Chapter-1

Introduction

1.1.1 Chirality: Definition and its types:

Until half a century ago, it was assumed that the forces of nature were symmetric and that they did not distinguish between right and left, between image and mirror image. The discovery of the violation of parity in 1956 was more than a sensation, for some it was a shock. It implied that the universe displays handedness, or chirality, and that it is fundamentally asymmetric.[1] The idea of chirality has been known in chemistry since chiral chemistry got impetus from pioneering work by Louis Pasteur, a French chemist and biologist, who physically separated the two isomers of sodium ammonium tartrate in 1848 although it would be nearly a hundred years before chemists began using this term. In fact, in the first edition of Eliel's "Stereochemistry of Carbon Compounds" in 1962, the word chiral is not mentioned.[2] 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.*[3]"

As Mislow has pointed out, Kelvin's geometric definition of chirality is equivalent to that given many years later by Vladimir Prelog in his 1975 Nobel Prize lecture:

"*An object is chiral if it cannot be brought into congruence with its mirror image by translation or rotation.*"

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. Chiral molecules are differentiated on the basis of type of chiral entity present in the molecules.

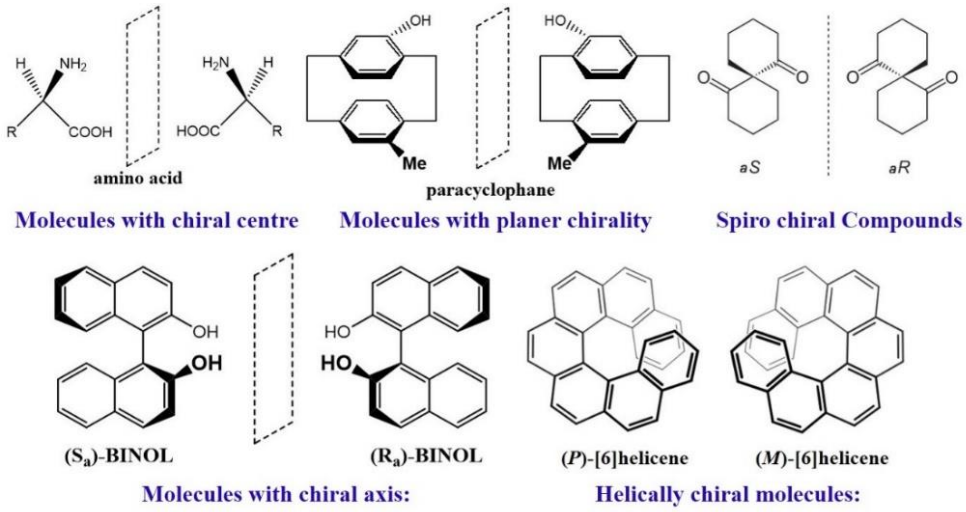


Figure 1.1: Types of chiral molecules

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).

1.1.2 Asymmetric synthesis

Synthesis of chiral molecule in an achiral environment using achiral starting material results in equimolar mixture of both enantiomers. In order to make single enantiomer, some enantioenriched material must be present in the reaction medium. 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. Asymmetric synthesis involves synthesis of chiral molecules using i) Chiral catalyst and ii) Chiral Auxilliary.

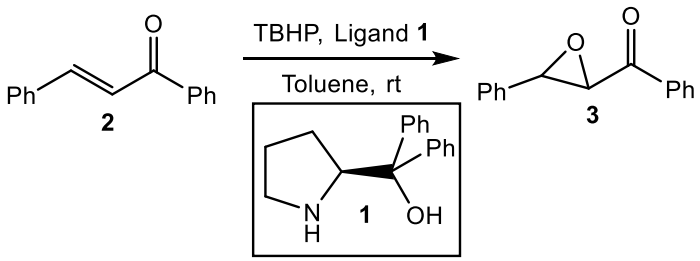
1.1.2.1 Chiral Catalyst:

In the field of asymmetric synthesis, chiral catalysts hold a special appeal due to their ability to produce large quantities of desired enantiomerically pure compounds from simple feedstocks and relatively small quantities of enantio-enriched chiral catalysts. Naturally occurring chiral molecules like amino acid, alkaloids, chiral acids, etc have been frequently used as catalysts for asymmetric transformations. Over the years chiral catalysis has been categorized into: a) Organo-metallic catalysis, b) Organo-catalysis and c) **Biocatalysis.**

Although organo-metallic catalysts have been more commonly employed for the asymmetric synthesis of important chiral molecules over the years, the focus has now been shifted on application of chiral organo-catalysts for asymmetric induction. The major advantages of organo-catalyst over metal catalysts are inertness towards moisture and oxygen, demanding reaction conditions (inert atmospheres, low temperatures, absolute solvents etc.) are usually not required, absence of transition metals make them attractive for synthesis of pharmaceutical products.[4b]

The field of organo-catalysis took off after the pioneering work by List et al when they employed proline as chiral organo-catalyst in asymmetric aldol reaction.[4a] Since then

many organic molecules have been employed as chiral catalysts in asymmetric transformations. In 2005, Lattanzi et al, investigated the role of α,α-Diphenyl-L-prolinol (β-amino alcohol-**1**), as recyclable catalyst, and TBHP as asymmetric oxidant for epoxidation of 2,3-enones.[5]



Scheme 1.1: Application of α,α-diphenyl prolinol as catalyst in asymmetric epoxidation

Biocatalysis:

Another important class of chiral catalysis, biocatalysis, involves the use of natural enzymes for performing organic transformations. The term biocatalysis represents the transformation of a substrate into desired target product through enzyme catalyzed step. The use of biocatalysis possesses certain advantages over conventional catalytic processes.[6]

Biocatalytic processes have high chemo-, regio-, and stereo-selectivities.

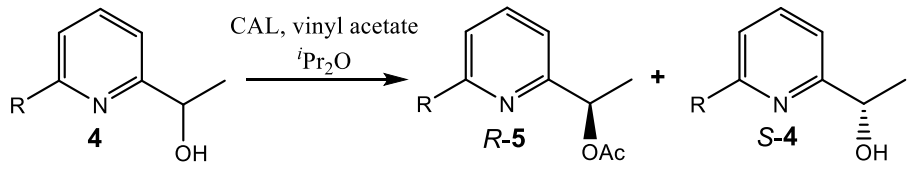
The reactions require mild reaction conditions and thus provide great advantages for successful applications especially in cases where either the substrates or the products of the reaction are chemically labile.[7]

Biocatalysis can be performed in an aqueous environment as well as in solvent mixtures, liquid–liquid two-phase systems, and even in pure organic solvents.

The biocatalytic transformations can be performed without introduction of protecting groups.

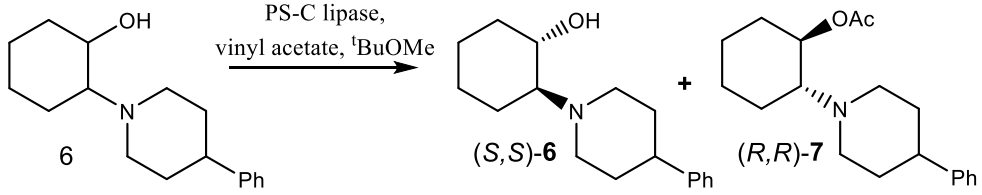
Amongst organic reactions biocatalysis has been commonly utilized for fermentation reactions, biotransformations and enzyme mediated reactions. However, the enzyme mediated acylation reactions are most popularly explored. The role of enzymes in kinetic resolution of alcohols by stereoselective acylation in presence of lipase enzyme has been the center of attraction for synthetic organic chemists.[8] The resolution of racemic 1-(2-pyridyl)ethanols, including the 2,2′-bipyridyl and isoquinolyl derivatives, by lipase-catalyzed asymmetric acetylation with vinyl acetate was reported by Nakamura et al

using *Candida antarctica lipase* (CAL) to give (*R*)-acetate and unreacted (*S*)-alcohol with excellent enantiomeric purities in good yields (Scheme 1.2).[8]



Scheme 1.2: Enzymatic resolution of 1-(2-pyridyl)ethanols using CAL as biocatalyst

The major advantage of enzyme catalyzed reaction is its ability to perform transformations without prior protection of other functional groups. Gotor et al have employed enzymatic resolution protocol for the chiral resolution of various trans-2-(*N*,*N*-dialkylamino)cyclohexanols including Vesamicol, a cyclohexanol based experimental drug used in inhibiting the transport of acetylcholine (Scheme 1.3).[9]



Scheme 1.3: Lipase mediated asymmetric synthesis of Vesamicol

The efficiency of enzyme mediated kinetic resolution is being represented by calculating the inherent enantioselectivity which is termed as enantiomeric ratio (*E*).[10] The equation to calculate the (*E*) value is presented as:

$$E = \{\ln [ee_P\,(1 - ee_S)/(ee_S + ee_P)]\}/\{\ln [ee_P\,(1 + ee_S)\,/\,(ee_S + ee_P)]\}$$

where ee_S = ee of Substrate and ee_P = ee of Product

In general, for any enzymatic kinetic resolution if the (*E*) value is >200 it is considered to be highly enantioselective, while (*E*) value lower than 15 is considered to be practically unacceptable.

1.1.2.2 Chiral Auxiliary:

Other variants of diastereoselective syntheses include the use of chiral auxiliary molecules (these can be either from chiral pool or synthetic). A chiral auxiliary is a chemical compound or unit that is temporarily incorporated into an organic synthesis 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 cleaved from the substrate and is typically recovered for future use. Chiral auxiliary allows enantioselective synthesis via diastereoselective reaction.

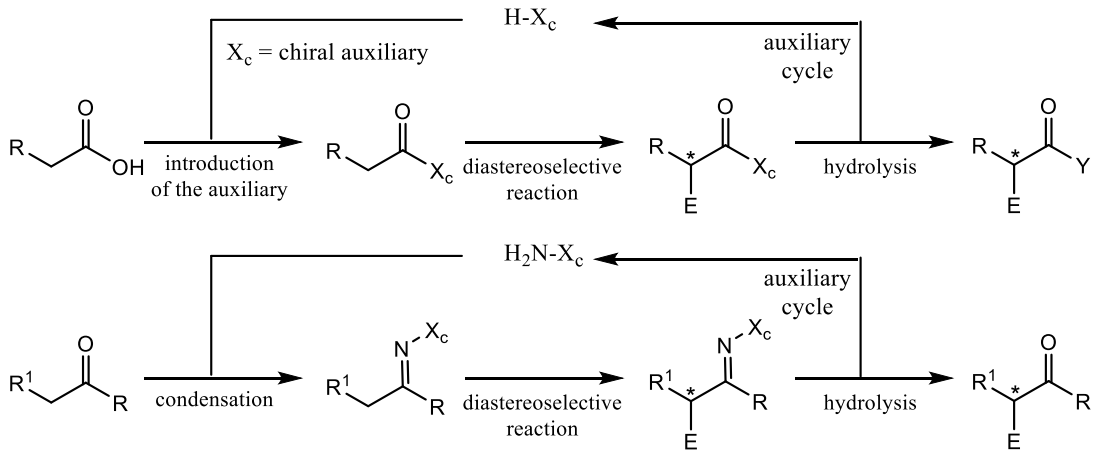


Figure 1.2: Schematic representation of reaction scheme involving the use of chiral auxiliary[11]

Generally the major issues to be addressed in the development of diastereoselective transformations using chiral auxiliary is threefold in nature.[11]

1) Subsequent to facile introduction, the chiral auxiliary must provide a strong predisposition for a highly selective enolization process. 2) It must provide a strong bias for enolate diastereoselectivity in the new bond construction. 3) Its non-destructive and mild cleavage must occur without racemization of desired products.

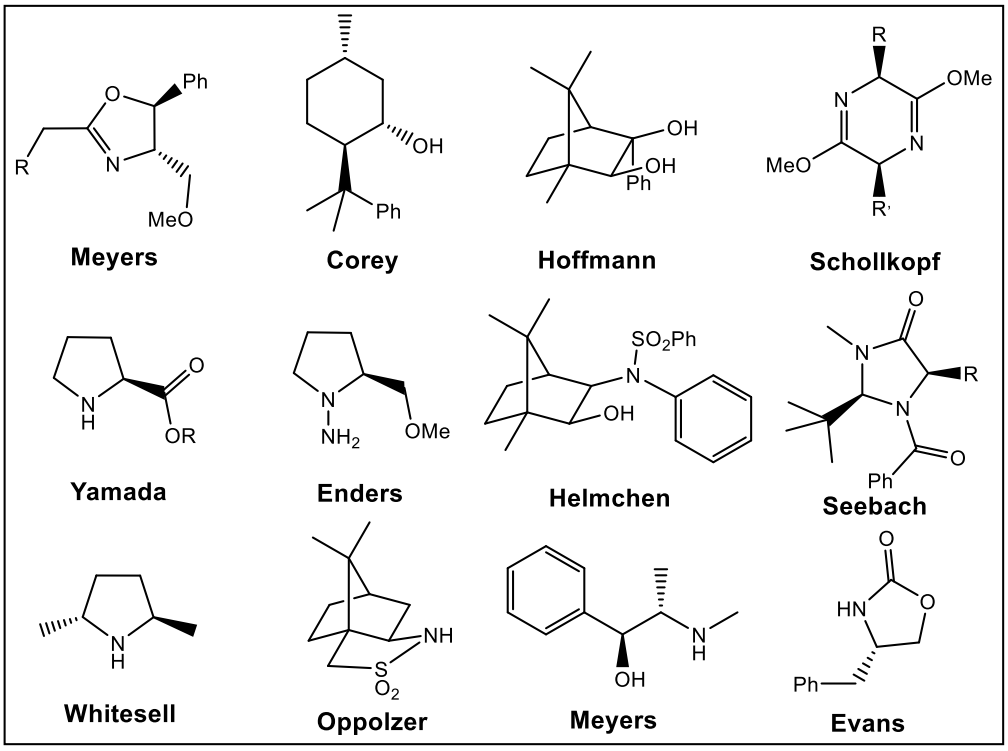
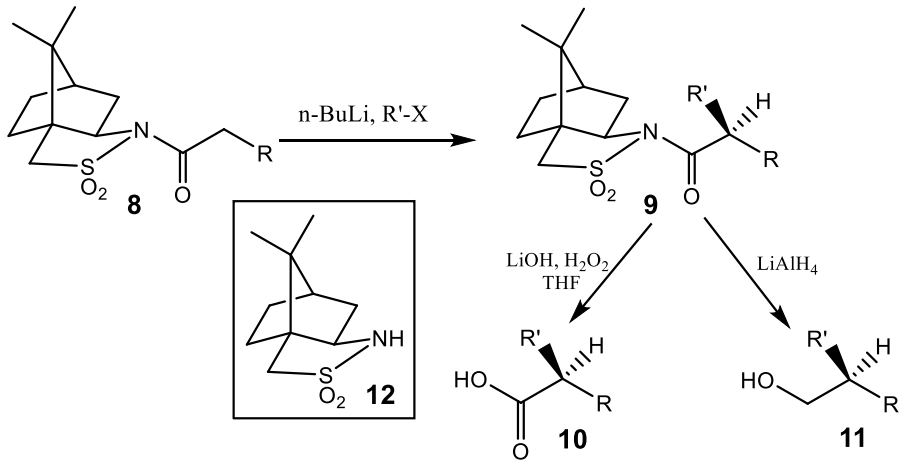


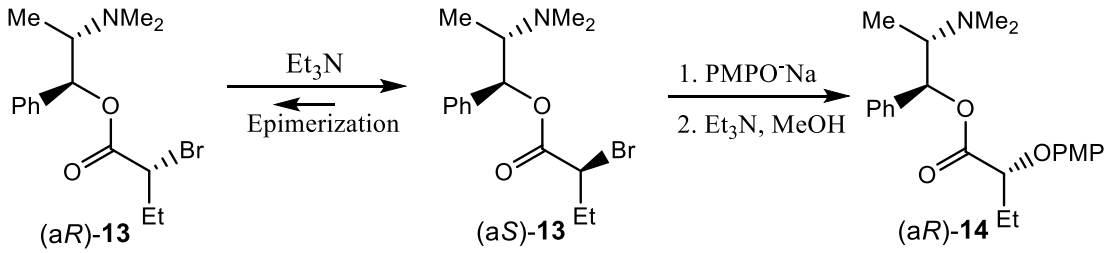
Figure 1.3: Popularly used chiral auxiliary[11]

The asymmetric alkylation using chiral auxiliary camphorsultam was employed by Oppolzer et al in 1989 for successive treatment of acylsultams with n-BuLi and primary alkyl halides, followed by crystallization to yield enantiomerically pure acids (**10**) or alcohols (**11**).[12]



Scheme 1.4: Application of Camphorsultam as chiral auxiliary in asymmetric alkylation

In addition to the use of chiral auxiliaries for asymmetric alkylation reactions, chiral auxiliaries have also been designed and successfully used for asymmetric Diels-Alder reaction, aldol reaction, asymmetric ene reaction, asymmetric reduction, etc.[13] However the use of auxiliaries in dynamic thermodynamic resolution has been rather restricted to very few reports. The use of ephedrine based chiral auxliary in the nucleophilic substitution reactions of α-bromo ester electrophiles via dynamic thermodynamic resolution for asymmetric syntheses of α-hydroxy carboxylic acid derivatives was employed by Park et al.[14]



Scheme 1.5: Epimerization of ephedrine based α-bromo ester followed by nucleophilic substitution.

The determination of optical purity of chiral compounds is of profound significance. The conventional methods used in determination of optical purity of chiral molecules involve chromatography based separation techniques (HPLC or GC) where chiral solid stationary phase are used for separation.[15] These chromatography based determination involves

molecular recognition which is highly substrate specific. Also chromatography based methods are time consuming and often require pre derivatization of substrates for proper analysis. Over the years other techniques such as mass spectrometry,[16] IR & UV spectroscopy,[17] CD & electrophoresis,[18] competitive immunoassay,[19] etc have evolved for accurate determination of the ratio of chiral isomers.

1.1.3.1 Molecular recognition by NMR Spectroscopy:

Amongst these methods, the role of NMR spectroscopy and fluorescence spectroscopy have gained significant interest due to rapid and accurate analysis. The NMR based methods for determination of optical purity have been classified into three types on the basis of reagents used for determination:

1) Chiral Lanthanide Shift Reagent (CLSR)

CLSR based recognition involves complex formation between the analytes and paramagnetic lanthanide reagents for differentiation of NMR signal.[20] Most frequently used CLSR are Eu and Pr-based complexes of camphor derivatives. CLSRs are paramagnetic materials resulting in broadening of NMR signals thus limiting their application in molecular recognition.

2) Chiral Derivatizing Agent (CDA)

Chiral derivatizing agents are basically chiral auxiliaries that bind with the enantiomers of substrate converting them to diastereomers in order to determine the enantiomeric excess by calculating the difference in chemical shift corresponding to enantiomers.[21] However, prior derivatization and purification required for CDA possess a major limitation to its use.

3) Chiral Solvating Agent (CSA)

Chiral Solvating Agents are optically pure compounds which bind in situ to the substrate comprising of mixture of enantiomers through non covalent, intermolecular forces. CSAs are usually chiral compounds which 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 is the source of discrimination in NMR spectroscopy.[22]

CSA provides an added advantage over CDA as prior derivatization is not required. Moreover there is no deracemization of substrates in case of CSA. The concept of CSA got its boost from the pioneering work of Pirkle et al when they used 2,2,2-trifluoro-1-

(9-anthryl)ethanol (TFAE) as CSA for molecular recognition of alcohols and γ-lactones.[23] Over the past few decades considerable work has been done for the development of CSAs based on structural requirements of substrate molecules. Synthesis of new chiral solvating agents has been the focus of extensive investigation to determine the enantiomeric purity and understand the basic mechanism of host–guest complexation, particularly for carboxylic acids, such as chiral amides, amines, ureas and thioureas, BINOL and their derivatives, crown ethers and macrocycles, etc.

1.1.3.2 Amide based Chiral Solvating Agent:

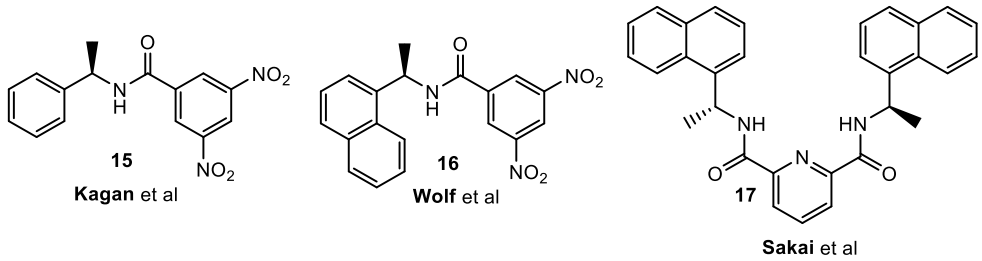


Figure 1.5: Some representative examples of Kagan's type amide based CSAs.[22g,24]

An important class of CSAs have been based on amide type molecules. Since the initial report of amide based CSA by Kagan et al for molecular recognition of chiral sulphoxide derivatives (Figure 1.6), the amide type CSAs have been successfully employed in chiral recognition of amines, amides, sulfoxides, multifunctional *tert*-alcohols, phosphine oxides, etc.[24]

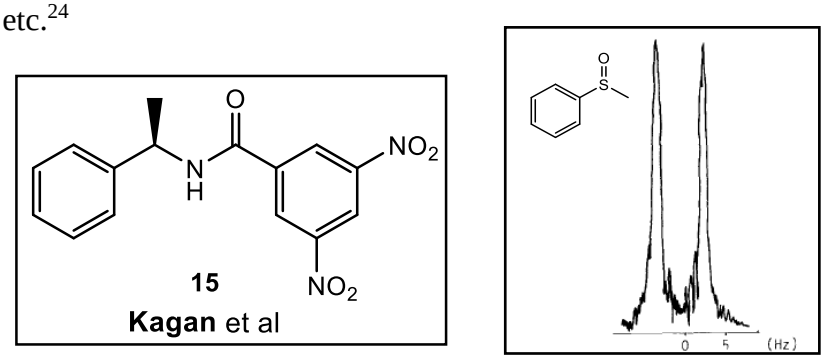


Figure 1.6: Application of Kagan's amide as CSA for sulphoxide

1.1.3.3 Urea and Thiourea based CSAs:

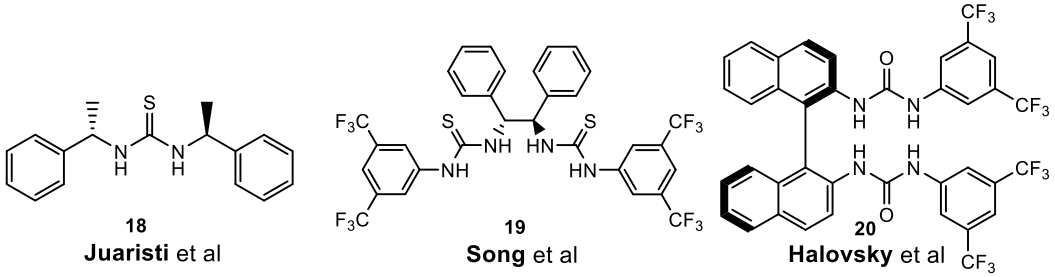


Figure 1.7: Representative examples of Urea and Thiourea derivatives as CSA.[25]

In the recent years many reports have indicated that chiral urea and thiourea derivatives have been efficiently used as organocatalysts in diverse asymmetric reactions due to existence of multiple H-bonding interactions which lead to the development of thioureas as chiral solvating agents for neutral molecules and acid anions. Song et al have successfully explored the chiral bis-thiourea derivative (**19**) as chiral solvating agent for the molecular recognition of carboxylic acids in presence of DMAP as base.[25b]

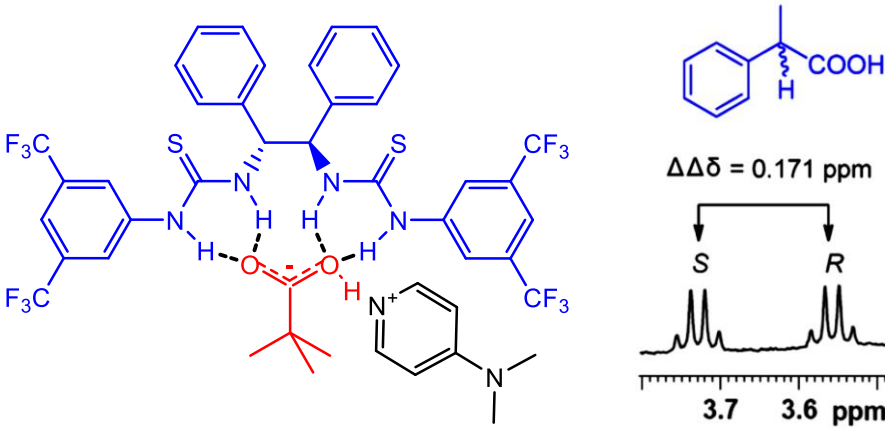


Figure 1.8: Chiral bisthiourea as CSA for molecular recognition of acids.

1.1.3.4 Chiral crown ethers and macrocycles as CSA:

Amongst the realm of CSA, the chiral crown ethers and macrocycles have acquired a very prominent position. Since the initial molecular recognition studies by Lehn et al and Cram et al, chiral crown ethers have been most popularly used for chiral recognition.[26] The chiral cavity of crown ethers is known to bind with the enantiomers of chiral guests. Usually two kinds of interactions with opposite effects on complex formation exist in chiral host-guest systems. These are attractive bonding interactions between macrocyclic hosts and guest enantiomers and a steric repulsive interaction between the groups at the chiral centers of the guests and the macrocyclic ligand. The attractive interaction provides stability to the complex while the latter reduces the stability.

To sum up, *in order to obtain effective enantiomeric recognition, a primary requirement is that chiral macrocyclic receptors form reasonably stable complexes with guest enantiomers so that the repulsive interactions can effectively lessen the stability of the complex of one enantiomer*. An ultimate case is that one enantiomer forms a stable complex with the macrocyclic receptor but the other one does not interact with the receptor at all.[27]

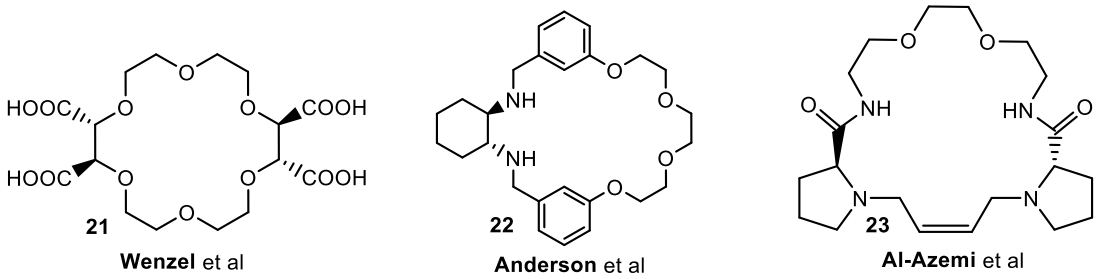


Figure 1.9: Representative examples of chiral crown ethers and macrocyles as CSA[27]

The chiral crown ethers and macrocycles have been conventionally used for enantiodiscrimination of quaternary ammonium salts and amino acids. Chiral amines and amino alcohols are an important part of drug molecules. Many chiral crown ethers have been designed for chiral discrimination of amines and amino alcohols. Wenzel et al have successfully employed (-)-(18-crown-6)-2,3,11,12-tetracarboxylic acid (**21**) as CSA for enantiomeric recognition of pipyridine derivative.[27b]

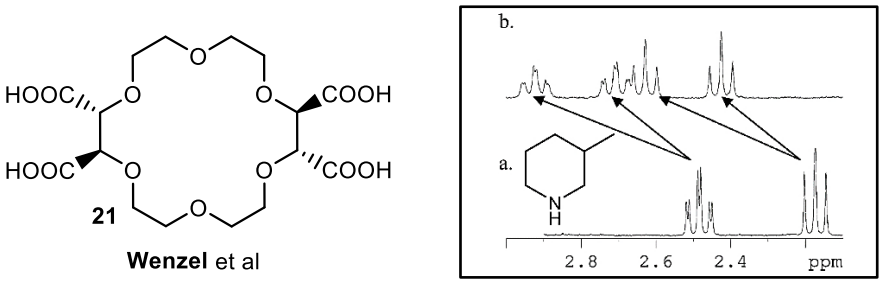


Figure 1.10: Tetracarboxylic acid based crown ether as CSA for chiral pipyridine

In addition to amines, CSAs have been mostl commonly used for enantiomeric recognition of carboxylic acids. Amine based chiral solvating agents are being used for chiral discrimination of carboxylic acids. Anderson et al used chiral macrocycle (**22**), containing *trans*-1,2-diaminocyclohexane and arene-oligo ethylene glycoderived subunit as CSA in enantiodiscrimination of mandelic acid.[27c]

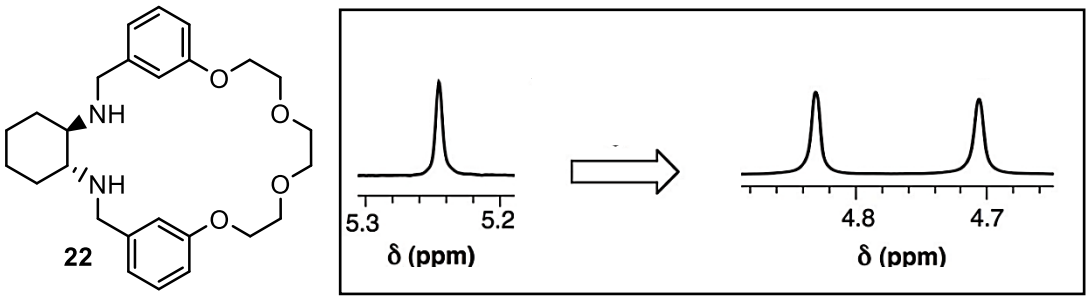


Figure 1.11: Chiral aza-crown ether as CSA for mandelic acid.

1.1.4.1 Molecular recognition by Fluorescence Spectroscopy:

Over the years optical methodologies, especially those based on fluorescence spectroscopic techniques, have drawn substantial interest of researchers, working in molecular recognition, owing to their advantageous features such as simplicity, low cost,

high sensitivity and real-time analysis, and diverse signal output modes. Not only do fluorometric methods enable fast in situ determinations of the enantiomeric compositions of chiral analytes. Fluorescent sensors that are capable of differentiating between the two enantiomers of a chiral compound should provide a real time technique in the rapid chiral assays with many unique advantages.[28] Significant progress has been made in the development of enantioselective sensors.

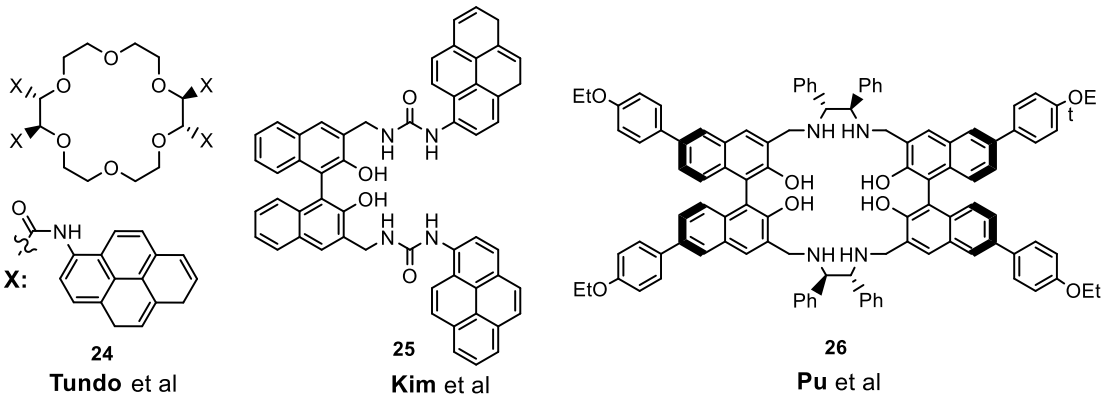


Figure 1.11: Some representative examples of Chiral fluorescent sensors.[29]

Studying the chiral discrimination of organic fluorophores began with the work on their fluorescent responses to chiral amines and amino alcohols. These nitrogen-containing molecules often served as quenchers to reduce the fluorescent intensity of the fluorophores. Both dynamic and static fluorescence quenchings were observed. The dynamic quenching often involved the formation of an exciplex between the amines and the excited fluorophores, and the static quenching might be due to their non-fluorescent ground state hydrogen bonded complexes or the base promoted deprotonation. In case of fluorescent sensors majority of sensors have been designed around BINOL core as it not only provides rigidity but also acts as an efficient fluorophore in chiral recognition of enantiomers. Kim et al have utilized BINOL derived chiral fluorescent host (**25**) for the recognition of amino acids which bears two urea groups and two pyrene groups. The sensor displayed a larger K_a value with D-amino acid derivatives than with L-isomers.[29c]

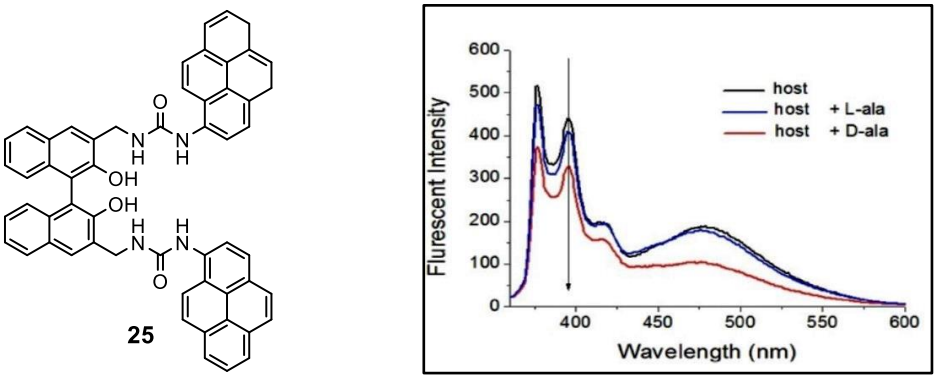


Figure 1.12: Fluorescent Spectra of *D* and *L*-alanine with sensor.

The binaphthyl core of BINOL derivatives has played a vital role in chiral discrimination of amino acids and amino alcohols. The 6,6'-substituted BINOL derived macrocycle synthesized by Pu et al was successfully used for the fluorescent recognition of mandelic acid in methylene chloride solution (Figure 1.13). The fluorescence spectra of (*S*)-**26** in the presence of (*R*)- and (*S*)-mandelic acid exhibits large fluorescence enhancement of the 6,6'-*p*-ethoxyphenyl substituted macrocycle (*S*)-**26** at λ_{short} when treated with mandelic acid. The fluorescence enhancement at λ_{short} was enantioselective with an *ef* of 2.[29b]

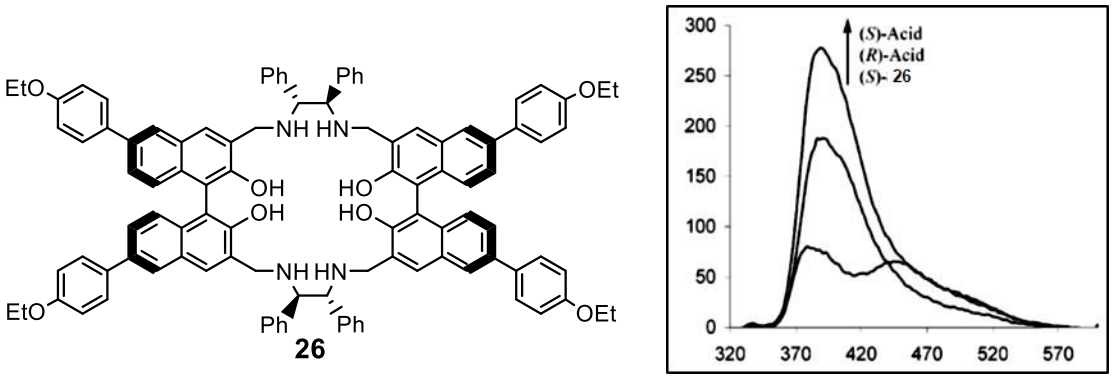


Figure 1.13: Chiral recognition of mandelic acid by fluorescence spectroscopy using macrocycle.

In addition to molecular recognition, fluorescence spectroscopy has also been utilized for accurate determination of enantiomeric purity of chiral substrates. Furthermore, Anzenbacher et al have also developed a method for determination of enantiomeric purity by fluorescence spectroscopy and its validation using statistical methods.[29c]

1.1.5 Aim of the thesis:

The aim of the thesis is to design synthesis of new chiral molecules based on cyclohexanol core and utilize these molecules for asymmetric synthesis and molecular recognition studies. The contents of the thesis are divided into 4 chapters. **Chapter 1** deals with introduction.

Chapter 2 deals with synthesis and applications of novel chiral aza-crown ethers and aza-macrocycles. This involves synthesis of amino alcohols by ring opening of meso cyclohexenoxide with (S)-phenyl-ethyl amine resulting in formation of diastereomeric amino alcohols. These diastereomeric alcohols were then step wise converted to diols which were subsequently converted to chiral aza-crown ethers. These crown ethers were screened as chiral solvating agents for chiral carboxylic acid and phosphoric acids. The

preliminary screening indicated the need of further modification required in the chiral core of chiral aza-crown ethers for improving the molecular recognition process. The other set of diastereomeric crown ethers were synthesized by carefully incorporating aromatic ring in the chiral core of crown ethers. The modified crown ethers were fully characterized and used for enantiomeric discrimination of chiral acid substrates. The results indicated that further rigidity of chiral cavity would be needed for enhanced chiral recognition. Based on these observations, new set of chiral aza-macrocycles have been synthesized and their crystal structure has been solved which indicates interesting aspects about the orientation of phenyl rings of pendent groups. The aza-macrocycles with (*S*,*S*,*S*)-configuration showed partially closed cavity while the other diastereomer with (*R*,*R*,*S*)-configuration exhibited much more accessible cavity. These macrocycles were then employed for molecular recognition of organic phosphoric acids and phosphonic acids. The NMR analysis indicated a clear pattern of match-mismatch effect which was reversed for the latter type of substrates. The chiral recognition of binaphthyl phosphoric acid was also studied by fluorescence spectroscopy utilizing the fluorescent property of binaphthyl phosphoric acid. The fluorescence analysis showed better recognition for the (*R*,*R*,*S*) diastereomer which was in agreement with the NMR data.

Chapter 3 deals with the synthesis, resolution and application of cyclohexanol based chiral auxiliaries. The auxiliaries were synthesized by ring opening of meso cyclohexenoxide with naphthoxides generated in-situ. These cyclohexanol derivatives were then resolved by employing enzymatic kinetic resolution in presence of Steapsin lipase. The absolute configuration of resolved alcohols were determined by converting alcohols to chiral esters by coupling with chiral acid of known optical purity. The single crystal X-ray analysis of chiral esters revealed the absolute configuration of resolved alcohols. These chiral alcohols were then screened as chiral auxiliaries for deracemization of α-halo acid substrates. The chiral alcohols were coupled with racemic acids under standard coupling conditions and their diastereomeric ratios were determined. The mechanism of deracemization has been studied in detail by conducting series of experiments by varying the conditions of experiment. The mechanism of deracemization has been further supported by performing computational studies.

Chapter 4 deals with synthesis and resolution of cyclohexane derived quinolin-yl cyclohexanol and amino alcohol and their applications in chiral discrimination. The quinoline derived alcohol was resolved by enzymatic resolution and its absolute configuration was established by converting it to its ester by coupling with chiralacid of

known chiral purity. The chiral alcohol was analysed by single crystal X-ray analysis which indicated interesting packing which results in formation of helical assemblies assisted with water molecule. The (*R,R*) isomer resulted in *P*-helical assembly while the other enantiomer gave *M*-assembly. The resolved alcohol has been screened as chiral solvating agent for α-substituted carboxylic acids, BINOL derivatives, binaphthyl phosphoric acid and cyclic phosphoric acid derivatives. The fluorescent alcohol has also been employed as chiral fluorescent sensor for chiral recognition of amino acids. In addition to amino acids the sensor was also screened for some dipeptide derivatives with optimum chiral recognition. Furthermore, the practical utility of sensor has also been established by validating the enantiomeric purity of unknown samples. In the 2nd part, β-amino alcohol has been synthesized by epoxide opening of meso cyclohexenoxide by *N*-methyl aniline and the corresponding alcohol was resolved by subjecting it to enzymatic resolution. The resolved amino alcohol was converted to chiral pyridine containing diester which was screened as CSA for chiral acid derivatives.

1.2 References:

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