ASYMMETRIC SYNTHESIS OF BIOACTIVE MOLECULES AND CATALYSIS BY NOVEL PALLADIUM COMPLEXES IN C-C BOND FORMATION

A THESIS

SUBMITTED TO THE

UNIVERSITY OF PUNE

FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

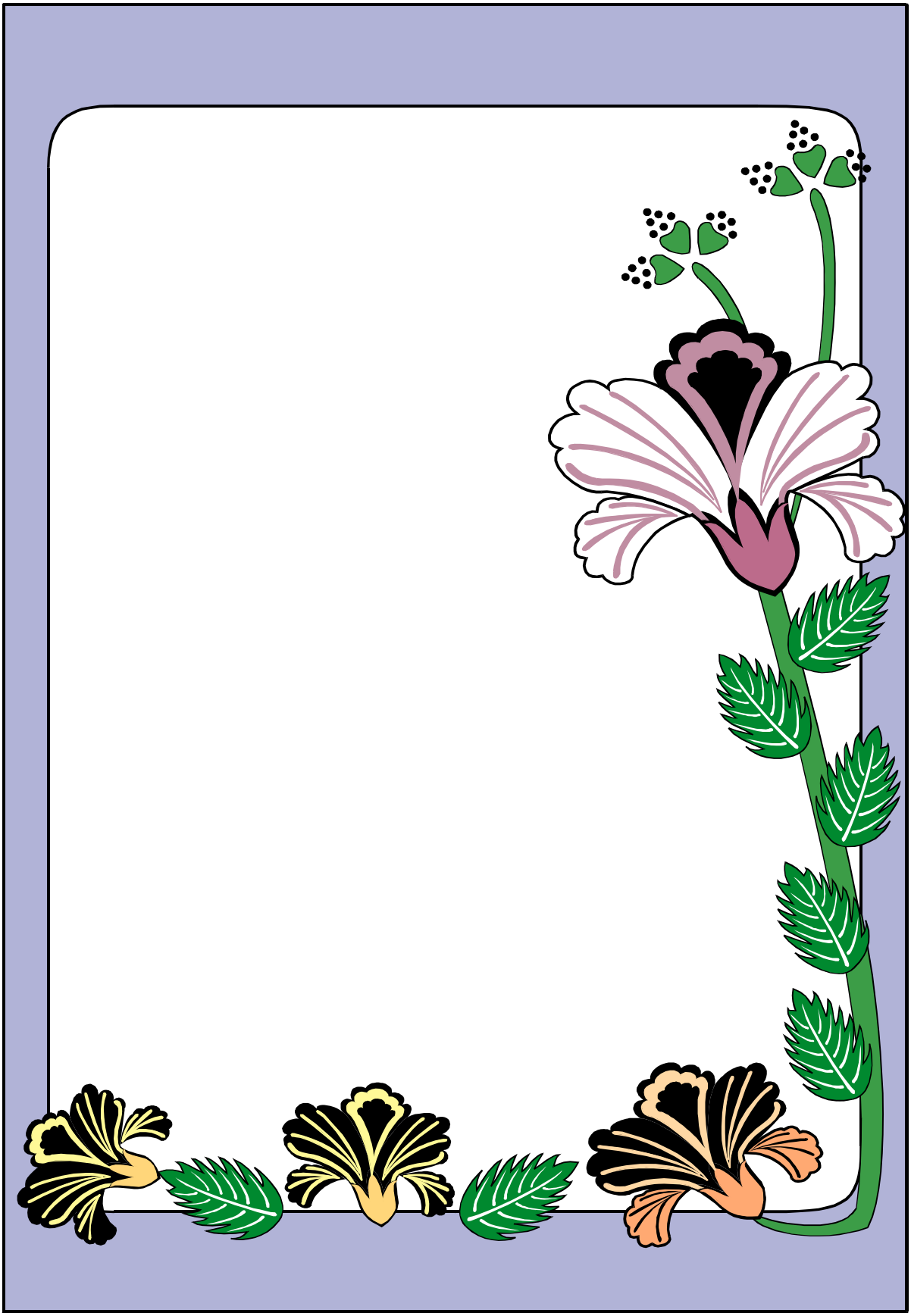
IN

CHEMISTRY

C. RAMESH KUMAR

Chemical Engineering and Process Development Division
National Chemical Laboratory
Pune-411008, INDIA

September 2007



NATIONAL CHEMICAL LABOATORY
Dr. A. Sudalai
Scientist
Chemical Engineering & Process Development Division,
Pune – 411 008, India
Phone (O) : 0091-20-25902174, Fax: 0091-20-25902676,
e-mail: a.sudalai@ncl.res.in

CERTIFICATE

Certified that the work incorporated in the thesis entitled "**Asymmetric Synthesis of Bioactive Molecules and Catalysis by Novel Palladium Complexes in C-C Bond Formation**" 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.

September 2007 **(Dr. A. Sudalai)**

Pune Research Supervisor

NATIONAL CHEMICAL LABORATORY

DECLARATION

I here by declare that the thesis entitled **"Asymmetric Synthesis of Bioactive Molecules and Catalysis by Novel Palladium Complexes in C-C Bond Formation"** submitted for the degree of Doctor of Philosophy in Chemistry to the University of Pune, has not been submitted by me to any other university or institution. This work was carried out at the National Chemical Laboratory, Pune, India.

September 2007
Pune

C. Ramesh Kumar
CE & PD Division
National Chemical Laboratory
Dr. Homi Bhabha Road
Pune – 411 008 INDIA.

CONTENTS

ACKNOWLEDGEMENT

I wish to express my sincere gratitude towards my research guide, Dr. A. Sudalai, I will be always obliged to him for his suggestions, criticisms and constant encouragement. I sincerely thank him for his splendid guidance, constant support, inspiration and personal freedom rendered to me during my research period. His endless enthusiasm and receptive attitude will always remain a source of inspiration for me.

I thank Dr. B. D. Kulkarni, Deputy Director and Head, CE-PD division, for his help and support. My special thanks go to Dr. S. Gurunath for his constant encouragement and moral support. I am immensely thankful to my seniors Drs. Milind, Gajanan, Vinay, Iliyas and Abhimanyu for useful training in the initial phase of my career which made me what I am today. I would like thank my teachers Mr. B. Venkatramani, Mr. R. Sarangapani, Dr. V. Ramalingam, Mr. Vasikaran Williams, Mr. Jekar Cellaraj and Dr. T. Venkatachalam for teaching me discipline in life along with science.

I am very thankful to Dr. Kulkarni for her help in the GCMS analysis. I am also thankful to Dr. Chavan for his help in the HPLC analysis. I thank NMR group and CMC group for their help in obtaining the analytical data. I thank PD office staff Mr. Bhosale, Mrs. Puranik and Mr. Kakade for their cooperation. It's my privilege to thank the Director, NCL for giving me this opportunity and providing all necessary infrastructure and facilities. Financial assistance from CSIR, New Delhi is greatly acknowledged.

I wish to thank my friendly and cooperative lab mates Drs. Sivakumar, Srinu and Shriram, Arun, Victor, Pandu, Emmanuvel, Tanveer, Shyla, Santhosh, Gajanan, Kuppu swamy, Sawant, Asif, Sudhir, Ravi, Ramachandra, Deepak, Nana, Balaji, Prakash, Bharat, Mohan, Amol, Vijay, Hari, Satish, Santosh, Shaheen, Deepali, Payal, Shobhana, Divya, Vandana, Vaishali, Sheema, Geetanjali, Alka, Sheetal, Rohini, Ram prakash, Shanmuga vel, Arvind, Balamurugan, Rubas, Paramasivam, Rakesh, Sandeep, Raja, Mudasir, Baba and Ruchi for providing a cheerful atmosphere in the lab.

I am deeply indebted to my friends at NCL, Drs Murugan, Pasupathy, Krishnaswamy, Sivappa, Shankar, Mangaleswar, Easwar, Subbu, Jayanthi, Selvakannan, Vijayaraj, Suresh, Thiru, Chidambaram, Venketesh and B. Senthil Kumar, Malli, Elango, Mari, Sasi, Sachin, Ramesh, Jitan, Francis, Ramanujam, Pradeep, Dharmaraja, Kannan,

Baag, Amol, Bala, Kesari, Murali, Venkat, Shankar, Murugan, Kishore, Viji, Kaja, Selva, Nagaraj, vijay and sunil.

I am greatly indebted to my friend Dr. Radha Krishnan. My special thanks go to friends, Gopi, Praveen, Maheswari, Bhuvana, Suresh, Anandamurugan, Anandaraj, Vinitha, Prem, Vijay, Muthu, Thiyagu, Nanadagopal, Sivabalan, Anniappan, Jadav, Patil, Jaya and Mari for making Home away from Home.

Without understanding what I am doing, my beloved parents have supported me through out my career with lots of patience. I am indeed very grateful to them whose constant love, care, support and encouragement have been the main force and motivation so far and will continue so in the days to come. The best wishes of my brother Suresh, sister Anusha have made me what I am and I owe much to them.

I wish to thank great scientific community whose achievements are constant source of inspiration for me. I appreciate the efforts of all those authors and directors whose books and movies were entertaining, inspiring and enlightening.

Finally, I thank God Almighty for His enormous blessings.

ABBREVATIONS

Ac	Acetyl
Ar	Aryl
Bn	Benzyl
n-Bu	n-Butyl
n-BuLi	n-Butyl Lithium
CAN	Cerric ammonium nitrate
Cbz	Benzyloxy carbonyl
CH_2Cl_2	Methylene chloride
$CHCl_3$	Chloroform
CH_3CN	Acetonitrile
$CuSO_4$	Copper(II) sulfate
DBAD	Dibenzyl azodicarboxylate
DBU	1,8-Diazabicyclo[5.4.0]undecene-7
DIBAL-H	Diisobutyl alulinum hydride
DET	Diethyl Tartarate
DMF	Dimethyl formamide
DMSO	Dimethyl sulphoxide
DMAP	N,N-dimethyl-4-aminopyridine
ee	Enantiomeric excess
Et	Ethyl
Et_3N	Triethylamine
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
EtOH	Ethyl alcohol
g	Grams
h	Hours
HCl	Hydrochloric acid
HPLC	High pressure liquid chromatography
H_2SO_4	Sulfuric acid
IR	Infra red
IBX	2-Iodoxybenzoic acid
K_2CO_3	Potassium carbonate
KOH	Potassium hydroxide
$LiAlH_4$	Lithium aluminum hydride
LDA	Lithium diisopropyl amide
M+	Molecular ion
Me	Methyl
MeOH	Methyl alcohol
min	Minutes
mL	Milliliter
mp	Melting point
MS	Mass spectrum
Ms	Mesyl
$NaBH_4$	Sodium borohydride

$NaHCO_3$	Sodium bicarbonate
NaOH	Sodium hydroxide
Na_2SO_4	Sodium sulfate
NH_4Cl	Ammonium chloride
NH_4OH	Ammonium hydroxide
NIS	*N*-iodosuccinimide
NMR	Nuclear Magnetic Resonance
NMO	*N*-Methyl morpholine *N*-oxide
Pd/C	Palladium on activated charcoal
Pet. ether	Petroleum ether
Ph	Phenyl
p-TSA	*p*-Toluene sulfonic acid
PhNO	Nitrosobenzene
Py	Pyridine
TBS	*tert*-Butyldimethylsilyl
TBHP	*tert*-Butyl hydroperoxide
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TBAF	Tetrabutylammonium fluoride
TBDMSCl	*tert*-Butyldimethylsilyl chloride
TBDPSCl	*tert*-Butyldiphenylsilyl chloride
TFA	Trifluoroacetic acid
TMSCN	Trimethylsilyl cyanide
Ts	Tosyl

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 °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 aluminum plates coated with silica gel (5-25 m) 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 Brucker FT AC-200 and MSL-300 MHz instruments using TMS as an internal standard. The following abbreviations were used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, brs = broad singlet, dd = doublet of doublet, dt = doublet of triplet and ddd = doublet of 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 °C using sodium D light.

10. HPLC analyses were performed on Waters Alliance separation module-2695; equipped with 2487 UV-Visible detector.

11. All melting points and boiling points are uncorrected and the temperatures are in centigrade scale.

12. Elemental analysis was done on Carlo ERBA EA 110B instrument.

13. The compounds, scheme and reference numbers given in each chapter refers to that particular chapter only.

14. L-proline, D-proline, DL-proline, DBAD, DBU were purchased from Aldrich

ABSTRACT

The thesis entitled "**Asymmetric Synthesis of Bioactive Molecules and Catalysis by Novel Palladium Complexes in C-C Bond Formation**" is divided into four chapters.

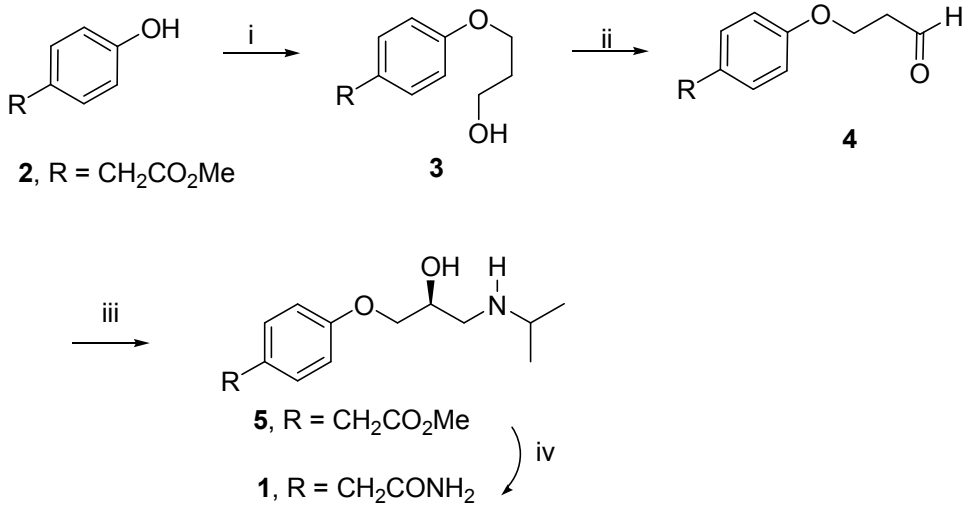
The title of the thesis clearly reflects the objective, which is to synthesize enantiomerically pure bioactive molecules and to interface synthetic organic chemistry for the development of new synthetic methodologies. **Chapter 1** presents the enantioselective synthesis of several *β*-adrenenergic blockers namely (*S*)-atenolol (**1**), (*S*)-celiprolol (**8**), (*S*)-sotalol (**18**) and (*R*)-nifenalol **(19)** *via* proline-catalyzed *α*-aminooxylation of the corresponding aldehydes as well as cobalt-catalyzed kinetic resolution of racemic epoxides. **Chapter 2** deals with enantioselective synthesis of two antifungal agents, namely miconazole (**27**) and ketoconazole (**28**) *via* cobalt-catalyzed hydrolytic kinetic resolution of epoxides. **Chapter 3** describes the enantioselective synthesis of L-DOPA (**42**) and formal synthesis of levoflaoxacin (**47**) *via* proline-catalyzed *α*-amination of aldehydes. **Chapter 4** presents the synthesis of novel water soluble palladium complexes and their applications in the synthesis of non-steroidal anti-inflammatory drugs and cinacalcet (**74**). This chapter also presents the cobalt-catalyzed chemoselective transfer hydrogenation of carbonyl and nitro compounds using 2-propanol as hydrogen source.

CHAPTER 1

Asymmetric Synthesis of *β*-Adrenergic Blockers *via* Kinetic Resolution of Epoxides and Proline-catalyzed *α*-Aminooxylation of Aldehydes

In recent years, organocatalysis is gaining importance in asymmetric synthesis, complementing bio-and metal-catalysis. Particularly, proline, an abundant, inexpensive

amino acid available in both enantiomeric forms, has emerged as arguably the most practical and versatile organocatalyst for α-functionalization of carbonyl compounds.[1] *β*-Adrenergic blocking agents (*β*-blockers) are important drugs, widely used for the treatment of hypertension and angina pectoris.[2] Generally, the (*S*)-isomers are known to be much more effective (50-500 fold) than the (*R*)-isomers, which often possess toxicity. Hence, the administration of optically pure (*S*)-isomers are highly desirable. This chapter describes the asymmetric synthesis of four *β*-blockers namely (*S*)-atenolol (**1**), (*S*)-celiprolol (**8**), (*S*)-sotalol (**18**) and (*R*)-nifenalol (**19**).

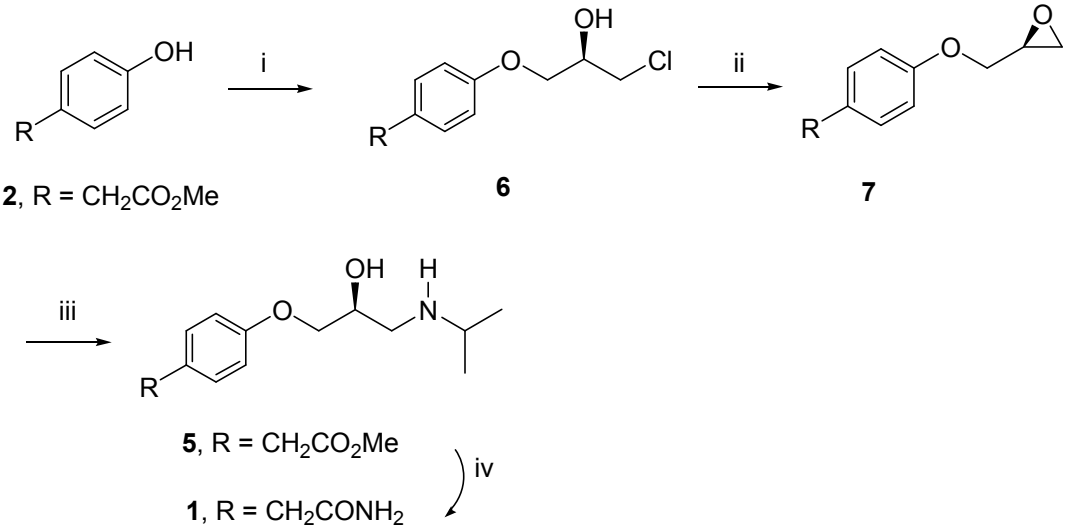


Scheme 1: (i) 3-bromopropan-1-ol, K_2CO_3, acetone, 75 °C, 80%; (ii) IBX, DMSO, 25 °C, 78%; (iii) (a) L-proline, CH_3CN, PhNO, -20 °C, 24 h; (b) isopropylamine; iii) 10% Pd/C, H_2 (1 atm.), 25 °C, CH_3OH, 68%, 94% ee; (iv) NH_4OH, CH_3OH, 25 °C, 72 %, 94% ee.

(i) (*S*)-Atenolol: The asymmetric synthesis of (*S*)-atenolol (**1**) was achieved in 4 steps starting from phenolic ester **2**. Thus, phenol **2** was *O*-alkylated with 3-bromopropan-1-ol to afford the corresponding alcohol **3**, which was readily oxidized using IBX to give aldehyde **4** in 78% yield. Aldehyde **4** was readily transformed into chiral amino alcohol **5** in an one-pot procedure by carrying out proline-catalyzed *α*-aminooxylation strategy using nitrosobenzene followed by reductive amination using catalytic hydrogenation.

Ammonolysis of ester **5** afforded (*S*)-atenolol (**1**) in 94% ee with 30.6% overall yield (**Scheme 1)**.

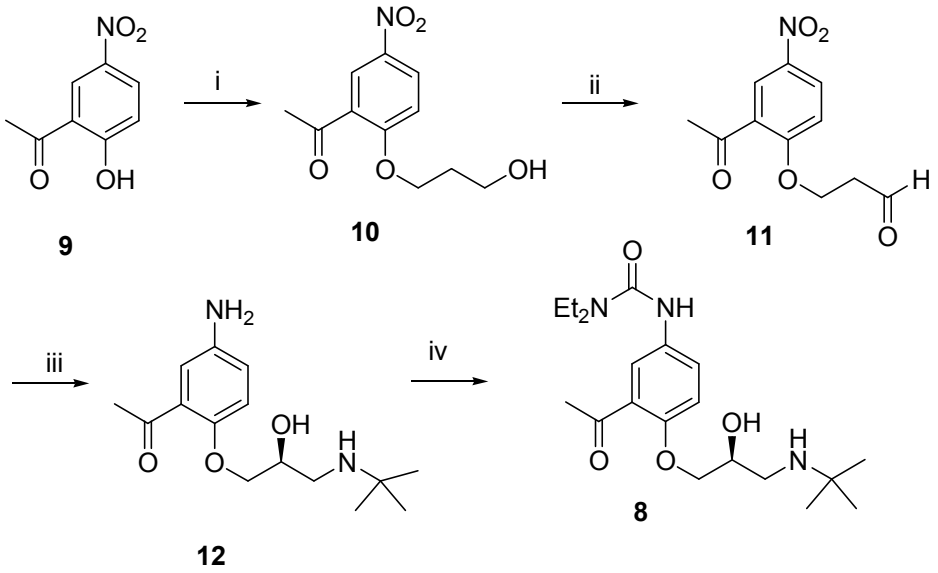
The low ee (94%) as well as low overall yield of this route prompted us to use the cobalt-catalyzed kinetic resolution of commercially available (±)-epichlorohydrin with phenol **2** as the nucleophile.[3] Thus, (±)-epichlorohydrin was subjected to asymmetric kinetic resolution using *(R,R)*-(salen)Co.$OCOCF_3$ to give the corresponding chloro alcohol **6** in 98% ee. Chloro alcohol **6** was converted into epoxide **7**, which underwent regiospecific ring opening with isopropylamine to give amino alcohol **5** in 90% yield with 98% ee. Ammonolysis of ester **5** afforded (*S*)-atenolol (**1**) in 98% *ee* with 45.4% overall yield (**Scheme 2**).



Scheme 2: (i) Epichlorohydrin, (*R,R*)-Co(salen).$OCOCF_3$, 25 °C, 24 h, 87%. (ii) K^{t}OBu, THF, 0 °C, 93%, 98% ee; (iii) isopropylamine, H_2O, 25 °C, 78%, 98% ee; (iv) NH_4OH, CH_3OH, 25 °C, 72%, 98% ee.

(ii) (*S*)-Celiprolol: The enantioselective synthesis of (*S*)-celiprolol (**8**) was achieved in 4 steps starting from phenol **9**. *O*-Alkylation of phenol **9** with 3-bromopropan-1-ol and oxidation of the resulting alcohol **10** with IBX gave aldehyde **11** in 65% yield. Aldehyde **11** was transformed into chiral amino alcohol **12** in an one-pot procedure by carrying out

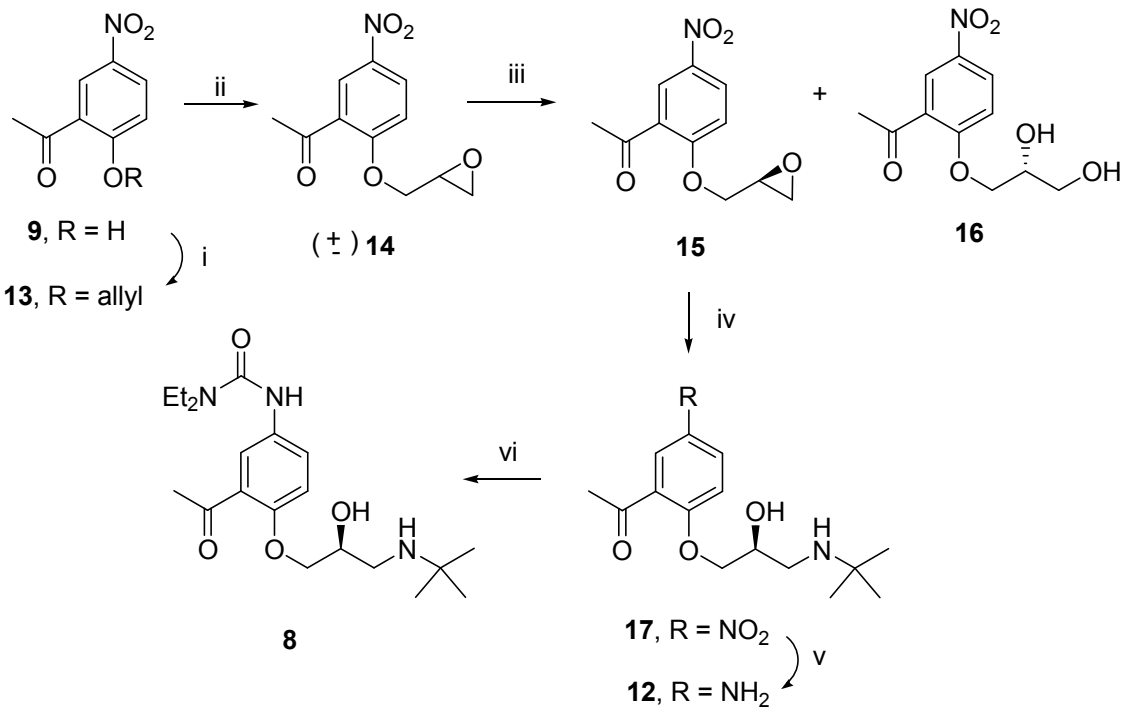
L-proline catalyzed α-aminooxylation using nitrosobenzene followed by reductive amination using catalytic hydrogenation. Selective *N*-acylation of anilinic function was achieved using *N,N'*-diethylcarbamoyl chloride to furnish (*S*)-celiprolol (**8**) in 22.3% over all yield with 88% ee (**Scheme 3**).



Scheme 3: (i) 3-bromopropan-1-ol, K_2CO_3, acetone, 75 °C, 68%; (ii) IBX, DMSO, 25 °C, 65%; (iii) (a) L-proline, CH_3CN, PhNO, -20 °C, 24 h; (b) *t*-butylamine; (iii) 10% Pd/C, H_2 (20 psig), 25 °C, CH_3OH, 56%, 88% ee. (iv) DECC, Et_3N, THF, 40 °C, 48 h, 90%, 88% ee.

To enhance the ee and overall yield, the enantioselective synthesis of (*S*)-celiprolol (**8**) was undertaken using cobalt-catalyzed hydrolytic kinetic resolution of racemic epoxide **14.** The hydrolytic kinetic resolution (HKR) of terminal epoxides catalyzed by chiral (*R,R*)(salen) Co(III).OAc afforded both recovered unreacted epoxide and 1,2-diol product in highly enantioenriched form.[4] Racemic epoxide **14**, prepared from allyl ether **13**, was subjected to hydrolytic kinetic resolution using (*R,R*)-Co(Salen).OAc with 0.55 equivalent of water to produce chiral epoxide **15** in 45% yield and 95 % ee along with its diol 3**2** in 49% yield and 92% ee. Regiospecific ring opening of epoxide **15** with *t*-butylamine gave amino alcohol **17** in 86% yield, which was converted into (*S*)-celiprolol

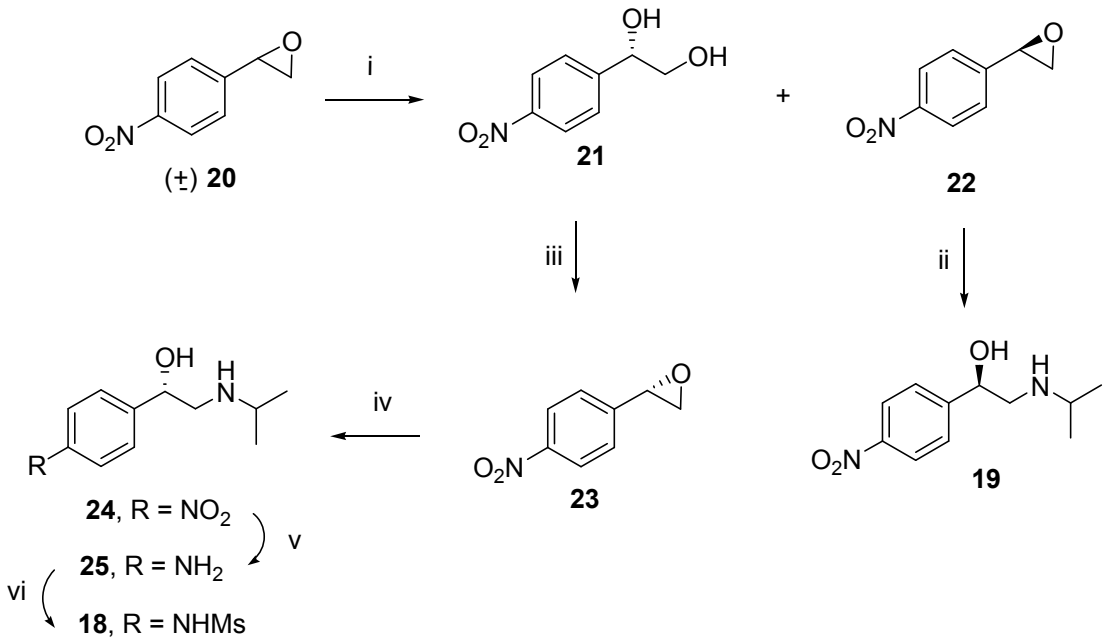
(**8**) in 2 steps, namely reduction of nitro functionality to amine followed by *N*-acylation of anilinic function using *N, N'*- diethylcarbamoyl chloride to furnish (*S*)-celiprolol (**8**) (**Scheme 4**).



Scheme 4: (i) allyl bromide, K_2CO_3, acetone, 75 °C, 96%; (ii) *m*-CPBA, $CHCl_3$, 25 °C, 95%; (iii) (*R,R*)-Co(salen).OAc, H_2O (0.55 equiv.), THF, 0 °C, (45% yield and 95% ee for **15** and 49% yield and 92% ee for **16**); (iv) *tert*-butylamine, H_2O, 25 °C, 86%, (v) 10% Pd/C, H_2(20 psig), CH_3OH, 25 °C, 92%. (iv) DECC, Et_3N, THF, 40 °C, 48 h, 90%, 95% ee.

(iii) (*S*)-Sotalol and (*R*)-Nifenalol: Finally, the synthesis of two *β*-blockers (*S*)-sotalol (**18**) and (*R*)-nifenalol (**19**) were also undertaken by using cobalt-catalyzed hydrolytic kinetic resolution approach. Thus, racemic epoxide **20** was subjected to hydrolytic kinetic resolution catalyzed by (*R,R*)-Co(salen).OAc to afford chiral epoxide **22** in 45% yield and 96% ee along with its diol **21** in 49% yield and 93% ee. Nucleophilic ring opening of epoxide **22** with isopropylamine furnished (*R*)-nifenalol (**19**) in 89% yield with 96% ee. Diol **21** was transformed into epoxide **23**, which was subjected to nucleophilic ring

opening with isopropylamine to give amino alcohol **24** in 89% yield. Finally, amino alcohol **24** was transformed into (*S*)-sotalol (**18**) with 93% ee in two steps of reduction of nitro functionality to amine group followed by *N*-mesylation with methanesulfonyl chloride (**Scheme 5**).



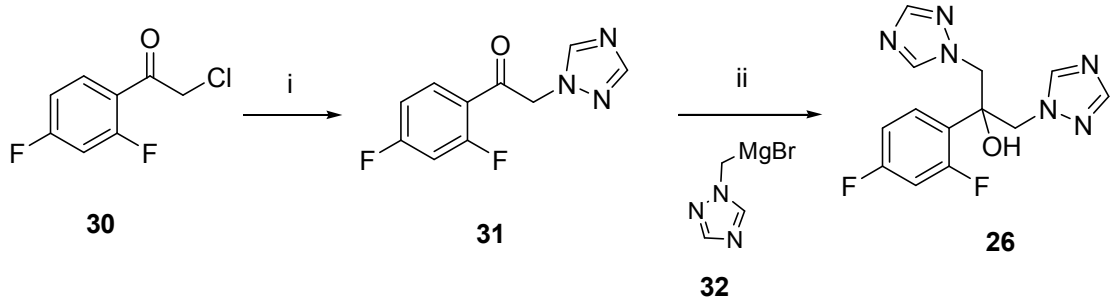
Scheme 5: (i) (*R,R*)-Co(salen).OAc, H_2O (0.5 equiv.), 25 °C, 24 h, (45% yield, 96% ee for **22** and 49% yield, 93% ee for **21**); (ii) isopropylamine, H_2O, 25 °C, 85%, 96% ee; (iii) DIAD, PPh_3, benzene, reflux, 78%; (iv) isopropylamine, H_2O, 25 °C, 89%, 93% ee; (v) 10% Pd/C, H_2(20 psig), CH_3OH, 25 °C, 92%, (vi) MsCl, pyridine, 25 °C, 72%, 93% ee.

CHAPTER 2

Asymmetric Synthesis of Antifungal Agents *via* Hydrolytic Kinetic Resolution of epoxides

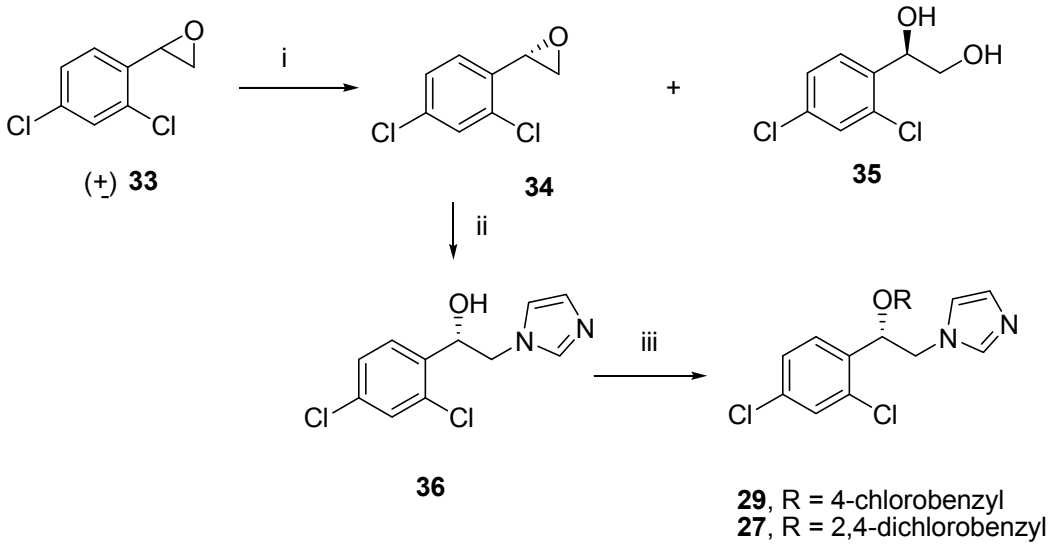
Fluconazole (**26**), miconazole (**27**), ketoconazole (**28**) are widely used for the treatment of fungal diseases.[5] In this chapter, we have employed hydrolytic kinetic resolution of terminal epoxides as a key step for the synthesis of these antifungal agents.

Firstly, fluconazole (**26**) was synthesized in 2 steps starting from phenacyl chloride **30**. Ketone **31** was readily prepared by condensation of triazole with **30**. Grignard reagent **32**, prepared from the corresponding 1-(bromomethyl)-1*H*-1,2,4-triazole, was reacted with ketone **31** to afford fluconazole(**26**) in 85% yield (**Scheme 6**).



Scheme 6: (i) 1,2,4-triazole, K_2CO_3, CH_3CN, 65 °C, 88%; (b) **32**, THF, -40 °C, 85%;

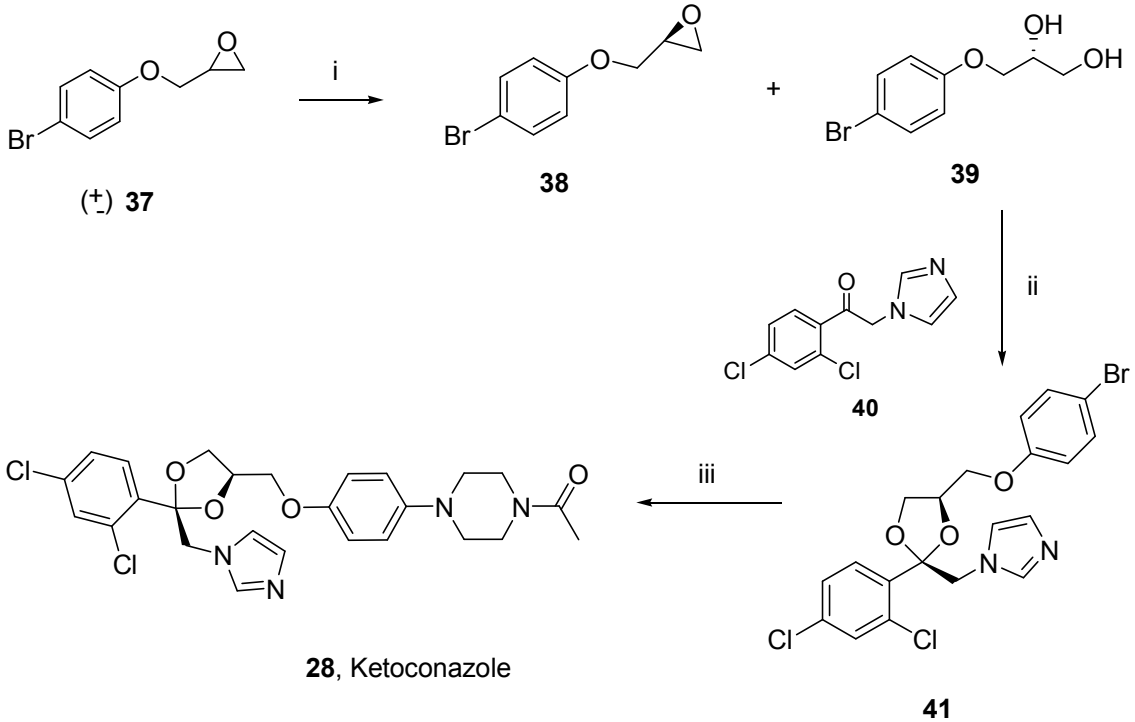
Secondly, enantioselective synthesis of myconazole (**27**) and econazole (**29**) were achieved in 3 steps utilizing cobalt-catalyzed hydrolytic kinetic resolution of epoxide **33**.



Scheme 7: (i) (S,*S*)-Co(salen).OAc, H_2O (0.55 equiv.), 0 °C, 24 h, (46 %, 96% ee for **34** and 49% yield, 93% ee for **35)**; (ii) imidazole, reflux, EtOH, 88%, 96% ee; (iii) NaH, DMF, 2, 4-dichlorobenzyl bromide, 25 °C, 78%; (iii) NaH, DMF, 4-chlorobenzyl bromide, 25 °C, 73%.

Thus, the racemic epoxide **33** was subjected to hydrolytic kinetic resolution using (*S,S*)-Co(salen).OAc to afford chiral epoxide **34** in 46% yield and 96% ee along with its diol **35** in 49% yield and 93% ee. Subsequently, the regiospecific ring opening of epoxide **35** with imidazole afforded aminoalcohol **36**, which was *O*-alkylated with the corresponding substituted benzyl bromide to afford miconazole (**43**) and econazole (**45**) in 24.7% and 23.1% overall yields respectively (**Scheme 7**).

Finally, synthesis of ketoconazole (**28**) was achieved in 3 steps utilizing kinetic resolution of epoxide **37** using water as nucleophile. Thus, the racemic epoxide **37**, was subjected to hydrolytic kinetic resolution using (*R,R*) Co (salen).OAc to afford chiral epoxide **38** in 48% yield along with its diol **39** in 42% yield. The resulting diol **39** was protected as its ketal derivative **41** with ketone **40.** Finally, copper-catalyzed amination of **41** with *N*-acetylpiperazine afforded ketoconazole (**28**) in 78% yield (**Scheme 8)**.



Scheme 8: (i) (*S,S*)-Co(Salen).OAc, H_2O (0.45 equiv.), 0 °C, 24 h, 48%, 93% ee for **38**, 42%, 96% ee for **39**; (ii) *p*TSA, benzene, 110 °C, 82%. (iii) *N*-acylpiperazine, CuI, Cs_2CO_3, DMF, 150 °C,

78%.

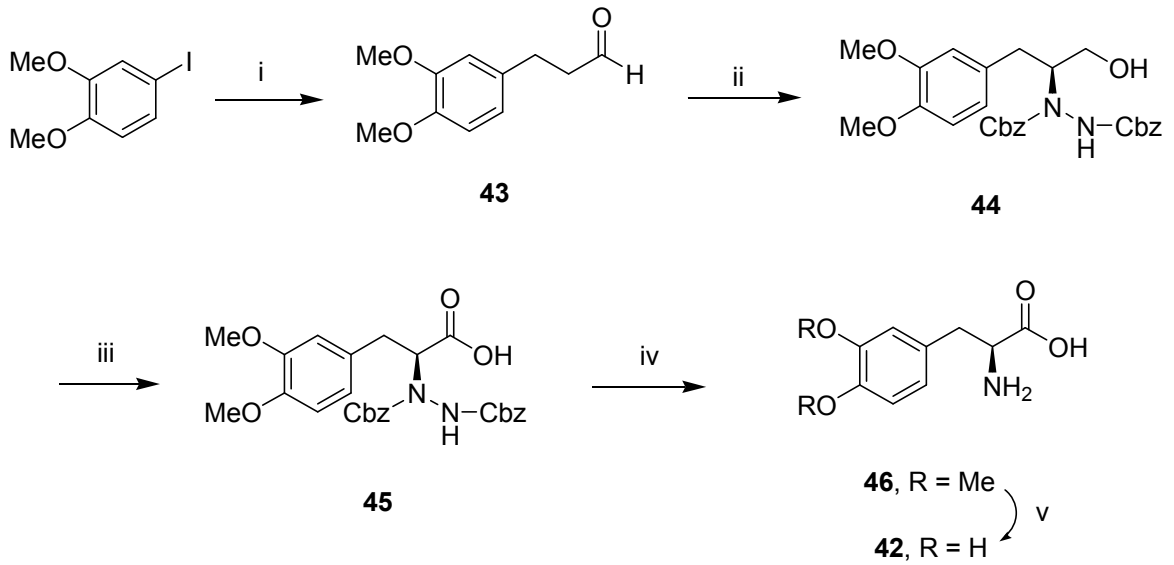
CHAPTER 3

Asymmetric Synthesis of L-DOPA and Formal Synthesis of Levofloxacin using Proline-Catalyzed *α*-Functionalization of Aldehydes

This chapter describes proline-catalyzed *α*-functionalization strategy for the enantioselective synthesis of L-DOPA (**42**) and formal synthesis of levofloxacin (**47)**.

SECTION 1: Enantioselective Synthesis of L-DOPA *via* Proline-Catalyzed *α*-Amination of Aldehyde

L-DOPA (**42**) is one of the principal drugs administered to patients with Parkinson's disease since 1967.[6] This section describes the enantioselective synthesis of L-DOPA *via* D-proline-catalyzed α-amination of 3-(3,4-dimethoxyphenyl)propanal (**43**).

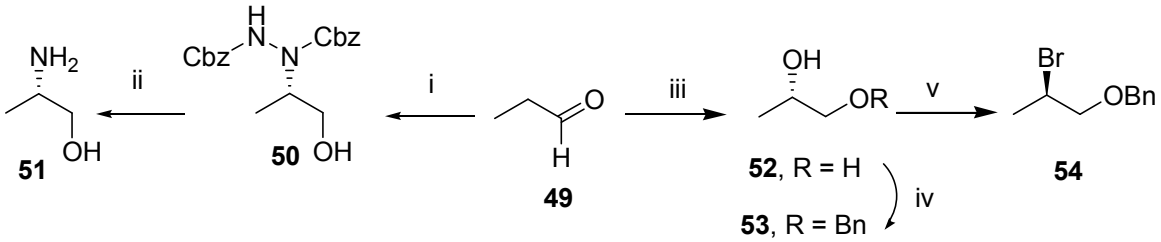


Scheme 9: (i) allyl alcohol, $Pd_2(dba)_3$, $P(cy)_3$, K_2CO_3, DMF, 100 ºC, 86%; (ii) dibenzyl azodicarboxylate , D-proline (10 mol%), CH_3CN, 0-25 ºC, 3 h then $NaBH_4$, EtOH, 62%; (iii) $NaClO_2$, NaClO, TEMPO, CH_3CN, phosphate buffer, 25 °C, 78%; (iv) H_2 (70 psig), Raney-nickel, MeOH, AcOH, 25 °C; (v) BBr_3, CH_2Cl_2, 0 ºC, 58%, 94% ee.

Thus, 4-iodo-1,2-dimethoxybenzene, prepared readily by the iodination[7] of 1,2-dimethoxybenzene, was arylated with allylic alcohol using Pd-catalyst to produce aldehyde **43** in 86% yield. Aldehyde **43** was then subjected to *α*-amination catalyzed by D-proline using dibenzyl azodicarboxylate as the amine source, followed by its *in situ* reduction with $NaBH_4$ gave the protected amino alcohol **44** in 62% yield. Mild oxidation of alcohol **44** was carried out with $NaClO_2$, NaOCl, 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) to produce the corresponding diazo acid **45**, which was then subjected to reduction [H_2 (70 psig), Raney Ni] to give amino acid **46**, followed by demethylation of **46** using BBr_3 afforded L-DOPA (**42**) in 78% yield (**Scheme 9**).

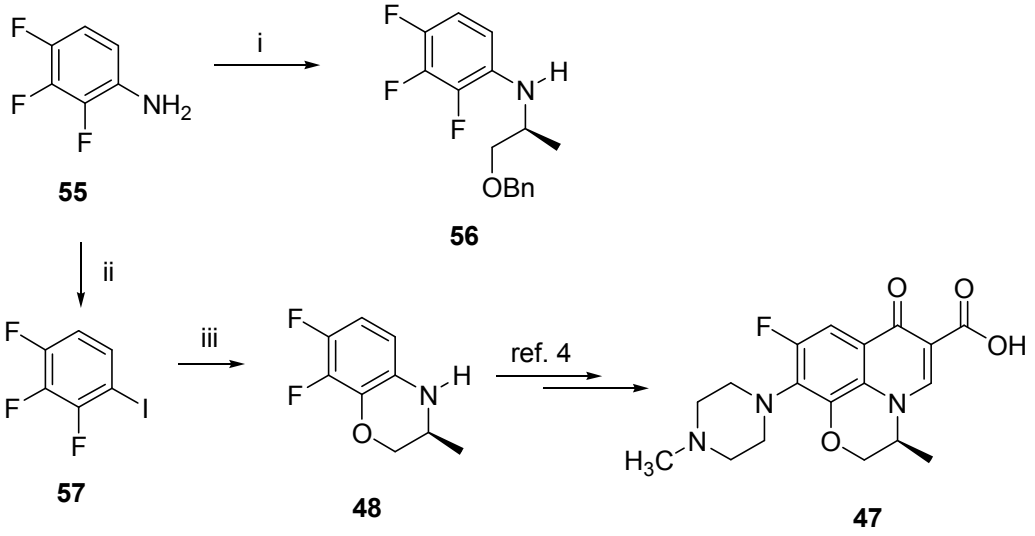
SECTION 2: Formal Synthesis of Levofloxacin *via* Proline- Catalyzed *α*-Amination and α-aminooxylation of Aldehydes

Levofloxacin (**47**) is a potent antibacterial agent that exhibits potent activity against both gram-negative and gram-positive bacteria.[8] This section describes the enantioselective synthesis of the key intermediate benzoxazine **48** *via* proline-catalyzed α-amination and α-aminooxylation of 1-propanal. We envisaged compounds **51** and **54** to be the key chiral intermediates for the synthesis of levofloxacin (**47**).



Scheme 10: (i) Dibenzyl azodicarboxylate, D-proline (10 mol%), CH_3CN, 0-20 ºC, 3 h then $NaBH_4$, EtOH, 92%; (ii) H_2 (70 psig), Raney-nickel, MeOH, AcOH, 25 °C, 70%, 96% ee; (iii) (a) PhNO, D-proline (25 mol%), CH_3CN, -20 ºC, 24 h then MeOH, $NaBH_4$, 85%; (b) H_2 (1atm.), 10% Pd/C, MeOH, 25 °C, 12 h, 90%, 98% ee; (iv) Bu_2SnO, toluene, reflux, 12 h then Bu_4NBr, BnBr, reflux, 24 h, 93%; (v) PPh_3, CBr_4, imidazole, CH_2Cl_2, 25 °C, 96%.

Thus, 1-propanal was subjected to D-proline-catalyzed α-amination using dibenzyl azodicarboxylate as the amine source followed by its subsequent reduction with $NaBH_4$ to give the protected amino alcohol **50** in 92% yield. Catalytic hydrogenation of **50** using Raney Ni, H_2 (70 psig) produced (*S*)-2-aminopropan-1-ol (**51**) in 70% yield and 96% ee. Similarly, D-proline-catalyzed α-aminooxylation of 1-propanal followed by its reduction with $NaBH_4$ gave diol **52** in 85% yield. Selective protection of the primary alcohol in diol **52** followed by the conversion of secondary alcohol to bromo derivative **53** with CBr_4 and PPh_3 afforded **54** in 96% yield (**Scheme 10**). Having obtained chiral intermediates **51** and **54** in high enantiopurity, in the first approach synthesis of **56** was achieved using copper-catalyzed amination of iodo-compound **57** with amino alcohol **51** in two steps.



Scheme 11: (i) **54**, NaH, DMF, 135 °C, 79%; (ii) Conc. HCl, $NaNO_2$, HCl, KI, 76%; (iii) (a) **51**, CuI, Cs_2CO_3, DMF, 25 °C, 88%; (b) KOH, THF, 70 ºC, 64%, 97% ee.

Thus, 1,2,3-trifluoro-4-iodobenzene (**57**), prepared by diazotization of aniline **55** followed by iodide displacement of diazonium ion, was subjected to copper-catalyzed amination with (*S*)-2-aminopropan-1-ol (**51**) to give (*S*)-7,8-difluoro-2,3-dihydro-3-

methyl-4*H*-1, 4-benzoxazine (**48**). In another route, synthesis of intermediate **15** was also achieved by *N*-alkylation of aniline **55** with bromo derivative **54** in presence of NaH, followed by removal of benzyl group by hydrogenolysis. Transformation of **48** to levofloxacin (**47**) has already been reported in six steps[8] (**Scheme 11**).

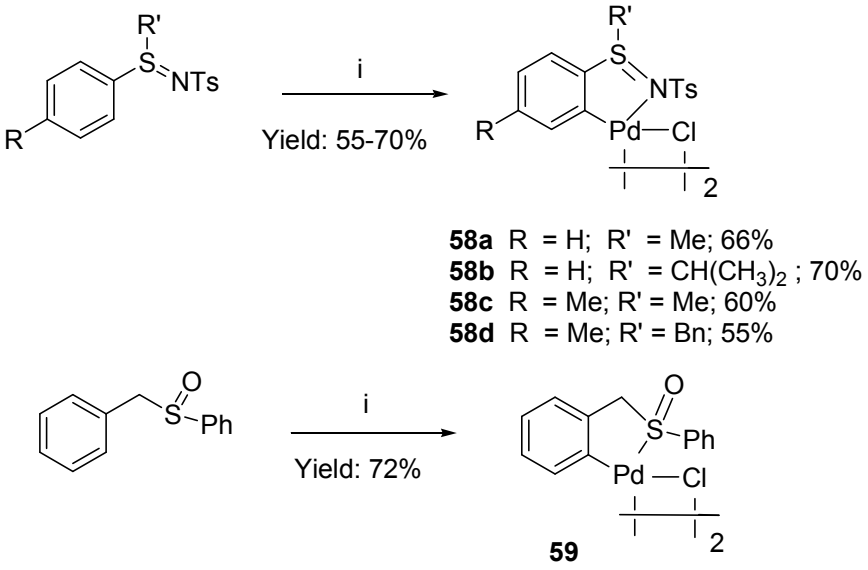
CHAPTER 4

Synthesis of Novel Transition Metal Complexes and their Applications in C-C Bond Formation

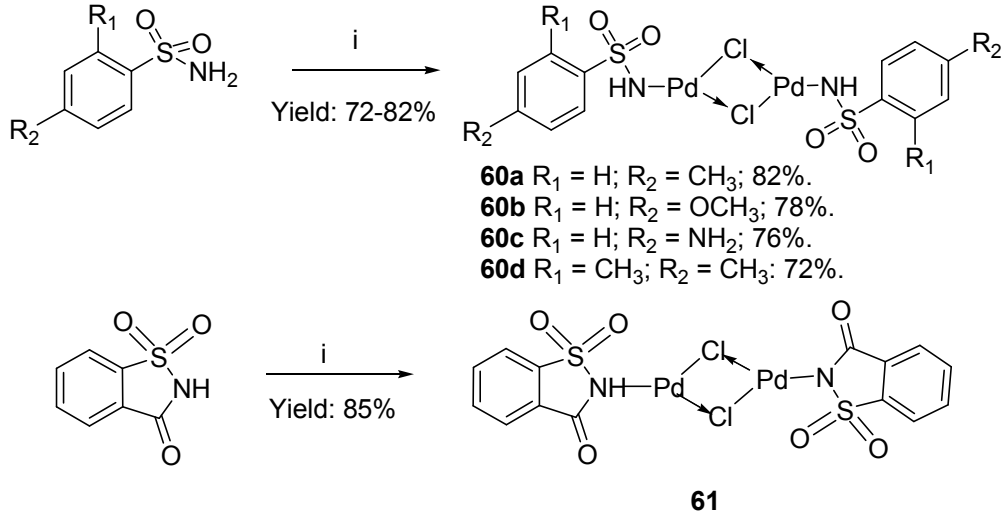
Palladium-catalyzed cross-coupling chemistry for the formation of C-C bond has recently emerged as a powerful method in organic synthesis.[9] This chapter describes the preparation of several new palladium complexes (**58-61**) and their application as efficient catalysts in the synthesis of bioactive molecules.

SECTION 1: Synthesis and Characterization of Novel Palladium Complexes and Their Catalytic Activity Studies

Palladacycles are efficient catalysts or catalyst precursors in the Pd- catalyzed C-C bond forming reactions such as Heck-Mizoroki, Suzuki-Miyaura, Sonogashira, etc. This section describes, for the first time, a novel method for the synthesis of several sulfilimine palladacycles **58a-d,** sulfoxide palladacycles **59,** *via* a carbopalladation reactions[10] (Scheme **12**) and also sulfonamide-based and water soluble saccharin-based palladium complexes **60a-d** and **61** respectively in high yields (**Scheme 13**).



Scheme 12: (i) Li_2PdCl_4, NaOAc, MeOH, 25 °C, 24 h.

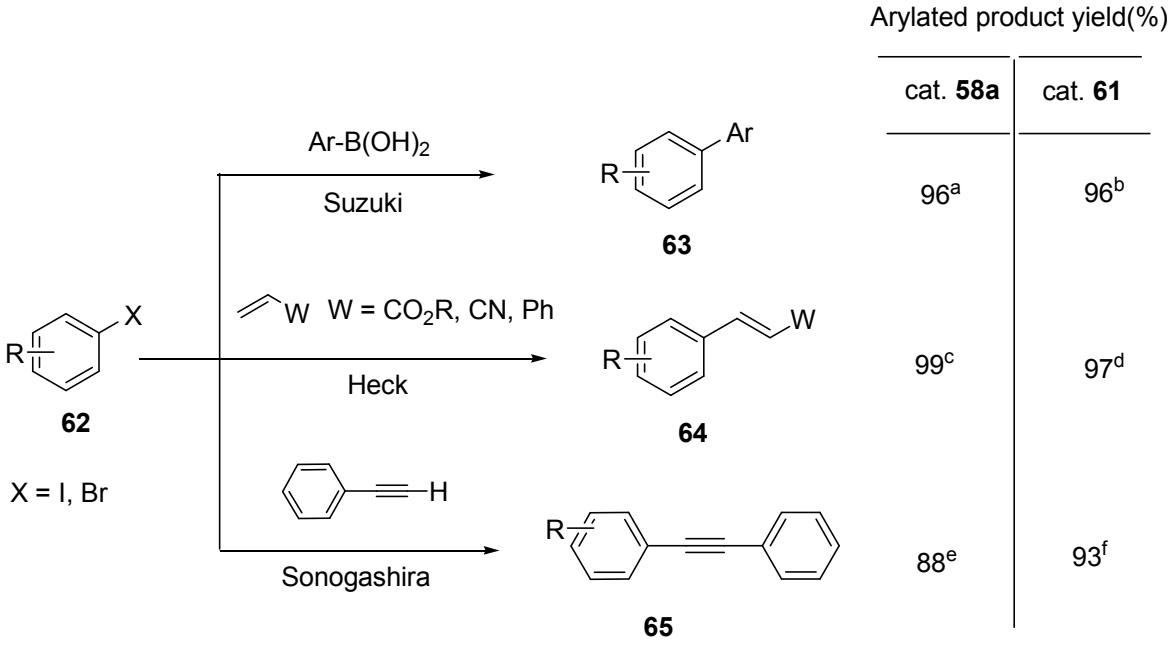


Scheme 13: (i) Li_2PdCl_4, NaOAc, MeOH, 25 °C, 24 h.

Among these sulfilimine palladacycles (**59a**) have shown to exhibit high activity for the Suzuki coupling for aryl halides (X = I, Br, Cl) with the variety of arylboronic acids to give biaryls (**63**) with a turn over number of (TON) 960. Heck arylation and vinylation of olefins with various aryl halides **62** were achieved using sulfilimine-based palladacycle **58a** in 99% with TON of 5, 94,000. Palladacycle **58a** was found to be effective catalyst

for Sonogashira reactions of phenylacetylene with aryl halides under totally copper-free conditions to give diphenylacetylene (**65**) in 88% yield with a TON of 352 (**Scheme 14**). Aqueous-phase palladium catalyzed reactions are of much interest as environmentally benign synthetic methods that would decrease the use of volatile organic solvents and simplify the catalyst recovery.[11]

Saccharin- palladium complex (**61)** is highly water soluble and has exhibited high activity for the Heck cross-coupling of aryl halides **62** with olefins in water medium to give the arylated products (**64**) in good yields with a TON of 3,72,000 (Scheme **14**).



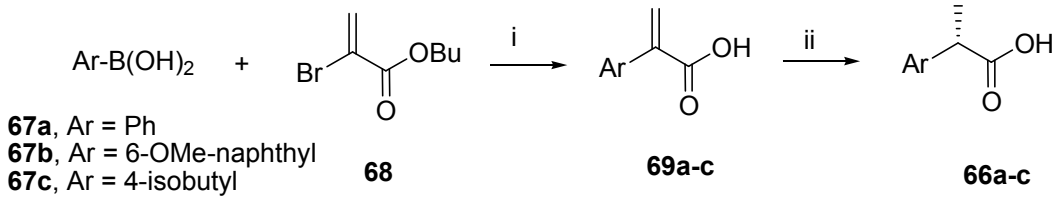
Scheme 14: a) K_2CO_3, toluene, 110 °C, 3 h. b) KOH, TBAB, H_2O, 25 °C, 3 h. c) Et_3N, NMP, 140 °C, 12 h. d) K_2CO_3, TBAB, H_2O, 100 °C, 6 h. e) Et_2NH, 80 °C, 12 h. f) KOH, TBAB, H_2O, 100 °C.

SECTION 2: Application of Saccharin Palladium Complexes in the Synthesis of Drugs

α-Arylpropionic acids (**66**) have emerged as an important class of non-steroidal anti-inflammatory agents during the past three decades.[12] This section describes the use of water soluble saccharin palladium complex **61** in the synthesis of aryl propionic acids

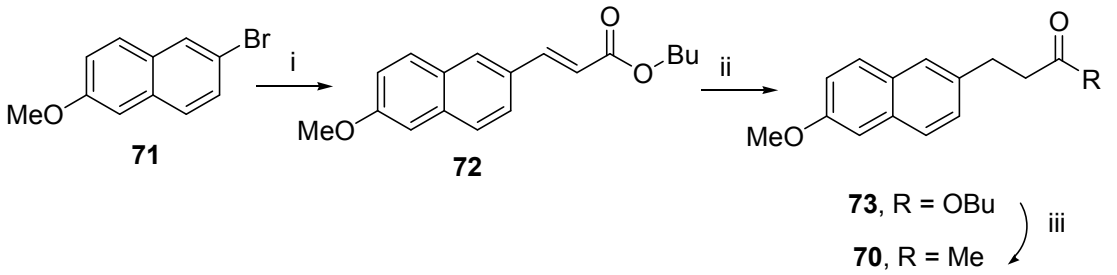
(**66a-c**), Nabumetone (**70**) and (*R*) Cinacalcet (**74**) *via* Suzuki and Heck coupling reactions respectively.

We have developed a new synthetic methodology for the synthesis of α-arylacrylic acids in good yields. Butyl-2-bromoacrylate (**68**) was prepared by the bromination of bromo acrylate followed by its dehydrobromination with base. Arylation of vinyl bromo ester **68** with arylboronic acids **67a-c** using palladium saccharin complex (**61)** gave α-arylacrylates in good yield. The key intermediates **69a-c** were obtained by the basic hydrolysis of α-arylacrylates. Finally, asymmetric reduction of unsaturated acids (**69a-c**) using [(S)-BINAP-Ru(acac)$_2$] provided (*S*)-aryl propionic acids in good yields and with high ee (**Scheme 15**).



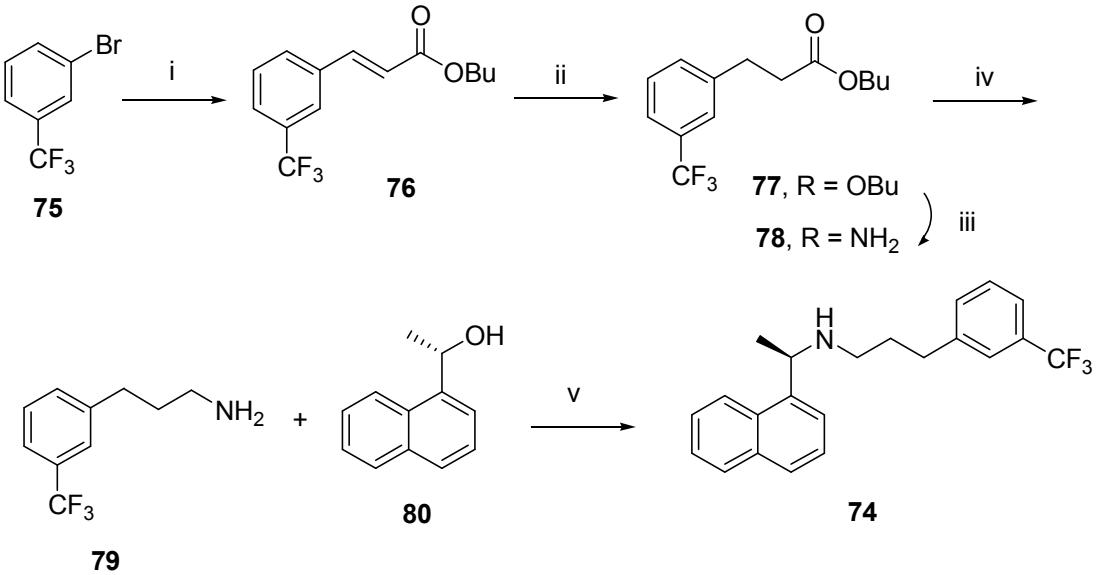
Scheme 15: (i) a) Palladium complex **61**, K_2CO_3, toluene, reflux; b) aq. KOH, reflux; (ii) [(S)-BINAP-Ru (acac)$_2$], H_2 (1000 psig), 25 °C, MeOH.

Secondly, palladium complex (**61**) was used for the Heck reaction of 2-bromo-6-methoxynaphthalene (**71**) and butyl acrylate to give unsaturated ester **72**, which is the key intermediate for the synthesis of non-steroidal anti-inflammatory drug, nabumetone (**70**)[13]. Chemoselective reduction of Heck product **72** to saturated ester **73** was achieved using $NaBH_4$ and $CoCl_2$. Finally, addition of methylmagnesium iodide on to ester provided nabumetone (**70**) in 64% yield (**Scheme 16)**.



Scheme 16: (i) Butyl acrylate, palladium complex **61**, Et_3N, NMP, 135 °C, 85%; (ii) $NaBH_4$, $CoCl_2.6H_2O$, MeOH, 25 °C, 95%; (iii) CH_3MgI, THF, 64%.

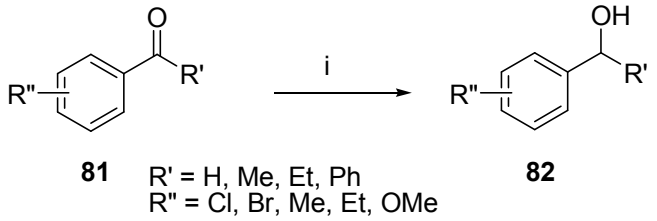
Another application is the use of palladium complex (**61**) in the synthesis of (*R*)-Cinacalcet. The Heck reaction between *m*-bromobenzotrifluoride (**75**) and butylacrylates gave unsaturated ester **76** in 95% yield. (*R*)-Cinacalcet (**74**), an oral calcimimetic,[14] was synthesized in 4 steps from unsaturated ester **76** (**Scheme 17**). Chemoselective reduction of Heck product **76** to saturated ester **77** was achieved using $NaBH_4$ and $CoCl_2$. Ammonolysis of ester **77** afforded amide **78,** which on reduction gave amine **79**. (*R*)-Cinacalcet (**74**) was then obtained by the Mitsunobu reaction of (*S*)-(-)-α-methyl-1-naphthalenemethanol (**80**) with amine **79**.



Scheme 17: (i) Butyl acrylate, palladium complex **61**, NaOAc, NMP, 135 °C, 90%; (ii) $NaBH_4$, $CoCl_2.6H_20$, MeOH, 25 °C, 95%; (iii) conc. ammonia, 24 h, 25 °C, 80%; (iv) $LiAlH_4$, THF, reflux, 2 h, 65%; (v) PPh_3, DEAD, THF, 0 °C, 82%.

SECTION 3: Cobalt Catalyzed Transfer Hydrogenation of Carbonyl Compounds using 2- Propanol as a Hydrogenation Source

Catalytic transfer hydrogenation has found wide spread application in organic synthesis.[15]



81 R' = H, Me, Et, Ph
R" = Cl, Br, Me, Et, OMe **82**

Scheme 18: (i) $CoCl(PPh_3)_3$, 2-propanol, KOH, 80 °C, 24 h.

In comparison with the catalytic reduction using molecular hydrogen, hydrogen donors such as ammonium formate, isopropyl alcohol, formic acid, and sodium formate have many advantages. This section presents $CoCl(PPh_3)_3$- catalyzed chemoselective transfer hydrogenation of carbonyl and nitro compounds in high yields using propan-2-ol as hydrogen source and KOH as co-catalyst (**Scheme 18**).

References

1. (a) Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Shoji, M. *Tetrahedron Lett.* **2003**, *44*, 8293. (b) Zhong, G. *Angew. Chem., Int. Ed. Engl*. **2003**, *42*, 4247. (c) Hayashi, Y.; Yamaguchi, J.; Sumiya, T.; Shoji, M. *Angew. Chem., Int. Ed. Engl.* **2003**, *43*, 1112.
2. (a) Barret, C.; *Brit. J. Pharmacol.* **1968**, *34*, 43. (b) Hansteen, V.; *Brit. Med. J.* **1982**, *284*, 155. (c) Fitzgerald, J. D.; in *"Pharmacology of Antihypertensive Drugs"* A. Acriabine, (Ed.), Raven Press, NY, **1980**, 195.
3. Ready, J. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 6086.
4. Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307.

5. (a) Aumaid, U.;Michael, D.; Josef, S.; Erwin, T.; *Fungal Genetics and Biology* **2005**, *42*, 719–725. (b) Heeres, J.; Backx, L. J. J.; Mostmans, J. H.; Cutsem, J. V *J. Med. Chem.* **1979***, 22*, 1003. (c) J. Heeres, J.; Hendrickx, R.; Cutsem, J. V *J. Med. Chem.* **1983***, 26*, 611.

6. Tolosa, E.; Marti, M. J.; Valldeoriola, F.; Molihuevo, J. L. *Neurology* **1995**, 50.

7. Emmanuvel, L; Shukla, R; Sudalai, A; Gurunath, S; Sivaram S. *Tetrahedron Lett*. **2006**, *47*, 4793.

8. Atarashi, S.; Yokohama, S.; Yamazaki, K.; Sakano, K.; Imamura, M.; Hayakawa, I. *Chem. Pharm. Bull.* **1987**, *35*, 1896.

9. (a) Tsuji, J. *Palladium Reagents and Catalysts;* Wiley: Chichester, **1995**; (b) Malleron, J. L.; Fiaud, J. C.; Legros, J. Y. *Handbook of Palladium-Catalysed Organic Reactions*; San Diego, **1997**; (c) *Transition Metals for Organic Synthesis*, Volumes 1 and 2; Beller, M.; Bolm, C., Eds. Wiley-VCH: Weinheim, **1998**.

10. Onoue, H.; Minami, K.; Nakagawa. K. *Bull. Chem. Soc. Jpn*. **1970**, *43*, 3480.

11. L. R. Moore**,** K. H. Shaughnessy, Org. Lett. **2004,** *6*, 225.

12 (a) Sonawane, H. R.; Bellur, N. S.; Ahuja, J. R.; Kulkarni, D. G.; *Tetrahedron Asymmetry* **1992**, *3*, 163. (b) Rieu, J. -P.; Boucherle, A.; Cousse, H.; Mouzin, G.; *Tetrahedron* **1986**, *41*, 4095.

13. Lake, A. W.; Rose, C. J. Prov. Patent GB 1,476,721, **1973**.

14. *Drugs Fut*. **2003**, *28*, 1024.

15. Johnstone, R. A. W.; Wilby, A. H.; Entwistle, I. D. *Chem. Rev*., **1985**, *85*, 129.

CHAPTER 1

Asymmetric Synthesis of *β*- Adrenergic Blockers *via* Kinetic Resolution of Epoxides and Proline-catalyzed *α*-Aminooxylation of Aldehydes

1.1 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] 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.[3] Biological systems, in most cases, recognize the members of a pair of enantiomers as different substances, and the 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. Since the biological activity in a racemic drug often resides in a single enantiomer, synthesizing such drugs in their optically pure form is becoming increasingly important.[4] 2-Amino alcohols are versatile intermediates for the synthesis of various biologically active natural products, unnatural amino acids, β-blockers, insecticidal agents, chiral auxiliaries and oxazolines.[5]

1.1.1 β-Adrenergic Blockers

β-Adrenergic blockers (**1-6**) were first reported to be useful for the treatment of glaucoma in 1967.[6] β-Adrenoreceptor antagonists are a group of compounds that competitively inhibit the effects of catecholamines at β-adrenergic receptors.[7] These agents are used widely in clinical medicine for the treatment of various conditions including

hypertension,[8] angina pectoris,[9] cardiac arrhythmias,[10] hypothyroidism[11] and glaucoma.[12] As the β-adrenoreceptor antagonists (β-blockers) have such a diverse range of clinical applications, the synthesis of these drugs becomes crucial. Most of the β-blockers possess a general structure containing Ar-O-$CH_2CH(OH)CH_2NHCH(CH_3)_2$ unit (**Fig. 1**) and have been used in the form of racemic mixtures.[13] They lowers high blood pressure by slowing down the heart rate and decreasing the force of contraction of the heart.

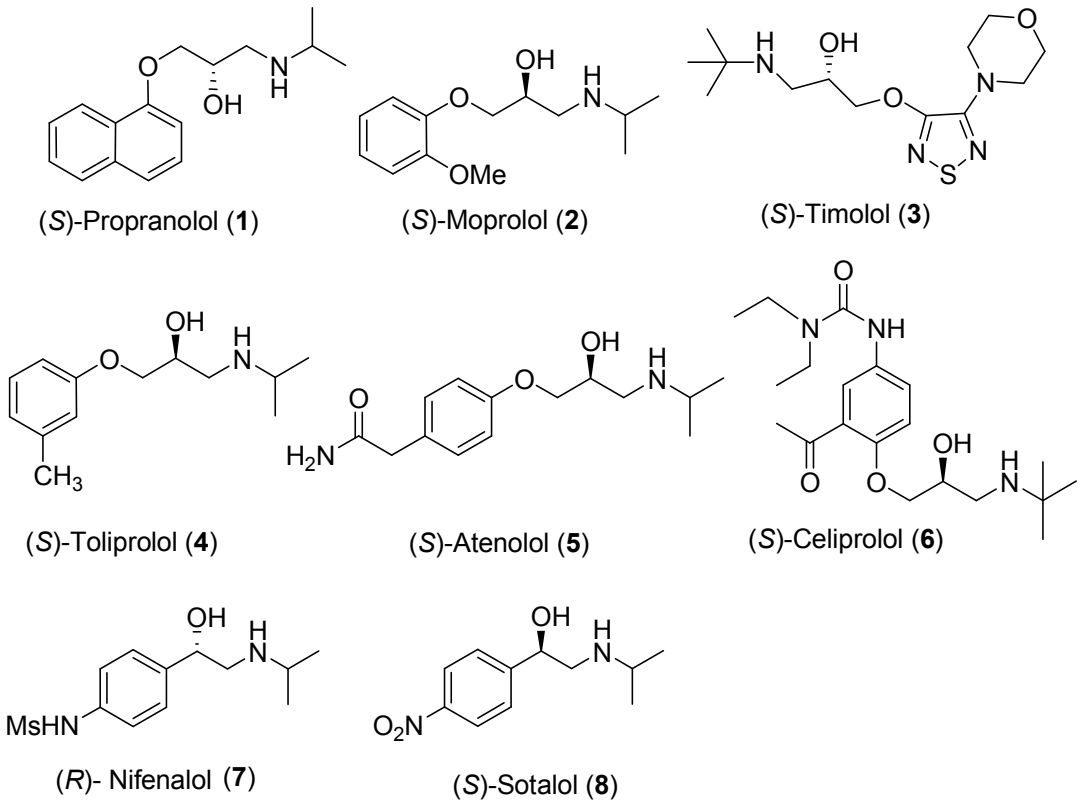


Fig. 1: Structures of various β-blockers

Three fundamental goals of cardiovascular drugs are: the lowering of blood pressure (antihypertensive), return of the heart to rhythmic beating (antiarrhythmics) and the general improvement of the heart muscle tone (cardiotonics).[14] Biochemically, the mechanism of action involves the adrenergic system in which the hormonal system

provides the communication link between the sympathetic nervous system and involuntary muscle.[15] There are four types of receptors for these molecules *α1*, *α2*, *β1* and *β2*. Blocking of *β*-receptor system reduces the overall activity of the sympathetic nervous system. Agents, which are *β*-blockers, are thus used to increase life expectancy after the heart attack. Although (*S*)-isomers are known to be much more effective (100-500 fold) than the (*R*)-isomer,[16] these antihypertensive drugs are presently sold as racemic mixtures. To avoid unnecessary stress or in some case toxicity to an organism caused by the (*R*)-isomers, the administration of optically pure (*S*)-isomer is thus desirable.

Among *β*-blockers, atenolol (**5**) is a widely used. While racemic atenolol is presently being marketed for the treatment of hypertension and angina and has shown promise in the treatment of post myocardial infarction, the *S* isomer has recently been found to avoid the occasional side effect of a lowered heart rate sometimes encountered with the racemate.[17] Celiprolol (**6**) is a new antihypertensive agent that represents a new generation of *β*-blockers. It combines cardio selective *β*-adrenergic antagonism (*β*-1) with a mild vasodilation *via* vasoselective *β*-adrenergic agonism (*β*-2). Results of animal studies show that celiprolol (**6**) has *β*-1 antagonist potency similar to that of propranolol and cardioselectivity slightly greater than that of atenolol.[18] Celiprolol distinguishes itself from other *β*-blockers by virtue of its cardioselectivity, vasorelaxation via *β*-2 agonism, and the lack of bronchoconstriction and cardiodepression.[19] (*S*)-Sotalol (**7**) and **(*R*)-**nifenalol (**8**) are also of great importance as *β*-adrenergic blockers bearing a structured unit of 2-amino-1-arylethanol**.** They are also used in the therapy of asthma, bronchitis and congestive heart failure.[20] Single enantiomers of chiral drugs are often more potent or have less side effects compared to their racemates.[21] There are several methods to obtain

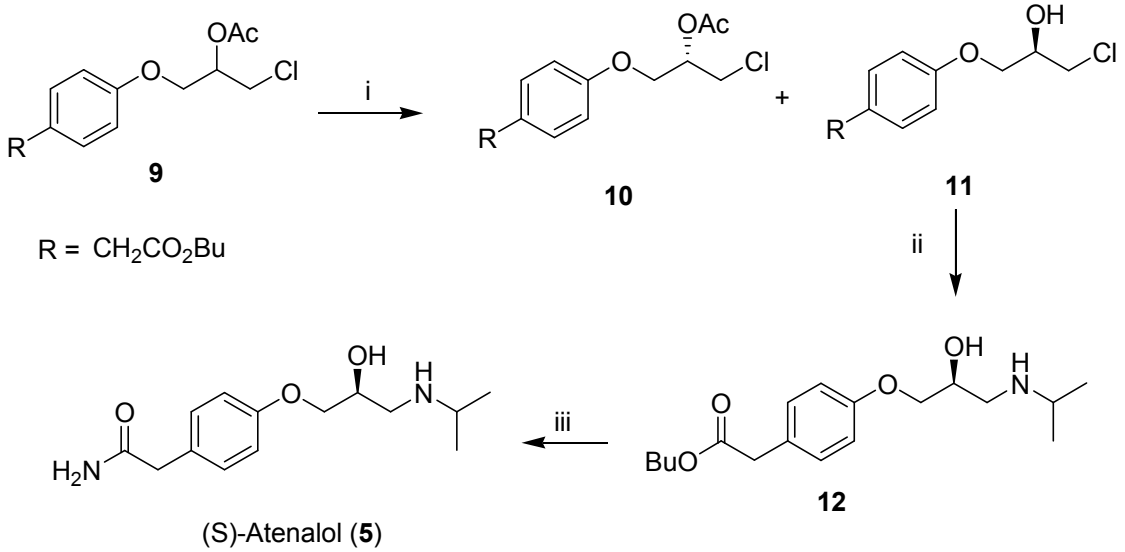
enantiomerically pure materials, which include classical resolution *via* diastereomers, chromatographic separation of enantiomers, enzymatic resolution, chiral kinetic resolution and asymmetric synthesis.[22]

1.2 Review of Literature

Literature search revealed that there are several reports available for the synthesis *β*-blockers namely (*S*)-atenolol (**5**), (*S*)-celiprolol (**6**), (*S*)-sotalol (**7**) and (*R*)-nifenalol (**8**). However, most of the reports deal with the synthesis of *β*-blockers in their racemic form and some methods known to obtain enantiomerically pure material mostly with resolution, chemo-enzymatic or enantioselective syntheses, which are described below.

Bevinakatti's approach (1992)[23]

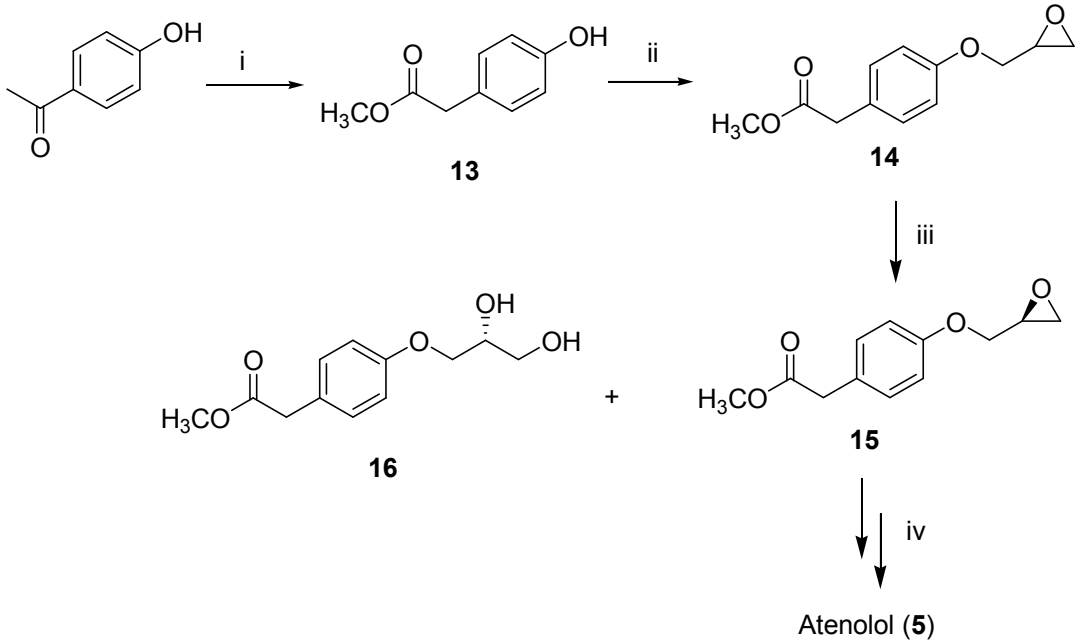
In this approach, chloro acetate **9** was subjected to LAPS-catalyzed hydrolysis of acetate under kinetic resolution condition to obtain chiral acetate **10** and the alcohol **11**. Alcohol **11** was subsequently transformed to (*S*)-atenolol (**5**) in 95% ee (**Scheme 1**).



Scheme 1: (i) LAPS catalyst, 25 °C, 95%; (ii) isopropylamine, 25 °C, 87%; (iii) aq. NH_4OH, MeOH, 25 °C, 65%.

Bose's approach (2005) [24]

In this approach, phenol **13** was allylated with allylbromide followed by epoxidation using *m*-CPBA to give racemic epoxide **14**, which on hydrolytic kinteic resolution using (*R,R*)-Co-Salen.OAc as catalyst resulted in chiral epoxide **15** and chiral diol **16** in excellent ee. Regioselective ring opening of the chiral epoxide **15** with isopropylamine and followed by ammonolysis gave atenolol (**5**) in 94% ee (**Scheme 2**).

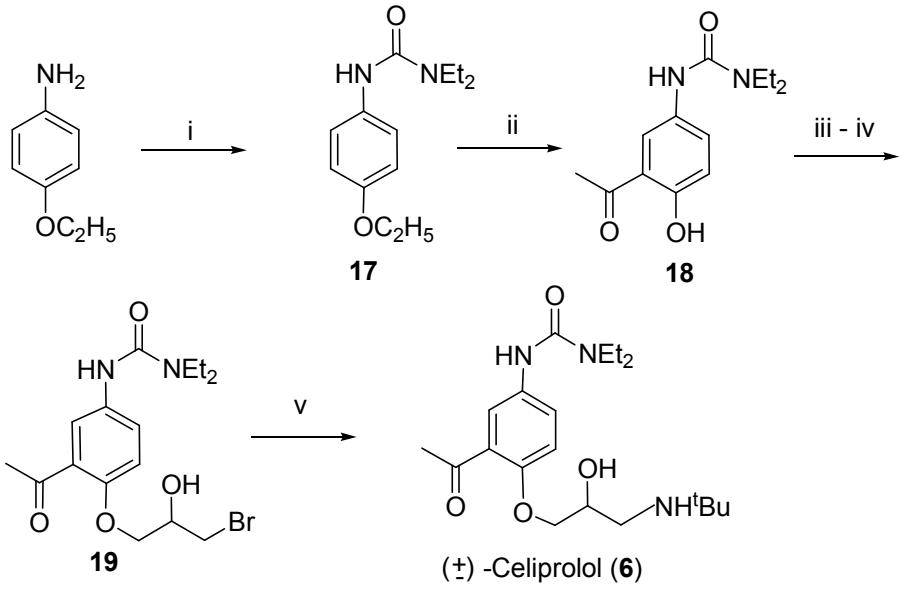


Scheme 2: (i) (a) sulfur, morpholine; (b) NaOH-EtOH; (c) MeOH, $SOCl_2$, 25 °C; (ii) (a) allylbromide, K_2CO_3, acetone; (b) *m*-CPBA, DCM; (iii) (*R,R*)-Salen Co(III), H_2O, 25 °C, 45%; (iv) (a) isopropylamine, 24 h, 25 °C, 91%; (b) aq. NH_4OH, MeOH, 24 h, 72 %.

Zoelss's approach (1983)[25]

In this approach, 4-ethoxyaniline was protected with diethylcarbamoyl chloride (DECC) in the presence of potassium bicarbonate to give *N*-*p*-ethoxyphenyl acetamide **(17).** Friedel-Crafts acylation using acetyl chloride and anhyd. aluminium chloride gave acyl derivative **18**, which on treatment with hydrobromic acid, gave bromohydrin **19**.

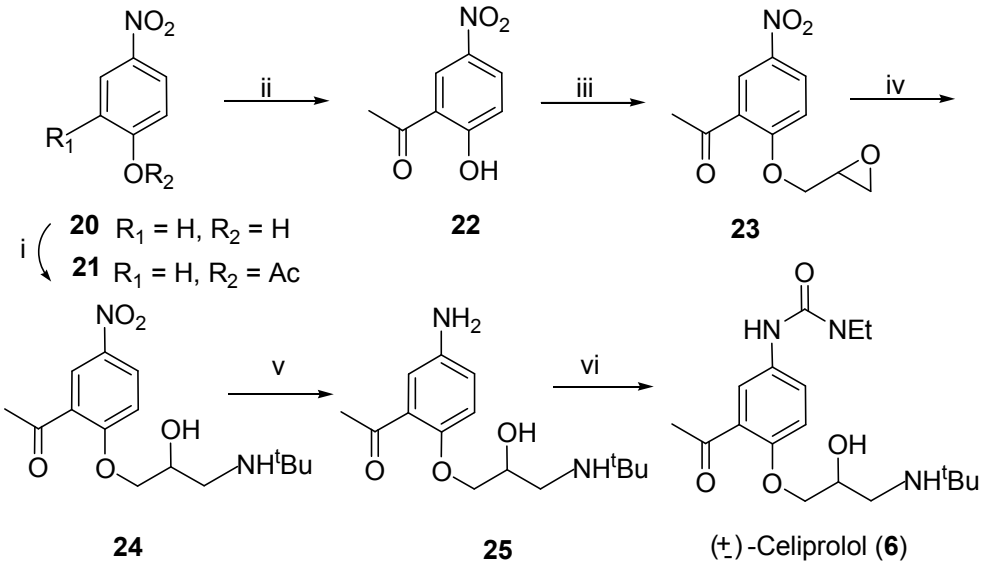
Bromohydrin **19** was converted into racemic celiprolol (**6**) in 71 % on reaction with *tert*-butylamine (**Scheme 3**).



Scheme 3: (i) $KHCO_3$, Et_2NCOCl, MeOH, 20-30 °C, 48 h, 92%; (ii) $AlCl_3$, AcCl, HCl, 6 h, 93%; (iii) epichlorohydrin; (iv) HBr, 71%; (v) EtN_3, *tert*-$BuNH_2$, 71%.

Joshi's approach (2001)[26]

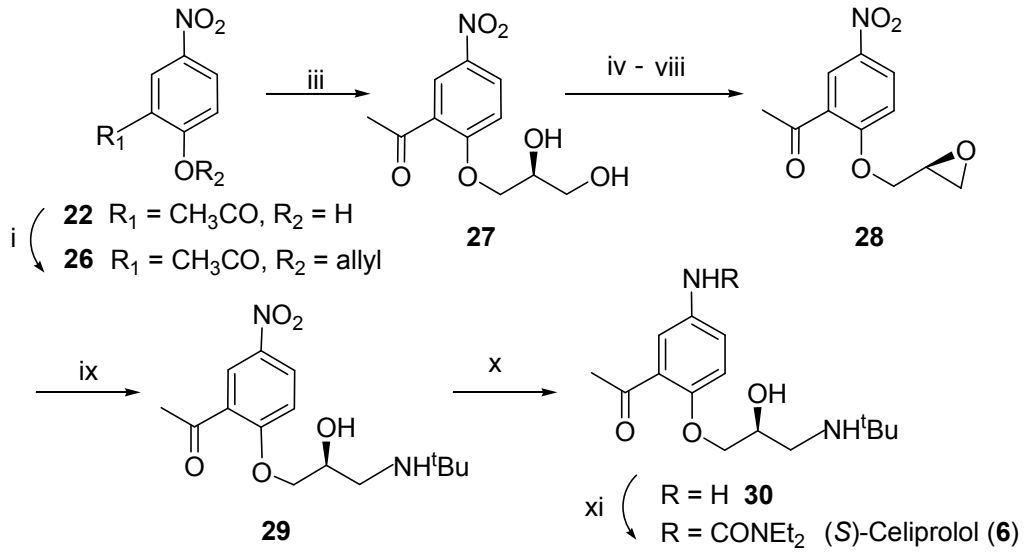
Joshi *et al.* have synthesized racemic celiprolol from 4-nitrophenol (**20**) in six steps. Fries' migration of phenyl acetate **21** using $AlCl_3$ in dry nitrobenzene gave 70% yield of 2-hydroxy-5-nitroacetophenone (**22**). *O*-Allylation of the phenol **22** with epichlorohydrin gave epoxide **23**, which underwent regiospecific ring with *tert*-butylamine in water to give **24**. Finally, catalytic reduction of nitro group followed by protection with *N,N*-diethylcarbamoyl chloride in THF and Et_3N as a base afforded racemic celiprolol (**6)** in 90% yield (**Scheme 4**).



Scheme 4: (i) NaOH, acetic anhydride, 90-95 °C, 10 min, 87%; (ii) $AlCl_3$, nitrobenzene, 140 °C, 6 h, 70%; (iii) K_2CO_3, benzyltriethylammonium chloride, 75 °C, 10 h, 96%; (iv) *tert*-$BuNH_2$, H_2O, 24 h, 86%; (v) H_2 (20 psig), MeOH, 10% Pd/C, 6 h, 92%; (vi) THF, Et_3N, DCC, 40 °C, 48 h, 90%.

Sudalai's approach (2006)[27]

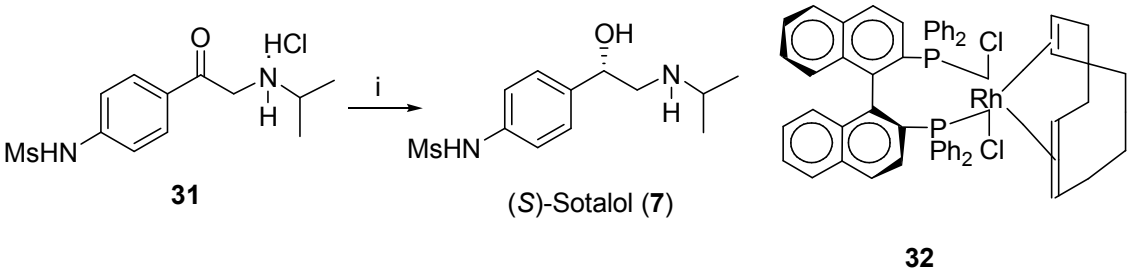
Sudalai *et al.* have synthesized (*S*)-celiprolol (**6**) in 97% ee. In this approach, the key reaction performed was asymmetric dihydroxylation [cat.OsO_4, $(DHQ)_2$-PHAL, $K_3Fe(CN)_6$] of allyl ether **26**, which gave the diol **27** in 97% ee. Diol **27** was transformed into chiral epoxide **28** in 4 steps *via* cyclic sulphate. Regiospecific ring opening of epoxide **28** with *tert*-butylamine followed by the catalytic reduction of nitro group and protection of amino function gave (*S*)-celiprolol (**6**) in 97% ee (**Scheme 5**).



Scheme 5: i) anhyd. $AlCl_3$, nitrobenzene, 140 °C, 6 h, 70%; (ii) K_2CO_3, allyl bromide, acetone, reflux, 24 h, 99%; (iii)) cat. OsO_4, $(DHQ)_2$-PHAL, $K_3Fe(CN)_6$, K_2CO_3, *tert*-BuOH:H_2O (1:1), 0-25 °C, 24 h, 96%, 97% ee; (iv) $SOCl_2$, Et_3N, CH_2Cl_2, 0 °C, 1 h, 98%; (v) cat. $RuCl_3$ $3H_2O$, $NaIO_4$, CH_3CN:H_2O, 0 °C, 30 min. 94%; (vi) LiBr, THF, 60 °C, 2 h; (vii) 20% H_2SO_4, Et_2O, 6 h; (viii) K_2CO_3, MeOH, 10-15 °C, 4 h, 85% overall in three steps; (ix) *t*-$BuNH_2$, H_2O, 24 h, 86%; (x) H_2 (20 psig), MeOH, 10% Pd/C, 6 h, 92%; (xi) THF, Et_3N, DCC, 40 °C, 48 h, 90%, 82% ee.

Smith's approach (1995)[28]

In this approach, (*S*)-sotalol (**7**) was prepared in 85% ee by the method of asymmetric hydrogenation of corresponding amino ketone **31** using Rh catalyst under high H_2 pressure (1000 psig) (**Scheme 15**).

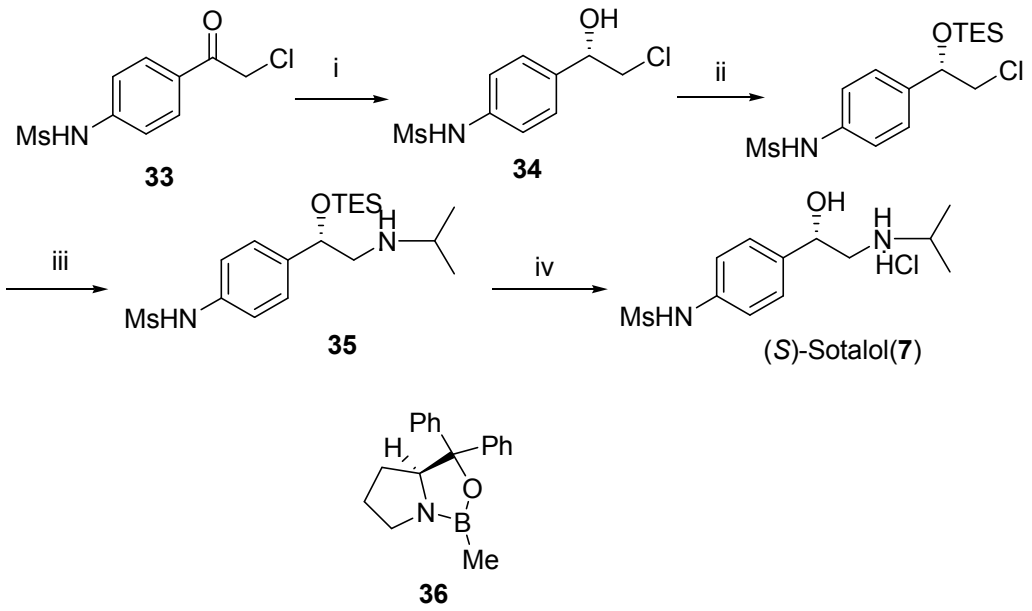


Scheme 6: (i) H_2, **32**, TEA, MeOH, 85% ee.

Brodfuhrer's approach (1997)[29]

In this approach, asymmetric reduction of chloro ketone **33** with catalytic amount of (*S*)-2-methyloxazaborolidine [(S)-Me-CBS-OB] in *tert*-butyl methyl ether gave chiral chloro

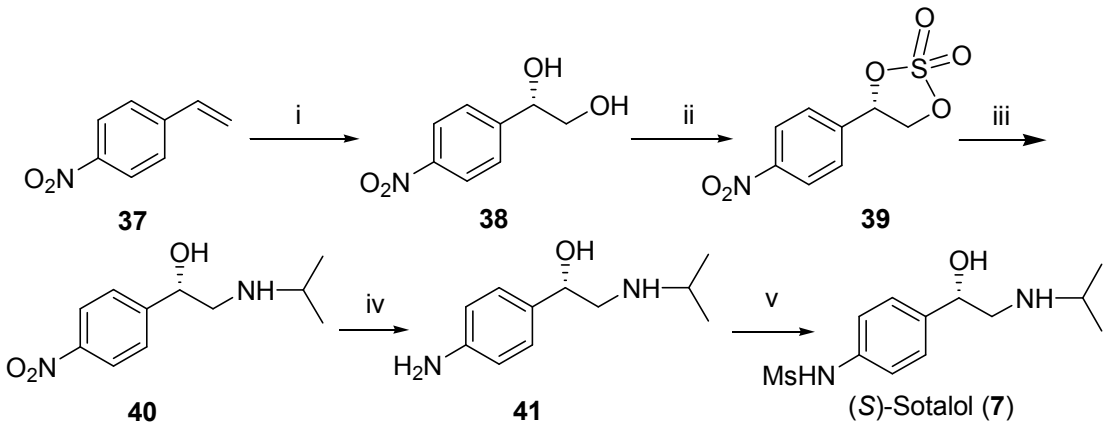
alcohol **34** in 96% ee. Nucleophilic displacement of chloro alcohol **34** with isopropylamine furnished (*S*)-sotalol as a free base in 58% yield, which on acidification furnished (*S*)-sotalol hydrochloride in 98% ee (**Scheme 7**).



Scheme 7: (i) **36**, 1M BH_3-THF, ^tBuOMe, 92%, 96% ee; (ii) Et_3SiCl, imidazole, DMF, 25 °C, 18 h, 80%; (iii) i-$PrNH_2$,130 °C, 17 h, Steel bomb, 30%; (iv) (a) TBAF, THF, reflux, 3 h, 58%; (b) 3.9N HCl in MeOH, IPA, 100%.

Phukan's approach (1997)[30]

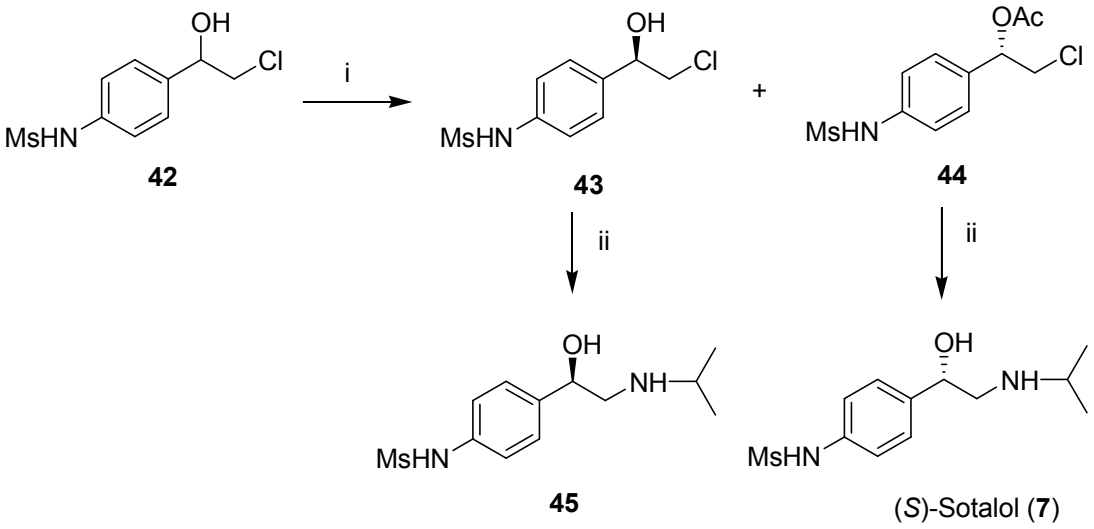
Phukan *et al.* have employed Os-catalyzed asymmetric dihydroxylation strategy, in which $(DHQ)_2$-PHAL was used as chiral ligand to furnish the chiral diol **38**. Then chiral diol **38** was first transformed into cyclic sulfate **39** in two steps ($SOCl_2$, pyridine; $NaIO_4$, $RuCl_3$, CH_3CN). Ring opening of the cyclic sulfate **39** with isopropylamine in THF followed by reduction of the nitro group (10% Pd/C, H_2 (20 psig)) and mesylation of the amine function gave sotalol (**7**) in 94% ee (**Scheme 8**).



Scheme 8: (i) $(DHQ)_2$-PHAL, OsO_4, *tert*-BuOH:H_2O; (ii) (a) $SOCl_2$, pyridine, (b) $RuCl_3$, $NaIO_4$, CH_3CN, $CCl_4.H_2O$; (iii) i-$PrNH_2$; (iv) H_2, Pd-C; (v) MsCl, pyridine.

Kamal's approach (2004)[31]

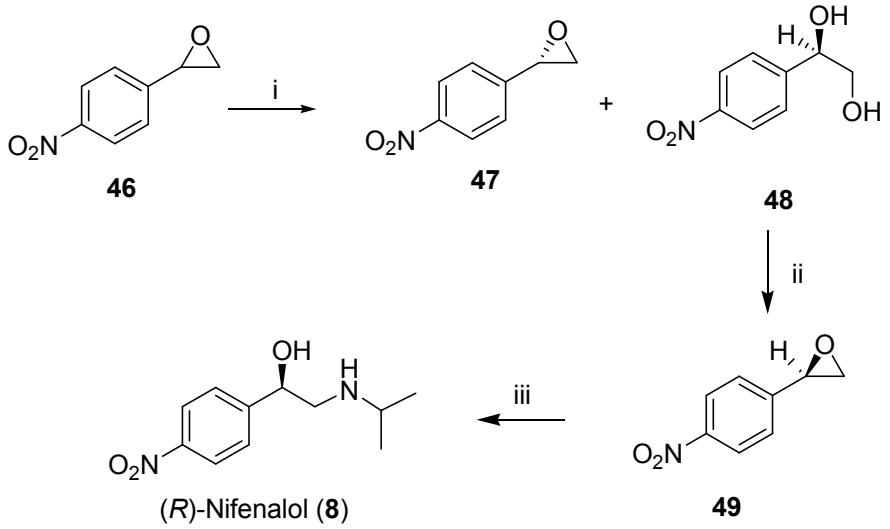
Kamal *et al.* have synthesized both the enantiomers of sotalol from the corresponding chloro alcohol. Thus, lipase mediated resolution of racemic chlorohydrin **42** gave alcohol **43** and acetate **44.** Nucleophilic displacement of chloride with isopropylamine in the presence of K_2CO_3 /MeOH gave both the enantiomers of sotalol in 90% yield and 94% ee (**Scheme 9**).



Scheme 9: i) lipase PS-C, isopropenyl acetate, 40 °C, 18 h; (ii) K_2CO_3, MeOH, isopropylamine, 25 °C, 12 h, 80%.

Moreau's approach (1997)[32]

Moreau *et al.* have synthesized (*R*)-nifenalol by enzymatic resolution of racemic epoxide **46** using A. niger whole cells followed by the acid-catalyzed hydrolysis in a one pot process to afford diol **48** in 80% ee. Epoxidation of the diol followed by treatement with isopropylamine gave (*R*)-nifenalol (**8**) (**Scheme 10**).



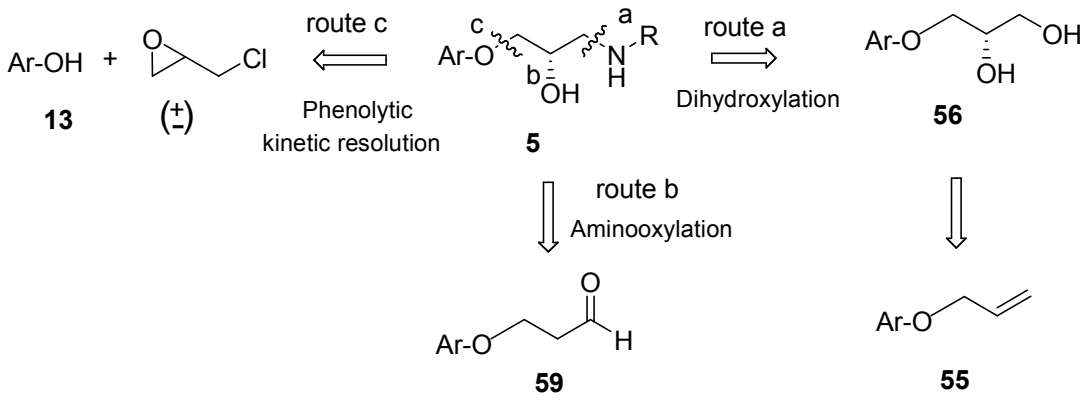
Scheme 10: (i) A.niger (whole cell or enzymatic powder); (ii) H_2SO_4; (iii) (a) recrystalization; (b) HBr/ acetic acid; (iv) i-$PrNH_2$.

1.3 Present Work

1.3.1 Objective

As can be seen from the above discussion, most of the methods reported for the syntheses of atenolol (**5**), celiprolol (**6**), sotalol (**7**) and nifenalol (**8**) suffer from several drawbacks such as the use of expensive enzymes and resolving agents, low-overall yields and optical purity, large number steps, *etc*. Hence, development of new catalytic methods for the synthesis of these *β*-adrenergic blockers **5**, **6**, **7** and **8** starting from the corresponding prochiral substrates is necessary. The general scheme of retrosynthetic analysis of these *β*-adrenergic blocking agent **5** is delineated in **Scheme 11**. There are three possible

disconnections of C-X bond envisaged (routes a, b and c) for the synthesis of these *β*-blockers. Overall, we visualized that these *β*-blockers can be synthesized either by asymmetric dihydroxylation of the respective olefin **55** (route a), *α*-aminooxylation of aldehyde **59** (route b) or by phenolytic kinetic resolution of epichlorohydrin with phenolic substrate **13** (route c).

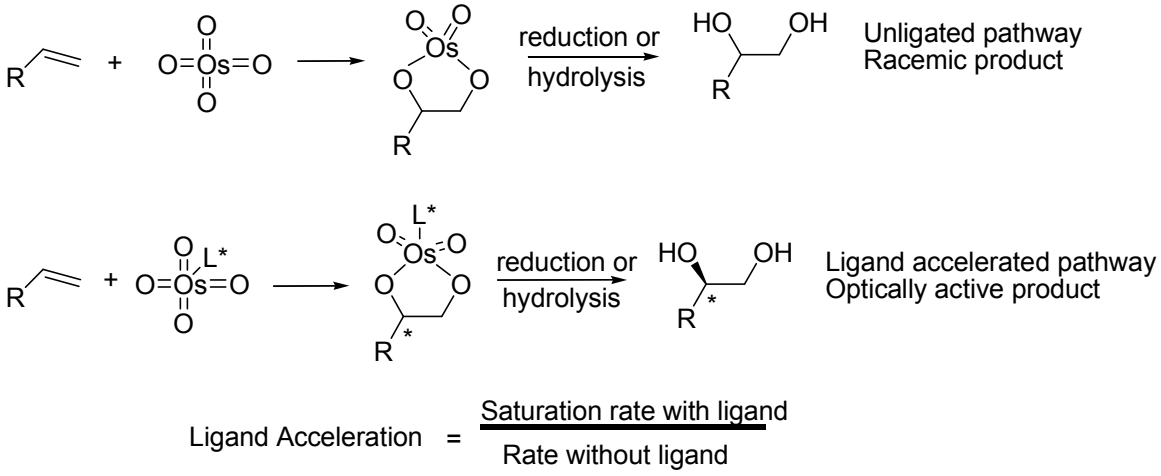


Scheme 11: General scheme of retrosynthetic analysis of *β*-blockers

This chapter describes new routes for the asymmetric synthesis of (*S*)-atenolol (**5**), (*S*)-celiprolol (**6**) and other *β*-blockers using most reliable enantioselective reactions such as asymmetric dihydroxylation, proline-catalyzed *α*-aminooxylation and phenolytic kinetic resolution. Since this Chapter deals with three important asymmetric reactions (Asymmetric dihydroxylation (ADH) of olefin, Co-catalyzed asymmetric kinetic resolution of terminal epoxides and proline catalyzed *α*-aminooxylation of carbonyl compounds), which introduce stereogenicity into the prochiral molecule, a brief account of ADH, Co-catalyzed asymmetric kinetic resolution of terminal epoxides and proline-catalyzed *α*-aminooxylation of carbonyl compounds is described as under).

1.3.2 Asymmetric Dihydroxylation (AD)

In recent years, much attention has been focused on the catalytic asymmetric synthesis. 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).[33] 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.[34]



Scheme 12: Mechanism of OsO_4-catalyzed dihydroxylation of olefin

In 1936, Criegee *et al.*[35] 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*.[34b] 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).[36]

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)**.

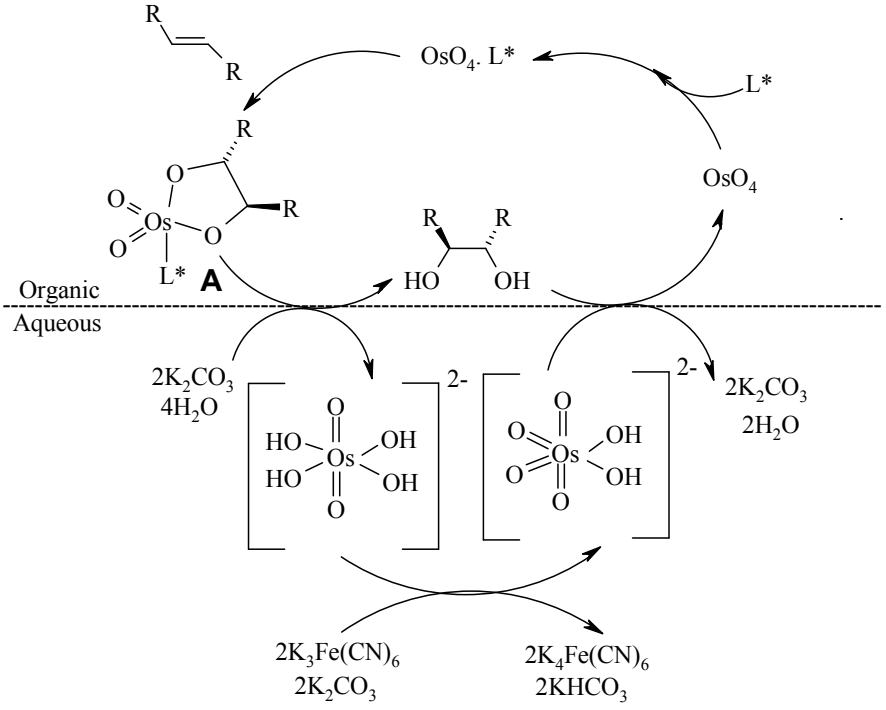


Fig. 2: Catalytic cycle for AD using $K_3Fe(CN)_6$ as co-oxidant

These conditions helped in protecting the organic osmate-(VI) monoglycolate ester (species **A**, **Fig. 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) obtains 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. Addition of methyl

sulfonamide also allowed carrying out the reactions of 1,2-di- tri- and tetra- substituted olefins at 0 ºC, which improved the selectivity as well as enantiomeric excess. 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 **50** or DHQD **51** ethers of phthalazine-1, 4-diol have proven to be the best for obtaining high enantioselective diols[37] **(Fig. 3)**.

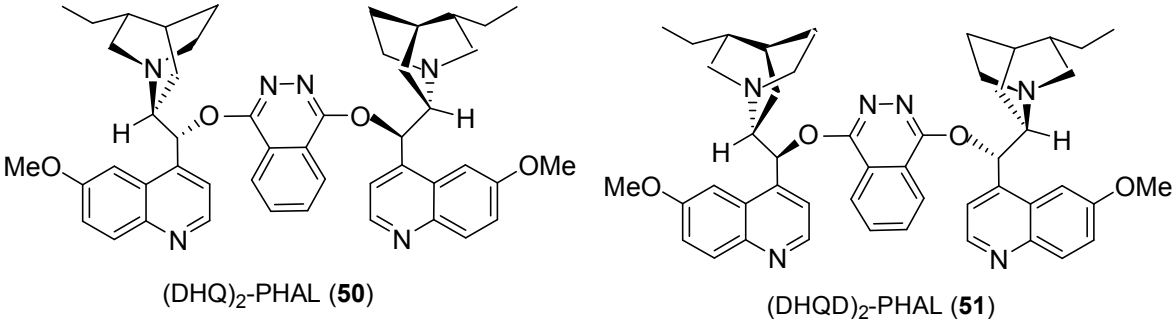


Fig. 3: Ligands for asymmetric dihydroxylation reaction

Studies have demonstrated the importance of enzyme-like binding pocket of the dimeric cinchona alkaloid for high enantioselectivity of the chiral diols.[38] Sharpless *et al*.[34] have shown that the facial selectivity for both ligands **50** and **51** 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.

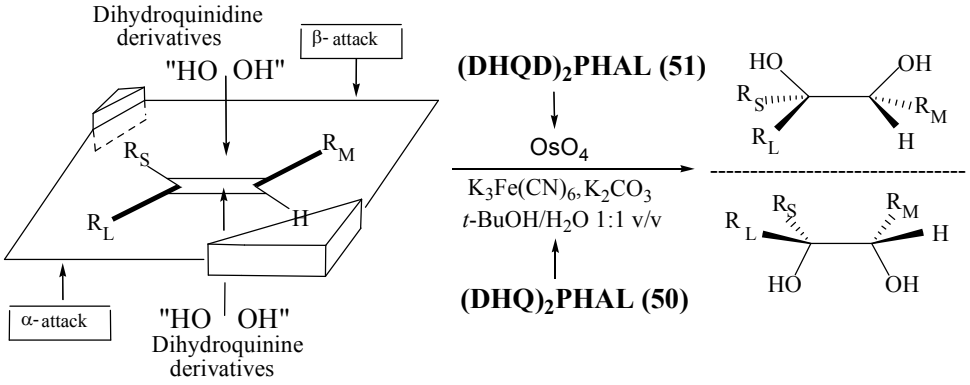


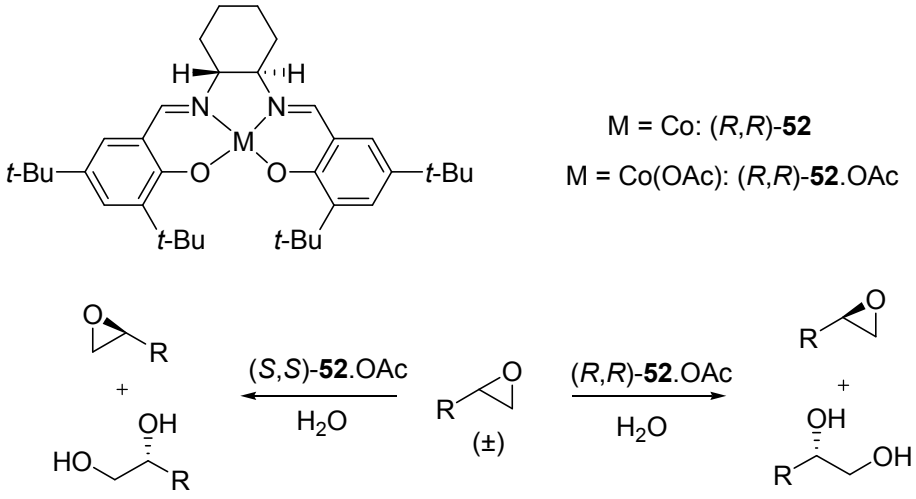
Fig. 4: Enantioselectivity mnemonic scheme

1.3.3 Hydrolytic Kinetic Resolution (HKR)

The importance of epoxides in organic synthesis arises partly from the occurrence of the strained three-membered ring unit in a number of interesting natural products[39] but more so because the ring opening of epoxides allows straightforward elaboration to useful new functionality, often with generation of new carbon-carbon bonds. Indeed, reactions of epoxides with nucleophiles, Lewis acids, radicals, reducing agents, oxidizing agents, acids, and bases have all been well documented and utilized in synthesis.[40] Thus epoxides are versatile building blocks for organic synthesis. However, terminal epoxides are arguably the most important subclass of these compounds, and no general and practical method exists for their production in enantiomerically pure form. Terminal epoxides are available very inexpensively as racemic mixtures, and kinetic resolution is an attractive strategy for the production of optically active epoxides, given an economical and operationally simple method. Readily accessible synthetic catalysts (chiral cobalt-salen complexes)[41] have been used for the efficient asymmetric hydrolysis of terminal epoxides. This process uses water as the only reagent, no added solvent, and low loadings

of a recyclable catalyst (0.5 mol %), and it affords highly valuable terminal epoxides and 1,2-diols in high yields with high enantiomeric enrichment.

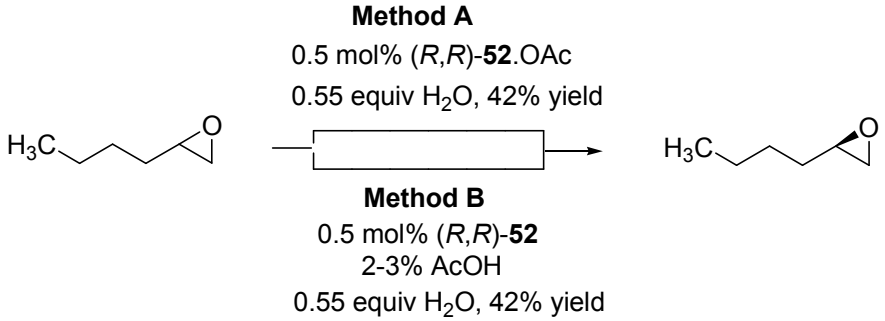
One of the most attractive features of kinetic resolution processes in general is the fact that the enantiomeric composition of unreacted substrate can be controlled by adjusting the degree of conversion, and virtually enantiopure material can be obtained at appropriately high conversions. This is an important consideration in the present case, since low-molecular weight terminal epoxides are typically liquids at room temperature and are not readily derivatized as salts, and therefore it is not a straightforward matter to upgrade their enantiomeric composition by crystallization. However, in the absence of straightforward substrate racemization protocols, kinetic resolutions have the significant disadvantage of a 50% maximum yield of substrate recovery. With a specific interest in devising a practical method for obtaining highly enantioenriched terminal epoxides, the following criteria must be met in order for a kinetic resolution approach to be viable.[42] (1) The racemic epoxides must be inexpensive or easily accessible from inexpensive commercial starting materials. (2) The catalyst for the resolution must be readily available in both enantiomeric forms. In the optimal case, the catalyst would be used in small quantities in the resolution and would be recyclable. (3) The nucleophile used for the ring opening should be inexpensive and easily handled. (4) The resolved epoxides must be obtained in good yield and very high enantiopurity and must be easily separated from the ring-opened products. (5) Ideally, although not necessarily, the ring-opened byproducts should also be valuable chiral building blocks and be obtainable in high enantiomeric excess. The Co (salen) complex **11** catalyzed the efficient hydrolytic kinetic resolution (HKR) of a variety of terminal epoxides (**Scheme 13**).[43]



Scheme 13: Hydrolytic Kinetic Resolution (HKR) Reaction

This new method appeared to hold considerable promise with regard to meeting all of the criteria outlined above. First, racemic 1,2-epoxides are generally available directly from commercial suppliers at low cost or are obtainable in one step from inexpensive olefins or aldehydes. In fact, certain racemic epoxides, such as propylene oxide, epichlorohydrin, styrene oxide, and butadiene monoepoxide, are commodity chemicals and are no more expensive than common organic solvents. Second, the ligands for catalyst **52** had previously been commercialized and manufactured on a ton scale in the context of (salen)Mn epoxidation catalysts. The cobalt analogues (*R*,*R*)-**52** and (*S*,*S*)-**52** proved equally accessible, and these are also now available in bulk. Third, water is perhaps the ideal reagent for effecting the resolution reaction: it is inexpensive and safe, and the rate of the ring-opening reaction can be controlled simply by modulating the rate of addition of water to the epoxide-catalyst mixture. Fourth, for those examples that were described in the preliminary report, highly enantioenriched epoxides were recovered from the HKR.

Finally, the HKR provided useful enantioenriched 1,2-diols, including many that are otherwise not readily accessible using existing asymmetric dihydroxylation methods.[44]



Scheme 14: Methods of catalyst preparation

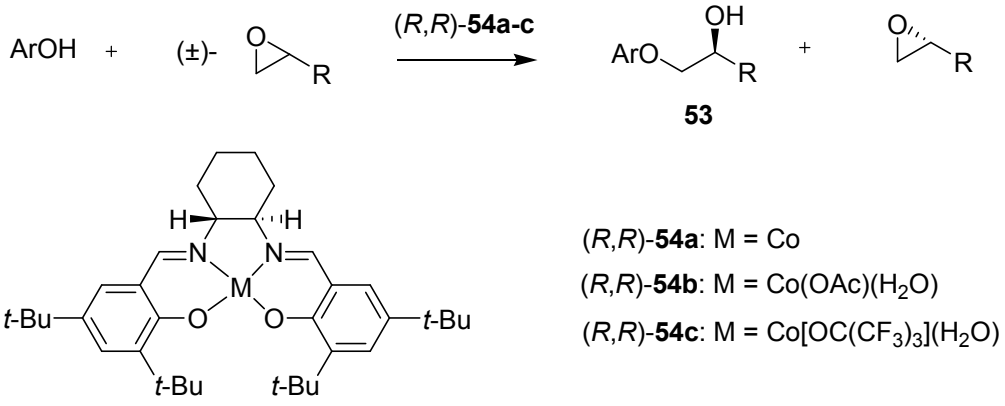
Two useful methods (A and B) for the generation of cobalt complex **52.**OAc have been developed (**Scheme 14**). Method A involves isolation of **52.**OAc as a crude solid prior to the HKR as given below. The Co(II) complex **52** is dissolved in toluene to generate ~ 1 M solution, and acetic acid (2 equiv.) is added. The resulting solution is stirred open to air at room temperature for 30 min, during which time the color of the mixture changes from orange to dark brown. All volatile materials are distilled off *in vacuo*, affording **52.**OAc as a brown solid crude product that can be used without further purification. Method B involves *in situ* generation of **52.**OAc under HKR conditions by suspension of the Co(II) complex **52** in epoxide or epoxide/solvent and addition of HOAc under an aerobic atmosphere.

1.3.4 Kinetic resolution of terminal epoxides *via* highly enantioselective ring opening with phenols

Enantiopure α-aryloxy alcohols (**53**) are valuable tarobtains for asymmetric synthesis as a result of their role as key synthetic intermediates in a variety of pharmaceutically important compounds.[45] In principle, access to these building blocks may be provided by

several routes, including asymmetric reduction of aryloxy ketones[46] or the ring opening of enantiopure terminal epoxides with phenols. Of these, the latter is probably the most versatile and direct, but available methods for the addition of phenols to epoxides are extremely limited.

The ready accessibility of terminal epoxides in racemic form renders kinetic resolution of terminal epoxides with phenols a potentially attractive route to **53** (**Scheme 15**). The high selectivities obtained in the recently reported hydrolytic kinetic resolution of terminal epoxides with catalyst **54b** suggested that (salen)Co(III) complexes might also serve as effective catalysts for the enantioselective addition of phenols to epoxides. This strategy has proven successful and the kinetic resolution of epoxides with phenols has been reported, with the isolation of 1-aryloxy 2-alcohols (**53**) in high ee's and yields.



Scheme 15: Kinetic resolution of terminal epoxides with phenols

Reaction of 2.2 equiv of (±)-epoxide with phenol in the presence of (salen)Co(OAc) complex **54b** (0.044 equiv) in *tert*-butyl methyl ether (TBME) led to 61% conversion of phenol after 55 h at room temperature, with 1-aryloxy 2-alcohols (**53**) generated in 94% ee. Encouraged by the observation of high enantioselectivity in this reaction, a variety of reaction parameters with the goal of identifying a more reactive system has been

evaluated. The identity of the counter ion for the (salen) cobalt complex proved to be important in this context, with the perfluoro *tert*-butoxide complex displaying superior reactivity. Thus, the use of complex **54c** under conditions otherwise identical to those outlined above resulted in 80% conversion of phenol in 18 h and formation of 1-aryloxy 2-alcohols (**53**) as the major product in 96% ee. Small amounts of 1,2-diol were also generated, presumably as a result of epoxide hydrolysis with adventitious water, but this pathway could be suppressed easily by the inclusion of 3 Å molecular sieves in the reaction mixture.

1.3.5 Asymmetric organocatalysis

The broad utility of synthetic chiral molecules as single-enantiomer pharmaceuticals, in electronic and optical devices, as components in polymers with novel properties, and as probes of biological function, has made asymmetric catalysis a prominent area of investigation. Until a few years ago, it was generally established that transition metal complexes and enzymes were the two main classes of very efficient asymmetric catalysts. Synthetic chemists have hardly used small organic molecules as catalysts throughout the last century, even though some of the very first asymmetric catalysts were purely organic molecules. Simple organic molecules can be highly effective enantioselective catalysts for a variety of important organic transformations,[47] this rediscovery has initiated an explosive growth of research activities in organocatalysis both in industry and in academia. The 1970s brought a milestone in the area of asymmetric organocatalysis, when two industrial groups led by Hajos and Wiechert published the first and highly enantioselective catalytic aldol reactions using the simple amino acid proline as the catalyst.

Organocatalysis is the catalysis of chemical transformations using a purely organic molecule, which is composed of mainly carbon, hydrogen, nitrogen, sulfur, and phosphorus, and does not contain any metals. The advantages of organocatalysts include their lack of sensitivity to moisture and oxygen, their ready availability, low cost, and low toxicity, which confers a huge direct benefit in the production of pharmaceutical intermediates when compared with transition metal catalysts. Organic molecules not only have ease of manipulation and a "green" advantage but also can be very efficient catalysts. Asymmetric organocatalysis may begin to catch up with the spectacular advancements of enantioselective transition metal catalysis.

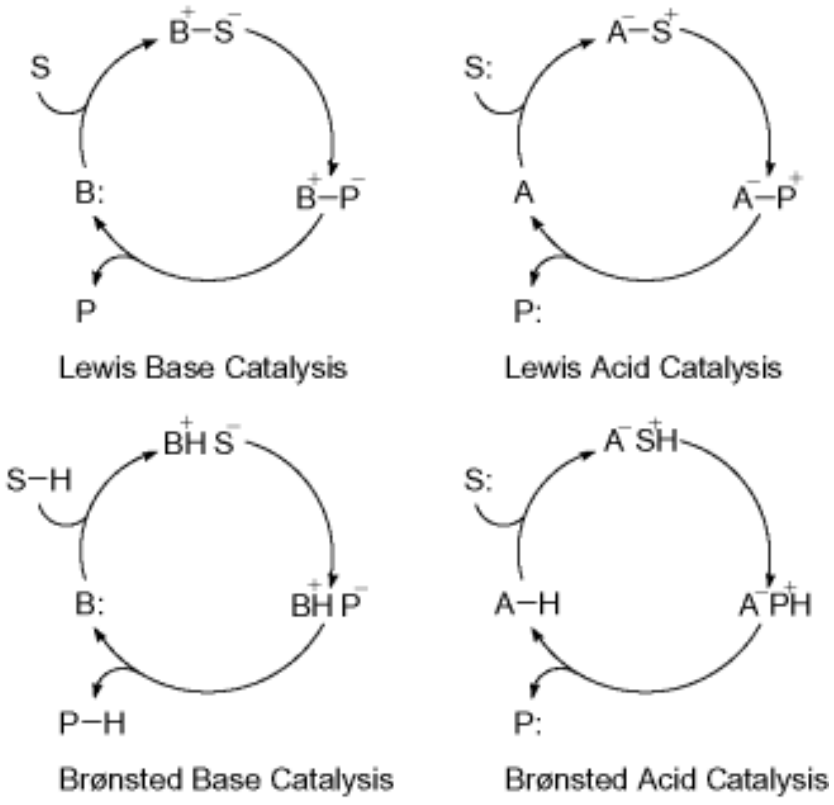


Fig. 5: Organocatalytic cycles

Recently, List[47] introduced a system of classification based on the mechanism of catalysis (**Fig. 5**). The four categories are Lewis base, Lewis acid, Bronsted base and Bronsted acid catalysis. Accordingly, Lewis base catalysts (B:) initiate the catalytic cycle *via* nucleophilic addition to the substrate (S). The resulting complex undergoes a reaction and then releases the product (P) and the catalyst for further turnover. Lewis acid catalysts (A) activate nucleophilic substrates (S:) in a similar manner. Brønsted base and acid catalytic cycles are initiated *via* a (partial) deprotonation or protonation, respectively.

1.3.5.1 Proline a "Universal catalyst"

Proline (**55**) has been defined as a "universal catalyst" because of its high utility in variety of asymmetric organic transformations. Proline is the only natural amino acid with a secondary amine functionality, which raises the pKa value and better nucleophilicity as compared to other amino acids. It can act as a nucleophile to carbonyl groups (iminium intermediate) or Michael acceptors (enamines).

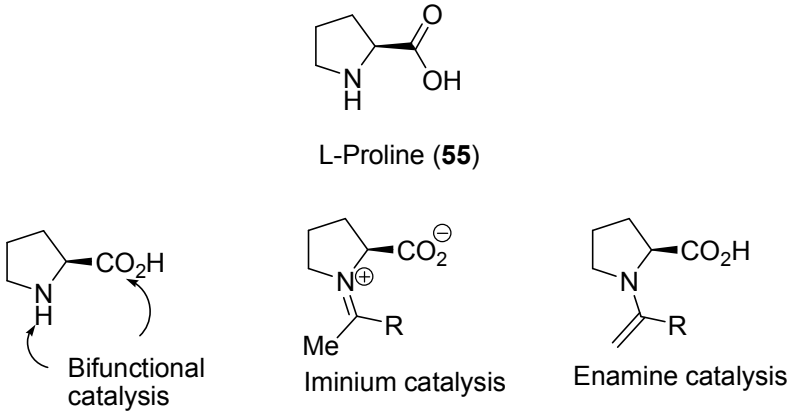


Fig. 6: Modes of proline catalysis

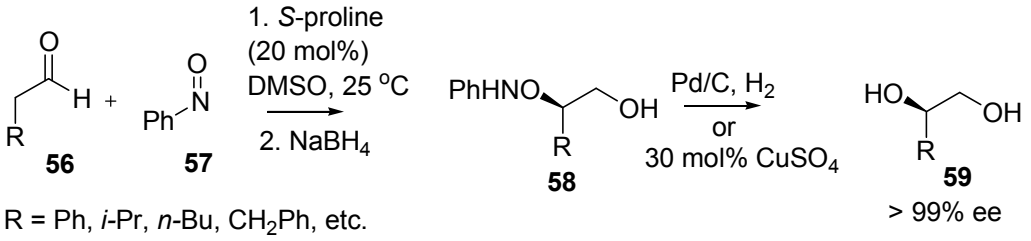
It can be regarded as a bifuctional catalyst as the secondary amine acts as Lewis base and the acid group acts as Bronsted acid (**Fig. 6**). The high stereoselectivity in the proline-catalyzed reactions is possibly due to its formation of organized transition states with

many hydrogen bonding frameworks. Proline is not the only molecule to promote catalysis, but it still seems to be one of the best in the diversity of transformations. Proline is known to catalyze aldol,[48] Diels-Alder,[49] Michael addition[50] and α-functionalization[51] among many other organic transformations.[52] Particularly proline-catalyzed α-aminooxylation[53] and α-amination[54] of carbonyl compounds are emerged as powerful transformations because chiral building blocks can be synthesized in effective manner starting from easily available materials.

1.3.5.2 Proline-catalyzed α-Aminooxylation

Optically active α-hydroxyaldehydes and ketones are important intermediates in organic synthesis as they are direct precursors to 1,2-diols. Because of this utility many methods have been developed for their preparation. The more prominent, well-established methods of enantioselective α-oxygenation include the use of Davis oxaziridine,[55a] Sharpless dihydroxylation of enol ethers,[55b] and Shi epoxidation of enol ethers.[55c] It is only rather recently that direct catalytic, asymmetric variants have been reported.[56] Most of these methods, however, require multiple manipulations and there is no direct method, nor catalytic asymmetric method for their synthesis from the corresponding aldehyde.

Recently, proline has been found to be an excellent asymmetric catalyst for α-aminooxylation[53] of carbonyl compounds. When an aldehyde **56** without substitution at α-position was reacted with nitrosobenzene **57** in presence of L-proline in DMSO at ambient temperature, aminooxylation of the aldehyde takes place at α-position. The aldehyde can be reduced in situ with sodium borohydride and the aminooxyl moiety undergoes hydrogenolysis with Pd/C, H_2 or $CuSO_4$ to give the corresponding diols **59** in very high enantioselectivities (**Scheme 16**).



Scheme 16: α-aminooxylation of aldehydes

The mechanism of the α-aminooxylation reaction is given in **Fig. 7**. The observed enantioselectivitiy of the catalytic α-aminoxylation of aldehydes can be rationalized by invoking an enamine mechanism operating through a chair transition state where the *Si* face of an *E*-enamine formed from the aldehyde and L-proline approaches the less-hindered oxygen atom of nitrosobenzene to provide a chiral α-aminoxyaldehyde with *R* configuration. Since proline is commercially available in both enantiopure forms, a one-pot sequential catalytic α-aminooxylation of aldehydes followed by in situ reduction with $NaBH_4$ affords *R*- or *S*- configured 1,2-diol units (the secondary alcohol "protected" by an *O*-amino group) with excellent enantioselectivities and in good yields.

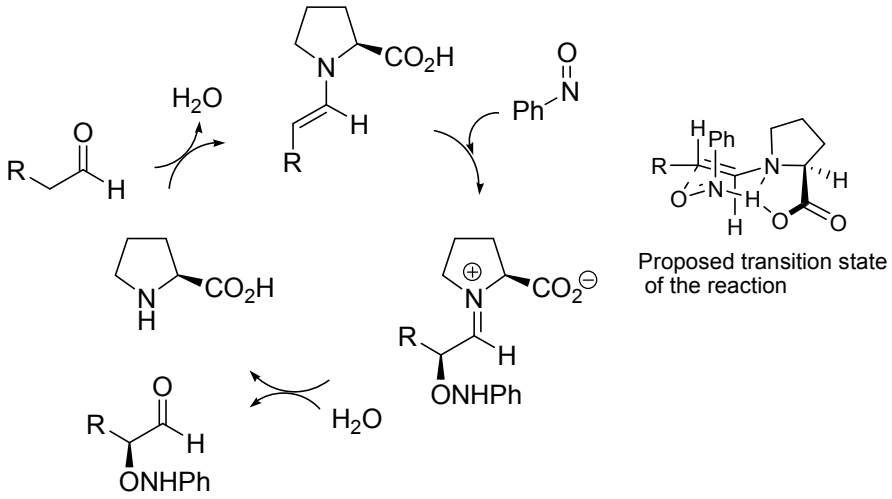
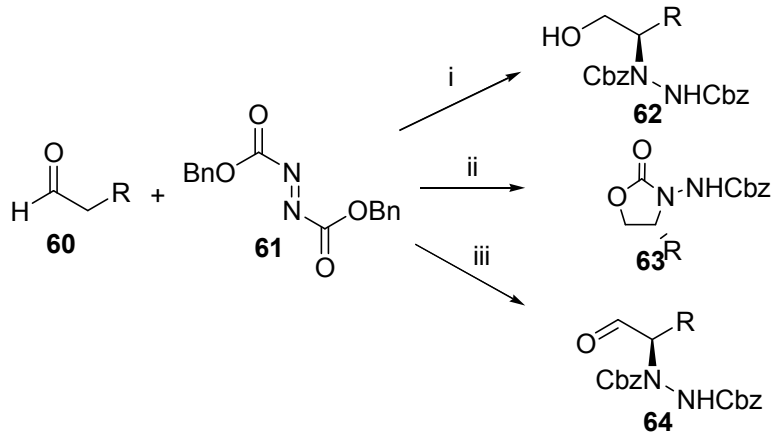


Fig. 7: Proposed mechanism of the α-aminooxylation reaction

1.3.5.3 Proline-catalyzed *α*-Amination

The motivation to investigate enantioselective α-amination of carbonyl compounds is provided by valuable synthetic targets such as α-amino acids and α-amino alcohols. The importance of optically active α-amino acids, α-amino aldehydes, and *α*-amino alcohols, formed by asymmetric catalysis, has stimulated an enormous development in synthetic strategies, and two different catalytic, enantioselective approaches are attractive: the C-C and the C-N bond-forming reactions. The catalytic enantioselective C-C bond-forming reactions include the addition to imines, such as the Strecker and Mannich reactions. The catalytic, enantioselective, direct C-N bond-forming reaction using aldehydes and a nitrogen source, such as azodicarboxylates, would constitute one of the simplest procedures for the construction of a stereogenic carbon center attached to a nitrogen atom.

Asymmetric α-amination[54] of aldehydes using proline-catalyzed reactions represent a burgeoning field of synthetic research as it is a tool for synthesizing chiral building blocks such as α-amino acids, α-amino aldehydes, and α-amino alcohols. The use of organocatalysis, in particular proline represents a drastic change in approach to asymmetric α-amination. Recently, both List[54a] and Jørgensen[54b] disclosed the asymmetric α-amination of aldehydes (**Scheme 17**) using catalytic quantities of proline. While these approaches parallel each other in many ways, minor variations in reaction conditions result in different products, as well as differences in yields and enantiomeric ratios.

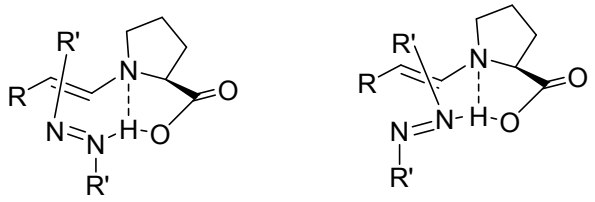


Scheme 17: (i) L-proline (10 mol%), CH_3CN, 0 °C, 3 h; $NaBH_4$, EtOH; (ii) L-proline (10 mol%), CH_2Cl_2, rt; $NaBH_4$, MeOH; 0.5 N NaOH; (iii) L-proline (10 mol %), CH_2Cl_2, rt; H_2O.

The reaction involves the addition of (*S*)-proline (10 mol%) to a solution of aldehyde and azodicarboxylate ester. List found that optimal enantiomeric enrichment of alcohol product **62** was obtained when the reaction temperature of 0 °C and in situ reduction with sodium borohydride was employed. Alternatively, Jørgensen found that aldehydes could be isolated directly, with diminished enantiomeric enrichment as reaction times increased, if the reaction was carried out in methylene chloride at room temperature. This procedure furnishes aldehyde products **64**; these could be converted to the fully protected α-amino acids via a multi-step protocol of oxidation, deprotection, protection, and hydrogenolysis. To access *N*-amino oxazolidinones, precursors to α-amino alcohols, Jørgensen's standard proline protocol was used, followed by addition of sodium borohydride and subsequent treatment with sodium hydroxide to facilitate cyclization to the desired product **63** (path b). These additional steps resulted in significantly diminished yields compared to List's route to α-amino alcohol precursors. Both List and Jørgensen were able to achieve high yields and excellent enantiomeric ratios using

sterically hindered substrates. This method is easily performed on gram scale using inexpensive chiral catalyst and can be performed in the absence of solvent.

The key shortcoming of this method is that excess aldehyde **60** is required, a serious disadvantage when using valuable aldehydes. Both List and Jørgensen proposed transition states that rationalize the observed stereochemical outcome. While these transition structures involve the anticipated enamine intermediate, they differ substantially in the prediction of the lowest energy conformation of the transition state. Jørgensen proposed a boat-like transition state **65**, whereas List a chair-like transition state **66**, analogous to that proposed for proline- catalyzed intramolecular aldol reaction.[57] It is worth mentioning that transition structure **66** lacks the hydrogen bond to the proline nitrogen, as Houk and coworkers have recently shown through a series of calculations that the N-H hydrogen bond does not lower the transition state energy in the corresponding aldol reaction.[58]



65 **66**

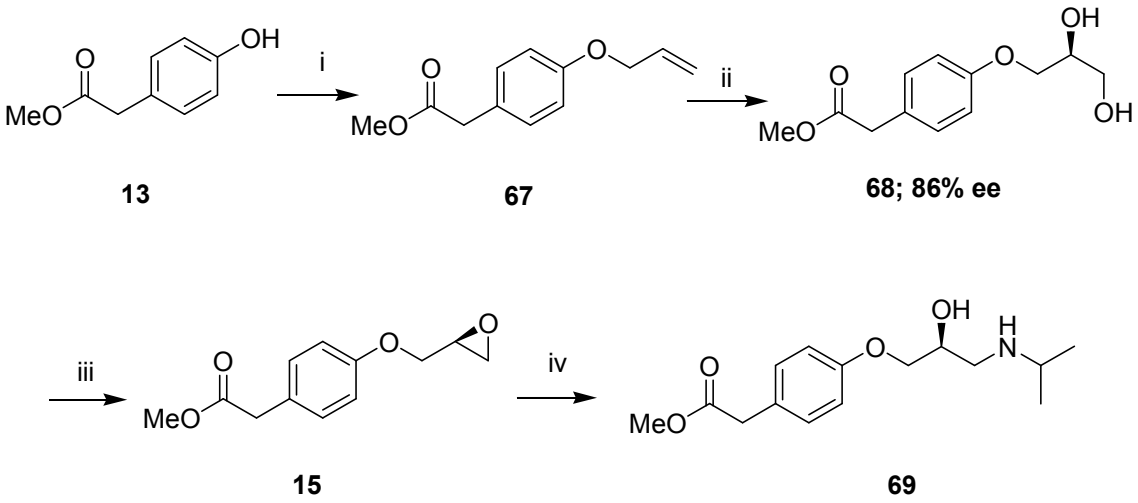
Fig. 8: Transition states for α-amination

While both transition structures lead to identical products directed by the hydrogen bond from the carboxylic acid of proline, they presumably possess unique energies, so one transition state should be the favored. However, the operative transition state has yet to be established.

1.4 Results and Discussion

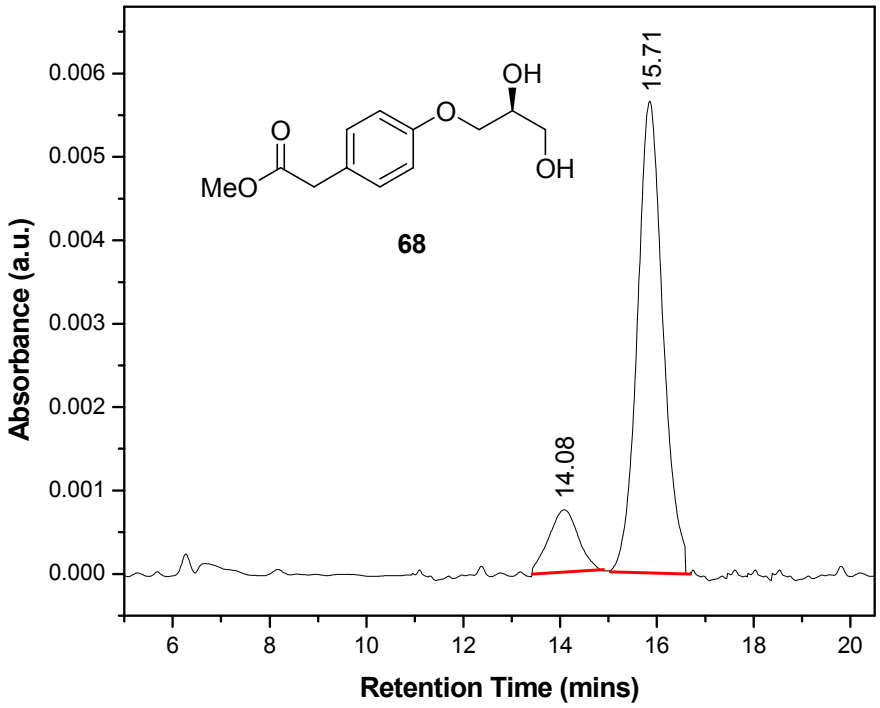
1.4.1 (*S*)-Atenolol

Amino alcohol **69,** the penultimate intermediate in the synthesis of (*S*)-atenolol (**5**), was synthesized using asymmetric dihydroxylation of allyl ether **67** as the key reaction (**Scheme 18**).



Scheme 18: (i) allyl bromide, K_2CO_3, acetone, 75 °C, 96%; (ii) $K_3Fe(CN)_6$, K_2CO_3, cat. OsO_4, $(DHQD)_2$-PHAL, *tert*-BuOH,H_2O (1:1), 92%, 86% ee; (iii) DEAD, PPh_3, benzene, reflux, 78%; (iv) isopropylamine, H_2O, 25 °C, 78%.

Accordingly, allylic ether **67**,[24] prepared by the *O*-allylation of phenolic ester **13** with allyl bromide in the presence of base, was subjected to Os-catalyzed asymmetric dihydroxylation using $(DHQD)_2$-PHAL as ligand in *tert*-BuOH:H_2O mixture at 0 °C to produce the corresponding chiral diol **68** in 86% ee; (chiral HPLC (**Fig. 9**)). The ^{1}H NMR spectrum of diol **68** showed signals at δ 3.78 (m) corresponding to methine (-OCH_2**C**H**O**H) and methylene (-**C**$\mathbf{H_2}$OH) protons. Its ^{13}C NMR showed typical signals at δ 63.5 and 70.3 corresponding to methine (-OCH_2**C**HOH) and methylene (-**C**H_2OH) carbons respectively.



Peak No.	Ret. Time (mins)	Area (mAU*s)	Area (%)
1	14.08	14113	6.99
2	15.71	187512	93.01

Fig. 9: HPLC Chromotogram of diol 68

The diol **68** was readily converted in a single step into epoxide **15** in 78% yield under Mitsunobu conditions[24] (i.e. diethyl azodicarboxylate and PPh_3). The ^1H NMR spectrum of epoxide **15** showed typical signals at δ 2.75 (dd) and 2.9 (dd) for methine (-**CH**O) and 3.3 (m) for methylene (-**CH$_2$**O) protons respectively. Its ^{13}C NMR spectrum showed characteristic signals at δ 44.4 and 68.5 for methylene carbons and a signal at δ 48.8 corresponds to the methine carbon of the epoxide moiety (**Fig. 10**).

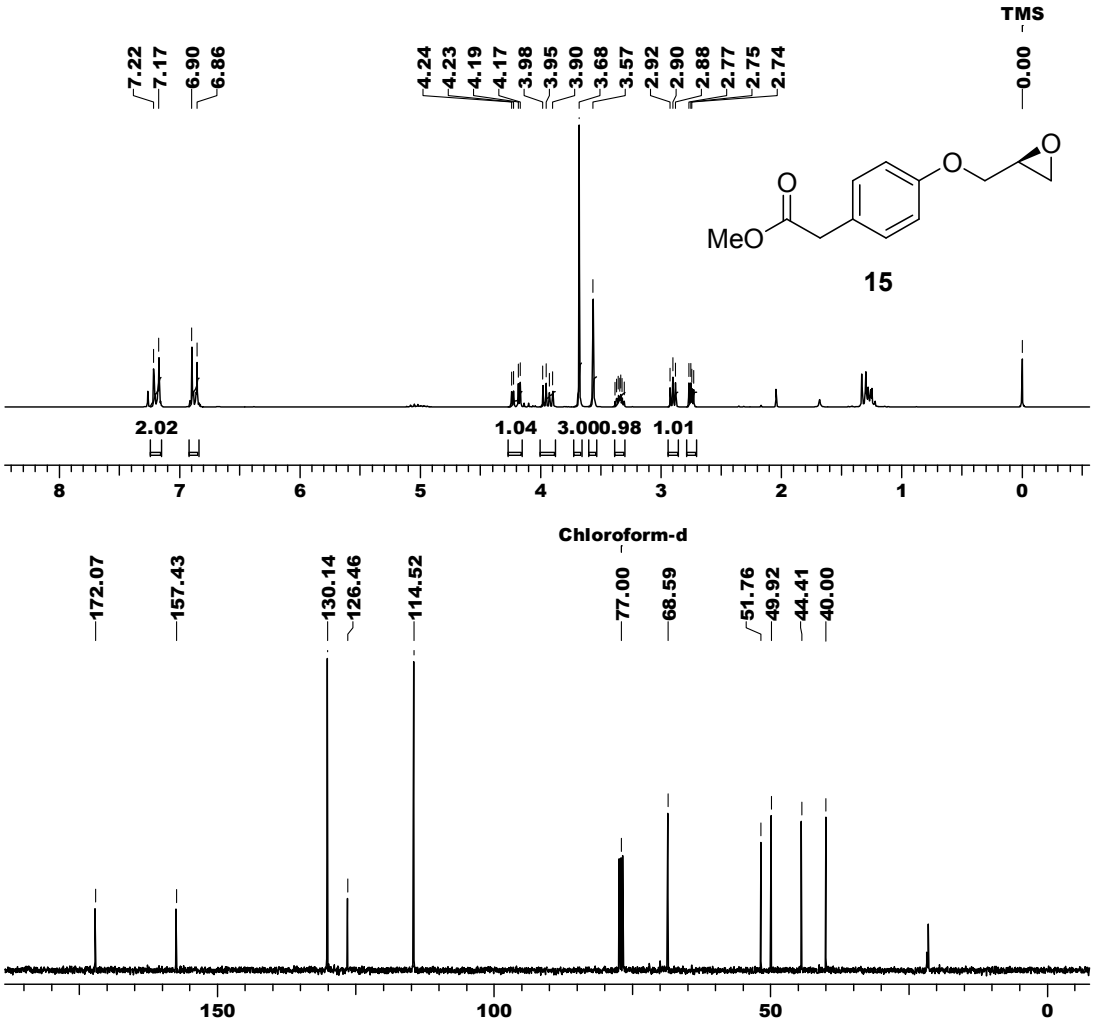


Fig. 10: ^{1}H and ^{13}C NMR spectra of epoxide 15

The regiospecific ring opening of epoxide **15** with isopropylamine was achieved to give amino alcohol **69** in 78% yield. The ^{1}H NMR spectrum of amino alcohol **69** showed a signal at δ 1.1 (d) for two methyl groups of isopropyl unit. Its ^{13}C NMR showed typical signals at δ 22.2 and 48.7 for methyl and methine carbons of the isopropyl group (**Fig. 11**).

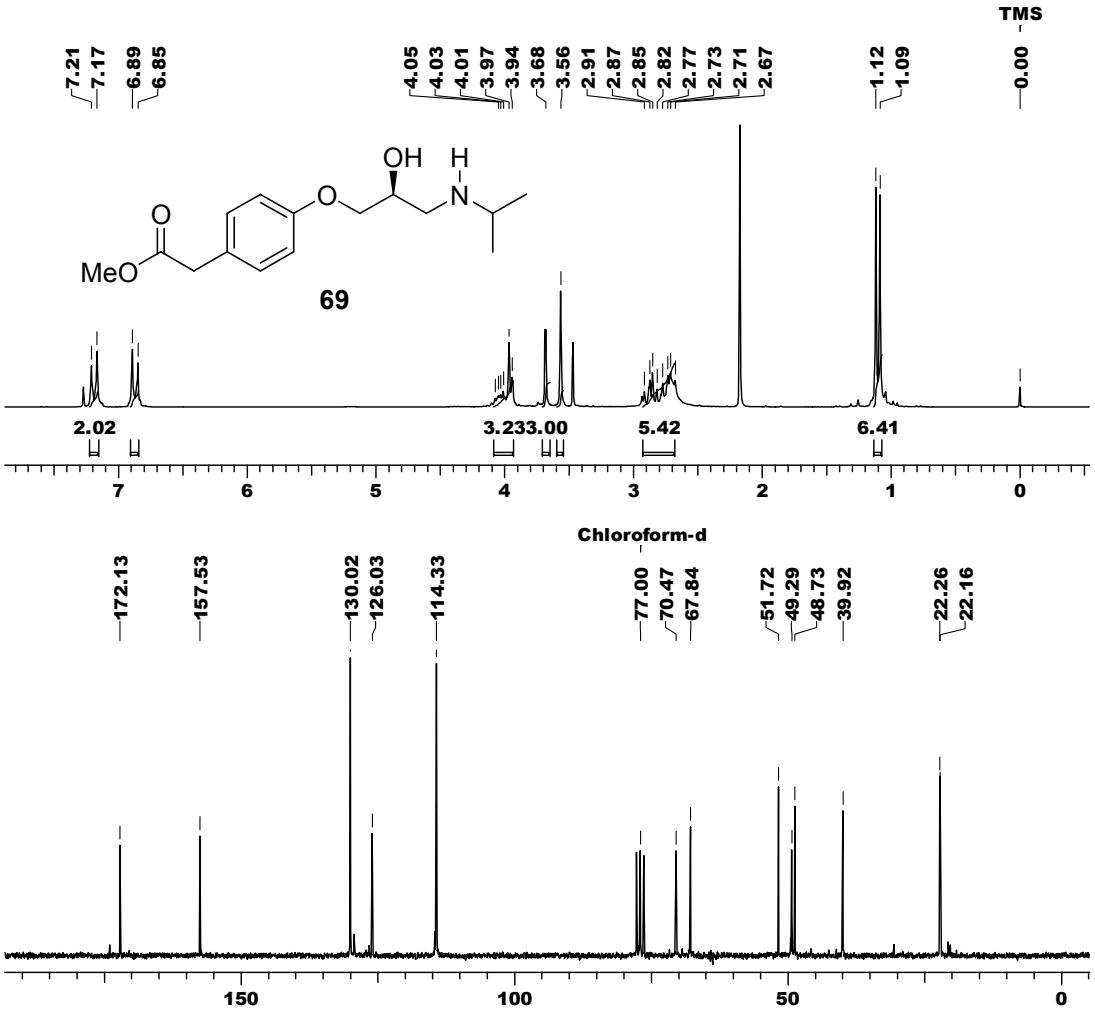
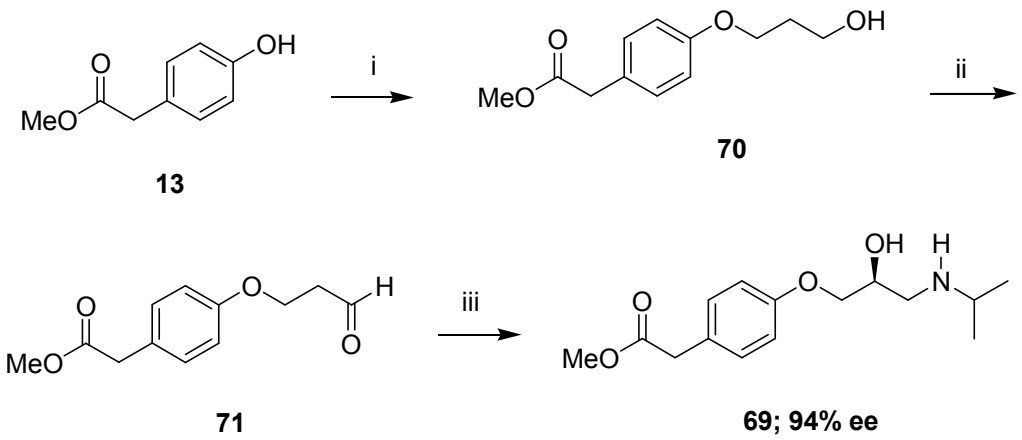


Fig. 11: ^{1}H and ^{13}C NMR spectra of amino alcohol 69

Although the ADH route to **69** was facile and high yielding, it suffers from low enantioselectivity (86% ee). Hence, it was of interest to provide an alternative, organocatalytic method by employing L-proline-catalyzed *α*-aminooxylation of aldehyde **71** as described below (**Scheme 19**).



Scheme 19: (i) 3-bromopropan-1-ol, K_2CO_3, acetone, 75 °C, 80%; (ii) IBX, DMSO, 25 °C, 1 h, 78%; (iii) (a) L-proline, CH_3CN, PhNO, -20 °C, 24 h; (b) isopropylamine; (c) 10% Pd/C, H_2 (1 atm.), 25 °C, CH_3OH, 68%, 94% ee.

In the second approach, *O*-alkylation of phenol **13** with 3-bromopropanol under basic conditions was carried out to afford alcohol **70** in 80% yield. The ^{1}H NMR spectrum of alcohol **70** showed signals at δ 3.83 (t) and 4.08 (t) corresponding to two methylene groups (**CH$_2$**O and **CH$_2$**OH) respectively. Its ^{13}C NMR spectrum displayed carbon signals at δ 31.8, 59.3, and 64.9 due to the methylene carbons of the propyl side chain. Alcohol **70** was subsequently oxidized with IBX in DMSO to give the corresponding aldehyde **71** in 78% yield. The ^{1}H NMR spectrum of the aldehyde **71** showed a singlet at δ 9.86 for aldehydic proton. Its ^{13}C NMR spectrum showed a characteristic signals at δ 200.1 due to carbonyl carbon (**Fig. 12**). Its IR spectrum exhibited a characteristic strong band at 1732 cm^{-1} indicating the presence of a carbonyl group. We have developed a one-pot procedure, for the first time, in which aldehyde **71** was transformed into chiral amino alcohol **69.** Thus, α-aminooxylation of aldehyde **71** with nitrosobenzene as the oxygen source and L-proline (10 mol%) at -20 °C gave aminooxy aldehyde *in situ*, which was treated with isopropylamine followed by *in situ* reduction of the resulting imine

intermediate with 10% Pd/C and H_2 (1 atm.), all occurring simultaneously to give amino alcohol **69** in 68% yield and 94% ee.

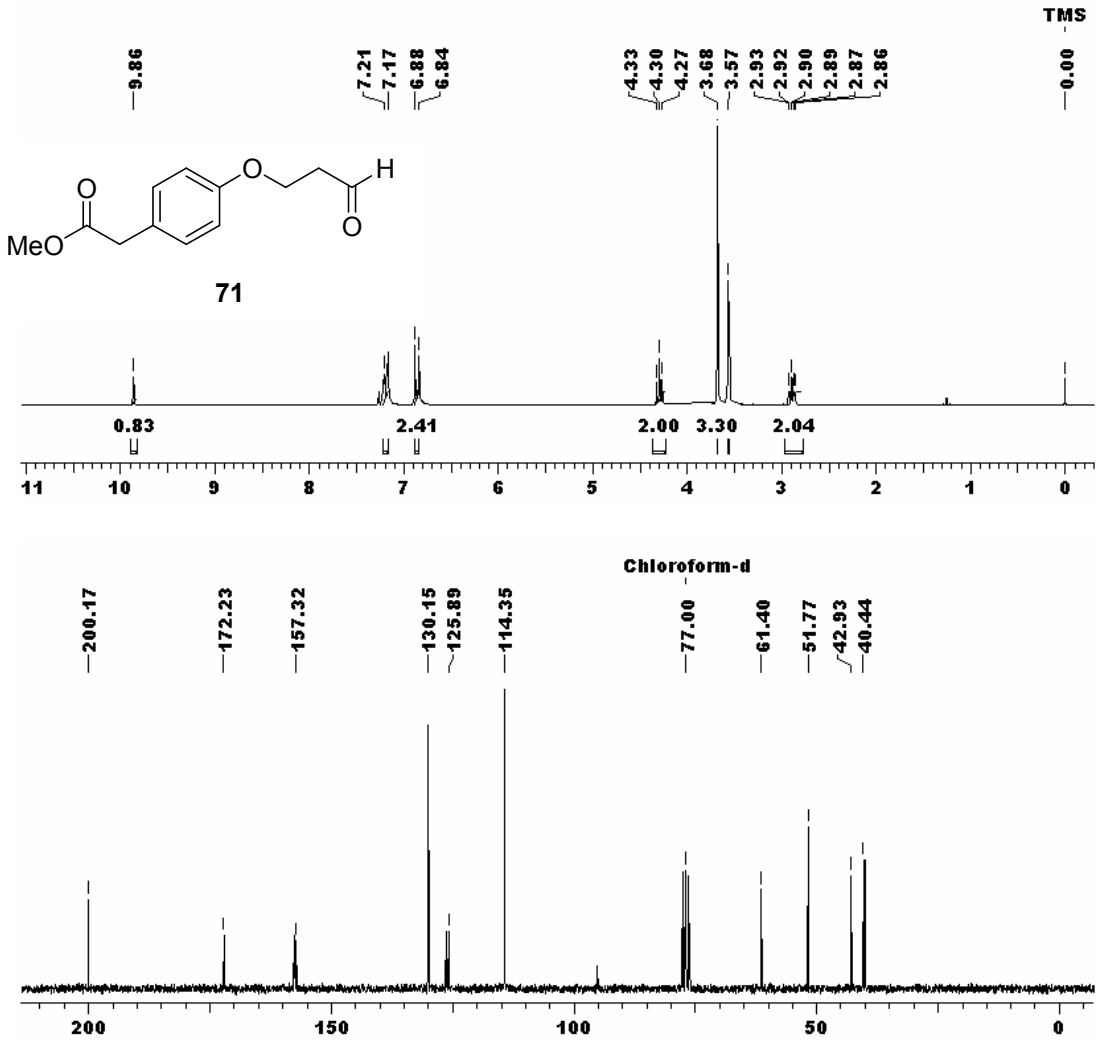
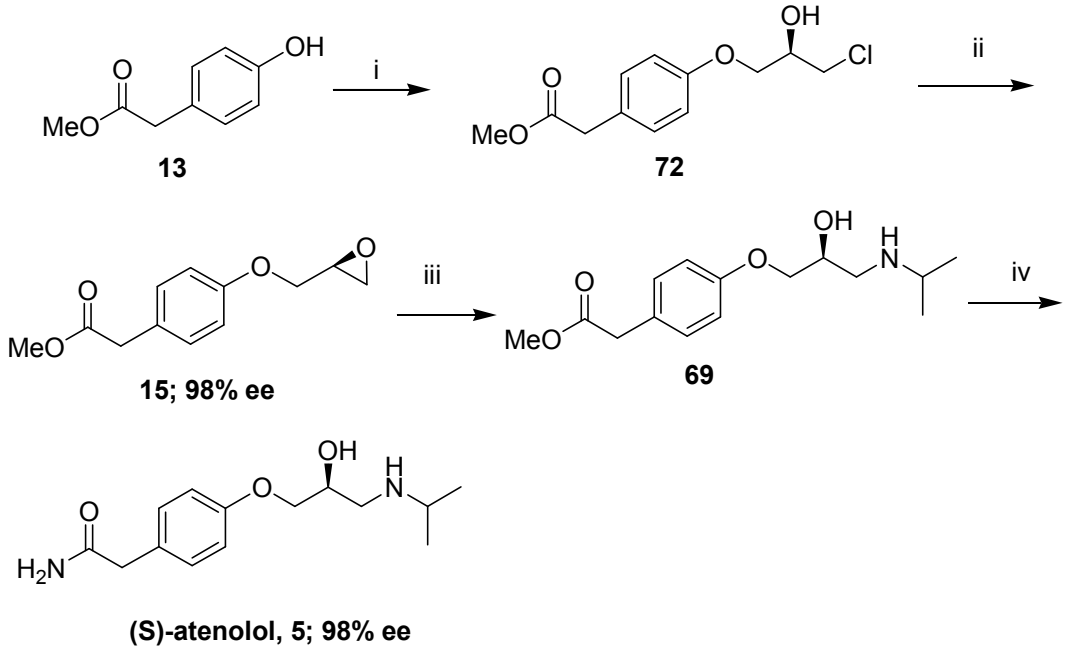


Fig. 12: ^{1}H and ^{13}C NMR spectra of aldehyde 71

Although the optical purity of (*S*)-atenolol (**5**) has increased considerably (94% ee) in L-proline-catalyzed α-aminooxylation route, the low overall yield (30.6%) of this route prompted us to use the cobalt-catalyzed kinetic resolution of commercially available (±)-epichlorohydrin with phenol **13** as the nucleophile. The synthetic route for (*S*)-atenolol

(**5**) using cobalt-catalyzed asymmetric kinetic resolution of (±)-epichlorohydrin is shown in **Scheme 20**.



Scheme 20: (i) epichlorohydrin, (*R,R*)-Co-(salen).$OCOCF_3$, 25 °C, 24 h, 87%; (ii) K^{t}OBu, THF, 0 °C, 93%, 98% ee; (iii) isopropylamine, H_2O, 25 °C, 78%, 98% ee; (iv) NH_4OH, CH_3OH, 25 °C, 72%, 98% ee.

In this approach, reaction of 2.2 equiv. of (±)-epichlorohydrin with phenol **13** in the presence of *(R,R)*-(salen)Co[$OCOCF_3$] complex (0.044 equiv) at 25 °C was carried out to give the chloro alcohol **72** in 87% yield based on phenol **13.** The ^{1}H NMR spectrum of the chloro alcohol **72** showed signals at δ 2.58 (brs) corresponding to the hydroxyl proton. Its ^{13}C NMR spectrum showed signals at 45.7 (**C**H_2Cl), 68.4 (**C**HOH) and 69.6 (**C**H_2O-Ar) corresponding to methylene and methine carbons of the propyl moiety (**Fig. 13**). Treatment of chloro alcohol **72** with base gave the corresponding epoxide **15** in 93% yield and 98% ee (chiral HPLC (**Fig. 14**)). The regiospecific ring opening of epoxide **15** with isopropylamine gave the amino alcohol **69** in 78% yield. Finally, ammonolysis of ester **69** with aq. ammonium hydroxide furnished atenolol (**5**) in 72% yield. The spectral

data obtained for (*S*)-atenolol (**5**) were in full agreement with the values reported in the literature.[24]

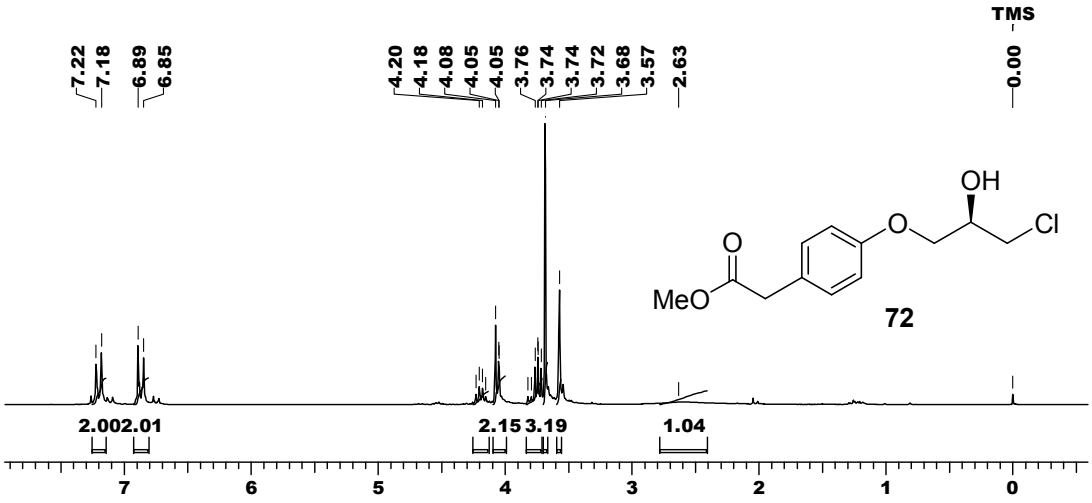
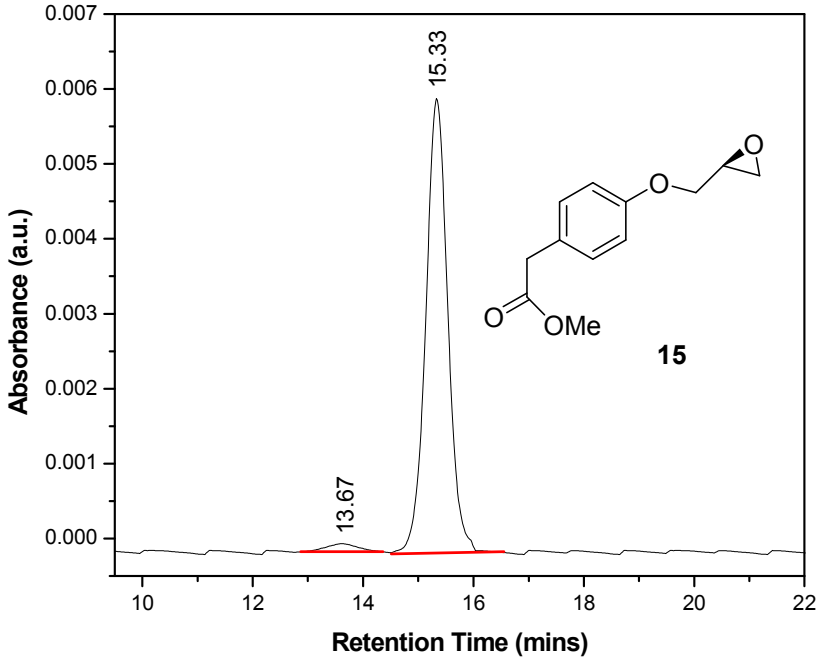


Fig. 13: ^{1}H NMR spectrum of chloro alcohol 72



Peak No.	Ret. Time (mins)	Area (mAU*s)	Area (%)
1	13.67	15.20	0.99
2	15.33	152052	99.01

Fig. 14: HPLC Chromotogram of epoxide 15

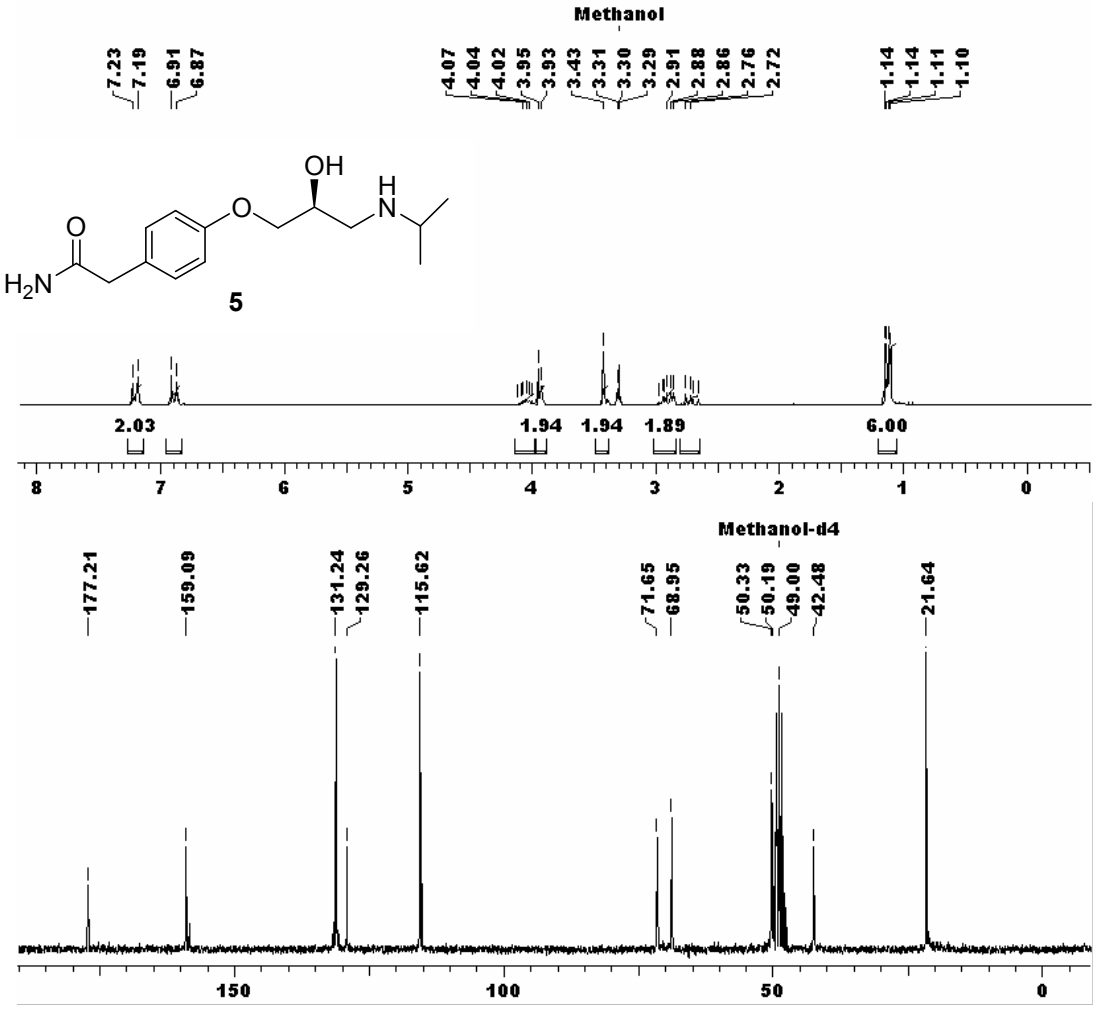
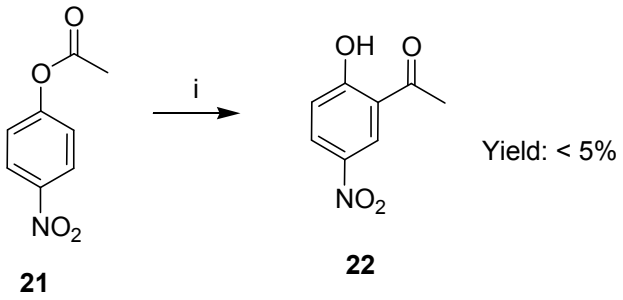


Fig. 15: ^{1}H and ^{13}C NMR spectra of (*S*) atenolol (5)

1.4.2 (*S*)-Celiprolol and other β-blockers

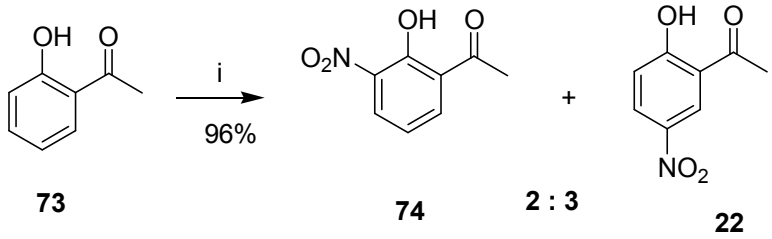
(*S*)-Celiprolol (**6**) is an important antihypertensive drug having 3-aryloxy-1,2-amino alcohol moiety. For the synthesis of (*S*)-celiprolol (**6**), Fries' migration (anhyd. $AlCl_3$, nitrobenzene, 140 °C) of 4-nitrophenyl acetate (**21**) by following the reported procedure[26] gave the Fries' migrated product **22** in <5% yield (**Scheme 21**).



21 22

Scheme 21: (i) anhyd. $AlCl_3$, nitrobenzene, 140 °C, 5 h, < 5%.

In order to prepare nitrophenol **22** in high yields, we have developed a new method of direct nitration of commercially available 2-hydroxyacetophenone (con. HNO_3, acetic acid, 25 °C), which produced a mixture of *ortho* and *para* nitrophenols in the ratio of 2:3. However, both **74** and **22** were readily separated by column chromatographic purification (**Scheme 22**).

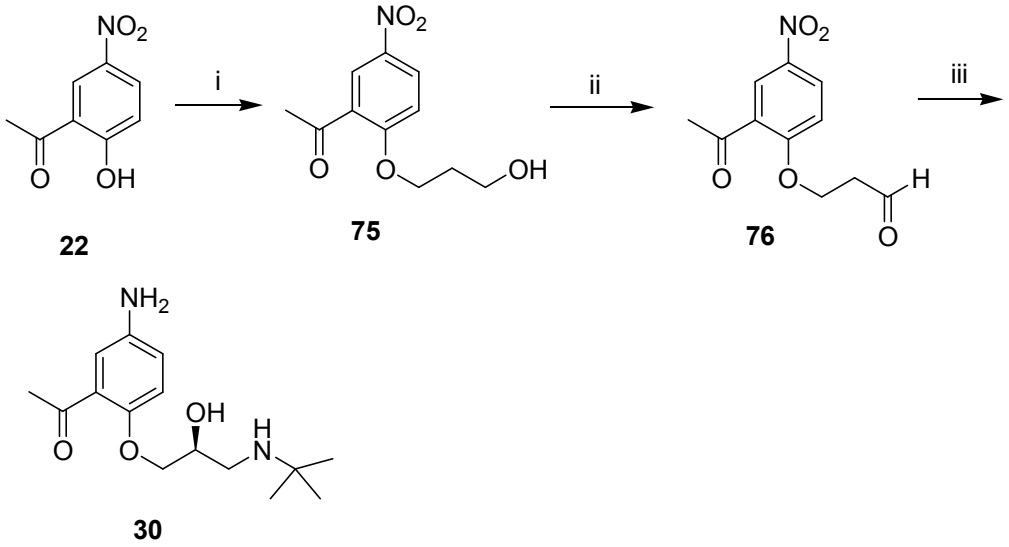


73 74 2 : 3 22

Scheme 22: (i) con. HNO_3, AeOH, 25 °C, 96% (ratio of *o:p* = 2: 3)

Having obtained 2-hydroxy-5-nitroacetophenone (**22**) in reasonable yield, its *O*-alkylation with 3-bromopropanol under basic conditions afforded the corresponding nitro alcohol **75** in 68% yield (**Scheme 23)**. The ^{1}H NMR spectrum of alcohol **75** showed signals at δ 3.91 (t) and 4.34 (t) corresponding to the methylene protons (**CH_2**O) of propyl group. A typical signal at δ 2.65 corresponds to methyl protons (ArCO**CH_3**). Also signal at δ 7.11 (d), 8.32 (dd) and 8.61 (d) are due to the aromatic protons. Its ^{13}C NMR spectrum displayed typical signals at δ 31.4, 58.8 and 66.7 corresponding to methylene

carbons of the propyl chain and a signal at δ 193.3 due to carbonyl carbon. The other signals at δ 112.6, 126.2, 127.5, 128.7, 140.6 and 162.5 are due to aromatic carbons.



Scheme 23: (i) 3-bromopropan-1-ol, K_2CO_3, acetone, 75 °C, 68%; (ii) IBX, DMSO, 25 °C, 2 h, 65%; (iii) (a) L-proline, CH_3CN, PhNO, -20 °C, 24 h; (b) *tert*-butylamine; (c) 10% Pd/C, H_2 (20 psig), 25 °C, CH_3OH, 56%, 88% ee.

Alcohol **75** was subsequently oxidized with IBX in DMSO to give the corresponding aldehyde **76** in 65% yield. The ^{1}H NMR spectrum of the aldehyde **76** showed a singlet at δ 9.93 for aldehydic proton. The other signals at δ 3.14 (t) and 4.56 (t) correspond to (O-CH_2-**CH_2**) and (O-**CH_2**-CH_2) protons respectively (**Fig. 16**). Its ^{13}C NMR spectrum showed a characteristic signal at δ 198.5 due to carbonyl carbon. Its IR spectrum also exhibited a characteristic strong bands at 1737 and 1513 cm^{-1} confirming the presence of aldehyde and nitro groups respectively.

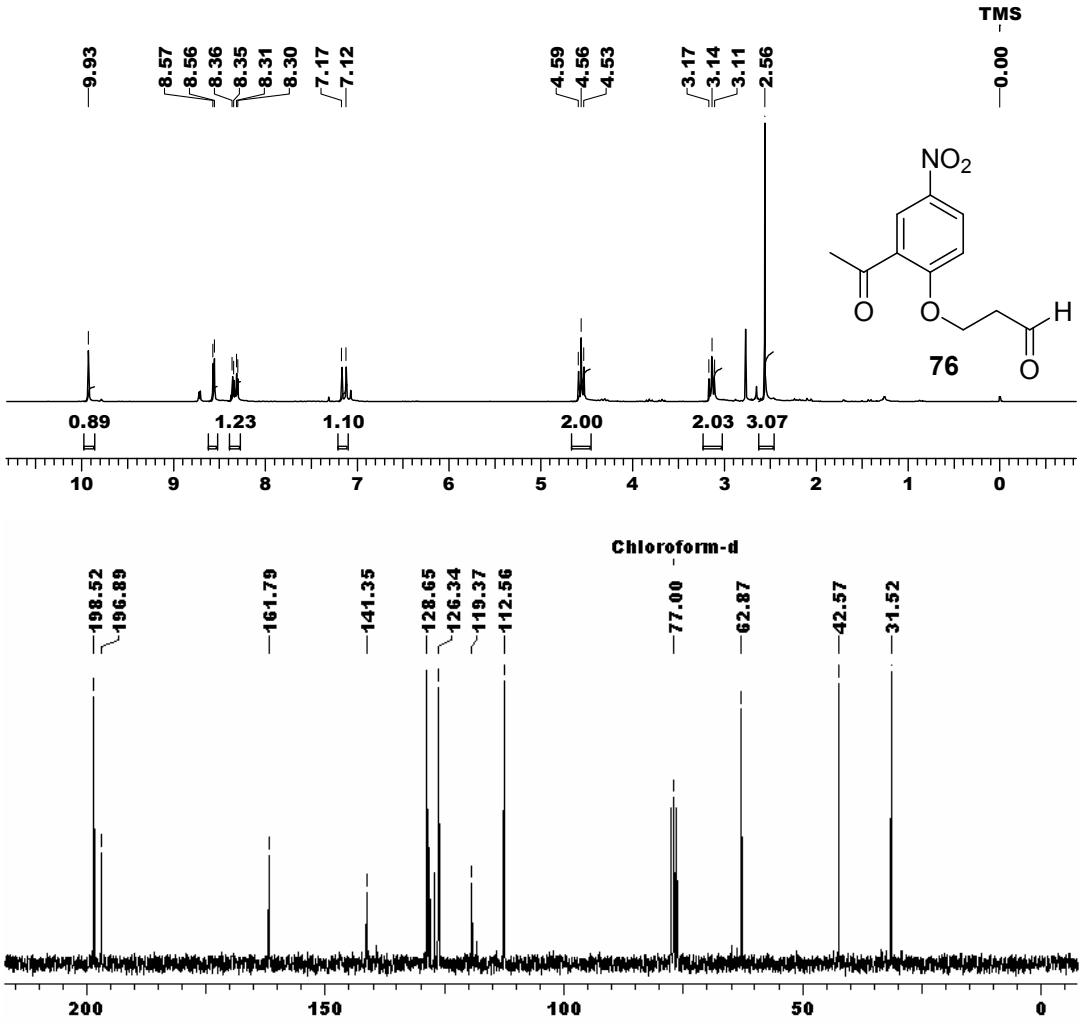


Fig. 16: ^{1}H and ^{13}C NMR spectra of aldehyde 76

We have developed a new, one-pot procedure in which aldehyde **76** was readily transformed into chiral amino alcohol **30** under mild conditions. Thus, *α*-aminooxylation of aldehyde **64** with nitrosobenzene as the oxygen source and L-proline (10 mol%) as catalyst gave aminooxy aldehyde *in situ,* which was then treated with *tert*-butylamine followed by its *in situ* reduction of the resulting imine with 10% Pd/C and H_2 (20 psig), all occurring sequentially afforded amino alcohol **30** in 56% yield. The ^{1}H NMR spectrum of amine **30** showed a singlet at δ 1.42 for methyl groups of *tert*-butyl moiety

(**Fig. 17**). Its ^{13}C NMR showed characteristic signals at δ 27.7 and 52.5 for methyl and quaternary carbons of the *tert*-butyl moiety respectively.

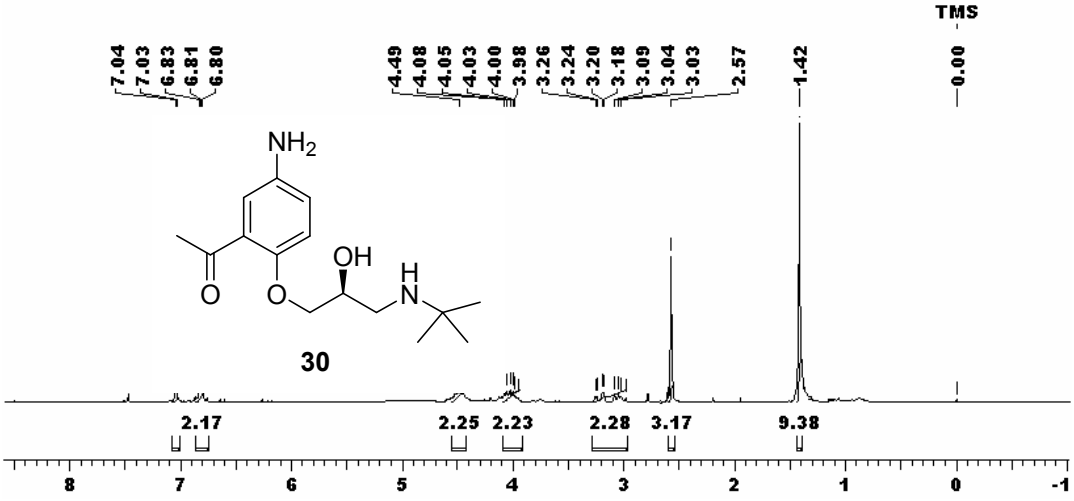
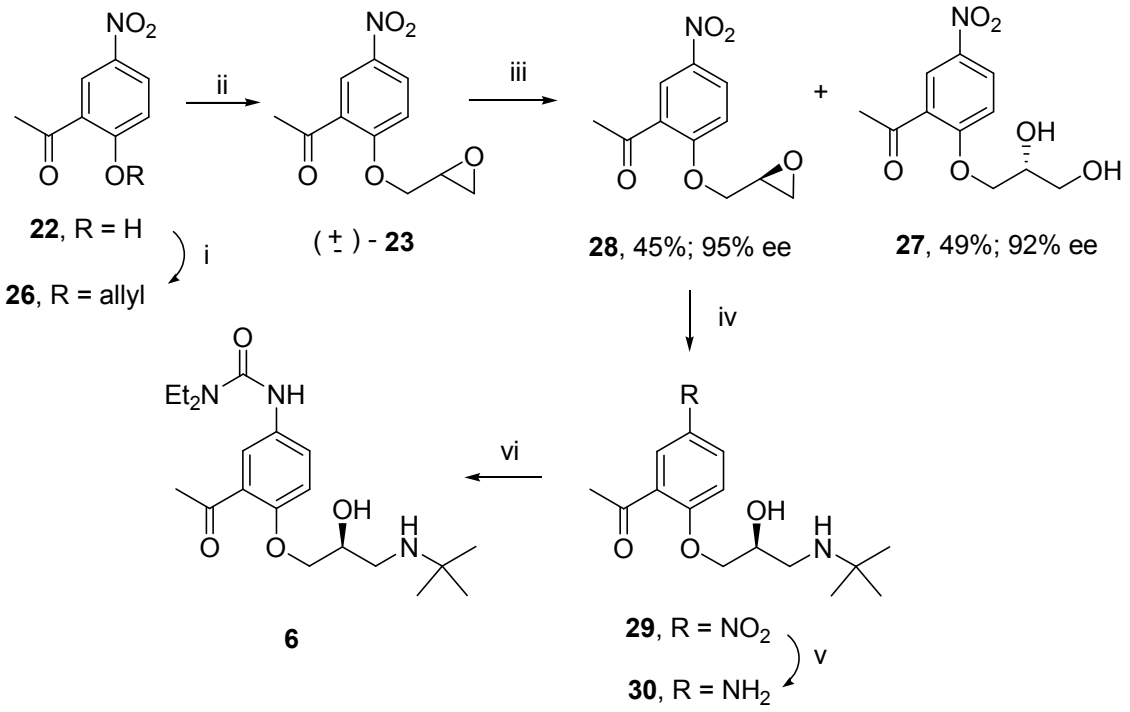


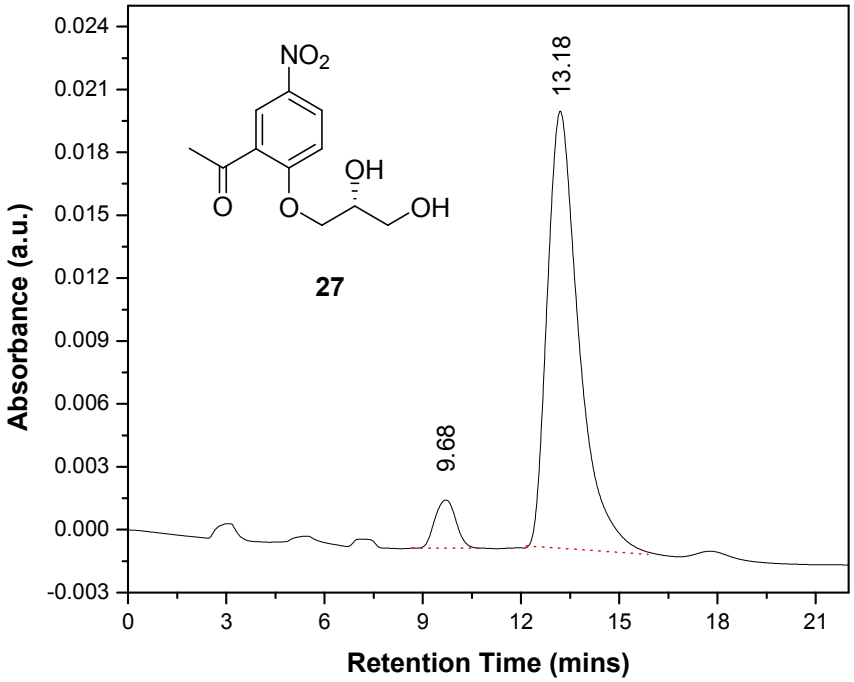
Fig. 17: ^{1}H NMR spectrum of amine 30

Although the proline catalyzed α-aminooxylation of aldehyde **64** gave chiral intermediate **30** in good yield, it suffers from low enantioselectivity (88% ee). Hence, it was of interest to provide an alternate synthesis of celiprolol (**6**) by employing cobalt-catalyzed hydrolytic kinetic resolution (HKR)[41] of epoxide **23**. The synthetic scheme for (*S*)-celiprolol (**6**) *via* HKR is shown in **Scheme 24**.



Scheme 24: (i) allyl bromide, K_2CO_3, acetone, 75 °C, 96%; (ii) *m*-CPBA, $CHCl_3$, 25 °C, 95%; (iii) (*R,R*)-Co(salen).OAc, H_2O (0.55 equiv.), THF, 0 °C, 24 h (45% yield and 95% ee for **28** and 49% yield and 92% ee for **27**); (iv) *tert*-butylamine, H_2O, 25 °C, 86%, (v) 10% Pd/C, H_2 (20 psig), CH_3OH, 25 °C, 92%. (vi) diethylcarbamoyl chloride, Et_3N, THF, 40 °C, 48 h, 90%, 95% ee.

In this approach, our attempts to prepare the racemic epoxide **23** by the direct *O*-alkylation of phenol **22** with epichlorohydrin under basic conditions following reported procedure[26] have failed. Hence, we have carried out two-step procedure of allylation of **22** with allyl bromide under basic condition to give allyl ether **26** in 96% yield, followed by epoxidation of allyl ether **26** using *m*-chloroperbenzoic acid in CH_2Cl_2 at 25 °C to give the corresponding racemic epoxide **23** in 95% yield. The racemic epoxide **23** was then subjected to hydrolytic kinetic resolution [(*R,R*)-salenCo(III).OAc (0.5 mol%), THF, distilled H_2O (0.55 equiv), 0 ºC, 24 h] to afford chiral epoxide **28** in 45% yield and 95% ee along with its diol **27** in 49% yield and 92% ee (chiral HPLC (**Fig. 18**)).



Peak No.	Ret. Time (mins)	Area (mAU*s)	Area (%)
1	9.68	52426	3.99
2	13.18	1258240	96.01

Fig. 18: HPLC Chromotogram of diol 27

The chiral epoxide **28** was readily separated from its diol **27** by column chromatographic purification. The ^{1}H NMR spectrum of epoxide **28** showed typical signals at δ 2.82 (dd) and 3.0 (dd) for methylene (CH-**C**$\mathbf{H_2}$-O) protons of epoxide. Its ^{13}C NMR spectrum showed characteristic signals at δ 44.1 and 70.4 corresponding to methylene carbons and a signal at δ 49.2 is due to the methine carbon of the epoxide moiety. A typical signal at δ 196.8 is due to carbonyl carbon and other signals at δ 112.9, 126.0, 128.0, 128.4, 141.1 and 161.7 are due to aromatic carbons (**Fig. 19**).

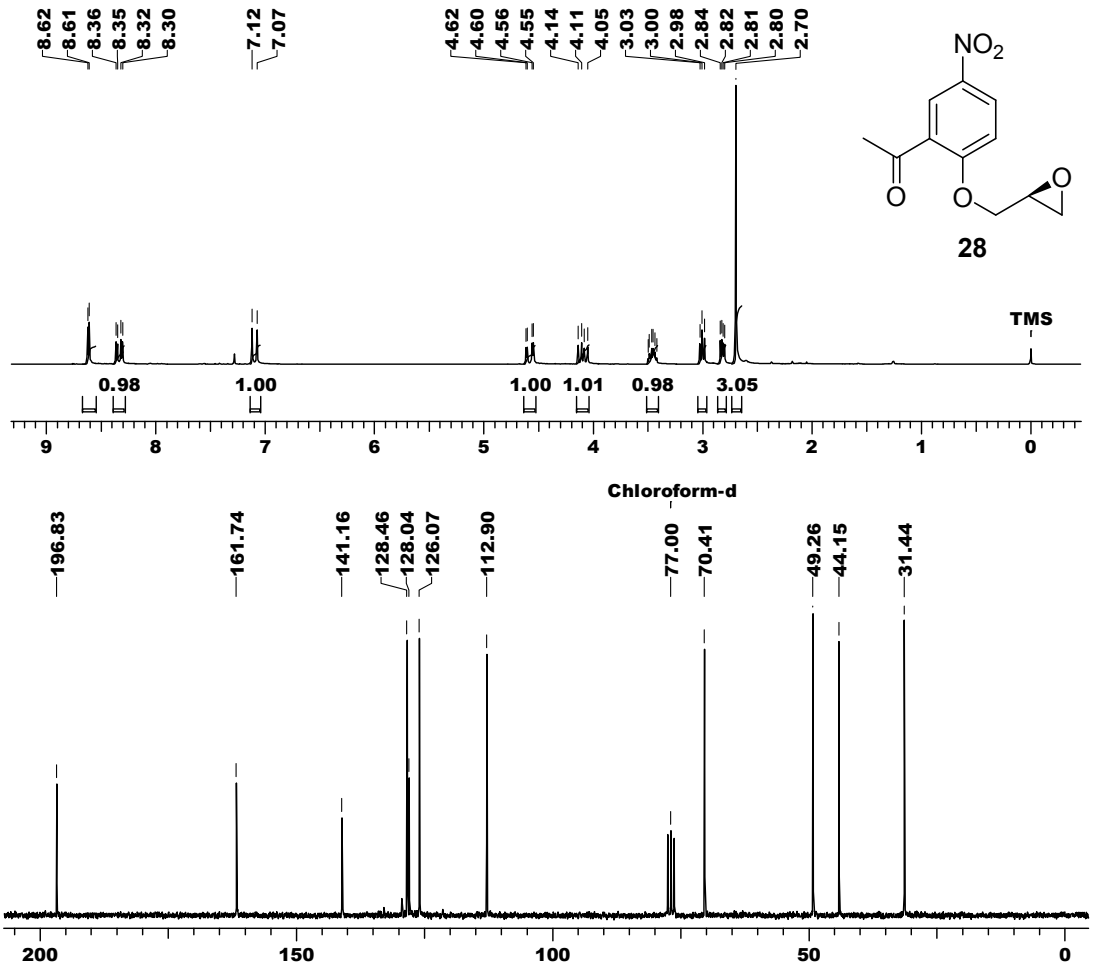


Fig. 19: ^{1}H and ^{13}C NMR spectra of epoxide 28

Regiospecific ring opening of the epoxide **28** with *tert*-butylamine afforded amino alcohol **29** in 86% yield. The ^{1}H NMR spectrum of amino alcohol **29** showed a singlet at δ 1.14 for methyl protons of *tert*-butyl group. Its ^{13}C NMR spectrum showed two typical signals at δ 28.3 and 31.5 for methyl and quaternary carbons of *tert*-butyl moiety respectively in addition to other characteristic signals. The nitro group in **29** was then hydrogenated [(20 psig H_2 pressure), 10% Pd/C, 25 ºC] to produce amino compound **30** in 92% yield. Finally, amino alcohol **30** was condensed with diethylcarbamoyl chloride (DECC) to afford (*S*)-celiprolol (**6**) in 90% yield with 95% ee (**Fig. 20**). The spectral data

obtained for (*S*)-celiprolol (**6)** were in full agreement with the values reported in the literature.[27]

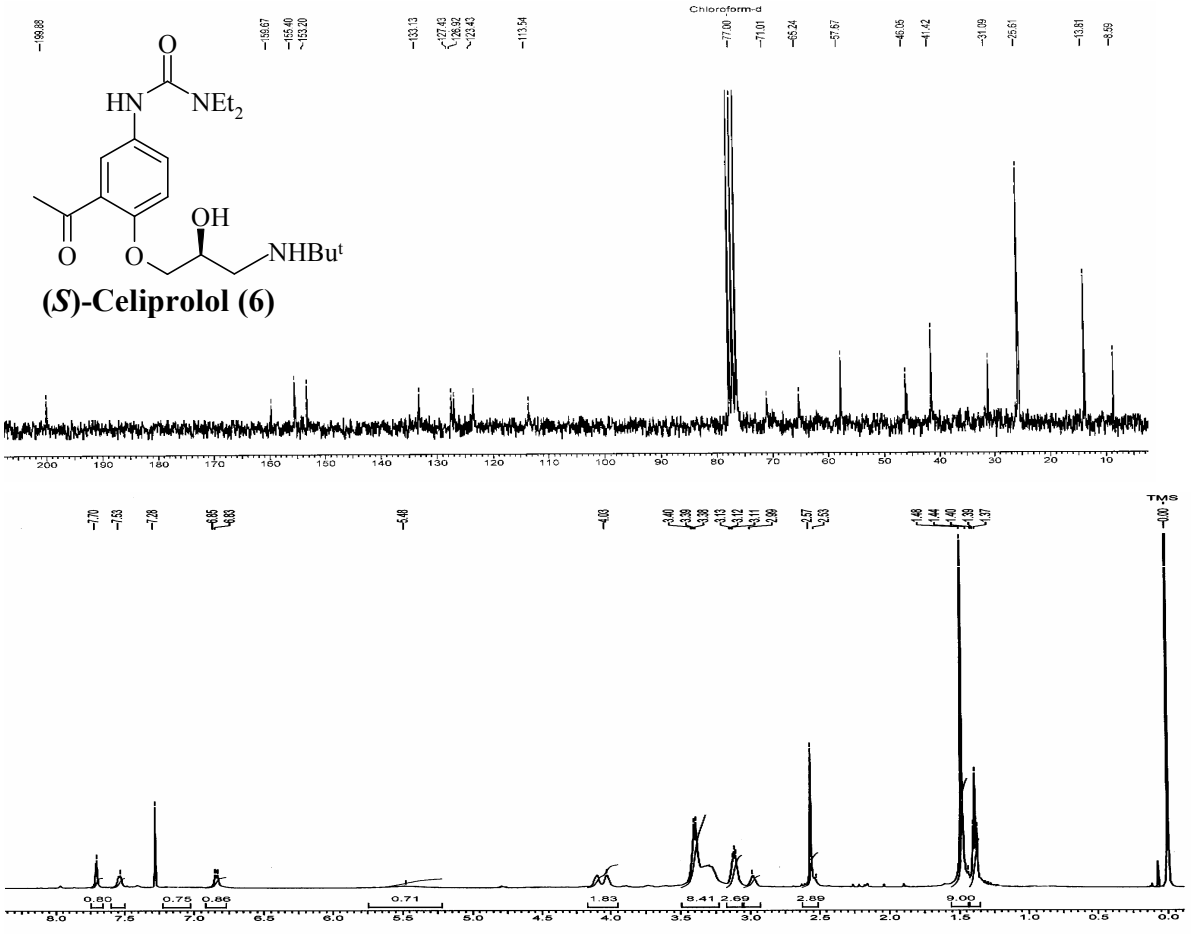
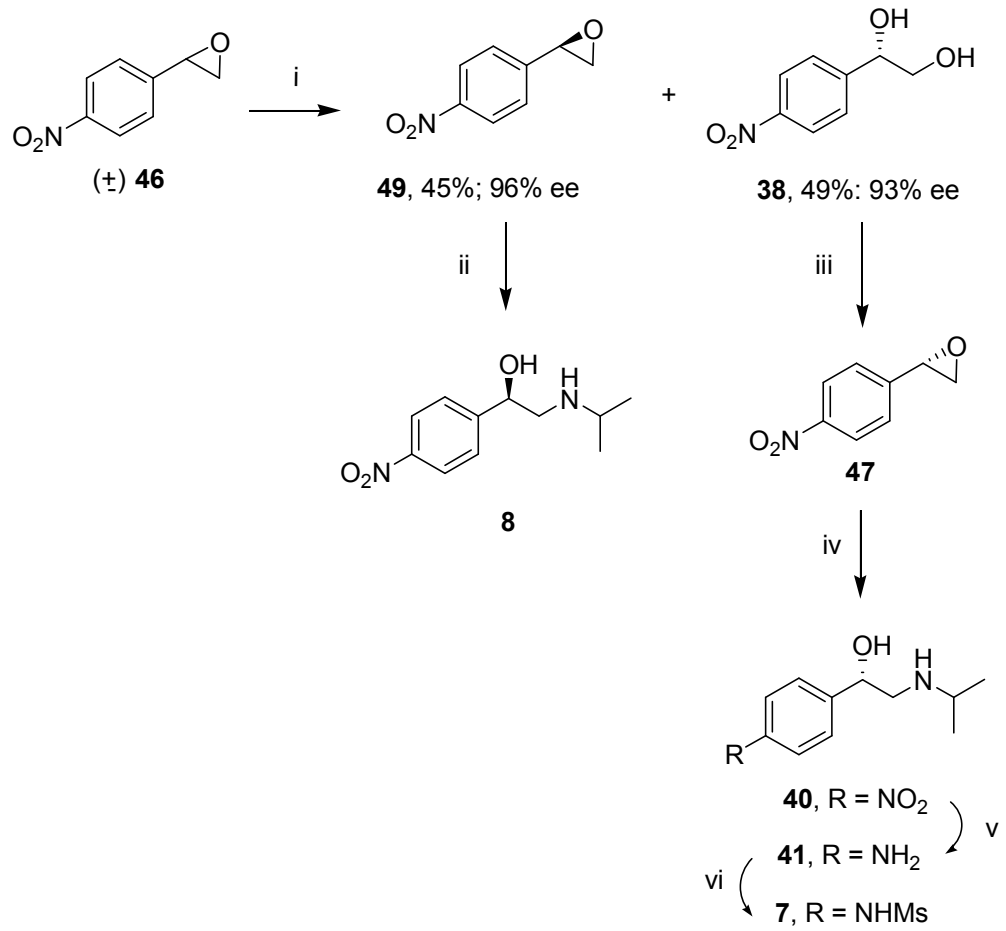


Fig. 20: ^{13}C and ^{1}H -NMR spectra of (*S*)-celiprolol (**6**)

(*S*)-Sotalol (**7**) and (*R*)-nifenalol (**8**) are some of the other important *β*-adrenergic blockers bearing a similar structural unit of 2-amino-1-arylethanol**.** We have employed cobalt-catalyzed hydrolytic kinetic resolution of epoxide **46** as a key step to synthesize both (*S*)-sotalol (**7**) and (*R*)-nifenalol (**8**) (**Scheme 25)**.



Scheme25: (i) (*R,R*)-Co(salen).OAc, H_2O (0.55 equiv.), 0 °C, 24 h, (45% yield, 96% ee for **49** and 49% yield, 93% ee for **38**); (ii) isopropylamine, H_2O, 25 °C, 85%, 96% ee; (iii) DEAD, PPh_3, benzene, reflux, 78%; (iv) isopropylamine, H_2O, 25 °C, 89%, 93% ee; (v) 10% Pd/C, H_2 (20 psig), CH_3OH, 25 °C, 92%, (vi) MsCl, pyridine, 25 °C, 72%, 93% ee.

The racemic epoxide **46**[32] when subjected to hydrolytic kinetic resolution[41] [(*R,R*)-salenCo(III).OAc (0.5 mol %), THF, distilled H_2O (0.55 equiv), 0 ºC, 24 h], gave the chiral epoxide **49** in 45% yield and 96% ee (chiral HPLC) along with its chiral diol **38** in 49% yield and 93% ee. The ^{1}H NMR spectrum of epoxide **49** showed two signals at δ 2.79 (dd) and 3.24 (dd) for methylene protons and 3.98 (dd) for methine protons. Its ^{13}C NMR spectrum displayed carbon signals at δ 51.2 and 51.5 corresponding to the

methylene and methine carbons respectively. Regiospecific ring opening of epoxide **49** with isopropylamine gave (*R*)-nifenalol (**8)** in 85% yield with 96% ee (**Fig. 21**).

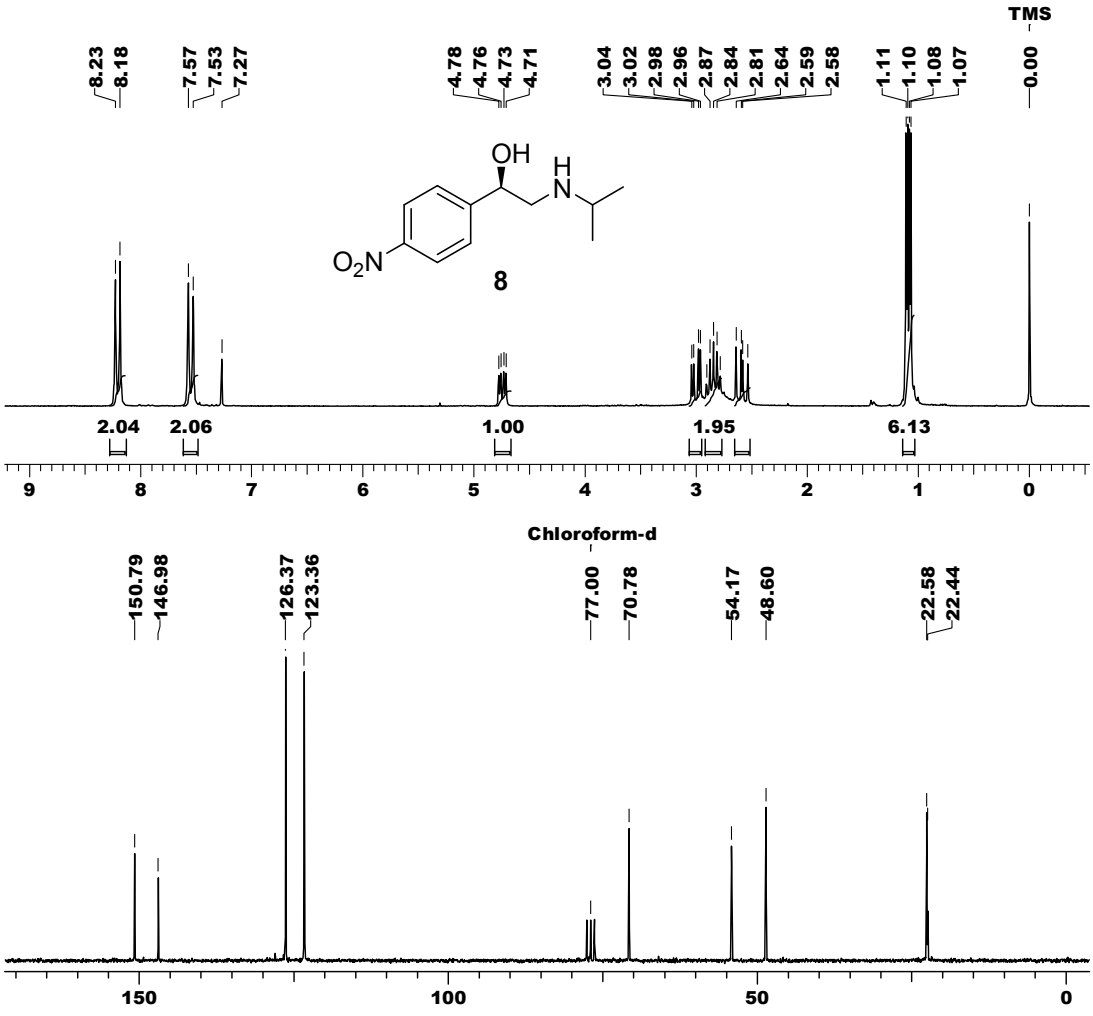


Fig. 21: ^{1}H and ^{13}C NMR spectra of nifenalol (8)

The ^{1}H NMR spectrum of diol **38** showed two distinct doublets at δ 4.69 and 4.89 for methylene protons. Its ^{13}C NMR spectrum displayed carbon signals at δ 67.2 and 73.3 for the methylene and methine carbons respectively. The diol **38** was successfully transformed into epoxide **47** in 78% yield under Mitsunobu conditions (i.e. diethyl azodicarboxylate and PPh_3). Regiospecific ring opening of epoxide **47** with isopropylamine gave amino alcohol **40** in 89% yield. The ^{1}H NMR spectrum of amino

alcohol **40** showed a typical signal at δ 1.15 (dd) for methyl protons of isopropyl group. Its ^{13}C NMR spectrum displayed carbon signals at δ 22.5 and 48.6 for the methyl and methine carbons of isopropyl moiety. Finally, the nitro group was reduced (10% Pd/C at 20 psig H_2) to obtain amine **41** in 92% yield followed by its mesylation gave (*S*)-sotalol (**7**) in 72% yield and 93% ee. The spectral data obtained for (*S*)-sotalol (**7**)[30] and (*R*)-nifenalol (**8**)[32] were in full agreement with the values reported in the literature.

1.5 Conclusion

In conclusion, we have successfully applied proline-catalyzed α-aminooxylation of aldehydes (**71** and **76**) towards the synthesis of (*S*)-atenolol (**5**) and (*S*)-celiprolol (**6**) respectively. The key feature is that intermediates, 3-aryloxy-1,2-amino alcohols (**69** and **30**) have been obtained in a single step from aldehydes (**71** and **76**) with good yields. We have also achieved the enantioselective synthesis of *β*-blockers namely (*S*)-atenolol (98% ee), (*S*)-celiprolol (95% ee), (*S*)-sotalol (93% ee) and (*R*)-nifenalol (96% ee) using cobalt-catalyzed kinetic resolution of terminal epoxides. In both approaches, the reactions are rapid; requiring a relatively low amount of cheap and nontoxic proline catalyst and catalytic amount of cobalt complex respectively.

1.6 Experimental Section

Methyl 2-(4-(allyloxy)phenyl)acetate (67):

To a stirred solution of methyl 2-(4-hydroxyphenyl)acetate (**13**) (3.32 g, 20 mmol) in dry acetone (50 mL), allyl bromide (3.630 g, 30 mmol) and anhyd. potassium carbonate (5.528 g, 40 mmol) was added at 25 °C. The reaction mixture was then refluxed for 12 h,

allowed to cool, and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were concentrated to give a crude product, which was purified by column chromatography using pet.ether: EtOAc (9:1) as eluent to obtain allyl ether **67**.

Yield: 3.96 g (96%); **IR** ($CHCl_3$, cm^{-1}): 823, 1018, 1178, 1243, 1512, 1613, 1738, 2952; ^{1}**H NMR** (200 MHz, $CDCl_3$): δ 3.54 (s, 2H), 3.67 (s, 3H), 4.50 (d, *J* = 5.3 Hz, 2H), 5.23-5.44 (m, 2H), 5.94-6.10 (m, 1H), 6.84 (d, *J* = 8.7 Hz, 2H), 7.16 (d, *J* = 8.7 Hz, 2H); ^{13}**C NMR** (50 MHz, $CDCl_3$): δ 40.2, 51.8, 68.7, 114.8, 117.4, 126.1, 130.2, 133.3, 157.75, 172.0; **Analysis: $C_{12}H_{14}O_3$** requires C, 69.88; H, 6.84; found C, 69.57, H, 6.92%.

Methyl 2-(4-((*S*)-2,3-dihydroxypropoxy)phenyl)acetate (68):

To a stirred mixture of $K_3Fe(CN)_6$ (8.92 g, 27.1mmol), K_2CO_3 (3.74 g, 27.1 mmol), $(DHQD)_2$-PHAL (0.140 g, 0.18 mmol) in *t*-BuOH:H_2O (1:1, 80 mL) was added a solution of OsO_4 (229 μl, 0.09 mmol, 0.5 M solution in toluene) at 0 °C. The resulting reaction mixture was stirred at the same temperature for 5 minutes and then allyl ether **67** (1.856 g, 9 mmol) was added. The reaction mixture was stirred at 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 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhyd. Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by column chromatography using pet.ether: EtOAc (7:3) as eluent to give pure diol **68**.

Yield: 1.99 g (92%); viscous liquid; $[\alpha]^{25}_D$ +6.14 (*c* 1, $CHCl_3$) {lit.[24] $[\alpha]^{25}_D$ +7.0 (*c* 1, $CHCl_3$)}; **HPLC**: 86% ee, Chiracel OD-H, λ = 254 nm, 2-propanol/hexane (20:80), 1 mL/min, retention time: (*R*)-enantiomer 14.08 min, (*S*)-enantiomer 15.71 min; **IR** ($CHCl_3$, cm^{-1}): 521, 606, 800, 824, 1044, 1114, 1178, 1248, 1301, 1514, 1725, 2932,

3401; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.33 (brs, 2H), 3.55 (s, 2H), 3.68 (s, 3H), 3.72-3.79 (m, 2H), 3.99-4.07 (m, 3H), 6.85 (d, *J* = 8.6 Hz, 2H), 7.18 (d, *J* = 8.5 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 40.1, 51.9, 63.5, 69.01, 70.3, 114.5, 126.5, 130.3, 157.5, 172.4; **Analysis: $C_{12}H_{16}O_5$** requires C, 59.99; H, 6.71; found C, 60.12; H, 6.74%.

Methyl 2-[4-{((*S*)-oxiran-2-yl)methoxy}phenyl]acetate (15):

A mixture of diol **68** (2.4 g, 10 mmol), PPh_3 (3.93 g, 15 mmol) and diethylazo dicarboxylate (2.612 g, 15 mmol) in benzene (30 mL) was refluxed for 18 h. After completion of the reaction, as monitored by TLC, the solvent was distilled off under reduced pressure and the crude product was diluted with ether to precipitate Ph_3PO, which was distilled off by filtration. The filtrate was concentrated and the crude product was purified by chromatography to afford (*S*)-epoxide as a colourless liquid.

Yield: 1.73 g (78%); 86% ee; **$[\alpha]^{25}_D$** +5.21 (*c* 1, $CHCl_3$); { lit.[24] **$[\alpha]^{25}_D$** +5.7 (*c* 1, $CHCl_3$ for 94% ee)}; **IR** ($CHCl_3$, cm^{-1}): 753, 827, 1159, 1243, 1435, 1513, 1613, 1732, 2952; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.75 (dd, *J* = 2.7, 4.9 Hz, 1H), 2.90 (dd, *J* = 4.2, 4.8 Hz,1H), 3.31-3.38 (m, 1H), 3.57 (s, 2H), 3.68 (s, 3H), 3.94 (dd, *J* = 5.7, 11.1 Hz, 1H), 4.21 (dd, *J* = 3.2, 11.0 Hz,1H), 6.88 (d, *J* = 8.7 Hz, 2H), 7.2 (d, *J* = 8.7 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 40.0, 44.4, 49.9, 51.7, 68.5, 114.5, 126.4, 130.1, 157.4, 172.0; **Analysis: $C_{12}H_{14}O_4$** requires C, 64.85; H, 6.35; found C, 64.62; H, 6.05%.

(*S*) 1-[4[(Methoxycarbonyl)methyl]phenoxy]-3-(isopropyl amino)propan-2-ol (69):

A mixture of (*S*)-epoxide **15** (0.666 g, 3 mmol), isopropylamine (2.5 mL, 30 mmol) and water (0.5 mL) was refluxed for 5 h and the isopropylamine was distilled off under reduced pressure. The crude product was diluted with water and extracted with ethyl acetate. The organic layers were dried over anhyd. Na_2SO_4 and concentrated to obtain the

crude product which was purified by column chromatography to afford amino alcohol, **69**.

Yield: 0.66 g (78%); 86% ee; $[\alpha]^{25}_{D}$ -3.66 (*c* 1, $CHCl_3$); {lit.[24] $[\alpha]^{25}_{D}$ -4.0 (*c* 1, $CHCl_3$ for 94% ee)}; **IR** ($CHCl_3$, cm^{-1}): 731, 823, 1038, 1177, 1246, 1513, 1613, 1737, 1891, 2965, 3305; ^{1}**H NMR** (200 MHz, $CDCl_3$): δ 1.11 (d, *J* = 6.3 Hz, 6H), 2.67-2.91 (m, 5H), 3.56 (s, 2H), 3.68 (s, 3H), 3.94-4.07 (m, 3H), 6.87 (d, *J* = 8.7 Hz, 2H), 7.19 (d, *J* = 8.6 Hz, 2H); ^{13}**C NMR** (50 MHz, $CDCl_3$): δ 22.2, 39.9, 48.7, 49.2, 51.7, 67.8, 70.4, 114.3, 126.0, 130.0, 157.5, 172.1; **Analysis: $C_{15}H_{23}NO_4$** requires C, 64.03; H, 8.24; N, 4.98; found C, 64.33; H, 8.04; N, 4.75%.

Methyl 2-(4-(3-hydroxypropoxy)phenyl)acetate (70):

To a stirred mixture of methyl 2-(4-hydroxyphenyl)acetate (**13)** (0.830 g, 5 mmol), and anhyd. K_2CO_3 (0.829 g, 6 mmol) in dry acetone (20 mL) was added 3-bromopropan-1-ol (0.765 g, 5.5 mmol). The reaction mixture was refluxed under stirring for 24 h, allowed to cool and extracted with ethyl acetate (3 x 20 mL). The combined ethyl acetate layers were concentrated to give crude product, which was purified by column chromatography using pet.ether: EtOAc (9:1) as eluent to furnish alcohol **70**.

Yield: 0.89 g (80%); viscous liquid; **IR** ($CHCl_3$, cm^{-1}): 731, 826, 952, 1060, 1246, 1514, 1614, 1738, 2952, 3409; ^{1}**H NMR** (200 MHz, $CDCl_3$): δ 1.95-2.07 (m, 2H), 2.20 (s, 1H), 3.54 (s, 2H), 3.67 (s, 3H), 3.83 (t, *J* = 5.8 Hz, 2H), 4.08 (t, *J* = 5.9 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 7.16 (d, *J* = 8.7 Hz, 2H); ^{13}**C NMR** (50 MHz, $CDCl_3$): δ 31.8, 40.0, 51.7, 59.3, 64.9, 114.3, 125.8, 130.0, 157.8, 172.1; **Analysis: $C_{12}H_{16}O_4$** requires C, 64.27; H, 7.19; found C, 64.12; H, 7.31%.

Methyl 2-(4-(2-formylethoxy)phenyl)acetate (71):

To a solution of alcohol **70** (0.673 g, 3 mmol) in DMSO (10 mL) was added iodoxybenzoic acid (IBX) (1.68 g, 6 mmol) and the reaction mixture was allowed to stir at 25 °C for 1 h. It was then quenched with water and extracted with ethyl acetate (3 x 20 mL). The combined ethyl acetate layers were concentrated to give crude product, which was purified by column chromatography using pet.ether: EtOAc (9:1) as eluent to give aldehyde **71**.

Yield: 0.52 g (78%); viscous liquid; **IR** ($CHCl_3$, cm^{-1}): 823, 1043, 1244, 1436, 1514, 1614, 1732, 2953; ^{1}**H NMR** (200 MHz, $CDCl_3$): δ 2.90 (dt, *J* = 1.5, 6.2 Hz, 2H), 3.57 (s, 2H), 3.68 (s, 3H), 4.3 (t, *J* = 6.2 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 7.19 (d, *J* = 8.6 Hz, 2H), 9.86 (t, *J* = 1.5 Hz, 1H); ^{13}**C NMR** (50 MHz, $CDCl_3$): δ 40.4, 42.9, 51.7, 61.4, 114.3, 125.89, 130.1, 157.3, 172.2, 200.1; **Analysis: $C_{12}H_{14}O_4$ requires** C, 64.85; H, 6.35; found C, 64.69; H, 6.16%.

(*S*) 1-[4[(Methoxycarbonyl)methyl]phenoxy]-3-(isopropyl amino)propan-2-ol (69):

To a stirred solution of aldehyde **71** (0.555 g, 2.5 mmol) and nitrosobenzene (0.321 g, 3 mmol) in acetonitrile (30 mL) was added L-proline (57 mg, 20 mol %) at –20 °C. After 24 h of stirring, isopropylamine (0.354 g, 6 mmol) was added and stirring was continued for 6 h at 25 °C. Solvent was distilled off under reduced pressure and the crude product was redissolved in 25 mL MeOH and hydrogenated with H_2 at 14 psig with 10% Pd/C (0.030 g) at 25 °C for 6 h. Solvent was distilled off under reduced pressure and the crude product was purified by column chromatography.

Yield: 0.48 g (68%); viscous liquid; $[\alpha]^{25}_D$ -3.98 (*c* 1, $CHCl_3$) 94% ee; {lit.[24] $[\alpha]^{25}_D$ -4.0 (*c* 1, $CHCl_3$ for 94% ee)}.

Methyl 2-(4-((*R*)-3-chloro-2-hydroxypropoxy)phenyl)acetate (72):

Preparation of Co-salen.OCOCF$_3$ complex: To a solution of (*R, R*)-Co(salen) (60 mg, 0.1 mmol) in toluene (0.5 mL) was added trifluoroacetic acid (0.24 g, 21 mmol) at 25 °C. The solution was allowed to stir at same temperature open to air for 30 min over which time the color changed from orange-red to a dark brown. The solution was concentrated under *vacuo* to leave a crude solid.

Co-salen complex *(R,R)*-(salen)Co.OCOCF$_3$ (0.072 g, 0.100 mmol), (±)-epichlorohydrin (0.462 g, 12 mmol), *tert*-butylmethylether (1 mL) and 3 A° molecular sieves (0.1 g) at 25 °C was added methyl 2-(4-hydroxyphenyl) acetate (**13)** (0.913 g, 5.5 mmol). The reaction mixture was stirred at 25 °C for 24 h and monitored by TLC for complete conversion of phenol, at which time pyridinium *p*-toluenesulfonate (0.2 g, 0.80 mmol) was added. The reaction mixture was filtered through a pad of silica and washed with 50% EtOAc/hexane (15 mL). The filtrate was concentrated *in vacuo* to give the crude product, which was purified by chromatography using EtOAc/Pet. ether (20:80) as eluent to give chloroalcohol **72** in 87% yield.

Yield: 1.23 g (87%); viscous liquid; **[α]$^{25}_{D}$** -2.88 (*c* 0.6, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 825, 1042, 1178, 1246, 1299, 1437, 1513, 1613, 1733, 2953, 3433; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.58 (brs, 1H), 3.57 (s, 2H), 3.68 (s, 3H), 3.72-3.82 (m, 2H), 4.05-4.08 (m, 2H), 4.15-4.23 (m, 1H), 6.87 (d, *J* = 8.7 Hz, 2H), 7.2 (d, *J* = 8.7 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): 40.0, 45.7, 51.9, 68.4, 69.6, 114.5, 126.5, 130.2, 157.2, 172.4; **Analysis**: **$C_{12}H_{15}ClO_4$** requires C, 55.71; H, 5.84; Cl, 13.70; found C, 55.51; H, 5.98; Cl, 13.58%.

Methyl 2-{4-[((*S*)-oxiran-2-yl) methoxy]phenyl}acetate (15):

To a solution of chloro alcohol **72** (0.776 g, 3 mmol) in dry THF (15 mL) at 0 °C was added potassium *tert*-butoxide (0.673 g, 6 mmol) and stirred for 1 h, diluted with H_2O (10 mL) and extracted with ether (3 × 20 mL). The collected organic layers were washed with brine and dried over anhyd. Na_2SO_4. Solvent was evaporated *in vacuo* to afford chiral epoxide **15** in 93% yield.

Yield: 0.62 g (93%); $\mathbf{[\alpha]^{25}_D}$ +5.94 (*c* 1, $CHCl_3$); { lit.[24] $\mathbf{[\alpha]^{25}_D}$ +5.7 (*c* 1, $CHCl_3$ for 94% ee)}; **HPLC**: 98% ee, Chiracel OD-H, λ = 254 nm, 2-propanol/hexane (10:90), 1 mL/min, retention time: (*R*)-enantiomer 13.67 min, (*S*)-enantiomer 15.33 min.

2-(4-((*S*)-2-hydroxy-3-(isopropylamino)propoxy)phenyl)acetamide{(*S*)-Atenolol} (5): A pre-cooled solution of ester **69** (0.530 g, 2 mmol), methanol (20 mL) and aq. 30% NH_4OH (8 mL) were mixed, stoppered, allowed to attain 25 °C and stirred for 24 h. After completion of the reaction, solvent was distilled off and the crude product was recrystallized with ethyl acetate to obtain pure (*S*)-atenolol (**5**).

Yield: 0.38 g (72%); **mp:** 146-149 °C (recrystallized from ethyl acetate); $\mathbf{[\alpha]^{25}_D}$ -17.72 (*c* 1, 1 N HCl) 98% ee; { lit.[24] $\mathbf{[\alpha]^{25}_D}$ -17.0 (*c* 1, 1 N HCl for 94% ee)}; **IR** ($CHCl_3$, cm^{-1}): 835, 968, 1054, 1139, 1263, 1329, 1506, 1596, 1687, 2839, 2950, 3170, 3325; ^{1}**H NMR** (200 MHz, methanol d_4): δ 1.12 (dd, *J* = 1.5, 6.3 Hz, 6H), 2.71 (dd, *J* = 8.5, 12.1 Hz, 1H), 2.86-2.98 (m, 2H), 3.43 (s, 2H), 3.93-4.11 (m, 3H), 6.89 (d, *J* = 8.7 Hz, 2H), 7.21 (d, *J* = 8.7 Hz, 2H); ^{13}**C NMR** (50 MHz, methanol d_4): δ 21.6, 42.4, 50.1, 50.3, 68.9, 71.6, 115.6, 129.2, 131.2, 159.0, 177.2; **Analysis:** $\mathbf{C_{14}H_{22}N_2O_3}$ requires C, 63.13; H, 8.33; N,10.52; found C, 63.03; H, 8.45; N, 10.34%.

1-(2-(3-Hydroxypropoxy)-5-nitrophenyl)ethanone (75):

To a slurry of 2-hydroxy-5-nitroacetophenone **(22)** (0.905 g, 6 mmol) and anhyd. K_2CO_3 (1.38 g, 10 mmol) in dry acetone (25 mL), 3-bromopropan-1-ol (0.828 g, 6 mmol) was added. The reaction mixture was refluxed under stirring for 24 h, allowed to cool, and extracted with ethyl acetate (3 x 20 mL). The combined ethyl acetate layers were concentrated to give crude product, which was purified by column chromatography to obtain alcohol **75**.

Yield: 0.98 g (68%); colorless solid; **mp**: 48 °C; **IR**: ($CHCl_3$, cm^{-1}): 653, 750, 1117, 1279, 1344, 1584, 1681, 3406; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.09-2.23 (m, 2H), 2.6 (s, 3H), 3.91 (t, *J* = 5.8 Hz, 2H), 4.36 (t, *J* = 6.1 Hz, 2H), 7.11 (d, *J* = 9.2 Hz, 1H), 8.32 (dd, *J* = 2.9, 9.2 Hz, 1H), 8.61 (d, *J* = 2.9 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 31.2, 31.4, 58.8, 66.9, 112.6, 126.2, 127.5, 128.7, 140.6, 162.5, 197.3; **Analysis**: **$C_{11}H_{13}NO_5$** requires C, 55.23; H, 5.48; N,5.86; found C, 55.03; H, 5.67; N, 5.65%.

3-(4-Nitro-2-acyl-phenoxy)propanal (76):

To a mixture of alcohol **75** (0.655 g, 3 mmol) and iodoxybenzoic acid (IBX) (1.68 g, 6 mmol), DMSO (10 mL) was added and stirred at 25 °C for 2 h. Then the reaction mixture was quenched with water and extracted with ethyl acetate (3 x 20 mL). The combined ethyl acetate layers were concentrated to give the aldehydes **76**.

Yield: 0.46 g (65%); viscous liquid; **IR**: ($CHCl_3$, cm^{-1}): 773, 1044, 1244, 1513, 1584, 1737, 2952; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.56 (s, 3H), 3.14 (dt, *J* = 0.89, 5.81 Hz, 2H), 4.53 (t, *J* = 5.8 Hz, 2H), 7.15 (d, *J* = 9.3 Hz, 1H), 8.33 (dd, *J* = 2.9, 9.1 Hz, 1H), 8.56 (d, *J* = 2.9 Hz, 1H), 9.92 (t, *J* = 0.9 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 31.5, 42.5, 62.8, 112.5, 119.3, 126.3, 128.6, 141.3, 161.7, 196.8, 198.5; **Analysis**: **$C_{11}H_{11}NO_5$** requires C, 55.7; H, 4.67; N, 5.9; found C, 55.4, H, 4.91; N, 5.65%.

1-(2-((S)-3-(tert-butylamino)-2-hydroxypropoxy)-5-aminophenyl)ethanone (30):

To a solution of aldehyde **76** (777 mg, 3.5 mmol) and nitrosobenzene (0.535 g, 5 mmol) in acetonitrile (30 mL), L-proline (0.08 g, 20 mol %) was added at –20 °C. After 24 h, *tert*-butylamine (0.637 mL, 6 mmol) was added and stirring was continued for 6 h at 25 °C. Solvent was distilled off under reduced pressure and the crude product was redisvolved in 50 mL MeOH and hydrogenated with H_2 at 20 psig with 10% Pd/C (0.030 g,) at 25 °C for 6 h. Solvent was distilled off under reduced pressure and the crude product was purified by column chromatography.

Yield: 0.55 g (56%); **mp** 105-107 °C; 88% ee; **$[\alpha]^{25}_D$** -9.66 (*c* 0.9, EtOH); {lit.[27] **$[\alpha]^{25}_D$** -10.65 (*c* 0.9, 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 1.42 (s, 9H), 2.57 (s, 3H), 2.98-3.09 (m, 1H), 3.18-3.26 (m, 1H), 3.95-4.20 (m, 3H), 4.49 (brs, 2H), 6.76-6.87 (m, 2H), 7.04 (d, *J* = 2.4 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 27.7, 31.2, 45.0, 52.5, 67.4, 71.8, 114.6, 116.3, 120.6, 128.2, 140.3, 150.8, 199.8; **Analysis**: **$C_{15}H_{24}N_2O_3$** requires C, 64.26; H, 8.63; N, 9.99; found C, 64.41; H, 8.61; N, 10.07%.

1-(2-(Allyloxy)-5-nitrophenyl)ethanone (26):

A mixture of 2-hydroxy-5-nitroacetophenone (**22**) (2.715 g, 15 mmol), allyl bromide (2.1 mL, 25 mmol), and anhyd. K_2CO_3 (4.14 g, 30 mmol) in dry acetone (40 mL) was refluxed under nitrogen atmosphere for 12 h (reaction monitored by TLC). The reaction mixture was then cooled to 25 °C, filtered through sintered funnel to remove K_2CO_3 and the filtrate was evaporated to dryness. Crude product was purified by column chromatography using pet. ether: EtOAc (9:1) as eluent to obtain pure allyl ether **26** in 96% yield.

Yield: 3.18 g (96%); colourless solid; **mp**: 72 °C; **IR**: ($CHCl_3$, cm^{-1}): 658, 748, 1118, 1224, 1277, 1354, 1520, 1605, 2453, 3030; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.67 (s, 3H), 4.79 (d, *J* = 5.4 Hz, 2H), 5.39-5.53 (m, 2H), 6.00-6.20 (m, 1H), 7.07 (d, *J* = 9.2 Hz, 1H), 8.33 (dd, *J* = 2.9, 9.2 Hz, 1H), 8.61 (d, *J* = 2.9 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 31.4, 70.1, 112.9, 119.2, 126.0, 128.2, 128.4, 131.0, 141.0, 162.0, 196.9; **Analysis**: **$C_{11}H_{11}NO_4$** requires C, 59.73; H, 5.01; N, 6.33; found C, 59.79; H, 5.43; N, 6.48%.

1-{2-[(Oxiran-2-yl)methoxy]-5-nitrophenyl}ethanone (23):

To a solution of allyl ether **26** (3.462 g, 15 mmol) in $CHCl_3$ (50 mL) was added 3-chloroperoxybenzoic acid (2.22 g, 15 mmol). The reaction mixture was stirred under nitrogen at 25 °C for 8 h. After the reaction was complete, (reaction monitored by TLC) water was added to the reaction mixture and extracted with several portions of $CHCl_3$ and the organic extracts were combined, dried with anhyd. Na_2SO_4, filtered and evaporated to dryness. The crude product was purified by column chromatography using pet. ether: EtOAc (8:2) as eluent to obtain pure epoxide **23** in 85% yield.

Yield: 3.38 g (95%); colorless solid; **mp**: 84 °C; **IR**: ($CHCl_3$, cm^{-1}): 487, 756, 1017, 1116, 1216, 1277, 1345, 1484, 1523, 1586, 1610, 1685, 2930, 3020; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.70 (s, 3H), 2.82 (dd, *J* = 2.7, 4.7 Hz, 1H), 3.00 (dd, *J* = 4.1, 4.6 Hz, 1H), 3.43-3.49 (m, 1H), 4.1 (dd, *J* = 6.3, 11.0 Hz, 1H), 4.57 (dd, *J* = 2.5, 11.1 Hz, 1H), 7.10 (d, *J* = 9.2 Hz, 1H), 8.34 (dd, *J* = 2.9, 9.1 Hz, 1H), 8.61 (d, *J* = 2.9 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 31.4, 44.1, 49.2, 70.4, 112.9, 126.0, 128.0, 128.5, 141.1, 161.7, 196.8; **Analysis**: **$C_{11}H_{11}NO_5$** requires C, 55.70; H, 4.67; N, 5.90; found C, 55.96; H, 4.58; N, 5.46%.

Hydrolytic kinetic resolution of 1-(2-((oxiran-2-yl)methoxy)-5-nitrophenyl)ethanone (23):

Preparation of Co-salen.OAc complex: To a solution of (*R, R*)-Co(salen) (0.06 g, 0.1 mmol) in toluene (0.5 mL) was added AcOH (0.126 g, 21 mmol) at 25 °C. The solution was allowed to stir at 25 °C open to air for 30 min over which time the color changed from orange-red to a dark brown. The solution was concentrated under *vacuo* to leave a crude solid.

Thus prepared, Co-salen complex (0.031 g, 0.5 mol%), was dissolved in THF and epoxide **23** (4.74 g, 20 mmol) was added at 25 °C, the solution was cooled to 0 °C and H_2O (0.198 g, 11 mmol) was added dropwise over 5 min. The reaction mixture was stirred for 24 h at the same temperature and purified by column chromatography to obtain epoxide **28** in 45% yield and diol **27** in 49% yield respectively

1-(2-((Oxiran-2-yl) methoxy)-5-nitrophenyl)ethanone (28):

Yield: 2.13 g (45%); colorless solid; **mp**: 80-83 °C; $[\alpha]^{25}_{D}$ –10.5 (*c* 0.9, EtOH) 95% ee; {lit.[27] $[\alpha]^{25}_{D}$ -10.7 (*c* 0.9, EtOH)}.

1-(2-Acetyl-4-nitrophenyl)-2, 3-propanediol (27):

Yield: 2.5 g (49%); viscous liquid; $[\alpha]^{25}_{D}$ +5.04 (*c* 1.1, EtOH); {lit.[27] $[\alpha]^{25}_{D}$ +5.31 (*c* 1.1, EtOH) for 97% ee}; **HPLC**: 92% ee, Chiracel OD-H, λ = 254 nm, 2-propanol/hexane (30:70), 1 mL/min, retention time: (*R*)-enantiomer 9.68 min, (*S*)-enantiomer 13.18 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, 1H), 8.33 (dd, *J* = 2.9, 9.0 Hz, 1H), 8.58 (d, *J* = 4.0 Hz, 1H); **^{13}C NMR** (50 MHz, acetone-d_6): δ 31.0, 62.8, 69.8, 70.4, 112.7, 125.6,

127.6, 128.2, 140.5, 162.1, 196.9; **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%.

2-(3'-*tert*-Butylamino-2'-hydroxypropoxy)-5-nitroacetophenone (29):

To a solution of chiral epoxide **28** (0.47 g, 2 mmol) in water (10 mL), *tert*-butylamine (0.637 mL, 6 mmol) was added and stirred at 25 °C for 12 h. Excess of *tert*-butylamine was distilled off under reduced pressure and the resulting crude product was extracted with EtOAc (2 x 10 mL). The organic layer was dried with anhyd. Na_2SO_4 and concentrated to give amino alcohol **29** in 86% yield.

Yield: 0.53 g (86%); yellow solid; **mp:** 105-107 °C; **$[\alpha]^{25}_D$** -10.13 (*c* 1.2, EtOH); **IR**: ($CHCl_3$, cm^{-1}): 754, 1022, 1119, 1288, 1345, 1522, 1613, 1668, 2977, 3335; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.14 (s, 9H), 2.41 (brs, 2H), 2.68 (s, 3H), 2.71-2.75 (m, 1H), 2.92 (dd, *J* = 4.1, 12.0 Hz, 1H), 3.12-3.17 (m, 1H), 4.06-4.22 (m, 2H), 7.10 (d, *J* = 9.2 Hz, 1H), 8.33 (dd, *J* = 2.9, 9.1 Hz, 1H), 8.61 (d, *J* = 2.9 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 28.5, 31.4, 44.4, 51.1, 67.7, 72.0, 112.9, 126.2, 128.2, 128.6, 141.1, 162.2, 197.1; **Analysis**: **$C_{15}H_{22}N_2O_5$** requires C, 58.05; H, 7.15; N, 9.03; found C, 58.21; H, 7.02; N, 8.89%.

2-(3'-*tert*-Butylamino-2'-hydroxypropoxy)-5-amino-acetophenone (30):

Nitro compound **29** (0.39 g, 1 mmol) in MeOH was hydrogenated [H_2 (20 psig), 10% Pd/C (0.030 g)] at 25 °C. After the reaction was complete (12 h), the catalyst was filtered off and the filtrate was concentrated under reduced pressure to afford the amino compound **30** in 92% yield.

Yield: 0.26 g (92%); yellow solid; **mp:** 105-107 °C; **$[\alpha]^{25}_D$** -10.43 (*c* 1, EtOH); {lit.[27] **$[\alpha]^{25}_D$** -10.65 (*c* 0.9, EtOH)}.

3-(4-((*S*)-3-(*tert*-Butylamino)-2-hydroxypropoxy)-3-acetylphenyl)-1,1-diethylurea {(*S*)-Celiprolol} (6):

To a solution of amino compound **30** (0.140 g, 0.53 mmol), trimethylamine (0.21 mL, 1.5 mmol) in THF (5 mL) at 40 °C, was added diethylcarbamoyl chloride (DECC) (0.2 mL) and the reaction progress was monitored by TLC. After 48 h the reaction mixture was extracted with EtOAc (3 x 5 mL) dried over anhyd. Na_2SO_4, and concentrated under reduced pressure. The crude product was dissolved in acetone (10 mL) and filtered through a short bed of neutral alumina. The filtrate was concentrated under reduced pressure to afford celiprolol in 90% yield.

Yield: 0.18 g (90%); yellow solid; **mp:** 117-118 °C (crystallized from acetone); $\mathbf{[\alpha]^{25}_D}$ -12.24 (*c* 1.76, EtOH) 95% ee; {lit.[27] $\mathbf{[\alpha]^{25}_D}$ -12.5 (*c* 1.76, EtOH)}; **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* = 10.1 Hz, 6H), 1.48 (s, 9H), 2.57 (s, 3H), 2.99 (bs, 1H) 3.11-3.13 (m, 3H), 3.38 (m, 4H), 4.01-4.05 (m, 2H), 6.84 (d, *J* = 10.2 Hz, 1H), 7.53 (d, *J* = 10.3 Hz, 1H), 7.70 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 8.5, 13.8, 25.6, 31.0, 41.4, 46.0, 57.6, 65.2, 71.0, 113.5, 123.4, 126.9, 127.4, 133.1, 153.2, 155.4, 159.6, 199.8; **Analysis**: $\mathbf{C_{20}H_{33}N_3O_4}$ requires C, 63.30; H, 8.76; N, 11.07; found C, 63.45; H, 8.89; N, 10.95%

Hydrolytic kinetic resolution of 2-(4-nitrophenyl)oxirane (46):

Preparation of Co-salen.OAc complex: (*R, R*)-Co(salen).OAc (0.031 g, 0.5 mol%) was dissolved in THF and racemic epoxide **46** (1.650 g, 10 mmol) was added at 25 °C. The reaction mixture was cooled to 0 °C, and H_2O (100 mg, 5.5 mmol) was added dropwise

over 5 min and stirred for 24 h. Reaction mixture was directly passed through silica gel to obtain epoxide **49** in 45% yield and diol **38** in 49% yield.

(*R*)-2-(4-Nitrophenyl)oxirane (49):

Yield: 0.74 g (45%); colorless solid; **mp**: 83 °C; **$[\alpha]^{25}_{D}$** -36.4 (*c* 1.25, $CHCl_3$); lit.[32] $[\alpha]^{25}_{D}$ -36 (*c* 1.25, $CHCl_3$) for 95% ee; **HPLC**: 96% ee, (*R,R*)- Whelk-O 1, λ = 254 nm, 2-propanol/hexane (1:99), 1 mL/min, retention time: (*R*)-enantiomer 12.65 min; **IR**: ($CHCl_3$, cm^{-1}): 461, 759, 859, 1106, 1203, 1344, 1520, 1603, 1932, 2925, 3071; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.79 (dd, *J* = 2.5, 5.7, 1H), 3.24 (dd, *J* = 4.2, 5.6 Hz, 1H), 3.98 (dd, *J* = 2.4, 4.0 Hz, 1H), 7.46 (d, *J* = 8.7 Hz, 2H), 8.22 (d, *J* = 8.7 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 51.3, 51.6, 123.7, 126.1, 145.2, 147.7; **Analysis: $C_8H_7NO_3$** requires C, 58.18; H, 4.27; N, 8.48; found C, 58.25; H, 4.49; N, 8.29%.

(*S*)-1-(4-Nitrophenyl) ethane-1,2-diol (38):

Yield: 0.89 g (49%); yellow solid; **mp**: 78 °C; **$[\alpha]^{25}_{D}$** +19 (*c* 1, MeOH) 93% ee; {lit.[32] $[\alpha]^{25}_{D}$ +13.5 (*c* 0.92, MeOH) for 66% ee}; **IR**: ($CHCl_3$, cm^{-1}): 855, 1036, 1352, 1538, 1610, 1940, 2964, 3401; **^{1}H NMR** (200 MHz, DMSO-d_6): δ 2.49 (brs, 2H), 4.69 (dd, *J* = 5.6, 10.4 Hz, 1H), 4.89 (t, *J* = 5.7 Hz, 1H), 5.62 (d, *J* = 4.4 Hz, 1H), 7.61(d, *J* = 8.6 Hz, 2H), 8.16 (d, *J* = 8.9 Hz, 2H); **^{13}C NMR** (50 MHz, DMSO-d_6): δ 67.2, 73.3, 123.2, 127.8, 146.7, 151.8; **Analysis**: **$C_8H_9NO_4$** requires C, 52.46; H, 4.95; N, 7.65; found C, 52.24; H, 5.11; N, 7.45%

(*R*)-2-(Isopropyl amino)-1-(4-nitrophenyl)ethanol {(*R*)-Nifenalol (8)}:

A mixture of (*R*)-epoxide **49** (1.645 g, 9.969 mmol), isopropylamine (5.892 g, 99.69 mmol) and water (0.5 mL) was refluxed for 5 h. After completion of the reaction, excess isopropylamine was distilled off under reduced pressure. The crude product was diluted

with water and extracted with ethyl acetate. The organic layer was dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography to afford the pure amino alcohol **8**.

Yield: 1.89 g (85%); yellow solid; **mp**: 120 °C; $[\alpha]^{25}_{D}$ -11.1 (*c* 1, EtOH) 96% ee; {lit.[32] $[\alpha]^{25}_{D}$ -11.4 (*c* 1, EtOH)}; **IR** ($CHCl_3$, cm^{-1}): 668, 757, 854, 1014, 1077, 1216, 1349, 1522, 1605, 2969, 3020; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.09 (d, *J* = 2.78 Hz, 6H), 2.59 (dd, *J* = 8.8, 12.1,1H), 2.78-2.91 (m, 2H), 3.00 (dd, *J* = 3.8, 12.3 Hz, 1H), 4.75 (dd, *J* =3.7, 8.9 Hz,1H), 7.55 (d, *J* = 8.6 Hz, 2H), 8.21 (d, *J* = 8.9 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 22.4, 22.5, 48.6, 54.1, 70.7, 123.3, 126.3, 146.9, 150.7; **Analysis: $C_{11}H_{16}N_2O_3$** requires C, 58.91; H, 7.19; N, 12.49; found C, 58.72; H, 7.38; N, 12.58%.

(*S*)-2-(4-Nitrophenyl)oxirane (47):

A mixture of 1, 2 diol **38** (1.83 g, 10 mmol), PPh_3 (3.93 g, 15 mmol) and diethylazo dicarboxylate (2.612 g, 15 mmol) in benzene (30 mL) was refluxed for 18 h. Then the solvent was distilled off under reduced pressure and the crude product diluted with ether to precipitate Ph_3PO, which was distilled off by filtration. The filtrate was concentrated and the crude product was chromatographed to afford epoxide **47**.

Yield: 1.29 g (78%); colorless solid; **mp**: 84 °C; **$[\alpha]^{25}_{D}$** +35.2 (*c* 1.25, $CHCl_3$) 93% ee; **IR**: ($CHCl_3$, cm^{-1}): 461, 759, 859, 1106, 1203, 1344, 1520, 1603, 1932, 2925, 3071; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.79 (dd, *J* = 2.5, 5.6, 1H), 3.24 (dd, *J* = 4.5, 5.6 Hz, 1H), 3.98 (dd, *J* = 2.4, 4.0 Hz, 1H), 7.46 (d, *J* = 8.7 Hz, 2H), 8.22 (d, *J* = 8.7 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 51.3, 51.6, 123.7, 126.1, 145.2, 147.7; **Analysis: $C_8H_7NO_3$** requires C, 58.18; H, 4.27; N, 8.48; found C, 58.25, H, 4.49, N, 8.29%.

(*S*)-2-(Isopropylamino)-1-(4-nitrophenyl)ethanol (40):

A mixture of (*S*)-epoxide **47** (1.645 g, 9.969 mmol), isopropylamine (5.892 g, 99.69 mmol) and water (0.5 mL) was refluxed for 5 h. After completion of the reaction, excess isopropylamine was distilled off under reduced pressure. The crude product was diluted with water and extracted with ethyl acetate. The organic layer was dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography to afford the pure amino alcohol **40**.

Yield: 1.99 g (89%); yellow solid; **mp:** 120 °C; **$[\alpha]^{25}_D$** +10.7 (*c* 1, EtOH) 93% ee; **IR** ($CHCl_3$, cm^{-1}): 668, 757, 854, 1014, 1077, 1216, 1349, 1522, 1605, 2969, 3020; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.09 (d, *J* = 2.9 Hz, 6H), 2.59 (dd, *J* = 8.8, 12.1, 1H), 2.78-2.91 (m, 1H), 3.00 (dd, *J* = 3.8, 12.3 Hz, 1H), 4.75 (dd, *J* = 3.7, 8.8 Hz, 1H), 7.55 (d, *J* = 8.6, 2H), 8.21 (d, *J* = 8.9 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 22.4, 22.5, 48.6, 54.1, 70.7, 123.3, 126.3, 146.9, 150.7; **Analysis: $C_{11}H_{16}N_2O_3$** requires C, 58.91; H, 7.19; N, 12.49; found C, 58.72; H, 7.38; N, 12.58%.

(*S*)-1-(4-Aminophenyl)-2-(isopropyl amino)ethanol (41):

Nitro compound, **40** (1.5 g, 6.7 mmol), 10% Pd/C (0.1 g) and 95% ethanol (50 mL) were charged into a reactor bottle and the mixture was pressurized with H_2 at 50 psig pressure for 2 h. The palladium catalyst was filtered over celite and filtrate was concentrated to obtain amine **41**.

Yield: 1.19 g (92%): yellow solid; **mp:** 135-138 °C; **$[\alpha]^{25}_D$** +13.5 (*c* 1, EtOH) 93% ee; **IR**: ($CHCl_3$, cm^{-1}): 559, 827, 1064, 1103, 1281, 1514, 1608, 1638, 1887, 2969, 3227, 3343, 3449; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.08 (d, *J* = 6.3 Hz, 6H), 2.61-2.90 (m, 5H), 3.61 (s, 2H), 4.60 (dd, *J* = 3.8, 9.1 Hz, 1H), 6.66 (d, *J* = 8.6 Hz, 2H), 7.15 (d, *J* = 8.2 Hz, 2H); **^{13}C NMR** (50 MHz, DMSO-d_6): δ 22.9, 48.1, 55.4, 71.7, 113.7, 126.8, 131.8, 147.7;

Analysis: $C_{11}H_{18}N_2O$ requires C, 68.01; H, 9.34; N, 14.42; found C, 67.89; H, 9.19; N, 14.59%.

(*S*)-2-(Isopropylamino)-1-(4-(mesylamino)phenyl)ethanol {(*S*)-Sotalol} (7):

Amino alcohol **41** (0.817 g, 3 mmol) was dissolved in pyridine (15 mL), cooled to -20 °C, treated drop wise with a solution of methanesulfonyl chloride (0.35 g, 3.1 mmol) in pyridine (10 mL) and stirred at the same temperature for 1 h. The reaction was quenched ice-water and was extracted with EtOAc. The combined organic extract was washed with brine, dried over anhyd. Na_2SO_4 and the crude product purified by column chromatography to afford (*S*)-sotalol.

Yield: 0.588 g (72%); yellow solid; **mp**: 203 °C; $[\alpha]^{25}_{D}$ +30.1 (*c* 1, H_2O) 93% ee; {lit.[31] $[\alpha]^{25}_{D}$ +34.7 (*c* 1, H_2O)}; **IR** ($CHCl_3$, cm^{-1}); 1040, 1125, 1210, 1495, 2850, 2960, 3260, 3350; ^{1}**H NMR** (200 MHz, $CDCl_3$): δ 1.1 (d, *J* = 6.5 Hz, 6H), 1.9 (brs, 1H), 2.3 (brs, 1H), 3.65 (m,1H), 3.0 (s, 3H), 3.8 (m, 1H), 4.0 (m, 1H), 4.95 (m, 1H), 7.1 (m, 4H); ^{13}**C NMR** (50 MHz, $CDCl_3$): δ 24.8, 38.5, 63.9, 67.4, 74.4, 121.4, 129.7, 134.1, 134.8; **Analysis:** $C_{12}H_{20}N_2O_3S$ requires C, 52.92; H, 7.40; N, 10.29; S, 11.77; found C, 52.78; H, 7.49; N, 10.49; S, 11.65%.

1.7 References

1. a) Agranat, I.; Canner, H; Cadwell, J. *Nature Reviews* **2002**, *1*, 753. b) Riddel, J. G.; Shanks, R. G. and Brogden, R. N. *Drugs* **1987**, *34*, 438.
2. a) Eichelbaum, M.; Gross, A. S. *Adv. Drug. Res*. **1996**, *28*, 1-64. b) Crossley, R. *Chirality and the Biological Activity of drugs* (CRC Press, Boca Raton, Florida, **1995**). c) Aboul-Enein, H.Y.; Wainer, I. W. *The impact of Stereochemistry on the*

Drug Development and use (Chemical Analysis Vol. 142) (Wiley New York, **1997**).

d) Rriggle, D. *J. Stereoselectivity of drug action, Drug Discov. Today* **1997**, *2*, 138.

e) Cadwell, J. Through the looking glass in chiral drug development. *Modern Drug Discov.***1999**, *2*, 51.

3. Stinson, S. C.; *C and EN*, **1998**, *77*, 83.
4. (a) Deutsch, D. H. *Chemtech* **1991,** *21,* 157. (b) Borman, S. *Chem. Eng. News* **1990,** *68*(28), 9.
5. Corey, E. J.; Zhang, F. *Angew. Chem. Int. Ed. Engl*. **1999**, *38,* 1931.
6. Phillips, C. I.; Howitt, G.; Rowlands, D. J. Br. *J. Ophthalmol.* **1967**, *51,* 222.
7. Barrett, M. A. *Beta-adrenoceptive agonists; in Recent Advances in Cardiology*, ed. Churchill Livingstone, Edinburgh, London, **1973**; p. 289.
8. (a) Pritchard, B. N. C. *Am. Heart J.* **1970**, *79*, 128. (b) Pritchard, B. N. C.; Gillam, P. M. S. *Brit. Med. J.* **1969**, *1*, 7.
9. Pritchard, B. N. C. *Cardiovascular Drugs Vol. 2*, *β-Adrenoceptor blocking drugs*, ed. G. S. Avery, ADIS Press, Seaforth, Australia, **1977**; p. 85.
10. (a) Jewitt, D. E.; Singh, B. N. *Prog. Cardiovasc. Dis.* **1973**, *16*, 421. (b) Singh, B. N; Jewitt, D. E. *Drugs* **1974**, *7*, 426.
11. Hamer, J.; Sowton, E. *Am. J. Cardiol.* **1966**, *18*, 354.
12. Bundgaard, H.; Buur, A.; Chang, S. C.; Lee, V. H. L. *Int. J. Pharm.* **1988**, *46*, 77.
13. (a) Howe, S. *Nature* **1966**, *210*, 1336. (b) Shiratsuchi, M.; Kawamura, K.; Akashi, T.; Ishihama, H.; Nakamura, M.; Takenaka, F. *Chem. Pharm. Bull.* **1987**, *35*, 3691.
14. Hanson, R. M. *Chem. Rev.* **1991**, *91*, 437.
15. Taylor, S. H.; Grimm, R. H. J. *Am. Heart J.* **1990**, *119*, 655.

16. (a) Leftheris, K.; Goodman, M. J. *J. Med. Chem.* **1990**, *33*, 216. (b) Shiratsuchi, M.; Kawamura, K.; Akashi, T.; Ishihama, H.; Nakamura, M.; Takenaka, F. *Chem. Pharm. Bull.* **1987**, *35*, 3691.

17. (a) Pearson, A. A.; Graffney, T. E.; Walle, T.; Privitera, P. J. *J. Pharmacol. Exp. Ther***.** **1989**, *250*, 759–768; (b) Sittig, M. Pharmaceutical Manufacturing Encyclopedia, 2nd ed.; Noyes Publications: Park Ridge, NJ, **1988**; Vol. 1, p 109.

18. Louis, W, J.; Drummer, O. H.: Tung, L. H. *Cardiovascular Drugs and Therapy/Sponsored by the International society of Cardiovascular Pharmacotherapy* **1991**, *4*, 1281.

19. Perrone, M. H.; Barrett, J. A. *Am. Heart J.* **1991***, 121*, 677.

20. Klleman, A.; Engel, J.; Kutscher, B.; Reichert, D. Pharmaceutical Substances: Syntheses, Patents, Applications, 3rd ed.; Verlag: New York, **1999**.

21. (a) Waldeck, B. *Chirality* **1993**, *5*, 350. (b) Ruffolo, R. R. Jr., *Tetrahedron* **1991**, *47*, 9953.

22. Johnson, R. A.; Sharpless, K. B. *Catalytic Asymmetric Synthesis* Ojima I.; (Ed.); VCH Publishers (New York), **1993**; Chap. 4, pp. 227-270.

23. Bevinakatti, H. S.; Banerji, A. A. *J. Org. Chem.* **1992,** 57, 6003.

24. Bose, D. S.; Narsaiah, A. V. *Bio org. Med. Chem.* **2005**, *13*, 627.

25. Zoelss, G. *Arzneim-Forsch*. **1983**, *33*, 2.

26. Joshi, R. A.; Gurjar, M. K.; Tripathy, N. K. *Org. Process Res. Dev.* **2001**, *5*, 176.

27. Sayyed, I. A.; Thakur, V. V.; Milind, D. N.; Dewkar, G. K.; Kotkar, S. P.; Sudalai, A. *Tetrahedron* **2005**, *61*, 2831.

28. Smith, P.; Brodfuehrer, P. R.; Dillon, J. L.; Vemishetti, P. *Synth. Commun* , **1995,**

25, 1093.

29. Brodfuhrer, P. R.; Smith, P.; Dillon, J. L; Vemishetti, P. *Org. Process Res. Dev.* **1997**, *1*, 176.
30. Phukan, P.; Jagtap, H. S; Sudalai, A. *Indian J. Chem*. **2000**, *39B*, 950.
31. Kamal, A.; Sandbhor, M. B.; Shaik, A. A. *Bio Org. Med. Chem. Lett*. **2004**, *14*, 4581.
32. Pedragosa, M. S.; Morisseau, C.; Baratti, J.; Zylber, J.; Archelas, A.; Furstoss, R. *Tetrahedron* **1997**, *53*, 9707.
33. (a) Jacobsen, E. N.; Marko, I.; France, M. B.; Svendsen, J. S.; Sharpless, K. B. *J. Am. Chem. Soc.* **1989**, *111*, 737. (b) Kolb, H. C.; Anderson, P. G.; Bennani, Y. L.; Crispino, G. A.; Jeong, K. S.; Kwong, H. L.; Sharpless, K. B. *J. Am. Chem. Soc.* **1993**, *115*, 12226.
34. (a) Hentges, S. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 4263.
35. (a) Criegee, R. *Justus Liebigs Ann. Chem.* **1996**, *522*, 75. (b) Criegee, R. *Angew. Chem. Int. Ed. Engl.* **1937**, *50*, 153. (c) Criegee, R.; Marchand, B.; Wannowias, H. *Justus Liegs*. *Ann. Chem.* **1942**, *550*, 99. (d) Sharpless, K. B.; Teranishi, A. Y.; Backwall, J. E. *J. Am. Chem. Soc.* **1977**, *99*, 3120. (e) Jorgensen, K. A.; Schioett, B. *Chem. Rev.* **1990**, *90*, 1483.
36. Gawley, R. A.; Aube, J. *Principles of Asymmetric Synthesis* Elesevier Science (Oxford), **1996**, Vol. 14, (Chap. 8), pp 314-350.
37. Sharpless K. B.; Amerg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K. S.; Kwong, H. L.; Morikawa, K.; Wang, Z. M.; Xu. D.; Zhang, X. L. *J. Org. Chem.* **1992**, *57*, 2768.

38. Amerg, W.; Bennani, Y. L.; Chadha, R. K.; Crispino, G. A.; Davis, W. D.; Hartung, J.; Jeong, K. S.; Ogino, Y.; Shibata, T.; Sharpless K. B. *J. Org. Chem.* **1993**, *58*, 844.

39. Some, among many, notable examples: (a) Fumagillin: Tarbell, D. S.; Carman, R. M.; Chapman, D. D.; Cremer, S. E.; Cross, A. D.; Huffman, K. R.; Kuntsmann, M.; McCorkindale, N. J.; McNally, J. G.; Rosowsky, A.; Varino, F. H. L.; West, R. L. *J. Am. Chem. Soc.* **1961**, *83*, 3096. (b) Ovalicin: Sigg, H. P.; Weber, H. P. *Helv. Chim. Acta* **1968**, *51*, 1395. (c) Coriolin: Takeuchi, T.; Iinuma, H.; Iwanaga, J.; Takahashi, S.; Takita, T.; Umezawa, H. *J. Antibiot.* **1969**, *22*, 215. (d) Bierl, B. A.; Beroza, M.; Collier, C. W. *Science* **1970**, *170*, 87.

40. For reviews and lead references, see: (a) Winstein, S.; Henderson, R. B. *Heterocyclic Compounds*, Vol. 1; Elderfield, R. C., Ed.; Wiley: New York, **1950**; Chapter 1. (b) Parker, R. E.; Isaacs, N. S. *Chem. Rev.* **1959**, *59*, 737. (c) Barto´k, M.; La´ng, K. L. *Small Ring Heterocycles In The Chemistry of Heterocyclic Compounds*, Vol. 42, Part 3; Hassner, A., Ed.; Wiley: New York, **1985**; Chapter 1.

41. (a) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936. (b) Furrow, M. E.; Schaus, S. E.; Jacobsen, E. N. *J. Org. Chem*. **1998**, *63*, 6776. (c) Jacobsen, N. E.; Schaus, E. S.; Brandes, D. B.; Larrow, F. J.; Tokunaga, M.; Hansen, B. K.; Gould, E. A.; Furrow, E. M. *J. Am. Chem. Soc* **2002**, *124*, 1307-1315.

42. For an in depth discussion of practical considerations in kinetic resolution reactions, see: Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth., Catal.* **2001**, *343*, 5.

43. (a) Larrow, J. F.; Jacobsen, E. N.; Gao, Y.; Hong, Y.; Nie, X.; Zepp, C. M. *J. Org.*

Chem. **1994**, *59*, 1939. (b) Larrow, J. F.; Jacobsen, E. N. *Org. Synth*. **1997**, *75*, 1.

44. For the most effective catalyst developed thus far for the asymmetric dihydroxylation of terminal olefins, see: Becker, H.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 448. For a general review of the AD reaction, see: Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev***. 1994**, *94*, 2483.
45. (a) Baker, N. R.; Byrne, N. G.; Economides, A. P.; Javeld, T. *Chem. Pharm. Bull*. **1995**, 1045. (b) Kirkup, M. P.; Rizvi, R.; Shankar, B. B.; Dugar, S.; Clader, J. W.; McCombie, S. W.; Lin, S.; Yumibe, N.; Huie, K.; Heek, M. V.; Compton, D. S.; Davis, H, R.; McPhail, A. T. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2069.
46. (a) Takahashi, H.; Sakuraba, S.; Takea, H.; Achiwa, K. *J. Am. Chem. Soc.* **1990**, *112*, 5877. (b) Gooding, O. W.; Colin, B. C.; Cooper, G. F.; Jackson, D. Y. *J. Org. Chem.* **1993**, *58*, 3681. (c) Yuan, R.; Watanabe, S.; Kuwabata, S.; Yoneyama, H. *J. Org. Chem.* **1997**, *62*, 2494. (d) Kang, S. B.; Ahn, E. J.; Kim, Y.; Kim, Y. H. *Tetrahedron Lett.* **1996**, *37*, 9317. (e) Guanti, G.; Banfi, L.; Narisano, E. *Tetrahedron Lett.* **1986**, *27*, 3547.
47. Seayad, J.; List, B. *Org. Biomol. Chem*. **2005**, *3*, 719.
48. List, B.; Lerner, R. A.; Barbas III, C. F. *J. Am. Chem. Soc.* **2000,** *122,* 2395.
49. (a) Sabitha, G.; Fatima, N.; Reddy, E.V.; Yadav, J. S. *Adv. Synth. Catal.* **2005**, *347*, 1353. (b) Ramachary, D. B.; Chowdari, N. S.; Barbas, C. F. III *Synlett* **2003**, 1910.
50. Hechavarria Fonseca, M. T.; List, B. *Angew. Chem., Int. Ed*. **2004**, *43*, 3958.
51. For α-functionalization reviews: (a) Franzen, J.; Marigo, M.; Fielenbach, D.; Wabnitz, T. C.; Kjarsgaard, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 18296. (b) Guillena, G.; Ramon, D. J. *Tetrahedron: Asymmetry* **2006**, *17*, 1465.

52. For a review of proline-catalyzed asymmetric reactions see: List, B. *Tetrahedron* **2002**, *58*, 5573.

53. (a) Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Shoji, M. *Tetrahedron Lett*. **2003**, *44*, 8293. (b) Zhong, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4247. (c) Hayashi, Y.; Yamaguchi, J.; Sumiya, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 1112. (d) Brown, S. P.; Brochu, M. P.; Sinz, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2003**, *125*, 10808. (e) Cordova, A.; Sunden, H.; Bøgevig, A.; Johansson, M.; Himo, F. *Chem. Eur. J*. **2004**, *10*, 3673.

54. (a) List, B. *J. Am. Chem. Soc*. **2002**, *124*, 5656. (b) Bogevig, A.; Juhl, K.; Kumaragurubaran, N.; Zhuang, W., Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1790. (c) Kumaragurubaran, N.; Juhl, K.; Zhuang, W., Bogevig, A.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2002**, *124*, 6254. (d) Vogt, H.; Vanderheiden, S.; Brase, S. *Chem. Commun.* **2003**, 2448. (e) Iwamura, H.; Mathew, S. P.; Blackmond, D. G. *J. Am. Chem. Soc.* **2004**, *126*, 11770.

55. (a) Davis, F. A.; Bang-Chi C. *Chem. Rev*. **1992**, *92*, 919. (b) Morikawa, K.; Park, J.; Andersson, P.G.; Hashiyama, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1993**, *115*, 8463. (c) Zhu, Y.; Tu, Y.; Yu, H.; Shi, Y. *Tetrahedron Lett*. **1998**, *39*, 7819.

56. Merino, P.; Tejero, T. *Angew. Chem. Int. Ed*. **2004**, *43*, 2995.

57. Cordova, A.; Watanabe, S.; Tanaka, F.; Notz, W.; Barbas, C. F., III *J. Am. Chem. Soc*. **2002**, *124*, 1866.

58. Bahmanyar, S.; Houk, K. N. *J. Am. Chem. Soc.* **2001**, *123*, 12911.

CHAPTER 2

Asymmetric Synthesis of Antifungal Agents *via* Hydrolytic Kinetic Resolution of Epoxides

2.1 Introduction

During the past two decades, infections caused by opportunistic fungal pathogens have increased substantially *in immuno* compromised patients. Amphotericin B, discovered in 1956, was the drug of choice for the treatment of most severe systemic infections. However, more recently, there has been an expansion in the number of antifungal drugs availability. Five major classes of antifungal compounds are currently in clinical use: polyenes, azole derivatives, allylamines, thiocarbamates, and fluoropyrimidines.[1] Numerous studies on the SAR (structure-activity relationships) of antifungal azoles have been developed since the discovery of the first imidazoles, and these studies have led to new compounds endowed with better biological and/or pharmacological properties. Although today's antifungal research is mainly focused on systemic fungal infections,[2] dermatomycoses are among the most widespread and common human superficial and cutaneous fungal infections.[3]

Triazole antifungal agents demonstrate potential drug to treat these infectious diseases because of their broad antifungal spectrum and low toxicity.[4] Azoles[5] such as ketoconazole (**1**), econazole (**2**), miconazole (**3**), itraconazole (**4**) and fluconazole (**5**) (**Fig. 1**), act as 14-α-demethylase inhibitors. These are potent broad-spectrum antimycotics, which show high *in vitro* activity against almost all fungi of clinical interest. They have also been successfully applied for topical use in many clinical trials, particularly in mucocutaneous candidosis of the vagina and in dermatophytosis. The major disadvantage of miconazole, econazole, and clotrimazole is that serum, urine, and body fluid levels after oral doses are disappointingly low, at best hardly sufficient to inhibit fungal growths.[6]

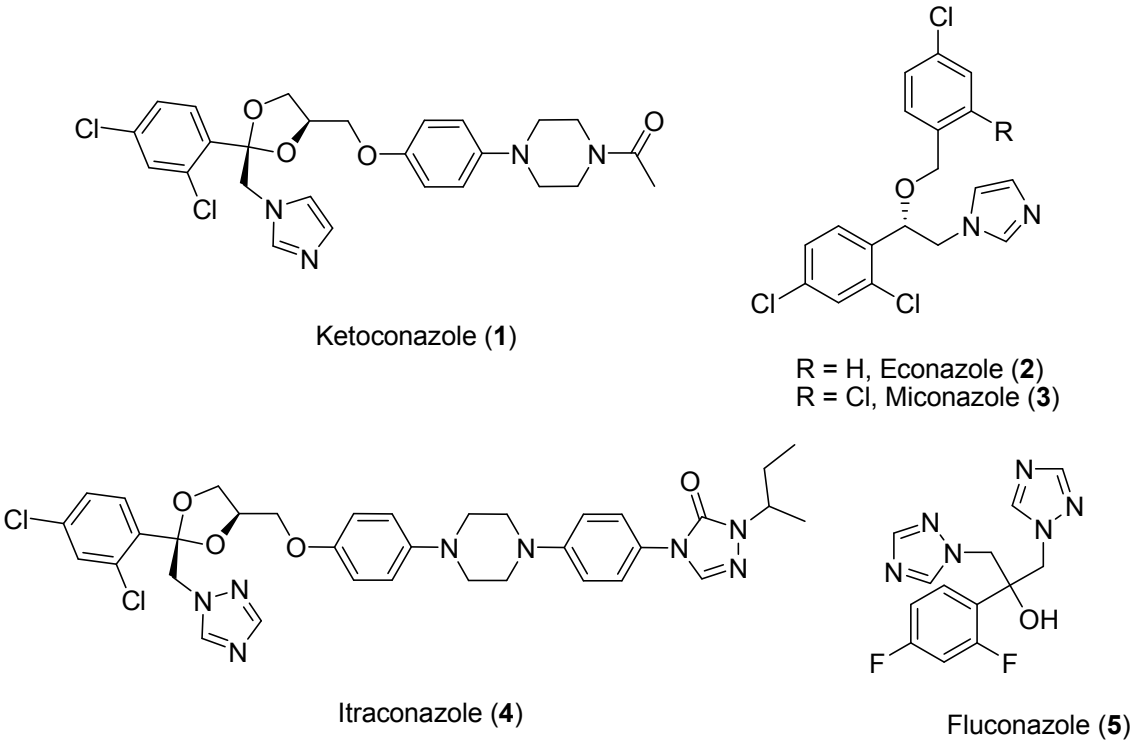


Fig. 1: Structures of antifungal agents

Unlike miconazole and clotrimazole, ketoconazole **(1)**, is a potent, orally active, broad-spectrum antifungal agent,[7] well absorbed in the bloodstream. It has been found to be highly effective against crop candidosis in turkeys, vaginal candidosis in rats, systemic candidosis in chickens, systemic and skin candidosis, as well as dermatophytosis, in guinea pigs and mice.[8] The basis of the antifungal activity of ketoconazole (**1**) and related azoles are blockade of the conversion of lanosterol to ergosterol, which is necessary for maintaining the integrity of the organism's cell membrane. Ketoconazole (**1**) has shown a similar inhibitory effect on the corresponding enzyme responsible for conversion of lanosterol to cholesterol in mammals[9] and has been demonstrated to lower cholesterol in humans.

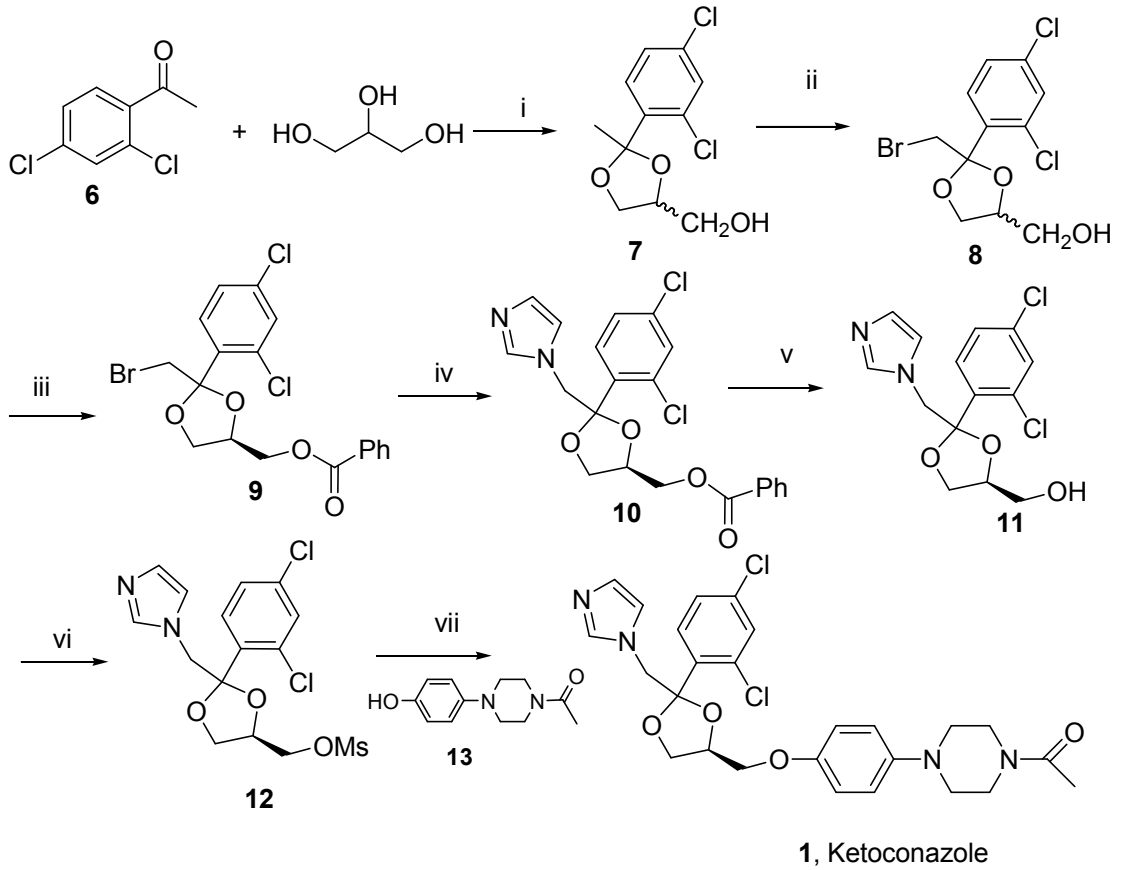
Fluconazole **(5)** is used to treat fungal infections, including yeast infections of the vagina, mouth, throat, esophagus, abdomen, lungs, blood, and other organs. It is also used to treat meningitis caused by fungus. Further, fluconazole, itraconazole, and voriconazole are clinically used representative antifungal drugs of this family. Therefore, the development of an efficient and convergent synthetic route that can be applied to large-scale synthesis of these antifungals is an important goal.

2.2 Review of Literature

Literature search revealed that there are few reports available for the synthesis antifungal agents namely ketoconazole (**1**), miconazole (**3**) and fluconazole (**5**). However, most of the reports deal with the racemic synthesis of these antifungal agents, while some methods are known to obtain enantiomerically pure material mostly with chiral pool approaches, which are enumerated below.

Heeres's approach (1979)[10]

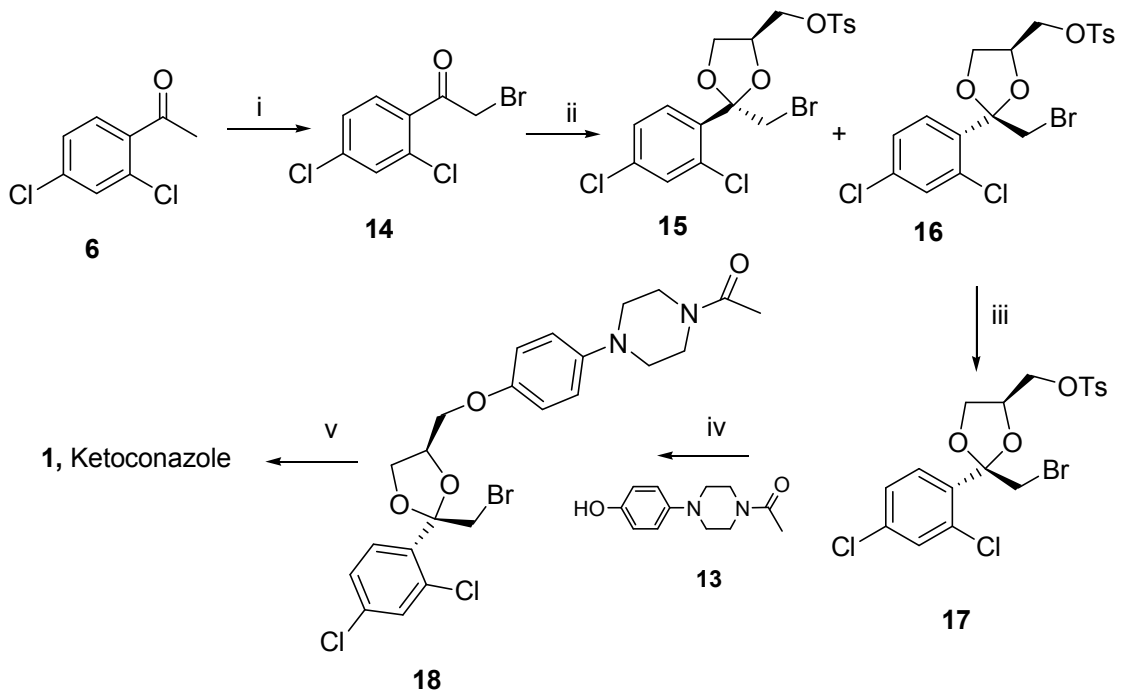
Heeres *et al.* have synthesized ketoconazole (**1**) starting from 2,4-dichloroacetophenone (**Scheme 1)**. The ketal **7**, obtained from **6** was brominated at 30 ^{o}C to give bromo ketal **8,** followed by its benzoylation afforded the corresponding ester as a *cis/trans* mixture, from which the *cis* form **9** was isolated by crystallization from EtOH. Coupling of bromo ketal **9** in dry dimethylacetamide (DMA) with imidazole gave the imidazole derivative **10,** which on saponification gave alcohol **11.** Alcohol **11** was converted to methanesulfonate **12**, which was coupled with the sodium salt of phenol **13** furnishing ketoconazole (**1**).



Scheme 1: (i) *p*-TsOH, *n*-BuOH, benzene; (ii) Br_2, 91%; (iii) (a) PhCOCl, pyridine, 50%; (b) EtOH; (iv) imidazole, DMA, 55%; (v) NaOH, dioxane, H_2O, 96%; (vi) pyridine, CH_3SO_2Cl, 87%; (vii) NaH (50%), Me_2SO, 59%.

Rotstein's approach (1992)[11]

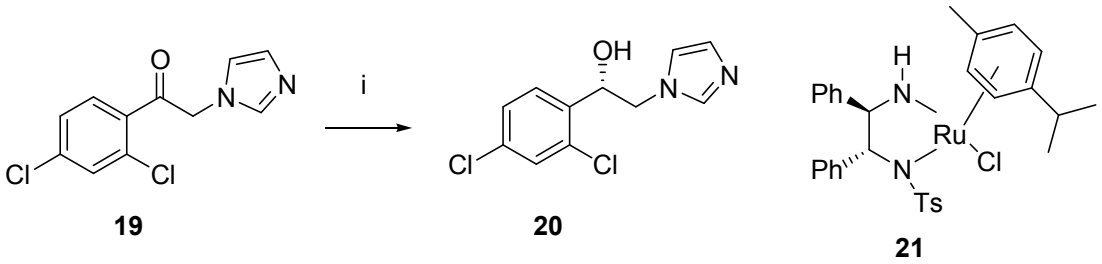
Rotstein *et al* have synthesized ketoconazole (**1**) starting from 2,4-dichloroacetophenone (**6**) (**Scheme 2)**. Bromination of **6** with copper(II) bromide in 1: 1 CH_2C1_2-EtOAc gave 2-bromo-2',4'-dichloroacetophenone (**14**), which on ketalization using (S)-solketal tosylate in the presence of *p*-TsOH and *n*-BuOH in refluxing toluene, accompanied by azeotropic removal of water, afforded a 1.2:l mixture of the *cis* and *trans* bromotosylates **15** and **16,** which were separated by chromatography. Displacement of bromide with excess imidazole in dimethylacetamide under reflux condition led to ketoconazole (**1)** after 4-16 h in 40-50% yields.



Scheme 2: (i) $CuBr_2$, EtOAc:CH_2Cl_2, reflux, 85%; (ii) (*R*)-solketal tosylte, *p*-TsOH, *n*-BuOH, toluene, reflux, 43%; (iii) NaH 50%, Me_2SO, 80 ^oC, 78%; (v) K_2CO_3, imidazole, DMF, reflux, 53%.

Lennon's approach (2005)[12]

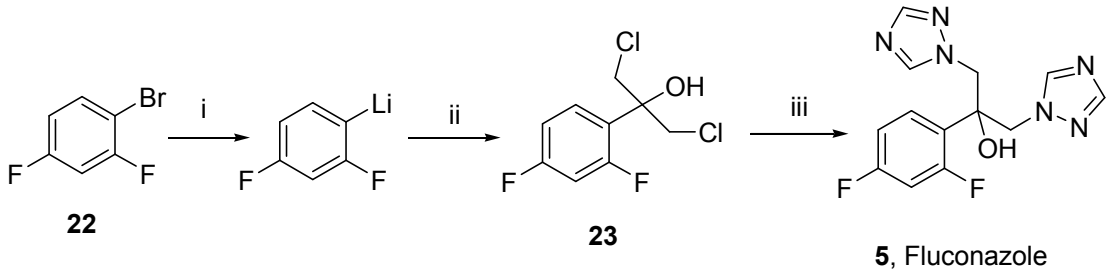
Lennon *et al*. have synthesized alcohol **20**, the key intermediate for myconazole, by carrying out the asymmetric transfer hydrogenation of amino ketone (**19**) with [(*R,R*)-TsDPEN]Ru(*p*-cymene)Cl (**21**) as catalyst and formic acid in triethylamine as hydrogen source which resulted in the formation of **20** in 91% ee (**Scheme 3**).



Scheme 3: (i) **21**, formic acid: triethylamine, CH_2Cl_2, 91% ee.

Richardson approach (1983)[13]

In this approach, fluconazole (**5**) was synthesized in 2 steps; (i) addition of 1-bromo-2, 4-difluoro-phenyllithium onto 1,3-dichloroacetone to afford 1,3-dichloro alcohol **23**; (ii) Nucleophilic displacement of the chloro derivative **23** with triazole furnished fluconazole (**5**) in 26% yield (**Scheme 4**).

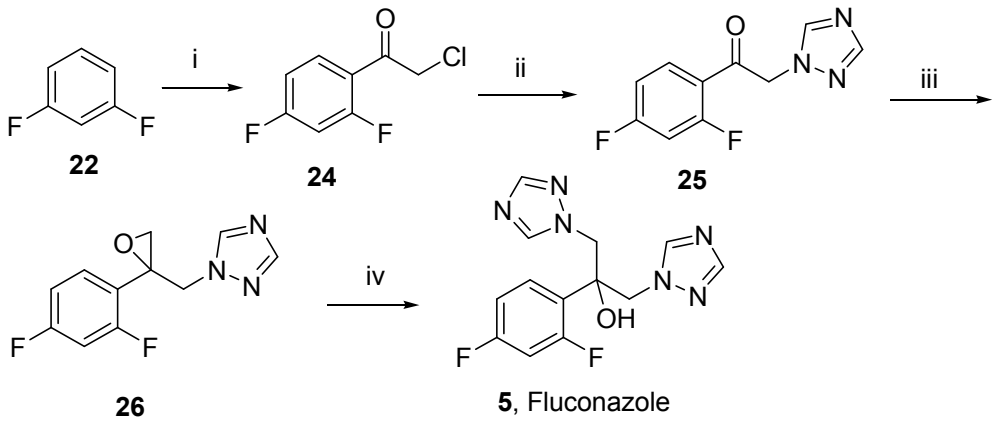


22 **23** **5**, Fluconazole

Scheme 4: (i) *n*-BuLi; (ii) 1,3-dichloro acetone; (iii) 1,2,4-triazole, K_2CO_3, 26%.

Veinberg approach (1996)[14]

In this approach, the first step involves the Friedel-Crafts' acylation of 1,3-difluorobenzene (**22**) with chloroacetyl chloride to give α-chloro-2,4-difluoro-acetophenone (**24).** Nucleophilic displacement of the chloro compound **24** with triazole, gave ketone **25,** which was epoxidized using sulfur ylide to give the epoxide **26** in 27% yield. Regiospecific ring opening of epoxide **26** with imidazole afforded fluconazole (**5)** (**Scheme 5**).



Scheme 5: (i) chloro acetylchloride, $AlCl_3$; ii) 1,2,4-triazole, Et_3N; iii) trimethylsulfoxonium iodide, NaH, 27%; iv) 1,2,4-triazole, K_2CO_3, 61%.

2.3 Present Work

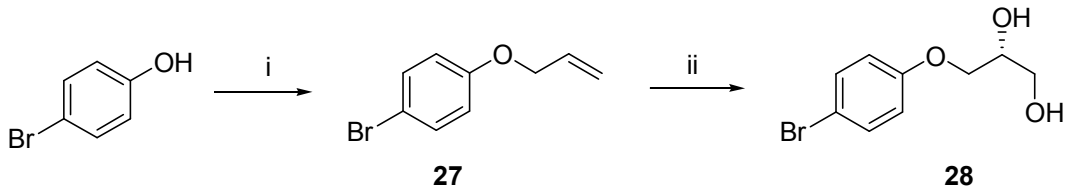
2.3.1 Objective

All the reported methods described above for the synthesis of these antifungal agents suffer from drawbacks such as use of expensive enzymes and resolving agents, low overall yields, low optical purity, *etc*. In order to develop a new general route for the asymmetric synthesis of these compounds, we have decided to make use of cobalt-catalyzed kinetic resolution of racemic epoxides. This chapter describes the new synthetic routes for the asymmetric synthesis of ketoconazole (**1**), econazole (**2**) and myconazole (**3**) using cobalt-catalyzed kinetic resolution of epoxides **29** and **32** respectively. (A brief account of Co-catalyzed asymmetric kinetic resolution of terminal epoxides is given in Chapter I).

2.4 Results and Discussion

2.4.1 Ketoconazole

For the synthesis of ketoconazole (**1**), chiral 1,2-diol **28** was visualized as the key intermediate, which could be prepared by the Os-catalyzed asymmetric dihydroxylation (ADH) of the corresponding allyl ether **27** (**Scheme 6)**.



27 **28**

Scheme 6: (i) allyl bromide, K_2CO_3, acetone, 75 °C, 96%; (ii) $K_3Fe(CN)_6$, K_2CO_3, OsO_4, $(DHQ)_2$-PHAL, *tert*-BuOH:H_2O (1:1), 92% yield, 83% ee.

Thus, the *O*-allylation of 4-bromophenol was carried out in the presence of K_2CO_3 to give allyl ether **27** in 96% yield. The ^{1}H NMR spectrum of allyl ether **27** showed typical a doublet at δ 4.49 for -O-CH_2 protons; other multiplets at δ 5.34 (2H) and 6.01 (1H) are due to olefinic protons. Its ^{13}C NMR spectrum showed characteristic signals at δ 117.6 and 132.7 due to olefinic carbons. Allylic ether **27** was then subjected to Os-catalyzed ADH using $(DHQ)_2$-PHAL as chiral ligand in *tert*-BuOH: H_2O mixture at 0 °C to produce the corresponding chiral diol **28** in 92% yield and 83% ee. The ^{1}H NMR spectrum of diol **28** showed a multiplet at δ 3.95 due to methine (-OCH_2**C**H**O**H) and methylene (-**C**$\mathbf{H_2}$OH) protons. Its ^{13}C NMR showed typical signals at δ 62.4 and 96.4 corresponding to methine (-OCH_2**C**HOH) and methylene (-**C**H_2OH) carbons respectively (**Fig. 2**).

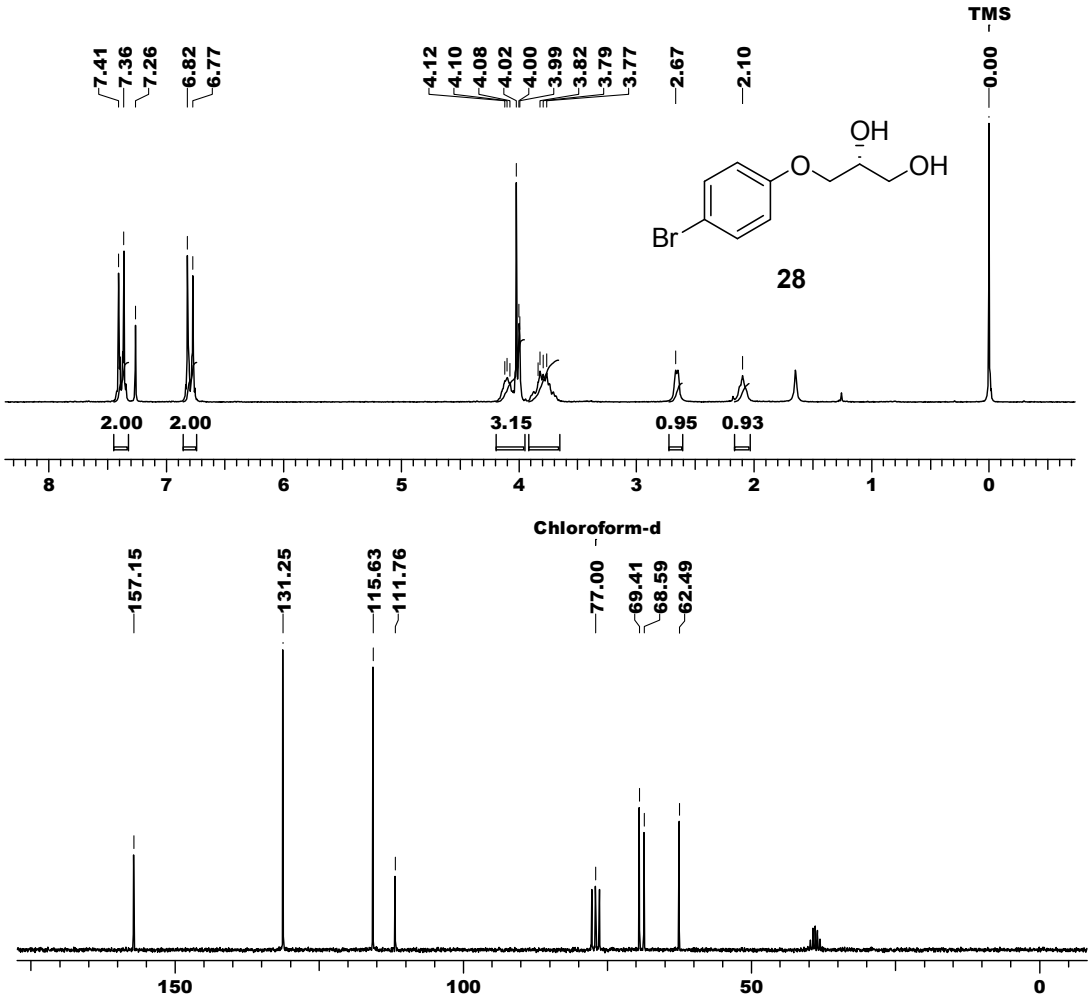
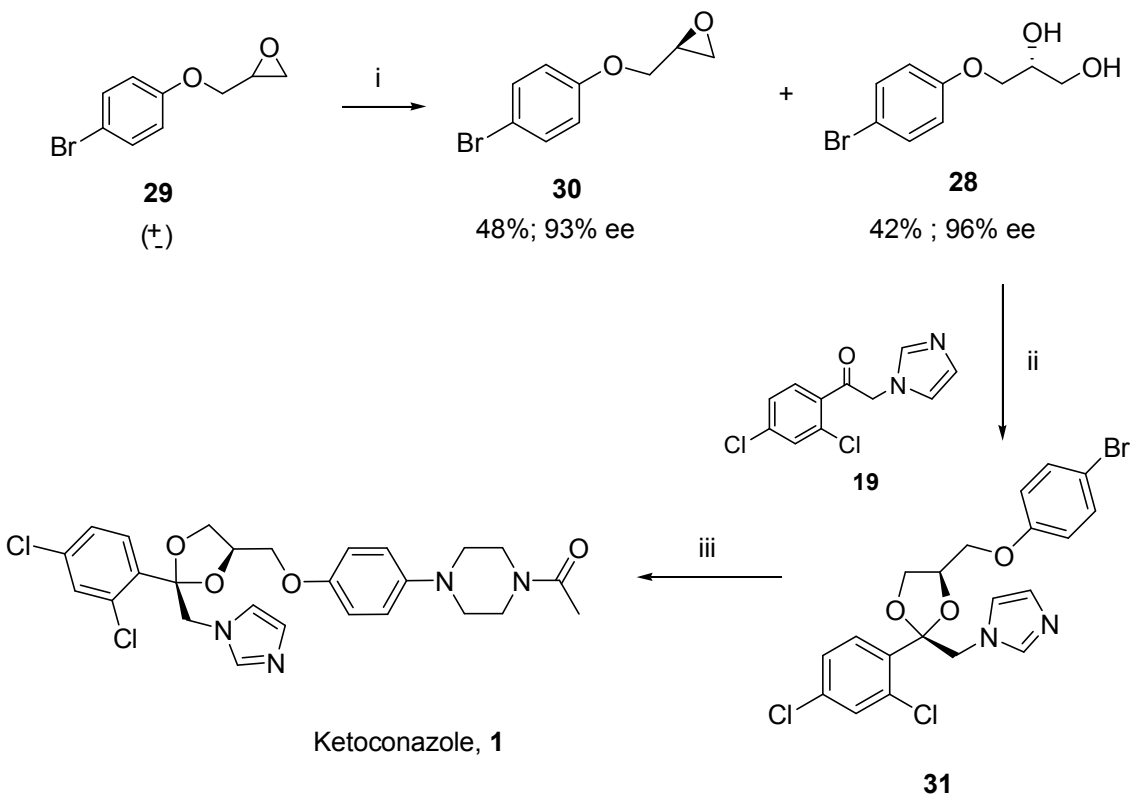


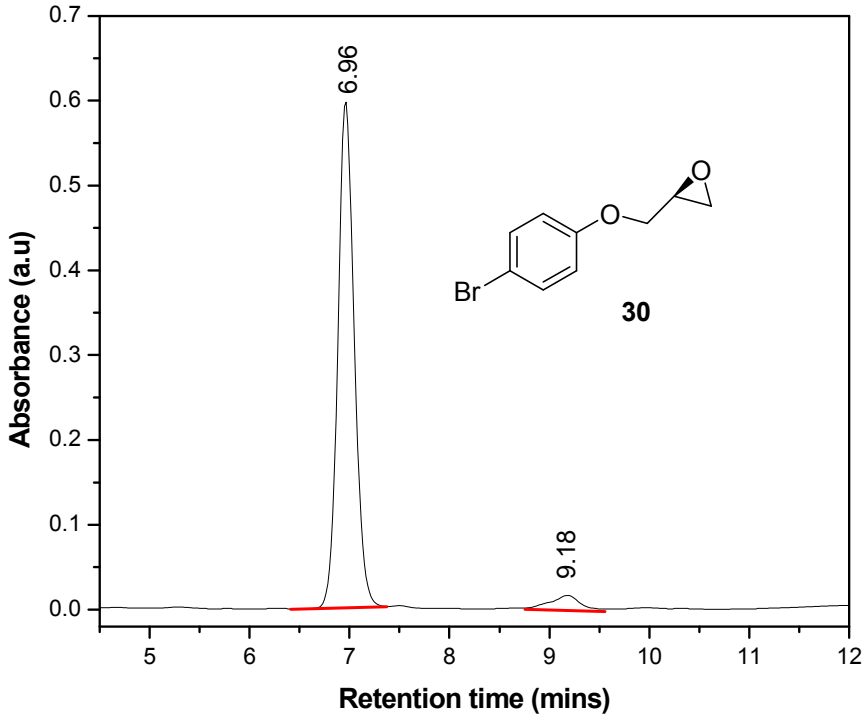
Fig. 2: ^{1}H and ^{13}C NMR spectra of (*R*)-3-(4-Bromophenoxy)propane-1, 2-diol (28)

Although the ADH route to diol **28** was facile and high yielding, it suffers from low enantioselectivity (83% ee). Hence, it was of interest to provide an alternate synthesis for **1** in which we have employed cobalt-catalyzed hydrolytic kinetic resolution (HKR) of racemic epoxide **29** as the key reaction (**Scheme 7**). The racemic epoxide, **29,** was subjected to hydrolytic kinetic resolution[15] [(*R,R*)-salen-Co(III).OAc (0.5 mol %), THF, distilled H_2O (0.45 equiv), 0 ºC, 24 h] to afford the chiral epoxide **30** in 48% yield and 93% ee (chiral HPLC (**Fig. 3**)) along with its diol **28** in 42% yield. The chiral diol **28** was readily separated from its epoxide **30** by column chromatographic purification.



Scheme 7: (i) (*R,R*)-Co(salen).OAc, H_2O (0.45 equiv.), 0 °C, 24 h, 48%, 93% ee for **30** and 42%, 96% ee for **28**; (ii) *p*-TSA, benzene, 110 °C, 82%; (iii) *N*-acylpiperazine, CuI, Cs_2CO_3, DMF, 150 °C, 78%.

The ^{1}H NMR spectrum of epoxide **30** showed typical signals at δ 2.74 (dd) and 2.90 (dd) for methylene -CH-**CH_2**-O protons of epoxide. Its ^{13}C NMR spectrum showed characteristic signals at δ 44.2 and 68.7 corresponding to methylene carbons and a signal at δ 49.7 is due to the methine carbon of the epoxide **30**.



Peak No.	Ret. Time (mins)	Area (mAU*s)	Area (%)
1	6.96	6851024	96.8
2	9.18	226480	3.2

Fig. 3: HPLC Chromotogram of (*S*)-epoxide (30)

The diol **28** was converted into its ketal derivative **31** by condensing with ketone **19**[12] (*p*-TSA, benzene, 100 ^{o}C). Finally, copper-catalyzed amination of bromoderivative **31** with *N*-acetylpiperazine in the presence of Cs_2CO_3 afforded ketoconazole (**1**) in 78% yield and 96% ee. The spectral data obtained for ketoconazole (**1**) were in complete agreement with the values reported in the literature[11] (**Fig. 4**).

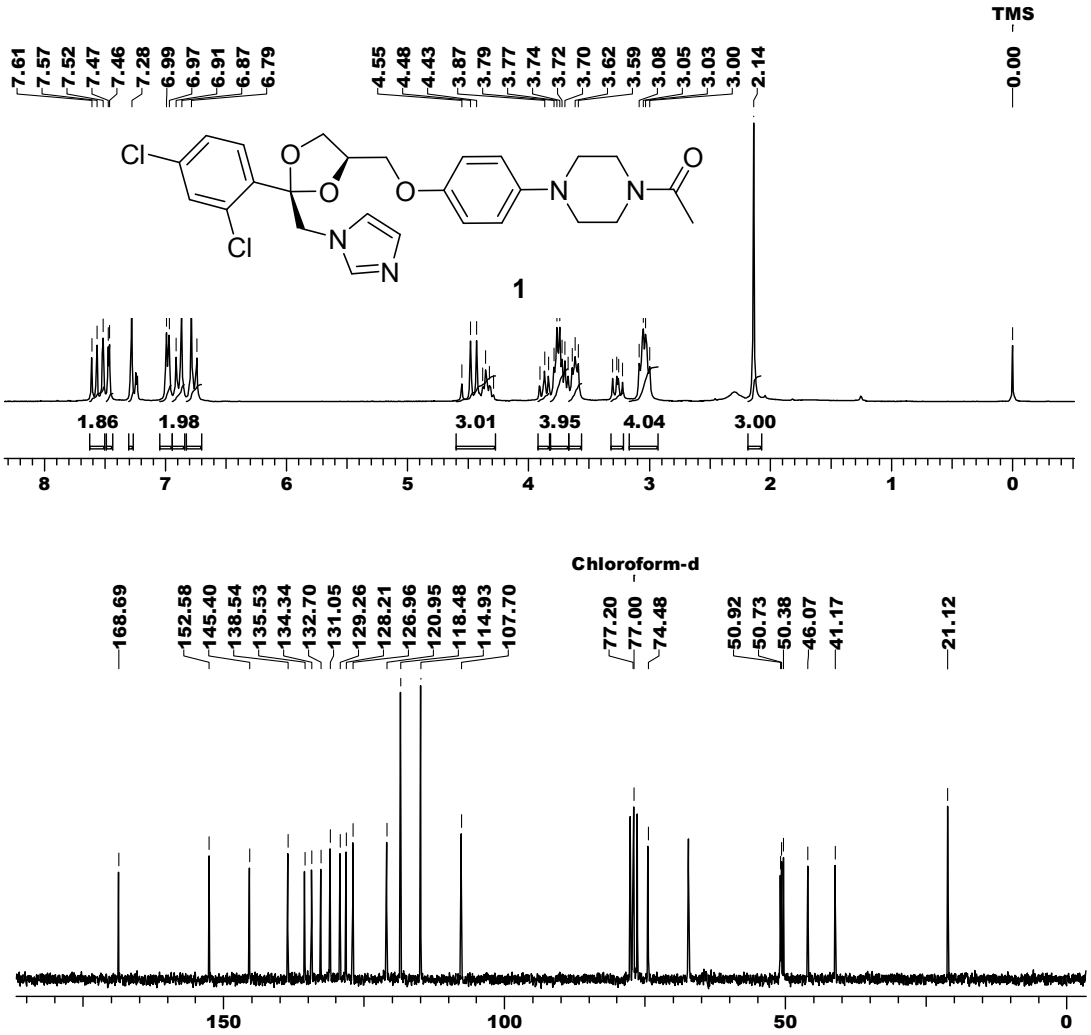
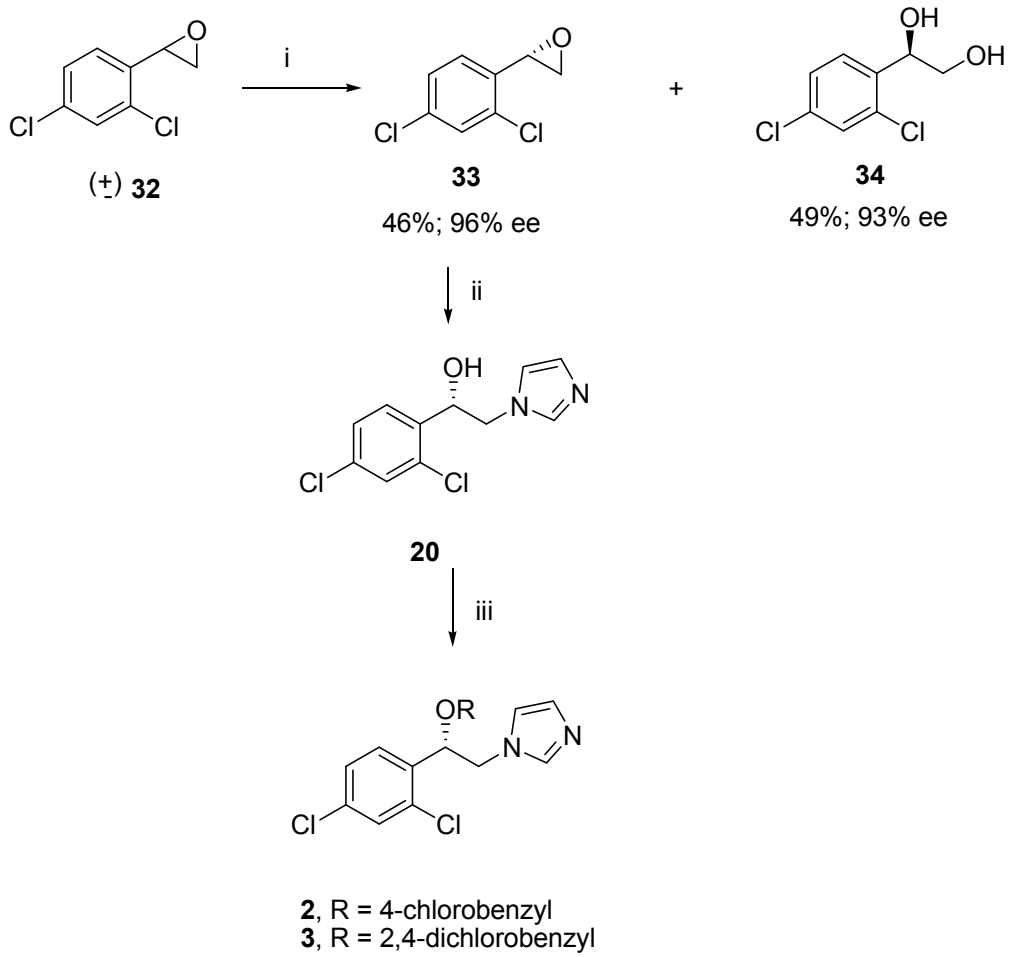


Fig. 4: ^{1}H and ^{13}C NMR spectra of ketoconazole (1)

2.4.2 Myconazole (2) and Econazole (3)

Synthetic route for (*S*)-econazole (**2**) and (*S*)-myconazole (**3**) is shown in **Scheme 8**, wherein HKR constitutes the key chiral inducing reaction.

Thus, the racemic epoxide **32** was subjected to hydrolytic kinetic resolution[15] [(*S,S*)-salen-Co(III).OAc (0.5 mol %), THF, distilled H_2O (0.55 equiv), 0 ºC, 24 h] to afford chiral epoxide **33** in 46% yield and 96% ee (chiral HPLC) along with its diol **34** in 49% yield and 93% ee. The chiral epoxide **33** was readily separated from the corresponding diol **34** by simple column chromatographic purification.



Scheme 8: (i) (*S,S*)-Co(salen).OAc, H_2O (0.55 equiv.), 0 °C, 24 h, (46%, 96% ee for **33** and 49% yield, 93% ee for **34**); (ii) imidazole, reflux, EtOH, 88%, 96% ee; (iii) NaH, DMF, 2,4-dichlorobenzyl bromide, 25 °C, 78%; or NaH, DMF, 4-chlorobenzyl bromide, 25 °C, 73%.

The ^{1}H NMR spectrum of epoxide **33** showed signals at δ 2.60 (dd) and 3.18 (dd) corresponding to methylene protons; other signal at δ 4.13 (dd) for methine proton. Its ^{13}C NMR spectrum showed typical signal at δ 49.4 and 50.4 due to methylene and methine carbons respectively. The ^{1}H NMR spectrum of diol **34** showed typical signals at δ 3.45 (dd) and 3.79 (dd) corresponding to -CH_2 protons; other signal at 4.45 (dd) due to methine proton. Its ^{13}C NMR showed signal at δ 65.9 and 70.9 corresponding to methylene and methine carbons respectively. Regiospecific ring opening of epoxide **33**

with imidazole in ethanol gave amino alcohol **20** in 88% yield and 96% ee. The ^{1}H NMR spectrum of amino alcohol **20** showed signals at δ 3.85 (dd) and 4.20 (dd) corresponding to methylene -CH_2 protons (**Fig. 5**).

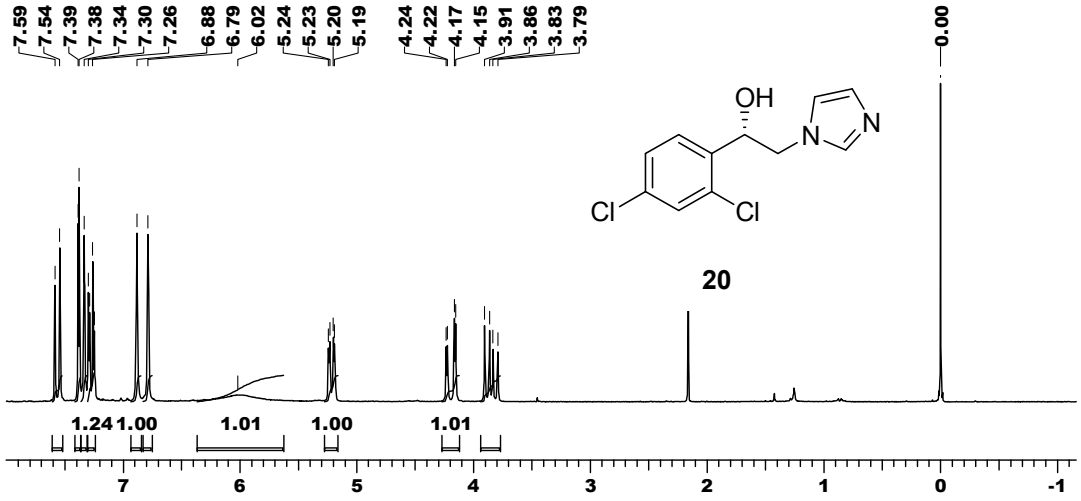
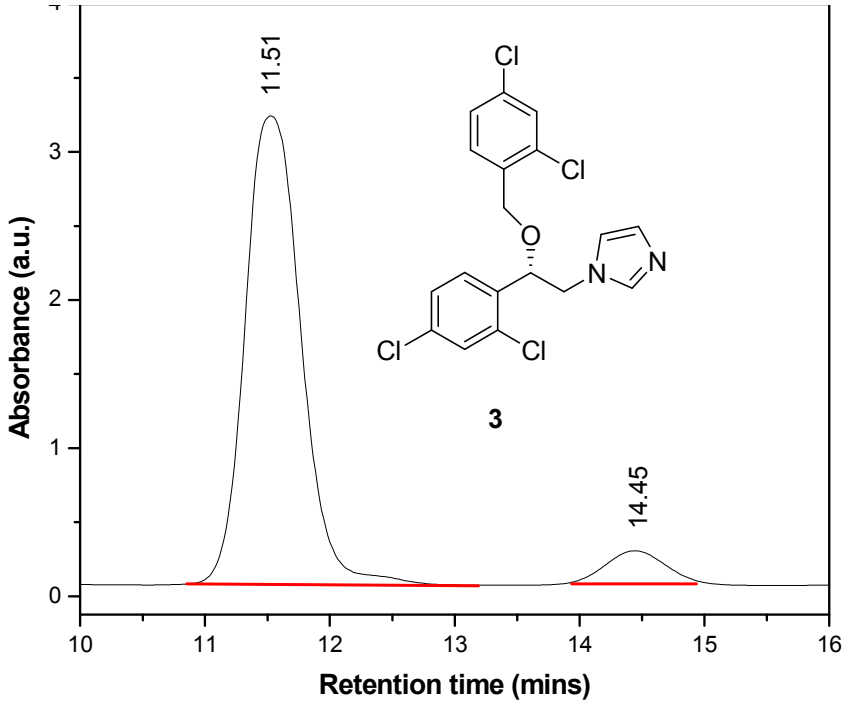


Fig. 5: ^{1}H NMR spectrum of amino alcohol (20)

Finally, *O*-alkylation of the amino alcohol **20** either with 2,4-dichlorobenzyl bromide or 4-chlorobenzyl bromide under basic conditions in DMF afforded (*S*)-miconazole (**3**) and econazole (**2**) in 78% and 73% yield and 96% ee respectively (chiral HPLC (**Fig. 7**)). The ^{1}H NMR spectrum of miconazole (**3**) showed typical signals δ 4.07 (dd) and 4.24 (dd) corresponding to -CH_2-N protons; other signal at δ 4.42 (dd) due to Ar-CH_2 protons. Its ^{13}C NMR showed typical benzylic carbon signals at δ 51.2 and 68.1 corresponding to -CH_2-N and Ar-CH_2 respectively (**Fig. 6**).



Peak No.	Ret. Time (mins)	Area (mAU*s)	Area (%)
1	11.51	103332642	98.04
2	14.45	2065809	1.96

Fig. 7: HPLC Chromotogram of Miconazole (3)

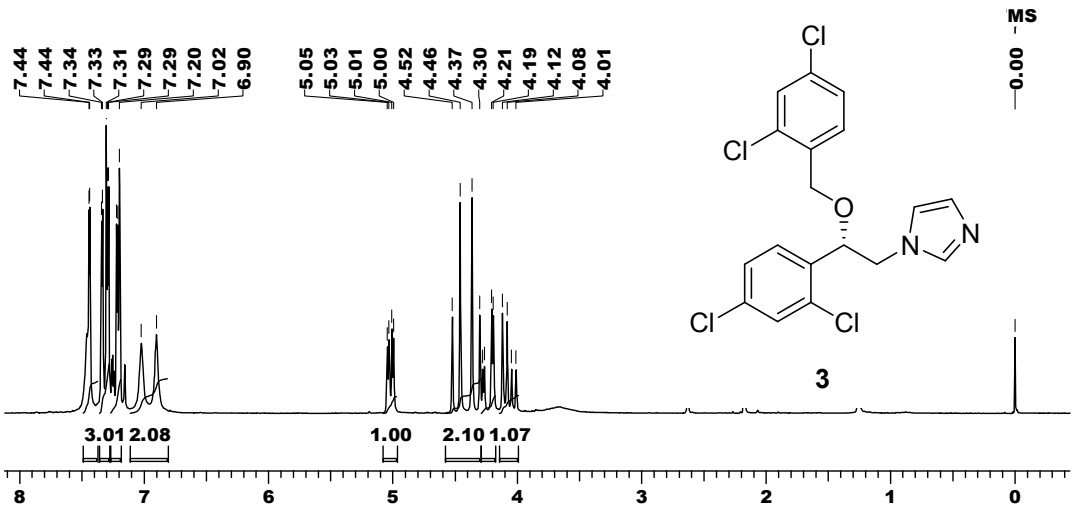


Fig. 6a: ^{1}H NMR spectrum of miconazole (3)

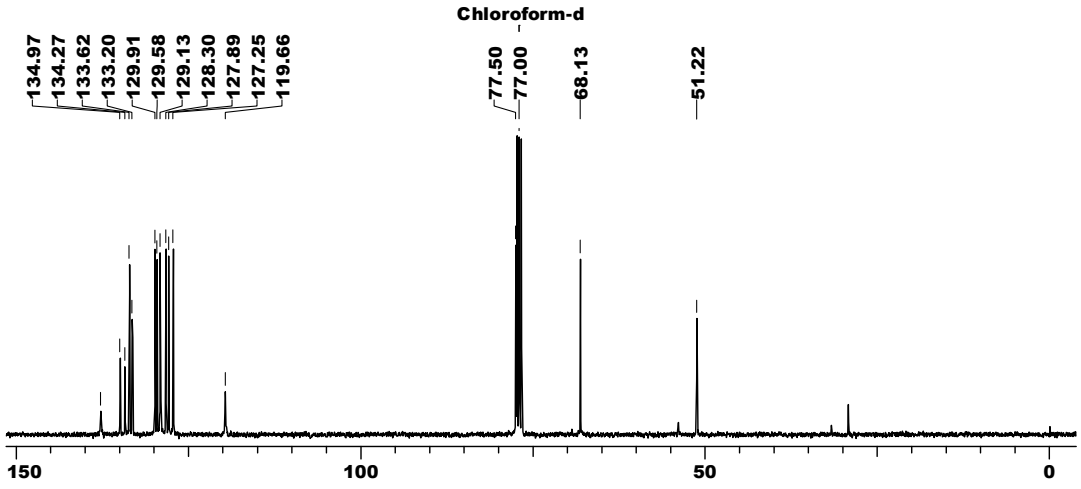
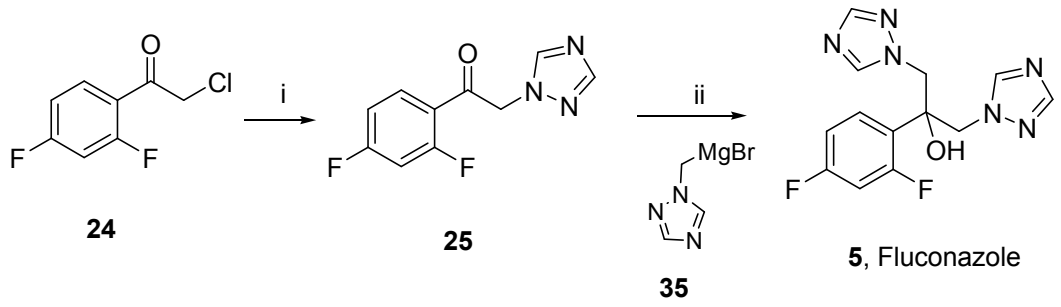


Fig. 6b: ^{13}C NMR spectrum of miconazole (3)

2.4.3 Fluconazole

The synthetic route for fluconazole (**5**), a class of antifungals, is shown in **Scheme 9**.



Scheme 9: (i) 1,2,4-triazole, K_2CO_3, CH_3CN, 65 °C, 88%; (ii) **35**, THF, -40 °C, 85%.

We have begun our synthesis with the preparation of ketone **25,** which was readily achieved in 96% yield by the condensation of 1,2,4-triazole with 2-chloro-1-(2,4-difluorophenyl)ethanone (**24)** in refluxing CH_3CN. The ^1H NMR spectrum of ketone **25** showed a doublet at δ 5.60 for -CH_2 protons. Its ^{13}C NMR showed characteristic signals at δ 58.1 and 187.5 corresponding to -CH_2 and C=O carbons respectively. Its IR spectrum

has exhibited a characteristic strong band at 1702 cm^{-1} indicating the presence of a carbonyl group.

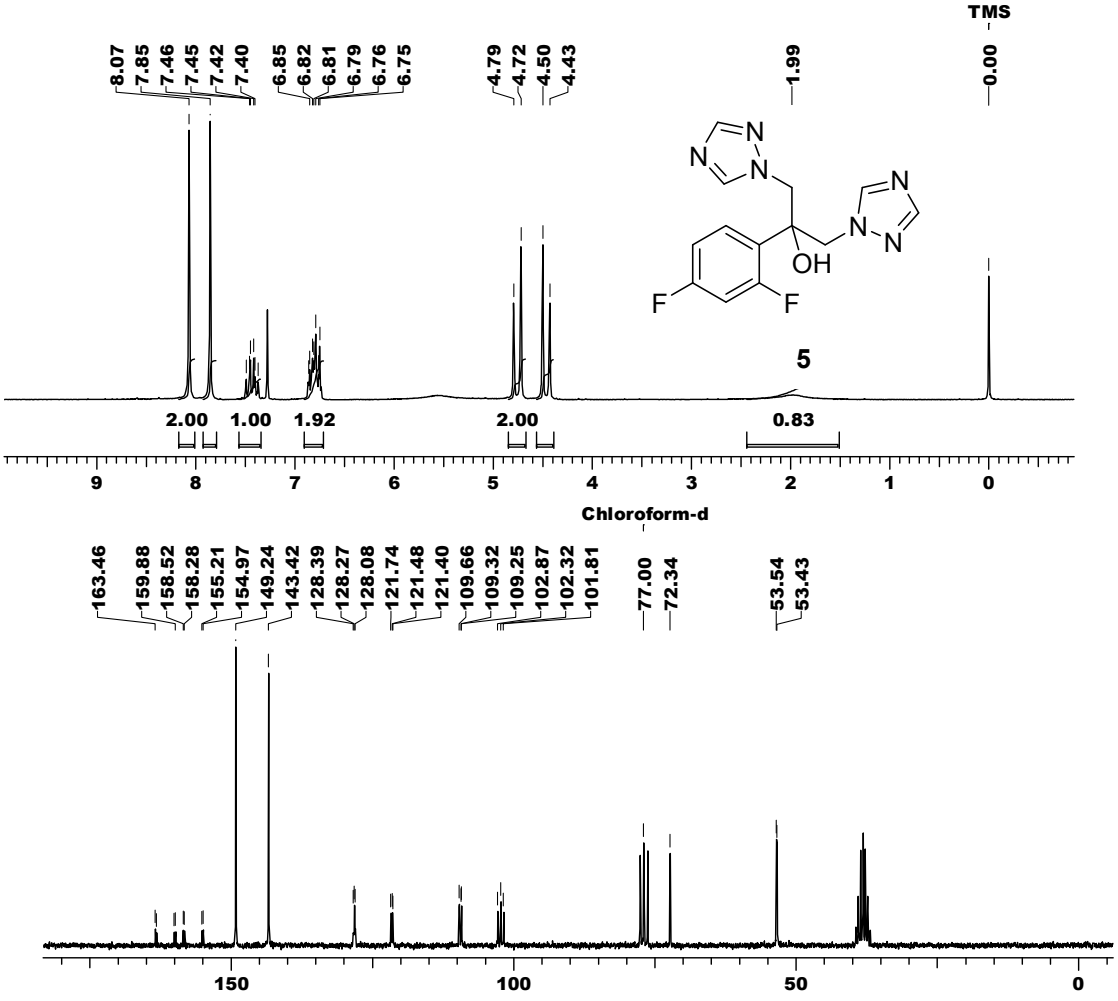


Fig. 8: ^{1}H and ^{13}C NMR spectra of fluconazole (5)

Finally, the Grignard reagent **35**, prepared by a modified procedure from the corresponding 1-(bromomethyl)-1*H*-1,2,4-triazole,[16] with Mg, was added to ketone **25** to afford fluconazole (**5**) in 85% yield. The ^{1}H NMR spectrum of fluconazole (**5**) showed characteristic two doublets at δ 4.47(d) and 4.76 (d) corresponding to -CH_2-N protons. Its ^{13}C NMR showed typical signals at δ 72.3 and 53.4 due to -CH_2-N and –C-OH carbons

respectively (**Fig. 8**). A broad band at 2900-3200 cm^{-1} in its IR spectrum confirms the presence of OH group in the molecule.

2.5 Conclusion

In conclusion, we have successfully applied cobalt-catalyzed kinetic resolution of terminal epoxides (**29** and **32**) for obtaining ketoconazole (**1**), (*S*)-econazole (**3**) and (*S*)-myconazole (**3**) respectively in high optical purities. The reactions are rapid, and require only catalytic amount of cobalt chiral catalyst. The high yields and less number of steps associated with our approach render our method a good alternative to the known procedures.

2.6 Experimental Section

1-(Allyloxy)-4-bromobenzene (27):

To a stirred mixture of 4-bromophenol (8.65 g, 50 mmol), allyl bromide (12.1 g, 100 mmol) and anhyd. K_2CO_3 (13.8 g, 100 mmol) in dry acetone (100 mL) was refluxed under nitrogen atmosphere for 12 h. The reaction mixture was then cooled to 25 ^oC, filtered through sintered funnel to remove solid crude product and the filtrate was evaporated to dryness. The crude product was purified by column chromatography using pet. ether: EtOAc (9:1) as eluent to obtain pure allyl ether **27** in 96% yield.

Yield: 10.2 g (96%); viscous liquid; **IR** ($CHCl_3$, cm^{-1}): 823, 914, 1031, 1072, 1242, 1286, 1488, 1577, 1589, 2925, 3001, 3058; ^{1}**H NMR** (200 MHz, $CDCl_3$): δ 4.47-4.50 (m, 2H), 5.25-5.43 (m, 2H), 5.92-6.11 (m, 1H), 6.77 (d, *J* = 9.0 Hz, 2H), 7.35 (d, *J* = 9.0 Hz, 2H); ^{13}**C NMR** (50 MHz, $CDCl_3$): δ 68.8, 112.8, 116.3, 117.6, 132.0, 132.7, 157.5; **MS** (m/z,

% relative intensity): 212 (M+, 8), 143 (9), 133 (16), 105 (12), 63 (19), 41 (100, base peak); **Analysis: C_9H_9BrO** requires C, 50.73; H, 4.26; found C, 50.90; H, 4.51%.

(*R*)-3-(4-Bromophenoxy)propane-1, 2-diol (28):

To a solution of $K_3Fe(CN)_6$ (8.93 g, 27.1mmol), K_2CO_3 (3.74 g, 27.1 mmol), $(DHQ)_2$-PHAL (0.140 g, 0.18 mmol) in *tert*-BuOH:H_2O (1:1, 80 mL) was added a solution of OsO_4 (229 μl, 0.09 mmol, 0.5 M solution in toluene) at 0 °C. The resulting reaction mixture was stirred at the same temperature for 5 minutes and then allyl ether **27** (1.917 g, 9 mmol) was added. The reaction mixture was stirred at 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). The combined organic layers were washed with brine (25 mL), dried over anhyd. Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by column chromatography using pet.ether: EtOAc (7:3) as eluent to give pure diol **28**.

Yield: 2.04 g (92%); **mp**: 82 °C; **$[\alpha]^{25}_D$** -10.52 (*c* 1, EtOH) 83% ee; {lit.[17] $[\alpha]^{25}_D$ -12.3 (*c* 1, EtOH) 97% ee}; **IR** ($CHCl_3$, cm^{-1}): 669, 756, 823, 1043, 1215, 1242, 1488, 1591, 2879, 2931, 3018; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.10 (brs, 1H), 2.67 (s, 1H), 3.17-3.84 (m, 2H), 3.99-4.12 (m, 3H), 6.80 (d, *J* = 9.1 Hz, 2H), 7.39 (d, *J* = 9.0 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 62.4, 68.5, 69.4, 111.7, 115.6, 131.2, 157.1; **MS** (m/z, % relative intensity): 246 (M+, 10), 172 (100, base peak), 157 (7), 136 (7), 93 (17), 75 (19), 65 (36), 43 (48); **Analysis: $C_9H_{11}BrO_3$** requires C, 43.75; H, 4.49; found C, 43.59; H, 4.58%.

Hydrolytic kinetic resolution of 2-[(4-Bromophenoxy)methyl]oxirane (29):

Preparation of Co-salen.OAc complex: To a solution of (*R,R*)-Co(salen) (0.06 g, 0.1 mmol) in toluene (0.5 mL) was added AcOH (0.126 g, 21 mmol) at 25 °C. The solution

was allowed to stir at 25 °C open to air for 30 min over which time the color changed from orange-red to a dark brown. The solution was concentrated under *vacuo* to leave a crude solid.

Thus prepared, Co-salen complex (0.031 g, 0.5 mol%), was dissolved in THF and epoxide **29** (4.58 g, 20 mmol) was added at 25 °C, the solution was cooled to 0 °C and H_2O (0.162 g, 9 mmol) was added dropwise over 5 min. The reaction was allowed to 25 °C and stirred for 48 h. Mixture containing epoxide and diol was purified by column chromatography to obtain epoxide **30** in 48% yield and diol **28** in 42% yield respectively

(*S*)-2-[(4-Bromophenoxy)methyl]oxirane (30):

Yield: 1.09 g (48%); $\mathbf{[\alpha]^{25}_D}$ +5.02 (*c* 2.1, $CHCl_3$); **HPLC**: 93% ee, Chiracel OD-H, λ = 254 nm, 2-propanol/hexane (10:90), 1 mL/min, retention time: (*S*)-enantiomer 6.96 min, (*R*)-enantiomer 9.18 min; **IR** ($CHCl_3$, cm^{-1}): 823, 1031, 1072, 1174, 1242, 1286, 1488, 1577, 1589, 2925, 3001, 3058; ^{1}**H NMR** (200 MHz, $CDCl_3$): δ 2.74 (dd, *J* = 2.7, 4.8 Hz, 1H), 2.90 (dd, *J* = 2.6, 4.3 Hz, 1H), 3.30-3.37 (m, 1H), 3.89 (dd, *J* = 5.8, 11.1 Hz, 1H), 4.21 (dd, *J* = 2.9, 11.0 Hz, 1H), 6.80 (d, *J* = 9.1 Hz, 2H), 7.37 (d, *J* =9.1 Hz, 2H); ^{13}**C NMR** (50 MHz, $CDCl_3$): δ 44.2, 49.7, 68.7, 113.1, 116.2, 132.0, 157.3; **Analysis:** $\mathbf{C_9H_9BrO_2}$ requires C, 47.19; H, 3.96, Br, 34.88; found C, 47.28; H, 3.88; Br, 35.02%.

(*R*)-3-(4-Bromophenoxy)propane-1, 2-diol (28):

Yield: 1.04 g (42%); **mp**: 82 ^oC; $\mathbf{[\alpha]^{25}_D}$ -12.1 (*c* 1, EtOH) 96% ee; {lit.[17] $[\alpha]^{25}_D$ -12.3 (*c* 1, EtOH), 97% ee}.

1-(2,4-Dichlorophenyl)-2-(1*H*-imidazol-1-yl)ethanone (19):

A mixture of 2-chloro-1-(2,4-dichlorophenyl)ethanone (2.23 g, 10 mmol), imidazole (1.02 g, 25 mmol), and anhydrous K_2CO_3 (2.07 g, 15 mmol) in dry CH_3CN (20 mL) was

refluxed under nitrogen atmosphere for 12 h (reaction monitored by TLC). The reaction mixture was then cooled to 25 °C, 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 amino ketone (**19**) in 96% yield.

Yield: 1.83 g (82%); ^{1}**H NMR** (200 MHz, $CDCl_3$): δ 5.72 (s, 2H), 7.07 (s, 1H), 7.35 (m, 1H), 7.67 (dd, *J* = 2.1, 6.3 Hz, 1H), 7.83 (d, *J* = 2.0 Hz, 1H), 7.97-8.06 (m, 2H); ^{13}**C NMR** (50 MHz, $CDCl_3$): δ 55.5, 120.0, 127.9, 129.8, 130.8, 131.1, 132.5, 134.1, 138.1, 139.2, 193.7; **Analysis:** $\mathbf{C_{11}H_8Cl_2N_2O}$ requires C, 51.79; H, 3.16; N, 10.98; found C, 51.92; H, 3.32; N, 10.75%.

1-{[(2*S*,4*R*)-4-[(4-Bromophenoxy)methyl]-2-(2,4-dichlorophenyl)-1,3-dioxolan-2-yl]methyl}-1*H*-imidazole (31):

To a stirred suspension of ketone **19** (2.55 g, 10 mmol), (*R*)-1,2-diol **28** (2.47 g, 10 mmol), and *n*-butanol (2.5 mL) in toluene (50 mL) was added *p*-toluenesulfonic acid (3.44 g, 20 mmol) at 25 ^{o}C. The resulting reaction mixture was heated at reflux through a Dean-Stark trap. After 12 h, the reaction mixture was cooled to 25 ^{o}C and evaporated to dryness. The residue was extracted with EtOAc (3 x 50 mL), organic layers were washed with saturated sodium bicarbonate, brine and dried over anhyd. Na_2SO_4, evaporated under reduced pressure and purified by column chromatography.

Yield: 3.97 g (82%); **mp**: 150-151 ^{o}C; $\mathbf{[\alpha]^{25}_D}$ -10.9 (*c* 1.0, $CHCl_3$); ^{1}**H NMR** (200 MHz, $CDCl_3$): δ 3.27 (dd, *J* = 6.8, 9.4 Hz, 1H), 3.59-3.64 (m, 2H), 3.83-3.91 (m, 1H), 4.29-4.55 (m, 3H), 6.77 (d, *J* = 9.0 Hz, 2H), 6.89 (d, *J* =9.0 Hz, 2H), 6.97 (br, 1H), 6.99 (br, 1H), 7.28 (br, 1H), 7.47 (d, *J* = 1.8 Hz, 1H), 7.52-7.61 (m, 2H); ^{13}**C NMR** (50 MHz, $CDCl_3$):

δ 41.1, 50.7, 50.9, 67.2, 67.3, 74.4, 77.2, 107.7, 113.4, 116.3, 120.9, 126.9, 128.2, 129.2, 131.0, 132.2, 132.7, 134.3, 135.5, 145.4, 152.5; **Analysis:** $\mathbf{C_{10}H_{17}BrCl_2N_4O_3}$ requires C, 49.61; H, 3.54; N, 5.79; found C, 49.52; H, 3.72; N, 5.85%.

1-(4-(4-(((2S,4R)-2-((1*H*-Imidazol-1-yl)methyl)-2-(2,4-dichlorophenyl)-1,3-dioxolan-4-yl)methoxy)phenyl)piperazin-1-yl)ethanone {Ketoconazole} (1):

To a stirred mixture of copper(I) iodide (0.019 g, 0.1 mmol), aryl bromide **31** (0.968 g, 2 mmol) and Cs_2CO_3 (1.3 g, 4.0 mmol) in DMF (5 mL) was added 1-acylpiperazine (0.248 g, 2.2 mmol) at 25 ^oC and heated to 150 ^oC. After 12 h, the reaction mixture was cooled to 25 ^oC, diluted with dichloromethane and filtered to remove inorganic salts. Solvent was removed under reduced pressure. The resulting residue was purified by column chromatography to obtain ketoconazole.

Yield: 0.83 g (78%); **mp**: 157-158 ^oC; $\mathbf{[\alpha]^{25}_D}$ -10.16 (*c* 0.5, $CHCl_3$) 96% ee {lit.[11] $[\alpha]^{25}_D$ -10.58 (*c* 0.4, $CHCl_3$); ^{1}**H NMR** (200 MHz, $CDCl_3$): δ 2.14 (s, 3H), 3.00-3.08 (m, 4H), 3.27 (dd, *J* = 6.8, 9.4 Hz, 1H), 3.59-3.64 (m, 2H), 3.67-3.79 (m, 4H), 3.83-3.91 (m, 1H), 4.29-4.55 (m, 3H), 6.77 (d, *J* = 9.0 Hz, 2H), 6.89 (d, *J* =9.0 Hz, 2H), 6.97 (br, 1H), 6.99 (br, 1H), 7.28 (br, 1H), 7.47 (d, *J* = 1.8 Hz, 1H), 7.52-7.61 (m, 2H); ^{13}**C NMR** (50 MHz, $CDCl_3$): δ 21.1, 41.1, 46.0, 50.3, 50.7, 50.9, 67.2, 67.3, 74.4, 77.2, 107.7, 114.9, 118.4, 120.9, 126.9, 128.2, 129.2, 131.0, 132.7, 134.3, 135.5, 138.5, 145.4, 152.5, 168.6; **Analysis:** $\mathbf{C_{26}H_{28}Cl_2N_4O_4}$ requires C, 58.76; H, 5.31; Cl, 13.34; N, 10.54; found C, 58.59; H, 5.52; Cl, 13.45; N, 10.47%.

Hydrolytic kinetic resolution of 2-(2, 4-dichlorophenyl)oxirane (32):

Preparation of Co-salen.OAc complex: To a solution of (*S,S*)-Co(salen) (0.06 g, 0.1 mmol) in toluene (0.5 mL) was added AcOH (0.126 g, 21 mmol) at 25 °C. The solution

was allowed to stir at 25 °C open to air for 30 min over which time the color changed from orange-red to a dark brown. The solution was concentrated under *vacuo* to leave a crude solid.

Thus prepared, Co-salen complex (0.031 g, 0.5 mol%), was dissolved in THF and epoxide **32** (3.78 g, 20 mmol) was added at 25 °C, the solution was cooled to 0 °C and H_2O (0.198 g, 11 mmol) was added dropwise over 5 min. The reaction was allowed to 25 °C and stirred for 48 h. Mixture containing epoxide and diol was purified by column chromatography to obtain epoxide **33** in 46% yield and diol **34** in 49% yield respectively

(*S*)-2-(2,4-Dichlorophenyl)oxirane (33):

Yield: 1.739 g (46%); viscous liquid; **$[\alpha]^{25}_{D}$** +62.36 (*c* 1.2, $CHCl_3$); **HPLC**: 96% ee, (*R,R*)- Whelk-O 1, λ = 220 nm, 2-propanol/hexane (0.1:99.9), 1 mL/min, retention time: (*S*)-enantiomer 4.53 min; **IR**: ($CHCl_3$, cm^{-1}): 817, 952, 1130, 1162, 1380, 1467, 1648, 2933, 3297, 3370; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.60 (dd, *J* = 2.5, 3.1 Hz, 1H), 3.18 (dd, *J* = 4.1, 1.6 Hz, 1H), 4.13 (dd, *J* = 2.5, 1.6 Hz, 1H), 7.14-7.26 (m, 2H), 7.36-7.37 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 49.4, 50.4, 126.5, 127.3, 128.8, 133.7, 133.9, 134.3; **Analysis**: **$C_8H_6Cl_2O$** requires C, 50.83; H, 3.20; Cl, 37.51; found C, 50.72; H, 3.45; Cl, 37.62%.

(*R*)-1-(2, 4-Dichlorophenyl)ethane-1,2-diol (34):

Yield: 2.028 g (49%); viscous liquid; **$[\alpha]^{25}_{D}$** -52.4 (*c* 1, $CHCl_3$); **IR**: ($CHCl_3$, cm^{-1}): 759, 1046, 1216, 1472, 1563, 1670, 3020, 3390; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.45 (dd, *J* = 8.1, 11.5 Hz, 1H), 3.79 (dd, *J* = 2.8, 11.6 Hz, 1H), 4.04 (brs, 2H), 4.45 (dd, *J* = 2.7, 8.1 Hz, 1H), 7.18-7.24 (m, 1H), 7.30-7.31 (m, 1H), 7.41-7.45 (m, 1H); **^{13}C NMR** (50 MHz,

$CDCl_3$): δ 65.9, 70.9, 127.3, 128.3, 129.0, 132.2, 133.9, 136.2; **Analysis**: $\mathbf{C_8H_8Cl_2O_2}$ requires C, 46.41; H, 3.89; Cl, 34.25; found C, 46.48; H, 3.75; Cl, 34.41%.

(*S*)-1-(2,4-Dichlorophenyl)-2-(1*H*-imidazol-1-yl)ethanol (20):

To a stirred solution of epoxide **33** (0.945 g, 5 mmol) in ethanol (15 mL) was added imidazole (0.340 g, 5 mmol) at 25 ^oC. The reaction mixture was refluxed under N_2 for 12 h (reaction monitored by TLC). The reaction mixture was then cooled and the solvent was removed under reduced pressure. The residue was purified by column chromatography using pet. ether: EtOAc (3:7) as eluent to get amino alcohol **20** in 88% yield.

Yield: 1.13 g (88%); **mp**: 129-130 ^oC; $\mathbf{[\alpha]^{25}_D}$ +85.5 (*c* 1, MeOH) 96% ee; {lit.[12] $[\alpha]^{25}_D$ +88 (*c* 1.06, MeOH) 98.8% ee}; **IR** ($CHCl_3$, cm^{-1}): 669, 759, 1081, 1216, 1512, 1590, 2400, 3020, 3351; ^{1}**H NMR** (200 MHz, $CDCl_3$): δ 3.85 (dd, *J* = 8.2, 14.2 Hz, 1H), 4.20 (dd, *J* = 2.4, 14.2 Hz, 1H), 5.22 (dd, *J* = 2.3, 8.2 Hz, 1H), 6.02 (bs, 1H), 6.79 (br, 1H), 6.88 (br, 1H), 7.28 (dd, *J* = 2.0, 8.3 Hz, 1H), 7.34 (br, 1H), 7.39 (d, *J* = 2.0, 1H), 7.57 (d, *J* = 8.5, 1H); ^{13}**C NMR** (50 MHz, $CDCl_3$): δ 58.4, 69.7, 120.4, 128.0, 129.1, 129.9, 132.3, 133.4, 137.9; **Analysis:** $\mathbf{C_{11}H_{10}Cl_2N_2O}$ requires C, 51.38; H, 3.92; N, 10.90; found C, 51.54; H, 3.72; N, 10.75%.

1-((*S*)-2-(4-Chlorobenzyloxy)-2-(2,4-dichlorophenyl)ethyl)-1*H*-imidazole {Econazole} (2):

To a stirred mixture of NaH (88 mg, 2.2 mmol) in dry DMF (5 mL) was added 4-chlorobenzyl bromide (0.452 g, 2.2 mmol) at 0 ºC. The reaction mixture was stirred for 30 min at 25 ºC followed by addition of amino alcohol **20** (0.514 g, 2 mmol). After completion of reaction (TLC), the reaction mixture was extracted with EtOAc (3 x 50

mL). The combined organic layer was dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography to afford **2**.

Yield: 0.557 g (73%); **$[\alpha]^{25}_D$** +40.29 (*c* 2, acetone) 96% ee; **IR** ($CHCl_3$, cm^{-1}): 758, 819, 1044, 1094, 1216, 1382, 1472, 1506, 1590, 1695, 2953, 3018, 3390; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 4.03 (dd, *J* = 7.6, 14.5 Hz, 1H), 4.15-4.24 (m, 2H), 4.40-4.16 (m, 1H), 4.96 (dd, *J* = 2.9, 7.6 Hz, 1H), 6.90 (bs, 1H), 7.04-7.08 (m, 3H), 7.26-7.32 (m, 4H), 7.44 (d, *J* = 1.3, 2H); **Analysis: $C_{18}H_{15}Cl_3N_2O$** requires C, 56.64; H, 3.96; N, 7.34; found C, 56.54; H, 3.72; N, 7.15%.

1-((*S*)-2-(2,4-Dichlorobenzyloxy)-2-(2,4-dichlorophenyl)ethyl)-1*H*-imidazole {Miconazole} (3):

To a stirred mixture of NaH (88 mg, 2.2 mmol) in dry DMF (5 mL) was added 2,4-chlorobenzylbromide (0.48 g, 2 mmol) at 0 ºC. The reaction mixture was stirred for 30 min at 25 ºC followed by addition of amino alcohol **20** (0.514 g, 2 mmol). After completion of reaction (TLC), the reaction mixture was extracted with EtOAc (3 x 50 mL). The combined organic layer was dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography to afford **2**.

Yield: 0.649 g (78%); $[\alpha]^{25}_D$ +44.16 (*c* 2, acetone); **HPLC**: 96% ee, Chiracel OD-H, λ = 220 nm, diethylamine/2-propanol/hexane (0.1:20:80), 1 mL/min, retention time: (*S*)-enantiomer 11.51 min, (*R*)-enantiomer 14.45 min; **IR** ($CHCl_3$, cm^{-1}): 758, 819, 1044, 1094, 1216, 1382, 1472, 1506, 1590, 1695, 2953, 3018, 3390; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 4.07 (dd, *J* = 7.3, 14.5 Hz, 1H), 4.24 (dd, *J* = 2.8, 14.5 Hz, 1H), 4.42 (dd, *J* = 12.6, 31.6 Hz, 2H), 5.02 (dd, *J* = 2.8, 7.3 Hz, 1H), 6.90 (br, 1H), 7.02 (br, 1H), 7.20-7.22 (m, 2H), 7.29-7.34 (m, 3H), 7.44 (d, *J* = 1.4, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 51.2,

68.1, 77.5, 119.6, 127.2, 127.8, 128.3, 129.0, 129.1, 129.5, 129.9, 133.1, 133.2, 133.6, 134.2, 134.9, 137.7; **Analysis: $C_{18}H_{14}Cl_4N_2O$** requires C, 51.95; H, 3.39; N, 6.73; found C, 52.08; H, 3.54; N, 6.97%.

1-(2, 4-Difluorophenyl)-2-(1*H*-1, 2, 4-triazol-1-yl)ethanone (25):

A mixture of 2-chloro-1-(2, 4-difluorophenyl)ethanone (**24**) (2.23 g, 10 mmol), 1,2,4-triazole (1.726 g, 25 mmol), and anhydrous K_2CO_3 (2.07 g, 15 mmol) in dry CH_3CN (20 mL) was refluxed under nitrogen atmosphere for 12 h (reaction monitored by TLC). The reaction mixture was then cooled to 25 ^oC, 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 amino ketone **25** in 96% yield.

Yield: 1.96 g (88%); **mp**: 110 ^oC; **IR** ($CHCl_3$, cm^{-1}): 538, 678, 827, 881, 970, 1104, 1147, 1278, 1437, 1515, 1613, 1702, 2967, 3071, 3134; ^{1}**H NMR** (200 MHz, $CDCl_3$): δ 5.60 (d, *J* = 3.7 Hz, 2H), 6.94-7.10 (m, 2H), 8.00-8.11 (m, 2H), 8.22 (s, 1H); ^{13}**C NMR** (50 MHz, $CDCl_3$): δ 58.1, 104.6, 112.8, 118.7, 132.7, 144.7, 151.5, 160.3, 163.8, 165.4, 169.1, 187.5; **Analysis: $C_{10}H_7F_2N_3O$** requires C, 53.82; H, 3.16; N, 18.83; found C, 53.59; H, 3.32; N, 18.71%.

1-(Bromomethyl)-1*H*-1, 2, 4-triazole (35):

A mixture of 1,2,4-triazole (0.235 g, 3.4 mmol), paraformaldehyde (0.510 g, 17 mmol), 33 wt% HBr/acetic acid (4 mL) was kept at 70-80 ^oC for 3 h, cooled and then poured over ice. The aqueous solution was immediately extracted with CH_2Cl_2 (2 x 25 mL), and the organic extracts were washed with 10% $NaHCO_3$ solution, brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column

chromatography using pet. ether: EtOAc (9:1) as eluent to give bromomethyl derivative **35**.

Yield: 0. 519 g (82%); **IR** ($CHCl_3$, cm^{-1}): 634, 679, 883, 979, 1064, 1157, 1281, 1473, 1518, 1582, 1632; ^{1}**H NMR** (200 MHz, DMSO-d_6): δ 5.46 (s, 2H), 7.98 (s, 1H), 8.58 (s, 1H); ^{13}**C NMR** (50 MHz, $CDCl_3$): δ 71.4, 144.3, 151.8; **Analysis: $C_3H_4BrN_3$** requires C, 22.24; H, 2.49; N, 25.94; found C, 22.45; H, 2.64; N, 26.11%.

2-(2,4-Difluorophenyl)-1,3-di(1H-1,2,4-triazol-1-yl)propan-2-ol {Fluconazole} (5):

To a stirred mixture of magnesium (1.2 mmol, 28 mg) in THF (10 mL) was added 1-(bromomethyl)-1*H*-1,2,4-triazole (186 mg, 1 mmol) at 0 ^oC and was refluxed for 1 h. A solution of ketone **25** (1 mmol, 223 mg) in 10 mL was added dropwise to the above prepared Grignard reagent at 25 ^oC. The reaction mixture was refluxed for 2 h, cooled to 25 ^oC, quenched with 2 M HCl (20 mL) and extracted with ether. The combined organic layers were washed with brine, dried over anhyd. Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by column chromatography using pet.ether: EtOAc (7:3) as eluent to give fluconazole.

Yield: 0.260 g (85%); **IR** (KBr, cm^{-1}): 571, 654, 834, 853, 967, 1140, 1276, 1421, 1505, 1516, 1619, 1726, 3107, 3116; ^{1}**H NMR** (200 MHz, $CDCl_3$): δ 1.99 (brs, 1H), 4.57 (d, *J* = 14.3 Hz, 2H), 4.76 (d, *J* = 14.3 Hz , 2H), 6.75-6.86 (m, 2H), 7.37-7.49 (m, 1H), 7.85 (s, 2 H), 8.07 (s, 2H); ^{13}**C NMR** (50 MHz, $CDCl_3$): δ 53.4, 72.3, 102.3, 109.4, 121.5, 128.2, 143.4, 149.2, 155.1, 158.4, 160.0, 163.3; **Analysis: $C_{12}H_{12}F_2N_6O$** requires C, 50.98; H, 3.95; N, 27.44; found C, 50.83; H, 4.11; N, 27.59%.

2.7 References

1. Onishi, J.; Meinz, M.; Thompson, J.; Curotto, J.; Dreikorn, S.; Rosenbach, M.; Douglas, C.; Abruzzo, G.; Flattery, A.; Kong, L.; Cabello, A.; Vicente, F.; Pelaez, F.; Diez, M. T.; Martin, I.; Bills, G.; Giacobbe, R.; Dombrowski, A.; Schwartz, R.; Morris, S.; Harris, G.; Tsipouras, A.; Wilson, K.; Kurtz, M. B. *Antimicrob. Agents Chemother.* **2000**, *44*, 368.
2. Fostel, J. M.; Lartey, P. A. *Drug Discov. Today* **2000**, *5*, 25.
3. Kane, J.; Summerbell, R. C. 7th ed.; Murray, P. R., et al., Eds.; ASM Press: Washington, DC, **1999**; p 1275.
4. Como, J. A.; Dismukes, W. J. *New Engl. J. Med*. **1994**, *330*, 263.
5. Maertens, J. A. *Clin. Microbiol. Infec.* **2004**, *10*, 1.
6. Holt, R. J. *Drugs* **1975**, *9*, 401.
7. Heel, R. C.; Brogden, R. N.; Carmine, A.; Morley, P. A.; Speight, T. M.; Avery, G. S. *Drugs* **1982**, *23*, 1.
8. Boeache, H. V. *Curr. Top. Med. Mycol.* **1985**, *1*, 313.
9. (a) Strandberg, T. E.; Tilvis, R. S.; Miettinen, T. A. *Lipids* **1984**, *22*, 1020. (b) Kraemer, F. B.; Spilman, S. D. *Pharmacol. Exp. Ther.* **1986**, 238, 905.
10. Heeres, J.; Backx, L.J. J.; Mostmans, J. H.; Van Cutsem, J. *J. Med. Chem,* **1979,** *22***,** 1003.
11. Rotstein, D. M.; Kertesz, D. J.; Walker, K. A. M.; Swinney, D. C. *J. Med. Chem,* **1992,** *35***,** 2818.
12. Lennon I. C.; Ramsden, J. A. *Org. Process Res. Dev.* **2005**, *9*, 110.
13. Richardson, K. US patent 1983/4404216.

14. Veinberg, A.; Senderichin, A. US patent 1996/5484936.

15. (a) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936. (b) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307.

16. Desai, R. C.; Farrell, R. P.; Kuo, G. H.; Hlasta, D. J. *Synlett* **1994**, *11*, 933.

17. Theil, F.; Weidner, J.; Ballschuh, S.; Kunath, A.; Schick, H. *J. Org. Chem.* **1994**, *59*, 388.

CHAPTER 3

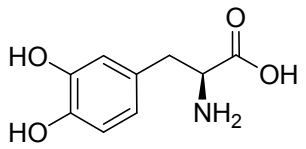
Asymmetric Synthesis of L-DOPA and Formal Synthesis of Levofloxacin using Proline-Catalyzed α-Functionalization of Aldehydes

SECTION 1:

Enantioselective Synthesis of L-DOPA via Proline-Catalyzed α-Amination of Aldehyde

3.1.1 Introduction

L-DOPA [(*S*)-3,4-dihydroxyphenylalanine] (**1**) is a naturally occurring amino acid derived from post-translational modification of tyrosine.[1] It is one of the principal agents administered to patients with Parkinson's disease since 1967.[2] Although rarely found in proteins, L-DOPA (**1**) was detected in high yield (ca. 10%) in marine mussel adhesive proteins. The ubiquitous nature of (*S*)-3,4-dihydroxyphenylalanine, {L-DOPA (**1**)} touches biological fields ranging from medicine to engineering. Most commonly known for pharmacological value, L-DOPA (**1**) has been the treatment of choice to alleviate Parkinson's disease symptom **(Fig. 1)**.[3]



L-DOPA (**1**)

Fig. 1 Structure of *L*-DOPA(1)

Parkinsonism is a chronic neurological disorder characterized by tremor, rigidity of the limbs and poverty of movement (hypokenesia). In most cases, however, no cause can be identified. Pathological examination of the brain reveals widespread degenerative changes in the basal ganglia, particularly the *substantia nigra* and *corpus striatum*.

3.1.1.1 Pharmacology of L-DOPA

Parkinson's disease is caused by a shortage of a particular chemical that is produced in the brain. This chemical is called dopamine. Without this chemical messenger, the signals from the brain do not get through to the spinal cord and then to the various muscles of the body, hence muscular function is impaired. Dopamine is synthesized within nerve cells. Chemically, L-tyrosine is converted to (*S*)-dihydroxyphenylalanaine [L-DOPA (**1**)] and then to dopamine in a two-step process.[4]

The symptoms appear when there is not enough dopamine in the brain. Dopamine is a naturally occurring chemical (neurotransmitter) that allows nerve cells to transmit messages between each other and then to muscles to allow normal movement to take place. In Parkinson's disease, many of these cells are died. The remaining cells cannot produce enough dopamine. Most drug therapy replaces dopamine in the brain. Parkinson's disease is believed to be related to low levels of dopamine in certain parts of the brain. When L-DOPA is taken orally, it crosses through the "blood-brain barrier." Once it crosses, it is converted to dopamine. The resulting increase in brain dopamine concentrations is believed to improve nerve conduction and assist the movement disorders in Parkinson's disease. Carbidopa does not cross the blood-brain barrier and added to L-DOPA (**1**) to prevent the breakdown of L-DOPA before it crosses into the brain. The addition of carbidopa allows lower doses of L-DOPA to be used. This reduces the risk of side effects from L-DOPA such as nausea and vomiting.

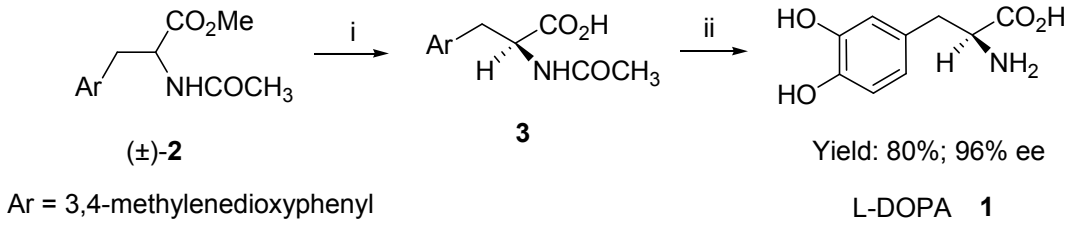
3.1.2 Review of Literature

Literature search reveals that there are various methods available for the enantioselective synthesis of L-DOPA (**1**). Most of these methods make use of classical kinetic resolution

of diastereomeric derivatives of L-DOPA, others on oxidation of L-tyrosine and probably the dominating industrial procedure is based upon catalytic asymmetric hydrogenation. Some of the recent approaches to L-DOPA have been described below.

Tyagi's approach (1992)[5]

This approach describes the synthesis of L-DOPA (**1**) utilizing enzymatic resolution as a key step. Thus, racemic *N*-acetyl-3,4-methylenedioxyphenylalanine methyl ester **2** on enzymatic hydrolysis by alcalase provided (*S*)-*N*-acetyl-3,4-methylenedioxyphenylalinine (**3**), which was converted to L-DOPA (**1**) in high optical purity by known sequence of reactions (**Scheme 1**).



(±)-**2**

Ar = 3,4-methylenedioxyphenyl

3

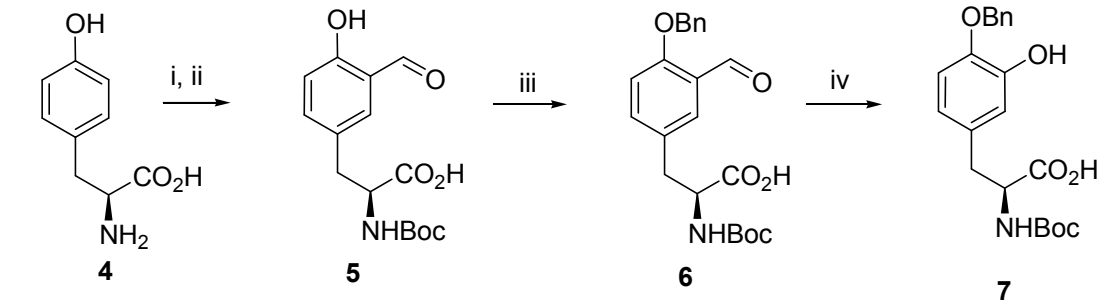
Yield: 80%; 96% ee

L-DOPA **1**

Scheme 1: (i) Alcalase, pH: 7.5; (ii) PhOH, HCl, reflux.

Jung's approach (1997)[6]

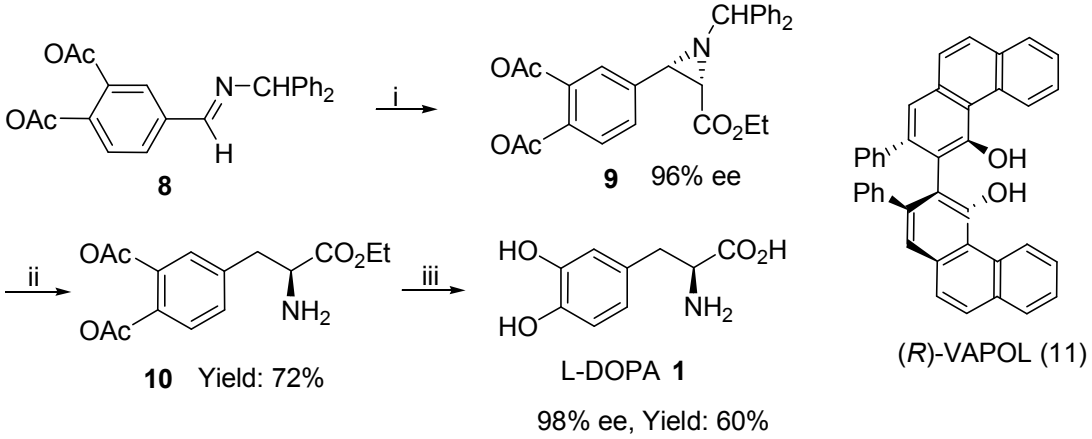
Synthesis of *N*-Boc-*L*-3-[3hydroxy-4-(phenylmethoxy)phenyl]alanine (**7**) was achieved *via* Reimer-Tiemann formylation followed by Dakin reaction as key steps. Thus, formylation of *N*-Boc *L*-tyrosine (**4**) provided 2-formyl derivative **5**. Further, benzylation followed by reaction with 30% H_2O_2 in the presence of diphenyl diselenide gave the aryl formate, which on subsequent treatment with methanolic ammonia afforded the desired phenol **7** in 78% yield (**Scheme 2**).



Scheme 2: (i) $(BOC)_2O$, Et_3N, dioxane, H_2O, 92%; (ii) $CHCl_3$, NaOH, H_2O, heat, 4 h, 64%; (iii) K_2CO_3, BnBr, $CHCl_3$, MeOH; (iv) 30% H_2O_2, 4% $(PhSe)_2$, CH_2Cl_2, NH_3, 1 h, 78%.

Antilla's approach (2000)[7]

Antilla and co-workers have synthesized L-DOPA (**1**) by using asymmetric aziridination approach. Thus, reaction of imine **8** with ethyl diazoacetate (EDA) in the presence of catalytic amount of (*R*)-VAPOL (**11**) and triphenylborate afforded the chiral aziridines **9** in 96% ee. Hydrogenation of aziridine **9** at the *N*-benzylic bond occurred with cleavage of the benzhydral group to give the amino ester **10** in 72% yield. On hydrolysis of **10** L-DOPA (**1**) was obtained in 60% yield and 98% ee (**Scheme 3**).

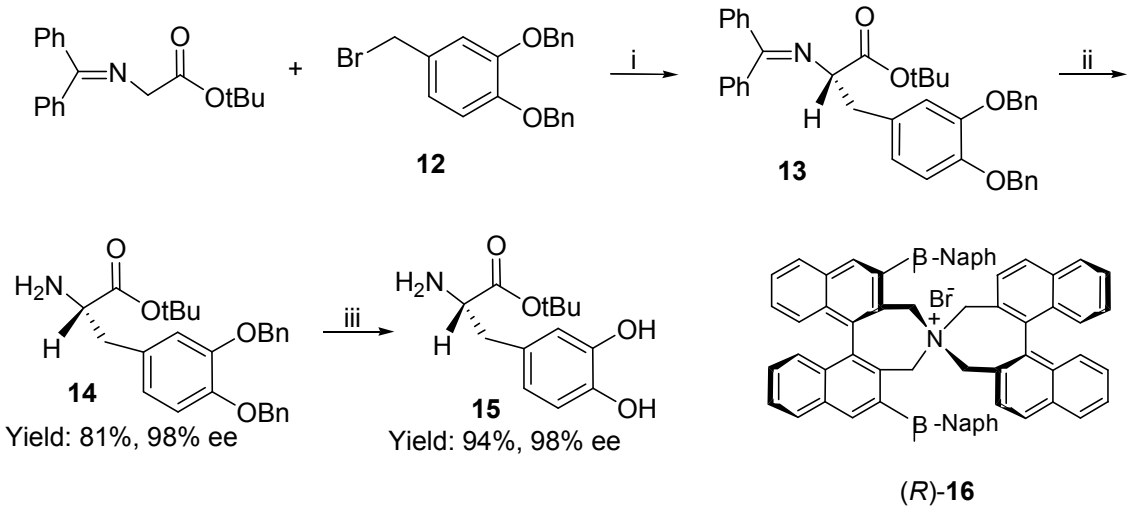


Scheme 3: (i) 1.1 equiv. EDA. (*R*)-VAPOL (**11**)/ $B(OPh)_3$, 8 h (2.5 mol%), 0 °C, 6 h, 22 °C, 14 h; (ii) Pd black, HCO_2H/ MeOH, 25 °C; (iii) 3N HCl, acetone, 90 °C, 20 h.

Takashi's approach (2000)[8]

Takashi *et al.* have described synthesis of L-DOPA ester **15** by using chiral quaternary ammonium salt **16** as a phase-transfer catalyst. Thus, alkylation of imine with bromide **25**

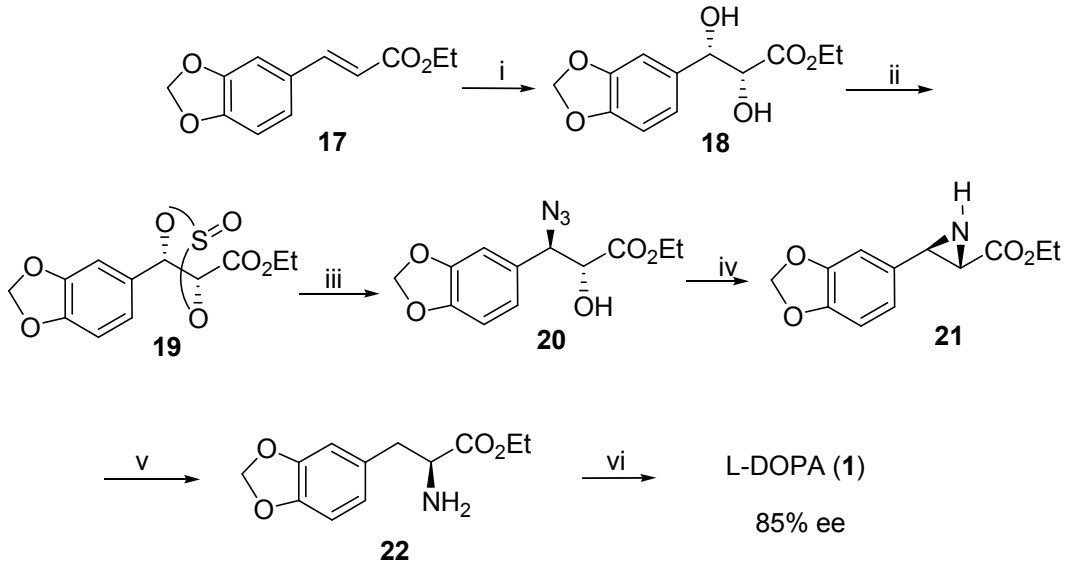
in the presence of (*R*)-**16** gave *tert*-butyl ester **13**, which was subsequently treated with 1M citric acid to afford the corresponding amino ester **14** in 81% yield. Debenzylation of amine **14** afforded the desired *tert*-butyl ester of L-DOPA **15** in 98% ee (**Scheme 4**).



Scheme 4: (i) (*R*)-**16** (1 mol%), toluene, 50% *aq*. KOH, 0 ^{o}C; (ii) 1M citric acid, THF, 25 ^{o}C, 10 h; (iii) 10% Pd-C, 25 ^{o}C, THF, 25 ^{o}C, 5 h.

Sudalai's approach (2004)[9]

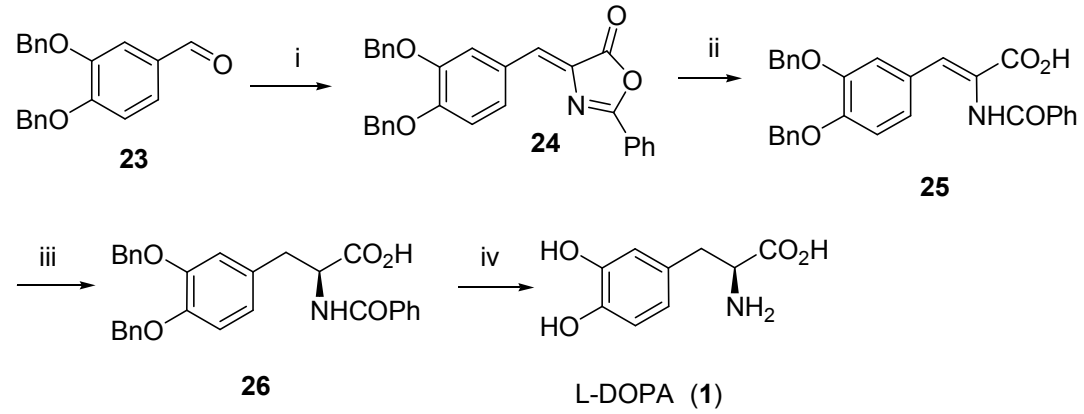
In this approach, α,β-unsaturated ester **17** was subjected to ADH to give chiral diol **18** in excellent optical purity. The vicinal diol **18** on treatment with $SOCl_2$ in presence of Et_3N in CH_2Cl_2 at 0 ^{o}C gave the corresponding cyclic sulfite **19**. Cyclic sulfite **19** was treated with sodium azide, to get azido alcohol **20,** which was converted into aziridine **21.** Aziridine **21** underwent stereospecific and regioselective ring opening at the benzylic position to produce amine **22**. Aminoester **22** was hydrolyzed with acid to furnish L-DOPA (**1**) in 85% ee (**Scheme 5**).



Scheme 5: (i) Cat. OsO_4, $(DHQ)_2$-PHAL, $K_3Fe(CN)_6$, K_2CO_3, *tert*-BuOH:H_2O, 0 ^oC, 85%; (ii) $SOCl_2$, Et_3N, CH_2Cl_2, 0 ^oC, 88%; (iii) NaN_3, acetone: H_2O, 80 ^oC, 82% yield, 95% ee; (iv) PPh_3, CH_3CN, 90%; (v) 10% Pd/C, HCO_2NH_4, MeOH, reflux, 92%; (vi) 6 N HCl, PhOH, AcOH, 130-135 ^oC, 24 h, 70% yield, 85% ee.

Valdes's approach (2004)[10]

Valdes *et al.* have demonstrated the synthesis of L-DOPA (**1**) by Pd/C catalyzed asymmetric hydrogenation of *N*-benzoylamino-3-(3',4'-dibenzyloxyphenyl)-2-propenoic acid (**25)** using cinchonine as ligand (**Scheme 6**).

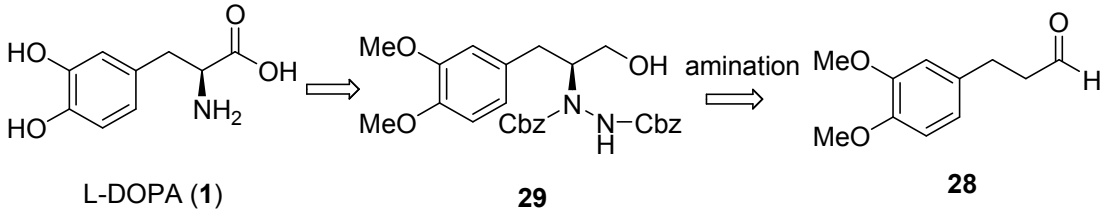


Scheme 6: (i) Ac_2O, NaOAc, N-benzoylglycine, 77%; (ii) (a) 2 M NaOH; (b) conc. HCl, 93%; (iii) THF, Pd/C, cinchonine, H_2, 65%; (iv) conc. HBr, 60%.

3.1.3 Present Work

3.1.3.1 Objective

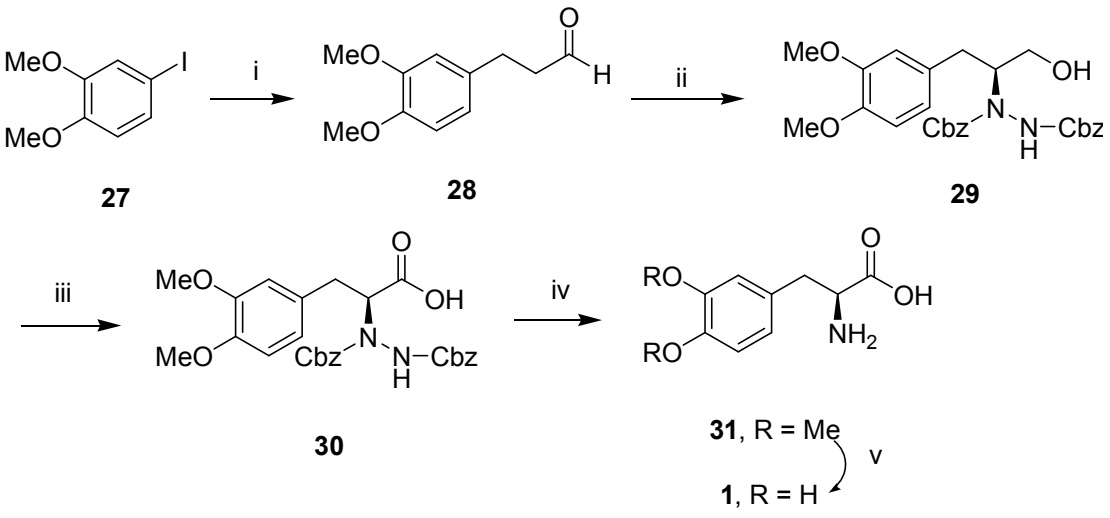
All the reported methods described above for the synthesis of L-DOPA (**1**) suffer from drawbacks such as use of expensive enzymes and resolving agents, low overall yields, low optical purity, the need for separation of diastereomers *etc*. As can be seen from the retrosynthetic analysis (**Scheme 7)**, the synthesis of L-DOPA (**1**) is visualized to be achieved by the D-proline-catalyzed α-amination[11] of aldehyde **28**.



Scheme 7: Retrosynthetic analysis for L-DOPA (1)

3.1.4 Results and Discussion

The synthetic route for L-DOPA (**1**) is shown in **Scheme 8**.



Scheme 8: (i) allyl alcohol, $Pd_2(dba)_3$, $P(Cy)_3$, K_2CO_3, DMF, 100 ºC, 86%; (ii) dibenzyl azodicarboxylate , D-proline (10 mol%), CH_3CN, 0-25 ºC, 3 h then $NaBH_4$, EtOH, 62%; (iii) $NaClO_2$, NaClO, TEMPO, CH_3CN, phosphate buffer, 25 °C, 78%; (iv) H_2 (70 psig), Raney-nickel, MeOH, AcOH, 25 °C; (v) BBr_3, CH_2Cl_2, 0 ºC, 58%, 94% ee.

Our synthesis started with the preparation of aldehyde **28**, which was obtained with a yield of 86% by the arylation of 4-iodo-1,2-dimethoxybenzene (**27**) with allylic alcohol using $Pd_2(dba)_3$ as catalyst. The ^1H NMR spectrum of aldehyde **28** showed a typical singlet at δ 9.82 for aldehydic proton; other typical singlets at δ 3.85 and 3.87 are due to two -OMe protons. Its ^{13}C NMR spectrum showed an aldehydic carbon at δ 201.67. Its IR spectrum exhibited a characteristic strong band at 1712 cm^{-1} indicating the presence of a carbonyl group. Aldehyde **28** was then subjected to *α*-amination using D-proline as catalyst, dibenzyl azodicarboxylate as the amine source, followed by its *in situ* reduction with $NaBH_4$ gave the protected amino alcohol **29** in 62% combined yield. The ^1H NMR spectrum of **29** showed signals at δ 5.17 corresponding to -O-CH_2 protons of Cbz groups; other multiplet at δ 4.21 is due to -N-CH proton. Its ^{13}C spectrum showed signals at δ 67.9 and 156.38 corresponding to -O-CH_2- and carbonyl carbon of Cbz groups respectively (**Fig. 2**).

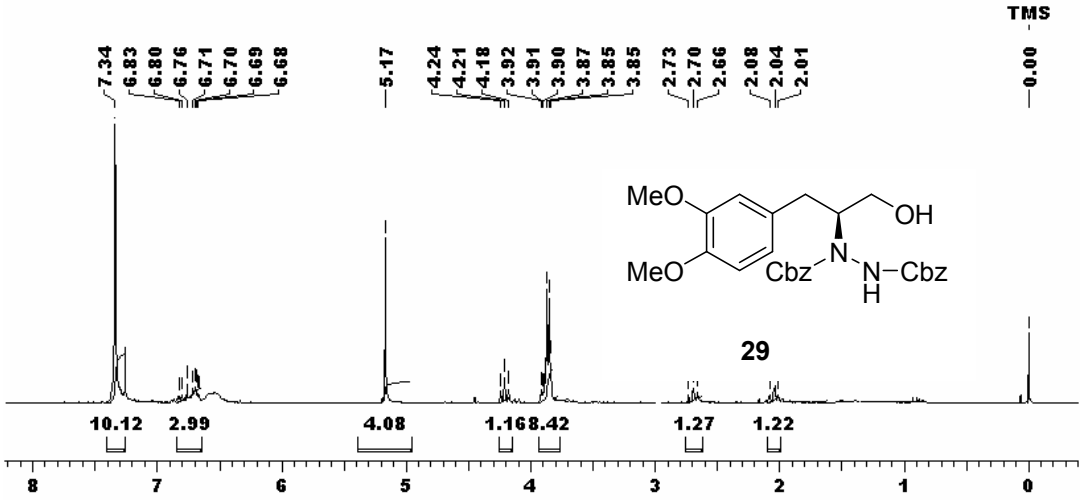


Fig. 2: ^1H spectrum of amino alcohol 29

Mild oxidation of alcohol **29** was carried out with $NaClO_2$, NaOCl, 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) as catalyst to produce the corresponding acid **30**. The ^1H NMR spectrum of **30** showed signals at δ 5.13 corresponding to -O-CH_2- protons of Cbz groups. Its ^{13}C spectrum showed signals at δ 67.8 and 172.12 corresponding to -O-CH_2- of Cbz groups and acid carbonyl respectively.

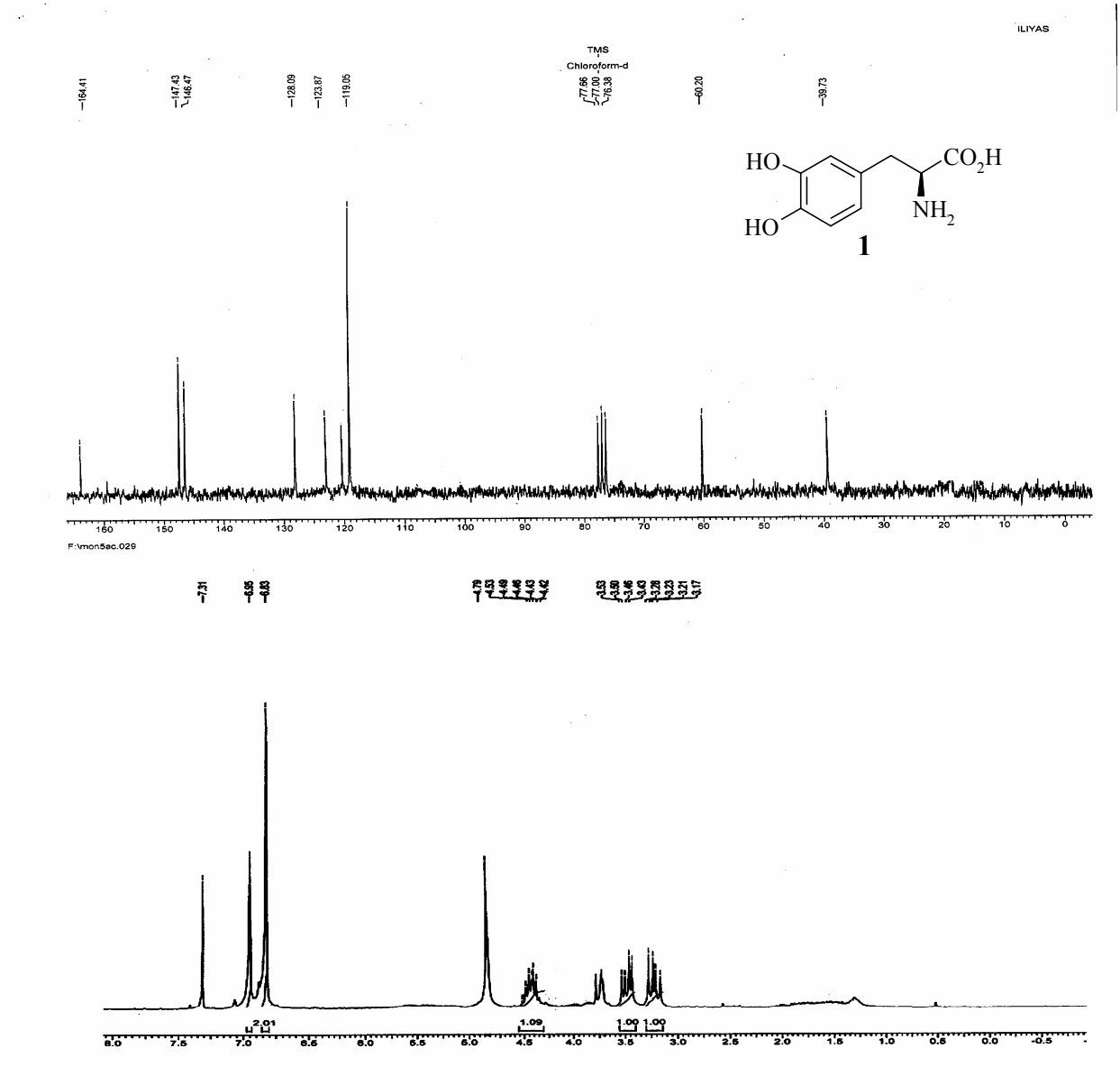


Fig. 3: ^{13}C NMR and ^1H spectra of L-DOPA (1)

Reductive removal of both Cbz groups as well as *N*-*N* bond cleavage were achieved with Raney-Nickel (H_2, 70 psig), followed by demethylation using BBr_3, thus afforded L-DOPA (**1**) in 78% yield with 94% ee. The spectral data obtained for L-DOPA were in full agreement with the values reported in the literature[9] (**Fig. 3**).

3.1.5 Conclusion

In conclusion, synthesis of L-DOPA (**1**) was achieved in 94% ee *via* D-proline-catalyzed *α*-amination of aldehyde **28**. These reactions are operationally simple, rapid and require a relatively low amount of an inexpensive and nontoxic proline-catalyst. Excellent yields, simple and environment friendly procedures and easy availability of starting materials are some of the merits of this synthesis.

3.1.6 Experimental Section

3-(3,4-Dimethoxyphenyl)propanal (28):

To a stirred mixture of 4-iodo-1,2-dimethoxybenzene (**27**) (2.64g, 10 mmol), $Pd_2(dba)_3$ (0.045 g, 0.5 mol%), $P(Cy)_3$ (0.028 g, 1 mol %) and K_2CO_3 (2.76 g, 20 mmol) in DMF (15 mL) was added allyl alcohol (1.68 g, 30 mmol). The resulting mixture was stirred at 100 °C for 6 h. Then the reaction mixture was cooled to 25 ^oC and extracted with ethyl acetate (3 x 20 mL), washed with brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. The crude product was purified on column chromatography using 5% ethyl acetate in pet. ether as eluent to afford the pure aldehyde **28** as colorless liquid.

Yield: 1.668 g (86%); colourless liquid; **IR:** ($CHCl_3$, cm^{-1}): 757, 831, 1033, 1178, 1247, 1308, 1463, 1514, 1612, 1681, 1712, 2057, 2362, 2837, 2933, 3006; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.73-2.81 (m, 2H), 2.88-2.99 (m, 2H), 3.85 (s, 3H), 3.87 (s, 3H), 6.71-6.82 (m, 3H), 9.82 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 24.3, 45.1, 55.5, 55.6, 111.1, 111.3, 119.8, 132.6, 147.1, 148.6, 201.6; **Analysis: $C_{11}H_{14}O_3$** required C, 68.02; H, 7.27; found C, 67.89; H, 7.45%.

(S)-3-(3,4-Dimethoxyphenyl)-2-(1,2-dibenzyloxycarbonylhydrazinyl)propanol (29):

To a mixture of dibenzyl azodicarboxylate (1.324 g, 4 mmol) and D-proline (0.140 g, 20 mol%) in CH_3CN (200 mL) at 0 ºC was added 3-(3,4-dimethoxyphenyl)propanal (1.17 g, 6 mmol) and the reaction mixture was allowed to stir at the same temperature for 2 h and then warmed to 20 ºC within 1 h. After the reaction mixture became colorless it was cooled to 0 ºC again and then treated with EtOH (20 mL) and $NaBH_4$ (0.38 g) for 5 min at 0 ºC. After completion of reaction, it was quenched with aq. ammonium chloride solution and extracted with ethyl acetate (100 mL X 3). The combined organic layers were dried over anhyd. Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to get **29**.

Yield: 1.532 g (62%); **$[\alpha]_D^{25}$** +9.6 (*c* 0.14, $CHCl_3$); **IR:** ($CHCl_3$, cm^{-1}): 665, 929, 1027, 1060, 1217, 1361, 1454, 1514, 1724, 2401, 2937, 2958, 3020; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.04 (t, *J* = 7.3 Hz, 1H), 2.70 (t, *J* = 7.4 Hz, 1H), 3.85 (s, 3H), 3.87 (s, 3H), 3.89-3.92 (m, 2H), 4.18-4.24 (m, 1H), 5.17 (s, 4H), 6.67-6.83 (m, 3H), 7.34 (m, 10 H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 31.1, 53.1, 55.8, 55.9, 67.9, 68.7, 111.5, 111.9, 120.3, 128.3, 128.4, 128.6, 132.7, 135.5, 147.6, 149.1, 156.3; **Analysis: $C_{27}H_{30}N_2O_7$** required C, 65.57; H, 6.11; N, 5.66; found C, 65.42; H, 6.13; N, 5.78%.

(S)-3-(3,4-dimethoxyphenyl)-2-(1,2-dibenzyloxycarbonylhydrazinyl)-propanoic acid (30):

To a stirred solution of alcohol **29** (1.48 g, 3 mmol), TEMPO (33 mg, 0.21 mmol), $NaClO_2$ (0.5 g, 6 mmol) and phosphate buffer (12 mL) in CH_3CN (15 mL) at 25 ºC was added NaClO (5%, 0.15 mL). After stirring the reaction mixture for 5 h at 25 ºC, 7.2 mL of 2N NaOH was added and the mixture was added to an ice-cold solution of sodium sulfite (92 mg in 30 mL). After stirring for 30 min, the reaction mixture was acidified with 2N HCl to pH 3-4 and extracted with ethyl acetate (50 mL X 3). The combined organic layers were washed with brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give the acid **30** as a viscous liquid.

Yield: 1.189 g (78%); $[\alpha]_D^{25}$ +5.33 (*c* 0.36, $CHCl_3$); **IR:** ($CHCl_3$, cm^{-1}): 667, 698, 1027, 1217, 1261, 1514, 1593, 1605, 1733, 2937, 2960, 3018, 3066, 3294; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.05-3.14 (m, 1H), 3.27-3.29 (m, 1H), 3.82 (s, 6H), 5.11-5.20 (m, 4H), 6.63-6.78 (m, 3H), 7.30-7.36 (m, 10H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 34.5, 55.7, 67.8, 68.6, 111.2, 111.9, 120.7, 127.8, 128.3, 128.4, 134.8, 135.3, 147.7, 148.8, 155.19, 172.1; **Analysis:** $C_{27}H_{28}N_2O_8$ requires C, 63.77; H, 5.55; N, 5.51 found C, 63.91; H, 5.38; N, 5.59%.

(S)-2-Amino-3-(3,4-dihydroxyphenyl)propanoic acid (L-DOPA) (1):

The acid **30** (0.763 g, 1.5 mmol) was dissolved in MeOH (20 mL), AcOH (10 drops) and treated with Raney nickel (1 g, excess) for 24 h under 70 psig hydrogen pressure. The reaction mixture was filtered over pad of celite and concentrated. To the crude amino acid dry CH_2Cl_2 (5 mL) was added BBr_3 (1 mL, excess) at 0 ºC and stirred for 6 h at 25

ºC. After completion of reaction, solvents were removed under reduced pressure and purified by column chromatography to get pure product.

Yield: 0.171 g (58%); **mp:** 298 ºC; lit. **mp:** 295 ºC; $\mathbf{[\alpha]^{25}_D}$ -12.1 (*c* 1.0, 1N HCl); {lit.[9] $\mathbf{[\alpha]^{25}_D}$ -12.3 (*c* 1.0, 1N HCl)}; **IR** (KBr, cm^{-1}): 840, 985, 1245, 1454, 1514, 1591, 1610, 1654, 1696, 2599, 2854, 2925, 3203, 3500; **^{1}H NMR** (200 MHz, D_2O): δ: 3.20 (dd, *J* = 6.0, 6.0 Hz, 1H), 3.50 (dd, *J* = 6.0, 6.0 Hz, 1H), 3.60 (brs, 2H) 4.45 (m, 1H), 6.80-7.05 (m, 3H), 11.8-12.6 (brs, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 39.73, 60.20, 119.05, 120.20, 123.87, 128.09, 146.47, 147.43, 164.41. **Analysis: $C_9H_{11}NO_4$** requires C, 54.82; H, 5.62; N, 7.10 found C, 54.69; H, 5.55; N, 6.94%.

SECTION 2:

Formal Synthesis of Levofloxacin *via* Proline-Catalyzed *α*-Amination and *α*-Aminooxylation of Aldehydes

3.2.1 Introduction

3.2.1.1 Quinolone Antibacterial agents

Quinolone antibacterial agents are among the most attractive drugs in the anti-infective chemotherapy field. A tremendous amount of synthetic effort has been channeled into the synthesis of Quinolone Antibacterial agents.[12] These research efforts have been rewarded by very significant improvements in antibacterial potency has resulted from changes in the basic quinolone nucleus.[13] The contribution of many research facilities have allowed to reach a point where quinolones are some of the potent antibacterial.

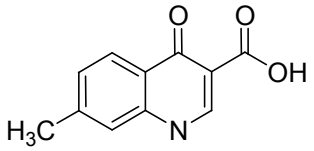
3.2.1.2 Activity of Quinolone Antibacterial agents

Studies on the *N*-substituent of the 4-pyridone nucleus showed that an ethyl substituent or some other substituents with comparable steric requirements *i.e*., vinyl, fluoroethyl, methoxy, methyl amino or cyclopropyl groups were favorable for antibacterial activity. Particularly, *N*-cyclopropyl derivatives were found to possess excellent antibacterial activity. In the studies of the relationships between physicochemical properties and pharmacokinetics of new compounds, it was found that introduction of fluorine into *N*-substituent reduced the lipophilicity of the molecules, suggesting that there should be a possibility for preparing less toxic compounds with reduced distribution to the central nervous system (CNS). The series of fluorinated compounds showed lower

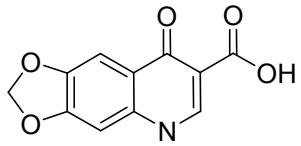
hydrophobicity than the corresponding nonfluorinated derivatives and some of them retained similar antibacterial activity with that of ciprofloxacin (**35**).

3.2.1.3 Fluoroquinolones

The first quinolone antibiotic called nalidixic acid (**32**) was introduced in 1962. Since then, structural modifications have resulted in the second, third and fourth generation of fluoroquinolone antibiotics having excellent activity against gram-positive organisms (**Fig. 4-7**).

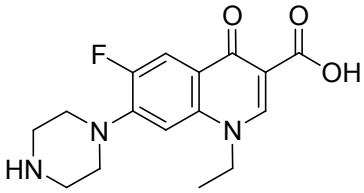


Nalidixic acid (**32**)

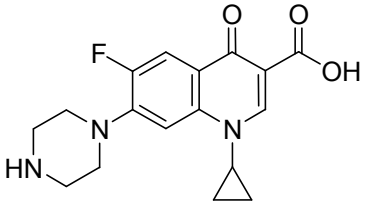


Cinoxacin (**33**)

Fig. 4: 1st Generation Quinolone Antibiotics

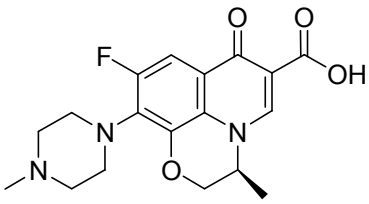


Norfloxacin (**34**)

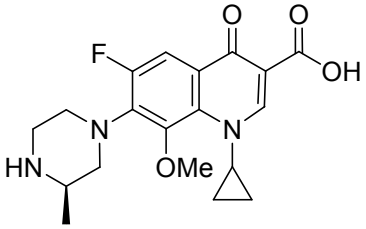


Ciprofloxacin (**35**)

Fig. 5: 2 nd Generation Quinolone Antibiotics



Levofloxacin (**36**)



Gatifloxacin (**37**)

Fig. 6: 3rd Generation Quinolone Antibiotics

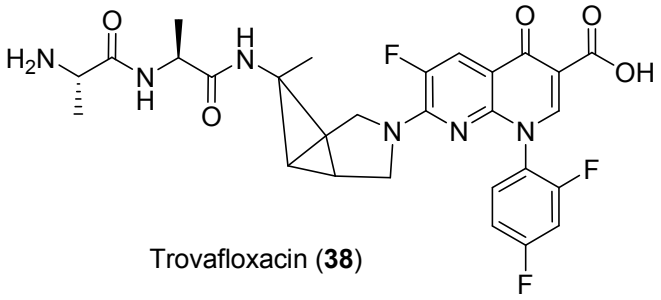


Fig. 7: 4th Generation Quinolone Antibiotics

Fluoroquinolones were primarily used to treat genitourinary tract infections but now they are used to treat a variety of infections – upper and lower respiratory infections, gastrointestinal infections, gynecologic infections, sexually transmitted diseases, and some skin and soft tissue infections. Most quinolones have excellent oral bioavailability**,** with few adverse effects. While fluoroquinolones are excellent antibiotics, the organisms it affects are known to develop multi-pathway resistance to fluoroquinolones. This is because, genetic mutations are very rapid and frequent during the course of antibiotic treatment. It is imperative therefore, that fluoroquinolones are used judiciously.

3.2.1.4 Mode of Action of Fluoroquinolones

Quinolones rapidly inhibit DNA synthesis by promoting cleavage of bacterial DNA in the DNA-enzyme complexes of DNA gyrase and type IV topoisomerase, resulting in rapid bacterial death. It has also been established that it binds to Bacterial topoisomerase IV in case of gram-negative organisms while it binds to DNA gyrase in gram-positive organisms. Quinolones are known to bind specifically to single stranded DNA but not to gyrase or double stranded DNA. The excellent potency of quinolones may be attributed to the fact that they are well absorbed following oral administration, with moderate to

excellent bioavailability. Quinolones are effective in the treatment of prostatitis because of their excellent penetration into prostatic tissue.[14]

3.2.1.5 Importance of fluorine compounds

More than one million compounds containing one or more carbon-fluorine bonds are known, and since barely more than ten of those occur natural. Organofluorine chemistry is virtually a completely man-made branch of organic chemistry.[15] In the medicinal chemistry the introduction of fluorine atoms into molecules of biological interest such as steroids, carbohydrates, antitumor agents, and other biologically important molecules, occupies an increasing position in the recent scientific literature. This growing interest is due to the particular effects that fluorine can exert on the properties of the compound without altering its steric bulk. Electron withdrawal by fluorine results in a strong polarization of the C-F bond and the pronounced electronic effects associated to poor steric demands can have implications for reactions at an adjacent center that is for drug-target interactions.

Many selectively fluoro substituted organic compounds show a peculiar biological activity in fields such as biotechnologies, agriculture, and medicine. In the present case, fluoroamines, fluoroaminoacids and fluorinated peptidomimetics can find use in medicinal field as antitumor, anti-HIV and antithrombotic agents; the chiral fluorinated pheromones can be effective in the integrated biological fight against insects and parasites. The great demand for fluoroaromatics as building blocks in the synthesis of pharmaceuticals and pesticides has led to the search for attractive preparative routes.

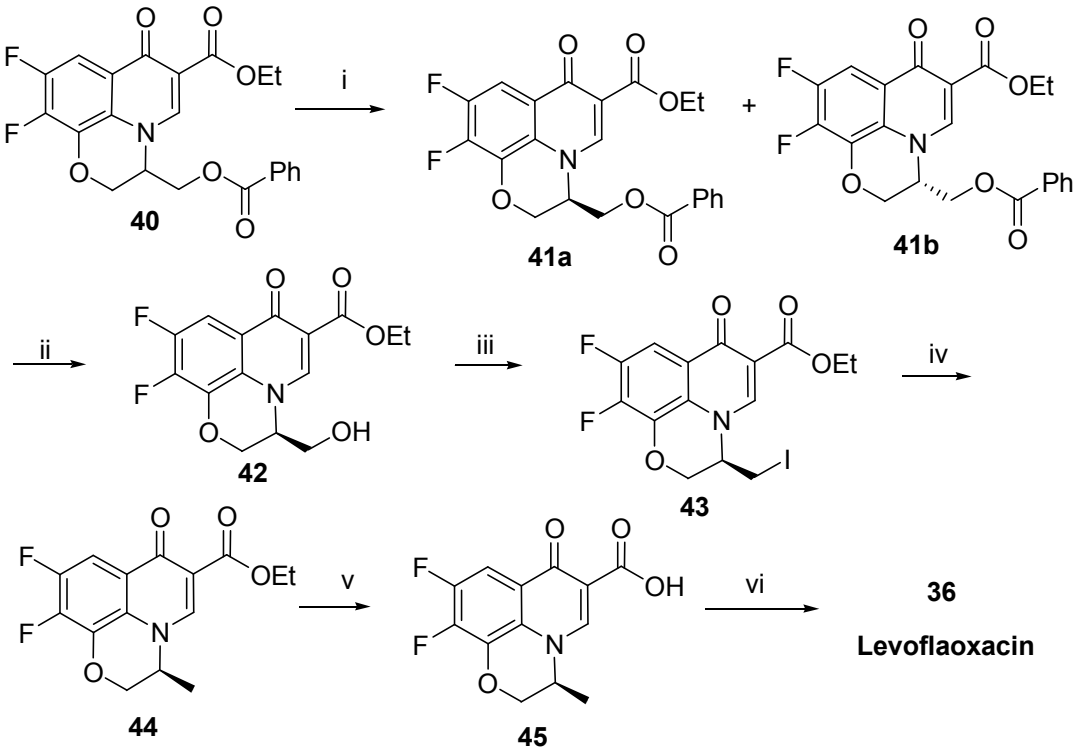
Research efforts concerning the use of fluorinated organic compounds are of considerable interest as there are numerous examples wherein fluorine dramatically alters the chemical

and biological properties of a molecule. Among the quinolone antimicrobial agents, relatively few fused tricyclic analogues have been found to be possessing outstanding antibacterial activity. Levofloxacin (**36**) has been developed as a highly active new quinoline antibacterial agent against gram-positive and gram-negative pathogens.[16]

3.2.2 Review of Literature

Literature search revealed that there are few reports available for the synthesis of (*S*)-(-)-7,8-difluoro-2,3-dihydro-3-methyl-4*H*-1,4-benzoxazine (**39),** the key intermediates for Levofloxacin (**36**). However, the reports deal with the synthesis of the intermediate using a stoichiometric amount of chiral reducing agents, *N*-alkylation of sulfonanilides with chiral sulfonates and mitsunobu cyclization, a brief account of which are described below.

Hayakawa *et al* (1986)[17]

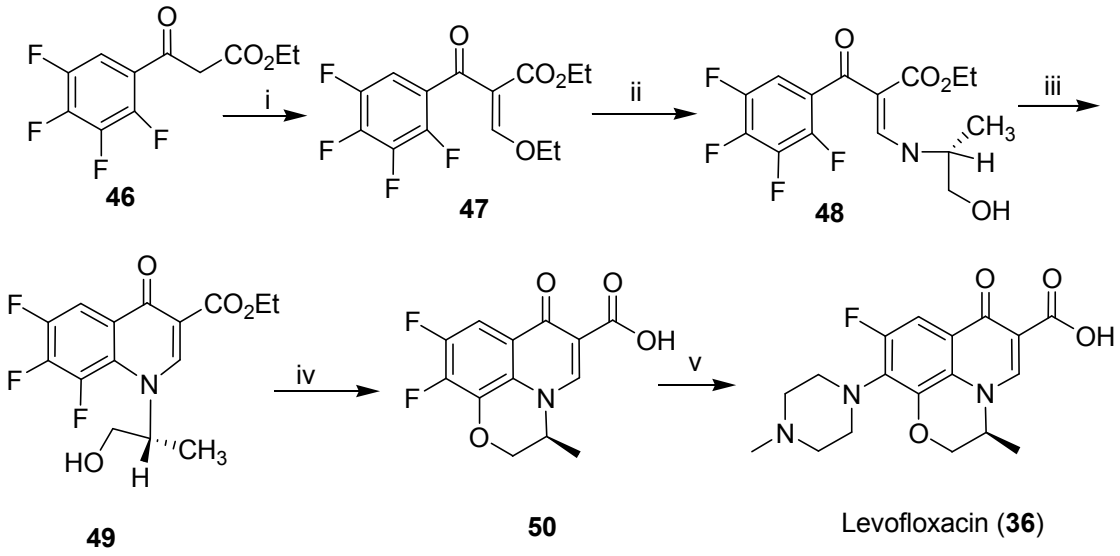


Scheme 9: (i) HPLC separation; (ii) aq. $NaHCO_3$, EtOH (iii) $P(OPh)_3$.MeI, DMF; (iv) Bu_3SnH, EtOH; (v) conc HCl-CH_3COOH (2:1); (vi) 1-methylpiprazine, DMSO, reflux.

Hayakawa *et al.* have synthesized both isomers of levofloxacin (**36**) by HPLC separation of **9** to give optically pure benzoyl esters **41a** and **41b**. The benzoyl ester **41a** was hydrolyzed with an ethanolic aqueous $NaHCO_3$ solution to yield alcohol **42** which was converted to iodide **43** with triphenylphosphite methiodide in DMF. Reduction of iodide **43** with tri-*n*-butyltin hydride in ethanol, followed by hydrolysis of resulting ester **44** gave **c**arboxylic acid **45**. Finally, acid **45** was treated with 1-methylpiprazine in DMSO yielded (-)-levofloxacin **36** (**Scheme 9**).

Mitscher's *et al* (1987)[13]

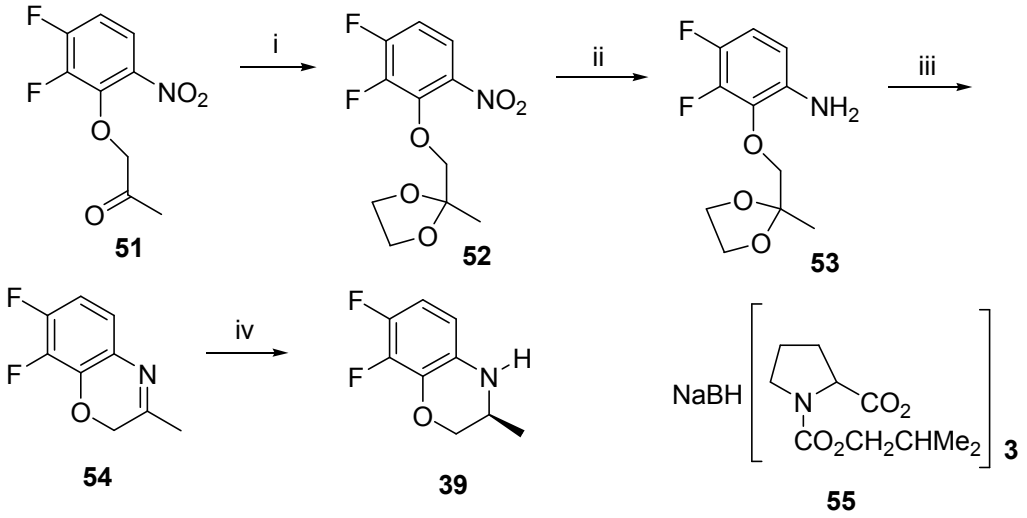
Mitscher and coworkers have synthesized levofloxacin by condensation of 2,3,4,5-tetrafluorobenzoylacetate (**46**) with triethyl orthoformate which on reaction with (*S*)–(+)–2-amino-1-propanol followed by cyclisation with sodium hydride in dimethyl sulfoxide yielded ethyl 1,4-dihydro-fluoroquinoline (**49**) in 59% yield. Ester **49** on heating with aqueous potassium hydroxide followed by condensation with *N*-methyl-piperazine yielded levofloxacin (**36**) (**Scheme 10**).



Scheme10: (i) triethyl orthoformate, Ac_2O, reflux; (ii) (*S*)-(+)-2-amino-1-propanol, 57%; (iii) NaH, DMSO, 25 ºC, 59%; (iv) KOH, THF, 65 ºC, 70%; (v) *N*-methyl-piperazine, pyridine.

Atarashi *et al* (1991)[18]

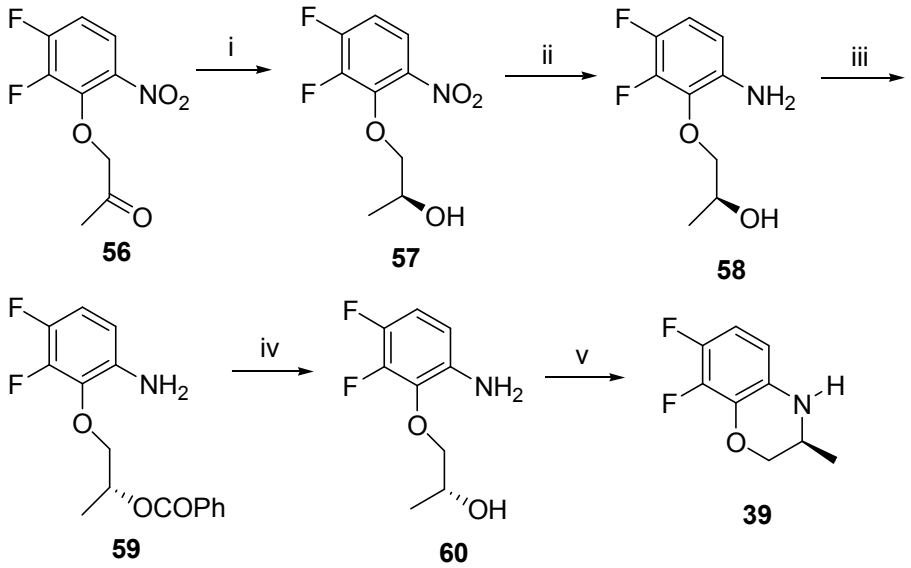
Atarashi *et al.* have synthesized the key intermediate of levofloxacin **36** by asymmetric reduction of imine **54** using chiral sodium triacyloxyborohydride **55** (**Scheme 11**). Protection of ketone **51** as its ketal with ethyleneglycol and *p*-toluenesulfonic acid in benzene afforded **52**, which was hydrogenated on 5% palladium on charcoal in methanol gave amine **53**. Deprotection of the ketal in acidic conditions afforded imine **54**, which on asymmetric reduction using **55** in DCM gave **39** in 95% ee.



Scheme 11: (i) ethylene glycol, *p*-TSA, benzene; (ii) 5% Pd/C, ethanol; (iii) conc. HCl, aqueous ammonia; (iv) CH_2Cl_2, **55**.

Kang *et al* (1996)[19]

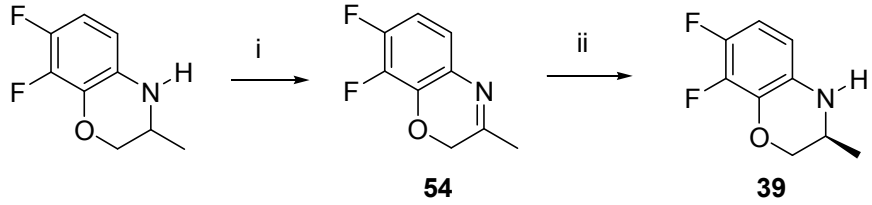
Kang *et al.* have synthesized the key intermediate of levofloxacin (**7**) by enzymatic reduction of ketone **56** to afford alcohol **57** in 91% yield with >99% ee. Reduction of nitro group with 10% Pd/C followed by Mitsunobu inversion of alcohol gave ester **59** in 95% yield. The mild hydrolysis of **59** with potassium cyanide in MeOH at 25 ºC yielded the alcohol **60** with 99% ee. Cyclization of **60** under Mitsunobu reaction conditions afforded benzoxazine **39** in 95% yield (**Scheme 12**).



Scheme 12: (i) Bakers' yeast, MeOH/H_2O, 35 ºC, 91%, 99% ee; (ii) Pd/C, H_2, THF, 25 ºC, 99%; (iii) Ph_3P, DEAD, $PhCO_2H$, THF, 25 ºC, 95%; (iv) KCN, MeOH, 25 ºC, 99 %, 99% ee; (v) Ph_3P, DEAD, $ZnCl_2$, CH_3CN, reflux, 95%.

Satoh *et al* (1998)[20]

Satoh *et al.* have synthesized the key intermediate of levofloxacin (**36**) by enantioselective reduction of imine **54** using $[Ir(COD)Cl]_2$ and (2*S*,4*S*)-BPPM as ligand at 40 bar H_2 pressure (**Scheme 13**).



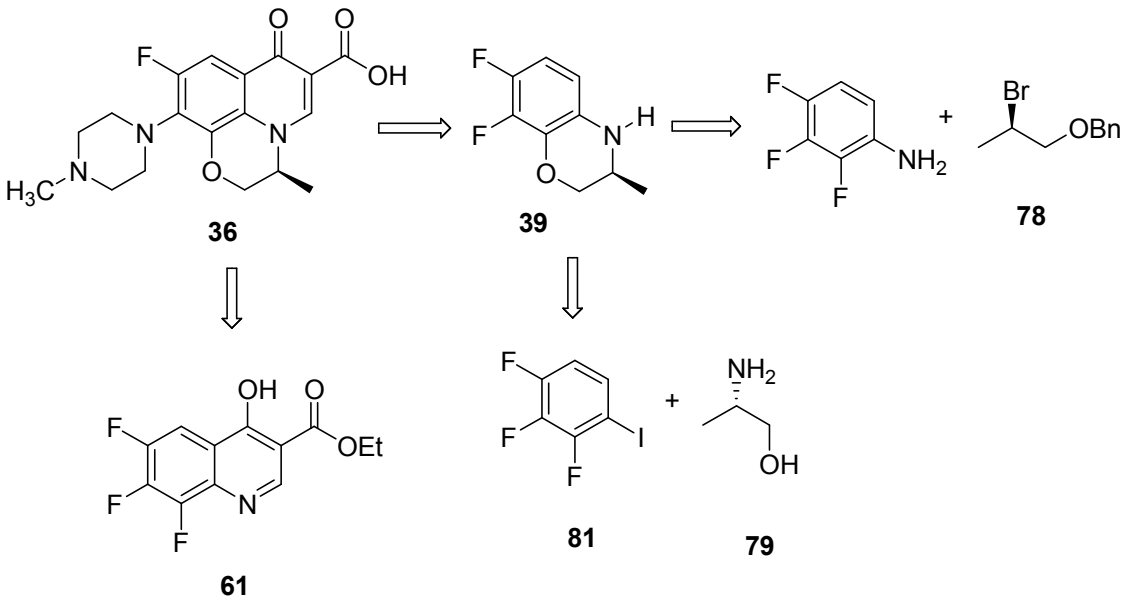
Scheme 13: (i) Et_3N, Br_2, EtOAc; (ii) $[Ir(COD)Cl]_2$, (2*S*, 4*S*)-BPPM, benzne: MeOH (1:1), BiI, H_2 (40 bar);

3.2.3 Present Work

3.2.3.1 Objectives

As can be seen from the above discussion, most of the methods reported for the synthesis of (-)-levofloxacin (**36**), either require use of expensive chiral starting materials in

stoichiometric amounts or adopt classical resolution strategies. The retrosynthetic analysis of (-)-levofloxacin (**36**) shows that benzoxazine **39** could serve as the key intermediate, which was visualized to be synthesized by employing proline catalyzed amination (**Scheme 14)**.



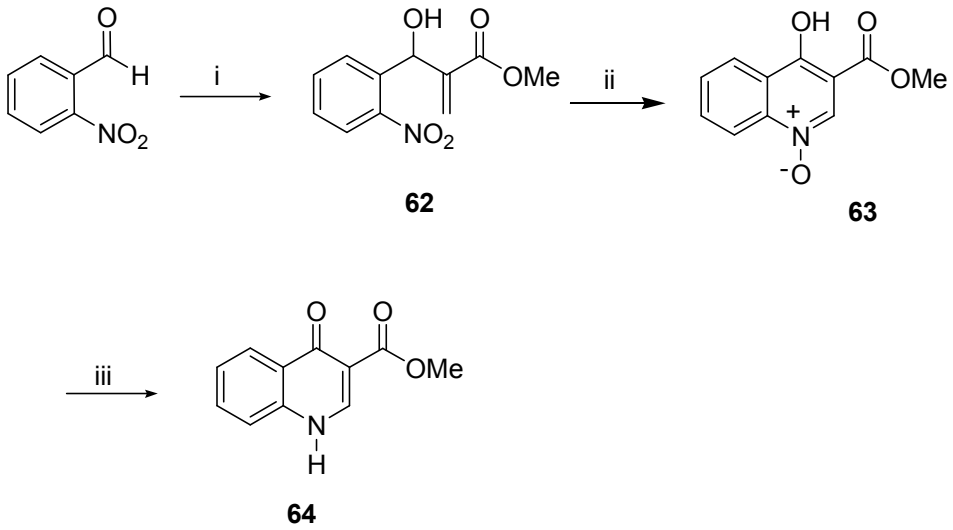
Scheme 14: Retrosynthesis of (-)- Levofloxacin

This section describes the asymmetric synthesis of the intermediate benzoxazine **39** using proline-catalyzed *α*-amination as well as *α*-aminooxylation of 1-propanal.

3.2.4 Results and Discussion

We have visualized that benzoxazine **39** and quinoline derivative **61** are the key intermediates in our synthetic strategy. Firstly, we planned to synthesize the intermediate **61** by employing Bayllis-Hillman reaction of 3,4,5-trifluoro-2-nitrobenzaldehyde **(67)** with methyl acrylate. Initially, a model study was carried out using *o*-nitrobenzaldehyde and methyl acrylate as substrates in the presence of DABCO to obtain ethyl 4-hydroxyquinoline-3-carboxylate (**62**) in 90% yield (**Scheme 15)**. The ^{1}H NMR spectrum

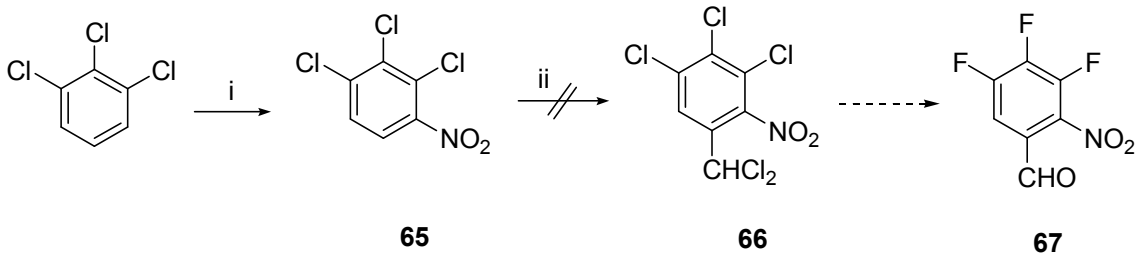
of **62** showed a singlet at δ 3.74 corresponding to methoxy proton; other signals at δ 5.96 and 6.29 are due to olefinic protons. Its IR spectrum exhibited a characteristic strong band at 1720 cm^{-1} indicating the presence of a carbonyl group. Cyclization of **62** with trifluoroacetic acid resulted in the formation of *N*-oxide **63** in 85% yield. The ^1H NMR spectrum of *N*-oxide **63** showed a singlet at δ 8.69 corresponding to the aromatic proton *ortho* to nitrogen atom; also the disappearance of the signals at δ 5.96 and 6.29 confirmed the nitrone formation. The reduction of *N*-oxide moiety in **63** using $NaBH_4$ gave the quinolone **64** in 65% yield. The ^1H NMR spectrum of quinolone derivative **64** showed a typical singlet at δ 8.71 corresponding to an aromatic proton *ortho* to nitrogen atom.



Scheme 15: (i) DABCO, methyl acrylate, 25 ºC, 90%; (b) CF_3CO_2H, 60 °C, 85%; (c) $NaBH_4$, MeOH, 25 °C, 24 h, 65%.

Next, the synthesis of fluoro substituted nitrobenzaldehyde **67**, the required starting material for the Bayliss-Hillman reaction was envisaged from 1,2,3-trichlorobenzene (**Scheme 16**). Thus, the nitration of 1,2,3-trichlorobenzene in conc. HNO_3 and H_2SO_4 mixture at 0 ºC gave the mono nitrated product **65** in 96% yield. The ^1H NMR spectrum of **65** showed two doublets at δ 7.56 and 7.67 corresponding to two aromatic protons.

Vicarious nucleophilic substitution on nitro compound **65** using K^{t}OBu and $CHCl_3$ did not give the dichloro intermediate, **66.**

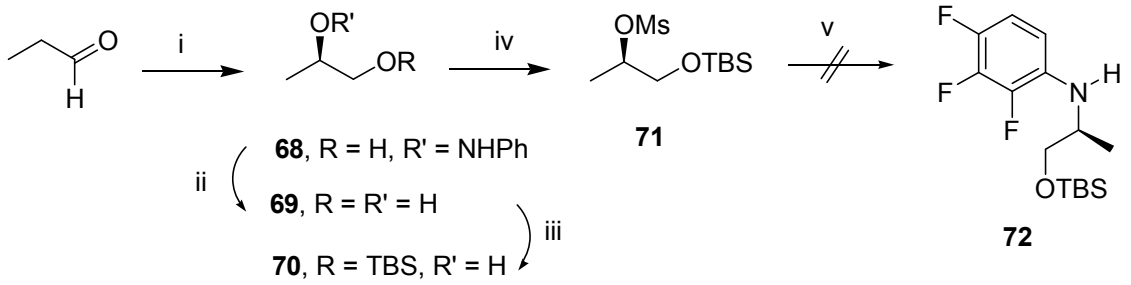


65 **66** **67**

Scheme 16: (i) conc. HNO_3–H_2SO_4, 0 ºC, 2 h, 96%; (ii) K^{t}OBu, $CHCl_3$, THF-DMF, 25 °C, 3 min then AcOH in MeOH.

Alternately, L-proline-catalyzed *α*-aminooxylation[21] of 1-propanal was carried out using nitrosobenzene and L-proline (25 mol%) at -20 ºC to furnish the aminooxy aldehyde, which was reduced *in situ* with sodium borohydride to afford (*R*)-α-aminooxy alcohol **68** in 85% yield. The aminooxy alcohol **68** was then hydrogenated over 10% Pd/C to furnish (*R*)-1,2-propanediol **69** in 90% yield. The ^{1}H NMR spectrum of diol **69** showed typical signal at δ 3.39 (dd) corresponding to the methine proton (-**CH**OH); other doublet at δ 1.15 is due to methyl proton. Its ^{13}C NMR spectrum displayed signals at δ 67.5 and 68.1 due to the methine and methylene carbons respectively. Selective monoprotection of diol **69** was carried out using TBSCl in CH_2Cl_2 to give the TBS ether **70** in 90% yield. The appearance of signals at δ 0.06 (s) and 0.89 (s) in the ^{1}H NMR spectrum of **70** due to methyl and *tert*-butyl protons of TBS group confirms the formation of silyl ether **70**. Mesylation of the silyl protected alcohol **70** using mesyl chloride under basic conditions afforded mesyl compound **71** in 95% yield. The ^{1}H NMR spectrum of **71** showed typical signal at δ 3.01 (s) corresponding to the methyl protons of mesyl group. Its ^{13}C NMR spectrum displayed signal at δ 38.1 corresponding to methyl carbon of mesyl group.

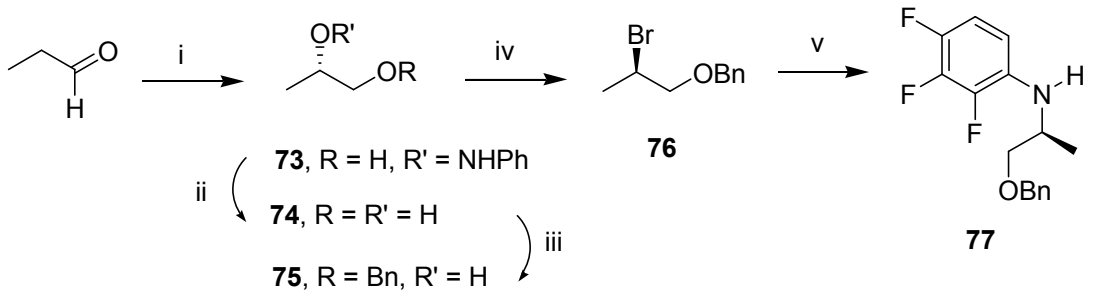
However, *N*-alkylation of 2,3,4-trifluoroaniline with chiral mesyl compound **71** under the basic conditions gave mixture of products (**Scheme 17**).



Scheme 17: (i) PhNO, L-proline (25 mol%), CH_3CN, -20 ºC, 24 h then MeOH, $NaBH_4$, 85%; (ii) H_2 (1atm.), 10% Pd/C, MeOH, 25 °C, 12 h, 90%, 98% ee; (iii) imidazole, TBSCl, CH_2Cl_2, 0 °C, 2 h, 90%; (iv) Et_3N, CH_3SO_2Cl, CH_2Cl_2, 0 °C, 2 h, 95%; (v) 2,3,4-trifluoroaniline, Et_3N, DMF, 0-25 °C.

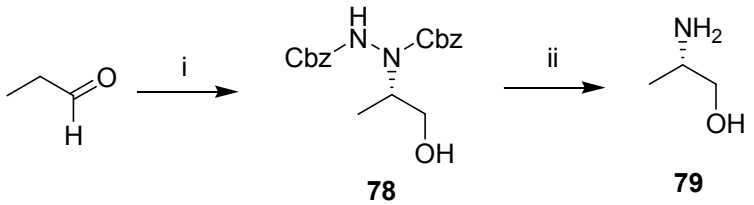
In our next attempt, D-proline-catalyzed α-aminooxylation[21] of 1-propanal was carried out using nitrosobenzene and D-proline (25 mol%) at -20 ºC to furnish the aminooxy aldehyde, which was reduced *in situ* with sodium borohydride to afford (*S*)-α-aminooxy alcohol **73** in 85% yield. The aminooxy alcohol **73** was then hydrogenated over 10% Pd/C to furnish (*S*)-1,2-propanediol **74** in 90% yield. Selective monobenzylation of diol **74** was carried out with benzyl bromide in presence of Bu_2SnO and to give **75** in 93% yield. The appearance of signals at δ 4.55 (s) and 7.32 (m) in the ^{1}H NMR spectrum of the **75** corresponding to the benzylic and aromatic protons confirms the benzylic protection. The hydroxy function in alcohol **75** was converted into bromo derivative **76** in 95% yield using CBr_4 and PPh_3 in the presence of imidazole. The ^{1}H NMR spectrum of bromo intermediate **76** showed typical signal at δ 1.70 (d) corresponding to the methyl proton; other signal at δ 4.57 is due to benzylic proton. Its ^{13}C NMR spectrum displayed signals at δ 67.5 and 68.1 due to the methine and methylene carbons respectively. Among the several conditions tried, *N*-alkylation of bromo derivative **76** with 1,2,3-

trifluoroaniline in the presence of NaH, in reflux DMF gave the required product **77** although in low yield (< 5%). The ^{1}H NMR spectrum of **77** showed typical singlet at δ 4.54 corresponding to benzylic protons; other two multiplets at δ 6.43 and 6.75 corresponding to aromatic protons. At this stage, purification of the required product was not successful to continue the process of debenzylation and cyclization (**Scheme 18**).



Scheme 18: (i) PhNO, *D*-proline (25 mol%), CH_3CN, -20 ºC, 24 h then MeOH, $NaBH_4$, 85%. (ii) H_2 (1atm.), 10% Pd/C, MeOH, 25 °C, 12 h, 90%, 98% ee; (iii) Bu_2SnO, toluene, reflux, 12 h then Bu_4NBr, BnBr, reflux, 24 h, 93%; (iv) PPh_3, CBr_4, imidazole, CH_2Cl_2, 25 °C, 6 h, 95%; (v) 2,3,4-trifluoroaniline, NaH, DMF, 135 °C, 6 h, 5%.

In the new strategy, D-proline-catalyzed α-amination[11] of 1-propanal using dibenzyl azodicarboxylate as the amine source followed by its subsequent reduction with $NaBH_4$ gave the protected amino alcohol **78** in 92% yield. Catalytic hydrogenation of **78** using Raney Ni, H_2 (70 psig) produced (*S*)-2-aminopropan-1-ol (**79**) in 70% yield and 96% ee (**Scheme 19**).



Scheme 19: (i) dibenzyl azodicarboxylate, D-proline (10 mol%), CH_3CN, 0-20 ºC, 3 h then $NaBH_4$, EtOH, 92%; (ii) H_2 (70 psig), Raney-nickel, MeOH, AcOH, 25 °C, 70%, 96% ee.

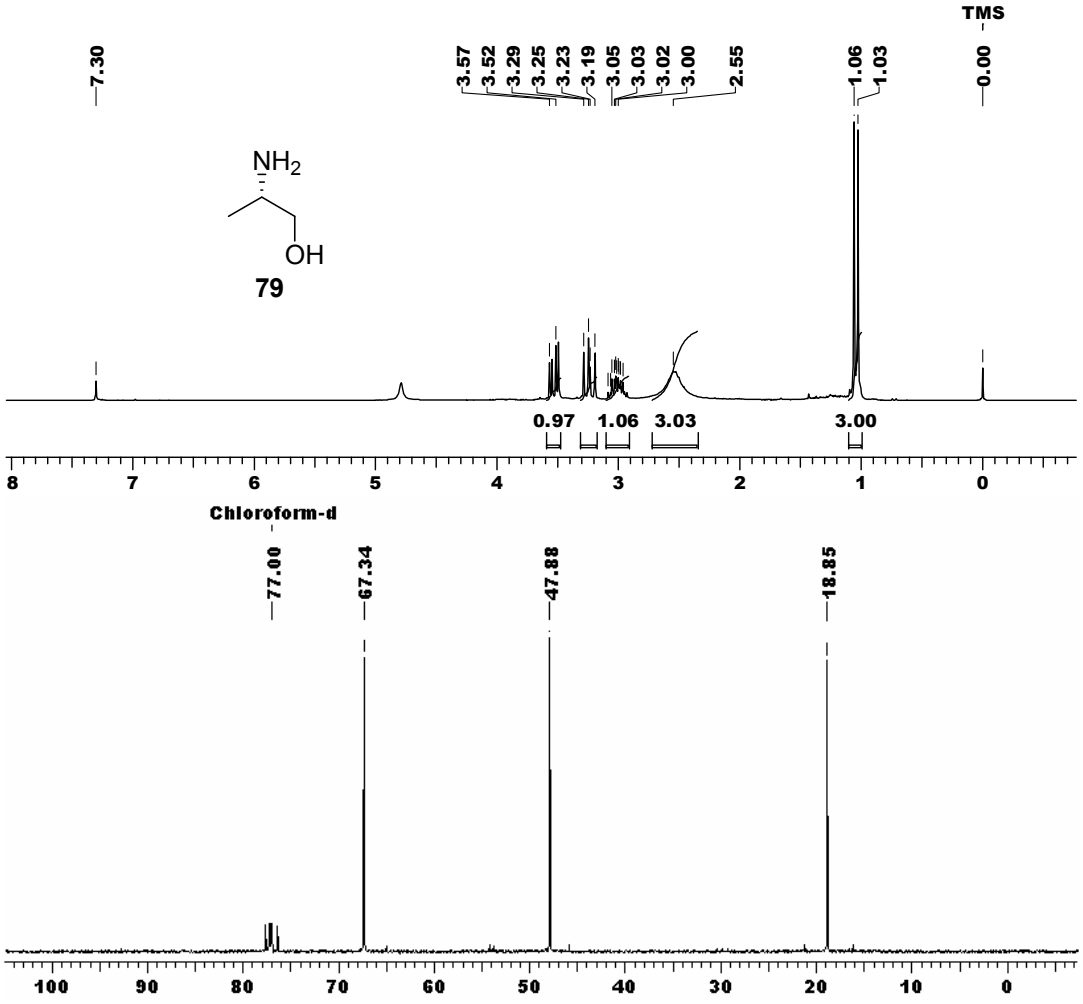
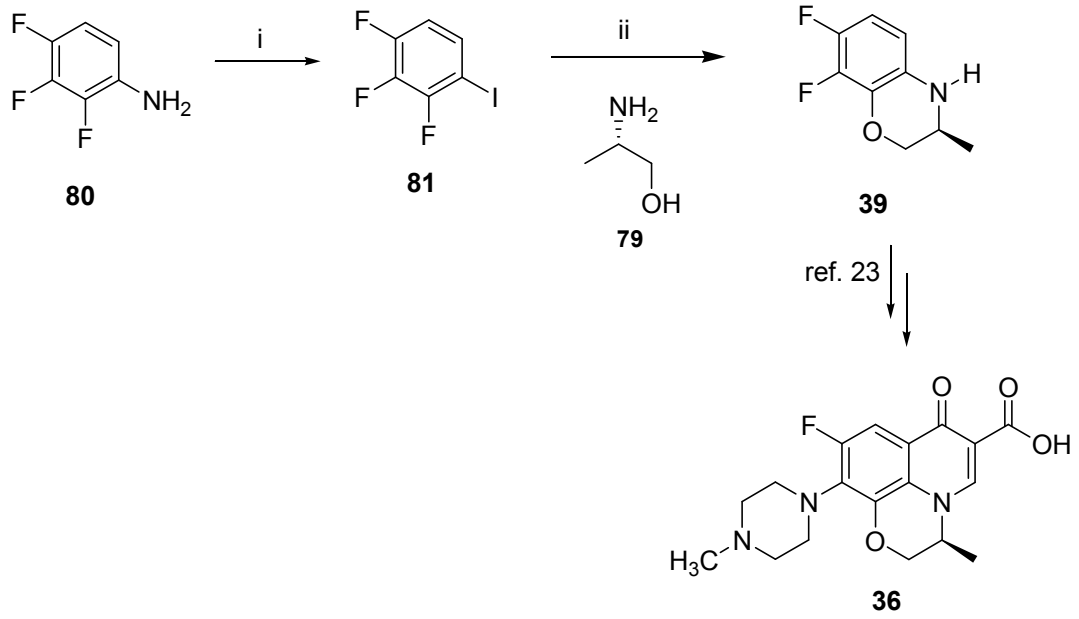


Fig. 8: ^{1}H and ^{13}C NMR spectra of amino alcohol 79

In order to complete the synthesis, 1,2,3-trifluoro-4-iodobenzene (**81**) was prepared in 76% yield by diazotization of the corresponding 2,3,4-trifluoroaniline (**80**) (**Scheme 20**). The ^{1}H NMR spectrum of **81** showed two multiplets at δ 6.82 and 6.47 corresponding to aromatic protons. Buchwald amination[22] (CuI, Cs_2CO_3, 2-acetylcyclohexanone) of aryl iodide **81** with (*S*)-2-aminopropan-1-ol (**79**) was carried out to give the amino alcohol *in situ,* which was subjected to cyclization under basic conditions to give benzoxazine **39** in 64% yield. The spectral data obtained for benzoxazine **39** were in full agreement with the

values reported in the literature.[20] The synthesis of levofloxacin (**36**) has already been reported from **39** in six steps.[23]



Scheme 20: (i) conc. HCl, $NaNO_2$, HCl, KI, 76%; (ii) (a) CuI, 2-acetylcyclohexanone, Cs_2CO_3, DMF, 25 °C; (b) KOH, THF, 65 ºC, 64%, 96% ee.

3.2.5 Conclusion

In conclusion, we have successfully applied proline-catalyzed α-aminooxylation and α-amination strategies towards the synthesis of the chiral intermediates **71, 76** and **79**, in high enantioselectivity (98, 98 and 96%). The reactions are rapid, and require a relatively low amount of an inexpensive and nontoxic proline-catalyst. The synthesis of the intermediate benzoxazine **39** has been achieved in three steps with 96% ee, thus completing the formal synthesis of (-)- levofloxacin (**36**).

3.2.6 Experimental Section

3-[Hydroxy(2-nitrophenyl)methyl]but-3-en-2-one (62):

To a stirred solution of 2-nitrobenzaldehyde (3.02 g, 20 mmol) and methyl acrylate (15 mL) was added DABCO (2.24 g, 20 mmol) at 25 ºC and stirred at the same temperature for 24 h. The reaction mixture was poured into water, and extracted with dichloromethane (3 x 25 mL). The combined organic layers were washed with brine (50 mL), dried over anhyd. Na_2SO_4, and evaporated under reduced pressure. The crude product was purified by column chromatography using pet.ether: EtOAc as eluent to give pure hydroxy ester **62**.

Yield: 3.978 g (90%); **IR** ($CHCl_3$, cm^{-1}): 752, 788, 859, 964, 1051, 1082, 1194, 1297, 1351, 1440, 1527, 1633, 1720, 2954, 3004, 3456; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.64 (brs, 1H), 3.69 (s, 3H), 5.67 (s, 1H), 6.29 (s, 1H), 7.45-7.97 (m, 4H); **Analysis:**

$C_{11}H_{11}NO_4$ required C, 59.73; H, 5.01; N, 6.33; found C, 59.54; H, 5.23; N, 6.52%.

3-Methoxycarbonyl-4-hydroxyquinoline *N*-oxide (63):

A stirred solution of hydroxy ester **62** (1.020 g, 5 mmol) in trifluoroacetic acid (10 mL) was heated at 60-70 °C for 2 h. After cooling to 25 °C, the reaction mixture was poured into water and extracted with chloroform (2 x 30 mL). The combined organic layers were washed with brine (50 mL), dried over anhyd. Na_2SO_4, and evaporated under reduced pressure. The crude product was purified by column chromatography using CH_2Cl_2: MeOH (14:1) as eluent to give nitrone **63**.

Yield: 0.863 g (85%); colourless solid; **mp**: 182-183 °C; **IR** (KBr, cm^{-1}): 779, 974, 1057, 1099, 1145, 1227, 1306, 1357, 1421, 1458, 1484, 1536, 1616, 1700, 2563, 2871, 2959, 3106; **^{1}H NMR** (200 MHz, DMSO-d_6): δ 3.72 (s, 3H), 7.49 (m, 1H), 7.81 (m, 2H), 8.17 (m, 1H), 8.69 (m, 1H); **Analysis: $C_{11}H_9NO_3$** required C, 65.02; H, 4.46; N, 6.89; found C, 64.85; H, 4.31; N, 6.97%.

3-Acetylquinolin-4(1*H*)-one (64):

A stirred solution of nitrone **63** (0.420 g, 2 mmol) in methanol (8 mL) was added sodium borohydride (0.152 g, 4 mmol) at 25 °C and stirred for 24 h. The reaction mixture was poured into water, and extracted with dichloromethane (3 x 25 mL). The combined organic layers were washed with brine (50 mL), dried over anhyd. Na_2SO_4, and evaporated under reduced pressure. The crude product was purified by column chromatography using pet.ether: EtOAc as eluent to give pure quinolone **64**.

Yield: 0.243 g (65%); yellow solid; **mp**: 204-206 °C; **IR** (KBr, cm^{-1}): 789, 1056, 1251, 1298, 1497, 1572, 1628, 1717, 2986, 3000, 3082; **^{1}H NMR** (200 MHz, DMSO-d_6): δ 3.77 (s, 3H), 7.38-7.73 (m, 2H), 8.21-8.36 (m, 2H), 8.71 (m, 1H); **Analysis: $C_{11}H_9NO_2$** required C, 70.58; H, 4.85; N, 7.48; found C, 70.41; H, 4.81; N, 7.52%.

1,2,3-Trichloro-4-nitrobenzene (65):

To 1,2,3-trichlorobenzene (10 g, 55 mmol), nitrating mixture (5ml conc. H_2SO_4 + 4ml conc. HNO_3) was added at 0 ºC. The reaction mixture was stirred at 25 ºC for 10 h and poured carefully onto a mixture of ice/water. The resulting mixture was extracted with dichloromethane (3 x 150 mL) and the combined organic layers were washed with brine (50 mL), dried over anhyd. Na_2SO_4, and evaporated under reduced pressure. The crude product was purified by column chromatography using pet.ether: EtOAc (9:1) as eluent to give pure nitro compound **65**.

Yield: 11.98 g (96%); **mp**: 54-55 °C; **IR** (KBr, cm^{-1}): 575, 616, 739, 766, 828, 899, 1143, 1173, 1262, 1348, 1432, 1526, 1563, 1911, 2866, 2981, 3078, 3129, 3433; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.54 (d, *J* = 8.8 Hz, 1H), 7.69 (d, *J* = 8.8 Hz, 1H); **^{13}C NMR** (50 MHz,

$CDCl_3$): δ 123.1, 127.6, 128.5, 134.5, 138.4, 147.7; **Analysis: $C_6H_2Cl_3NO_2$** required C, 31.82; H, 0.89; Cl, 46.97; N, 7.82; found C, 31.95; H, 1.04; Cl, 47.13; N, 7.74%.

(2*R*)-(*N*-Phenylaminooxy)propan-1-ol (68):

To a stirred mixture of propanal (5.5 mL, 75 mmol) and nitrosobenzene (2.675 mg, 25 mmol) in CH_3CN (60 mL) was added L-proline (0.575 g, 20 mol%) at -20 ºC. The reaction mixture was allowed to stir at the same temperature for 24 h followed by addition of MeOH (75 mL) and $NaBH_4$ (2.8 g, 75 mmol) to the reaction mixture followed by stirring for 10 min. After addition of phosphate buffer, the resulting mixture was extracted with EtOAc (3 × 60 mL) and the combined organic layers were dried over Na_2SO_4. Purification by column chromatography over silica gel (Pet ether: EtOAc = 80:20) afforded aminooxy alcohol as a brownish liquid.

Yield: 3.55 g (85%); **$[\alpha]^{25}_D$** +4.38 (*c* 1.2, $CHCl_3$) {lit.[21b] $[\alpha]^{25}_D$ +1.21 (*c* 0.8, $CHCl_3$)}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.25 (d, *J* = 6.4 Hz, 3H), 2.40 (brs, 1H), 3.70-3.78 (m, 2H); 4.05-4.18 (m, 1H), 6.94-7.01 (m, 3H), 7.24-7.31 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 15.5, 66.5, 80.0, 114.6, 122.3, 128.9, 148.3.

(*R*)-Propane-1,2-diol (69):

To a solution of alcohol **68** (3.0 g, 18 mmol) in MeOH (15 mL) was added 10% Pd/C (1 g) at 25 ºC. The reaction mixture was then stirred in the hydrogen atmosphere (1 atm) for 6 h. After completion of reaction (monitored by TLC) the reaction mixture was filtered through celite pad, concentrated to near dryness. The crude product was then purified by silica gel chromatography using pet ether: EtOAc (30:70) as eluent to afford pure diol **69** as colourless liquid.

Yield: 1.23 g (90%); **$[\alpha]^{25}_{D}$** -25.22 (*c* 2.8, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 811, 922, 1045, 1132, 1264, 1428, 1716, 2933, 3706; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.15 (d, *J* = 6.3 Hz, 3H), 3.39 (dd, *J* = 8.0, 11.1 Hz, 1H), 3.63 (m, 1H), 3.93 (m, 1H), 4.35 (brs, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 18.5, 67.5, 68.1; **Analysis: $C_3H_8O_2$** required C, 47.35; H, 10.6; found C, 47.51; H, 10.69%.

(*R*)-1-(*tert*-Butyldimethylsilylhydroxy)propan-2-ol (70):

To a stirred mixture of diol **69** (0.76 g, 10 mmol) and imidazole (0.783 g, 11 mmol) in CH_2Cl_2 was added *tert*-butyldimethylsillyl chloride (1.73 g, 11 mmol) at 0 ºC. The reaction mixture was stirred at same temperature for 1 h and quenched with $NaHCO_3$ solution. The resulting mixture was extracted with dichloromethane (3 x 150 mL) and the combined organic layers were washed with brine (50 mL), dried over anhyd. Na_2SO_4, and evaporated under reduced pressure. The crude product was purified by column chromatography to give pure silyl protected alcohol **70**.

Yield: 1.67 g (90%); **$[\alpha]^{25}_{D}$** -4.25 (*c* 0.9, acetone); **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.04 (s, 6H), 0.89 (s, 9H), 1.08 (d, 3H), 2.46 (brs, 1H), 3.32 (m, 1H), 3.60 (m, 1H), 3.80 (m, 1H); **Analysis: $C_9H_{22}O_2Si$** required C, 56.79; H, 11.65; found C, 56.51; H, 11.52%.

(*R*)-1-(*tert*-Butyldimethylsilylhydroxy)-propan-2-yl methanesulfonate (71):

To a stirred mixture of alcohol **70** (0.95 g, 5 mmol) and Et_3N (0.9 mL, 6 mmol) in CH_2Cl_2 (20 mL) was added $MeSO_2Cl$ (0.5 mL, 6 mmol) at 0 ºC. The reaction mixture was allowed to stir at 25 ºC for 6 h. the solvent was removed under reduced pressure to get crude product. The crude product was purified by silica gel column chromatography using pet ether: ethyl acetate (85:15) to obtain bromo derivative **71.**

Yield: 1.27 g (95%); **[α]$^{25}_{D}$** -6.58 (*c* 1.2, $CHCl_3$); **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.05 (s, 6H), 0.88 (s, 9H), 1.37 (d, 3H), 3.01 (s, 3H), 3.66 (m, 2H), 4.72 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.3, 14.1, 21.9, 22.8, 28.9, 30.7, 31.8, 33.7, 42.2, 42.3, 42.6; **Analysis: $C_{10}H_{24}O_4SSi$** required C, 44.74; H, 9.01; S, 11.94; found C, 44.51; H, 9.1; S, 12.08%.

(2*S*)-(*N*-Phenylaminooxy)propan-1-ol (73):

To a stirred mixture of propanal (5.5 mL, 75 mmol) and nitrosobenzene (2.675 mg, 25 mmol) in CH_3CN (60 mL) was added D-proline (0.575 g, 20 mol%) at -20 ºC. The reaction mixture was allowed to stir at the same temperature for 24 h followed by addition of MeOH (75 mL) and $NaBH_4$ (2.8 g, 75 mmol) to the reaction mixture followed by stirring for 10 min. After addition of phosphate buffer, the resulting mixture was extracted with EtOAc (3 × 60 mL) and the combined organic layers were dried over Na_2SO_4. Purification by column chromatography over silica gel (Pet ether: EtOAc = 80:20) afforded aminooxy alcohol as a brownish liquid.

Yield: 3.55 g (85%); **[α]$^{25}_{D}$** -4.38 (*c* 1.2, $CHCl_3$); {lit.[21b] **[α]$^{25}_{D}$** -1.21 (*c* 0.8, $CHCl_3$)}.

(*S*)-Propane-1,2-diol (74):

To a solution of alcohol **73** (3.0 g, 18 mmol) in MeOH (15 mL) was added 10% Pd/C (1 g) at 25 ºC. The reaction mixture was then stirred in the hydrogen atmosphere (1 atm) for 6 h. After completion of reaction (monitored by TLC) the reaction mixture was filtered through celite pad, concentrated to near dryness. The crude product was then purified by silica gel chromatography using pet ether: EtOAc (30:70) as eluent to afford pure diol **74** as colourless liquid.

Yield: 1.23 g (90%); **[α]$^{25}_{D}$** +25.22 (*c* 2.8, $CHCl_3$).

(*S*)-1-(Benzyloxy)propan-2-ol (75):

A mixture of diol **74** (0.76 g, 10 mmol) and Bu_2SnO (2.98 g, 12 mmol) in toluene (100 mL) was refluxed for 12 h with azeotropic removal of water. Then, tetrabutylammonium bromide (1.6 g, 5 mmol) and benzyl bromide (1.84 g, 12 mmol) were added and the mixture was refluxed for 20 h. The solution was concentrated in vaccuo, and silica gel chromatography (pet ether: EtOAc 80:20) afforded alcohol **75.**

Yield: 1.55 g (93%); $[\alpha]_D^{25}$ +7.31 (*c* 1.08, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 698, 740, 1095, 1253, 2361, 2928, 2967, 3331; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.14 (d, *J* = 6.4 Hz, 3H), 3.26 (dd, *J* = 8.2, 9.2 Hz, 1H), 3.46 (dd, *J* = 3.1, 9.3 Hz, 1H), 3.91-4.06 (m, 1H), 4.55 (s, 2H), 7.32 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 18.6, 66.4, 73.3, 75.8, 127.7, 127.8, 128.4, 137.9; **MS** (m/z, % relative intensity): 166 (11), 107 (18), 91 (100, base peak), 75 (6), 65 (12), 45 (19); **Analysis: $C_{10}H_{14}O_2$** requires C, 72.26; H, 8.49; found C, 72.09; H, 8.54%.

1-[{(*R*)-2-Bromopropoxy}methyl]benzene (76):

To a stirred mixture of alcohol **75** (0.835 g, 5 mmol), PPh_3 (1.44 g, 5.5 mmol) and imidazole (0.37 g, 5.5 mmol) in CH_2Cl_2 (20 mL) was added CBr_4 (1.82 g, 5.5 mmol) at 0 ºC. The reaction mixture was allowed to stir at 25 ºC for 6 h. the solvent was removed under reduced pressure to get crude product. The crude product was purified by silica gel column chromatography using pet ether: ethyl acetate (85:15) to obtain bromo derivative **76.**

Yield: 5.4 g (95%); $[\alpha]_D^{25}$ -6.58 (*c* 1, $CHCl_3$); **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.70 (d, *J* = 6.7 Hz, 3H), 3.56 (dd, *J* = 6.8, 10.1 Hz, 1H), 3.68 (dd, *J* = 5.9, 10.1 Hz, 1H), 4.08-4.24 (m, 1H), 4.57 (s, 2H), 7.32 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 22.7, 46.3, 73.0,

75.4, 127.5, 127.8, 128.4, 137.9; **Analysis: $C_{10}H_{13}BrO$** requires C, 52.42; H, 5.72; Br, 34.88; found C, 52.49; H, 5.86; Br, 34.96%.

***N*-((*S*)-1-(benzyloxy)propan-2-yl)-2,3,4-trifluorobenzenamine (77):**

To a stirred mixture of NaH (0.88 g, 2.2 mmol), 2,3,4-trifluoroaniline aniline (0.516 g, 2 mmol) and bromo compound **76** (0.165 g, 2.2 mmol) in DMF (5 mL) was refluxed at 135 °C for 6 h. Solvent was removed under reduced pressure. The resulting residue was purified by column chromatography to obtain **77**.

Yield: 5%; colorless liquid; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.14 (d, *J* = 6.4 Hz, 3H), 3.28 (dd, *J* = 8.0, 9.2 Hz, 1H), 3.46 (dd, *J* = 3.2, 9.3 Hz, 1H), 3.93-4.02 (m, 1H), 4.54 (s, 2H), 6.36-6.46 (m, 1H), 6.71-6.79 (m, 1H), 7.32 (m, 5H).

(*S*)-2-(1, 2-Dibenzyloxycarbonylhydrazinyl)-1-prapanol (78):

To a mixture of dibenzyl azodicarboxylate (8.25 g, 25 mmol) and D-proline (287 mg, 2.49 mmol, 10 mol%) in CH_3CN (200 mL) at 0 ºC was added 1-propanal (2.175 g, 37.5 mmol) and the reaction mixture was allowed to stir at the same temperature for 2 h and then warmed to 20 ºC within 1 h. After the reaction mixture became colorless it was cooled to 0 ºC again and then treated with EtOH (150 mL) and $NaBH_4$ (1.2 g) for 5 min at 0 ºC. After completion of reaction it was quenched with aq. ammonium chloride solution and extracted with EtOAc (100 mL x 3). The combined organic layers were dried over anhyd. Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using pet ether: ethyl acetate (85:15) to obtain alcohol **78**.

Yield: 8.24 g (92%); yellow solid; **mp:** 82-83 °C; **$[\alpha]_D^{25}$** +26.9 (*c* 0.9, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 702, 732, 755, 1049, 1064, 1209, 1264, 1338, 1432, 1702, 1722, 2979,

3032, 3252, 3524; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.00 (d, *J* = 6.6 Hz, 3H), 1.77 (bs, 1H), 3.46 (m, 2H), 4.49 (m, 1H), 5.16 (m, 4H), 6.72 (bs, 1H), 7.34 (m, 10 H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.5, 56.1, 62.9, 68.2, 127.68, 128.1, 128.4, 128.5, 135.0, 135.6, 156.3; **Analysis: $C_{19}H_{22}N_2O_5$** required C, 63.67; H, 6.19; N, 7.82; found C, 63.85; H, 6.05; N, 7.74%.

(*S*)-2-Aminopropan-1-ol (79):

The alcohol **78** (5.73 g, 16 mmol) was dissolved in MeOH (40 mL), AcOH (10 drops) and treated with Raney nickel (10 g, excess) for 24 h under 5 bar of hydrogen. The reaction mixture was filtered over celite pad and concentrated to give the corresponding amino alcohol **79**.

Yield: 0.84 g (70%); colorless liquid; 96% ee; **$[\alpha]^{25}_D$** +23.02 (*c* 1.3, MeOH); {**$[\alpha]^{25}_D$** +23.5 (*c* 1, MeOH) for 98% ee}; **IR** ($CHCl_3$, cm^{-1}): 701, 1043, 1376, 1454, 1648, 2873, 2972, 3029, 3296; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.05 (d, *J* = 6.4 Hz, 3H), 2.55 (bs, 3H), 2.96-3.07 (m, 1H), 3.24 (dd, *J* = 7.8, 10.6 Hz, 1H), 3.54 (dd, *J* = 3.9, 10.4 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 18.8, 47.8, 67.3; **Analysis: C_3H_9NO** required C, 47.97; H, 12.08; N, 18.65; found C, 47.79; H, 11.88; N, 18.81%.

2,3,4-Trifluoro-iodobenzene (81):

2,3,4-Trifluoroaniline (2.852 g, 19.4 mmol) was dissolved in con. HCl (8.5 mL) and water (8.5 mL). The reaction mixture was cooled to 0-5 °C in an ice-bath and solution of sodium nitrite (2.249 g, 32.6 mmol) in 10.8 mL of water was added in small portions. It was stirred vigorously with a thermometer and the temperature was maintained below 10 °C, but preferably at about 5 °C by adding a little crushed ice to the mixture. To the diazonium mixture was added a solution of KI (5.41 g, 32.6 mmol) in 5 mL of water with

shaking and allowed to reflux for 1 h. The reaction mixture was cooled to 25 °C, 10% NaOH was added and extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine (25 mL), dried over anhyd. Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by column chromatography using pet.ether: EtOAc (9:1) as eluent to give pure iodo compound **81**.

Yield: 3.8 g (76%); **IR** ($CHCl_3$, cm^{-1}): 839, 1023, 1229, 1250, 1501, 2837, 2931, 3076; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 6.76-6.90 (m, 1H), 7.41-7.53 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 75.4, 114.0, 132.1, 139.7, 148.9, 153.9; **Analysis: $C_6H_2F_3I$** requires C, 27.93; H, 0.78; found C, 27.88; H, 0.75%.

(*S*)-7,8-Difluoro-3,4-dihydro-3-methyl-4*H*-1,4-benzoxazine (39):

To a srirred mixture of copper (I) iodide (0.019 g, 0.1 mmol), aryl iodide **81** (0.516 g, 2 mmol), aminoalcohol **79** (0.165 g, 2.2 mmol) and Cs_2CO_3 (1.3 g, 4.0 mmol) in DMF (5 mL) was added 2-acetylcyclohexanone (56 mg, 0.4 mmol) at 25 ^oC for 12 h. The reaction mixture was diluted with dichloromethane and filtered to remove inorganic salts and solvent was removed under reduced pressure. To the crude mixture in THF (25 mL) was added 10% aqueous solution of KOH (5 mL), and the reaction mixture was heated at 70 ^oC for 2 h. The reaction mixture was concentrated under reduced pressure and extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine (25 mL), dried over anhyd. Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by column chromatography to give amino compound **39**.

Yield: 0.237 g (64%); colorless liquid; 96% ee; **$[\alpha]^{25}_D$** -5.86 (*c* 3, $CHCl_3$) {lit[20] **$[\alpha]^{25}_D$** -5.5 (*c* 3, $CHCl_3$) 90% ee}; **IR** (neat, cm^{-1}): 1558, 1610, 1683, 1716, 2871, 2976, 3388; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.18 (d, *J* = 6.3 Hz, 3H), 3.43-3.54 (m, 1H), 3.64 (bs, 1H),

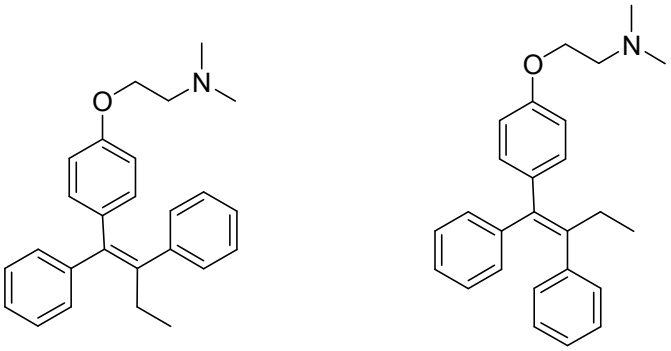
3.77 (dd, *J* = 8.3, 10.4 Hz, 1H), 4.26 (dd, *J* = 2.7, 10.4 Hz, 1H), 6.21-6.34 (m, 1H), 6.54 (m, 1H); **Analysis: $C_9H_9F_2NO$** required C, 58.38; H, 4.90; N, 7.56; found C, 58.21; H, 5.04; N, 7.69%.

SECTION 3:

Synthesis of (*Z*)-Tamoxifen via Palladium-Catalyzed Suzuki coupling

3.3.1 Introduction

Antiestrogens are used clinically for controlling mammary and endometrial carcinomas and managing a number of endocrine disorders.[24] Tamoxifen (1,2-diphenyl-l-[4[2-dimethylamino)ethoxylphenyl]-l-butene) **82** is the potent antiestrogen, which block the action of estrogens. It inhibits the development and growth of mammary tumors in rats and is effective in treating estrogen-dependent, metastatic breast cancer in human.[25] *In vivo*, tamoxifen (**82**) is transformed to hydroxytamoxifen, which has a much higher binding affinity for the estrogen receptor and appears to be the compound responsible, in part, for the biological actions of tamoxifen. (*E*)-Tamoxifen, usually referred to as *cis*-tamoxifen has no clinical uses.



82, (*Z*) **82**, (*E*)

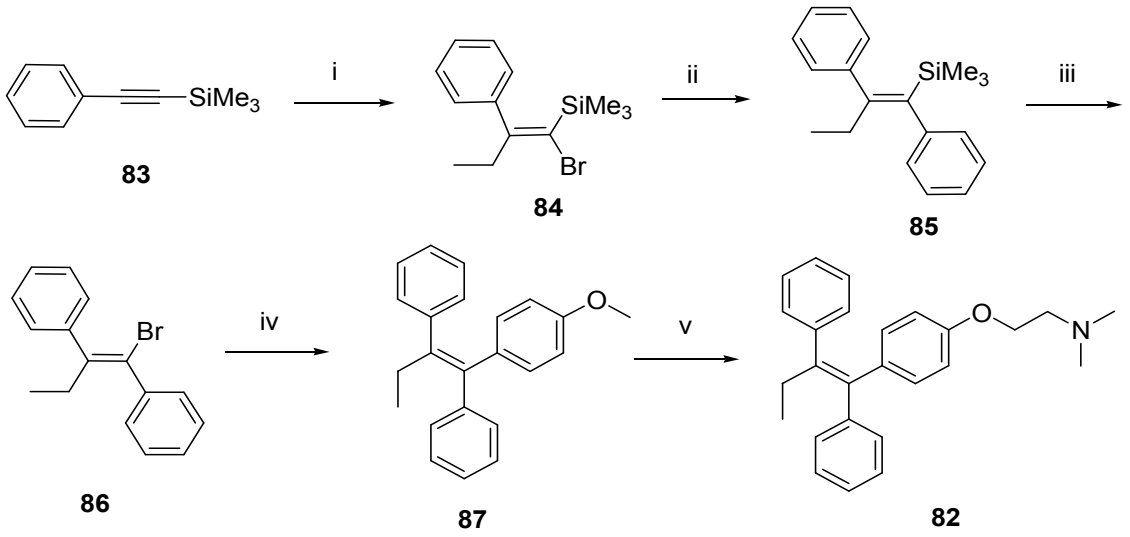
Fig. 9: Structures of (*Z*) and (*E*)-tamoxifen

3.3.2 Review of Literature

Literature search revealed that there are several reports available for the synthesis of (*Z*)-tamoxifen (**82).** However, most of the reports deal with the carbometalation of alkynes with diethylaluminium chloride, triethylaluminum, phenylmagnesium chloride, etc. Other methods produce *Z/E* mixture of tamoxifen from dehydration of the corresponding tertiary alcohol, a brief account of which is presented below.

Miller *et al* (1985)[25]

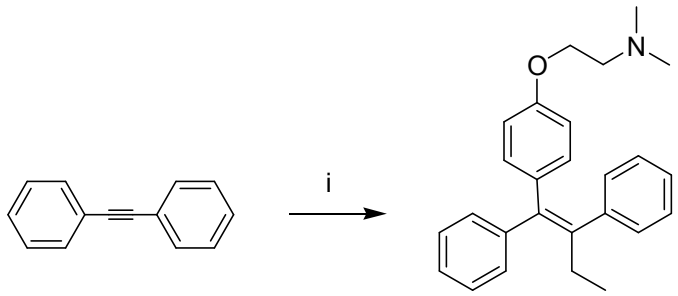
In this approach, phenyl(trimethylsilyl)acetylene was carbometalated with diethylaluminium chloride-titanocene to give *in situ* an organometallic intermediate, which was cleaved by NBS at -78 ºC to afford the bromo compound **84**. Palladium-catalyzed successive Negishi coupling was carried out using arylzinc to give ethyl triaryl olefin **87** in 84% yield. Finally, the methoxy compound **87** was demethylated and the resulting phenol was condensed with 2-(dimethylamino)ethyl chloride to furnish tamaxifen (**82**) (**Scheme 21**).



Scheme 21: (i) Et_2AlCl, Cp_2TiCl_2, CH_2Cl_2; (b) NBS, -78 ºC, 85%; (ii) PhZnCl, $Pd(PPh_3)_4$, THF, 95%; (iii) Br_2, CH_2Cl_2, NaOMe/MeOH, -78 ºC, 85%; (iv) *p*-$MeOC_6H_4ZnCl$, $Pd(PPh_3)_4$, THF, reflux, 84%; (v) (a) NaSEt, DMF, reflux; (b) $ClCH_2CH_2NMe_2$.HCl, NaOEt, EtOH, reflux; (c) HCl (g), Et_2O; (d) 0.5 N NaOH, 60%.

Mohammed *et al* (1987)[26]

In this approach, synthesis of tamoxifen (**82**) was achieved *via* carbometallation of diphenylacetylene (**88**) with trimethyl aluminium followed by palladium-catalyzed cross coupling using 2-(4-bromophenoxy)-1-dimethylaminoethane (**Scheme 22**).

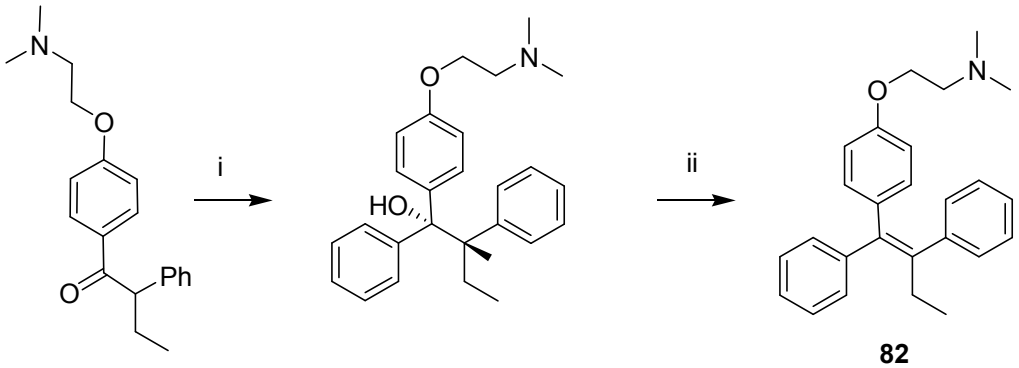


88 **82**

Scheme 22: (i) (a) $(C_2H_5)_3Al$, toluene, 90 ^oC, 24 h; (b) $(CH_3)_2N(CH_2)_2OC_6H_4Br$-*p*, THF, Pd(0), reflux, 24 h, 35%.

Raymond *et al* (1987)[27]

In this approach, tertiary alcohol **90** was prepared by reaction of 1-(*p*-dimethylamino ethoxy)-2-phenylbutan-1-one (**89**) with phenyl magnesium bromide. Acid catalyzed dehydration of the tertiary alcohol **90** gave tamoxifen as a *Z/E* mixture in the ratio of 2: 1 (**Scheme 23**).



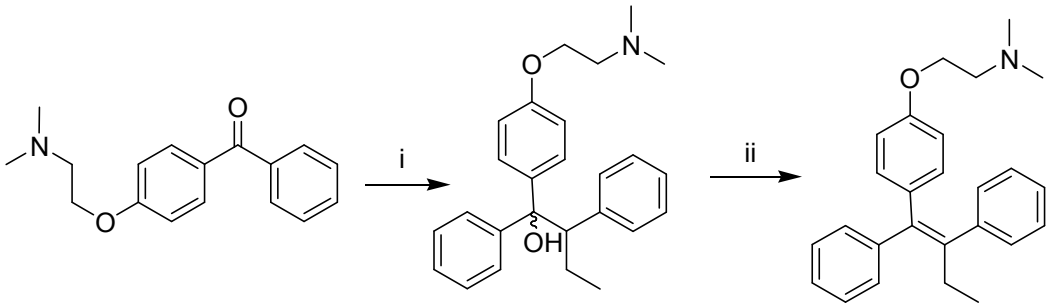
89 **90** **82**

Z:E (2:1)

Scheme 23: (i) PhMgBr, Et_2O; (ii) HCl (aq), EtOH, 80 ºC.

Chantal *et al* (1995)[28]

In this approach, propylbenzene anion, generated using *n*-BuLi -K^{t}OBu-TMEDA was added on to the substituted benzophenone **91**, to give the corresponding carbinol 92. Acid catalyzed dehydration of carbinol **92** gave tamoxifen (**82**) as a *cis/trans* mixture in 50% yield (**Scheme 24**).

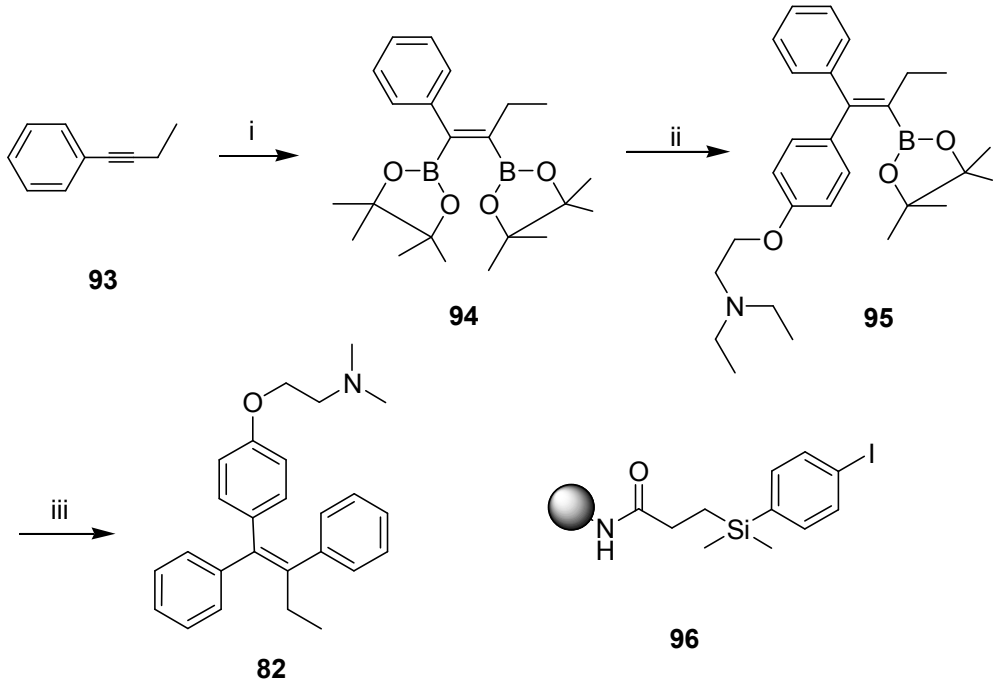


91 **92** **82**

Scheme 24: (i) propyl benzene, *n*-BuLi -K^{t}OBu -TMEDA, hexane, 25 ºC, then **10**, Et_2O, - 70 ºC; then 0 ºC, 5 h; (ii) 32% H_2SO_4, 16 h, 50 º C.

Brown *et al* (1997)[29]

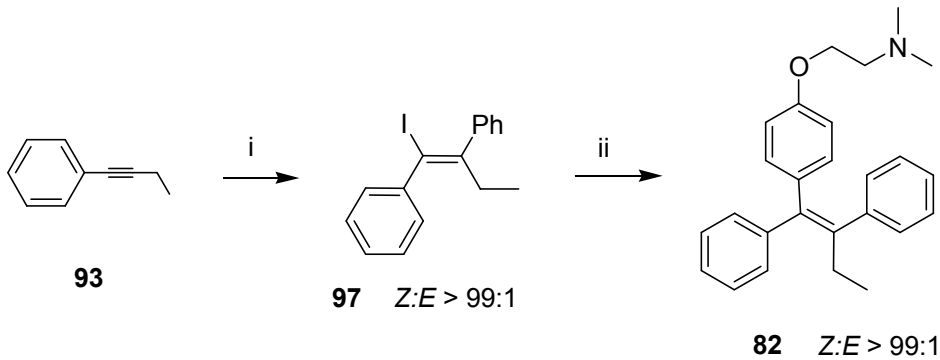
In this approach, alkyne **93** was converted into bis(boryl)alkene **94** by platinum catalyzed addition of diborate. Suzuki coupling of this intermediate **94** with bromobenzene gave the arylated product **95** which was treated with solid supported resin **96** for second Suzuki coupling. Tamoxifen (**82**) was cleaved from the polymer as amine salts using trifluoroacetic acid (**Scheme 25**).



Scheme 25: (i) $Pt(PPh_3)_4$, DMF, 80 ºC; (ii) Pd(dppf), 3,5-dimethoxyphenol, 6 M KOH, DME, 25 ºC, 18 h; (iii) (a) **96**, 6 M KOH, 25 º C, 18 h; (b) 30% TFA, CH_2Cl_2.

Thomas *et al* (1997)[30]

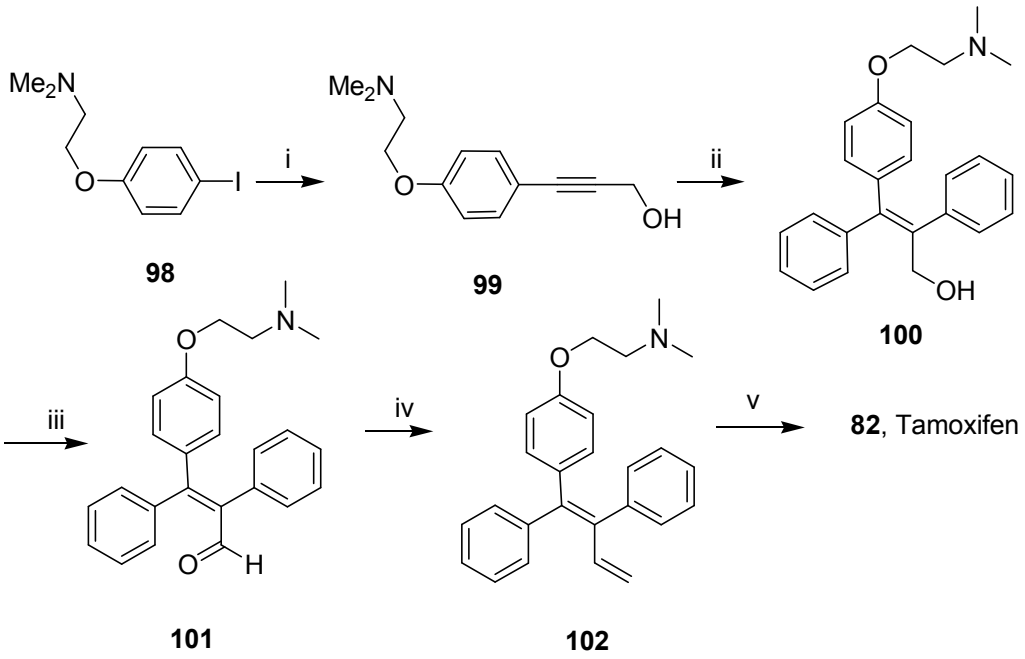
In this approach, addition of diphenylzinc on 1-phenyl-1-butyne (**93**) in the presence of $Ni(acac)_2$ and subsequent iodolysis gave *Z* alkene **97** in 88% yield (*Z:E* > 99:1). Then the reaction of alkene **97** with the arylzinc bromide in the presence of $Pd_2(dba)_3$ provided tamoxifen (**82**) in 75% yield (**Scheme 26**).



Scheme 26: (i) (a) Ph_2Zn, THF, NMP, [$Ni(acac)_2$], -35 ºC, 3 h; (b) I_2, 88%; (ii) $(CH_3)_2N(CH_2)_2OC_6H_4ZnBr$-*p*, $Pd_2(dba)_3$, PPh_3, THF, 55 º C, 10 h, then HCl, 75%.

Pierre *et al* (2003)[31]

In this approach, Sonogashira cross-coupling of aryl halide **98** with propargyl alcohol gave alkynol **99** in 83% yield. Then carbometallation of **99** with phenylmagnesium chloride followed by the addition of $Pd(PPh_3)_4$ and phenyl iodide as the cross coupling partner gave alkenol **100** in 72% yield. The alkenol **100** was converted into diene **102** followed by the selective reduction of the less hindered double bond afforded (*Z*)-tamoxifen (**82**) in 69% yield (**Scheme 27**).

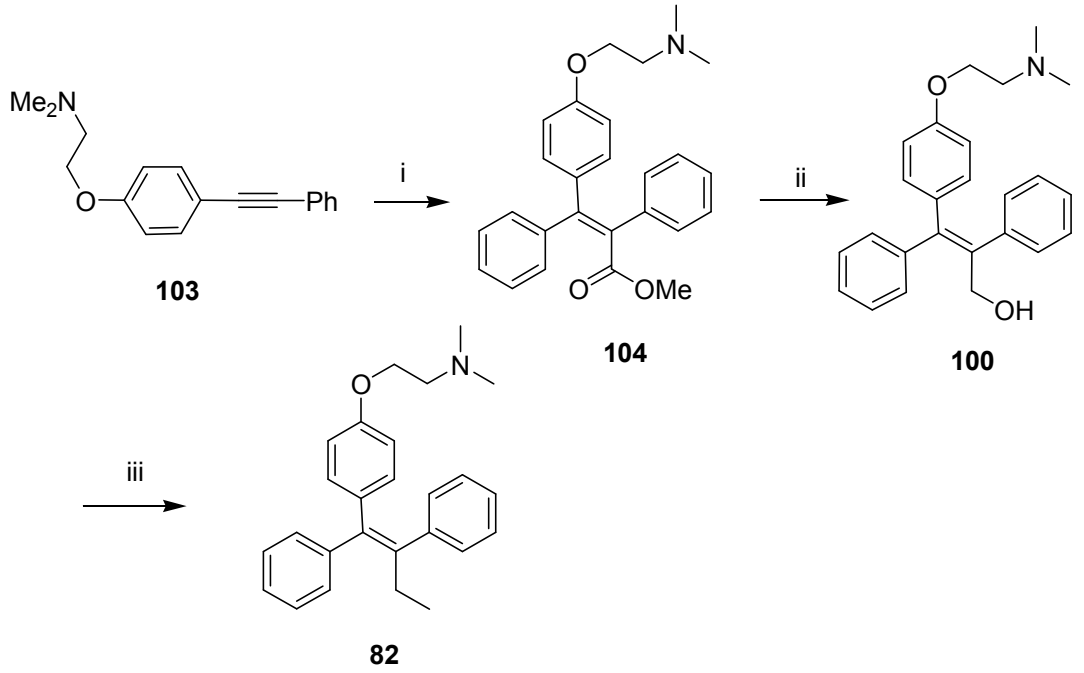


Scheme 27: (i) propargyl alcohol, $PdCl_2(PPh_3)_2$, CuI, THF, 22 ºC, 18 h, 83%; (ii) (a) PhMgCl, toluene, reflux; (b) $Pd(PPh_3)_4$, PhI, 72%; (iii) DMP, $CHCl_3$, 22 ºC, 12 h, 96%; (iv) K^tOBu, PPh_3CH_3Br, THF, reflux, 16 h, 81%; (v) H_2, Pd/C, EtOAc, 22 ºC, 2 h, 85%.

Kazuya *et al* (2006)[32]

In this approach, the key intermediate tetrasubstituted alkene was obtained from disubstituted alkyne **103** using nickel catalyzed arylative carboxylation followed by esterification with diazomethane. Unsaturated ester **104** was reduced into alkenol **100** using DIBAL-H in quantitative yield. The alkenol **100** was converted into diene by

oxidation followed by Wittig olefination. Then the selective reduction of the less hindered double bond afforded (*Z*)-tamoxifen in 71% yield (**Scheme 28**).



Scheme 28: (i) (a) CO_2, $Ni(COD)_2$, DBU, Ph_2Zn, THF, 40 ºC, 20 h; (b) CH_2N_2, 63%; (ii) DIBAL-H, CH_2Cl_2, -78 ºC, 2 h, 99%; (iii) (a) DMP, $CHCl_3$, 22 ºC, 12 h, 96%; (b) K^{t}OBu, PPh_3CH_2Br, THF, reflux, 16 h, 81%; (c) H_2, Pd/C, EtOAc, 22 ºC, 2 h, 85%.

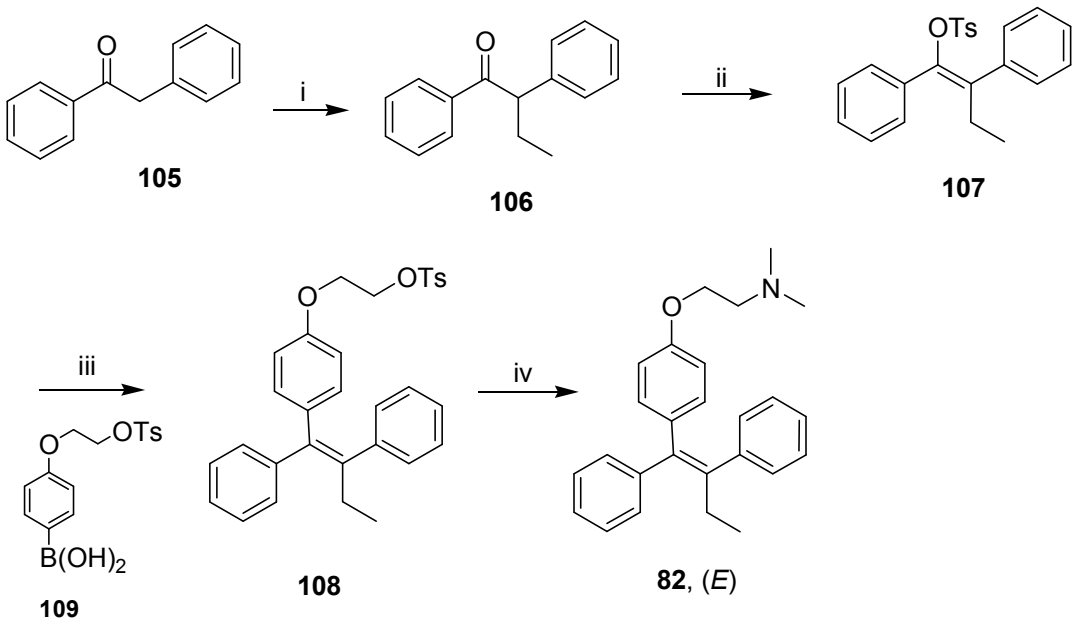
3.3.3 Present Work

3.3.3.1 Objective

As can be seen from the above discussion, many methods are known in the literature for the synthesis of tamoxifen. However, many of these methods have limitations such as producing mixture of *Z* and *E* isomers of tamoxifen as well as low overall yields. In this section, we have used palladium-catalyzed Suzuki coupling for the synthesis of tamoxifen, the details of which are described as follows.

3.3.4 Results and Discussion

The synthetic route for (*Z*)-tamoxifen (**82**) by palladium-catalyzed Suzuki coupling is shown in **Scheme 29**. Alkylation at the α-position of ketone **105** under basic conditions gave ketone **106** in 91% yield. The ^{1}H NMR spectrum of **106** showed typical triplets at δ 0.90 and 4.40 due to -CH_3 and -CH protons respectively. Its ^{13}C NMR spectrum also showed characteristic signals at δ 12.1 and 55.3 corresponding to methyl and methine carbons respectively.



Scheme 29: (i) EtBr, KO^{t}Bu, DMF, 25 ºC, 24 h, 91%; (ii) NaH, LiCl, THF, reflux, TsCl, 6 h, 82%; (iii) $Pd_2(dba)_3$, Na_2CO_3, THF, reflux, 12 h, 56%; (iv) dimethyl amine, metanol, reflux, 3 h, 78%.

Ketone **106** was transformed into vinyl tosylate **107** (NaH, TsCl) in 82% yield. The ^{1}H NMR spectrum of **107** showed a typical singlet at δ 2.49 for Ar-CH_3 protons. Palladium-catalyzed Suzuki coupling of tosylate **107** with arylboronic acid **109** (prepared from the corresponding bromo compound) in the presence of K_2CO_3 in THF at 65 °C gave tetra substituted olefin, **108** in 56% yield. The ^{1}H NMR spectrum of **108** showed a typical singlet at δ 2.34 for Ar-CH_3 proton; two triplets at δ 4.17 and 3.91 are due to -O-**CH_2**-

CH_2-OSO_2- protons respectively. Its ^{13}C NMR spectrum showed characteristic signal at δ 21.4 for Ar-**C**H_3 carbons; other signals at δ 67.9 and 64.9 are due to -O-**C**H_2-**C**H_2-OSO_2- carbons respectively (**Fig. 10**).

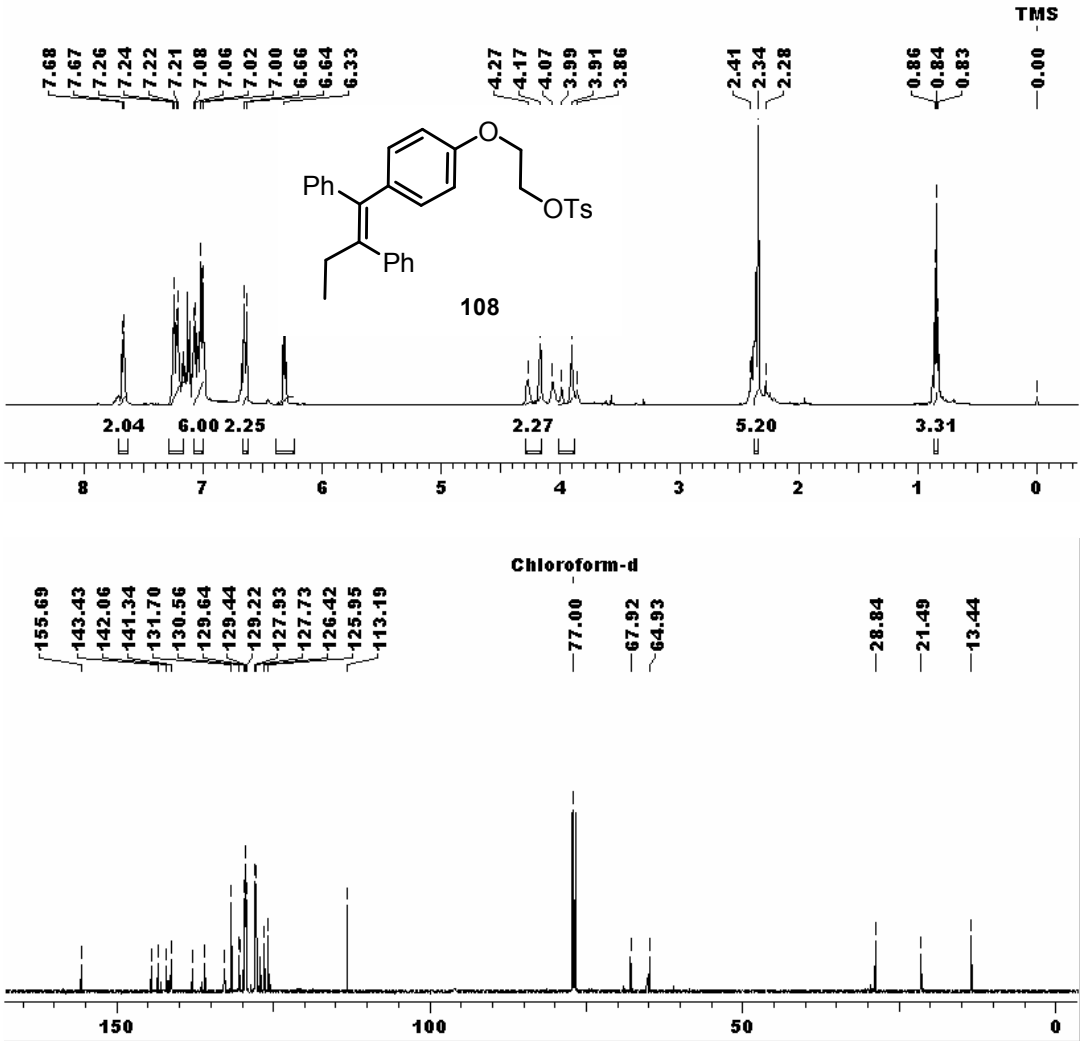


Fig. 10: ^1H and ^{13}C NMR spectra of 108

Nucleophilic displacement of the OTs group with 2 M methanol solution of dimethyl amine resulted in the formation of (*Z*)-tamoxifen (**82**) in 78% yield. The spectral data obtained for (*Z*)-tamoxifen (**82**) were in full agreement with the values reported in the literature[25] (**Fig. 11**).

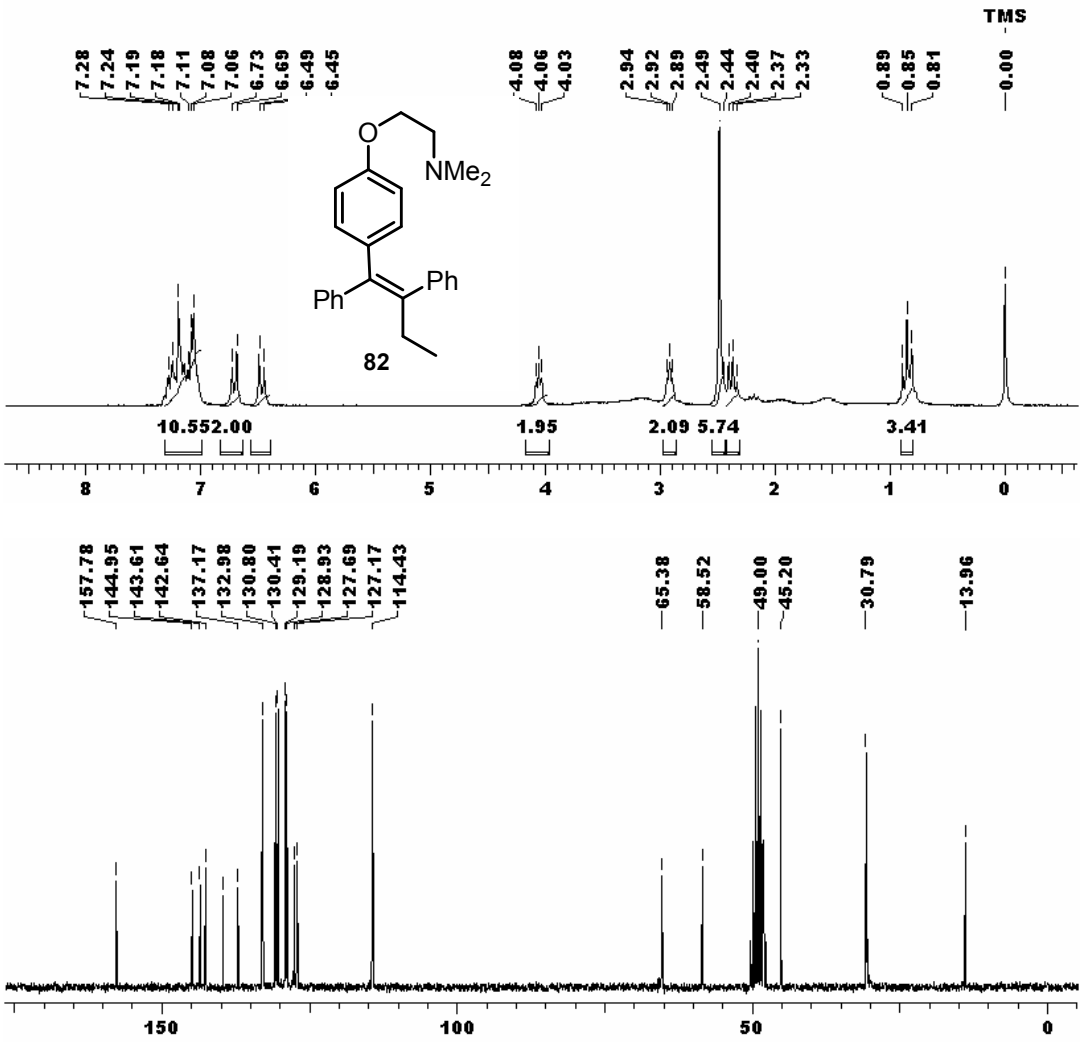


Fig. 11: ^{1}H and ^{13}C NMR spectra of (*Z*)-tamoxifen (82)

3.3.5 Conclusion

Synthesis of (*Z*)-tamoxifen was achieved in four steps with the overall yield (32.6%) using the palladium catalyzed Suzuki coupling. The reactions are rapid; requiring a relatively low amount of Pd-catalyst.

3.3.6 Experimental Section

1,2-Diphenylbutan-1-one (106):

To a stirred mixture of 1,2-diphenylethanone (**105)** (5.88 g, 30 mmol), and K^{t}OBu (6.72 g, 60 mmol) in dry DMF (50 mL) was added ethyl bromide (6.54 g, 60 mmol) at 0 ^oC. The reaction mixture was stirred at 25 ^oC for 24 h and extracted with ethyl acetate (3 x 20 mL). The combined ethyl acetate layers were concentrated to give crude product, which was purified by column chromatography using pet.ether: EtOAc (9:1) as eluent to furnish **106**.

Yield: 6.12 g (91%); **mp**: 74 °C; **IR** ($CHCl_3$, cm^{-1}): 669, 1174, 1215, 1263, 1379, 1448, 1490, 1596, 1679, 2875, 2875, 2931, 2968, 3018; ^{1}**H NMR** (200 MHz, $CDCl_3$): δ 0.90 (t, *J* = 7.3 Hz, 3H), 1.77-1.92 (m, 1H), 2.13-2.27 (m, 1H), 4.40 (t, *J* = 7.2 Hz, 1H), 7.14-7.45 (m, 8H), 7.91-7.95 (m, 2H); ^{13}**C NMR** (50 MHz, $CDCl_3$): δ 12.1, 27.0, 55.3, 126.8, 128.1, 128.3, 128.5, 128.7, 132.6, 136.9, 139.5, 199.9; **Analysis: $C_{16}H_{16}O$** requires C, 85.68; H, 7.19; found C, 85.64; H, 7.31%.

(*Z*)-1,2-Diphenylbut-1-enyl 4-methylbenzenesulfonate (107):

To a stirred mixture of NaH (0.22 g, 5.5 mmol), LiCl (0.231 g, 5.5 mmol) in dry THF (25 mL) was added ketone **106** (1.12 g, 5 mmol) at 0 ºC. The reaction mixture was stirred for 30 min at the same temperature followed by addition of *p*-toluenesulfonyl chloride (1.05 g, 5.5 mmol). Then the reaction mixture was refluxed for 6 h, and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography to afford **107**.

Yield: 1.5 g (82%); ^{1}**H NMR** (200 MHz, $CDCl_3$): δ 0.85 (t, *J* = 7.5 Hz, 3H), 2.39 (q, *J* = 7.3 Hz, 2H), 2.49 (s, 3H), 7.23-7.7.48 (m, 10H), 7.90-7.98 (m, 4H); ^{13}**C NMR** (50 MHz,

$CDCl_3$): δ 13.4, 21.4, 28.8, 103.5, 126.6, 128.0, 128.4, 129.3, 130.4, 132.9, 134.4, 136.4, 139.4, 142.2, 146.8, 169.3; **Analysis: $C_{23}H_{22}O_3S$** requires C, 72.99; H, 5.86; S, 8.47; found C, 73.12; H, 5.81; S, 8.55%.

2-(4-((*Z*)-1,2-Diphenylbut-1-enyl)phenoxy)ethyl 4-methylbenzenesulfonate (108):

To the enol tosylate (0.756 g, 2 mmol), arylboronic acid (1.005 g, 3 mmol), and $Pd_2(dba)_3$ (0.018 g, 1 mol%), THF (25 mL) was added followed by 2 M Na_2CO_3 (3.5 mL, 7.5 mmol). The reaction mixture was refluxed for 12 h and product was isolated by extraction with dichloromethane (3 x 25 mL). The combined organic extracts were washed with brine and dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give the crude product, which was purified by column chromatography to afford **108**.

Yield: 0.558 g (56%); **IR** ($CHCl_3$, cm^{-1}): 669, 929, 1031, 1215, 1508, 1600, 2399, 2927, 2972, 3018; ^{1}**H NMR** (200 MHz, $CDCl_3$): δ 0.84 (t, *J* = 7.3 Hz, 3H), 2.28-2.44 (m, 5H), 3.86-4.27 (m, 4H), 6.32 (d, *J* = 8.3 Hz, 2H), 6.65 (d, *J* = 8.5 Hz, 2H), 7.00-7.08 (m, 6H), 7.21-7.26 (m, 6H), 7.68 (d, *J* = 7.5 Hz, 2H); ^{13}**C NMR** (50 MHz, $CDCl_3$): δ 13.4, 21.4, 28.8, 64.9, 67.9, 113.1, 125.9, 126.4, 127.7, 127.8, 127.9, 129.2, 129.4, 129.6, 130.4, 130.5, 131.7, 132.8, 135.8, 137.8, 141.3, 142.0, 143.4, 144.5, 155.6; **Analysis: $C_{31}H_{30}O_4S$** requires C, 74.67; H, 6.06; S, 6.43; found C, 74.59; H, 5.91; S, 6.59%.

1,2-Diphenyl-l-[4[2-dimethylamino)ethoxylphenyl]-l-butene (Tamoxifen) (82):

A mixture of tosylate **108** (0.498 g, 1 mmol) and 2 M methanol solution of dimethylamine (2.5 mL, excess) was refluxed for 3 h and the excess dimethylamine was distilled off under reduced pressure. The crude product was diluted with water and extracted with ethyl acetate. The organic layers were dried over anhyd. Na_2SO_4 and

concentrated to obtain the crude product, which was purified by column chromatography to afford tamoxifen **82**.

Yield: 0.29 g (78%); **mp** 95-98 °C; **IR:** ($CHCl_3$, cm^{-1}): 667, 703, 1029, 1174, 1215, 1228, 1440, 1461, 1508, 1606, 1672, 2854, 2927, 2964, 3016; ^{1}**H NMR** (200 MHz, $CDCl_3$): δ 0.85 (t, *J* = 7.5 Hz, 3H), 2.39 (q, *J* = 7.3 Hz, 2H), 2.49 (s, 6H), 2.92 (t, *J* = 5.0 Hz, 2H), 4.06 (t, *J* = 5.0 Hz, 2H), 6.47 (d, *J* = 8.5 Hz, 2H), 6.71 (d, *J* = 8.5 Hz, 2H), 7.06-7.28 (m, 10H); ^{13}**C NMR** (50 MHz, $CDCl_3$): δ 13.9, 30.7, 45.2, 58.5, 65.3, 114.4, 127.1, 127.6, 128.9, 129.1, 130.4, 130.8, 132.9, 137.1, 139.7, 142.6, 143.6, 144.9, 157.7; **Analysis:** **$C_{26}H_{29}NO$** requires C, 84.06; H, 7.87; N, 3.77; found C, 83.94; H, 7.81; N, 3.85%.

3.3.7 References

1. Longo, R.; Castellani, R.; Tibolla, M. *Phytochemistry* **1974**, *13*, 167.
2. Tolosa, E.; Marti, M. J.; Valldeoriola, F.; Molihuevo, J. L. *Neurology* **1995**, 50.
3. Mendis, T.; Suchowerski, O.; Lang, T.; Gauthier, S. *Can. J. Neur. Science* **1999**, 26, 89.
4. a) Calne, D. B.; Sandler, M. *Nature* **1970**, *226*, 21. b) Sourkes, T. L. *Pharmacol. Rev.* **1966**, *18*, 53. c) Tissort, R.; Bartholini, G.; Pletscher, A. *Arch. Neurol.* **1969**, *20*, 187.
5. Tyagi, O. D.; Boll, P. M.; Parmar, V. S.; Taneja, O.; Singh, S. K. *Indian J. Chem., Sec-B.* **1992**, *31*, 851.
6. Jung, M. E.; Lazarova, T. I. *J. Org. Chem.* **1997**, *62*, 1553.
7. Antilla, J. C.; Wulff, W. D. *Angew. Chem., Int. Ed.* **2000**, *39*, 4518.
8. Takashi, O.; Kameda, M.; Tannai, H.; Maruoka, K. *Tetrahedron Lett.* **2000**, *41*, 8339.
9. Sayyed, I. A.; Sudalai, A. *Tetrahedron: Asymmetry* **2004***, 15,* 3111.
10. Valdes, R. H.; Puzer, L.; Gomes, Jr. M.; Marques, C. E. S. J.; Aranda, D. A. G.; Bastos,

M. L.; Gemal, A. L.; Antunes, O. A. C. *Catalysis Communications* **2004**, 631.

11. List, B. *J. Am. Chem. Soc*. **2002**, *124*, 5656.
12. Fernandes, P. B; Chu, D. T. W. *Annu. Rep. Med. Chem.* **1987***, 22,* 117.
13. Mitscher, L. A.; Sharma, P. N.; Chu, D. T. W.; Shen, L. L.; Pernet, A. G. *J. Med. Chem.* **1987***, 30,* 2283.
14. Catherine O. M.; Gary G. M. *Clinical Pharmacology* **2002**, *65*, 455.
15. Chu, C. K.; Kim, J. H.; Kim, D. W.; Chung, K. H.; John A. K.; Chi, D. Y. *Bull. Korean Chem. Soc.* **2005**, *26*, 599.
16. Sato, K.; Matsuura, Y.; Inoue, M.; Une, T.; Osada, Y.; Ogawa, H.; Mitsuhashi, S. *Antimicrob. agents Chemother.* **1982**, *22*, 548.
17. Hayakawa, I.; Atarashi, S.; Yokohama, S.; Imamura, M.; Sakano, K. I.; Furukawa, M. *Antimicrob. agents chemother.* **1986**, *29*, 163.
18. Atarashi, S.; Tsurumi, H.; Fujiwara, T.; Hayakawa, I. *J. Heterocyclic Chem*. **1991**, *28*, 329.
19. Kang, S. B.; Ahn, E. J.; Kim, Y.; Kim, Y. H. *Tetrahedron lett.* **1996**, *37*, 9317.
20. Satoh, K.; Inenaga, M.; Kanai, K. *Tetrahedron: Asymmetry* **1998**, *9*, 2657.
21. (a) Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Shoji, M. *Tetrahedron Lett*. **2003**, *44*, 8293. (b) Cordova, A.; Sunden, H.; Bøgevig, A.; Johansson, M.; Himo, F. *Chem. Eur. J*. **2004**, *10*, 3673.
22. Shafir, A.; Lichtor, P.A.; Buchwald, S. L. *J. Am. Chem. Soc*. **2007**, *129*, 3490.
23. Atarashi, S.; Yokohama, S.; Yamazaki, K.; Sakano, K.; Imamura, M.; Hayakawa, I. *Chem. Pharm. Bull.* **1987**, *35*, 1896.
24. Robertson, D. W.; Katzenellenbogen, J. A. *J. Org. Chem*. **1982**, *47*, 2387.

25. Miller, R. B.; Al-Hassan, M. I. *J. Org. Chem*. **1985**, *50*, 2121.

26. Al-Hassan, M. I. *Synthsis* **1987**, 816.

27. McCague, R. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1011.

28. Olier-Reuchet, C.; Aitken, D. J.; Bucourt, R.; Husson, H, P. *Tetrahedron Lett.* **1995**, *36*, 8221.

29. Brown, S. D.; Armstrong, R. W. *J. Org. Chem*. **1997**, *62*, 7076.

30. Studemann, T.; Knochel, P. *Angew. Chem., Int. Ed. Engl*. **1997**, *36*, 93.

31. Tessier, P. E.; Penwell, A. J.; Souza, F. E. S.; Fallis, A. G. *Org. Lett.* **2003**, *5*, 2989.

32. Shimizu, K.; Takimoto, M.; Mori, M.; Sato, Y. *Synlett* **2006**, 3182.

CHAPTER 4

Synthesis of Novel Transition Metal Complexes and their Applications in C-C Bond Formation

SECTION 1:

Synthesis and Characterization of Novel Palladium Complexes and Their Catalytic Activity Studies

4.1.1 Introduction

Transition metal mediated reactions are becoming increasingly important in organic synthesis as organic chemists become familiar with the myriad of organometallic mechanisms involved in these processes. Homogeneous palladium catalysts are used in the commercial production of acetaldehyde, cinnamates and other products.[1] Palladium undergoes many reactions with organic systems and, apart from the well-known hydrogenation and oxidation (Wacker) processes, it acts as a catalyst for many key C-C bond forming reactions. Palladium catalyzed C-C bond formation reactions are widely exploited in academic research, but industrial applications are limited. Palladium-catalyzed cross-coupling chemistry for the formation of carbon-carbon bonds has recently emerged as a powerful method in organic synthesis.[2]

In these context, three areas are particularly important: the reaction of π-allyl-(η-allyl) palladium cations with nucleophiles, the cross coupling of organometallic reagents (such as organotin, organoboron and organozinc reagents) with organic halides, and the reaction of organic halides (usually aryl/alkenyl halides) with alkenes. The first of these was extensively developed by Trost, the second by Kumada and later by Stille, Suzuki and others and the last by Heck. The catalytically active component in these reactions is frequently a Pd(0) species. However, the added material is often a Pd(II) salt as in these cases the Pd(0) is generated *in situ* by reduction with the organometallic reagent, solvent

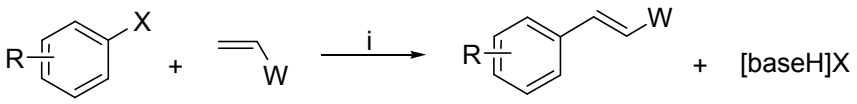
or some other species in the reaction mixture. It is important to note that the ready oxidative addition of the aryl halides and triflates to the Pd(0) species reverses the conventional concepts of reactivity in aryl systems: in nucleophilic displacement processes, as normally encountered, the alkyl halides are more reactive while in the palladium-catalyzed reactions, the alkyl halides are the least reactive species.

Coupling of organopalladium(II) halide or triflate moieties occurs with a variety of substrates including alkenes (Heck-Mizoroki arylation[3]), organoboron compounds (Suzuki-Miyaura reactions[4]), amines (Hartwig-Buchwald amination[5]) or organotin compounds (Stille coupling[6]). Although these reactions can be mediated by a variety of simple and highly reactive Pd(0) and Pd(II) salts in the presence of various phosphine ligands as well as phosphine-free palladium-carbene catalyst precursors,[7] several challenges remain to be achieved for industrial applications such as the use of aryl chlorides as substrates, the possibility of using aqueous conditions,[8] the recovery of catalyst[9] and the desire to simplify the catalyst by working under phosphine-free conditions.[10] In this context, recent developments for the utilization of aryl chlorides in C-C, C-N and C-O bond-forming reactions have largely focused on Pd-catalysts containing bulky, electron-rich phosphine ligands,[11] the synthesis of which often involves multistep synthesis using air-sensitive substances. In order to improve the stability of Pd-based catalysts and to increase their efficiency in coupling reactions, a new family of Pd-based catalyst precursors has recently been reported. Palladacycles have recently emerged as one of the most promising classes of catalysts or catalyst precursors in the Pd- catalyzed C–C bond forming reactions. In the last decade, a number of new types of ligands such as heterocyclic carbenes,[12] thiourea,[13] oximes,[14] diazabutadienes,[15] and 2-

aryl-2-oxazolines[16] were employed in these cross-coupling reactions. However, a high loading of catalysts and an inert atmosphere in most reactions especially involving phosphapalladacycles[17] and phosphines-free *N*-heterocyclic carbenes are generally required for achieving better conversions. The sulfur and nitrogen containing palladacycles have emerged as alternative catalyst precursors for the phosphine palladacycles due to their high stability towards moisture, air and high temperature. The discovery of these catalyst precursors allows arylation and vinylation reactions to be performed with activated and non-activated aryl halides using very low catalyst concentrations. Aqueous-phase palladium catalyzed reactions are of much interest as environmentally benign synthetic methods that would decrease the use of volatile organic solvents and simplify the catalyst recovery. The use of water as a solvent is very attractive because of the economy and safety.

4. 1. 1.1 Heck Reaction

The palladium-catalyzed arylation of olefins with aryl halides generally referred to as the Heck reaction has received increasing attention in the last two decades.[3] This is primarily due to the enormous synthetic potential of this versatile method for generating new C-C bonds (**Scheme 1**).



R = H, alkyl, CHO etc.
X = I, Br, Cl
W = CO_2R, Ph, CN etc.

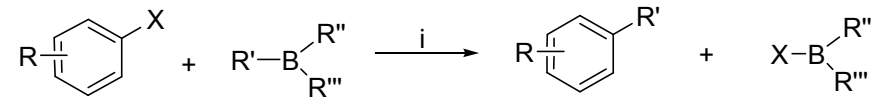
Scheme 1: Heck coupling reaction, (i) Pd-catalyst, base, solvent.

This reaction represents a powerful and popular method for the formation of C-C bonds; in particular, the preparation of aryl-functionalized alkenes in synthetic organic chemistry as applicable to pharmaceutical industry.[18] Recent developments in the catalysts and reaction conditions have resulted in a much broader range of donors and acceptors being amenable to the Heck reaction. One of the benefits of the Heck reaction is its outstanding *trans* selectivity. Traditionally, variety of palladium sources such as $Pd(OAc)_2$, $PdCl_2$, $PdCl_2(PPh_3)_2$, $Pd(dba)_2$, $Pd_2(dba)_3$, *etc*. were used as catalysts with or without phosphine (for e.g. PPh_3) ligands. Palladium-catalyzed reaction needs a stoichiometric use of base, high temperature (100 °C) and long time (24 h) for complete conversion. Some alternative conditions, such a high pressure, phase-transfer conditions or water-soluble phosphine-ligand catalysts were proposed and many Heck arylations are known to proceed smoothly in water or in water/organic solvent mixtures. However, these catalytic systems suffer from some severe limitations, such as non-applicability of this reaction on industrial scale. Typically a relatively large amount of catalyst (1-5 mol%) is needed for reasonable conversions and the catalyst recycling is often hampered by early precipitation of palladium black.[19] Due to the fast catalyst deactivation the turn over number (TON= mole of product/mole of Pd) and turn over frequency (TOF= mole of product/mole of Pd h^{-1}) was very low for all these conventional catalysts. During the past few years very active systems have been developed in order to improve the stability of palladium-based catalysts and to increase their efficiency.[20] Particularly, carbometalated Pd^{II} complexes, especially palladacycles have emerged as very promising catalysts for Heck reactions. The discovery of these palladacycles allowed Heck reactions to be performed with

activated and nonactivated aryl halides using very low catalyst concentrations (down to ppm in case of aryl iodides).[21]

4.1.1.2 Suzuki coupling

Palladium-catalyzed cross coupling of organic halides or perfluorinated sulfonates with organoboron derivatives proceeding with high stereo- and regioselectivity is referred to as the Suzuki coupling (**Scheme 2**).



R = H, alkyl etc.
X = I, Br, Cl

Scheme 2: Suzuki coupling reaction, (i) Pd-catalyst, base, solvent.

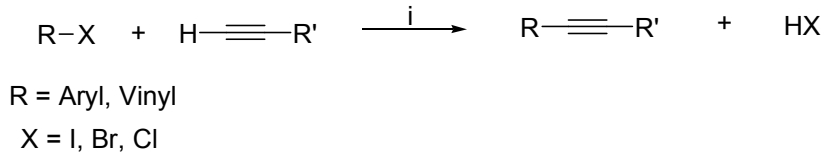
The Suzuki coupling has been successfully applied in the synthesis of pharmaceuticals, herbicides and natural products as well as in conducting polymers and liquid–crystalline materials.[22] Recent research has focused on the development of improved conditions for the Suzuki reaction for the synthesis of such biaryl units. Their preparation, when effected through the palladium-catalyzed Suzuki cross-coupling of aryl halides with arylboronic acids, is both extremely versatile and very convenient: boronic acids, being generally non-toxic, thermally stable and insensitive to air and moisture, are much easier to handle than other commonly used cross-coupling reagents.[23] The minimum criteria for an optimum system that must be met include: i) a broad substrate scope, ii) the ability to make truly hindered biaryls, iii) the ability to operate at low levels of catalyst for a range of substrates not just with the most simple examples (e.g., other than phenyl boronic

acid), and iv) the ability to operate at room temperature. Moreover, it is most desirable to develop protocols that do not necessitate the use of a glovebox.[24]

There has recently been considerable interest in the development of a new, high-activity catalyst that can be used in low loadings in such reactions, and palladacyclic complexes have played a significant role in this regard. Some of the challenges associated with cross-coupling partners in view of their attractive cost and readily available diversity. Efforts aimed at developing catalytic system that perform at mild reaction temperatures in short times using low catalyst loadings are an ongoing effort.

4.1.1.3 Sonogashira coupling

The palladium catalyzed coupling of vinyl or aryl halides with terminal acetylenes generally referred to as the Sonogashira reaction [25] (**Scheme 3**).



Scheme 3: Sonogashira coupling reaction, (i) Pd,Cu-catalyst, base, solvent.

Substituted acetylenes has been applied in the synthesis of antimycotics,[26] antibiotics,[27] liquid crystals, polymers, and optical or electronic materials.[28] While aryl bromides and aryl iodides are well known to undergo this reaction in the presence of suitable catalysts, there is no efficient protocol for the Sonogashira coupling of alkynes with aryl chlorides, which would be the most attractive starting materials because of the wide variety of cheaply available chloro derivatives.

Several modifications of the original Sonogashira protocol have been developed during the last few years, prominent among which are the phase transfer and copper-free

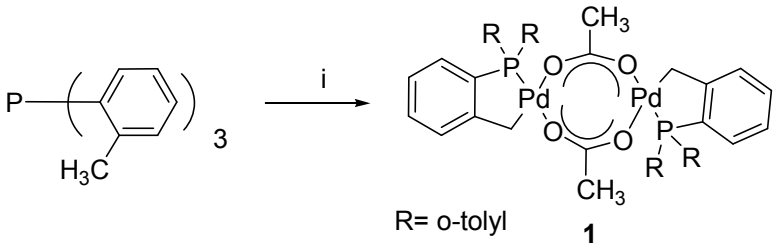
conditions, and the use of more active catalyst systems, including those having N-heterocyclic carbene (NHC) ligands for reaction with the less reactive bromo- and chloroarenes. The effect of different solvents has also been probed including aqueous–organic solvent mixtures in the presence of water soluble phosphine ligands and ionic liquids.[29]

4.1.2 Review of Literature

Literature search revealed that there are several reports on use of palladium complexes with ligands such as phosphorous and nitrogen for C-C bond formation reactions like Heck reaction, Suzuki coupling, *etc*. Some of the recent reports on the palladacycles synthesis and their application in C-C bond formation reactions are discussed below.

Herrmann's approach (1995)[30]

Palladacycle **1** was synthesized and used as efficient catalyst for the Heck reaction of aryl bromides as well as aryl chlorides. Turn over number (TON, mmol of product/mmol of Pd) upto 2,00,000 was achieved in case of Heck reaction of aryl bromides (**Scheme 4**).

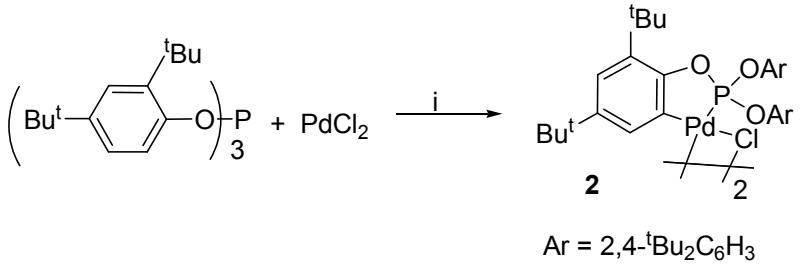


Scheme 4: (i) $Pd(OAc)_2$, toluene, 50 °C, 93%.

Herrmann *et al.*[31] have reported the use of the same catalyst **1** for the Suzuki coupling to yield biphenyl 21-92% with TON upto 74,000.

Bedford's approach (1998)[35]

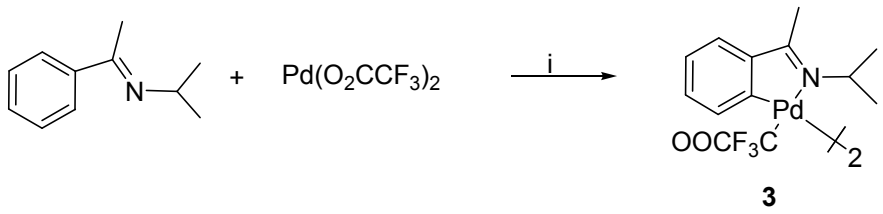
The reaction of tris(2,4-di-*tert*-butylphenyl)phosphite with $PdCl_2$ afforded the orthometallated dimer **2.** For Suzuki coupling TON upto 10,00,000 and TOF (turn over frequency) upto 9,00,000 were obtained. In case of Stille reaction, TON upto 8,30,000 were achieved (**Scheme 5**).



Scheme 5: (i) toluene, 96%.

Milstein's approach (1999)[33]

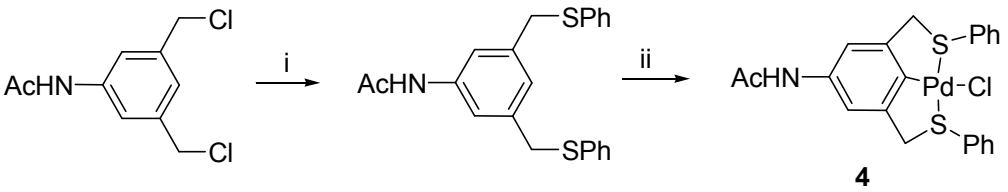
The cyclopalladated phosphine-free, air and thermally stable imine complex **3** was synthesized and applied for the Suzuki cross coupling with aryl bromides where in a TON upto 590 x 10^3 was obtained (**Scheme 6**).



Scheme 6: (i) THF, 93%.

Osburn's approach (1999)[34]

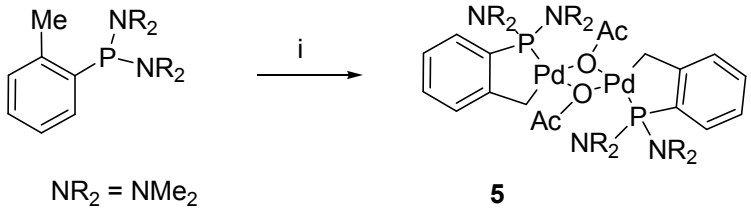
Sulfur palladacycle **4** was synthesized and used as an efficient catalyst for the Heck reaction of aryl iodides with olefins to yield *β*-substituted olefins in 91-96% yields (**Scheme 7**).



Scheme 7: (i) PhSH, K_2CO_3, DMF, 70 °C, 16 h, 89%; (ii) $Pd(PhCN)_2Cl_2$, MeCN, reflux, 14 h, 85%.

Brunel's approach (2000) [35]

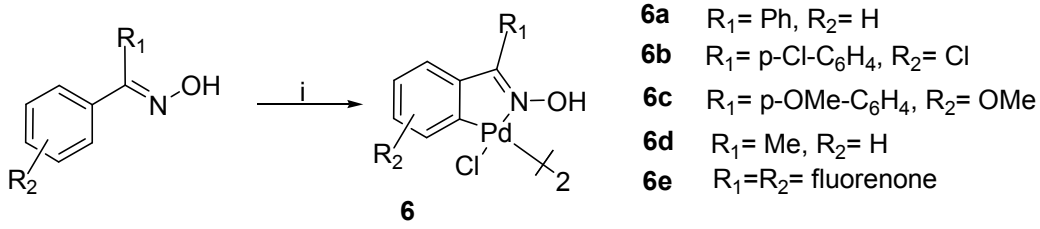
Brunel *et al*. synthesized palladacycle **5**, and used it as a catalyst for the hydroarylation of norbornene. Very high TON upto 196 x 10^6 was observed in presence of hydrogen donor like NEt_3/HCO_2H (**Scheme 8**).



Scheme 8: (i) $Pd(OAc)_2$, toluene, 110 °C, 2 h, 90%.

Alonso's approach (2000)[36]

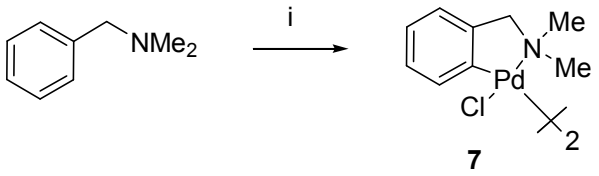
Several oxime palladacycles **6a-e** were prepared from very cheap starting materials such as corresponding oximes and these were used as versatile catalysts for different C-C bond forming reactions (**Scheme 9**).



Scheme 9: (i) Li_2PdCl_4, NaOAc, MeOH, 25 °C, 72 h, 90%.

Iyer's approach (2000)[37]

Amine based palladacycle **7** was found to be excellent catalysts for the Heck reaction. High TON upto 1, 45,454 were obtained. (**Scheme 10**)

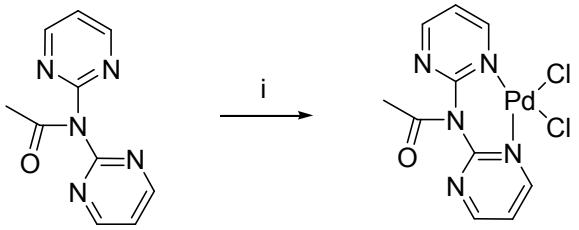


7

Scheme 10: (i) Li_2PdCl_4, MeOH, 25 °C, 93%.

Buchmeiser's approach (2001)[38]

Buchmeiser *et al.* have synthesized Pd-complex N-acetyl-N,N-bis(pyrimid-2-yl)aminepalladiumdichloride (**9**) from **8**. It was found to be excellent catalysts for the Heck reaction with TON upto 7300 was obtained (**Scheme 11**).

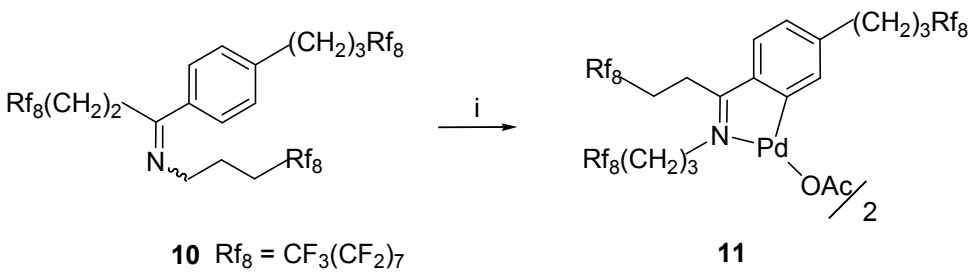


8 **9**

Scheme 11: (i) H_2PdCl_4, MeOH, 25 °C, 80%.

Gladysz's approach (2002)[39]

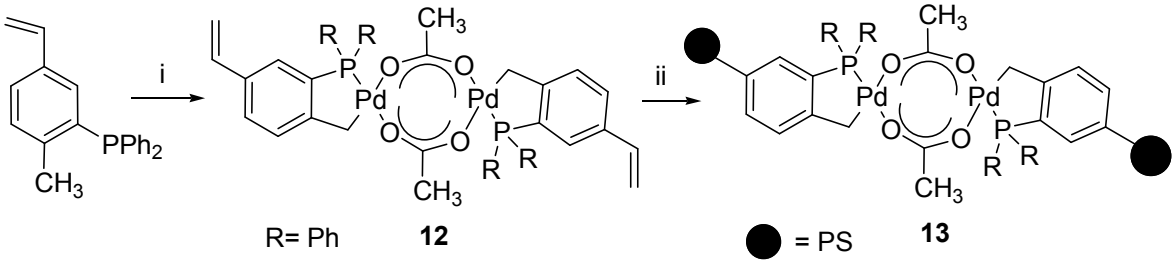
The fluorous Schiff base **10** was prepared and cyclopalladated to afford highly effective catalyst precursor **11.** TON up to 14,61,000 was obtained for Heck reaction (**Scheme 12**).



Scheme 12: (i) $Pd(OAc)_2$, AcOH, 95 °C, 87%.

Lin's approach (2003)[40]

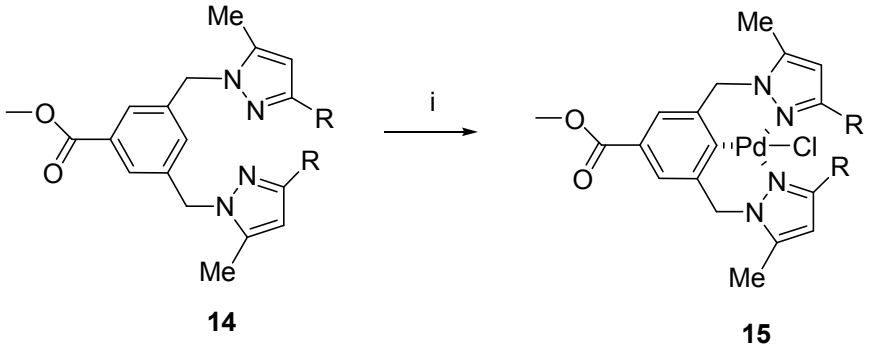
A new type of soluble polystyrene-supported palladacycle **13** was synthesized for carbon carbon bond formation in Heck, Suzuki and Sonogashira reactions (**Scheme 13**).



Scheme 13: (i) $Pd(OAc)_2$, toluene, 50 °C, 74%; (ii) styrene, benzene, 70 °C, 40 h, 66%.

Churruca's approach (2005)[41]

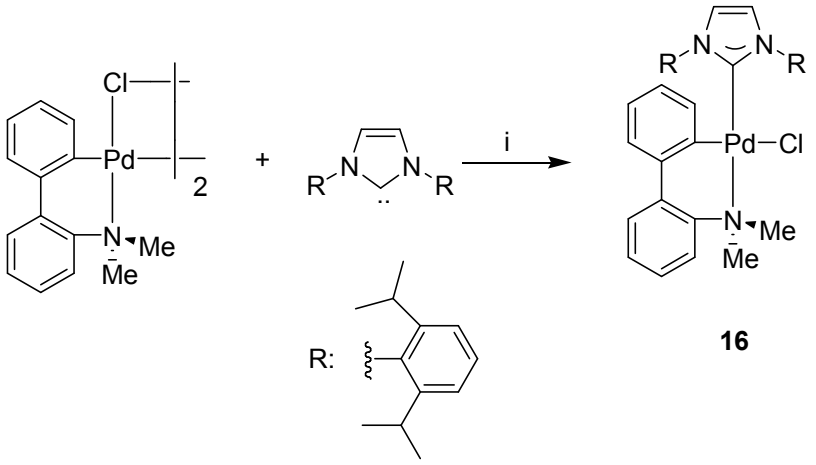
N-Heterocyclic NCN-Pincer palladium complex (**15**) was synthesized and successfully employed as catalysts in a range of C–C bond-forming reactions (**Scheme 14**).



Scheme 14: (i) (a) $Pd(OAc)_2$, AcOH, 95 °C, 20 h; (b) LiCl, acetone, H_2O, 48h, 81%.

Navarro's approach (2006)[42]

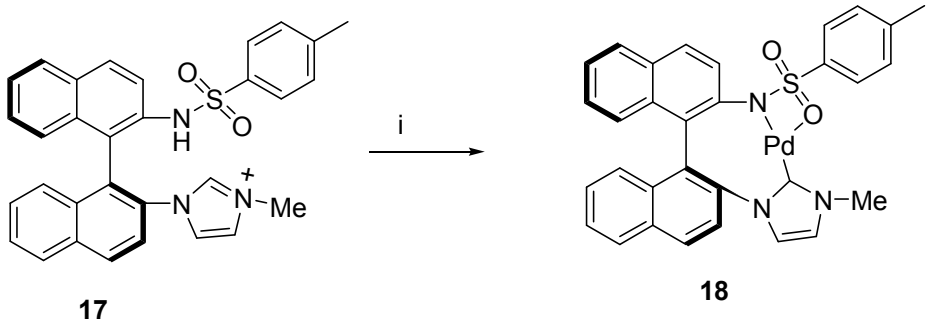
Suzuki Miyaura cross-coupling reaction involving unactivated arylchlorides and triflates with arylboronic acids at room temperature in technical grade 2-propanol is achieved using N-Heterocyclic carbene palladacycles **16.** This complex also displays very high activity for α-arylation of ketones with activated and unactivated aryl chlorides (**Scheme 15**).



Scheme 15: (i) THF, 25 °C, 2 h, 67%.

Chen's approach (2006)[43]

A novel tridentate NHC–Pd(II) complex derived from binaphthyl-2,2- diamine (BINAM) (**18**) had been synthesized. This NHC–Pd (II) complex was fairly effective in Suzuki and Heck-type cross-coupling reactions and gave the arylated in good to excellent yields (**Scheme 16**).

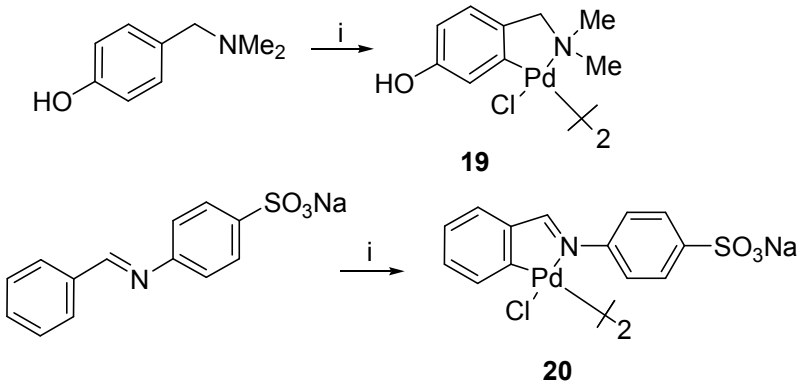


17 **18**

Scheme 16: (i) $Pd(OAc)_2$, THF, reflux, 56%.

Huang's approach (2006)[44]

A family of water-soluble palladacycles (**19** and **20**) were prepared from *N,N*-dimethyl-*p*-hydroxybenzyl amine and sodium 4-(N-benzylideneamino) benzenesulfonate. They exhibit high activity for the Suzuki coupling of aryl bromides and activated aryl chlorides in combination with (2-di-tert-butylphosphinoethyl)-trimethylammonium chloride (*tert*-Bu-Amphos) (**Scheme 17**).



Scheme 17: (i) $PdCl_2$, NaOAc, MeOH, 25 °C, 81%; (ii) $PdCl_2$, NaOAc, MeOH, 25 °C, 52%.

4.1.3 Present Work

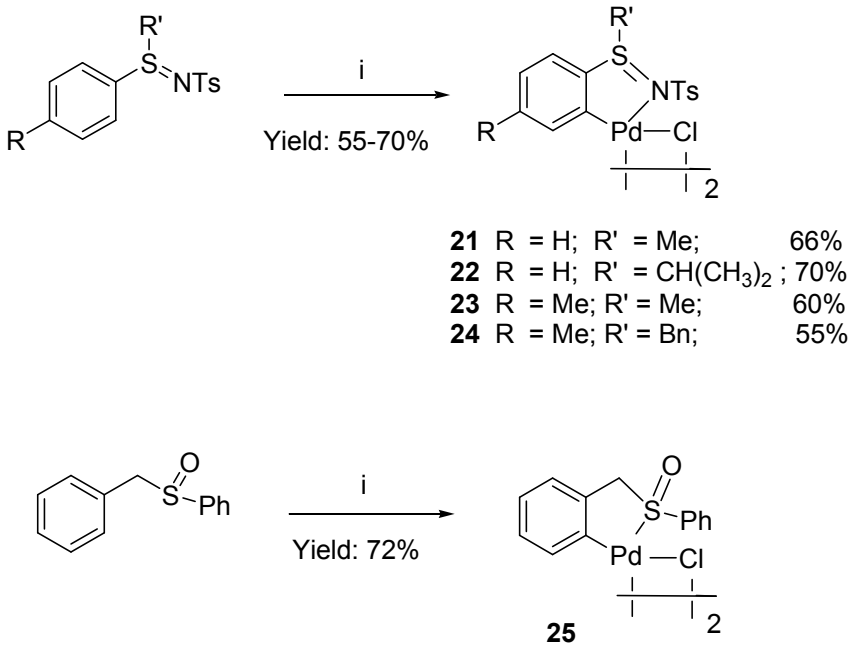
4.1.3.1 Objective

Although there are several palladium complexes reported for the C-C bond forming reactions namely Heck, Suzuki and Sonogashira coupling reactions, some of them suffer from several drawbacks: low turn over number (TON), multi-step synthesis of Pd-complexes, use of highly moisture and air-sensitive phosphine ligands, etc. In this context, the sulfur-and nitrogen-containing Pd-complexes are superior to phosphine-based Pd-complexes due to their high stability towards moisture, air and high temperature. Our aim was to develop methods for synthesizing new palladium complexes from readily accessible air-stable ligands such as sulfilimine, sulfoxide, sulfonamide and saccharin, etc. This section describes, the synthesis, characterization and catalytic activity studies of some of the new Pd-complexes in several C-C bond forming cross-coupling reactions, particularly with water as the solvent.

Results and Discussion

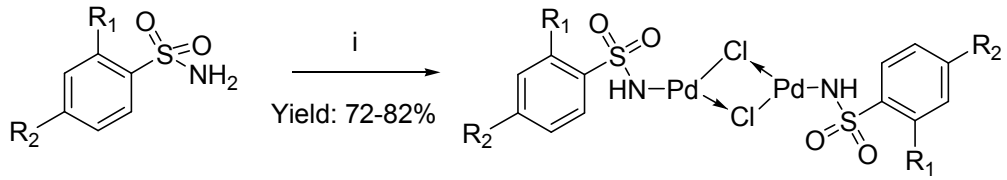
4.1.4.1 Synthesis of Pd- complexes (21-30)

We have, for the first time, synthesized several, novel palladium complexes, **21-30,** *via* a carbopalladation reaction,[45] in which lithium tetrachloropalladate in MeOH and NaOAc were used at 25 °C. These sulfilimine and sulfoxide-based palladacycles (**21-25)** were readily prepared in high yields (55-72%) from the corresponding sulfilimines[46] and sulfoxide precursors respectively (**Schemes 18** and **19**).

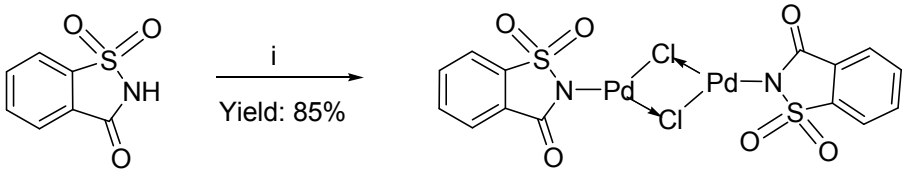


Scheme 18: (a) Li_2PdCl_4, NaOAc, MeOH, 25 °C, 24 h.

For example, sulfilimine palladacycles, **21-24,** with a variety of substitution in it (CH_3, $CH(CH_3)_2$, CH_2Bn) and sulfonamide-based palladium complexes (**26-30)** were synthesized in 55-70% and 72-85% yields respectively. In the case of saccharin, the Pd-complex was precipitated after 6 h and filtered off. Interestingly, we found that the saccharin-based palladium complex, **30,** was completely soluble in water at ambient conditions.



26 R_1 = H; R_2 = CH_3; 82%.
27 R_1 = H; R_2 = OCH_3; 78%.
28 R_1 = H; R_2 = NH_2; 76%.
29 R_1 = CH_3; R_2 = CH_3: 72%.



30

Scheme 19: (i) Li_2PdCl_4, NaOAc, MeOH, 25 °C, 24 h.

4.1.4.2 Characterization of Pd- complexes (21-30)

These palladium catalysts (**21-30**) were fully characterized by elemental C, H, N, S analysis, IR, ^1H & ^{13}C NMR spectroscopy and atomic absorption spectroscopy (AAS). The IR spectrum of all palladium complexes (**26-30**) showed a shift of 40-60 cm^{-1} in the sulfone stretching frequency compared to the parent sulfonamide ligands. For example, in the case of saccharin palladium complex **30**, the sulfone stretching frequency was observed at 1287 cm^{-1} and 1154 cm^{-1} while for the parent saccharin it was observed at 1331 cm^{-1} and 1176 cm^{-1}. Also the carbonyl stretching frequency for the complex **30** was observed at 1664 cm^{-1}, while the parent saccharin displayed at 1730 cm^{-1}. The percentage of palladium content in the palladium complexes (**21-30**) was analyzed from atomic absorption spectroscopy (AAS). For example, the palladium percentage in the palladium complex **30** was found to be 33.42% (requires theoretically 33.99%). The ^1H NMR spectrum of palladacycle **21** showed singlets at δ 2.32 and δ 2.95 for Ar-CH_3 and the S-

CH_3 protons respectively. Its ^{13}C NMR spectrum showed typical carbon signals at δ 20.8 and 37.4 for Ar-CH_3 and S-CH_3 carbons respectively; other signals at δ 125.7, 126.1, 129.2, 129.8, 132.2, 136.2, 141.2 and 141.3 are due to aromatic carbons (**Fig. 1**).

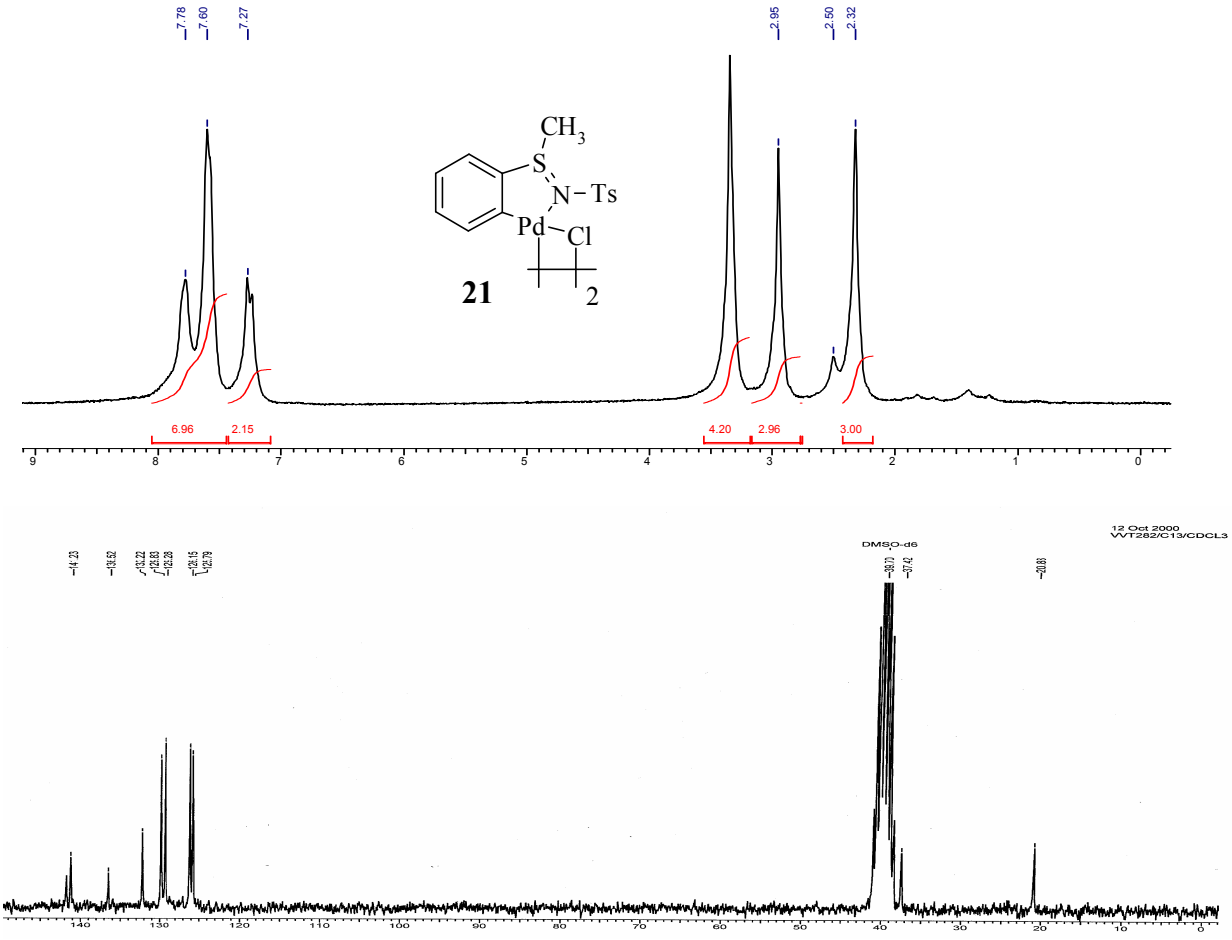


Fig. 1: ^{1}H and ^{13}C NMR spectra of palladacycle 21

As a second example, **Fig. 2** shows the ^{1}H and ^{13}C NMR spectra of saccharin palladium complex **30.** The ^{1}H NMR spectrum showed a multiplet at δ 7.64 (4H) corresponding to aromatic protons. Its ^{13}C NMR spectrum showed typical carbon signals at δ 119.7, 123.1, 131.9, 133.3, 134.6 and 145.2 due to aromatic carbons. Only two aromatic carbon signals

at δ 134.6 and 145.2 have disappeared in its DEPT-NMR, which confirms that no palladacycle was formed.

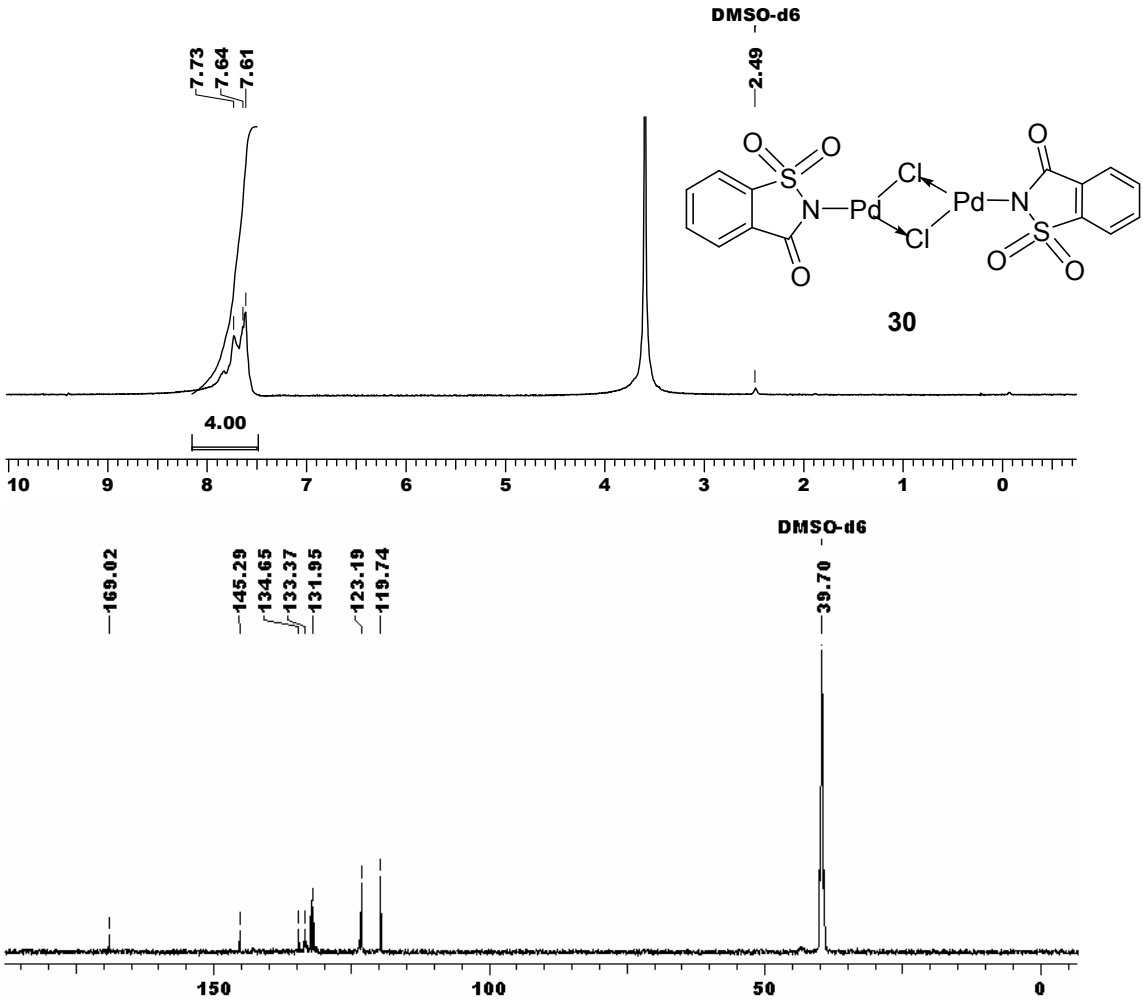


Fig. 2: ^{1}H and ^{13}C NMR spectra of palladium complex 30

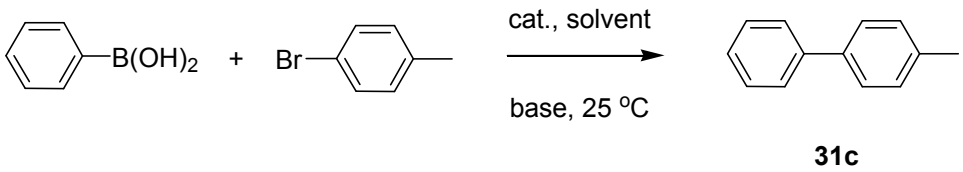
4.1.4.3 Catalytic activity studies of Pd-catalysts (21-30)

A. Catalytic Suzuki cross-coupling reactions

The catalytic activity of palladacycles **21-30** for C-C bond forming reactions was evaluated systematically. Initially, we have conducted experiments for Suzuki coupling

of 4-bromotoluene with phenylboronic acid using palladium complexes, **21-30,** and the results are summarized in Table **1**.

Table 1. Suzuki coupling of 4-bromotoluene with phenylboronic acid: Screening of palladium complexes[a]



31c

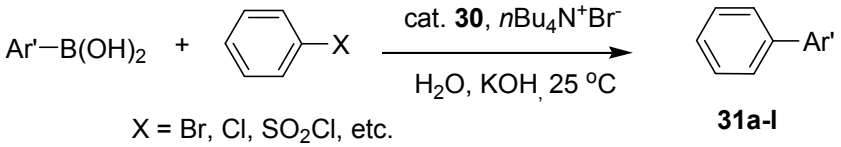
Entry	Pd-cat.	Solvent	Base	Yield of **31c** (%)[b]	TON[c]
1	**21**	toluene	K_2CO_3	76	76000
2	**21**	water	K_2CO_3	60	60000
3	**22**	toluene	K_2CO_3	75	75000
4	**23**	toluene	K_2CO_3	72	72000
5	**24**	toluene	K_2CO_3	59	59000
6	**25**	toluene	K_2CO_3	54	54000
7	**26**	water	KOH	73	73000
8	**26**	toluene	K_2CO_3	93	93000
9	**27**	toluene	K_2CO_3	92	92000
10	**28**	toluene	K_2CO_3	89	89000
11	**29**	toluene	K_2CO_3	90	90000
12	**30**	toluene	K_2CO_3	93	93000
13	**30**	water	KOH	95	95000

[a] Conditions: 4-bromotoluene (5 mmol), phenylboronic acid (7.5 mmol), base (10 mmol), palladium catalyst ($5x10^{-5}$ mmol), solvent (15 mL), 25 °C, 3 h. [b] isolated yields after chromatographic purification. [c] TON = mmol of product/ mmol of Pd.

Among the bases (K_2CO_3, KO^tBu, KOH and Cs_2CO_3) screened, KOH gave the best yield. From table 1, we found that palladium complex **30** showed the highest catalytic activity in terms of yield (95%) and TON (95000), when water was used as solvent. However,

sulfilimine and sulfoxide-based palladacycles (**21-25)** were generally found to show low catalytic activity in the coupling reaction resulting in moderate yields (54-76%).

Table 2: Suzuki coupling of aryl halides with arylboronic acids catalyzed by 30[a]



Entry	Ar'	ArX	Biaryl Product	Yield (%)[b]
1	Ph	4-Bromoanisole	**31a**	81
2	Ph	2-Bromoanisole	**31b**	78
3	Ph	4-Bromotoluene	**31c**	95
4	Ph	1-Bromo-4-fluorobenzene	**31d**	90
5	Ph	Bromobenzene	**31e**	96
6	Ph	2-Bromonaphthalene	**31f**	89
7	Ph	3-Bromobenzotrifluoride	**31g**	90
8	Ph	4-Chloroacetophenone[c]	**31h**	78
9	Ph	2-Nitrochlorobenzene[c]	**31i**	75
10	Ph	4-Toluenesulfonyl chloride	**31c**	80
11	Ph	Benzenesulfonyl chloride	**31e**	78
12	4-Acetyl Ph	Bromobenzene	**31h**	71
13	3-Chloro Ph	4-Nitrobromobenzene	**31j**	78
14	3-Chloro Ph	4-Bromotoluene	**31k**	71
15	3-Chloro Ph	Bromobenzene	**31l**	86
16	2-Naphthyl	Bromobenzene	**31f**	81

[a] Reaction conditions: aryl halide (5 mmol), phenylboronic acid (7.5 mmol), KOH (10 mmol), palladium catalyst **30** ($5x10^{-5}$ mmol), tetrabutylammonium bromide (5 mmol), water (15 mL), 25 ^{o}C , 3 h. [b] Isolated yields after chromatographic purification. [c] Reaction was carried out at 100 ^{o}C.

Substrate scope for Suzuki coupling using Pd-catalyst **30** was evaluated by taking aryl bromides and boronic acids as coupling partners. Under the optimized conditions (KOH,

TBAB, H_2O), various activated and unactivated aryl bromides underwent coupling successfully with wide range of phenylboronic acids with water as the solvent (Table **2**).

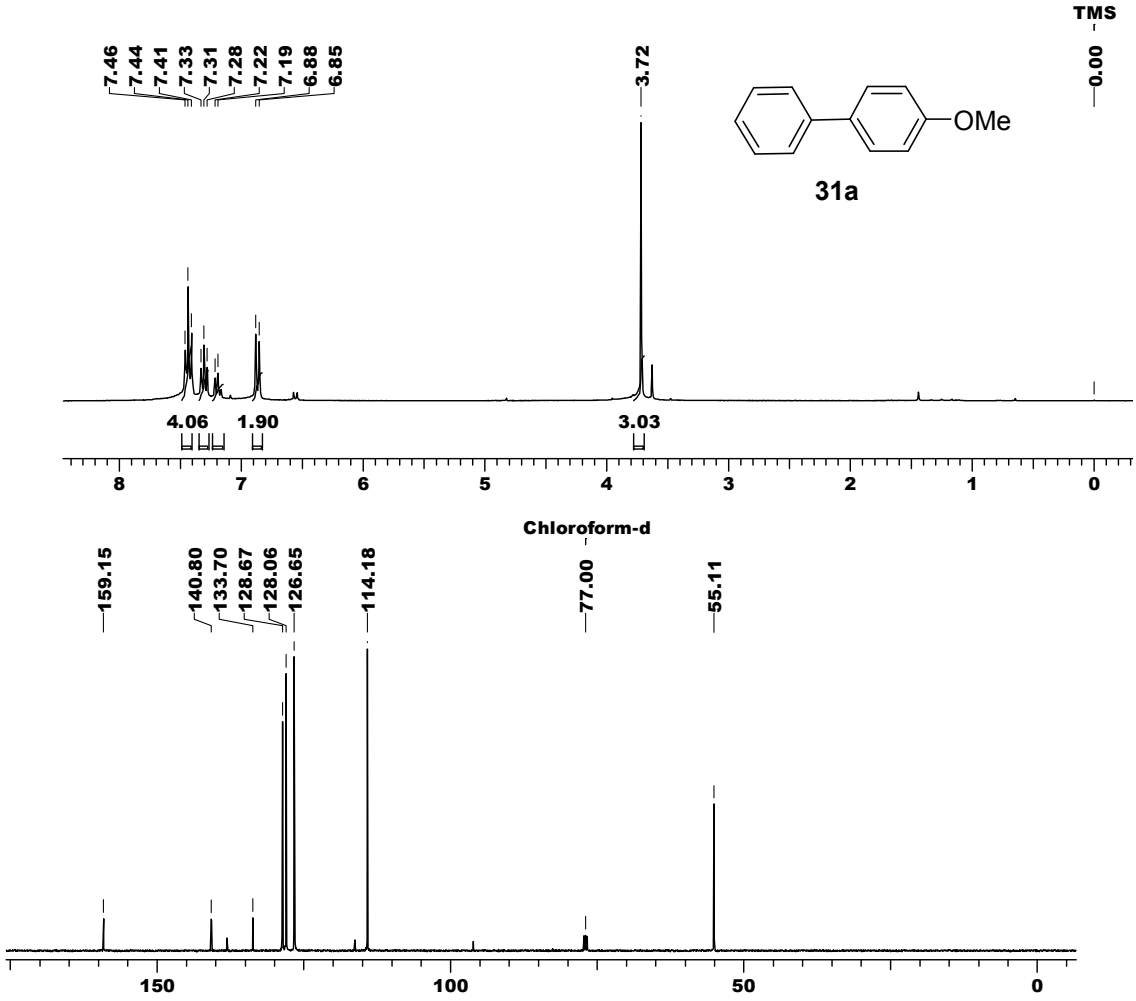


Fig. 3: ^{1}H and ^{13}C NMR spectra of 4-Methoxybiphenyl (31a)

It is remarkable that good yields of biaryls were obtained for the aryl chlorides having electron-withdrawing groups like acyl and nitro (entry 8 and 9). The coupling of 4-chloroacetophenone with phenylboronic acid gave the corresponding biphenyl **31h** in 78% with a TON of 78,000. As a representative example, the ^{1}H NMR spectrum of biphenyl **31a** is shown in (**Fig. 3**); which showed a singlet at δ 3.72 for Ar-O**CH$_3$** protons. Its ^{13}C NMR spectrum showed characteristic signal at δ 55.1 due to Ar-O**C**H$_3$ carbon.

B. Catalytic Heck Arylation Reaction

A variety of aryl bromides and olefins were subjected to the Heck reaction using Pd-complex **30** and the results are shown in Table **3**. For both activated and unactivated aryl bromides, excellent conversions were obtained within 6 h. However, in the case of activated aryl chlorides (entries 14 & 15; Table **3**) only a moderate yield was realized. For example, the ^{1}H NMR spectrum of **32a** showed a singlet at δ 2.5 for Ar-**C**$\mathbf{H_3}$ protons. Its ^{13}C NMR spectrum showed characteristic signals at δ 127.3 and 127.8 due to olefinic carbons (**Fig. 4**).

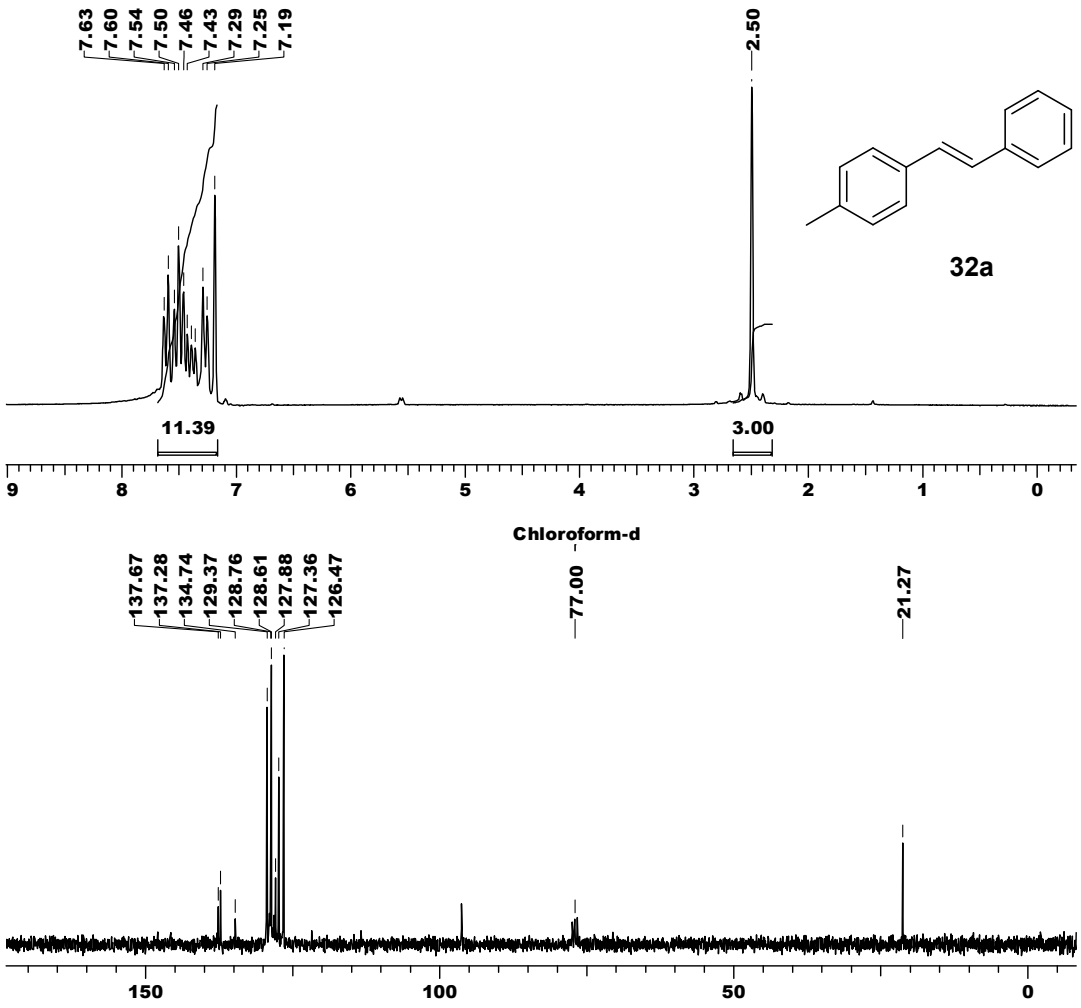
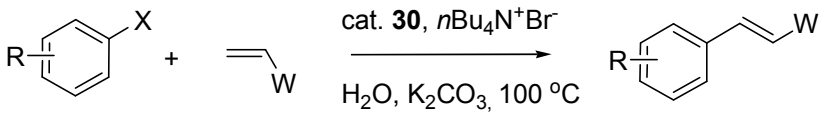


Fig. 4: ^{1}H and ^{13}C NMR spectra of 1-(4-Methylphenyl)-2-phenylethylene (32a)

Table 3: Heck reaction between aryl halides and olefinic substrates catalyzed by 30[a]



X = I, Br, Cl

W = CO_2R, Ph, etc.

32a-o

Entry	ArX	W	Product	Yield (%)[b]
1	4-Bromotoluene	Ph	**32a**	86
2	1-Bromonaphthalene	CO_2Me	**32b**	89
3	1-Bromonaphthalene	$CO_2{}^nBu$	**32c**	81
4	3-Bromobenzotrifluoride	$CO_2{}^nBu$	**32d**	94
5	3-Bromobenzotrifluoride	CO_2Et	**32e**	95
6	Bromobenzene	$CO_2{}^nBu$	**32f**	95
7	Bromobenzene	CO_2Me	**32g**	96
8	Bromobenzene	Ph	**32h**	94
9	Bromobenzene	CN	**32i**	88
10	1-Bromo-4-nitrobenzene	CO_2Et	**32j**	96
11	4-Bromoanisole	CO_2Et	**32k**	78
12	4-Bromoanisole	Ph	**32l**	81
13	2-Bromo-6-methoxynaphthalene	$CO_2{}^nBu$	**32m**	87
14	4-Chloronitrobenzene	CO_2Et	**32n**	45
15	4-Chloronitrobenzene	Ph	**32o**	56

[a] Reaction conditions: aryl halide (2 mmol), olefin (3 mmol), K_2CO_3 (4 mmol), palladium complex **30** ($5x10^{-6}$ mmol), tetrabutylammonium bromide (2 mmol), water (6 mL), 100 °C, 6 h. [b] Isolated yields after chromatographic purification.

C. Catalytic Sonogashira coupling reactions

In order to reduce the amount of diacetylene formation in the Sonogashira reaction, various copper-free conditions have recently been developed. The effectiveness of Pd-catalyst **30** for Sonogashira coupling reactions under totally copper-free conditions using

water in the presence of KOH was evaluated (Table **4**). Excellent yields of acetylenic compounds were obtained for the aryl iodides, although the Pd-catalysts have shown only the moderate activity for aryl bromides as well as chlorides. The ^{1}H NMR spectrum of **33c** showed a singlet at δ 2.46 for Ar-CH_3 protons. Its ^{13}C NMR spectrum showed characteristic signals at δ 88.8 and 89.6 due to acetylenic carbons (**Fig. 5**).

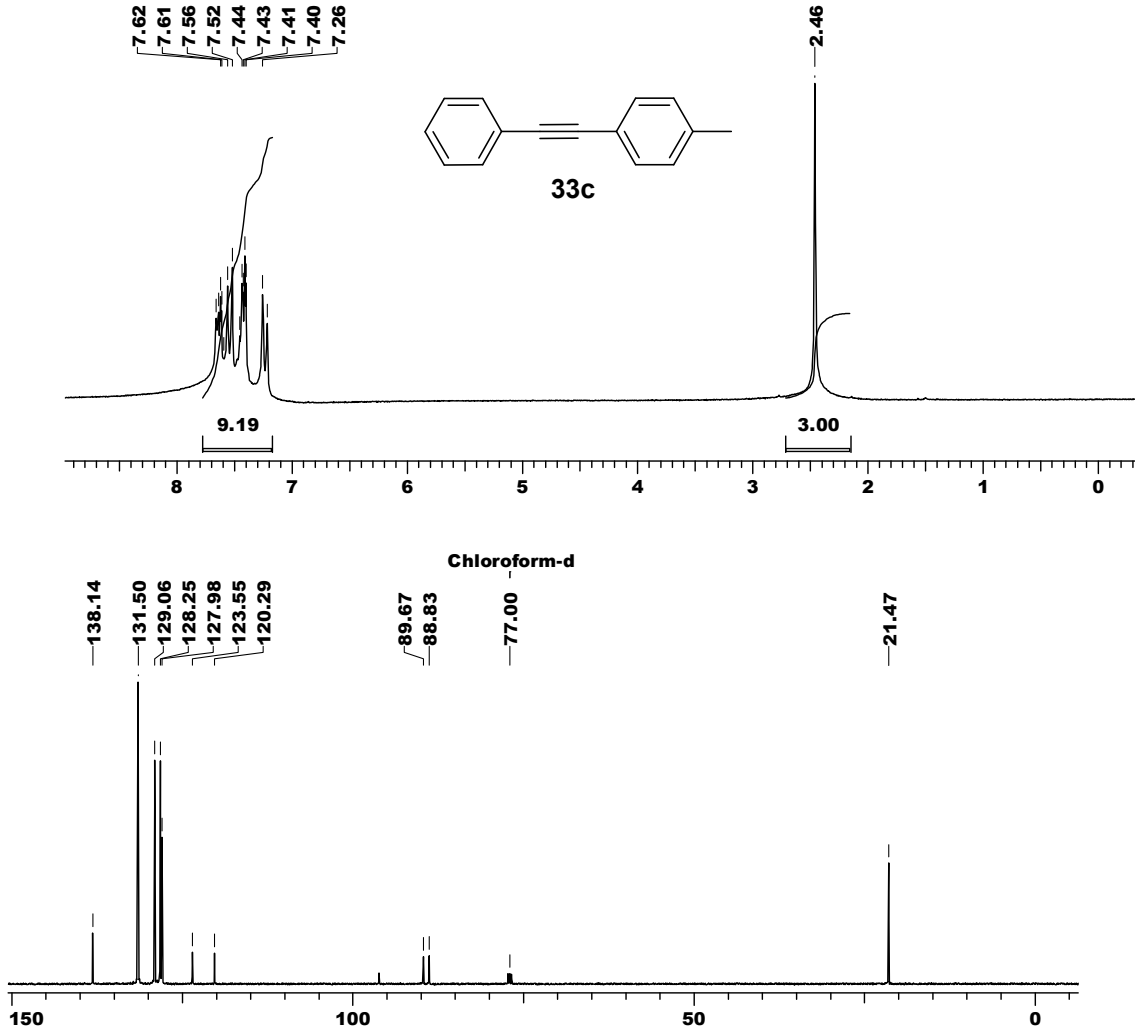
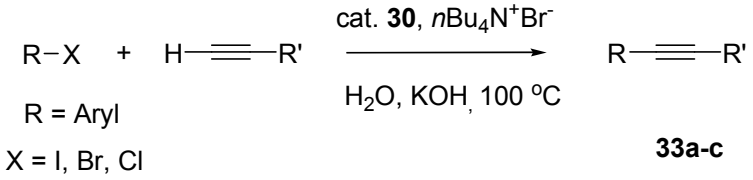


Fig. 5: ^{1}H and ^{13}C NMR spectra of 1-methyl-4-(2-phenylethynyl)benzene (33c)

Table 4: Sonogashira coupling catalyzed by water-soluble saccharin Pd-complex 30[a]



Entry	Aryl halides (Ar-X)	Alkynes (R')	Product	Yield (%)[b]
1	C_6H_5I	C_6H_5	**33a**	90
2	4-$O_2NC_6H_4I$	C_6H_5	**33b**	93
3	C_6H_5Br	C_6H_5	**33a**	70
4	C_6H_5Br	4-MeC_6H_4	**33c**	66
5	4-$O_2NC_6H_4Br$	C_6H_5	**33b**	72
6	4-MeC_6H_4Br	C_6H_5	**33c**	57
7	C_6H_5Cl	C_6H_5	**33c**	20

[a] Reaction conditions: aryl halide (5 mmol), alkyne (7.5 mmol), KOH (10 mmol), tetrabutylammonium bromide (5 mmol), water (15 mL), palladium complex **30** ($5x10^{-4}$ mmol), 100 °C, 6 h. [b] Isolated yields after chromatographic purification.

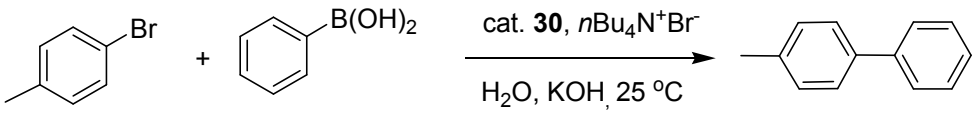
D. Reusability study of the catalyst 30

In order to make the process economically viable, recovery and recycling of the Pd-catalyst becomes necessary. We have thus studied the reusability of Pd-catalyst **30** for Suzuki coupling of 4-bromotoluene with phenylboronic acid under optimized condition (Table **5**).

In the first cycle the coupling product **31c** was obtained with the yield of 95%. After the product was separated by extracting with diethyl ether, a fresh batch of new starting material was added to aqueous layer that contained the palladium catalyst from the first reaction. After stirring for 3 h, the mixture produced the coupling product with the yield

of 95% in the second cycle. Similarly, the third cycle afforded a yield of 93% and the fourth 90% yield.

Table 5: Reusability study of the palladium complex 30 for the Suzuki coupling of 4-bromotoluene with phenylboronic acid[a]



31c

Entry	Reaction cycle	Yield of **31c** (%)[b]
1	1	95
2	2	95
3	3	93
4	4	90
5	5	88

[a] Reaction conditions: aryl halide (5 mmol), phenylboronic acid (7.5 mmol), KOH (10 mmol), palladium catalyst **30** ($5x10^{-5}$ mmol), tetrabutylammonium bromide (5 mmol), water (15 mL), 25 ^{o}C , 3 h. [b] Isolated yields after chromatographic purification.

The X-ray photoelectron spectroscopy (XPS) analysis of the recovered Pd-catalyst (30) and the fresh Pd-catalyst (30) shows that the binding energy of $3d_{5/2}$ orbital of recovered catalyst (336.1 eV) was very close with the $3d_{5/2}$ orbital of Pd(0) reported in the literature (335.3 eV) (Fig. 6). In these reaction conditions, the oxidation state of Pd-catalyst (30) was converted into Pd(II) to Pd(0). The high activity of Pd-catalyst was due to active Pd(0) species, which was formed in the course of the reaction. The transmission electron microscope (TEM) measurement for the aqueous medium of the Suzuki reaction (**Fig. 7**) confirmed the presence of Pd(0) nanoparticles of spherical morphology varying in diameter from 10 to 12 nm.

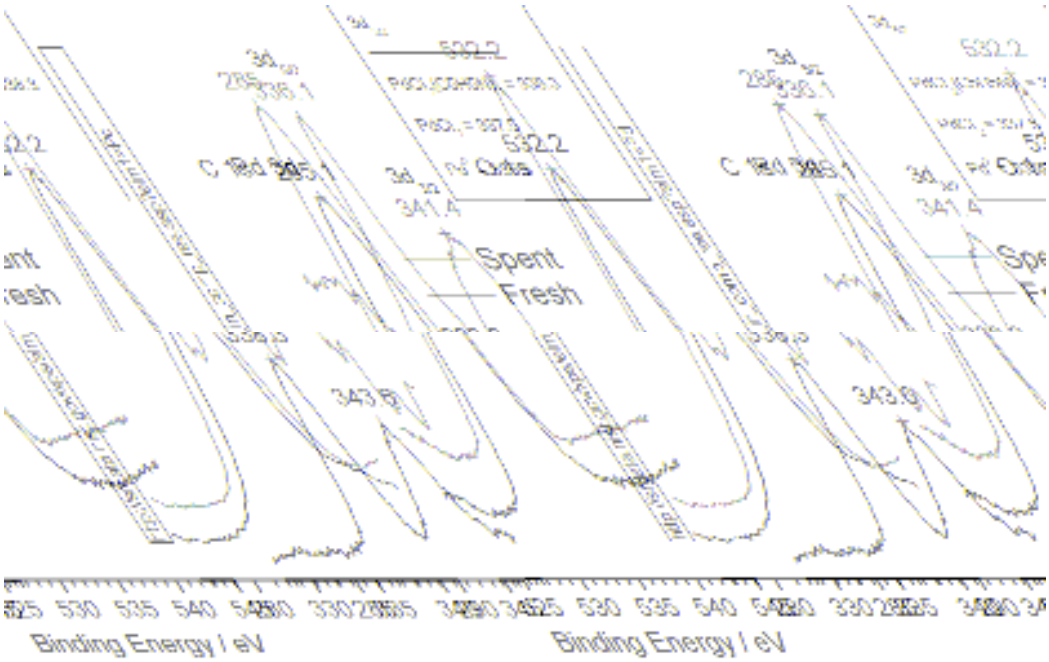


Fig. 6: ESCA of palladium-catalyst **30**

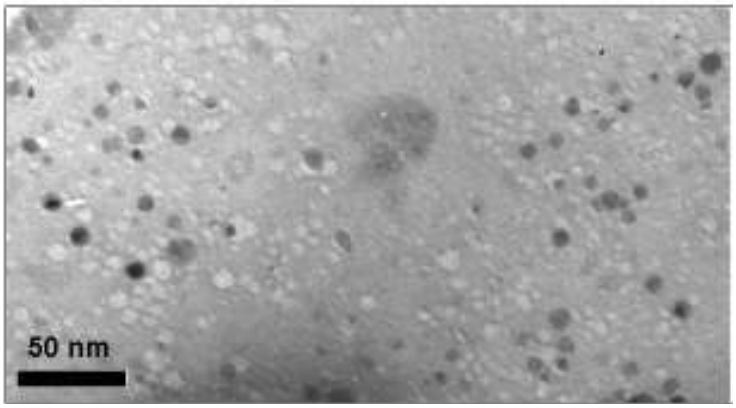


Fig. 7: TEM image of Pd nanoparticles of Pd-catalyst **30** in aqueous medium.

Mechanism

The mechanism of Heck reactions involves the mediation of Pd^0 and Pd^{II} species. The mechanism for the Heck reaction is shown in **Fig. 8**. In the first step of catalytic cycle (step **I**) haloarene oxidatively add to palladacycle to generate Pd^{II} species. This then

undergoes *syn*-addition on alkene (step **II**). The internal rotation (step **III**) followed by *β*-hydride elimination (step **IV**) results in formation of *trans*-1,2-disubstituted olefin. The catalyst is regenerated after the reductive elimination of HX in presence of base.

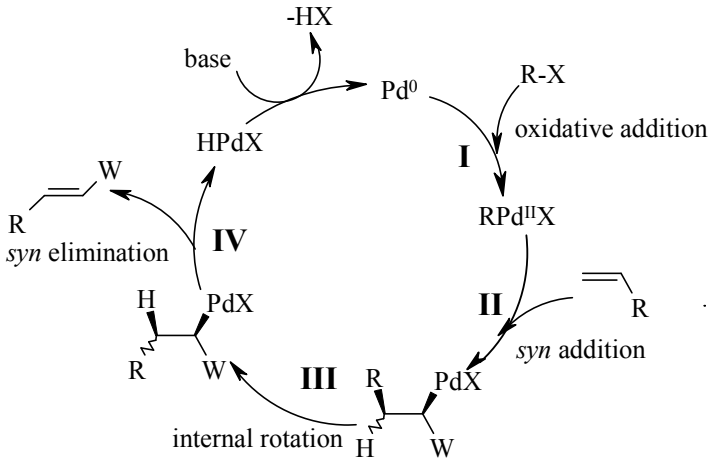


Fig. 8: **Catalytic cycle for the Heck reaction**

4.1.5 Conclusion

In summary, syntheses of a novel family of sulfonamide-based palladium complexes (**25-30**) and sulfilimine and sulfoxide-based palladacycles (**20-25)** have been achieved from easily available precursors. These novel Pd-catalysts are air, moisture-stable and some are completely soluble in water (Pd-catalyst **30**), and used for C-C bond forming reactions like Suzuki, Heck and Sonogashira coupling using aryl halides (X = I, Br, Cl). All the reactions in aqueous media and totally phosphine-free conditions are some of the salient features of this study. Other advantages include the easy separation and reusability of the Pd catalyst (**30**) for several times without loss of catalytic activity. The stability of these palladium catalysts against moisture, temperature and the fact that they can be synthesized from inexpensive starting materials render them as promising catalysts.

4.1.6. Experimental Section

Preparation of Sulfilimine Palladacycles (21-24):

To a stirred mixture of LiCl (0.100 g, 2.4 mmol) in MeOH (2 mL) was added $PdCl_2$ (0.177 g, 1 mmol) at 25 °C. After 2.5 h, a solution of NaOAc (0.123 g, 1.5 mmol) and sulfilimine (1 mmol) in MeOH (2 mL) was added to the reaction mixture. The resulting reaction mixture was stirred at 25 °C for 72 h. Then, distilled water (6 mL) was added to it and the resulting precipitate was filtered on sintered funnel, washed with water and dried under reduced pressure (5 mm) for 3 h to afford palladacycles **21-24** as brown colored solids.

Palladacycle 21: Yield: 0.143 g (66%); **mp**: 135-141 °C (decomp.); **IR** (KBr, cm^{-1}): 547, 576, 688, 746, 825, 933, 1087, 1141, 1280, 1296, 1446, 1539, 1595, 2866, 2922, 3024; **^{1}H NMR** (200 MHz, DMSO-d_6): δ 2.32 (s, 3H), 2.95 (s, 3H), 7.23 (d, J = 8.1 Hz, 2H), 7.60-7.78 (m, 6H); **^{13}C NMR** (50 MHz, DMSO-d_6): δ 20.8, 37.4, 125.7, 126.1, 129.2, 129.8, 132.2, 136.2, 141.2, 141.3; **Analysis: $C_{14}H_{14}ClNS_2O_2Pd$** requires C, 38.70; H, 3.25; Cl, 8.17; N, 3.23; S, 14.77; found C, 38.68; H, 3.50; Cl, 8.24; N, 3.34; S, 14.77%.

Palladacycle 22: **Yield:** 0.161 g (70%); **mp**: 96-98 °C (decomp.); **IR** (KBr, cm^{-1}): 568, 765, 948, 1089, 1145, 1280, 1352, 1601, 1827, 2576, 3419; **^{1}H NMR** (200 MHz, DMSO-d_6): δ 1.00 (dd, J = 6.3, 20.1 Hz, 6H), 2.30 (s, 3H), 3.37 (bs, 1H), 7.23 (bs, 2H), 7.60 (bs, 4H), 7.73-7.75 (bs, 2H); **^{13}C NMR** (50 MHz, DMSO-d_6): δ 14.8, 16.4, 20.7, 52.8, 125.7, 126.6, 129.0, 129.5, 131.9, 141.5; **Analysis: $C_{16}H_{18}ClNS_2O_2Pd$** requires C, 41.55; H, 3.93; Cl, 7.67; N, 3.03; S, 13.88; found C, 41.39; H, 3.40; Cl, 7.45; N, 3.34; S, 13.94%.

Palladacycle 23: Yield: 0.134 g (60%); **mp:** 78-80 °C (decomp.); **IR** (KBr, cm^{-1}): 573, 665, 762, 813, 942, 1087, 1145, 1279, 1350, 1401, 1493, 1595, 2922, 3428; **^{1}H NMR** (200 MHz, DMSO-d_6): δ 2.32 (s, 3H), 2.35 (s, 3H), 2.91 (s, 3H), 7.23-7.40 (m, 3H), 7.57-7.69 (m, 4H); **^{13}C NMR** (50 MHz, DMSO-d_6): δ 20.7, 37.2, 125.6, 126.0, 129.1, 130.1, 133.0, 141.0, 141.6, 142.4; **Analysis: $C_{15}H_{16}ClNS_2O_2Pd$** requires C, 40.17; H, 3.6; Cl, 7.91; N, 3.13; S, 14.31; found C, 40.41; H, 3.50; Cl, 8.04; N, 3.34; S, 14.47%.

Palladacycle 24: Yield: 0.148 g (55%); **mp**: 156-159 °C (decomp.); **IR** (KBr, cm^{-1}): 553, 570, 755, 809, 882, 915, 964, 1087, 1139, 1282, 1454, 1493, 1599, 1916, 2581, 2859, 2937, 3626**; ^{1}H NMR** (200 MHz, DMSO-d_6): δ 2.27 (s, 3H), 2.35 (s, 3H), 4.37-4.54 (m, 2H), 7.05-7.66 (m, 12H); **^{13}C NMR** (50 MHz, DMSO-d_6): δ 20.7, 20.7, 56.8, 125.3, 126.5, 128.2, 128.5, 128.6, 128.9, 130.0, 130.8, 131.3, 140.6, 141.2, 142.5; **Analysis: $C_{21}H_{20}ClNS_2O_2Pd$** requires C, 48.83; H, 3.75; Cl, 6.59; N, 2.60; S, 11.93; found C, 48.68; H, 3.59; Cl, 6.54; N, 2.84; S, 12.14%.

Preparation of Sulfoxide Palladacycle 25:

To a stirred mixture of LiCl (0.100 g, 2.4 mmol) in MeOH (2 mL) was added $PdCl_2$ (0.177 g, 1 mmol) at 25 °C. After 2.5 h, a solution of NaOAc (0.123 g, 1.5 mmol) and phenyl benzyl sulfoxide (0.216 g, 1 mmol) in MeOH (2 mL) was added to the reaction mixture. The stirring was continued at 25 °C for 72 h (monitored by TLC). Then distilled water (8 mL) was added to the reaction mixture, which resulted in precipitation of yellow colored solid. The solid was filtered on a sintered funnel, washed with distilled water and dried under reduced pressure (5 mm) for 3 h to afford palladacycle **25** as yellow colored solid.

Yield: 0.129 g (72%); **mp**: 143-146 °C (decomp.); **IR** (KBr, cm^{-1}): 495, 694, 744, 765, 1037, 1085, 1442, 1456, 1494, 2910, 2960, 3060; **^{1}H NMR** (200 MHz, DMSO-d_6): δ 4.06 (d, *J* = 12.2 Hz, 1H), 4.25 (d, *J* = 12.2 Hz, 1H), 7.08-7.51 (m, 9H); **^{13}C NMR** (50 MHz, DMSO-d_6): δ 61.7, 124.3, 127.8, 128.1, 128.9, 130.4, 130.9, 143.5; **Analysis:** **$C_{13}H_{11}ClSOPd$** requires C, 43.70; H, 3.11; Cl, 9.93; S, 8.98; found C, 43.42; H, 3.13; Cl, 9.88; S, 8.89%.

Preparation of Sulfonamide palladium complexes (26-29):

To a stirred mixture of LiCl (0.1 g, 2.4 mmol) in MeOH (2 mL) was added $PdCl_2$ (0.177 g, 1 mmol) at 25 °C. After 2.5 h, a solution of NaOAc (0.123 g, 1.5 mmol) and 4-methylsulfonamide (0.171 g, 1 mmol) in MeOH (2 mL) was added to the reaction mixture. The resulting reaction mixture was stirred at 25 °C for 24 h. Then, distilled water (6 mL) was added to it and the resulting precipitate was filtered on a sintered funnel, washed with water and dried under reduced pressure (5 mm of Hg) for 3 h to afford palladium complexes **26** as yellow colored solid (0.256 g, 82%).

Palladium complex 26: Yield: 0.256 g (82%); pale-yellow solid; **mp**: 195-198 °C (decomp.); **IR** (KBr, cm^{-1}): 559, 721, 813, 1083, 1157, 1305, 1340, 1377, 1463, 1521, 2358, 2675, 2727, 2852, 2916; **^{1}H NMR** (200 MHz, DMSO-d_6): δ 2.19 (s, 3H), 7.11-7.19 (m, 2H), 7.54-7.55 (m, 2H); **^{13}C NMR** (50 MHz, DMSO-d_6): δ 21.1, 125.4, 129.5, 141.5, 142.1; **Analysis: $C_{14}H_{16}Cl_2N_2O_4Pd_2S_2$** requires C, 26.92; H, 2.58; Cl, 11.36; N, 4.48; S, 10.27; found C, 26.88; H, 2.45; Cl, 11.54; N, 4.55; S, 10.19%.

Palladium complex 27: Yield: 0.256 g (78%); pale-yellow solid; **mp**: 198-201 °C (decomp.); **IR** (KBr, cm^{-1}): 561, 680, 721, 804, 1022, 1085, 1153, 1261, 1301, 1375, 1456, 1538, 1652, 1683, 2673, 2852, 2923; **^{1}H NMR** (200 MHz, DMSO-d_6): δ 3.75 (s,

3H), 7.01-7.12 (m, 2H), 7.79-7.82 (m, 2H); **^{13}C NMR** (50 MHz, DMSO-d_6): δ 55.9, 114.4, 128.0, 136.2, 162.0; **Analysis: $C_{14}H_{16}Cl_2N_2O_6Pd_2S_2$** requires C, 25.61; H, 2.46; Cl, 10.81; N, 4.27; S, 9.78; found C, 26.75; H, 2.35; Cl, 10.97; N, 4.23; S, 9.87%.

Palladium complex 28: Yield: 0.238 g (76%); pale-yellow solid **mp**: 305-308 °C (decomp.)**; IR** (KBr, cm^{-1}): 559, 678, 721, 891, 1087, 1151, 1313, 1375, 1456, 1506, 1558, 1652, 1683, 1733, 2671, 2854, 2923; **^{1}H NMR** (200 MHz, DMSO-d_6): δ 6.72-6.84 (m, 2H), 7.63-7.78 (m, 2H). **^{13}C NMR** (50 MHz, DMSO-d_6): δ 112.9, 127.8, 130.3, 152.3; **Analysis: $C_{12}H_{14}Cl_2N_4O_4Pd_2S_2$** requires C, 23.00; H, 2.25; Cl, 11.33; N, 8.95; S, 10.24; found C, 23.25; H, 2.17; Cl, 11.21; N, 8.74; S, 10.44%.

Palladium complex 29: Yield: 0.235 g (72%); pale-yellow solid; **mp**: 220-223 °C (decomp.); **IR** (KBr, cm^{-1}): 721, 1130, 1149, 1168, 1317, 1340, 1377, 1456, 1463, 1558, 1652, 1683, 2852, 2923, 2954; **^{1}H NMR** (200 MHz, acetone-d_6): δ 2.25 (s, 3H), 2.58 (s, 3H), 6.59-7.76 (m, 3H); **^{13}C NMR** (50 MHz, acetone-d_6): δ 20.0, 20.9, 127.0, 128.2, 133.4, 136.8, 139.7, 143.1; **Analysis: $C_{16}H_{20}Cl_2N_2O_4Pd_2S_2$** requires C, 29.44; H, 3.09; Cl, 10.87; N, 4.30; S, 9.84; found C, 29.66; H, 2.98; Cl, 10.74; N, 4.45; S, 9.72%.

Preparation of Saccharin palladium complex 30:

To a stirred mixture of LiCl (0.1 g, 2.4 mmol) in MeOH (2 mL) was added $PdCl_2$ (0.177 g, 1 mmol) at 25 °C. After 2.5 h, a solution of NaOAc (0.123 g, 1.5 mmol) and saccharin (0.183 g, 1 mmol) in MeOH (2 mL) was added to the reaction mixture. The resulting reaction mixture was stirred at 25 °C for 6 h. Then, the resulting precipitate was filtered on a sintered funnel, dried under reduced pressure (5 mm of Hg) for 3 h to afford palladium complex **30** as yellow colored solid (0.275 g, 85%).

Yield: 0.275 g (85%); pale-yellow solid; **mp**: 237-240 °C (decomp.); **IR** (KBr, cm^{-1}): 594, 756, 984, 1154, 1287, 1287, 1456, 1664, 1951, 3590; **^{1}H NMR** (200 MHz, DMSO-d_6): δ 7.61-7.73 (m, 4H); **^{13}C NMR** (50 MHz, DMSO-d_6): δ 119.7, 123.1, 131.9, 133.3, 134.6, 145.2, 169.0; **Analysis:** **$C_{14}H_8Cl_2N_2O_6Pd_2S_2$** requires C, 25.93; H, 1.24; Cl, 10.94; N, 4.32; S, 9.9; found C, 25.87; H, 1.40; Cl, 11.05; N, 4.15; S, 9.78%.

General Procedure for Suzuki Coupling:

To a stirred mixture aryl halide (5.0 mmol), arylboronic acid (7.5 mmol), KOH (0.58 g, 10 mmol), tetrabutylammonium bromide (1.612 g, 5 mmol) in water (15 mL) was added palladium complex **30** (0.03 mg, $5x10^{-5}$ mmol) at 25 °C at specified time (Table **2**) (the progress of the reaction was monitored by TLC). After the specified time, the product was isolated by extraction with dichloromethane (3 x 25 mL). The combined organic extracts were washed with brine and dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to afford the crude product. The crude product was then purified by column chromatography on silica gel using pet. ether and ethyl acetate as eluent to afford biphenyls (**31a-l**).

4-Methoxybiphenyl (31a): **Yield**: 0.745 g (81%); colorless solid; **mp**: 87 °C [lit.[47] 86-87 °C]; **IR** ($CHCl_3$, cm^{-1}): 566, 703, 776, 845, 1051, 1130, 1198, 1304, 1414, 1462, 1530, 1615, 2917, 2970, 3065; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.72 (s, 3H), 6.85-7.46 (m, 9H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 55.1, 114.1, 126.6, 128.0, 128.6, 133.7, 140.8, 159.1; **MS** (m/z, % relative intensity): 184 (M^+**,** 100), 169 (44), 141 (38), 115 (26), 63 (4); **Analysis:** **$C_{13}H_{12}O$** requires C, 84.75; H, 6.56; found C, 84.55; H, 6.81%.

2-Methoxybiphenyl (31b): **Yield:** 0.718 g (78%); viscous liquid; **IR** ($CHCl_3$, cm^{-1}): 565, 612, 667, 698, 732, 753, 800, 1028, 1055, 1122, 1236, 1259, 1463, 1504, 1597, 2834,

2956, 3011, 3061; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.71 (s, 3H), 6.75-7.49 (m, 9H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 55.3, 111.3, 120.8, 121.6, 126.6, 127.7, 128.4, 128.5, 129.4, 130.7, 133.2, 138.6, 156.4; **Analysis: $C_{13}H_{12}O$** requires C, 84.75; H, 6.57; found C, 84.85; H, 6.49%.

4-Methylbiphenyl (31c): **Yield**: 0.798 g (95%); viscous liquid; **IR** ($CHCl_3$, cm^{-1}): 546, 667, 760, 822, 1038, 1352, 1598, 1907, 2589, 3065; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.36 (s, 3H), δ 7.20-7.57 (m, 9H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.1, 126.8, 126.9, 127.1, 128.7, 129.4, 136.8, 138.4, 141.2; **MS** (m/z, % relative intensity): 168 (M^+**,** 100), 167 (68), 165 (22), 152 (20), 115 (6); **Analysis: $C_{13}H_{12}$** requires C, 92.81; H, 7.19; found C, 92.64; H, 7.40%.

4-Fluorobiphenyl (31d): Yield: 0.774 g (90%); **mp:** 76 ºC; **IR** (nujol, cm^{-1}): 667, 761, 836, 907, 1007, 1105, 1164, 1264, 1351, 1394, 1451, 1594, 1893, 2559, 2853, 2923, 3062; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.15-7.59 (m, 9H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 115.4, 115.6, 126.9, 127.2, 128.6, 128.6, 128.7, 137.3, 140.2, 161.5, 163.4; **Analysis**: **$C_{12}H_9F$** requires C, 83.7; H, 5.27; found C, 83.52; H, 5.55%.

Biphenyl (31e): **Yield**: 0.739 g (96%); **mp**: 71-72 °C; **IR** (Nujol, cm^{-1}): 698, 734, 1008, 1074, 1261, 1377, 1431, 1463, 1481, 1568, 2854, 2923, 2954; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.37-7.47 (m, 10H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 126.7, 126.8, 128.3, 140.8; **Analysis**: **$C_{12}H_{10}$** requires C, 93.46; H, 6.54; found C, 93.43; H, 6.52%.

2-Phenylnaphthalene (31f): **Yield**: 0.908 g (89%); colorless solid; **mp**: 105 °C; **IR** ($CHCl_3$, cm^{-1}): 668, 688, 758, 770, 820, 860, 892, 1076, 1216, 1452, 1496, 1598, 1948, 3106, 3058; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.40-8.27 (m, 12H); **^{13}C NMR** (50 MHz,

$CDCl_3$): δ 125.3, 125.7, 125.9, 126.0, 126.9, 127.1, 127.6, 128.2, 130.0, 131.6, 133.8, 140.2, 140.8; **Analysis: $C_{16}H_{12}$** requires C, 94.08; H, 5.92; found C, 94.29; H, 5.70%.

3-Trifluoromethylbiphenyl (31g): **Yield**: 0.999 g (90%); viscous liquid; **IR** ($CHCl_3$, cm^{-1}): 615, 659, 701, 758, 805, 899, 1022, 1097, 1166, 1261, 1424, 1456, 1483, 1593, 2927, 3037, 3063; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.57-8.01 (m, 9H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 123.9, 127.2, 128.0, 129.2, 130.3, 139.8, 142.2; **Analysis: $C_{13}H_9F_3$** requires C, 70.27; H, 4.08; found C, 70.15; H, 3.95%.

1-Biphenyl-4-yl-ethanone (31h): **Yield**: 0.764 g (78%); colorless solid; **mp**: 118 °C; **IR** ($CHCl_3$, cm^{-1}): 595, 668, 697, 756, 1007, 1216, 1267, 1358, 1604, 1680, 3019; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.59 (s, 3H), 7.40-7.47 (m, 3H), 7.56-7.65 (m, 4H), 7.97-8.01 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 26.3, 127.0, 128.0, 128.7, 135.6, 139.6, 145.4, 196.8; **MS** (m/z, % relative intensity): 196 (M^+, 51), 181 (100), 153 (33), 152 (51), 76 (13), 43 (4); **Analysis: $C_{14}H_{12}O$** requires C, 85.68; H, 6.16; found C, 85.59; H, 6.42%.

2-Nitrobiphenyl (31i): **Yield**: 0.746 g (75%); viscous liquid; **IR** ($CHCl_3$, cm^{-1}): 515, 666, 698, 740, 771, 782, 833, 1355, 1473, 1525, 1561, 1606, 2868, 2927, 3032, 3063; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.35-7.63 (m, 8H), 7.84-7.88 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 123.8, 127.8, 128.0, 128.1, 128.5, 131.8, 132.0, 132.9, 136.2, 137.4, 149.4; **Analysis: $C_{12}H_9NO_2$** requires C, 72.35; H, 4.55; N, 7.03; found C, 72.49; H, 4.37; N, 6.89%.

3-Chloro-4'-nitrobiphenyl (31j): **Yield**: 0.909 g (78%); yellow solid; **mp**: 91 °C [lit.[48] 89 °C]; **IR** (nujol, cm^{-1}): 574, 684, 704, 750, 786, 856, 1350, 1514, 1524, 1568, 1592, 1814, 3074; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 6.78-7.67 (m, 8H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 124.1, 125.4, 127.5, 127.7, 128.8, 130.3, 135.2, 140.5, 145.9, 147.5; **Analysis:**

$C_{12}H_8ClNO_2$ requires C, 61.69; H, 3.45; Cl, 15.17; N, 5.99; found C, 61.82; H, 3.65; Cl, 15.37; N, 6.21%.

4-Methyl-3'-chlorobiphenyl (31k): **Yield**: 0.72 g (71%); viscous liquid; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.45 (s, 3H), 7.26-7.60 (m, 8H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.2, 125.0, 126.9, 127.1, 129.6, 129.9, 134.7, 137.0, 137.5, 143.0; **Analysis: $C_{13}H_{11}Cl$** requires C, 77.04; H, 5.47; found C, 77.09; H, 5.47%.

3-Chlorobiphenyl (31l): **Yield**: 0.811 g (86%); colorless liquid; **IR** ($CHCl_3$, cm^{-1}): 523, 624, 766, 803, 892, 1014, 1061, 1114, 1420, 1604, 1694, 1766, 1810, 1884, 1957, 3033, 3086; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.16-7.44 (m, 9H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 125.2, 127.1, 127.2, 127.3, 127.8, 128.8, 129.9, 134.7, 139.8, 143.1; **Analysis: $C_{12}H_9Cl$** requires C, 76.4; H, 4.81; Cl, 18.79; found C, 76.12; H, 4.95; Cl, 18.54%.

General Experimental Procedure for the Heck Reaction:

To a stirred mixture of aryl halide (2.0 mmol), K_2CO_3 (0.552 g, 4.0 mmol), olefin (3.0 mmol), tetrabutylammonium bromide (0.644 g, 2 mmol) in water (6 mL) was added palladium complex **30** (0.003 mg, 5x 10^{-6} mmol). The reaction mixture was then heated in an oil bath at specified temperature and time (**Table 3**). The progress of the reaction was monitored by TLC. The reaction mixture was then allowed to cool to 25 °C and extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with brine and dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to afford the crude product. The crude product was then purified by column chromatography on silica gel using pet.ether and ethyl acetate as eluents to afford arylated products (**32a-o**).

1-(4-Methylphenyl)-2-phenylethylene (32a): **Yield**: 0.334 g (86%); viscous liquid; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.00 (s, 3H), 6.68-7.30 (m, 11H); **^{13}C NMR** (50 MHz,

$CDCl_3$): δ 21.3, 126.5, 127.4, 127.8, 129.4, 134.6, 137.3, 137.6; **Analysis:** $C_{15}H_{14}$ requires C, 92.74; H, 7.26; found C, 92.79; H, 7.27%.

Methyl-*(E)*-3-(1-naphthyl)propenoate (32b): **Yield:** 0.377 g (89%); viscous liquid; **IR** ($CHCl_3$, cm^{-1}): 1023, 1219, 1632, 1704, 2833, 2945, 3010, 3368, 3630; **^{1}H NMR** (200 MHz, $CDCl_3$)**:** δ 3.87 (s, 3H), 6.56 (d, *J* = 8.0 Hz, 2H), 7.48-7.54 (m, 3H), 7.88 (d, *J* = 8.1 Hz, 2H), 8.21 (d, *J* = 6.2 Hz, 1H), 8.57 (d, *J* = 12.1 Hz, 1H). **^{13}C NMR** (50 MHz, $CDCl_3$): δ 51.5, 120.3, 123.3, 124.8, 125.2, 126.0, 126.7, 128.6, 130.3, 131.3, 131.6, 133.6, 141.7, 166.8; **MS** (m/z, % relative intensity): 212 (M^+, 23), 181 (12), 153 (100), 151(71), 76 (58); **Analysis:** $C_{14}H_{12}O_2$ requires C, 79.22; H, 5.70; found C, 79.27; H, 5.79%.

Butyl-(*E*) -3-(1-naphthyl)propenoate (32c): **Yield**: 0.411 g (81%); viscous liquid; **IR** ($CHCl_3$, cm^{-1}): 698, 759, 799, 855, 977, 1038, 1087, 1175, 1346, 1464, 1634, 1707, 2933, 2960, 3019; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.91 (t, *J* = 6.6 Hz, 3H), 1.36-1.41 (m, 2H), 162-1.67 (m, 2H), 4.16 (t, *J* = 6.5, 2H), 6.41 (d, *J* = 15.5, 1H), 7.34-7.44 (m, 3H) 7.62 (d, *J* = 7.6 Hz, 2H), 7.74 (d, *J* = 7.6 Hz, 1H), 8.08 (d, *J* = 8.2 Hz, 1H), 8.41 (d, *J* = 16.4, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.7, 19.0, 30.7, 64.1, 120.7, 123.2, 124.7, 125.2, 125.9, 126.6, 128.5, 130.0, 130.2, 131.7, 133.5, 141.3, 166.3; **Analysis:** $C_{17}H_{18}O_2$ requires C, 80.28; H, 7.13; found C, 80.29; H, 7.17%.

Butyl-*(E)*-3-[(3-trifluoromethyl)-phenyl]propenoate (32d): **Yield**: 0.511 g (94%); viscous liquid; **IR** ($CHCl_3$, cm^{-1}): 803, 865, 902, 984, 1076, 1096, 1134, 1177, 1196, 1219, 1270, 1311, 1335, 1387, 1439, 1643, 1709, 2963; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.95 (t, *J* = 7.4 Hz, 3H), 1.33-1.48 (m, 2H), 1.60-1.74 (m, 2H), 4.19 (t, *J* = 6.7 Hz, 2H), 6.47 (d, *J* = 16.1 Hz, 1H), 7.44-7.74 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.4, 19.0,

30.7, 64.2, 120.3, 124.4, 126.2, 129.1, 130.7, 131.2, 131.6, 135.3, 142.2, 165.8; **MS** (m/z, % relative intensity): 272 (M^+, 9), 253 (7), 216 (57), 199 (100), 171 (31), 151 (59), 102 (14), 56 (47), 41 (50); **Analysis: $C_{14}H_{15}F_3O_2$** requires C, 61.76; H, 5.55; found C, 61.55; H, 5.81%.

Ethyl-*(E)*-3-[(3-trifluoromethyl)phenyl]propenoate (32e): **Yield**: 0.463 g (95%); viscous liquid; **IR** ($CHCl_3$, cm^{-1}): 1041, 1077, 1096, 1134, 1169, 1178, 1196, 1219, 1263, 1311, 1335, 1369, 1440, 1643, 1709, 2985; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.32 (t, *J* = 7.1 Hz, 3H); 4.24 (q, *J* = 7.1 Hz, 2H); 6.45 (d, *J* = 16.1 Hz, 1H); 7.25-7.73 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.0, 60.2, 120.3, 124.4, 126.2, 129.1, 130.7, 135.3, 142.2, 165.6; **MS** (m/z, % relative intensity): 244 (M^+, 34), 225 (16), 216 (45), 199 (100), 171 (60), 151 (97), 131 (12), 102 (24), 75 (22), 45 (26); **Analysis: $C_{12}H_{11}F_3O_2$** requires C, 59.02; H, 4.54; found C, 59.31; H, 4.25%.

***(E)*-^{n}Butyl 3-phenyl-2-propenoate (32f): Yield:** 0.388 g (95%); viscous liquid; **IR** (Nujol, cm^{-1}): 572, 684, 711, 979, 1026, 1172, 1201, 1255, 1280, 1311, 1326, 1384, 1450, 1496, 1577, 1639, 1712, 2873, 2933, 2960; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.90 (t, *J* = 7.1 Hz, 3H), 1.27-1.42 (m, 2H), 1.54-1.68 (m, 2H), 4.12 (t, *J* = 7.1 Hz, 2H), 6.33 (d, *J* = 16.1 Hz, 1H), 7.25-7.45 (m, 5H), 7.57 (d, *J* = 16.1 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.3, 18.8, 30.5, 63.7, 118.1, 127.6, 128.4, 129.7, 134.2, 144.0, 166.1; **MS** (m/z, % relative intensity): 204 (12, M^+), 148 (57), 131 (93), 103 (80), 77 (100); **Analysis: $C_{13}H_{16}O_2$** requires C, 76.44; H, 7.90; found C, 76.41; H, 7.86%.

***(E)*-Methyl 3-phenyl-2-propenoate (32g): Yield:** 0.311 g (96%); **IR** (Nujol, cm^{-1}): 689, 716, 776, 986, 1014, 1030, 1169, 1183, 1202, 1514, 1531, 1722, 2863, 2946, 3029; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.81 (s, 3H), 6.45 (d, *J* = 16.1 Hz, 1H), 7.29-7.64 (m, 5H),

7.73 (d, *J* = 16.1 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 51.5, 117.9, 128.0, 128.8, 130.2, 134.4, 144.7, 167.2; **MS** m/z (% relative intensity): 162 (M^+, 100), 131 (52), 103 (28), 77 (17); **Analysis: $C_{10}H_{10}O_2$** requires C, 74.06; H, 6.21; found C, 74.12; H, 6.18%.

***trans*-Stilbene (32h): Yield:** 0.338 g (94%); **mp:** 123-124 °C; **IR** (Nujol, cm^{-1}): 766, 962, 1378, 1452, 1464, 1496, 1598, 2866, 2869, 2926, 2966; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.07 (s, 2H), 7.22-7.36 (m, 6H), 7.48 (d, *J* = 8.0 Hz, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 126.5, 127.6, 128.6, 137.3; **MS** (m/z, % relative intensity): 180 (M^+, 100), 165 (31), 152 (6), 89 (14), 76 (10); **Analysis: $C_{14}H_{12}$** requires C, 93.29; H, 6.71; found C, 93.24; H, 6.67%.

***(E)*-2-Phenylacrylonitrile (32i): Yield**: 0.227 g (88%); viscous liquid; **IR** (Neat, cm^{-1}): 690, 749, 967, 1206, 1449, 1578, 1622, 2218, 3020, 3062; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 5.86 (d, *J* = 17.1 Hz, 1H), 7.32-7.40 (m, 6H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 94.8, 95.8, 117.5, 127.0, 128.7, 130.8, 133.3, 149.9; **MS** (m/z, % relative intensity): 129 (100, M^+), 102 (47), 76 (23), 63 (20); **Analysis: C_9H_7N** requires C, 83.69; H, 5.46; N, 10.85; found C, 83.69; H, 5.26; N, 10.78%.

Ethyl-*(E)*-3-(4-nitrophenyl)propenoate (32j): **Yield:** 0.425 g (96%); yellow solid; **mp**: 139-140 °C; **IR** ($CHCl_3$, cm^{-1}): 873, 1000, 1166, 1211, 1356, 1525, 1644, 1720, 2855, 2956, 3075; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.26 (t, *J* = 6.3 Hz, 3H), 4.21 (q, *J* = 6.3 Hz, 2H), 6.84 (d, *J* = 16.2 Hz, 1H), 7.72 (d, *J* = 16.2 Hz, 1H), 8.00 (d, *J* = 9.1 Hz, 2H), 8.22 (d, *J* = 9.1 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.9, 60.2, 122.3, 123.7, 129.2, 140.3, 141.5, 147.9, 165.4; **MS** (m/z, % relative intensity): 221 (M^+, 31), 193 (32), 177

(12), 176 (100), 160 (16), 129 (19), 102 (33), 76 (10); **Analysis: $C_{11}H_{11}NO_4$** requires C, 59.73; H, 5.01; N, 6.33; found C, 59.68; H, 5.21; N, 6.25%.

***(E)*-Ethyl 3-(4-methoxyphenyl)-2-propenoate (32k): Yield:** 0.321 g (78%); viscous liquid; **IR** (Neat, $CHCl_3$): 820, 844, 970, 1020, 1177, 1298, 1340, 1435, 1510, 1580, 1620, 1722, 2998, 3018; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.33 (t, *J* = 6.2 Hz, 3H), 3.82 (s, 3H), 4.24 (q, *J* = 6.2 Hz, 2H), 6.30 (d, *J* = 16.1 Hz, 1H), 6.89 (d, *J* = 8.2 Hz, 2H), 7.46 (d, *J* = 8.2 Hz, 2H), 7.64 (d, *J* = 16.1 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.9, 54.8, 59.8, 113.9, 115.4, 126.8, 129.3, 143.8, 161.0, 166.8; **MS** (m/z, % relative intensity): 206 (100, M^+), 178 (19), 161 (99), 134 (57), 118 (20), 89 (44), 77 (38), 63 (51); **Analysis: $C_{12}H_{14}O_3$** requires C, 69.88; H, 6.85; found C, 69.79; H, 6.82%.

1-(4-Methoxyphenyl)-2-phenylethylene (32l): **Yield:** 0.34 g (81%); colorless solid; **mp**: 138 °C ; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.85 (s, 3H), 6.89 (d, *J* = 10.2 Hz, 2H), 7.02 (d, *J* = 10.2 Hz, 2H), 7.24-7.51 (m, 7H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 55.1, 114.1, 126.3, 126.7, 127.2, 127.7, 128.3, 128.6, 130.2, 137.7, 159.3; **Analysis: $C_{15}H_{14}O$** requires C, 85.68; H, 6.71; found C, 85.61; H, 6.79%.

***(E)*-Butyl 3-[(6-methoxy)-2-naphthyl]propenoate (32m)**: **Yield:** 0.494 g (87 %); viscous liquid; **IR** ($CHCl_3$, cm^{-1}): 852, 981, 1031, 1168, 1251, 1309, 1344, 1392, 1483, 1600, 1623, 1704, 2873, 2950, 3108. **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.98 (t, *J* = 7.2 Hz, 3H), 1.36-1.55 (m, 2H), 1.64-1.78 (m, 2H), 3.92 (s, 3H), 4.22 (t, *J* = 6.3 Hz, 2H), 6.48 (d, *J* = 16.1 Hz 1H), 7.09-7.17 (m, 2H), 7.60-7.83 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.6, 19.1, 30.6, 55.1, 64.2, 105.7, 119.2, 124.0, 127.3, 128.4, 129.4, 129.5, 129.9, 135.4, 135.4, 144.6, 158.6, 167.1; **Analysis: $C_{18}H_{20}O_3$** requires C, 76.03; H, 7.09; found C, 76.18; H, 7.19%.

***(E)*-Ethyl 3-(4-nitrophenyl)-2-propenoate (32n): Yield:** 0.199 g (45%); **mp**: 139-140 °C; **IR** (Nujol, cm^{-1}): 873, 1000, 1166, 1211, 1356, 1525, 1644, 1720, 2855, 2956, 3075; **^{1}H NMR** (200 MHz, $CDCl_3$): 1.26 (t, *J* = 6.3 Hz, 3H), 4.21 (q, *J* = 6.3 Hz, 2H), 6.84 (d, *J* = 16.2 Hz, 1H), 7.72 (d, *J* = 16.2 Hz, 1H), 8.00 (d, *J* = 9.1 Hz, 2H), 8.22 (d, *J* = 9.1 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.9, 60.2, 122.3, 123.7, 129.2, 140.3, 141.5, 147.9, 165.4; **MS** (m/z, % relative intensity): 221 (M^+, 31), 193 (32), 177 (12), 176 (100), 160 (16), 129 (19), 102 (33), 76 (10); **Analysis: $C_{11}H_{11}NO_4$** requires C, 59.73; H, 5.01; N, 6.33; found C, 59.68; H, 5.21; N, 6.25%.

***(E)*-1-(4-Nitrophenyl)-2-phenylethylene (32o): Yield**: 0.252 g (56%); **mp**: 155-157 °C; **IR** (Nujol, cm^{-1}): 788, 1378, 1449, 1463, 1510, 1596, 1632, 2854, 2925, 2966; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.12 (d, *J* = 16.1 Hz, 1H), 7.24 (d, *J* = 16.1 Hz, 1H), 7.31-7.58 (m, 7H), 8.00 (d, *J* = 8.6 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 123.8, 126.1, 126.6, 126.8, 128.5, 128.6, 133.1, 136.0, 143.7, 146.6; **MS** (m/z, % relative intensity): 225 (100, M^+), 179 (77), 165 (8), 152 (14), 89 (10), 77 (6); **Analysis**: **$C_{14}H_{11}NO_2$** requires C, 74.65; H, 4.92; N, 6.22; found C, 74.62; H, 4.88; N, 6.24%.

General Procedure for Sonogashira Coupling:

To a stirred mixture of aryl halides (5 mmol), alkynes (7.5 mmol), KOH (0.58 g, 10 mmol), tetrabutylammonium bromide (1.61 g, 5 mmol) in water (15 mL) was added palladium complex **30** (0.3 mg, $5x10^{-4}$ mmol). The resulting mixture was stirred at 100 °C for 6 h. Then the reaction mixture was extracted with ethyl acetate (3 x 20 mL) and washed with brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. This crude product was purified on column chromatography using 10% ethyl acetate in pet. ether as eluent to afford acetylenic products (**33a-c**).

1,2-Diphenylethyne (33a): **Yield:** 0.801 g (90%); colorless solid; **mp**: 62 °C [lit.[49] 60 °C]; **IR** ($CHCl_3$, cm^{-1}): 689, 755, 916, 1026, 1069, 1351, 1496, 1598, 1882, 2708, 3061; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.33-7.38 (m, 3H), 7.55-7.57 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 89.4, 123.3, 128.1, 128.2, 131.5; **Analysis: $C_{14}H_{10}$** requires C, 94.35; H, 5.65; found C, 94.15; H, 5.9%.

1-(-2-(4-Nitrophenyl)ethynyl)benzene (33b): **Yield:** 1.037 g (93%); yellow solid; **mp:** 118 °C [lit.[50] 119-120 °C]; **IR** ($CHCl_3$, cm^{-1}): 660, 689, 764, 857, 921, 1027, 1107, 1177, 1351, 1509, 1594, 1828, 2217, 2345, 2441, 3062; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 7.36-7.41 (m, 3H), 7.51-7.56 (m, 2H), 7.63-7.67 (m, 2H), 8.19-8.24 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 87.5, 96.1, 122.0, 123.4, 128.4, 129.1, 130.0, 131.7, 132.1, 146.9; **Analysis: $C_{14}H_9NO_2$** requires C, 75.33; H, 4.06; N, 6.27; found C, 75.5; H, 4.31; N, 6.12%.

1-(-2-4-Tolylethynyl)benzene (33c): **Yield:** 0.634 g (66%); colorless solid; **mp**: 71 °C [lit.[49] 70 °C]; **IR** ($CHCl_3$, cm^{-1}): 512, 627, 669, 690, 756, 818, 928, 1045, 1215, 1442, 1510, 1596, 2400, 2423, 2976, 3018, 3438; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.46 (s, 3H), 7.22-7.64 (m, 9H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.4, 88.8, 89.6, 120.2, 123.5, 127.9, 128.2, 129.0, 131.5, 138.1; **MS** (m/z, % relative intensity): 192 (M^+**,** 100), 165 (17), 115 (8), 82 (25), 63 (10), 51 (8); **Analysis: $C_{15}H_{12}$** requires C, 93.71; H, 6.29; found C, 93.65; H, 6.40%.

SECTION 2:

Application of Saccharin Palladium Complexes in organic Synthesis

This section describes the use of water-soluble saccharin palladium complex **30** as catalyst for the synthesis of arylpropionic acids (**34, 35** and **36**), nabumetone (**37**) and (*R*)-cinacalcet (**38**), all drug molecules, *via* Suzuki and Heck arylation reactions respectively.

4.2.1 Introduction

Nonsteroidal antiinflammatory drugs have been used extensively in the treatment of some reproductive disorders and are promising for many others.[51] These have a similar mode of action *i. e.* they stop the arachidonic acid cascade to prostaglandins and thromboxane A_2 by cyclooxygenase inhibition, which are responsible for the inflammation mechanism. α-Arylpropionic acids (**34** and **35**) are an important class of non-steroidal anti-inflammatory agents during the past three decades.[52]

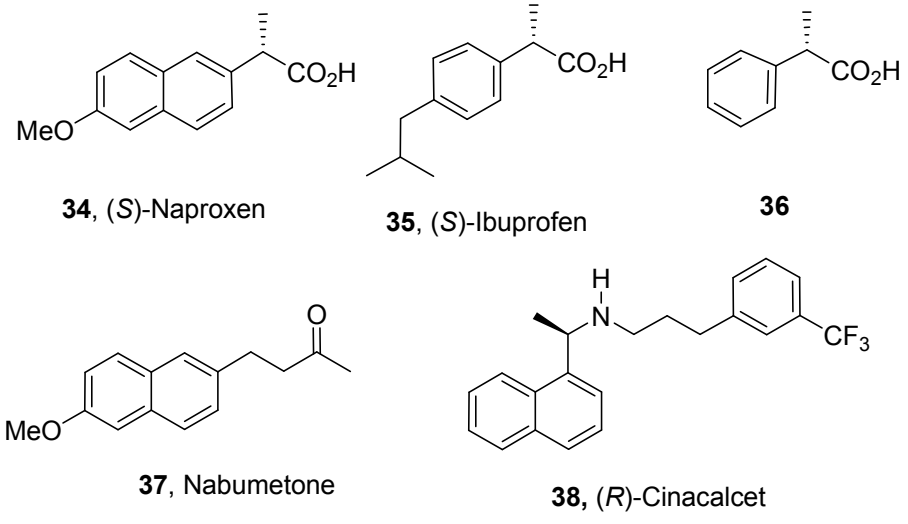


Fig. 9: Structures of Non-steroidal anti-inflammatory drugs

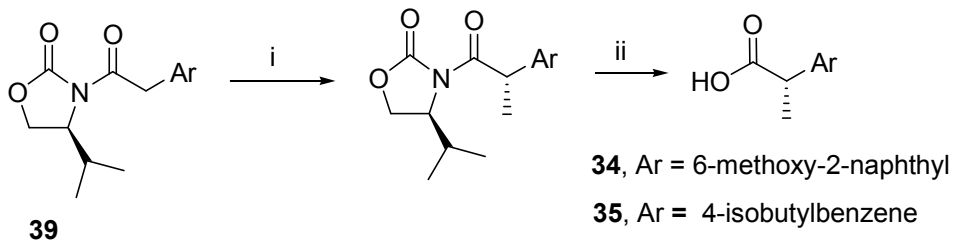
Nabumetone (**37**) is also a member of the non-steroidal anti-inflammatory drug, which reduces inflammation, pain, temperature, tenderness, stiffness caused by osteoarthritis and rheumatoid arthritis.[53] Cinacalcet (**38**) is an oral calcimimetic with a unique mechanism that modulates the behavior of the calcium sensing receptor on the parathyroid gland,[54] which produces a hormone, for maintaining blood calcium homeostasis.

4.2.2 Review of Literature

Literature search revealed that while there are several methods known[52a] for the synthesis of α-arylpropionic acids, only a few reports are available in the case of synthesis of nabumetone (**37**) and cinacalcet (**38**). Most of these methods make use of enzymatic resolution or asymmetric catalysis to create the chiral center. Some of the recent reports on the asymmetric syntheses of arylpropionic acids and synthesis of nabumetone (**37**) and cinacalcet (**38**) are described as follows.

Fadel's approach (1992)[55]

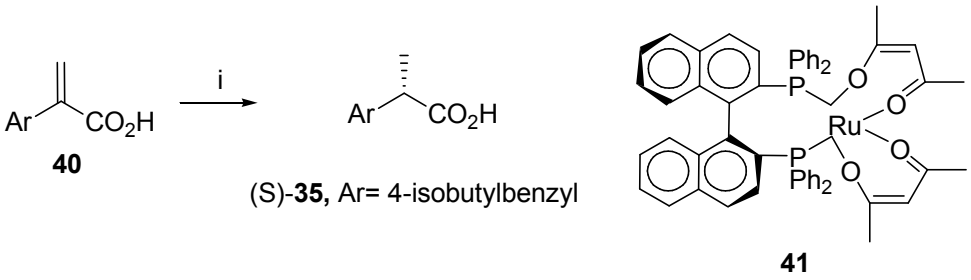
The Evans' chiral auxiliary, **39** was alkylated using methyl iodide and subsequent removal of the chiral auxiliary provided (*S*)-2-arylpropionic acids **34** and **35** in 98% ee respectively (**Scheme 20**).



Scheme 20: (i) NaHMDS, MeI, $CHCl_3$, –78 to –30 °C; (ii) LiOOH, dioxane or LiOH, THF-H_2O, 98% ee.

Fronczek's approach (1993)[56]

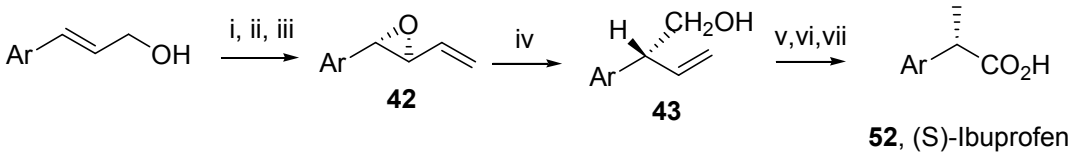
Chiral ruthenium complexes such as (*S*)-BINAP-Ru(acac)$_2$ (**41)** was prepared from BINAP and Ru(acac)$_3$. High pressure hydrogenation of **40** (1000 psig H_2 pressure) afforded (*S*)-ibuprofen (**35**) in 88% ee (**Scheme 21**).



Scheme 21: (i) Ru-catalyst **41**, H_2 (1000 psig), MeOH, 88% ee.

Jung's approach (1997)[57]

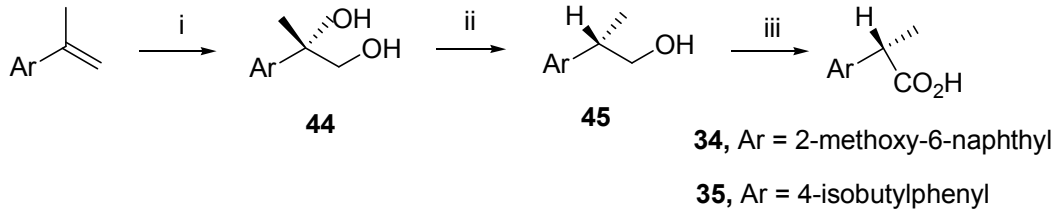
In this approach, (S)-ibuprofen (35) was synthesized via Sharpless epoxidation of cinnamyl alcohol, followed by Swern oxidation and Wittig olefination gave the key substrate 42. Rearrangement of epoxide 42 using triethylsilane afforded the desired alcohol 43 in 67% yield and 84% ee. Further transformation like tosylation followed by reduction with super-hydride®, and oxidative cleavage of the alkene with $RuCl_3$ and periodate gave (S)-ibuprofen (35) in 84% ee (**Scheme 22**).



Scheme 22: (i) $Ph_3P{=}CHCO_2Me$; (ii) DIBAL-H; (i) TBHP, (+)-DIPT, $Ti(O^iPr)_4$, 65% yield, 84% ee; (ii) Swern oxidation; (iii) Wittig; (iv) Et_3SiH, $BF_3{:}Et_2O$, 67% yield, 84% ee; (v) TsCl, pyridine; (vi) $LiEt_3BH$; (vii) $RuCl_3.3H_2O$, $NaIO_4$, $CH_3CN/CCl_4/H_2O$, 57% yield.

Ishibashi's approach (1999)[58]

Ishibashi *et al.* have reported the preparation of (*S*)-aryl-1,2-propanediols (**44**) by asymmetric dihydroxylation of the corresponding α-methyl styrenes with AD-mix-α . Hydrogenolysis at the benzylic position of **44**, over Pearlman's catalyst, gave (*S*)-2-aryl-1-propanol **45**, which was oxidized by Jones'reagent to give **34** and **35** in 98 and 90% ee respectively (**Scheme 23**).



44 **45**

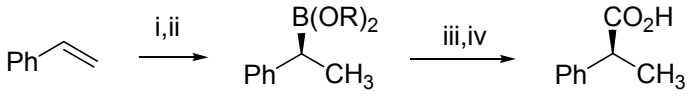
34, Ar = 2-methoxy-6-naphthyl

35, Ar = 4-isobutylphenyl

Scheme 23: (i) AD-mix-α; (ii) H_2, Pd $(OH)_2$/C; (iii) Jones' oxidation (CrO_3, H_2SO_4).

Crudden's approach (1999)[59]

Crudden *et al.* have employed asymmetric hydroboration of styrene, the key reaction to obtain chiral boronate ester **46,** which was then homologated with $LiCHCl_2$ followed by oxidation to afford (*S*)-phenylpropionic acid (**36**) in 91% ee (**Scheme 24**).

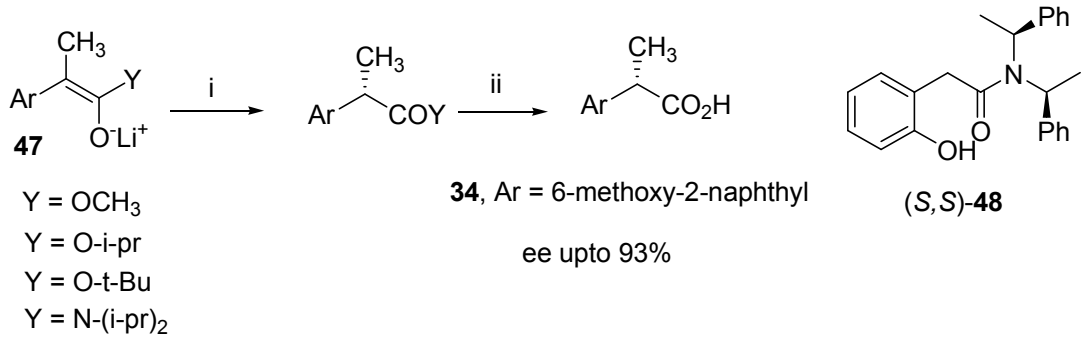


46 (S)-**36** 91% ee

Scheme 24: (i) catechol borane, $[Rh(COD)_2]^+$ BF_4^-, (S)-BINAP (2%); (ii) pinacol; (iii) $LiCHCl_2$, $ZnCl_2$; (iv) $NaClO_2$ oxidation.

Omar's approach (2003)[60]

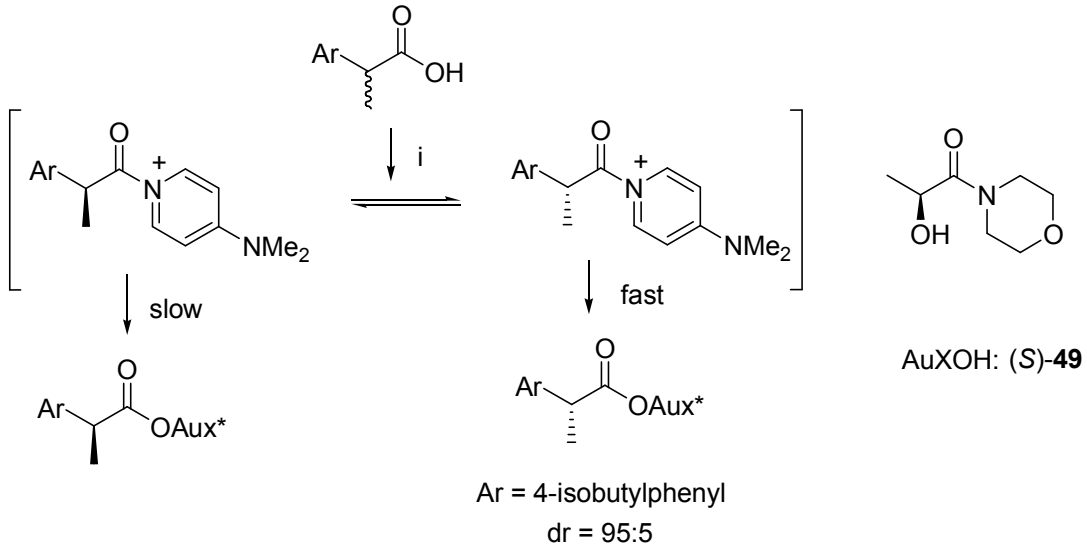
Omar *et al.* have synthesized (*S*)-naproxen (**34**) by the asymmetric protanation of the ester enolates **47**, prepared from the corresponding racemic ester (**Scheme 25**).



Scheme 25: (i) (*S, S*) **48**; (ii) I N NaOH, 93% ee.

Alessandra's approach (2006)[61]

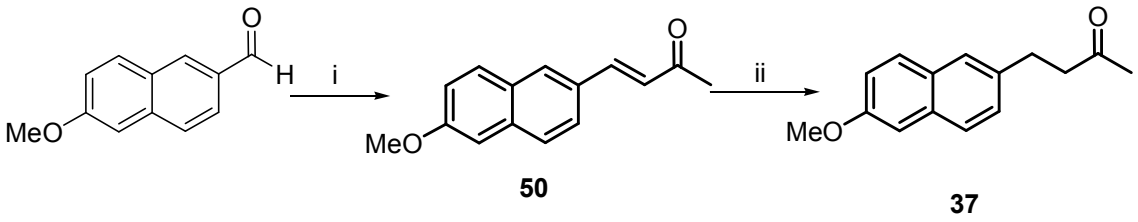
Alessandra *et al*. have synthesized (*S*)-ibuprofen (**35**) by asymmetric esterification of racemic ibuprofen with lactamide **49** mediated dynamic kinetic resolutions, in the presence of DCC and DMAP (**Scheme 26**).



Scheme 26: (i) (S)-**49**, DCC, DMAP, toluene, 0 °C,

Goudie's approach (1978) [62]

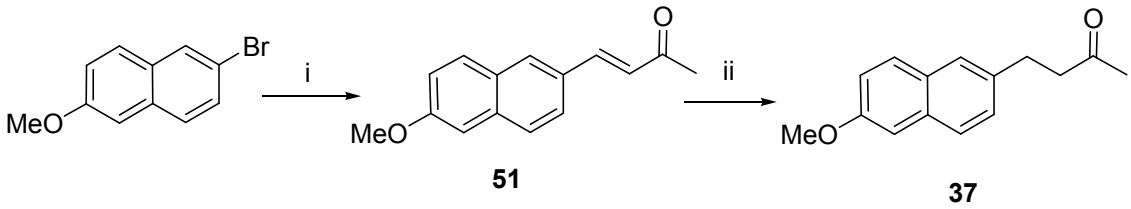
Goudie *et al.* have reported the condensation of 6-methoxy-2naphthaldehyde with acetone in dilute NaOH to afford the *α, β*- unsaturated ketone **50**, which on selective reduction with H_2 over 10% Pd/C in acetic acid gave nabumetone **37** (**Scheme 27**).



Scheme 27: (i) aq. NaOH, acetone; (ii) 10% Pd/C.

Aslam's approach (1989)[63]

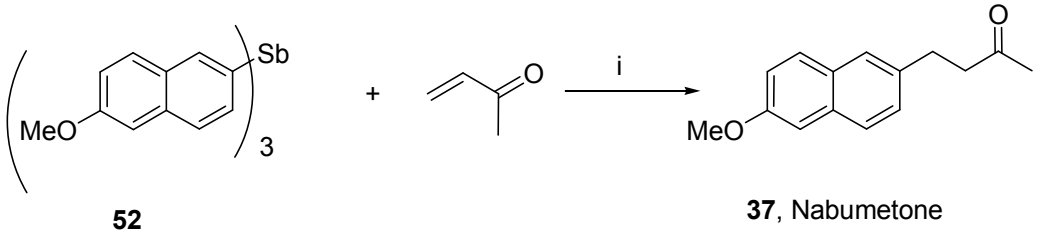
Aslam *et al.* have reported the palladium catalyzed coupling of 6-methoxy-2-bromo naphthalene with 3-buten-2-ol to give enol form of diketone **51,** which on further selective reduction gave nabumetone **37** in 65%yield (**Scheme 28**).



Scheme 28: (i) but-3-en-2-ol, $PdCl_2(PPh_3)_3$, $NaHCO_3$, NMP, 140 ºC; (ii) 10% Pd/C, H_2 (1 atm), 60%.

Uemura's approach(1996)[64]

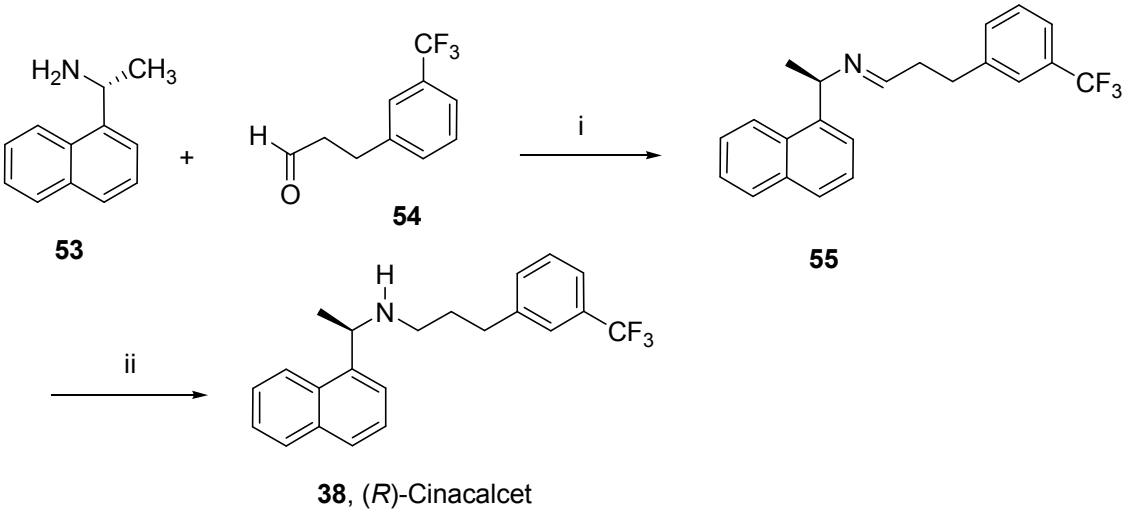
In this approach, nabumetone was synthesized by the $Pd(OAc)_2$-catalyzed conjugate addition of tris (6-methoxy-2-naphthyl) stibine **52** on to methyl vinyl ketone in acetic acid (**Scheme 29**).



Scheme 29: (i) $Pd(OAc)_2$, AgOAc, AcOH, 25 ºC, 99%.

Sorbera's approach (2002)[65]

Sorbera *et al.* have reported the synthesis of cinacalcet **38** by treating (*R*)-(1)- naphthyl amine **53** with 3-[(3- trifluoromethyl)phenyl]propionaldehyde **54** in the presence of $Ti(OiPr)_4$ to afford imine **55**, which was then reduced with $NaBH_3CN$ in ethanol to give (*R*)-cinacalcet **38** (**Scheme 30**).



Scheme 30: (i) $Ti(OiPr)_4$; (ii) $NaBH_3CN$.

4.2.3 Present Work

4.2.3.1 Objective

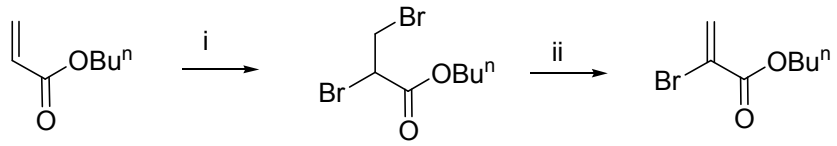
As can be seen from the above discussion, many methods are reported in the literature for the synthesis of α-arylpropionic acids. These methods have several limitations such as use of chiral starting materials, involving more number of steps, use of costly enzymes in case of kinetic resolutions (KR) and often resulting in low overall yields. For nabumetone (**37**) and (*R*)-cinacalcet (**38**), a few reports are available for their synthesis. In this section, we have explored the usefulness of water-soluble saccharin palladium complex **30**, (for its synthesis, see Section 1 of this Chapter) for the synthesis of α-arylpropionic acids

namely (*S*)-naproxen (**34**), (*S*)-ibuprofen (**35**) and (*S*)-phenylpropionic acid (**36**) *via* Suzuki coupling and nabumetone (**37**) and (*R*)-cinacalcet (**38**) *via* Heck reactions respectively.

4.2.4 Results and Discussion

(i) Asymmetric synthesis of arylpropionic acids

We have developed a simple procedure by which butyl 2-bromoacrylate (**57**), key component required as Suzuki coupling partner, was prepared in two steps of bromination of *n*-butyl acrylate followed by its dehydrobromination (**Scheme 31)**.



56 **57**

Scheme 31: (i) Br_2, AcOH, 0 °C, 96%; (ii) DBU, toluene, -20 °C, 98%.

The ^{1}H NMR spectrum of butyl 2,3-dibromopropanoate (**56**) showed two characteristic signals at δ 3.68 (dd) and 4.44 (dd) for –**C**$\mathbf{H_2}$Br protons; other signal at δ 3.93 is due to –**CH**Br proton. Its ^{13}C NMR spectrum displayed typical signals at δ 29.6 and 41.1 corresponging to –**C**H_2Br and –**C**HBr carbons respectively. The ^{1}H NMR spectrum of butyl 2-bromoacrylate (**57**) showed typical signals at δ 6.25 (d) and 6.95 (d) due to olefinic protons, while its ^{13}C NMR spectrum showed characteristic signals δ 121.3 and 131.9 corresponding to olefinic carbons; other signal at δ 161.74 due to carbonyl carbon (**Fig. 10**).

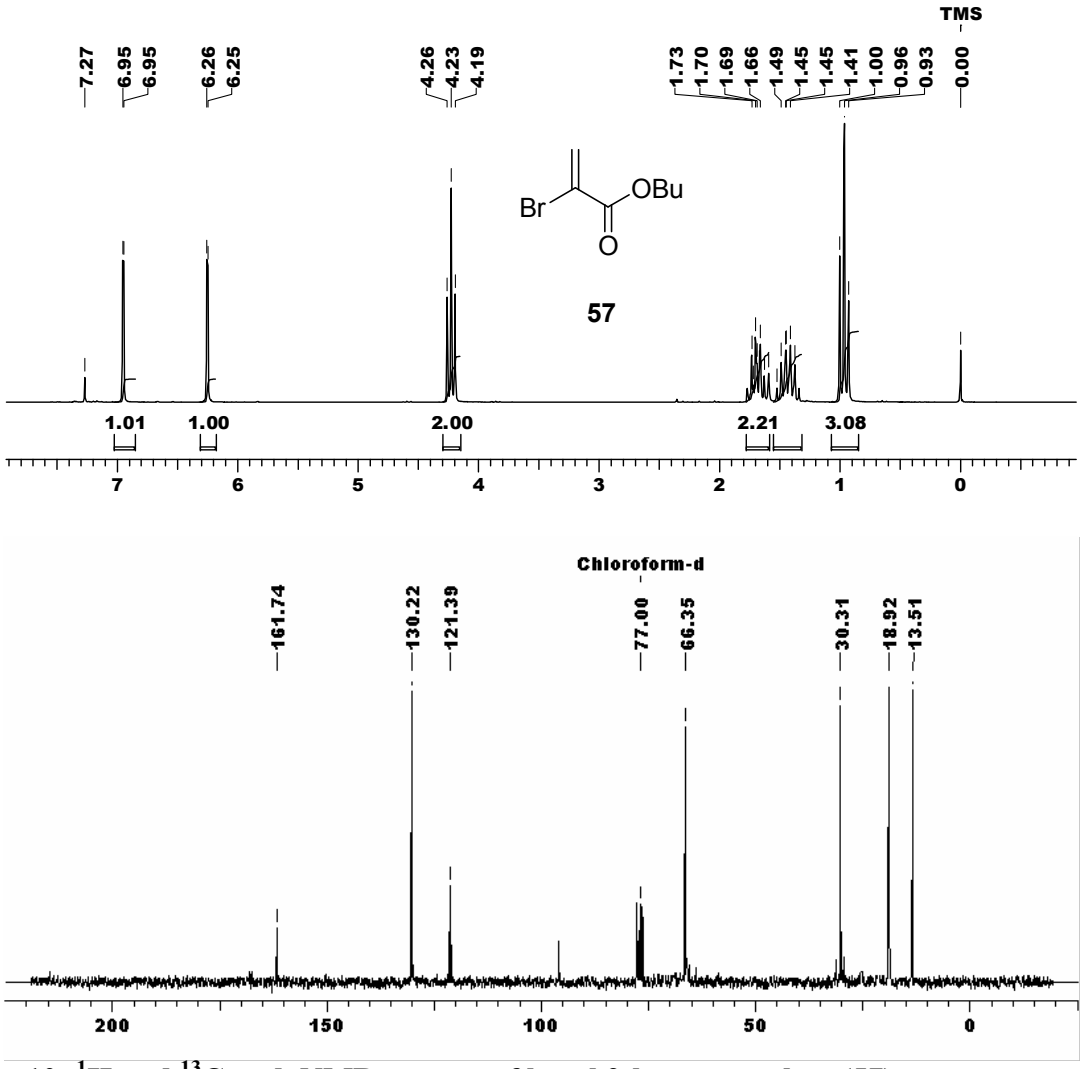
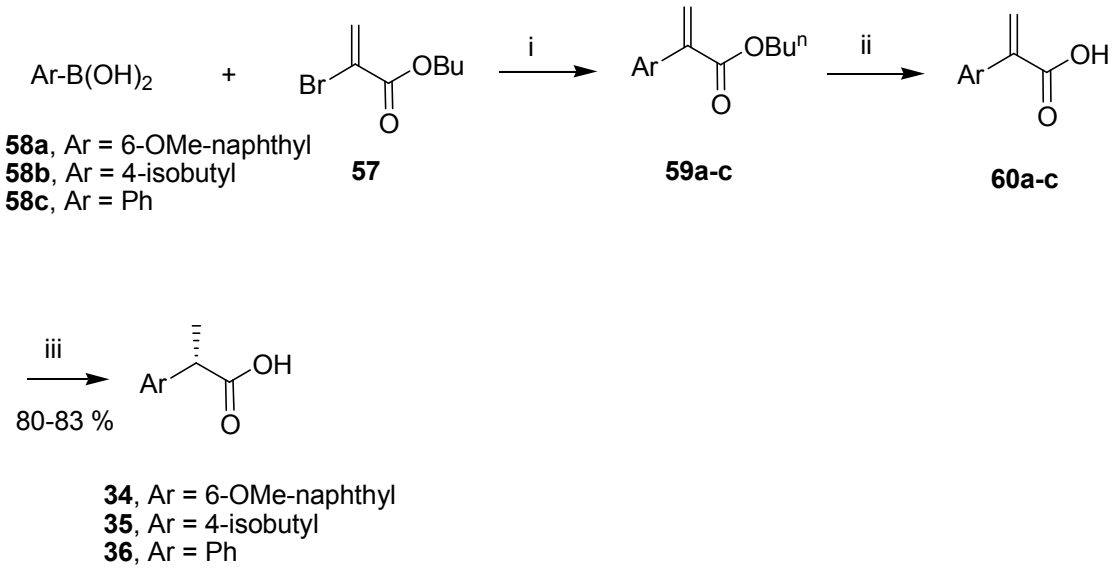


Fig. 10: ^{1}H and ^{13}C and NMR spectra of butyl 2-bromoacrylate (57)

Arylboronic acids (**58a-c**), the other coupling partners in Suzuki coupling, were prepared by the lithiation of the respective aryl bromides followed by the addition of trimethyl borate. Our next step was the arylation of vinyl bromo ester **57** with arylboronic acids **58a-c** using palladium saccharin complex (**30)** in the presence of K_2CO_3 to give α-aryl acrylates (**59a-c**). Hydrolysis of arylacrylates under basic conditions afforded the acrylic acids (**60a-c)** in 42-53% yields (**Scheme 32)**.



Scheme 32: (i) palladium complex **30**, K_2CO_3, toluene, reflux; ii) aq. KOH, reflux, 42-53%; (iii) [(S)-BINAP-Ru (acac) $_2$], H_2 (1000 psig), 25 °C, MeOH, 17 h, 80-83%.

The ^{1}H NMR spectrum of 2-(2-methoxynaphthalen-6-yl)acrylic acid (**60a**) showed typical signals at δ 6.12 (d) and 6.58 (d) due to olefinic protons; other signal at δ 3.93 correspond to Ar-O**CH$_3$** protons. Its ^{13}C NMR spectrum showed characteristic signals δ 117.5 and 132.7 corresponding to olefinic carbons; other signal at δ 166.4 is due to carbonyl carbon. The asymmetric reduction of acrylic acids (**60a-c**) using cobalt catalyst with semicorrin[66] in the presence of $NaBH_4$ proceeded smoothly to give reduced product, but with no optical induction. However, hydrogenation[67] of acrylic acids (**60a-c**) using [(S)-BINAP-Ru(acac)$_2$] at 1000 psig H_2 proceeded to give (*S*)-aryl propionic acids in good yields and with moderate enantioselectivity (84-88% ee). The spectral data obtained for (*S*)-naproxen (**34**) and (*S*)-ibuprofen (**35**)[67] were in full agreement with the values reported in the literature.

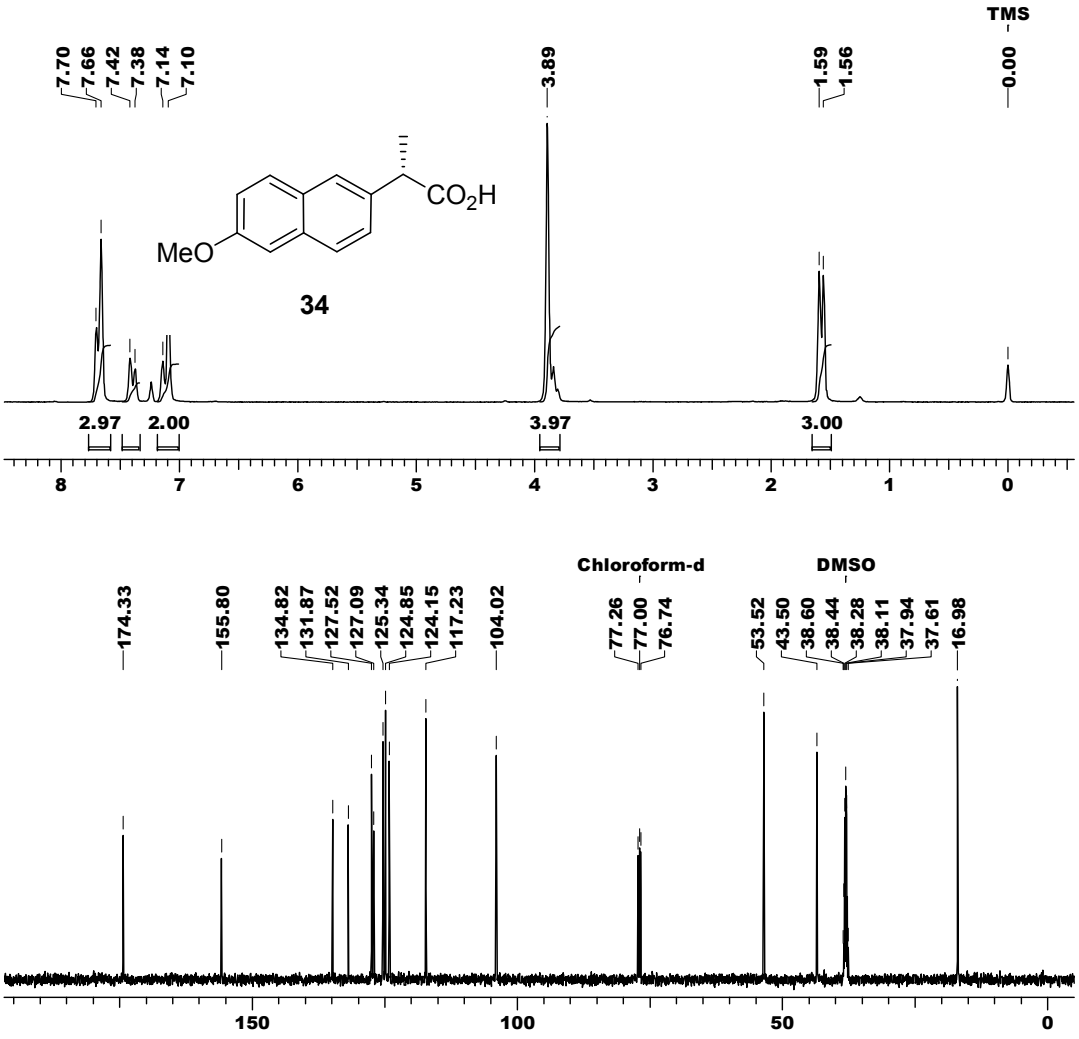
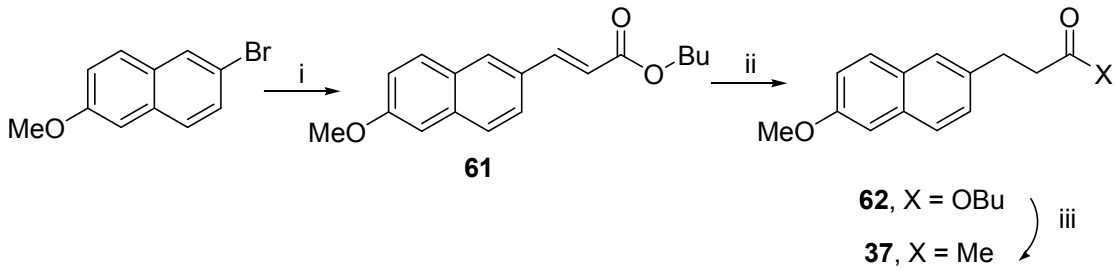


Fig. 11: ^{1}H and ^{13}C NMR spectra of naproxen (34)

(ii) Synthesis of nabumetone

We have successfully employed saccharin palladium complex (**30**) for another application in the synthesis of nabumetone, **37**, a non-steroidal anti-inflammatory drug (**Scheme 33)**. Heck arylation of 2-bromo-6-methoxynaphthalene with *n*-butyl acrylate in NMP and triethylamine in the presence of Pd-catalyst (**30**) at 135 °C gave unsaturated ester **61** in 85% yield. The ^{1}H NMR spectrum of unsaturated ester **61** showed a doublet at δ 6.48 corresponding to olefinic proton; other signal at δ 3.92 due to Ar-O**C**$\mathbf{H_3}$ proton. Its

^{13}C NMR spectrum showed signal at δ 167.1 corresponding to ester carbonyl carbon. The GC-MS of **61** showed the molecular ion peak at m/z 284.



Scheme 33: (i) *n*-butyl acrylate, palladium saccharin complex **30** ($5x10^{-4}$ mmol), Et_3N, NMP, 135 °C, 85%; (ii) $NaBH_4$, $CoCl_2.6H_2O$ (5 mol%), MeOH, 25 °C, 95%; (iii) CH_3MgI, THF, 2 h, 64%.

Reduction of C=C in unsaturated ester **61** with $CoCl_2/NaBH_4$[68] in methanol at 25 °C produced the saturated ester **62** in 95% yield. The ^{1}H NMR spectrum of the saturated ester **62** showed two triplets at δ 2.86 and 3.06 corresponding to Ar-CH_2-**CH_2**- and Ar-**CH_2**-CH_2- protons respectively. Its ^{13}C NMR spectrum showed typical signal at δ 30.5 and 35.7 corresponding to Ar-CH_2-**C**H_2- and Ar-**C**H_2-CH_2- carbons respectively; other signal at δ173.2 is due to ester carbonyl carbon. The GC-MS of **62** showed the molecular ion peak at m/z 286 confirming the formation of the saturated ester. The reaction of one equivalent of methyl magnesium iodide with the saturated ester, **62** in THF afforded nabumetone (**37**) in 64% yield. The ^{1}H NMR spectrum of nabumetone (**37)** showed singlet δ 2.13 corresponding to –CH_2CO**CH_3** protons. Its ^{13}C NMR spectrum showed a signal at δ 207.5 due to the carbonyl carbon. The GC-MS of **37** showed the molecular ion peak at m/z 228 confirming the formation of ketone **37** (**Fig. 12**).

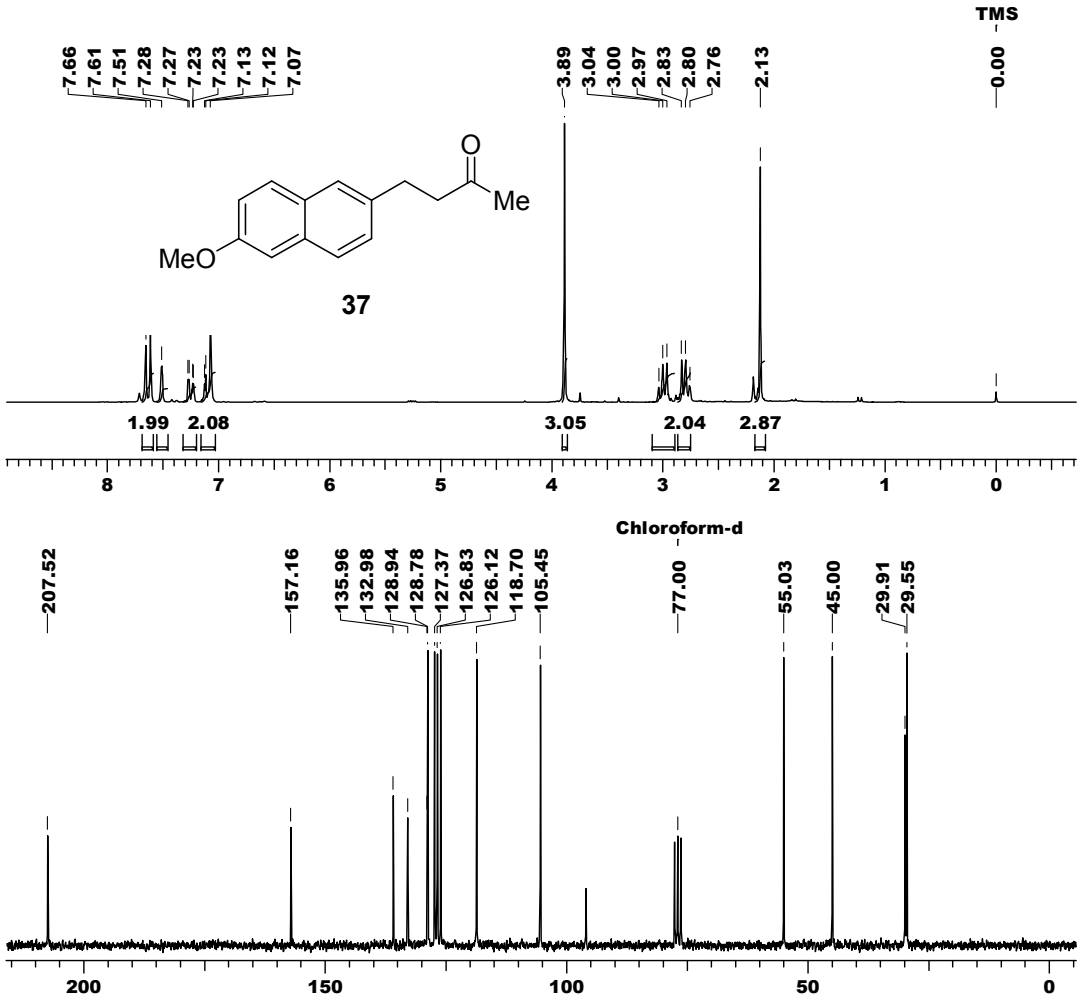
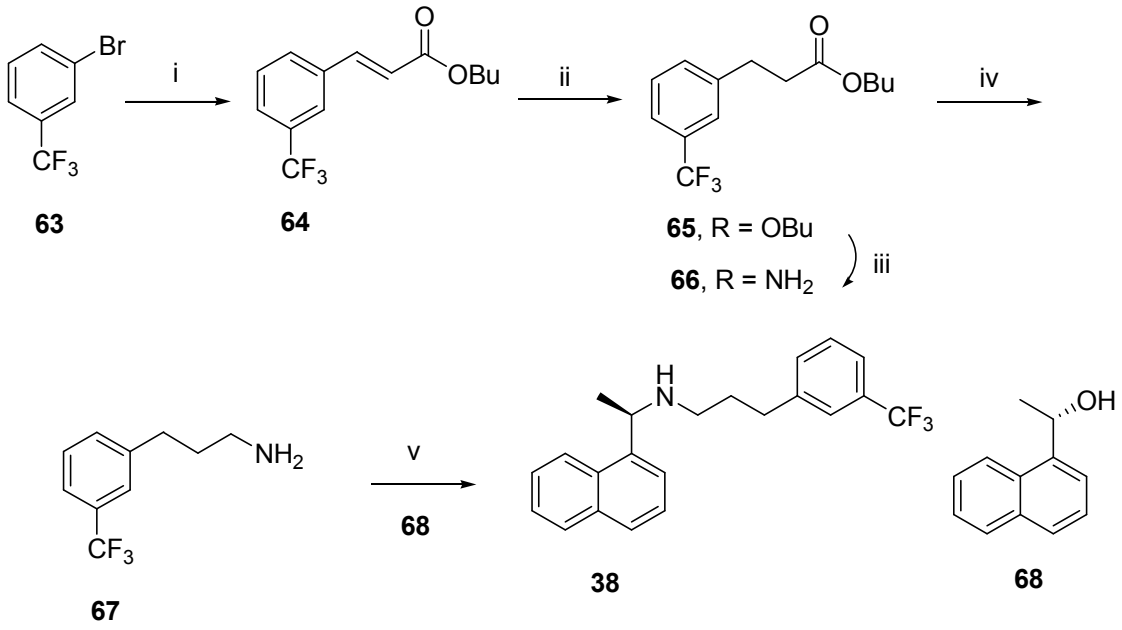


Fig. 12: ^{1}H and ^{13}C NMR spectra of nabumetone (37)

(iii) Asymmetric synthesis of (*R*)-cinacalcet

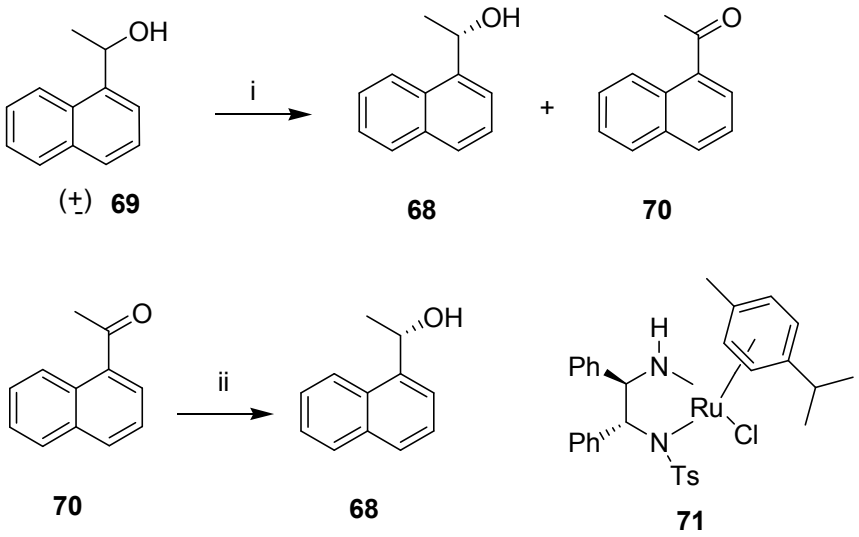
Another application of palladium complex (**30**) for arylation reaction relates to in the synthesis of (*R*)-cinacalcet (**38**) (**Scheme 34)**. The Heck arylation of *m*-bromobenzotrifluoride (**63**) with *n*-butyl acrylate catalyzed by palladium complex (**30**), in NMP and triethylamine at 135 °C gave the unsaturated ester **64.** The ^{1}H NMR spectrum of **64** showed a doublet at δ 6.47 for one of the olefinic protons. Its ^{13}C NMR spectrum showed a typical signal at δ 165.8 for ester carbonyl carbon.



Scheme 34: (i) *n*-butyl acrylate, palladium complex **30**, NaOAc, NMP, 135 °C, 90%; (ii) $NaBH_4$, $CoCl_2.6H_20$ (5 mol%), MeOH, 25 °C, 95%; (iii) conc. ammonia, 24 h, 25 °C, 80%; (iv) $LiAlH_4$, THF, reflux, 2 h, 65%; (v) PPh_3, DEAD, THF, 0 °C, 82%, $[\alpha]^{25}_D$ -7 (*c* 1.0, $CHCl_3$).

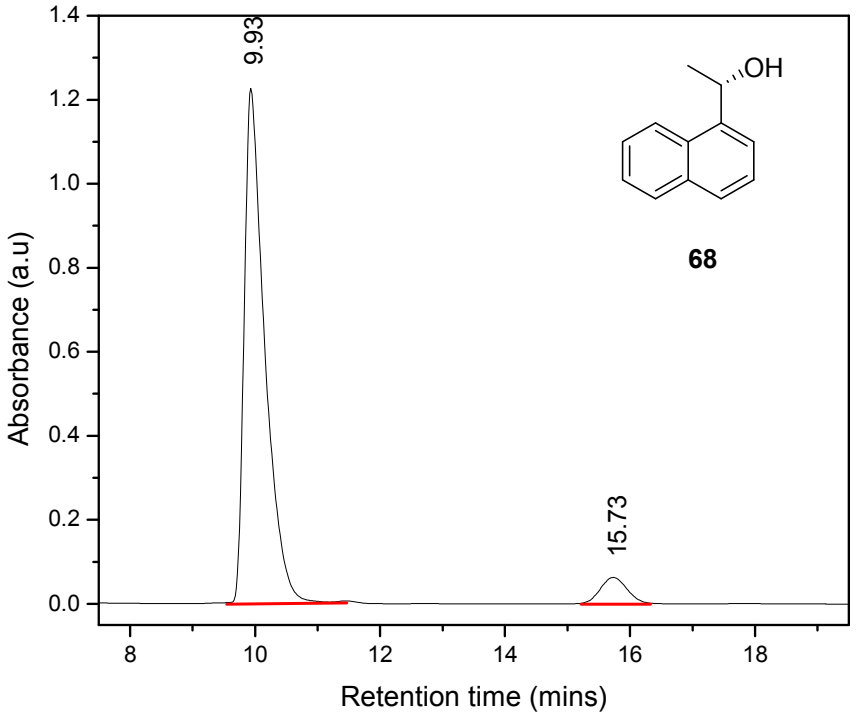
Reduction of the unsaturated ester **64** with $CoCl_2/NaBH_4$[68] in methanol at 25 °C produced the saturated ester **65** in 95% yield. The ^{1}H NMR spectrum of the saturated ester **65** showed two triplets at δ 2.63 and 3.00 corresponding to Ar-CH_2-**CH_2**- and Ar-**CH_2**-CH_2- protons respectively. Its ^{13}C-NMR spectrum showed a typical signal at δ 172.2 due to carbonyl carbon. Ammonolysis of saturated ester **65** with con. ammonia afforded amide **66** in 80% yield. The ^{1}H NMR spectrum of amide **66** showed two doublets at δ 2.50 and 2.97 corresponding to Ar-CH_2-**CH_2**- and Ar-**CH_2**-CH_2- protons respectively. Its ^{13}C NMR spectrum showed a typical signal at δ 175.2 due to carbonyl carbon. Reduction of amide **83** using lithium aluminum hydride in THF furnished amine **67** in 50% yield. The ^{1}H NMR spectrum of amine **67** showed multiplet at δ 1.92 for –**CH_2**-CH_2-NH_2 protons.

For the completion of the synthesis of **38**, we required (*S*)-(+)-α-methyl-1-naphthalenemethanol (**68**), which was prepared by two routes (i) by the oxidative kinetic resolution ($Pd(OAc)_2$ (5 mol %), (–)-sparteine (20 mol %), O_2 (1 atm.), toluene, MS 3 Å) of the racemic alcohol **69** which gave **68** in 88% ee; (ii) the other route involves asymmetric transfer hydrogenation[69] ($[RuCl_2(p\text{-cymene})]_2$, ligand **71**, IPA) of the corresponding ketone **70** in 96% ee (chiral HPLC (**Fig. 13**)) (**Scheme 35)**.



Scheme 35: (i) $Pd(OAc)_2$ (5 mol %), (–) sparteine (20 mol %), O_2 (1 atm.), toluene, MS 3 Å, 80 °C, 41%. (ii) $[RuCl_2(p\text{-cymene})]_2$, ligand **71**, 2-propanol, KOH, 25 °C, 83%, 96% ee.

The ^1H NMR spectrum of alcohol **68** showed a characteristic doublet at δ 1.57 for –CH-**CH_3** protons and a quartet at δ 5.5 for –**CH**-CH_3 proton. Its ^{13}C NMR spectrum also showed signals at δ 24.1 and 66.2 due to methyl and methine carbons respectively. Its IR spectrum exhibited characteristic strong bands at 1218 cm^{-1} (C-O stretching frequency) and 3011 cm^{-1} (O-H stretching frequency) confirming the presence of alcohol group. The synthesis of (*R*)-cinacalcet (**38**) was completed by reacting alcohol **68** with amine **67** under Mitsunobu conditions (diisopropylazo dicarboxylate and PPh_3).



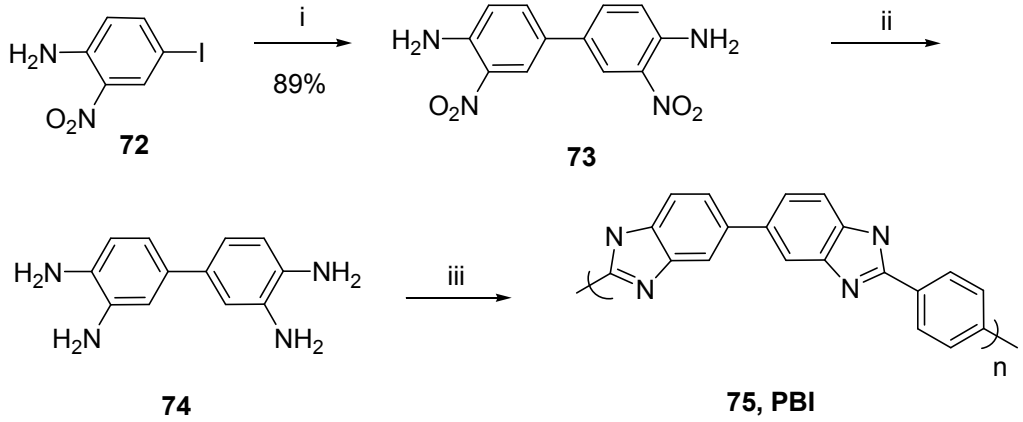
Peak No.	Ret. Time (mins)	Area (mAU*s)	Area (%)
1	9.93	28087622	97.96
2	15.73	584216	2.04

Fig. 13: HPLC Chromotogram of alcohol (68)

(iv) Synthesis of 3,3′, 4,4′-Tetraminobiphenyl

Another application of palladium complex (**30**) for homo coupling reaction is in the synthesis of polybenzimidazole (**75)** (**Scheme 36)**. 3,3′,4,4′-Tetraminobiphenyl (**74**) (TAB) is used as monomer in the preparation of polybenzimidazole (**4)** (PBI) polymers, which are widely used as proton-conducting materials for fuel cell applications. TAB is also used as an antioxidant and as an agent for stabilizing epoxide resins. We envisioned a simple route which involved water soluble palladium complex **30** as catalyst for the

homo-coupling of 4-iodo-2-nitroaniline (**72**), which could serve as the cost-effective synthesis of polybenzimidazole (**75**) with high yield and purity.



Scheme 36: i) palladium complex **30**, Et_3N, toluene, 110 °C, 89%; ii) $SnCl_2$. $2H_2O$, HCl, 25-40 °C, 2 h, 73% iv) isophthalic acid, polyphosphoric acid, 120 - 220 °C, 19 h, 92%.

The biaryl homocoupling of 4-iodo-2-nitroaniline (**72**)[70] using water soluble palladium complex **30** in the presence of triethylamine in toluene gave 3,3′-dinitro-4,4′-diaminobiphenyl (**73**) in 89% yield, which was insoluble in toluene and precipitated out after the reaction. The ^{1}H NMR spectrum of biphenyl **73** showed two doublets at δ 7.09 and 7.73; also a singlet at δ 8.12 corresponding to aromatic protons. The nitro groups were reduced to amines in 73% yield using $SnCl_2.2H_2O$. The ^{1}H NMR spectrum of tetramine **74** showed a multiplet at δ 6.5 (4H) and a singlet at δ 6.67 corresponding to aromatic protons (**Fig. 14**). Tetramine was polymerized with isophthalic acid in the presence of polyphosphoric acid to give polybenzimidazole (**75**) which showed inherent viscosity of 1.9 dL/g. The interesting feature of this method is that none of the above step requires purification by column chromatography. These polymers of high thermal and mechanical stability are widely used as proton-conducting materials for fuel cell applications.

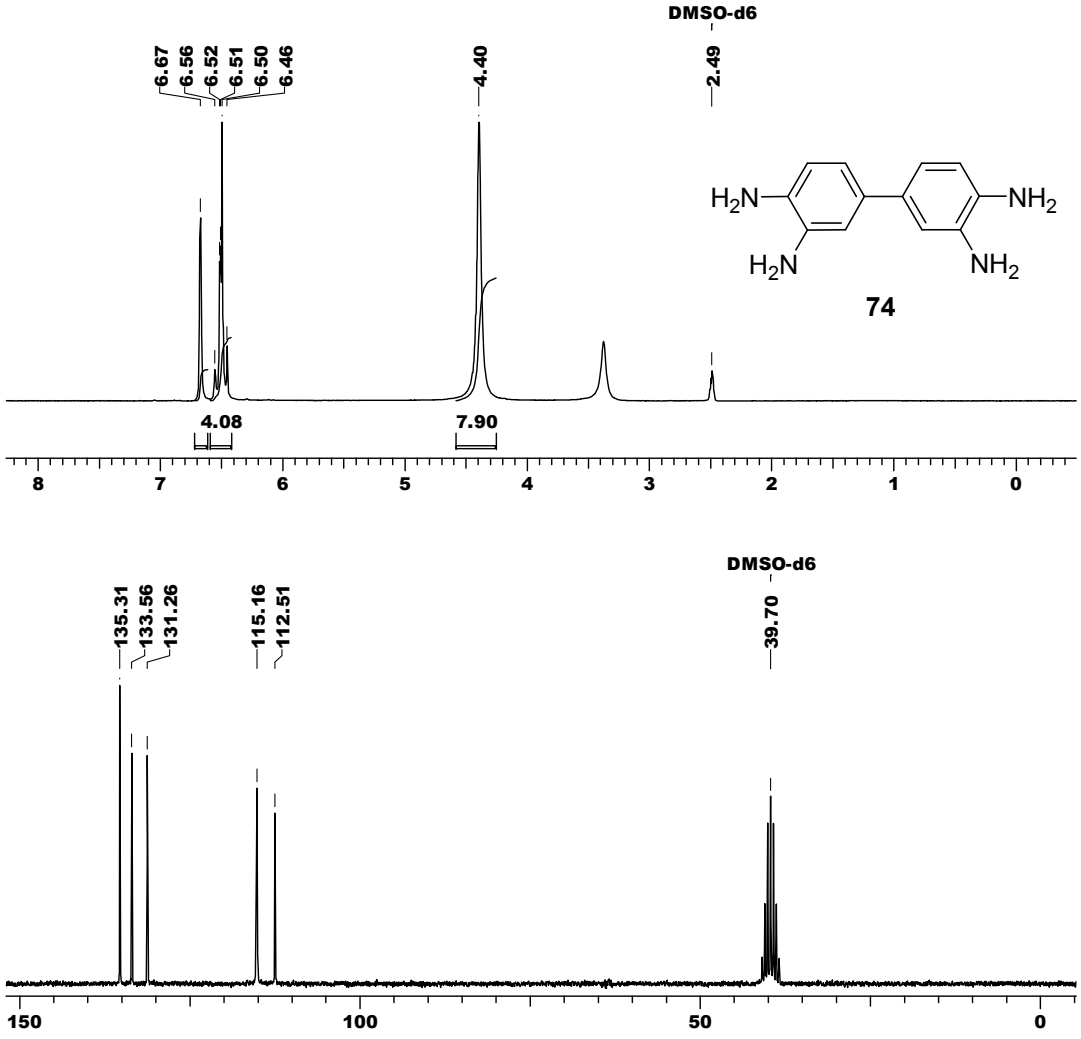


Fig. 14: ^{1}H and ^{13}C NMR spectra of 3,3′, 4,4′-Tetraminobiphenyl (74)

4.2.5 Conclusion

We have successfully demonstrated the use of water soluble saccharin palladium complex (**30**) for Suzuki coupling of butyl 2-bromoacrylate with arylboronic acids, for the synthesis of α-arylpropionic acids (**34-35**). We have also used saccahrin palladium complex in the synthesis of nabumetone (**37**) and (*R*)-cinacalcet (**38**) *via* Heck reaction. We have also synthesized tetraminobiphenyl (**74**), which is used as monomer in the

preparation of polybenzimidazole (**75**). The reactions are rapid, requiring a relatively low amount of Pd-catalyst.

4.2.6 Experimental Section

Butyl 2,3-dibromopropanoate (56):

To a stirred solution of butyl acrylate (12.8 g, 100 mmol,) in acetic acid (50 mL) was added bromine (22.5 g in 50 mL of acetic acid) at 0 °C. The reaction mixture was stirred at 25 °C for 2 h, poured into crushed ice and the precipitate formed was filtered off and washed with saturated sodium thiosulfate solution to give butyl 2,3-dibromopropanoate **56**.

Yield: 27.649 g (96%); **mp**: 62-63 ºC; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.95 (t, J = 7.2 Hz, 3H), 1.33-1.52 (m, 2H), 1.62-1.76 (m, 2H), 3.68 (dd, J = 4.4, 9.8 Hz, 1H), 3.93 (t, J = 11.3 Hz, 1H), 4.25 (t, J = 6.5 Hz, 2H), 4.44 (dd, J = 4.4, 11.3 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.5, 18.8, 29.6, 30.2, 41.1, 66.1, 167.3; **Analysis: $C_7H_{12}Br_2O_2$** requires C, 29.20; H, 4.20; Br, 55.49; found C, 29.41; H, 4.37; Br, 55.61%.

Butyl 2-bromoacrylate (57):

To a stirred solution of butyl 2,3-dibromopropanoate 56 (14.4 g, 50 mmol,) in toluene was added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (8.37 g, 55 mmol,) at -20 ^{o}C. The reaction mixture was stirred at the same temperature for 1 h. The hydro bromide salt of DBU was filtered out and the filtrate was evaporated to get butyl 2-bromoacrylate **57** as colorless oil.

Yield: 10.146 g (98%); **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.96 (t, *J* = 7.2 Hz, 3H), 1.38-1.52 (m, 2H), 1.59-1.73 (m, 2H), 4.23 (t, *J* = 6.7 Hz, 2H), 6.26 (d, *J* = 1.5 Hz, 1H), 6.95 (d, *J* = 1.5 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.5, 18.9, 30.3, 66.3, 121.3, 131.9, 161.7; **Analysis: $C_7H_{11}BrO_2$** requires C, 40.60; H, 5.35; Br, 38.59; found C, 40.72; H, 5.28, Br, 38.74%.

2-Arylacrylic acids (60a-c):

To a stirred mixture of arylboronic acids (7.5 mmol), K_2CO_3 (1.38 g, 10 mmol), Pd-catalyst **30** (3 mg, 0.005 mmol), in toluene (15 mL) was added butyl 2-bromoacrylate (1.035 g, 5 mmol) at 25 °C. The reaction mixture was heated in an oil bath at 100 °C. The progress of the reaction was monitored by TLC. After the completion of the reaction it was then allowed to cool to 25 °C, quenched with water (20 mL) and extracted with ethyl acetate (3 x 25 mL). The combined organic extracts were concentrated under reduced pressure to afford crude acrylic esters. To the crude ester, 6 M NaOH solutions (5 mL) was added and refluxed at 100 °C. After 1 h, con. HCl was added to remove excess base and the reaction mass was extracted with ethyl acetate (3 x 25 mL) washed with water, brine and dried over anhyd. Na_2SO_4. The combined organic extracts were concentrated under reduced pressure to afford crude acrylic acids. It was then purified by column chromatography on silica gel using pet. ether and ethyl acetate as eluent to obtain pure arylacrylic acids (**60a-c**).

2-(2-Methoxynaphthalen-6-yl)acrylic acid (60a): **Yield**: 0.907 g (53%); **mp**: 92-93 ºC; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.93 (s, 3H), 6.12 (d, *J* = 1.01 Hz, 1H), 6.58 (d, *J* = 1.14 Hz, 1H), 7.13-7.18 (m, 2H), 7.53 (dd, *J* = 1.8, 8.5 Hz, 1H), 7.74 (dd, *J* = 3.4, 8.5 Hz, 2H), 7.87 (d, *J* = 1.7 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 54.8, 104.0, 117.2, 117.8,

124.1, 124.8, 125.3, 127.0, 127.5, 131.8, 132.2, 134.8, 155.8, 178.2; **Analysis**: $\mathbf{C_{14}H_{12}O_3}$ requires C, 73.67; H, 5.30; found C, 73.51; H, 5.48%.

2-(4-Isobutylphenyl)acrylic acid (60b): **Yield**: 0.643 g (42%); gum; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.89 (d, *J* = 7.1 Hz, 6H), 1.81-1.86 (m, 1H), 2.41 (d, *J* = 7.1 Hz, 2H), 6.07 (d, *J* = 1.0 Hz, 1H), 6.59 (d, *J* = 1.1 Hz, 1H), 7.09 (d, *J* = 8.0 Hz, 2H), 7.23 (d, *J* = 8.1 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 22.3, 30.1, 48.1, 117.8, 127.2, 129.3, 132.5, 136.9, 140.7, 188.9; **Analysis**: $\mathbf{C_{13}H_{16}O_2}$ requires C, 76.44; H, 7.90; found C, 76.58; H, 8.02 %.

2-Phenylacrylic acid (60c): Yield: 0.533 g (48%); gum; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 6.00 (d, *J* = 1.3 Hz, 1H), 6.54 (d, *J* = 1.3 Hz, 1H), 7.31-7.44 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 117.5, 126.3, 126.4, 127.3, 132.7, 133.3, 166.4; **Analysis**: $\mathbf{C_9H_8O_2}$ requires C, 72.96; H, 5.44; found C, 73.07; H, 5.58%.

(*S*)(+)-α-arylpropionic acids:

A 100-mL Parr autoclave was charged with ruthenium (II) acetylacetonate (44 mg, 0.1 mmol), (*S*)-(-)-2,2'-bis(diphenylphosphino)-l,l'-binaphthyl ((*S*)-BINAP) (75 mg, 0.12 mmol), arylacrylic acid (2 mmol) and methanol (30 mL). The reactor was pressurized to 1000 psig with H_2 followed by stirring at 25 °C for 17 h to afford the corresponding α-arylpropionic acids (**34**, **35** or **36**) in pure form.

(*S*)-2-(2-methoxynaphthalen-6-yl)propanoic acid, (*S*)-naproxen (34):**Yield**: 0.382 g (83%); **mp**: 155-157 ºC; **$[\alpha]^{25}_D$** +56.9 (*c* 1, $CHCl_3$) 86% ee {lit.[67] **$[\alpha]^{25}_D$** +66 (*c* 1, $CHCl_3$)}; **IR** (Nujol, cm^{-1}): 896, 926, 1029, 1159, 1176, 1260, 1378, 1606, 1630, 1664, 1728, 2866, 2925, 2954; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.58 (d, *J* = 7.1 Hz, 3H), 3.81-3.89 (m, 4H), 7.10-7.42 (m, 3H), 7.66-7.70 (m, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 16.9,

43.5, 53.5, 104.0, 117.2, 124.1, 124.8, 125.3, 127.0, 127.5, 131.8, 134.8, 155.8, 174.3; **MS** (m/z, % relative intensity): 230 (M^+, 53), 185 (100), 170 (10), 154 (7), 141 (11), 115 (9), 77 (2), 63 (2); **Analysis**: **$C_{14}H_{14}O_3$** requires C, 72.40; H, 6.08; found C, 72.52; H, 6.19%.

(*S*)-2-(4'-Isobutylphenyl)propionic acid, (S)-ibuprofen (35): **Yield**: 0.338 g (82%); **mp**: 50-52 ^oC; **$[\alpha]^{25}_D$** +52.7 (*c* 2, EtOH) 88% ee {lit.[67] **$[\alpha]^{25}_D$** +59 (*c* 2, EtOH)}; **IR** ($CHCl_3$, cm^{-1}): 729, 947, 1137, 1413, 1459, 1601, 1707, 2946, 2982, 3088; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.89 (d, *J* = 7.1 Hz, 6H), 1.49 (d, *J* = 7.2 Hz, 3H), 1.80-1.84 (m, 1H), 2.44 (d, *J* = 7.1 Hz, 2H), 3.70 (q, *J* = 7.2 Hz, 1H), 7.09 (d, *J* = 8.1 Hz, 2H), 7.21 (d, *J* = 8.1 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 17.9, 22.3, 30.1, 45.0, 127.2, 129.3, 136.9, 140.7, 181.4; **MS** (m/z, % relative intensity): 206 (M^+, 50), 163 (94), 161 (100), 119 (42), 107 (30), 91 (49); **Analysis**: **$C_{13}H_{18}O_2$** requires C, 75.69; H, 8.80; found C, 75.52; H, 8.79%.

(*S*)-(+)-2-Phenylpropanoic acid (36): **Yield**: 0.24 g (80%); gum; **$[\alpha]^{25}_D$** +63.2 (*c* 1.6, $CHCl_3$) 84% ee {lit. [67] **$[\alpha]^{25}_D$** +73 (*c* 1.6, $CHCl_3$, 97% ee)}; **IR** ($CHCl_3$, cm^{-1}): 698, 729, 937, 1130, 1413, 1454, 1600, 1706, 2935, 2981, 3087; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.49 (d, *J* = 8.1 Hz, 3H), 3.69 (q, *J* = 8.1 Hz, 1H), 7.20-7.29 (m, 5H), 11.19 (bs, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 18.2, 45.5, 127.6, 128.6, 139.8, 180.9; **MS** (m/z, % relative intensity): 150 (M^+, 13), 105 (100), 91 (13), 77 (50), 63 (13); **Analysis**: **$C_9H_{10}O_2$** requires C, 71.98; H, 6.71; found C, 71.82; H, 6.66%.

(*E*)-Butyl 3-[(6-methoxy)-2-napthyl]-2-propenoate (61):

To a stirred mixture of diethylamine (0.585 g, 8 mmol), 2-bromo-6-methoxynaphthalene (0.948 g, 4 mmol), palladium complex (**30**) (0.3 g, $5x10^{-4}$ mmol) in NMP (10 mL) was

added *n*-butyl acrylate (0.769 g, 6 mmol) at 135 °C. After completion of the reaction, the mixture was cooled and poured into water (25 mL) and extracted with ethyl acetate (2 x 50 mL). The collected organic layers were washed with water (3 x 25 mL), brine (25 mL) and dried over anhyd. Na_2SO_4. The organic layer was evaporated under reduced pressure and purified by column chromatography.

Yield: 0.967 g (85%); **mp**: 45 °C; **IR** ($CHCl_3$, cm^{-1}): 852, 981, 1031, 1168, 1251, 1309, 1344, 1392, 1483, 1600, 1623, 1704, 2873, 2950, 3108; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.98 (t, *J* = 7.2 Hz, 3H), 1.36-1.55 (m, 2H), 1.64-1.78 (m, 2H), 3.92 (s, 3H), 4.22 (t, *J* = 6.3 Hz, 2H), 6.48 (d, *J* = 16.1 Hz, 1H), 7.09-7.17 (m, 2H), 7.60-7.83 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.6, 19.1, 30.6, 55.1, 64.2, 105.7, 119.2, 124.0, 127.3, 128.4, 129.4, 129.5, 129.9, 135.4, 144.6, 158.6, 167.1. **Analysis: $C_{18}H_{20}O_3$** requires C, 76.03; H, 7.09. Found: C, 76.18; H, 7.19%.

Butyl 3-[(6-methoxy)-2-napthyl]-2-propanoate (62):

To a stirred mixture of unsaturated ester **61** (0.568 g, 2 mmol), $CoCl_2.6H_2O$ (0.012 g, 5 mol%) in methanol (25 mL) was added sodium borohydride (0.227 g, 6 mmol) at 25 °C. Evolution of hydrogen gas was observed and then black precipitates appeared during the addition of remaining sodium borohydride. Reaction mixture was stirred for 1 h, quenched with water (25 mL) and extracted with ethyl acetate (2 x 15 mL). The collected organic layers were washed with water (3 x 25 mL), brine (25 mL) and dried over anhyd. Na_2SO_4. The solvent was evaporated under reduced pressure and the crude product purified by column chromatography.

Yield: 0.544 g (95%); **mp:** 47 °C; **IR** ($CHCl_3$, cm^{-1}): 757, 854, 1031, 1062, 1161, 1174, 1228, 1263, 1292, 1332, 1417, 1461, 1485, 1506, 1606, 1633, 1731, 2871, 2935, 2968,

3012. **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.87 (t, *J* = 7.3 Hz, 3H), 1.24-1.35 (m, 2H), 1.51-1.58 (m, 2H), 2.68 (t, *J* = 7.1 Hz, 2H), 3.05 (t, *J* = 7.2 Hz, 2H), 3.87 (s, 3H), 4.05 (t, *J* = 6.7 Hz, 2H), 7.09-7.14 (m, 2H), 7.25-7.29 (m, 1H), 7.54 (s, 1H), 7.63-7.67 (m, 2H)**;** **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.3, 18.8, 30.3, 30.6, 35.7, 54.9, 64.2, 105.3, 118.4, 126.0, 126.7, 127.1, 128.7, 128.8, 132.9, 135.3, 157.0, 173.2; **MS** (m/z, % relative intensity); 286 (34), 184 (39), 171 (100), 153 (5), 141 (18), 128 (20), 115 (13), 92 (11), 55 (16), 41 (32); **Analysis: $C_{18}H_{22}O_3$** requires C, 75.50; H, 7.74; found C, 75.64, H, 7.84%.

4-(6-Methoxy-2-napthyl)butan-2-one; Nabumetone (37):

To a stirred mixture of saturated ester (0.286g of 1 mmol) in THF (10 mL) was added methyl magnesium iodide (prepared by addition of methyl iodide (0.142 g of 1 mmol) to magnesium (0.024 g) in 10 mL of THF) at -55 ^oC. After completion of the reaction (2 h), the reaction mixture was quenched with 2 M HCl (20 mL) and extracted with ether. The organic layer was washed with brine and dried over anhyd. Na_2SO_4, evaporated under reduced pressure and the crude product purified by column chromatography.

Yield: 0.146 g (64%); **mp**: 80 °C; **IR** ($CHCl_3$, cm^{-1}): 757, 850, 1031, 1770, 1221, 1266, 1363, 1390, 1485, 1605, 1633, 1712, 2360, 2840, 2937, 2966, 3016. **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.13 (s, 3H), 2.80 (t, *J* = 7.1 Hz, 2H), 3.00 (t, *J* = 7.2 Hz, 2H), 3.89 (m, 3H), 7.07-7.13 (m, 2H), 7.23-7.28 (m, 2H), 7.51 (s, 1H), 7.61-7.66 (m, 2H)**;** **^{13}C NMR** (50 MHz, $CDCl_3$): δ 29.5, 29.9, 45.0, 55.0, 105.4, 118.7, 126.1, 126.8, 127.3, 128.7, 132.9, 135.9, 157.1, 207.5. **MS** (m/z, % relative intensity); 228 (34), 185 (11), 171 (100), 158 (5), 141 (9), 128 (23), 115 (14), 63 (7), 43 (64); **Analysis: $C_{15}H_{16}O_2$** requires C, 78.92; H, 7.06; found C, 78.81, H, 7.24%.

(*E*)-Butyl 3-[(3-trifluoromethyl)phenyl]-2-propenoate (64):

To a stirred mixture of 3-bromobenzotrifluoride **(63)** (2.25 g, 10 mmol), triethylamine (2.02 g, 20.0 mmol), *n*-butyl acrylate (2.56 g, 20 mmol) in NMP (30 mL) was added Pd-catalyst **30** (0.3 mg, $5x10^{-4}$ mmol) in NMP at 25 °C. The reaction mixture was heated in an oil bath at 120 °C for 3 h and was then allowed to cool to room temperature. It was then quenched with 10% HCl (5 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were washed with water, brine and dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to afford crude product, which was purified by column chromatography on silica gel using pet. ether and ethyl acetate as eluents to afford unsaturated ester **64**.

Yield: 2.45 g (90%); viscous liquid; **IR** ($CHCl_3$, cm^{-1}): 803, 865, 902, 984, 1076, 1096, 1134, 1177, 1196, 1219, 1270, 1311, 1335, 1387, 1439, 1643, 1709, 2963; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.95 (t, *J* = 7.4 Hz, 3H), 1.33- 1.48 (m, 2H), 1.60- 1.74 (m, 2H), 4.19 (t, *J* = 6.7 Hz, 2H), 6.47 (d, *J* = 16.1 Hz, 1H), 7.44-7.74 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.4, 19.0, 30.7, 64.2, 120.3, 124.4, 126.2, 129.1, 130.7, 131.2, 131.6, 135.3, 142.2, 165.8; **MS** (m/z, % relative intensity): 272 (M^+, 9), 253 (7), 216 (57), 199 (100), 171 (31), 151 (59), 102 (14), 56 (47), 41 (50); **Analysis: $C_{14}H_{15}F_3O_2$** requires C, 61.76; H, 5.55. Found: C, 61.55; H, 5.81%.

Butyl 3-[(3-trifluoromethyl)phenyl]propanoate (65):

To a stirred mixture of unsaturated ester **64** (2.178 g, 8 mmol) and $CoCl_2.6H_2O$ (0.189 g, 10 mol%) in methanol (25 mL) was added sodium borohydride (0.908 g, 24 mmol) at 25 °C. Evolution of hydrogen gas was observed and then black precipitate appeared during the addition of sodium borohydride. When the addition was complete, stirring was

continued for 1 h at 25 °C. After completion of the reaction, the mixture was cooled, poured into water (25 mL) and extracted with ethyl acetate (2 x 15 mL). The collected organic layers were washed with water (3 x 25 mL), brine (25 mL) and dried over anhyd. Na_2SO_4. The solvents were evaporated under reduced pressure and crude product purified by column chromatography.

Yield: 2.08 g (95%); viscous liquid; **IR** ($CHCl_3$, cm^{-1}): 659, 702, 802, 893, 1074, 1124, 1199, 1330, 1438, 1596, 1737, 2341, 2875, 2958; ^{1}**H NMR** (200 MHz, $CDCl_3$): δ 0.91 (t, *J* = 7.3 Hz, 3H), 1.26-1.36 (m, 2H), 1.52-1.61 (m, 2H), 2.63 (t, *J* = 8.1 Hz, 2H), 3.00 (t, *J* = 8.1 Hz, 2H), 4.05 (t, *J* = 6.6 Hz, 2H), 7.37-7.45 (m, 4H); ^{13}**C NMR** (50 MHz, $CDCl_3$): δ 13.6, 19.1, 30.7, 30.8, 35.5, 64.4, 125.1, 128.9, 131.7, 141.5, 172.2; **MS** (m/z, % relative intensity) 274 (M+, 6), 255 (3), 218 (31), 198 (14), 172 (100), 159 (43), 133 (17), 109 (7), 57 (69), 41 (86); **Analysis:$C_{14}H_{17}O_2F_3$** requires C, 61.31; H, 6.25; found C, 61.25; H, 6.52%.

3-[(3-Trifluoromethyl)phenyl]propanamide (66):

To a stirred solution of saturated ester **65** (1.096 g, 4 mmol) in methanol (20 mL) was added con. ammonia (8 mL) at 0 °C and stirred at 25 °C. After completion of the reaction, as monitered by TLC, the solvent was removed under reduced pressure and the crude amide was purified by column chromatography.

Yield: 0.695 g (80%); viscous liquid; ^{1}**H NMR** (200 MHz, $CDCl_3$): δ 2.51 (t, *J* = 7.3 Hz, 2H), 2.98 (t, *J* = 7.3 Hz, 2H), 6.01 (s, 1H), 6.46 (s, 1H), 7.28-7.43 (m, 4H); ^{13}**C NMR** (50 MHz, $CDCl_3$): δ 30.8, 36.9, 121.3, 122.9, 126.7, 128.7, 131.6, 141.5, 175.2; **MS** (m/z, % relative intensity) 217 (M+, 43), 198 (9), 172 (24), 159 (34), 151 (9), 133 (21), 119 (3),

109 (10), 72 (29), 55 (10), 44 (100); **Analysis: $C_{10}H_{10}OF_3N$** requires C, 55.3; H, 4.64; N, 6.45; found C, 55.15; H, 4.52; N, 6.25%.

3-[(3-Trifluoromethyl)phenyl]propylamine (67):

To a stirred mixture of lithium aluminium hydride (0.68 g, 18 mmol) in THF (15 mL) was added a solution of 3-(3-trifluoromethylphenyl)propanamide **(66)** (0.434 g, 2 mmol) in THF at 0 °C and the mixture was refluxed for 2 h. After cooling to 25 °C, it was quenched with ethyl acetate and water. The crude product was extracted with ethyl acetate (3 x 60 mL). The organic layer was washed with brine (50 mL), dried over anhyd. Na_2SO_4. After evaporation of the solvent under reduced pressure, the crude amine was purified by column chromatography.

Yield: 0.264 g (65%); viscous liquid; **IR** ($CHCl_3$, cm^{-1}): 659, 704, 800, 1020, 1074, 1164, 1330, 1406, 1566, 2854, 2923, 3450; ^{1}**H NMR** (200 MHz, $CDCl_3$): δ 1.92 (m, 2H), 2.77 (t, *J* = 6.2 Hz, 2H), 3.3 (t, *J* = 6.2 Hz, 2H), 7.34-7.51 (m, 4H); ^{13}**C NMR** (50 MHz, $CDCl_3$): δ 31.8, 33.9, 61.5, 122.6, 125.0, 128.6, 131.7, 142.8; **MS** (m/z, % relative intensity) 203 (M+, 3), 186 (62), 172 (2), 159 (31), 141 (5), 133 (17), 117 (100), 109 (16), 91 (28), 77 (7), 57 (7), 43 (10); **Analysis: $C_{10}H_{12}F_3N$** requires C, 59.11; H, 5.95; N, 6.89; found C, 58.9; H, 5.75, N, 7.31%.

α-Methyl-1-naphthalenemethanol (69)

To a stirred mixture of 1-acetylnaphthalene (5.1 g, 30 mmol) in methanol (50 mL) was added $NaBH_4$ (1.665 g, 45 mmol) portion wise at 0 °C. The reaction mixture was stirred for 3 h and solvent was evaporated. The residue was taken up in H_2O (25 mL) and extracted with CH_2Cl_2 (3x 30 mL). The organic layer was washed with brine (25 mL),

dried over anhyd. Na_2SO_4. After evaporation of the solvent under reduced pressure, the crude product was purified by column chromatography to give the alcohol **69**.

Yield: 95 %; **mp:** 50 °C; **IR** ($CHCl_3$, cm^{-1}): 1010, 1056, 1108, 1168, 1218, 1256, 1328, 1374, 1445, 1509, 1597, 3011; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.48 (d, *J* = 6.3 Hz, 3H), 3.01 (s, 1H), 5.40 (q, *J* = 6.3 Hz, 1H), 7.31- 7.90 (m, 7H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 24.1, 66.2, 121.7, 122.9, 124.9, 125.1, 125.3, 127.2, 128.4, 129.9, 133.4, 141.2; **MS** (m/z, % relative intensity) 172 (M+, 29), 157 (34), 153 (21), 129 (100), 115 (3), 102 (3), 76 (16), 63 (14), 43 (38); **Analysis: $C_{12}H_{12}O$** requires C, 83.68; H, 7.03; found C, 83.33, H, 7.31%.

(*S*)-(+)-α-Methyl-1-naphthalenemethanol (68): Oxidative Kinetic Resolution of racemic alcohol 69:

To a stirred mixture of molecular sieves (0.5 g, MS3Å), Pd $(OAc)_2$ (0.033 g, 5 mol%,) in toluene (15 mL) was added (-)-sparteine (0.14 g, 20 mol%). The flask was vacuum evacuated and filled with O_2, then heated to 80 °C for 15 min. A solution of alcohol (0.516 g, 3 mmol) in toluene (2 mL) and *t*-BuOH (3 mL) was added to the reaction mixture was maintained at 80 °C. The progress of the reaction was monitored by TLC. After 12 h, it was filtered through a pad of silica, evaporated and purified by column chromatography.

Yield: 0.352 g (41%); **mp:** 50 °C; **$[\alpha]^{25}_D$** -67.76 (*c* 1, MeOH) {lit.[71] $[\alpha]^{25}_D$ -77 (*c* 1, MeOH)}; **HPLC**: 88% ee, Chiracel OD-H, λ = 254 nm, 2-propanol/hexane (91:9), 1 mL/min, retention time: (*S*)-enantiomer 9.66 min, (*R*)-enantiomer 15.32 min;

(*S*)-(-)-α-Methyl-1-naphthalenemethanol (68): Transfer hydrogenation using (1*S*, 2*S*)-*N*-*p*-toluenesulfonyl-1,2-diphenyl ethylenediamine (71)

A solution of (*p*-cymene)ruthenium(II) chloride dimer (0.075 g, 0.015 mmol) and (1*S*, 2*S*)-*N*-*p*-toluenesulfonyl-1,2-diphenylethylenediamine (**71**) (0.009 g, 0.06 mmol) in dry propan-2-ol (5 mL) was heated at 80 °C for 20 min. under nitrogen. After cooling to 25 °C, the light brown solution was transferred to reaction mixture containing ketone (0.85 g, 5 mmol), KOH (1.25 mL, 2.5 mol%, 0.125 mmol, 0.1 M in propan-2-ol) and dry propan-2-ol (45 mL). The whole reaction mixture was stirred at 25 °C for 12 h and the dark brown solution was filtered through a pad of silica. The filtrate was concentrated *in vacuo* to give the crude α-methyl-1-naphthalenemethanol **(68),** which was purified by column chromatography.

Yield: 0.713 g (83%); **mp:** 50 °C; **$[\alpha]^{25}_{D}$** -73.9 (*c* 1, MeOH) {lit.[71] $[\alpha]^{25}_{D}$ -77 (*c* 1, MeOH)}; **HPLC**: 96% ee, Chiracel OD-H, λ = 254 nm, 2-propanol/hexane (91:9), 1 mL/min, retention time: (*S*)-enantiomer 9.93 min, (*R*)-enantiomer 15.73 min;

(*R*)-Cinacalcet (38):

To a stirred solution of amine **67** (0.152 g, 0.75 mmol), alcohol **68** (0.206 g, 1.2 mmol) and triphenylphosphine (0.289 g, 1.1 mmol) in ether (20 ml) was added dropwise diisopropyl azodicarboxylate (0.222 g, 1.1 mmol) at 0 °C under nitrogen atmosphere. After stirring at 0 °C for 4 h, the mixture was concentrated to get crude residue which was purified by column chromatography to give (*R*)-cinacalcet (**38**).

Yield: 0.22 g (82%); **$[\alpha]^{25}_{D}$** -7 (*c* 1.0, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 1028, 1164, 1255, 1328, 1403, 1452, 1541, 1666, 1720, 2854, 2923, 3261, 3435; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.15 (d, *J* = 8Hz, 3H), 1.15-1.68 (m, 2H), 2.53 (t, *J* = 6.3 Hz, 2H), 3.07 (q, *J* = 6.3 Hz, 1H), 4.03 (t, *J* = 6.2 Hz, 2H), 6.76-7.30 (m, 11H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 22.5,

29.9, 32.5, 48.6, 60.6, 122.5, 124.2, 124.3, 124.5, 125.6, 125.8, 126.1, 126.5, 126.9, 128.6, 129.2, 131.1, 131.5, 132.6, 133.5, 139.4, 141.6.

3,3′-Dinitro,4,4′-diaminobiphenyl (73):

To a stirred mixture of 4-iodo-2-nitroaniline **(72)** (10 g, 37.87 mmol), triethylamine (7.65 g, 75.8 mmol) in toluene (50 mL) was added Pd-catalyst **30** (25 mg, 0.1 mol %) at 25 °C. The reaction mixture was heated in an oil bath at 110 °C for 15 h and was then allowed to cool to room temperature. The coupled product 3, 3'-dinitrobenzidine (DNB), separated from the solvent by simple filtration. The crude biphenyl was washed with petroleum ether followed by dichloromethane to obtain 3,3′-dinitro,4,4′-diaminobiphenyl almost in pure form.

Yield: 4.62 g (89%); **mp**: 280 ˚C decomp.; **IR** (KBr, cm^{-1}): 764, 819, 1095, 1188, 1250, 1298, 1353, 1408, 1463, 1511, 1551, 1638, 3084, 3173, 3364, 3476; **^{1}H NMR** (200 MHz, DMSO- d_6) δ 7.09 (d, *J* = 8.8 Hz, 2H), 7.51 (bs, 4H), 7.73 (d, *J* = 8.5 Hz, 2H), 8.12 (s, 2H); **^{13}C NMR** (50 MHz, DMSO- d_6): δ 121.1, 122.2, 126.8, 131.3, 134.6, 146.0; **Analysis:** $\mathbf{C_{12}H_{10}N_4O_4}$ requires C, 52.56; H, 3.68; N, 20.43; found: C, 52.72; H, 2.55, N, 20.38%.

3,3′, 4,4′-Tetraminobiphenyl (74):

To a stirred mixture of $SnCl_2.2H_2O$ (27.8 g, 123.21 mmol), 3,3′-dinitro,4,4′-diaminobiphenyl (5 g, 18.24 mmol) was added con. HCl (50 mL) at 25 ºC. Then the reaction mixture was stirred for 2 h at 40 ºC for complete reduction. The hydrochloride salt of tetramine was precipitated out, which was made basic with cold 10% NaOH solution and the free amine was filtered out, washed with water dried under vacuum to give 3, 3'-diaminobenzidine (**74**).

Yield: 2.853 g (73%); **mp**: 175-176 ˚C (recrystallized from hot water); **IR** (KBr, cm^{-1}): 720, 763, 822, 1088, 1165, 1277, 1410, 1502, 1575, 1634, 1876, 3018, 3050, 3185, 3302, 3388; **^{1}H NMR** (200 MHz, DMSO- d_6) δ 4.40 (bs, 8H), 6.46-6.56(m, 4H), 6.67 (s, 2H); **^{13}C NMR** (50 MHz, DMSO- d_6): δ 112.5, 115.1, 115.2, 131.2, 133.5, 135.3; **Analysis:** **$C_{12}H_{14}N_4$** requires C, 67.27; H, 6.59; N, 26.15; found: C, 67.18; H, 6.67, N, 26.38%.

Polybenzimidazole (PBI) (75):

Polyphosphoric acid (450 g) was taken in a 3 neck round bottomed flash equipped with overhead mechanical stirrer and heated at 120 ºC with continuous flow of dry nitrogen. Tetraminobiphenyl (15 g, 70 mmol) was added at the same temperature and the reaction mixture was heated to 145 ºC with stirring. Isophthalic acid (11.63 g, 70 mmol) was added at 145 ºC and the temperature was increased to 170 ºC. After stirring for 5 h, the reaction mixture temperature was increased to 200 ºC and kept at the same temperature for 14 h. Then it was cooled to 120 ºC and added slowly to cold distilled water with vigorous stirring to get the polymer threads.

Yield: 22.18 g (92%); **Inherent viscosity:** 1.9 dL/g in H_2SO_4.

SECTION 3:

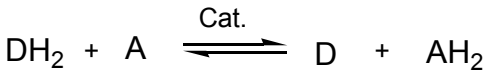
Cobalt Catalyzed Transfer Hydrogenation of Carbonyl Compounds using 2- Propanol as a Hydrogenation Source

4.3.1 Introduction

4.3.1.1 Transfer Hydrogenation

Reduction of organic compounds is an important reaction both in laboratory and industry. Particularly, catalytic transfer hydrogenation[72] has found wide spread use in organic synthesis.[73] In comparison with the catalytic reduction using molecular hydrogen,[74] hydrogen donors such as ammonium formate, isopropyl alcohol, formic acid, and sodium formate have real and potential advantages.[75] Transfer hydrogenation provides mild conditions, offers enhanced selectivity and avoids the risk and constraints associated with high-pressure reactors. Additionally, the rate and selectivity of the reaction can be favorably affected by selecting the most appropriate hydrogen donors.[76]

The process entails hydrogen abstraction from the reagent (hydrogen donor) by means of a catalyst, followed by hydrogen addition to the unsaturated functional group of the substrate (hydrogen acceptor) (**scheme. 36**)



DH_2 = Hydrogen donor

A = Hydrogen acceptor

Scheme. 37: Transfer hydrogenation

Several different substrates have been successfully reduced by transfer hydrogenation in the presence of heterogeneous and homogeneous catalysts.[76] The list of hydrogen acceptors include α, β- unsaturated acids, esters, imines and nitro compounds. Alkaline bases often act as crucial co-catalysts.

4.3.1.2 Hydrogen donors

Hydrogen donors can, in principle, is any organic compound whose oxidation potential is sufficiently low so that the hydrogen transfer can occur under mild conditions. The choice of hydrogen donor is generally determined by the ease of reaction and availability. The most popular hydrogen donors are alcohols and formic acid. Others include cyclohexene, cyclohexadiene, indene, tetraline, tetrahydroquinoline, dihydrofuran, dioxane, ethanol, 2-methoxyethanol, benzyl alcohol, polyvinyl alcohol, ascorbic acid, and hydrazine etc. Since dehydrogenation of formic acid derivatives is an irreversible and exothermic process, the use of such H-donors is recommended in reactions where unfavorable energetic balances are expected. Secondary alcohols are better H-donors than primary alcohols and can be successfully employed even in the reduction of ketones. Among secondary, 2-propanol is the most popular donor, because of its simplicity, cheapness and ease of acetone. 2-Propanol is a useful hydrogen donor for catalytic transfer hydrogenation of ketones, however the unfavorable ketone: alcohol equilibrium ratio often prevents a high conversion. Use of formic acid, another well behaving and inexpensive reducing agent, avoids these problems.

4.3.1.3 Types of Catalysts

A. Homogeneous Catalysts

Compounds of most of the elements from the second transition metal series in the periodic table are suitable for catalytic homogeneous reduction. Both salts and complexes of Pd, Pt, Ru, Ir, Rh, Fe, Ni, & Co have been used as the catalysts for the transfer of hydrogen from hydrogen donors to organic substrates. Generally, the most active catalysts are to be found in the salts and complexes of Rh, Ru and Pd. The catalytic activity of the transition metal salts and complexes is the result of a delicate balance of valence state and strength of chemical bonds.[78]

No catalytic activity is observed if the hydrogen donor and the transition metal form a stable compound. For the transfer of hydrogen to the substrate to occur, the hydrogen source must be accommodated by the transition metal.

B. Heterogeneous Catalysts

The most active catalysts for heterogeneous transfer reaction are based on Pd metal. Catalyst may be a pure bulk metal, finely divided, dispersed on various carriers, as with Pd on C, Pd/ $CaCO_3$, Pd/$BaSO_4$ and asbestos or be of a porous or skeletal type. Less versatile catalysts are derived from Ni, Rh, Ru, Pt, Os, and Co, again as finely divided metals, as metals supported on carbon (charcoal) or as skeletal metals like Raney Ni. Alloys of many metals have been investigated for catalytic activity towards hydrogenation, dehydrogenation and hydrogenolysis in industrial processes, but with a few exceptions such as Pd-Ru and Ni-Cu, these alloys have created only modest interest.

The major factor that need to be considered in the preparation of a heterogeneous catalysts are (a) the type of metal salt to be reduced to the metal, (b) the kind of reducing agent used (c) procedures adopted for washing the prepared catalyst and (d) the purity and physical state of the supporting material. In most cases, homogeneous catalysts show

better reactivity than its heterogeneous counterpart. Generally heterogeneous catalysts need more reaction time and higher temperature to achieve same performance of homogeneous one. The main advantage of heterogeneous catalyst is it can be reused several times for the same type of reaction before its activity is noticeably diminished.

4.3.1.4 Promotors

Strong bases like NaOH or KOH or sodium alkoxides are commonly used as promoters in transfer hydrogenation reactions since they exert a beneficial effect on the reaction rates. In the reduction of ketones with 2- propanol, base is essential for the activity. Base is believed to be effective by removing a proton from the reacting species. **Fig. 15** indicates how base promotes the transfer of hydride ion from an alkoxy radical to an adjoining coordinated ketone.

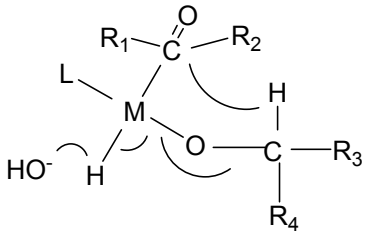


Fig. 15: Transfer of hydride ion from donor to acceptor

4.3.1.5 Effect of temperature and solvent

Generally increase in temperature leads to increased rates of reduction for most systems. However, the other factors such as catalyst, hydrogen acceptor, and solvent also have to be taken into account to get the optimal condition. Increase of temperature may lead to unwanted side reactions such as over reduction, isomerisation or decomposition of the substrates. At higher temperatures, the rate of reverse reaction also increases as well. However, a reaction condition for the forward reaction is different from the reverse reaction and lead to an overall acceleration in the forward reaction.

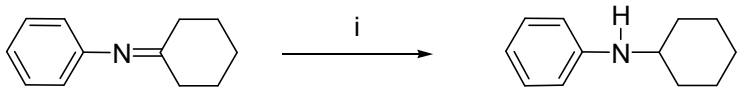
Proper choice of solvent is an important factor governing the activity of catalyst in transfer hydrogenation. Some metal catalysts are active in solutions only after dissociation of one or more ligands from the central metal atom with less than its maximum coordination number, thereby facilitating oxidative addition. The coordinate link between the solvent and catalyst should not be stronger than the binding of donor or acceptor.

4.3.2 Review of literature

In literature a wide variety of homogeneous and heterogeneous catalytic systems in combination with different hydrogen donors have been employed to selectively reduce most major functional groups attached to aliphatic and aromatic structures. The discovery of more active catalysts and efficient hydrogen donors has made this process more popular. Some of the recent developments on this reaction are discussed below.

Botta *et al.* (1985)[79]

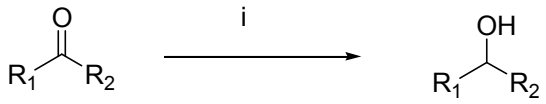
The reduction of several *N*-alkyl and *N*-aryl ketimines to the corresponding secondary amines have been achieved in high yields with isopropyl alcohol, aluminium isopropoxide in the presence of Raney Nickel (**Scheme 38**).



Scheme 38: (i) Raney Nickel, 2-propanol, $Al(O^iPr)_3$, reflux, 1 h, 80%.

Ratan *et al.* (1991)[80]

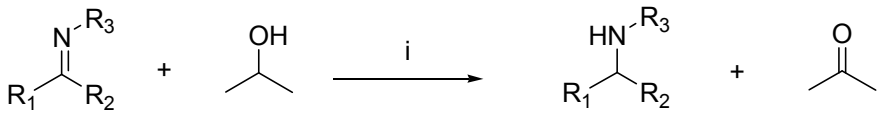
Ratan and co-workers have reported efficient reduction of both aliphatic and aromatic ketones using $RuCl_2(PPh_3)_3$ as catalyst and 2-propanol as hydrogen donor in the presence of NaOH as co-catalyst (**Scheme 39**).



Scheme 39: (i) $RuCl_2(PPh_3)_3$, 2-propanol, NaOH, reflux, 6 h, 89%.

Wang *et al.* (1992)[81]

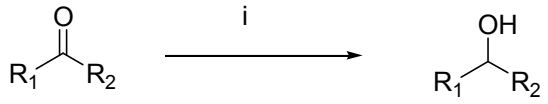
Wang and his co-workers have reported efficient transfer hydrogenation of imines using $RuCl_2(PPh_3)_3$ as catalyst and 2-propanol as hydrogen donor in the presence of NaOH as co-catalyst (**Scheme 40**).



Scheme 40: (i) $RuCl_2(PPh_3)_3$, K_2CO_3, reflux, 18 h, 93%.

Iyer *et al.* (1995)[82]

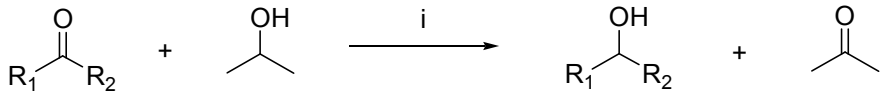
Iyer *et al* have reported transfer hydrogenation of aliphatic and aromatic ketones and aldehydes using $RuCl_2(PPh_3)_3$ as catalyst and 2-propanol as hydrogen donor in the presence of NaOH as co-catalyst (**Scheme 41**).



Scheme 41: (i) $NiCl_2(PPh_3)_2$ (5 mol %), 2-propanol, NaOH, reflux, 24 h, 82%.

Boldrini *et al.* (1995)[83]

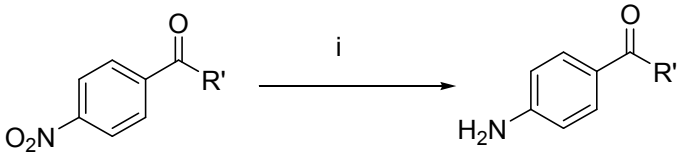
Boldrini *et al* have reported transfer hydrogenation of alkenes and carbonyl compounds using activated metallic nickel prepared by the thermal decomposition of nickel diisopropoxide in boiling 2-propanol (**Scheme 42**).



Scheme 42: (i) $NiCl_2$, LiO^iPr, 2-propanol, reflux, 3 h, 92%.

Upadhya *et al* .(1997)[84]

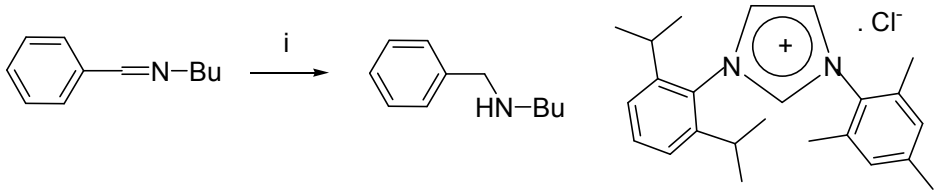
Upadhya *et.al*. have reported a convenient method for the chemo selective reduction of nitroarenes, aldehydes and ketones using Nickel stabilized Zirconia as catalyst and 2-propanol, KOH. The study established the reactivity order: NO_2 >> C=O > C-X >> C=C (**Scheme 43**).



Scheme 43: (i) $Zr_{0.8}Ni_{0.2}O_2$, 2-propanol, KOH, reflux, 3 h, 96%.

Kuhl *et al.* (2003)[85]

Transfer hydrogenation of imines to the corresponding amines catalyzed by Ni(0) / N-Hetero cyclic carbene species has been studied by Kuhl and coworkers. A variety of aldimines and ketimines were reduced in good to excellent yields under mild conditions (**Scheme 44**).



76

Scheme 44: (i) Ni(0), **76**, Et_2CHONa, dioxane, 100 °C, 6 h, 97%.

4.3.3 Present Work

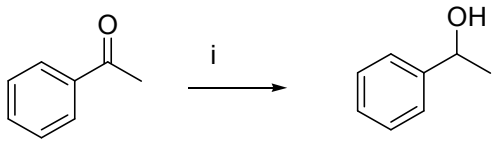
4.3.3.1 Objective

Although there are many methods available in the literature for transfer hydrogenation of carbonyl compounds using a variety of metal catalysts under homogeneous conditions, they suffer from certain drawbacks such as use of expensive metals like Pd, Pt, Ru, Rh etc., substrate scope, cumbersome experimental procedures and poor selectivity in product distribution. Further reduction of carbonyl compounds can be accomplished by classical Meerwein-Ponndorf-Verley reduction; however, the use of aluminium isopropoxide in stoichiometric amounts with drastic conditions leads to many side products. Moreover, metal complexes of Ni and Co have not been studied extensively for the transfer hydrogenation of ketones. In this section, we describe the results on cobalt salts-catalyzed transfer hydrogenation of carbonyl and nitro compounds using 2-propanol as hydrogen source and KOH as the base.

4.3.4 Results and Discussion

In our search for a much cheaper and effective catalytic system, we have chosen the simplest catalyst i.e. tris (triphenylphosphine)cobalt(I) chloride [$CoCl(PPh_3)_3$] which was

synthesized from $CoCl_2$ with PPh_3. For our initial studies, reduction of acetophenone in 2-propanol containing catalytic amount of $CoCl(PPh_3)_3$ and KOH under reflux condition gave 1-phenethanol in 95 % yield (**Scheme 45**).



Seheme 45: (i) $CoCl(PPh)_3$ (5 mol%), 2-propanol, KOH, 80 °C, 95%.

Out of several catalysts screened {$CoCl_2.6H_2O$, $Co(OAc)_2.4H_2O$, $CoCl_2(PPh_3)_2$, Co(salen) and $Co(DAC)Cl_2$ and $CoCl(PPh_3)_3$}, $CoCl(PPh_3)_3$ was found to be effective (95% yield). The reaction failed in the absence of either base or catalyst. We have also carried out the transfer hydrogenation of acetophenone using formic acid and ammonium formate as hydrogen source, using catalytic amount of $CoCl(PPh_3)_3$, but the reaction failed.

Table 6: Transfer hydrogenation of acetophenone to 1-phenethanol: Screening of transition metal complexes [a]

S.No	Catalyst	Yield (%)[b]
1	$CoCl_2.6H_2O$	85
2	$MnCl_2$	78
3	$NiCl_2.4H_2O$	82
4	5%Pd/C	66
5	$CoCl_2(PPh_3)_2$	77
6	$CoCl(PPh_3)_3$	95
6	$CoCl_2(DAC)$[c]	76
7	$Co(OAc)_2.4H_2O$	79
8	Co(salen)[d]	70

[a]Reaction condition: acetophenone (5 mmol), catalyst (5 mol%), KOH (5 mmol), 2-propanol (25 mL), 80 °C, 12 h. [b]Isolated yields. [c]Diaminocyclohexane. [d]Salen = salicylaldehyde + ethylene

diamine.

We have systematically studied the transfer hydrogenation reaction using $CoCl(PPh_3)_3$ as catalyst with a variety of carbonyl and nitro compounds in 2-propanol and the results are summarized in table 7.

Table 7: $CoCl(PPh_3)_3$-catalyzed transfer hydrogenation of carbonyl compounds using 2-propanol as a hydrogen source and KOH as co-catalyst

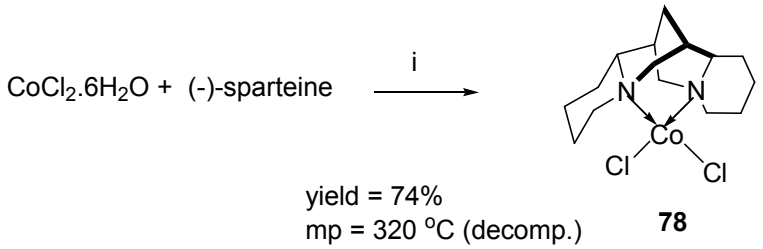
Entry	Substrate	Product (77a-u)	Yield (%)[b]
1	Acetophenone	1-Phenylethanol	95
2	4-Fluoroacetophenone	1-(4-Fluorophenyl)ethanol	92
3	4-Chloroacetophenone	1-(4-Chlorophenyl)ethanol	93
4	2,4-Dichloroacetophenone	1-(2,4-Dichlorophenyl)ethanol	92
5	4-Isobutylacetophenone	1-(4-Isobutylphenyl)ethanol	88
6	4-Methylacetophenone	1-(4-Methylphenyl)ethanol	89
7	4-Ethylacetophenone	1-(4-Ethylphenyl)ethanol	86
8	4-Methoxyacetophenone	1-(4-Methoxyphenyl)ethanol	73
9	3,4-Methoxyacetophenone	1-(3,4-Dimethoxyphenyl)ethanol	71
10	Propiophenone	1-Phenylpropanol	89
11	4-Bromopropiophenone	1-(4-Bromophenyl)propanol	87
12	1-Acetylnaphthalene	1-Naphthylethanol	90
13	6-Methoxy-2-acetylnaphthalene	1-(6-Methoxynaphthyl)ethanol	74
14	Cyclohexanone	Cyclohexanol	55
15	Benzaldehyde	Benzyl alcohol	86
16	4-Chlorobenzaldehyde[c]	4-Chlorobenzyl alcohol	80
17	4-Methoxybenzaldehyde[c]	4-Methoxybenzyl alcohol	73
18	4-Nitrobenzaldehyde[c]	4-Nitrobenzyl alcohol	78
19	2-Nitrobenzaldehyde[c]	2-Nitrobenzyl alcohol	74
20	Nirtobenzene	Aniline	87
21	2-Chloronirtobenzene	2-Chloroaniline	81

[a]Reaction condition: substrate (5 mmol), catalyst (5 mol%), KOH (5 mmol), 2-propanol (25 mL), 80 °C, 12 h. [b]isolated yields. [c]reactions was done at 25 °C .

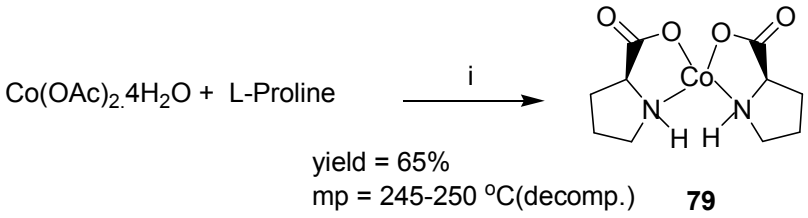
As can be seen from the table 7, the reaction proceeds very well with both electron-releasing and electron-withdrawing substituents present in the aromatic ring; however, the rate of reduction is faster in the case of substitution with electron-withdrawing groups (Table 7, entry 3 and 8). This catalytic system is also applicable for both aliphatic and aromatic carbonyl compounds. Interestingly, aldehydes were reduced at a faster rate than ketones; reactions proceed at 25 °C in such conditions, we also observed that even the nitro group was not reduced. This catalyst was also efficient for the reduction of nitro compounds into amines in reflux condition (entry 20 and 21). The alcohols formed were confirmed by ^{1}H, ^{13}C NMR, IR and Mass spectroscopy. For example, the ^{1}H NMR spectrum of 1-(4-fluorophenyl)ethanol (**77b**) showed a typical doublet at δ 1.43 and a quartet at δ 4.82 due to methyl and methine protons respectively. Its ^{13}C NMR spectrum showed characteristic signals at δ 24.9 and 69.3 corresponding to methyl and methine carbons respectively.

Asymmetric transfer hydrogenation using chiral cobalt complexes

In order to carry out the asymmetric version of transfer hydrogenation, we have prepared the chiral cobalt complexes using naturally occurring ligands such as (-)-sparteine and (L)-proline (**Scheme 46** and **47**).



Seheme 46: (i) $CoCl_2.6H_2O$, (-)- sparteine, EtOH, trimethoxyorthoformate, 2 h.



Seheme 47: (i) $CoCl_2.6H_2O$, (L)- proline, Et_3N, MeOH, 25 °C, 24 h.

Surprisingly, when catalysts such as **78** and **79** were used for the asymmetric reduction of ketones under transfer hydrogenation conditions, the reduced product was obtained in high yields with no optical induction. Other chiral auxiliaries such as (-)-diethyl tartarate (DET) and hydroquinidine, etc. were also tried for the asymmetric transfer hydrogenation, but with no optical induction.

4.3.5 Conclusion

In conclusion, the catalytic system comprising $CoCl(PPh_3)_3$ in combination with 2-propanol and KOH was found to be an excellent system for the reduction of carbonyl and nitro compounds *via* transfer hydrogenation. Cheaper metal and mild condition are the advantages of the current methodology.

4.3.6 Experimental Section

General experimental procedure for the transfer hydrogenation:

To a stirred mixture of carbonyl compound (5 mmol), KOH (5 mmol, 290 mg) in 2-propanol (25 mL) was added $CoCl(PPh_3)_3$ (5 mol%, 220 mg) at 25 °C. The reaction mixture was refluxed for 12 h and allowed to cool to 25 °C. Solvent was removed under reduced pressure and the residue was extracted with ethyl acetate (3 x 25 mL). The combined organic extracts were washed with water, brine, dried over anhyd. Na_2SO_4 and

concentrated under reduced pressure to afford crude product which was then purified by column chromatography on silica gel using pet. ether and ethyl acetate as eluent to afford the product in pure form.

1-Phenethanol (77a): Yield: 0.580 g (95%); colorless liquid; **IR** (nujol, cm^{-1}): 669, 761, 907, 1078, 1204, 1461, 1493, 2973, 3029, 3365; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.42 (d, *J* = 6.3 Hz, 3H), 2.55 (brs, 1H), 4.79 (q, *J* = 6.3 Hz, 1H), 7.21-7.3 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 24.9, 69.8, 125.2, 127.0, 128.1, 145.8; **MS** (m/z, % relative intensity) 122 (M^+, 35), 107(100), 79 (76), 77 (38), 51 (16), 43(17).

1-(4-Fluorophenyl)ethanol (77b): **Yield**: 0.645 g (92%); colorless liquid; **IR** (nujol, cm^{-1}): 543, 836, 899, 1014, 1085, 1157, 1223, 1296, 1372, 1510, 1605, 2894, 2976, 3319; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.43 (d, *J* = 6.5 Hz, 3H), 2.52 (brs, 1H), 4.82 (q, *J* = 6.4 Hz, 1H), 6.95-7.04 (m, 2H), 7.26-7.33 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 24.9, 69.3, 114.9 (d, *J* = 21.2 Hz, 1H), 126.9 (d, *J* = 8.0 Hz, 1H), 141.4 (d, *J* = 2.9 Hz, 1H), 161.8 (d, *J* = 244.8 Hz, 1H); **Analysis**: **C_8H_9FO** requires C, 68.56; H, 6.47; found C, 68.39; H, 6.71%.

1-(4-Chlorophenyl)ethanol (77c): **Yield**: 0.728 g (93%); colorless liquid; **IR** (nujol, cm^{-1}): 762, 1019, 1069, 1207, 1290, 1414, 1590, 2959, 3254; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.5 (d, *J* = 6.7 Hz, 3H), 2.1 (brs, 1H), 4.85 (q, *J* = 7.4 Hz, 1H), 7.3 (m, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 24.9, 69.2, 126.6, 128.2, 132.6, 144.0; **MS** (m/z, % relative intensity): 156 (M^+, 21), 141 (100), 111 (22), 107 (29), 91 (5), 77 (38); **Analysis**: **C_8H_9ClO** requires C, 61.35; H, 5.79; Cl, 22.64; found C, 61.21; H, 5.89; Cl, 22.48%.

1-(2,4-Dichlorophenyl)ethanol (77d): **Yield**: 0.879 g (92%); gum; **IR** (nujol, cm^{-1}): 571, 709, 816, 901, 1046, 1094, 1385, 1473, 1562, 2930, 2976, 3318; **^{1}H NMR** (200 MHz,

$CDCl_3$): δ 1.42 (d, *J* = 6.3 Hz, 3H), 2.68 (bs, 1H), 4.85 (q, *J* = 6.3 Hz, 1H), 7.21-7.26 (m, 1H), 7.30-7.31 (m, 1H), 7.45-7.49 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 23.4, 66.3, 127.2, 127.3, 128.9, 131.9, 133.1, 141.6; **Analysis**: **$C_8H_8Cl_2O$** requires C, 50.29; H, 4.22; Cl, 37.11; found C, 50.41; H, 4.23; Cl, 37.27%.

1-(4-Isobutylphenyl)ethanol (77e): Yield: 0.784 g (88%); viscous liquid; **IR** (nujol, cm^{-1}): 669, 920, 1080, 1204, 1461, 1493, 1540, 2903, 3029, 3382; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.89 (d, *J* = 6.31 Hz, 6H), 1.44 (d, *J* = 6.20 Hz, 3H), 1.78-1.91 (m, 1H), 2.45 (d, *J* = 6.1 Hz, 2H), 4.80 (q, *J* = 6.2 Hz, 1H), 7.08 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 22.4, 25.1, 30.2, 45.2, 70.2, 125.2, 129.1, 140.7, 143.2; **MS** (m/z, % relative intensity): 178 (M^+, 20), 162 (100), 134 (33), 122 (30), 120 (37), 117(40), 114 (27), 90 (53); **Analysis: $C_{12}H_{18}O$** requires C, 80.85; H, 10.18; found C, 80.63, H, 10.21%.

1-(4-Methylphenyl)ethanol (77f): **Yield**: 0.606 g (89%); colorless liquid; **IR** (nujol, cm^{-1}): 895, 1010, 1070, 1360, 1435, 1510, 2920, 3150, 3500; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.47 (d, *J* = 7.4 Hz, 3H), 2.1 (brs, 1H), 2.41 (s, 3H), 4.84 (q, *J* = 7.4 Hz, 1H), 7.15 (d, *J* = 9.2 Hz, 2H), 7.25 (d, *J* = 9.2 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 20.9, 24.8, 69.9, 125.2, 128.94, 136.7, 142.8; **MS** (m/z, % relative intensity): 136 (M^+, 29), 121 (97), 103 (10), 91 (100), 77 (62), 65 (23); **Analysis: $C_9H_{12}O$** requires C, 79.37; H, 8.88; found C, 79.12; H, 8.81%.

1-(4-Ethylphenyl)ethanol (77g): Yield: 0.646 g (86%); viscous liquid; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.23 (t, *J* = 6.3 Hz, 3H), 1.47 (d, *J* = 6.3 Hz, 3H), 2.64 (d, *J* = 6.3 Hz, 2H), 4.85 (q, *J* = 6.3 Hz, 1H), 7.18 (d, *J* = 9.1 Hz, 2H), 7.28 (d, *J* = 9.1 Hz, 2H); **^{13}C**

NMR (50 MHz, $CDCl_3$): δ 15.3, 24.7, 28.2, 69.7, 125.2, 127.5, 129.9, 142.9; **Analysis:** **$C_{10}H_{14}O$** requires C, 79.96; H, 9.39; found C, 80.03; H, 9.12%.

1-(4-Methoxyphenyl)ethanol (77h): **Yield**: 0.555 g (73%); **IR** (nujol, cm^{-1}): 767, 812, 870, 1027, 1141, 1235, 1263, 1465, 1519, 1594, 2837, 2936, 2971, 3711; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.45 (d, *J* = 6.3 Hz, 3H), 1.91 (brs, 1H), 3.78 (s, 3H), 4.8 (q, *J* = 6.3 Hz, 1H), 6.83 (d, *J* = 8.3 Hz, 2H), 7.25 (d, *J* = 8.8 Hz, 2H); **Analysis**: **$C_9H_{12}O_2$** requires C, 71.03; H, 7.95; found C, 71.21; H, 7.84%.

1-(3,4-Dimethoxyphenyl)ethanol (77i): **Yield**: 0.647 g (71%); **IR** (nujol, cm^{-1}): 767, 812, 870, 1027, 1141, 1235, 1263, 1465, 1519, 1594, 2837, 2936, 2971, 3711; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.46 (d, *J* = 6.3 Hz, 3H), 2.2 (bs, 1H), 3.85 (s, 3H), 3.87 (s, 3H), 4.81 (q, *J* = 6.3 Hz, 1H), 6.76-6.90 (m, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 24.7, 55.1, 55.2, 69.1, 108.4, 110.5, 117.0, 138.4, 147.6, 148.4; **Analysis**: **$C_{10}H_{14}O_3$** requires C, 65.91; H, 7.74; found C, 66.08; H, 7.54%.

1-Phenylpropanol (77j): **Yield**: 0.606 g (89%); colorless liquid; **IR** (nujol, cm^{-1}): 764, 975, 1014, 1097, 1454, 1494, 2877, 2934, 2966, 3030, 3339; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.89 (t, *J* = 7.3 Hz, 3H), 1.64-1.85(m, 2H), 2.22 (brs, 1H), 4.55 (t, *J* = 6.8 Hz, 1H), 7.31 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 9.8, 31.5, 75.4, 125.8, 127.0, 128.0, 144.4; **Analysis**: **$C_9H_{12}O$** requires C, 79.37; H, 8.88; found C, 79.51; H, 9.02%.

1-(4-Bromophenyl)propan-1-ol (77k): **Yield**: 0.936 g (87%); gum; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.86 (t, *J* = 7.3 Hz, 3H), 1.61-1.78 (m, 2H), 2.56 (brs, 1H), 4.49 (t, *J* = 6.7 Hz, 1H), 7.16 (d, *J* = 8.3 Hz, 2H), 7.43 (d, *J* = 8.3 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 9.8, 31.6, 74.9, 120.8, 127.5, 131.1, 143.3; **Analysis**: **$C_9H_{11}BrO$** requires C, 50.26; H, 5.15; Br, 37.15; found C, 50.11; H, 5.29; Br, 37.28%.

1-Naphthylethanol (77l): Yield: 0.775 g (90%); **mp:** 50 °C; **IR** ($CHCl_3$, cm^{-1}): 1010, 1056, 1108, 1168, 1218, 1256, 1328, 1374, 1445, 1509, 1597, 3011; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.48 (d, *J* = 6.2 Hz, 3H), 3.01 (s, 1H), 5.40 (q, *J* = 6.2 Hz, 1H), 7.31-7.90 (m, 7H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 24.1, 66.2, 121.7, 122.9, 124.9, 125.1, 125.3, 127.2, 128.4, 129.9, 133.4, 141.2; **MS** (m/z, % relative intensity): 172 (M+, 29), 157 (34), 153 (21), 129 (100), 115 (3), 102 (3), 76 (16), 63 (14), 43 (38); **Analysis:** **$C_{12}H_{12}O$** requires C, 83.68; H, 7.03; found C, 83.33; H, 7.31%.

1-(6-Methoxy-1-naphthyl)ethanol (77m): Yield: 0.748 g (74%); **mp:** 62-63 °C; **IR** (nujol, cm^{-1}): 761, 907, 1088, 1200, 1461, 1593, 2953, 3029, 3465; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.62 (d, *J* = 6.2 Hz, 3H), 3.83 (s, 3H), 5.67 (q, *J* = 6.2 Hz, 1H), 7.14 (d, *J* = 10.1 Hz, 1H), 7.25-7.44 (m, 2H), 7.64-7.75 (m, 2H), 8.09 (d, *J* = 10.1 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 23.6, 56.0, 65.6, 113.1, 122.8, 123.3, 125.4, 126.3, 128.3, 129.2, 131.1, 153.9, 159.4; **MS** (m/z, % relative intensity): 202 (M^+, 20), 187 (70), 163 (13), 157 (23), 144 (55), 127 (39), 115 (100), 89 (29), 77 (30), 62 (39); **Analysis:** **$C_{13}H_{14}O_2$** requires C, 77.20; H, 6.98; found C, 77.14; H, 7.10%.

Cyclohexanol (77n): **Yield**: 0.275 g (55%); colorless liquid; **IR** (nujol, cm^{-1}): 889, 963, 971, 1026, 1067, 1453, 2858, 2934, 3623; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.18 -1.22 (m, 5H), 1.51 -1.85 (m, 5H), 2.69 (brs, 1H), 3.52-3.61 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 23.8, 25.2, 35.0, 69.6; **MS** (m/z, % relative intensity): 100 (M^+, 4), 82 (45), 71 (34), 67 (48), 57 (100), 54 (32); **Analysis**: **$C_6H_{12}O$** requires C, 71.95; H, 12.08; found C, 71.78; H, 11.95%.

Benzylalcohol (77o): **Yield**: 0.465 g (86%); colorless liquid; **IR** (neat, cm^{-1}): 596, 698, 736, 1018, 1039, 1370, 1454, 2875, 2932, 3065, 3088, 3326; **^{1}H NMR** (200 MHz,

$CDCl_3$): δ 3.0 (brs, 1H), 4.65 (s, 2H), 7.2-7.45 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 64.7, 126.9, 127.3, 128.3, 140.9; **MS** (m/z, % relative intensity): 108 (M^+, 95), 91 (30), 79 (100), 63 (23).

4-Chlorobenzylalcohol (77p): **Yield**: 0.57 g (80%); colorless liquid; **IR** (neat, cm^{-1}): 1070, 1350, 1430, 1580, 2990, 3356; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.8 (brs, 1H), 4.7 (s, 2H), 7.26-7.35 (m, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 64.2, 128.1, 128.54, 133.2, 139.1; **MS** (m/z, % relative intensity): 142 (M^+, 11), 125 (4), 113 (8), 107 (24), 77 (78), 51 (100), 31 (60), 29 (81) ; **Analysis**: **C_7H_7ClO** requires C, 58.97; H, 4.95; Cl, 24.86; found C, 58.84; H, 4.74; Cl, 24.98%.

4-Methoxybenzylalcohol (77q): **Yield**: 0.504 g (73%); **IR** (neat, cm^{-1}): 573, 818, 1034, 1175, 1248, 1464, 1515, 1612, 2837, 2936, 3676; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.72 (brs, 1H), 3.79 (s, 3H), 4.58 (s, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 7.26 (d, *J* = 8.7 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 54.9, 64.3, 113.6, 128.4, 133.1, 158.8.

4-Nitrobenzylalcohol (77r): **Yield**: 0.597 g (78%); **mp**: 91-92 ºC; **IR** (neat, cm^{-1}): 1330, 1360, 1435, 1485, 2850, 3350; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.1 (brs, 1H), 4.85 (d, *J* = 5.0 Hz, 2H), 7.52 (d, *J* = 8.7 Hz, 2H), 8.20 (d, *J* = 8.7 Hz, 2H); **^{13}C NMR** (50 MHz, DMDO-d_6): δ 62.2, 123.4, 127.1, 146.5, 150.9; **MS** (m/z, % relative intensity): 153 (M^+, 37), 136 (30), 124 (20), 77 (16), 51 (35), 39 (21), 30 (100); **Analysis**: **$C_7H_7NO_3$** requires C, 54.90; H, 4.61; N, 9.15; found C, 54.81; H, 4.44; N, 9.28%.

2-Nitrobenzylalcohol (77s): **Yield**: 0.567 g (74%); **mp**: 70-71 ºC; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.53 (brs, 1H), 4.97 (s, 2H), 7.43-7.51 (m, 1H), 7.62-7.77 (m, 2H), 8.08-8.12 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 61.9, 124.7, 128.0, 129.2, 133.8, 136.9, 147.2;

Analysis: $C_7H_7NO_3$ requires C, 54.90; H, 4.61; N, 9.15; found C, 54.78; H, 4.87; N, 9.04%.

Aniline (77t): **Yield**: 0.405 g (87%); colorless liquid; **IR** (nujol, cm^{-1}): 600, 690, 1117, 1174, 1275, 1500, 2906, 3013, 3395, 3480; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.45 (bs, 2H), 6.3-6.6 (m, 3H), 6.9-7.25 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 115.0, 118.3, 129.2, 146.51.

2-Chloroaniline (77u): **Yield**: 0.517 g (81%); colorless liquid; **IR** (nujol, cm^{-1}): 678, 745, 929, 1078, 1262, 1384, 1451, 1487, 1617, 2925, 3026, 3382, 3471; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.91(bs, 2H), 6.61-6.74 (m, 2H), 6.99-7.07 (m, 1H), 7.19-7.24 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 115.6, 118.7, 118.9, 127.4, 129.1, 142.7; **MS** (m/z, % relative intensity): 127 (M^+, 100), 100 (10), 92 (18), 65 (43), 63 (18), 52 (14).

4.3.7 References

1. (a) Tsuji. J. *Palladium Reagents and Catalysts* Wiley: Chichcster, **1995**. (b) Mallcron, J. L.; Fiaud. J. C.; Lcgros. J. Y. *Handbook of Palladium-Catalysed Organic Reactions*; San Diccgo, **1997**.
2. (a) *Transition Metals for Organic Synthesis*, Volumes 1 and 2; Beller, M.; Bolm, C., Eds. Wiley-VCH: Weinheim, **1998.** (b) *Metal Catalysed Cross Coupling Reactions*; Diederich, F.; Stang, P. J., Eds. Wiley-VCH: Weinheim, **1998.** (c) Li, J. J.; Gribble, G. W. In *Palladium in Heterocyclic Chemistry*; Pergamon: Oxford, **2000.** (d) *Handbook of Organopalladium Chemistry for Organic Synthesis*, Volume 2; Negishi, E.I.; de Meijere, A., Eds. Wiley: New York, **2002.** (e) Dupont, J.; Pfeffer, M.; Spencer, J. *Eur. J. Inorg. Chem.* **2001**, *2001,* 1917-1927.

3. (a) Heck, R. F. *Palladium Reagents in Organic Synthesis;* Academic Press: London, **1985.** (b) Grushin, V. V.; Alper, H. *Chem. Rev.* **1994**, *94*, 1047. (c) Herrmann, W. A.; Brossmer, C.; Ofele, K.; Reisinger, C-P; Priermeier, T.; Beller, M.; Fischer, H. *Angew. Chem. Int. Ed.* **1995**, *34*, 1844. (d) Ohff. M.; Ohff, A.; Boom, M. E.; Milstein, D. *J. Am. Chem. Soc.* **1997**, *119*, 11687.

4. (a) Miyaura, N.; Suzuki, A. *Chem. Rev*. **1995**, *95*, 2457. (b) Suzuki, A. *J. Organomet. Chem*. **1999**, *576*, 147. (c) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633. (d) Pramick, M. R.; Rosemeier, S. M.; Beranek, M. T.; Nickse, S. B.; Stone, J. J.; Stockland, R. A.; Jr; Baldwin, S. M.; Kastner, M. E. *Organometallics* **2003***, 22*, 523.

5. (a) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158. (b) Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc*. **2003**, *125*, 6653. (c) Viciu, M. S.; Kelly III, R. A.; Stevens, E. D.; Naud, F.; Studer, M.; Nolan, S. P. *Org. Lett*. **2003**, *5*, 1479.

6. Milstein, D.; Stille, J. K. *J. Am. Chem. Soc*. **1979**, *101*, 4992.

7. Selvakumar, K.; Zapf, A.; Beller, M. *Org. Lett*. **2002,** *4*, 3031.

8. (a) *Aqueous-Phase Organometallic Catalysis, Concepts and Application;* Cornils, B.; Herrmann, W, A., Eds. Wiley-VCH: Weinheim, **1998.** (b) Botella, L.; Najera, C. *Angew. Chem. Int. Ed.* **2002**, *41*, 179. (C) Najera, C.; Gil-Molto, J.; Karlstrom, S.; Falvello, L. R. *Org. Lett.* **2003**, *5*, 1451.

9. (a) Bergbreiter, D.E.; Osburn, P. L.; Liu, Y. S. *J. Am. Chem. Soc*. **1999**, *121*, 9531.

10. (a) Reetz, M. T.; Westermann, E.; Lohmer, R.; Lohmer, G. *Tetrahedron Lett.* **1998**, *39*, 8449. (b) Consorti, C. S.; Zanini, M. L.; Leal, S.; Ebeling, G.; Dupont, J. *Org. Lett*. **2003**, *5*, 983.

11. (a) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc*. **1998**, *120*, 9722. (b) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc***. 1999**, *121*, 9550. (c) Wolfe, J. P.; Buchwald, S. L. *Angew. Chem. Int. Ed*. **1999**, *38*, 2413. (d) Li, G. Y. *Angew. Chem. Int. Ed*. **2001**, *40*, 1513. (e) Schnyder, A.; Indolese, A. F.; Studer, M.; Blaser, H-U. *Angew. Chem. Int. Ed*. **2002**, *41*, 3668.

12. (a) Bourissou, D.; Guerret, O.; Gabbai, F. P.; Bertrand, G.; *Chem. Rev*. **2000**, *100*, 39. (b) Herrmann, W. A. *Angew. Chem. Int. Ed.* **2002**, 41, 1290. (c) Lebel, H.; Janes, M. K.; Charette, A. B.; Nolan,S. P. *J. Am. Chem. Soc.* **2004**, *126*, 5046.

13. (a) Dai, M.; Liang, B.; Wang, C.; Chen, J.; Yang, Z. *Org. Lett.* **2004**, *6*, 221. (b) Yang, D.; Chen, Y-C.; Zhu, N-Y.; *Org. Lett.* **2004**, *6*, 1577. (c) Xiong, Z.; Wang, N.; Dai, M.; Li, A.; Chen, J.; Yang, Z. *Org. Lett.* **2004**, *6*, 3337. (d) Yang, D.; Chen, Y-C.; Zhu, N-Y. *Org. Lett.* **2004**, *6*, 4635.

14. (a) Alonso, D. A.; Najera, C.; Pacheco, M. C. *J. Org. Chem*. **2002**, *67*, 5588.

15. Grasa, G. A.; Hillier, A. C.; Nolan, S. P. *Org. Lett.* **2001**, *3*, 1077.

16. Mata, Y.; Dieguez, M.; Pamies, O.; Claver, C. *Org. Lett.* **2005**, *7*, 5597.

17. Frey, G. D.; Schutz, J.; Herdtweck, E.; Herrmann, W. A. *Organometallics* **2005**, *24*, 4416.

18. (a) Grushin, V. V.; Alper, H. *Chem. Rev.* **1994**, *94*, 1047.

19. Heck, R. F.; "*Vinyl Substitutions with Organopalladium Intermediates"* in "*Comprehensive Organic Synthesis"*, Trost, B. M.; Fleming, I.; (Eds.), Pergamon, Oxford, **1991**, ch. 4.3, pp. 833.

20. (a) Littke, A. F.; Fu, G. C.; *J. Org. Chem.* **1999**, *64*, 10. (b) Reetz, M. T.; Lohmer, G.; Schwickardi, R. *Angew. Chem. Int. Ed.* **1998**, *37*, 481. (c) Portnoy, M.; Ben-David, Y.;

Milstein, D. *Organometallics* **1993**, *12*, 4734.

21. (a) Herrmann, W. A.; Bohm,V. P. W.; Reisinger, C-P. *J. Organomet. Chem.* **1999**, *576*, 23. (b) Miyazaki, F.; Yamaguchi, K.; Shibasaki, M. *Tetrahedron Lett.* **1999**, *40*, 7379.
22. Stanforth, S.P. *Tetrahedron* **1998**, *54*, 263.
23. Dupuis, C.; Adiey, K.; Charruault, L.; Michelet, V.; Savignac, M.; Genet, J-P. *Tetrahedron Lett.* **2001**, *42*, 6523.
24. Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2004**, *43*, 1871.
25. (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467. (b) Kollhofer, A.; Pullmann, T.; Plenio, H. *Angew. Chem. Int. Ed.* **2003**, *42*, 1056.
26. Beutler, U.; Mazacek, J.; Penn, G.; Schenkel, B.; Wasmuth, D. *Chimia* **1996,** *50*, 154.
27. Grissom, J. W.; Gunawardena, G. U.; Klingberg, D.; Huang, D. *Tetrahedron* **1996**, *52*, 6453.
28. a) Anastasia, L.; Negishi, E. *Org. Lett.* **2001**, *3*, 3111. b) Yang, C.; Nolan, S. P. *Organometallics* **2002**, *21*, 1020. c) Plenio, H.; Hermann, J.; Sehring, A. *Chem. Eur. J.* **2000**, 6, 1820. d) Alami, M.; Crousse, B.; Ferri, F. *J. Organomet. Chem.* **2001**, *624*, 114. e) Batey, R. A.; Shen, M.; Lough, A. J. *Org. Lett.* **2002,** *4*, 1411.
29. Bhattacharya, S.; Sengupta, S. *Tetrahedron Lett.* **2004**, *45*, 8733.
30. Herrmann, W. A.; Brossmer, C.; Ofele, K.; Reisinger, C-P.; Priermeier, T.; Beller, M.; Fischer, H. *Angew. Chem. Int. Ed. Engl*. **1995**, *34*, 1844.
31. Beller, M.; Fischer, H.; Herrmann, W. A.; Ofele, K.; Brossmer, C. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1848.
32. Albisson, D. A.; Bedford, R. B.; Scully, P. N.; Lawrence, S. E. *Chem. Commun.* **1998**, 2095.

33. Weissman, H.; Milstein, D. *Chem. Commun.* **1999**, 1901.

34. (a) Bergbreiter, D. E.; Osburn, P. L.; Liu, Y-S. *J. Am. Chem. Soc.* **1999**, *121*, 9531. (b) Bergbreiter, D. E.; Osburn, P. L.;Wilson, A.; Sink, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 9058.

35. Brunel, J. M.; Heumann, A.; Buono, G. *Angew. Chem. Int. Ed.* **2000**, *39*, 1946.

36. Alonso, D. A.; Najera, C.; Pacheco, M. C. *Org. Lett.* **2000**, *2*, 1823.

37. Iyer, S.; Ramesh, C. *Tetrahedron Lett.* **2000**, *41*, 8981.

38. Buchmeiser, M. R.; Schareina, T.; Kempe, R.; Wurst, K. *J. Organomet. Chem.* **2001**, *634*, 39.

39. Rocaboy, C.; Gladysz, J. A. *Org. Lett.* **2002**, *4*, 1993.

40. Lin, C.; Luo, F. *Tetrahedron Lett*. **2003**, *44*, 7565.

41. Churruca, F.; SanMartin, R.; Tellitu, I.; Domínguez, E. *Synlett* **2005**, 3116.

42. Navarro, O.; Marion, N.; Oonishi, Y.; Kelly III, R. A.; Nolan, S. P. *J. Org. Chem.* **2006**, *71*, 685.

43. Chen, T.; Gao, J.; Shi, M. *Tetrahedron* **2006**, *62*, 6289.

44. Huang, R.; Shaughnessy, K. H. *Organometallics* **2006**, *25*, 4105.

45. Onoue, H.; Minami, K.; Nakagawa. K. *Bull. Chem. Soc. Jpn*. **1970**, *43*, 3480.

46. Marzinzik, A. L.; Sharpless, K. B. *J. Org. Chem*. **2001**, *66,* 594.

47. Tao, B.; Boykin, D. W. *J. Org. Chem.* **2004**, *69*, 4330.

48. Shih, C.; Hey, D.H.; William, G. H. *J. Chem. Soc.* **1958**, 2600.

49. Gholap, A.R.; Venkatesan, K.; Pasricha, R.; Daniel, T.; Lahoti, R. J.; Srinivasan, K. V. *J. Org. Chem.* **2005**, *70*, 4869.

50. Stephens, R. D.; Castro, C. E. *J. Org. Chem.* **1963**, *28*, 3313.

51. Mitchell, J. A.; Akaraseveenont, P.; Thiemermann, C.; Flower, R. J.; Vane, J. R. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, 90, 11693.

52. (a) Sonawane, H. R.; Bellur, N. S.; Ahuja, J. R.; Kulkarni, D. G. *Tetrahedron: Asymmetry* **1992**, *3*, 163. (b) Rieu, J. P.; Boucherle, A.; Cousse, H.; Mouzin, G. *Tetrahedron* **1986**, *42*, 4095.

53. Lake, A. W.; Rose, C. J. Prov. Patent GB 1,476,721, **1973**.

54. *Drugs Fut*. **2003**, *28*, 1024.

55. Fadel, A. *Synlett* **1992**, 48.

56. Fronczek, F. R.; Watkins, S. E.; Manimaran, T.; Wu, T. C.; Klobucar, W. D.; Kolich, C.H.; Stahly, P. *Organometallics* **1993**, *12*, 1467.

57. Jung, M. E.; Anderson, K. L. *Tetrahedron Lett.* **1997**, *38*, 2605.

58. Ishibashi, H.; Maeki, M.; Yagi, J.; Ohba, M.; Kanai, T. *Tetrahedron* **1999**, *55*, 6075.

59. (a) Chen, A. C.; Ren, L.; Crudden, C. M. *Chem. Commun.* **1999**, 611. (b) Chen, A.; Ren, L.; Crudden, C. M. *J. Org. Chem.* **1999**, *64*, 9704.

60. Omar, M. M.; Eusebio, J. *Tetrahedron Lett.* **2003**, *44*, 2023.

61. Alessandra, A.; Rosa, A.; Giancarlo, B.; Barbara, D. F.; Marialuigia, F.; Letizia, G.; Cristina, M.; Maria, L. T. *Eur. J. Org. Chem.* **2006**, *18*, 4088.

62. Goudie, A. C.; Gaster, L. M.; Lake, A. W.; Rose, C. J.; Freeman, P. C.; Hughes, B. O.; Miller, D. *J. Med. Chem.* **1978**, *21*, 1260.

63. Mohammad, A.; Varadaraj, E.; Kenneth, D. G. *Synthesis* **1989**, 869.

64. Uemura, S.; Cho, C. S.; Motofusa, S.; Ohe, K. *Bull. Chem. Soc. Jpn.* **1996,** *69*, 2341.

65. Sorbera, L. A.; Castaner, R. M.; Bayes, M. *Drugs Fut*. **2002**, *27*, 831.

66. Leutenegger, U.; Madin, A.; Pfaltz, A. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 60.

67. Fronczek, F. R.; Watkins, S. E. *Organometallics* **1993**, *12*, 1467.

68. Satoh. T.; Suzuki, S.; Suzuki, Y.; Miyaji, Y.; Imai, Z. *Tetrahedron Lett.* **1969**, *10*, 4555.

69. (a) Hashiguchi, S.; Fujii, A.; Takehara, J.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc*. **1995**, *117*, 7562. (b) Palmer, M. J.; Kenny, J. A.; Walsgrove, T.; Kawamoto, A. M.; Wills, M. *J. Chem. Soc., Perkin Trans. 1*, **2002**, *3*, 416. (c) Rhyoo, H. Y.; Park, H. J.; Chung, Y. K. *Chem. Commun.* **2001**, *20*, 2064.

70. Emmanuvel, L; Shukla, R; Sudalai, A; Gurunath, S; Sivaram S. *Tetrahedron Lett*. **2006**, *47*, 4793.

71 Kano, T.; Sasaki, K.; Maruoka, K. *Org. Lett.* **2005**, *7*, 1347.

72. Brieger, G.; Nestrick, T.J. *Chem. Rev.* **1974**, *74*, 567.

73. Johnstone, R. A. W.; Wilby, A. H.; Entwistle, I. D. *Chem. Rev*. **1985**, *85*, 129.

74. Rylander, P. N. Hydrogenation Methods, Acadamic Press, London, **1985**.

75. (a) Andrews, M. J.; Pillai, C. N. *Ind. J. Chem., Sect B*, **1978**, *16*, 465. (b) Augustine, R. L. *Hetrogeneous Catalysis for the Synthetic Chemist*, Marcel Dekker, Inc., New York, **1996**.

76. Zassinovich, G.; Mestroni, G.; Gladiali, S. *Chem. Rev.* **1992***, 92*, 1051.

77. Johnstone, R. A. W.; Wilby, A.H.; Entwistle, I.D. *Chem. Rev.* **1985***, 85*, 129.

78. Masters, C "Homogeneous *Transition metal catalysis*" Chapman and Hall; London **1987**, 1.

79. Botta, M.; Angelis, F. D; Gambacorto, A.; Labbiento, L.; Nocoletti, R. *J. Org. Chem.* **1985**, *50*, 1916.

80. Chowdhary, R. L.; Backvall, J. E. *J. Chem. Soc., Chem. Commun.* **1991**, 1063.

81. Wang, G. Z.; Backvall, J. E. *J. Chem. Soc., Chem. Commun.* **1992**, 980.

82. Iyer, S.; Varghese, J. P. *J. Chem. Soc., Chem. Commun.* **1995**, 465.

83. Boldrini, G. P.; Savoia, D.; Tagliavini, E.; Trombini, C.; Ronchi, A. U. *J. Org. Chem.* **1985**, *50*, 3082.

84. Upadhya, T. T.; Katdare, S. P.; Sabde, D. P.; Ramaswamy, V.; Sudalai, A. *Chem. Commun*. **1997**, 1119.

85. Kuhl, S.; Schneider, R.; Fort, Y. *Organomettalics* **2003**, *22*, 4184.

LIST OF PUBLICATIONS

- ”Sulfilimine palladacycles: Stable and efficient catalysts for carbon-carbon coupling reactions” N. S. C. Ramesh Kumar, V. V. Thakur and A. Sudalai Tetrahedron *Letters* **2004**, *45*, 2915-2918.
- “Pd-catalyzed oxidative kinetic resolution of 2-azido-1-arylethanols” N.S.C. Ramesh Kumar, Iliyas A. S and A. Sudalai *Indian Journal of Chemistry*, **2005**, *44B*, 1533-1535.
- ‘‘Sulfonamide-and hydrazine-based palladium catalysts: stable and efficient catalysts for C-C coupling reactions in aqueous medium” N.S.C. Ramesh Kumar, I. Victor Paul Raj and A. Sudalai *Journal of molecular catalysis. A Chemical* **2007**, *269*, 218-224
- “$CoCl(PPh_3)_3$ Catalyzed Transfer Hydrogenation of Carbonyl Compounds using 2- Propanol as a Hydrogenation Source” N.S.C. Ramesh Kumar and A. Sudalai (manuscript under preparation).

PATENTS

- “A New Catalytic Process for the Production of 3,3′, 4,4′-Tetraminobiphenyl” N. S. C. Ramesh Kumar, Asif maner, Sudhir Bavikar, A. Sudalai and S. Sivaram US 6,979,749 **2005**

  “A New Catalytic Process for the Preparation of High Quality 3,3’-Diaminobenzedine (3, 3’, 4, 4’-Tetraaminobiphenyl) and their Analogues” N. S. C. Ramesh Kumar, L. Emmanuvel, S. Ravi, S. Gurunath, A. Sudalai and S. Sivaram **US patent filed 2006**