2.1 Introduction

A chiral molecule is a type of molecule that lacks an internal plane of symmetry and has a non superimposable mirror image. The feature that is most often the cause of chirality in molecules is the presence of an asymmetric carbon atom. Asymmetry in molecules is very important to the biological activity of the molecule. Because almost all molecules in an organism, such as occur in cell membranes, enzymes, receptors, and nucleic acids are asymmetric, they interact differently with different enantiomers. Thus the enantiomers of limonene, both formed naturally, smells differently- one of the enantiomers (S)-limonene smells of lemon, while (R)-limonene, the opposite enantiomer, smells of oranges (Fig. 1).

![Fig. 1](image-url)
We distinguish between these enantiomers because our nasal receptors are also made of chiral molecules. Insects use chiral chemical messengers (pheromones) as sex attractants and chemists have discovered that one of the enantiomers of the insect pheromone, olean, attracts male fruit flies, while its mirror image operates on the female of the species.

2.2 Asymmetric Synthesis

Asymmetric synthesis is one of the most challenging but rapidly evolving areas of modern chemistry. The efficient and enantioselective synthesis of complex chiral organic molecules, such as those demanded by pharmaceutical industry, remains one of the most important objectives in all of chemistry, and one of the most problematic.

The two enantiomers of an asymmetric molecule have identical physical properties, except that they rotate plane-polarized light in opposite directions. The ability to rotate plane-polarized light (referred to as optical activity) is a property that only asymmetric molecules possess. One pure enantiomer will rotate the plane of polarization in one direction, and the opposite enantiomer will rotate the plane of polarization the same number of degrees but in the opposite direction. By knowing the specific rotation of a pure enantiomer, it is possible to calculate the relative amounts of each enantiomer (the so called optical purity) in any unequal mixture.

Another distinguishing property of two enantiomers is that each will react with a single enantiomer of another chiral molecule at a different rate. This process is related to the existance of diastereomers, which are stereo isomers that are not enantiomers. Diastereomers can occur in many forms. One common manifestation is the case where a molecule possesses two (or more) stereogenic carbon centres. Diastereomers, unlike enantiomers, possess
different physical and chemical properties; they have different free energies while enantiomers are identical in energy. Therefore if a reaction is designed so that it passes through two possible pathways, each involving transition states which are diastereomeric, to produce two possible stereoisomers of the product, then the pathway which involves the lower-energy transition state will proceed faster; thus one stereoisomer of the product will predominate in the mixture. The greater the difference between the energies of the transition states, the greater the predominance of one product stereoisomer. This is the basis of asymmetric synthesis.

Asymmetric synthesis originated in 1800s when Emil Fischer first reacted L-arabinose with hydrogen cyanide to obtain two optically active products, and a vast amount of research has since been directed towards providing many elegant methods for the introduction of chiral centres into organic molecules. These efforts have culminated in the Nobel Prize in Chemistry being awarded to Ryoji No-yori, William S. Knowles and K. Barry Sharpless for their work in asymmetric reductions and oxidations, as well as in realizing countless beautiful total syntheses of challenging natural products.

A common strategy to achieve asymmetric synthesis is to place a chiral centre in proximity to the location where the new stereogenic centre is to be introduced when the reaction proceeds, the configurations of the new stereogenic centres being formed are influenced by the chirality of the chiral reactant; the chiral reactant “induces” chirality at the newly formed stereogenic centres.

In some case, a chiral solvent or a chiral catalyst is used to induce chirality. In all case, the existing chiral entity in the reaction (reactant or solvent or catalyst) is involved in the transition state, resulting in diastereomeric states of which the lower-energy one is formed.
Another strategy for synthesizing predominantly one enantiomer of a product is to react a racemic mixture of a starting material with a chiral reagent or catalyst that reacts faster with one of the enantiomers of the starting material than the other so that one enantiomer is consumed and the other not. A kinetic resolution strategy for asymmetric synthesis is not as desirable as an asymmetric reaction strategy, because half of the starting material is left behind as the unwanted stereoisomer.

2.3 Asymmetric dihydroxylation of olefins

The cis hydroxylation of olefins first reported early last century is one of the most useful oxidation reactions. The original dihydroxylation used stoichiometric amounts of osmium tetroxide, which is expensive, volatile and toxic, with the result that even small scale reactions were inconvenient. Methods for the conversion of olefins to diols with only catalytic amounts of osmium tetroxide and stoichiometric co oxidant have been known almost as long as the reaction itself. A useful stoichiometric co oxidant is N-methyl morpholine N-oxide (NMO).

2.3.1 Catalytic Asymmetric Dihydroxylation

K. Barry Sharpless and coworkers\cite{141} have discovered and developed a catalytic system in which 1, 2-diols are produced in high enantiomeric excess. The reagent is made from potassium osmate mixed with potassium ferricyanide, an oxidant that generates OsO₄ in situ and a dimeric ligand. The latter is obtained by coupling a linear molecule with a chiral amine made from the optically active cinchona alkaloids, quinine and quinidine. The reagents, which are commercially available, are termed AD-mix α and AD-mix β. AD stands for asymmetric dihydroxylation, and the α and β indicates which face of the double bond undergoes addition under prescribed conditions.
Two phthalazine derivatives\textsuperscript{141}, (DHQD)\textsubscript{2}PHAL (45) and (DHQ)\textsubscript{2}PHAL (46) have been used in conjunction with potassium osmate that has resulted in the two commercial catalysts AD- mix $\beta$ (using 45) and AD- mix $\alpha$ (using 46). The abbreviations shown here refer to the reagents used to make each catalyst.

Catalyst 45 is prepared from dihydroquinidine (DHQD) and 1,4- dichloro phthalazine (PHAL). Similarly, 46 is prepared from dihydroquinine (DHQ) and (PHAL). The actual oxidizing medium labeled AD-mix $\alpha$ or $\beta$ uses 46 or 45, respectively, mixed with potassium osmate [K\textsubscript{2}OsO\textsubscript{2} (OH)\textsubscript{4}], powdered K\textsubscript{3}Fe(CN)\textsubscript{6}, and powdered K\textsubscript{2}CO\textsubscript{3} in an aqueous solvent mixture. The solvent that is normally used comprises a 1:1 mixture of tert- butyl alcohol and water, and, for all non- terminal alkenes, methane sulfonamide is also added.
The process is quite general for most alkenes, and simply using the other reagent switches the stereochemical outcome of the transformation. The optical yields are not identical, however, because (DHQ)$_2$ PHAL and (DHQD)$_2$PHAL are not enantiomers but rather diastereomers. Terminal alkenes do not react as enantioselectively as di- and trisubstituted alkenes do, and cis- disubstituted olefins are hydroxylated less selectively than trans-compounds.

The osmium- catalyzed dihydroxylation reaction has been the centre of extensive mechanistic investigations and two different mechanisms have been suggested. Boseken and Criegee originally proposed a concerted (3+2) pathway$^{142}$ (scheme 25, path A), while Sharpless and coworkers suggested a stepwise reaction$^{143}$ which is initiated by a (2+2)- like addition of the olefin across an Os=O bond (path B), followed by the rearrangement of the resulting osmaoxetane intermediate to the glycolate product.

![Scheme 25](image-url)
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The recent observation of a nonlinear Eyring relationship between ee and temperature is inconsistent with Criegee’s one-step (3+2) mechanism, but it can be explained by a reaction pathway with at least two selectivity determining steps which are weighted differently according to temperature owing to their different activation parameters, $\Delta H^\ddagger$ and $\Delta S^\ddagger$. Hence this observation suggests that the stepwise (2+2)-like mechanism is operative.

The chirality of the cinchona alkaloid is important since it provides the facial selectivity for the complexation of the alkene as well as orientational control via the steric interactions. Sharpless introduced a model shown in figure (1)\textsuperscript{141}, to predict the enantioselectivities of Ad-mix $\alpha$ and AD-mix $\beta$.

Top ($\beta$)- attack

Bottom ($\alpha$)- attack

**Figure (1)**

With $R_L$, $R_M$ and $R_S$ substituents of the alkene arranged as shown, the AD- mix $\beta$ catalyst gives dihydroxylation from the top, whereas the AD- mix $\alpha$ catalyst gives dihydroxylation from the bottom as shown.

Recently, a molecular mechanics model for explaining the facial selectivity and rate trends has been developed based on experimental
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This model assumes that the reaction proceeds through a stepwise (2+2)-like pathway (cf. scheme 25, path B), involving an osmaoxetane as intermediate, since this is the mechanism which fits the experimental observations best. The molecular mechanics model suggests that the enantiofacial selectivity is governed mainly by two factors: stabilizing stacking interaction between one of the substituents \( R'' \) on the oxetane and the OR substituent on C9 of the ligand, and destabilizing repulsive interactions between another oxetane substituent (a hydrogen) and H9 of the ligand. Those effects are depicted in structures 47 and 48.

47 and 48 are diastereomers whose only essential difference is that the carbon and oxygen atoms connected to osmium metalloxetane have been interchanged. Both 47 and 48 are in rotameric forms which allow engagement of the attractive interaction between \( R'' \) and C9 of OR substituent, leading to overall enhancement of reaction rate in each case. However, partaking of these attractive interactions comes at a greater cost for 48 than for 47 because of an attendant repulsive interaction between the ligand’s C9 hydrogen and the
proximate oxetane substituent. For 47 this repulsion is minimal since the C9 hydrogen is juxtaposed with the oxetane oxygen. But due to the aforementioned oxetane “interchange”, relating structures 47 and 48, the C9 hydrogen in 48 experiences a bad repulsive interaction with oxetane hydrogen. This model provides a simple rationale for the AD’s face selectivity. If it is correct, then intriguingly the AD is primarily dependent on a noncovalent attractive interaction for its high selectivity. The role of attractive interaction is to favor a transition state arrangement where a repulsive steric effect presents a substantial problem for one diastereomer 48 but not for the other 47. In this scenario, the AD’s enantioselectivity arises from the interplay of two simple effects, attraction and repulsion. Primacy is assigned to the attractive effect since it ordains the decisive role played by the repulsive interaction.

2.3.2 Immobilization of Osmium Catalysts for Asymmetric Dihydroxylation of Olefins

Osmium-catalyzed asymmetric dihydroxylation provides powerful synthetic routes to optically active 1,2-diols from olefins with high enantioselectivity. In spite of the significant advances in this transformation, high toxicity and volatility of the osmium components as well as possible contaminations of osmium species in the products have been obstacles for industrial applications. In order to address this issue, many efforts have been devoted to immobilization of the osmium catalyst. Several promising methods for immobilization of the osmium component have recently been reported.

2.3.2.1 Microencapsulation

In 1998, S. Nagayama and co-workers have reported the microencapsulation of osmium tetroxide\textsuperscript{145}. Microcapsules have been used for coating and isolating substances until their activity is needed, and their
applications in medicine and pharmacy have been extensively studied\textsuperscript{146}. This microencapsulation technique was applied as a method for immobilization of catalysts onto polymers. That is, catalysts would be physically enveloped by thin films of polymers, and at the same time immobilized by interaction between π electrons of the benzene rings of the polystyrene, which is used as a polymer backbone, and vacant orbitals of the catalysts (metal compounds).

Microcapsules including the osmium component were prepared by addition of methanol to a solution of linear polystyrene and osmium tetroxide in cyclohexane\textsuperscript{147}. This poly styrene-microencapsulated (PS-MC) Os catalyst was found to promote the non-enatioselective dihydroxylation of various simple alkenes with N-methyl morpholine N-oxide (NMO) as the co-oxidant in H$_2$O/ acetone/CH$_3$CN (1:1:1). Although attempts to utilize PS-MC Os for asymmetric dihydroxylation were unsatisfactory, the use of acrylonitrile-butadiene-polystyrene (ABS) polymer was found to be effective\textsuperscript{148}. ABS-MC Os was prepared by addition of methanol to a solution of ABS polymer and osmium tetroxide in THF. The catalyst showed a good catalytic performance with NMO as a co-oxidant.

The use of K$_3$Fe(CN)$_6$ as a co-oxidant was of particular interest, since NMO requires slow addition of the substrate to prevent the second catalytic cycle leading to a low enantioselectivity\textsuperscript{149}. Under the conditions with K$_3$Fe(CN)$_6$ in t- BuOH/H$_2$O (1:1), ABS-MC Os showed good catalytic activity and was reused three times without loss of yield and selectivity. On the other hand, polystyrene (PS) or poly (acrylonitrile-co-styrene) (AS) supported MC Os showed almost no catalytic activity under these conditions. Swollen-resin magic angle spinning (SR-MAS) $^1$H NMR analysis\textsuperscript{150} of ABS-MC Os indicated that the olefin moiety derived from butadiene in the ABS polymer was oxidized by osmium to form diol units. It was speculated that the diol
moiety serves as a hydrophilic part to realize effective contact of osmium species with the co-oxidant under the two-phase conditions. The search for a more effective design of the hydrophilic moiety led to the finding that poly-[4-(phenoxy ethoxy methyl) styrene- co- styrene] (PEM) was effective as the polymer support. The PEM-MC Os system was applied to several olefins and, the desired diols were obtained in good yields with high enantiomeric excess. PEM-MC Os is recovered by simple filtration, and reused.

The asymmetric dihydroxylation using PEM-MC Os was also found to proceed in water as the sole solvent when Triton X-405, a non-ionic surfactant, was used. No controlled addition of the co-oxidant and the base was required in this case.

It was further revealed that cross linked polystyrene (PS resin, cross linked by 1 mol% 1,4- divinyl benzene) could be used as the polymer support. PS resin- MC Os showed a similar activity to PEM-MC Os and worked in water in the presence of Triton X-405 with successful recovery and reuse for five times.

2.3.2.2 Immobilization by ionic interaction

In 2001, Choudary and co-workers reported an ion- exchange technique for immobilization of an osmium catalyst. They employed layered double hydroxide (LDH) with the composition Mg_{1-x}Al_{x}(OH)_{2}(Cl)_x·Z H_2O and quaternary ammonium salts bound to a polymer resin or a silica gel as the polymer support (here x=0.25). K_2OsO_4 as an aqueous solution was introduced to these ionic supports by an ion- exchange technique to generate LDH-Os, Resin-Os, and SiO_2- Os, respectively (Figure 2).
These immobilized catalysts were successfully applied to asymmetric dihydroxylation using NMO, K₃ Fe (CN)₆ and even O₂ co-oxidants. LDH- Os could be reused several times with NMO co-oxidant, but rapid deactivation during recycle stages was observed when K₃Fe(CN)₆/ K₂CO₃ and O₂/ phosphate co-oxidants were used, probably due to ion- exchange by co-existing anions. On the other hand, resin- Os and SiO₂- Os showed superior reusability with all co-oxidant systems. The difference between these anion-exchanged materials probably arises from the hydrophobic nature of the supports: LDH (hydrophilic), and resin (highly hydrophobic). Resin- Os was reused five times with consistent activity and enantioselectivity.

The LDH- Os was recovered quantitatively by simple filtration, and the chiral ligand was also recovered by simple acid- base extraction. The recovered catalyst along with the replenished chiral ligand was reused, and consistent activity was noticed even after the fifth cycle. Thus the LDH- Os catalyst is superior in terms of activity, enantioselectivity and scope of the reaction on comparison with that of Kobayashi catalyst (micro encapsulated osmium tetroxide).
2.3.2.3 Osmium catalyzed asymmetric dihydroxylation of olefins in ionic liquids

The concept for immobilization of osmium catalysts by ionic interaction has been further extended to the utilization of room temperature ionic liquids as a stationary phase. Room temperature ionic liquids are a relatively new and peculiar media that has been intensely studied during the last decade and applied in different areas, such as electrochemical transformations, fuel cells, solar cells, analytical and preparative separation and nanochemistry. Ionic liquids (ILs) are also appealing as reaction media in organic chemistry, with special focus in organometallic catalysis, organocatalysis and biocatalysis. During the last years, it has been demonstrated that ILs are in fact a unique alternative reaction media for a considerable range of catalytic reactions, with many examples of similar or better enantioselectivities to the ones in traditional organic solvents.

Their nonvolatility, as well as the possibility to modulate the solubility properties relative to either common organic solvents, water, catalysts, organic reactants or products by appropriate combination of the cation and anion, allow for a very simple, robust and efficient method for catalyst reuse, simply by immobilizing the catalyst in the IL under homogeneous conditions.

Room temperature ionic liquids (RTILs), especially those based on the 1,3- dialkyl imidazolium cation have been adopted as a new approach for catalyst recycling, which is based on catalyst immobilization in the ionic liquid due to their higher partition in the ionic liquid phase. Additionally, the reaction product can be selectively removed from the ionic phase by water or organic solvent, supercritical CO₂ extraction and pervaporation. Very recently, has been described in two communications the recyclable and reusable OsO₄- catalyzed olefin dihydroxylation using the co oxidant N-
methyl morpholine oxide (NMO) in 1-n- butyl-3-methyl imidazolium hexa fluoro phosphate [C₄mim][PF₆]/ water/ tert-butanol¹⁵⁸ solvent system and in 1-ethyl-3-methyl imidazolium tetra fluoro borate, [emim][BF₄]¹⁵⁹. A simple and practical approach to reuse and recycle the catalytic system of the AD reaction using the ionic liquid [C₄mim][PF₆] as a co solvent and the co oxidants K₃Fe(CN)₆ and NMO, respectively has been reported by Song and coworkers¹⁶⁰.

The use of room temperature ionic liquids (RTILs) in the Sharpless catalytic asymmetric dihydroxylation (AD) as a cosolvent or replacement of the tert-butanol was studied in detail by L.C.Branco and coworkers¹⁶¹. The AD reaction is faster in 1-n-butyl-3-methyl imidazolium hexa fluoro phosphate [C₄mim] [PF₆] as a cosolvent than in the conventional system of tert- butanol/ water. Comparable or even higher yields and enantiomeric excess (ee) were found using [C₄mim] [PF₆] or 1-n-octyl-3-methyl imidazolium hexa fluoro phosphate [C₈mim] [PF₆] compared to the conventional solvent system. Due to high affinity of the catalytic/ ligand system to the ionic liquid, the use of ionic liquid/water (biphasic) or ionic liquid/ water/ tert- butanol (monophasic) solvent systems provides a recoverable, reusable, efficient, and simple system for the AD reaction.

L.C. Branco and coworkers¹⁶² have also reported on catalyst immobilization in ionic liquids only, without any other reaction solvents, by combining it with supercritical CO₂ extraction, in order to enhance product quality, minimize osmium catalyst loss and make its reuse possible. Supercritical CO₂ (scCO₂) is the most commonly used supercritical fluid, due to its advantageous properties-relatively low and easily reachable critical parameters (t°C = 31°C, pbar = 73.8 bar), non-flammability, low cost and low toxicity. Due to their ionic nature and negligible vapor pressure, ionic liquids
exhibit no appreciable solubility in scCO\textsubscript{2}; at the same time, scCO\textsubscript{2} is remarkably soluble in most ionic liquids, and can be used to extract numerous organic substances from them without any IL contamination in the final product.

A. Serbanovic and coworkers\textsuperscript{163} have reported the IL- scCO\textsubscript{2} system being used for osmium catalysed AD reaction. As it is possible to achieve homogeneous catalysis, with high selectivity and atom efficiency, by immobilizing the catalyst in IL, the extraction of the product with scCO\textsubscript{2} that follows introduces, in principle, easy product recovery and catalyst recycle.

Provided that the AD reaction proceeds efficiently in ILs, the application of this concept requires that scCO\textsubscript{2} will be selective towards the reaction products, and that it will not extract the catalyst. The solvent power of scCO\textsubscript{2} is easily tunable, because it depends essentially on its density, which varies rapidly with pressure and temperature. ScCO\textsubscript{2} was used at the lowest possible density where it can still dissolve to some extent the reaction products, but does not carry any catalyst out of the ionic liquid solution. In these high selectivity conditions, the lower solubility of the products in scCO\textsubscript{2} can be compensated by extracting with higher amounts of the supercritical solvent. The combination of ionic liquids as solvents in the asymmetric dihydroxylation with the use of scCO\textsubscript{2} in the separation process does not need the use of organic solvents either for the reaction or for the separation of the products and allows the isolation of the diol, in high yield and enantiomeric excess without contamination with osmium.

A combined use of an osmium catalyst immobilized on quaternary ammonium salts bound to silica gel (TentaGel-Os) (49), monoquaternized bis-alkaloid ligand(L) (50), and an ionic liquid ([bmim]PF\textsubscript{6}) was reported\textsuperscript{163} with
only 0.5 mol % of the osmium catalyst and 2.0 mol% of the chiral ligand, ten recycles were achieved without significant loss of activity.

A polymer support bearing pyridinium ion moities ([P/S- PEG₃][BF₄]) was utilized for the immobilization of osmium. The polymer was prepared from pol (4-vinyl pyridine-co-styrene) and a tri ethylene glycol derivative. Osmium was introduced by shaking OsO₄ and the ionic polymer in H₂O/CH₃CN to give [P/S- PEG₃][BF₄]-Os. This catalyst exhibited good catalytic performance for asymmetric dihydroxylation and was reused five times, although a gradual loss of activity was observed.

2.3.2.4 Miscellaneous approaches

A silica gel-supported chitosan (SiO₂-CS) was utilized for immobilization of osmium and as a chiral ligand. The catalyst (SiO₂-CS-Os) was prepared from this supported chitosan and OsO₄ in the presence of t-BuOOH and was used for asymmetric dihydroxylation using K₃Fe(CN)₆ as co oxidant in t- BuOH/H₂O. SiO₂-CS-Os can be recovered by simple filtration and reused several times without significant loss of activity. Similarly, chitin, a poly (N-acetyl glucosamine) was used as a support by another group.

S.K. Cheng and co workers have demonstrated a novel soluble polymer-anchored mono- cinchona alkaloid ligand with anthraquinone as
coupling moiety. The catalytic activity and enantioselectivity of 51 are comparable to those of the free ligand $(DHQ)_2 AQN^{168}$ in the AD reaction.

After recycling five times, there is no obvious decrease in catalytic activity or enantioselectivity.

An aqueous solution of a sugar (sucrose) was used as a new, inexpensive immobilization medium in combination with $(QN)_2 PHAL$(Tetra Hydroxylated in situ) for recovery of osmium and the chiral ligand$^{169}$. Although the activity decreased gradually, the catalyst was reused three times with constant enantioselectivity without further addition of OsO$_4$ and the chiral ligand after the first run.

J.H. Miao and coworkers have used the natural bio polymer wool to prepare a new chiral polymer-metal complex, wool-osmium tetroxide complex (Scheme 26)
Wool-OsO₄ has been found to catalyze the asymmetric dihydroxylation of compounds like allyl amine and allyl chloride. The reaction has been carried out in the presence of K₃Fe(CN)₆, K₂CO₃, t-BuOH, and water at room temperature and under atmospheric pressure. The wool-OsO₄ complex is stable and can be reused without any remarkable change in the optical activity.

2.3.3 Osmium-catalyzed asymmetric Dihydroxylation using sodium chlorite

Sodium chlorite is an efficient stoichiometric oxidant in Sharpless asymmetric dihydroxylation. Double bonds are dihydroxylated extremely fast with NaClO₂ as the stoichiometric oxidant even without an added base. One sodium chlorite provides the reaction with the stoichiometric number of electrons and hydroxide ions needed to hydroxylate two olefins without the
consumption of any additional base. 100% conversion in sodium chlorite asymmetric dihydroxylation of styrene was achieved twice as fast as in the established Sharpless K₃[Fe(CN)₆] dihydroxylation.

Equation 3 shows that a total of four electrons are transferred during the reduction of NaClO₂ to NaCl which corresponds to the number of electrons needed to oxidise two K₂Os(VI)O₂(OH)₄ to two K₂Os(VIII)O₄(OH)₂. Four electrons correspond also to the number of electrons needed to oxidize two olefins to two diols (eqns. 1 and 2). Hydrolysis of the intermediate cyclic osmate-ester requires hydroxide ions. Two osmate-ester intermediates consume four hydroxide ions (eqn.2), which is the same number of hydroxide ions generated after two K₂Os(VIII)O₄(OH)₂ are transformed into two Os(VIII)O₄ (eqn.4).
Use of 1 mmole of NaClO₂ can oxidize 2 mmoles of olefins to corresponding diols. NaClO₂ AD process is also hydroxide ion efficient because it provides the dihydroxylation with the stoichiometric number of hydroxide ions. The dihydroxylation reaction can be controlled by the addition rate of NaClO₂. Enantioselectivities of the NaClO₂ AD-process are comparable with the enantioselectivities of the other AD-processes.