ASYMMETRIC SYNTHESIS OF BIOACTIVE MOLECULES AND SYNTHETIC METHODS INVOLVING OXIDATION OF N-H, O-H BONDS AND OXIDATIVE HALOGENATION OF ARENES AND ALKENES

A THESIS

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By

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dedicated to my sister Shobha

dedicated to my sister Shobha

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CERTIFICATE

Certified that the work incorporated in the thesis entitled "**Asymmetric Synthesis of Bioactive Molecules and Synthetic Methods Involving Oxidation of N-H, O-H Bonds and Oxidative Halogenation of Arenes and Alkenes**" was carried out by the candidate under my supervision. Such material as had been obtained from other sources has been duly acknowledged in the thesis.

(Dr. A. Sudalai)

Research Supervisor

CONTENTS

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Gajanan K. Dewkar

ABBREVATIONS

AD	Asymmetric Dihydroxylation
AIBN	2,2'-Azobisisobutyronitrile
Ac	Acetyl
bp	Boiling Point
Boc	N-*tert*-Butoxycarbonyl
DHQ	Dihydoquinine
DHQD	Dihydroquinidine
DMF	Dimethyl formamide
DMSO	Dimethyl sulphoxide
DECC	Diethyl carbamoyl chloride
DMAP	4-Dimethylaminopyridine
ee	Enantiomeric excess
ESR	Electron Spin Resonance
Et	Ethyl
EtOAc	Ethyl acetate
EtOH	Ethyl alcohol
g	Grams
h	Hours
HPLC	High pressure liquid chromatography
IR	Infra red
M^+	Molecular ion
Me	Methyl
min	Minutes
ml	Milliliter
mp	Melting point
MS	Mass spectrum
NMR	Nuclear Magnetic Resonance
NBS	N-Bromosuccinimide
NCS	N-Chlorosuccinimide
Pet. ether	Petroleum ether
Ph	Phenyl
PTSA	*p*-Toluene sulfonic acid
RT	Room Temperature
TG/DTA	Differential Thermal Gravimetric Analysis
THF	Tetrahydrofuran

TLC Thin layer chromatography

GENERAL REMARKS

1. All solvents were distilled and dried before use.
2. Petroleum ether refers to the fraction collected in the boiling range 60-80^{o}C.
3. Organic layers after every extraction were dried over anhydrous sodium sulfate.
4. Column Chromatography was performed over silica gel (60-120 mesh).
5. TLC analyses were performed over glass plates coated with silica gel (5-25 μ) containing UV active G-254 additive.
6. IR spectra were recorded on a Perkin-Elmer model 683 B or 1605 FT-IR and absorptions were expressed in cm^{-1}.
7. ^{1}H and ^{13}C-NMR spectra were recorded on Bruker FT AC-200, MSL-300 and 500 MHz instruments using TMS as an internal standard. The following abbreviations were used. s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, bs = broad singlet, and dd = doublet of doublet.
8. Mass spectra (MS) were recorded on an automated finnigan MAT 1020C mass spectrometer using ionization energy of 70eV.
9. Optical rotations were carried out on JASCO-181 digital polarimeter at 25^{o}C using sodium D light.
10. TG/DTA was performed on a TG/DTA 22, TG/DTA 32 system (Seiko Instruments) in the range of 30-400^{0}C at 10^{0}C min^{-}.
11. EPR spectra were recorded on a Bruker EMX spectrometer at 9.76 GHz and 298 K, and g values were determined relative to a standard marker: α,α'-diphenyl-β-picryl hydrazyl (DPPH, g = 2.0036)
12. All melting points and boiling points are uncorrected and the temperatures are in centigrade scale.
13. Cyclic Voltammetry recorded using Ag/AgCl reference electrode.
14. Elemental analysis was done on Carlo ERBA EA 110B instrument.
15. The compounds, scheme and reference numbers given in each chapter refers to that particular chapter only.
16. The ligands DHQD, $(DHQ)_2$-PHAL, $(DHQD)_2$-PYR, $(DHQ)_2$-PYR were purchased from Aldrich

ABSTRACT

The thesis entitled **"Asymmetric Synthesis of Bioactive Molecules and Synthetic Methods Involving Oxidation of N-H, O-H Bonds and Oxidative Halogenation of Arenes and Alkenes**" is divided into four chapters.

The title of the thesis clearly reflects the objective, which is to synthesize enantiomerically pure bioactive molecules and to interface synthetic organic chemistry for the development of new synthetic methodologies. **Chapter 1** involves the development of new procedure of asymmetric dihydroxylation (AD) of *N*-Boc allyl amines **2** and its application for the synthesis of anticonvulsant drug, (S)-2-(3'-diethylamino-2'-hydroxypropylamino)pyridine (**9**). **Chapter 2** describes the enantioselective synthesis of two *β*-adrenergic blockers (R)-Celiprolol (*N*-[3-acetyl-4-(3'-*tert*-butylamino-2-hydroxy)propoxy]-phenyl-*N*-diethylurea) (**19**), and Levcromakalim [(3S,4R)-3-hydroxy-2,2-dimethyl-4-(2-oxo-1-pyrrolidinyl)-6-chromane carbonitrile] (**28**). **Chapter 3** provides a novel synthesis of Titanium Superoxide **31** performing as a new heterogeneous catalyst and its application in the oxidation of N-H bond of amines and O-H bond of phenols. **Chapter 4** presents the $NaIO_4$-catalyzed oxidative halogenation of arenes and alkenes using alkali metal halides as halogen sources.

CHAPTER – 1

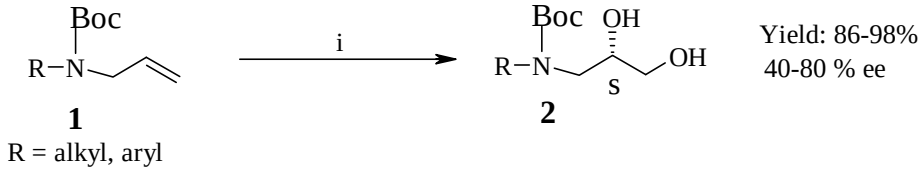
Os-Catalyzed Asymmetric Dihydroxylation of *N*-Boc Allyl Amines and Enantioselective Synthesis of (*S*)- 2-(3'-Diethylamino-2'-hydroxypropylamino)pyridine

This chapter is divided into two sections. While Section I deals with OsO_4-catalyzed asymmetric dihydroxylation of *N*-Boc aromatic, aliphatic as well as allylic amines, Section II deals with the enantioselective synthesis of (*S*)-2-(3'-diethylamino-2'-hydroxypropylamino)pyridine.

SECTION I: Os-Catalyzed Asymmetric Dihydroxylation of *N*-protected Allyl Amines

The value of enantiopure trisubstituted amino alcohols such as **2** lies in their utility as important chiral intermediates for the enantioselective synthesis of optically active drugs.

Asymmetric dihydroxylation (AD) of *N*-di protected allylic and homoallylic amines and α,β and β,γ-unsaturated amides are known in the literature,[1] but no AD methods are reported for *N*-Boc protected aromatic as well as aliphatic amines. This section describes, for the first time, asymmetric dihydroxylation of *N*-Boc protected allyl amines **1** to yield the corresponding optically pure amino alcohol **2** in high yield and optical purity (**Scheme 1**).



1

R = alkyl, aryl

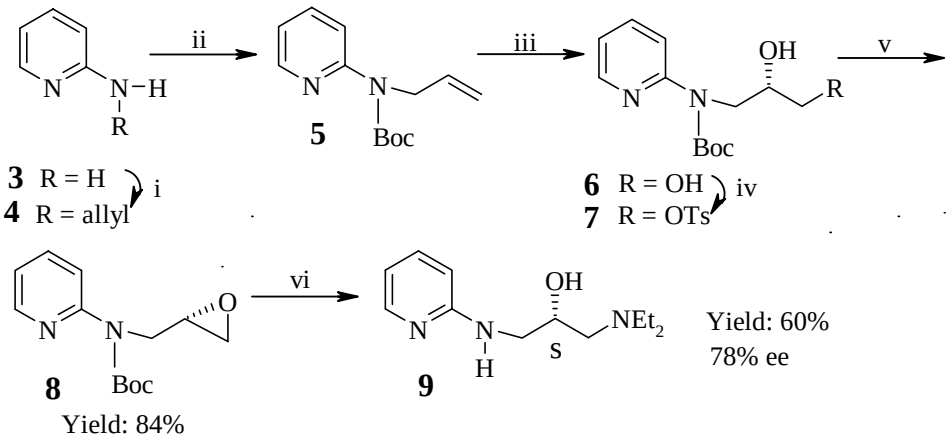
2

Scheme: 1 (i) cat. OsO_4, $(DHQ)_2$-PHAL, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH:H_2O (1:1), 0-25^{0}C, 18-24 h, 86-98%, 40-80% ee.

SECTION II: Enantioselective Synthesis of (S)-2-(3'-Diethylamino–2'-hydroxypropylamino)pyridine

Pyridine derivatives are important for the anticonvulsant, cardiotonic and antihypertensive β-adrenergic blocking activity. Aminopropanes are reported to possess CNS depressant, neuroleptic, antiarrhythmic, hypotensive and β-adrenergic blocking activity.[2] Therefore, it was envisaged that chemical entities with both pyridine and aminopropane moieties would result in compounds of interesting biological activities. These drugs, at present, are sold as racemic mixtures. To avoid unnecessary stress or in some cases toxicity to an organism caused by the other isomer, the administration of optically pure isomer is mandatory. This section describes enantioselective synthesis of one such drug i.e. (*S*)-2-(3'-diethylamino-2'- hydroxypropylamino)pyridine (**9**) (**Scheme 2**).

The synthesis starts with *N*-allylation of 2-aminopyridine (**3**) to give allyl amine **4**, which is protected using di-*tert*-butyldicarbonate to afford *N*-boc allyl amine **5**. The *N*-Boc protected allyl amine **5** was subjected to AD in the presence of $(DHQ)_2$-PHAL [hydroquinine 1,4-phthalazinediyl diether] as chiral ligand to give chiral diol **6.** Diol **6** was converted to its epoxide **8** in two steps. The regiospecific opening of epoxide by diethyl amine gave the corresponding drug **9** in 60% yield and 78% ee.



Scheme 2: (i) allyl bromide, THF, 60^0C 12 h, 98%; (ii) $(Boc)_2O$, Et_3N, cat. DMAP, CH_2Cl_2, RT 12 h, 95%; (iii) cat. OsO_4, $(DHQ)_2$-PHAL, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH:H_2O (1:1), 0-25^0C, 24 h, 96%, 80% ee. (iv) *p*-TsCl, pyridine, CH_2Cl_2 0^0C 24 h, 80%; (v) K_2CO_3, MeOH, 0^0C 12 h, 84%; (vi) Et_2NH, MeOH, reflux, 24 h, 60%, 78% ee.

CHAPTER – 2

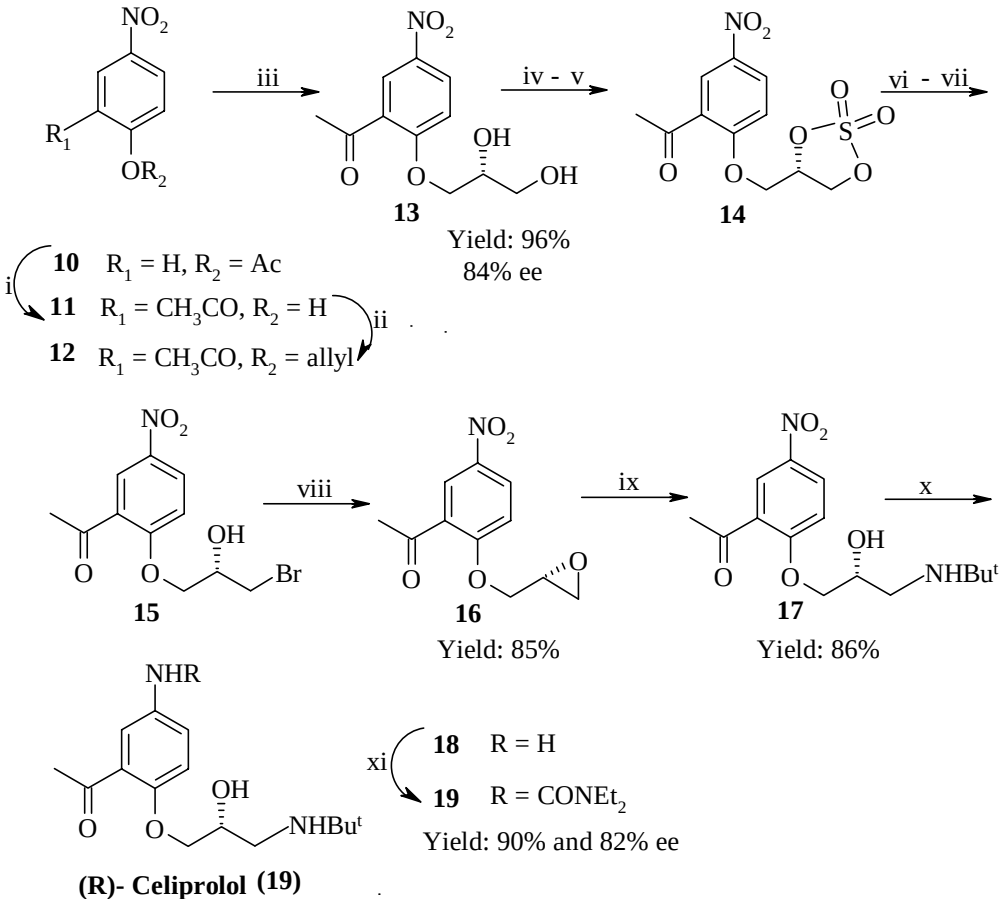
Asymmetric Synthesis of *β*-Adrenergic Blockers *via* OsO_4-Catalyzed Asymmetric Dihydroxylation

OsO_4-catalyzed asymmetric dihydroxylation (AD) of olefins is one of the most important and practical reactions to yield *vicinal* 1,2 *cis*-diols with high degree of optical purity and excellent yields.[3] Cinchona alkaloids such as dihydroquinine, dihydroquinidine and their derivatives are used as chiral ligands in AD reactions to induce chirality in the resulting diols. This chapter presents two sections. While Section I deals with the enantioselective synthesis of (*R*)-Celiprolol (**19**), **Section II** presents the enantioselective synthesis of Levcromakalim (**28**).

SECTION I: Enantioselective Synthesis of (*R*)-Celiprolol

β-Adrenergic blocking agents (*β*-blockers) are important drugs widely used for the treatment of hypertension and angina pectoris.[4] They are used to increase life expectancy after the occurrence of the heart attack. However these antihypertensive drugs are sold as racemic mixtures. (*R*)-Celiprolol **19** is one such *β*-blocker with promising antihypertensive activities. Literature search[5] revealed that only racemic synthetic methods are available for its synthesis.

Hence it is of interest to provide an asymmetric catalytic method for the synthesis of (*R*)-Celiprolol, which is presented in this chapter (**Scheme 3)**.



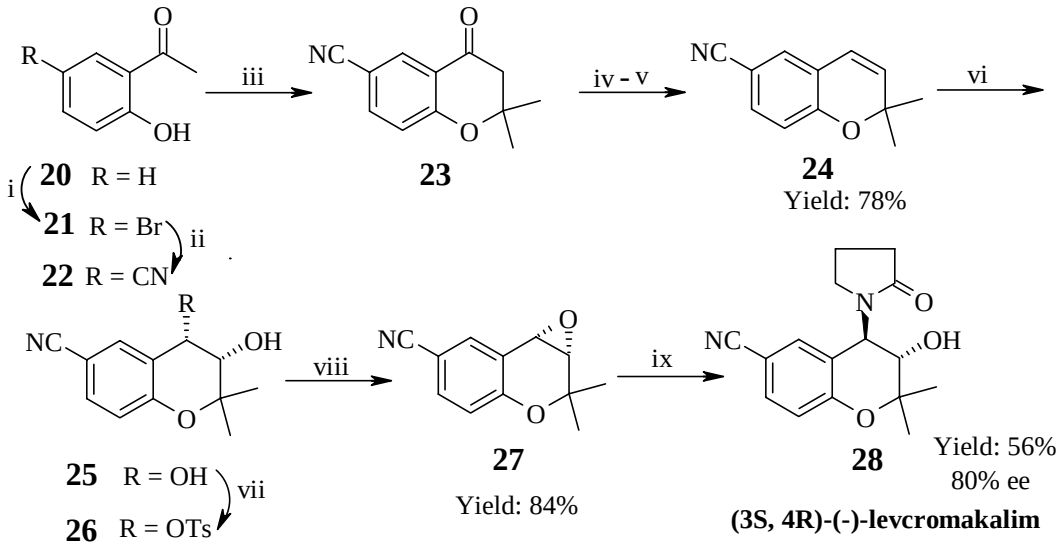
Scheme: 3 i) $AlCl_3$, nitrobenzene, 140^0C, 6 h, 70%; (ii) K_2CO_3, CH_2=$CHCH_2Br$, acetone, reflux, 24 h, 99%; (iii)) cat. OsO_4, $(DHQ)_2$-PHAL, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH:H_2O (1:1), 0-25^0C, 24 h, 96%, 84% ee; (iv) $SOCl_2$, Et_3N, CH_2Cl_2, 0^0C, 1 h, 98%; (v) cat. $RuCl_3$ $3H_2O$, $NaIO_4$, CH_3CN:H_2O, 0^0C, 30 min. 94%; (vi) LiBr, THF, 60^0C, 2 h; (vii) 20% H_2SO_4, Et_2O, 6 h; (viii) K_2CO_3, MeOH, 10-15^0C, 4 h, 85% overall in three steps; (ix) *t*-$BuNH_2$, H_2O, 24 h, 86%; (x) H_2 (20 psi), MeOH, 10% Pd/C, 6 h, 92%; (xi) THF, Et_3N, DCC, 40^0C, 48 h, 90%, 82%.

4-Nitrophenol was converted into 4-nitrophenylacetate **10** in 87% yield using acetic anhydride and NaOH. The Fries migration of phenyl acetate **10** using $AlCl_3$ in nitrobenzene gave 70% yield of 2-hydroxy-5-nitroacetophenone **(11)**. O-Allylation of **11** gave allyl ether **12** which was subjected to ADH in the presence $(DHQ)_2$-PHAL [hydroquinine 1,4-phthalazinedily diether] as a chiral ligand to yield chiral diol **13** in 96% yield, and 84% ee. The diol **13** was converted to cyclic sulfate **14** in two steps. Nucleophilic opening of cyclic sulfate **14** with *tert*- butyl amine gave the sulfate, which was difficult to hydrolyze. Hence the

cyclic sulfate was further converted to the corresponding epoxide **16** in three steps. The regiospecific opening of epoxide **16** by *tert*- butyl amine gave amino alcohol **17** in high yield. The nitro group was hydrogenated over catalytic Pd/C in methanol to afford the amine **18** in 92% yield. Finally, the introduction of *N*,*N*-diethyl carbamoyl chloride (DECC) in the presence of base gave the corresponding drug **19** in 90% yield and 82% ee.

SECTION II: Asymmetric Synthesis of Levcromakalim

Potassium channel blocking agents are important drugs widely used for the treatment of heart diseases. Cardiac arrhythmias are still a major cause of death in the western world, especially in patients with ischemic heart disease.[6] These irregularities are caused by abnormalities in the electrical activities of the heart. Levcromakalim **28** is one such potassium channel blocker, the asymmetric synthesis of which is presented in this section using ADH as a key reaction to introduce stereogenic center in the molecule (**Scheme 4**).



Scheme 4: (i) NBS, CH_3CN, 60^0C, 12 h, 90%; (ii) CuCN, DMF, reflux, 12 h, 50%; (iii) acetone, pyrrolidine, toluene, 4 h with a Dean-Stark apparatus, 94%; (iv) $NaBH_4$, MeOH, $0\text{-}25^0C$, 2 h, 98% yield; (v) *p*-TSA, toluene, Dean-Stark with 4 h, 78%; (vi)) cat. OsO_4, $(DHQD)_2$-PYR, $K_3Fe(CN)_6$, K_2CO_3, $MeSO_2NH_2$ *t*-BuOH:H_2O (1:1), $0\text{-}25^0C$, 24 h, 90% yield, 58% ee. (vii) *p*-TsCl, pyridine, CH_2Cl_2 0^0C 24 h, 80%, (viii) K_2CO_3, MeOH, 0^0C 12 h 84%; (ix) NaH, DMSO, 2-pyrrolidone, 25^0C, 6 h, 56%, 80% ee.

2-Hydroxyacetophenone (**20**) was brominated using NBS to give 2-hydroxy-5-bromoacetophenone **21** in 90% yield. Nucleophilic displacement of bromide with cyanide afforded 3-acetyl-4-hydroxybenzonitrile **(22)** in 50% yield which was subsequently cyclized

with acetone in presence of catalytic amount of pyrrolidine as a base to give 6-cyano-2,2-dimethyl chromanone (**23)** in 94% yield. Reduction of chromanone **23** with $NaBH_4$ gave 4-chromanol which on acid catalyzed dehydration gave 6-cyano-2,2-dimethyl chromene **(24)** in 78% yield. Chromene **24** was subjected to ADH in the presence of $(DHQD)_2$-PYR [hydroquinidine 1,4-phthalazinediyl diether] as a chiral ligand to yield chiral diol **25** in 90% yield and 58% ee. The diol **25** was then converted into epoxide **27** in two steps. Finally, the epoxide **27** was opened with 2-pyrrolidone, regio and stereoselectively to afford the corresponding drug **28** in 56% yield and 80% ee.

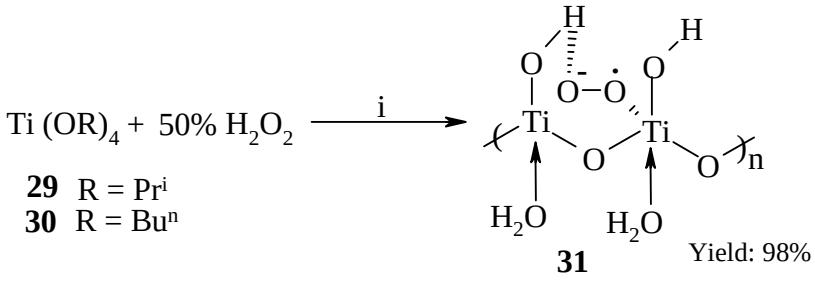
CHAPTER-3

Novel Synthesis of Titanium Superoxide as Heterogeneous Catalyst for Organic Functional Group Transformations

This chapter is divided into three sections. While Section I describes a new method of synthesis of Ti-Superoxide (**31**), **Section II** and **Section III** describe the application of Ti-Superoxide as a new heterogeneous catalyst for simple oxidation of N-H and O-H bonds.

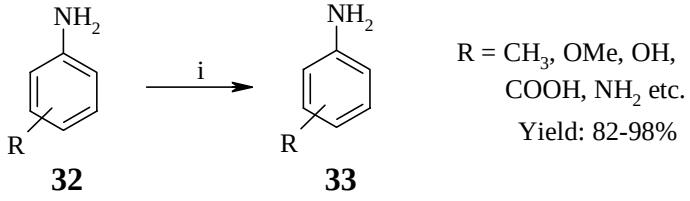
SECTION I: A New Method of Synthesis of Ti-Superoxide[7] and Its Application to Oxidation of Amines: A High Yield Synthesis of Nitro Compounds

Superoxide ion ($O_2^{-\cdot}$), an active oxygen species, plays important roles in various diseases caused by oxygen toxicity such as ischemia, carcinogenesis, inflammation, diabetes, and aging.[8] Literature search[9] reveals that the generation of $O_2^{-\cdot}$ is achieved by electrolytic reduction of O_2 in DMF or by enzymes such as xanthine-xanthine oxidase. Also, the generation of superoxide was described on the lattice of metal oxides such as MgO/CaO, ZnO, ZrO_2 and TiO_2 by using photoinduced electron-transfer process.[10] However, these methods are not suitable for large-scale synthesis. This section describes a novel and new method for the generation and spectroscopic characterization of $O_2^{-\cdot}$ on the solid hydrated titanium matrix. The light yellow-coloured catalyst **31** was prepared by the action of 50% H_2O_2 on Ti $(OR)_4$ in methanol at 25^0C (**Scheme 5**).



Scheme 5: (i) anhydrous methanol, 25^0C, 1 h, under N_2, 98%.

The oxidation of amines as generally complicated by the several other competing reaction pathways yielding range of product.[11] This section presents the results of various N-H bonds of amines when subjected to oxidation with 50% H_2O_2 as the oxidant and Ti-Superoxide as catalyst at 25^0C. The reaction proceeds selectively to afford the corresponding nitro derivatives in 82-90% yield (**Scheme 6**).

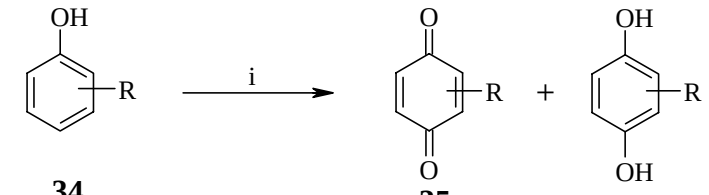


Scheme 6: (i) cat. titanium superoxide (**31**) 25 wt %, 50% H_2O_2 (4 equiv.), MeOH, 25^0C, 30 min, 82-90%.

Remarkably, even aryl amines with electron withdrawing groups such as CO_2H, NO_2, *etc* are efficiently oxidized to the corresponding nitro arenes, which otherwise may be difficult to obtain by the conventional methods.

SECTION II: Ti-Superoxide-Catalyzed Oxidation of Phenols: A High Yield Synthesis of Quinones

Quinones are an important class of compounds in industry (e.g., anthraquinone dyestuffs), in organic synthesis as dienophiles in Diels-Alder reactions and in Nature, where they have a vital role in electron transport in the respiratory and photosynthetic elements of biological systems.[12] In view of the synthetic utility and biological activity of quinones, this section describes the application of titanium superoxide for the selective oxidation of phenols to quinones in good to excellent yields (**Scheme 7**).



34 **35**

R = H, alkyl, halide, etc. Yield: 32-98 Yield: 0.6-3.1

Scheme 7: (i) cat. titanium supeoxide **(31)** (20 wt%), 30% H_2O_2 (20 mmol), AcOH, 0-25^{0}C, 1-2 h.

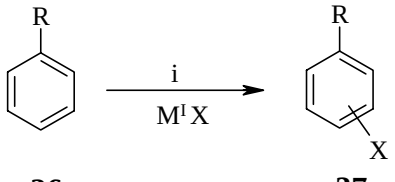
CHAPTER-4

$NaIO_4$-Mediated Regioselective Oxidative Halogenation of Arenes and Alkenes using Alkali Metal Halides

This chapter describes the use of $NaIO_4$ as a novel catalyst in organic synthesis and is divided into two sections. While **Section I** presents the halogenation of arenes, **Section II** describes the new catalytic method for synthesis of halohydrin from alkenes.

SECTION I: $NaIO_4$-Mediated Regioselective Oxidative Halogenation of Arenes Using Alkali Metal Halides as Halogen source

The halogenation of arenes is one of the prominent organic reactions that have seen numerous laboratory uses and industrial applications. The introduction of chlorine onto aromatic rings by electrophilic substitution is an important synthetic transformation because chlorinated hydrocarbons are recognized as versatile starting materials and additives in the production of high quality insecticides, fungicides, dyes, pharmaceuticals etc.[13] This section describes the $NaIO_4$ catalyzed regioselective oxidative halogenation of a variety of arenes using NaCl and LiBr as halogen sources (**Scheme 8**).



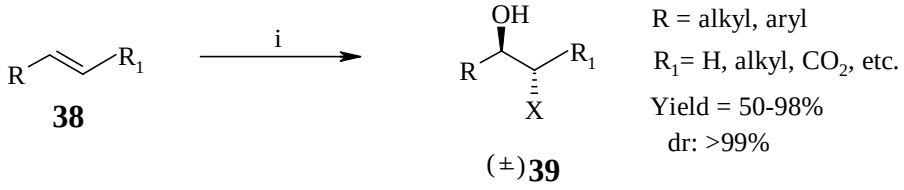
36 **37**

R = H, CH_3, OMe, etc.
M = Na, Li
X = Cl, Br
Yield: 20-83%

Scheme 8: (i) $M^I X$ (M = Na, Li: X = Cl, Br), $NaIO_4$ (20 mol%), H_2SO_4 (10 mmol), CH_3CN: H_2O (2:1), 80^{0}C, 3 h, 20-83%.

SECTION II: $NaIO_4$-Mediated Regioselective Oxidative Halogenation of Alkenes using Alkali Metal Halide as Halogen source: A High Yield Preparation of Halohydrins

The functionalization of olefins by addition of the two different functional groups in a single step is an important transformation for e.g. aminohydroxylation, haloazidation, halohydrin, etc. Among all these, halohydrin is one of the most useful reactions as the halogens can be replaced by a variety of nucleophiles such as N_3, CN, OAc, OMe, NHR, SR etc[14] there-by providing a new class of functionalized reactive intermediates in organic synthesis. This section describes the synthesis of halohydrins **39** from the corresponding alkenes **38** using $NaIO_4$ as the catalyst and metal halide as the halogen source **(Scheme 9)**.



38 (±)**39**

Scheme 9: (i) $NaIO_4$ (25 mol%), MX = (M = Li, Na; X = Cl, Br) (1.2 mmol),H_2SO_4 (10 mmol), CH_3CN: H_2O (2:1), 25^0C, 1-3 h, 50-98%.

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CHAPTRER 1

Os-Catalyzed Asymmetric Dihydroxylation of N-Boc Allyl Amines and Enantioselective Synthesis of (S)-2-(3'-Diethylamino-2'-hydroxypropylamino)pyridine

SECTION I:

Os-Catalyzed Asymmetric Dihydroxylation of *N*-protected Allyl Amines

1.0.1 Introduction

During the last two decades a number of powerful asymmetric reactions have emerged as a result of the growing need to develop efficient and practical synthesis of biologically active compounds. Catalytic asymmetric reactions provide an especially practical entry into chiral world due to their economical use of asymmetric inducing agents.[1] A number of processes have gained wide acceptance, and some of them are even used on an industrial scale. Among the most prominent examples are the "Monsanto Process" for the asymmetric hydrogenation of dehydroamino acids[2] and the enantioselective isomerization of allylic amines,[3] used in the "Takasago Process" for the manufacture of (-)-menthol. The asymmetric epoxidation of unfunctionalized olefins, catalyzed by manganese-salen complexes, and asymmetric dihydroxylation of olefins, catalyzed by osmium[4] also have considerable potential.[5]

Asymmetric dihydroxylation of *N*-protected aromatic allyl amines is one of the important synthetic reactions in organic chemistry. Our current interest in asymmetric dihydroxylation of *N*- allyl aromatic amines is due to the fact that such products possess many biological properties like anticonvulsants[6], such as 2-(3'-diethylamino-2'-hydroxypropylamino)pyridine, 2-(3'-diphenylamino-2'-hydroxypropylamino)pyridine, 2-(3'-piperidine-2'-hydroxypropylamino)pyridine *etc*. (**1-6**) (**Fig.1**)

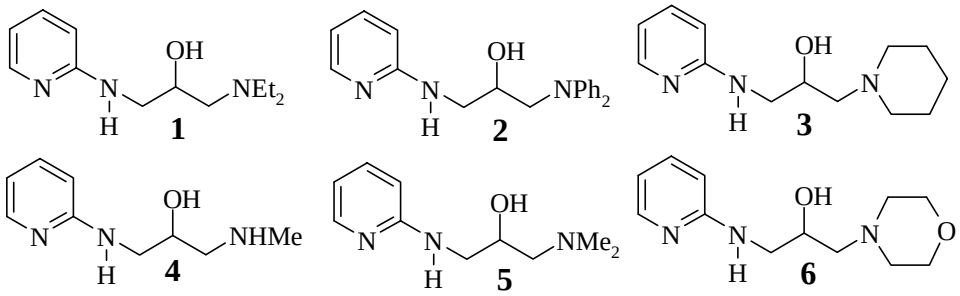


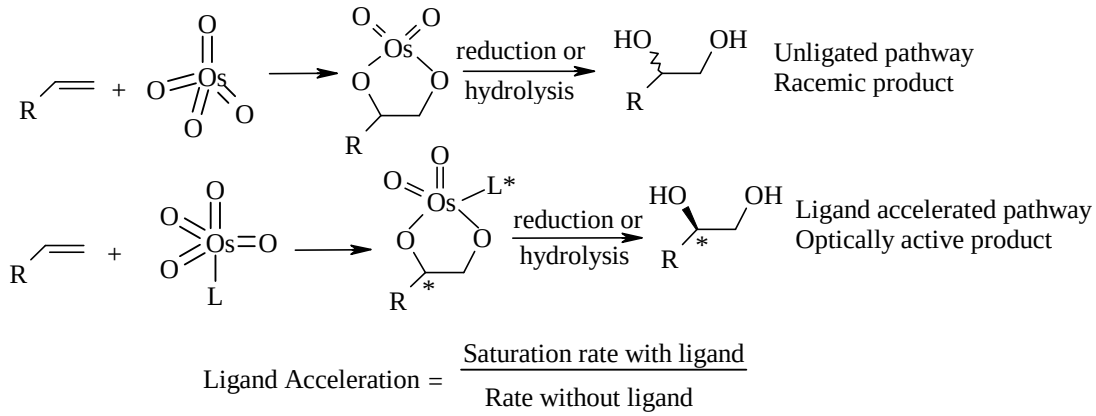
Fig. 1: Some of anticonvulsant drugs

1.0.2 Asymmetric Dihydroxylation (AD)

In recent years much attention has been focused on the catalytic asymmetric synthesis. There are several methods to obtain enantiomerically pure compounds that include classical optical resolution, chromatographic separation of enantiomers, enzymatic resolution and asymmetric synthesis.[7] It often has significant economic advantages over stoichiometric asymmetric synthesis for industrial-scale production of enantiomerically pure compounds. All these asymmetric reactions crucially depend on ligand acceleration effect (LAE).[8] Among all these reactions, Sharpless Catalytic Asymmetric Dihydroxylation (AD) is one of the most important practical and widely used reaction in organic synthesis. It has become the most general method for the preparation of optically active *vicinal-cis*-diols from activated as well as inactivated olefins.[9]

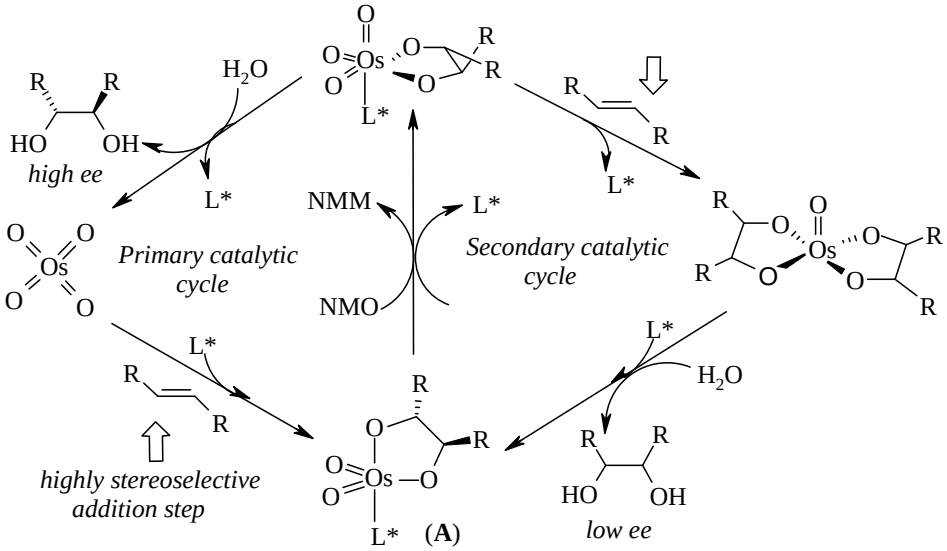
In 1936, Criegee *et al.*[10] have found that addition of pyridine or any other tertiary amine to osmylation of olefins, accelerates the rate of reaction considerably. A major breakthrough has occurred in the field of asymmetric oxidation when Sharpless *et al.*[9b] demonstrated that asymmetric induction could be achieved when chiral amines were added to OsO_4-mediated asymmetric oxidation of olefins. Among the various ligands screened best results were obtained with ligands which were representatives of the cinchona alkaloid family, dihydroquinidine (DHQD) and dihydroquinine (DHQ).[11] A number of recent methods employ

chiral diamine ligands for the asymmetric osmylation of olefins. The simplified mechanism of achiral and chiral dihydroxylation is given in **Scheme 1**.



Scheme 1: Mechanism of OsO_4-catalyzed dihydroxylation of olefin

In order to develop a catalytic method, several co-oxidants such as sodium or potassium chlorate,[12] hydrogen peroxide,[13] *tert*-butyl hydroperoxide[14] and *N*-methylmorpholine *N*-oxide (NMO)[15] were introduced.



Scheme 2: Catalytic cycle for AD using NMO as co-oxidant.

The idea to use these co-oxidants was to minimize the amount of toxic and costly osmium so as to make the process more economical.

Sharpless *et al.*[16] have established that the most practical and suitable catalytic method is with NMO as co-oxidant but the ee's of the diol was less than those produced by the stoichiometric reactions (primary catalytic cycle, **Scheme 2**). The reason was thought to be the involvement of second catalytic cycle (secondary catalytic cycle, **Scheme 2**), which results in low or no ee at all. To improve the %ee of the chiral diol, the second catalytic cycle of AD should be avoided and this was achieved by employing the $K_3Fe(CN)_6$ as reoxidant and using biphasic conditions **(Fig. 2)**.[7,17]

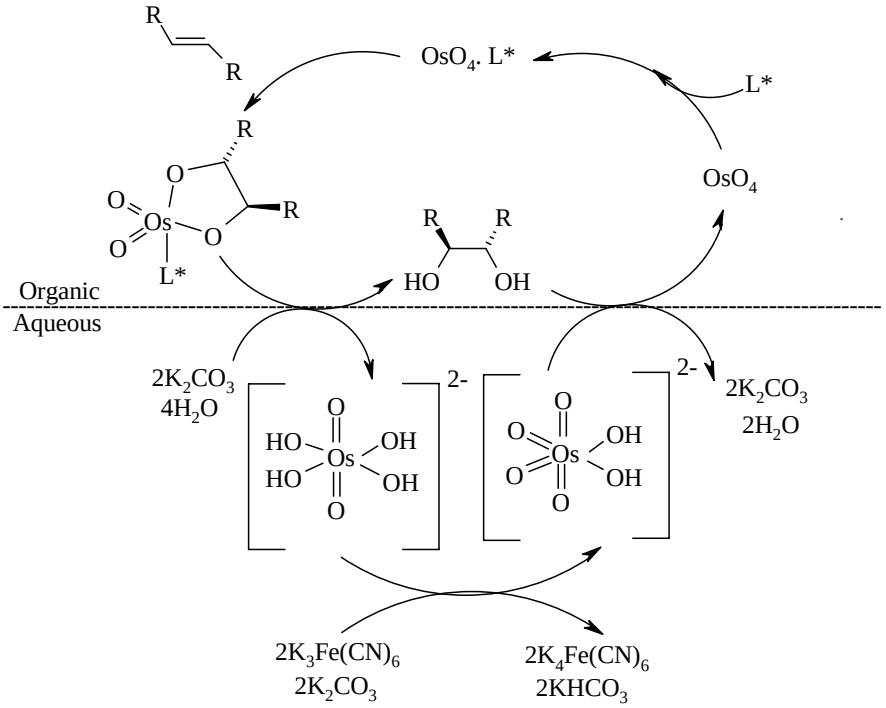
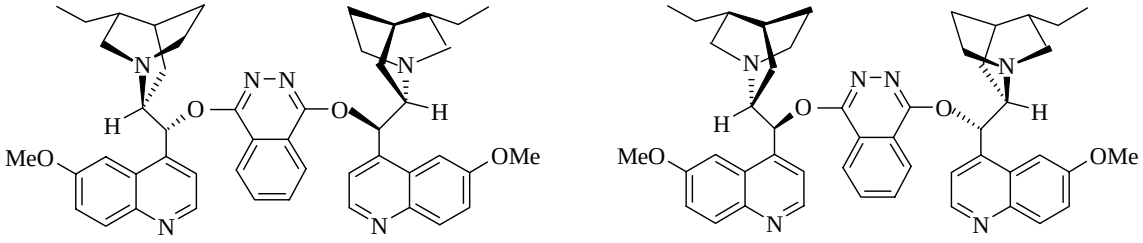


Fig. 2: Catalytic cycle for AD using $K_3Fe(CN)_6$ as co-oxidant.

These conditions helped in protecting the organic osmate-(VI) monoglycolate ester (species **A**, **Scheme 2**) from inopportune oxidation prior to hydrolysis and thereby releasing the diol and ligand to the organic phase and osmium-(VI) to the aqueous phase. Subsequently, osmium-(VI) gets reoxidized and recycled into the catalytic cycle. Further improvement in the AD was realized by the addition of methyl sulfonamide ($MeSO_2NH_2$) to the reaction mixture.

It also helps to accelerate the hydrolysis of the species **A**, thus facilitating the dihydroxylation smoothly.[7] Addition of methyl sulfonamide also allowed carrying out the reactions of 1,2-di-tri- and tetra- substituted olefins at 0^0C, which improved the selectivity as well as %ee.

In order to develop the asymmetric version of the Os-catalyzed AD reaction, Sharpless and coworkers have screened various chiral ligands and found out that the derivatives of cinchona alkaloids gave excellent results. Among all the 250 derivatives of cinchona alkaloid ligands screened, the *bis*-DHQ **7** or DHQD **8** ethers of phthalazine-1, 4-diol have proven to be the best for obtaining high enantioselectivities of the chiral diols[18] **(Fig. 3)**.



$(DHQ)_2$-PHAL (7) **$(DHQD)_2$-PHAL (8)**

Fig. 3: Ligands for asymmetric dihydroxylation reaction

The recent studies have demonstrated the importance of enzyme-like binding pocket of the dimeric cinchona alkaloid for high enantioselectivity of the chiral diols.[18, 19] Sharpless *et al*.[9] have shown that the facial selectivity for both ligands **7** and **8** is different, based on their ability to induce the ee into the diols. This observation has led to the development of mnemonic model **(Fig. 4)** in which olefin with the constraints will be attacked either from the top (i. e. β) face in the presence of dihydroquinidine (DHQD) derivatives or from the bottom (i.e. α) face in the presence of dihydroquinine (DHQ) derived ligand.

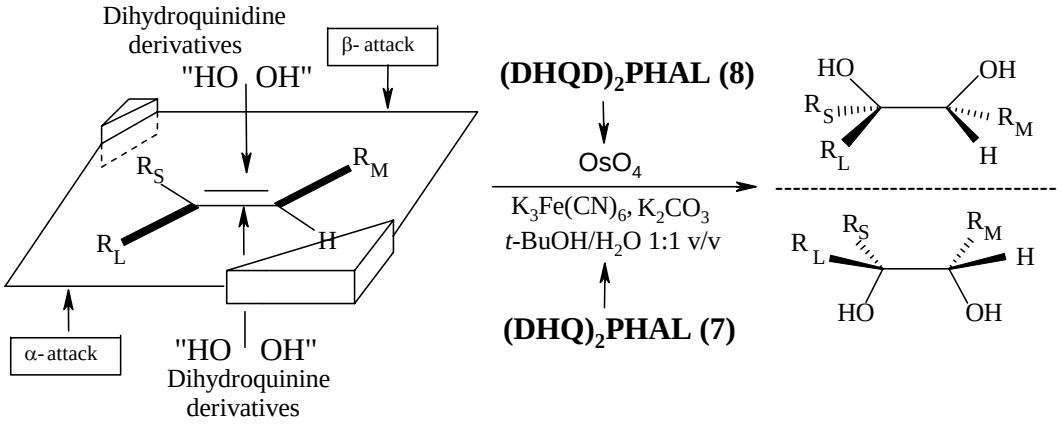


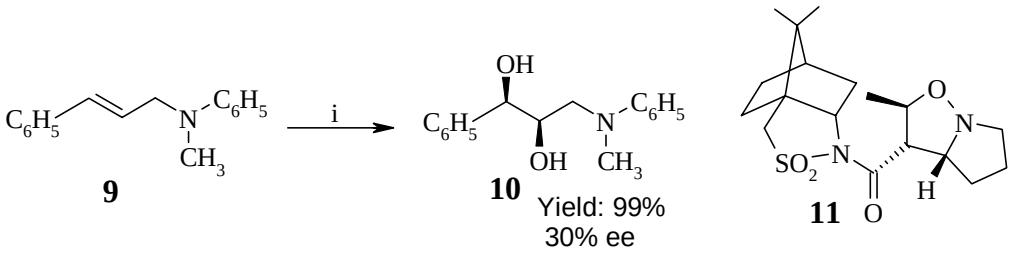
Fig. 4: Enantioselectivity mnemonic scheme

1.0.3 Review of Literature

Literature search revealed that there are no reports available on the asymmetric dihydroxylation of *N*-boc protected aromatic allylic amines. However, some of the related reports on the asymmetric dihydroxylation of allylic and homoallylic amines and amides are known in the literature as shown below.

Yasushi's approach (1992)[20]

Yasushi *et al.* have developed Os-catalyzed asymmetric dihydroxylation of allylamine **9** using chiral isoxazolidine ligands **11** derived from camphorsulfonic acid to give the corresponding diol **10** in good yield and moderate enantiomeric excess (**Scheme 3**).

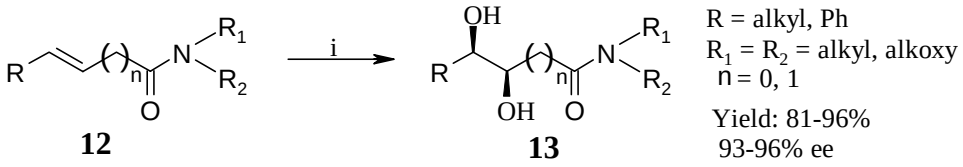


9 **10** **11**

Scheme 3: (i) OsO_4 (cat.), ligand **8**, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH-H_2O, 25^0C.

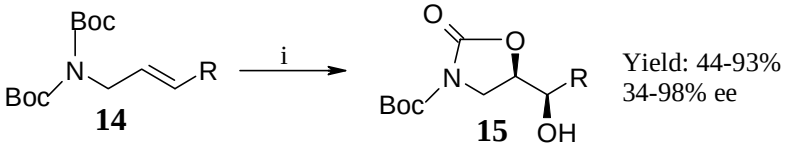
Sharpless' approach (1993)[21]

Sharpless *et al*. have developed a modified AD-mix-β^{TM} obtained by increasing the ligand, $(DHQD)_2$-PHAL, **8** and the potassium osmate content in the AD-mix-β^{TM} five-fold (5 mol% ligand and 1 mol% osmate respectively). The new modified AD-mix-β^{TM} was successfully used for the asymmetric dihydroxylation of *N*,*N*-dialkyl and *N*-methoxy-*N*-methyl α,β-and β,γ-unsaturated amides **12** to give the corresponding diols **13** in excellent yields and ee's (**Scheme 4**).



Scheme 4: (i) modified AD-mix-β^{TM}, $CH_3SO_2NH_2$, *t*-BuOH-H_2O, 0^0C or 25^0C

Sharpless *et al*.[22] have also successfully applied asymmetric dihydroxylation to substrate such as *N*-diBoc allylic and homoallylic amines **14**. This methodology has the advantage that the initial diol product cyclizes spontaneously to give the Boc-protected carbamate **15**, thereby differentiating the newly introduced hydroxyl groups.



Scheme 5: (i) AD-mix-β, $MeSO_2NH_2$, *t*-BuOH-H_2O, 0^0C

1.0.4 Present Work

1.0.4.1 Objective

Although there are some methods reported in the literature related to the asymmetric dihydroxylation of *aliphatic N,N*-dialkyl α,β-and β,γ-unsaturated amides and *N*-diBoc allylic and homoallylic amines, there is no method available on the asymmetric dihydroxylation of *N*-protected *aromatic* allylic amines. However, the existing methods suffer from the following drawbacks: (i) use of stoichiometric amount of methane sulfonamide; (ii) use of modified AD-mix-β^{TM}; (iii) low optical purity for the terminal olefins. In order to overcome these difficulties, there is a definite need to develop a convenient method for the asymmetric dihydroxylation of aromatic allylic amines.

Inspired by Sharpless' work on asymmetric dihydroxylation of *N*-diBoc allylic and homoallylic amines, we became interested to subject various *N*-protected aromatic allylic amines to asymmetric dihydroxylation protocol. The results of this methodology are presented in this section.

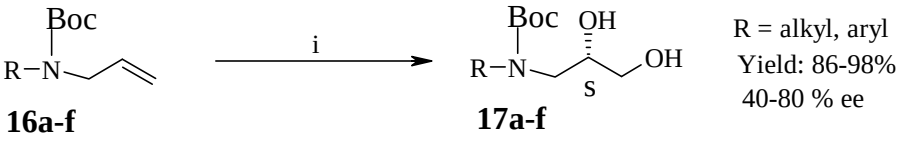
1.0.5 Results and Discussion

Our initial attempt to dihydroxylate *N*-allylanilines in chiral fashion has resulted in a surprisingly very low yield and enantiomeric excess. It may be due to the presence of free lone pair of electron on nitrogen atom coordinating with the osmium tetraoxide during the dihydroxylation process. To avoid this problem, the nitrogen atom is protected as the *N*-Boc derivative.

The *N*-Boc-*N*-allylanilines (**16a-f**) were readily obtained from the corresponding substituted anilines in a two-step sequence by following the known literature procedures.[23]

Thus, aniline on treatment with di-*tert*-butyl dicarbonate (Boc anhydride) in presence of triethylamine and catalytic amount of 4-dimethylaminopyridine (DMAP) in dichloromethane at 0^0C to 25^0C gave *N*-Boc-aniline which was allylated using allyl bromide in presence of sodium hydride as base to give the protected allylamine (**16a-f**) in almost quantitative yield.

When the various substituted *N*-Boc-*N*-allylanilines (**16a-f**) were subjected to osmium catalyzed asymmetric dihydroxylation using $(DHQ)_2$-PHAL [dihydroquinine 1,4-phthalazinediyl diether] (**7**) as a ligand in *t*-BuOH:H_2O system at 0^0C to 25^0C, it gave the corresponding diols (**17a-f**) in 86-98% yield and 40-80% ee (**Scheme 6)**.



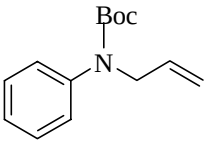
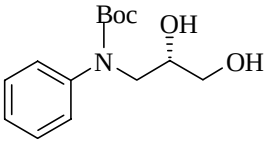
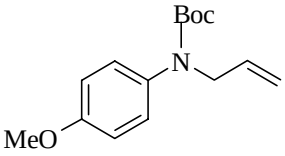
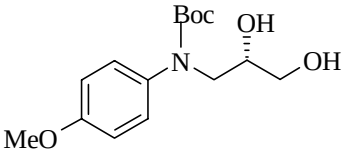
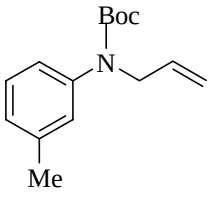
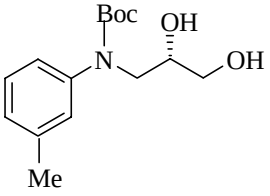
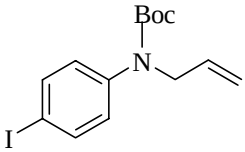
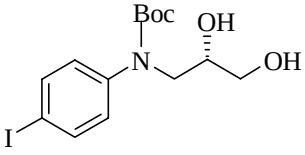
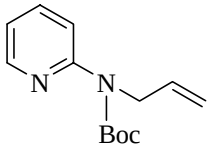
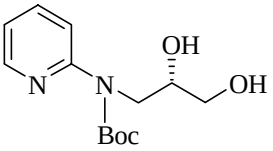
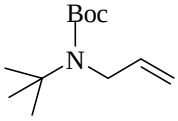
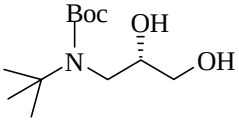
16a-f **17a-f**

Scheme 6: (i) cat. OsO_4, $(DHQ)_2$-PHAL, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH:H_2O (1:1), 0-25^0C, 18-24 h, 86-98%, 40-80% ee.

The optical purity of diols (**17a-f**) was determined by Mosher's ester and HPLC analysis using Chiralcel OD (25 cm) column. Thus, Mosher's esters were prepared by cyclization of diols to oxazolidinones using NaH as base at 0^0C by following literature procedure[22] and free OH were esterified with (R)-α-methoxy-α-trifluromethylphenyl acetic acid (Mosher's acid). For example, measurement of the diastereomeric methyl singlets of **18** at δ 3.51 and 3.54 in ^{1}H-NMR spectrum in $CDCl_3$ demonstrated the ester to be of 48% diastereomeric excess. Also its ^{19}F spectrum showed two signals in the ratio 74:26 further confirming the diastereomeric excess of 48%.

The results of the asymmetric dihydroxylation of various *N*-Boc-*N*- allylsubstituted anilines (**16a-f**) are presented in **Table 1**. As can be seen from **Table 1**, a variety of *N*-Boc-*N*-allylanilines can be subjected for asymmetric dihydroxylation to afford the corresponding

Table 1: Os-catalyzed Asymmetric Dihydroxylation of *N*-protected Allylamines **16**(**a-f**)[a]

Entry	Substrates (16a-f)	Product[b] (17a-f)	Yield (%)[c]	$[\alpha]^{D}_{25}$ in EtOH	ee (%)[d]
a			93	- 2.07 (c 2, EtOH)	40
b			98	- 1.6 (c 1, EtOH)	48
c			96	- 2.10 (c 2, EtOH**)**	45
d			86	- 2.10 (c 2, EtOH**)**	e
e			96	- 29.35 (c 2.2, EtOH)	80
f			96	- 2.50 (c 2, EtOH)	e

a) reaction conditions: allylamine (**16a-f**) (2.1 mmol), OsO_4 (0.02 mmol), $K_3Fe(CN)_6$ (6.4 mmol), K_2CO_3 (6.4 mmol), $(DHQ)_2$-PHAL (0.04 mmol) and *t*-BuOH : H_2O (1:1), 0-25^{0}C, 18-24 h; b) absolute configuration (S) as determined by sign of $[\alpha]_D$ reported in literature; c) yields refer to isolated product after column chromatography; d) %ee based on Mosher ester and HPLC analysis; e) %ee is not determined.

enantiopure diols (**17a-f**) in excellent yield and moderate optical purity. In order to improve the enantioselectivity we increased the amount of ligand (upto 5 mol%), which does not have any significant effect on the enantiomeric excess of the product. We observed that in all the cases studied, the yields of the diols are excellent. The 2-(*N*-Boc-*N*-2',3'-

dhydroxyproplamino)pyridine **17e** showed the excellent yield and good enantiomeric excess than the *N*-boc-*N*-2,3-propanediolanilines (**17a-c**). Asymmetric dihydroxylation of *N*-Boc-*N*-allyl-2-aminopyridine **17e** provides the corresponding diol in excellent yield and good enantiomeric excess, which was determined by Mosher's ester and HPLC analysis using Chiralcel OD (25 cm) column. The formation of diols (**17a-f**) was confirmed by spectroscopic techniques such as ^{1}H and ^{13}C-NMR, IR and GC-Mass. The IR spectrum of all diols (**17a-f**) showed broad bands in the region of 3334-3428 cm^{-1} indicating the presence of hydroxyl functionality in the molecule.

Example 1: The ^{1}H-NMR spectrum of **17c** showed a singlet at δ 1.40 for nine *t*-butyl protons, a broad singlet at δ 3.32 for two OH protons and a shift of allylic protons at δ 3.63-3.745 confirming the presence of *t*-butoxy group and 3,4 dihydroxypropane moiety in the molecule. The ^{13}C-NMR spectrum also showed specific signals at δ 27.79, 80.64 and 52.19, 63.69, 70.20 due to the presence of *t*-butyl carbons and *N*-propane carbons respectively. Its IR spectrum showed a strong absorption band at 3417 cm^{-1} for hydroxy functionality. Its mass spectrum showed molecular ion peak at m/z 281 confirming the formation of diol **17c** (**Fig. 5**).

Example 2: The ^{1}H-NMR spectrum of **17f** showed two singlets at δ 1.39 and δ 1.50 for nine protons each confirming the presence of two *t*-butyl groups in the molecule. Its ^{13}C-NMR showed signals at δ 28.22, 29.58 and 46.86, 63.51, 72.44 for *t*-butyl carbons and *N*-propane carbons respectively. Its IR spectrum also showed a strong absorption band at 3396 cm^{-1} confirming the presence of hydroxy functionality in the molecule (**Fig. 6**).

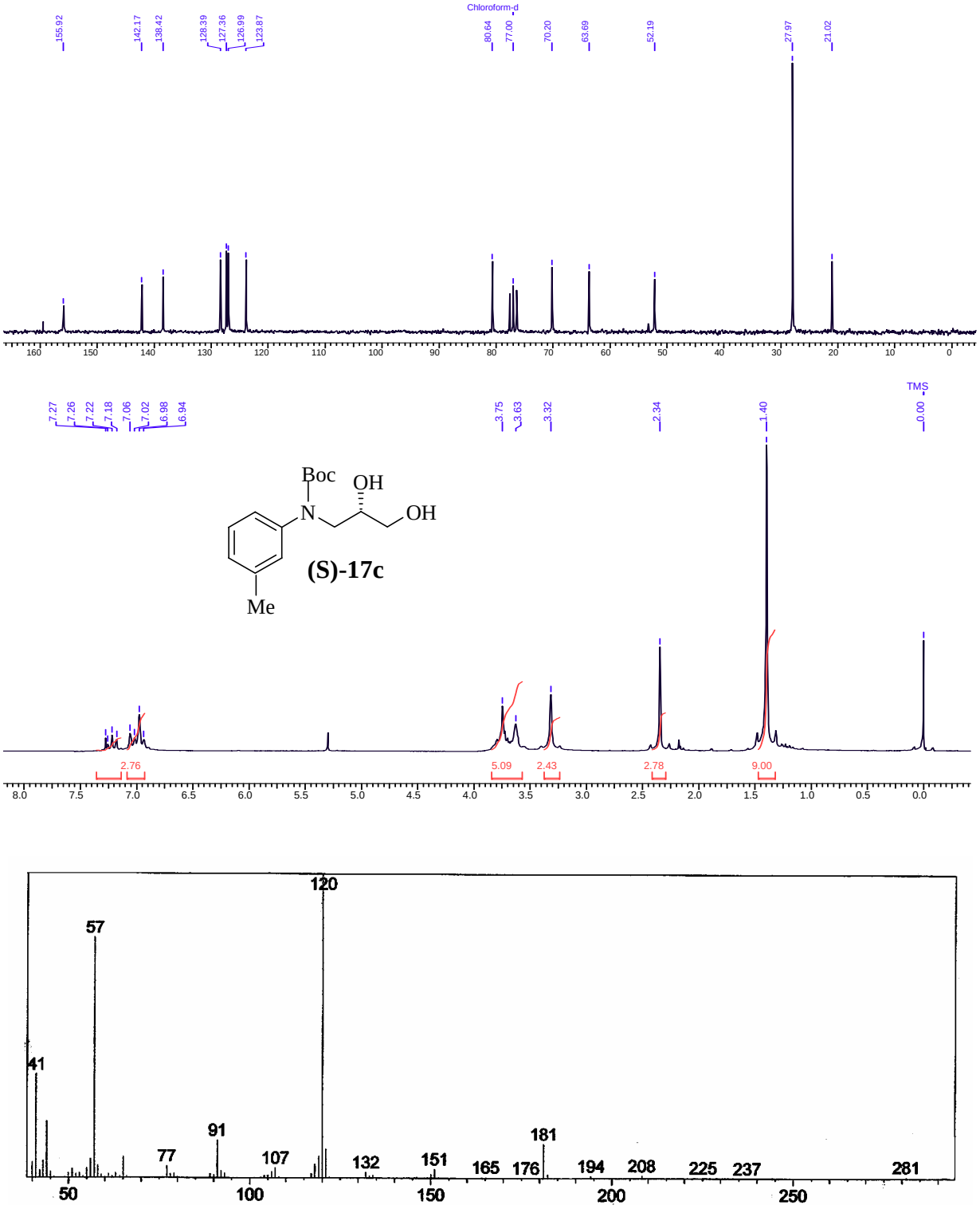


Fig. 5: ^{13}C, ^{1}H -NMR and GC-Mass spectra of 17c

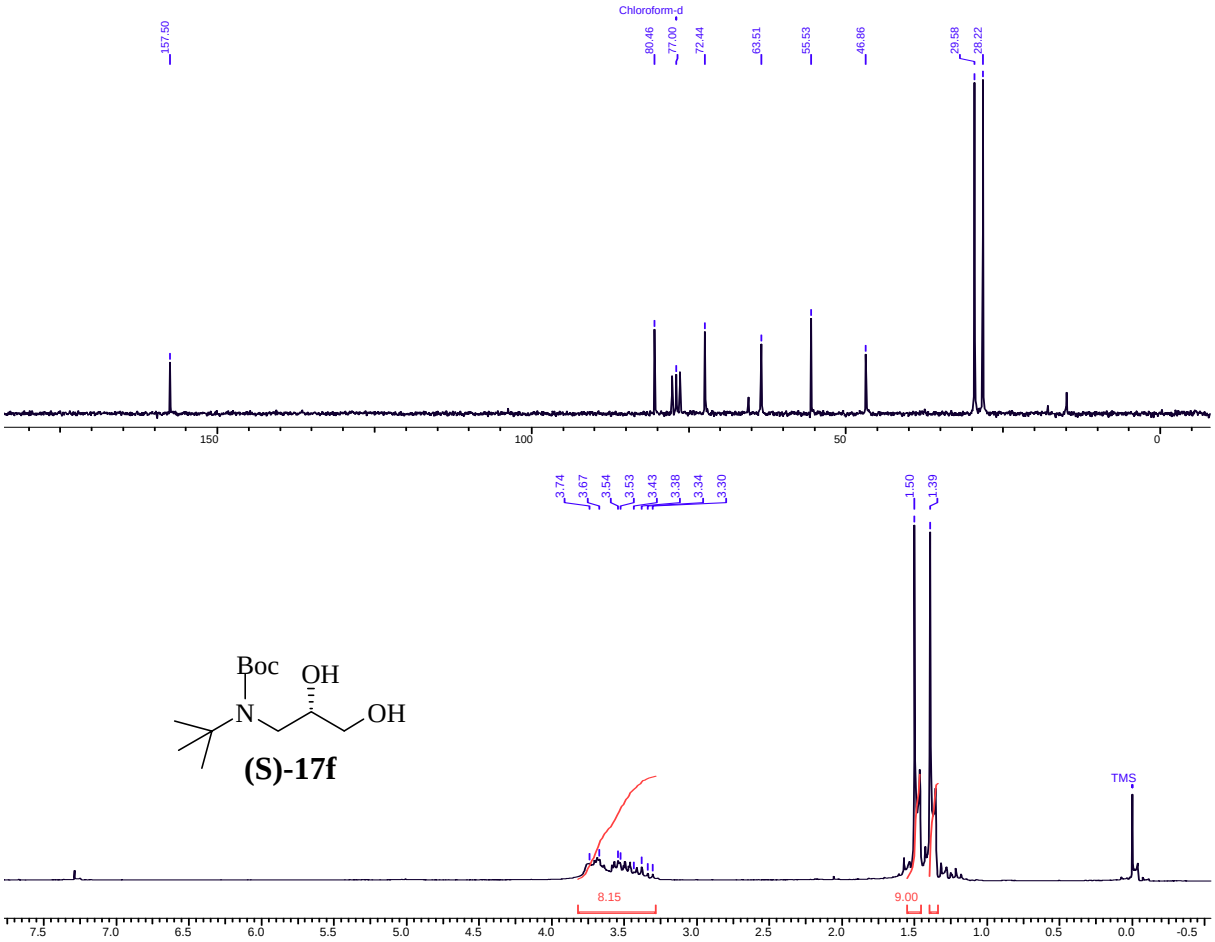


Fig. 6: ^{13}C and ^{1}H -NMR spectra of 17f

1.0.6 Conclusion

In conclusion, we have developed, for the first time, a general method for the asymmetric dihydroxylation of *N*-Boc-*N*-allylanilines by using OsO_4 as catalyst and $(DHQ)_2$-PYR as a ligand to prepare optically active diols in 86-98% yield and 40-80% ee.

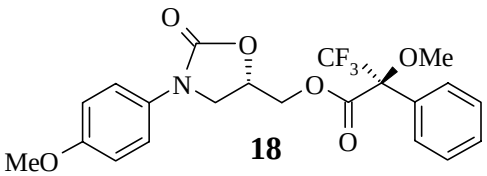
1.0.7 Experimental Section

General procedure for the asymmetric dihydroxylation of *N*-Boc *N*- allyl aromatic amines

A 100 ml RB flask was charged with $K_3Fe(CN)_6$ (2.1 g, 6.4 mmol), K_2CO_3 (0.89 g, 6.4 mmol), $(DHQ)_2$-PHAL (0.038 g, 0.04 mmol) and *t*-BuOH : H_2O (1:1, 40 ml) and the resulting mixture was stirred for 10 minutes at 25^0C. It was then cooled to 0^0C and a solution of OsO_4 (50 μl, 0.02 mmol, 0.5 M solution in toluene) was added. The resulting reaction mixture was stirred at 0^0C for 5 minutes and then the olefin (**16a-f**) (0.5 g, 2.1 mmol) was added. The reaction mixture was stirred at 0-25^0C for 18-24 h (monitored by TLC). It was quenched with sodium sulfite (2.0 g) and extracted with ethyl acetate (4 x 20 ml). Combined organic layers ware washed with brine (15 ml), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by column chromatography using 25% EtOAc in pet. ether as eluent to yield pure diols (**17a-f**) as gum in 86-98% yield.

Preparation of the Mosher ester of diol 17b

A two neck 25 ml flask with septum was charged with (44 mg, 0.206 mmol) *N*,*N*'-dicyclohexylcarbodiimide (DCC), catalytic amount of 4-dimethylaminopyridine (DMAP) and CH_2Cl_2 (5 ml) under nitrogen atmosphere. The flask was allowed to cool to 0^0C for 10 min and a solution of diol **17b** (0.179 mmol) in CH_2Cl_2 (5 ml) was introduced through syringe. It was allowed to stir for additional 10 min, followed by drop-wise addition of (R)-α-methoxy-α-trifluromethylphenyl acetic acid (46 mg, 0.196 mmol) in CH_2Cl_2 was done. This reaction mixture was then stirred at 0^0C for additional one hour and at 25^0C temperature for over night. The solvent was evaporated under reduced pressure to get crude material, which was then purified by column chromatography eluting 20% ethyl acetate in petroleum ether to get the Mosher ester **18** of diol **17b**.



18

Yield: 90%: mp: 110^{0}C: **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.51 (s, 2.23H), 3,54 (s, 0.77H), 3.66-3.71 (m, 1H), 3.80 (s, 3H), 3.97-4.09 (m, 1H), 4.39-4.50 (m, 1H), 4.63-4.70 (m, 1H), 4.82-4.91 (m, 1H), 6.85-6.92 (m, 1H), 7.25-7.52 (m, 7H). **^{19}F-NMR** (200 MHz, $CDCl_3$): δ 10.50 (s, 2.22), 10.65 (s, 0.78).

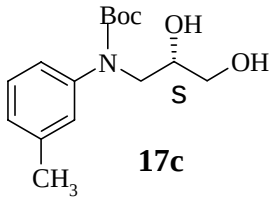
(S)-*N*-Boc-*N*-2,3-propanediolaniline (17a)

Yield: 93%; gum; **$[\alpha]^{25}_D$**: - 2.07 (c 3.5, EtOH); **Mosher ester**: 40% ee: **IR**: ($CHCl_3$, cm^{-1}): 448, 700, 749, 861, 1167, 1398, 1457, 1500, 1597, 1656, 1704, 2923, 2977, 3417; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.39 (s, 9H), 3.49 (bs, 2H), 3.59-3.61 (m, 2H), 3.72-3.74 (m, 3H), 7.15-7.38 (m, 5H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 28.00, 52.41, 63.80, 70.38, 80.79, 126.26, 126.92, 128.64, 142.50, 155.96; **MS** (m/z, % relative intensity): 267 (M^+**,** 10) 252 (2), 211 (8), 194 (20), 180 (24), 167 (100), 162 (5), 150 (15), 137 (100), 118 (80), 106, 93, 77, 57, 41; **Analysis**: $C_{14}H_{21}NO_4$ requires C, 62.92; H, 7.86; N, 5.24; found C, 62.80; H, 7.95; N, 5.28%.

(S)-*N*-Boc-*N*-2,3-propanediol-4-methoxyaniline (17b)

Yield: 98%; **mp**: 96-98^{0}C; **$[\alpha]^{25}_D$**: - 1.6 (c 1, EtOH); **Mosher ester**: 48% ee; **IR**: ($CHCl_3$, cm^{-1}): 475, 700, 830, 1036, 1151, 1295, 1512, 1671, 3017, 3418; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.38 (s, 9H), 3.49 (bs, 2H), 3.62-3.67 (m, 2H), 3.68-3.76 (m, 3H), 3.80 (s, 3H), 6.85 (d, *J* = 8.0 Hz, 2H), 7.07 (d, *J* = 8.8 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 28.08, 52.74, 55.24, 63.84, 7049, 80.68, 114.02, 128.06, 135.58, 156.43, 157.90; **Analysis**: $C_{15}H_{23}NO_5$ requires C, 60.60; H, 7.74; N, 4.71; found C, 59.96; H, 7.90; N, 4.98%.

(S)-*N*-Boc-*N*-2,3-propanediol-3-methylaniline (17c)

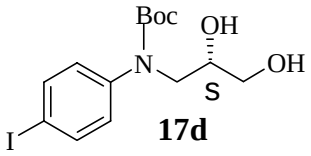


17c

Yield: 96%; gum; **$[\alpha]^{25}_D$**: - 2.15 (c 2, EtOH); **Mosher ester**: 45% ee; **IR**: ($CHCl_3$, cm^{-1}): 464, 700, 770, 845, 863, 977, 1170, 1495, 1586, 1688, 1742, 2880, 2987, 3428; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.40 (s, 9H), 2.34 (s, 3H), 3.32 (bs, 2H) 3.63 (bs, 2H), 3.75 (bs, 3H), 6.94-7.06 (m, 3H), 7.18-7.27 (m, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 21.02, 27.97, 52.19, 63.69, 70.20, 8064, 123.87, 126.99, 127.36, 128.39, 138.42, 142.17, 155.92; **MS** (m/z, % relative

intensity): 281 (4), 181 (10), 151 (5), 132 (3), 120 (100), 107 (5), 91 (10), 77 (6), 57 (80), 41 (30); (**Analysis**: $C_{15}H_{23}NO_4$ requires C, 64.05; H, 8.18; N, 4.98.

(S)-*N*-Boc-*N*-2,3-propanediol-4-iodoaniline (17d)



17d

Yield: 86%; gum; $[\alpha]^{25}_{D}$: - 2.10 (c 2, EtOH); **IR**: ($CHCl_3$, cm^{-1}): 469, 502, 725, 759, 808, 867, 990, 1135, 1486, 1586, 1656, 1704, 2869, 2977, 3428; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.39 (s, 9H), 3.45 (bs, 2H), 3.57-3.61 (m, 2H), 3.71 (bs, 3H), 6.95 (d, *J* = 8.0 Hz, 2H), 7.65 (d, *J* = 8.0 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 28.00, 52.26, 63.73, 70.20, 81.08, 90.78, 128.83, 137.69, 142.32, 155.29; **Analysis**: $C_{14}H_{20}INO_4$ requires C, 32.36; H, 3.85; I, 48.74; N, 2.69; found C, 32.20; H, 3.95; I, 48.80; N, 2.68%.

(S)-2-(*N*-Boc-*N*-2',3'-dihydroxypropylamino)pyridine (17e)

NMR Data is given under **Experimental Section II**

(S)-*N*-Boc-*N*-2,3-propanediol-*t*-butylamine (17f)

Yield: **96%;** gum; $[\alpha]^{25}_{D}$: - 2.50 (c 2, EtOH); **IR**: ($CHCl_3$, cm^{-1}): 443, 749, 861, 920, 953, 1285, 1393, 1452, 1688, 1710, 2902, 2977, 3396; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.39 (s, 9H), 1.50 (s, 9H), 3.41-3.57 (m, 8H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 28.22, 29.58, 46.86, 55.53, 63.51, 72.44, 80.46, 157.50; **Analysis**: $C_{12}H_{25}NO_4$ requires C, 58.29; H, 10.12; N, 5.66; found C, 59.20; H, 9.95; N, 5.68%.

SECTION II:

Enantioselective Synthesis of (S)-2-(3'-Diethylamino-2'-hydroxypropylamino)pyridine

1.1.1 Introduction

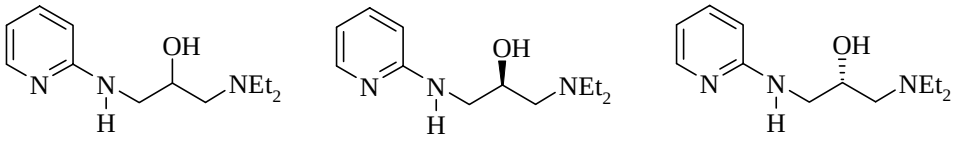
Chiral drugs have long been used as therapeutic agents, but in most cases only in racemic form. Over the last 20 years, however, great advances in production technology and quality control techniques have made chirality an important issue. In the development process of a new drug, differentiation due to chirality is now an integral part of preclinical and clinical investigations. The choice of racemate must be justified and the criteria for this will become more demanding in the future. [24]

The members of a pair of enantiomers often show different pharmacological and metabolic characteristics. The synthesis of homochiral drugs has become a key issue not only in academic research but also in the pharmaceutical industry.[25] Biological systems, in most cases, recognize the members of a pair of enantiomers as different substances, and the two enantiomers will exhibit different responses. Thus, one enantiomer may act as a very effective therapeutic drug whereas the other enantiomer is highly toxic. It has been shown for many pharmaceuticals that only one enantiomer contains all the desired activity, and the other is either totally inactive or highly toxic.

There are several methods to obtain enantiomerically pure materials, which include classical resolution *via* diastereomers, chromatographic separation of enantiomers, enzymatic resolution, chiral kinetic resolution and asymmetric synthesis. OsO_4-catalyzed asymmetric

dihydroxylation (AD), developed by Sharpless *et al.*[26] is a simple, efficient and the most reliable method for asymmetric synthesis of chiral vicinal diols.

1.1.2 The Pharmacology of (S)-2-(3'-Diethylamino-2'-hydroxypropylamino)pyridine



(±)-1 **(R)-(+)-1a** **(S)-(-)-1b**

Fig. 7:

Pyridine derivatives were reported to be associated with anticonvulsant,[27] cardiotonic,[28]antihypertensive[29] and β- adrenergic blocking activity.[30] Aminopropanes were reported to possess CNS depressant,[31] neuroleptic,[32] antiarrhythmics,[33] hypotensive[34] and β-adrenergic blocking activity.[35] Therefore, it was envisaged that chemical entities with both pyridine and aminopropane moieties would result in compounds of interesting biological activities. Joseph *et al.*[36] first time synthesized racemic pyridine derivative 2-(3'-diethylamino-2'-hydroxypropytlamino)pyridine **1**.

All the 2-(3'-substituted-2'-hydroxypropylamino)pyridine (**Section I, Fig. 1**) have exhibited significant anticonvulsant activity but 2-(3'-diethylamino-2'-hydroxypropytlamino)pyridine **1** was found to exhibit the highest anticonvulsant activity. The anticonvulsant activity of the racemic pyridine derivative, 2-(3'-substitued-2'-hydroxypropylamino)pyridine (**Fig. 1**) were tested against maximal electroshock induced convulsions in rats.[37]All the compounds were soluble in water and administrated to the

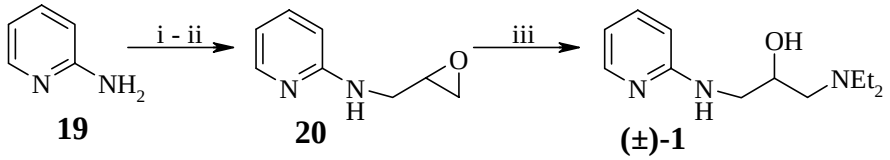
animals as a solution in distilled water. The racemic pyridine derivatives were also screened for cardiac activity[38] on isolated frog heart.

1.1.3 Review of Literature

Literature search revealed that only one report is available on the racemic synthesis of 2-(3'-diethylamino-2'-hydroxypropytlamino)pyridine, (±)-**1** which is described below.

Joseph's approach (2002)[36]

Joseph *et al*. have synthesized racemic 2-(3'-diethylamino-2'-hydroxypropylamino)pyridine (±)-**1**, from 2-aminopyridine **19** followed by alkylation with epichlorohydrin to form epoxide **20** intermediate. The epoxide was then subjected to regiospecific nucleophilic opening with diethylamine to afford the corresponding racemic drug, 2-(3'-diethylamino-2'-hydroxypropylamino)pyridine (±)-**1** (**Scheme 8**).



19 **20** **(±)-1**

Scheme 8: (i) Sodium methoxide, methanol, 65^{0}C, 1h; (ii) epichlorohydrin, DMF, 25^{0}C, 1h, 34%; (iii) diethylamine, methanol, 65^{0}C, 24h, 45%.

1.1.4 Present Work

1.1.4.1 Objective

Literature search revealed that only one report is available on the synthesis of racemic 2-(3'-diethylamino-2'-hydroxypropylamino)pyridine (±)-**1**. However, not much attention has been focused on its asymmetric version. Thus, the objective of the present work is to synthesize optically active (S)- 2-(3'-diethylamino-2'-hydroxypropylamino)pyridine (**1b**) using Sharpless Asymmetric Dihydroxylation as a key reaction. The pyridine derivative 2-(3'-diethylamino-2'-hydroxypropylamino)pyridine (**1b**) is a new anticonvulsant agent that represents a new generation of β-blockers. The cardiac activity exhibited by these compounds may be correlated to the presence of the pharmacophore similar to the chemical functionality present in β-adrenergic blocking agent so that its asymmetric synthesis is highly desirable. The present strategy for the asymmetric synthesis of (S)- 2-(3'-diethylamino-2'-hydroxypropylamino)pyridine (**1b**) is shown in **Scheme 9.** The retrosynthetic analysis of 2-(3'-diethylamino-2'-hydroxypropylamino)pyridine is shown in **Fig. 8.** There are three possible routes visualized to synthesize this molecule; our approach is based on the **route b**.

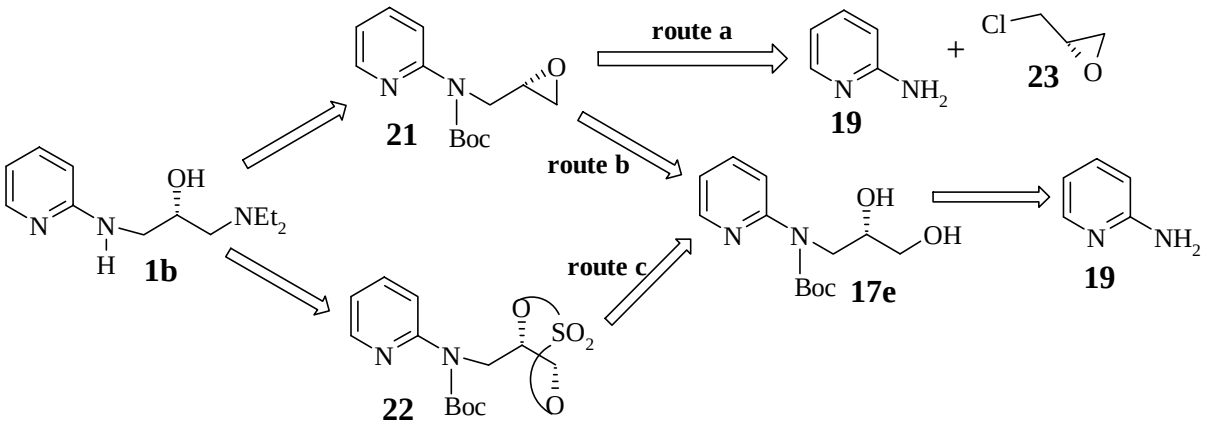
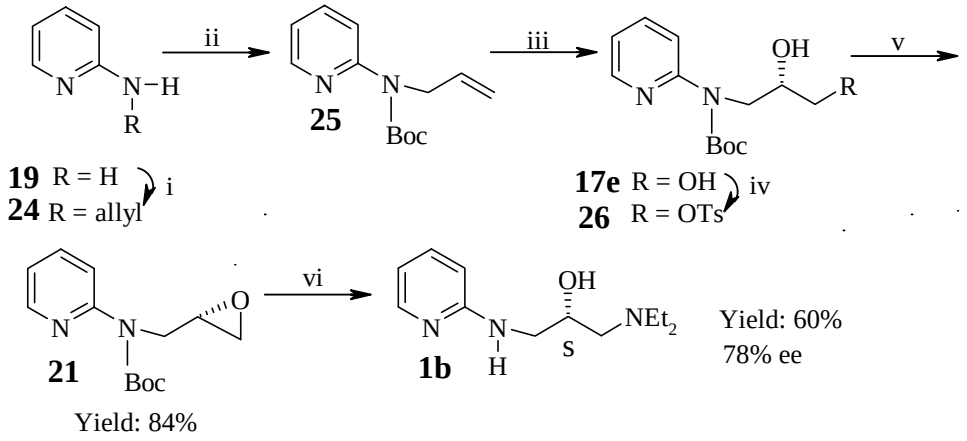


Fig. 8: Retrosynthetic analysis of (S)-2-(3'-diethylamino-2'-hydroxypropylamino)pyridine (1b)

1.1.5 Results and Discussion

The synthetic strategy for (S)-2-(3'-diethylamino-2'-hydroxypropylamino)pyridine **1b** is shown in **Scheme 9** wherein Os-catalyzed asymmetric dihydroxylation (AD) constitutes a key step in introducing chirality into the molecule.



Scheme 9: (i) allyl bromide, THF, 60^0C 12 h, 98%; (ii) $(Boc)_2O$, Et_3N, cat. DMAP, CH_2Cl_2, RT. 12 h, 95%; (iii) cat. OsO_4, $(DHQ)_2$-PHAL, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH:H_2O (1:1), 0-25^0C, 24 h, 96% , 80% ee. (iv) *p*-TsCl, pyridine, CH_2Cl_2 0^0C 24 h, 80%; (v) K_2CO_3, MeOH, 0^0C 12 h, 84%; (vi) Et_2NH, MeOH, reflux, 24 h, 60%, 78% ee.

The readily available 2-aminopyridine (**19**) was converted into *N*-allyl-2-aminopyridine (**24**) in 98% yield by alkylation with allyl bromide. The ^{1}H-NMR spectrum of **24** showed typical pattern for the allylic functionality in the region of δ 4.83 - 5.94 and the ^{13}C-NMR spectrum showed signals for the carbons of the allylic functionality in the region of δ 54.62 - 114.94. Allylamine **24** was protected with di-*tert*-butyldicarbonate (Boc anhydride) in the presence of triethylamine and catalytic amount of 4-dimethylaminopyridine (DMAP) to give Boc protected allylamine **25** in 95% yield. The ^{1}H-NMR spectrum of **25** showed a singlet of nine protons at δ 1.54 and its ^{13}C-NMR spectrum showed signals for the carbon of the *tert*-butoxy group at δ 28.26 and carbonyl carbon at δ 161.54, which confirmed the presence of *tert*-butoxy group in the molecule (**Fig. 9**).

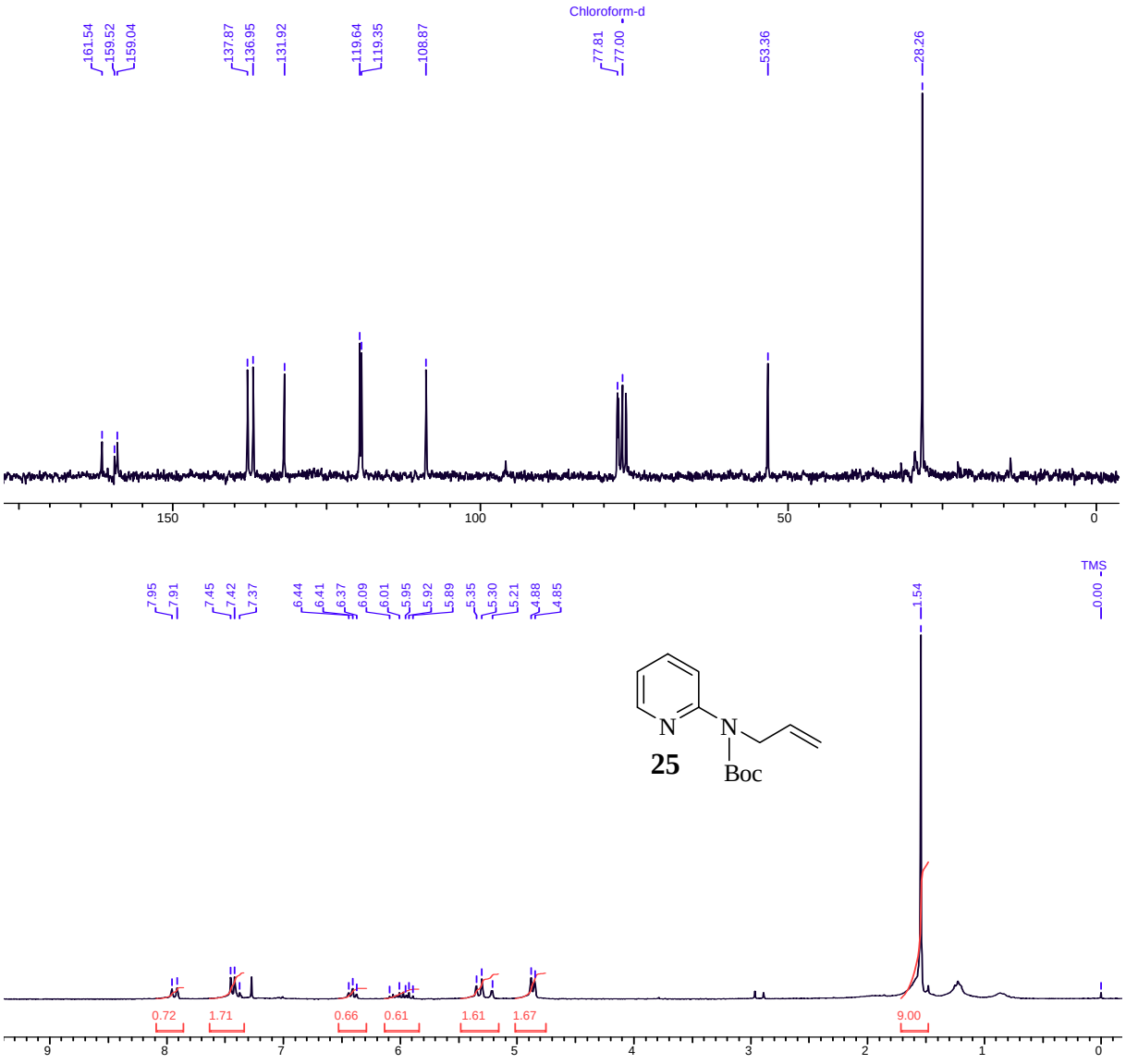
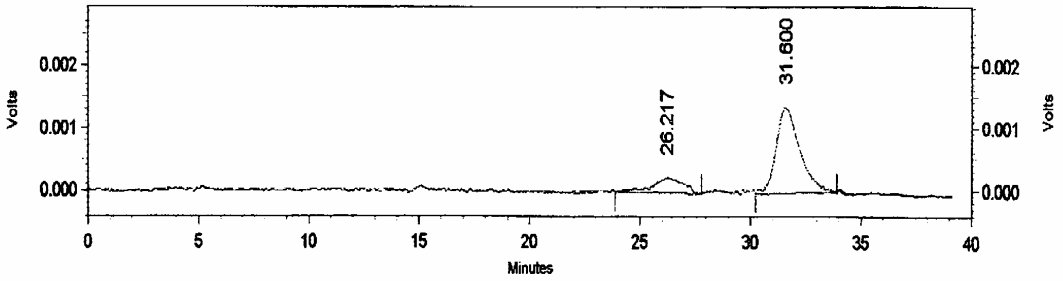


Fig. 9: ^{13}C and ^{1}H -NMR spectra of *N*-Allyl-*N*-boc-2-aminopyridine (25)

N-Protected allylamine **25** was subjected to ADH in the presence of $(DHQ)_2$-PHAL [hydroquinine 1,4-phthalazinediyl] as a chiral ligand in the presence of $K_3Fe(CN)_6/K_2CO_3$ as a co-oxidant/base to give optically active diol **17e** in 96% yield and 80% ee. The optical purity of diol **17e** was determined both by Mosher's ester and by HPLC analysis using Chiralcel OD (25 cm) column and was found to be 80% ee (**Fig. 10**)



Detector A - 1
(254nm)

Pk #	Retention Time	Area	Area %	Height %	Name
1	26.217	23100	10.195	14.776	
2	31.600	103859	89.805	85.224	
Totals		126959	100.000	100.000	

Fig. 10: HPLC Chromatogram of chiral diol 17e

The IR spectrum of diol **17e** showed a broad band in the region of 3300-3356 cm^{-1} indicating the presence of hydroxyl functionality in the molecule. The ^{1}H-NMR spectrum showed disappearance of signal for allylic protons in the region of δ 4.85 - 6.44. Multiplets in the region of δ 3.34 – 3.57 and 4.32 - 4.49 for four protons, 3.96 – 4.04 for one proton and a broad singlet for two OH protons confirmed the formation of diol. The ^{13}C-NMR spectrum of diol **17e** showed typical signals at δ 28.11, 78.47 and at δ 55.09, 62.00, 70.57 due to the presence of *t*-butyl carbons and *N*-propane carbons respectively in the molecule (**Fig. 11**).

We attempted to convert the diol **17e** into the corresponding cyclic sulfite. However, the formation of cyclic sulfite did not take place. Various other conditions such as the low temperature, change of base etc. were tried to get cyclic sulfite but all of them failed. We also tried to obtain epoxide **21** in one step by following the standard Sharpless method from diol **17e** but it resulted in very low yield of epoxide **21**.

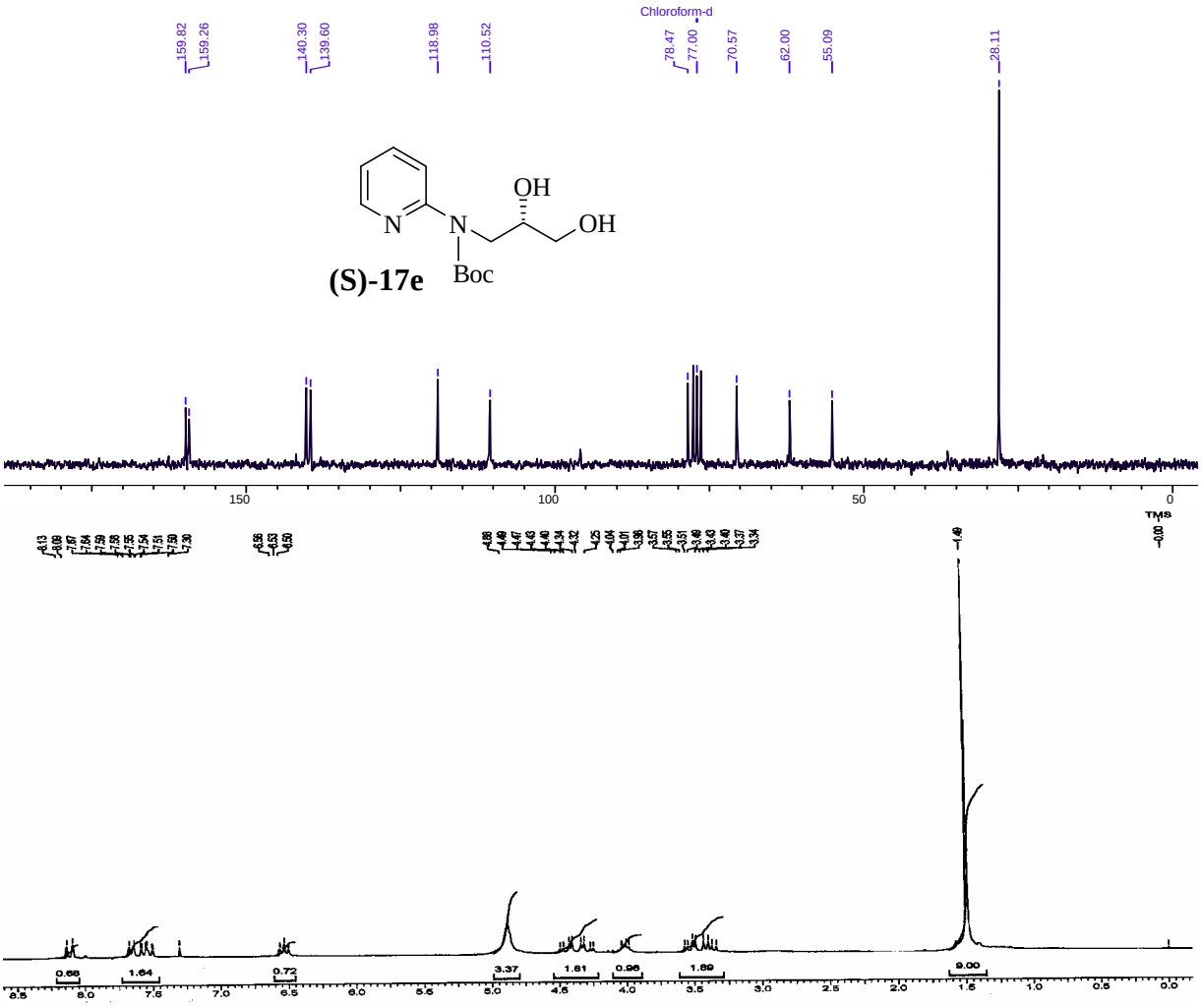


Fig. 11: ^{13}C and ^{1}H -NMR spectra of chiral diol 17e

Hence, we decided to convert the diol **17e** into the corresponding epoxide **21** using a two-step procedure. Thus, diol **17e** was treated with tosyl chloride and pyridine in CH_2Cl_2 at 0^0C to give monotosylate **26**. The monotosylate **26** was treated with anhydrous K_2CO_3 in methanol at 0^0C to give the epoxide **21** in 84% yield. Its IR spectrum showed the disappearance of OH peak in the region of 3356 cm^{-1}. Its ^{1}H-NMR spectrum showed an upfield signals for epoxide protons. The ^{13}C-NMR spectrum showed the upfield shift in case of the epoxide carbon signals at δ 57.30, and 62.22 confirming the formation of epoxide moiety in the molecule (**Fig. 12**).

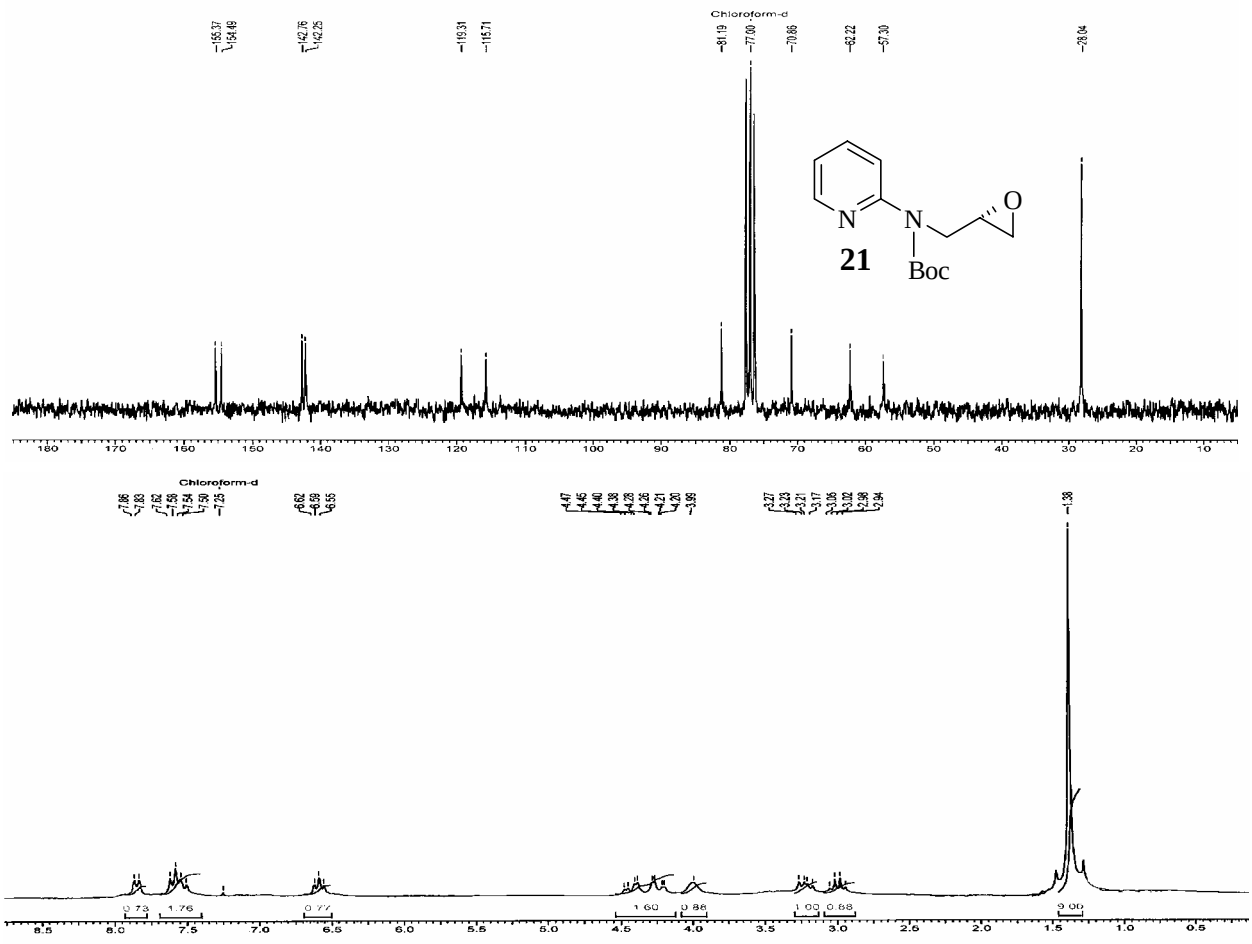


Fig. 12: ^{13}C and ^{1}H -NMR spectra of epoxide 21

The epoxide **21** was subjected to regio and stereoselective opening with diethylamine in dry methanol at reflux temperature for 24 h to afford the final drug (S)-2-(3'-diethylamino-2'-hydroxypropylamino)pyridine **1b** in 60% yield and 78% ee. Here deprotection of Boc-group also occurred simultaneously. The IR spectrum of **1b** showed strong band in the region of 3024 – 3342 cm^{1}. Its ^{1}H-NMR spectrum showed a specific signal of ethyl group at δ 1.25 as triplet for six protons and a quartet at δ 2.99 for four protons confirming the presence of diethylamino group in the molecule. The ^{13}C-NMR spectrum also showed signals of ethyl carbons at δ 11.59 and 43.57 which confirmed the formation (S)-2-(3'-diethylamino-2'-hydroxypropylamino)pyridine **1b** (**Fig. 13)**.

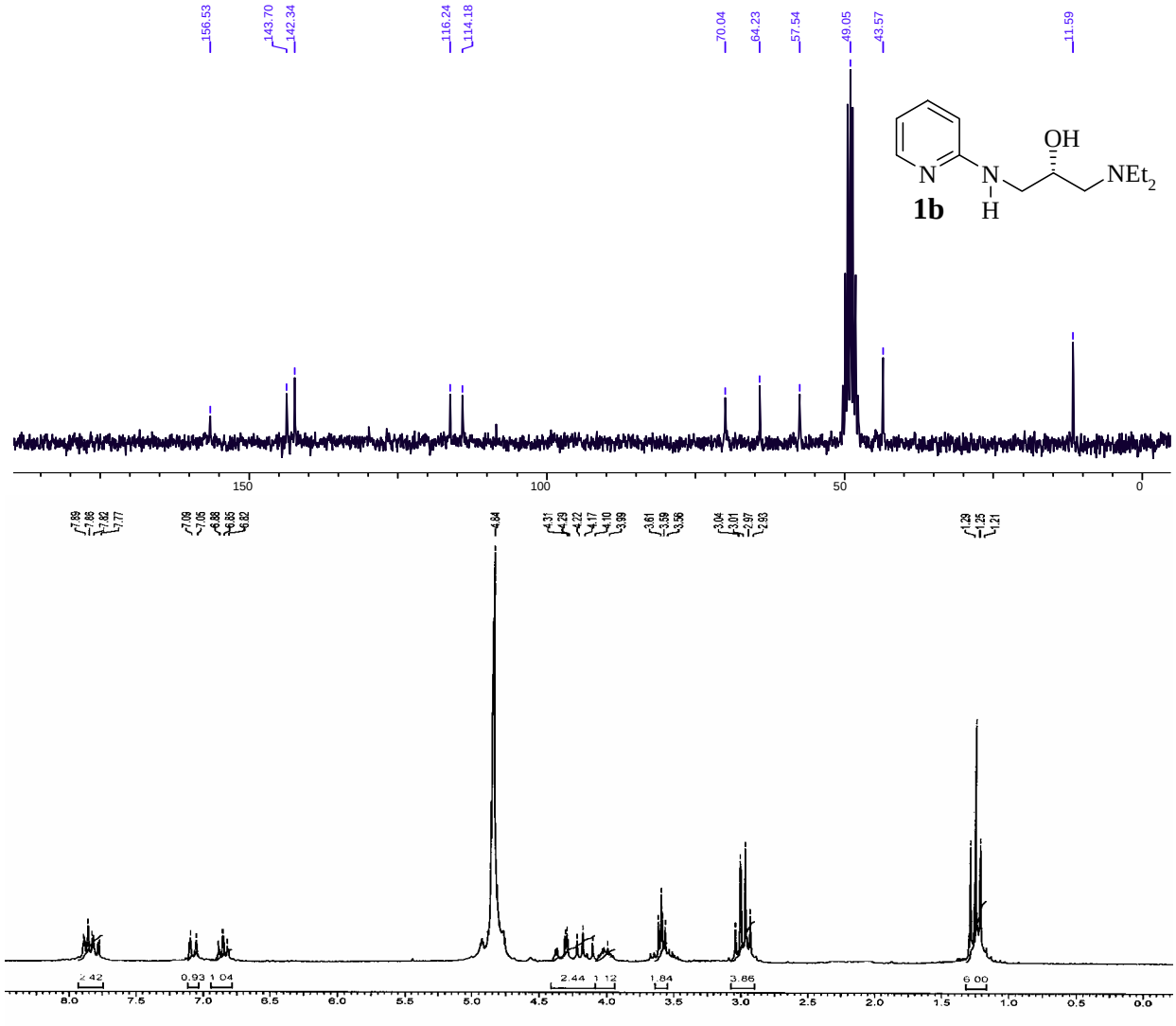


Fig. 13: ^{13}C and ^{1}H -NMR spectra of (S)-2-(3'-Diethylamino-2'-hydroxypropylamino)pyridine (1b)

1.1.6 Conclusion

In conclusion, we have developed a simple and practical method of asymmetric dihydroxylation of aromatic protected allylic amines and successfully applied this methodology for the enantioselective synthesis of anticonvulsant drug (S)-2-(3'-diethylamino-2'-hydroxypropylamino)pyridine (**1b**) [36% overall yield, 78% ee] in overall six steps starting from 2-aminopyridine.

1.1.7 Experimental Procedure

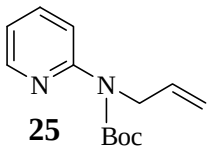
Preparation of *N*-allyl-2-aminopyridine (24):

To a mixture containing 2-aminopyridine (5 g, 53.3 mmol) and allyl bromide (5.9 ml, 63.8 mmol) in 40 ml THF was stirred at 60^0C, 12 h under nitrogen atmosphere (monitored by TLC). After the reaction was over, the product precipitated out; filtered the product washed with ethyl acetate to give pure product **24** (6.9 g).

Yield: 98%; white solid **mp**: 70-74^{0}C; **IR** ($CHCl_3$, cm^{-1}): 770, 899, 1055, 1162, 1264, 1387, 1538, 1656, 2964, 3084, 3350; **^{1}H-NMR** (200 MHz, DMSO-d_6): δ 4.83 (d, *J* = 4.0 Hz, 2H), 5.10 (dd, *J* = 18 and 26 Hz, 2H), 5.80-5.94 (m, 1H), 6.75 (t, *J* = 8.0 Hz, 1H), 7.18 (d, *J* = 8.0 Hz, 1H), 7.69 (t, *J* = 8.0 Hz, 1H), 7.89 (d, *J* = 6 Hz, 1H) 8.44 (bs, 1H); **^{13}C-NMR** (50 MHz, DMSO-d_6): δ 54.62, 113.25, 114.94, 118.99, 130.42, 139.98, 142.59, 153.76; **MS** m/z (% rel. intensity): 134 (M^+, 20), 133 (30) 119 (28), 106 (15), 94 (100), 86 (5), 80 (75), 67 (80), 57 (10); **Analysis**: $C_8H_{10}N_2$ requires C, 71.64; H, 7.46; N, 20.89%; found C, 70.89; H, 8.10; N, 19.97%.

Preparation of *N*-Boc-*N*-allyl-2-aminopyridine (25):

To a stirred mixture of *N*-allyl-2-aminopyridine (3 g, 22.3 mmol), triethylamine (7.7 ml, 56 mmol) and catalytic amount of 4-dimethylaminopyridine (DMAP) in CH_2Cl_2 (25 ml) at 0^0C was added di-*tert*-butyldicarbonate (Bocanhydride) (5.1 ml, 4.88 mmol) drop-wise under nitrogen atmosphere. The reaction mixture was further starred at 0-25^{0}C for 12 h (monitored by TLC). The reaction mixture was concentrated under reduced pressure to give the crude product, which was further purified by column chromatography on silica gel using petroleum ether: EtOAc (50:50) as eluent to afford a white crystalline solid **25** in 95% yield.



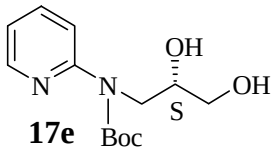
25

Yield: 95%; White solid **mp**: 80-82^{0}C; **IR** ($CHCl_3$, cm^{-1}): 759, 834, 942, 1001, 1151, 1280, 1361, 1430, 1532, 1613, 1672, 2934, 3034; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.54 (s, 9H), 4.87 (d, *J* = 6.0 Hz, 2H), 5.21-5.35 (m, 2H), 5.89-6.09 (m, 1H), 6.4 (t, *J* = 8.0 Hz, 1H), 7.37-7.45 (m, 2H), 7.93 (d, *J* = 8.0 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 28.26, 53.36, 77.81, 108.87,

119.35, 119.64, 131.92, 136.95, 137.87, 159.04, 159.52, 161.54; **MS** m/z (% rel. intensity): Electrospray ionization technique (solvent: methanol + water + ammonium acetate) 234.34 (M^+, 40), 217.44 (2), 177.24 (100), 159.53 (5), 133.72 (20), 119.91 (10), 90.50 (5); **Analysis**: $C_{13}H_{19}N_2O_2$ requires C, 66.38; H, 8.08; N, 11.91; found C, 66.18; H, 8.46; N, 11.68%.

Preparation of (S)-2-(*N*-Boc-*N*-2',3'-dihydroxypropylamino)pyridine (17e):

See **Section I**, Exptal for its detailed procedure



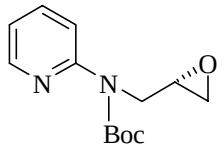
17e

(S)-2-(*N*-Boc-*N*-2',3'-dihydroxypropylamino)pyridine (17e)

Yield: 96%; **mp**: 108-110^{0}C; **[α]$^{25}_D$**: – 29.35 (c 2.2, EtOH); HPLC: 80% ee, λ-250, Chiralcel OD (25 cm), 5% isopropanol/hexane, 1ml/min, Retention time (R): 26.217 min, (S): 31.600 min **IR**: ($CHCl_3$, cm^{-1}): 407, 433, 772, 1157, 1215, 1389, 1513, 1657, 2980, 3017, 3356; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.49 (s, 9H), 3.38 (dd, *J* = 6.0 and 12 Hz, 1H), 3.53 (dd, *J* = 4.0 and 12 Hz, 1H), 3.98-4.04 (m, 1H), 4.29 (dd, *J* = 4.0 and 12 Hz, 1H), 4.37 (dd, *J* = 4.0 and 12 Hz, 1H), 4.88 (bs, 2H), 6.53 (t, *J* = 6.0 Hz, 1H), 7.50-7.67 (m, 2H), 8.11 (d, *J* = 8.0 Hz, 1H) ; **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 28.11, 55.09, 62.00, 70.57, 78.47, 110.52, 118.98, 139.60, 140.30, 159.26, 159.82; **Analysis**: $C_{13}H_{20}N_2O_4$ requires C, 58.20; H, 7.46; N, 10.44; found C, 59.00; H, 6.95; N, 10.68%.

Preparation of (S)- 2-(*N*-Boc-*N*-2',3'-epoxypropylamino)pyridine (21):

To a stirred solution of diol **17e** (1.5 g, 5.6 mmol) and pyridine (0.54ml, 6.7 mmol) in dry CH_2Cl_2 (20 ml) at 0^{0}C was added TsCl (1 g, 5.6 mmol) portion-wise using solid addition funnel. After starring for 24 h, the mixture was poured into ice-cold water (30 ml), washed with $NaHCO_3$, and brine dried over anhydrous sodium sulfate and evaporated under reduced pressure. The crude product (2 g. 5.1 mmol) and K_2CO_3 (2.8 g. 20 mmol) were stirred in dry methanol (30 ml) at 0^{0}C for 24 h (monitored by TLC). The reaction mixture was filtered through sintered funnel and methanol evaporated under reduced pressure. The crude product was purified by column chromatography using 50% EtOAc in petroleum ether as eluent to yield epoxide in 84%.

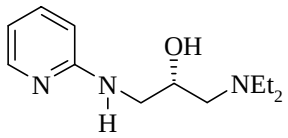


21

Yield: 84%; **mp**: 120-124^{0}C; $[\alpha]^D_{25}$: – 14.8 (c 1.4, EtOH); **IR** ($CHCl_3$, cm^{-1}): 412, 687, 763, 1157, 1216, 1251, 1269, 1522, 1651, 1712, 2984, 3016; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.38 (s, 9H), 3.00 (dd, J = 8.0 and 16 Hz, 1H), 3.22 (dd, J = 8.0 and 16 Hz, 1H), 3.9-4.05 (m, 1H), 4.23 (dd, J = 2 and 12 Hz, 1H), 4.42 (dd, J = 2, 12 Hz, 1H), 6.59 (t, J = 8 Hz, 1H), 7.50-7.62 (m, 2H), 7.84 (d, J = 6 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 28.04, 57.30, 62.22, 70.86, 81.19, 115.71, 119.31, 142.25, 142.76, 154.49, 155.37; **Analysis**: $C_{13}H_{18}N_2O_3$ requires C, 62.40; H, 7.20; N, 11.20; found C, 63.10; H, 6.93; N, 12.10%.

Preparation of (S)-2-(3'-diethylamino-2'-hydroxypropylamino)pyridine (1b):

A solution of epoxide (1 g. 4 mmol) and diethylamine (0.5 ml, 4.8 mmol) in 40 ml of methanol was refluxed for 24 h under N_2 atmosphere. The product obtained was filtered; vacuum dried and recrystallized using 1:1 chloroform-ether to afford the corresponding drug **1b** in 60% yield.



(S)-1b

Yield: 60%; **mp**: 242^{0}C, {Lit.[36] 240-241^{0}C}; $[\alpha]^D_{25}$: + 6.19 (c 2.5, EtOH); HPLC: 78% ee, Chiralcel OD-H, 25% EtOH/hexane 1 ml/min.. Retention time: (R): 20.34 min. (S): 22.78 min.; **IR** (KBr, cm^{-1}): 734, 780, 1296, 1334, 1460, 2924, 3342; **^{1}H-NMR** (200 MHz, Methanol-d4): δ 1.25 (t, *J* = 8.0 Hz, 6H), 2.99 (q, *J* = 8.0 Hz, 4H), 3.59 (t, *J* = 6.0 Hz, 2H), 3.90-4.10 (m, 1H), 4.10-4.31 (m, 2H), 6.85 (t, *J* = 6.0 Hz, 1H), 7.07 (d, *J* = 8.0 Hz, 1H), 7.82-7.89 (m, 2H); **^{13}C-NMR** (50 MHz, Methanol-d_4): δ 11.59, 43.57, 57.54, 64.23, 70.04, 114.18, 116.24, 142.34, 143.70, 156.53; **Analysis**: $C_{12}H_{21}N_3O$ requires C, 64.54; H, 9.48; N, 18.82; found C, 65.05; H, 9.68; N, 18.68%.

1.1.8 References

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CHAPTRER 2

Asymmetric Synthesis of β-Adrenergic Blockers via OsO_4-Catalyzed Asymmetric Dihydroxylation

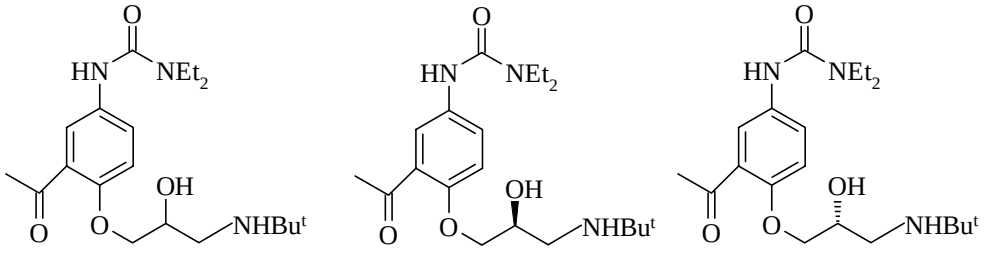
SECTION-I:

Enantioselective Synthesis of (R)-Celiprolol

2.0.1 Introduction

Chiral drugs continue to be a significant force in the pharmaceutical market. Most of the new drugs reaching the market today are single enantiomers, rather than the racemic mixtures that dominated till ten years ago.[1] The issue of drug chirality is now a major theme in the design, discovery and development of new drugs, underpinned by a new understanding of the role of molecular recognition in many pharmacological relevant events.[2] Drugs that modulate the physiological and pathophysiological action of serotonine are potentially useful in treating a variety of major psychiatric and metabolic problems.[3] One can manipulate actions of serotonine by using drugs that interfere with its biosynthesis, stimulate its release from presynaptic storage vesides, occupy one or more of the serotonine receptor subtypes and antagonize enzymes responsible for catabolism of serotonine.[4]

2.0.2 The Pharmacology of Celiprolol

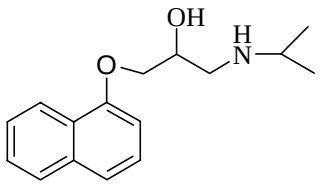


(±)-Celiprolol **(1)** (S)-(-)-Celiprolol **(1a)** (R)-(+)-Celiprolol **(1b)**

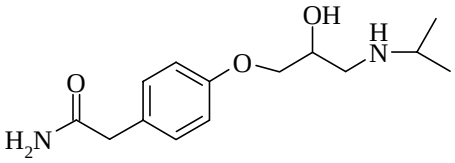
Fig.1

β - Adrenoceptor blocking drugs are widely used for the treatment of cardiovascular diseases such as arterial hypertension, coronary heart diseases and supraventricular and ventricular tachyarrhythmias. They may also be beneficial in the hyperkinetic heart syndrome, hypotensive circulatory disorders, portal hypertension, hyperthyroidism, tremour, migraine, anxiety, psychosomatic disorder or glaucoma. In recent years, even patients with heart failure have been successfully treated with β-blockers initially given at very low doses. A great number of β - adrenoceptor blocking drugs are now available for clinical use, which differ widely with respect to their pharmacodynamic and pharmacokinetic properties.[5]

Celiprolol (1) is a new antihypertensive agent that represents a new generation of β-blockers. It combines cardioselective β-adrenergic antagonism (β-1) with a mild vasodilation *via* vasoselecyive β-adrenergic agonism (β-2).[6] Results of animal studies show that Celiprolol (1) has β-1 antagonist potency similar to that of propranolol (2) and atenolol (3) and cardioselectivity slightly greater than that of atenolol (3) (Fig, 2).[7]



(±)-Propranolol (2)



(±)-Atenolol (3)

Fig.2

Celiprolol (1) does not produce bronchoconstriction but has mild propranolol-resistant bronchodilatory properties in cat. This compound also relaxes vascular smooth muscle in a propranolol sensitive fashion, suggesting a mechanism of β-2 agonism. The β-2 agonism results in a selective downregulation in β-2 receptor number and response in tissue culture, as well as in peripheral tissue from Celiprolol-treated volunteers. The decreases in β-2 receptors

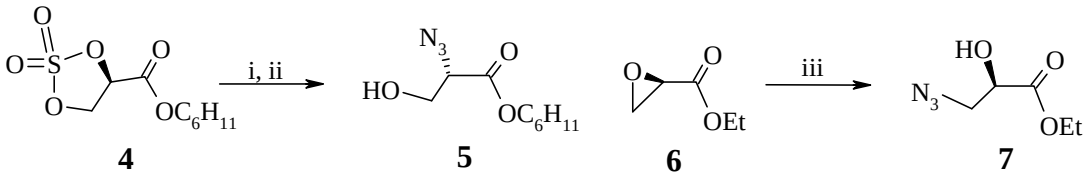
are blocked by concomitant treatment with propranolol. Celiprolol is devoid of cardiac depressant activity and in fact as mild cardiostimulatory actions. The cardiostimulation is not *via* β-1 stimulation, since it is not abolished by β -blocking doses of propranolol (2). In a model of server myocardial ischemia, Celiprolol (1) attenuates the ischemia-induced myocardial acidosis and improves the regional segment function. These results are suggestive of myocardial protection. In summary, celiprolol distinguishes itself from other β-blockers by virtue of its cardioselectivity, vasorelaxation via β-2 agonism, and the lack of bronchoconstriction and cardiodepression.[8]

2.0.3 Chemistry of Cyclic Sulfites and Sulfates

The chemistry of cyclic sulfites and sulfates is very old.[9] These are esters of 1,2; 1,3 or 1,4 diols and possess properties similar to epoxides. Unlike epoxide, chemistry of cyclic sulfites and sulfates is less explored in organic synthesis due to lack of an efficient method for their preparation. The significant role of cyclic sulfates in organic synthesis is realized due to their unique properties such as (i) high reactivity towards nucleophiles which is comparable to epoxides (ii) attack of nucleophile is regiospecific and thereby serving as a protecting group at a second position (iii) nucleophilic opening of five-membered cyclic sulfates generates two contiguous stereocenters.[10] The recent developments in Ru-catalyzed oxidation of the cyclic sulfites with sodium periodate extend the scope of cyclic sulfates in organic synthesis.[11] Cyclic sulfates are important intermediates in obtaining bioactive molecules containing hydroxyl functionality.[10] Chiral cyclic sulfates are easily prepared from the corresponding chiral glycols, which could be obtained from a variety of olefins by OsO_4-catalyzed asymmetric dihydroxylation.

2.0.4 Reactivity of Cyclic Sulfates

The cyclic sulfates (1,3,2-dioxathiolane-2,2-dioxde) are more reactive than their immediate cyclic sulfites (1,3,2-dioxathiolane-2-oxide). The high reactivity of the cyclic sulfate has been attributed to the ring strain and partial double bond character between ring oxygen and sulfur and also due to 2p(O)-3d(S) orbital interaction[12] The good leaving ability of the $ROSO_3^-$ moiety also enhances the reactivity of cyclic sulfates towards various nucleophilic reagents. The reactivity of cyclic sulfates and epoxides are similar in nature towards nucleophiles but vary in regioselective approach (**Scheme 1**). For example, the reactions of cyclic sulfate **4** with sodium azide in acetone: water system preferentially gave α-azido-product **5**, whereas epoxyester **6**, under similar reaction conditions gave β-azido-product **7**.[13]

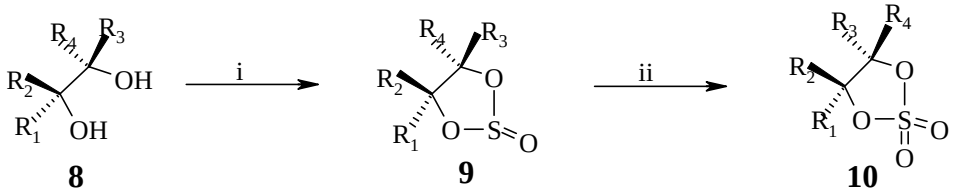


4 **5** **6** **7**

Scheme 1: Reactivity pattern of cyclic sulfate *vs* epoxide i) NaN_3; ii) H_2SO_4; iii) NaN_3, H_2O.

2.0.5 Preparation of Cyclic Sulfites and Sulfates

Cyclic sulfites **9** are conveniently prepared by condensation of 1,2-, 1,3- and 1,4-diols **8** with thionyl chloride (**Scheme 2**).[11,14] In case of acid sensitive substrates, triethyl amine or



8 **9** **10**

Scheme 2: i) $SOCl_2$, Et_3N, CH_2Cl_2, 0^0C; ii) cat. $RuCl_3.3H_2O$, $NaIO_4$, CH_3CN:H_2O.

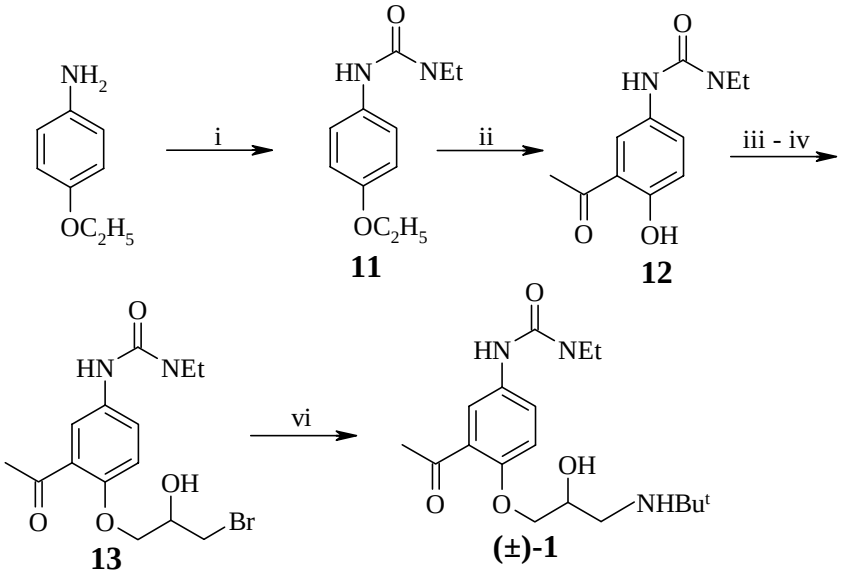
pyridine is required to scavenge the hydrogen chloride generated in the reaction. It is then transformed to cyclic sulfates **10** by Ru-catalyzed oxidation with $NaIO_4$.[10,11]

2.0.6 Review of Literature

Literature search revealed that only few reports are available for the synthesis of celiprolol (**1**).[15,16,17] However, most of the reports deal with the synthesis of celiprolol in their racemic form as shown in the following reactions. There are some methods known to obtain enantiomerically pure material by classical resolution via formation of diastereomers and separation of enantiomers by chiral liquid chromatography.[18]

Zoelss's approach (1983)[15]

Zoeless's approach is the first approach for the synthesis of racemic celiprolol (**1**). In this approach, racemic synthesis was achieved from 4-ethoxyaniline (**Scheme 3**).



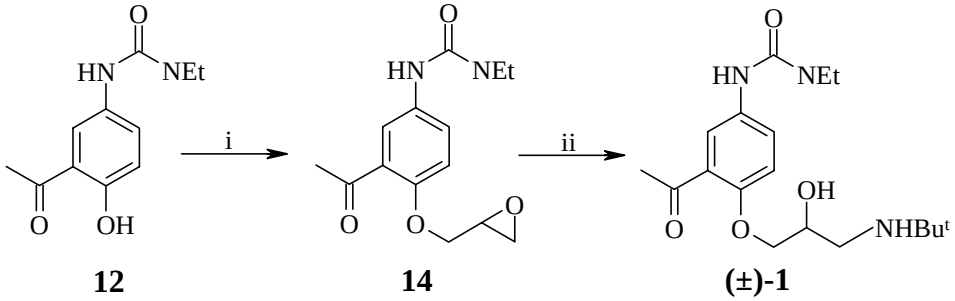
Scheme 3: (i) $KHCO_3$, Et_2NCOCl, MeOH, 20-30^{0}C, 48h, 91.6% yield; (ii) $AlCl_3$, AcCl, HCl 6h, 93.4%; (iii) epichlorohydrin; (iv) HBr, 71.38% yield; (vi) EtN_3, ^{t}Bu NH_2, 71.2% yield

4-Ethoxyaniline was treated with diethylcarbamoyl chloride (DECC) in the presence of potassium bicarbonate to give N-p-ethoxyphenyl acetamide (**11**). Friedel-Crafts, acylation

using acetyl chloride and anhydrous aluminium chloride gave urea derivative **12**. Reactoin of the urea derivative **12** with epichlorohydrin followed by treatment with hydrobromic acid gave bromohydrin **13**. The racemic celiprolol (**1**) is then obtained in 71.2% by the reaction of bromohydrin **13** with *tert*-butylamine in the presence of triethylamine.

Zhijuns's approach (1997)[16]

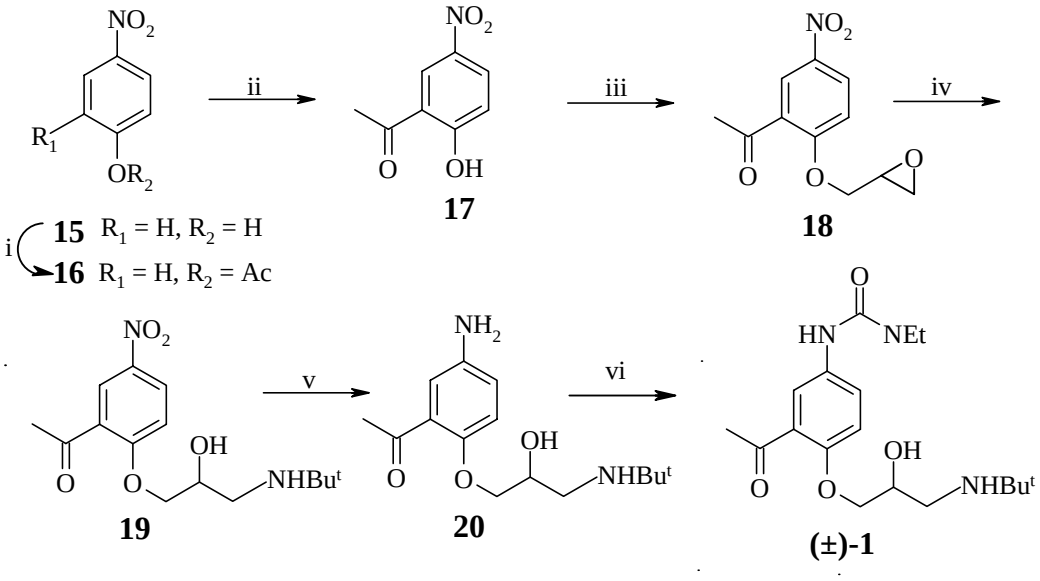
Zhijun *et al.* have synthesized racemic celiprolol via opening of epoxide **14** with tert-butylamine as a key reaction to afford celiprolol (**1**) in 84% yield (**Scheme 4**).



Scheme 4: (i) Epichlorohydrin; ii) Et_3N, *t*-Bu NH_2, 84% yield

Joshi's approach (2001)[17]

Joshi *et al.* have synthesized racemic celiprolol. In this approach, 4-nitrophenol (**15**) was converted into 4-nitrophenylacetate (**16**) in 87% yield using acetic anhydride and NaOH.[19] The Fries migration[20] of phenyl acetate **16** using $AlCl_3$ in dry nitrobenzene give 70% yield of 2-hydroxy-5-nitroacetophenone (**17**). O-Allylation of **17** with epichlorohydrin gave epoxide **18**. The ring opening of the epoxide **18** with *tert*-butylamine in water gave the solid amino alcohol derivative **19** in 86% yield. The nitro group was hydrogenated over Pd/C catalyst in methanol to afford the amine **20** in 92% yield. Finally, the introduction of N,N-diethyl carbamoyl group was achieved to give the corresponding drug celiprolol (**1)** in 90% yield (**scheme 5**).



Scheme 5: (i) NaOH, acetic anhydride90-95^{0}C, 10 min, 87%; (ii) $AlCl_3$, nitrobenzene, 140^{0}C, 6 h, 70%; (iii) K_2CO_3, benzyltriethylammonium chloride, 75^{0}C, 10h, 96%:(iv) *t*-$BuNH_2$, H_2O, 24 h, 86%; (v) H_2 (20 psi), MeOH, 10% Pd/C, 6 h, 92%; (vi) THF, Et_3N, DCC, 40^{0}C, 48 h, 90%.

2.0.7 Present Work:

2.0.7.1 Objective

Literature search revealed that although there are few reports available on the synthesis of racemic (±) celiprolol, not much attention has been focused on its asymmetric version. Thus, the objective of the present work is to synthesize optically active (R)-(+)-Celiprolol (**1b**) using Sharpless asymmetric dihydroxylation as a key reaction. Celiprolol is a new antihypertensive agent that represents a new generation of β-blockers in its relationship to some β-adrenoceptor antagonists so that its asymmetric synthesis is highly desirable. The present strategy for the asymmetric synthesis of (R)-(+)-Celiprolol (**1b**) is shown in **Scheme 6**. The retrosynthetic analysis of celiprolol (**1b**) is shown in **Fig 3**.

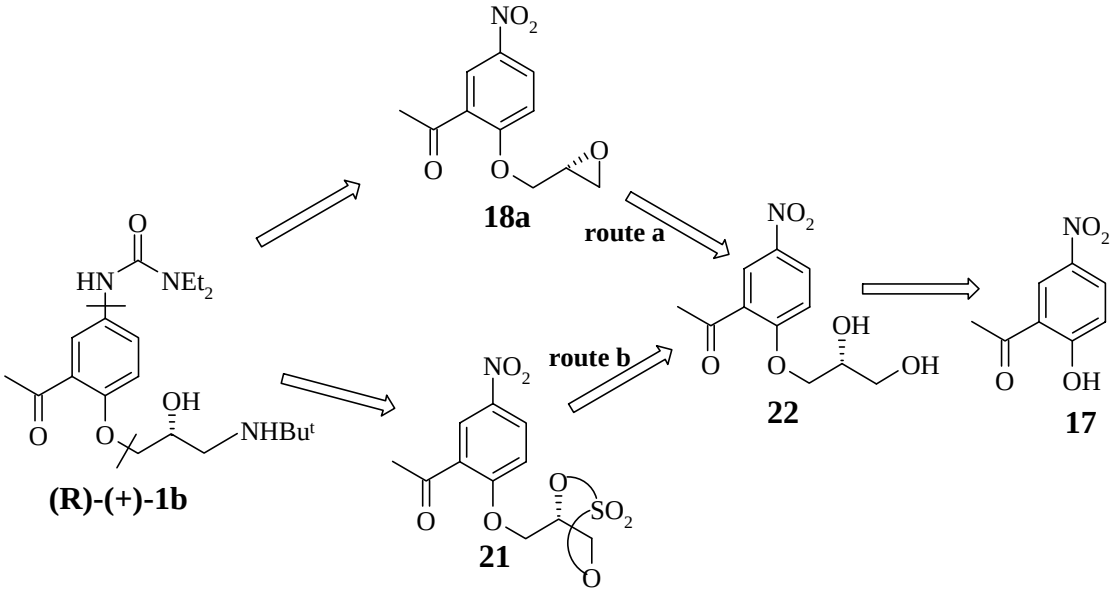
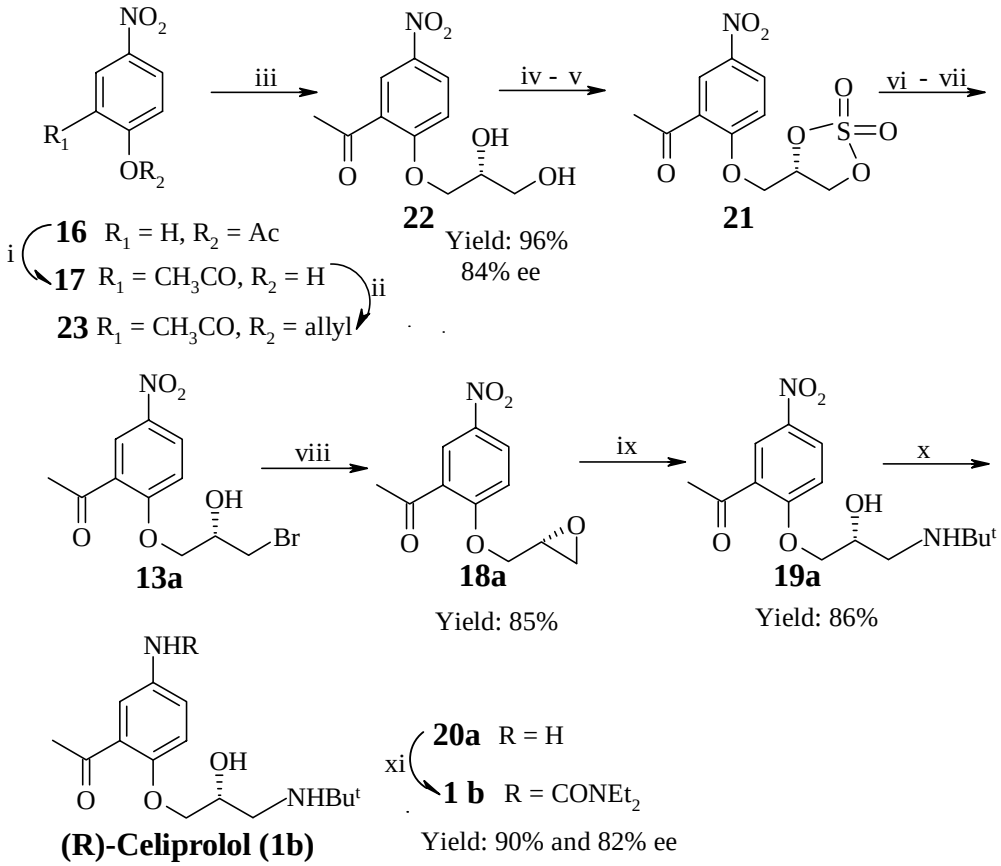


Fig 3: Retrosynthetic analysis of (R)-Celiprolol (1b)

2.0.8 Results and Discussion

The synthetic strategy employed for (R)-celiprolol (1b) is shown in **Scheme 6** wherein Os-catalyzed asymmetric dihydroxylation (AD) constitutes a key step in introducing chirality into the molecule (**Scheme 6**).

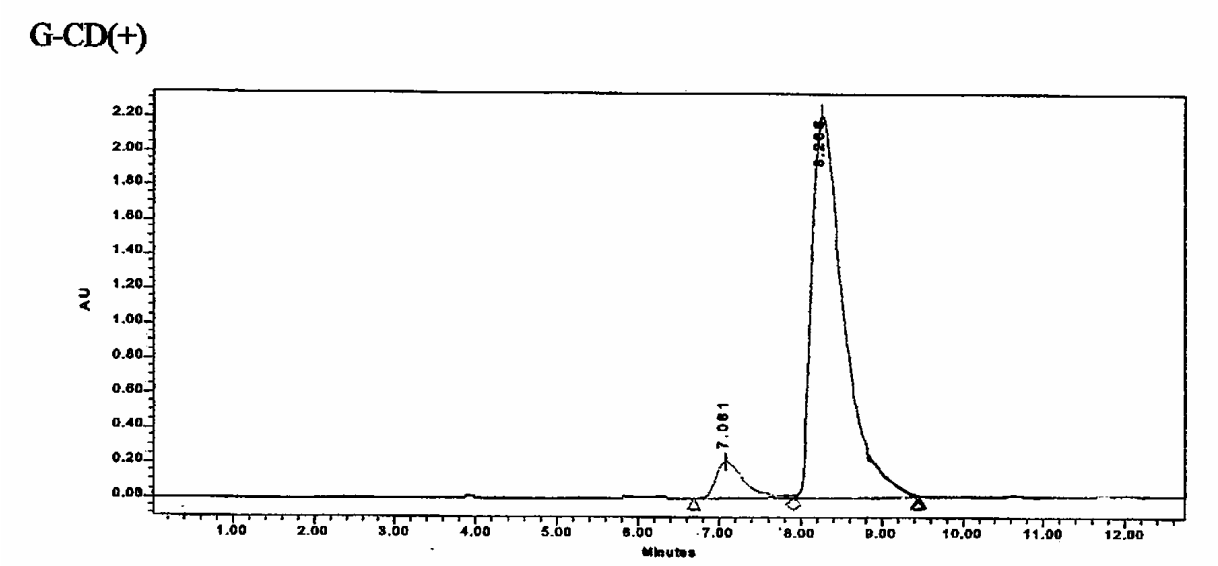


Scheme 6: i) $AlCl_3$, nitrobenzene, 140^0C, 6 h, 70%; (ii) K_2CO_3, CH_2=$CHCH_2Br$, acetone, reflux, 24 h, 99%; (iii)) cat. OsO_4, $(DHQ)_2$-PHAL, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH:H_2O (1:1), 0-25^0C, 24 h, 96%, 84% ee; (iv) $SOCl_2$, Et_3N, CH_2Cl_2, 0^0C, 1 h, 98%; (v) cat. $RuCl_3$ $3H_2O$, $NaIO_4$, CH_3CN:H_2O, 0^0C, 30 min. 94%; (vi) LiBr, THF, 60^0C, 2 h; (vii) 20% H_2SO_4, Et_2O, 6 h; (viii) K_2CO_3, MeOH, 10-15^0C, 4 h, 85% overall in three steps; (ix) *t*-$BuNH_2$, H_2O, 24 h, 86%; (x) H_2 (20 psi), MeOH, 10% Pd/C, 6 h, 92%; (xi) THF, Et_3N, DCC, 40^0C, 48 h, 90%, 82% ee.

The readily availably 4-nitrophenol (**15**) was transformed into 4-nitrophenylacetate (**16**) in 87% yield using acetic anhydride and NaOH. The ^{1}H-NMR spectrum showed a singlet for CH_3 proton at δ 2.37 and the ^{13}C-NMR spectrum showed the carbonyl of ester at δ 168.31. The Fries-migration of phenyl acetate using $AlCl_3$ in dry nitrobenzene gave 70% yield of 2-hydroxy-5-nitroacetophenone (**17**). The ^{1}H-NMR showed a singlet of CH_3 proton at δ 2.76,

OH proton at δ 12.88 and the ^{13}C-NMR showed the carbonyl at δ 203.96. *O*-Allylation of **17** with allylbromide gave allyl ether **23** in 99% yield. Its ^{1}H-NMR spectrum showed typical pattern for the allylic functionality in the region of δ 4.50- 6.50 and the ^{13}C-NMR spectrum showed signals for the carbons of the allylic functionality in the region of δ 70 - 120.

Allylic ether **23** was subjected to ADH in the presence of $(DHQ)_2$-PHAL [hydroquinine 1,4-phthalazinediyl diether] as a chiral ligand in the presence of $K_3Fe(CN)_6$ / K_2CO_3 as a co-oxidant/base to give optically active diol **22** in 96% yield and 84%ee.The optical purity of diol **22** was determined by both Mosher's ester and by HPLC analysis using Chiralcel OD-H (25cm) column and was found to be 84% ee (**Fig. 4**).



	Name	Retention time	Area	% Area	Height	Int Type	Amount	Unites	Peak Type	Codes
1		7.081	4977999	7.915	209984	BV			Unknown	
2		8.266	57951914	92.08	2223373	VV			Unknown	

Fig. 4: HPLC Chromatogram of chiral diol 22

The IR spectrum of this diol showed a broad band in the region of 3400-3500 cm^{-1} indicating the presence of hydroxyl functionality in the molecule. The ^{1}H-NMR spectrum

showed disappearance of signal for allylic protons in the region of δ 4.50 to 6.50. Multiplets in the region of δ 3.73 – 3.83 and δ 4.15 – 4.35 for the five protons and a broad singlet at δ 3.25 confirmed the formation of the diol. The ^{13}C-NMR spectrum of diol **22** showed typical signals at δ 31.09 and 196.98 for the CH_3 of acetate and carbonyl groups respectively and at δ 62.85, 69.50, 70.49 for the three aliphatic carbons bearing oxo-functionality in the molecule (**Fig. 5**)

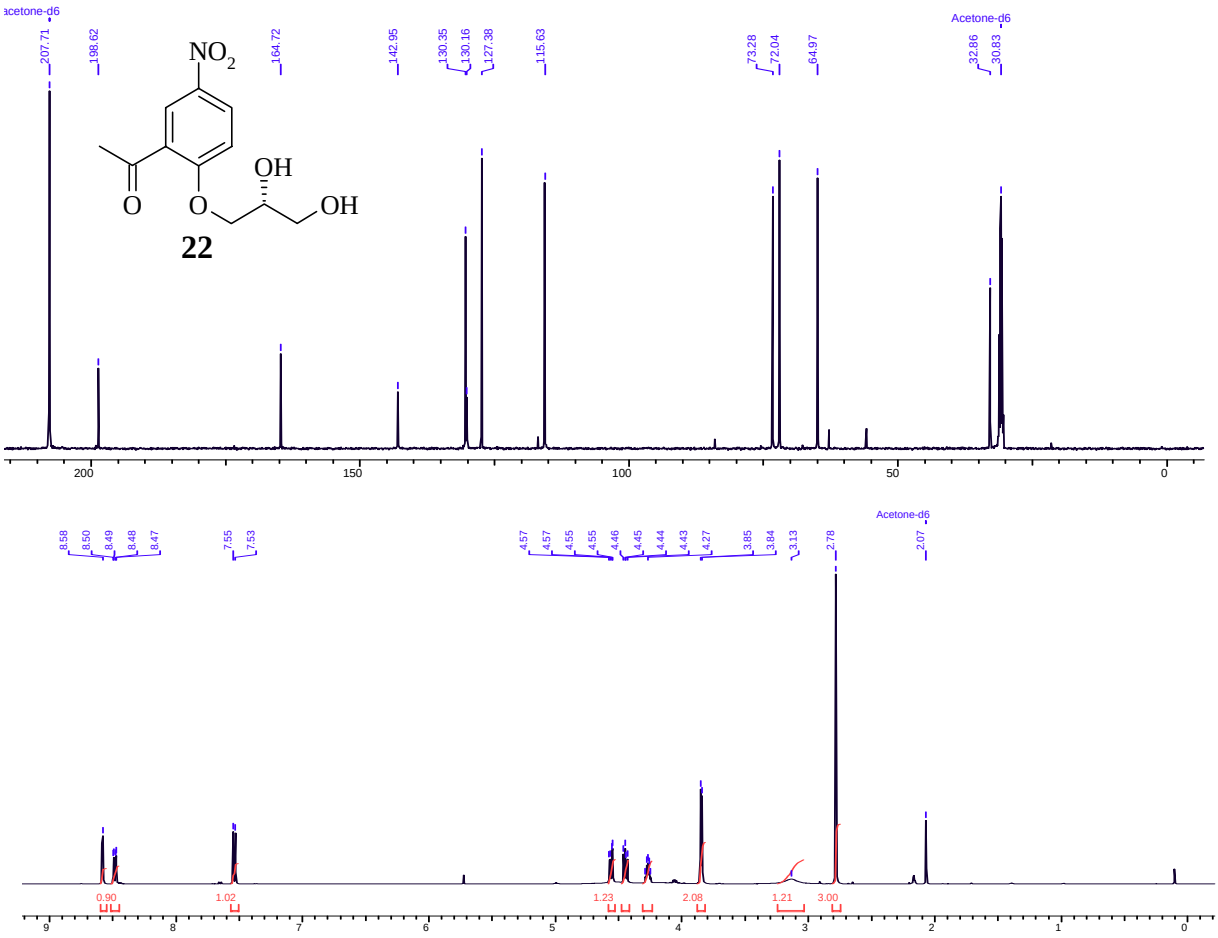


Fig. 5: ^{13}C and ^{1}H -NMR spectra of the diol 22

The diol **22** was treated with freshly distilled $SOCl_2$, Et_3N in CH_2Cl_2 at 0^0C to afford the corresponding cyclic sulfite in 98% yield. The formation of cyclic sulfite was clearly evident from the appearance of multiplets in its ^{1}H-NMR in the region δ 4.30-5.47 due to the presence of diastereomeric mixtures.

The cyclic sulfite of the diol was converted into cyclic sulfate **21** in 94% yield using Ru-catalyzed oxidation with $NaIO_4$ as the oxidant. The ^{1}H-NMR spectrum of cyclic sulfate **21** showed the disappearance of multiplets in the region δ 4.30-5.47 due to diastereomeric cyclic sulfite mixtures. The ^{13}C-NMR spectrum of **21** also showed simplified pattern because of the absence of diastereomeric mixtures. Its Mass spectrum showed molecular ion peak (m/e 317), which confirms the formation of cyclic sulfate moiety (**Fig. 6**).

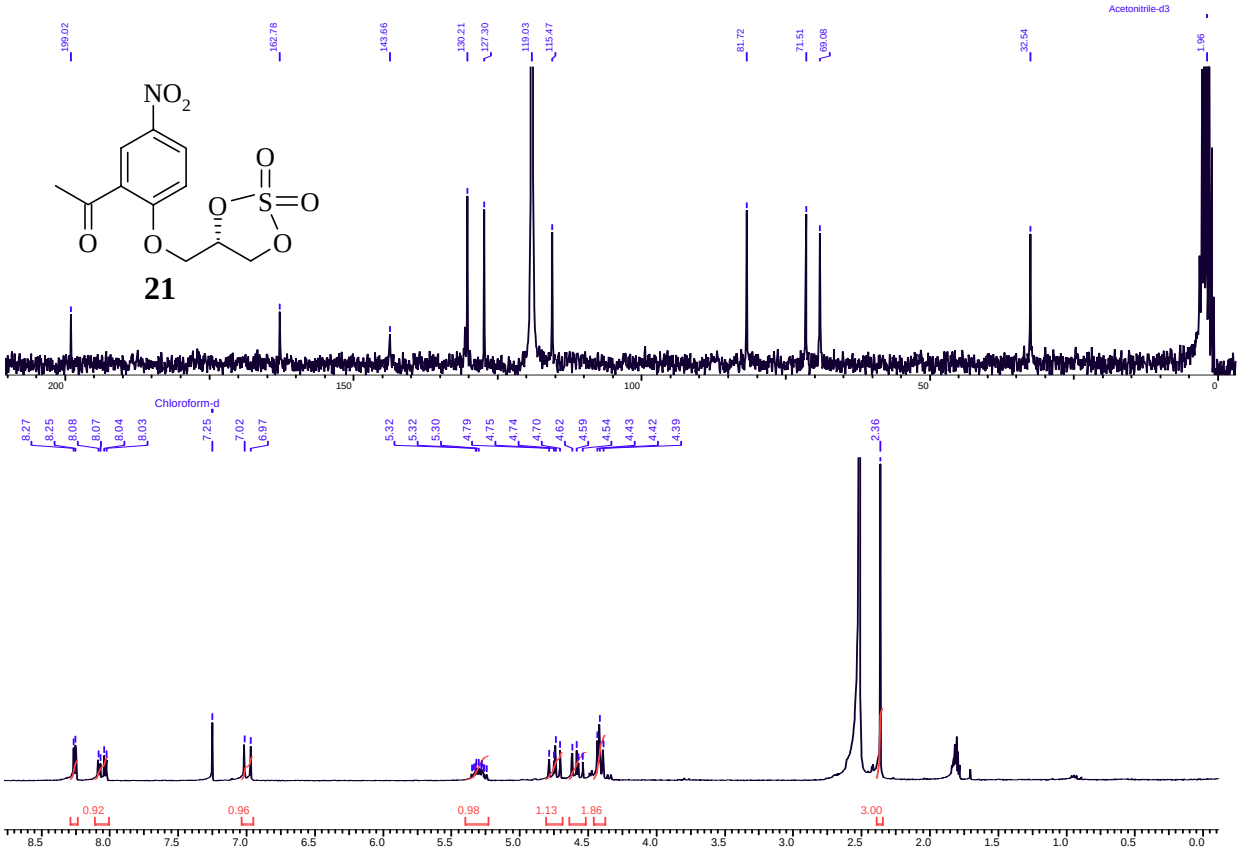


Fig. 6: ^{13}C and ^{1}H -NMR spectra of the cyclic sulfate 21

The cyclic sulfate **21** was subjected to nucleophilic displacement with *tert*-butylamine followed by hydrolysis of the resulting salt afforded the corresponding amino alcohol **19a**. However, the hydrolysis of the ester of the cyclic sulfate **21** was not successful. Various reaction conditions such as 20% H_2SO_4 in ether, 50% H_2SO_4 in ether, 20% HCl, concentrated HCl, 20% aqueous NaOH and 50% aqueous NaOH were tried but failed to hydrolyze the salt**.**

Hence, we decided to convert this cyclic sulfate **21** into the corresponding epoxide **18a** using a three-step procedure to produce epoxide **18a** in overall yield of 85%. Thus, cyclic sulfate **21** was first treated with anhydrous LiBr, then with 20% aqueous H_2SO_4 in ether to give bromoalcohol. It was then treated with K_2CO_3 in MeOH at -15^0C to afford the corresponding epoxide **18a.**

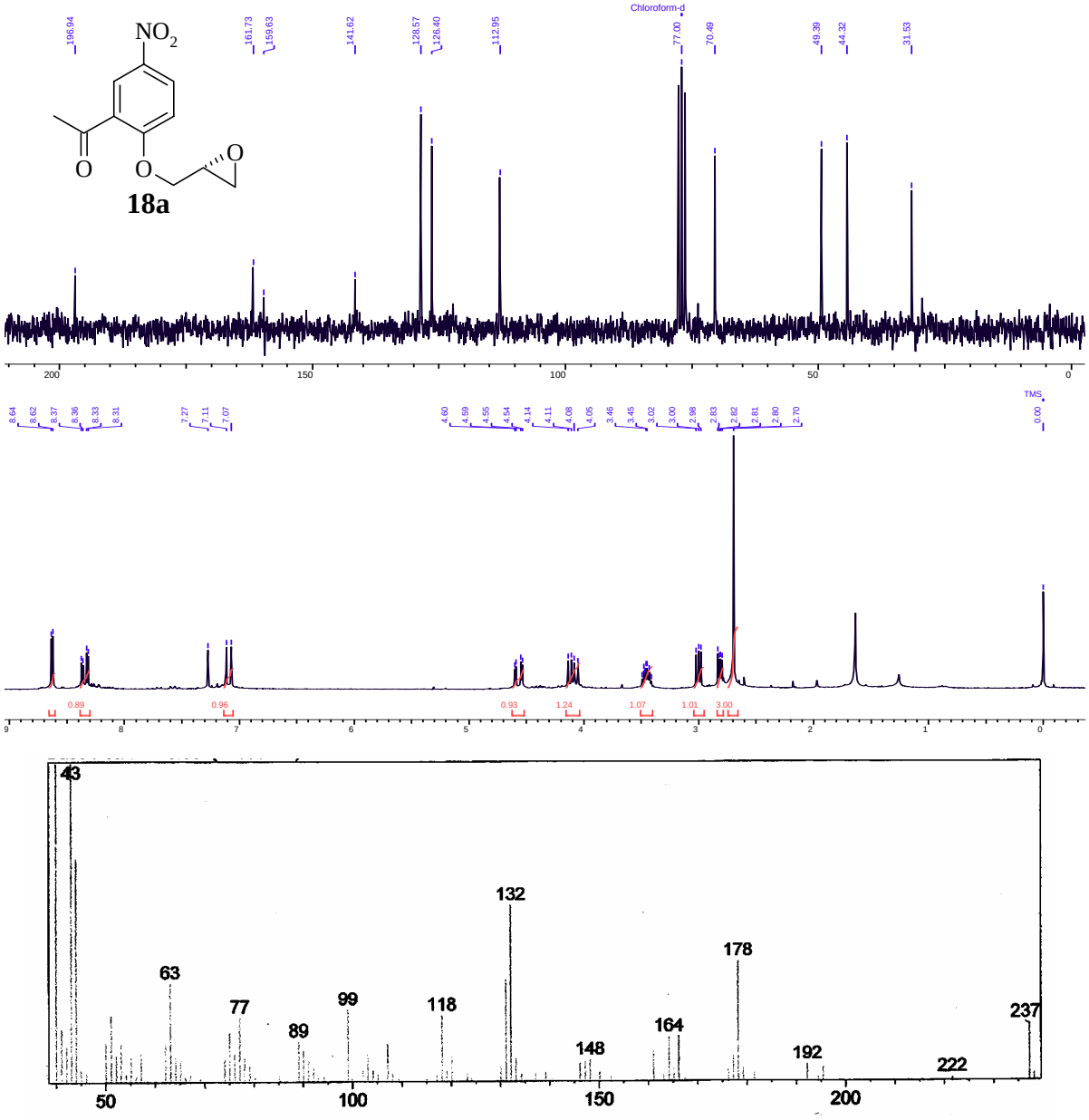


Fig. 7: ^{13}C, ^{1}H-NMR and GC-Mass spectra of the epoxide 18a

The ^{1}H-NMR of epoxide **18a** showed typical signals at δ 2.82 (dd, *J* = 2, 6 Hz, 1H), 3.00 (dd, *J* = 2, 6 Hz, 1H), 3.43 – 3.49 (m, 1H), 4.09 (dd, *J* = 6, 12 Hz, 1H) and 4.57 (dd, *J* = 2, 10 Hz, 1H); which indicate the presence of the epoxide functionality. The ^{13}C-NMR spectrum also showed the upfield shift in case of the carbons belonging to *O*-side chain at δ 44.32, 49.39 and 70.39. Its Mass spectrum showed molecular ion peak (m/e 237), which confirms the formation of epoxide **18a** as shown in **Fig. 7**

The epoxide **18a** was subjected to regiospecific nucleophilic attack with *tert*-butylamine in water to afford the corresponding amino alcohol **19a** in good yield (86%). Its ^{1}H-NMR spectrum showed a singlet of *tert*- butyl protons at δ 1.17 whereas its ^{13}C-NMR showed two typical signals at δ 28.32,and 31.51which confirmed the formation of amino alcohol **19a** (**Fig. 8**).

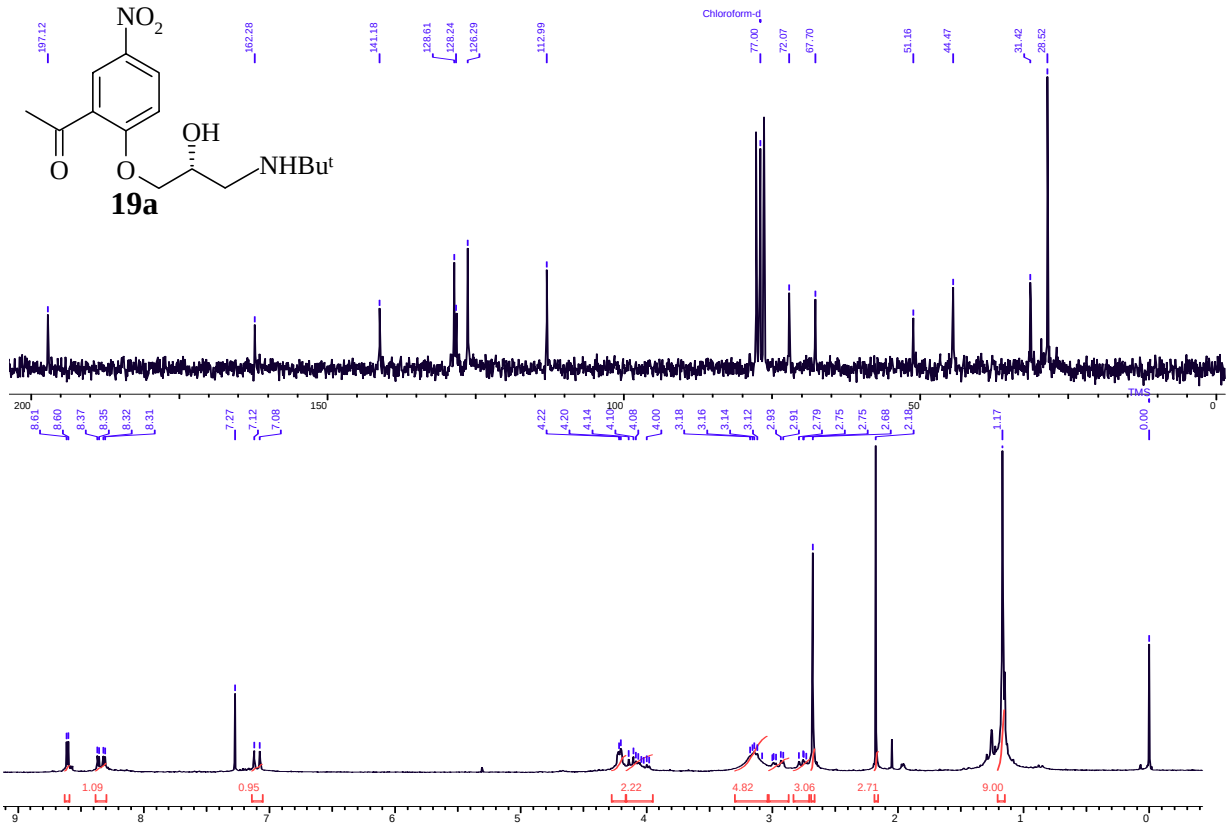


Fig. 8: ^{13}C and ^{1}H -NMR spectra of 19a

The nitro group in **19a** of celiprolol intermediate was hydrogenated at 20 psi H_2 pressure with 10% Pd/C as catalyst at room temperature. After complete reduction, the amino compound **20a** was produced in 92% yield.

The amine **20a** was condensed with diethyl carbamoyl chloride (DECC) to afford the corresponding (R)-celiprolol in excellent yield (90%). Its ^{1}H-NMR spectrum showed the typical ethyl peak of a triplet at δ 1.21 (t, *J* = 10 Hz, 6H) and a quartet at δ 3.39 (q, *J* = 10 Hz, 4H) confirming the formation of (R)-celiprolol (**1b**) (**Fig. 9**). Its optical purity 73% ee was determined from HPLC analysis using Chiral-OD column.

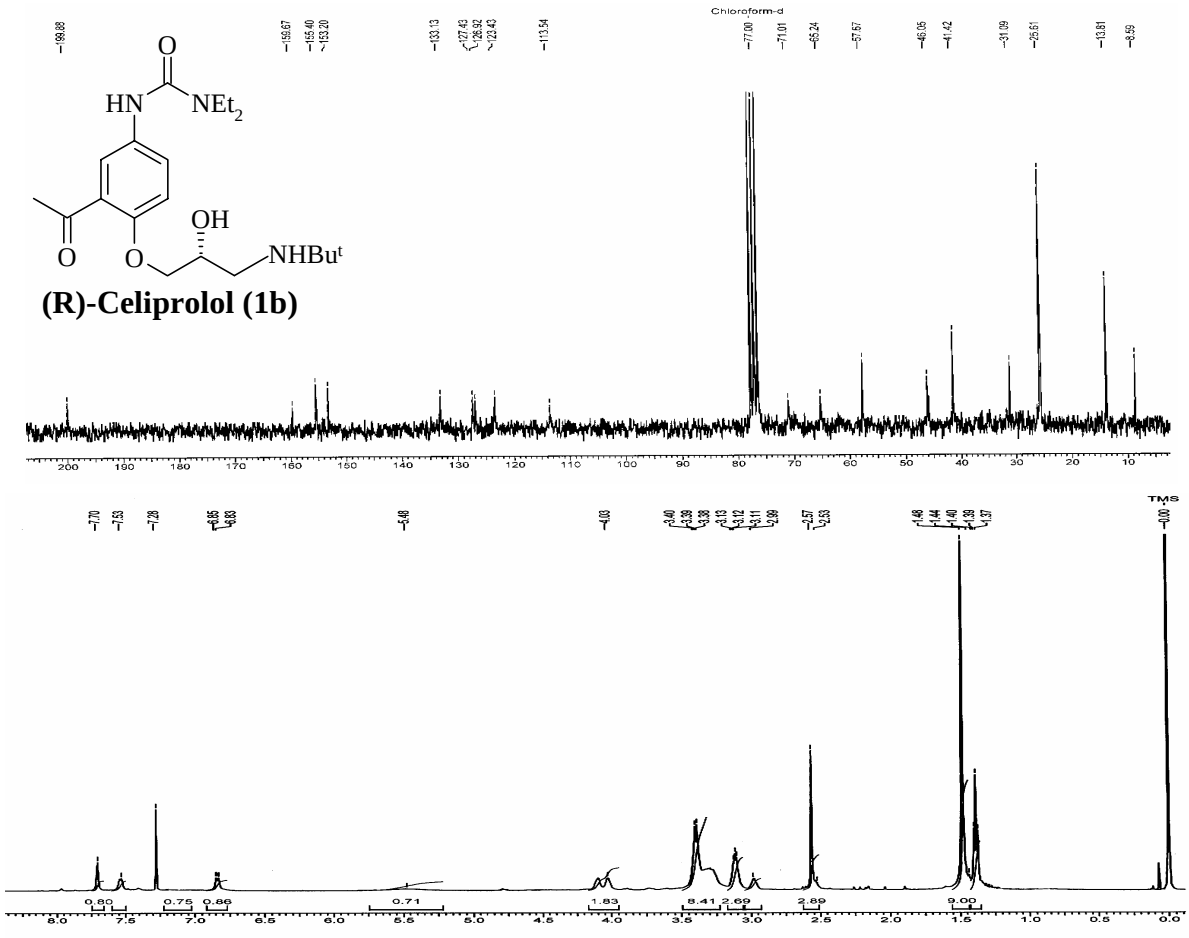


Fig. 9: ^{13}C and ^{1}H -NMR spectra of (R)-celiprolol (1b)

2.0.9 Conclusion

In conclusion, we have achieved for the first time a simple and efficient asymmetric synthesis of (R)-celiprolol using ADH in the presence of $(DHQ)_2$-PHAL [hydroquinine 1,4-phthalazinediyl diether] as ligand with a over all yield of 32.27%, and optical purity of 82% ee in twelve steps starting from the readily availably 4-nitrophenol. We have also developed a simple and efficient method for the conversion of cyclic sulfate **21** to the corresponding epoxide **18a** in high yield (85%) using a three-step procedure

2.0.10 Experimental Section

Preparation of 4-nitrophenylacetate (16):

4-Nitrophenol **15** (5 g, 35.9 mmol), was slowly added to a solution of NaOH (2.1 g, 53.6 mmol, 20 ml water). The reaction mixture was heated at 90-95^{0}C with stirring until a homogenous solution was obtained. Acetic anhydride (5.3 ml, 51.9 mmol) was added in 10 min to the above hot solution. Then the reaction mixture was immediately cooled at 20^{0}C. The product was crystallized and collected by filtration. The precipitated solid was washed with water to give white crystalline solid of 5.6 g of **16**.

Yield: 87% white solid; **mp**: 81^{0}C, lit.[19] mp 83^{0}C; **IR**: ($CHCl_3$, cm^{-1}): 593.3, 706.0, 872.5, 920.8, 1017.4, 118.7, 1210.7, 1361.1, 1527.5, 1763.8, 1806.7, 2977.2, 3106.0; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.37 (s, 3H), 7.30 (d, *J* = 9.3 Hz, 2H), 8.29 (d, *J* = 9.3 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 20.19, 122.32, 125.04, 145.19, 155.29, 168.31; **Analysis**: $C_8H_7NO_4$ requires C, 53.03; H, 3.86; N,7.73; found C, 53.27, H, 3.85; N, 7.78%.

Preparation of 2-hydroxy-5-nitroacetophene (17):

To a stirred solution of acetate **16** (5 g, 27.6 mmol) in 20 ml of dry nitrobenzene was added a solution of anhydrous $AlCl_3$ (3.6 g, 27.6 mmol) in 20 ml of nitrobenzene over a period of 15 min at room temperature. The reaction mixture was heated at 140^{0}C for 6 h, allowed to cool to room temperature, and then poured into 200 g crushed ice and 15 ml of concentrated HCl with vigorous stirring. The nitrobenzene layer was separated and washed with water (50 ml) followed by 10% aq. NaOH (2 x 15 ml). The combined alkali layers were acidified to pH 5 with concentrated HCl and extracted with ethyl acetate (3 x 20 ml). The combined ethyl acetate layers were concentrated to give a residue, which was subjected to Soxhlet extraction using n-hexane as a solvent to yield 3.5 g, of **17**.

Yield: 70% white solid; **mp**: 102^{0}C, lit.[21] mp 102-103^{0}C; **IR**: ($CHCl_3$, cm^{-1}): 652.3, 759.7, 818.8, 963.8, 1124.8, 1302.0, 1527.5, 1656.4, 2912.8, 3106.0; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.76 (s, 3H), 7.10 (d, *J* = 9.3 Hz, 1H), 8.35 (dd, *J* = 2.9, 9.0 Hz, 1H), 8.72 (d, *J* = 2.9 Hz, 1H), 12.88 (s, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 26.46, 118.32, 119.23, 126.99, 130.81, 139.38,

166.87, 203.96; **Analysis**: $C_8H_7NO_4$ requires C, 53.03; H, 3.86; N,7.73; found C, 54.02, H, 3.75; N, 8.14%.

Preparation of Allyl-2-acetyl-4-nitrophenyl ether (23):

A mixture of 2-hydroxy-5-nitroacetophenone **17** (3 g, 13.5 mmol), allyl bromide (1.4 ml, 16.2mmol), and anhydrous K_2CO_3 (2.7 g, 20.3 mmol) in dry acetone (30 ml) was refluxed under N_2 for 24 h (reaction monitored by TLC). The reaction mixture was then cooled to room temperature, filtered through sintered funnel to remove solid residue and the filtrate was evaporated to dryness. The residue was purified by column chromatography using pet. ether: EtOAc (9:1) as eluent to get pure allyl ether **23** in 99% yield.

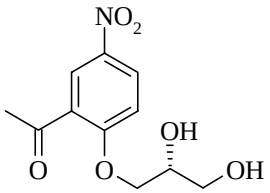
Yield: 99% white solid; **mp**: 78-80^{0}C: **IR**: ($CHCl_3$, cm^{-1}): 669.23, 756.98, 1117.37, 1215.72, 1275.13, 1345.80, 1523.81, 1609.22, 3020.21, 2405.23; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.66 (s, 3H), 4.78 (d, *J* = 4 Hz), 5.38-5.52 (m, 2H), 6.00-6.19 (m, 1H), 7.06 (d, *J* = 9.3 Hz), 8.31 (dd, *J* = 2.9, 9 Hz), 8.61 (d, *J* = 2 Hz); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 31.42, 70.16, 112.99, 119.27, 126.07, 128.31, 131.03, 141.00, 159.52, 161.95, 196.94; **Analysis**: $C_{11}H_{11}NO_4$ requires C, 59.72; H, 4.92; N, 6.33; found c, 59.79; H, 5.43; N, 6.48%

Preparation of (2R)-1-(2-acetyl-4-nitrophenyl)-2,3-propanediol (22):

A 250 ml RB flask was charged with $K_3Fe(CN)_6$ (8.93 g, 27.1mmol), K_2CO_3 (3.74 g, 27.1 mmol), $(DHQ)_2$-PHAL (0.140 g, 0.18 mmol) and *t*-BuOH : H_2O (1:1, 80 ml) and the resulting mixture was stirred for 10 minutes at 25^{0}C. It was then cooled to 0^{0}C and a solution of OsO_4 (229 μl, 0.09 mmol, 0.5 M solution in toluene) was added. The resulting reaction mixture was stirred at 0^{0}C for 5 minutes and then the olefin **23** (2 g, 9 mmol) was added. The reaction mixture was stirred at 0^{0}C for 20-24 h (monitored by TLC). It was quenched with sodium sulfite (5.0 g) and extracted with ethyl acetate (4 x 30 ml). Combined organic layer was washed with brine (25 ml), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by column chromatography using 25% EtOAc in pet. ether as eluent to yield pure diols **22** as gum in 96% yield.

Yield: 96% yellow gum; **$[\alpha]^{25}_D$**: + 5.31 (c 1.1, EtOH); **HPLC**: 84% ee, Chiralcel-OD (25 cm) λmax: 254 nm, 70:30 petroleum ether/ isopropanol, 1ml/min. Retention time: (R): 7.08 min. (S): 8.26 min.; **IR**: (CHCl, cm^{-1}): 740, 780, 845, 993, 1020, 1130, 1257, 1379, 1390, 1458, 1515, 1598, 2845, 2910, 3280; **^{1}H-NMR** (200 MHz, acetone-d_6): δ 2.66 (s, 3H), 3.83-3.87 (m,

2H), 4.16-4.34 (m, 3H), 7.10 (d, *J* = 9.3 Hz), 8.33 (dd, *J* = 2.9, 9 Hz), 8.58 (d, *J* = 4 Hz); **^{13}C-NMR** (50 MHz, acetone-d_6): δ 31.09, 62.85, 69.85, 70.49, 112.77, 125.63, 127.62, 128.24, 140.55, 162.13, 196.98; **Analysis**: $C_{11}H_{13}NO_6$ requires C, 51.76; H, 4.31; N, 5.49; found c, 50.24; H, 5.21; N, 5.45%



22

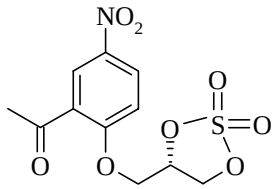
Preparation of cyclic sulfate (4R)- 4-[(2-acetyl-4-nitrophenyl)methyl]-1,3,2-dioxathiolane-2,2-dioxide (21):

[A] To a solution of diol **22** (6 mmol) and triethylamine (3.32 ml, 24 mmol) in CH_2Cl_2 (15 ml) at 0^0C was added freshly distilled thionyl chloride (0.65 ml, 9 mmol) drop-wise under nitrogen atmosphere. The reaction mixture was stirred at 0^0C for 30-40 minutes (monitored by TLC). The reaction mixture was quenched by the addition of cold water (10 ml). The organic layer was separated and the aqueous layer extracted with EtOAc (3 x 15 ml). The combined organic extracts were washed with water, brine and dried over anhydrous Na_2SO_4. Evaporation of solvent under reduced pressure yielded yellow colored liquid, which was purified by the column chromatography using 10% EtOAc in pet. ether as a eluent to afford the corresponding cyclic sulfite as viscous dark yellow gum in 96% yield.

Yield: 96% yellow gum; **$[\alpha]^{25}_{D}$**: + 13.10 (c 2.5, EtOH); **IR**: ($CHCl_3$, cm^{-1}): 410, 434, 477, 668, 770, 1117, 1217, 1276, 1347, 1486, 1523, 1611, 1685, 2927, 3021; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.67 (s, 3H), 4.35-4.38 (m, 1H), 4.53-4.59 (m, 1H), 4.72-4.77 (m, 1H), 4.93-4.98 (m, 1H), 5.38-5.46 (m, 1H), 7.05-7.12 (m, 1H), 8.31-8.37 (m, 1H), 8.57 (d, *J* = 4 Hz); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 31.35, 67.99, 77.29, 79.54, 112.73, 112.88, 126.11, 128.46, 141.62, 160.95, 196.68; **Analysis**: $C_{11}H_{11}NSO_7$ requires C, 43.85; H, 3.65; N, 4.65; S, 10.63 found C, 43.88; H, 3.55; N, 4.78; S, 10.60%.

[B] To a solution of cyclic sulfite (4 mmol) in CH_3CN: H_2O mixture (9:1, 10 ml) at 0^0C was added solid $NaIO_4$ (1.27 g, 6 mmol) and $RuCl_3.3H_2O$ (0.008 g, 0.030 mmol). The reaction mixture was stirred for 30-40 minutes at 0^0C (monitored by TLC). After the reaction

mixture was completed, it was filtered was through a pad of celite. Solvent evaporated under reduced pressure to give the crude product, which was purified by column chromatography using pet. ether: EtOAc (9:1) as eluent to afford cyclic sulfate **21** in 98% yield



21

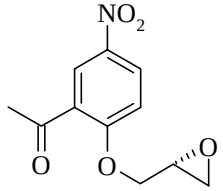
Yield: 98% white solid; **mp**: 138-140^{0}C; **[α]$^{25}_D$**: + 2.97 (c 0.4, EtOH); **IR**: ($CHCl_3$, cm^{-1}): 651, 753, 984, 1024, 1130, 1213, 1255, 1460, 1510, 1600, 1688, 2854, 2940; **^{1}H-NMR** (200 MHz, acetonitrile-d_3): δ 2.36 (s, 3H), 4.39-4.54 (m, 2H), 4.59 (dd, *J* = 4 ,9 Hz, 1H), 4.74 (dd, *J* = 4, 9 Hz. 1H), 5.29-5.35 (m, 1H), 7.00 (d, *J* = 9.3 Hz, 1H), 8.05 (dd, *J* = 2.9, 9 Hz, 1H), 8.26 (d, *J* = 4 Hz, 1H); **^{13}C-NMR** (50 MHz, acetonitrile-d_3): δ 32.54, 69.08, 71.51, 81.72, 115.47, 127.30, 130.21, 143.66, 162.78, 199.02; **Analysis**: $C_{11}H_{11}NSO_8$ requires C, 41.64; H, 3.47; N, 4.41; S, 10.09; found C, 41.62; H, 3.45; N, 4.46; S, 9.78%.

Preparation of epoxide 18a:

[A] To a solution of the cyclic sulfate **21** (0.79 g, 2.5 mmol) in dry THF (15 ml) was added anhydrous LiBr (0.87 g, 10 mmol) and the resulting reaction mixture was stirred for 40 minutes (monitored by TLC for the disappearance of cyclic sulfate) at 25^{0}C. After completion of the reaction, the solvent was removed under reduced pressure. In the resulting residue diethyl ether (25 ml), and 20 % H_2SO_4 (25 ml) was added and stirred at 25^{0}C for 4-5 h (monitored by TLC). After completion of the reaction the two layer was separated, the aq. layer extracted with diethyl ether (3x15 ml), combined organic extract was washed with saturated $NaHCO_3$, water and brine, dried over anhydrous sodium sulfate and evaporated under reduced pressure to give the corresponding bromoalcohol **13a**.

[B] The crude bromoalcohol **13a** (2.5 mmol) was dissolved in dry MeOH (20 ml) and treated with anhydrous K_2CO_3 (1.3 g, 10 mmol) at 0^{0}C. The resulting reaction mixture was stirred at 0^{0}C for 2 h (monitored by TLC). After completion, the reaction was quenched by the addition of saturated NH_4Cl solution (10 ml) and extracted with CH_2Cl_2 (4 x 15 ml), with water and brine, dried over anhydrous sodium sulfate and evaporated under reduced pressure

to give the crude product. It was then purified by column chromatography using pet. ether: EtOAc (8:2) as eluent to give pure epoxide **18a** as solid (85% yield).



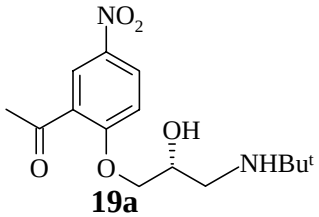
18a

(2R)-2-[(2',3',-epoxy)-propoxyl-5-nitro-acetophenone

Yield: 85% white solid; **mp**: 80-83^{0}C; **[α]$^{25}_D$**: + 10.74 (c 0.9, EtOH); **IR**: ($CHCl_3$, cm^{-1}): 413, 430, 440, 459, 471, 487, 756, 1017, 1116, 1216, 1277, 1345, 1485, 1523, 1586, 1610, 1685, 2930, 3020; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.70 (s, 3H), 2.28 (dd, *J* = 2, 9 Hz, 1H), 3.00 (dd, *J* = 2, 9 Hz, 1H), 3.43-3.49 (m, 1H), 4.57 (dd, *J* = 2, 10 Hz, 1H), 7.09 (d, *J* = 9.3 Hz, 1H), 8.34 (dd, *J* = 2.9, 9 Hz, 1H), 8.63 (d, *J* = 4 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 31.53, 44.32, 49.39, 70.39, 112.95, 126.40, 128.57, 141.62, 159.63, 161.73, 196.94; **MS** m/z (%rel. intensity): 237 (M^+, 20), 192 (8), 178 (40), 164 (18), 148 (10), 132 (60), 118 (30), 99 (35), 89 (10), 77 (20), 63 (35), 43 (100); **Analysis**: $C_{11}H_{11}NO_5$ requires C, 55.69; H, 4.64; N, 4.90; found C, 54.96; H, 4.58; N, 4.46%.

Preparation of 2-(3'-*tert*-Butylamino-2'-hydroxypropoxy)-5-nitro-acetophenone 19a:

Glycidyl ether **18a** (0.47 g, 2 mmol), *tert*-butylamine (0.637 ml, 6mmol) and water (10 ml) were combined and stirred at room temperature for 12 h. Excess of tert-butylamine was removed under reduced pressure, and the resulting residue was extracted with EtOAc (2 x 10). The organic layer was dried with anhydrous sodium sulfate and concentrated to give amino alcohol **19a** in 86% yield. The amino alcohol was recrystallized from diisopropyl ether and ethyl acetate (5:1).



19a

Yield: 86% yellow solid; **mp** 105-107; **$[\alpha]^{25}_{D}$**: + 10.34; (c 1.76, EtOH); **IR**: ($CHCl_3$, cm^{-1}): 754, 1022, 1119, 1288, 1345, 1522, 1613, 1668, 2977, 3335; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.17 (s, 9H), 2.67-2.75 (m, 4H), 2.92 (dd, *J* = 2, 12 Hz, 1H), 3.12-3.17 (m, 1H), 4.06-4.22 (m, 2H), 7.10 (d, *J* = 8 Hz, 1H), 8.33 (dd, *J* = 2, 8 Hz, 1H), 8.61 (d, *J* = 2Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 28.52, 31.42, 44.47, 51.16, 67.70, 72.07, 112.99, 126.29, 128.24, 128.61, 141.18, 162.28, 197.12

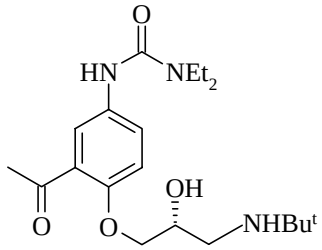
Preparation of 2-(3'-*tert*-Butylamino-2'-hydroxypropoxy)-5-amino-acetophenone 20a:

Amino alcohol **19a** (0.39 g, 1 mmol) in MeOH was hydrogenated at 20 psi with 10% Pd/C (0.030 g,) at room temperature. The reaction mixture was monitored by (TLC). After complete reduction (12 h), the catalyst was filtered, and the filtrate was concentrated under vacuum to afford the amino compound **20a** in 92% yield.

Yield: 92% solid; **mp** 105-107; **$[\alpha]^{25}_{D}$**: + 10.65; (c 1.76, EtOH); **IR**: ($CHCl_3$, cm^{-1}): 810, 1024, 1065, 1117, 1157, 1205, 1229, 1263, 1304, 1359, 1439, 1494, 1583, 1673, 2970, 3360; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.27 (s, 9H), 2.64 (s, 3H), 2.86-2.92 (m, 1H), 3.01-3.15 (m, 1H), 3.74- 4.22 (m, 7H), 6.81 (d, *J* = 2 Hz, 1H), 7.05 (dd, *J* = 2, 4 Hz, 1H), 7.27 (s, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 27.78, 31.27, 45.06, 52.52, 67.48, 71.82, 114.64, 116.37, 120.63, 128.28, 140.30, 150.81, 199.84;

Preparation of (R)-Celiprolol (1b)

To the amino compound **20a** (0.140 g, 0.53 mmol) in THF (5 ml) containing trimethylamine (0.21 ml, 1.5 mmol) and maintained at 40^0C, was added diethyl carbamoyl chloride (DECC) (0.2ml), and the reaction progress was monitored by TLC. After 48 h the reaction mixture was concentrated, extracted with ethyl acetate (3 x 5 ml) dried over anhydrous sodium sulfate, and concentrated. The residue was dissolved in acetone (10 ml) and filtered through a short bed of neutral alumina. The filtrate was concentrated under vacuum to afford Celiprolol base 90% yield and crystallized from acetone.



(R)-Celiprolol (1b)

Yield: 90% solid; **mp** 116-118^{0}C lit[15]; **mp** 117-118^{0}C; **[α]$^{25}_D$**: + 12.54; (c 1.76, EtOH), 82% ee; **HPLC**: 82% ee, Chiralcel-OD 10% diethylamine/2-propanol, 1 ml/mim. Retention time: (R): 12.67 min. (S): 10.35 min.; **IR**: ($CHCl_3$, cm^{-1}): 673, 759, 824, 1044, 1076, 1162, 1221, 1307, 1382, 1430, 1500, 1651, 1677, 2794, 2966, 3320; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.39 (t, *J* = 10 Hz, 6H), 1.48 (s, 9H), 2.57 (s, 3H), 2.99 (bs, 1H) 3.11-3.13 (m, 3H), 3.38 (m, 8H), 4.01-4.05 (m, 2H), 6.84 (d, *J* = 10 Hz, 1H), 7.53 (d, *J* = 10 Hz, 1H), 7.70 (s, 1H **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 8.59, 13.81, 25.61, 31.09, 41.42, 46.05, 57.67, 65.24, 71.01, 113.54, 123.43, 126.92, 127.43, 133.13, 153.20, 155.40, 159.67, 199.88.

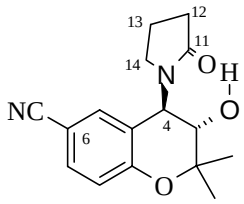
SECTION II:

Asymmetric Synthesis of Levcromakalim

2.1.1 Introduction

The study of potassium ion channel biochemistry, physiology, pharmacology, and medicinal chemistry has flourished in recent decades.[22] The reasons for this are manifold: ion channels, including sodium (Na), potassium (K), and calcium (Ca) channels, are present in all mammalian cells and play pivotal roles in the control of a variety of physiological processes, because they are ubiquitous and are integrally involved in normal cellular homeostasis. Levcromakalim (**24**) is one of the potassium channel activator (an antihypertensive agent) has been known since 1970.[23] Potassium channels regulated by changes in intra cellular levels of adenosine triphosphate are called ATP-sensitive potassium channel or K_{ATP} channels and an important class of ionic channels. Sodium channel blockers have been used for many years as local anesthetics and antiarrhythmics. Subsequently, calcium channel blockers underwent a vigorous development resulting in a number of drugs that are now widely used in a range of the therapeutic potential substances that modulate potassium channels.[24] There are three prototypes of these class of compounds; Pinacidil, a peripheral vasodilator; Nicorandil, an antianginal agent, and Cromakalim, a highly potent antihypertensive drug.[25] The existence of a powerful electron-withdrawing group located at C-6 in benzopyran compounds as well as a 4-(cyclic amido) group is essential for good blood pressure lowering action in the spontaneously antihypertensive rat (SAR).[26] Solution phase and solid state data suggest that the lactam and benzopyran rings of levcromakalim (**Fig. 10**) prefer to be orthogonal to one another with the carbonyl parallel to the C4-H bond.[27] Information on the biologically active

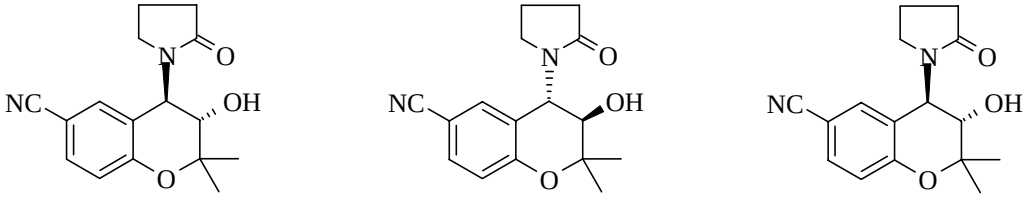
conformation of levcromakalim could lead ultimately to more potent or selective potassium channel activators.[28]



24

Fig. 10:

2.1.2 The Pharmacology of Levcromakalim



(±)-Levcromakalim **(24)** (3R,4S)-Levcromakalim **(24a)** (3S,4R)-Levcromakalim **(24b)**

Fig. 11:

The cell membrane is made up of an electrically isolating material known as the bilipid layer. To ensure the exchange of ions, channels are inserted. Most channels proteins are specialized in the transport of inorganic ions such as sodium, potassium, calcium and chloride, and connect the intracellular with the extra cellular space. Every second more than 10 million ions can pass through an ion channel[29] enabling inorganic ions to diffuse rapidly along the electrochemical gradient through the membrane. However, this does not mean that channels are just water filled pores in the membrane since they normally exhibit a high selectivity of certain ions. In addition, they are not permanently open but controlled by so-called gates, which are open for a short period of time and then closed again. The opening of gates is controlled by specific stimulus such as a change in the membrane potential (i.e., voltage-

dependant ion channels), mechanical stress (i.e., mechanically controlled ion channels) or binding of a messenger molecule (i.e., ligand-coupled ion channels). These ion channels are responsible for the electrical excitability of nerve and muscle cells, the secretion of hormones, volume regulation of cells, as well as other important life supporting activities.[30]

Because of the prominent physiological significance of K channels, some of the K channel activators (**25-32**) (**Fig. 12**) have important pharmacological effect on variety of tissues, including smooth and cardiac muscle eg. hypertension, asthma, urogenital malfunction, cardiac effect, CNS effects and miscellaneous effects.[31] Extensive clinical studies demonstrated potassium channel activator in case of enantiomers of cromakalim have been compared in vivo and in vitro, the (-)- enantiomer (levcromakalim) (**24b**) is approximately 100-200 times more potent than the (+)- enantiomer.[26, 32]

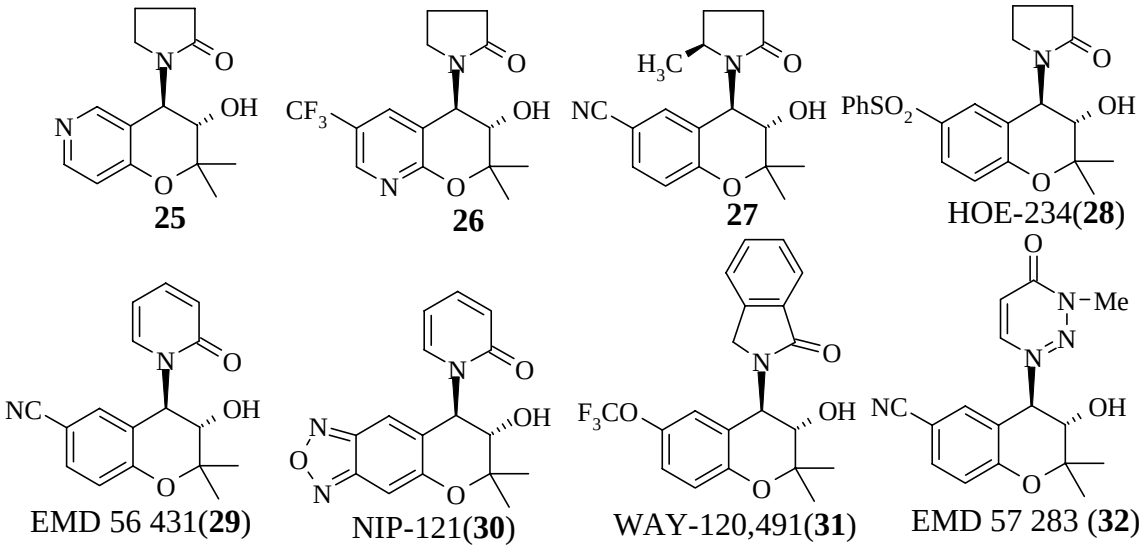


Fig. 12: Potassium Channel Activators

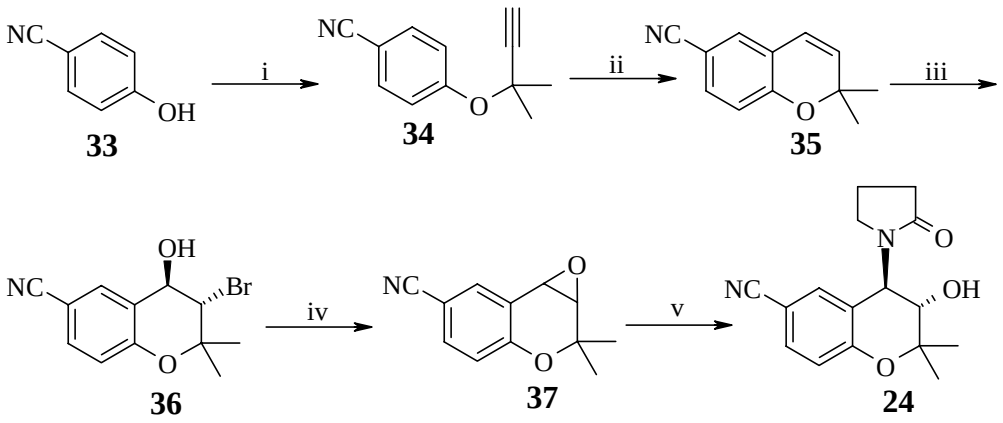
2.1.3 Review of Literature

Literature search revealed that only few reports are available for the synthesis of levcromakalim (**24b**). However, most of the reports are concerned with the synthesis of

levcromakalim in their racemic form and only two repots are available on asymmetric synthesis both of which are described below.

John's approach (1983)[33]

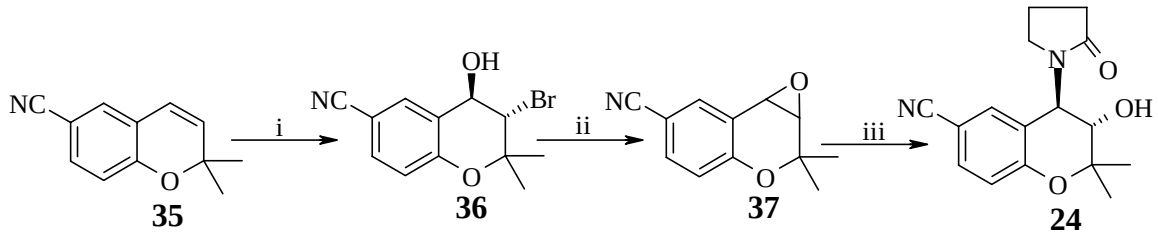
It is the first report on synthesis of the levcromakalim in its racemic form (**Scheme 7**). In this approach 4-cyanophenol (**33**) was heated with 3-chloro-3-methylbutyne in acetone in the presence of K_2CO_3 and KI to obtain the propargyl ether **34**. Propargyl ether **34** was cyliced by heating with *N*,*N*-diethylaniline to gave benzopyrans **35**. The cyclized product was converted in to epoxide **37** *via*- bromoalcohol and finally the epoxide was opened with cyclic amide to afford the racemic levcromakalim (**24**).



Scheme 7: (i) 3-chloro-3-methylbutyne, K_2CO_3, KI, dry acetone, reflux, 18 h, 72%; (ii) *N*,*N*-diethylaniline, reflux, 12 h, 84%; (iii) NBS, DMSO:H_2O, RT, 0.5 h; (iv) KOH, Et_2O, 4 days, 95%; (v) 2-pyrolidinone, EtOH, RT, 18 h.

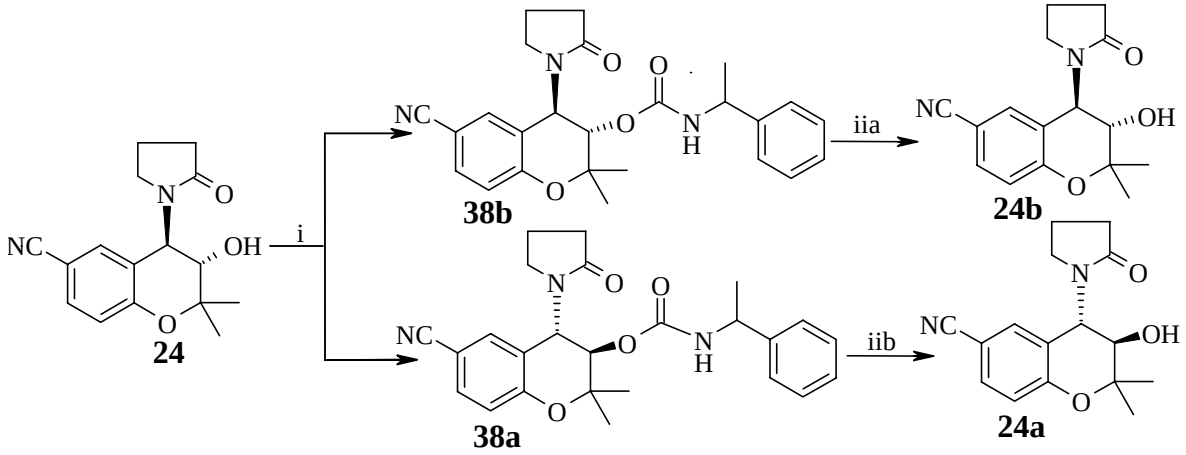
Valerie's approach (1986)[26]

[A] Valerie's *et al.* have synthesized derivatives of racemic levcromakalim. Starting from olefin **35** to epoxide **37** via bromoalcohol **36**, finally opening of epoxide with different cyclic amides to afford derivatives of racemic levcromakalim (**24**) (**Scheme 8**).



Scheme 8: (i) NBS, DMSO:H_2O, RT, 40 Min, 89%; (ii) NaOH, dioxane:H_2O, RT, 3 h, 65%; (iii) 2-pyrolidinone, 80% NaH, DMSO, RT, 2-6 h.

[B] Valerie's *et al.* have also synthesized derivatives of optically active levcromakalim (**24a** and **b**) via diastereomeric separations. Racemic levcromakalim (**24**) was resolved by reaction with (-)-α-methylbenzylisocyanate. Fractional crystallization gave two diastereomeric carbamates **38a** and **38b**, which were hydrolyzed by treatment with trichlorosilane-triethylamine to yield the enantiomer of levcromakalim **24a** and **24b** as shown in **Scheme 9**.

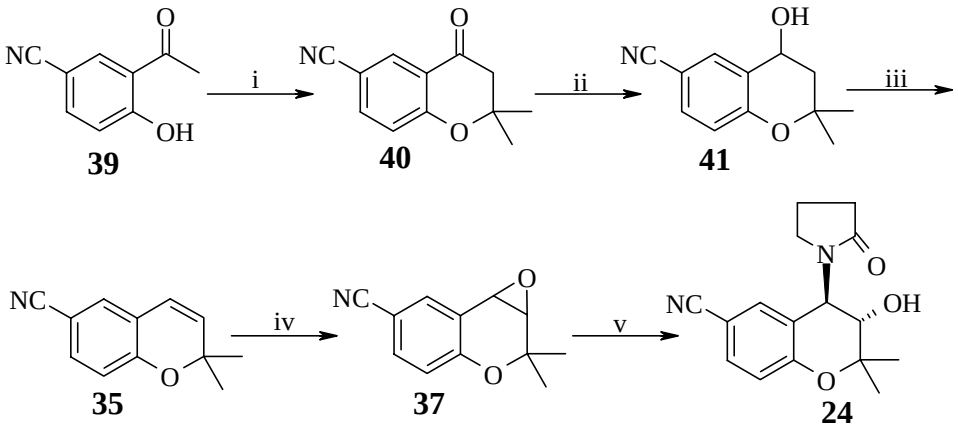


Scheme: 9 (i) toluene, (-)-α-methylbenzylisocyanate, 43 h (ii) Et_3N, H Si Cl_3, toluene.

Rolf Bergmann's approach (1990)[25]

Rolf Bergman *et al*. have reported a simple practical method for synthesis of racemic levcromakalim (**24**). In this approach 3-acetyl-4-hydroxybenzonitrile (**39**) was cyclized with acetone in the presence of catalytic amount of pyrrolidine as a base to give 6-cyano-2,2-

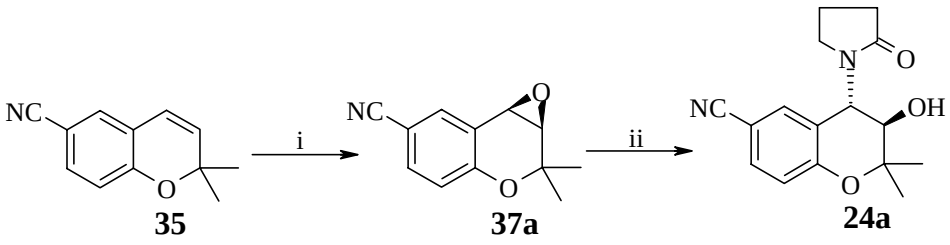
dimethylchromanone (**40**). Reduction of chromanone **40** with $NaBH_4$ gave 4-chromanol **41**, which on acid catalyzed dehydration gave chromene **35**. Chromene **35** was subjected to epoxidation using *m*-CPBA. Finally, the epoxide was opened with 2-pyrrolidone to afford the racemic drug levcromakalim **24** in 56% yield (**Scheme 10**).



Scheme 10: (i) acetone, pyrrolidine, toluene, 4 h with a Dean-Stark apparatus, 94%; (ii) $NaBH_4$, MeOH, 0-25^{0}C, 2 h, 98% yield; (iii) *p*-TSA, toluene, Dean-Stark with 4 h, 78%; (iv) *m*-CPBA, CH_2Cl_2, 5^{0}C, 12 h, 59%; (v) NaH, DMSO, 2-pyrrolidone, RT, 6 h, 56%.

Lee's approach (1991)[34]

This is the first approach for the asymmetric synthesis of levcromakalim as shown in **Scheme 11**. Lee *et al*. have developed Mn (salen) complex catalyzed asymmetric epoxidation of chromene derivatives. Finally, the epoxide **37a** was opened with 2-pyrrolidine to afford the corresponding optically active drug (**24a**) with excellent optical purity 97% ee and 56% yield.



Scheme 11: NaOCl, CH_2Cl_2, (R, R)-Jacobsen-catalyst, at pH = 11.3, 0^{0}C, 9 h, 81%; (ii) NaH, DMSO, 2-pyrrolidone, RT, 6 h, 56%, 99% ee.

2.1.4 Present Work

2.1.4.1 Objective

Although racemic β-blockers have been administered over the last two decades, there is now a great demand for enantiomerically pure isomers, which show higher affinity to β-receptors. All the reported methods described above for the synthesis of levcromakalim both in racemic as well as in optically active forms suffer from drawbacks such as the use of stoichiometric resolving agents, low overall yields, *etc.* To develop a new and practical method for the asymmetric synthesis of levcromakalim (**24b**) with good optical purity and yield, we have decided to make use of Sharpless Asymmetric Dihydroxylation (AD). In this work, we have developed a simple and practical method for the synthesis of (3S, 4R)-levcromakalim (**24b**), starting from 2-hydroxyacetophenone. The retro synthetic analysis of levcromakalim (**24b**) is shown in **Fig. 13.**

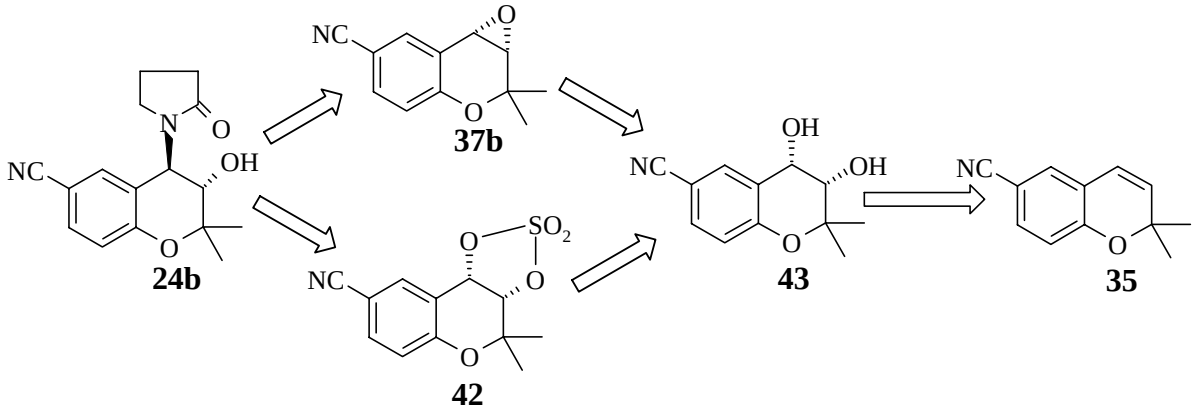
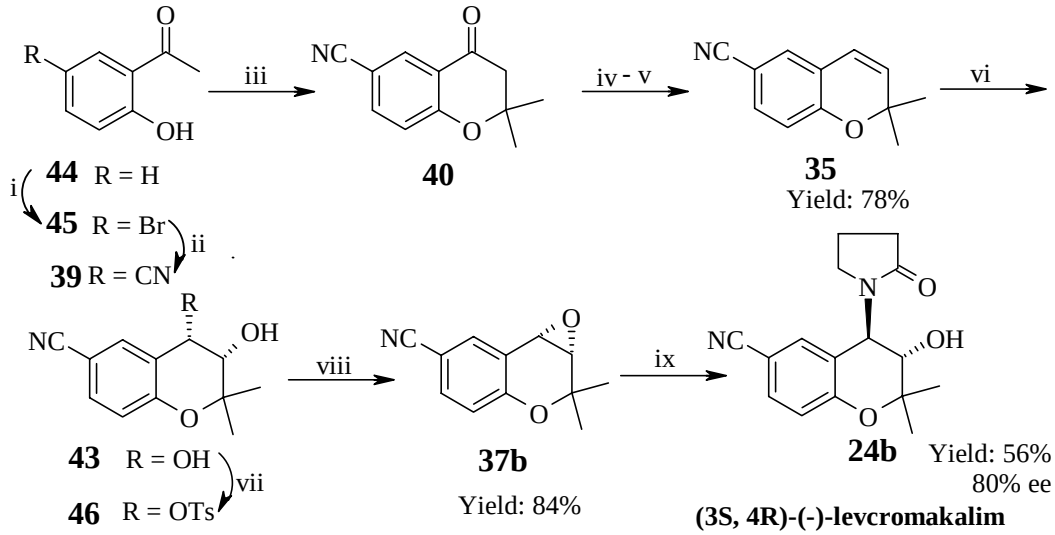


Fig. 13: The retrosynthetic analysis of levcromakalim (24b)

2.1.5 Results and Discussion

The synthetic strategy for levcromakalim (**24b**) is shown in **Scheme 12** wherein Os-catalyzed asymmetric dihydroxylation (AD) constitutes a key step in introducing chirality into the molecule based on retrosynthetic analysis.



Scheme 12: (i) NBS, CH_3CN, 60^0C, 12 h, 90%; (ii) CuCN, DMF, reflux, 12 h, 50%; (iii) acetone, pyrrolidine, toluene, 4 h with a Dean-Stark apparatus, 94%; (iv) $NaBH_4$, MeOH, $0\text{-}25^0C$, 2 h, 98% yield; (v) *p*-TSA, toluene, Dean-Stark with 4 h, 78%; (vi)) cat. OsO_4, $(DHQD)_2$-PYR, $K_3Fe(CN)_6$, K_2CO_3, $MeSO_2NH_2$ *t*-BuOH:H_2O (1:1), $0\text{-}25^0C$, 24 h, 90% yield, 58% ee. (vii) *p*-TsCl, Et_3N, CH_2Cl_2 0^0C 24 h, 80%, (viii) K_2CO_3, MeOH, 0^0C 12 h 84%; (ix) NaH, DMSO, 2-pyrrolidone, 25^0C, 6 h, 56%, 80% ee.

2-Hydroxyacetophenone (**44**) was brominated using *N*-bromosuccinimide (NBS) to give 2-hydroxy-5-bromoacetophenone (**45**) in 90% yield. Nucleophilic displacement of bromide with cyanide function was achieved with CuCN to afford 3-acetyl-4-hydroxybenzonitrile (**39**) in 50% yield. The IR spectrum of this cyano compound showed a strong band in the region of 2236 cm^{-1} indicating the presence of CN group in the molecule. Its ^{13}C-NMR spectrum has also displayed the appearance of extra carbon signal at δ 165.05 due to the presence of CN carbon in the molecule (**Fig. 14**).

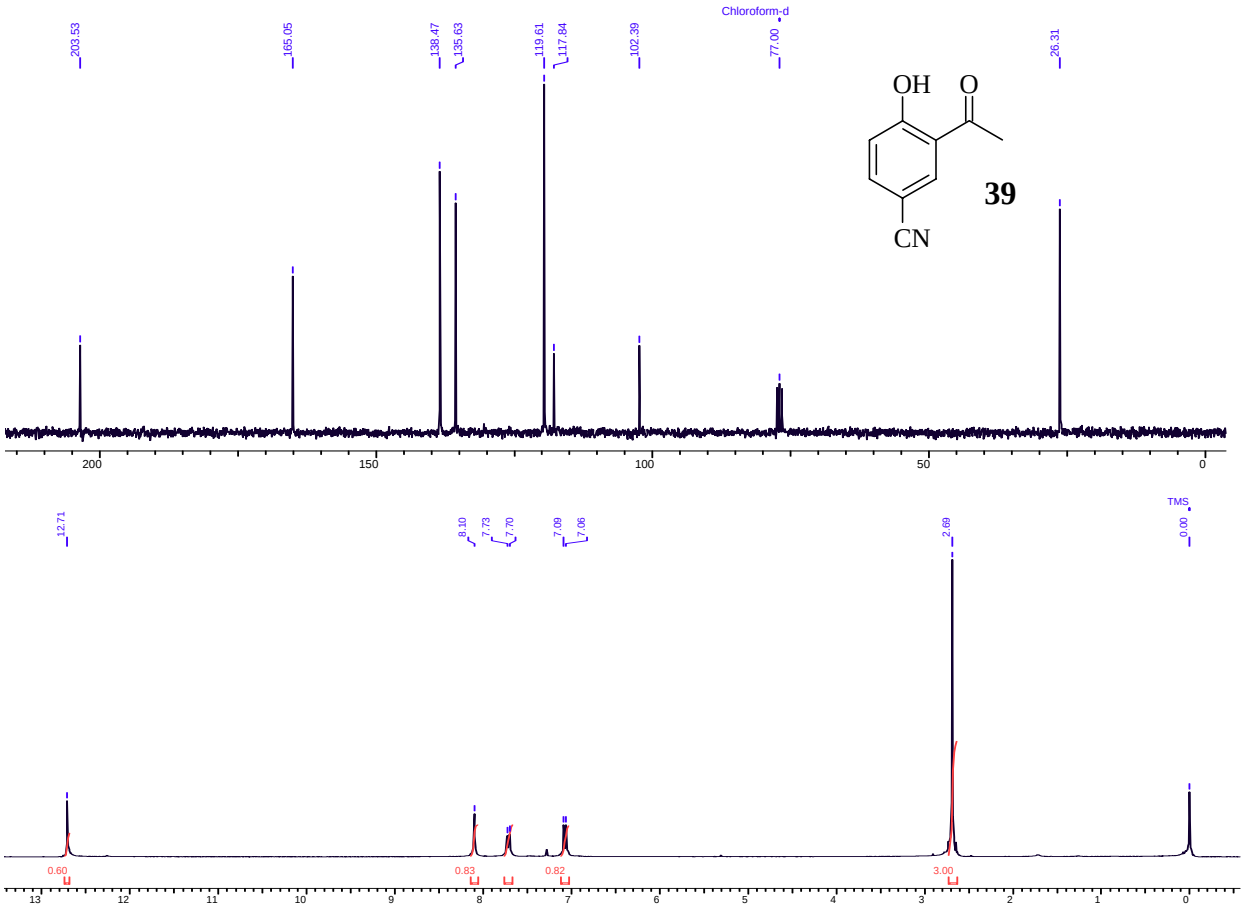


Fig. 14: ^{13}C and ^{1}H -NMR spectra of the 3-acetyl-4-hydroxybenzonitrile (39)

The cyano compound **39** was subsequently cyclocondensed with acetone in the presence of catalytic amount of pyrrolidine as base to give 6-cyano-2, 2-dimethylchromanone (**40**) in 94% yield. Its IR spectrum showed peaks in the regions 2236 and 1699 cm^{-1} indicating the presence CN and carbonyl groups respectively. The ^{1}H-NMR spectrum showed a singlet for dimethyl protons at δ 1.50. Its ^{13}C-NMR spectrum also showed a characteristic signal at δ 203.35 for carbonyl carbon indicating the presence of 6-cyano-2, 2-dimethylchromanone (**40**). Reduction of chromanone **40** with $NaBH_4$ in methanol gave 4-chromanol (**41**) in 98% yield. Its IR spectrum showed a broad band at 3428 cm^{-1} indicating the presence of hydroxy functionality in the molecule. The ^{1}H-NMR spectrum showed two singlets for methyl protons

at δ 1.32 and 1.46 due to the presence of diastereotopic methyl group, a triplet for CH proton bearing OH at δ 4.84 and its ^{13}C-NMR spectrum showed disappearance of carbonyl carbon peak in the molecule (**Fig. 15**).

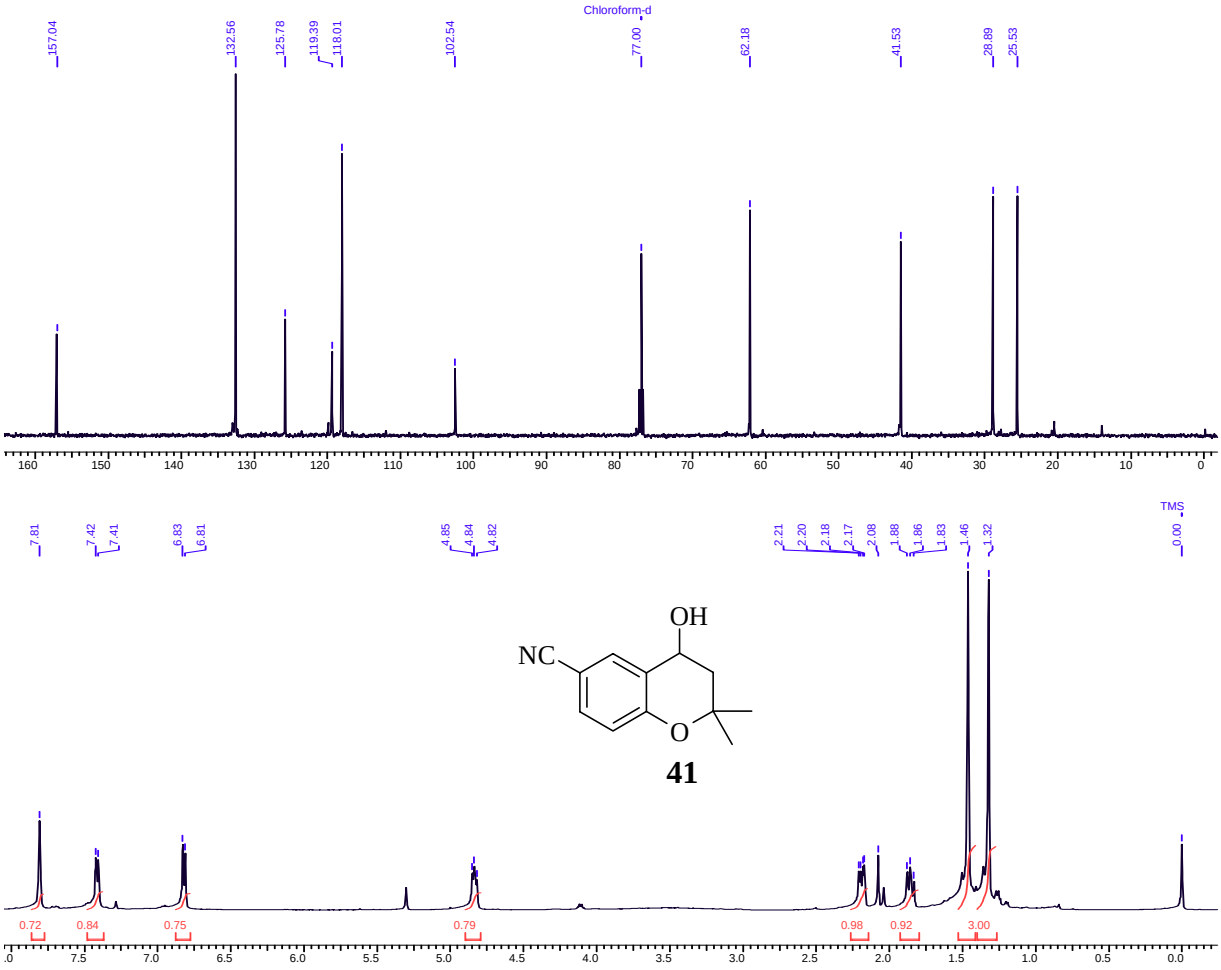


Fig. 15: ^{13}C and ^{1}H -NMR spectra of 6-cyano-2,2-dimethylchromanol (41)

The acid catalyzed dehydration of 4-chromanol (**41**) gave 6-cyano-2, 2-dimethylchromene (**35**) in 78% yield. Its ^{1}H-NMR spectrum showed the specific two doublets for olefin protons at δ 5.70 and 6.28. The ^{13}C-NMR spectrum showed the two olefinic carbon peaks at δ 77.60 and 103.53, which confirmed the presence of olefin in the molecule (**Fig. 16**).

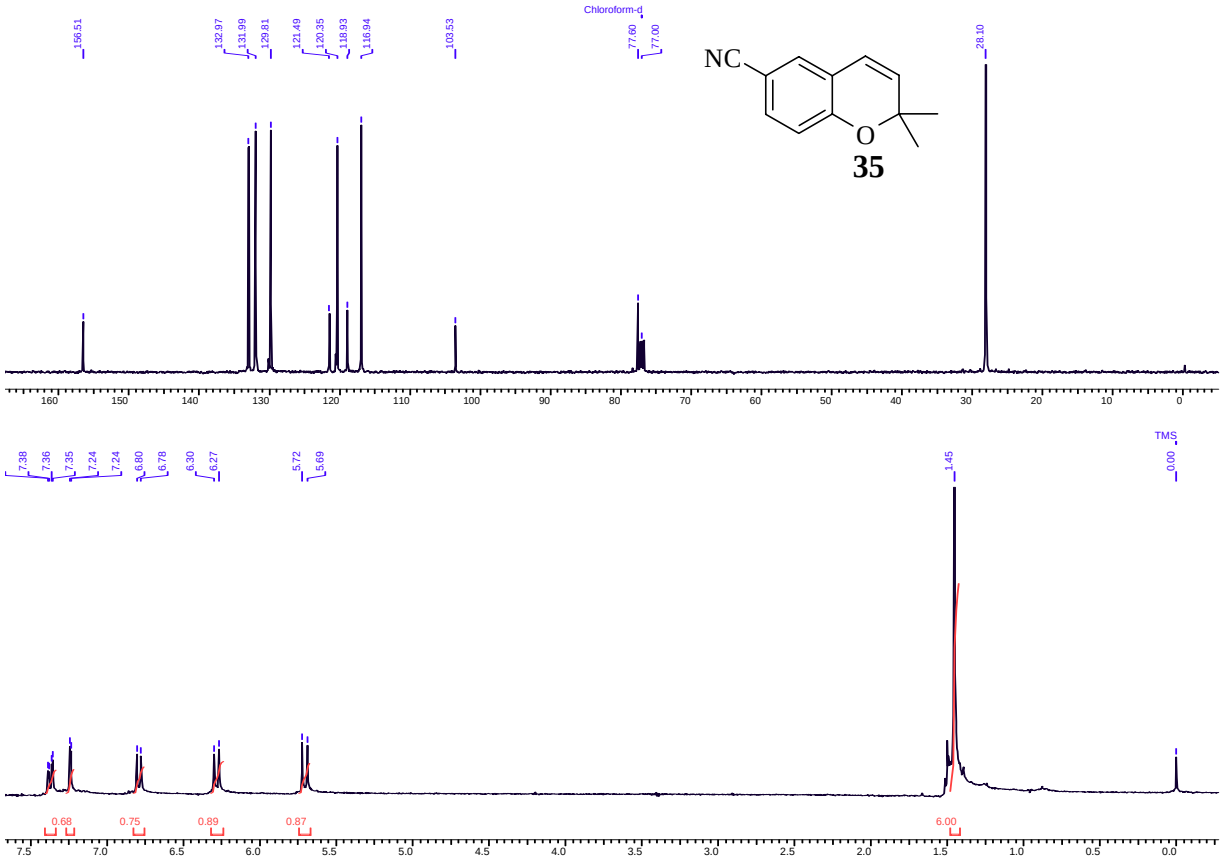


Fig. 16: ^{13}C and ^{1}H -NMR spectra of 6-cyano-2,2-dimethylchromene (35)

The chromene **35** was subjected to the Os-catalyzed Sharpless Asymmetric Dihydroxylation (AD) using $(DHQD)_2$-PYR [hydroquinidine 1,4-phthalazinediyl diether] as chiral ligand in presence of $K_3Fe(CN)_6/K_2CO_3$ as co-oxidant/base to give the optically active diol **43** in 90% yield and 58% ee (determined by chiral HPLC using Chiralcel OD-H column). The ^{1}H-NMR of the diol **43** showed disappearance of signals for olefinic protons in the region of δ 5.70-6.28. The appearance of three signals at δ 3.60 for two OH protons and two doublets at δ 4.02 and 5.13 confirmed the formation of diol **43**. The IR spectrum of diol **43** showed a broad band in the region of 3400-3500 cm^{-1} indicating the presence of hydroxy functionality in the molecule. The ^{13}C-NMR spectrum for diol showed two characteristic carbon signals at 65.23 and 71.59 (**Fig. 17**).

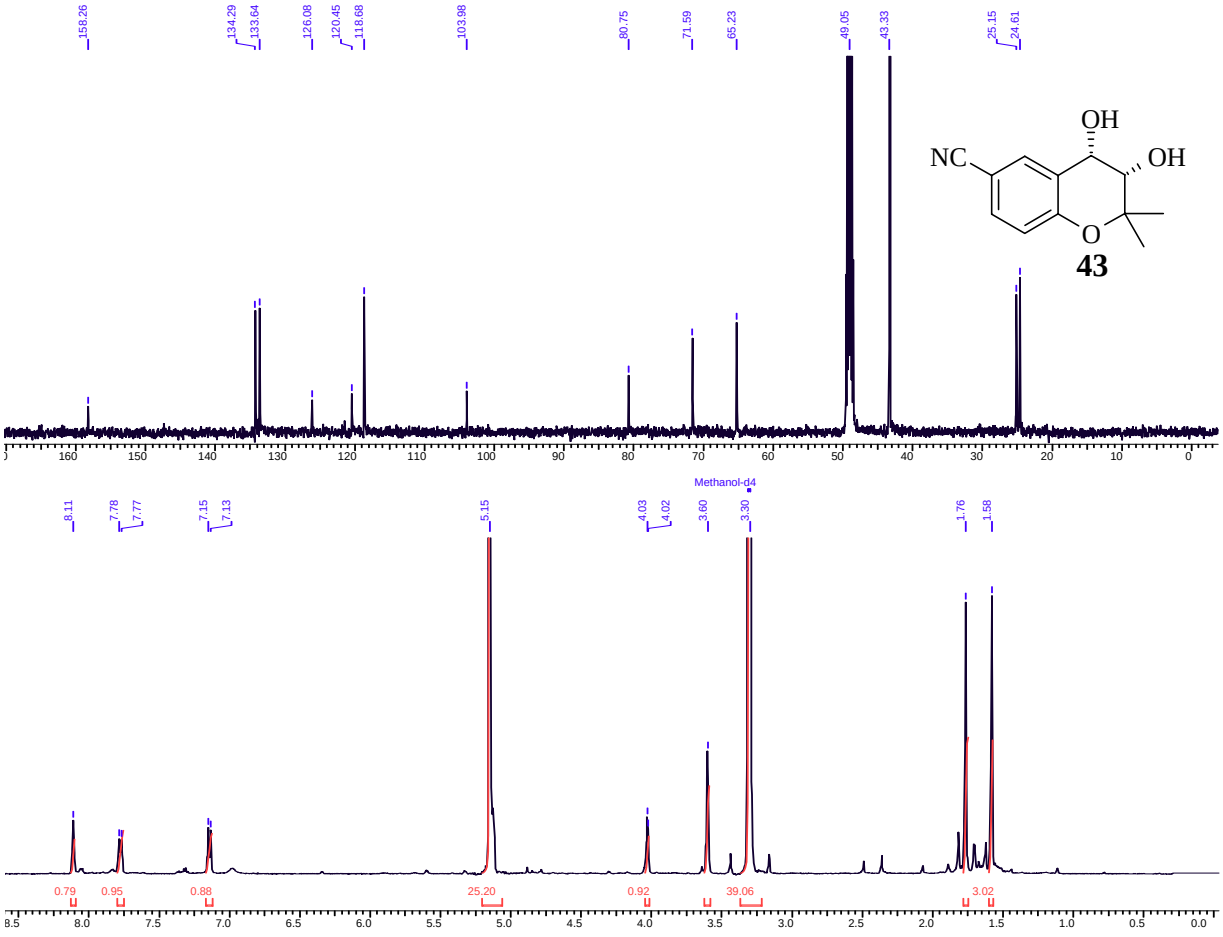


Fig. 17: ^{13}C and ^{1}H -NMR spectra of (S,S)-Diol (43)

The diol **43** was treated with freshly distilled $SOCl_2$ and Et_3N in CH_2Cl_2 at 0^0C to afford the corresponding cyclic sulfite in 96% yield. However, our attempts to oxidize this cyclic sulfite using Ru-catalyst to the corresponding cyclic sulfate were unsuccessful. Hence, the cyclic sulfite was subjected directly to nucleophilic displacement with 2-pyrolidone followed by hydrolysis of the salt in order to obtain levcromakalim. However, the opening and hydrolysis of the cyclic sulfite resulted in no reaction. Various other reaction conditions such as change of solvents temp. *etc*. were tried to obtain levcromakalim (**24b**) but all of them failed. We also tried to get epoxide from diol by following single step Sharpless[35] procedure using various conditions but resulted in very low yield of epoxide.

Hence, we have decided to convert the diol **43** into the corresponding epoxide **37b** using a two-step procedure. Thus, diol **43** was treated with tosyl chloride and Et_3N in CH_2Cl_2 at 0^0C to give monotosylate **46**. The monotosylate **46** was treated with anhydrous K_3CO_3 in MeOH at 0^0C to give the epoxide **37b** in 84% yield and 64% ee **(**determined by HPLC using Cyclodex-B capillary column). Its ^{1}H-NMR spectrum showed characteristic two doublets of epoxide protons at δ 3.53 and 3.90. The ^{13}C-NMR spectrum also showed the upfield shift in case of the epoxide carbon signals at δ 49.74 and 62.18. The IR spectrum showed the disappearance of OH peak (**Fig. 18**).

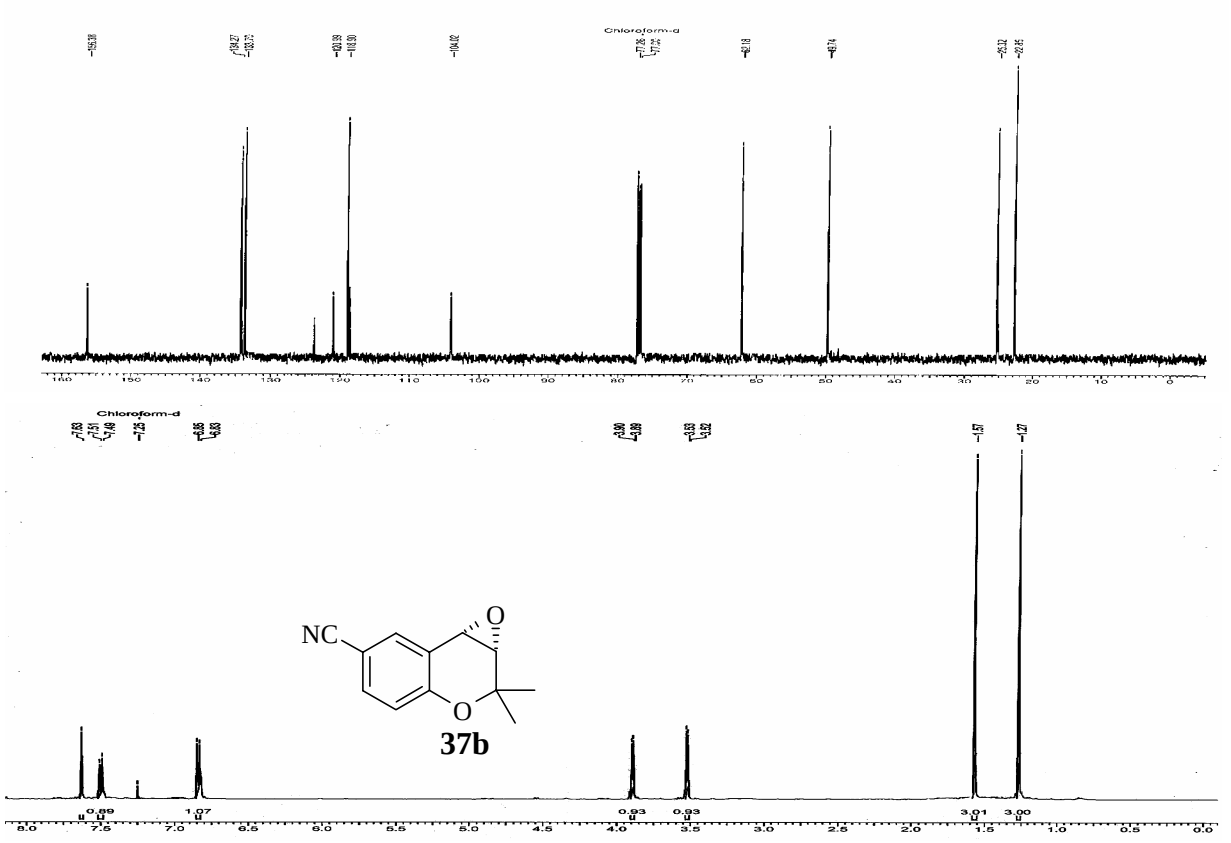


Fig. 18: ^{13}C and ^{1}H -NMR spectra of (S,S)-Epoxide (37b)

Finally, the epoxide **37b** was subjected to regio- and stereoselective opening with 2-pyrrolidone in dry DMSO using sodium hydride as base to afford (3S,4R)-levcromakalim

(**24b**) in 56% yield and 80% ee (optical rotation compared with lit.[26] value). The ^{1}H-NMR spectrum of **24b** showed multiplets of CH_2 protons [C (13)] at δ 2.09-2.17, multiplet of CH_2 protons [C (12)] at δ 2.58-2.64 and two multiplets of CH_2 protons [C (14)] at δ 3.05-3.08, δ 3.09-3.38.[27] Its ^{13}C-NMR showed three CH_2 carbon signals at δ 18.16, 31.18, 42.72 and one carbonyl at δ 178.12. The IR spectrum showed strong bands at 3353 and 1661 cm^{-1} due to OH and C=O functions respectively, thus confirming the formation of levcromakalim (**24b**) (**Fig. 19**).

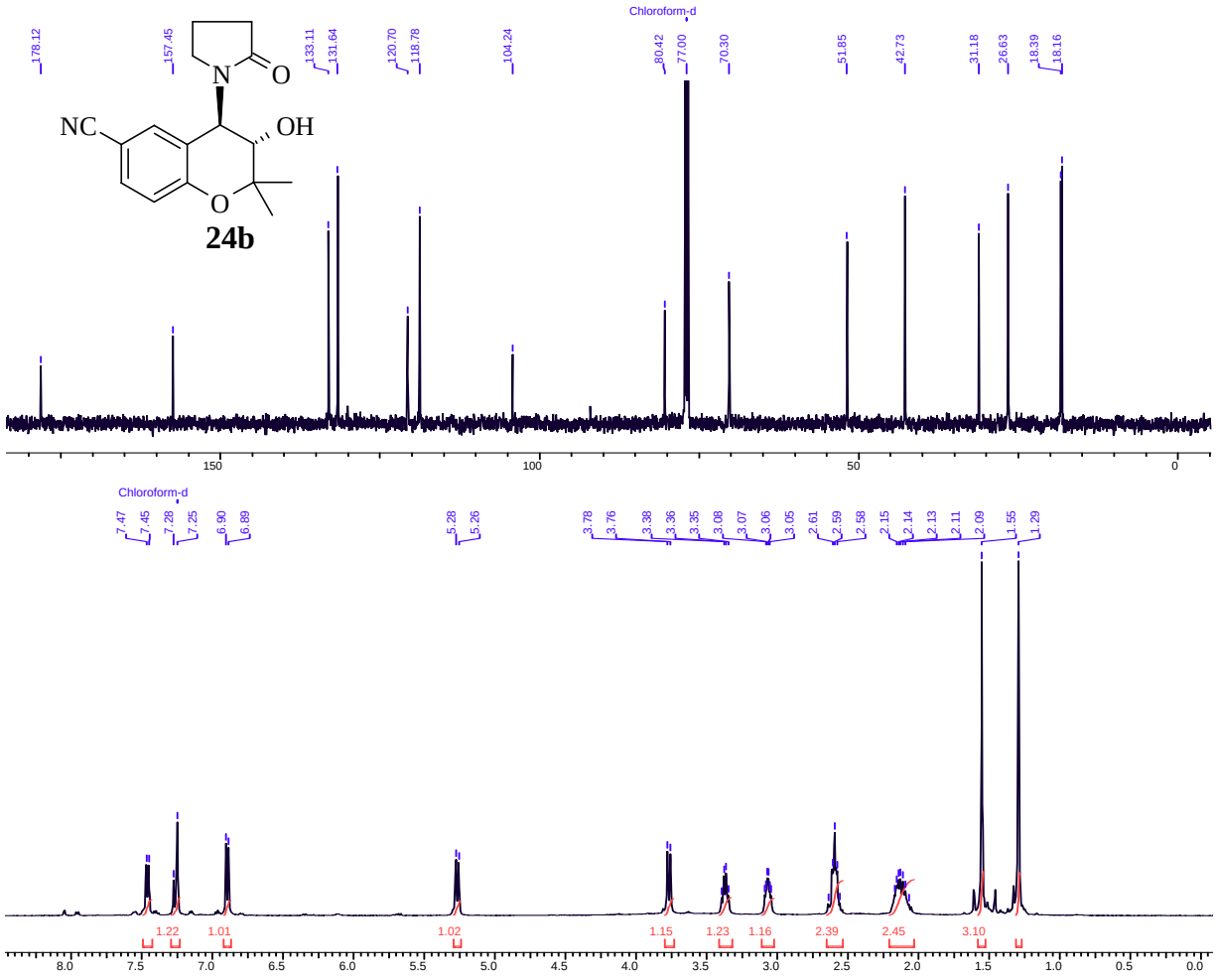


Fig. 19: ^{13}C and ^{1}H -NMR spectra (3S,4R)-(-)- Levcromakalim (24b)

The ^{1}H-NMR and ^{13}C-NMR spectral data of (3S, 4R)-(-)-levcromakalim **24b** matched very well with that of the published values.[36]

2.1.6 Conclusion

In conclusion, we have achieved a simple and efficient method for the asymmetric synthesis of (3S, 4R)-(-)-levcromakalim **24b** [10.95% overall yield, 80% ee], in overall nine steps starting from 2-hydroxyacetophenone.

2.1.7 Experimental Section

All solvents were distilled and dried before use. Chromatography was performed over silica gel (60-120 mesh). IR spectra were recorded on a Perkin-Elmer 137 E spectrometer. ^{1}H-NMR and ^{13}C-NMR were recorded on Bruker FT 200 and 500 MHz instruments using TMS as an internal standard. The optical rotations were recorded on JASCO-181 digital polarimeter at 25^{0}C using sodium D light.

Preparation of 5-bromo-2-hydroxyacetophenone (45):

A mixture of 2-hydroxyacetophenone (5.5 g, 40 mmol) and NBS (8.63 g, 48 mmol) in acetonitrile (40 ml) was stirred at 60^{0}C under N_2 for 24 h (monitored by TLC). The reaction mixture was then cooled to room temperature, diluted with water and extracted with CH_2Cl_2 (3 x 60 ml). Combined organic extracts were washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by column chromatography using only petroleum ether as eluent to yield white solid in 90% yield.

Yield: 90%; **mp**: 60-61^{0}C{Lit[37] **mp**: 62^{0}C}; **IR (**$CHCl_3$, cm^{-1}**)**: 3470, 2977, 1650, 1530, 1480, 1330, 850,754, 650; **^{1}H-NMR (**500 MHz, $CDCl_3$**)**: δ 2.62 (s, 3H), 6.89 (d, *J* = 15 Hz, 1H), 7.53 (d, *J* = 15 Hz, 1H), 7.83 (s, 1H), 12.17 (s, 1H); **^{13}C-NMR (**50 MHz, $CDCl_3$) δ 26.49, 110.27, 120.34, 120.77, 132.76, 138.89, 161.17, 203.35; **Analysis:** $C_8H_7BrO_2$ requires C, 45.93; H, 3.34; Br, 38.27; found C, 46.60; H, 3.20; Br, 38.56%.

Preparation of 2-hydroxy-5-cyanoacetophenone (39):

A mixture of 5-bromo-2-hydroxyacetophenone (6.5 g, 30 mmol) and CuCN (3.2 g, 36 mmol) in dry DMF (60 ml) was refluxed under N_2 for 24 h (monitored by TLC). The reaction mixture was then cooled to room temperature, diluted with water and extracted with ethyl acetate (3 x 60 ml). Combined organic extracts were washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by column chromatography using 25% ethyl acetate in petroleum ether as eluent to yield white solid in 50% yield.

Yield: 50%; **mp**: 100^{0}C {Lit[38] **mp**: 100-101^{0}C}; **IR (**$CHCl_3$, cm^{-1}**)**: 3460, 2934, 2859, 2236, 1656, 1575, 1484, 1307, 1200, 840, 775, 652; **^{1}H-NMR (**500 MHz, $CDCl_3$**)**: δ 2.69 (s, 3H),

7.08 (d, *J* = 15 Hz, 1H), 7.73 (d, *J* = 15 Hz, 1H), 8.11 (s, 1H), 12.72 (s, 1H); **^{13}C-NMR (**50 MHz, $CDCl_3$): δ 26.31, 102.39, 117.84, 119.61, 135.63, 138.47, 165.05, 203.53; **Analysis:** $C_9H_7NO_2$ requires C, 67.08; H, 4.34; N, 8.69; found C, 66.60; H, 4.20; N, 8.86%.

Preparation of 2,2-dimethyl-6-cyanochroman-4-one (40):

A mixture of 3-acetyl-4-hydroxybenzonitrile (**39**) (3 g, 18.5 mmol), acetone (2 ml, 27.7 mmol), and pyrrolidine (0.3 ml, 3.7 mmol) was refluxed in dry toluene (60 ml) for 4 h with a Dean-Stark apparatus. The solvent was evaporated and the residue purified by column chromatography using 20% ethyl acetate in petroleum ether as eluent to yield yellow solid in 94% yield.

Yield: 94%; **mp**: 120-122^{0}C; **IR (**Nujol, cm^{-1}**)**: 2934, 2848, 2236, 1699, 1613, 1468, 1382, 1291, 1189, 834; **^{1}H-NMR (**200 MHz, $CDCl_3$**)**: δ 1.50 (s, 6H), 2.76 (s, 2H), 7.02 (d, *J* = 8.0 Hz, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 8.15 (s, 1H); **^{13}C-NMR (**50 MHz, $CDCl_3$): δ 26.42, 48.22, 80.64, 104.68, 117.62, 119.71, 120.34, 131.55, 138.09, 162.31, 189.48; **Analysis:** $C_{12}H_{11}NO_2$ requires C, 71.64; H, 5.47; N, 6.96; found C, 71.60; H, 5.20; N, 6.86%.

Preparation of 2,2-dimethyl-6-cyanochroman-4-ol (41):

Ketone **40** (2.5 g, 1.2 mmol) in MeOH (40 ml) was stirred with $NaBH_4$ (0.70 g, 1.8 mmol). The solvent was evaporated, and the residue was taken up in H_2O (50 ml) and extracted with Et_2O (3 x 60 ml). The combined ether extracts were washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by column chromatography using 22% ethyl acetate in petroleum ether as eluent to yield yellow gum of chromanol in 98% yield.

Yield: 98%; gum; **IR (**$CHCl_3$, cm^{-1}**)**: 3428, 2987, 2934, 2236, 1704, 1613, 1575, 1495, 1377, 1130, 1076, 915, 829, 759, 555; **^{1}H-NMR (**500 MHz, $CDCl_3$**)**: δ 1.32 (s, 3H), 1.46 (s, 3H), 1.83-1.88 (m, 1H), 2.17-2.21 (m, 1H), 4.84 (t, *J* = 10 Hz, 1H), 6.82 (d, *J* = 10 Hz, 1H), 7.42 (d, *J* = 5.0 Hz, 1H), 7.81 (s, 1H); **^{13}C-NMR (**50 MHz, $CDCl_3$): δ 25.53, 28.89, 41.53, 62.18, 77.00, 102.54, 118.01, 119.39, 125.78, 132.56, 157.04; **Analysis:** $C_{12}H_{13}NO_2$ requires C, 70.93; H, 6.40; N, 6.89; found C, 71.20; H, 6.20; N, 7.40%.

Preparation of 2,2-dimethyl-6-cyanochromene (35):

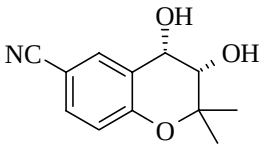
A mixture of 2,2-dimethyl-6-cyanochroman-4-ol (**41**) (2.46 g, 12 mmol) and *p*-toluenesulfonic acid hydrate (0.126 g, 0.66 mmol) was refluxed in dry toluene (60 ml) for 4 h

with a Dean-Stark apparatus. The solvent was evaporated under reduced pressure and the residue purified by column chromatography using 10% ethyl acetate in petroleum ether as eluent to yield yellow viscous liquid in 78% yield.

Yield: 78%; yellow viscous liquid; **IR (**$CHCl_3$, cm^{-1}**)**: 2977, 2923, 2236, 1651, 1602, 1484, 1377, 1280, 1221, 1151, 1130, 969, 899, 765, 727; **^{1}H-NMR (**500 MHz, $CDCl_3$**)**: δ 1.45 (s, 6H), 5.70 (d, *J* = 15 Hz, 1H), 6.28 (d, *J* = 15 Hz, 1H), 6.79 (d, *J* = 15 Hz, 1H), 7.24 (d, *J* = 5.0 Hz, 1H), 7.37 (dd, *J* = 5.0 and 15 Hz, 1H); **^{13}C-NMR (**50 MHz, $CDCl_3$): δ 28.10, 77.60, 103.53, 116.94, 118.93, 120.35, 121.49, 129.81, 131.99, 132.97, 156.51; **Analysis:** $C_{12}H_{11}NO$ requires C, 77.83; H, 5.94; N, 7.56; found C, 78.20; H, 6.10; N, 7.40%.

Preparation (3S,4S)-(+)-2,2-dimethyl-6-cyano-3,4-dihydroxychroman (43):

A 250 ml round-bottomed flask equipped with a magnetic stirrer, was charged with $K_3Fe(CN)_6$ (5.33 g, 16.2 mmol), K_2CO_3 (2.23 g, 16.2 mmol), $(DHQD)_2$-PHAL (0.095 g, 0.10 mmol), $MeSO_2NH_2$ (0.5 g, 5.4 mmol) and *t*-BuOH : H_2O (1:1, 80 ml) and the resulting mixture was stirred for 10 minutes at 25^0C. It was then cooled to 0^0C and a solution of OsO_4 (137 μl, 0.05 mmol, 0.5 M solution in toluene) was added. The resulting reaction mixture was stirred at 0^0C for 5 minutes and then the olefin **35** (1 g, 5.4 mmol) was added. The reaction mixture was stirred at 0^0C for 24 h (monitored by TLC). It was quenched with sodium sulfite (5.0 g) and extracted with ethyl acetate (4 x 30 ml). The combined organic layers were washed with 2N KOH (30 ml) and brine (30 ml), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by column chromatography using 50% EtOAc in pet. ether as eluent to yield pure diols **43** as gum in 90% yield.



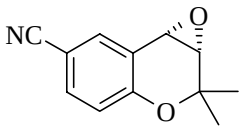
(3S,4S)-43

Yield: 90%; gum; **[α]$^{25}_D$ –** 32.15 (c 2, MeOH**)** 58% ee ; **IR (**$CHCl_3$, cm^{-1}**)**: 3428, 2980, 2936, 2228, 1806, 1716, 1610, 1594, 1576, 1386, 1308, 1268, 1188, 1066, 980; **^{1}H-NMR (**500 MHz, methanol-d_4**)**: δ 1.58 (s, 3H), 1.76 (s, 3H), 3.60 (s, 2H), 4.02 (d, *J* = 5.0 Hz, 1H), 5.13 (d, *J* = 5.0 Hz, 1H) 7.13 (d, *J* = 10 Hz, 1H), 7.78 (d, *J* = 10 Hz, 1H), 8.11 (s, 1H); **^{13}C-NMR (**50 MHz, methanol-d_4): δ 24.61, 25.15, 65.23, 71.59, 80.75, 103.98, 118.68, 120.45, 126.08,

133.64, 134.29, 158.26; **Analysis:** $C_{12}H_{13}NO_3$ requires C, 65.75; H, 5.93; N, 6.39; found C, 65.80; H, 6.07; N, 6.40%.

Preparation of (3S,4S)-(+)-2,2-dimethyl-6-cyano-3,4-epoxychroman (37b):

To a solution of diol **43** (0.5 g, 2.2 mmol) and Et_3N (0.194 g, 2.7 mmol) in dry CH_2Cl_2 (20 ml) at -15^0C was added TsCl (0.433 g, 2.2 mmol) portion-wise using solid addition funnel. After stirring for 24 h, the mixture was poured into ice water (30 ml), washed with $NaHCO_3$, and brine dried over anhydrous sodium sulfate and evaporated under reduced pressure. The crude product (0.8 g, 2.1 mmol) and K_2CO_3 (1.1 g, 8.5 mmol) was stirred in dry MeOH (50 ml) at 0^0C 24 h (monitored by TLC). The reaction mixture was filtered through sintered funnel and methanol evaporated under reduced pressure. The crude product was purified by column chromatography using 20% EtOAc in petroleum ether as eluent to yield epoxide **37b** in 84%.



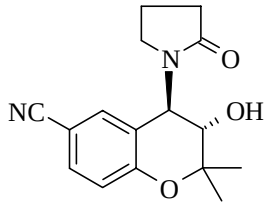
(3S,4S)-37b

Yield: 84%; **mp**: 120-122^{0}C {Lit.[33] 120^{0}C}; **$[\alpha]^{25}_D$:** - 28.45 (c 2, MeOH) after recrystallization from 50% EtOH; **HPLC**: 64% ee, Cyclodex-B capillary column 10% EtOH/hexane, 1 ml/min. Retention time: (S,S): 51.45 min. (R,R): 53.14 min.; **IR (**$CHCl_3$, cm^{-1}**)**: 2928, 2934, 2226, 1698, 1614, 1578, 1458, 1404, 1386, 1370, 1344, 1236, 1134, 1040, 816, 792, 766, 734, 672, 594, 572; **^{1}H-NMR (**500 MHz, $CDCl_3$**)**: δ 1.27 (s, 3H), 1.57 (s, 3H), 3.53 (d, *J* = 5.0 Hz, 1H), 3.90 (d, *J* = 5.0 Hz, 1H), 6.84 (d, *J* = 10 Hz, 1H), 7.50 (d, *J* = 10 Hz, 1H), 7.63 (s, 1H); **^{13}C-NMR (**50 MHz, $CDCl_3$): δ 22.85, 25.32, 49.74, 62.18, 77.26, 104.02, 118.90, 120.99, 123.99, 133.70, 134.27, 156.38. **Analysis:** $C_{12}H_{11}NO_2$ requires C, 71.64; H, 5.47; N, 6.96; found C, 71.80; H, 5.54; N, 6.90%

Preparation of (3S,4R)-3-hydroxy-2,2-dimethyl-4-(2-oxo-1-pyrroldinyl)-6-chromancarbonitrile (24b):

A dry two-necked 25 ml RB was charged with NaH (0.114 g, 60%, 3 mmol). The flask was then evacuated, filled with argon and then dry DMSO (10 ml) was introduced through syringe. 2-Pyrrolidone was added through syringe and stirred for 30 min at RT and finally epoxide (0.3 g, 1.5 mmol) was added through syringe. The reaction mixture was stirred for 2 h

(monitored by TLC) diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine and dried over Na_2SO_4 evaporated under reduced pressure. The crude product was recrystallized three times in ethyl acetate to yield 56% levcromakalim (**24b**).



(3S,4R)-(-)-Levcromakalim (24b)

Yield: 56%; **mp:** 243^{0}C {Lit.[26] **mp** 242-244^{0}C}; **[α]$^{25}_D$ –** 41.76 (c 1, $CHCl_3$) 80% ee after three time recrystallization from EtOAc, {Lit.[26] – 52.2 (c 1, $CHCl_3$}; **IR (**$CHCl_3$, cm^{-1}**)**: 3353, 2987, 2934, 2363, 2236, 1661, 1489, 1464, 1291, 1124, 1080, 1000, 978, 914, 832, 754, 668, 584, 496; **^{1}H-NMR (**500 MHz, $CDCl_3$**)**: δ 1.29 (s, 3H), 1.55 (s, 3H), 2.14 (m, 2H), 2.60 (m, 2H), 3.06 (m, 1H), 3.36 (m, 1H), 3.77 (d, *J* = 10 Hz, 1H), 5.27, (d, *J* = 10 Hz, 1H), 6.90 (d, *J* = 5.0 Hz, 1H), 7.25 (s, 1H), 7.46 (d, *J* = 10Hz, 1H); **^{13}C-NMR (**50 MHz, $CDCl_3$): δ 18.16, 18.39, 26.63, 31.18, 42.73, 51.85, 70.30, 80.42, 104.24, 118.78, 118.90, 120.70, 131.64, 133.11, 157.45, 178.18; **Analysis:** $C_{16}H_{18}N_2O_3$ requires C, 67.13; H, 6.29; N, 9.79; found C, 68.80; H, 6.54; N, 9.90%

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CHAPTRER 3

Novel Synthesis of Titanium Superoxide as Heterogeneous Catalyst for Organic Functional Group Transformations

SECTION I:

A New Method of Synthesis of Ti-Superoxide and Its Application to Oxidation of Amines: A High Yield Synthesis of Nitro Compounds

3.0.1 Introduction

Superoxide name has prompted many in recent years to assume an exceptional degree of reactivity for superoxide anion ($O_2^{-\cdot}$), especially as a strong oxidant and as an initiator of radical reactions. The name superoxide, was first proposed for the potassium salt of the radical anion $O_2^{-\cdot}$ in 1934.[1] It was selected because the stoichiometry for KO_2 differed from that for the products of combustion for most metals, e.g., NaOH (hydroxide), Na_2O (oxide), Na_2O_2 (peroxide), NaO_2H (hydroperoxide), and Na_2O_3 (ozonide). For many years, superoxide was considered to be little more than an interesting chemical curiosity.[2] Ionic salt of superoxide (yellow solid), which generally were performed from the reaction of dioxygen with metals such as potassium, rubidium, or cesium, were found to be paramagnetic with one unpaired electron per two oxygen atoms.[3]

The superoxide ion $O_2^{-\cdot}$ is one of the most extensively studied radical species because of its participation in a wide range of chemical and biochemical process.[4] In 1974 Kokes had first reported the formation of $O_2^{-\cdot}$ on ZnO surfaces.[5] The studies on adsorption of oxygen on the surfaces of oxides, metal oxides, supported catalysts, and zeolites have been investigated[6] using ESR. The main circumstances under which stable superoxide anions are formed at surfaces; include (i) the direct surface-oxygen electron transfer, (ii) the photoinduced electron

transfer (iii) surface intramolecular electron transfer and (iv) the decomposition of hydrogen peroxide.[7] The adsorbed superoxide species is different from the oxygen and peroxide and characterized by the presence of three electrons in the two $2\pi^*$ antibonding orbitals (**Fig. 1**), thus rendering it a paramagnetic species.[8]

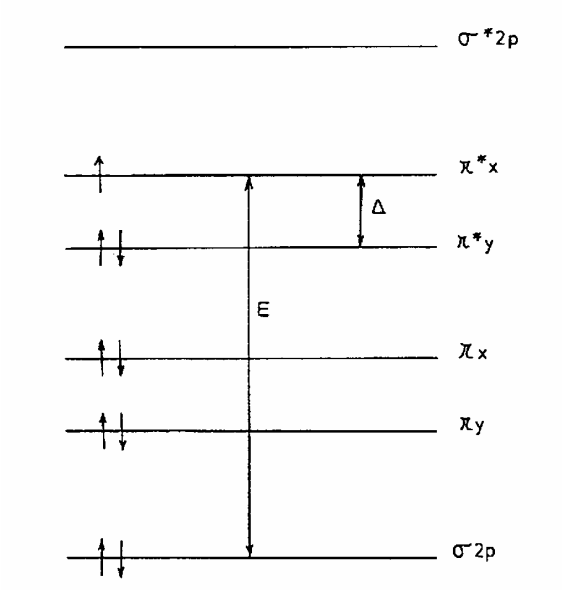


Fig. 1: Energy levels for the superoxide $O_2^{-\cdot}$ radical ion adsorbed on a surface

3.0.2 Review of Literature

Literature search[9] revealed that there are various methods known for the generation of superoxide ($O_2^{-\cdot}$) including electrolytic reduction of oxygen in DMF or by using enzymes such as xanthine-xanthine oxidase. Recently, the generation of $O_2^{-\cdot}$ was described on the lattice of metal oxides such as MgO/CaO, ZnO, ZrO_2, and TiO_2 by using a direct oxide-dioxygen electron transfer and photoinduced electron transfer processes.[7,10]

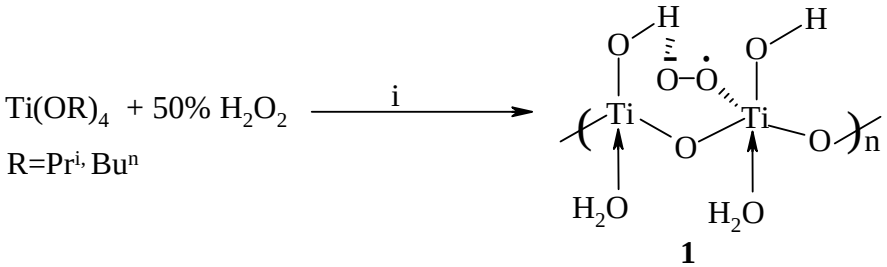
3.0.3 Present Work

3.0.3.1 Objective

The superoxide radical ion ($O_2^{-\cdot}$) is one of the most extensively studied radical species because of its participation in a wide range of chemical and biochemical processes such as self-contained breathing apparatus in which potassium superoxide, mixed with transition metal oxide catalyst, was used both to adsorb CO_2 and to generate O_2.[11] Most of the studies have been carried out to characterize the adsorbed oxygen species and to elucidate the role of oxygen in the surface reaction for the catalytic oxidation of inorganic molecules, as well as the oxidation and oxidative dehydrogenation of hydrocarbons.[12] Literature methods such as electrolytic reduction, oxide-dioxide electron transfer and photo-induced electron transfer process *etc*. However, these methods are not suitable for large-scale synthesis of adsorbed superoxide on transition metals. This chapter describes a new and practical method for the generation of $O_2^{-\cdot}$ on a solid hydrated titanium matrix and its catalytic activity towards the oxidation of N-H bonds of aromatic and aliphatic primary amines as well as O-H bonds of phenols.

3.0.4 Synthesis of Titanium Superoxide

The light yellow titanium superoxide (**1**) was readily prepared by the action of aq. 50% H_2O_2 on $Ti(OR)_4$ in anhydrous methanol at 25^0C in good yield (**Scheme 1**).[13]



1

Yield: 98%

Scheme 1: (i) anhydrous methanol, 25^0C, 1 h, 98%.

We have thoroughly characterized the generation of superoxide species **1** on the hydrated titanium matrix by various spectroscopic techniques such as FTIR, Raman spectroscopy, XRD, ESR, TG/DTA, and chemical analysis as follows. Its IR spectrum showed characteristic absorption bands at 3720 (w), 3665 (w), and 3450 (s) cm^{-1} indicating the presence of vibrational modes of coordinated water molecules at Ti^{4+} site and of surface Ti-OH groups.[14] The other IR absorption bands at 1027 (s) and 1157 (m) indicates the presence of superoxide radical ion in the solid material.[10b, 15] It also has IR bands in the range of 900-538 (m) cm^{-1} corresponding to the presence of Ti-O-Ti linkages. An intense line at 900 cm^{-1} in the Raman spectrum of the catalyst **1** further confirmed the presence of Ti-O-Ti linkages. The other weak Raman lines observed in the range of 1025-1119cm^{-1} assigned for the $O_2^{-\cdot}$.

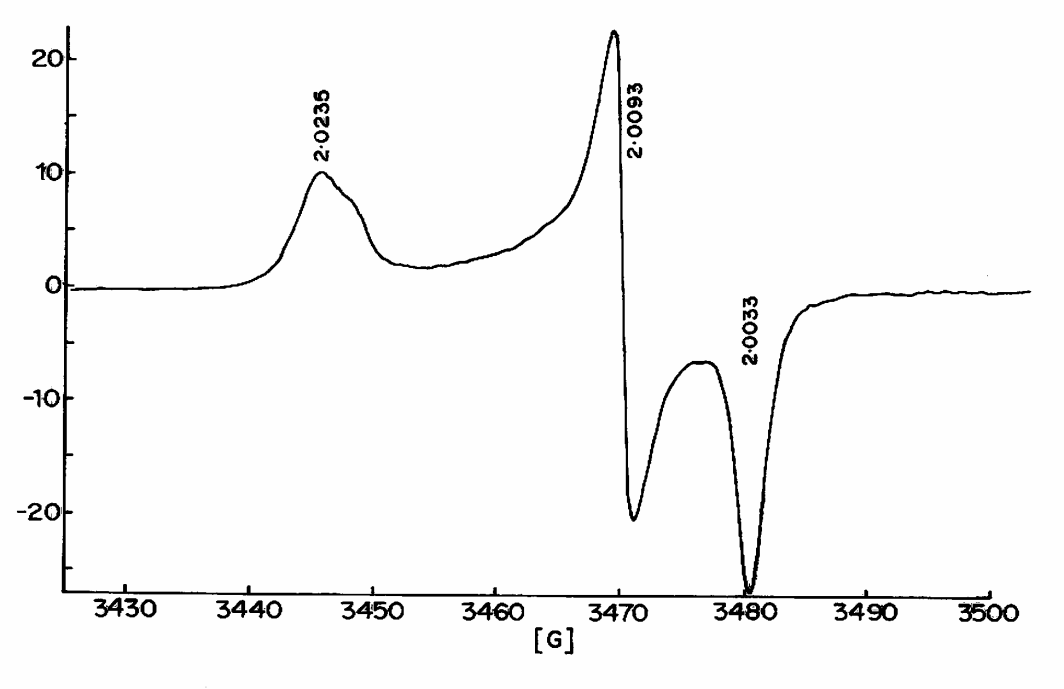


Fig. 2: ESR spectrum of 1 at 298 K.

The XRD pattern of Ti superoxide **1** showed that the material is amorphous in nature, as there are no sharp peaks observed in the spectrum. A sample of **1** dried at 25^{o}C (3 mm Hg) showed characteristic ESR signals at g_1 = 2.024, g_2 = 2.009 and g_3 = 2.003 (**Fig. 2**), which

strongly suggest the presence of unpaired electrons of the stable superoxide radical anion generated by the decomposition of H_2O_2 over Ti-matrix (**Fig. 2**).[10c,10f,16] However, the characteristic ESR signals disappeared when its ESR was recorded at 90°C.

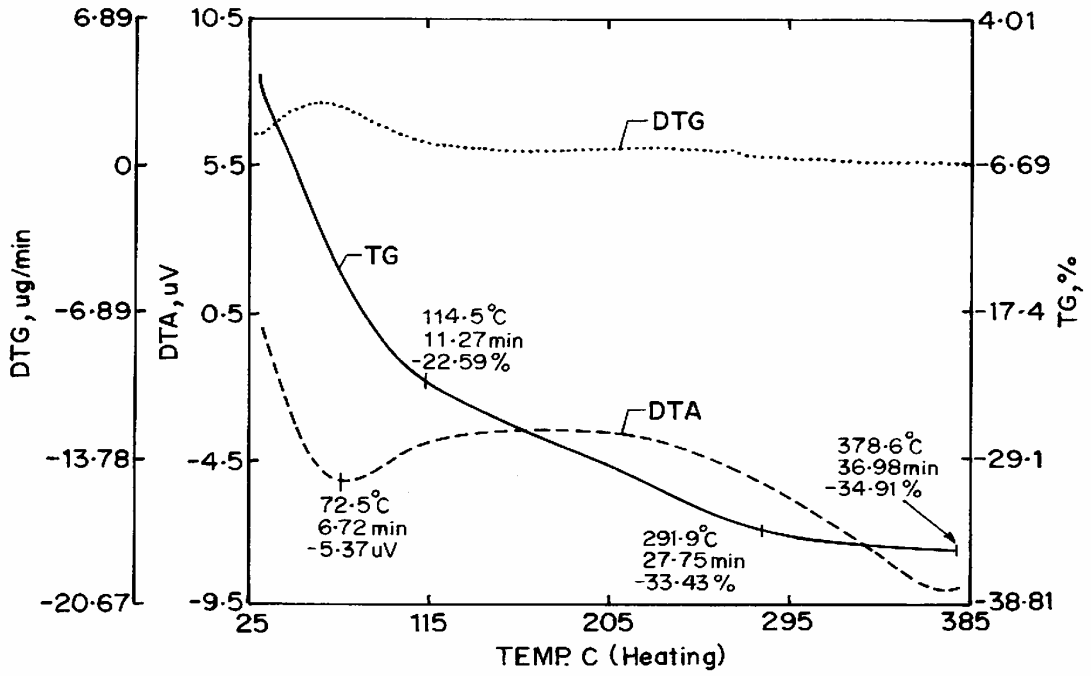


Fig. 3: TG/DTA spectrum of 1

The TG/DTA analysis of **1** (**Fig. 3**) showed a weight loss of 22.59% at 114°C and 10.84% at 291°C due to the loss of coordinated H_2O molecules and superoxide radical anion, respectively. Volumetric analysis [17] of **1** gave Ti-content of 41.7% and the surface area, determined by Braunner-Emmette-Teller method, was 310 m^2/g. Based on these data, the structure of titanium superoxide was deduced as shown in **1**. We then turned our attention on to systematically evaluate its catalytic oxidative properties towards both N-H and O-H bonds.

Oxidation of N-H Bonds of Amines: A High Yield Synthesis of Nitro Compounds

3.0.5 Introduction

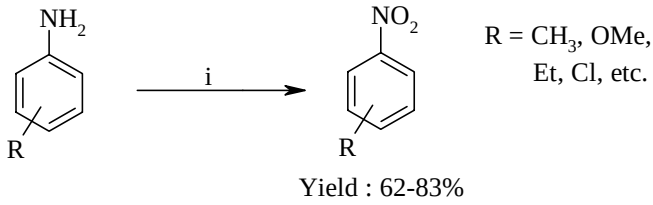
The direct oxidation of primary amines into the corresponding nitro derivatives is one of the most useful reactions for fundamental and industrial application, particularly for the selective synthesis of its oxygenated derivatives such as hydroxylamine, nitroso, azo, azoxy, and nitro compounds representing various oxidation levels. Among these, the preparation of nitro, oxime, and azoxy compounds has assumed special importance as synthetically useful intermediates. Consequently, a variety of oxidation methods have been reported.[18] For example, arylamines can be oxidized not only with stoichiometric oxidants such as peracetic acid,[19] MnO_2,[20] $Pb(OAC)_4$[21] and $Hg(OAc)_2$[22] but also with hydroperoxides by catalytic process using *t*-BuOOH:M (M= Ti, Mo, W),[23] Ru-H_2O_2[24] etc. Obviously, the reaction selectivity to produce specific oxygenated product is of crucial importance. However, it is generally complicated by the several other competing reaction pathways resulting in range of products in various oxidation states and the product composition depends on the oxidants, catalysts, and reaction conditions employed. Therefore, it assumes great importance to have effective control over selectivity in such reactions.

3.0.6 Review of Literature

Literature search reveals that there are various catalytic as well as non-catalytic methods known for the preparation of nitro compounds from amino compounds. Some of the important methods are described below.

William's[19]

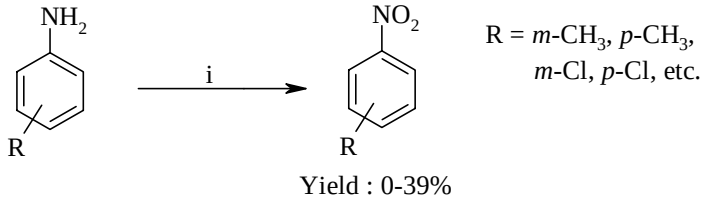
The various substituted aromatic primary amines were oxidized using peracetic acid into the corresponding nitro compounds in 62-83 % yield (**Scheme 2**).



Scheme 2: (i) peracetic acid, $CHCl_3$, 0^0C, 45 min.

Howe *et al.*

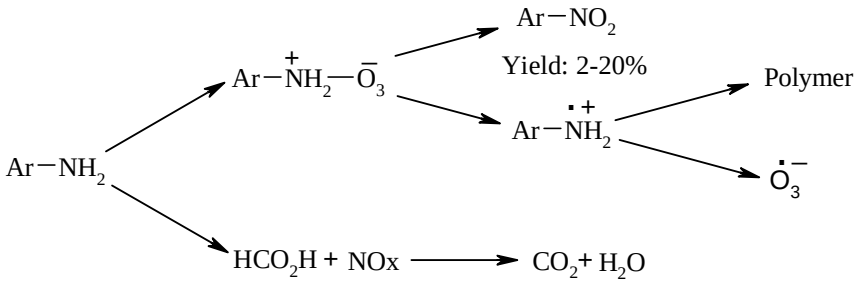
Howe *et al.*[25] have studied effect of substituent in the oxidation of aniline to nitrobenzene using *tert*-butyl hydroperoxide in the presence of catalytic quantities of molybdenum and vanadium compounds (**Scheme 3**).



Scheme 3: (i) *tert*-butyl hydroperoxide, benzene:$CHCl_3$, vanadium oxyacetylacetonate.

Ehud *et al.*

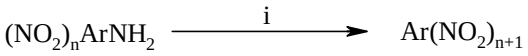
Ehud et al.[26] have developed an efficient synthetic method for the oxidation of primary amines into their nitro derivatives. The alkyl and aryl amines were adsorbed on dry silica gel and a stream of 3% ozone (in oxygen) (generated from a Welsbach ozonizer) passed through it to give nitro compounds. The dependence of product yields on several experimental factors was investigated (**Scheme 4**).



Scheme 4: (i) stream of ozone, -70^{0}C.

Arnold *et al.*[27]

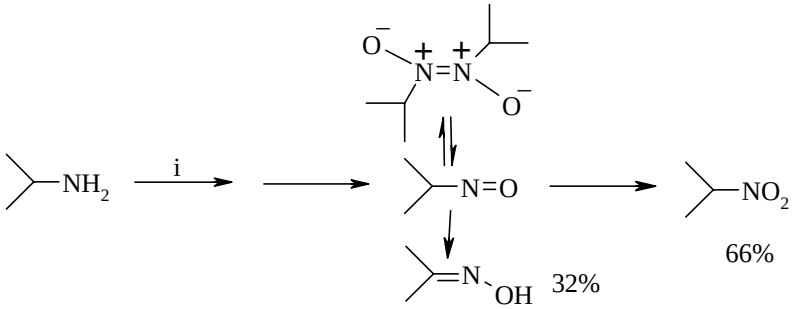
Peroxydisulfuric acid in sulfuric acid solution was prepared by reaction of hydrogen peroxide with excess oleum (100% H_2SO_4), oxidizes primary polynitroarylamines and their *N*-acetamido derivatives to polynitro aromatics in good to excellent yields (**Scheme 5**).



Scheme 5: (i) $H_2S_2O_8$, H_2SO_4, -10^{0}C, 30 min.

Gilbert *et al.*[28]

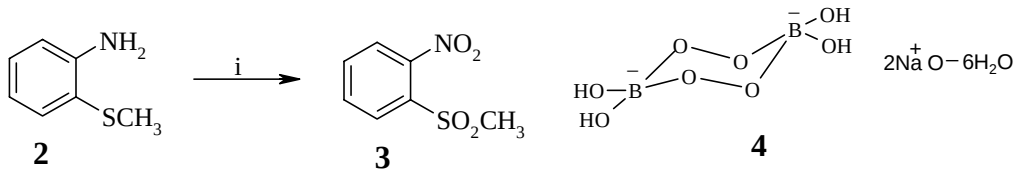
Gilbert and coworkers have developed a method for the oxidation of aliphatic amines to nitro compounds using *m*-chloroperbenzoic acid (*m*-CPBA) as an oxidant (**Scheme 6**).



Scheme 6: (i) *m*-CPBA (4 eq.), $CHCl_3$, 61^{0}C, 3 h, 30-66%.

Alexander *et al.*

Alexander *et al.*[29] have reported sodium perborate **4** in acetic acid as an effective reagent for the oxidation of anilines **2** having thioether substituted to the corresponding nitro sulfone compounds **3**; it is also highly effective for the oxidation of sulfides to either, sulfoxides or sulfones in 80% yield (**Scheme 7**).

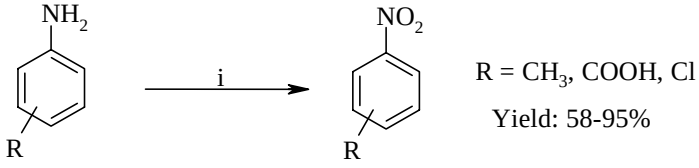


2 **3** **4**

Scheme 7: (i) cat. 4, acetic acid, 50-55^{0}C.

Murray *et al.*[30]

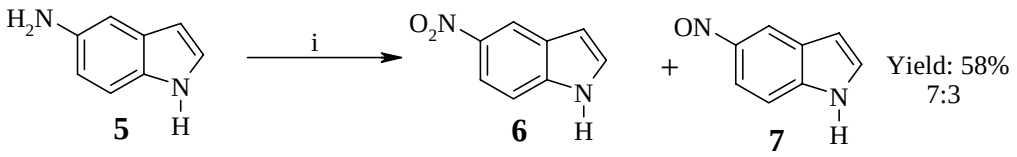
Murray and co-workers have carried out oxidation of variety of primary amines to the corresponding nitro compounds using dimethyldioxirane as a reagent (**Scheme 8**).



Scheme 8: (i) dimethyldioxirane, acetone, dark, 30 min.

Zabrowski *et al.*

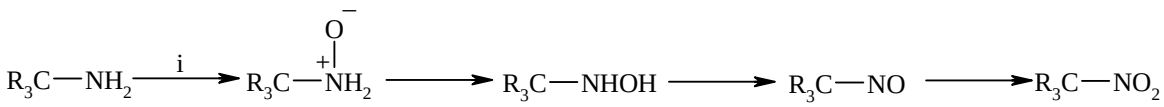
Zabrowski *et al.*[31] have used oxone for the oxidation of aromatic amines to the corresponding nitro substituents **6** and **7** in ratio (7:3) performing the reaction under mild, nonacetic condition in the presence of highly nucleophilic aromatic systems such as indoles and furans (**Scheme 9**).



Scheme 9: (i) Oxone (3.2 eq), acetone, nBu_4NHSO_4, CH_2Cl_2, Na_2HPO_4 aq. buffer, pH ≅ 8, 0^0C.

Barens et al.

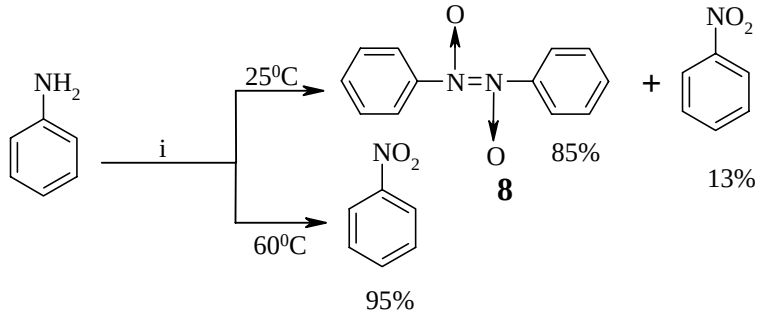
Barens *et al.*[32] have used potassium permanganate in aqueous acetone in the presence of magnesium sulfate, as an oxidizing agent for the oxidation of variety of tertiary alkyl primary amines into nitro compounds in 70-80% yield (**Scheme 10**).



Scheme 10: (i) K_2CO_3, $MgSO_4$, aq. acetone, 2 h, 70-80%.

Sigeki *et al.*[23]

Sigeki and co-workers have studied temperature effect on the oxidation of anilines with 30 % aq. H_2O_2 catalyzed by peroxotungstophosphate (PCWP) at room temperature in chloroform under two-phase condition, which afforded nitrosobenzene (**8**) with high selectivity. When the same reactions were carried out at reflux temperature, nitrobenzenes were obtained in good yields (**Scheme 11**).



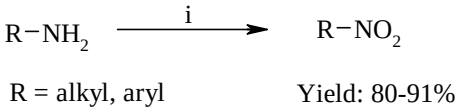
Scheme 11: PCWP (10 wt %), 30% aq. H_2O_2, $CHCl_3$, 24 h.

Rozn *et al.*[33]

Rozn *et al***.** have developed HOF-MeCN as oxygen transfer agent, prepared from F_2, H_2O and CH_3CN and successfully employed for the oxidation of primary aliphatic and aromatic amines to their corresponding nitro compounds.

Sudalai *et al.*[34]

Our groups have developed a simple method for the oxidation of various primary amines to the corresponding nitro compounds using chromium silicate as a catalyst and 70% *tert*-butyl hydroperoxide as the oxidant (**Scheme 12**).



Scheme 12: CrS-2 (10% m/m), 70% TBHP (3 eq.) MeOH, 65^0C.

3.0.7 Present Work

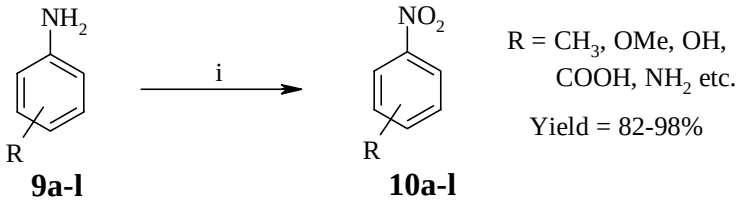
3.0.7.1 Objective

Although there are many methods available in the literature for the oxidation of amines to nitro compounds, they suffer from certain drawbacks like low product selectivity, use of stoichiometric oxidants, difficulty in handling hazardous nature of the anhydrous peracids, toxicity, drastic reaction conditions etc. There are very few reports available on the catalytic oxidation of primary amines to direct nitro compounds. In order to overcome these difficulties, a new catalytic method for oxidation of primary amines to direct nitro compound is highly desirable.

The oxidation of aliphatic amines possessing α-C-H bond activated by allylic or benzylic positions occupies a unique position in that there has by always been a problem of exclusive formation of one of the oxygenated products. For example, when such amines are oxidized, one would obtain a variety of higher oxygenated products such as hydroxylamine, nitroso compound, or oxime. Although there are many reports available in the literature, the existing methods suffer from the low yield of oximes. The chemistry of the superoxide radical ion remains to be completely characterized. We have decided to explore the use of superoxide radical ion **1** as a catalyst in combination with H_2O_2 as oxidant for effecting oxidation of amines to nitro compounds directly.

3.0.8 Results and discussion

When aniline was treated under nitrogen atmosphere with 50% aq. H_2O_2 (6 eq.) in the presence of catalytic amount of Ti-superoxide **1** (25 wt %) in methanol, nitrobenzene was obtained in high yield and selectivity (98%). Among the various solvents employed such as acetone, acetonitrile, THF, methanol, only methanol gave the high selectivity of nitrobenzene (**Scheme 13**).



9a-l **10a-l**

Scheme 13: Ti-superoxide (25 wt %), 50% aq. H_2O_2 (6 eq.), methanol, 25^0C, 30 min.

Various substituted primary aromatic amines (**9a-l**) were oxidized to the corresponding nitro compounds (**10a-l**) in excellent yield and selectivity (82-98%). However, aliphatic primary amines (**11a-e**) were oxidized to the corresponding oximes (**12a-e**) in good yield (75-90%).

Table 1: Ti-superoxide (**1**)[a] catalyzed oxidation of primary aromatic amines (**9a-l**).

Sr. No	Substrate	Time (min)	(%) Conversion	(%) Product[b] selectivities[c]			
				NB	NSOB	AB	AZOB
a	Aniline	30	100	98.18	1.82	--	--
b	2-Methylaniline	30	100	97.35	1.50	--	1.15
c	3-Methylaniline	35	100	90.00	6.60	1.50	1.90
d	4-Methylaniline	30	100	98.00	1.57	--	0.43
e	2-Methoxyaniline	30	100	97.15	1.00	0.80	1.05
f	2-Methoxy-5-nitroaniline	35	100	95.60	3.05	--	1.35
g	4-Methoxyaniline	30	100	97.05	1.13	0.37	1.45
h	4-Hydroxyaniline	45	100	89.22	3.01	3.62	4.15
i	2-Methyl-6-ethylaniline	35	100	90.98	4.50	1.87	2.65
j	4-Chloroaniline	35	100	91.22	5.00	1.50	2.28
k	4-Nitroaniline	45	100	82.50	9.01	3.19	5.31
l	2-Aminobenzoic acid	45	100	85.05	8.05	4.09	2.81

a) catalyst was recovered and reused without any loss of activity and selectivity; b) products were characterized by mp, IR, ^{1}H NMR, MS and GC-MS; c) selectivities are based on gas chromatographic analysis, NB–nitobenzene, NSOB–nitrosobenzene, AB–azobenzene, AZOB–azoxybenzene.

The results of oxidation of both aromatic and aliphatic amines are summarized in **Table 1** and **2.** As mentioned in **Table 1** a variety of aromatic primary amines are oxidized to give nitro

compounds along with minor products such as azoxybenzene, azobenzene, nitrosobenzene (0-5%) which were characterized by the GC-MS and GC. In case of the substrates with electron-withdrawing groups lower selectivity was observed than the substrates with electron-donating groups. Remarkably, even aryl amines with electron withdrawing groups such as NO_2 and COOH are efficiently oxidized to the corresponding nitroarenes (entry **10k** and **10l**), which otherwise may be difficult to obtain by conventional methods. It may be noted that Zeolites such as TS-I, TS-2, NaY, CrS-2 and HY as heterogeneous catalysts are known to oxidize arylamines to azoxybenzenen, azobenzene, and nitrobenzene with poor selectivity.[35]

Under similar oxidation conditions, aliphatic primary amines **11a-e** having α-CH bonds were selectively converted to oximes **12a-e** (65-94%) along with ketones (6-12%) formed by partial hydrolysis (**Table 2**).

Table 2: Ti-superoxide (**1**)[a] catalyzed oxidation of aliphatic amines **11a-e**.

Sr. No	Substrate	Time (min)	(%) Conversion	(%) Product[b] selectivities[c]	
				Oxime	Ketone
a	Cyclohexyl amine	45	90	88.88	11.11
b	Benzylamine	45	85	94.11	5.88
c	Ethylenediamine	45	80	87.5	12.5
d	4-Methoxybenzylamine	45	89	90.34	9.66
e	1-Tetralylamine	45	75	80.97	19.03

a) catalyst was recovered and reused without any loss of activity and selectivity; b) products were characterized by mp, IR, ^{1}H NMR, MS and GC-MS; c) selectivities are based on gas chromatographic analysis,

The influence of the amount of Ti-superoxide catalyst **1** on oxidative process was evaluated using aniline as a representative case. It is observed that no nitrobenzene was formed in the absence of catalyst Ti-superoxide. Increasing the catalyst to either 5 or 10 wt %

has resulted in the formation of nitrobenzene in 40% yield. However, further increase of catalyst (25 wt%) improved the excellent yield and selectivity of nitrobenzene.

The formation of nitro compounds (**10a-l**) and oximes (**12a-e**) was conformed by ^{1}H, ^{13}C-NMR, IR and Mass spectroscopy. The mass spectra of nitro compounds showed typical prominent peaks resulting from elimination of an NO_2 radical (M – 46, the base peak in nitrobenzene), and of a neutral NO molecule with rearrangement to form the phenoxy cation (M-30); both are good diagnostic peaks. Loss of HC≡CH from the M – 46 ion accounts for a strong peak at M – 72: loss of CO from the M – 30 ions gives a peak at M – 58. A prominant peak at m/z 30 results from the NO^{+} ion. The IR spectrum of all the nitro compounds showed the typical absorption band at 1500 - 1524 cm^{-1} because of asymmetric N=O stretching and symmetric N=O stretching frequencies at 1300 - 1350 cm^{-1} region.

In case of the oximes (**12a-e**) the IR showed typical absorption band in the region of 1600 –1650 cm^{-1} due to the presence of C=N stretching and in the region of 3200-3430 cm^{-1} due to the presence of hydroxy group. For example, IR spectrum of 2,4-dinitroanisole (**10f**) showed the typical absorption band at 1457 cm^{-1} because of N=O asymmetric stretching and at 1296 cm^{-1} due to symmetric stretching. Its mass spectrum showed the molecular ion peak at m/z 198 (**Fig. 4**)

As another example, the ^{1}H-NMR spectrum of cyclohexanone oxime (**12a**) showed multiplets in the region at δ 1.56-2.57 for ten protons and a broad singlet at δ 8.75 for one hydroxy proton. Its ^{13}C-NMR spectrum showed signals at δ 24.47, 25.58, 25.83, 26.86, 32.05 for $(CH_2)_5$ carbons, and a signal at δ 160.81 for (C=N) oxime carbon. The IR spectrum showed typical absorption band at 3218 cm^{-1} due to presence of hydroxy group and its mass spectrum showed molecular ion peak at m/z 113 (**Fig. 5**).

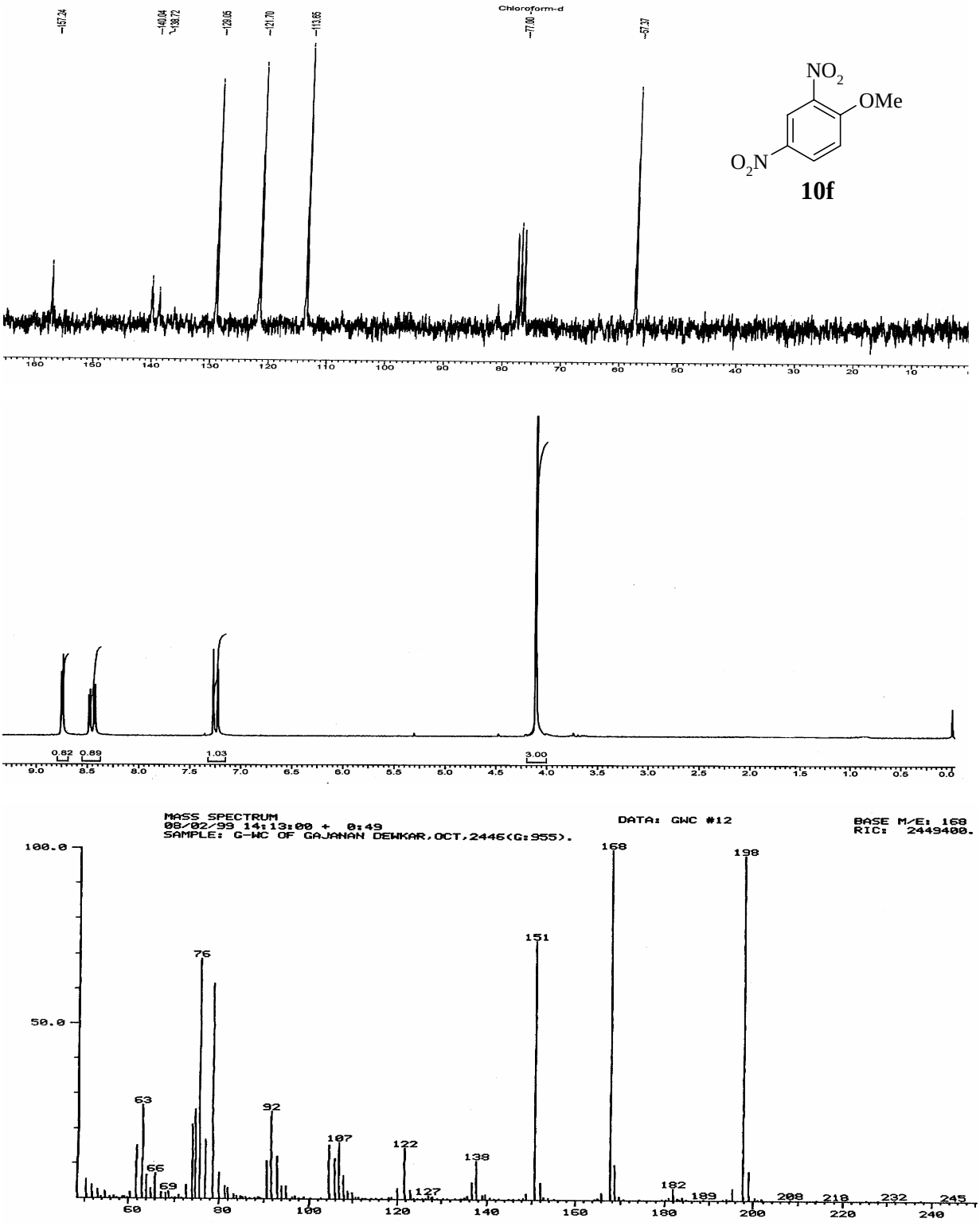


Fig. 4: ^{13}C, ^{1}H -NMR and Mass spectra of 2,4-dinitroanisole (10f)

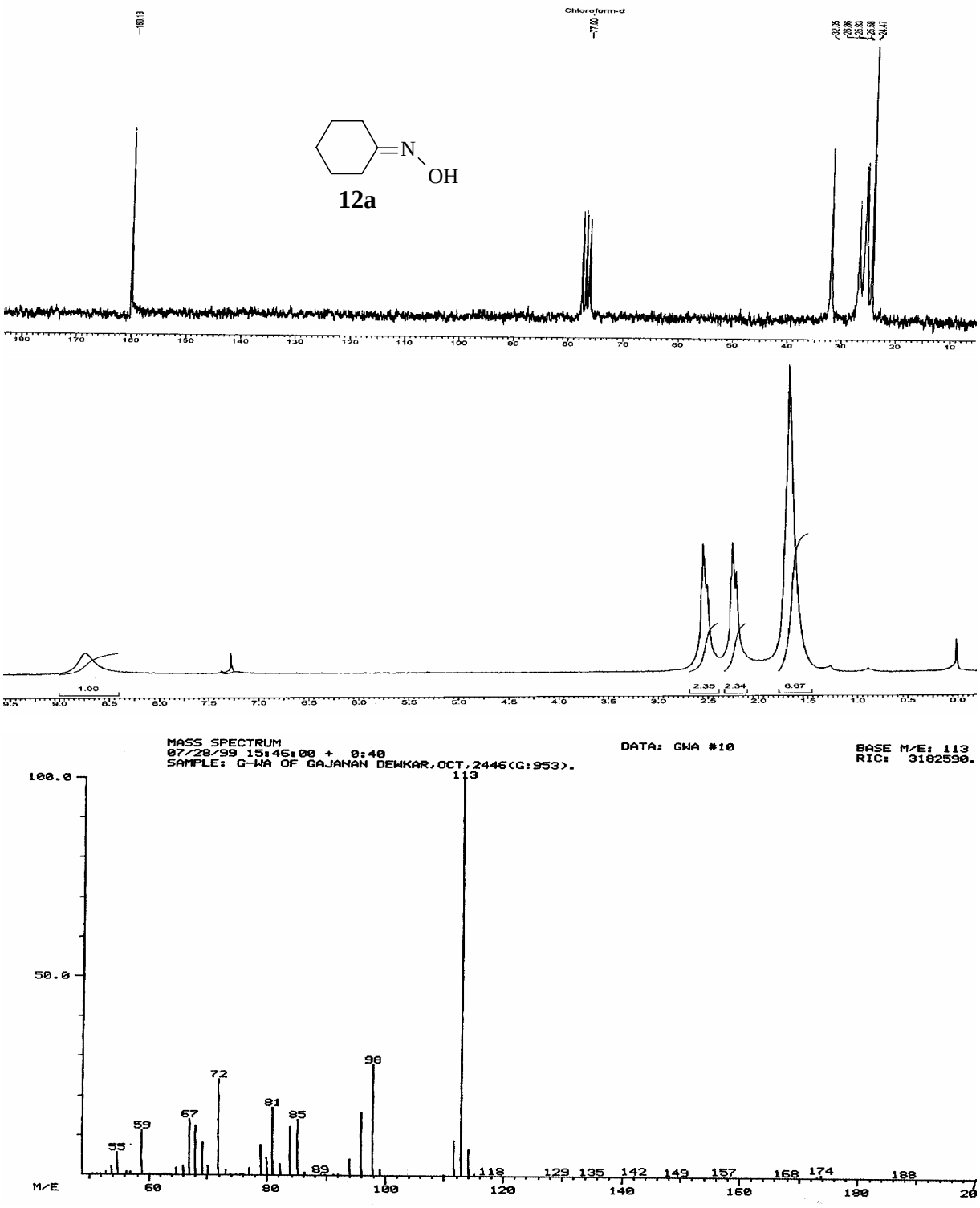
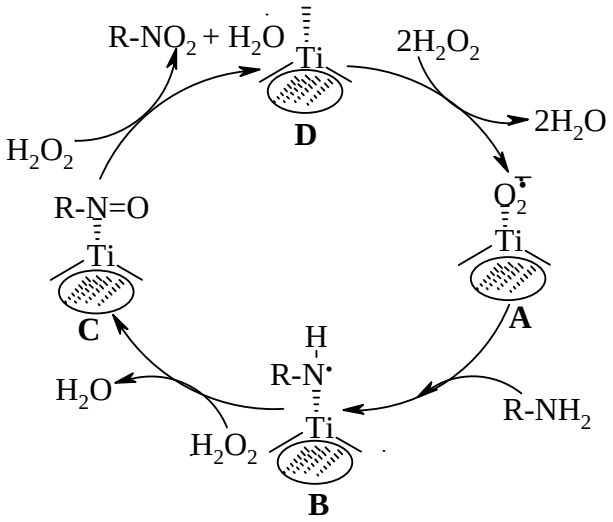


Fig. 5: ^{13}C, ^{1}H -NMR and Mass spectra of cyclohexanone oxime (12a)

Mechanism

On the basis of experimental and spectroscopic study we proposed a catalytic cycle for the oxidation of primary amines. The oxidation of aniline with aq. 50% H_2O_2 and Ti-superoxide catalyst (**1)** was monitored by ESR spectroscopy. When the catalyst 1 was added to a solution of aniline in methanol, the ESR signal of the catalyst disappeared. However, the ESR signal reappeared on the addition of a few drops of aq. 50% H_2O_2. As the reaction progressed, this signal again became weak and finally disappeared. The oxidation of primary amines did not take place when a radical quencher was added to the reaction mixture. On the basis of these results, the catalytic cycle shown in **Scheme 14** is proposed.



Scheme 14: Proposed catalytic cycle for the oxidation of amines

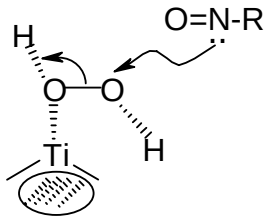
The first step is the absorption of a hydrogen atom from the amine by the superoxide radical ion **A** to generate the transient $RNH^{\cdot}$ radical **B**, which is oxidized by H_2O_2 to nitroso species **C**. Further oxidation of **C** with one mole of H_2O_2 generates nitrobenzene and liberates

D. Finally, the superoxide catalyst **A** is generated by decomposition of hydrogen peroxide on the Ti^{4+} surface [Eqs. (1) and (2)].

$$Ti^{4+} + H_2O_2 \longrightarrow 2\,{}^{\bullet}OH \qquad \textbf{(1)}$$

$${}^{\bullet}OH + H_2O_2 \longrightarrow H_2O + O_2^{\bullet -} + H^{+} \qquad \textbf{(2)}$$

Under similar oxidation conditions, aliphatic primary amines possessing α–CH bonds were selectivity converted to oximes along with its partially hydrolyzed product, ketone. It may be reasoned that the presence of α–CH protons of the species **C** (**Scheme 14**) undergoes prototropic rearrangement to a more stable enol form. It is also possible that the attack of nitroso species **C** on the electrophilic oxygen of the associated peroxide with Ti-matrix is preferred due to high basicity of the nitroso compared to its oxime counterpart (**Scheme 15**).



Scheme 15: Attack of nitroso species on the electrophilic oxygen atom of the peroxide associated with the Ti matrix

In order to understand whether the catalyst behaves in a truly heterogeneous manner or not, the superoxide catalyst was filtered out at the end of the reaction and an additional amount each of aniline and H_2O_2 was added to the reaction mixture. It was found that no nitrobenzene was obtained with the complete recovery of aniline. Further, the catalyst recovered by simple filtration was successfully reused at least four times for the oxidation of aniline without affecting its reactivity and selectivity.

3.0.9 Conclusion

In conclusion, we have successfully demonstrated a novel method for the preparation of stable Ti-superoxide catalyst (**1**) from readily and cheaply available $Ti(O^iPr)_4$. The catalyst **1** is heterogeneous in nature and found to be very effective for the selective oxidation of amines, particularly for the anilines and aliphatic primary amines to their corresponding nitrobenzenes and oximes respectively.

3.0.10 Experimental Section

Preparation of Ti-superoxide 1:

50% aq. H_2O_2 (5.98 g, 0.175 mol) was added slowly to a solution of Ti (O*i*Pr)$_4$ (5.0 g, 0.0175 mol) in anhydrous MeOH (50 ml) over 40 min under nitrogen atmosphere with stirring at room temperature. The yellow precipitate formed was collected by filtration on a sintered funnel, washed with anhydrous methanol, and dried under reduced pressure (3 mm Hg) at 25^0C for 1 h to give superoxide in 98% yield. EPR spectra were recorded on a Bruker EMX spectrometer at 9.76 GHz and 298 K, and g values were determined relative to a standard marker: α,α'-diphenyl-β-picryl hydrazyl (DPPH, g = 2.0036). TG/DTA was performed on a TG/DTA 22, TG/DTA 32 system (Seiko Instruments) in the range of 30-400^{0}C at 10^{0}C/ min.

General procedure for oxidation of primary aromatic 9a-l and aliphatic amines 11a-e

50% aqueous H_2O_2 (2.19 g, 0.064 mmol) was added slowly to a mixture of anilines **9a-l** (1.0 g, 0.011 mmol), catalyst superoxide (0.25 g, 25 wt %), and anhydrous methanol (15 ml) under nitrogen atmosphere with stirring over 10 min. The reaction was exothermic and the color changed from yellow to reddish brown during addition of H_2O_2. The reaction was monitored by TLC (15%) ethyl acetate in petroleum ether and after completion, catalyst was filtered off, and methanol evaporated under reduced pressure to give nitrocompounds in 82-98% yield. The nitrocompounds were analyzed by gas chromatography.

Nitrobenzene (10a): **Yield**: 98%, yellow liquid; **IR** (Neat, cm^{-1}): 346, 764, 1022, 1162, 1478, 1524, 1605, 3112; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 7.5 (m, 3H), 8.3 (m, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): 124.02, 129.21, 135.11; **MS**: (% rel. intensity): 123 (47), 107 (10), 93 (17), 77 (85), 74 (18), 65 (31); **Analysis**: $C_6H_5NO_2$ requires C, 58.05; H, 4.06; N, 11.38; found C, 57.89; H, 5.10; N, 11.56%.

2-Nitrotoluene (10b): **Yield**: 97%, yellow liquid; **IR** (Neat, cm^{-1}): 857, 1215, 1348, 1523, 1610, 3069, 3110; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.6 (s, 3H), 7.3 (m, 2H), 7.5 (d, *J* = 8 Hz, 1H), 8.0 (d, *J* = 10 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): 21.05, 125.29, 127.02, 131.24, 133.00, 134.19, 150.33.

3-Nitrotoluene (10c): **Yield**: 90%, yellow liquid; **IR** (Neat, cm^{-1}): 757, 800, 1349, 1479, 1526, 2957, 3072; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.5 (s, 3H), 7.3-7.5 (m, 2H), 8.0 (m, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): 21.17, 121.02, 125.33, 130.23, 135.00, 135.93, 140.22, 148.56.

4-Nitrotoluene (10d): **Yield**: 98%, Yellow solid; **mp**: 45^0C; IR (Nujol, cm^{-1}): 800, 1104, 1342, 1401, 1457, 1516, 1598, 2922, 3023, 3148; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.4 (s, 3H), 7.3 (d, *J* = 8.14 Hz, 2H), 8.1 (d, *J* = 8.14 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): 22.01, 124.12, 129.10, 148.00; **MS**: (% rel. intensity): 137 (80), 121 (5), 107 (35), 91 (92), 77 (39), 65 (100); **Analysis**: $C_7H_7NO_2$ requires C, 61.31; H, 5.10; N, 10.21; found C, 60.95; H, 6.00; N, 12.10%.

2-Nitroanisole (10e): **Yield**: 97%, yellow liquid; IR (Neat, cm^{-1}): 854, 1016, 1155, 1352, 1400, 1462, 1489, 1524, 1606, 2943, 3113; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.9 (s, 3H), 7.1 (m, 2H), 7.6 (dd, J = 8.1 Hz, 1H), 7.8 (d, J = 8.1 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): 56.02, 114.92, 120-.16, 125.00, 136.73, 139.41, 154.05.

2,4-Dinitroanisole (10f): **Yield**: 95%, yellow solid; **mp**: 82^0C; **IR** (Nujol, cm^{-1}): 1107, 1236, 1293, 1457, 1596, 2854, 2922, 3130, 3161; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 8.8 (s, 1H), 8.4 (d, *J* = 8.5 Hz, 2H), 7.2 (d, *J* = 8.5 Hz, 2H), 4.1 (s, 3H); **MS**: (% rel. intensity): 198 (99), 182 (5), 168 (100), 151 (75), 138 (10), 122 (16), 107 (17), 92 (26), 69 (3), 66 (8), 63 (28); **Analysis**: $C_7H_6N_2O_5$ requires C, 42.42; H, 3.03; N, 14.14; found C, 43.12; H, 3.32; N, 14.12%.

4-Nitroanisole (10g): **Yield**: 97%, greenish solid; **mp**: 59^0C; **IR** (Nujol, cm^{-1}): 848, 1017, 1372, 1460, 1497, 1591, 2854, 2924, 3113; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.9 (s, 3H), 7 (d, *J* = 8.5 Hz, 2H), 8.2 (d, *J* = 8.5 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): 57.09, 116.54, 125.90, 142.77, 165.18; **MS**: (% rel. intensity): 153 (42), 137 (10), 123 (42), 107 (18), 95 (52), 77 (51), 64 (100). **Analysis**: $C_8H_7NO_3$ requires C, 54.90; H, 4.75; 9.15; found C, 54.23; H, 4.80; N, 10.24%.

4-Nitrophenol (10h): **Yield**: 89%, white solid; **mp**: 112^0C; **IR** (Nujol, cm^{-1}): 853, 1160, 1330, 1462, 1490, 1586, 1742, 1920, 2923, 3084, 3119, 3352; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.3 (bs, 1H), 6.9 (d, *J* = 8.5 Hz, 2H), 8.2 (d, *J* = 8.5 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$: DMSO-d_6): 155.06, 126.18, 140.44, 164.67; **MS**: (% rel. intensity): 139 (100), 123 (6), 109 (32), 93 (14), 81 (9), 65 (12); **Analysis**: $C_6H_5NO_3$ requires C, 51.79; H, 3.59; N, 10.07; found C, 52.04; H, 3.60; N, 10.24%.

2-Methyl-6-ethylnitrobenzene (10i): **Yield**: 90, gum; **IR** (Neat, cm^{-1}): 849, 1369, 1481, 1527, 1605, 2973, 3109; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.2 (t, *J* = 8.2 Hz, 3H), 2.3 (s, 3H), 2.6 (q, *J* = 8.2 Hz, 2H), 7.1 (m, 2H), 7.3 (q, *J* = 6.8 Hz, 1H); **MS**: (% rel. intensity): 165 (5), 148 (43), 130 (7) 120 (23), 115 (28), 106 (29), 91 (100), 77 (85), 65 (72); **Analysis**: $C_9H_{11}NO_2$ requires C, 65.45; H, 6.66; N, 8.48; found C, 64.98; H, 7.90; N, 9.50%.

4-Chloronitrobenzene (10j): **Yield**: 91%, yellow solid; **mp**: 85^{0}C; **IR** (Nujol, cm^{-1}): 738, 843, 1279, 1381, 1425, 1469, 1515, 1574, 1601, 2822, 3098; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 7.1 (d, *J* = 8.5 Hz, 2H), 7.9 (d, *J* = 8.5 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): 125.07, 131.45, 131.22, 143.98, 147.77; **MS**: (% rel. intensity): 157 (100), 141 (4), 127 (52), 111 (84), 99 (32), 85 (8), 74 (50); **Analysis**: $C_6H_4ClNO_2$ requires C, 45.85; H, 2.54; Cl, 22.29; N, 8.91; found C, 46.03; H, 2.34; Cl, 22.45; N, 9.13%.

1,4-Dinitrobenzene (10k): **Yield**: 82%, yellow solid; **mp**: 171^{0}C; **IR** (Nujol, cm^{-1}): 709, 837, 1319, 1375, 1459, 1553, 2854, 2923; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 8.4 (s, 4H); **^{13}C-NMR** (50 MHz, $CDCl_3$: DMSO-d_6): 126.79, 153.56; **MS**: (% rel. intensity): 168 (100), 122 (30), 92 (18), 75 (57); **Analysis**: $C_6H_4N_2O_4$ requires C, 42.85; H, 2.38; N, 16.66; found C, 43.13; H, 2.54; N, 17.32%.

2-Nitrobenzoic acid (10l): **Yield**: 85%, white solid; mp: 147^{0}C; **IR** (Nujol, cm^{-1}): 1292, 1352, 1452, 1525, 1679, 2945; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 7.1-7.2 (m, 2H), 7.4-7.5 (m, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$: DMSO-d_6): 124.11, 128.98, 130.00, 134.12, 135.67, 149.00, 168.34; **MS**: (% rel. intensity): 167 (100), 150(6), 137 (8), 123 (50), 109 (13), 93 (80), 77 (25), 65 (34); **Analysis**: $C_7H_5NO_4$ requires C, 50.29; H, 2.99; N, 8.38; found C, 49.90; H, 3.26; N, 8.89%.

Cyclohexanoneoxime (12a): Yield: 90%, white solid; mp: 89^{0}C; **IR** ($CHCl_3$, cm^{-1}): 756, 894, 954, 988, 1219, 1444, 1660, 2858, 2932, 3110, 3218; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.5 (s, 6H), 2.2 (s, 2H), 2.6 (s, 1H), 8.7 (bs, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): 24.25, 26.90, 27.98, 28.77, 34.77, 161.76; **MS**: (% rel. intensity): 113 (100), 98 (28), 85 (15), 81 (18), 72 (25), 67 (15), 58 (12), 55 (6); **Analysis**: $C_6H_{11}NO$ requires C, 63.71; H, 9.73; N, 12.38; found C, 64.13; H, 10.14; N, 13.14%.

Syn-Benzylaldoxime (12b): Yield: 94%, viscous liquid; **IR** ($CHCl_3$, cm^{-1}): 644, 690, 755, 868, 955, 1209, 1292, 1448, 1494, 2980, 3090, 3325; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 7.5-7.4

(m, 3H), 7.6 (d, *J* = 8.5 Hz, 2H), 8.3 (s, 1H), 9.3 (s, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): 127.10, 129.24, 132.45, 134.76, 135.23, 146.54, 153.85; **MS**: (% rel. intensity): 121 (47), 103 (72), 99 (3), 94 (22), 89 (8), 77 (56), 66 (25); **Analysis**: C_7H_7NO requires C, 69.42; H, 5.78; N, 11.57; found C, 70.24; H, 5.89; N, 12.04%.

Glyoxime (12c): **Yield**: 87%, white solid; **mp**: 179^{0}C; **IR** ($CHCl_3$, cm^{-1}): 770, 1217, 1383, 1405, 1641, 2924, 3430, 3430; **MS**: (% rel. intensity): 88 (100), 70 (15); **Analysis**: $C_2H_4N_2O_2$ requires C, 27.27; H, 4.54; N, 31.81; found C, 28.10; H, 5.10; N, 31.98%.

4-Methoxybenzaldoxime (12d): 80%; mp: 65^{0}C; IR: (Nujol, cm^{-1}); 690, 750, 930, 1050, 1026, 1320, 1350, 1470, 3300; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 4.03 (s, 3H), 7.06 (d, *J* = 10 Hz, 2H), 7.7 (d, *J* = 10 Hz, 2H), 8.20 (bs, 1H).

1-Tetralone oxime (12e): 65%; **mp**: 92^{0}C; IR: (Nujol, cm^{-1}); 750, 900, 970, 1050, 1270, 1360, 1450, 1610, 3400; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.8-2.0 (m, 2H), 2.6-2.9 (m, 4H), 5.5 (bs, 1H), 7.0-72 (m, 3H), 7.9 (m, 1H).

SECTION II:

Ti-Superoxide-Catalyzed Oxidation of Phenols: A High Yield Synthesis of Quinones

3.1.1 Introduction

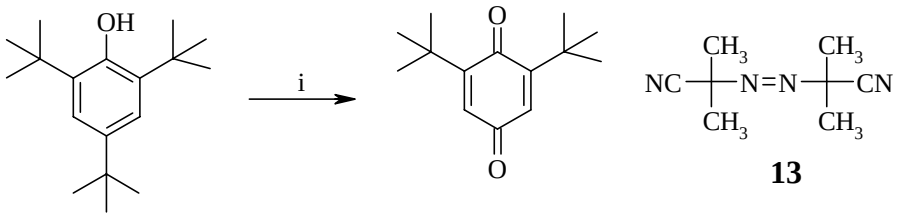
It is well known that many quinone derivatives possess bioactivity e.g. anthrocycline antibiotics[36] and the tetracyclic quinone stretonigrin.[37] Some quinones are also important class of compounds in industry (e. g., anthraquinone dyestuffs), in organic synthesis as a dienophiles in Diels-alder reactions and in Nature, where they have a vital role in electron transport in the respiratory and photosynthetic elements of biological systems.[38] They also well known for possessing pronounced bioactivity and consequently, are important for medicine.[38c] For example, 2-methyl,-1,4-napthoquinine, vitamin K_3, constituents an important additives in animal feed, which is used commercially in large quantities. Further more, alkyl-substituted *p*-benzoquinones serve as a useful dienophiles in Diels-Alder reactions and are versatile starting materials in the synthesis of many natural products. Thus, trimethyl-*p*-benzoquinones and 2,3-dimethoxy-5-methyl-*p*-benzoquinone are especially valuable starting materials for the synthesis of vitamin E and coenzyme Q.[39]

3.1.2 Review of Literature

Literature search revealed that there are various catalytic as well as non-catalytic methods available for the oxidation of phenols to *p*-quinones. Some of the important methods are described bellow.

Bickel *et al.*[40]

During an evaluation of the antioxidant properties of 2,6-di-t-butyl-*p*-cresol in lubricating oils, a yellow crystalline substance, m.p. 65-66^{0}C, which was identified as 2,6-di-*t*-butylquinone, was formed in the condenser of the test apparatus after few days. This substance has been shown to result from the action of 2,2'-azoisobutyronitrile [**AIBN**] (**13**) on 2,4,6-tri-*t*-butylphenol in the presence of oxygen (**Scheme 16**).



13

Scheme 16: (i) AIBN, oxygen, water.

Metro's[41]

Metro's method deals with the oxidation of 2,6-di-*t*-butylphenol to the corresponding quinone using copper-iron catalyst in the presence of molecular oxygen.

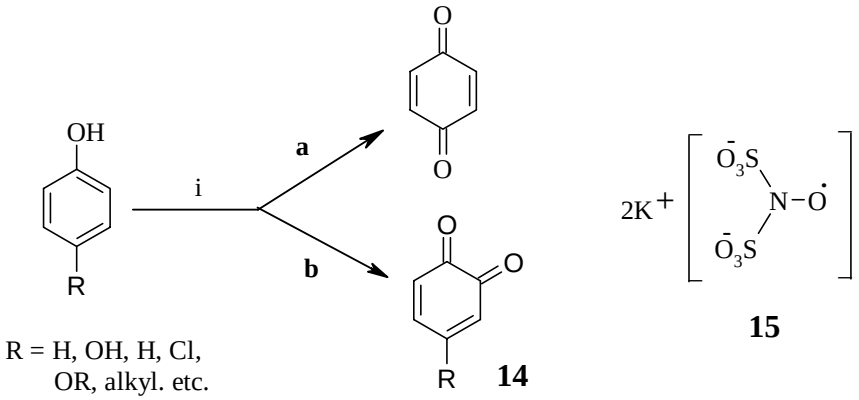
Bryce-Smith *et al.*[42]

Bryce *et al.* have developed a method for oxidation of 2,5-dimethylphenol to the corresponding quinone using a mixture of sulfuric acid and acetic acid.

Hans Zimmer *et al.*[43]

The oxidation of phenols with potassium nitrosodisulfonate **15** (Fremy's radical) represents an excellent synthetic method for the preparation of either *o*-or *p*-benzoquinones, under very mild conditions. When the *para* position to the hydroxyl group is unsubstituted (R = H), *p*-benzoquuinone is formed (path **a**). If the position *para* to the hydroxyl group is substituted (R = OR, alkyl), oxidation leads to the formation of *o*-benzoquinones **14** (path **b**).

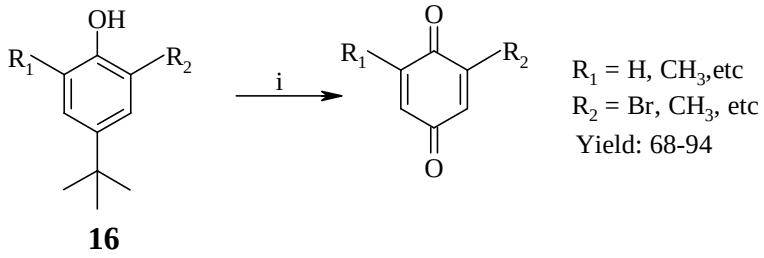
One exception has been reported that if the para position to the hydroxyl group is substituted with halide it leads to *p*-benzoquinones with the loss of halide (**Scheme 17**).



Scheme 17: (i) potassium nitrosodisulfonate **15,** acetone, 25^0C.

McKillop *et al.*[44]

On treatment of 2,6-disubstitued-4-*t*-butylphenols (**16**) with thallium (III) trifluoroacetate in either trifluoroacetic acid or tetrachloride as solvent results in loss of the 4-*t*-butyl substituent as isobutene and formation in high yield of the corresponding 2,6-disubstitued *p*-quinones (**Scheme 18**).



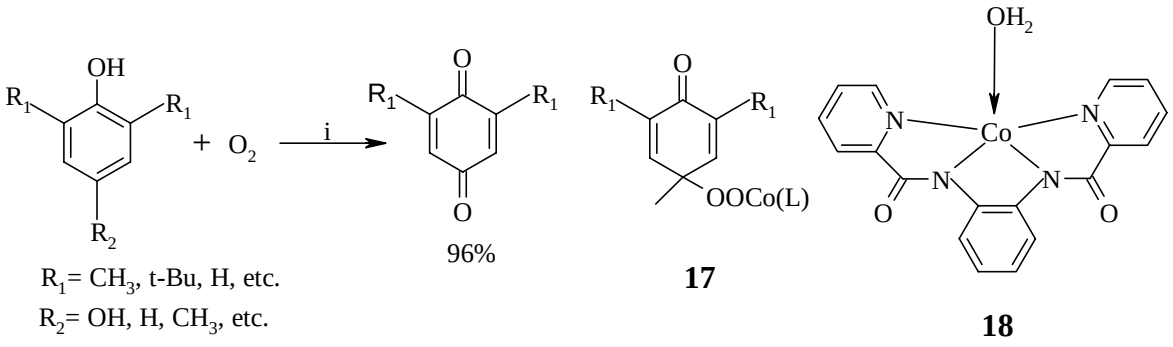
Scheme 18: (i) Thalium (III) tyrifluroacetate (TTFA) (0.11 mmol), TFA, 25^0C, 2 h.

Fischer *et al.*

Fischer *et al.*[45] have developed a simple method for oxidation of hydroquinone, catechols and phenols to the corresponding quinones using cericammonium nitrate and ammonium dichromate coated on silica in dichloromethane at 0^0C.

Ganeshpure *et al.*[46]

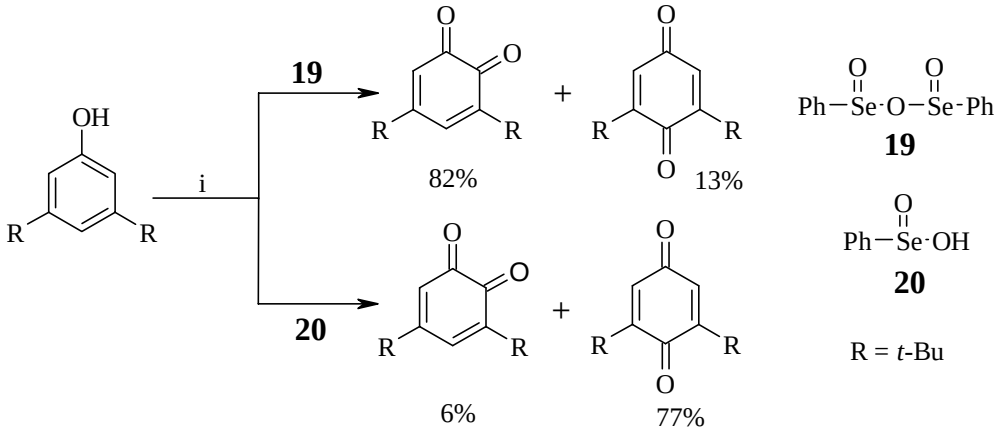
Cobalt (II) bis-amide chelate **18** selectively catalyzed oxidation of substituted phenols with molecular oxygen to give the corresponding 1,4-benzoquinones. If alkyl group is present on the *para* position the formation of a pale yellow precipitate of peroxy-*p*-quinalato-cobalt complex **17** was observed (**Scheme 19**).



Scheme 19: (i) cat **18**, acetonitrile, 25^0C, 2 h,

Derek *et al.*

Derek e*t al*.[47] studied the activity of benzeneselenic anhydride **19** and benzeneselenic acid **20** for the oxidation of *t*-butyl substituted phenols to the corresponding quinones and the role of various solvents on product selectivity was also discussed (**Scheme 20**).



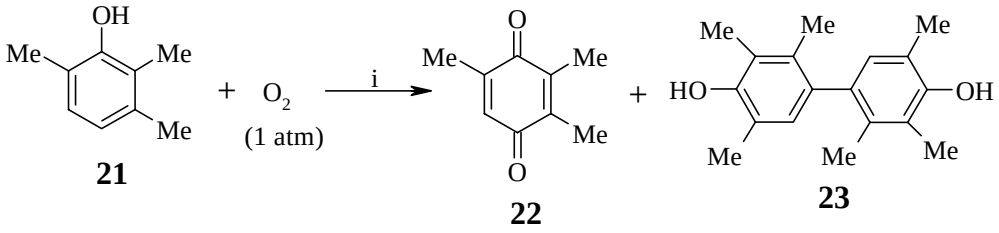
Scheme 20: (i) cat **19,** benzene, 4 h, reflux; cat **20** dichloromethane, 2 h, 25^0C.

Forni *et al.*

Forni *et al.*[48] oxidized phenol using La-Eu cuprates as catalysts but the selectivity of quinone was very poor.

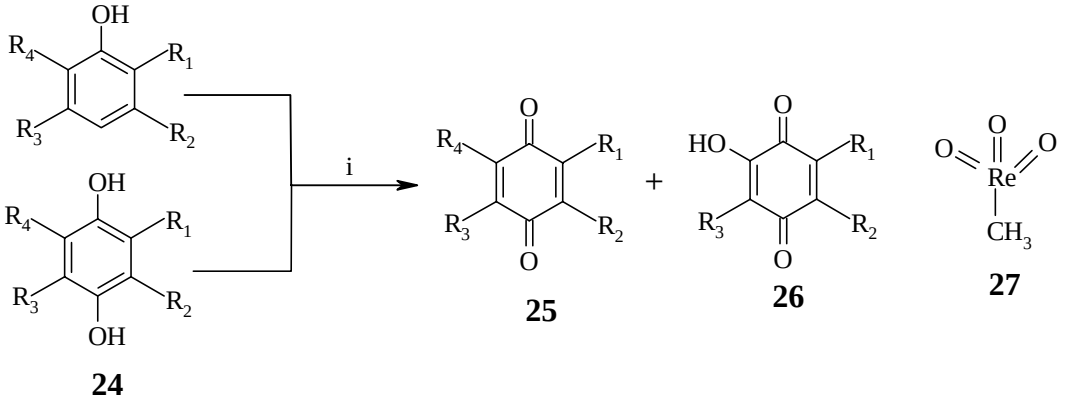
Fujibayashi *et al.*[49]

Vanadomolybdophosphate supported on active carbon is used as a catalyst for the oxidation of 2,3,6-trimethylphenol (**21**) in the presence of dioxygen to give *p*-benzoquinone **22** and 4,4'-dihydroxy-2,2',3,3',3,5,5'-hexamethylbiphenyl (**23**) in (75:3) ratio (**Scheme 21**).



Scheme 21: (i) cat. NPV_6Mo_6/C, acetic acid: water (1:1 v/v), 60^0C, 5 h.

Waldemar *et al.*[50]



Scheme 22: (i) cat. MTO, acetic acid, 85% H_2O_2, 20-40^0C, 4 h.

Methyltrioxorhenium (VII) **27** (CH_3ReO_3, MTO) in presence of hydrogen peroxide is step-wise converted into the mono- and bis(peroxo)rhenium complex $CH_3Re(O_2)O.H_2O$,

which was found to be an excellent catalyst for the oxidation of hydroxyarenes **24** to *p*-quinones **25** and **26** with 83% H_2O_2 in selectivity and 9-70% yield (**Scheme 22**).

Sudalai *et al.*[51]

Our group has developed a simple method for the selective oxidation of substituted phenols to the corresponding *p*-quinones using chromium silicate-2 as a catalyst and 70% aq. *tert*-butyl hydroperoxide or 30% aq. H_2O_2 as an oxidant in 30-42% yield.

Mohammed *et al.*[52]

Mohammed *et al.* have found Co and Mn salts of *p*-aminobenzoic acid supported on silica gel as an efficient heterogeneous catalyst for the selective oxidation of various substituted phenols to *p*-quinones with molecular oxygen in 36-65% yield.

3.1.3 Present Work

3.1.3.1 Objective

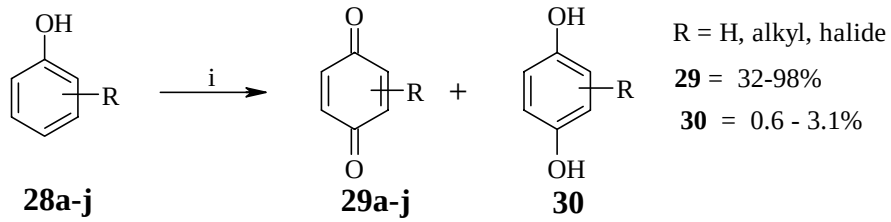
Although there are many catalytic methods available in the literature for oxidation of phenols to quinones, they suffer from certain drawbacks like reactions were performed under homogenous, non-catalytic conditions, low product selectivity in terms of product distribution *etc*. In order to overcome these difficulties a new catalytic method for oxidation of phenols to quinones is highly desirable.

Initially, we were interested in developing a simple and efficient procedure for the hydroxylation of phenol using aq. H_2O_2 and Ti-superoxide as catalyst. When phenol was subjected to oxidation with titanium superoxide **1,** formation of 1,4-hydroquinone was observed in low yields; rest being tar. Change of various conditions such as change of catalyst concentration, change of temperature, change of solvent did not yield the desired result. The progress of the reaction was monitored by GC analysis. It was interesting to find that phenol, when subjected to oxidation with aq. 30% H_2O_2 catalyzed by titanium superoxide, undergoes oxidation firstly to form 1,4-benzoquinone and then subsequently to 1,4-hydroquinone in low yields. However, by optimizing certain parameters H_2O_2:AcOH (1:1) and at elevated temperature, it was possible to obtain 1,4-hydroquinone in good yields. We have evaluated the use of titanium superoxide radical ion as a heterogeneous catalyst in combination with aq. H_2O_2 as oxidant for effecting oxidation of phenol to *p*-quinone, the results of which are discussed in this section.

3.1.4 Results and Discussion

Thus, when phenols were subjected to oxidation with aq. 30% H_2O_2 (20 mol%) in the presence of catalytic amount of Ti-superoxide **1** (20 wt%) in acetic acid as solvent, the

corresponding 1,4-benzoquinones were obtained in very high yield (32-98%) with excellent product selectivity (**Scheme 23**)



Scheme 23: (i) cat **1** (20 wt%), aq. 30% H_2O_2 (20 mmol), acetic acid, 50^0C, 1-2 h.

Phenol was selected as a model substrate for studying its oxidative behavior (**Scheme 23**). Various solvent systems such as acetonitrile, acetone, methanol, water and acetic acid were screened for the selective oxidation of phenol to *p*-quinone the results of which are summarized in **Table 3**.

Table 3: Ti-superoxide (**1**) catalyzed oxidation of phenol to quinone: effect of solvents[a]

Entry	Solvent	Time (h)	Yield[b] (%)
a	Acetonitrile	2	48
b	Acetone	1	50
c	Methanol	1	55
d	Water	2	56
e	Acetic acid	1	80

a) reaction condition: catalyst (20 wt%), aq. 30% H_2O_2 (20 mmol), 50^0C, solvent; b) yields refer to isolated yields after column chromatography.

Among all the systems studied, a combination of Ti superoxide, aq. 30% H_2O_2 in acetic acid was found to be the best choice (80% yield), which was taken for further studies. As can be seen from **Table 4,** a variety of substituted phenols **28a-j** were oxidized to give the corresponding *p*-quinones **29a-j** in excellent yields (32-98%) and selectivity along with 1,4-hydroquinones **30** (0.6-3%). These were characterized by the IR, ^{1}H, ^{13}C-NMR, GC-MS and GC analysis. In case of the substrates with electron donating groups (**28b-f)** excellent

selectivity was observed but substrates with electron-withdrawing groups such as CN, NO_2 resulted in no reaction. Surprisingly, 1,4-hydroquinone and *para* alkyl substituted phenols when subjected to oxidation resulted in no reaction. Remarkably, phenol with 2,6-di-*tert*-butyl groups (**28f**) is efficiently oxidized to 1,4-quinone. Even phenols with halide substitutions at 4-positions in the nucleus underwent smooth oxidation affording 1,4-quinones in high yields and selectivity.

Table 4: Ti-superoxide (**1**)[a] catalyzed oxidation of phenols to *p*-quinones and hydroquinones with aq. 30% H_2O_2.

Entry	Substrate	Time (h)	Conversion (%)	Product (%)[b]		Selectivity (%)[c]
				PBQ	HQ	
a	Phenol	1	83.00	79.90	3.1	96.26
b	2-Methylphenol	1	97.60	96.20	1.4	98.72
c	3-Methylphenol	1	99.28	98.68	0.6	99.39
d	2,6-Dimethylphenol	2	99.65	97.05	2.6	97.39
e	2-*tert*-Butylphenol	2	99.89	98.49	1.4	98.59
f	2,6-Di-*tert*-butylphenol	3	80.98	80.98	--	100
g	4-Iodophenol	1	75.77	75.77	--	100
h	4-Bromophenol	1	65.93	65.93	--	100
I	4-Chlorophenol	1	41.29	39.91	1.38	96.65
j	2,6-Dichlorophenol	2	32.30	32.30	--	100

a) catalyst was recovered and reused without any loss of activity and selectivity; b) products were characterized by mp, IR, ^{1}H, ^{13}C-NMR, GC and GC-MS. c) selectivity are based on gas chromatographic analysis, PBQ- *p*-benzoquinone, HQ- hydroquinone.

We tried to convert all quinones to hydroquinones with our modified conditions, by the addition of H_2O to the reaction mixture and stirring at 120^0C for 3 h. This resulted in good yields of 1,4-hydroquinones (60%) but this method is applicable only to phenol and not for substituted phenols. We tried various solvent systems but all of them failed.

The influence of the amount of Ti-superoxide catalyst **1** on oxidation of phenol was evaluated. It was observed that in the absence of Ti-superoxide, the rate of the oxidation was very slow. For example, when phenol was subjected to oxidation less than 10% of *p*-quinone was obtained after 12 h at 60^0C and no product was formed in substituted phenol. Increasing the catalyst concentration to either 5 to 10 wt% has resulted in the formation of *p*-quinone in 30% yield.

The formation of *p*-quinones was confirmed by ^{1}H, ^{13}C-NMR, IR, and GC-MS spectroscopy. The IR spectrum of all the *p*-quinones showed typical absorption band in the region 1655-1690 cm^{-1} for C=O stretching. Its ^{13}C- NMR spectra showed typical carbonyl carbon signals in the region at δ 186-188 confirming the presence of *p*-quinone. For example, IR spectrum of 2-methyl-1,4-benzoquinone **29b** showed the typical absorption band at 1634 cm^{-1} due to C=O stretching. Its ^{13}C-NMR spectrum showed carbonyl carbon signals at δ 186.91 and 187.16 confirming the formation of *p*-quinone moiety. Its GC-MS spectrum also showed the molecular ion peak as the base peak at m/z 198 (**Fig. 6**). As another example, the IR spectrum of 2,6-di-*tert*-butyl-1,4-benzoquinone **29f** showed a typical absorption band at 1652 cm^{-1} due to C=O stretching. Its ^{13}C-NMR spectrum showed signals at δ 29.18, 35.28 for *t*-butyl carbons and at δ 187.46, 188.34 for carbonyl carbons confirming the formation of 2,6-di-*tert*-butyl-1,4-benzoquinone. Its GC-MS spectrum also showed the prominent molecular ion peak at m/z 220 (**Fig. 7**).

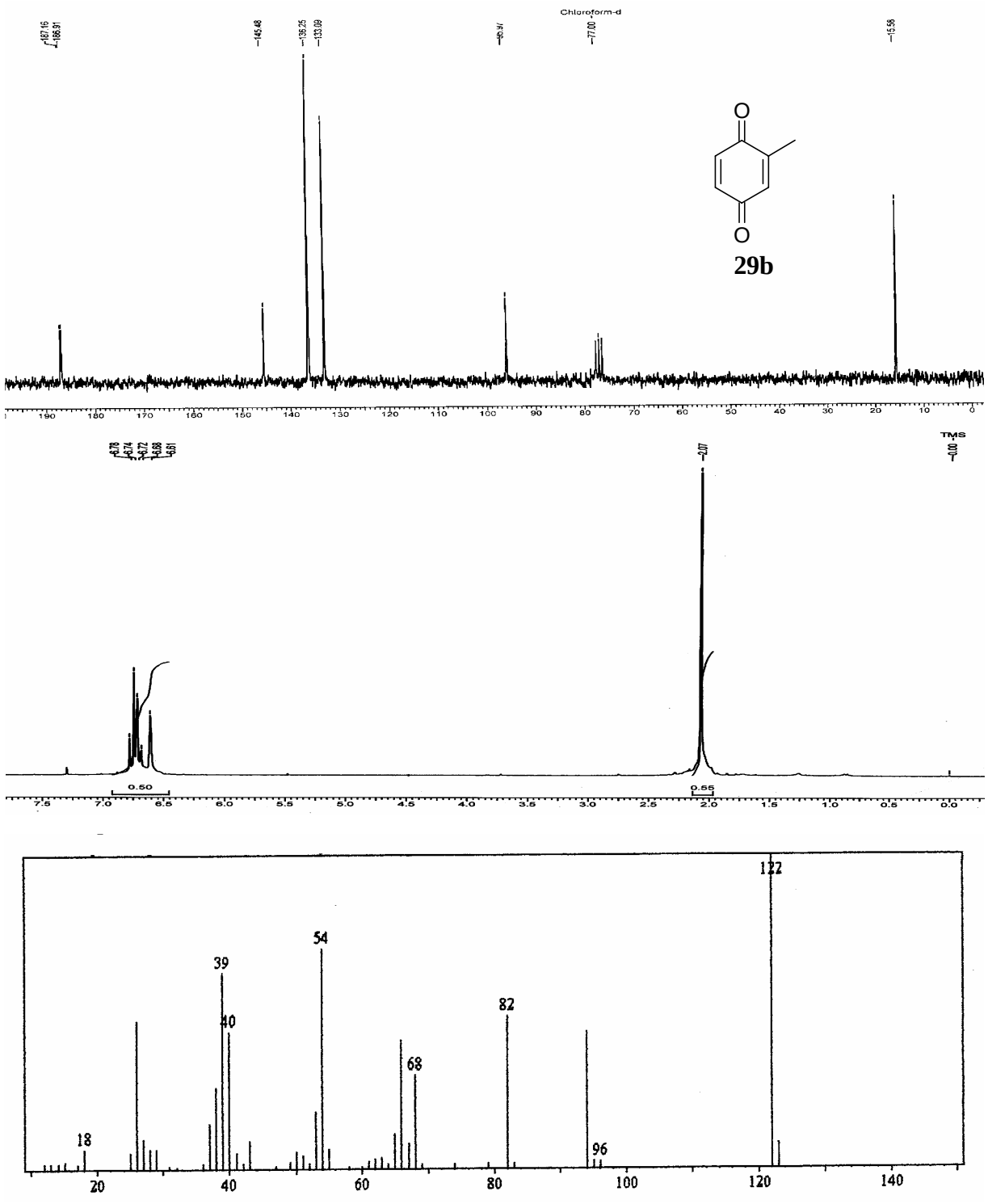


Fig 6: ^{13}C, ^{1}H -NMR and GC-MS spectra of 2-methyl-1,4-benzoquinone (29b)

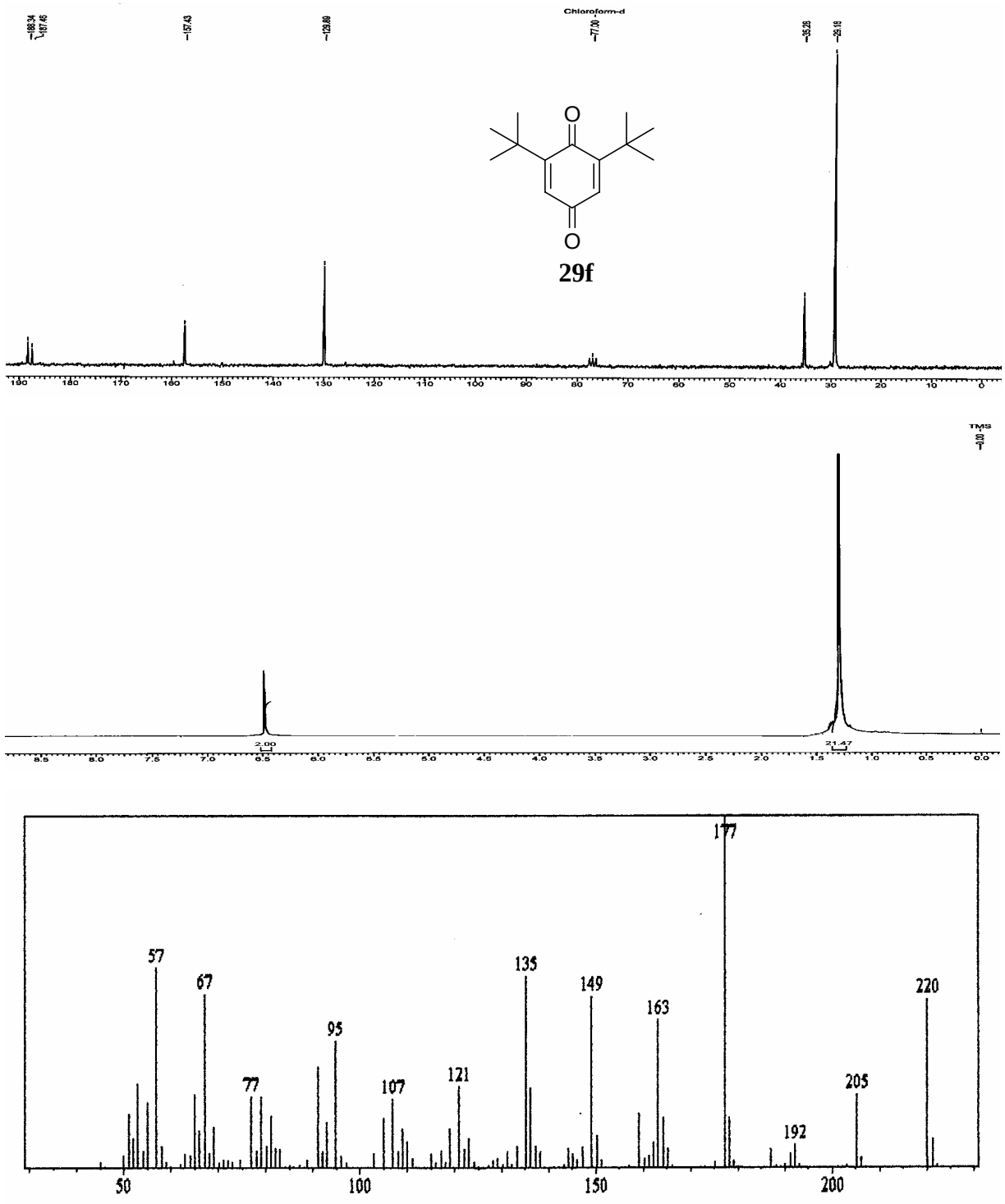
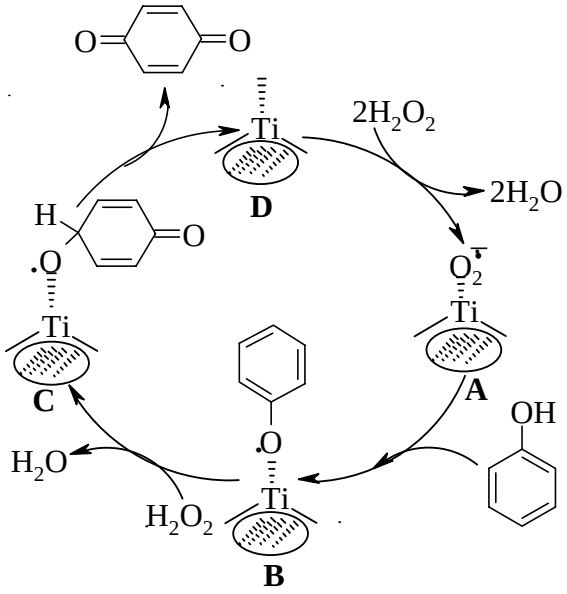


Fig 7: ^{13}C, ^{1}H -NMR and GC-MS spectra of 2,6 –di-*t*-butyl-1,4-benzoquinone (29f)

Mechanism

It has been well-established[53] in the literature that the superoxide ions have the capacity to absorb protons from amines, phenols, etc, there by producing aminyl and phenoxy radicals respectively. We also proved the existence of radical species in case of amine oxidations (See **Section I**). Based on these informations, a catalytic cycle for the oxidation of phenols is proposed in **Scheme 24**.



Scheme 24: Proposed catalytic cycle for the oxidation of phenols

The first step probably involves the absorption of hydrogen atoms from phenols by the superoxide radical ion **A** to generate the transient PhO radical **B**, which in presence of H_2O_2 will be converted into species **C**. Species **C** is then decomposed to generate *p*-quinones and species **D**. Finally, the superoxide catalyst **A** is regenerated by the reaction of hydrogen peroxide on the Ti^{4+} surface.

3.1.5 Conclusion

In conclusion, we have successfully demonstrated the application of a novel Ti-superoxide catalyst, for the first time, to the selective oxidation of phenols to *p*-quinones. The catalytic system is also very effective for the sterically hindered phenols **29e** and **29f** to give the corresponding *p*-quinones in 80-98% yield.

3.1.6 Experimental section

General procedure for the oxidation of phenols

The mixture of phenols **28a-j** (5 mmol) and Ti-superoxide catalyst **1** (20 wt%) in acetic acid (5 ml) was stirred at 50^0C. To this reaction mixture 30% aq. H_2O_2 (20 mmol) was added drop-wise. After stirring for a specified time (**Table 1**), the reaction mixture was diluted with water and extracted with dichloromethane (3 x 15 ml). The combined organic phase was washed with $NaHCO_3$, 5% NaOH solution to remove unreacted phenols, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude reaction mixture was purified on column chromatography using pet. ether and EtOAc (9:1) as eluent to afford the *p*-quinones **29a-j** in (32-98%) yield.

General procedure for the hydroxylation of phenol

The mixture of phenol **28a** (5 mmol) and Ti-superoxide catalyst **1** (20 wt%) in acetic acid (5 ml) was stirred at 50^0C. To this reaction mixture 30% aq. H_2O_2 (20 mmol) was added drop-wise. After stirring for a specified time (**Table 1**), 5 ml of water was added to the reaction mixture and stirred at 120^0C for 3 h. It was then diluted with water and extracted with dichloromethane (3 x 15 ml). The combined organic layer was washed with $NaHCO_3$ solution, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude reaction mixture was purified on column chromatography using pet. ether and EtOAc (1:1) as eluents to afford the 1,4-hydroquinone (**30)** 60% yield.

1,4-Benzoquinone (29a): Yield: 80%, Yellow solid; **mp**: 113^0C {Lit. 114^0C}; **IR** ($CHCl_3$, cm^{-1}): 3073, 1645, 1586, 1307, 1087, 942, 894; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 6.85 (s, 4H); **GC-MS** m/z (% rel. intensity): 108 (M^+, 80), 98 (5), 82 (20), 79 (18), 54 (100), 50 (10), 26 (90); **Analysis**: $C_6H_4O_2$ requires C, 66.66; H, 3.70; found C, 66.98; H, 3.86%.

2-Methyl-1,4-benzoquinone (29b): **Yield**: 96%, yellow solid; **mp**: 69^0C; **IR** ($CHCl_3$, cm^{-1}): 3056, 2960, 1652, 1674, 1424, 1348, 1038, 1282, 1092, 924; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.07 (s, 3H); 6.61-6.78 (m, 3H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 15.58, 95.97, 133.09, 136.25, 145.48, 186.91, 187.16; **GC-MS** m/z (% rel. intensity): 122 (100), 96 (2), 94 (40), 82 (45), 68 (20), 66 (30), 54 (80), 40 (45), 39 (75), 18 (5); **Analysis**: $C_7H_6O_2$ requires C, 68.85; H, 4.91; found C, 68.98; H, 4.90%.

2,6-Dimethyl-1,4-benzoquinone (29d): **Yield**: 97%; **mp**: 72^{0}C; **IR** ($CHCl_3$, cm^{-1}): 3067, 2980, 1645, 1349, 1282, 1090, 884, 824; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.05 (s, 6H), 6.54 (s, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 15.69, 133.13, 145.59, 187.35, 187.90; **GC-MS** m/z (% rel. intensity): 136 (M^+, 60), 121 (2), 108 (40), 96 (25), 79 (50), 68 (100), 53 (10); **Analysis**: $C_8H_8O_2$ requires C, 70.58; H, 5.88; found C, 70.62; H, 5.94%.

2-*tert*-Butyl-1,4-benzoquinone (29e): **Yield**: 98; **mp**: 59^{0}C; **IR** ($CHCl_3$, cm^{-1}): 3065, 2987, 1650, 1460, 1345, 1250, 1053, 947, 830; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.29 (s, 9H), 6.58 (s, 1H), 6.67 (s, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 28.63, 34.69, 130.96, 134.45, 138.09, 155.15, 186.72, 187.42; **GC-MS** m/z (% rel. intensity): 164 (M^+, 80), 149 (100), 136 (20), 121 (85), 107 (15), 93 (80), 77 (75), 67 (20), 54 (50); **Analysis**: $C_{10}H_{12}O_2$ requires C, 73.17; H, 7.31; found C, 73.24; H, 7.30%.

2,6-Di –*tert*-butyl-1,4-benzoquinone (29f): **Yield**: 81% ; **mp**: 65-67^{0}C; **IR** ($CHCl_3$, cm^{-1}): 3073, 2966, 2343, 1652, 1468, 1371, 1242, 942, 880; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.26 (s, 18H), 6.45 (s, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 29.18, 35.28, 129.89, 157.43, 187.46, 188.34; **GC-MS** m/z (% rel. intensity): 220 (M^+, 30), 205 (15), 192 (5), 177 (100), 163 (40), 149 (55), 135 (60), 121 (15), 107 (10), 95 (25), 77 (20), 67 (50), 57 (70); **Analysis**: $C_{14}H_{20}O_2$ requires C, 76.36; H, 9.09; found C, 76.45; H, 9.10%.

2-Chloro-1,4-benzoquinone (29j): **Yield**: 32%; **mp**: 57^{0}C; **IR** ($CHCl_3$, cm^{-1}): 3045, 2830, 1649, 1475, 1324, 1078, 942, 831; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 6.82 (s, 1H), 6.95 (s, 1H), 7.05 (s, 1%); **GC-MS** m/z (% rel. intensity): 142 (100), 116 (18), 114 (30), 88 (80), 82 (92), 60 (45), 54 (90); **Analysis**: $C_6H_3O_2$ Cl requires C, 50.70; H, 2.11; Cl 24.64; found C, 50.75; H, 2.10; Cl 24.75%.

1,4-Hydroquinone: Yield: 60% **mp**: 172-175^{0}C; **IR** ($CHCl_3$, cm^{-1}): 3373, 3045, 1595, 149, 1470, 1224,810, 752; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 6.62 (s, 4H), 8.33 (bs, 2H); **GC-MS** m/z (% rel. intensity): 110 (100), 95 (2), 81 (20), 69 (2), 63 (5), 53 (25), 39 (18); **Analysis**: $C_6H_6O_2$ requires C, 65.45; H, 5.45; found C, 65.50; H, 5.46%.

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CHAPTRER 4

$NaIO_4$-Mediated Regioselective Oxidative Halogenation of Arenes and Alkenes using Alkali Metal Halides

SECTION I:

$NaIO_4$-Mediated Regioselective Oxidative Halogenation of Arenes Using Alkali Metal Halides as Halogen source

4.0.1 Introduction

Halogenated aromatic compounds are an important class of molecules in synthetic organic chemistry. They are the key intermediates in the preparation of organometalic reagents[1] and play vital role in transition mediated coupling reactions.[2] Numerous industrially valuable products such as pesticides, insecticides, herbicides, pharmaceutically and medicinally active molecules, fire retardants and other newer materials carry halogen functionality. The chlorinated hydrocarbons are recognized as versatile starting materials and additives in the production of high quality of dyes.[3] Since 1940, large quantities of chlorobenzene have been used in the production of DDT, a widely used insecticide. 1,4-Dichlorobenzene is a solid at room temperature and is used as mothballs and room deodorant blocks. The major use of *p*-chlorotoluene is in the manufacture of p-chlorobenzotrifluoride.

Traditionally, aromatic chloro and bromo compounds are prepared by the reaction with elemental halogens in the presence of a metal catalyst, and often involving harsh reaction conditions.[4] The handling of chlorine gas and liquid bromine is cumbersome due to their hazardous nature while special equipment and care are needed for the transfer of these materials in large scale. Moreover, halogenation of aromatic substrates with elemental halogens involves a substitution reaction with the formation of hydrohalic acid as a by-product, effectively reducing the atom efficiency by 50%. The hydrophalic acid waste that is generated must be neutralized before it can be discharged as effluent.

4.0.2 Review Literature

Various methods of halogenation of aromatics are known in the literature. Some of the important methods so far known are described below.

Russell's[5]

Glein studied the solvent effect in the ring chlorination reaction of free radicals and atoms. He found that photochemical chlorination and sulfuryl chloride chlorination give different products in the chlorination of branched-chain hydrocarbons.

Marsh *et al.*[6]

Marsh *et al.* have found that dichlorine monoxide (Cl_2O) is a powerful and selective reagent for either side-chain or ring chlorination of deactivated aromatic substrates, and it gives excellent yields under mild conditions where conventional reagents fail or require harsh conditions.

Keith *et al.*[7]

Keith Smith and coworkers improved the process for ring chlorination by using t-butyl hypochlorite as halogen source and silica as a catalyst in carbon tetrachloride. He also observed that several other chlorine containing organic compounds such as *N*-chlorosuccinimide and *N*-chloroamines also serve as effective electrophilic chlorinating agents in the presence of silica.

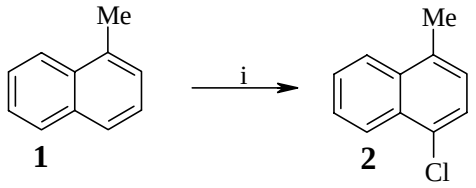
David's[8]

David Watson of Dow Chemical Company studied the regioselective *para* chlorination of phenol using Friedel-Crafts catalyst with sulfuryl chloride in combination with diphenyl sulfide. They found that sulfuryl chloride on reacting with diphenyl sulfide gave diphenyl

sulfur dichloride and aluminium complex which is bulky. Hence attack at the more accessible *para* position is preferred.

Mitsuo *et al.*[9]

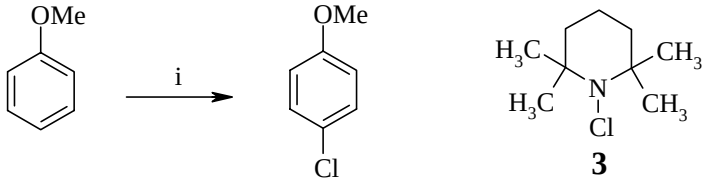
Mitsuo have *et al*. have absorbed copper (II) chloride on alumina and used it for selective halogenation of poly aromatic hydrocarbons. The formation of mono and dihalo compounds was obtained in high yields depending upon the reaction conditions (**Scheme 1**).



Scheme 1: (i) CuX (X = Cl, Br) /$AlCl_3$, chlorobenzene, 130^0C, 2 h.

John *et al.*[10]

John *et al*. have developed a simple, method for highly selective aromatic chlorination and studied the kinetics and mechanism of chlorination of electron-rich aromatic compounds by *N*-chloroamines **3** in acidic solution (**Scheme 2**).

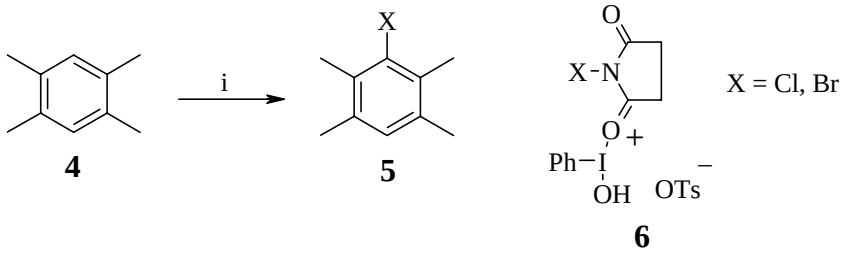


Scheme 2: (i) *N*-chloro-2, 2,6,6-tetramethylpiperidine, trifluoroacetic acid, 25^0C.

Pakorn *et al.*[11]

1-Bromo-2,5-pyrrolidinedione (NBS) and 1-chloro-2,5-pyrrolidinedione (NCS) with catalytic quantities of *p*-toluenesulphonic acid have been used for ring halogenation of polyalkylbenzenes. Pakorn *et al.* found that NBS in the presence of *p*-toluenesulphonic acid,

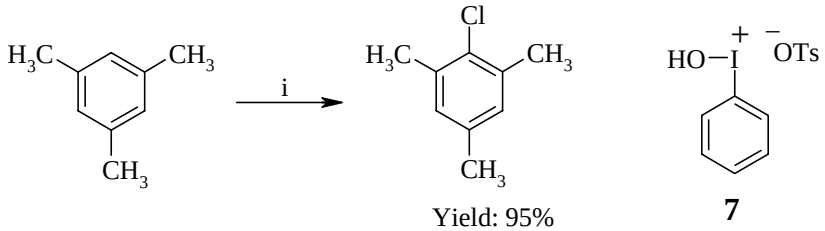
will form [hydroxy(tosyloxy)iodo]benzene (Koser's reagent, HTIB) **6**, which was used as a effective catalyst for ring halogenation (**Scheme 3**).



4 **5** **6**

Scheme 3: (i) NIX, TsOH, HITB, MeOH, 25^0C.

Pakorn *et al*[12]. have developed another simple method for ring chlorination of polyalkylbenzenes such as mesitylene have been carried out at room temperature with LiBr, NaCl and stoichiometric amounts of hydroxy(tosyloxy)iodobenzene (HTIB, Koser's reagent) **7**. This procedure is also applied for the brominations and iodinations (**Scheme 4**).



7

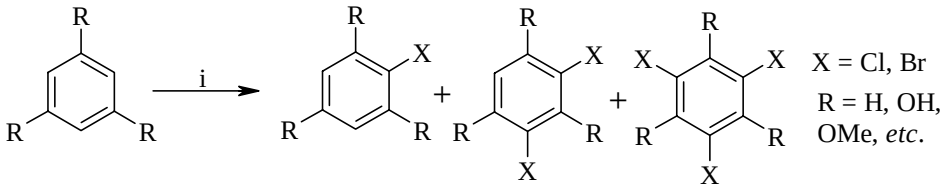
Scheme 4: (i) NaCl, HTIB, CH_2Cl_2 or H_2O, 25^0C, overnight, 95%.

Delaude *et al.*[13]

Delaude *et al.* have developed a method for chlorination of arenes using thionyl chloride as a halogen source and HNaX zeolites as catalyst.

Chimmanamada *et al.*[14]

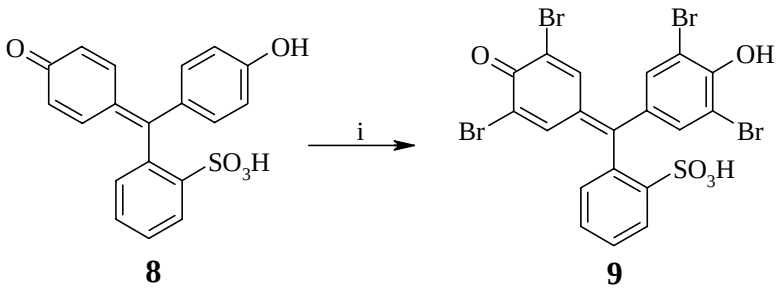
Chimmanamada *et al.* have studied the mimicking vanadat-dependent marine metalloenzymes as a catalyst for the halognation of selected organic compounds (**Scheme 5**).



Scheme 5: (i) KX (X = Cl, Br), aq. H_2O_2 (30%), hyperchloric acid, ammonium metavanadate (AMV), CH_2Cl_2, 25^0C. 15 h.

Jerrylaine *et al.*[15]

Jerryaline *et al.* have studied peroxidative halogenation of organic substrates catalyzed by transition-metal-ion-grafted mesoporous silicate materials (**Scheme 6**).

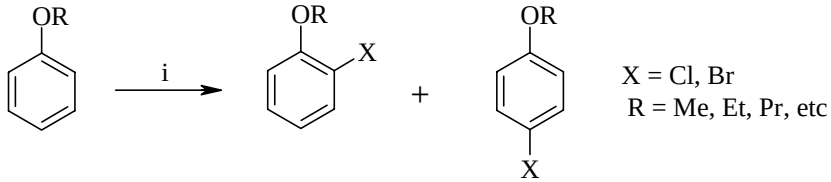


8 **9**

Scheme 6: (i) Ti/MCM-48, phenol red, KBr, aq. H_2O_2, Hepes buffer, pH 6.5.

Masao *et al.*[16]

Masao *et al.* have developed a simple method for regioselective chlorination and brominations of C_6H_5OR (R = C_1-C_8 alkyl, Butyl, allyl, cyclohexyl, benzyl) to 4-XC_6H_4OR (X = Cl and Br, respectively) using $NaClO_2$, $Mn(acac)_3$ in CH_2Cl_2 in the presence of catalyst moist kaolin (**Scheme 7**).



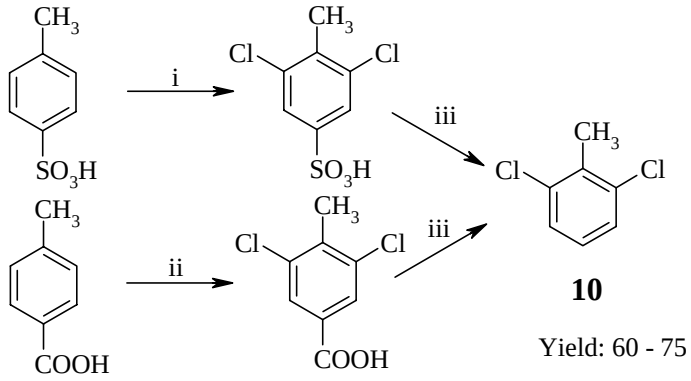
Scheme 7: (i) $NaClO_2$, $Mn(acac)_3$, moist kaolin, NaX (X = Cl, Br), CH_2Cl_2, 25_0C.

Istvan *et al.*[17]

Istvan *et al.* have found out that under mild conditions *t*-butyl hypochlorite is an excellent, highly regioselective aromatic ring chlorinating agent.

Mukhopadhyay *et al.*[18]

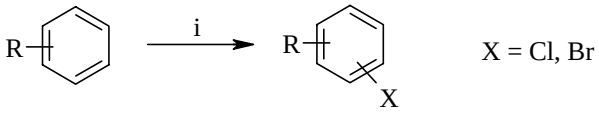
Mukhopadhyay *et al* have developed alternative manufacturing process for 2,6-dichlorotoluene, 2,6-dichloroaniline and 2,6-dichlorophenol, involving oxidative chlorination, which involved protection of the starting material in the *para* position followed by deprotection involving either desulphonation or decarboxylation. For example, oxidative chlorination of 4-methylbenzenesulphonic acid, 4-methylbenzoic acid, 4-aminobenzoic acid, and 4-hydroxybenzoic acid by using HCl-H_2O_2, and their subsequent desulphonation or decarboxylation, gave a 60-75% yield of the desired products (**Scheme 8**).



Scheme 8: (i) HCl, H_2O_2, Cl_2 gas; (ii) HCl, H_2O_2, acetic acid/water, (iii) sulphuric acid.

Barhate *et al.*[19]

Barhate *et al.* have developed a simple method for halogenation of arenes utilizing a combination of aqueous hydrogen peroxide (34%) or *tert*-burylhydroperoxide (70%) and hydrohalic acid (**Scheme 9**).



Scheme 9: (i) HX (X = Cl, Br), H_2O_2, TBHP, CCl_4, 25^0C, 50%.

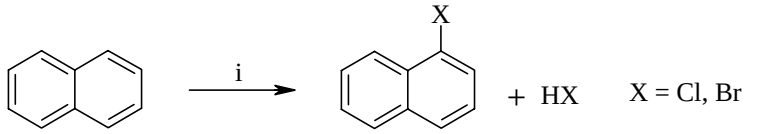
Roxana *et al*.[20]

Roxana *et al*. have studied the kinetics of halogenation and the bromination of phenol red to bromophenol blue was studied at pH 6.5, in the presence of perxovanadium (V) species generated by acid decomposition of $[O\{VO(O_2)_2\}_2]^{4-}$.

Hussni's [21]

Hussni have developed a new mild and efficient method for aromatic halogenation with a wide variety of halides in presence of sodium bismuthate ($NaBO_3$) in acetic acid. Hussni has used metal halides of groups Ia, IIa, IIIa, Iva, Va, and the first row of transition elements. He found that the rate of halogen production increases from the top of the group to the bottom (**Scheme 10**).

Hussni also first reported (**1996**) the chlorination of aromatic compounds using tin (IV) chloride and lead tetraacetate.

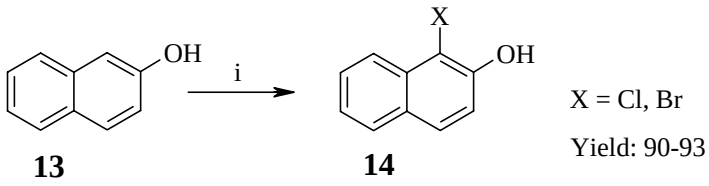


Scheme 10: (i) NaX (X = Cl, Br), $NaBiO_3$, AcOH, 25^0C, 68-80%.

Vyas *et al.*[22]

Vyas *et al* have developed a simple and efficient procedure for chlorination and brominations of aromatic amines, hydrocarbons and naphthols by the action of aqueous

hydrohalic acid on hydrogen peroxide. This environmentally clean and safe procedure involves *in situ* generation of the active halogen (**Scheme 11**).



13 **14**

Scheme 11: (i) con. HCl, 30% aq. H_2O_2, MeOH, 25^0C, 20 h, 90-93%.

4.0.3 Present Work

4.0.3.1 Objective

Although there are many methods available in the literature for halogenation of arenes, they suffer from certain drawbacks like low regioselectivity, low yield, use of elemental halogens, cumbersome experimental procedures, *N*-alkyl halides as halogen source etc.

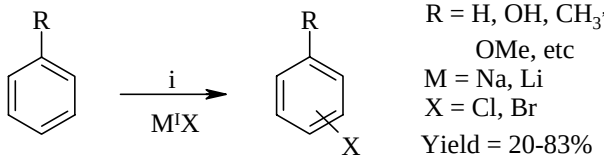
In order to overcome some of these problems, a new and environmentally safe procedure is envisioned which involves *in situ* preparation of positive halogen species by the oxidation of a chloride or bromide anion using a suitable oxidant. This reactive electrophilic halogen species can thus effect halogenation of organic substrates under suitable reaction conditions. This concept has been inspired by the enzymes, vanadium dependent bromoperoxidases found in marine algae, which have the ability to catalyze oxidation of bromide ions, by hydrogen peroxide in the biosynthesis of brominated compounds[23]. Some authors[24] have designed synthetic catalysts based on Nature's model to assist oxidation of a bromide anion with hydrogen peroxide in bromination reactions.

In our studies we explored the oxidation of alkali metal halides by $NaIO_4$ to generate halogen species *in situ* for effective halogenation of alkenes[25] (See **Section II** for details). As a logical extension, the oxidative halogenation of aromatics was carried out and the corresponding halogenated products were obtained in good yield with excellent regioselectivity, the results of which are presented in this section.

4.0.4 Results and Discussion

When anisole (**15a**) was treated with alkali metal halides in the presence of $NaIO_4$ (25 mol%) under acidic conditions in acetonitrile:water system (2:1), the corresponding halogenated products were obtained in good yields with excellent regioselectivity.

Importantly, excellent regioselectivity in bromination has been observed with metal bromides rather than metal chlorides (**Scheme 12**).[25]



15a-i **16a-i**

Scheme 12: (i) M^IX (M = Na, Li; X = Cl, Br), $NaIO_4$, CH_3CN:H_2O (2:1), aq. H_2SO_4, 80^0C, 3 h, 20-83%.

We turned our attention to systematically study the effectiveness of various alkali metal halides, under the influence of $NaIO_4$ on oxidative halogenation of arenes. Accordingly, different metal halides were screened as halogen sources (**Table 1**).

Table 1: $NaIO_4$-mediated oxidative halogenation of anisole (**15a**) with metal halides[a]

Sr. No.	Halogen source	Yield (%)[b]	Selectivity[c]	
			4-X	2-X
a	NaCl	53	60	40
b	NaBr	69	>99	-
c	LiCl	80	70	30
d	LiBr	74	>99	-
e	Cl_2	83	100	-

a) reaction conditions: $NaIO_4$ (25 mol%), anisole (10 mmol), alkali metal halide (12 mmol), CH_3CN/H_2O (2:1, 15 ml), 30% aq. H_2SO_4 (0.5ml, 10 mmol), 80^0C, 3h. b) Isolated yield after column chromatography; c) determined from GC-MS; X = Cl, X = Br.

Among the various alkali metal halides screened, sodium bromide and lithium bromide were found to give excellent regioselectivity in brominations. However, in the case of chlorinations, the excellent regioselectivity has been observed with chlorine gas rather than lithium chloride or sodium chloride.

Table 2: $NaIO_4$-mediated oxidative halogenation of arenes with sodium chloride[a]

Sr. No.	Arenes (15b-i)	Yield (%)[b]	Selectivity[c]	
			4-X	2-X
b	Benzene	30	100[d]	-
c	Chlorobenzene	25	60	40
d	Toluene	39	58	42
e	Mesitylene	80	100	
f	2-Nitroanisole	59	100[e]	-
g	Acetophenone	75	100[f]	-
h	4-Chloroacetophenone	80	100[g]	
i	Phenol	20	75	25

a) reaction conditions: $NaIO_4$ (25 mol%), anisole (10 mmol), alkali metal halide (12 mmol), CH_3CN/H_2O (2:1, 15 ml), 30% aq. H_2SO_4 (0.5ml, 10 mmol), 80^0C, 3h.; b) Isolated yield after column chromatography; c) determined GC-MS; d) monochlorobenzene; e) 2-nitro-4-chloroanisole; f) α-chloroacetophenone; g) 2-chloro-1-(4-chlorophenyl)ethanone

It was of interest to subject various substituted arenes (**15a-i)** for chlorinations using cheaply available alkali metal halides such as sodium chloride. As can be seen from **Table 2**, various substituted arenes underwent chlorinations with $NaIO_4$ and sodium chloride to give the corresponding chlorinated products (**16a-i**) in good yields. In case of acetophenone, we obtained the side chain α-chlorinated product in good yield and in case of substrates such as toluene, anisole and phenol we obtained both the *ortho* and *para* products but the selectivity of *para* chlorinated product being much higher. In case of benzene mono chlorinated product was obtained in poor yield with excellent selectivity.

The formation of chlorinated products (**16a-i**) were confirmed by ^{1}H-NMR, ^{13}C-NMR, GC and GC-MS. For example, the ^{1}H-NMR spectrum of 2-chloro-1-(4-chlorophenyl)ethanone

(**16h**) showed the typical singlet of methyl proton at δ 4.68 confirming the formation of 2-chloro-1-(4-chlorophenyl)ethanone. Its GC-MS spectrum showed the molecular ion peak at m/z 188.

Mechanism

[For the mechanism of generation of halogens, see **Section II** in this **Chapter** for details].

4.0.5 Conclusion

In conclusion, we have shown that $NaIO_4$ oxidizes alkali metal halides efficiently in aqueous medium to halogenate arenes to produce the corresponding halo derivatives in good yields (20-83%) and excellent selectively

4.0.6 Experimental Section

General experimental procedure for halogenation of arenes (15a-i)

A mixture of arenes (10 mmol), alkali metal halide (12 mmol), 30% aq. H_2SO_4 (0.5 ml, 10 mmol) and $NaIO_4$ (25 mol%) in acetonitrile: water (2:1, 15ml) was stirred at 80^0C. The reaction was monitored by GC analysis. After completion of the reaction, it was diluted with dichloromethane (20 ml) and washed with water and brine. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to give the crude products, which were purified by column chromatography on silica gel using petroleum ether as eluent to afford the pure product.

4-Chloroanisole (16a): Yield: 53%; liq. **bp.** 199-201^{0}C (198-202^{0}C); **^{1}H-NMR (200 MHz, $CDCl_3$)**: δ 3.80 (s, 3H), 6.85 (d, *J* = 8.5 Hz, 2H), 7.20 (d, *J* = 8.5 Hz, 2H); **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 56.12, 115.34, 125.56, 130.45, 158.78; **GC-MS** m/z (% rel. intensity): 142 (100), 127 (75), 111 (5), 99 (60), 73 (15), 63 (20), 50 (15).

Chlorobenzene (16b): Yield: 30%; liq. **bp.** 129-131^{0}C (Lit. 132^{0}C); **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 7.10-7.40 (m, 5H); **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 126.20, 128.12, 130.10, 135. 29; **GC-MS** m/z (% rel. intensity): 112 (100), 77 (75), 56 (10), 51 (50).

1,4-Dichlorobenzen (16c): Yield: 25%; liq. **bp.** 53^{0}C (Lit. 52-54^{0}C); **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 7.85 (s, 4H); **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 130.56, 138.32.

4-Chlorotoluene (16d): Yield: 39%; liq. **bp.** 159-160^{0}C (Lit. 162^{0}C); **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 2.3 (s, 3H), 7.09 (d, *J* = 8.5 Hz, 2H), 7.20 (d, *J* = 8.5 Hz, 2H), **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 21.20, 130.34, 132.67, 133.45, 135.98; **GC-MS** m/z (% rel. intensity): 126 (10), 91 (100), 65 (20), 51 (10).

α-Chloroacetophenone (16g): Yield: 75%; **gum**; **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 4.68 (s, 2H), 6.8-7.5 (m, 5H); **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 4.35 (s, 2H), 7.34-7.87 (m, 5H): **GC-MS** m/z (% rel. intensity): 154 (5), 105 (100), 91 (10), 77 (80), 65 (8), 51 (60).

2-Chloro-1-(4-chlorophenyl)ethanone (16h): Yield: 80%; mp: 80-82^{0}C **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 4.68 (s, 2H), 7.48 (d, *J* = 8.5 Hz, 2H), 7.91 (d, *J* = 8.5 Hz, 2H), **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 45.61, 129.01, 129.75, 132.28, 140.26, 189.77.

4-Chlorophenol (16i): Yield: 20%; liq. **bp.** 39-42^{0}C (Lit. 43-45^{0}C); **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 5.25 (bs, 1H), 6.85 (d, *J* = 8.5 Hz, 2H), 7.20 (d, *J* = 8.5 Hz, 2H), **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 115.23, 127.15, 130.45, 155.67; **GC-MS** m/z (% rel. intensity): 128 (100), 102 (5), 100 (10), 73 (10), 65 (75), 53 (15).

SECTION II:

$NaIO_4$-Mediated Regioselective Oxidative Halogenation of Alkenes using Alkali Metal Halides as Halogen Source: A High Yield Preparation of Halohydrins

4.1.1 Introduction

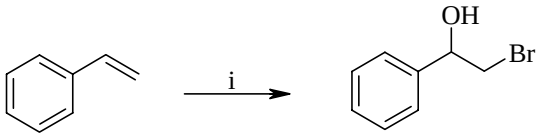
The 1,2-functionalization of olefins by the selective addition of two different functional groups, such as water or alcohols and halogens (halohydroxylation, haloalkoxylation), in a highly regio- and enantioselective manner, remains important and challenging to organic chemists.[26] Such halo derivatives are widely used in the synthesis of pharmaceuticals, dyes, flame-retardants, additives and plasticizers, agrochemicals and speciality chemicals.[27] The vicinal halohydroxy functionality presents a very useful structural moiety in synthetic organic chemistry as the halo functionality can be replaced by a variety of nucleophiles such as azido (N_3), cyano (CN), acetate (OAc), alkoxy (OR), amino (NHR), thio (SR), *etc.* thereby providing a new class of functionalized reactive intermediates in organic synthesis. On treatment with base the vicinal halohydroxy can be converted to the corresponding epoxides, which are important building blocks in organic synthesis. Thus, the vicinal halohydroxy represents a very useful class of compounds in organic synthesis.[28]

4.1.2 Review of Literature

Literature search revealed that there are various catalytic as well as non-catalytic methods available for the synthesis of halohydroxylation of olefin. All these methods, which involve use of halides, *N*-halides, metal halides and water sources, are described below.

John *et al.*[29]

John *et al*. studied the action of bromine water on styrene in hot aqueous potassium bromide solution to give styrene bromohydrine in 96% yield. The product is formed based on Markonikov's rule (**Scheme 13**).



Scheme 13: (i) Br_2, KBr, hot water, 90^0C, 1 h, 96%.

Winstein *et al*.[30]

Winstein *et al*. have synthesized bromohydrins using *N*-bromoacetamide-water system. It was then converted into epoxide in basic conditions. The role of neighboring group's participation in halide replacement reactions was also discussed.

Robert *et al.*[31]

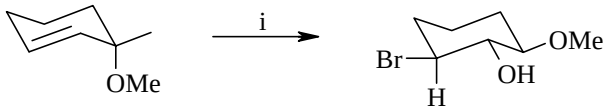
Robert *et al*. have developed a simple method for the synthesis of styrene bromohydrins using *N*-bromoacetamide in aqueous dioxane as solvent.

Josef *et al.*[32]

Josef *et al*. have synthesized 9α-halo derivatives of cortisone and hydrocortisone using hypobromus acid.

Bannard *et al.*[33]

Bannard *et al*. have studied the stereochemistry of 1α-methoxy-2β-bromo-3α-hydroxycyclohexane (**18**), which was synthesized using aqueous *N*-bromosuccinimide and 1-methoxycyclohex-2-ene (**17**) (**Scheme 14**).



17 **18**

Scheme 14: (i) aq. NBS.

David *et al.*[34]

David *et al.* have converted a number of olefins to their respective bromohydrins by using of *N*-bromosuccinimide (NBS) and moist dimethyl sulfoxide and studied the role of dimethyl sulfoxide in synthesis of bromohydrins (**Fig. 1**).

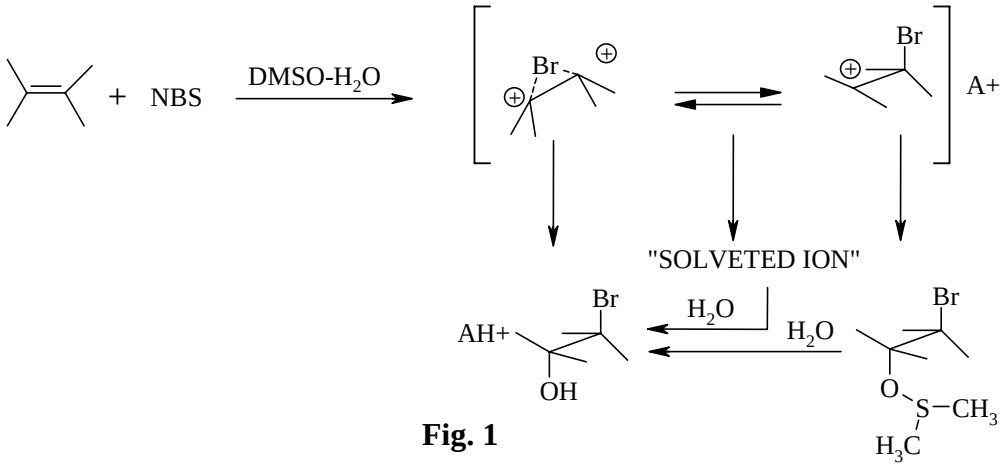
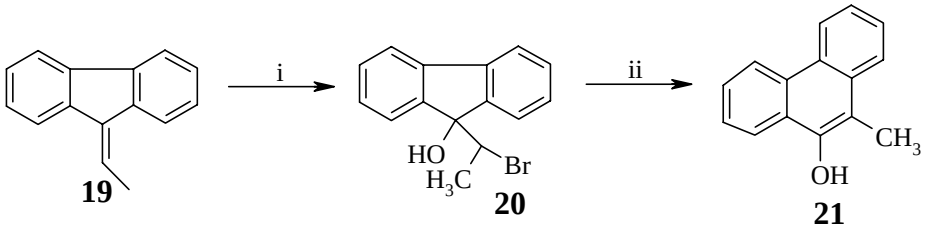


Fig. 1

Anthony[35]

Anthony developed a new ring expansion procedure *via* bromohydrins **20**, which was synthesized using NBS and aq. DMSO (**Scheme 15**)

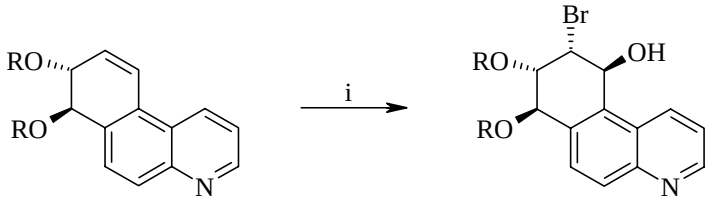


19 **20** **21**

Scheme 15: (i) DMSO, NBS, H_2O; (ii) benzene, methylmagnesium bromide, 60^0C.

Dubey *et al.*[36]

Dubey *et al*. have synthesized epoxide of benzo[*f*]quinoline *via* bromohydrin **23,** which was synthesized from **22** using NBA and HCl in water (**Scheme 16**).



22 **23**

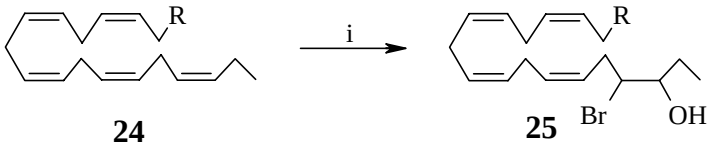
Scheme 16: (i) *N*-bromoacetamide (NBA), 30% HCl, water.

Shih *et al.*[37]

Shih *et al*. have discovered the NBA as a selective reagent for the functionalization of the 10,11 double bond of Avermectin B1a.

Tabahiro *et al.*[38]

Tabahiro *et al.* have synthesized bromohydrins **25** from terminal olefin of **24** in fatty acid using NBS in aqueous glyme (**Scheme 17**).

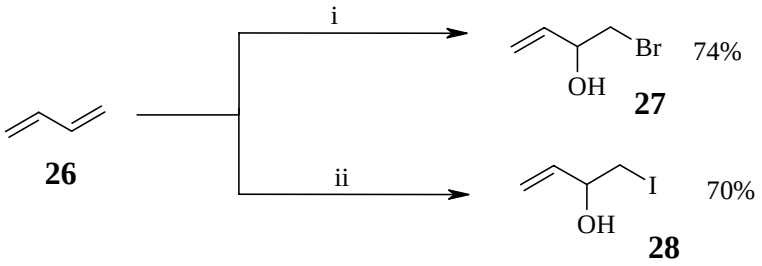


24 **25**

Scheme 17: (i) NBS, glyme, 0^0C.

Haruyoshi *et al.*[26b]

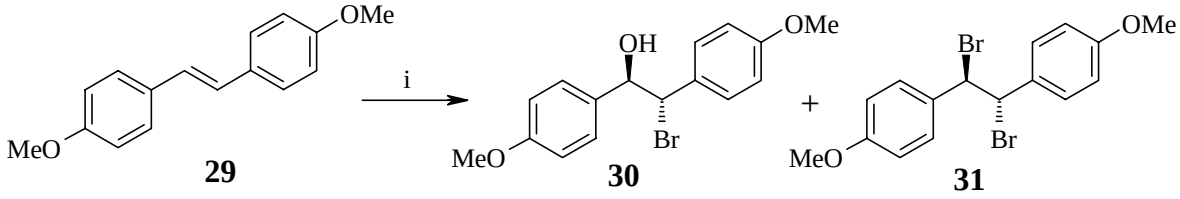
Hypohydrous acids such as hypoiodous acid (IOH) and hypobromous acid (BrOH) were easily generated from H_5IO_6 and $NaBrO_3$ respectively in the presence of an appropriate reducing agent such as $NaHSO_3$, which is well known for the synthesis of halohydrins. Haruyoshi *et al.* have thus, synthesized various iodohydrins **28** and bromohydrins **27** derivatives using H_5IO_6 or $NaBrO_3$ and $NaHSO_3$ in good yield (**Scheme 18**).



Scheme 18: (i) $NaBrO_3$, $NaHSO_3$, CH_3CN/H_2O (2/3 v/v%), 0^0C, 2 h; (ii) H_5IO_6, $NaHSO_3$, CH_3CN/H_2O (2/3 v/v%), 25^0C, 2 h

Malin *et al.*[39]

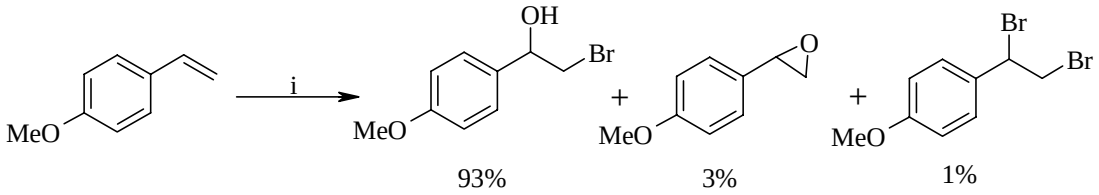
Malin *et al.* have developed bromoperoxidases mimicking systems using H_2O_2, KBr and NH_4VO_3 in water-dichloromethane two-phase system, which was applied for the brominations/bromohydroxylation of the arenes and alkenes (**Scheme 19**).



Scheme 19: (i) NH_4VO_3, H_2O_2, KBr, CH_2Cl_2/H_2O (1:1), 700rpm, 25^0C,

Sels *et al.*[40]

Sels *et al.* have developed a new heterogeneous catalyst WO_4^{2-} supported on layered double hydroxides ((Ni,Al)LDH-WO_4^{2-}, which is used for mild oxidative brominations and bromide-assisted epoxidation with H_2O_2 as the oxidant leading to bromohydroxylations, alkoxyhydroxylations and epoxidations (**Scheme 20**).



Scheme 20: (i) WO_4^{2-} on (Ni, Al) LDH-Cl^-, 25% aq. H_2O_2, NH_4Br, H_2O; CH_3CN (3:7).

4.1.3 Present Work

4.1.3.1 Objective

Although there are many methods available in the literature for halohydroxylation of olefins, they suffer from certain drawbacks such as use of elemental bromine, which are pollutants, and generate hazardous HX as by products.[41] In contrast to Br_2, other stoichiometric brominating reagents, such as *N*-bromosuccinimide (NBS), *N*-bromoacetamide, bromodimethylsulfonamide or chloramine T[42] do not produce HX in halogenation of organic molecules, but they are expensive and generate organic wastes. Recently, the oxidative halogenation of olefins by metal halides has emerged as an important alternative for the synthesis of such halo derivatives.[43] However, such oxidative halogenations involve the use of heavier metals in stoichiometric amounts, often resulting in poor yield and selectivity.

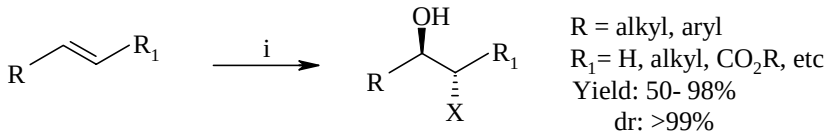
However, catalytic protocols with most V-BPO[44] biomimics still contain major disadvantage, such as the use of chlorinated solvents and more seriously, when milder pH conditions are required, almost stoichiometric amounts of metal must be used to ensure satisfactory activity.

$NaIO_4$ is well known reagent for oxidation reactions like metal oxidations,[45a] oxidative cleavage of 1,2-diols,[45b] oxidation of sulfides,[45c] phenols,[45d] indoles,[45e] etc. However, oxidation of alkali metal halides with $NaIO_4$ has not been reported. We have decided to oxidize cheaply available alkali metal halides and use them as a halogen source for selective oxidative halogenation of alkenes and arenes. When as a model substrate, we tried to halogenate styrene using $NaIO_4$, in combination with lithium bromide in THF, we got the dibromo product in low yield (10%). We tried to increase the yield by using various solvents such as acetone, acetonitrile, methanol, dimethyl sulfoxide, or acetic acid. We found that

acetic acid medium helped to give excellent yield of dibrominated product (98%). We then thought that use of water could produce bromohydroxylated product along with o-acetate product. We studied this reaction carefully by employing various solvents in combination with water, which resulted in very poor yield of bromohydroxylation along with dibrominated product. Then we studied the role of pH in our reaction protocol. We found that only in acidic conditions $NaIO_4$ readily oxidizes halides and liberates halogens. After studying various solvent-water systems in presence of acidic conditions we found that acetonitrile-water is the best solvent system for bromohydroxylation of alkenes and styrenes (up to 98%); the results of which are discussed in this section.

4.1.4 Results and Discussion

When styrene was treated with lithium bromide (1:1.2) in the presence of $NaIO_4$ (25 mol%), 30% aq. H_2SO_4/HCl (10 mmol) in acetonitrile water (2:1) system, the corresponding bromohydroxy product was obtained in very high yield (upto 98%) with high regioselectivity (>99%) (**Scheme 21**).[25]



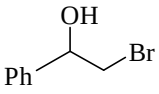
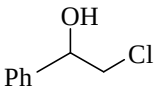
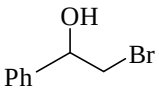
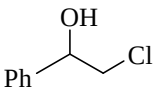
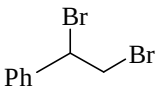
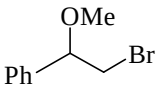
32a-p **33a-p**

Scheme 21: (i) LiBr (1.2 mmol), $NaIO_4$ (25 mol%), aq. H_2SO_4 (10 mmol), CH_3CN/H_2O (2:1), 25^0C, 1-3 h, 50-98%.

As can be seen from **Table 3** we turned our attention to the role of $NaIO_4$ in oxidative halogenation of alkenes in the presence of various alkali metal halides using various solvent systems. When styrene was subjected to oxidative halogenation in presence of 25 mol% of $NaIO_4$, the corresponding halogenated product was obtained in high yields. In the absence of $NaIO_4$, no reaction took place; lowering the molar ratio of $NaIO_4$ also resulted in the reduced

yield. It is found that the use of 25 mol% of $NaIO_4$ and the proper choice of solvent under acidic conditions (H_2SO_4 or HCl) are critical in achieving high conversion level of olefins with excellent product selectivity. Thus, while a mixture of CH_3CN and water at pH = 6.2 (initial pH = 2.17 rose to 6.2 within 10 min.) was found to be the best solvent for halohydrin formation, the formation of dibromides was facilitated in presence of acetic acid as solvent requiring no strong acidic conditions. However, when HIO_4 and $PhI(OAc_2)$ were employed in catalytic amounts for the halobromination of styrene with LiBr, mixtures of bromo alcohols and dibromides were obtained in low yield (25%).

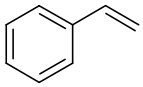
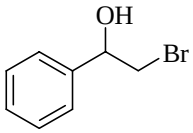
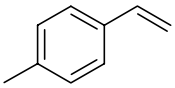
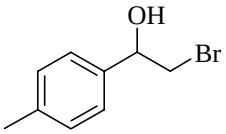
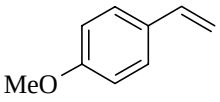
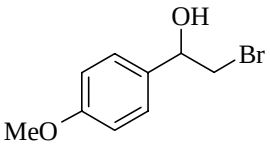
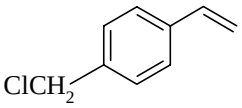
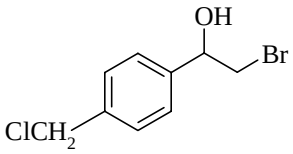
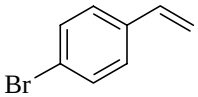
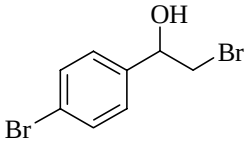
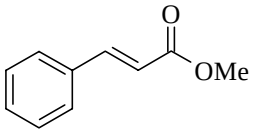
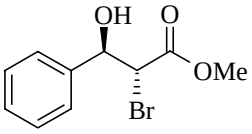
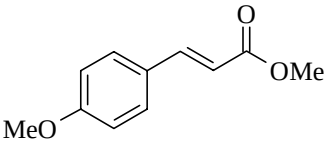
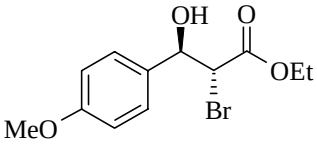
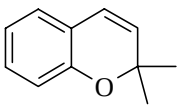
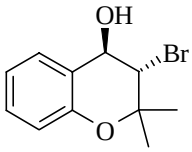
Table 3: $NaIO_4$-mediated oxidative halogenation of styrene using alkali metal halides[a]

Entry	Metal halide	Solvent[b]	Product	Yield (%)[c]
1	LiBr	CH_3CN/H_2O (2:1)		91[d]
2	LiCl	CH_3CN/H_2O (2:1)		81[d]
3	NaBr	CH_3CN/H_2O (2:1)		86[d]
4	NaCl	CH_3CN/H_2O (2:1)		80[d]
5	LiBr	AcOH		98
6	LiBr	$MeOH/H_2O$ (3:1)		57[d]

a) conditions: substrate (10 mmol), $NaIO_4$ (25 mol%), metal halides (12 mmol), 30% aq.H_2SO_4 (0.5 ml, 10 mmol); b) solvent 15 ml: CH_3CN:H_2O (2:1), AcOH, MeOH:H_2O (3:1); c) isolated yield after column chromatography; d) 5-10% of the corresponding dihalides are also formed.

As can be seen from **Table 4,** a various substituted styrenes and α,β-unsaturated carbonyl compounds **32a-h** underwent oxidative brominations to give the corresponding bromohydroxylation **33a-h** in excellent yield. α,β-Unsaturated carbonyl compounds (**32f-g**) also gave excellent yield of bromohydrins **33f-g** but the rate was very slow.

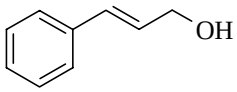
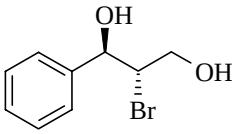
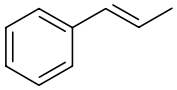
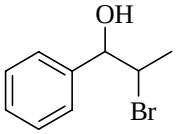
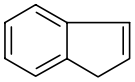
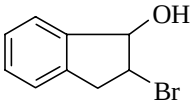
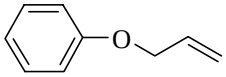
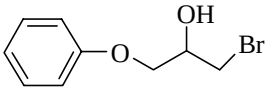
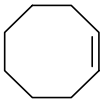
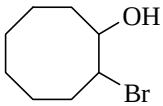
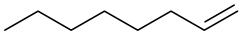
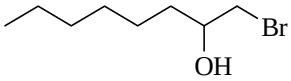
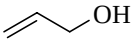
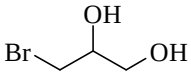
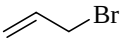
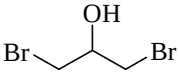
Table 4: $NaIO_4$-mediated oxidative bromohydroxylation of styrenes and α,β-unsaturated carbonyl compounds with LiBr

Sr. No.	Olefins (32a-h)	Time (h)	Product (33a-h)	Yield (%)[b]	Mp (^{0}C)
a		1		91	gum
b		1		95	gum
c		1		90	gum
d		1		85	63-65
e		1		80	73-75
f		3		90[c]	56-58
g		3		95[c]	60-62
h		3		95[c]	120

a) reaction conditions: alkene (10 mmol), $NaIO_4$ (25 mol%), LiBr (12 mmol), 30% aq.H_2SO_4 (0.5 ml, 10 mmol), solvent 15 ml: CH_3CN:H_2O (2:1); b) yields refers to isolated product after column chromatography; c) only *erythro* products were observed.

In all styrenic substrates, the incoming hydroxy function entered at the benzylic position exclusively. Remarkably, in the case of 1,2-disubstituted olefins, *anti*-isomers of the corresponding halo derivatives with dr >99% (**33f-i**) were obtained exclusively.

Table 5. $NaIO_4$-mediated oxidative bromohydroxylation of olefins with LiBr[a]

Sr. No.	Olifins (32i-p)	Time (h)	Product (33i-p)	Yield (%)[b]	Mp (^{0}C)
i		3		80[c]	65
j		2		86[d]	gum
k		1		98[d]	198-200
l		3		80[d]	gum
m		3		85	gum
n		1		96[d]	gum
o		1		58[d]	gum
p		1		50[d]	gum

a) reaction conditions: alkene (10 mmol), $NaIO_4$ (25 mol%), LiBr (12 mmol), 30% aq.H_2SO_4 (0.5 ml, 10 mmol), solvent 15 ml: CH_3CN:H_2O (2:1); b) yields refers to isolated product after column chromatography; c) only *erythro* products were observed; d) regioisomers were formed nearly in 1:1 ratio as determined from ^{1}H and ^{13}C-NMR.

As can be seen from **Table 5** a variety of aliphatic olefins and allylic alcohol **32i-p** underwent oxidative brominations with lithium bromide and $NaIO_4$ (25 mol%) to give the corresponding bromohydrins **33i-p** in excellent yield. In case of substrates such as allyl

alcohol (**32o**) and allyl bromide (**32p**), dibromide was obtained in higher yield along with lower yield of bromohydrins. For aliphatic olefins the regioisomers were formed nearly in 1:1 ratio as determined from ^{1}H and ^{13}C-NMR spectra respectively.

The formation of bromohydrins **33a-p** was confirmed by ^{1}H, ^{13}C-NMR, IR and Mass spectroscopy. The Mass spectra of the bromohydroxy compounds showed typical molecular ion peak and M + 2 peak almost equal in intensity because of the presence of a molecular ion containing the ^{81}Br isotope. The IR spectrum of all bromohydroxy compounds showed the typical absorption band in the region of 3400-3475cm^{-1} confirming the presence of hydroxy group in the molecule. ^{1}H-NMR spectrum also showed the broad singlet at δ 2-3 due to the presence of hydroxy proton.

For example, the IR spectrum of 2-bromo-1-(4-bromophenyl)ethanol (**33e**) showed a typical absorption band in the region 3425 cm^{-1} confirming the presence of hydroxy group in the molecule. Its ^{1}H-NMR spectrum showed the broad singlet at δ 2.82 for OH proton. Its ^{13}C-NMR also showed typical bromohydrins carbon signal at δ 39.25 and 72.85. The mass spectrum of 4-bromo styrene bromohydrins **33e** showed the molecular ion peak at m/z 280 (**Fig. 2**).

As another example, the IR spectrum of ethyl-2-bromo-3-hydroxy-3-(4-methoxyphenyl)propionate (**33g**) showed the typical absorption band in the region 3474 cm^{-1} confirming the presence of hydroxy group in the molecule. Its ^{1}H-NMR spectrum showed the broad singlet at δ 2.64 for OH proton. Its ^{13}C-NMR also showed typical carbon signals for bromohydrins at δ 48.07 and 74.32. The mass spectrum of ethyl-2-bromo-3-hydroxy-3-(4-methoxyphenyl)propionate (**33g**) showed the molecular ion peak at m/z 304 (**Fig. 3**)

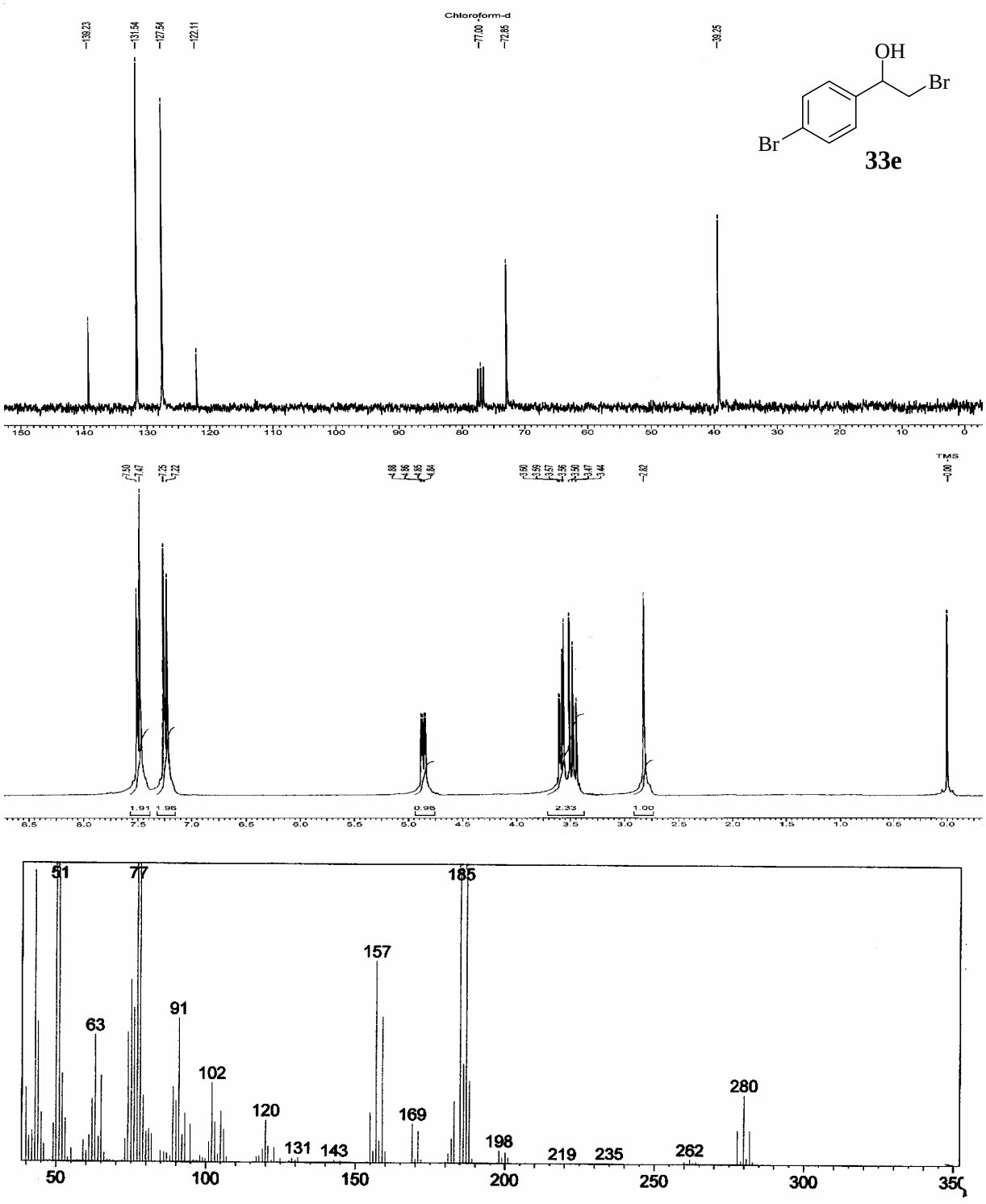


Fig. 2: ^{13}C, ^{1}H -NMR and GC-Mass spectra of 2-bromo-1-(4-bromophenyl)ethanol (33e)

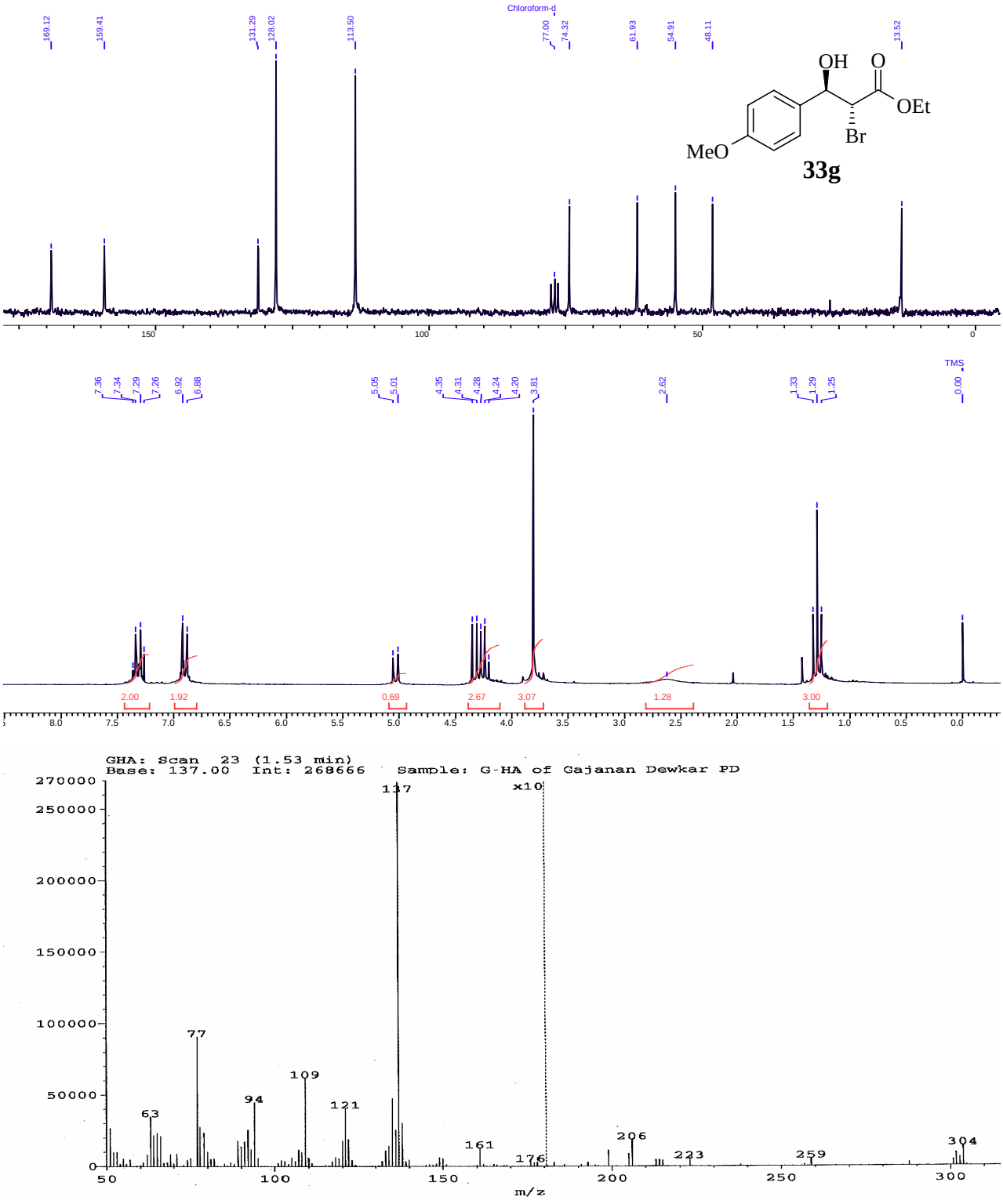
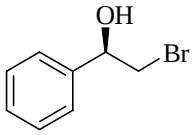
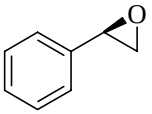
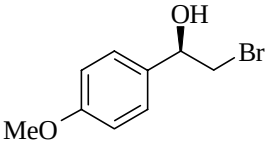
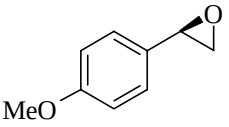
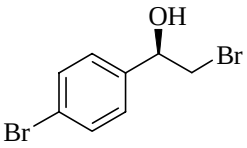
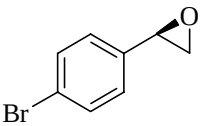
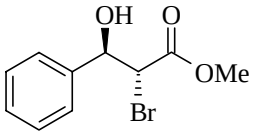
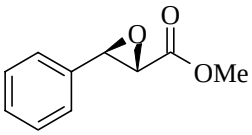
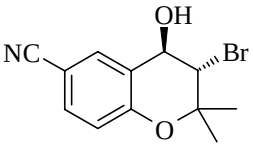
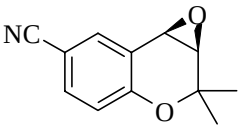


Fig. 3: ^{13}C, ^{1}H -NMR and Mass spectra of ethyl-2-bromo-3-hydroxy-3-(4-methoxyphenyl)propionate (33g)

Table 6: $NaIO_4$-mediated asymmetric oxidative bromohydroxylation of β-CD complexes of styrenes[a] and conversion to their epoxides[b]

Sr. No.	bromohydrin (%) (34a-e) product	yield[c]	epoxide (%) (35a-e) product[d]	yield[c]	ee[e]
a		55		90	25
b		50		80	34
c		60		90	22
d		50		85	55
e		64		89	20

a) conditions: (β-CD) complex of the corresponding styrenes (10 mmol), $NaIO_4$ (25 mol%), Libr (12 mmol), 30% aq. H_2SO_4 (0.5 ml, 10 mmol), CH_3CN/H_2O 2:1 (25 ml), 25^0C, 12 h. b) 1-2-bromoalcohol (2 mmol), K_2CO_3 (4 mmol), acetone (10 ml), 25^0C, 24 h. c) isolated yield after columan chromatography. d) absolute configuration assigned on the basis of the sign of rotation. [e]determined from chiral HPLC analysis.

The result of the asymmetric version of oxidative bromohydroxylation is presented in **Table 6**. As can be seen from **Table 6**, the asymmetric version of bromohydroxylation of β-cyclodextrin (β-CD) complexes of styrenes took place readily followed by their conversion into the corresponding chiral epoxides. However, the yield and enantioselectivity of the process were found to be moderate. Change of temperature, solvent or molar ratio of $NaIO_4$

did not yield improved %ee. Thus, when *β*-cyclodextrin (*β*-CD) complexes[46] of the styrenes were subjected to oxidative brominations under the reaction conditions ($NaIO_4$, LiBr, H^+), the corresponding chiral bromohydrins (**34a-e**) were obtained in good yields. Subsequently, these bromohydrins were converted under basic conditions into their respective epoxides (**35a-e**) in high yields and moderate enantioselectivity.

For example, the IR spectrum of methyl-3-phenyloxiranecarboxylate (**35d**) showed the disappearance of absorption band in the region 3400-3475 cm^{-1} confirming the formation of epoxide. Its ^{1}H-NMR spectrum showed the typical doublet at δ 3.50 and 4.10 for epoxy protons. Its ^{13}C-NMR also showed typical epoxy carbon signals at δ 56.49 and 57.78 (**Fig. 4**).

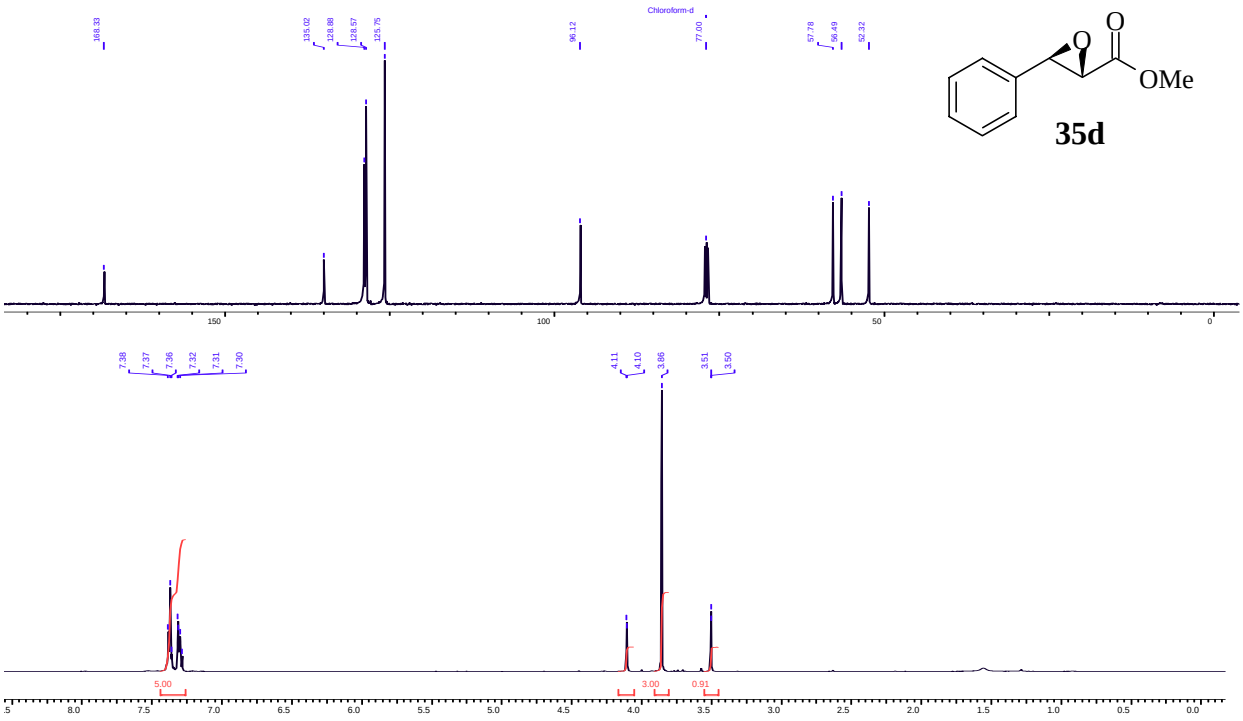
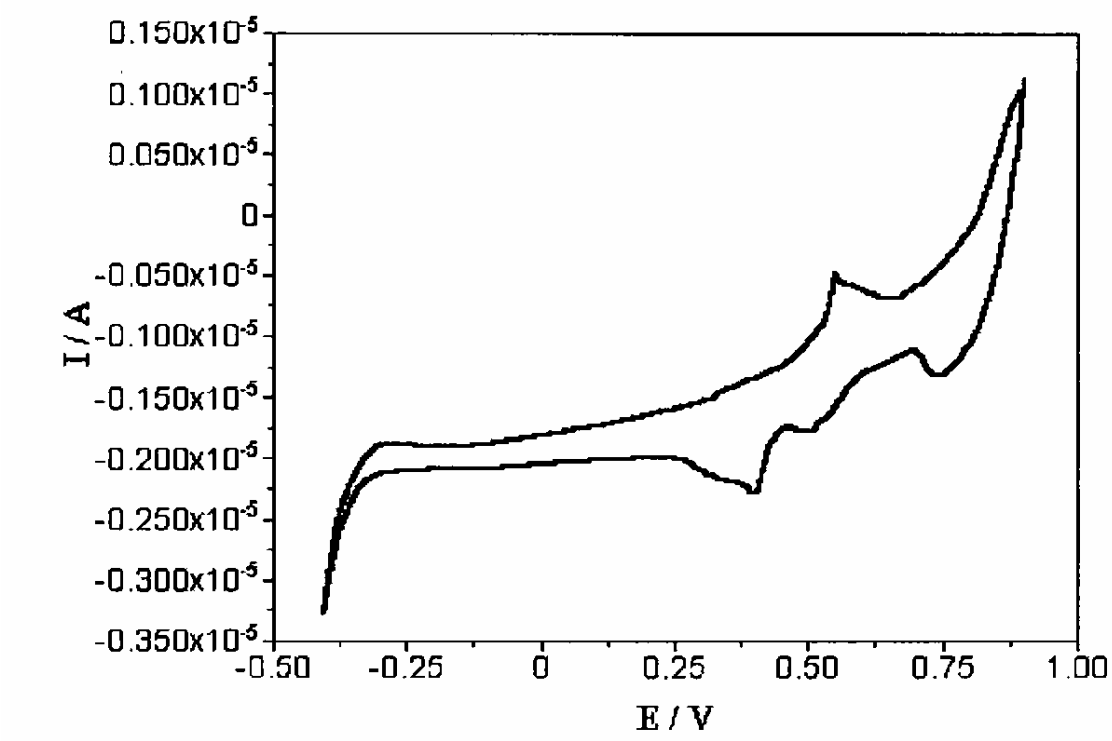


Fig. 4: ^{13}C and ^{1}H -NMR spectra of epoxide 35d

Mechanism

With the help of Cyclic Voltammetry (CV) study, the mechanism of the reaction can be deduced. The Cyclic Voltammetry (Figure **5**) of the reaction shows, for the forward oxidation scan at 500 mV/s, an irreversible oxidation peak at Ep_a = 0.565 V [$Br^- \rightarrow Br_2$ equn (1)] and, for the reverse reduction scan, three irreversible reduction peaks at Ep_c = 0.720 V, 0.490 V and 0.390 V corresponding to the reduction of IO_4^-, IO_3^- and I_2 respectively [equns (2)-(4)].[47]



Voltage vs. Ag/AgCl reference

Fig. 5: CV of reaction mixture containing $NaIO_4$ (25 mol%), styrene (10 mmol), LiBr (12 mmol), 30% aq. H_2SO_4 (0.5 ml, 10 mmol), CH_3CN/H_2O 2:1 (20 ml) at 25^0C

$$2Br^- \longrightarrow Br_2 + 2e^- \quad \text{----------(1)}$$

$$IO_4^- + 2H^+ + 2e^- \longrightarrow IO_3^- + H_2O \quad \text{----------(2)}$$

$$IO_3^- + 6H^+ + 6e^- \longrightarrow I^- + 3H_2O \quad \text{----------(3)}$$

$$I_2 + 2e^- \xrightarrow{\text{fast}} 2I^- \quad \text{----------(4)}$$

Thus, CV reveals that X_2 (X = Br, Cl) generated *in situ* from metal halides by oxidation with $NaIO_4$, rapidly halogenates olefins or aromatic to produce the halo derivatives. The fact that such halogenations take place in *anti* fashion in the case of 1,2-disubstituted olefins probably proves the involvement of bromonium ions.

4.1.5 Conclusion

In conclusion, we have shown that a stable, commercially available $NaIO_4$ oxidizes alkali metal halides efficiently in aqueous medium to halogenate alkenes and produce the corresponding halo derivatives in excellent regio and diastereoselective fashion. The present system also demonstrates the asymmetric version of bromohydroxylation using a β-cyclodextrin complex of the respective styrenes, although with low enantiomeric excess.

4.1.6 Experimental section:

General experimental procedure for bromohydrin of olefins:

To a stirred mixture of olefin (10 mmol), LiBr (12 mmol), and 30% aq. H_2SO_4 (0.5 ml, 10 mmol) in CH_3CN:H_2O (2:1, 15 ml) at 10-15^{0}C, $NaIO_4$ (25 mol%) was added portion-wise. The reaction was monitored by TLC. After completion of the reaction, it was diluted with water and extracted with CH_2Cl_2 (25 ml x 3). The organic layers were washed with dilute solution of Na_2SO_3 and brine. It was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude products, which were purified on column chromatography packed with silica gel using petroleum ether and ethyl acetate (9:1) as eluent to afford the pure products.

2-Bromo-1-phenylethanol (33a): Yield: 91%; **gum**; **IR** (Neat, cm^{-1}): 592, 666, 762, 916, 1026, 1060, 1216, 1296, 1452, 1492, 1758, 2892, 2960, 3408; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.60 (1H, brs), 3.55-3.70 (2H, m), 4.90-5.00 (1H, dd, *J* = 8.10 and 4.00 Hz), 7.20-7.60 (5H, m), **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 39.62, 73.54, 125.63, 125.85, 140.33, 128.20, 128.42; **MS m/z** (% rel. intensity): 200(M^+, 1), 141 (1), 127 (1), 121 (10), 107 (100), 94 (25), 84 (60), 79 (75), 65 (18), 55 (14); **Analysis**: C_8H_9BrO requires C, 47.76; H, 4.47; Br, 39.80; found C, 47.75; H, 4.67; Br, 40.14%.

2-Bromo-1-(4-methylphenyl)ethanol (33b): Yield: 95%; **gum**; **IR** (Neat, cm^{-1}): 682, 764, 818, 916, 1016, 1612, 2920, 2958, 3424; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.34 (s, 3H), 2.55 (bs, 1H), 3.57-3.64 (m, 2H), 4.86 (dd, *J* = 18.15 and 3.7 Hz, 1H), 7.17 (d, *J* = 8.3 Hz, 2H), 7.25 (d, *J* = 8.3 Hz, 2H), **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 20.91, 39.43, 73.32, 125.52, 125.70, 128.98, 137.39, 137.72, 138.20; **Analysis**: $C_9H_{11}BrO$ requires C, 50.23; H, 5.11; Br, 37.20; found C, 50.30; H, 5.23; Br, 37.45%.

2-Bromo-1-(4-methoxyphenyl)ethanol (33c): Yield: 90%; **gum**; **IR** (Neat, cm^{-1}): 680, 750, 1030, 2930, 2964, 3475; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.54 (bs, 1H); 3.40 - 3.51 (m, 2H), 3.83 (s, 3H), 4.81 (dd, *J* = 8.9 and 3.95 Hz, 1H), 7.31 (d, *J* = 8.5 Hz, 2H), 6.91 (d, *J* = 8.5 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 15.43, 55.28, 73.73, 114.05, 126.99, 133.31, 164.15; **Analysis**: $C_9H_{11}BrO_2$ requires C, 46.75; H, 4.76; Br, 34.63; found C, 47.02; H, 5.01; Br, 34.69%.

2-Bromo-1-(4-chloromethylphenyl)ethanol (33d): Yield: 85%; **mp:** 63-65^{0}C; **IR** ($CHCl_3$, cm^{-1}): 654, 744, 838, 916, 1066, 1418, 1512, 2960, 3028, 3414; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.58 (bs, 1H) 4.58 (s, 2H), 3.49 – 3.65 (m, 2H), 4.90 (dd, *J* = 3.5 and *J* = Hz, 1H), 7.32 – 7.65 (m, 4H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 39.69, 45.68, 73.21, 126.29, 128.76, 137.50, 140.52; **Analysis**: $C_9H_{10}BrClO$ requires C, 43.37; H, 4.01; Br, 32.12; Cl, 14.05; found C, 43.47; H, 4.13; Br, 32.01; Cl, 13.97%.

2-Bromo-1-(4-bromophenyl)ethanol (33e): Yield: 80%; **mp:** 73-75^0**C**; **IR** ($CHCl_3$, cm^{-1}): 670, 830, 1130, 1212, 1460, 1500, 2960, 3026, 3425; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.82 (1H, brs), 3.44-3.50 (m, 2H), 4.86 (dd, *J* = 8 and 6 Hz, 1H), 7.35 (d, *J* = 8 Hz, 2H), 7.48 (d, *J* = 8 Hz, 2H),; **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 139.23, 13154, 127.54, 122.11, 72.85, 39.25; **MS m/**z (% rel. intensity): 280 (30), 198 (5), 185 (100), 169 (15), 157 (70), 120 (10), 102 (20), 91 (50), 77 (100), 63 (40), 51 (100); **Analysis**: $C_8H_8Br_2O$ requires C, 34.28; H, 2.85; Br, 57.14; found C, 34.30; H, 2.90; Br, 57.12%.

(±)-*trans*-Methyl-2-bromo-3-hydroxy-3-phenylpropionate (33f): Yield: 90%; **mp**: 56-58^{0}C; **IR** ($CHCl_3$, cm^{-1}): 1017, 1146, 1282, 1454, 1740, 2954, 3032, 3499; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.97 (bs, 1H), 3.81 (s, 3H), 4.39 (d, *J* = 8.15 Hz, 1H), 5.08 (d, *J* = 8.15 Hz, 1H), 7.4 (m, 5H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 47.52, 53.00, 75.61, 126.95, 128.46, 128.68, 139.09, 140.52; **Analysis**: $C_{10}H_{11}BrO_3$ requires C, 46.33; H, 4.24; Br, 30.88; found C, 46.35; H, 4.20; Br, 30.90%.

(±)-*trans*-Ethyl-2-bromo-3-hydroxy-3-(4-methoxyphenyl)propionate (33g): Yield: 95%; **mp:** 60-62^{0}C; **IR** ($CHCl_3$, cm^{-1}): 668, 770, 833, 1032, 1177, 1216, 1251, 1302, 1514, 1613, 1735, 2984, 3018, 3474; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.29 (t, *J* = 8.15 Hz, 3H), 2.64 (bs, 1H), 4.21 (d, *J*= 8 Hz, 1H), 3.81 (s, 3H), 5.03 (d, *J* = 8 Hz, 1H), 6.90 (d, *J* = 8.15 Hz, 2H), 7.31 (d, *J* = 8.15 Hz, 2H), **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 13.52, 48.11, 54.91, 61.93, 74.32, 113.50, 128.02, 131.29, 169.12; **MS** m/z (% rel. intensity): 304 (7), 259 (3), 223 (3), 206 (11), 161 (7), 137 (100), 121 (14), 109 (22), 94 (18), 77 (33), 64 (14); **Analysis**: $C_{12}H_{15}BrO_4$ requires C, 47.36; H, 4.93; Br, 26.31; found C, 47.39; H, 4.90; Br, 26.35%.

2,2-Dimethylcoumarin bromohydrin (33h): Yield: 95%; **mp:** 120^{0}C; **IR** ($CHCl_3$, cm^{-1}): 750, 1054, 1132, 1474, 1592, 2960, 3032, 3354; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 7.41 (d, *J* = 10.17 Hz, 1H), 1.34 (s, 3H), 1.53 (s, 3H), 4.08 (d, *J* = 10.15 Hz, 1H), 4.86 (d, *J* = 10.15 Hz,

1H), 6.73 (d, *J* = 10.17 Hz, 1H), 6.91 (m, 1H), 7.14 (m, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 19.78, 28.77, 62.88, 70.28, 78.82, 116.93, 121.13, 122.30, 127.52, 129.70, 151.93; **Analysis**: $C_{11}H_{13}BrO_2$ requires C, 51.36; H, 5.05; Br, 31.12; found C, 51.40; H, 5.10; Br, 32.34%.

(±)-*trans*-2-Bromo-1-hydroxy–1-phenylpropanol (33i): Yield: 80%; **mp:** 65^{0}C; **IR** ($CHCl_3$, cm^{-1}): 590, 658, 766, 894, 958, 1078, 1216, 1494, 2932, 3032, 3406; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.45 (bs, 1H), 3.50 – 3.67 (m, 1H), 4.03 – 4.12 (m, 2H), 4.25 – 4.44 (m, 1H), 6.75 – 7.45 (m, 5H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 34.77, 51.93, 63.99, 68.55, 69.24, 69.39, 114.64, 116.29, 121.48, 129.49, 138.28, 159.56; **MS** m/z (% rel. intensity): 232 (2), 149 (3), 133 (30), 107 (99), 91 (20), 79 (100), 65 (10); **Analysis**: $C_9H_{11}BrO_2$ requires C, 46.75; H, 4.76; Br, 34.63; found C, 46.60; H, 4.67; Br, 34.84%.

(±)-*trans*-2-Bromo-1-phenyl-1-hydroxypropane (33j): Yield: 91%; **gum**; **IR** ($CHCl_3$, cm^{-1}): 574, 700, 820, 1068, 1176, 1268, 1450, 1603, 2974, 3030, 3418; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.54 (d, *J* = 6.4 Hz, 3H). 2.34 (bs, 1H), 4.40-4.43 (m, 1H), 5.005 (d, *J* = 3.5 Hz, 1H), 7.34 – 7.35 (m, 5H), **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 18.19, 55.09, 76.60, 125.70, 127.25, 127.54, 139.01; **Analysis**: $C_9H_{11}BrO$ requires C, 50.23; H, 5.11; Br, 37.20; found C, 50.21; H, 5.00 Br, 37.28%.

(±)-*trans*-2-Bromo-1-hydroxy indane (33k): Yield: 98%; **mp:** 198-200^{0}C; **IR** ($CHCl_3$,cm^{-1}): **^{1}H-NMR** (200 MHz, DMSO-D_6): δ 2.49 (bs, 1H), 3.15 – 3.38 (m, 1H), 3.53 – 3.64 (m, 1H), 4.18–4.33 (m, 1H), 5.30-5.41 (m, 1H), 7.23-7.45 (m, 4H), **^{13}C-NMR** (50 MHz, DMSO-D_6): δ 39.89, 41.86, 54.21, 82.33, 83.98, 123.54, 123.76, 126.70, 127.95, 139.16, 140.33, 141.91, 159.37, 206.50; **Analysis**: C_8H_7BrNO requires C, 45.07; H, 3.28; Br, 37.55; N, 6.57 found C, 45.10; H, 3.45; Br, 37.56; N, 6.60%.

1-Phenoxy-3-bromo-2-propanol (33l): Yield: 80%; **gum**; **IR** ($CHCl_3$, cm^{-1}): 504, 690, 756, 1074, 1238, 1288, 1460, 1592, 2874, 2930, 3402; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.12 (bs, 1H), 4.12-4.30 (m, 2H), 4.27-4.57 (m, 1H), 5.17-531 (m, 2H), 7.39 (s, 5H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 52.26, 59.25, 64.28, 127.58, 128.42, 128.79, 138.72, 139.64, 159.41; **Analysis**: $C_9H_{11}BrO_2$ requires C, 46.75; H, 4.76; Br, 34.63; found C, 46.50; H, 4.70; Br, 34.91%.

(±)-*trans*-2-Bromo-1-hydroxy cyclooctane (33m): **Yield:** 85%; **gum**; **IR** ($CHCl_3$, cm^{-1}): 1050, 1250, 1452, 1510, 1725, 2923, 3030, 3453; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.49–1.74

(m, 2H), 1.75–1.95 (m, 8H), 1.98–2.19 (m, 2H), 3.82–3.89 (m, 1H), 4.37–4.75 (m, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 21.57, 24.25, 32.23, 32.74, 34.47, 56.60, 70.79; **Analysis**: $C_8H_{15}BrO$ requires C, 46.37; H, 7.24; Br, 38.64; found C, 46.40; H, 7.43; Br, 38.73%.

1-Bromo-2-octanol (33n): Yield: 96%; **gum; IR** ($CHCl_3$, cm^{-1}): 662, 726, 1030, 1126, 1238, 1376, 1740, 2858, 2928, 3420; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.89 (t, J = 6Hz, 3H), 1.29-1.54 (m, 10), 2.05 (s, 1H), 3.34-3.47 (m, 2H), 3.52 (m, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 13.92, 22.54, 26.61, 28.37, 31.46, 35.98, 36.20, 52.92; **Analysis**: $C_8H_{17}BrO$ requires C, 46.37; H, 7.24; Br, 38.64; found C, 46.30; H, 7.45; Br, 38.70%.

1,2-dihydroxy-3-bromopropane (33o): Yield: 58%**; gum; IR** ($CHCl_3$, cm^{-1}): **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.23 (bs, 1H), 3.66–3.98 (m, 4H), 4.01–4.35 (m, 1H), **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 32.80, 52.63, 63.55, **Analysis**: $C_3H_7BrO_2$ requires C, 23.22; H, 4.51; Br, 51.61; found C, 23.45; H, 4.67; Br, 51.65%.

1,3-dibromo-2-hydroxypropane (33p): Yield: 50%; **gum**; **IR** ($CHCl_3$, cm^{-1}): **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.26 (bs, 1H), 3.36-4.01 (m, 4H), 4.03-4.35 (m, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 31.79, 53.18, 63.99; **Analysis**: $C_3H_6Br_2O$ requires C, 17.82; H, 2.97; Br, 79.20; found C, 17.90; H, 2.98; Br, 79.20%.

4.1.7 References

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