)	5414(3)	-78(2)	54(1)
N(5)	-1326(2)	2852(2)	-171(1)	49(1)
C(76)	-1006(3)	6625(3)	520(2)	56(1)
C(75)	2091(3)	6775(3)	478(2)	56(1)
C(74)	1076(3)	4695(3)	426(2)	51(1)
C(73)	155(3)	3378(3)	60(2)	53(1)
C(72)	-1480(3)	5945(3)	649(2)	56(1)
C(71)	1253(3)	7294(3)	394(2)	46(1)
C(70)	247(4)	4090(3)	-172(2)	63(1)

C(69)	-2077(3)	4563(3)	525(2)	55(1)
C(68)	1017(3)	3965(3)	649(2)	56(1)
C(67)	711(3)	4737(3)	5(2)	66(2)
C(66)	-371(3)	2677(3)	-141(2)	66(2)
C(65)	-97(3)	7392(3)	-53(2)	61(1)
C(64)	1458(4)	8175(3)	520(2)	67(2)
C(63)	-880(3)	6085(3)	-207(2)	54(1)
C(62)	-2009(4)	1828(3)	354(2)	67(2)
C(61)	1486(3)	5427(3)	643(2)	57(1)
C(60)	-679(3)	6691(3)	91(2)	51(1)
C(59)	-2981(4)	3088(3)	796(2)	65(2)
C(58)	557(3)	3322(3)	472(2)	58(1)
C(57)	-3297(3)	4489(3)	-12(2)	56(1)
C(56)	-3178(4)	2206(4)	897(2)	78(2)
C(55)	2358(4)	6898(3)	975(2)	71(2)
C(54)	-1758(4)	2571(3)	-581(2)	64(2)
C(53)	1351(4)	7506(3)	-430(2)	71(2)
C(52)	-1564(4)	1690(4)	-722(2)	96(2)
C(51)	2564(4)	7770(3)	1095(2)	82(2)
C(50)	2797(4)	5526(3)	173(2)	88(2)
C(49)	1759(5)	8291(4)	1003(2)	87(2)
C(48)	-2364(4)	1704(4)	828(2)	81(2)
C(47)	-4150(4)	4486(4)	273(2)	89(2)
C(46)	-3496(4)	4185(3)	-482(2)	85(2)
C(45)	3065(6)	5822(4)	-286(3)	138(3)
C(44)	-1529(4)	3136(4)	-969(2)	95(2)
C(43)	1173(5)	8385(4)	-568(2)	102(2)
C(42)	3593(4)	5510(4)	498(3)	142(4)
C(41)	1180(6)	6954(5)	-840(2)	131(3)
N(4)	4844(2)	1544(2)	2402(1)	45(1)
N(3)	217(2)	3383(2)	2218(1)	48(1)
C(40)	4064(3)	274(3)	2160(2)	44(1)
C(39)	1230(3)	2251(3)	2044(2)	48(1)
C(38)	2101(3)	834(3)	2327(2)	55(1)
C(37)	2805(3)	3990(3)	2723(2)	50(1)
C(36)	4946(3)	747(3)	2190(1)	42(1)
N(2)	1234(2)	4388(2)	2835(1)	48(1)
C(35)	3942(3)	2812(3)	2349(2)	45(1)
N(1)	3539(2)	273(2)	2571(1)	49(1)
C(34)	4453(3)	2154(3)	2109(2)	50(1)

C(33)	3041(3)	3301(3)	2949(2)	62(1)
C(32)	3736(3)	3523(3)	2124(2)	56(1)
C(31)	1375(3)	1613(3)	1755(2)	63(1)
C(30)	1799(4)	924(3)	1899(2)	66(2)
C(29)	3594(3)	2715(3)	2767(2)	54(1)
C(28)	1508(3)	2164(3)	2479(2)	60(1)
C(27)	131(3)	4271(3)	2195(2)	51(1)
C(26)	843(3)	3044(3)	1897(2)	57(1)
C(25)	-593(3)	2897(3)	2257(2)	60(1)
C(24)	741(4)	5629(3)	2401(2)	73(2)
C(23)	4245(4)	-562(3)	1959(2)	65(2)
C(22)	2599(3)	106(3)	2489(2)	68(2)
C(21)	3188(3)	4097(3)	2308(2)	59(1)
C(20)	935(3)	4711(3)	2404(2)	50(1)
C(19)	1939(3)	1470(3)	2619(2)	64(2)
C(18)	3924(4)	-131(3)	2959(2)	65(2)
C(17)	-6(4)	4609(4)	1721(2)	74(2)
C(16)	4632(4)	-509(4)	1493(2)	85(2)
C(15)	5594(3)	1858(3)	2663(2)	66(2)
C(14)	5367(3)	770(3)	1723(2)	61(1)
C(13)	-1234(4)	2920(5)	1860(2)	106(2)
C(12)	2169(3)	4583(3)	2929(2)	63(2)
C(11)	5494(4)	-50(4)	1506(2)	73(2)
C(10)	631(4)	4480(3)	3222(2)	65(2)
C(9)	599(5)	5946(4)	1932(2)	97(2)
C(8)	-1088(4)	3090(3)	2686(2)	80(2)
C(7)	702(4)	5266(4)	3491(2)	95(2)
C(6)	3749(4)	-1042(3)	3006(2)	90(2)
C(5)	5681(5)	1412(4)	3107(2)	104(2)
C(4)	759(5)	3752(4)	3529(2)	93(2)
C(3)	3605(5)	297(4)	3385(2)	110(3)
C(2)	-157(5)	5513(4)	1708(2)	89(2)
C(1)	6498(4)	1885(4)	2427(3)	104(2)

LIST OF PUBLICATIONS

1. Toward Homogeneity of Chirality via Selective Formation of Homochiral or Heterochiral Aggregates, Periasamy, M.; Sivakumar, S.; Reddy, M. N.; **Padmaja**, **M**. *Org. Lett*. **2004**, *6*, 265.
2. Synthesis of *trans*-1,2-diamines via Sequential Opening of Cyclohexene Oxide and Aziridinium ions, Periasamy, M.; Seenivasaperumal, M.; **Padmaja**, **M**.; Rao, V. D. *Arkivoc* **2004**, *(viii)*, 4.
3. The Synthesis of Novel Chiral Macrocyclic and Polymeric Amines Containing a *trans*-1,2-Diaminocyclohexane System, **Padmaja**, **M**.; Periasamy, M. *Tetrahedron: Asymmetry* **2004**, *15*, 2437.
4. Synthesis, Resolution and Enhancement of Enantiomeric Purity of *trans*-*N*,*N*-dialkyl-1,2-diaminocyclohexanes, **Padmaja**, **M**.; Periasamy, M. (to be communicated).
5. Application of Chiral Macrocyclic Amines containing *trans*-1,2-Cyclohexane Moiety as Chiral NMR Solvating Agents for Carboxylic Acids, **Padmaja**, **M**.; Periasamy, M. (to be communicated).
6. Synthesis of Chiral Macrocyclic and Oligomeric Macrocyclic Amines containing *trans*-1,2-Diaminocyclohexane System, **Padmaja**, **M**.; Periasamy, M. (manuscript under preparation).
7. Synthesis of Chiral Quaternary Ammonium Salts containing *trans*-1,2-Diaminocyclohexane System, **Padmaja**, **M**.; Periasamy, M. (manuscript under preparation).

POSTERS/PRESENTATIONS

1. Design and Synthesis of Chiral Macrocyclic and Polymeric Amines, **M. Padmaja**, M. Periasamy, *Indo-US Conference* on 'Organometallic Catalysis and Olefin Polymerisation' IIT Madras, December 10-12, 2003.
2. Synthesis of Chiral 1,2-Diaminocyclohexane based Novel Diamines, Macrocycles and Polymers, **M**. **Padmaja**, M. Periasamy, *Chemfest 2004*, School of Chemistry, University of Hyderabad, March 12, 2004.
3. Synthesis of (*R*,*R*)-1,2-Diaminocyclohexane based Diamines, Macrocycles, Polymers and Quaternary Ammonium Salts, **M**. **Padmaja**, M. Periasamy, *Chemfest 2005*, School of Chemistry, University of Hyderabad, February 19, 2005.