Abstract

of the thesis entitled

"Development of Novel Methodologies in Asymmetric Synthesis"

to be submitted

as a partial fulfilment for the award of the degree of

DOCTOR OF PHILOSOPHY

in

CHEMISTRY

by

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Abstract of Thesis

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DOCTOR OF PHILOSOPHY

in

CHEMISTRY

Research Student	: **Hiten Bharatbhai Raval**
Title of Thesis	: **Development of Novel Methodologies in Asymmetric Synthesis**
Supervisor	: **Prof. Ashutosh V. Bedekar** **Professor**
Department	: **CHEMISTRY**
Faculty	: **SCIENCE**
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The thesis will be presented in the form of following chapters –

Chapter 1

Introduction

Chapter 2

Synthesis and study of fluorine containing Kagan's amides as chiral Solvating agents

Chapter 3 [I]

One-pot preparation of chiral arylalkyl carbinols by Mitsunobu Protocol

Chapter 3 [II]

Silver-Mediated Conversion of Alcohols to Carbonates with Dialkylazodicarboxylate

Chapter 4

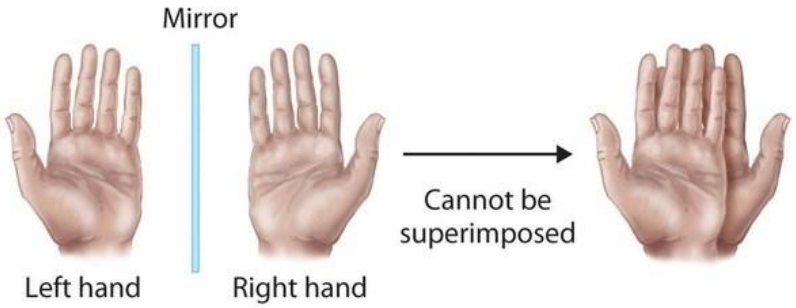
Synthesis, Resolution and Application study of Thiourea derivatives

Chapter-1

Introduction

1.1 Chirality

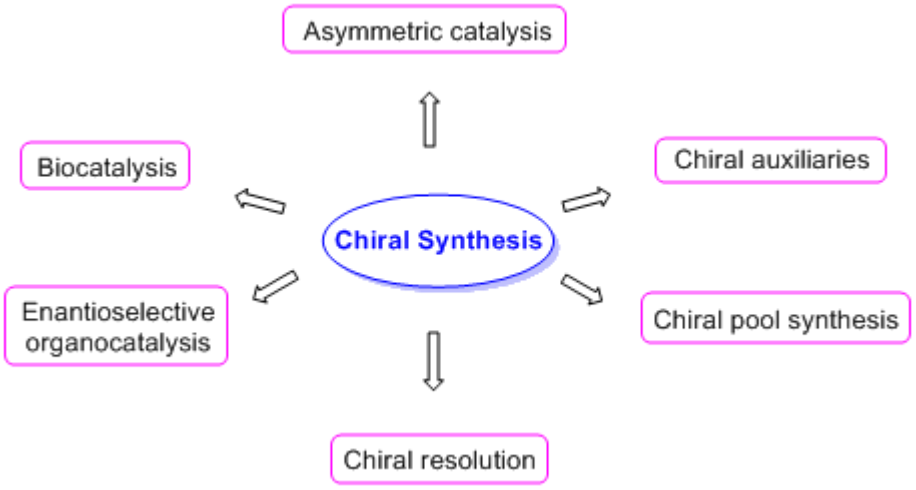
Chirality is a vital component in nature. Greek word cheir is the root of the phrase Lord Kelvin used to describe chirality in 1873. When racemic sodium ammonium tartrate tetrahydrate crystallised from an aqueous solution, Louis Pasteur found spontaneous resolution. This discovery was quickly acknowledged as being of utmost significance to the molecular chirality or chemistry. The optical rotation of the molecules, which have the same absolute value but the opposite sign, is the only difference between them. The first method of resolving a racemate was also discovered with the spontaneous resolution of sodium ammonium tartrate. Chirality basically means '**mirror-image, non-superimposable molecules**'



As chiral molecules make up the majority of cells, chirality is a key term in biology. Amino acids and sugars are examples of small chiral compounds that serve as the building blocks for larger chiral molecules, like proteins and nucleic acids. Chirality plays a crucial role in the synthesis and development of pharmaceuticals. The majority of newly discovered medicines are chiral. Interaction of drugs with biological targets such proteins, nucleic acids, and biological membranes can be used to identify their pharmacological activity. A chiral medication may have one of its two enantiomers that is a treatment for a certain ailment, whereas the other enantiomer of the molecule may not be inactive but can be harmful. As a result, chirality is important in the world of pharmaceuticals.

1.2 Synthesis of Chiral Compounds

Enantioselective synthesis, also known as asymmetric synthesis or chiral synthesis, is the process of synthesize a molecule in such a way as to promote the development of a particular enantiomer or diastereomer. It is a crucial procedure in contemporary chemistry and is especially significant in the area of medicinal chemistry since a molecule's various enantiomers or diastereomers can have different biological functions. For a wide range of possible uses, particularly in the pharmaceutical industry, the enantioselective synthesis of chiral compounds is essential.

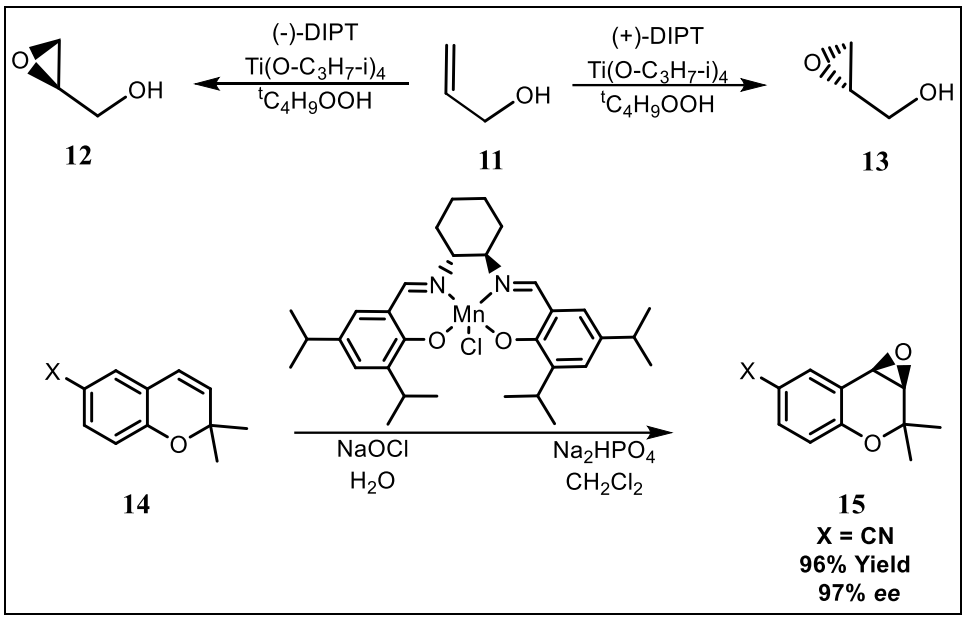


1.2.1 Asymmetric Catalysis

The pharmaceutical industry's growing need for optically pure chiral intermediates and the adoption of green and sustainable chemistry principles in the production of high value-added fine chemicals have spruced up the growth of asymmetric catalytic techniques.

Several developments have contributed in the growth of defined transition metal complexes for asymmetric catalysis. The ability to synthesize and characterize well defined transition metal complexes improved intensely. Access to defined complexes set the stage for understanding the effect of structure for function, which resulted in the development of defined transition metal complexes, typically hybrids of organic molecules and transition metals, for chemical catalysis.[11a,b] an enantioselective chemical reaction to prepare 2,3-epoxyalcohols **12,13** from primary **11** allylic alcohols **(Scheme 1)**. The oxidizing agent is *tert*-butyl hydroperoxide. The method relies on a catalyst formed from titanium

tetra(isopropoxide) and diethyl tartrate.[11c] Synthesis of the chiral epoxide **15** can be achieved using Jacobsen catalyst with high optical yield **(Scheme 1)**.[11d]



Scheme 1: Asymmetric epoxidation of allylic Alcohol

BINAP complexes of rhodium provide exceptional enantioselectivity in such modifications, again drawing on catalytic hydrogenation. Because the initially formed adduct is an enol boron species, it can be caught in a highly diastereoselective aldol process in addition to protonation, resulting in the formation of three stereogenic centres in a single asymmetric catalytic event.

Chapter-2

2.5 Development of New Chiral Solvating Agent

The literature has a variety of chiral ligands or auxiliaries, each of which is unique to molecules that contain a particular functional group. However, ongoing research is being done to find additional compounds or ligands to add to the CSA library.

Result and Discussion

2.6 Synthesis of new chiral amide

Chiral amide **22** prepared from suitable amine and 3,5-dinitro benzoic acid was first reported by Kagan and screened for a variety of optically active analytes for the discrimination of signals in NMR.[53-56] (figure 2.5). In our previous study we have modified Kagan's amine by introducing two trifluoro methyl groups on the amide side, thereby attempting to strengthen the proposed hydrogen bonding between its N-H and the carbonyl group of the chiral analyte, by the inductive effect.[57] A considerable improvement in the recognition ability of **23a** was established as compared to **22** in a large number of neutral as well as acidic analytes. We also studied slight improvement by introduction of a para chloro group on the acid side of the amide in **23b** and tested enhanced molecular recognition in few of the examples.[58] Prior to our modifications, there are also few more derivatives of **22** reported in the literature, such as **24a**,[59] **24b**,[60] where the chiral amine is replaced by different aromatic moieties, or by **24c**,[61] where it is substituted by a bicyclic isobornyl amine.

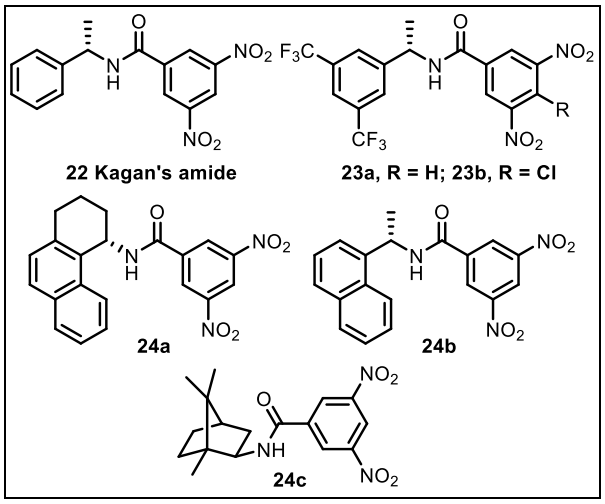


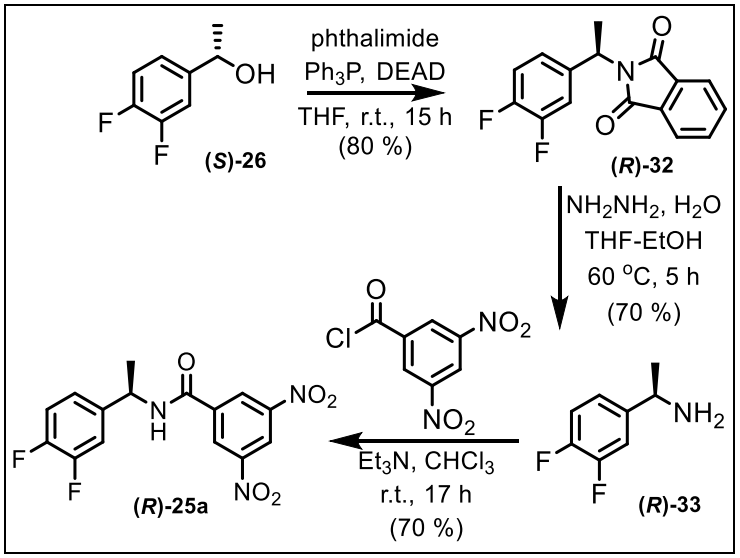
Figure 2.6: Kagan's amide and its variants

All these derivatives have been explored as efficient Chiral Solvating Agents for the successful discrimination of few selected signals of chiral analytes in the NMR analysis

by focusing hydrogen as well as few other active nuclei.

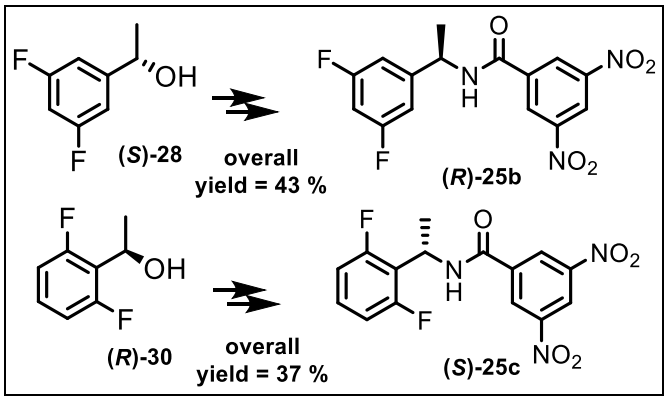
2.6.2 Synthesis of amides

The sample of optically pure alcohols were then converted to the corresponding proposed Kagan's amides by the previously reported synthetic sequence.[57] The alcohol (*S*)-**26** was treated with phthalimide under the standard Mitsunobu conditions to get (*R*)-**32** with inversion of absolute configuration **(Scheme 3)**. The optically pure amine (*R*)-1-(3,4-difluorophenyl)ethan-1-amine (*R*)-33 was obtained from the hydrazine mediated cleavage in good overall yield, which was condensed with 3,5-dinitrobenzoyl chloride to furnish the amide (*R*)-**25a**.



Scheme 3: Synthesis of (*R*)-**25a** from chiral alcohol

The other two alcohols (*S*)-**28** and (*R*)-**30** were similarly converted to the other two amides, (*R*)-**25b** and (*S*)-**25c** with adequately inverting the configuration in moderate overall yields (Scheme 4).



Scheme 4: Similar synthesis of (*R*)-**25b** and (*S*)-**25c**

Chapter 3 [I]

3.I.2 Result and Discussion

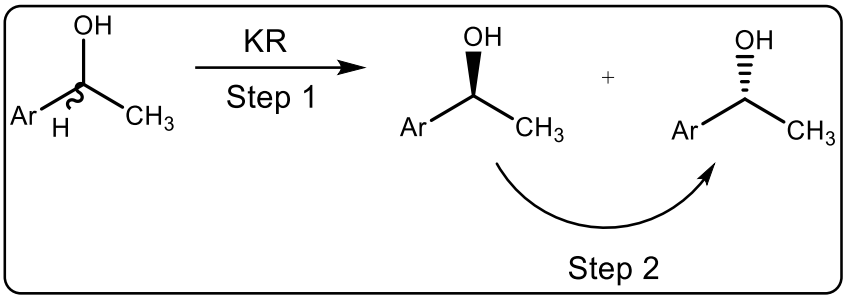
Many different types of enzymes' stereoselectivity is used to produce optically active molecules. Particularly crucial are the lipase-catalyzed kinetic resolutions of carboxylic acid derivatives and racemic alcohols through acylation in organic solvents (**Scheme 1**). One of the enantiomers is isolated as a free alcohol and the other is obtained as a (or unreactive) ester derivative simultaneously with high enantiomeric purities when the value of the enantiomeric ratio (E; the ratio of the specificity coefficients of the enantiomers) [39] for such a reaction is high sufficiently.

Chromatographic processes can be time-consuming when separating these resolution products. A more significant flaw of conventional resolutions (chemical or enzymatic) is that for some uses, 50% of the initial material has the opposite absolute configuration. Our goal has been to present a one-pot method that can be employed to get the necessary enantiorner with a theoretical yield of 100% when computed using the racemic starting material while avoiding the above-mentioned drawbacks of lipase-catalyzed resolution. Racemization of the isomer *in situ* during the reaction or subsequent resolution after the unwanted enantiomer has been separated from the resolved mixture have both been used as methods of recycling unwanted enantiomers as a method of accomplishing this.[40-42] An inversion at the stereogenic centre has been suggested as another method for producing the correct stereochemistry. As a reasonable option for the enantioconvergent S_N2 step in one-pot synthesis, we reverted to this method and used resolution followed by the Mitsunobu reaction of a free alcohol enantiomer using redox couple of diethyl azodicarboxylate (DEAD)-triphenylphosphine (PPh3) and a carboxylic acid (**Scheme 1**). The chemically produced and original optically active esters become configurationally identical when the RCOOH of the S_N2 step matches to the acid constituent of the ester in the resolved mixture, increasing the chemical yield of the ester enantiomer to 100% in principle.

3.I.3.0 One pot Kinetic Resolution-Mitsunobu Reaction

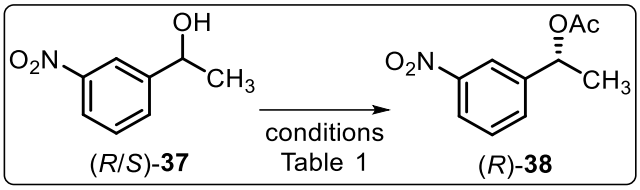
In this chapter we shall discuss our approach to use a one-pot strategy of combining enzyme mediated KR and Mitsunobu esterification. In the present reaction we chose to use metal acetates as source of nucleophile. The acetate ion is more readily available in the salt of acetic acid due to its enhanced ionic character. Conversion of less reactive isomer of alcohol to the acetate by inversion of

configuration by Mitsunobu reaction is done with acetic acid as the source of acetate ion.



Scheme 15: Separation of isomers by KR.

The nucleophilicity of acetate ions in the metal salt of AcOH will be appreciably more and will favor the displacement procedure. With this aim we have screened number of metal acetates for the Mitsunobu step in the one-pot sequence of this reaction. The standard reaction was performed on 1-(3-nitrophenyl)ethan-1-ol (*R*/*S*-**37**), where the first step of KR was done with suitable immobilized bio-catalyst and with vinylacetate as source for acetylation. After standardizing conditions for this step, we performed parallel set of example, where the reaction mixture was immediately subjected to Mitsunobu conditions with metal acetates to convert unreacted alcohol to acetate (**Scheme 16**).



Scheme 16: One-pot KR-Mitsunobu with MOAc as nucleophile

The first step of KR was performed using Novozyme-435 as the immobilized enzyme and vinyl acetate as the acetylating agent. The conditions of using excess vinyl acetate (10 eq.), diethyl ether as solvent, with the beads of Novozyme-435 (50 % w/w) as biocatalyst and performing the reaction at room temperature was optimized after several experiments. After the KR is achieved, the reaction mixture was filtered to remove the solid matrix of immobilized enzyme and the reaction mixture was treated with metal acetate, DEAD and Ph_3P for the Mitsunobu reaction step (Table 1). The reaction with AgOAc was smooth at room temperature and high conversion to acetate **38** was achieved. The product was isolated and its

optical purity measured by HPLC analysis on chiral column. The overall reaction furnished the desired acetate in excellent chemical yield and optical purity.

Table-1 Screening of different MOAc for one-pot KR-Mitsunobureaction[a]

No	MOAc	Acetate (*R*)-38	
		Yield (%)	e.e. (%)b
1	AgOAc	94	96.2
2	$Hg(OAc)_2$	81	91.4
3	$Pb(OAc)_2$	70	76.2
4	$Cu(OAc)_2$	84	84.9
5	$Mn(OAc)_2$	78	86.2
6	$Mg(OAc)_2$	82	73.9
7	$Co(OAc)_2$	76	66.9
8	$Ni(OAc)_2$	80	83.3

*[a]For (R/S)-**37** (0.30 g); vinyl acetate (10.0 eq.); Novozyme-435 (0.15 g; 50 % w/w); dry Et_2O (10 mL); r.t. (24 h for KR step-1 & 24 h for Mitsunobu step-2); For step-2: dry CH_3CN (15 mL); DEAD (2.0 eq.); Ph_3P (2.0 eq.); MOAc (2.0 eq.). Reaction for step 2 required reflux conditions, except for entry 1. [b]Determined by HPLC*

Similarly, $Hg(OAc)_2$, like AgOAc, too has less charge density on metal ion and hence will have weaker metal-acetate bond, and show good nucleophilic nature. Our results with one-pot reaction with $Hg(OAc)_2$ also furnished the product in good conversion and purity; however, the reaction mixture was needed to be held at reflux temperature. We extended the study to compare efficacy of different metal acetates as source of acetate ion for the second step of this one-pot sequence. In most of the cases moderate yields were obtained, though good selectivity was observed. The other metal acetates have stronger M-OAc bonds and were not as effective; however, their lower cost and other considerations may offer some advantage.

Another experiment was conducted where the reagents for Mitsunobu step were introduced without removing the biocatalyst. With (*R*/*S*)-**37**, the acetate (*R*)-**38** was isolated in comparable parameters (89 % Y and 92 % ee).

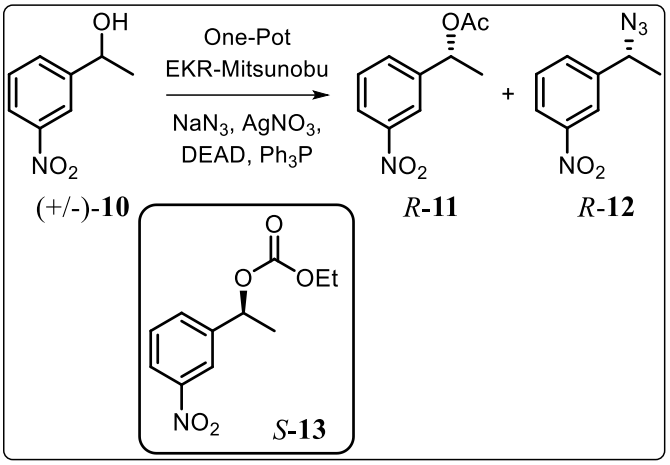
Chapter 3 [II]

3.II.3 Result and Discussion

In this Chapter we share our observations on the unexpected formation of alkyl carbonate during the one-pot enzyme mediated Kinetic Resolution and Mitsunobu reaction with less reactive nucleophiles. To widen the scope of our approach we investigated second step of Mitsunobu reaction with sodium azide as nucleophile, assisted by the presence of silver salts. During this investigation we observed formation of ethyl carbonate as an impurity. The Mitsunobu reagent, DEAD, provides the source of ethyl carbonate in this silver mediated conversion. We further investigate this unexpected observation with more examples and offer a plausible explanation.

3.II.4 Mitsunobu reaction with azide Nucleophile

Reaction of secondary aryl carbinol was investigated for one-pot enzyme mediated Kinetic Resolution and Mitsunobu reaction. The efficacy of enzyme to discriminate the optical isomers has been established in our earlier work. The one-pot reactions are often challenging to understand due to the interactions of different components in the medium. The standard reaction was optimized with 1-(3-nitrophenyl)ethan-1-ol (*R*/*S*-**10**) (**Scheme 4**). The optically enriched acetate *R*-**11** and azide *R*-**12** were obtained in high selectivity. In order to explore utility of this approach we were keen to use different nucleophiles in the second step of Mitsunobu reaction. Initial experiments with sodium azide furnished poor yield of azide *R*-**12** (12%), hence, silver nitrate was added to *in situ* convert it to more reactive silver azide. We have already established the efficiency of silver salts in such reactions.[1] As expected there was marked improvement in the formation of the azide *R*-**12** in presence of silver nitrate (41%). In the best conditions the combined yield of both these isolated materials was about 86%. Careful observation of the reaction mixture revealed formation of another byproduct, which was confirmed to be the ethyl carbonate **13**. Analysis of this product on chiral stationary phase HPLC indicated that it was formed almost as a single enantiomer (9% Yield, 99% ee).



Scheme 4: One-Pot EKR-Mitsunobu reaction

3.II.5 Synthesis of Organic Carbonates.

This unexpected formation of the ethyl carbonate in presence of silver nitrate prompted us to further explore this one-pot reaction. Several practical methods are available for the preparation of carbonates from corresponding alcohols, such as using sodium borohydride in dialkyl carbonate solvents,[8,,9] catalyst CsF supported on α-alumina,[10] Organotin-oxomolybdate coordination polymer.[11] Although the present reaction was not designed to prepare carbonates from alcohols, its serendipitous formation merits more investigation. Furthermore, the high optical purity of this ethyl carbonate **13** was an encouraging observation and the scope of this stereospecific reaction is attractive.

3.II.5.1 Optimisation condition for the carbonate formation

The reaction of carbonate formation was examined with 1-(3-nitrophenyl)ethan-1-ol (**10**) to determine the role of each reagents (Table 1). The reaction with DEAD in the absence of Ph_3P and silver salt did not proceed at all. The same reaction with DEAD and Ph_3P, under the well established Mitsunobu condition furnished only traces of carbonate **13**. However, in presence of silver nitrate (1.0 eq.) along with DEAD/Ph_3P, the reaction proceeded smoothly to give a good yield of carbonate **13**. Interestingly, the reaction with DEAD and silver nitrate in absence of Ph_3P, also resulted in the formation of **13** in good isolated yield. This observation is interesting as the smooth conversion without triphenylphosphine may indicate deviation from Mitsunobu type reaction pathway. As expected, the reaction did not proceed without DEAD, hence, eliminating the possibility of contamination of any other source of carbonate during the reaction. All the reactions were performed under the inert atmosphere of nitrogen gas.

Scheme 5: Mitsunobu reaction with **$AgNO_3$**

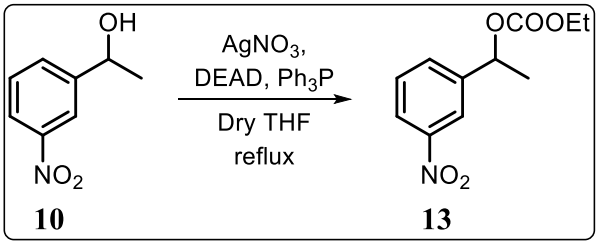


Table 1. Screening of conditions for carbonate formation[a]

No	$AgNO_3$ (eq.)	DEAD (eq.)	Ph_3P (eq.)	Time (h)	Yield (%)
1	--	2.0	--	72	NR
2	--	--	2.0	72	NR
3	--	2.0	2.0	72	< 2
4	1.0	2.0	2.0	24	74
5	1.0	2.0	--	48	85
6	1.0	--	2.0	72	NR

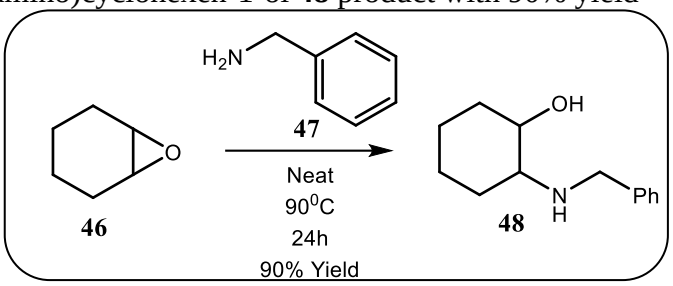
[a]Isolated Yield; Ratio, with respect to **10**; NR = No Reaction on TLC.

Chapter 4

4.2 Synthesis of ligand (*R*,*R*,*R*)-**56**, (*R*,*R*,*S*)-**57**, (*R*,*R*)-**58**

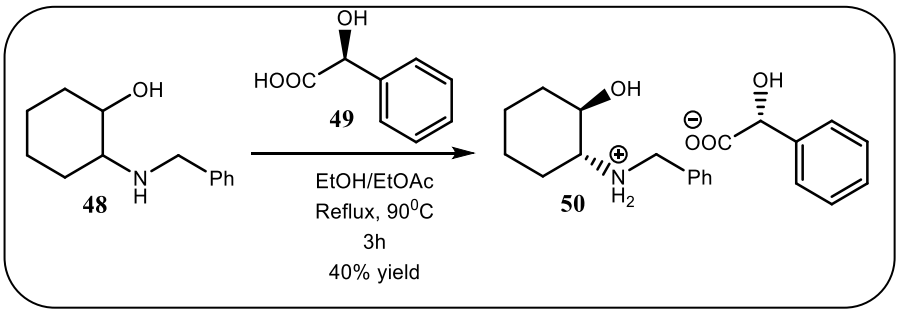
By studying a literature on thiourea based organic molecules which has many applications in the various fields like organocatalysis and work as a chiral solvating agent in organic chemistry, we have started our work to synthesize a thiourea based organic-molecules. To synthesize a effective thiourea based organocatalyst two different groups attached at two different nitrogen sites of thiourea should be such that it should easily form a interaction with substrate and favour a confirmation from a particular direction.

Synthesis of ligand (*R*,*R*,*R*)-**56**, (*R*,*R*,*S*)-**57**, (*R*,*R*)-**58** were started by epoxide ring opening reaction of epoxyclohexene **46** with the help of benzyl amine **47** to form a racemic 2-(benzylamino)cyclohexen-1-ol **48** product with 90% yield



Scheme 12: Epoxide ring opening reaction of epoxyclohexene **46.**

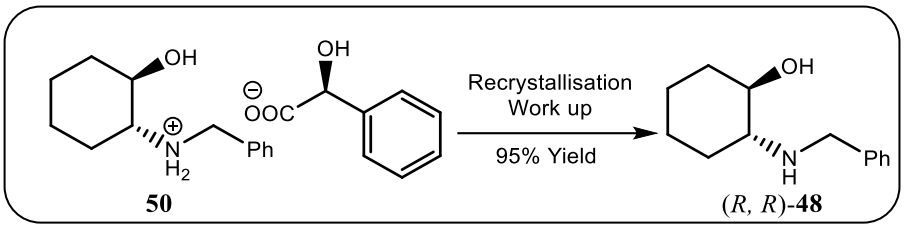
As amino alcohols are potent to form a supramolecular interaction like H-bonding with suitable analytes due to availability of lone pair of electrons, racemic 2-(benzylamino)cyclohexen-1-ol **48** which contains equimolar mixture of (*R*,*R*) and (*S*,*S*) was resolved by the treatment with optically active *S*-mandelic acid **49** in a reflux condition. (*R*,*R*)- **48** form a diastereomeric salt with *S*-mandalic acid **49**. This diastereomeric salt then purified by recrystallisation with good yield. Solvent used for recrystallization was EtOH/EtOAc mixture in a (20:80) ratio.



Scheme 13: Diastereomeric salt formation of racemic 2-(benzylamino) cyclohexen-1-ol **48.**

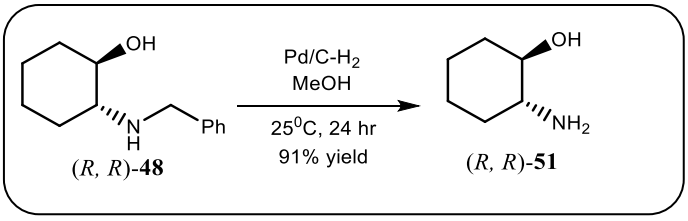
Compound **50** which is diastereomeric salt of (*R*,*R*) 2-(benzylamino)cyclohexen-1-ol and

S mandelic acid. This diastereomeric salt **50** then cleaved in a EtOAc/H_2O (50:50) biphasic mixture to get enantioenriched (*R,R*) 2-(benzylamino)cyclohexen-1-ol. Optically pure (*R,R*)-**48** can be achieved by recrystallisation. Optical activity was measured in HPLC by chiral amylose column which indicate the purity of the compound **50** to be >99%



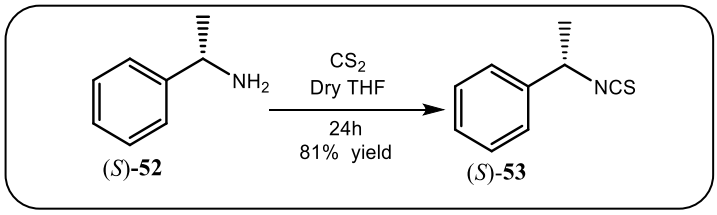
Scheme 14: Cleavage of (*R,R*)-2-(benzylamino)cyclohexen-1-ol **48** and *S*-mandelic acid**.**

Optically pure compound **48** then reduced in presence of Pd/C -H_2 for 24 hours at room temperature to get enantiomerically pure (*R,R*)- 2-aminocyclohexan-1-ol **51** with 91% yield.



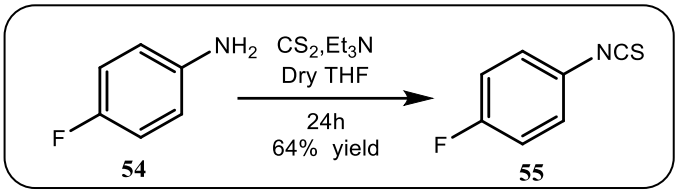
Scheme 15: Cleavage of (*R,R*) 2-(benzylamino)cyclohexen-1-ol **48** and *S*-Mandelic acid**.**

The isothiocyanates are very reactive. The (*S*)-1-phenylehane-1-amine is treated with carbon disulphide in the THF to get (*S*)-(1-isothiocyanatoethyl)benzene **53** with more then 80% yield.



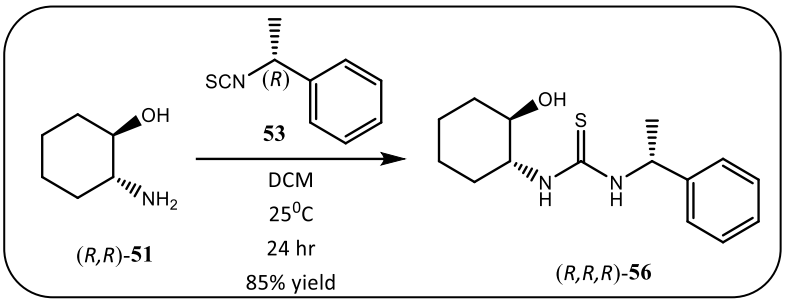
Scheme 16: Synthesis of (*S*)-(1-isothiocyanatoethyl)benzene **53**

1-fluoro-4-isothiocyanatobenzene **55** was synthesised by reacting 4-fluoroaniline **54** in presence of triethyl amine and carbon disulphide in dry THF.



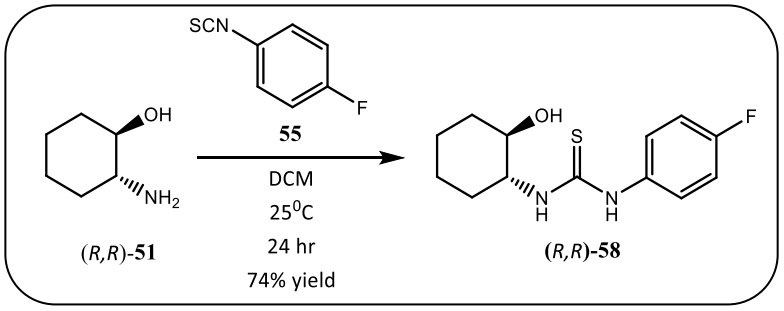
Scheme 17: Synthesis of 1-fluoro-4-isothiocyanatobenzene **55**

(*R*,*R*)- 2-aminocyclohexan-1-ol **51** is condensed with (*S*)-(1-isothiocyanatoethyl)benzene **53** in dichloromethane at ambient temperature for 24 hours to furnish 1-((1R,2R)-2-hydroxycyclohexyl)-3-((R)-1-phenylethyl)thiourea **56**.

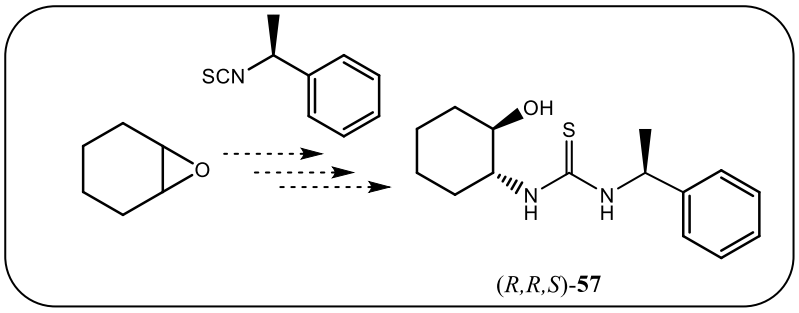


Scheme 17: Synthesis of 1-((1R,2R)-2-hydroxycyclohexyl)-3-((R)-1-phenylethyl)thiourea **56**

By applying same strategy, molecules 1-((1R,2R)-2-hydroxycyclohexyl)-3-((S)-1-phenylethyl)thiourea **57** and 1-(4-fluorophenyl)-3-((1R,2R)-2-hydroxycyclohexyl)urea **58** were also synthesized.



Scheme 18: Synthesis of compound 1-(4-fluorophenyl)-3-((1R,2R)-2-hydroxycyclohexyl)thiourea **58**



Scheme 19: Synthesis of compound **57.**

These three ligands **56, 57, 58** contain thiourea moiety and cyclohexyl ring system which

will allow them to interact with substrate molecules. Here both NH hydrogens of thiourea moity are acidic enough to make a supramolecular interaction with electron donating atoms like oxygen, sulfer or halogens while rigid cyclohexyl ring gives the substrate a particular cavity by which substrate molecule can form interaction in a particular direction with thiourea moity.