Chapter 1

Asymmetric Oxidation
1.1 Introduction

Catalysis is a process in which the rate of a reaction is enhanced by a small amount of different substance called catalyst [1]. Like other reagent it actively participate in the reaction to direct the reaction through a relatively lower energy transition state path to increase the reaction rate, but does not undergo any permanent change itself. The term catalysis was coined by Jöns Jakob Berzelius in 1835 [2] to describe reactions that are accelerated by substances that remain unchanged after the reaction. Later on in the 1880s, Wilhelm Ostwald was awarded with the Nobel Prize in Chemistry in 1909 [3] for his investigation on acid and base catalyzed reaction. He found that chemical reactions occur at finite rates and these rates can be used to determine the strengths of acids and bases. Thereafter this field has been studied extensively to develop new catalytic systems and implemented in different field such as pharmaceutical, agrochemicals, fine chemicals, flavour and fragrance etc. of synthetic chemistry to synthesize variety of chiral as well as non-chiral synthetic intermediates or products.

The French physicist Jean Baptiste Biot for the first time reported phenomenon of ‘chirality’ in a molecule in 1815 [4]. However, in 1849 the French chemist and microbiologist Louis Pasteur discovered the concept of molecular chirality by the manual separation of the crystals of left-handed and right-handed tartaric acid (Figure 1.1). His first ever chiral separation laid the foundation for stereochemistry [5].

![Figure 1.1](image)

**Figure 1.1** Crystal structure of the two enantiomers of tartaric acid separated by Louis Pasteur.

In 1874, the basis of molecular chirality was explained by Dutch physical chemist Jacobus Hendricus Van’t Hoff [6] and the French chemist Achille Le Bel [7] simultaneously. They conclude the origin of Pasteur’s observation is the presence of asymmetric carbon, a carbon atom with four different atom or group attached with it, in the tartaric acid and Van’t Hoff proposed tetrahedral geometry for asymmetric carbon atom.
1.2 Chirality: an integral part of life

Most of the building blocks of life are chiral such as amino acids, sugars, nucleic acids, hormones and in nature these exist in only one enantiomeric form, e.g. amino acids are available in the L-form and sugars in the D-form. Therefore, all the receptor or reactive sites in the living organism made up of optically pure molecules having definite geometry in the three dimension space (Figure 1.2), making receptors or reactive sites overall chiral in nature.

**Figure 1.2** The 3D structure of D and L alanine, arrangement of groups in 3D space.

When these sites come in contact with any chiral molecules (having definite geometry in three dimensional space), only one enantiomer of the substrate having complementary geometry can (or may) bind suitably over the other enantiomer. Hence their biological activities found to be different in most of the cases (Figure 1.3). For example, the natural compound Carvone, having two enantiomers, (4S)-(+) -carvone, which has a distinct caraway odor, as compared to (4R)-(−)-carvone which has a characteristically sweet spearmint odor [8] (Figure 1.4). In case of asparagine the absolute configuration of the product determines the taste, (S)-isomer of asparagine is sweet whereas the (R)-isomer is bitter in taste (Figure 1.4).

**Figure 1.3** Graphical presentation of binding of the substrate with the reactive site of enzyme
Figure 1.4 Dependence of odor and taste on the absolute configuration.

Chiral molecules play distinct role not only in food and flavor industries but also in pharmaceutical industry. The real impetus for this demand came after the cause of the ill-famous Thalidomide tragedy, where “wrong “ enantiomers was found to be the cause for genetic malfunction in new-born (Figure 1.5). Since then it was made mandatory by the FDA (and other Drug control authorities world over) that if there is a chiral center in the drug molecule then all the enantiomers should be treated as different compounds and all pharmacological studies should be carried out separately for individual isomer as biological activity of such molecules greatly controlled by the absolute configuration of the drug molecule. This led to the requirement of all isomers in their chirally pure form, hence the need for methodologies to produce them. Besides, the classical resolution of racemates, last two-decades have seen tremendous development in the area of asymmetric synthesis, especially asymmetric catalyst for various organic transformations to synthesize chirally pure products.

Figure 1.5 Influence of chirality on the biological activity.

1.3 Methods to synthesize optically pure molecules

The need of optically pure compounds brings a challenge to the chemist to develop methods to produce chirally pure molecule and can be classified mainly in three categories
(Scheme 1.1), a) Resolution of the racemates, b) The chiral pool synthesis and c) Asymmetric synthesis.

![Scheme 1.1 General routes to synthesize enantiopure compounds.](image)

1.3.1 Resolution of the racemates

The separation of racemic mixture into enantiomers called chiral resolution [9]. After the discovery of chiral resolution by Louis Pasteur this method was developed extensively. Recently it involves crystallization, resolution using resolving agent, chiral chromatographic separation of enantiomers and kinetic resolution. The resolution of racemate is an important tool for the production of optically pure drugs. But the main disadvantage is that only 50% of the desired isomer is obtained and all the compounds are not crystallizable.

1.3.1.1 Resolution by crystallization

Under certain specific condition enantiomers from a racemic mixture are known to crystallize separately hence caused resolution of racemic mixture [10]. Louis Pasteur was the first to conduct chiral resolution when he discovered the concept of optical activity by the manual separation of left-handed and right-handed tartaric acid crystals in 1849. Thereafter, several compounds were successfully resolved, such as methadone and hydrobenzoin. This process is spontaneous and need no external reagent for crystallization. Since all compounds are not crystallisable, so this method is not applicable to resolve all the compounds and sometime it needs several cycle of crystallization to achieve high optical purity, viz. after 15 cycles 97% optical purity for (-)-hydrobenzoin can be obtained from solution of (±)-hydrobenzoin in ethanol.
1.3.1.2  Resolution with resolving agent

In this method racemic mixture is derivatized with optically pure resolving agent forming diastereomeric derivative of two enantiomers, thereafter separated by conventional techniques in physical chemistry and finally by means of chemical reaction diastereomeric derivative is transformed to its original enantiomeric form. For example, the resolution of mandelic acid (Scheme 1.2).

![Scheme 1.2 Resolution of mandelic acid with (S)-phenylethylamine as resolving agent.](image)

Though this method is quite efficient to resolve racemates, but the use of stoichiometric amount of optically pure resolving agent makes this process very expensive, besides this the unavailability of the suitable resolving agent makes it less applicable in large scale resolution.

1.3.1.3 Resolution by chromatography

In chiral column chromatography the stationary phase is chirally modified with a single enantiomer of a chiral compound rather than being achiral as in case of column chromatography. When racemic analyte passed through the column, both enantiomers differ in affinity to the chiral stationary phase and therefore they exit the column at different times, hence cause the separation of racemate. Most commonly used optically pure compounds are cellulose or cyclodextrin derivatives for the preparation of chiral stationary phase [11].

1.3.1.4 Kinetic resolution

The kinetic resolution is a method to differentiate two enantiomers in a racemic mixture on the basis of different reaction rates in chemical reaction with a chiral catalyst or reagent, resulting in an enantioenriched sample of the less reactive enantiomer [12] (Scheme 1.3). In contrast to chiral resolution, kinetic resolution does not rely on different physical properties of diasteremeric products, rather on the reaction rates of the
The enantiomeric excess of the unreacted starting materials increases with the conversion. In an ideal case the 50% of the substrate can be obtained in 100% enantiomeric excess after the conversion of 50% only if one enantiomer does not undergo any reaction in the reaction condition.

Scheme 1.3 General scheme for the kinetic resolution.

1.3.2 *The chiral pool synthesis*

Chiral pool synthesis is a strategy in synthetic organic chemistry to synthesize optically pure product, starting from naturally available starting material referred as chiral pool such as amino acids, sugars etc. [13]. For the synthesis of pharmaceutically important benzodiazepine (Scheme 1.4) the source of chirality in the product comes from the chiral alanine used as chiral pool. This method is highly suitable for the synthesis of exclusively one enantiomer of the product, provided the desired product bears a great resemblance to cheap enantiopure natural products (chiral pool) is available.

Scheme 1.4 Use of alanine as chiral pool for the synthesis of benzodiazepine derivative.
1.3.3 Enantioselective synthesis

Enantioselective synthesis or asymmetric synthesis is defined by IUPAC as: a chemical reaction (or reaction sequence) in which one or more new elements of chirality are formed in a substrate molecule and which produces the stereoisomeric (enantiomeric or diastereoisomeric) products in unequal amounts. This is a key process in the modern chemistry for the synthesis of optically pure products from prochiral starting materials using a) chiral auxiliary, b) bio-catalyst and c) chiral catalyst as shown in (Scheme 1.1).

1.3.3.1 Chiral Auxiliary

Chiral auxiliary is an optically pure organic compound that is incorporated in the initial stage of organic synthesis to bind with the prochiral substrate to control the stereochemical outcome of the synthesis [14, 15] (Scheme 1.5). Thereafter it is cleaved from the chiral product and recovered to reuse. This strategy was introduced by E. J. Corey in 1978 with chiral 8-phenylmenthol and by B. M. Trost in 1980 with chiral mandelic acid. The use of the stoichiometric amount of chiral compound, two additional steps of labeling of substrate with auxiliary and cleavage of auxiliary from the product restricts this process for practical application.

![Scheme 1.5 Use of chiral auxiliary in asymmetric synthesis.](image)

1.3.3.2 Bio-catalysis

Bio catalysis is one of the oldest chemical transformation known to humans, for brewing predates recorded history. The oldest records of brewing are about 6000 years old and refer to the Sumerians. This method use the natural catalyst such as protein, enzymes, and whole cells as catalyst to catalyze asymmetric organic transformations [16, 17]. The significance of enzyme catalyzed reactions are (a) they are highly chemo-, regio- and stereoselective, (b) environment friendly and (c) works well under very mild reaction condition. The main disadvantage is that they are sensitive, highly substrate selective and
unstable at extreme reaction conditions. They generally function well only at physiological pH values at very dilute solutions of the substrate.

1.3.3.3 Chiral Catalysis

In enantioselective synthesis, the use of chiral catalyst is the most interesting and most investigated topic in the last decades. Organic reactions are performed in presence of a catalytic amount of chirally pure compound called catalyst to synthesize enantiopure desired product directly from the prochiral substrates in a single step. Depending on the nature of the catalyst, chiral catalysis can be subdivided in two categories a) Organo catalysis and b) Metal complex catalysis.

Organo catalysts are derivatives of enantiopure molecules usually having acidic or basic functionality within the molecule which can activate substrate, reagent or both and hence initiate or accelerate the reaction rate [18, 19]. The main advantage of organo catalysis over the bio-catalysis is the flexibility in the choice of chirality in the product. Besides this, as the product obtained by this process are free from metal contamination, the study on organo catalysis being increasing day by day for various types of organic transformations.

Metal complex catalyzed methods were found to be more active and atom-efficient method as a single chiral catalyst molecule is able to produce thousands of product molecules [20]. Moreover, this methodology can be conducted in higher concentrations thus gives higher turnover of the product as compared to a reactor size used in bio-catalysis. The metal part of the catalyst is responsible to catalyze the reaction and the chiral steric environment of the ligand control the enantioselectivity in the product. The availability of number of metals with different relativities and properties are great advantages in favor of chiral metal catalyzed asymmetric organic transformations. Several breakthroughs have been achieved in the area of metal complex catalyzed catalysis [21-24]. In 2001 the Nobel Prize in Chemistry was awarded to Dr. William S. Knowles, Professor Ryoji Noyori, and Professor K. Barry Sharpless for their contributions in the development of catalytic asymmetric synthesis [25]. The achievements of these three chemists are of great significance in academic research, industrial synthesis of pharmaceutical products and others biologically active substances [26]. In the initial stage of asymmetric catalysis using chiral metal complexes, most of the preferred metals were belonging from the second row transition metal series such as Pd, Ru, Rh, Ir and Pt etc. Though these metal catalysts were found to be very reactive and enantioselective, the tedious reaction condition, sometimes low stability and sensitivity of the catalysts and catalyst poisoning guided chemists to
search for the alternative metal catalysts to carry out enantioselective organic transformations. The first row transition metal catalyst are extensively being studied in recent years as an alternative of second row transition metals. Besides this more emphasis is being given to minimize metal contamination in the product as well as on the recyclability of the metal catalyst.

1.3.3.4 The cause of enantioinduction in chiral catalysis

In catalysis a catalyst actively participate in the reaction to start or increase the rate of the reaction by guiding the reaction through a lower energy transition state (TS). The reason behind the unequal formation of enantiomers in chiral catalysis is that both enantiomer pass through two separate diastereomeric transition state (Scheme 1.6) in presence of chiral catalyst having different energy. In such condition the enantiomer which pass through less energy transition state forms as a major enantiomer. The energy difference between two diastereomeric transition states is approximately 4 kJ/mol.

![Energy profile diagram for the enantioselective reaction](image)

**Scheme 1.6** Energy profile diagram for the enantioselective reaction

1.4 Oxidative kinetic resolution (OKR) of secondary alcohols

The application of optically pure secondary alcohol as synthetic intermediates in pharmaceutical, agrochemical and fine chemical industries [27] makes it a key process in organic synthesis. Two approaches were extensively studied for the synthesis of optically pure alcohols 1) asymmetric reduction of prochiral ketones and 2) oxidative kinetic resolution of racemic secondary alcohols. Though both bio catalyst [28] and metal catalyst [29] were proved to be efficient for the asymmetric reduction to produce alcohol in high enantiomeric excess. There has been significant interest on oxidative kinetic resolution of secondary alcohols as the achiral product of this reaction (ketone) can easily be converted...
to the racemic starting material by simple hydrogenation (Scheme 1.7), which increase the efficiency of this process. Towards the goal, enzymes have been well explored as catalyst [30-33]. Recently more emphasis has been given for the development of non-enzymatic catalytic protocols using molecular oxygen and in situ generated HOBr as oxidant.

Scheme 1.7 general scheme for the OKR of secondary alcohols

1.4.1 OKR of secondary alcohols using molecular oxygen

The use of air/oxygen as oxidant in oxidative organic transformations are highly desirable in order to make the catalytic process economically favorable, clean, atom efficient and environmentally benign as it produce water as the byproduct. In the field of OKR of secondary alcohols Stoltz et al. and Sigman et al. reported Pd and naturally occurring diamine (--)sparteine (1) as a chiral ligand based catalytic protocol using molecular oxygen as oxidant [34-40]. This system provided excellent enantioselectivity (>99%) of the unreacted alcohol with very high yield (Scheme 1.8). Later on this catalytic protocol was successfully employed for the synthesis of several alkaloids viz. enantioselective syntheses of the alkaloids (--)aurantioclavine, (+)amuresinine, (--)lobeline, and (+)sedamine [41].

Scheme 1.8 In situ generated Pd(--sparteine complex catalyzed OKR of 1-phenylethanol.

Ikariya et al. [42] developed chiral bifunctional amido complex (Figure 1.6) of Ir (2-5), Rh (6) and Ru (7) based oxidative kinetic resolution protocol for the secondary alcohols. The Ir based catalyst 4, 5 and Rh based catalyst 6 provided excellent
enantioselectivity (93-98%) as well as yield for the unreacted 1-phenylethanol at room temperature. But the results were poor in case of Ru catalyst.

**Figure 1.6** Chiral bifunctional amido complex of Ir, Rh, and Ru.

Chiral BINOL derived (NO)Ru salen catalyst (8-10) (**Figure 1.7**) was successfully used by Katsuki et al. [43] for the photo-induced aerobic enantioselective oxidation of racemic secondary alcohols. This study revealed that the addition of β-hydroxy ketone or 1,3-diketone had a significant influence on its activity. For example, the addition of 1,3-bis(p-bromophenyl)propane-1,3-dione 9 improved the relative reaction ratio up to 30 in kinetic resolution of simple racemic secondary alcohols. Under the optimized reaction condition catalyst 8 provided very high enantiomeric excess for the unreacted alcohols.

**Figure 1.7** Chiral BINOL derived (NO)Ru-salen catalyst for the photo-induced aerobic enantioselective oxidation of racemic secondary alcohols.

Besides, the second row transition metals, Yamada et al. [44] reported the use of Co(II) salen and bis(1,3-diketonato)cobalt(II) complexes as catalysts (11-16) using molecular oxygen as oxidant in presence of styrene as the oxygen acceptor (**Figure 1.8**). Initial complex screening experiments showed that Co(II) salen complex (11) does not
catalyzed the reaction at all whereas other bis(1,3-diketonato)cobalt(II) complexes smoothly catalyzed the oxidation of secondary alcohols. Among these complexes, the complex 15 provided the highest enantioselectivity with the $k_{rel}$ value of 8.8 which is found to be less effective compared to the previous reports. The maximum 86% enantioselectivity was obtained with the catalyst 15 with 48% of yield for the chromanol derivatives.

**Figure 1.8** Structure of chiral Co(II) catalyst for the OKR of secondary alcohol.

### 1.4.2 OKR of secondary alcohols using acetone as hydrogen acceptor

Besides, the enantioselective oxidation of secondary alcohols using molecular oxygen as oxidant, chiral Ru-complexes ([Figure 1.9](#)) were used for the oxidation using modified Oppenauer oxidation reaction. Uemura et al. [45] established catalytic OKR protocol with ferrocenyloxazolinylphosphine-ruthenium complexes 17 and 18. This system use acetone as solvent as well as proton acceptor. At the end of reaction acetone reduced to isopropyl alcohol and the substrate oxidized to the corresponding ketone providing very high optical purity for the unreacted secondary alcohols. The catalyst 17 provided excellent enantioselectivity for the different kind of acyclic benzylic secondary alcohols and proved to be the better over the catalyst 18. In case of cyclic alcohols the catalyst seems to be promising for 1-indanol derivatives. However, oxidative kinetic resolution of other cyclic alcohols such as 1,2,3,4-tetrahydro-1-naphthol and 6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol did not proceed so selectively under the same reaction conditions.

**Figure 1.9** Structure of chiral Ferrocenyloxazolinylphosphine-Ruthenium complexes.
1.4.3 OKR of secondary alcohols using PhI(OAc)\(_2\)/PhIO as oxidant

In the past decade, the use of hypervalent iodine in organic synthesis experienced a rapid development [46]. This growing interest is mainly due to the mild and highly selective oxidizing property, combined with their benign environmental character and commercial availability.

1.4.3.1 OKR of secondary alcohols using homogeneous Mn(III) salen complex

Katsuki and co-workers [47] have established new catalytic protocol based on BINOL-derived Mn(III) salen complex 19 and Jacobsen Mn(III) salen complex 20 as catalyst and hypervalent PhIO as an oxidant (Figure 1.10). Both complexes were highly reactive as the reaction complete in 1 h at 10 °C. But, only moderate enantioselectivity were achieved for the OKR of 3,3-dimethylindan-l-ol with the complex 19, whereas the complex 20 was very poor in terms of enantioselectivity.

![Figure 1.10 Structure of chiral Mn(III) salen complexes used for OKR with PhIO as oxidant.](image)

After the Katsuki’s reports on Mn(III) salen catalyzed OKR of secondary alcohols, several protocols have been reported with modified Mn(III) salen catalyst and diacetoxyiodobenzene (PhI(OAc)\(_2\)) as oxidant instead of PhIO. Xia et al. [48] reported the OKR in water as solvent using the complexes 21, 22, 23 and 26. Initially very poor enantioselectivity were obtained using dichloromethane and water as solvent comparatively enantioselectivity were higher in case of water (9% ee) then the dichloromethane (2% ee). Thereafter a tremendous improvement in enantioselectivity was observed when the reaction was carried out in presence of catalytic amount of the phase-transfer catalyst (PTC) tetraethylammonium bromide (84% ee). Under the optimum reaction condition both the catalysts 22 and 26 provided moderate to high enantioselectivity for para substituted 1-phenylethanol derivatives, but substrates with the substitution at the ortho position of the phenyl ring and substrates with bulkier groups in place of methyl group were poorly
resolved. Later on the same group[49] studied in detail on Mn(III) salen catalyzed OKR of secondary alcohols to explore the substituent effect on ligand, influence of counter ion, solvent, additive, role of chiral diamine, on the outcomes of the reaction. The most effective catalytic system was obtained in water-organic solvent biphasic reaction medium at room temperature. This study showed that the additive KBr is essential to oxidize secondary alcohols in an enantioselective manner as well as to increase the rate of the reaction. In absence of KBr they observed very poor conversion and no enantioselectivity for the unreacted alcohol. The substituent at the 5th position of the salen ligand also plays a crucial role for the enantioinduction. Complex 23 with methyl group at the 5th position provided very poor enantioselectivity. This result demonstrate the necessity of the tert butyl group at the 5th position of the salicyldehyde part in the complex. Moreover, the chiral cyclohexanediamine as the chiral part of the complex gave better result compare to the chiral diphenyldiamine. In this study the role of counter ion was examined, but it did not seems to be very specific as the catalyst 21, 24 and 25 with chloride, bromide and acetate counter ion respectively provided comparable enantioselectivity.

**Figure 1.11** Chiral Mn(III) salen complexes used for OKR with PhI(OAc)$_2$ as oxidant.

**1.4.3.2 OKR of secondary alcohols using recyclable homogeneous Mn(III) salen complexes**

With these basic understandings, several modified Mn(III) salen catalytic system have been successfully developed which are not only focused on the enantioselectivity but also on the recyclability of the catalyst. In homogeneous catalysis separation of the reaction mixture, the recovery of the catalyst need large amount of solvent. For the sake of economical and environmental reasons the recovery and reuse of chiral catalysts has become an important area of research [50-52]. Towards this goal, Abdi et al. reported [53, 54] dimeric and polymeric Mn(III) salen complexes (**Figure 1.12**) as homogeneous and
A recyclable catalyst for oxidative kinetic resolution of secondary alcohols. The strategy to recycle the catalyst was to manipulate the solubility of catalyst by increasing the molecular weight, so that the catalyst can be used as homogeneous catalyst for the reaction and after completion of the reaction it could be precipitated out by the addition of hexane to the reaction mixture. This strategy was found to be very successful as polymeric catalysts 28 and dimeric catalyst 31 were recycled 5 times without any loss in the reaction results. In terms of enantioselectivity, the catalysts 28 and 31 resulted in almost same enantioselectivity compare to their monomeric homogeneous catalyst but these catalytic systems also found to be inefficient for the substituent at the ortho position of the 1-phenylethanol and for the substrate having bulky group in place of methyl group of 1-phenylethanol.

![Figure 1.12 Structure of recyclable polymeric and dimeric Mn(III) salen catalyst](image)

Recently Tan and co-workers [55] tune the solubility of the catalyst by bridging two catalyst moiety with N, N-dialkylimidazolium ionic liquid at the C-5 position of the salicylaldehyde moieties (Figure 1.13). All these three catalysts 34, 35 and 36 induced similar enantioselectivity (98% ee) for the OKR of 1-phenylethanol in dichloromethane and water biphasic reaction medium at 20 °C. The catalyst 34 was precipitated out from the
reaction mixture by the addition of hexane and reused for the five successive catalytic runs after filtration.

![Figure 1.13 Structure of the IL-bridged chiral dimeric Mn(III) salen complexes](image)

The most innovative technique for the catalyst recycling is developed by the Yin et al. [56]. This group synthesized chiral Mn(III) salen complexes possessing a thermoregulated phase-transfer function by the introduction of thermoresponsive poly(n-isopropylacrylamide) group to the complex framework by attaching covalently to the salen ligand (37) and by axially grafting into the metal center of the complex (38) (Figure 1.14). The catalyst 37 showed better enantioinduction then the complex 38 under the identical reaction condition. Several para substituted 1-phenylethanol derivatives were resolved with high optical purity (up to 96%) with the catalyst 37. Being thermoresponsive, the catalyst is easily precipitated out from the reaction mixture and recovered for reuse by adjusting the temperature at 42 °C.

![Figure 1.14 Structure of chiral Mn(III) salen complexes possessing a thermoregulated phase-transfer function.](image)

1.4.3.3 **OKR of secondary alcohols using heterogeneous Mn(III) salen complexes**

Another method towards the same direction was simultaneously reported by the Kantam et al. [57]. This group used heterogeneous resin supported sulfonato-Mn(III) salen complex (Figure 1.15) to catalyze OKR of secondary alcohols using PhI(OAc)_2 as oxidant in water as reaction medium. Though the resin supported sulfonato-Mn(III) salen complex 40 was successfully recycled four times and showed similar reactivity as compare to the
homogeneous sulfonato-Mn(III) salen complex 39, however, moderate enantioselectivity was observed with both the catalysts 39 and 40.

Figure 1.15 Structure of the sulfonato-Mn(III) salen complex and resin supported sulfonato-Mn(III) salen complex

Halligudi et al. heterogenized the Xia’s catalytic system by the immobilization of chiral Mn(III) salen complex 21 into ionic liquid modified silica [58] (Scheme 1.9). Here chiral Mn(III) salen complex was immobilized over silica through a thin film of covalently anchored imidazolium ionic liquid. This system provided excellent enantioselectivity for 1-phenylethanol (99% ee), chloro (99% ee) and bromo (99% ee) substituted 1-phenylethanol at the para position of the phenyl ring under the heterogeneous reaction condition. Besides, this it showed similar reactivity as compare to the homogeneous catalyst and reused for four successive catalytic cycles after separating the catalyst by filtration without any significant change in the result.

Scheme 1.9 Scheme for the immobilization of chiral Mn(III) salen complex into ionic liquid modified SBA-15 (21a).
1.4.4 OKR of secondary alcohols using NBS as an oxidant

The enantioselective oxidation of secondary alcohol with Mn(III) salen-PhI(OAc)_2 was studied extensively over the last decade, though the substrate scope for these systems remained very narrow. Most of the catalytic systems were only effective for the 1-phenylethanol and its para substituted derivatives, especially for electron withdrawing substituent at the para position of the aryl moiety of the benzylic alcohols. Recently Sun et al. [59] demonstrated a new catalytic system based on Mn(III) salen complex (Figure 1.16) as catalyst and NBS as oxidant. Surprisingly all catalysts 21, 41-44 were efficient to resolve 1-phenylethanol with high enantiomeric excess (85-99% ee) however, the best result was obtained with the catalyst 41. This new protocol is very efficient (the ee were above 94% for most of the substrate) for the oxidative kinetic resolution of a wide range of secondary alcohols, including ortho-substituted benzylic alcohols.

![Figure 1.16](image)

Figure 1.16 Structure of the catalysts for Mn(III) salen-NBS catalytic protocol

1.5 Importance of optically pure sulfoxide

In the last three decades the optically pure sulfoxides have attracted an enormous interest due to their increasing use as chiral auxiliaries in a wide range of organic transformations, viz. carbon-carbon [60] and carbon-oxygen [61] bond forming reactions, cycloaddition reactions [62], radical addition reactions [63] and asymmetric catalysis [64]. The most important and increasing application of optically pure sulfoxides (Figure 1.17) as synthetic intermediate or as drug in the pharmaceutical industry [65-67]. For example, omeprazole was the highest selling drug in 1997, used for the treatment of acid-induced inflammation and ulcers having the sulfoxide functionality. It was initially marketed in racemic form, but later on the S-form of omeprazole, esomeprazole was launched. Likewise
modafinil and sulindac are sulfoxide drugs used for the treatment of narcolepsy and inflammation respectively.

Figure 1.17 Chiral sulfoxide derived drugs

1.6 General routes for the synthesis of optically pure sulfoxides

Recently the synthesis and use of optically pure sulfoxides is considered to be a developing field in organic synthesis. So far developed techniques for the synthesis of enantiomerically enriched sulfoxides can be classified into two categories: a) chiral auxiliary directed synthesis of sulfoxides and b) catalytic enantioselective oxidation of prochiral sulfides.

1.6.1 Chiral auxiliary directed synthesis of sulfoxides

The first synthetic method for the preparation of optically pure sulfoxides was pioneered by Andersen in 1962 [68, 69], using chiral auxiliary directed asymmetric synthesis, which involves three steps (Scheme 1.10)

- Condensation of toluene sulfinyl chloride with optically pure (-)-menthol to form a mixture of diastereomeric menthyl p-tolylsulfinate.
- Separation of diastereomeric menthyl p-tolylsulfinate by recrystallization.
- Nucleophilic substitution with organomagnesium halide reagent with clean inversion at the sulfur center following Gilman’s report [70].

Later on this synthetic method named as Andersen method and became the preferred approach while preparing enantiopure sulfoxides of known absolute configuration. Thereafter several modifications have been done to improve this methodology [71-73].
1.6.2 Catalytic enantioselective synthesis of sulfoxides

In 1984, the first synthetically efficient enantioselective catalytic systems were reported nearly simultaneously by Kagan [74] and Modena [75] using modified Sharpless catalytic system for epoxidation, which laid the foundation for the chiral metal catalyzed asymmetric sulfoxidation (Scheme 1.11). Both these methods used same titanium isopropoxide, \((R,R)\)-DET as ligand and tert-butyl hydroperoxide as oxidant. But there is a slight difference between two methods, Kagan method use water and Modena method worked without water.

Scheme 1.11 The first catalytic enantioselective sulfoxidation

After this invention, catalytic asymmetric sulfoxidation reaction was studied extensively globally and developed variety of catalytic systems with different metal catalysts using PhIO, TBHP, CHP, UHP, aqueous \(\text{H}_2\text{O}_2\) and molecular oxygen as oxidant, with chiral oxidant as well as with organo catalyst. In metal complex catalyzed asymmetric
sulfoxidation most commonly used and efficient metals are Ti, Fe, V and Mn. Besides these Cu, Al, Mo, Os, Zr and Nb based catalysts were also examined for this reaction.

1.6.2.1 Enantioselective sulfoxidation with Ti catalyst

Following the Kagana and Medona method, in titanium mediated asymmetric sulfoxidation reaction several chiral diols has been used (Figure 1.18) as a substituent of DET to improve the enantioselectivity of the product. Uemura et al. [76] used chiral BINOL, 45 as ligand with Ti(Oi-Pr)₄ and TBHP as oxidant in toluene at -20 °C. Though good yield was obtained but the enantioselectivity remained moderate (73% ee) for methyl (4-methylphenyl) sulfide.

![Figure 1.18 Chiral diol used as ligand for Ti mediated asymmetric sulfoxidation](image)

Imamoto et al. used the chiral hexanediol 46 as a ligand and CHP as oxidant [77]. This method provided sulfoxide with good yield and 95% of enantioselectivity for the same substrate. Unlike the Kagan and Uemura methods, this catalytic system works better in presence of molecular sieves. Rosini and co-workers [78] developed Ti based system using (S,S)-1,2-diphenylethan-1,2-diol 47 as ligand, TBHP as oxidant in carbontetrachloride at 0 °C. 80% enantiomeric excess was obtained for methyl (4-methylphenyl) sulfide with 62% of yield. Recently, the same group has reported [79] excellent enantioselectivity (99% ee) for benzyl phenyl sulfoxide with the diol 48. Bolm et al. [80] have reported the steroid derived BINOL ligand 49 under the same reaction condition as reported by Uemura. This ligand showed high enantioselectivity (92% ee) when compare to BINOL.

Out of the regular track, Bryliakov and Talsi [81] screened a series (Figure 1.19) of in situ generated Ti complex of amino alcohol derived Schiff base ligands 50-55 in Ti-mediated enantioselective sulfoxidation. Though poor enantioselectivity (60% ee) was observed, this system worked with >1% of catalyst loading and the use of environment benign and cheap aqueous hydrogen peroxide as oxidant is a significant advantage of this system.
Besides, amino alcohol derived Schiff base ligands Bryliakov and Talsi [82] also used in situ generated Ti-salen complex (56-64) (Figure 1.20) as well as their pre prepared corresponding Di-µ-oxo Ti salen complex for this reaction with 2 mol% of catalyst using aqueous H₂O₂ as oxidant at RT. This study revealed that pre-prepared complexes are more enantioselective over the in situ generated complexes. Among these complexes, Ti-complexes of 59, 61 and 64 provide moderate enantioselectivity, but they observed the increase in enantioselectivity (up to 97%) with lowering the selectivity when 1.6 fold H₂O₂ was used. This reflects that the subsequent oxidative kinetic resolution of the sulfoxide occurred in presence of excess of H₂O₂. This system worked better for benzyl phenyl sulfide compare to aryl alkyl sulfide.

**Figure 1.20** Structure of salen ligands used for the in situ generation of Ti-complex

### 1.6.2.2 Enantioselective sulfoxidation with Ti-chiral hydroperoxides

In Ti-mediated asymmetric sulfoxidation, Adam et al. [83] established a distinct method by the use of chiral (S)-(−)-1-phenylethyl hydroperoxide 65 for the oxidation as well as for asymmetric induction instead of chiral complex and oxidant (Figure 1.21). Results obtained were modest, with moderate to good enantiopurities (up to 80%), but significant over oxidation of the product took place under the reaction condition lowering the yield of
the product. Thereafter, Scettrì and co-workers [84-86] investigated several chiral hydroperoxides to improve the results in term of yield, enantioselectivity and selectivity of the desired product. The use of hydroperoxide 66 [84] provided better result in terms of yield and enantioselectivity. Later on the same group have used several camphor derived furyl hydroperoxides [87-89] and further improved the results. The (S)-norcamphor derived furyl hydroperoxides 67 gave up to 99% ee with 86 % of yield, which is the best result in this segment so far. In spite of the excellent result, the use of very expensive chiral stoichiometric oxidant is economically not feasible.

![Image](image_url)

**Figure 1.21** Chiral hydroperoxide based oxidants

### 1.6.2.3 *Enantioselective sulfoxidation with V-catalysts*

Vanadium is the second most investigated metal for asymmetric sulfoxidation. After the first report of Fujita in the 1986 [90], Bolm et al. [91] reported efficient enantioselective (85% ee with 69) catalytic system using amino alcohol Schiff base ligand 68 and 69 (Figure 1.22) with VO(acac)$_2$ which were selective towards substrates. The significant advantage of this method is that the reaction was carried out under atmospheric condition using environment benign aqueous H$_2$O$_2$. Inspired by this result, Ellman et al. [92] investigated a series of amino alcohol derived Schiff base ligands having different steric and electronic substituent at the 3$^{rd}$ and 5$^{th}$ position of the salicylaldehyde moiety. Their study conclude that the steric factor at the 5$^{th}$ position does not affect the outcomes of the reaction but electronic factor at 5$^{th}$ position and both steric as well as electronic factor at 3$^{rd}$ position are significant. Finally the ligand 69 was identified as the best for the oxidation of tert-butyl disulfide with 82% ee and 94% conversion were achieved. Maguire et al. [93, 94] used ligands 69-73 (Figure 1.22). The ligand 70 showed highest enantioselectivity. With this ligand 99% ee was obtained for benzyl phenyl sulfide derivatives. At the same time Gao’s [95] system with 74 and 75 having chiral valinol in the ligand gave better enantioselectivity compare to its tertiary leucinol analog.
Berkessel and co-workers [96] used more sterically hindered ligands 76 and 77. The ligand 77 provided better result for thioanisole whereas 77 was better for ortho substituted thioanisole. Encourage by Berkessel’s result, Katsuki et al. [97] established catalytic system based on the ligand 78 and Ahn et al. [98] utilized 79 and 80. All three ligands gave 86-96% ee with good yield (up to 90%) of the product.

Recently Li et al. [99] screened a number of Schiff base ligands (Figure 1.23) with two stereogenic centers in the oxidation of aryl alkyl sulfides. Ligand 90 gave the best results, producing sulfoxide with 81% yield and 99% ee for structurally different kind of substrate. The excellent enantioselectivity is the result of enantioselective oxidation followed by successive oxidative kinetic resolution.

**Figure 1.22** Structure of chiral amino alcohol derived Schiff base ligands

**Figure 1.23** Structure of chiral amino alcohol derived Schiff base ligands with two stereogenic centre
Besides, the amino alcohol derived Schiff base ligands, Zhu et al. [100] have used \textit{in situ} generated vanadium salen catalysts (Figure 1.24) and aqueous \( \text{H}_2\text{O}_2 \) as oxidant for the asymmetric sulfoxidation. Among the ligands (56, 57, 91-95), the ligand 57 was found to be the best which provided 95\% of ee with 78\% yield for methyl phenyl sulfide. Liu et al. [101] synthesized a new chiral NOO-type tridentate ligand 96 bearing a rigid tetrahydroquinoline framework. This system provided 77\% ee with 92\% yield for aryl methyl sulfide using aqueous \( \text{H}_2\text{O}_2 \) as oxidant.

![Figure 1.24 Structure of chiral salen ligands and NOO-type ligand.](image)

\textbf{1.6.2.4 Enantioselective sulfoxidation with Fe catalysts}

The use of environmentally benign and biologically less toxic metal catalyst for asymmetric transformation is of great interest as the toxic metal contamination in the bioactive product is a serious issue to concern. In this context the use of iron complex instead of other toxic metal complexes for asymmetric catalysis is highly desirable. Besides, this iron is very cheap, abundant and commercially available.

In asymmetric sulfoxidation, Groves and Viski [102] first used iron complex of porphyrin ligand 97 using iodosylbenzene (PhIO) as the oxidant (Figure 1.25). Modest result was obtained with this catalyst in terms of enantioselectivity even at 0 \( ^\circ \)C. The best result with this catalyst was 74\% yield with 48\% ee, obtained for methyl ortho-bromophenyl sulfide. Thereafter several Fe-porphyrin-PhIO system have been employed [103-105] but the enantioselectivity remained low to moderate in all cases even at very low temperature.
Figure 1.25 Structure of porphyrin ligand and iron pinene complex

Fontecave and co-workers used both monomeric and dimeric complex of iron with (-) 4,5-pinene-2,2'-bi-pyridine [106]. The highest enantiomeric excess was only 40%, for methyl \textit{para}-bromophenyl sulfide. The advantage of this system was that it works with H$_2$O$_2$ as oxidant.

Bolm et al. for the first time established efficient Fe mediated asymmetric sulfoxidation protocol [107] using aqueous H$_2$O$_2$ as oxidant with amino alcohol derived Schiff base ligand 70, developed earlier for vanadium catalyzed sulfoxidation reaction. Initially they achieved 59% ee with 36% of yield for methyl phenyl sulfide. Later on the same group improve the result [108, 109] significantly by the use of 4-methoxybenzoic acid or the lithium salt of 4-methoxybenzoic acid as additive. In presence of additive the same system oxidized methyl phenyl sulfide with 90% ee and 63% of yield (Scheme 1.12).

Scheme 1.12 Effect of additive on Bolm’s catalytic system
Bryliakov et al. [110] screened a long series of Fe-salen complex for this reaction using PhIO as oxidant and reported moderate result with catalysts 99, 100 and 101 (Scheme 1.13). All three ligands showed similar activity towards the oxidation of benzyl phenyl sulfide.

Scheme 1.13 Structure of active catalysts of Bryliakov’s system

The most efficient Fe-mediated catalytic protocol was reported by Katsuki [111, 112] using the catalyst 102 (Scheme 1.14) and aqueous H$_2$O$_2$ as oxidant in water as solvent. This system is very efficient for both aryl methyl and alkyl methyl sulfides, for sterically different kind of substrate 81-96% ee with high yield 76-99%.

Scheme 1.14 Katsuki’s catalytic system for asymmetric sulfoxidation

Recently, Simonneaux and Maux reported [113] Fe-porphyrin complex 103 to catalyse the oxidation using aqueous H$_2$O$_2$ as oxidant which provided 71-90% enantiomeric excess for various aryl alkyl sulfide, including ortho substituted sulfides. Almost
simultaneously List and Liao employed asymmetric counterion directed catalysis (ACDC) in asymmetric sulfoxidation using an achiral Fe-salen cation and a chiralphosphate counterion 104 as catalyst using PhIO as oxidant [114]. 66-96% enantiomeric with 79-94% yield were obtained with variety of aryl alkyl and di alkyl sulfides. Using this catalytic protocol a potent histone deacetylase inhibitor was synthesized with 98% of optical purity (Figure 1.26).

Figure 1.26 Structure Fe-porphyrin 103 and Fe-salen complex with a chiralphosphate counterion

1.6.2.5 Enantioselective sulfoxidation with Mn catalysts

Chiral Mn(III) salen complexes are one of the most investigated system in asymmetric metal complex catalyzed organic transformation. A wide range of organic reactions have been catalyzed by chiral Mn(III) salen complexes [115] (Figure 1.27). Jacobsen et al. [116] first successfully employed this in asymmetric sulfoxidation reaction with the use of catalyst 105 and aqueous H$_2$O$_2$ as oxidant. Though moderate enantioselectivity (34-68%) were observed for most of the substrates, but the yield (84-94%) was quite high with high level of selectivity for the desired product. This study was encouraging to study asymmetric sulfoxidation with Mn(III) salen complexes. Later on Katsuki et al. [117, 118] studied number of Mn(III) salen complex es for this reaction and found the catalyst 106 is best of all. They found that in some cases the addition of 4-phenylpyridine N-oxide (4-PPNO) as an additive increased the enantioselectivity. With this catalyst they obtained up 94% ee with very good yield of the product 97%, but the disadvantage was the use of PhIO as oxidant instead of aqueous H$_2$O$_2$. 
Fontecave and co-workers reported an in situ generated Mn complex using N4 ligand for oxidation reaction [119]. Both Mn(ClO4)2 and Mn(acac)2, were able to generate complex in situ, however better result was obtained with Mn(acac)2. Over all this system provided low to moderate (31-61% ee) enantioselectivity with moderate yield. Very recently Gao et al. [120] developed most reactive and enantioselective system with porphyrin-inspired in situ generated manganese complex 108 as catalyst and hydrogen peroxide as oxidant. This system completes the reaction within a short time (0.5-1.0 h) and was tested on 25 substrates having different steric as well as electronic properties. The lowest enantioselectivity was in the range of 87% and for most of the substrate it was >99% with very good yield (up to 92%).

1.6.2.6 Recent development in enantioselective sulfoxidation

In 2007, Katsuki et al. have reported chiral Al-salen complex 109 [121] for the enantioselective oxidation of prochiral sulfides using aqueous H2O2 as oxidant at RT. Excellent enantioselectivity (99%) were obtained for ortho, meta and para substituted methyl phenyl sulfides with very high yield (81-91%) (Figure 1.28). Later on the same group extended their study with Al-salen mediated sulfoxidation for cyclic dithioacetals [122, 123], excellent enantioselectivity and yield were achieved with the same catalyst 109. For most of the substrates, the ee value was 99 or >99% and yield was in the range of 72-98%. So far in this reaction, Cu complexes were found to be very poor in terms of yield and enantioselectivity. Magurie et al. [124] developed efficient Cu mediated catalytic system
with *in situ* generated complex using amino alcohol derived Schiff base ligand 110 and 111. These catalysts oxidized variety of alkyl phenyl sulfides and benzyl phenyl sulfides with 46-84% ee and 47-91% yield.

In asymmetric sulfoxidation metal mediated catalytic systems provided high activity and were most investigated. List et al. [125] introduced chiral Bronsted acid as catalyst for this reaction using aqueous H\(_2\)O\(_2\) as oxidant at RT. Only 2 mol% of the catalyst smoothly catalyzed the reaction in cyclohexane as solvent. This organo catalyst provided 90-98% of enantiomeric excess for number of aryl alkyl sulfides with excellent yield (89-99%). The synthetic value of this method was demonstrated by the asymmetric synthesis of NSAID (R)-sulindac with 98% of optical purity.

![Diagram](image)

**Figure 1.28** Recently developed efficient catalytic systems

### 1.7 Summary of the work done in the present thesis

**Chapter: 2**

*Macrocyclic Mn(III) salen complexes as recyclable catalyst for oxidative kinetic resolution of secondary alcohols*

This chapter describe the synthesis of new macrocyclic chiral Mn(III) salen complexes (1-8) (Figure 1.29) having non-chiral as well as chiral linker at 3,3’ positions of salicylaldehyde and keeping tert-butyl group at the 5\(^{th}\) position of the salicylaldehyde moiety. After the characterization of the complexes by various physico-chemical methods, these complexes were used as catalysts for oxidative kinetic resolution (OKR) of various secondary alcohols (Scheme 1.15) with diacetoxyiodobenzene (PhI(OAc)\(_2\)) and \(N\)-
bromosuccinimide (NBS) as co oxidant, in biphasic dichloromethane : water solvent mixture together with three previously reported catalysts. Good to excellent enantioselectivities (up to 99.5% ee) were achieved with catalyst 2 for several secondary alcohols having different steric environment. In general with catalyst 2, NBS as a co-oxidant showed better enantioselectivity than PhI(OAc)$_2$ in OKR. The catalyst 2 is highly stable in the oxidative condition and was easily retrieved from the reaction mixture by the addition of hexane and recycled seven times both with NBS and PhI(OAc)$_2$ as co-oxidants without losing its performance. Based on the experimental results and spectral studies a mechanism for OKR of racemic 1-phenylethanol has been proposed where ($R$,$R$)-Mn-salen preferably binds with ($S$)-1-phenylethanol to give ($R$)-1-phenylethanol in excess at the end of the reaction.

**Figure 1.29** Structure of the chiral Mn(III) salen complexes used for the OKR of secondary alcohols.

**Scheme 1.15** OKR of racemic secondary alcohols with catalyst 2.
Chapter 3

Titanium complexes of chiral amino alcohol derived Schiff bases as efficient catalysts in asymmetric oxidation of prochiral sulfides with hydrogen peroxide as an oxidant

In this chapter several chiral Schiff base ligands 9a-9i, 10 and 11 were synthesized by the condensation of (1S,2R)/(1R,2S)-2-amino-1,2-diphenylethanol with different salicylaldehyde derivatives (Figure 1.30) having different steric and electronic features. Thereafter their corresponding Ti complexes were generated in situ (Scheme 1.16) by treating ligands with Ti(Oi-Pr)$_4$ under inert atmosphere to catalyzed the asymmetric sulfoxidation (Scheme 1.17) using cheap and environmentally benign oxidant H$_2$O$_2$ at 0 °C.

![Figure 1.30](image1.png)

**Figure 1.30** Structure of the chiral Schiff base ligands 5'-7'.

![Scheme 1.16](image2.png)

**Scheme 1.16** Expected structure of the in situ generated Ti-complex.

Prochiral sulfides were converted to respective chiral sulfoxides efficiently (conversion, 93%; up to ee, 98%) with this system in 10 h at 0 °C. This study demonstrated a significant role of steric influence of the substituent attached on both aryl and alkyl moiety on the enantioselectivity. Based on the kinetic study in combination with UV-vis. spectral analysis of the reaction a catalytic cycle was proposed for the sulfoxidation reaction (Scheme 1.17).
Scheme 1.17 Catalytic asymmetric sulfoxidation of prochiral sulfides.

Chapter: 4

In-situ generated chiral iron complex as efficient catalyst for enantioselective sulfoxidation using aqueous H$_2$O$_2$ as an oxidant

This chapter describes the development of catalytic protocol for the enantioselective sulfide oxidation based on the most desired combination of chiral iron complex (in situ generated) as catalyst using environment benign aqueous H$_2$O$_2$ as a terminal oxidant. Towards this goal a series of ONONO donor ligands (8'-11') with different chiral amino alcohols were synthesized (Scheme 1.18) by the condensation of commercially available bis-aldehyde (a) and different chiral amino alcohols (b) and were characterized by standard analytical and spectroscopic techniques. Thereafter their iron complexes were synthesized in situ to catalyze the asymmetric oxidation of prochiral sulfide using aqueous H$_2$O$_2$ as a terminal oxidant. The complex generated from 8' was found to be very efficient catalyst for the enantioselective oxidation of methyl phenyl sulfide. During the optimization process the electron donating benzoic acid derivative or its Na salt as additive was found to be beneficial to improve both conversion and enantioselectivity. Finally the applicability of this catalyst was tested on different aryl alkyl sulfides (Scheme 1.19). This catalyst provided good to excellent enantioselectivity (75 to 96% ee) with good conversion and excellent chemo selectivity (up to 99%) for most of the substrates.
Scheme 1.18 Synthesis and structure of chiral ligands.

Scheme 1.19 Catalytic asymmetric sulfoxidation of prochiral sulfides.

Chapter 5

In situ generated dimeric titanium complex catalyzed enantioselective oxidation of thioethers using aqueous hydrogen peroxide as terminal oxidant

This chapter presents the synthesis of a series of chiral dimeric amino alcohol derived Schiff base ligands 12'-16' (Scheme 1.20) for the development of dimeric titanium complex mediated catalytic protocol for the enantioselective oxidation of thioethers using aqueous hydrogen peroxide as an oxidant. All the dimeric titanium complexes were generated in situ by the interaction of Ti(Oi-Pr)_4 with the ligands (Figure 1.31) under nitrogen atmosphere at room temperature. Based on our previous study with monomeric titanium complex for the same reaction, here we have developed more efficient catalytic protocol in terms of activity and enantioselectivity using ligand 12' and methanol as an additive. To ensure whether both reactive sites of the dimeric catalyst working independently or having cooperative effect, we have carried out the nonlinearity study. This
improved catalytic system showed high enantioselectivity for the various types of aryl alkyl sulfide (up to 98.5% ee) with good yield and selectivity for the desired product.

**Scheme 1.20** General scheme for the synthesis of chiral dimeric amino alcohol derived Schiff base ligands.

**Figure 1.31** Structure of dimeric amino alcohol derived Schiff base ligands.
1.8 References


Chapter 1


