Synopsis of thesis entitled

"Design, Synthesis and Applications of Novel Cyclohexanol Derived Chiral Molecules"

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Chapter 1: Introduction

Chiral chemistry got impetus from pioneering work of Louis Pasteur, the French chemist and biologist, who physically separated the two isomers of sodium ammonium tartrate in 1848. The definition of chirality was first given by Lord Kelvin in May 1893, during a conference of the Oxford University Junior Scientific Club:

"I call any geometrical figure, or group of points, chiral, and say it has chirality, if its image in a plane mirror, ideally realized, cannot be brought to coincide with itself." [1]

Chirality is defined as a property of object which is non superimposable with its mirror image resulting in a pair of stereoisomers referred as enantiomers. Study of stereoisomers is one of the most important and significant areas of modern organic chemistry. The role of chirality in drug development is on the rise in the past forty years, ever since the thalidomide case has triggered interest in the interactions of individual stereoisomers with bioreceptors. The demand for ready access to stereoisomers (both diastereoisomers and enantiomers) of drug molecules has stimulated in turn basic research in the field of stereoselective synthesis (either diastereoselective or enantioselective).

What is asymmetric synthesis?

The synthesis of chiral molecules from symmetrically constituted compounds with the use of optically active materials is regarded as asymmetric synthesis. It involves creation of stereogenic centers with high levels of enantio as well as diasteroselectivity. Diastereoselective syntheses involve syntheses of enantiomerically pure compounds from the pool of enantiomers available from the nature (or chiral pool), e.g. from amino acids, hydroxy acids, carbohydrate, terpenes, or alkaloids. Other variants of diastereoselective syntheses include the use of chiral auxiliary molecules (these can be either from chiral pool or synthetic).

Importance of optically active molecules in the field of medicine, fragrance and flavours, material science and supramolecular chemistry has already been well established. The supramolecular interactions in biological systems between the chiral receptors and guest substrates are generally more enantiospecific. Crown ethers and other macrocyclic compounds have a unique place in the field of supramolecular chemistry.[2-4] Chiral crown ethers and macrocyclic molecules have been widely employed as CSA for enantiomeric recognition on account of their ability to bind with optically active guest molecules.

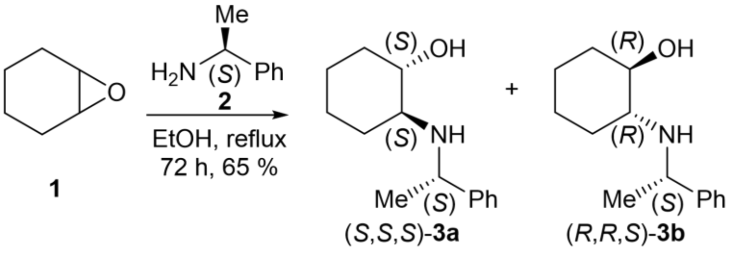
Chiral Solvating Agents are optically pure compounds which bind *in situ* to the substrate comprising of mixture of enantiomers through non covalent, intermolecular forces. These are usually designed in such a way as to have ability to participate through non covalent interactions such as hydrogen bonding, π-π interactions, C-*H*- π interactions and charge transfer complexes. Associated complexes of CSA with pair of enantiomers are diastereomers, which offers the source of discrimination in NMR spectroscopy.[5]

Chapter 2: *Synthesis and Application of chiral Aza-crown ethers*

Chiral Crown Ethers:

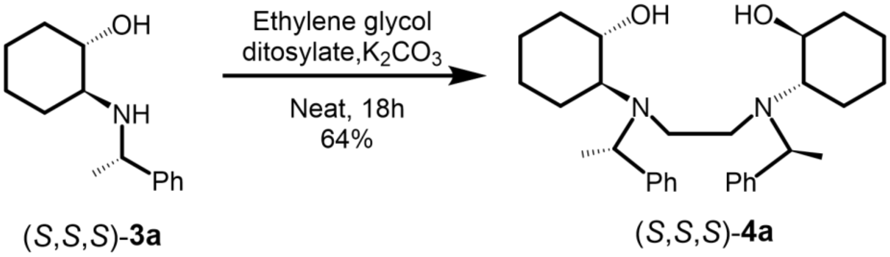
The chiral crown ethers have been widely applied as chiral selectors in differentiating the enantiomers of racemic mixture containing a primary amino group. Chiral aza crown ethers have been widely used in enantiomeric recognition of chiral acids. Optically pure crown ethers can be used for the determination of the enantiomeric excess of chiral compounds in NMR spectroscopy. In particular the chiral crown ethers are known to be effective chiral solvating agents. However, these crown ethers are shape and size selective in their molecular recognition. Due to this there is a constant need to synthesize and screen novel chiral crown ethers. In this effort we have synthesized and characterized new crown ether and will investigate its utility for the enantioselective discrimination and asymmetric synthesis.

In the present study diastereomeric mono and diaza crown ethers have been synthesized to study their chiral discriminating ability towards guest molecules. Synthesis of β-amino alcohol by ring opening of *meso* cyclohexenoxide using chiral (*S*)-phenylethyl amine resulting in formation of diastereomers **3a** and **3b** in the ratio of 54:46**.**



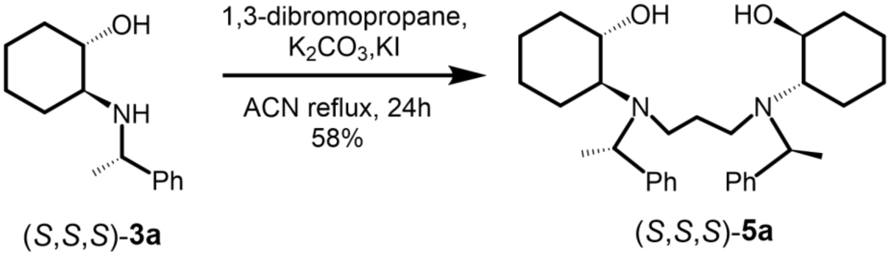
Scheme 1: Synthesis of diastrereomeric amino alcohols (**3**)

The separated diastereomer **3a** was converted to building block diamino diol **4a** for the synthesis of diaza 18-crown-6 derivative by treatment with ethylene glycol ditosylate and base under the solvent free condition.



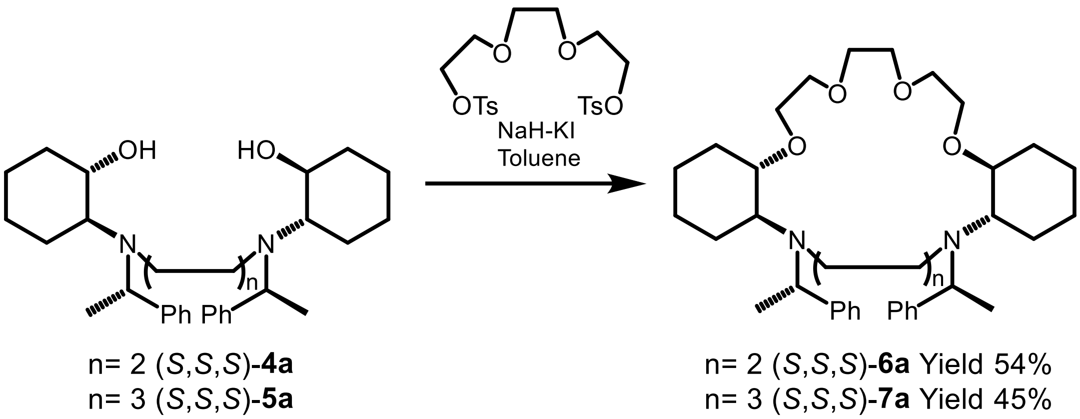
Scheme 2: Syntheis of diamino diol **4a**

The diastereomer **3a** on treatment with 1,3-dibromopropane in MeCN in presence of base yielded chiral diamino diol subunit **5a**. The reaction mixture was directly subjected to column chromatography on silica gel to yield diamino diol **5a**.



Scheme 3: Syntheis of diamino diol **5a**

The diamino diols **4a** & **5a** were treated with triethylene glycol ditosylate in dry toluene in presence of NaH base for 48h resulting in formation of diazacrown ethers **6a** & **7a**. The reaction was observed to progress upon the addition of KI. The reaction mixture was subjected to column chromatography yielding desired chiral aza crown ethers.



Scheme 4: Syntheis of aza crown ethers **6a** and **7a.**

Application as CSA:

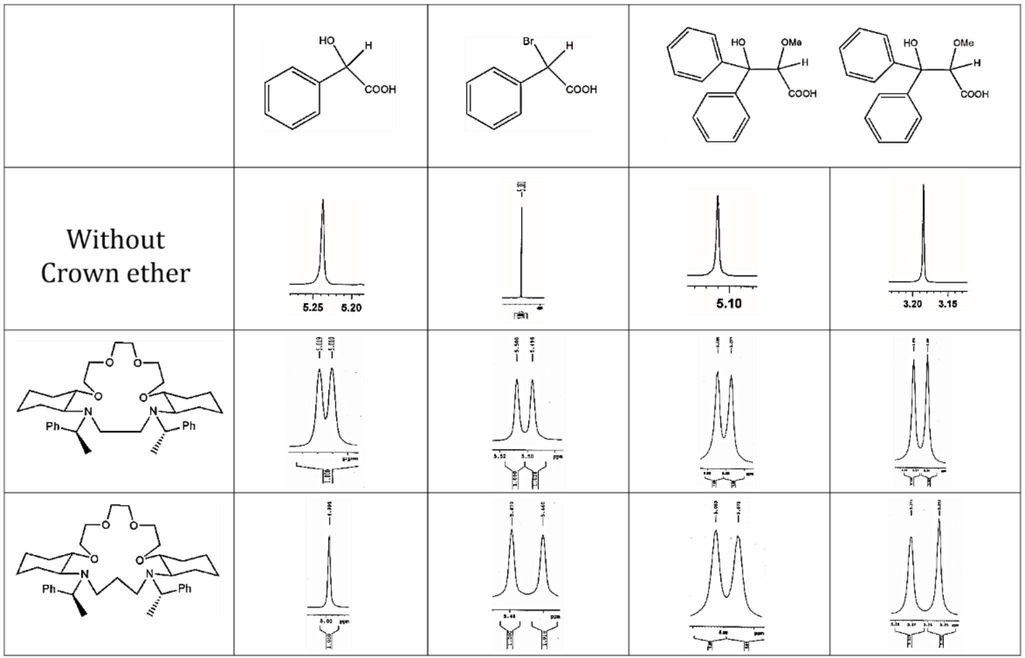
The use of chiral shift agents (CSA) for ^{1}H NMR spectroscopy is one of he most convenient methods to achieve a quick determination of enantiomeric excess of chiral compounds. This methods has advantage of easy performance without using any chiral derivatising agent. In CSA two different abbreviations are commonly used

i) Induced Chemical Shift

The difference between the signals in a solution of the analyte and the average of the signal of the two discriminated enantiomers after mixing the chiral additive which is represented as $\Delta\delta$

ii) Chemical Shift Non-equivalence

The difference between two resolved peaks after mixing the chiral additive which represented by $\Delta\Delta\delta$.

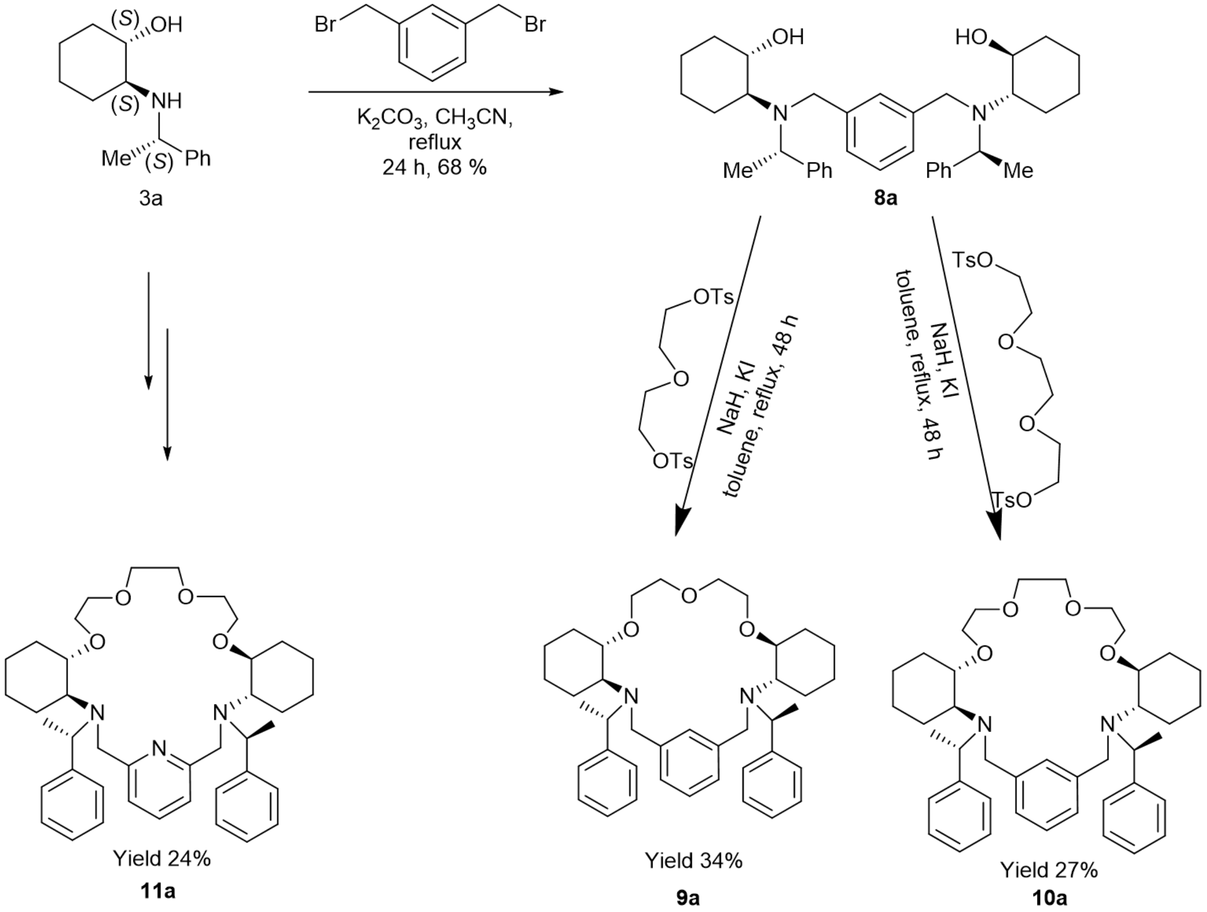


The chiral shift experiments were carried out by measuring the ^{1}H NMR spectra (400MHz) of a mixture crown ethers (**6a** & **7a**) and carboxylic acid (1:2 ratio) in CDCl$_3$ at room temperature.

The crown ethers **6a** and **7a** were used as CSA for racemic Mandelic acid, α-bromophenylacetic acid and α-methoxy acid. Crown ethers showed marginal separation with α-bromophenylacetic acid and α-methoxy acid while in case of mandelic acid the separation was low with crown ether **6**. This encouraged us to synthesize crown ethers with aromatic ring containing linkers which would facilitate more efficient π-π and C-H-π interactions.

Synthesis of Aza Crown ethers:

The separated diastereomer **3a** was converted to building block **8a** by treatment with 1,3-bisbromomethyl-xylene in presence of K_2CO_3 to yield diaminodiol building blocks **8a**. The diaminodiol building block was then treated with diethylene glycol ditosylate and triethylene glycol ditosylate inpresence of NaH and KI in dry toluene resulting in formation of crown ethers **9a** and **10a** respectively. Similarly aminoalcohol **3b** was converted to crown ethers **9b** and **10b** respectively. Moreover amino alcohol **3a** was treated with 2,6-bisbromomethyl-pyridine followed by treatment with triethylene glycol ditosylate resulting in formation of crown ether **11a**.



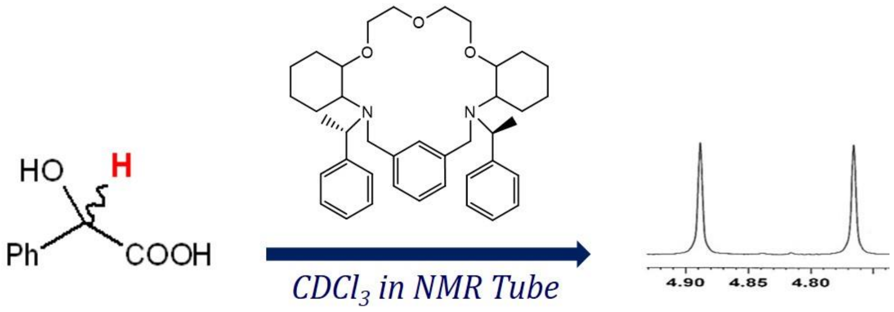
Scheme 5: Synthesis of crown ethers **9-11**

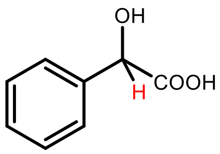
Having synthesized the aza-crown ethers, we characterized them by usual spectral and analytical techniques. The NMR spectras of crown ethers **9** and **10** are in agreement with the structure further confirmed by HRMS.

The objective of the preparation of the aza-crown ether is to scan them as CSAs for suitable chiral analytical substrates. The presence of aromatic ring in the bridge may aid the additional supramolecular interactions.

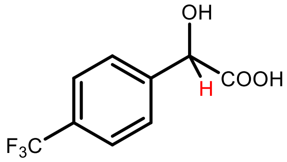
Application of crown ethers as CSA

The crownethers **9a**, **9b**, **10a** and **10b** have been used as CSA for acid substrates. CSA analysis indicate a clear pattern of match-mismatch between two diastereomers of crown ether **9** where diastereomer **9a** shows good separation for binaphthylphosphoric acid while **9b** shows no separation at all. Moreover the larger crown ethers **10** show no recognition for phosphoric acid.

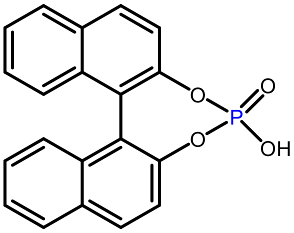




i) with **9a** ΔΔδ = 0.016
ii) with **9b** ΔΔδ = --
iii) with **10a** ΔΔδ = 0.008
iv) with **10b** ΔΔδ =--



i) with **9a** ΔΔδ = 0.010
ii) with **9b** ^{19}F ΔΔδ =0.008

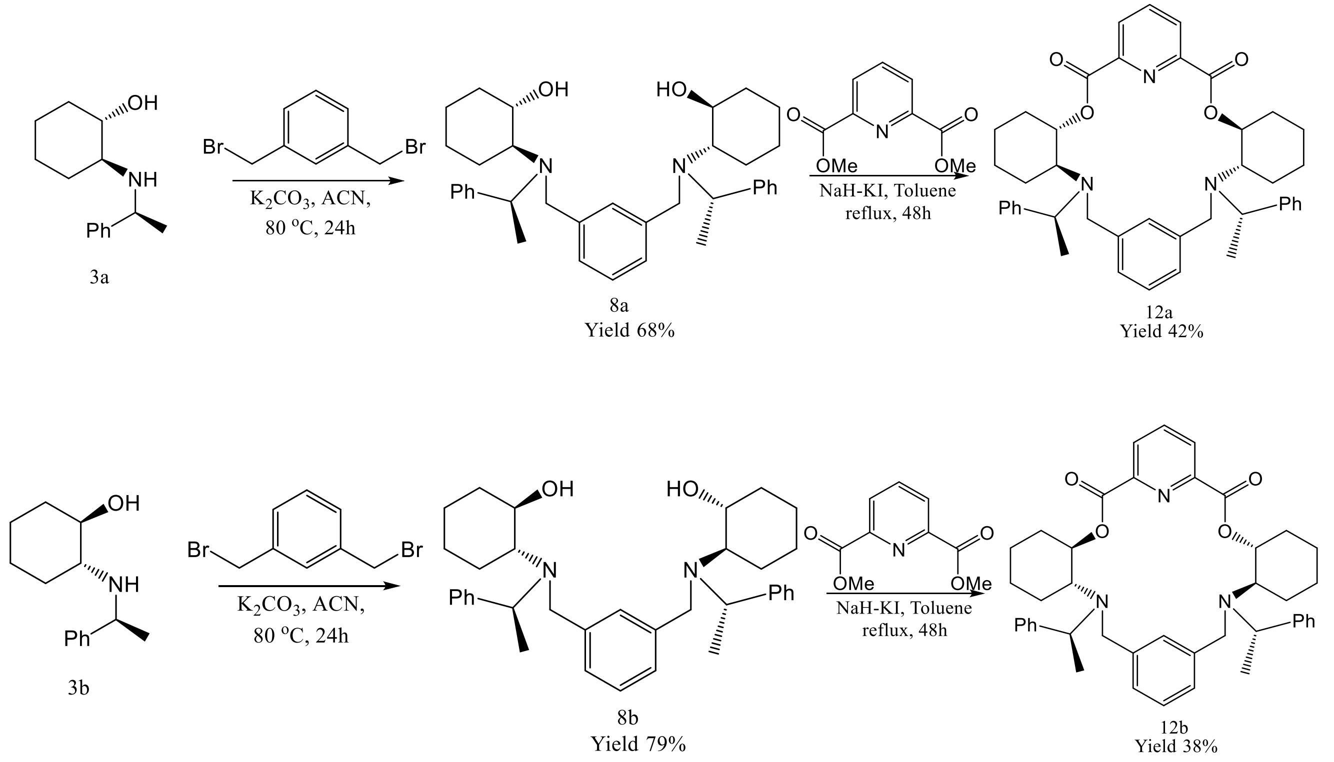


i) with **9a** ΔΔδ = 0.36
ii) with **9b** ΔΔδ = --
iii) with **10a** ΔΔδ =--
iv) with **10b** ΔΔδ =--

The synthesized crown ethers are screened for enantiodiscrimination of chiral acids by UV-Vis and fluorescence spectroscopy. Further screening of these crown ethers for enantiodiscrimination of chiral guest molecules is currently underway.

Synthesis of aza-macrocycle:

The separated diastereomers **3a** was treated with 1,3-bis-dibromomethyl-xylene in presence of K_2CO_3 to yield diaminodiol building blocks **8a**. The diamino diol **8a** was treated with dimethyl-2,6-pyridinedicarboxylate in dry toluene in presence of NaH as base for 48h resulting in formation of diazamacrocycle **12a**. The reaction was observed to progress upon the addition of KI. The reaction mixture was subjected to column chromatography yielding desired chiral aza macrocycle. The synthesis of diastereomeric macrocycle **12b** has been performed following similar scheme of reactions.



Scheme 6: Synthesis of Aza macrocycles **12a** and **12b**

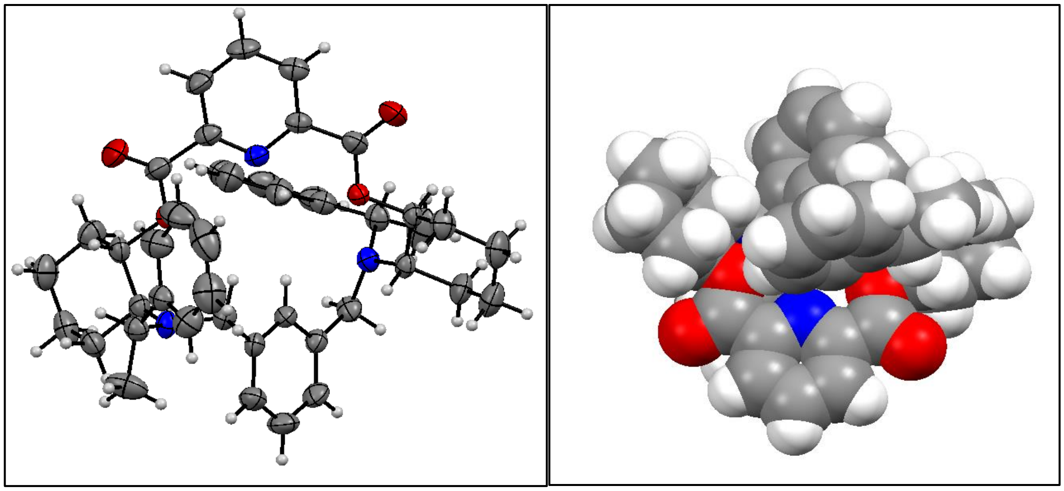


Figure 1: Crystal Structure and Space filled model for **12a**

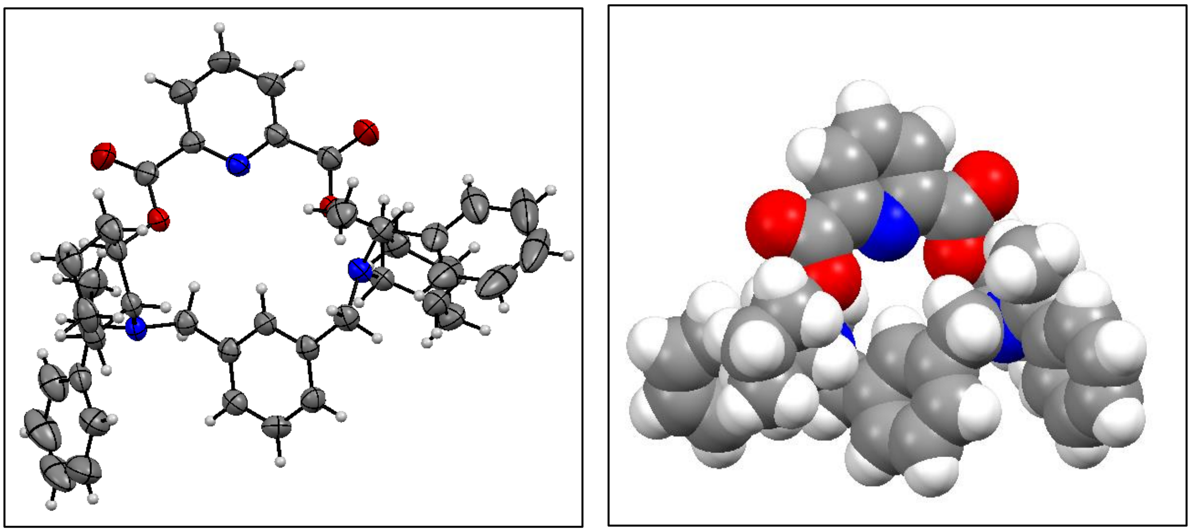
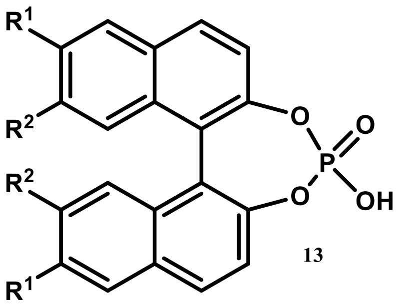


Figure 2: Crystal Structure and Space filled model for **12b**

Application as CSA for Heteronuclei: Study of Match/ Mismatch effect



13

The two derivatives of **13** were screened to study their ability to discriminate the ^{31}P NMR signals of derivatives of **13** by measuring the chemical shift non-equivalence ($\Delta\Delta\delta$) (Table 1). A clear pattern of better discrimination for (*R*,*R*,*S*)-**12b** was observed in all the examples, while the other derivative (*S*,*S*,*S*)-**12a**, with closed cavity was found ineffective

Table 1: Discrimination of Binaphthyl phosphoric acids **13**[a]

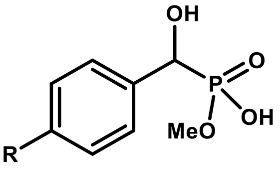
No.	Compound No.	R^1	R^2	ΔΔδ (ppm)	
				(S,S,S)-12a	(R,R,S)-12b
1	13a	H	H	0.03	0.78
2	13b	H	OMe	--[b]	0.64
3	13c	H	O^iPr	--[b]	0.76
4	13d	NO_2	H	--[b]	0.81
5	13e	Br	H	--[b]	0.40

[a]In CDCl_3 (20 mM), 162 MHz, ratio of 13:12 (2:1); [b]Not resolved.

Determination of nature of host-guest complex:

The nature of complex between **13** and the isomers of macrocycle was determined by IR spectroscopy. Complex of **13** with **12a** showed a weak band at 1098 cm^{-1} for phosphoryl bond stretching, but appears much stronger for **12b.** The static quenching is probably attributed to the deprotonation of phosphoric acid **12**, which is indicated by the appearance of a new peak in the UV-Vis spectra at a higher wavelength of 327 nm.

Table 2 Discrimination of monomethyl esters of substituted hydroxyl-phosphonic acids **14** to **16**[a]



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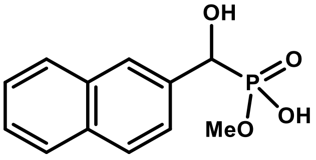

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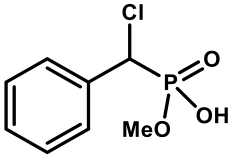


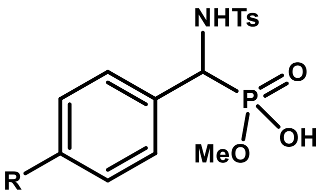
16

No.	Compound No.	R^1	ΔΔδ (ppm)	
			(S,S,S)-12a	(R,R,S)-12b
1	14a	H	0.17	0.04
2	14b	Me	0.19	--[b]
3	14c	Cl	0.16	--[b]
4	15	--	0.17	--[b]
5	16	--	--[b]	--[b]

[a]In CD_3OD (5%) in CDCl_3 (20 mM), 162 MHz, ratio of **14** to **16**:**12** (2:1); [b]Not resolved.

α-Hydroxy phosphonic acids and α-amino phosphonic acids have received considerable attention in the field of medicinal chemistry. Aminophosphonic acid derivatives, being structurally analogous to amino acids, have been incorporated into many drug molecules due to their physiological activity as antiviral, antibacterial, anticancer and neuroactive compounds.

Table 3 Discrimination of monomethyl esters of substituted amino-phosphonic acids **17** and **18**[a]



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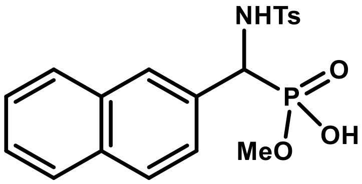


18

No.	**Compound No.**	**R¹**	**ΔΔδ (ppm)**	
			(S,S,S)-12a	**(R,R,S)-12b**
1	17a	H	0.40	--[b]
2	17b	Me	0.42	--[b]
3	17c	Cl	0.45	0.10
4	17d	OMe	0.43	--[b]
5	17e	NO_2	0.40	0.12
6	18	--	0.37	--[b]

[a] In CD_3OD (5%) in $CDCl_3$ (20 mM), 162 MHz, ratio of **17** to **18**:**12** (2:1); [b] Not resolved.

In summary synthesis of chiral azacrown ethers was achieved from amino alcohol, prepared by diastereomeric ring opening of *meso* cyclohexenoxide with chiral amine. The aza crown ethers were screened as CSA for enantiomeric recognition of α-functional carboxylic acids. The detailed investigation of crown ethers as CSA along with mechanistic study of binding with guest molecules is currently under progress. Furthermore, two diastereomeric N,O-macrocycles were synthesized and evaluated as CSA for effective discrimination by ^{31}P NMR signals and fluorescence quenching of several organo phosphoric and phosphonic acid derivatives. The study of combination of chirality on the backbone of macrocycle and of the pendant group was explored for molecular recognition of optically active hosts for quantifiable discrimination.

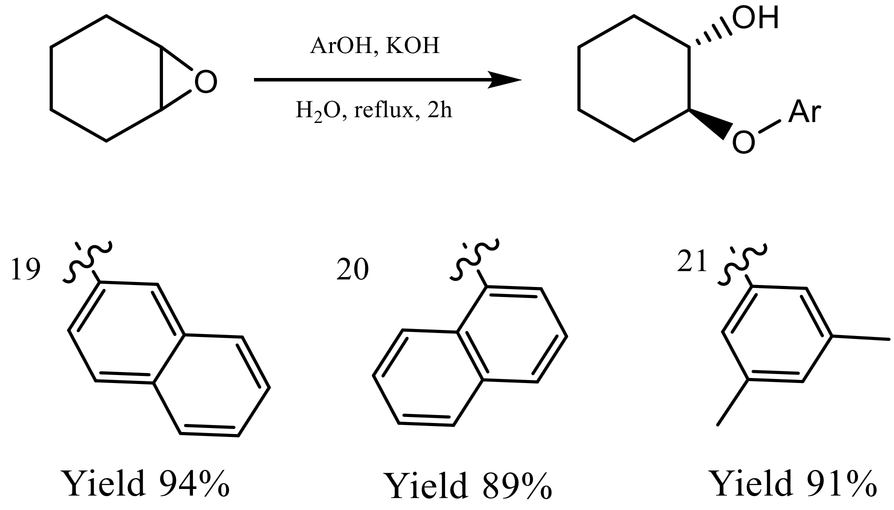
Cyclohexanol as Chiral Auxiliary:

A chiral auxiliary is a chemical compound or unit that is temporarily incorporated into an organic molecule in order to control the stereochemical outcome of the synthesis. The chirality present in the auxiliary can bias the stereoselectivity of one or more subsequent reactions. The auxiliary can be eventually cleaved from the substrate and is typically recovered for future use.

Application of cyclohexanol based chiral auxiliaries is known in asymmetric transformation. Notably 8-phenylmenthol and 2-phenylcyclohexanol have been previously used as auxiliaries in asymmetric reactions. Although these auxiliaries are known to show high levels of stereoinduction, availability of single enantiomeric form and tedious synthesis of auxiliary pose a major limitation. In the present study cyclohexanol based chiral auxiliary has been synthesized and resolved by enzymatic methods.

Synthesis of chiral Auxiliary:

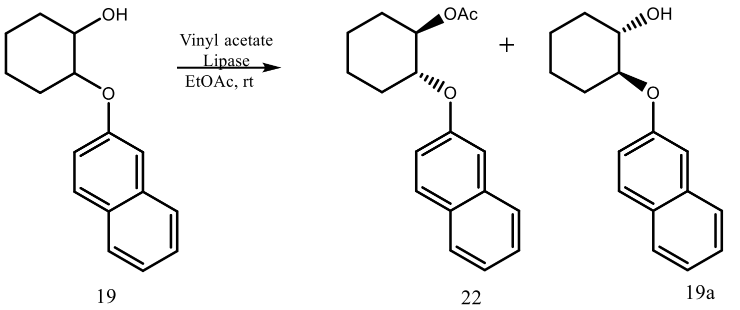
(±)-*trans*-2-Aryloxy cyclohexanols (19-21) have been prepared by using cyclohexene oxide (1 eq) and corresponding phenol (3 eq) in the presence of potassium hydroxide (3 eq) in water. The reaction mixture was then extracted with ethyl acetate and purified by column chromatography.



Scheme 7: Synthesis of Chiral Auxiliaries **19-21**

Enzymatic Resolution:

One important approach to obtain enantiomerically pure compounds is the kinetic resolution method by using a biocatalyst; this process is based on the difference in reaction rates (k_{fast}/k_{slow}) of two enantiomers. In our study we have used crude lipase *steapsin* as biocatalyst for the resolution of alcohols **(19, 20** and **21).**



Yield 48%
ee = > 99%

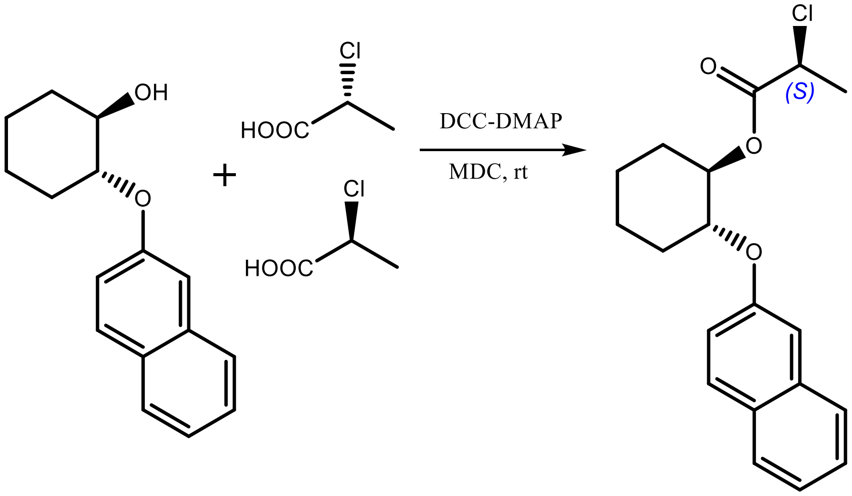
Yield 49%
ee = > 99%

Scheme 8: Enzymatic resolution of alcohol **19**

Similarly the cyclohexanol derivatives **20** and **21** have been synthesized and resolved using above conditions. The resolved alcohols were then converted to diastereomeric esters by reaction with (*R*)-*O*-acetyl-mandelic acid for determination of absolute configuration. The single crystal X-Ray analysis of crystals of chiral esters showed that *R*,*R*-isomer of alcohol undergoes enzymatic acylation while *S*,*S*-isomer remains unreacted.

Application of trans-2-aryloxy cyclohexan-1-ol as Chiral Auxiliary: Deracemization of 2-chloropropanoic acid

Racemic 2-chloropropanoic acid **(23)** was condensed with alcohol **(19b)** in the presence of DCC-DMAP. The diastereomeric ratio of the product has been established from the ^{1}H NMR signal for the α -C*H*- proton. It was clearly evident that only one set of signals of a quartet of ClC*H*(Me)COOR* at 4.29 to 4.34 δ was observed indicating absence of the other diastereomer (with C*H* at 4.22 to 4.28 δ).



19 23 24

Yield 99%
de = *>99%*

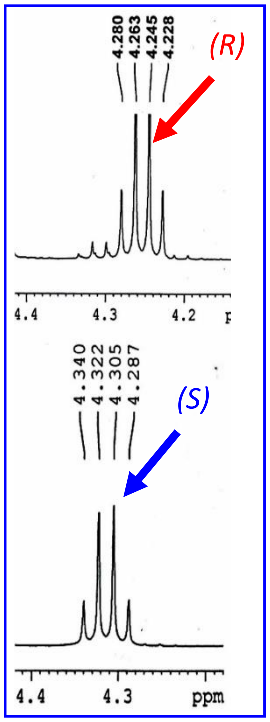
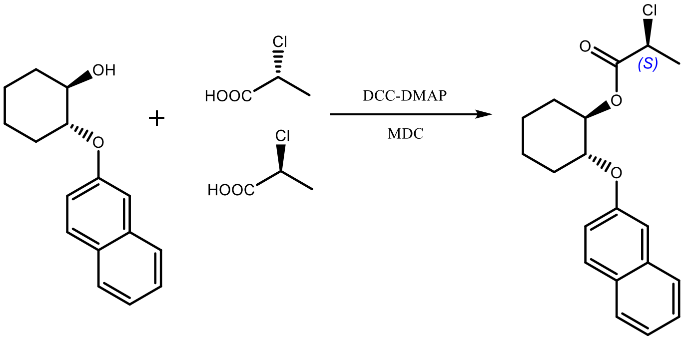


Table 4: Base study in deracemization of 2-chloropropanoic acid

Entry	**Base**	**Time (hours)**	**Diastereomeric Ratio (*dr*)**
1	DMAP	12	>99
2	DABCO	12	>99
3	Triethyl amine	12	98
4	K_2CO_3	12	97

Effect of temperature on diastereoselectivity

The esterification of alcohol **19** with 2-chloro-propanoic acid was monitored at different temperatures. The reaction with racemic 2-chloro-propanoic acid resulted in single diastereomer at 0 °C, rt and heating. Interestingly when a scalemic mixture of 33% (*R*)-2-chloro-propanoic acid was used, it resulted in formation of product with *dr* 72% *αS* at rt and reflux temperature but on cooling it showed decrease in diastereoselectivity to 50% *αS*.



19 23 24

Table 5: Effect of temperature on diastereomeric ratio

No	Initial Composition (*R:S*)	Time (hours)	Temperature	Product %dr (*αS*)
1	50:50	12	Rt	>99
2	50:50	12	Reflux	>99
3	50:50	12	0 °C	>99
4	67:33	12	Rt	72
5	67:33	12	reflux	72
6	67:33	12	0 °C	50

Effect of time on diastereomeric ratio:

The reaction of chiral alcohol **19** and 2-chloro propanoic acid was monitored at different times. The diastereomeric ratio of product **24** showed gradual increase with increase in time. When the reaction was stopped after 6 h the product showed *dr* of 69% whereas after 48 h it showed increase in *dr* up to 48%.

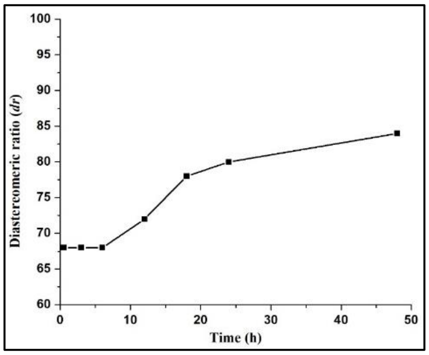
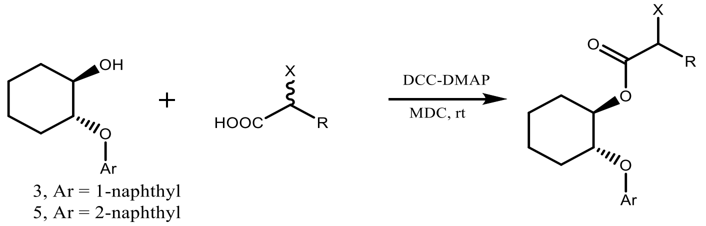


Table 6: Effect of substituents on diastereoselectivity



3, Ar = 1-naphthyl
5, Ar = 2-naphthyl

No	Auxiliary	R	X	Yield %	Diastereomeric ratio (% *dr*)
1	20	Me	Cl	98	68
2	19	Me	Cl	99	>99
3	19	Me	Br	98	66
4	19	Et	Cl	97	50
5	19	Et	Br	98	40
6	19	^{i}Pr	Cl	98	42
7	19	^{i}Pr	Br	96	46
8	19	Bn	Cl	94	43
9	19	Bn	Br	92	38
10	20	Ph	Br	95	10
11	19	Ph	Br	98	66*R*
12	19	Ph	Cl	94	34*R*

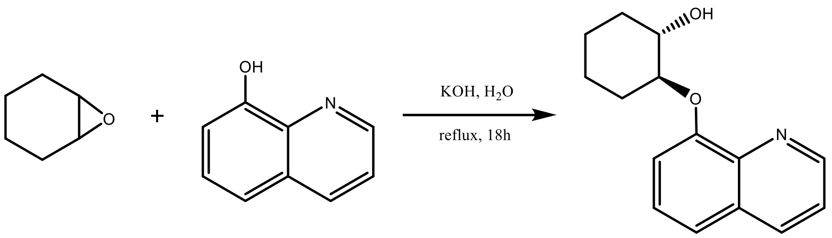
In summary, practical synthesis and resolution of *trans*-2-aryloxy cyclohexan-1-ols **19-21** have been carried out. The enzymatic resolution of *trans*-2-aryloxy cyclohexan-1-ols yield both the enantiomers in optically pure form. The naphthyloxy cyclohexanol derivatives have been further screened as chiral auxiliary for deracemization of *rac*-α-chloropropanoic acid. The results indicate diastereoselective ester formation in presence of DCC and DMAP. The diastereomeric ratio of the product has been established from the ^{1}H NMR signal for the α -C*H*- proton and by HPLC. The auxiliary **19** has been employed for deracemization of *a*-halo acids with varying alkyl groups and diastereomeric enrichment has been observed. The detailed mechanistic study and theoretical calculations for diastereoselective esterification are currently under progress.

Chapter 4: *Synthesis, Resolution and Application of Cyclohexanol derivatives in Enantiomeric Recognition:*

Amino alcohols and *α*-hydroxy-*β*-amino acid moieties are found in a large variety of biologically important compounds, e.g. natural products and peptides, as well as in a growing number of ligands and chiral auxiliaries for asymmetric synthesis. Amino alcohols also play an important role as chiral ligands and chiral auxiliaries in asymmetric synthesis and are most commonly derived from natural sources. A wide variety of amino alcohols have been derivatized and employed in enantiodiscrimination of chiral compounds using NMR spectroscopy and fluorescence spectroscopy. *β*-Amino alcohol is one of the most important pharmocophore because of its ubiquity in biologically active compounds such as antibiotics, alkaloids, enzyme inhibitors and *β*-blockers.

Synthesis of Quinolin-8-yl-cyclohexanol:

(±)-*trans*-2-(Quinolin-8-yloxy)cyclohexanol (**25**) has been prepared by using cyclohexene oxide (1 eq) and 8-hydroxyl quinoline (1 eq) in the presence of potassium hydroxide (1 eq) in water. The quinolinyl alcohol was further crystallized and subjected to enzymatic resolution.

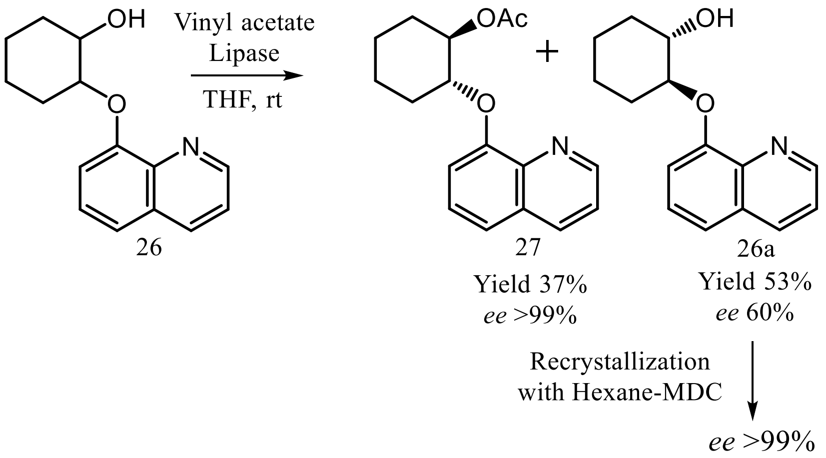


1 25 26

Scheme 9: Synthesis of Quinolinyl alcohol **26**

(**±**)-*trans*-2-(Quinolin-8-yloxy)cyclohexanol **25** has been subjected to enzymatic resolution in presence of Steapsin lipase and vinyl acetate as acyl donor.

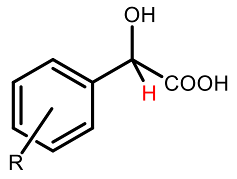
The unreacted alcohol with moderate optical purity (60% ee) was further recrystallized resulting in enhanced *ee* of over 99%.



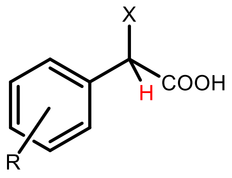
Scheme 10: Resolution of Quinolinyl alcohol **26**

Application of quinolinyl cyclohexanol as CSA

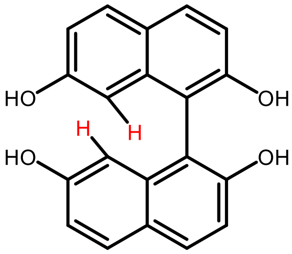
The resolved quinolinyl alcohol **26** was then subjected as CSA for chiral discrimination of acid substrates. The quinolinyl alcohol has been successful in enantiodiscrimination of variety of substrates ranging from mandelic acid derivatives to binol derivatives. Furthermore it has also been successful in recognition of binaphthyl phosphoric acid and cyclic phosphoric acid derivatives.



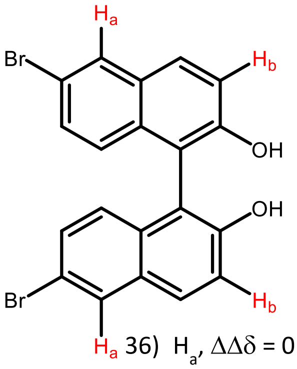
28) R = H, ΔΔδ = 0.027
29) R = 2-Cl, ΔΔδ = 0.019
30) R = 4-CF_3, ^{1}H ΔΔδ = 0.022
^{19}F ΔΔδ = 0.036



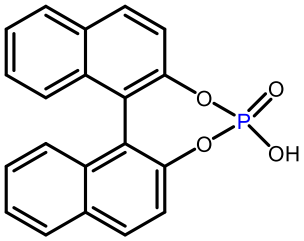
31) R = H, X = Cl, ΔΔδ = 0.016
32) R = 2-Cl, X = Cl, ΔΔδ = 0.024
33) R = 4-CF_3, X = Cl, ^{1}H, ΔΔδ = 0.012
^{19}F, ΔΔδ = 0.026
34) R = H, X = Br, ΔΔδ = 0.030



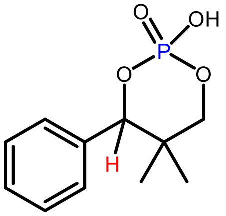
35) ΔΔδ = 0.058



36) H_a, ΔΔδ = 0.015
H_b, ΔΔδ = 0.022



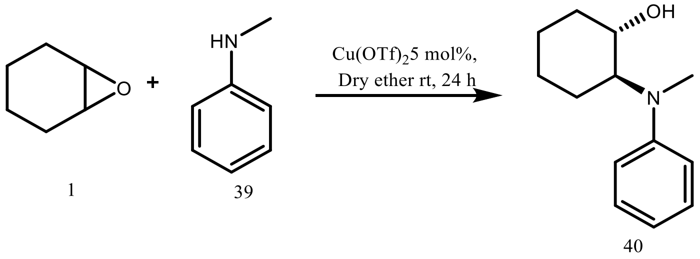
37) ΔΔδ = 0.56



38) ^{1}H, ΔΔδ = 0.020
^{31}P, ΔΔδ = 0.34

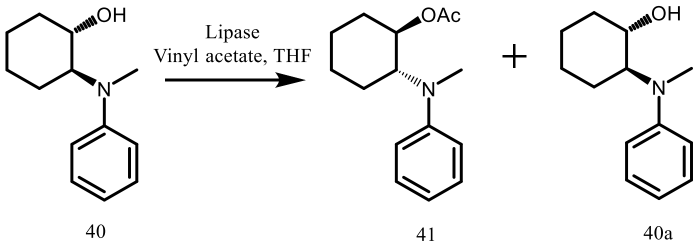
Synthesis and resolution of aminoalcohol:

Amino alcohol **40** was synthesized by ring opening of *meso* cyclohexenoxide (1eq) with N-methyl aniline (1eq) in presence of $Cu(OTf)_2$ in dry ether. The amino alcohol **40** was then subjected to enzymatic resolution in presence of lipase and vinyl acetate as acyl donor in THF.



Scheme 11: Synthesis of amino alcohol **40**

Enzymatic resolution of amino alcohol



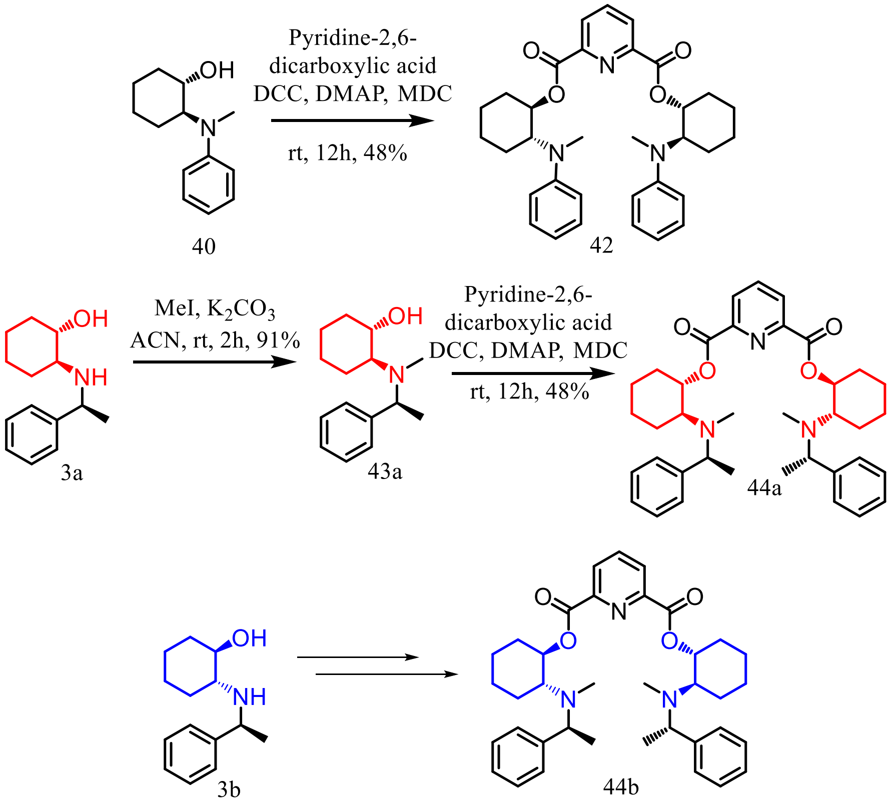
Scheme 12: Enzymatic resolution of amino alcohol **40**

Table 7: Conditions for enzymatic resolution of aminoalcohol **40**

No	Lipase (w/w)	Acyl donor	Solvent	Enantiomeric excess		C	E value
				Acetate (% *ee*)	Alcohol (% *ee*)		
1	CAL-B 30%	VA 2.5eq	THF	>99	7	10	>200
2	CAL-B 30%	VA 10eq	THF	>99	10	11	>200
3	CAL-B 60%	VA 5eq	THF	97	20	10	79
4	Steapsin 1eq	VA 5eq	THF	>99	34	28	>200
5	Steapsin 2.5eq	VA 10eq	THF	>99	80	42	>200
6	**Steapsin 3eq**	**VA 10eq**	**THF**	**>99**	**90**	**45**	**>200**

Synthesis of amino esters:

The resolved amino alcohol **40** was treated with pyridine-2,6-dicarboxylic acid in presence of DCC and DMAP in MDC resulting in formation of amino ester **42**. We wish to synthesis similar diastereomeric diesters **44** by reaction of diastereomeric amino alcohol **3a** and **3b** repectively with MeI in MeCN in presence of K_2CO_3 followed by esterification. These amino esters **42**, **44a** and **44b** would then be screened as CSA for enantiomeric recognition of acid substrates. We wish to examine the match mismatch effect in case of diastereomeric esters **44a** and **44b**. Also we would like to observe the effect of having *N*-Me group attached directly to aromatic ring and separated by single carbon atom which would enable us to fine tune the CSA by virtue of differing electronic as well as steric effects.



Scheme 13: Synthesis of amino esters **42**, **44a** and **44b**

In summary quinolinyl based amino alcohol has been synthesized by ring opening of cyclohexenoxide. The quinolinyl alcohol thus formed, has been resolved by enzymatic resolution and employed for enantiodiscrimination of chiral acids by NMR spectroscopy. Chiral amino esters have been prepared from amino alcohols **3** and **40** and screening of amino esters as CSA is currently underway.

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