PART A

Applications of Sharpless Dihydroxylation and Aminohydroxylation Processes
CHAPTER 1

General Introduction
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During the last few decades a number of powerful asymmetric reactions have emerged as a tool for obtaining enantiomerically pure compounds having biological importance. This area of asymmetric synthesis is growing considerably for the development of new synthetic approaches in the field of organic, medicinal as well as pharmaceutical chemistry. Catalytic asymmetric reactions paved the way to the chiral world due to their economical use of asymmetry inducing agents. The asymmetric oxidation of carbon-carbon double bonds into a variety of functionalised compounds is one of the most useful and routine transformations in synthetic organic chemistry. Olefins are the most important synthetic organic intermediates because of their inexpensive nature and ready availability. In addition, the resultant 1,2-oxidised compounds such as epoxides, diols, halohydrins or amino derivatives can be further transformed into other classes of compounds. The advancement in the field of asymmetric oxidation of olefins was pioneered by the discovery of Sharpless asymmetric epoxidation, Sharpless asymmetric dihydroxylation (AD), the Jacobsen and Katsuki Salen-asymmetric epoxidation (Salen-AE) and the Sharpless asymmetric aminohydroxylation (AA). This chapter comprises of a brief discussion of the Sharpless asymmetric dihydroxylation and Sharpless asymmetric aminohydroxylation processes.

1.1. Sharpless asymmetric dihydroxylation (AD)

Osmium tetroxide (OsO₄) has been the most reliable reagent for transforming an alkene to the corresponding cis-diol. The reaction between osmium tetroxide and alkene generally takes place in almost any solvent with all type of carbon-carbon double bond with the general trend that the reaction proceeds faster with electron-rich alkene than in electron-deficient system. The initial product of such an osmylation reaction is a dimeric Os(VI) glycolate (2) (Scheme 1.1) which is transformed via oxidative or reductive methods to the cis-diol (1)
Criegee was the first to report that certain tertiary amines like pyridine accelerate the reaction between osmium tetroxide and alkene. The amines dramatically increased the formation of Os(VI) ester complex. The complex formed is a monomeric osmium (VI)-glycinate bispyridine complex (3). Criegee’s pioneering observation of the pyridine ligand acceleration effect in the osmium tetroxide addition leads to the development of asymmetric dihydroxylation reaction, which was discovered by Hentages and Sharpless. At first, Hentages and Sharpless used chiral pyridine derivatives with only modest success. It was due to the low binding constant for these ligands with OsO₄. It was found that the binding constant of a ligand is extremely sensitive to the steric hindrance near the reacting center. The breakthrough came with cinchona alkaloid ligands (dihydroquinidine acetate and dihydroquinine acetate). Due to the quinuclidine ring in these alkaloids, these ligands coordinate much more strongly with OsO₄ to afford chiral diol with usually fair to good optical purity. The most appealing features of the cinchona alkaloids as chiral ligand is the pseudoenantiomeric relationship between dihydroquinine (DHQ) and dihydroquinidine (DHQD).

Discovery of other two independent cinchona alkaloid derivatives by Hartung and Crispino (Figure 1.1) attached to a heterocyclic spacer led to a considerable increase in both the enantioselectivity and the scope of the reaction. Apart from these, a number of other cinchona alkaloid derived ligand had been studied for the purpose of AD process with satisfactory results. These
improvements paved the way to obtain high enantioselectivities of the diol product with a broad range of olefins.

Apart from these cinchona alkaloids, there are a number of methods employing chiral monodentate\textsuperscript{10} and bidentate diamine ligands.\textsuperscript{11} Despite the good to excellent enantioselectivities that can be obtained with diamine ligand, their bidentate nature turned out to be problematic. They form very stable chelate complex with Os(VI) glycolate product which prevents in situ recycling of the Os and the ligand. So all reactions involving bidentate ligands are stoichiometric in both OsO\textsubscript{4} and chiral ligand.\textsuperscript{6} The catalytic version of the dihydroxylation reaction was achieved by using OsO\textsubscript{4} in presence of secondary oxidant that hydrolyze the intermediate osmium (VI) ester complex oxidatively to regenerate the tetroxide which can further undergo reduction by the substrate. A variety of oxidants have been used. The most popular reoxidants used are hydrogen peroxide,\textsuperscript{12} chlorates,\textsuperscript{13} N-methylmorpholine $N$-oxide (NMO)\textsuperscript{14} and potassium fericyanide (K\textsubscript{3}FeCN\textsubscript{6}).\textsuperscript{15} These observations lead to the development of catalytic asymmetric dihydroxylation (AD) process through combination of chiral ligand and suitable cooxidant. Initially the AD using derivatives of cinchona alkaloids were performed under stoichiometric condition but in 1987 Sharpless and Marko\textsuperscript{16} found that the process became catalytic when NMO was used as cooxidant. However the enantiomeric excess of the diol products obtained under these catalytic condition were poor than those obtained by stoichiometric condition. The origin of this problem was found to be the presence of a second catalytic cycle.\textsuperscript{17} (Scheme 1.2)
The participation of the osmium(VI) glycolate complex in a second catalytic cycle exhibit only low or non enantioselectivity of the diol product. The primary cycle proceeds with high enantioselectivity and turns over by hydrolysis of the osmium(VIII) trioxoglycolate complex, while the second cycle proceeds with low enantiocontrol and turn over by alkene addition with the same osmium(VIII) trioxoglycolate complex. Kwong\textsuperscript{18} had shown that the reaction can be performed under two-phase condition with K\textsubscript{3}Fe(CN)\textsubscript{6} as the stoichiometric reoxidant. Under these conditions there is no oxidant other than OsO\textsubscript{4} in the organic layer in contrast to the homogeneous NMO condition. Since the actual osmylation occur in the organic layer, the resulting monoglycolate ester undergo hydrolysis releasing the diol and the ligand to the organic layer and Os(VI) to the aqueous layer before its reoxidation can occur. So participation of the osmium glycolate into the second cycle is prevented (Scheme 1.3)
The use of K$_2$OsO$_2$(OH)$_4$ as a nonvolatile Os source in combination with an inorganic cooxidant K$_3$Fe(CN)$_6$, had allowed to formulate a premix containing all reagents including the ligand. The premix is known as “AD-mix”.

Another key discovery made by Amberg and Xu\textsuperscript{19} was that the rate of reaction can be accelerated considerably by methane sulfonamide (MeSO$_2$NH$_2$) addition. This allows high catalytic turn over even with sterically encumbered substrates and tetrasubstituted olefins. Due to this “sulfonamide effect” most AD reactions are carried at 0°C rather than at room temperature, which normally has a beneficial influence on the selectivity.\textsuperscript{20}

**Mechanistic study**

The osmium catalyzed dihydroxylation reaction has been the center of extensive mechanistic investigation and two different mechanisms have been suggested. Bösken and Criegee proposed a concerted [3+2] pathway\textsuperscript{21} (Scheme 1.4, path A) while Sharpless et al. suggested a stepwise reaction\textsuperscript{22} initiated by a [2+2]
like addition of olefin across Os=O bond (path B), followed by rearrangement of the resulting osmaoxetane intermediate to the glycolate product.

However observation of a non linear Eyring relationship between $ee$ and temperature$^{17}$ established that the stepwise $[2+2]$-like mechanism is operative. Recent ligand structure-activity studies showed light on the origin of enantioselectivity in the AD reaction.$^{23}$ It demonstrated the importance of an enzyme-like binding pocket present in the "dimeric" cinchona alkaloid ligand e.g. the phthalazine ligands. The cinchona alkaloid backbone is ideally suited for providing high ligand acceleration as well as enantioselectivity and the relationship between ligand structure and activity.$^{24}$

**Reaction condition**

The AD reaction is carried out in a solvent mixture containing 50% water and is best carried out under heterogeneous condition with 3 equivalents of both $K_3Fe(CN)_6$ and $K_2CO_3$ in order to avoid the second catalytic cycle.$^{15}$ Optimization studies showed that 1:1 mixture of water and tert-butyl alcohol is the best solvent system while less polar solvents can result in inferior enantioselectivities. The olefin concentration in the tert-butyl alcohol/H$_2$O solvent mixture is usually 0.1 M. While the reaction is normally run under basic condition ($K_2CO_3$, pH 12.2, aqueous layer), it is possible to buffer the system with 3 equivalents of NaHCO$_3$.$^{25}$ The buffering does not affect the $ee$, rather it can have a beneficial effect on the yield when base sensitive substrates are used or base sensitive products are formed (in case of allyl or cinnamyl halides) normally the reaction is carried out with 3 equivalents of $K_3Fe(CN)_6$ as the reoxidant, however the use of peroxodisulfate gives good result with comparable reaction rates to the original conditions.$^{26}$ Only 0.2 mol% of Os
reagent is added to the reaction mixture either as OsO₄ or as the nonvolatile 
K₂OsO₄(OH)₄ and 1 mol% of the ligand is sufficient for most olefinic substrates. 
The enantioselectivity of the AD reaction has proven to be quite insensitive to 
variations in the relative amount of Os and ligand. Terminal 1,2-disubstituted and 
trans-1,2-disubstituted as well as trisubstituted olefins can be regarded as “standard” 
substrates for the AD reaction. Since these substrates require very similar reaction 
condition, it is possible to use a premix of all the reactants called “AD-mixes”. 
These AD-mixes are commercially available and can be radily prepared. The 
currently recommended content in 1 Kg of AD-mix are as follows: K₃Fe(CN)₆, 699.6 g; K₂CO₃, 293.9 g; (DHQD)²- or (DHQ)²-PHAL, 5.52g and K₂OsO₄(OH)₄, 1.04 g. The standard AD procedure calls for 1.4 g of the AD mixes per milimol of 
the olefins. 1 equivalent of MeSO₂NH₂ should be added for all substrates other than 
terminal alkene to enhance hydrolysis of the osmate (VI) ester and the rate of 
catalytic turn over, especially in the case of tetrasubstituted olefins, enol eters, 
electron deficient olefins etc.¹⁶,²⁷

For the purpose of determining enantiomeric excess of optically active 
compounds, it is often necessary to make the racemic counterparts for chiral HPLC 
analysis. The pioneering work on racemic method for dihydroxylation reaction was 
developed by D. Y. Cha known as Upjohn Dihydroxylation.²⁸ It is a catalytic system 
using NMO as stoiciometric reoxidant with OsO₄. This is still used for the formation 
of cis-vicinal diols. However it is very slow and is prone to over-oxidation of the 
diols to diketone. In response to these problems, Stuart-Warren and coworkers had 
developed an identical reaction condition to the Sharpless asymmetric 
dihydroxylation using achiral quinuclidine to provide racemic diol.²⁹ Overall, a very 
few racemic versions of dihydroxylation reaction of olefins using Os has been 
reported.³⁰,¹²

1.2. Sharpless asymmetric Aminohydroxylation (AA)

The asymmetric aminohydroxylation facilitates a single step introduction of 
both amino and hydroxyl functionality to the olefinic bond. This process where 
alkene (4) undergo vicinal addition of an amino (protected) and a hydroxyl group 
(Scheme 1.5) is an extension of the asymmetric dihydroxylation process.
The characteristics features of this catalytic process is that it proceeds with a efficient enantio and regioselectivity to furnish β-amino alcohol (5). The β-amino alcohols are very important structural element in biologically active compounds as well as the starting point in designing many chiral ligands. Among these, nonhydrolysable hydroxyethylene and hydroxyethyl amine isostere peptidomimetics are best known for potent and selective HIV protease inhibitors. The area of asymmetric aminohydroxylation reaction has been extensively reviewed.

According to original protocol alkenes can be converted to racemic, N-tosyl protected β-amino alcohols in the presence of catalytic amount of OsO₄ using Chloramine-T as the nitrenoid source and water as the hydroxyl source (Scheme 1.6).

However unlike the AD process, the aminohydroxylation of unsymmetrical alkene can lead to the formation of two regioisomeric products, which was a drawback in the early stages of its development. The direct reaction of OsO₄ with the olefin could not be completely suppressed and diols were sometimes observed as side products. In a later stage of development, vicinal oxyamination was achieved by using N-chloro-N-argentocarbamates (Scheme 1.7) These were generated in situ by the reaction of corresponding N-chlorosodiocarbamates with AgNO₃ in acetonitrile. But the generation of Ag salt limited its utility.
Although the first, albeit stoichiometric example of asymmetric aminohydroxylation reaction had already been observed during 1980, the development of Ti-catalyzed asymmetric epoxidation during the same period probably also "interfered" with an earliest development of today's catalytic asymmetric aminohydroxylation process. Since the discovery of catalytic AD in 1987, there have been numerous attempts in the Sharpless group to render the old catalytic aminohydroxylation process asymmetric. Sharpless et al. in 1996, reported that the important chiral β-hydroxyamino unit can be synthesized directly from olefins in enantiomerically enriched form (Scheme 1.8). Exciting products were obtained with moderate to high enantioselectivity by using phthalazine ligands, (DHQ)$_2$PHAL and (DHQD)$_2$PHAL.

Other than the asymmetric induction, the most dramatic effect of the cinchona alkaloid ligand is the good regioselectivity. Another positive effect of the ligand is it's ability to suppress formation of diol by-product, which, in the absence of ligand, is substantial in this new system. However increase of temperature above 25°C leads to the formation of diol. The process in the present form leads to only modest enantioselectivities (33-81% ee), however 100% enantiomeric purity can be obtained by recrystallization of the product. Both MeCN:H$_2$O and i-BuOH:H$_2$O
(1:1) are used as the solvent system. The better enantioselectivity was obtained with \( t\text{-BuOH:H}_2\text{O} \).

Two important features of the Asymmetric Aminohydroxylation process are:

1. Even strongly electron-deficient olefins like dimethyl fumarate react readily with good \( ee \) (77%) whereas the AD reaction of the same is extremely slow.
2. \( cis\)-disubstituted olefins appears to be promising substrates, even with symmetrical compounds which give achiral meso diol in AD.

Ligand as well as different nitrogen sources in combination with the olefin control the enantioselectivity as well as regioselectivity of the product formation. By choosing the suitable ligand, it is possible to tune the enantioselectivity. However, setting a particular regioselectivity is a challenging task. A number of investigations have been carried out on the basis of steric and electronic contribution of the ligand, substrates and hydrophobic effects due to solvent. These are all mutually dependent on each other and experimental determination is a very hard work.

**Nitrogen sources**

There are three main classes of nitrogen sources for asymmetric aminohydroxylation reaction. They are (i) sulfonamide (ii) carbamates and (iii) amides. Optimized reaction conditions with respect to these sources had already been established. Most of the halogenated species are chloro-species which are used directly or prepared in situ via the use of \( tert\)-butyl hypochlorite in presence of a base. Apart from these, other alternative nitrogen sources had been developed like \( N\)-heterocycles. All these sources are used widely in combination with cinchona derived ligands like (DHQ)\(_2\)PHAL, (DHQ)\(_2\)AQN etc.

Some important sources:

**Chloramine-T and Chloramine-M**

The sulfonamide method was the first to be developed for aminohydroxylation reaction, where chloramine-T was used in a non asymmetric process. Chloramine-T remains the most frequently used reagent due to its low cost and commercial availability. Chlotramine-M \([\text{MsN(Na)}\text{Cl}]\) is another common
alternative, but must be prepared independently or in situ.\textsuperscript{44} Chloramine-M generally gives higher yield with good enatio and regioselectivity than Chloramine-T. This is probably due to the smaller substituent on the sulfur. The reaction is commonly carried out in 3 mol equivalents of the nitrogen source in 1:1 CH\textsubscript{3}CN/H\textsubscript{2}O or alcohol/water. In order to maximize the yield, the nitrogen source is also used in large excess (6 mol equiv.).\textsuperscript{45} The optimal solvent system depends on both the substrates and chloramines used. Chloramine-T in aqueous propanol was found to give lower yields and higher enantioselectivity than in acetonitrile\textsuperscript{46} while chloramine-M is more successful in propanol system. An interesting feature of chloramines-M is its faster reactivity in presence of DHQ/ DHQD ligand while chloramines-T reacts faster in absence of the ligand. The robust nature of the sulfonamide product is the major drawbacks of this method. Harsh reaction condition is necessary for deprotection to regenerate the free amine.\textsuperscript{47}

A number of alternative sulfonamide nitrogen sources had been studied, including the chloramines salts of \textit{p}-nitrophenylsulfonamide [NsN(Na)Cl],\textsuperscript{48} \textit{t}-butylsulfonamide\textsuperscript{48} etc. Another significant drawback of sulfonamide method is its limited substrate scope. \(\alpha,\beta\)- Unsaturated esters, phosphates as well as amides can be successfully subjected to aminohydroxylation while styrenes and vinyl arenes remained unsuccessful.

**Carbamates**

The development of carbamate based nitrogen sources\textsuperscript{49} expanded the scope of AA reaction which increases the substrate scope and selectivity. Under these new modified conditions, styrene became the best substrate for AA process like AD reaction. Moreover, they also obey the same face selection rule established for AD process.\textsuperscript{20} (Scheme 1.9)
This procedure leads to high selectivity and yield in case of substrates like methyl cinnamate (up to 99% ee). However styrene provides both the regioisomer. The regioselectivity is highly dependent on the nature of styrene as well as the choice of ligand, solvent and ligand-solvent combination. Phthalazine ligand (DHQ\textsubscript{2}PHAL or (DHQD)\textsubscript{2}PHAL in n-PrOH favor the benzylic amine (Scheme 1.9: 12, 14) over the benzylic alcohol regioisomer (13, 15).

The commonly used carbamates included ethyl, benzyl, \textit{t}-butyl and 2-(trimethylsilyl)ethyl carbamate (Teoc). Except Teoc, all are commercially available. The purity of benzyl carbamate was found to be of critical importance, recrystallization of the carbamate increases the AA yield from 33\% to 78\%.\textsuperscript{50} The carbamate is typically converted in situ to the corresponding chloramines salt by reaction with NaOH and 3 mol equivalents of \textit{t}-butylhypochlorite. Due to the unsuitability of \textit{t}-butylhypochlorite to use on a large scale two viable alternatives have already been developed: 1,4-dichloro-5,5-dimethylhydantoin and dichloroisocyanuric acid sodium salt.\textsuperscript{51} The choice of the solvent system in case of carbamate system depends on both substrate and carbamate. However in most cases, 1:1 propanol/water gives the best result. However use of \textit{t}-butyl carbamate as the nitrogen source posses drawbacks under this solvent system due to formation of diol by-product.\textsuperscript{41\textsuperscript{a}} However the diol formation can be minimized by using 2:1 propanol/\textsubscript{H\textsubscript{2}O} system along with using more amount of ligand. Acetonitrile/water (1:1) system had found to decrease or reverse the regioselectivity of the carbamate based
AA. Similar to sulfonamides, carbamates with less sterically demanding N-substituents were found to give better results. Ethyl carbamates salt give improved yield and selectivity than benzyl carbamate, which may be attributed to the suppression of second catalytic cycle in the catalytic cycle proposed. But deprotection of ethyl carbamate is not easy as in the case of benzyl carbamate. The 2-(trimethylsilyl)ethyl reagent generally gives the best yields and selectivities among all the carbamates. The fastest reaction rate of this reagent has allowed for the use of reduced osmium catalyst loading (2 mol% rather than 4 mol%). It is observed that the preferred regioselectivity and ee observed with benzyl carbamate as nitrogen source can be overturned by carrying out the reaction with (DHQ)$_2$AQN. (Scheme 1.10)

![Scheme 1.10](image)

### Scheme 1.10

The Teoc protecting group is readily removed with mild acid or fluoride sources.

### N-halocarboxamide

In the stages of development for AA reaction, N-halogenated amides have been demonstrated to act as a nitrogen source. These nitrogen sources are comparable in scope to carbamate-based method and works well with almost all kinds of olefins. Only one equivalent of haloamide is required to carry out the process and the isolation of the AA product is very simple. Since N-chloro carbamides are susceptible to Hofmann rearrangement, the lithium salt of commercially available N-bromoacetamide was found to be the most viable alternative (Scheme 1.11).
While comparing the (DHQ)$_2$PHAL mediated isopropyl cinnamate (18, Scheme 1.11), with either Teoc$^{52}$ or $N$-bromoacetamide, it was observed that both the reagent produced excellent enantio and regioselectivities. However, in the formation of AA products with amide mediated procedure affords higher yield. However in the formation of AA product 20 (Figure 1.2)$^{57}$ $N$-bromoacetamide was found to be superior to tert-butylcarbamate not only in terms of yield and regioselectivity but also in terms of chromatographic separation of the regioisomers. However AA of several acrylates (21, 22, Figure 1.2) with benzyl carbamate gave significantly better result than that with amide.

The amide mediated AA processes are carried out in either alcohol-water or acetonitrile-water solvent mixture. Amide exhibits a greater tendency than carbamate to provide the benzylic alcohol regioisomer in the AA of styrene substrates with the choice of solvent system affecting this tendency. In acetonitrile-water, the regioselectivity of the product was found to be opposite of that in alcohol-water system.$^{55a}$

Development of monobromination of primary amides leads to the development of more $N$-haloamides to be used as $N$-sources in AA process.$^{55b}$ Results are analogues to sulfonamides and carbamates version with less sterically demanding substituents over $N$-atom gives better result (Scheme 1.12).
Aliphatic amides provide highest yield as well as enantio- and regioselectivities. Electron deficient amides and aromatic amides were found to be less efficient.\textsuperscript{55b,58}

**Heterocycles**

Jerina et al. achieved a breakthrough via an adenine derivative as nitrogen source in the aminohydroxylation of a unique olefin\textsuperscript{59} and later on expanded the process in a general manner.\textsuperscript{60} With adenine derivatives, \textit{cis}-aminohydroxy products were obtained with racemic mixture. This methodology was applied successfully in the synthesis of adenosine conjugates of polycyclic aromatic hydrocarbon metabolites.\textsuperscript{59} Adenine nitrogen sources did not give rise to asymmetric induction. However it leads to the development for asymmetric version through the use of N-substituted heterocycles.\textsuperscript{61} Using EtOH: H\textsubscript{2}O (2:1) solvent system, stilbene (26, \textbf{Scheme 1.13}) was converted to either enantiomer of the aminoalcohol (27) with good to excellent yield and enantioselectivities (\textbf{Scheme 1.13}).
Mechanism of AA reaction

The mechanism of AA process proposed is closely based on mechanistic of its forerunner, the AD process. The intermediate in the key bond forming step is the imidotrioxoosmium (VIII) species (28, Scheme 1.14). This species adds with syn-stereospecificity to the alkene to give the azaglycolate complex (29). There are two pathways to explain this process. Both pathways explain the formation of 28 to effect aminohydroxylation rather than dihydroxylation and other key aspects such as enantio and regiselectivity. The two mechanistic paths are outlined below.

(a) Concerted [3+2] Mechanism

(b) Stepwise [2+2] Mechanism

Scheme 1.14. (a) Direct and concerted [3+2]-mechanism; (b) Stepwise [2+2]-addition

In the [2+2] cycloaddition pathway, addition of the alkene to 28 produce the osmaazetidine 30. This is followed by addition of ligand coordination to form 31 and 1,2-migration of the carbon-osmium bond to give the osmium azaglycolate addition product 29. The mechanism uses electronic arguments to account for the observed preference for the nitrogen to add regioselectively to the β-carbon of alkene bearing an electron withdrawing group. The beneficial effect of the ligands on the enantio- and regioselectivity of the AA reaction occur by influencing the position of equilibrium or by controlling the relative rate of final bond formation to provide 29. The concerted [3+2] cycloaddition reaction requires a simultaneous transfer of both the nitrogen and the osmium group from the osmium complex onto
the olefin. This irreversible oxidation step determines the final absolute configuration of the product. The active osmium complex responsible for the stereoselective reaction course is believed to be a cinchona alkaloid ligated complex 32. Although 32 exist in equilibrium with the free ligand and the uncomplexed mono imido compound 28, it reacts at a higher rate than the later. This ensures the formation of product via the chiral pathway involving the species 32.

Although the chemistry of isolated osmium(VIII) complex bearing alkylimido ligand has been well investigated, surprisingly few data are available on the nature and reactivity of respective compounds with carbamoylimido or tosylimido ligands. As a consequence, a full investigation for AA process is still not been complete.

To account for these observation, a mechanistic scheme has been proposed consisting of two catalytic cycles (Scheme 1.15).

![Scheme 1.15](image)

Both the cycles proceeds via three steps viz. addition, reoxidation and hydrolysis. The primary cycle proceeds in presence of the alkaloid derived ligand. The addition of the imidotrioxoosmium (VIII) species 28 to the alkene gives the azaglycolate species 29. Reoxidation of 29 by the N-source gives 33, which can undergo hydrolysis to regenerate the initial osmium species 28 and liberate the product. The oxidized azaglycolate species 33 may also enter in a second catalytic cycle and add
to a second alkene to form bis(azaglycolate)osmium species 34. Since this addition step is independent of the ligand participation, the product formed in this cycle proceeds with low enantio- and regioselectivity. The hydrolysis of 34 gives back 29 which can re-enter either the primary or secondary cycle. The hydrolysis of the azaglycolate species 33 or 34 is the turn-over limiting step in both the cycles. The oxidation pathway is controlled by conducting the reaction in aqueous solvent mixture which favour the hydrolysis of 33 and dominant the primary cycle. The AA process usually has been carried out under homogeneous condition and the suppression of the secondary cycle relies on effective hydrolysis of 33. There is considerable evidence that entry in to the deleterious second cycle is suppressed by any factor that favors the hydrolytic release of glycolate or azaglycolate product from osmium.

Sharpless reported the development of asymmetric oxidation procedures that based on secondary cycle. These observations resulted from the fact that aminohydroxylation of unsaturated carboxylate salt, amide and some esters afford racemic product even in the presence of excess ligand. The extension of this work led to the development of chiral aminoalcohol ligand bearing a carboxylic acid functional group which mediate the new aminohydroxylation or dihydroxylation process. This secondary cycle based aminohydroxylation is more efficient than the alkaloid ligand mediated reaction in that it proceeds with low catalyst loading and without diol formation, but suffer from poor regioselectivity as well as enantioselectivity.

**Reaction condition of AA**

Asymmetric aminohydroxylation of alkene can be considered as one of the easiest metal catalyzed reaction to perform. Generally the reaction is carried out in a solvent mixture containing 50% water. t-BuOH, n-PrOH and CH$_3$CN are most commonly used non-aqueous solvent. Usually 2-4 mol% of Os reagent and 5 mol% of the ligand is sufficient for the process. When sulfonamide or carbamte is used as nitrogen source, 3 equivalents of the reagent are used to maintain the primary cycle and to suppress the formation of diol by-product. In almost all cases the solvent-water ratio is maintained at 1:1. However depending on the N-source, ligand and
substrate combination, these compositions are made changeable to improve the selectivity.

This part of the thesis encloses development of synthetic pathways towards some important classes of bioactive molecules through Sharpless dihydroxylation and aminohydroxylation process. In chapter 2, we have shown a new synthetic pathway for the synthesis of unit-B (α-amino acid) of cryptophycin-24, a potent antitumour selective cytotoxin. Chapter 3 deals with synthesis of some new analogues of 1, 3-oxazinan-2-ones through sharpless dihydroxylation process. In chapter 4, we have developed an efficient synthetic pathway for the synthesis of 2,4,5-trisubstituted piperidines through asymmetric dihydroxylation of 1,2,3,6-tetrahydropyridine derivatives. The results on the use of a new nitrogen source namely bromamine-T for Sharpless asymmetric aminohydroxylation reaction have been incorporated in the chapter 5.
1.3. References


