CHAPTER 1

Introduction to Asymmetric Dihydroxylation, Hydrolytic Kinetic Resolution and Organocatalytic Aldol reaction
1.1. ASYMMETRIC DIHYDROXYLATION (AD)

1.1.1. Introduction

Asymmetric synthesis of bioactive molecules is in the forefront of synthetic organic chemistry due to its wide applications in pharmaceutical industries and biotechnologies. The main aim of asymmetric synthesis is to synthesize enantio-enriched compounds in a most efficient and practical manner. During the last few decades, extensive research has been done to synthesize biologically active compounds using asymmetric inducing agents. To synthesize bioactive molecules, the popular heteroatom-carbon bond forming reaction is widely applied, as the ensuing functionality can generate a wide variety of heterocyclic compounds. For that, a number of metal-mediated methods for the epoxidation, oxidative cyclization, halohydrin formation, dihydroxylation have been developed. "Ligand acceleration" is the general feature of all the above mentioned processes, where the presence of a metal induced coordinating ligands, make the process much faster.

The OsO₄ catalyzed asymmetric dihydroxylation (AD) of olefin producing two syn hydroxyl groups (Scheme 1) in the presence of cinchona alkaloid ligands (Figure 1) is perhaps one of the most reliable and useful transformations for an organic chemist.

![Scheme 1: Dihydroxylation of olefin](image)

Extensive research gave the best reaction conditions for asymmetric dihydroxylation reaction. In the presence of “dimeric” PHAL or PYR ligands (Figure 2), the biphasic reaction can be carried out in equal amounts of water: t-BuOH (1:1), using catalytic OsO₄ as an oxidant, K₃Fe(CN)₆ as the re-oxidant and K₂CO₃ as a base. (Figure 3)
Figure 1. Cinchona Alkaloid Ligands for AD under Catalytic Conditions.

Figure 2. The latest generation of “dimeric” PHAL and PYR ligands

Figure 3. Catalytic cycle of the AD reaction with K₃Fe(CN)₆ as the Co-oxidant
1.1.2. Empirical rules for predicting the face selectivity

Widely accepted ‘mnemonic device’ is used for predicting the facial selectivity of dihydroxylation reaction (Scheme 2).\(^8\) The plane of the olefin is divided into the four quadrants whereas the SE corner is inaccessible due to steric factor so only small hydrogen or hydrogen like small atom can be placed there. The NW quadrant, placed diagonally to the SE quadrant, is a little bit spacious and comparatively small groups (but bigger than hydrogen) can be placed while the NE corner is more spacious than NW and usually medium group used to be placed there. The SW quadrant due to its wide spacial arrangement, is perfectly suitable for large ligand group, mainly PYR ligand and aromatic part of PHAL ligands.\(^{8c}\) The olefin, placed in above constraints received two hydroxyl groups from β-face, when DHQD derived ligands is used but in the case of DHQ derivatives it encounters from α-face (Scheme 2).

![Scheme 2. Prediction of face selectivity by mnemonic device](image)

1.1.3. Reaction Conditions

The asymmetric dihydroxylation reaction is performed in equal mixture of water and \( t\)-BuOH and the olefin concentration is usually 0.1 M.\(^9\) The reagents are 3 equivalents of re-oxidant \( K_3Fe(CN)_6 \), 0.2-0.4 mol% osmium, 1 mol% of ligand, 3 equivalents of \( K_2CO_3 \) and 1 equivalent of \( CH_3SO_2NH_2 \). For recovery of PHAL ligand, the combined organic layers are extracted with 3% aq. \( H_2SO_4 \) saturated with \( K_2SO_4 \). The aqueous phase contains ligand as the salt of hydrogen sulphate and can be reused directly for the next dihydroxylation reaction. But in this present situation, \( K_2CO_3 \) is used in excess amount to neutralize excess \( H_2SO_4 \) and also to release the ligand salt as its free base.
1.1.4. The substrate preferences of cinchona alkaloid

**Phthalazine (PHAL) ligands**

PHAL (Phthalazine) ligands\textsuperscript{10} are readily available and widely used and this class of ligand reacts especially in the presence of aromatic groups and exhibits high enantioselectivity.\textsuperscript{11,12} However, in case of branched aliphatic olefins, these PHAL ligands show very poor enantioselectivity.

**Anthraquinone (AQN) ligands**

These type of ligands derivatives are a good choice for all type of aliphatic olefins\textsuperscript{13} specially in the case of diols obtained from allyl halides or allyl alcohols which show excellent enantiopurity. So, for the easy access of valuable chiral synthon, the AQN ligands are the automatic choice, except olefins with aromatic or sterically demanding substituents.

**Pyrimidine (PYR) ligands**

These type of ligands are used for sterically crowded branched olefins.\textsuperscript{14}

**Diphenyl pyrazinopyridazine (DPP) and diphenyl phthalazine (DP-PHAL) ligands**

Except for some typical terminal olefins, these ligands show somewhat better enantiopurity than anthraquinone or phthalazine ligands.\textsuperscript{15} The diphenyl pyrazinopyridazine (DPP) which is suitable for aromatic as well as substituted cis-olefins also shows little superiority than DP-PHAL ligands.

**Indoline (IND) ligands**

Olefins which show poor enantioselectivity with other ligands, e.g., dihydroxylation of cis-1,2-disubstituted olefins,\textsuperscript{16,17} sometime exhibit better results with this ligand.
1.2. HYDROLYTIC KINETIC RESOLUTION (HKR)

1.2.1. Introduction

In the last few decades, three-membered strained ring, specially chiral epoxides have attracted considerable attention from synthetic chemists due to its availability in a wide number of naturally occurring bioactive molecules.\textsuperscript{18} To generate new carbon-carbon bonds via opening of epoxide, a number of methods are presented in literature which mainly include the use of typical Lewis acids, nucleophiles and some selective reducing agents.\textsuperscript{19} Since the availability of those epoxides from natural sources are very low and natural chiral pool materials are not reliable, direct source of enantiopure epoxides, rather, chiral epoxides can be made from those chiral pool using multistep synthetic route.\textsuperscript{20} However, by this way we can get very limited chiral epoxide. As a consequence, during the last few decades, development of novel and general catalytic asymmetric olefin oxidation route to synthesize enantio-enriched epoxides has become an area of active research.

Sharpless asymmetric epoxidation of allylic alcohol has been one of the most popular methods for general access of chiral epoxide.\textsuperscript{21} Recently developed chiral (salen)Mn(III) catalyst mediated epoxidation of unfunctionalized conjugated olefins provide gram scale synthesis of certain chiral epoxide.\textsuperscript{22} But it is not applicable for all type of olefins. Nowadays, preparation of enantioenriched epoxide from simple olefin using chiral dioxirane moiety (Shi epoxidation) has become quite popular.\textsuperscript{23} In some specific contexts, Sharpless asymmetric dihydroxylation and its synthetic manipulation has become very significant.\textsuperscript{24} Despite all this progress in asymmetric catalytic synthesis of epoxides, no general methods has been developed for the direct preparation of highly enantio-enriched 1-oxiranes, which are the most valuable class of epoxides for organic synthesis.\textsuperscript{25} There are some effective routes for the synthesis of chiral epoxide like multistep synthetic manipulation of chiral glycidol\textsuperscript{26} or epichlorohydrin\textsuperscript{27} or enzymatic kinetic resolution of certain epoxide\textsuperscript{28} but all these methods also have some limitations.

Recently, Jacobsen discovered an excellent method of HKR for a wide range of terminal epoxides using (salen)Co complex \textbf{17 (Figure 6)}.\textsuperscript{29-31} To be practical, this new method
(Scheme 6) fulfills all the required criteria for kinetic resolution. Racemic terminal epoxides such as propylene oxide, epichlorohydrin, styrene oxide are commercially available or can be synthesized in one step from cheap olefins or aldehydes. Secondly, compared to (salen)Mn catalysts, (R,R)-17 and (S,S)-17 can be prepared easily in large scale.\textsuperscript{32,33} Apart from this, water is used as a nucleophile for kinetic resolution reaction and the kinetics of the reaction can be controlled simply by tuning the rate of water addition.\textsuperscript{34} Finally, from HKR reaction we not only get highly enantioenriched epoxide (ee > 99\%) but also the highly enantiomeric pure 1,2-diols that are not available from existing dihydroxylation methods.\textsuperscript{5,11}

![Figure 6. Jacobsen catalyst](image)

HKR emerged as a widely popular method and thus resulted into synthesis of several natural products.\textsuperscript{35} Using HKR conditions, many uncommon chiral epoxides are being manufactured industrially nowadays.\textsuperscript{33}

![Scheme 6. Hydrolytic kinetic resolution of propylene oxide.](image)
1.2.2. Preparation of Catalyst and General Experimental Considerations

Although both the enantiomers of 17 are commercially available, they can also be synthesized in laboratory from Co(OAc)$_2$. Before using HKR reaction, the inactive Co(II) complex 17 must be oxidized to its active (salen)Co(III) X form via aerobic oxidation of 17 in the presence of a mild Brønsted acid. Acetic acid is the most effective for this process. There are two methods for synthesizing 17.OAc.

In method A, crude solid of active (salen)Co(III).OAc is prepared before HKR reaction. In this method, to a stirred solution of Co(II) complex in toluene was added acetic acid (2 equiv) and the reaction mixture was stirred 30 min in open air at room temperature. During this time, the orange color of reaction mixture becomes dark brown. The reaction mixture was concentrated in vacuo to afford 17.OAc as a brown solid which is used for HKR without purification.

In method B, to the stirred solution of racemic epoxide and Co(II) complex 17, AcOH was added and the reaction mixture was stirred in open air at room temperature. For all types of terminal epoxide, the catalyst synthesized by both methods shows almost similar result and in that case method B is more popular, as in this case, the catalyst is generated in situ so we can easily avoid the preactivation step. But in some cases, less reactive epoxide shows better result in method A. Apart from the generation of active catalyst, another crucial step is the amount of catalyst loading and solvent choice. After extensive study, 0.5 mol% of catalyst with respect to epoxide and 0.55 equiv of water (for lipophilic substrates before addition of catalyst, epoxide was dissolved in water miscible organic solvents like THF, isopropanol) was found to be suitable for HKR.

![Method A and Method B](image-url)
Scheme 7. General reaction

\[ ((R,R)-N,N'\text{-Bis(3,5-di-}t\text{-}r\text{e}t\text{-}b}u\text{t}y\text{l}sa\text{lic}y\text{l}i\text{d}e\text{)}e\text{-})_{1,2}\text{-cyclohexanedi}a\text{amine(2-))cobalt(II)} \]

\((R,R)-17\). Under argon atmosphere, to a stirred solution of ligand \([(R,R)-N,N'\text{-bis(3,5-di-}t\text{-}r\text{e}t\text{-}b}u\text{t}y\text{l}sa\text{lic}y\text{l}i\text{d}e\text{-})_{1,2}\text{-cyclohexanedi}a\text{mine}] \) (10.9 g, 20.0 mmol) in degassed DCM (80 mL), cobalt(II) acetate tetrahydrate (5.98 g, 24.0 mmol) in MeOH (80 mL) was added dropwise. During addition of cobalt(II) acetate tetrahydrate, precipitation of a brick-red solid was observed. After complete addition, the reaction mixture was stirred at room temperature for 15 minutes and then for another 30 minutes at 0 °C. Filtration of the precipitate through vacuum followed by washing with excess cold methanol provides red solid \([(R,R)-N,N'\text{-bis(3,5-di-}t\text{-}r\text{e}t\text{-}b}u\text{t}y\text{l}sa\text{lic}y\text{l}i\text{d}e\text{-})_{1,2}\text{-cyclohexanedi}a\text{mine(2-))cobalt(II)} \]  \((R,R)-17\) (11.6 g, 19.2 mmol, 96%).
1.3 ORGANOCATALYTIC ALDOL REACTION

1.3.1. Introduction to organocatalysis

Synthesis of chiral molecules as pharmaceuticals has given an impetus to extensive research in the area of asymmetric catalysis. In the last few decades, the number of chemical transformations using small organic molecules have been reported but it was unexplored until late 1990’s at which time the field of organocatalysis was ‘born’. Now, it is widely accepted that organocatalysis is one of the most powerful tool for the enantioselective synthesis of chiral molecule and this has become one of the very popular research areas. Organocatalysts, composed of carbon, hydrogen, nitrogen, sulfur and phosphorus (but not any trace of metal) catalyzes organic transformations using purely small organic molecule and it is a complementary mode of metal catalyst. Apart from lots of “green” advantage, compared to metal catalysts, it also reduces the organic waste involved in chemical transformation and saves time and cost of manufacturing pharmaceutical leads. With an ecofriendly approach, organocatalysis has grabbed the attention of researchers worldwide and several studies are currently underway to find new organocatalysts with greater TON (turnover numbers), better efficiency and high reactivity.

1.3.2. Proline a “Universal catalyst”

In terms of diversity of organic transformations and high utility, proline is referred to as a “universal catalyst”. With the presence of a secondary amine group (which acts as a Lewis base) and carboxylic acid group (which acts as a Bronsted acid), proline is considered as a bifunctional catalyst. Due to the presence of organized hydrogen bonding in the transition state, many proline-catalyzed reactions like α-functionalization, both inter and intramolecular aldol reaction, Michael addition, Diels-Alder reaction show excellent selectivity.
1.3.3. Proline-catalyzed aldol reaction

**Beginnings**

In early 1970’s, during the synthesis of CD ring of steroids (Figure 8), Hajos and Parrish first identified the hydrindane dione intermediate 3 which is an intramolecular aldol product.\(^{41}\) This was the first reaction where proline was used as a catalyst in organic transformation and enantiomeric ratio of the aldol product was 96.5:3.5. This interesting result was reported in 1974, but unfortunately even after this breakthrough, the field remained unexplored until late 1990’s at which time Barbas and coworkers synthesized Wieland-Miescher ketone 4 via proline catalyzed Robinson annulation reaction.\(^{42}\)

![Diagram of the Hajos-Parrish-Eder Sauer-Wiechert reaction](image)

**Figure 8: Hajos-Parrish-Eder Sauer-Wiechert reaction**

This discovery encouraged several chemists to investigate new organocatalyst with better efficiency and better reactivity.
1.3.4 Mechanism of Aldol reaction

Very similar to "microaldolase" the secondary nucleophilic amine and caboxylic acid conjugately acting as a acid/base cocatalyst. After detailed study of the mechanism of aldol reaction (Figure 9), it is observed that the acid base cocatalyst plays an important role at each step of aldol reaction. In the first step (step a), a carbinol intermediate is formed by nucleophilic attack of the amine to the carbonyl, followed by dehydration (step b) furnishing the iminium species. Depotonation of the iminium species (step c) gives enamine which undergoes C-C bond formation reaction through enamine addition on the 're' face of the carbonyl (step d) to generate iminium-aldol adduct. Subsequent hydrolysis (step e) of iminium-aldol adduct and elimination (step f) gives hydroxy ketone and regenerates the catalyst.43

![Figure 9: Proposed enamine mechanism of the proline-catalyzed aldol reaction](image)

Using Zimmerman-Traxler transition state (Figure 10), we can predict the facial selectivity and enantioselectivity of the aldol reaction. From the pictorial diagram of possible transition state (Figure 10), it is observed that "re" face attack minimizes the steric interaction between the carbonyl and the enamine (8) whereas enamine on the 'si' face of the carbonyl leads to the unfavorable transition state (9). One of the most attractive feature is that both D and L- proline are readily available, so both enantiomers can be accessed easily.
1.3.5 Scope of the proline-catalyzed aldol reaction:

The renaissance of organocatalysis was intitated by Barbas $^{43,44,45}$ who first reported the cross aldol reaction between acetone and 4-nitrobenzaldehyde, using L-proline to give the aldol product in 68% yield with enantiomeric ratio of 88:12. (Scheme 4)

Scheme 8: First proline catalyzed direct asymmetric aldol reaction

An easy way to synthesize anti-1,2-diols from hydroxyacetone and various α-substituted aldehyde using proline as a catalyst adds extra importance of organocatalysis. Earlier, only branched aldehydes were used as acceptors because long chain aldehyde undergoes either self aldolization or gives dehydrated α,β-unsaturated ketone as a major product. $^{46,47}$ This problem was solved by Benjamin List who proposed that use of either pure acetone or 20% v/v acetone in chloroform or THF and long reaction time can supress the self-aldolization but in this reaction,
conditions er was not satisfactory. Later, MacMillan reported the proline catalyzed *anti* cross-aldol reaction with good er’s with different aldehyde acceptor and ketone donor in DMF solvent. α-Keto esters and fluoroacetone compounds as enamine acceptors have also been investigated. Interestingly, it was found that α- branched aldehydes are not good enolate donors, because these would lead to a β-hydroxyaldehyde with a quaternary α carbon. Four stereoisomers are possible from aldol reaction between cyclohexanone (as a donor) and different aldehyde (as a acceptor) that are *syn-* and *anti-* diastereomeric pair of enantiomers (Figure 11).

![Diagram](image)

**Figure 11**: Possible products from cyclohexanone enamine with aldehydes

MacMillian *et al.* showed in their report that the nature of α-substituted aldehydes plays an important role to get high regio- and stereoselectivity in cross aldol reaction. They found that protected α-oxyaldehydes act as both donors and acceptors in the aldol reaction: α-alkyl aldehydes with α-methylene protons act as donors in reaction
with protected α-oxyaldehydes whereas in the same reaction alkylaldehydes without α-methylene protons acts as an acceptor.\textsuperscript{52} Using the above concept, proline catalyzed cross aldol reaction has been used for the synthesis of carbohydrate. Córdova has reported the synthesis of hexose (\textbf{Scheme 9}) in multigram scale (29\% overall yield and 99.5:0.5 er) involving a two-step sequence of cross-aldol reaction involving both L and D-proline.\textsuperscript{53}

\textbf{Scheme 9. Córdova’s hexose synthesis}
1.4 References


33. For information, see: [http://www.rhodiachirex.com](http://www.rhodiachirex.com); [http://www.chem.harvard.edu](http://www.chem.harvard.edu); [http://www.chemistry.illinois.edu](http://www.chemistry.illinois.edu)

34. While it may be assumed that an “ideal” resolution would involve no added reagents *i.e.*, an enantiomer undergoing selective isomerization or polymerizations, the rate of such transformation may be difficult to control because of the exothermicity ($\Delta H > 30$ kcal/mol) associated with epoxide ring opening. This is a special concern with reactions carried out on a large scale. The fact that the rate of nucleophile addition can be adjusted to control reaction rate therefore has significant practical advantages.


44. List, B. *Synlett* **2001**, *11*, 1675.


