Asymmetric Synthesis of Bioactive Molecules *via* Hydrolytic Kinetic Resolution of Alkoxy Epoxides, Dihydroxylation of Alkenes and Synthetic Methodologies Involving Oxidative Cyclization of Styrenes and Esterification of Aldehydes

A THESIS

SUBMITTED TO THE

UNIVERSITY OF PUNE

FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

IN

CHEMISTRY

By

Chaithanya Kiran, I. N.

UNDER THE GUIDANCE OF

Dr. A. Sudalai

Chemical Engineering and Process Development Division

CSIR-National Chemical Laboratory

Pune-411008, INDIA

March 2014

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DEDICATED TO

MY BELOVED BROTHER

I. LAKSHMI NARAYANA

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CERTIFICATE

This is to certify that the work incorporated in the thesis entitled ***"Asymmetric Synthesis of Bioactive Molecules via Hydrolytic Kinetic Resolution of Alkoxy Epoxides, Dihydroxylation of Alkenes and Synthetic Methodologies Involving Oxidative Cyclization of Styrenes and Esterification of Aldehydes"*** which is being submitted to the ***University of Pune*** for the award of ***Doctor of Philosophy*** in ***Chemistry*** by ***Mr. Chaithanya Kiran, I. N.*** was carried out by him under my supervision at the CSIR-National Chemical Laboratory, Pune. Such material as has been obtained from other sources has been duly acknowledged in the thesis.

March 2014 **Dr. A. Sudalai**

Pune (Research Guide)

CSIR-NATIONAL CHEMICAL LABORATORY

DECLARATION

I hereby declare that the thesis entitled ***"Asymmetric Synthesis of Bioactive Molecules via Hydrolytic Kinetic Resolution of Alkoxy Epoxides, Dihydroxylation of Alkenes and Synthetic Methodologies Involving Oxidative Cyclization of Styrenes and Esterification of Aldehydes"*** 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 CSIR-National Chemical Laboratory, Pune, India.

March 2014
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CONTENTS

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Chaithanya Kiran, I. N.

ABBREVATIONS

Ac	Acetyl
Ar	Aryl
Bn	Benzyl
Boc	*N*-*tert*-Butoxycarbonyl
$(Boc)_2O$	Di*tert*-butyl dicarbonate
n-Bu	*n*-Butyl
n-BuLi	*n*-Butyl lithium
t-Bu	*tert*-Butyl
Cbz	Benzyloxy carbonyl
CH_2Cl_2	Methylene chloride
$CHCl_3$	Chloroform
CH_3CN	Acetonitrile
$CuSO_4$	Copper(II) sulfate
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DIBAL-H	Diisobutyl aluminium hydride
DMF	Dimethyl formamide
DMSO	Dimethyl sulphoxide
DMAP	*N,N*-dimethyl-4-aminopyridine
dr	Diastereomeric ratio
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
HNO_3	Nitric acid
imid.	Imidazole
IR	Infra red
IBX	2-Iodoxybenzoic acid
K_2CO_3	Potassium carbonate
KOH	Potassium hydroxide
$LiAlH_4$	Lithium aluminum hydride
LiHMDS	Lithium hexamethyldisilazide
M+	Molecular ion

Me	Methyl
MeOH	Methyl alcohol
MOM	Methoxymethyl
min	Minutes
mg	Miligram
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
NBS	*N*-Bromosuccinimide
NMR	Nuclear Magnetic Resonance
NMO	*N*-Methyl morpholine *N*-oxide
PCC	Pyridinium chlorochromate
Pd/C	Palladium on activated charcoal
PDC	Pyridinium dichromate
$Pd(OH)_2$	Palladium hydroxide
Ph	Phenyl
p-Ts	*p*-Tosyl
p-TSA	*p*-Toluene sulfonic acid
PhNO	Nitrosobenzene
Py	Pyridine
TBS	*tert*-Butyldimethylsilyl
TEMPO	(2,2,6,6-tetramethyl-1-piperidinyl)oxyl
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TBAF	Tetrabutylammonium fluoride
TBDMSCl	*tert*-Butyldimethylsilyl chloride
TBDPSCl	*tert*-Butyldiphenylsilyl chloride
TFA	Trifluoroacetic acid

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 (230-400 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 MHz, Brucker Avance 500 MHz and JEOL ECX 400 instruments using TMS as an internal standard. The following abbreviations were used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br s = broad singlet, dd = doublet of doublet, dt = doublet of triplet and ddd = doublet of doublet of doublet.

8. Optical rotations were carried out on JASCO-181 digital polarimeter at 25 °C using sodium D light.

9. Enantiomeric excesses were determined on Agilent HPLC instrument equipped with a chiral column.

10. HRMS data were recorded on a Thermo Scientific Q-Exactive, Accela 1250 pump.

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.

ABSTRACT

The thesis entitled "**Asymmetric Synthesis of Bioactive Molecules *via* Hydrolytic Kinetic Resolution of Alkoxy Epoxides, Dihydroxylation of Alkenes and Synthetic Methodologies Involving Oxidative Cyclization of Styrenes and Esterification of Aldehydes"** is divided into four chapters.

The title of the thesis clearly reflects the objective, which is to synthesize enantiomerically pure bioactive molecules, drugs and to interface synthetic organic chemistry for the development of new methodologies. **Chapter 1** describes a short enantioselective synthesis of (+)-goniodiol and (-)-polysphorin analog using hydrolytic kinetic resolution of alkoxy epoxides. **Chapter 2** presents the synthesis of 3-substituted chiral phthalides using CN-assisted oxidative cyclization of cyano cinnamates and styrene derivatives and its application in the synthesis of (-)-matteucen C and butylphthalide. **Chapter 3** deals with asymmetric synthesis of 3-amino-1,2-diols *via* proline catalyzed α-aminooxylation and its application in the synthesis of (+)-*epi*-cytoxazone and formal synthesis of *N*-thiolated-2-oxazolidinone. **Chapter 4** presents an organocatalyzed asymmetric synthesis of rasagiline and NHC catalyzed esterification of aromatic aldehydes.

CHAPTER 1

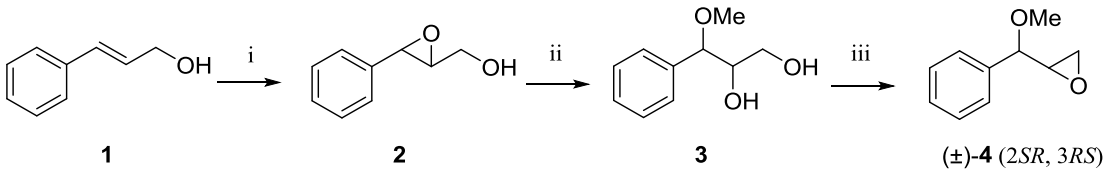
Short Enantioselective Synthesis of (+)-Goniodiol and (-)-Polysphorin Analog using Co-Catalyzed HKR of Alkoxy Epoxides

Jacobsen's Hydrolytic Kinetic Resolution (HKR) has emerged as an effective method for obtaining chiral epoxides and 1,2-diols in a highly enantioenriched forms.[1] These compounds are important intermediates in the synthesis of various bioactive molecules.[2] In view of easy availability of chiral ligands and the simplicity of the reaction conditions with water being used as the nucleophile, HKR is being used extensively for providing several chiral building blocks in the synthesis of biologically active compounds.[3] This chapter is divided into two sections. **Section I** deals with the enantioselective synthesis of (+)-goniodiol (**13**) and **Section II** describes enantioselective synthesis of (-)-polysphorin analog (**27**) using two-stereocentered HKR of alkoxy epoxides.

Section I: Concise Enantioselective Synthesis of (+)-Goniodiol, a Cytotoxic Lactone *via* Co-Catalyzed Hydrolytic Kinetic Resolution of *anti*-(2*SR*, 3*RS*)-3-Methoxy-3-phenyl-1,2-epoxypropane

(+)-Goniodiol (**13**), a styryl lactone, was isolated from petroleum ether extracts of leaves and twigs of *Goniothalamus sesquipedalis*.[4] It exhibits potent and selective cytotoxic activity against human lung carcinoma and leukemia cells.[5]

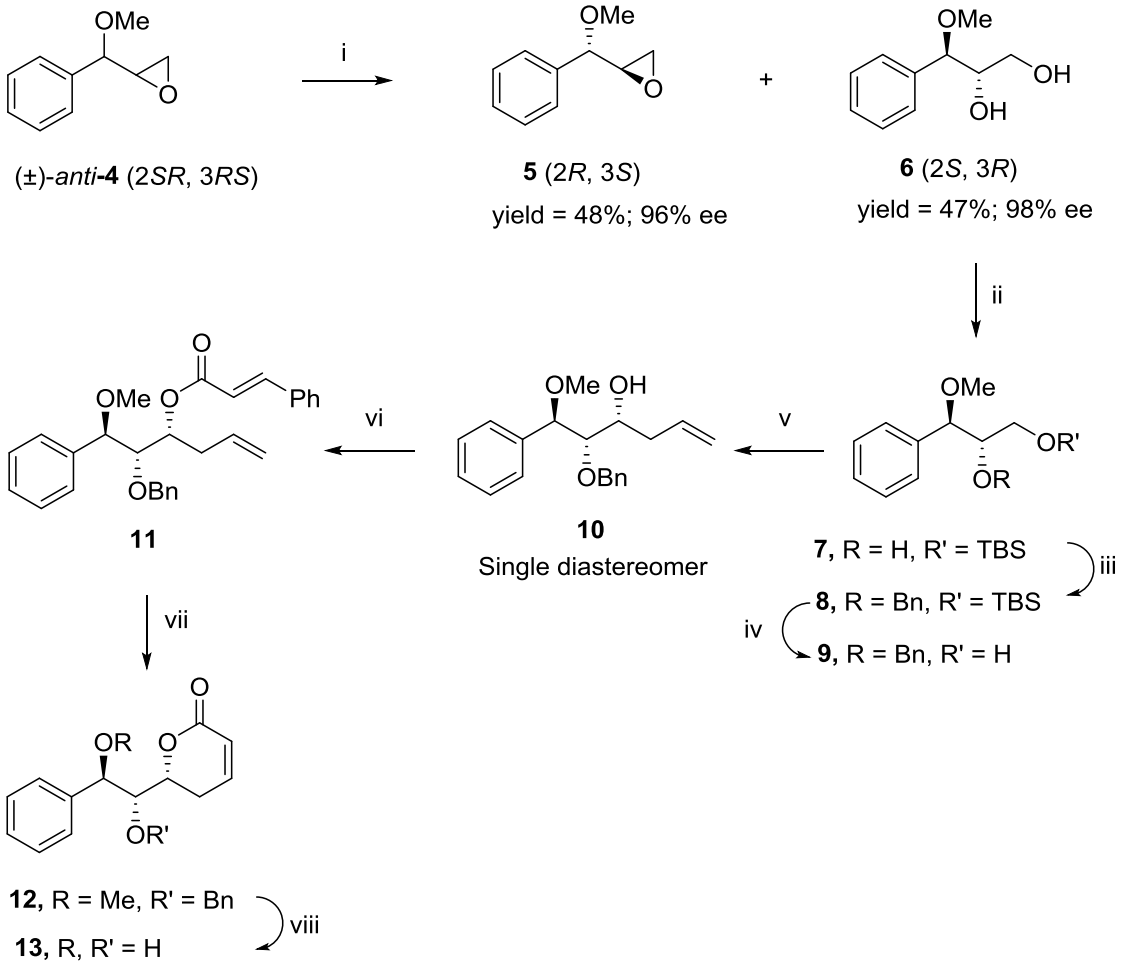
The asymmetric synthesis of (+)-goniodiol begins with commercially available cinnamyl alcohol and its transformation into racemic *anti*-methoxy epoxide **4** in 4 steps. Cinnamyl alcohol **1** on epoxidation with *m*CPBA gave the epoxy alcohol **2**. The regiospecific ring opening of epoxide **2** with MeOH was achieved quantitatively to give diol **3**, which was further converted to *anti*-methoxy epoxide **4** in a two-step reaction sequence: the selective monotosylation of primary alcohol (TsCl, Bu_2SnO, Et_3N, DMAP, CH_2Cl_2) followed by epoxide formation under basic conditions (K_2CO_3, MeOH) (**Scheme 1**).



Scheme 1: (i) *m*CPBA, CH_2Cl_2, 14 h, 0 °C, 88%; (ii) camphor sulfonic acid (10 mol %), MeOH, 1 h, 96%; (iii) (a) TsCl, Bu_2SnO (2 mol%), Et_3N, DMAP (10 mol%), CH_2Cl_2, 2 h; (b) K_2CO_3, MeOH, 3 h, 76% (over two steps).

Racemic *anti*-methoxy oxirane **4** was subjected to HKR by using (*S*, *S*)-salen-Co-OAc catalyst to give highly enantiomerically pure methoxy epoxide **5** (48% yield, 96% ee), and methoxy diol **6** (47% yield, 98% ee).[7] The primary hydroxyl group in **6** was selectively protected as its TBS ether **7**, followed by its secondary hydroxyl protection as its benzyl ether **8** (NaH, BnBr in DMF). Further TBS group was selectively deprotected to give the primary alcohol **9** in 91% yield, which was oxidized using IBX in DMSO to give the corresponding aldehyde. To this crude aldehyde in CH_2Cl_2 at -78 ^oC was added $TiCl_4$ and tributyl allyl stannane which produced homoallylic alcohol **10**, as a single diastereomer (^1H NMR analysis) in 73% yield.[6] Homo allylic alcohol **10** was esterified with (*E*)-cinnamoyl chloride to give cinnamate ester **11**, which on RCM Grubbs' second generation catalyst gave α-pyrone **12** in 76% yield. Both methyl and benzyl ethers in pyrone **12** were cleaved in a single

step using BBr_3 to afford (+)-goniodiol **13** in 12.25% overall yield and 98% ee (**Scheme 2**).[8]

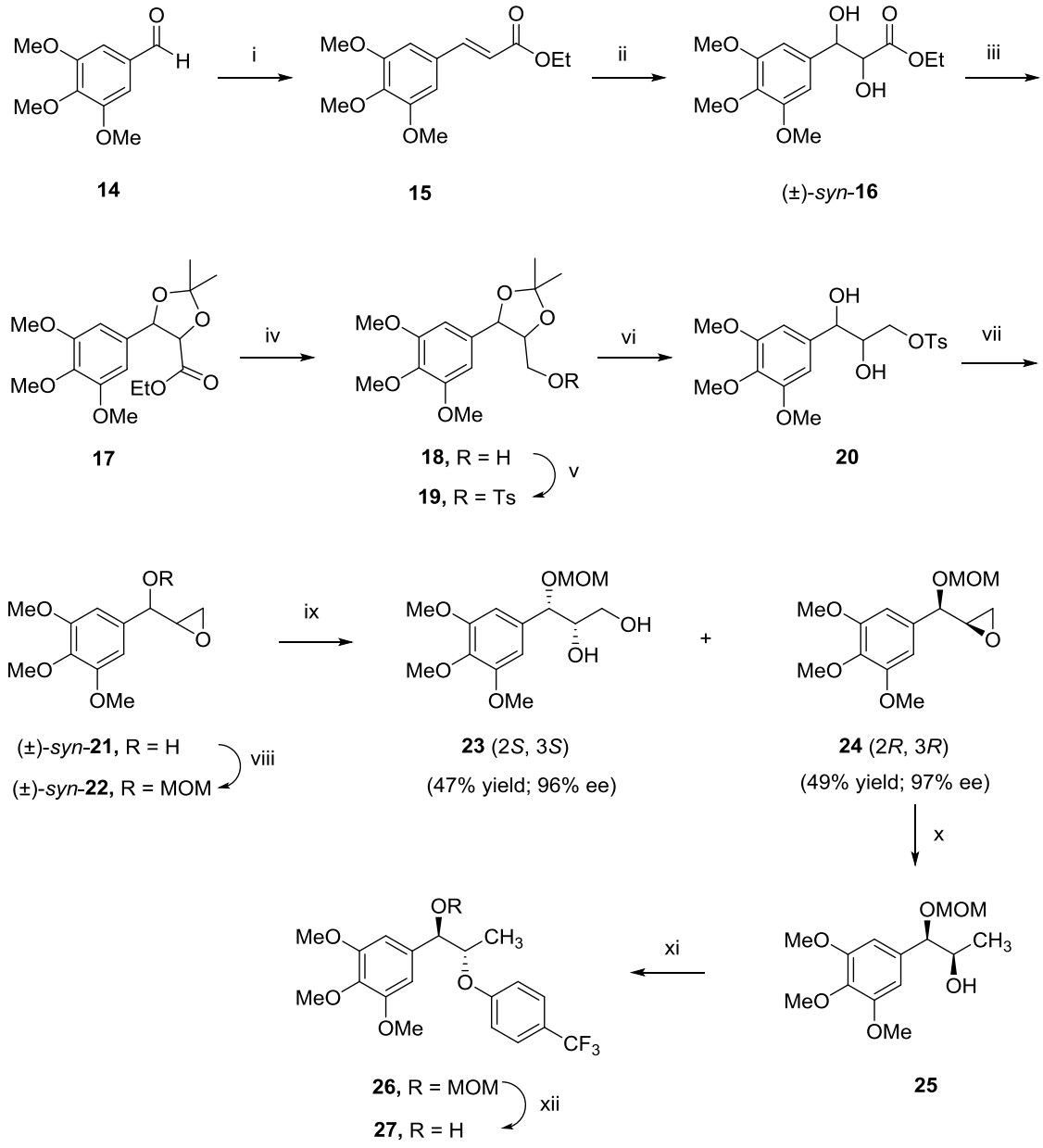


Scheme 2: (i) (*S, S*)-Co(salen)OAc, (0.5 mol%), THF, H_2O (0.5 equiv), 0 °C, 14 h; (ii) TBDMSCl, imid., CH_2Cl_2, 0 °C to 25 °C, 1 h, 90%; (iii) NaH, DMF, BnBr, 0 °C to 25 °C, 2 h, 95%; (iv) TBAF, THF, 25 °C, 8 h, 91%; (v) IBX, DMSO, 2 h, 25 °C then $TiCl_4$, tributyl allyl stannane, CH_2Cl_2, -78 °C, 30 min, 73% (over two steps); (vi) (*E*)-cinnamoyl chloride, dry pyridine, DMAP, CH_2Cl_2, 0 °C to 25 °C, 12 h, 64%; (vii) Grubbs' II generation catalyst (10 mol%), CH_2Cl_2 reflux, 8 h, 76%; (viii) BBr_3, CH_2Cl_2, -78 °C, 6 h, 71%.

SECTION II: Enantioselective Synthesis of (-)-Polysphorin Analog *via* Co-Catalyzed Hydrolytic Kinetic Resolution of *syn*-(2*SR*, 3*SR*)-3-(Methoxymethyl) oxy-3-(3,4,5-trimethoxyphenyl)-1,2-epoxypropane

Polysphorin neolignan isolated from *Piper polysphorum C* in China,[9] and from the leaves and stems of *Rhaphidopora decursiva* in Vietnam[10] was shown to possess *in vitro* antimalarial activity (IC_{50} 400ng/ml).[11] Several other members of this family of

neolignans have also been shown to display interesting biological properties. Polysphorin analog (**27**) was found to be highly effective against malaria during the hepatic phase of the disease.[12]



Scheme 3: (i) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, 25 °C, 5 h, 96%; (ii) $K_2OsO_4.2H_2O$ (2 mol%), NMO, acetone:H_2O (4:1), 0 to 25 °C, 20 h, 93%; (iii) 2,2-dimethoxypropane, camphor sulfonic acid (10 mol %), CH_2Cl_2, 25 °C, 6 h, 98%; (iv) $LiAlH_4$, THF, 0 to 25 °C, 1 h, 92%; (v) *p*-TsCl, Et_3N, DMAP (10 mol%), CH_2Cl_2, 25 °C, 4 h, 94%; (vi) camphor sulfonic acid (10 mol %), CH_3OH, 40 °C, 1 h, 96%; (vii) K_2CO_3, CH_3OH, 25 °C, 3 h, 88%; (viii) MOMCl, $^{i}Pr_2NEt$, CH_2Cl_2, 25 °C, 8 h, 92%; (ix) (*S*, *S*)-Co(salen)OAc (0.5 mol%), H_2O (0.5 equiv), 0 °C, 14 h; (x) $LiAlH_4$, THF, 0 to 25 °C, 4 h, 96%; (xi) PPh_3, $^{i}PrO_2C\text{-}N{=}N\text{-}CO_2Pr^{i}$, 4-(trifluoromethyl)phenol, THF, 70 °C, 12 h, 74%; (xii) conc. HCl, CH_3OH, 25 °C, 4 h, 86%.

The complete synthetic sequence for polysphorin analog (**27**), commencing from the precursor aldehyde **14**, is shown in **Scheme 3**. Wittig olefination of aldehyde **14** resulted in cinnamte ester **15** (96% yield), which was subjected to Os-catalyzed Upjohn dihydroxylation to give the *syn* dihydroxy ester **16** in 93% yield. Acetonide protection of diol in **16** was achieved in 98% yield (2,2 - dimethoxypropane, CSA in CH_2Cl_2). Reduction of ester **17** using $LiAlH_4$ furnished alcohol **18** in quantitative yield, which was further converted to epoxy alcohol **21** in a three-step reaction sequence: (i) tosylation of primary alcohol (TsCl, Et_3N, DMAP); (ii) acetonide deprotection (CSA, MeOH, 40 ^oC) followed by (iii) epoxide formation under basic conditions (K_2CO_3, MeOH). Secondary alcohol in epoxy alcohol **21** was protected as its MOM ether to give *syn*-racemic epoxide **22**, precursor for HKR in 92% yield. Racemic oxirane **22** was subjected to two-setereocentred HKR by using (*S, S*)-salen-Co-OAc catalyst to give highly enantiomerically pure diol **23** (47% yield, 96% ee) and epoxide **24** (49% yield, 97% ee).[7] Regioselective reductive ring opening of the epoxide **24** was achieved with $LiAlH_4$ to afford secondary alcohol **25** in 96% yield. The Mitsunobu reaction of alcohol **25** with *p*-trifluoromethyl phenol gave the protected neolignan **26** in 74% yield. Subsequent deprotection of MOM group in **26** using conc.HCl gave the (-)-polysphorin analog (**27**) in 86% yield.

CHAPTER 2

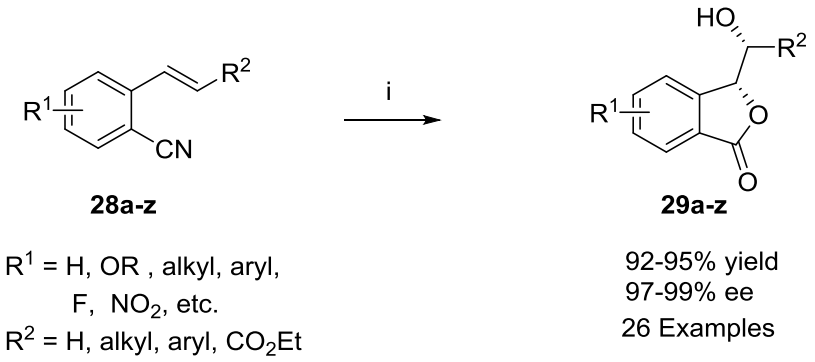
CN-Assisted Oxidative Cyclization of Cyano Cinnamates and Styrene Derivatives: A Facile Entry to 3-Substituted Chiral Phthalides and its Application to the Synthesis of (-)-Matteucen C and Butylphthalide

Sharpless asymmetric dihydroxylation (ADH) is one of the most effective methods for the preparation of chiral diols. This chapter deals with development of a novel method for the synthesis of chiral phthalides **29a-z** *via* CN-assisted oxidative cyclization of cyano cinnamates followed by its application in the synthesis of (-)-matteucen C and butylphthalide. This chapter is divided into two sections.

SECTION I: CN-Assisted Oxidative Cyclization of Cyano Cinnamates and Styrene Derivatives: a Facile Entry to 3-Substituted Chiral Phthalides

Chiral phthalides [isobenzofuran-1(3*H*)-ones] comprising of 5-membered lactones are found in a large number of plant products displaying broad and potent biological

activities such as anticonvulsant, anesthesia, antiischemic, antiHIV, anticancer and antibiotics.[13] In this section, we describe a single-step oxidative cyclization of cyanocinnamates and styrene substrates that affords 3-substituted phthalides in high yields *via* synergetic acceleration of CN and osmate ester groups present in proximity positions. When ethyl 2-cyanocinnamate **28a** was subjected to a typical AD-mix-β process for 7 h, with THF as co-solvent for better solubility, the corresponding chiral phthalide **29a** was obtained exclusively in 99% ee.



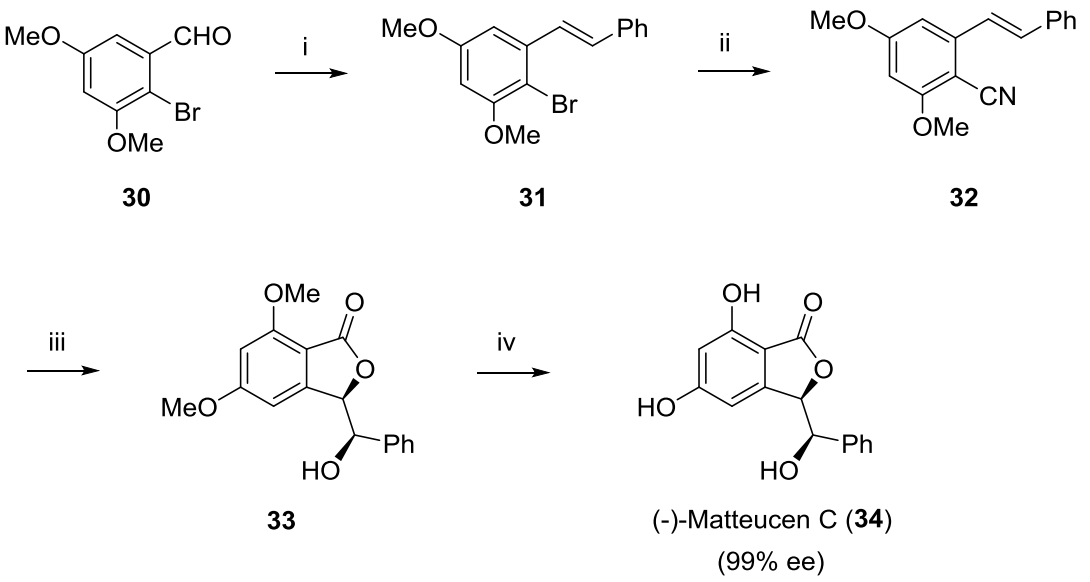
Scheme 4: (i) AD-mix-β, *tert*-BuOH:THF:H_2O (0.5:0.5:1), 25 °C, 3-7 h.

Encouraged by this result, we examined the scope of the reaction with other cyano cinnamate esters and styrene derivatives **28b-z**. In every case, the reaction proceeded rapidly in 3-7 h giving the desired phthalides **29b-z** in excellent yields and ees (upto 99%) (**Scheme 4**). The higher reactivity of cyano substituted cinnamates and styrenes were substantiated by carrying out several competitive experiments involving 1:1 molar equivalents of aromatic substrates with and without cyano substitution. The results clearly show that cyano substituted substrates react almost 10-12 times faster than the one without cyano substitution, giving excellent yields of chiral phthalides.

SECTION II: First Enantioselective Synthesis of (-)-Matteucen C and Facile Synthesis of antiIschemic Stroke Drug, 3-Butylphthalide

Matteucen C (**34**), isolated from Chinese medicinal herb, is used in the treatment of hemostatics and relieving ostalgia.[14] 3-butylphthalide (**40**), is an anticonvulsant drug for the treatment of stroke.[15] This section describes a short and practical enantioselective synthesis of (-)-matteucen C (**34**) and 3-butylphthalide (**40**), by employing CN-assisted oxidative cyclization of the corresponding *o*-cyano styrene

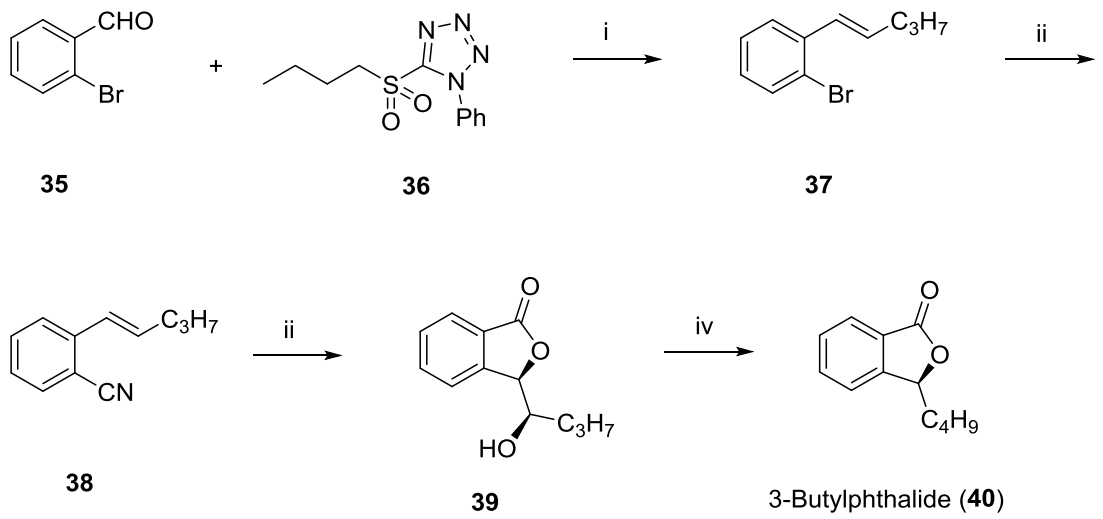
derivative **32** and **38** as the key step. Our synthesis of (-)-matteucen C commenced with 2-bromo-3,5-dimethoxy benzaldehyde (**30**), which was subjected to Wittig reaction to afford *trans*-stilbene derivative **31** in 82% yield. Rosenmund-von Braun reaction of bromo stilbene **31** gave cyano stilbene **32** with excess of CuCN under reflux conditions in DMF. Cyano stilbene **32** was then subjected to AD-mix-β process to give chiral phthalide **33** in 93% yield and 99% ee *via* CN-assisted "one-pot" oxidative cyclization. Demethylation of chiral phthalide **33** with BBr_3 in CH_2Cl_2 gave (-)-matteucen C in 43.67% overall yield and 99% ee (**Scheme 5**). Synthesis of (-)-matteucen C (**34**) was achieved for the first time, thereby confirming its structural and stereochemical assignments.



Scheme 5: (i) $PhCH_2Ph_3P^+I^-$, *n*-BuLi, THF, 0 to 25 °C, 3 h, 82%; (ii) CuCN (3.5 equiv), DMF, reflux, 14 h, 83%; (iii) AD-mix-β, *tert*-BuOH:THF:H_2O (0.5:0.5:1), 25 °C, 7 h, 93%; (iv) BBr_3, CH_2Cl_2, 25 °C, 12 h, 69%.

Similarly, our synthesis of 3-butylphthalide (**40**), started with *o*-bromobenzaldehyde (**35**), which on Julia-Kocienski olefination with butyl sulfone **36** gave (*E*)-2-bromostyrene **37** in 82% yield. Rosenmund-von Braun reaction of bromostyrene **37** with CuCN gave cyanostyrene **38**, which was then subjected to AD-mix-β process to give chiral phthalide **39** in 93% yield and 99% ee *via* CN-assisted "one-pot" oxidative

cyclization. Barton-McCombie protocol was utilized for deoxygenation of alcohol **39** to give 3-butylphthalide (**40**) in 86% yield (**Scheme 6**).



Scheme 6: (i) NaHMDS, THF, -78 ^{o}C to 25 ^{o}C, 14 h, 82%; (ii) CuCN (3.5 equiv), dry DMF, reflux, 14 h, 87%; (iii) AD-mix-β, *tert*-BuOH:THF:H_2O (0.5:0.5:1), 25 ^{o}C, 7 h, 93%; (iv) (a) 1,1-thiocarbonyldiimidazole, DMAP (10 mol%), CH_2Cl_2, 18 h; (b) AIBN (10 mol%), Bu_3SnH, toluene, reflux, 15 min, 86%.

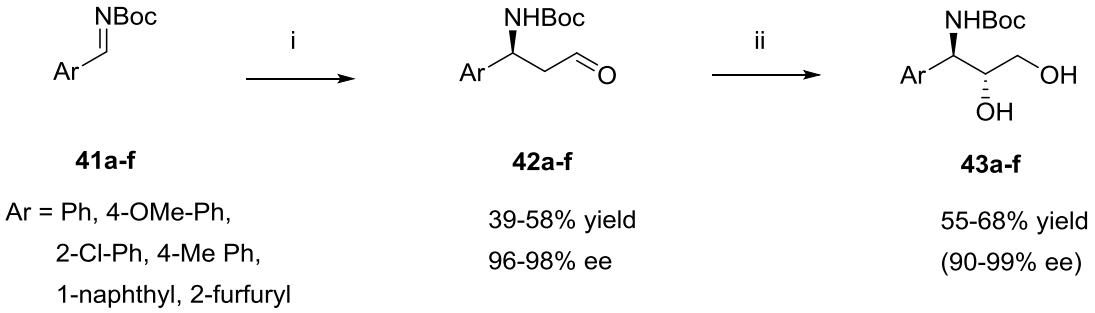
CHAPTER 3

A New Concise Method for the Synthesis of Chiral 3-Amino-1,2-Diols, (+)-*epi* -Cytoxazone and Formal Synthesis of *N*-Thiolated-2-Oxazolidinone *via* Proline-Catalyzed α-Aminooxylation of β-Aminoaldehydes

Asymmetric organocatalysis in organic chemistry has provided several new methods for obtaining chiral compounds in an environmentally benign manner. This chapter is divided into two sections. **Section I** deals with the development of novel flexible organocatalytic route to the synthesis of chiral 3-amino-1,2-diols *via* proline catalyzed α-aminooxylation of chiral β-aminoaldehydes. **Section II** describes the application of this protocol for the enantioselective synthesis of (+)-*epi*-cytoxazone and formal asymmetric synthesis of *N*-thiolated-2-oxazolidinone.

SECTION I: Proline-Catalyzed α-Aminooxylation of β-Aminoaldehydes: A Highly Stereoselective Synthesis of 3-Amino-1,2-Alkane Diols

The enantiomerically pure *syn*- or *anti*-3-amino-1,2-alkane diols[16] are valuable building blocks for asymmetric synthesis of numerous biologically active natural products and pharmacologically relevant therapeutic agents such as taxol side chain, glycosphingolipids, (-)-cytoxazone, (+)-*epi*-cytoxazone, oxazolidinones, etc. Proline, an abundant, inexpensive aminoacid available in both enantiomeric forms has emerged as a practical and versatile organocatalyst, efficient for α-functionalization[17] of aldehydes and ketones. In this section, an elegant and efficient protocol for the synthesis of chiral 3-amino-1,2-diols **43a-f** as single diastereomer *via* proline catalyzed α-aminooxylation of β-aminoaldehydes **42a-f** in good yields and high ee is described. Chiral pure β-aminoaldehydes **42a-f**, the starting materials for α-amino oxylation were efficiently prepared from the corresponding Boc-protected aryl aldimines **41a-f** following literature protocol (L-proline, CH_3CN, 0 ºC).

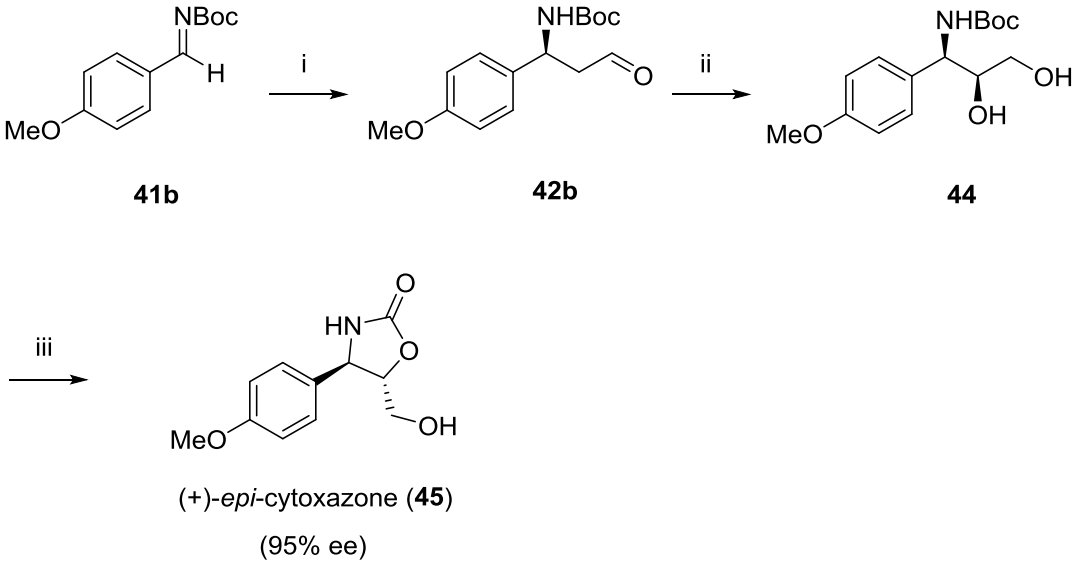


Scheme 7: (i) CH_3CHO, L-proline (20 mol%), CH_3CN, 0 °C, 3 h; (ii) (a) PhNO (0.8 equiv), L-proline (20 mol%), CH_3CN, -10 °C, 20 h then $NaBH_4$ CH_3OH, 10 min; (b) $Cu(OAc)_2.H_2O$ (15 mol%), CH_3OH, 25 °C, 10 h.

Several β-aminoaldehydes **42a-f** when subjected to L-proline catalyzed α-amino oxylation with PhNO followed by its reduction with $NaBH_4$ gave the corresponding 3-amino-1,2-diol derivatives **43a-f**. In every case, the reaction proceeded smoothly to give a single diastereomer of *anti*-3-amino-1,2-diols **43a-f**, with the intact of excellent enantioselectivity. For instance, substrates having electron-rich or electron-deficient substituent on the aromatic ring including 1-naphthyl ring system and heteroaryl gave the desired *anti*-3-amino-1,2-diols in excellent stereoselectivity (**Scheme 7**).

<u>SECTION II</u>: Enantioselective Synthesis of Cytokine Modulator (+)-*epi*-Cytoxazone and Formal Synthesis of Antibacterial *N*-Thiolated-2-Oxazolidinone

(+)-*epi*-Cytoxazone (**45**) containing a novel 4,5-disubstituted-2-oxazolidinone moiety was isolated from *Streptomyces sp.*[18] and was found to exhibit cytokine-modulating activity by inhibiting the signaling pathway of Th2 cells. Recently, studies have shown that *N*-thiolated 2-oxazolidinone (**50**) possesses antibacterial activity against methicillin-resistant *Staphylococcus aureus* and *Bacillus anthracis*.[19] In this section, a concise protecting group-free enantioselective synthesis of (+)-*epi*-Cytoxazone (**45**) and 2-oxazolidinone (**49**) using proline catalyzed α-aminooxylation of β-amino aldehyde is presented (**Scheme 8** and **9**).

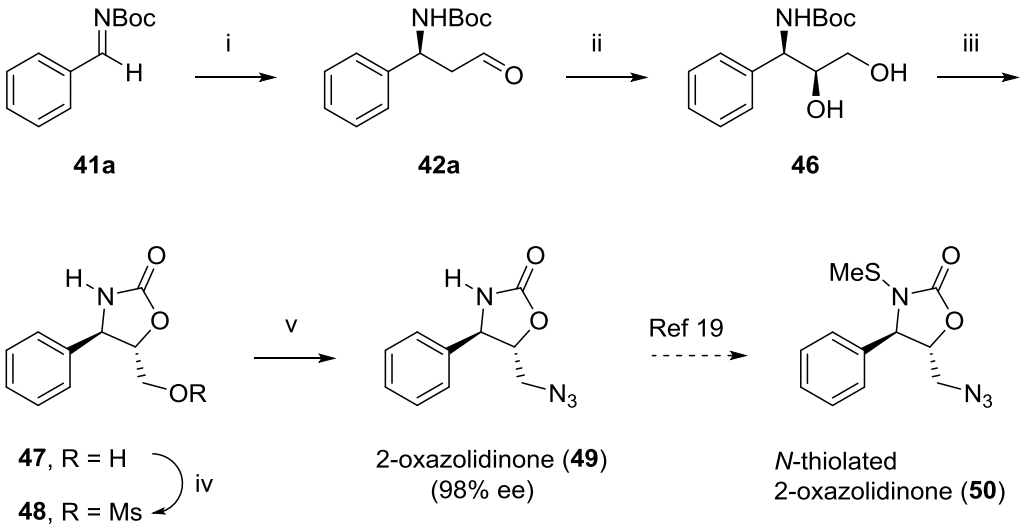


<u>Scheme 8</u>: (i) CH_3CHO, L-proline (20 mol%), CH_3CN, 0 °C, 3 h, 56%; (ii) (a) PhNO (0.8 equiv), D-proline (20 mol%), CH_3CN, -10 °C, 18 h; then $NaBH_4$, CH_3OH, 0 °C, 10 min; (b) $Cu(OAc)_2.H_2O$, CH_3OH, 25 °C, 16 h, 68% (over two steps); (iii) NaH, dry THF, 25 °C, 3 h, 90%.

The L-proline-catalyzed Mannich reaction of acetaldehyde with N-Boc-arylaldimine **41b** gave enantiopure β-aminoaldehyde **42b** in 56% yield and 98% ee.[20] The β-amino aldehyde **42b** was then subjected to D-proline catalyzed α-aminooxylation, which involves a two-step reaction sequence: (i) reaction of β-aminoaldehyde **42b** with

nitrosobenzene as the oxygen source in the presence of D-proline in CH_3CN at -10 °C followed by treatment with $NaBH_4$ in MeOH gave the crude aminooxy alcohol *in situ* and (ii) subsequent reduction of the crude aminoxy product with 30 mol% $Cu(OAc)_2.H_2O$ yielded chiral 3-amino-1,2-diol **44** in 68% yield, >99% dr and 98% ee (over two steps). Finally, the regioselective intramolecular cyclization of **44** has been achieved to give (+)-*epi*-Cytoxazone (**45**) (**Scheme 8**).

The synthetic strategy utilized for the synthesis of (+)-2-oxazolidinone (**49**), precursor to *N*-thiolated-2-oxazolidinone (**50**) (**Scheme 9**) was similar to the one employed for (+)-*epi*-cytoxazone (**45**) (see **Scheme 8**). Thus oxazolidinone (**49**) was prepared in 3 steps [(i) Mannich reaction, (ii) proline-catalyzed α-aminooxylation and (iii) intramolecular cyclization] starting from imine **41a** in 33% yield (over three steps). Mesylation of primary alcohol **47** gave the mesylate **48**, which on treatment with NaN_3 in DMF at 60 °C afforded (+)-2-oxazolidinone (**49**) in 98% ee.



Scheme 9: (i) CH_3CHO, L-proline (20 mol%), CH_3CN, 0 °C, 3 h, 55%; (ii) (a) PhNO (0.8 equiv), D-proline (20 mol%), CH_3CN, -10 °C, 18 h; then $NaBH_4$, CH_3OH, 0 °C, 10 min; (b) $Cu(OAc)_2.H_2O$, CH_3OH, 25 °C, 16 h, 64% (over two steps); (iii) NaH, dry THF, 25 °C, 3 h, 94%; (iv) MsCl, Et_3N, CH_2Cl_2, 0 °C, 1 h; (v) NaN_3, DMF, 60 °C, 12 h, 82% (over two steps).

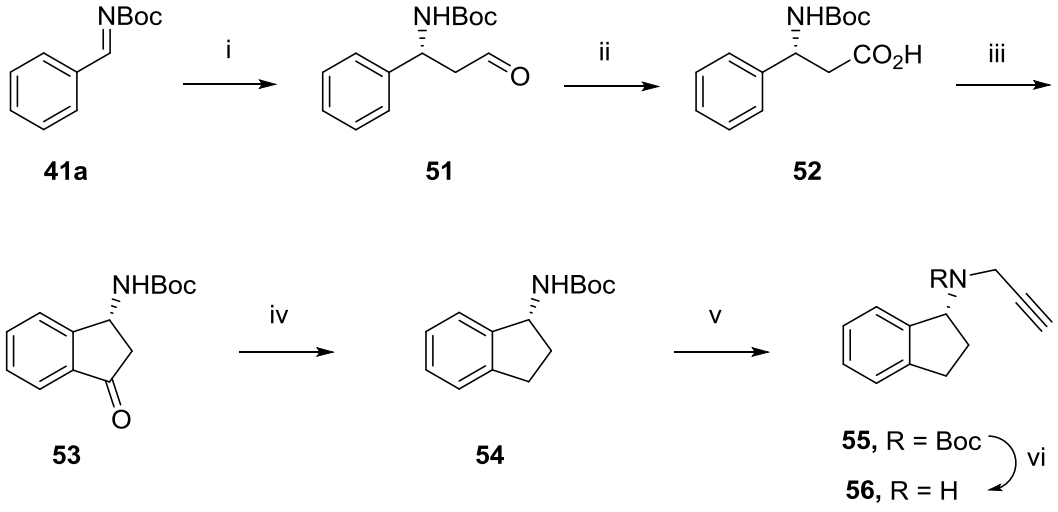
CHAPTER 4

Asymmetric Synthesis of Rasagiline and NHC-catalyzed Esterification of Aromatic Aldehydes

This Chapter is divided into two sections. **Section I** deals with the asymmetric synthesis of anti-Parkinson drug, rasagiline *via* proline-catalyzed Mannich reaction and **Section II** describes the esterification of aromatic aldehydes with alcohols under aerobic condition using *N*-heterocyclic carbene as catalyst.

SECTION I: Enantioselective Synthesis of Rasagiline an anti-Parkinson Drug

Rasagiline (Azilect) (**56**) is an irreversible inhibitor of monoamine oxidase[21a] used as a monotherapy in early Parkinson's disease or as an adjunct therapy in more advanced cases.[21b] The present section describes the enantioselective synthesis of rasagiline (**56**) *via* proline-catalyzed Mannich reaction, followed by Friedel-Crafts' intramolecular acylation as the key reactions (**Scheme 10**). Our synthesis of rasagiline (**56**) started from Boc-protected benzaldimine **41a**, which on Mannich reaction with acetaldehyde (D-proline, CH_3CN, 0 ºC) afforded β-aminoaldehyde **51** in 62% yield and 98% ee.

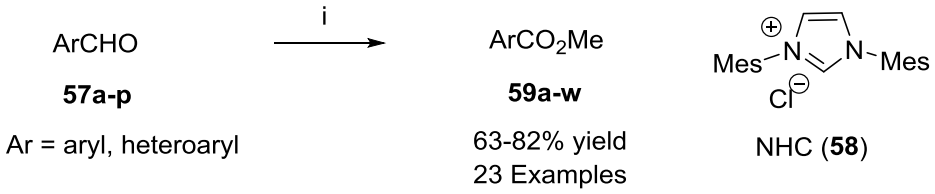


Scheme 10: (i) CH_3CHO, D-proline (20 mol%), CH_3CN, 0 °C, 3 h, 62%; (ii) $NaClO_2$, NaH_2PO_4, *tert*-BuOH:H_2O (5:1), 25 °C, 30 min, 93%; (iii) $ClSO_3H$, CH_2Cl_2, 25 °C, 2 h, then $(Boc)_2O$, Et_3N, cat. DMAP, CH_2Cl_2, 25 °C, 3 h, 83%; (iv) $NH_2NH_2.H_2O$, KOH, diethylene glycol, reflux, 4 h, 88%; (v) NaH, propargyl bromide, DMF, 25 °C, 4 h, 81%; (vi) 37% aq. HCl, dioxane, 25 °C, 30 min, 97%.

The Pinnick oxidation of β-aminoaldehyde **51** with $NaClO_2$ and NaH_2PO_4 gave the corresponding β-amino carboxylic acid **52**, which on Friedel-Crafts' intramolecular acylation reaction with $ClSO_3H$, followed by the protection of primary amine [$(Boc)_2O$, Et_3N, cat. DMAP] afforded indanone **53**. Wolff-Kishner reduction of indanone **53** afforded carbamate **54** in 88% yield. Alkylation of carbamate **54** followed by subsequent deprotection of the Boc protecting group with 37% aq. HCl in dioxane furnished rasagiline (**56**).

SECTION II: ***N*-Heterocyclic Carbene-Catalyzed Esterification of Aromatic Aldehydes with Alcohols under Aerobic Condition**

Aromatic esters are important and useful structural elements finding tremendous applications in wide range of fields encompassing solvents, lubricants, plasticizing agents, perfumes, pharmaceuticals, agrochemicals, etc. In recent years, *N*-heterocyclic carbenes (NHCs) have emerged as an important and powerful class of organocatalysts[22] with tremendous applications in a variety of synthetic transformations and as versatile ligands in transition metal catalysis. In this section, we describe a simple, organocatalytic procedure for the direct oxidative esterification of a variety of aromatic aldehydes **57a-p** with various alcohols that affords the corresponding aromatic esters **59a-w** in good yields using imidazolium NHC (**58**) as catalyst and molecular O_2 as oxidant at ambient conditions (**Scheme 11**).



Scheme 11: (i) NHC (**58**) (10 mol%), DBU (20 mol%), alcohol (1.2 equiv), O_2 (1 atm).

Several aromatic aldehydes underwent oxidative esterification with methanol smoothly under mild conditions. Remarkably, substrates with electron-withdrawing groups showed higher reactivity as compared to electron-releasing substituents. Heteroaromatic aldehydes such as 3-pyridine carboxaldehyde and furfural also gave the corresponding esters in high yields.

A wide range of alcohols were then examined for oxidative esterification with 4-nitrobenzaldehyde as the substrate, both primary and secondary alcohols including allylic, propargylic and benzylic alcohols underwent this reaction to give the corresponding esters in excellent yields. In order to gain insight into the mechanistic details of the reaction, control experiments were carried out and based on result and literature precedents,[23] a catalytic cycle was propsed.

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CHAPTER 1

Short Enantioselective Synthesis of (+)-Goniodiol and (-)-Polysphorin Analog using Co-Catalyzed HKR of Alkoxy Epoxides

Section I:

Concise Enantioselective Synthesis of (+)-Goniodiol, a Cytotoxic Lactone *via* Co-Catalyzed Hydrolytic Kinetic Resolution of *anti*-(2*SR*, 3*RS*)-3-Methoxy-3-phenyl-1,2-epoxy propane

1.1.1 Introduction

The genus *Goniothalamus* (Annonoceae) consists of over 115 species of shrubs and treelets growing abundantly in the rain forests of tropical Asia.[1] The extracts and leaves of *Goniothalamus* species have traditionally been used as folk medicine: e.g. in the treatment of edema and rheumatism,[2] abortifacient,[3] labor pain,[4] etc. Recently, (+)-goniodiol (**1**), belonging to styryllactone family, was isolated from *Goniothalamus sesquipedalis*.[4]

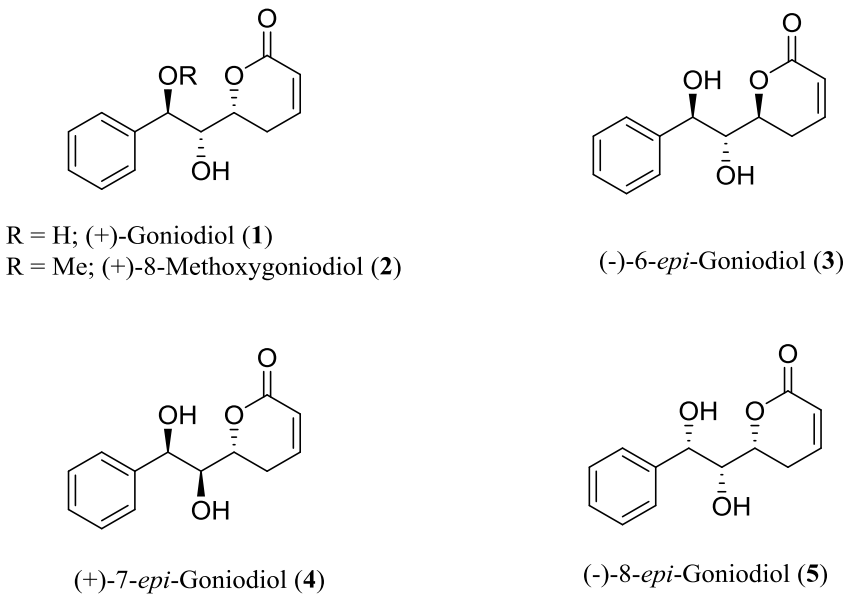


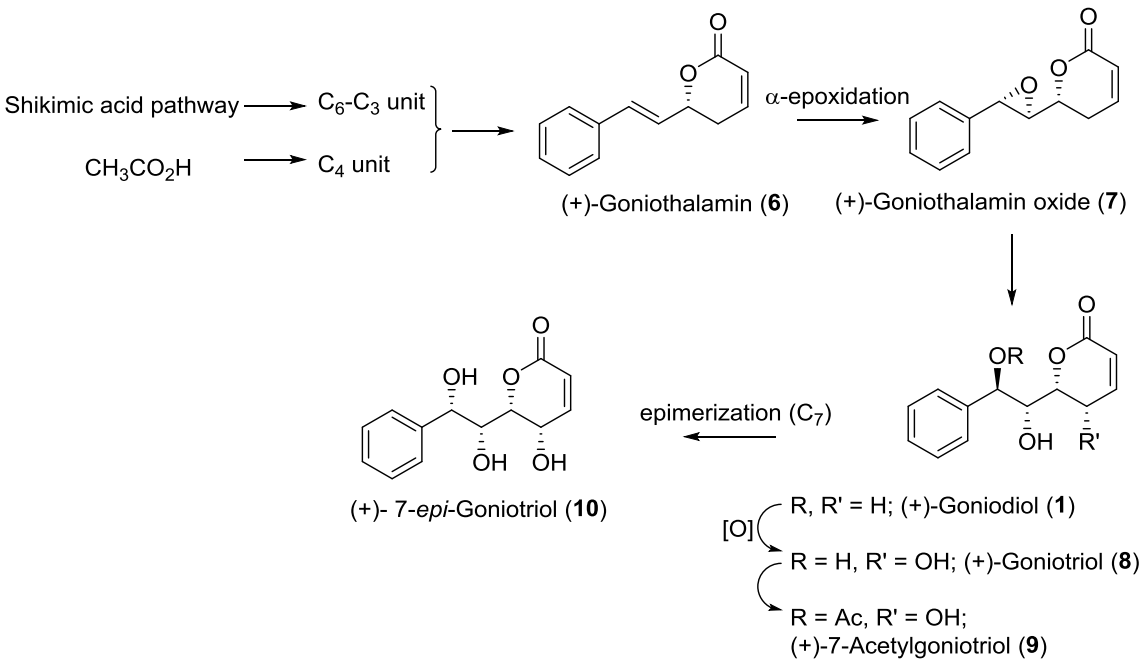
Fig. 1: Structures of bioactive styryllactones

Fig. 1 shows the structures of some of the isomers of goniodiol **1-5**. These bioactive natural products (**1-5**) with relatively small and densely functionalized molecules are

found to exhibit significant cytotoxic activity[5] including antimicrobial and antifungal properties as well as antibiotic potential. In particular, (+)-goniodiol (**1**) was found to show significant cytotoxic selectivity against several human tumor cell lines e.g. human lung carcinoma (A-549) (ED_{50} $1.22x10^{-1}$ µg/ml).[4a,6] Its unique structural features coupled with potent biological activities make them ideal targets for testing new synthetic methodology. Consequently, there have been consistent efforts toward styryllactones **1**-**5** resulting in a number of their total synthesis.[7-18]

1.1.2 Pharmacology and Mode of Action

The structure and relative configuration of (+)-goniodiol (**1**) were established by NMR spectral studies [4a,6] and X-ray crystallography.[6] (+)-Goniodiol (**1**) contains a 6-substituted 5,6-dihydro-α-pyrone moiety, which is widely distributed in the plant kingdom. Natural products containing this lactone unit also possess a wide range of biological activity such as insect antifeedants, antifungal, plant growth inhibitors, etc.



Scheme 1: Proposed biosynthetic pathways for styryllactones

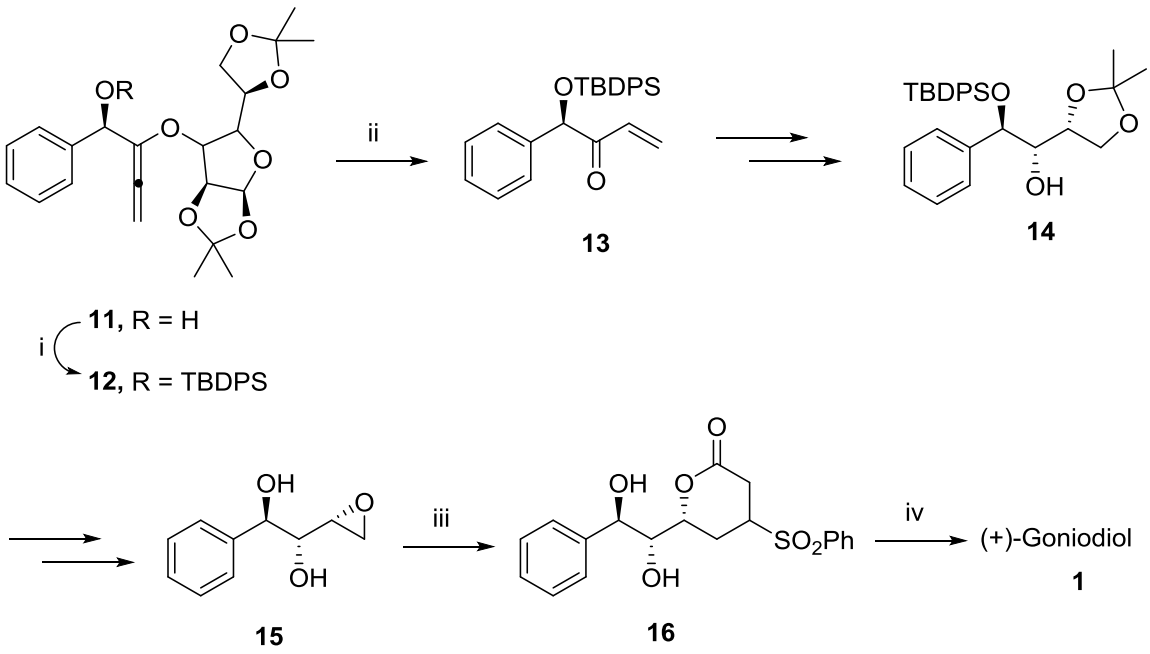
The α,β-unsaturated δ-lactone functionality is presumed to be responsible for the biological activities, due to its ability to act as a Michael acceptor, enabling these molecules to bind to a target enzyme. Literature reveals that (+)-goniodiol (**1**) is considered to be the biosynthetic precursor to other styryllactones. Thus, (+)-goniodiol (**1**) may be more important and can be an immediate precursor to many higher order functionalized styryllactones **8**-**10** (**Scheme 1**).[19]

1.1.3 Review of Literature

Literature search revealed that several reports are available for the synthesis of (+)-goniodiol (**1**) involving chiral pool, chemo-enzymatic approach or enantioselective syntheses, several of which are described below.

Vatele's approach (1996)[7]

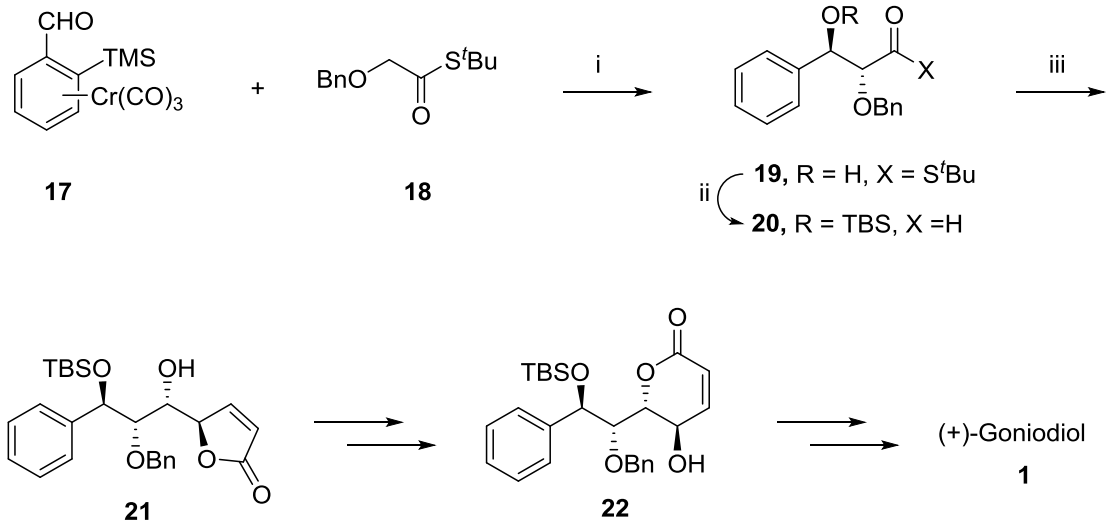
Vatele *et al.* have achieved the synthesis of (+)-goniodiol (**1**) using a chiral pool approach commencing from allenic alcohol **11**, which was derived from D-glucose by a diastereoselective addition of the lithium salt of 3-O-allenyl diacetone-D-glucose to benzaldehyde. The allenic alcohol **11** was subjected to O-silylation **12,** followed by acidic hydrolysis to give unsaturated ketol **13**. Protected ketol **13** was converted to alcohol **14** (dr = 92:8) using simple standard transformations, where diastereoselective dihydroxylation and reduction using L-Selectride served as key steps. Epoxide **15** was obtained from alcohol **14** in four linear steps. Further, epoxide **15** was treated with lithio derivative of methyl 3-phenylsulfonyl orthopropionate in the presence of $BF_3.Et_2O$ to give the sulfonyl lactone **16**. Finally, DBU-induced elimination gave (+)-goniodiol (**1**) (**Scheme 2**).



Scheme 2: (i) *t*-$BuPh_2SiCl$, DMAP, CH_2C1_2, 3 days; (ii) 50% CF_3CO_2H-CH_2Cl_2, 3 h, 81% (over 2 steps); (iii) (a) 2-methoxypropene, camphorsulfonic acid, CH_2C1_2, 10 min, 25 °C, 68%; (b) methyl-3-phenylsulfonyl orthopropionate , *n*-BuLi, $BF_3.Et_2O$, THF, -78 °C, 2 h; then 3M H_2SO_4, 50 °C, 3 h; (iv) DBU, CH_2C1_2, 1 h, 0 °C, 60%.

Hanaoka's approach (1997)[8]

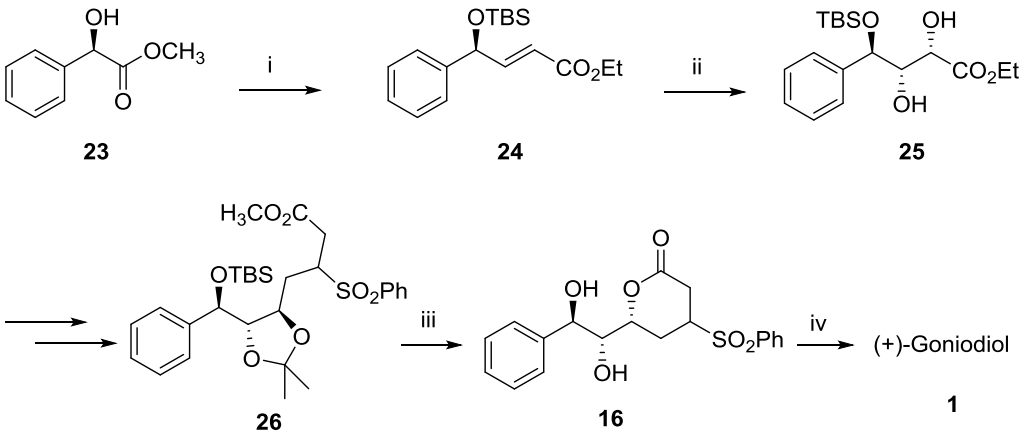
Hanaoka *et al*. have reported a useful method of synthesis of (+)-goniodiol **1** using a highly stereoselective asymmetric aldol reaction of chromium complexed *o*-TMS-benzaldehyde **17** as key step. Reaction of aldehyde **17** with ethanethioate **18** in the presence of $TiCl_4$ afforded the *anti*-aldol product **19** in 59% yield. *anti*-Aldol product **19** was then converted to aldehyde **20** using simple transformations; Further, aldol reaction of aldehyde **20** with 2-trimethylsilyloxy furan in the presence of $Ti(O^iPr)_2Cl_2$ produced δ-lactone **21** in 56% yield. Five-membered δ-lactone **21** was then converted to six-membered lactone **22** in two steps, which was finally transformed to (+)-goniodiol (**1**) in five linear steps (**Scheme 3**).



Scheme 3: (i) $TiCl_4$, Et_3N, CH_2Cl_2, -78 °C, 2 h then TBAF- HF, CH_3CN:THF, -78 °C to 0 °C, 30 min then hυ, Et_2O, 0 °C, 2 h, 67%; (ii) (a) thallium trinitrate, CH_3OH, 4 h, 71%; (b) TBSCl, imid., CH_2Cl_2, 71%; (c) DIBAL-H, benzene, 25 °C, 3 h; (iii) $Ti(O^iPr)_2Cl_2$, 2-trimethyl silyloxyfuran, CH_2Cl_2, -78 °C, 2 h, 56%.

Vatele's approach (1998)[9]

Vatele *et al*. have commenced their synthesis from commercially available methyl (*R*)-mandelate **23**.

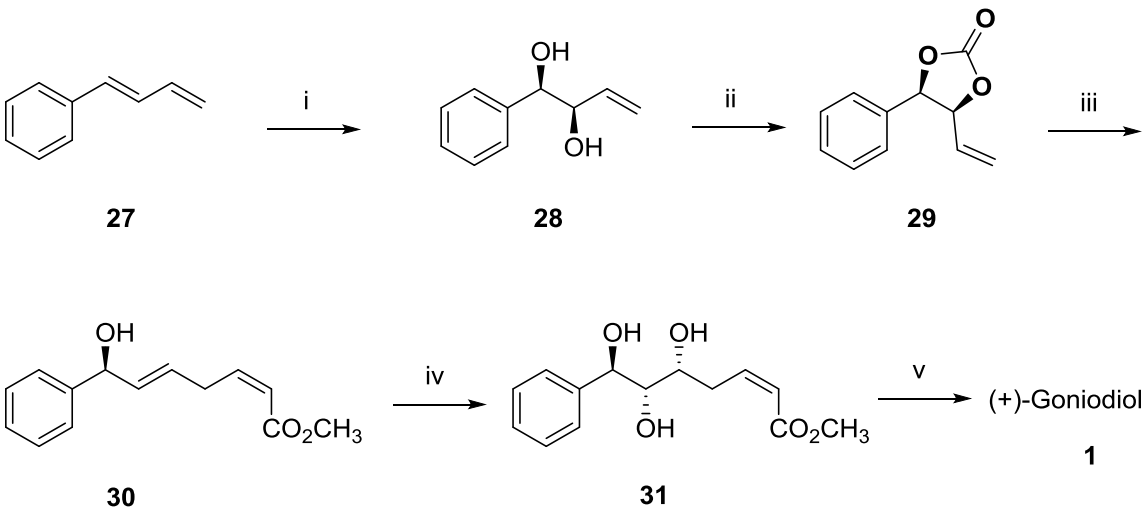


Scheme 4: (i) (a)TBDMSCl, imid., DMF, 25 °C, 12 h, 98%; then DIBAL-H, Et_2O, hexane, -78 °C, 20 min, 82%; (b) $Ph_3P{=}CHCO_2Et$, toluene, reflux, 30 min, 94%; (ii) cat. OsO_4, NMO, acetone:H_2O (5:1), 25 °C, 5 h, 85%; (iii) CF_3CO_2H:H_2O (4:1), 25 °C, 18 h, 83 %; (iv) DBU, CH_2C1_2, 0 °C, 1 h, 97 %.

The (*E*)-unsaturated ester **24** was obtained from methyl (*R*)-mandelate **23** by sequential protection of the hydroxy group, reduction of ester and Wittig reaction. Ester **24** on OsO_4-catalyzed diastereoselective dihydroxylation gave dihydroxy ester **25**, with high *anti* selectivity (89:11 ratio) in 85% yield. Sulfone **26** obtained from dihydroxy ester **25** in four steps; was then converted to known intermediate **16** under acidic condition. Finally, DBU-induced elimination afforded goniodiol (**1**) (**Scheme 4**).

Lin's approach (2002)[10]

Lin *et al.* have reported the synthesis of (+)-goniodiol (**1**) by employing Sharpless asymmetric dihydroxylation as the key reaction. Thus, (*E*)-1-phenyl-1,3-butadiene **27** was subjected to regioselective asymmetric dihydroxylation, which resulted in a slightly greater preference for the internal double bond over terminal double bond with a ratio of 2.2 to 1 and an ee of 95% for diol **28**.



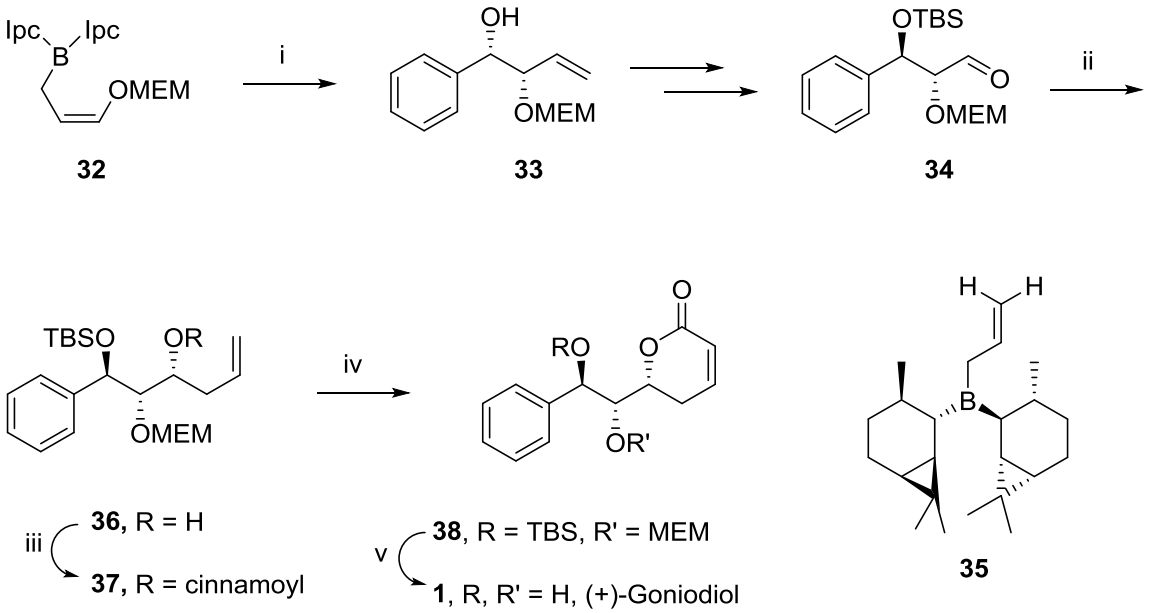
Scheme 5: (i) AD-mix-β, $CH_3SO_2NH_2$, 0 °C, 30 h, 58%; (ii) triphosgene, Et_3N, CH_2Cl_2, 0 °C, 2 h, 98%; (iii) cat. $PdCl_2(CH_3CN)_2$, (*Z*)-vinyltributylstannane, DMF:H_2O (4:1), 0 °C, 1 h, 71%; (iv) AD-mix-β, $CH_3SO_2NH_2$, 0 °C, 22 h, 83%; (v) *p*-TSA, toluene, 80 °C, 84%.

Protection of diol **28** with triphosgene furnished allylic cyclic carbonate **29**, which was coupled with (*Z*)-vinyltributylstannane in the presence of $PdCl_2(CH_3CN)_2$ (5

mol%) to afford the (*E*)-substituted allylic alcohol **30.** Sharpless dihydroxylation of **30** with AD-mix-β furnished the triol **31** (de 96:4). Finally, lactone formation under acidic condition provided (+)-goniodiol (**1**) (**Scheme 5**).

Ramachandran's approach (2002)[11]

Ramachandran *et al.* have employed asymmetric alkoxyallylboration as the key reaction. Thus, alkoxyallylboration of benzaldehyde with (+)-*B*-γ-methoxyethoxy methoxyallyl diisopinocamphenylborane **32** afforded α-alkoxyhomoallylic alcohol **33** in 71% yield and 98% ee.



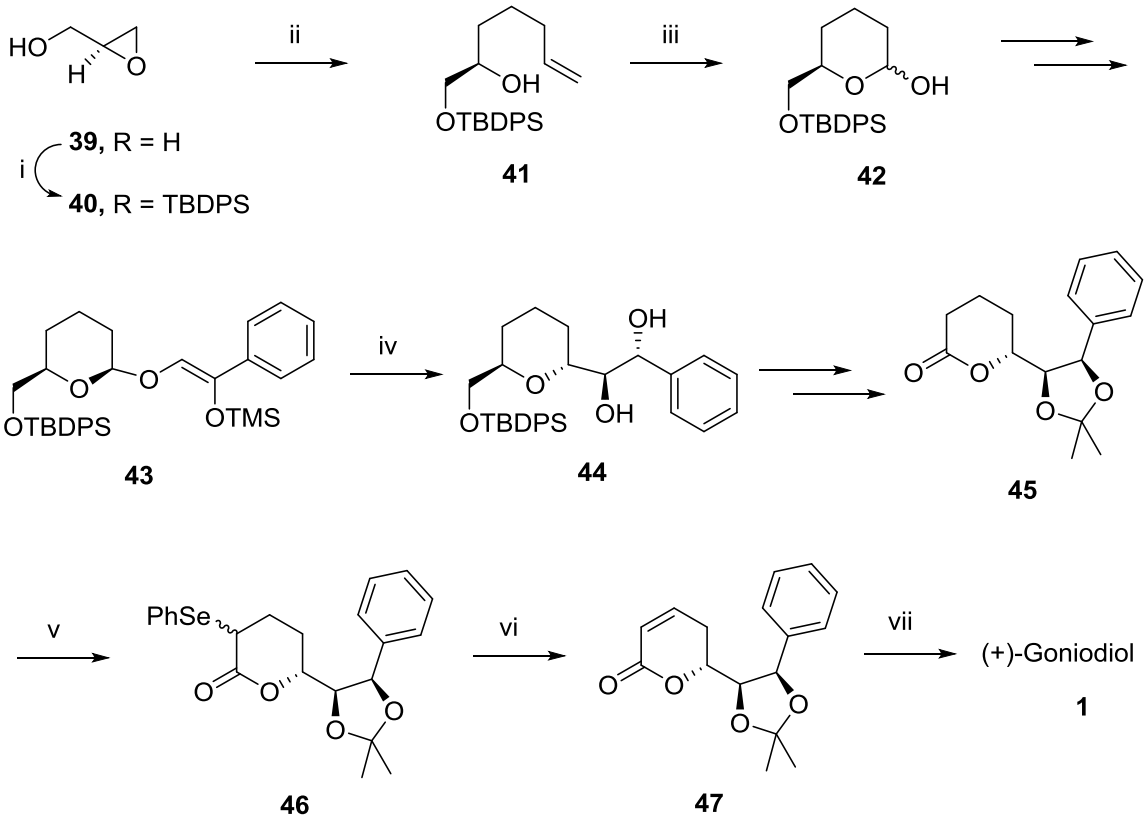
Scheme 6: (i) (a) PhCHO, -100 °C; (b) $NaOH/H_2O_2$, 25 °C, 71%; (ii) (a) (+)-**35**, ether:pentane, -100 °C; (b) NaOH, H_2O_2, 25 °C, 6 h, 76%; (iii) (*E*)-cinnamoyl chloride, pyridine, DMAP, CH_2Cl_2, 0 °C, 15 h, 63%; (iv) Grubbs' I generation catalyst, toluene, 120 °C, 3 h, 76%; (v) HCl:THF(1:8), 65%.

With simple transformations, α-alkoxyhomoallylic alcohol **33** was converted to aldehyde **34**, allylboration of which with **35**, provided the corresponding homoallylic alcohol **36** in 76% yield and 92% diastereomeric excess. The alcohol **36** was converted as its cinnamate ester **37** followed by ring closing metathesis with Grubbs'

first generation catalyst provided α-pyrone **38**. Both TBS and MEM groups were deprotected in a single step with HCl in THF to afford (+)-goniodiol (**1**) (**Scheme 6**).

Ley's approach (2006)[12]

Ley *et al.* have achieved the synthesis of (+)-goniodiol (**1**) using a chiral pool approach starting from (*S*)-(-)-glycidol **39**. Silyl protection of alcohol and subsequent regioselective addition of but-3-enylmagnesium bromide afforded alkenol **41.**



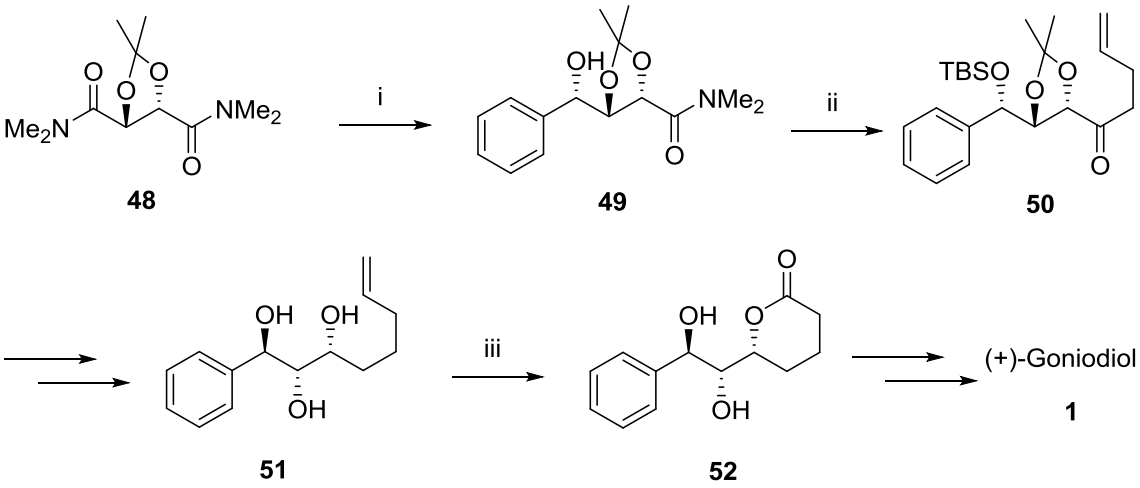
Scheme 7: (i) TBDPSCl, DMAP, Et_3N, CH_2Cl_2, 25 °C, 3 days, 86%; (ii) $CH_2=CH(CH_2)_2MgBr$, Li_2CuCl_4, THF, -30 °C, 100%; (iii) O_3, CH_2Cl_2, -78 °C, then PPh_3, 25 °C, 100%; (iv) (a) TMSOTf, CH_2Cl_2, -30 °C, 43%; (b) $NaBH_4$, CH_3OH, 0 °C, 100%; (v) LDA, THF, -78 °C then PhSeBr; (vi) CH_2Cl_2:30% aq. H_2O_2 (2 : 1), 0 °C, 10 min, 82% (over 2 steps); (vii) 50% aq. AcOH, 80 °C, 30 min, 97%.

Ozonolysis of olefin in **41** followed by reductive work-up gave lactol **42**. Lactol **42** was then converted to *anti*-diol **44** (d.e. = 95%) through silyl enol ether **43** using

simple transformations, where Grignard addition and diastereoselective reduction served as key steps. Subsequent protection and oxidations produced lactone **45** in five steps from *anti*-diol **44**. Introduction of α,β-unsaturation into the lactone molecule was achieved efficiently in two steps *via* sequential treatment with PhSeBr under basic condition to give selenide **46**, followed by oxidative elimination with H_2O_2 resulting in lactone **47**. Finally, deprotection of acetonide group gave (+)-goniodiol (**1**) (**Scheme 7**).

Prasad's approach (2007)[13]

Prasad *et al*. have employed chiral pool approach commencing from *D*-(-)-iso propylene dioxy tartaric amide **48**, which on reaction with PhMgBr and stereoselective reduction under Luche condition resulted in the formation of alcohol **49** (dr = 94:6) in 82% yield.



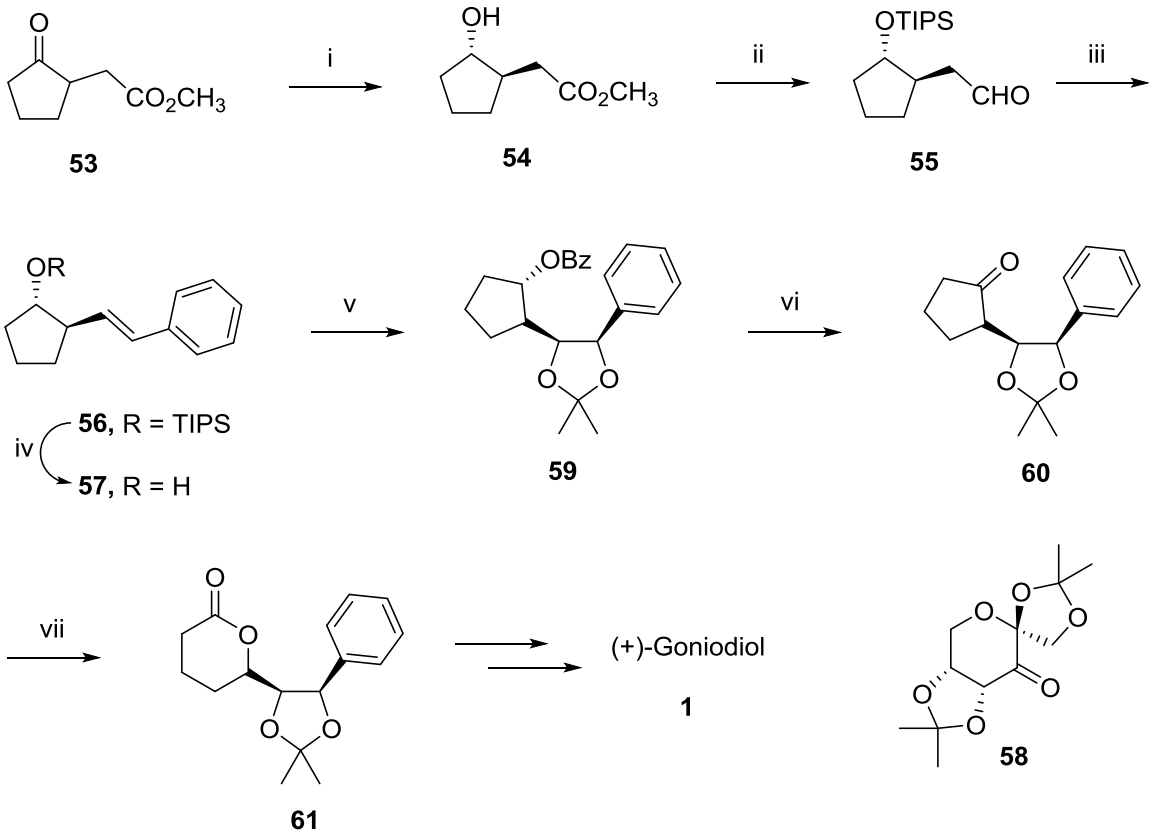
Scheme 8: (i) (a) PhMgBr, THF, -10 °C, 0.5 h, 92%; (b) $NaBH_4$, $CeCl_3$, -78 °C, 2 h; (ii) (a) TBDMSCl, imid., DMAP, DMF, 25 °C, 6 h, 90%; (b) 3-butenylmagnesium bromide, -10 °C, THF, 0.5 h, 93%; (iii) (a) O_3/Me_2S, CH_2Cl_2:MeOH, -78 °C, 6 h; (b) Ag_2CO_3/Celite, toluene reflux, 0.5 h, 76%.

Protection of the benzylic hydroxy group followed by the addition of 3-butenyl magnesium bromide afforded ketone **50**. Triol **51** was obtained from ketone **50** using simple transformations, where in Barton-McCombie deoxygenation and Mitsunobu

reactions served as key steps. Ozonolysis of olefin moiety followed by oxidation of the resulting lactol with Ag_2CO_3, gave lactone **52**. Selenation and deselenation of lactone **52** resulted in α,β-unsaturated lactone, which afforded (+)-goniodiol (**1**) (**Scheme 8**).

Yamauchi's approach (2008)[14]

Yamauchi *et al.* have reported the synthesis of (+)-goniodiol (**1**) by employing the enzymatic reduction of keto ester as the key reaction.

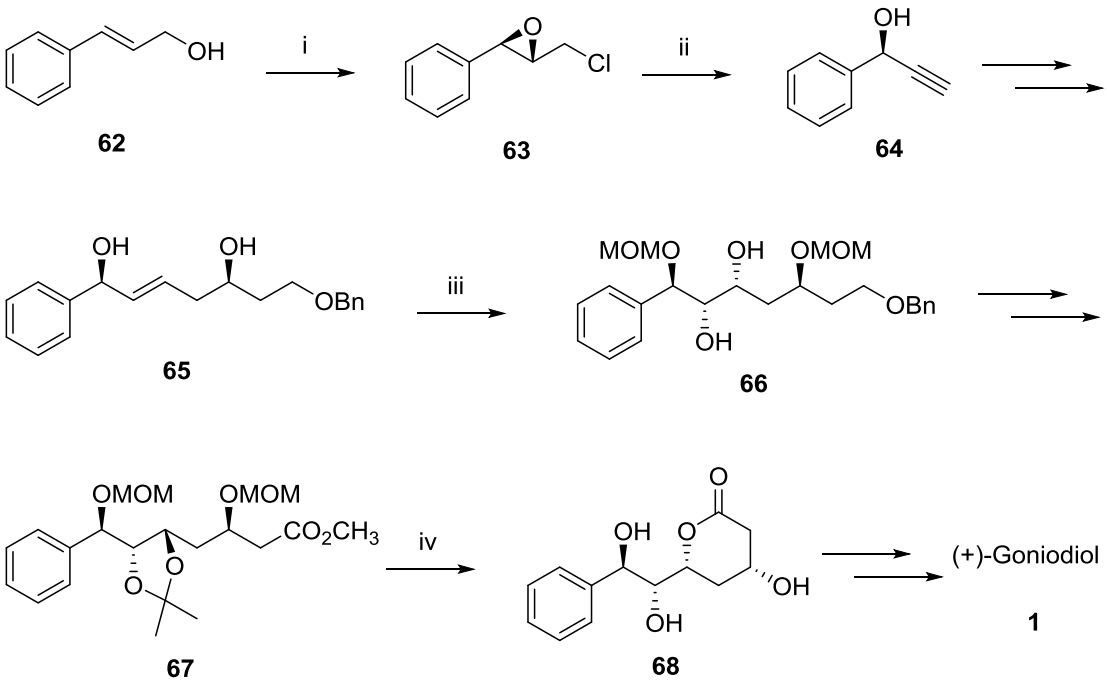


Scheme 9: (i) Baker's yeast, 30 °C, 48 h, 36%; (ii) (a)TIPSOTf, 2,6-lutidine, CH_2Cl_2, 25 °C, 20 h, 99%; (b) $LiAlH_4$, 0 °C, 1 h; (c) PCC, CH_2Cl_2, 25 °C, 16 h, 82%; (iii) (a) PhMgBr, 0 °C, 20 min, 94%; (b) $KHSO_4$, toluene reflux, 1.5 h, 84 %; (iv) TBAF, THF, 25 °C, 4 h, 100%; (v) (a) ketone **58**, 25 °C, 18 h, 83%; (b) BzCl, pyridine, 25 °C, 9 h, 98%; (c) 2-methoxypropene, *p*-TSA, DMF, 25 °C, 8 h, 41%; (vi) (a) NaOH, EtOH, 25 °C, 14 h, 97 %; (b) PCC, CH_2Cl_2, 25 °C, 22 h, 91% (over 2 steps); (vii) *m*CPBA, CH_2Cl_2, 25 °C, 8 h, 74%.

Thus, the racemic keto ester **53** was subjected to enzymatic reduction with Baker's yeast to give (1*R*, 2*S*)-hydroxy ester **54** in 36% yield. The hydroxy group of **54** was protected as its silyl ether, followed by reduction of ester group and oxidation of alcohol with PCC gave aldehyde **55**. Aldehyde **55** was subjected to Grignard reaction followed by dehydration, giving *trans*-olefin **56** as a single isomer. Desilylation and treatment of olefin **57** with D-fructose-derived ketone **58** gave epoxides as an inseparable diastereomers in 83% yield. Pure stereoisomer **59** was however obtained after benzoylation; Hydrolysis of epoxide to diol under acidic condition followed by its protection as acetonide was carried out. Base hydrolysis followed by PCC oxidation of **59** gave ketone **60**. Ketone **60** was then converted to the known lactone **45** by Baeyer-Villiger oxidation, thus constituting a formal synthesis of (+)-goniodiol (**1**) (**Scheme 9**).

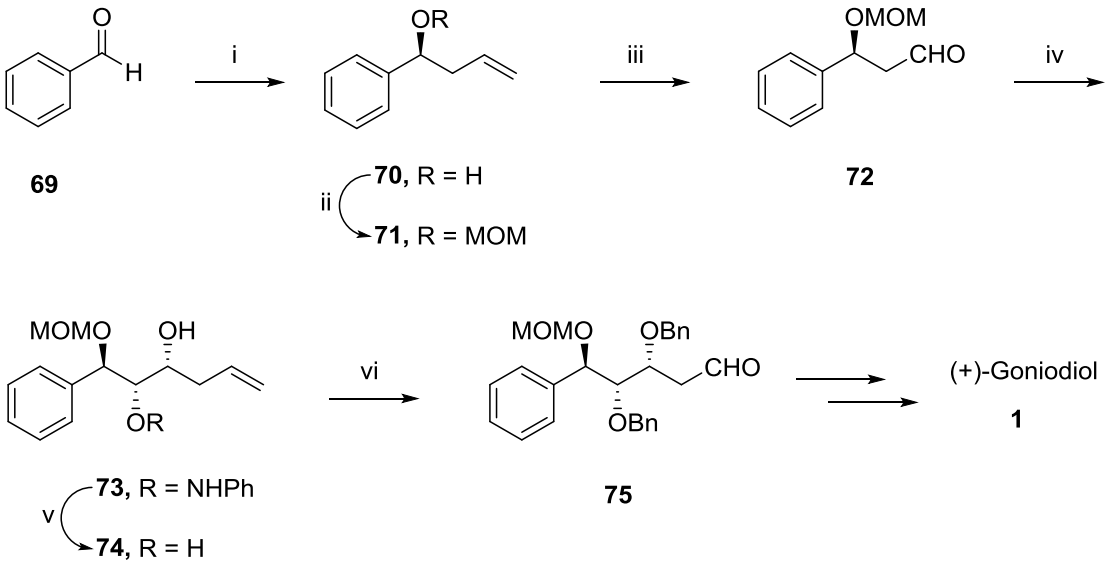
Yadav's approach (2008), (2011)[15,16]

Yadav *et al*. have achieved the synthesis of (+)-goniodiol (**1**) by employing Sharpless asymmetric epoxidation as the key reaction. Thus, Sharpless asymmetric epoxidation of cinnamyl alcohol **62** gave the desired epoxyalcohol in 82% yield, which was subsequently converted to chiral propargylic alcohol **64** in 72% yield. Regioselective ring opening of (*S*)-2-(2-(benzyloxy)ethyl)oxirane by reaction with lithium acetylide from **64**; followed by reduction with $LiAlH_4$ gave allylic alcohol **65**. Protection of diol **65** as its MOM ether and Sharpless asymmetric dihydroxylation afforded diol **66** in 80% yield. Ester **67** was obtained from diol **66** using simple transformations in four steps. Cyclization of ester **67** was achieved using *p*-TSA to afford lactone **68**, which was further converted to (+)-goniodiol (**1**) by elimination of hydroxyl group in the lactone moiety (**Scheme 10**).



Scheme 10: (i) (a) D-(-)-DET, $Ti(O^iPr)_4$, TBHP, CH_2Cl_2, 30 °C, 82%; (b) Ph_3P, CCl_4, $NaHCO_3$, 88%; (ii) *n*-BuLi, THF, 72%; (iii) (a) MOMCl, Hunig's base, CH_2Cl_2, 25 °C, 92%; (b) AD-mix-β, $CH_3SO_2NH_2$, *tert*-BuOH:H_2O (1:1), 0 °C; (iv) MeOH, *p*-TSA, 78%.

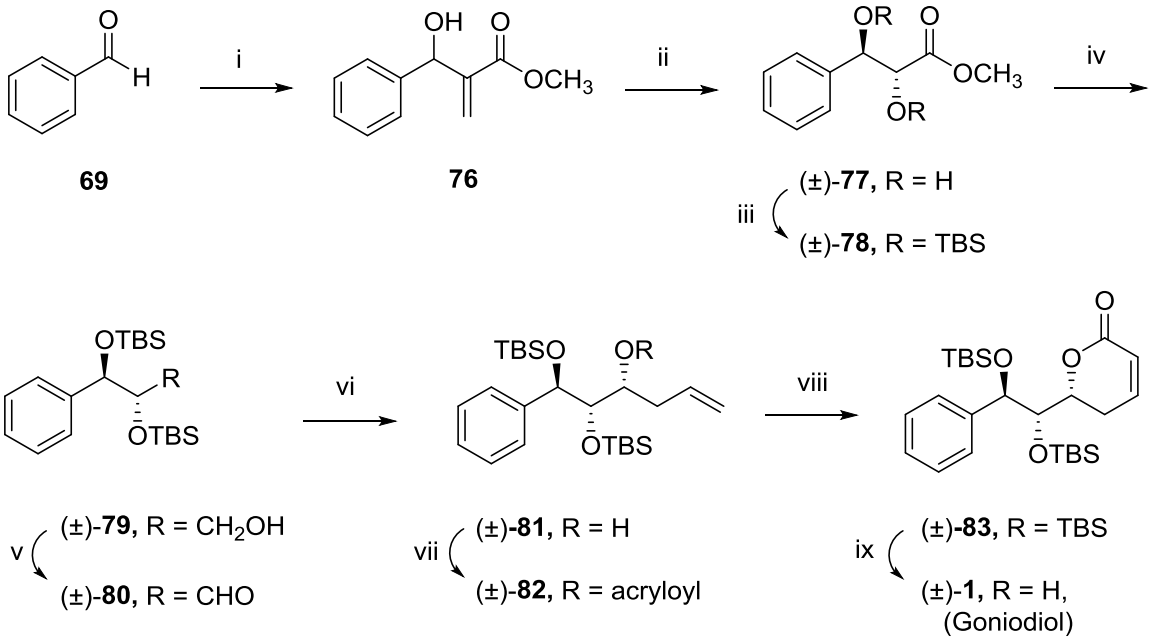
Yadav *et al.* have also developed another approach commencing from commercially available benzaldehyde **69**, which was converted to homoallylic alcohol **70** (98% ee) *via* Keck allylation using (*S*)-BINOL. The protection of alcohol **70** and subsequent oxidative cleavage provided aldehyde **72**. *L*-Proline-catalyzed α-aminoxylation of aldehyde **72** followed by *in situ* In-mediated allylation provided *syn*-alcohol **73** in 65% yield**,** dr = 6:4 (*syn*:*anti*). *syn*-Alcohol **73** was subjected to oxidative cleavage to provide aldehyde **75,** which on chain elongation with Wittig ylide and under cyclization conditions provided (+)-goniodiol (**1**) (**Scheme 11**).



Scheme 11: (i) (*S*)-BINOL, $Ti(O^iPr)_4$, CH_2Cl_2 reflux, 2 h, 25 °C, 10 min, then allyltributyltin, - 78 °C, 24 h, 91%; (ii) $^iPr_2NEt$, MOMCl, CH_2Cl_2, 25 °C, 15 h, 92%; (iii) (a) cat. OsO_4, NMO, acetone:H_2O (2:1), 25 °C, 24 h; (b) $NaIO_4$, THF:H_2O(2:1), 85%; (iv) PhNO, *L*-proline, $CHCl_3$, 0 °C, 4 h, allyl bromide, NaI, In, DMSO, 25 °C, 90 min, 65%; (v) Cu $(OAc)_2$, EtOH, 12 h, 25 °C; (vi) (a) NaH, BnBr, THF, 25 °C, 12 h, 90%; (b) cat. OsO_4, NMO, acetone:H_2O (2:1), 25 °C, 24 h; (c) $NaIO_4$, THF:H_2O, 85%.

Coelho's approach (2011)[17]

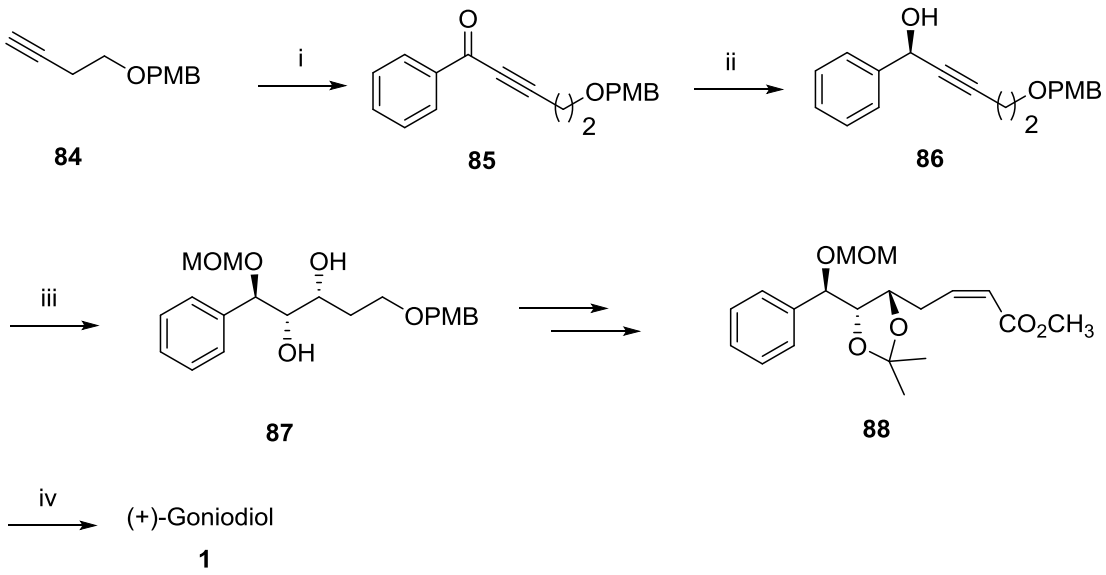
Coelho *et al.* have synthesized (±)-goniodiol (**1**) using Morita-Baylis-Hillman adduct. The reaction between benzaldehyde **69** and methyl acrylate gave the Morita-Baylis-Hillman adduct **76** in 85% yield. Ozonolysis under reductive conditions afforded *anti*-dihydroxylated ester **77** (95% de), which was protected as its silyl ether **78**. The aldehyde **80** was obtained by reduction of ester **78**, followed by the oxidation of alcohol **79** with IBX. Allylation using allyltributylstanane on aldehyde **80** gave allyl alcohol **81** (*syn*:*anti* = 83:17) in 79% yield, which on reaction with acryloyl chloride provided ester **82**. Ring closing metathesis of ester **82** gave α,β-unsaturated cyclohexenone **83**, which on treatment with HF/pyridine gave (±)-goniodiol (**1**) (**Scheme 12**).



Scheme 12: (i) methyl acrylate, 25 °C, 96 h, 85%; (ii) (a) O_3, MeOH, - 78 °C, then $(CH_3)_2S$, 1 h; (b) $NaBH_4$, CH_2Cl_2, -78 °C, 12 h, 70%; (iii) TBSCl, imid., 25 °C, 12 h, 98%; (iv) DIBAL-H, CH_2Cl_2, -78 °C, 1 h, 79%; (v) IBX, DMSO, 25 °C, 1 h, 88%; (vi) allyltributyltin, $TiCl_4$, CH_2Cl_2, -78 °C, 1 h, 79%; (vii) acryloyl chloride, NEt_3, CH_2Cl_2, 0 °C, 83%; (viii) cat. Grubbs' I generation, CH_2Cl_2 reflux, 18 h, 64%; (ix) HF, pyridine, CH_3CN, 25 °C, 24 h, 74%.

Sabitha's approach (2011)[18]

Sabitha *et al*. have developed a useful synthetic method for (+)-goniodiol (**1**) using CBS-reduction and Sharpless asymmetric dihydroxylation as the key reactions. Thus, asymmetric CBS-reduction of ketone **85** derived from homopropargylic alcohol derivative **84,** gave chiral propargylic alcohol **86** (99% ee) in 66% yield. Reduction of propargylic alcohol **86** with $LiAlH_4$ followed by Sharpless asymmetric dihydroxylation with AD-mix-β provided diol **87** as a single isomer in 90% yield. Ester **88** was obtained from diol **87** in four steps, where Still-Gennari reagent was used for chain elongation. Finally, the ester **88** on treatment with catalytic amount of *p*-TSA afforded (+)-goniodiol (**1**) *via* tandem deprotection and *in situ* cyclization process (**Scheme 13**).



Scheme 13: (i) (a) LHMDS, benzaldehyde, THF, -78 °C to 25 °C, 3 h, 90%; (b) IBX, DMSO, CH_2Cl_2, 0 °C to 25 °C, 92%; (ii) (*R*)-(Me)-CBS, $BH_3.SMe_2$, THF, -25 °C, 1 h, 66%; (iii) (a) $LiAlH_4$, THF, 0 °C to 25 °C, 3 h, 90%; (b) MOMCl, $^iPr_2NEt$, CH_2Cl_2, 0 °C to 25 °C, 3 h, 96%; (c) AD-mix-β, $CH_3SO_2NH_2$, *tert*-BuOH:H_2O (1:1), 0 °C, 10 h, 90%; (iv) *p*-TsOH, EtOH, 50 °C, 16 h, 84%.

1.1.4 Present Work:

1.1.4.1 Objective:

Even though several methods are reported for the synthesis of (+)-goniodiol (**1**),[7-18] some of them suffer from certain limitations such as use of chiral building blocks, exotic reagents, involvement of longer reaction sequences, expensive and hazardous reagents, low overall yields, low diastereomeric ratios, etc. In this context, a more practical method for the synthesis of (+)-goniodiol (**1**) is highly desirable.

Retrosynthetic analysis of (+)-goniodiol (**1**) reveals that homoallylic alcohol **103** could be visualized as the key intermediate. The homoallylic alcohol **103** could be achieved by means of Lewis acid-mediated diastereoselective allylation of aldehyde obtained from *anti*-methoxy diol **99**. The *anti*-methoxy diol **99** could in turn be obtained by performing Co-catalyzed two-stereocentered hydrolytic kinetic resolution

of the corresponding racemic *anti*-methoxy epoxide **97**. The requisite racemic *anti*-methoxy epoxide **97** could be easily prepared from cinnamyl alcohol **62** (**Fig. 2**).

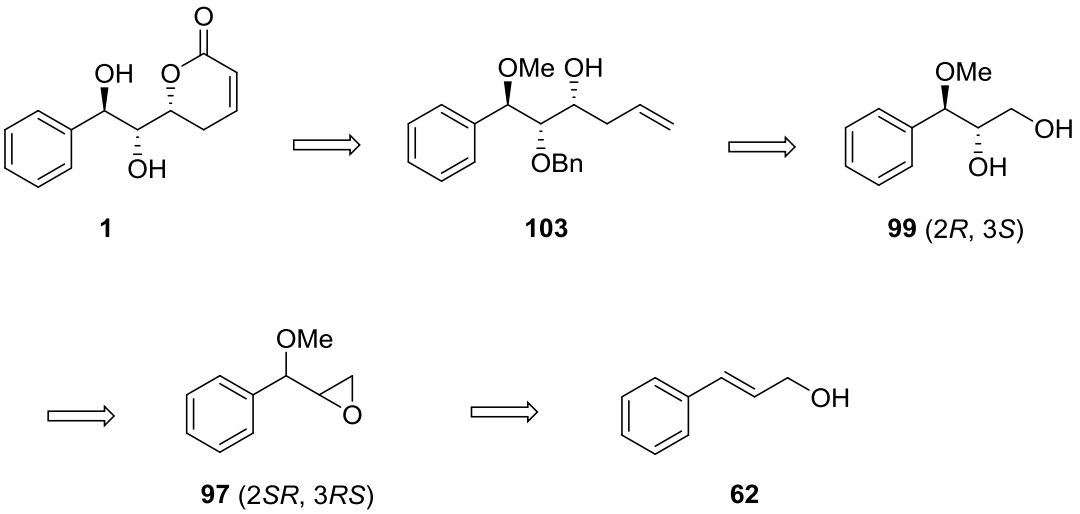


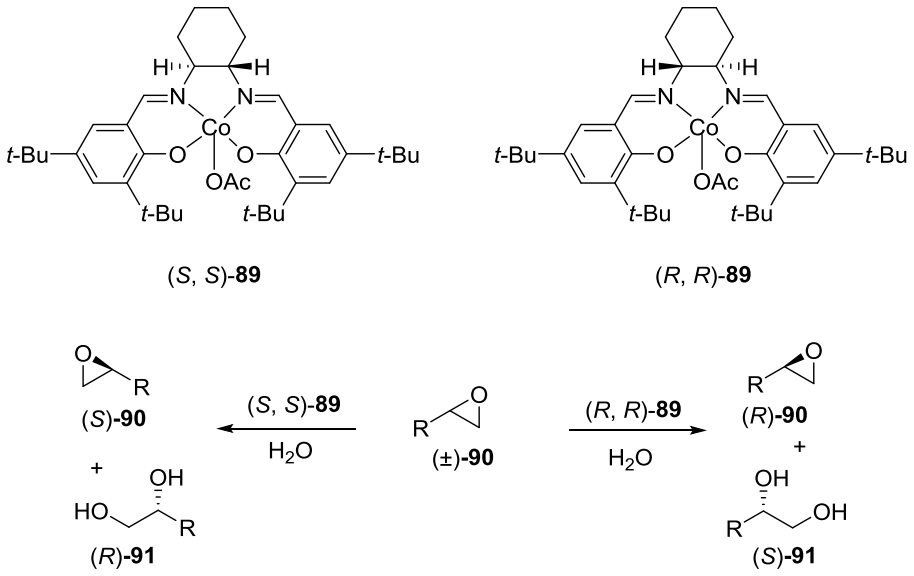
Fig. 2: Retrosynthetic analysis of (+)-goniodiol (**1**)

Since this chapter employs Co-catalyzed two-stereocentered HKR (Hydrolytic Kinetic Resolution),[20] as a key chiral inducing step, a brief account of the same is presented in the following section.

1.1.4.2 Hydrolytic Kinetic Resolution (HKR)

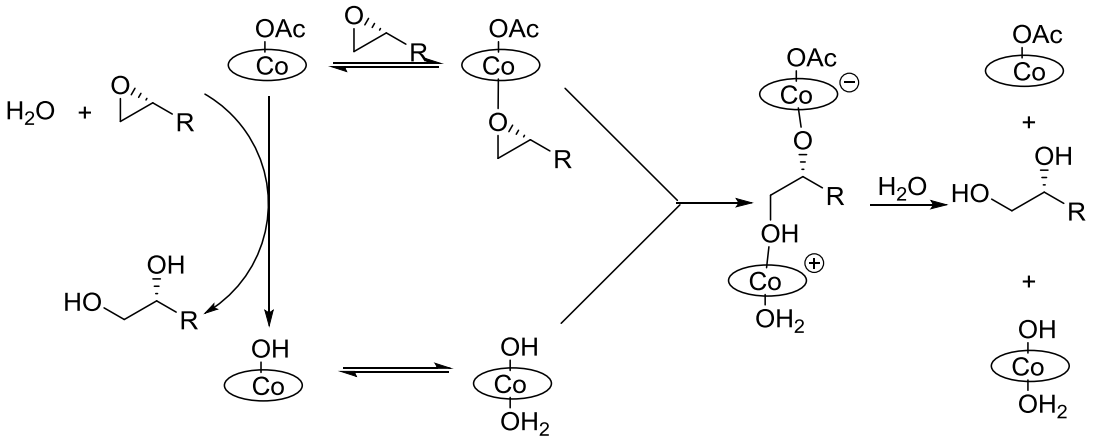
The importance of epoxides in organic synthesis arises partly from the occurrence of the strained three-membered ring unit in a number of interesting natural products[21] but more so because the ring opening of epoxides allows straightforward elaboration to useful new functionality, often with generation 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.[22] 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 (for example: chiral cobalt-salen complexes, **89**)[23] 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. 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:[24] (1) The racemic epoxides must be inexpensive or easily accessible from commercial starting materials; (2) The catalyst for the resolution must be readily available in both enantiomeric forms. 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, the ring-opened byproducts should also be valuable chiral building blocks and be obtainable in high enantiomeric excess.



Scheme 14: Jacobsen's Hydrolytic Kinetic Resolution (HKR) of racemic epoxide, (±)-**90**

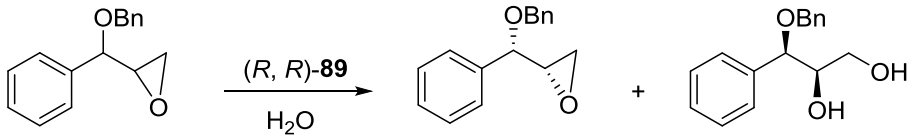
The (salen)Co complex **89** has been well-established to catalyze the efficient hydrolytic kinetic resolution (HKR) of a variety of terminal epoxides **90** (**Scheme 14**).[25] One of the most remarkable features of this method is the consistently high stereoselectivity obtained in the hydrolysis of a wide range of terminal epoxides, with the relative rate of reaction for the two enantiomers of the substrate (k_{rel}) >500 for some substrates and >100 for almost all examined.[26] The asymmetric induction in epoxide opening is imparted by both chiral complexes working cooperatively rather than by either complex alone. A mechanistic picture have been disclosed wherein the rate and stereoselectivity-determining step involves one Co(III) complex acting as a Lewis acid to activate the epoxide while another serves to activate water as a nucleophile *via* a (salen)Co−OH complex (**Scheme 15**).[27] The rate of this step, and therefore of the overall reaction, depends strongly on the identity of the counterion in the (salen)Co-OAc precatalyst.[28] In contrast, the stereoselectivity in the HKR was shown to be quite insensitive to counterion effects.[28a]



Scheme 15: Proposed catalytic mechanism for epoxide hydrolysis

This method appeared to hold considerable promise with regard to meeting all of the five 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 **89** had previously been commercialized and manufactured on a ton scale in the context of (salen)Mn epoxidation catalysts.[29] The cobalt analogues (*R*, *R*)-**89** and (*S*, *S*)-**89** 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.[30] Two useful methods for the generation of complex **89** have been developed.

Method A involves isolation of **89** as a crude solid prior to the HKR. The Co(II) salen complex 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. All volatile materials are removed *in vacuo*, affording **89** as a brown solid residue that can be used without further purification. Method B involves *in situ* generation of **89** by suspension of the Co(II) salen complex in epoxide and addition of HOAc under an aerobic atmosphere. Despite these achievements, HKR has only been applied to the resolution of simple terminal epoxides with one stereocentre.[31] To overcome this drawback, Sudalai *et al.* have extended the scope of the applicable substrates to cover multi-functionalized molecules with two stereocentres. This study related to HKR of alkoxy epoxides (*ex*: benzyloxy epoxide **92**) with two stereocentres, wherein the relative stereochemistry between the alkoxy and the epoxide functions are established prior to the HKR step and thus a single asymmetric reaction is employed to form compounds with two asymmetric centers (**Scheme 16**).[20a]

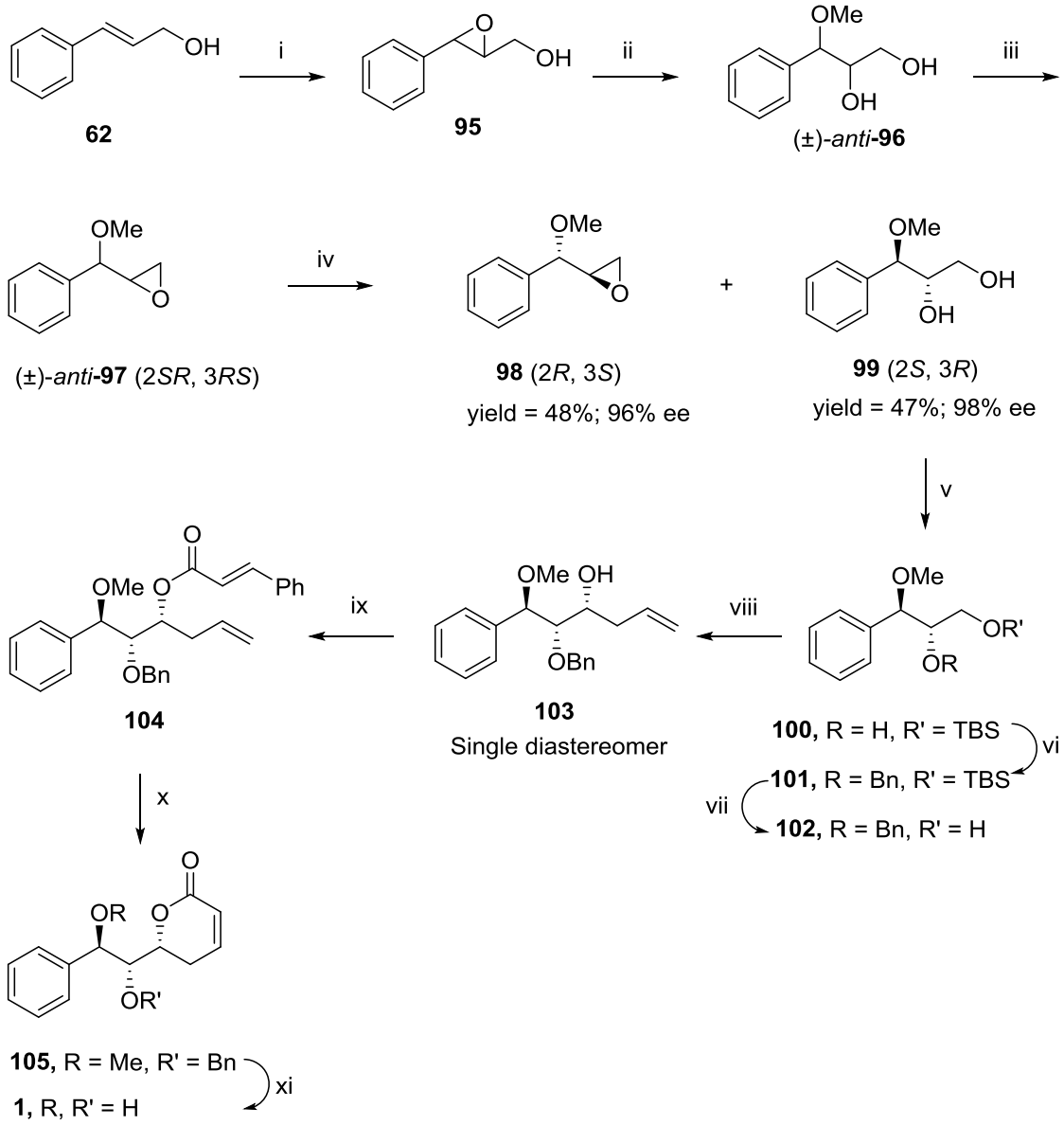


92 (2*SR*, 3*SR*) **93** (2*S*,3*S*) **94**

Scheme 16: Hydrolytic Kinetic Resolution (HKR) of two-stereocentered benzyloxy epoxide, **92**

1.1.5 Results and Discussion

The synthetic scheme for (+)-goniodiol (**1**), wherein two-stereocentred Co-catalyzed HKR of racemic epoxide and Lewis acid-mediated diastereoselective allylation of aldehyde constituting two key steps for the introduction of chirality into the molecule is shown in **Scheme 17**.



Scheme 17: (i) *m*CPBA, CH_2Cl_2, 14 h, 0 °C, 88%; (ii) camphor sulfonic acid (10 mol %), MeOH, 1 h, 96%; (iii) (a) TsCl, Bu_2SnO (2 mol%), Et_3N, DMAP (10 mol%), CH_2Cl_2, 2 h; (b) K_2CO_3, MeOH, 3 h, 76% (over two steps); (iv) (*S*, *S*)-Co(salen)OAc, (0.5 mol%), THF, H_2O (0.5 equiv), 0 °C, 14 h; (v) TBDMSCl, imid., CH_2Cl_2, 0 °C to 25 °C, 1 h, 90%; (vi) NaH, DMF, BnBr, 0 °C to 25 °C, 2 h, 95%; (vii) TBAF, THF, 25 °C, 8 h, 91%; (viii) IBX, DMSO, 2 h, 25 °C then $TiCl_4$, tributyl allyl stannane, CH_2Cl_2, -78 °C, 30 min, 73% (over two steps); (ix) (*E*)-cinnamoyl chloride, dry pyridine, DMAP, CH_2Cl_2, 0 °C to 25 °C, 12 h, 64%; (x) Grubbs' II generation catalyst (10 mol%), CH_2Cl_2 reflux, 8 h, 76%; (xi) BBr_3, CH_2Cl_2, -78 °C, 6 h, 71%.

The present synthesis of (+)-goniodiol (**1**) started from commercially available cinnamyl alcohol **62**, which on epoxidation with *m*CPBA gave the epoxy alcohol **95** in 88% yield. The formation of epoxy alcohol **95** was confirmed from its ^{1}H NMR spectrum, which showed a doublet at δ 3.92 (d, J = 2.2 Hz, 1H) and a multiplet at δ 3.19-3.23 (m, 1H) corresponding to two methine protons of epoxide moiety. Its ^{13}C NMR spectrum showed two typical carbon signals at δ 55.6 and 62.5 indicative of the methine carbons of epoxide, thus confirming the formation of epoxy alcohol **95** (**Fig. 3**).

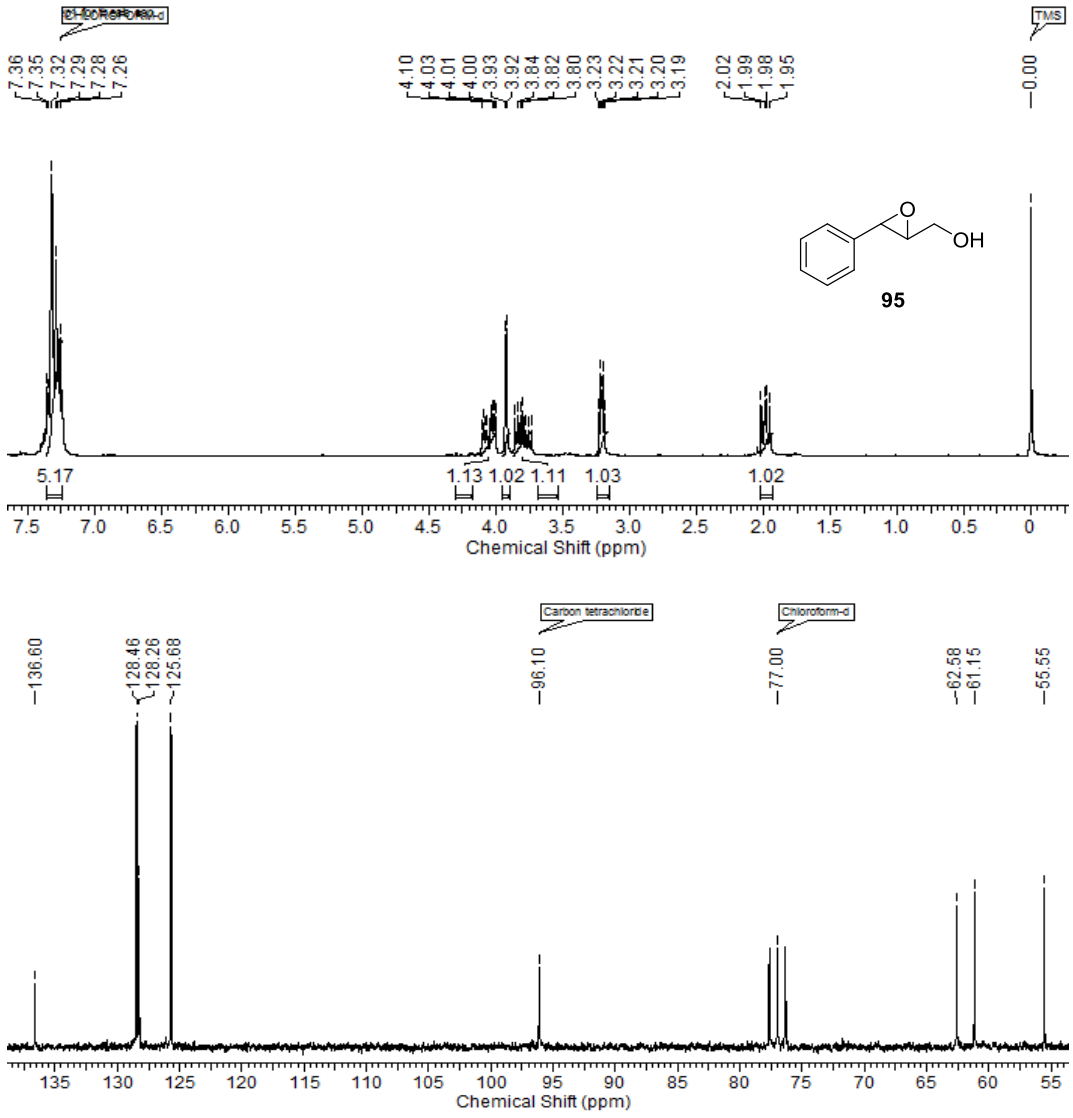


Fig. 3: ^{1}H and ^{13}C NMR spectra of epoxy alcohol **95**

The regiospecific opening of epoxide **95** with MeOH was accomplished quantitatively to give the racemic *anti*-methoxy diol **96**. Its ^{1}H NMR spectrum showed a characteristic multiplet at δ 3.63-3.75 (m, 3H) for methylene (-CH_2-OH) protons while its ^{13}C NMR spectrum showed two characteristic carbon signals at δ 62.2 and 75.7 due to methylene and methine carbons attached to hydroxyl groups respectively (**Fig. 4).**

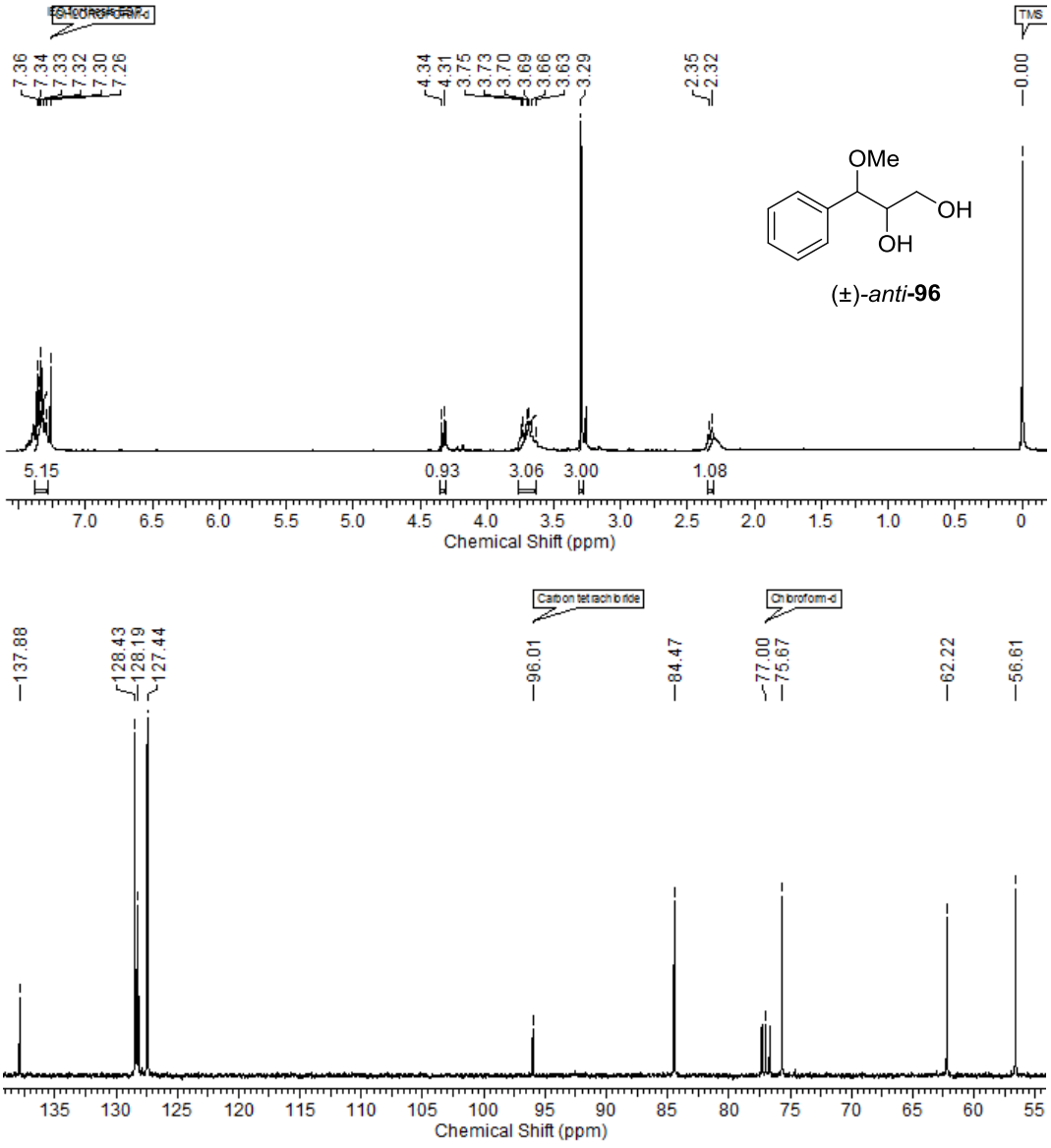


Fig. 4: ^{1}H and ^{13}C NMR spectra of racemic *anti*-methoxy diol **96**

Racemic *anti*-methoxy diol **96** was further converted to racemic *anti*-methoxy epoxide **97** in a two-step reaction sequence: i) selective monotosylation of primary alcohol (TsCl, cat. Bu_2SnO, Et_3N, DMAP, CH_2Cl_2); ii) formation of epoxide under basic conditions (K_2CO_3, MeOH). The formation of racemic *anti*-methoxy epoxide **97** was confirmed from its ^1H NMR spectrum, which showed typical proton signals at δ 2.59 (dd, *J* = 2.6, 4.8 Hz, 1H), 2.73 (t, *J* = 4.2 Hz, 1H) and 3.14-3.21 (m, 1H) corresponding to methylene and methine protons of epoxide respectively. Its ^{13}C NMR spectrum showed characteristic carbon signals at δ 43.8 and 55.0 corresponding to methylene and methine carbons of the epoxide moiety respectively (**Fig. 5)**.

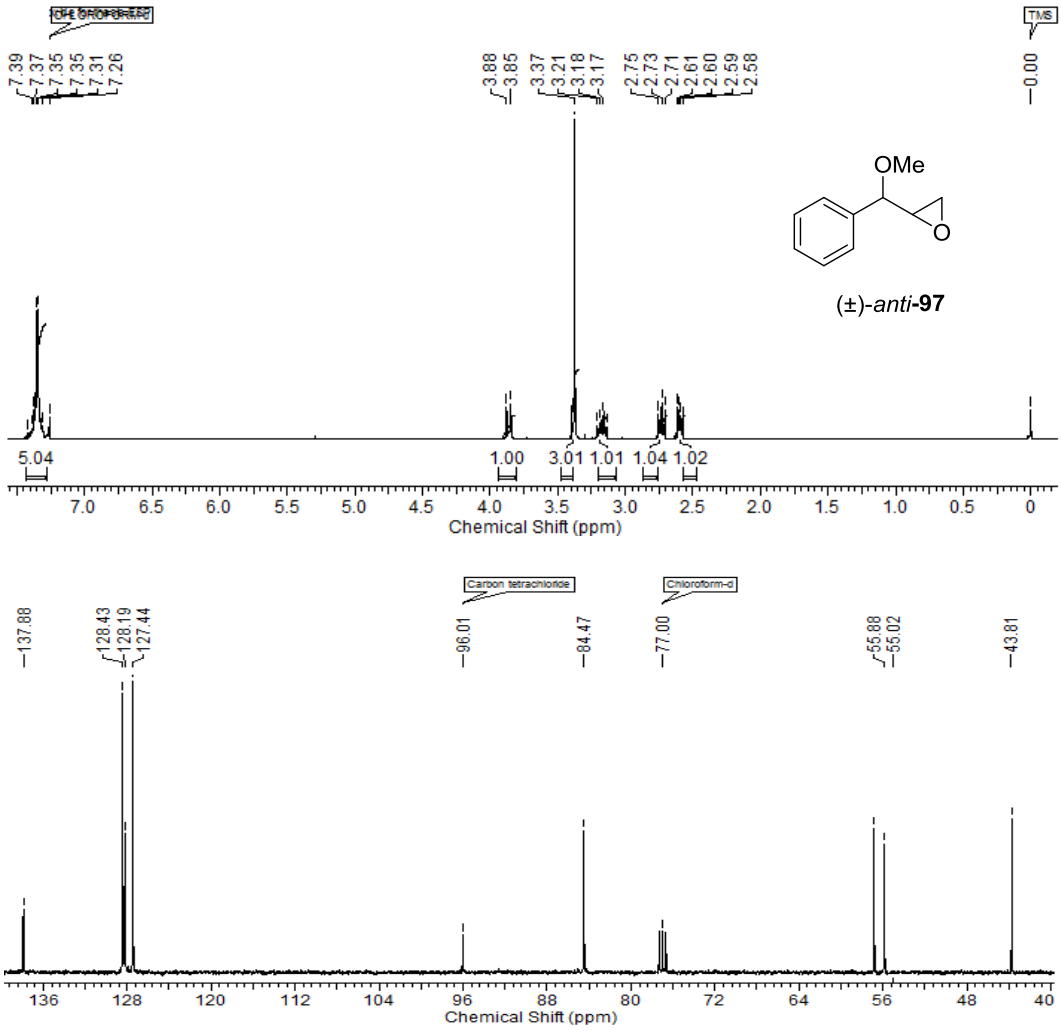
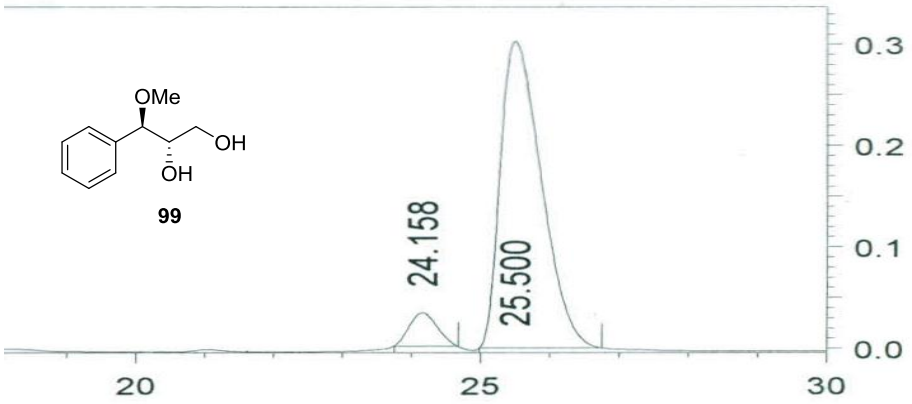


Fig. 5: ^1H and ^{13}C NMR spectra of racemic *anti*-methoxy epoxide **97**

Then, *anti*-(2*SR*, 3*RS*)-3-methoxy-3-phenyl-1,2-epoxypropane **97** was subjected to HKR with (*S, S*)-salen Co(OAc) complex[20a,b] (0.5 mol%) and H_2O (0.5 equiv), which produced the corresponding chiral epoxide **98** (48% yield, 96% ee) and chiral *anti*-diol **99** (47% yield, 98% ee) in high optical purity.



No	Ret. Time min	Height µ AU	Area µ AU* min	Rel. Area %
1	24.16	349.879	130.443	1.08
2	25.50	15012.384	11932.889	98.92

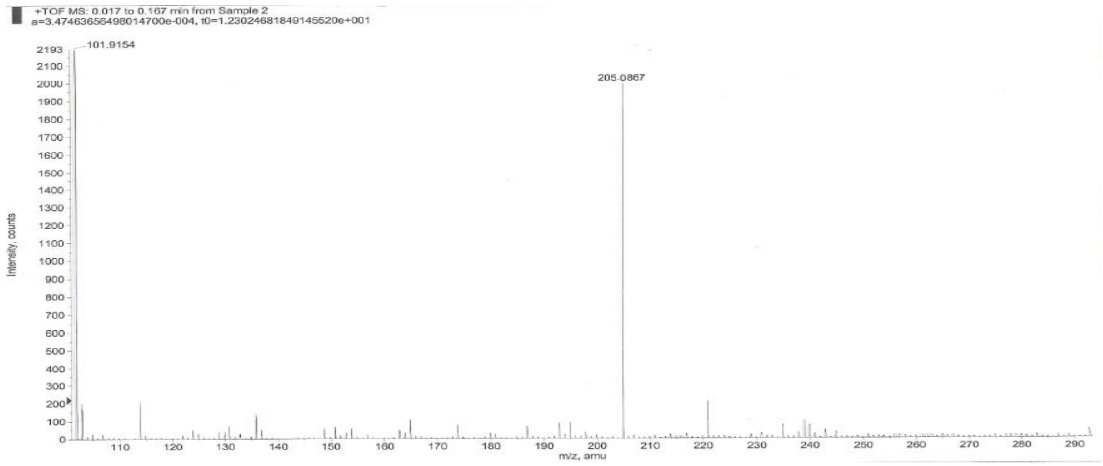


Fig. 6: HPLC chromatogram and mass spectra of chiral *anti*-methoxy diol **99**

The chiral diol **99** was readily separated from epoxide **98** by the column chromatographic purification. The optical purity of chiral diol **99** was determined to be 98% ee from chiral HPLC analysis (Chiralcel OJ-H, *n*-hexane/ ^{i}PrOH, 86:14, 0.5

mL/min) retention time 24.16 (1.08%) and 25.50 (98.92%). The mass spectrum also confirmed the formation of diol **99** (**Fig**.**6**).

The primary hydroxyl function in diol **99** was selectively protected as TBS ether (TBSCl, imid.)[32] to give the corresponding silyl ether **100** in 90% yield. The formation of silyl ether **100** was confirmed from its ^{1}H NMR spectrum, which showed a doublet at δ 0.07 (d, J = 2.5 Hz, 6H) corresponding to methyl protons attached to silicon atom.

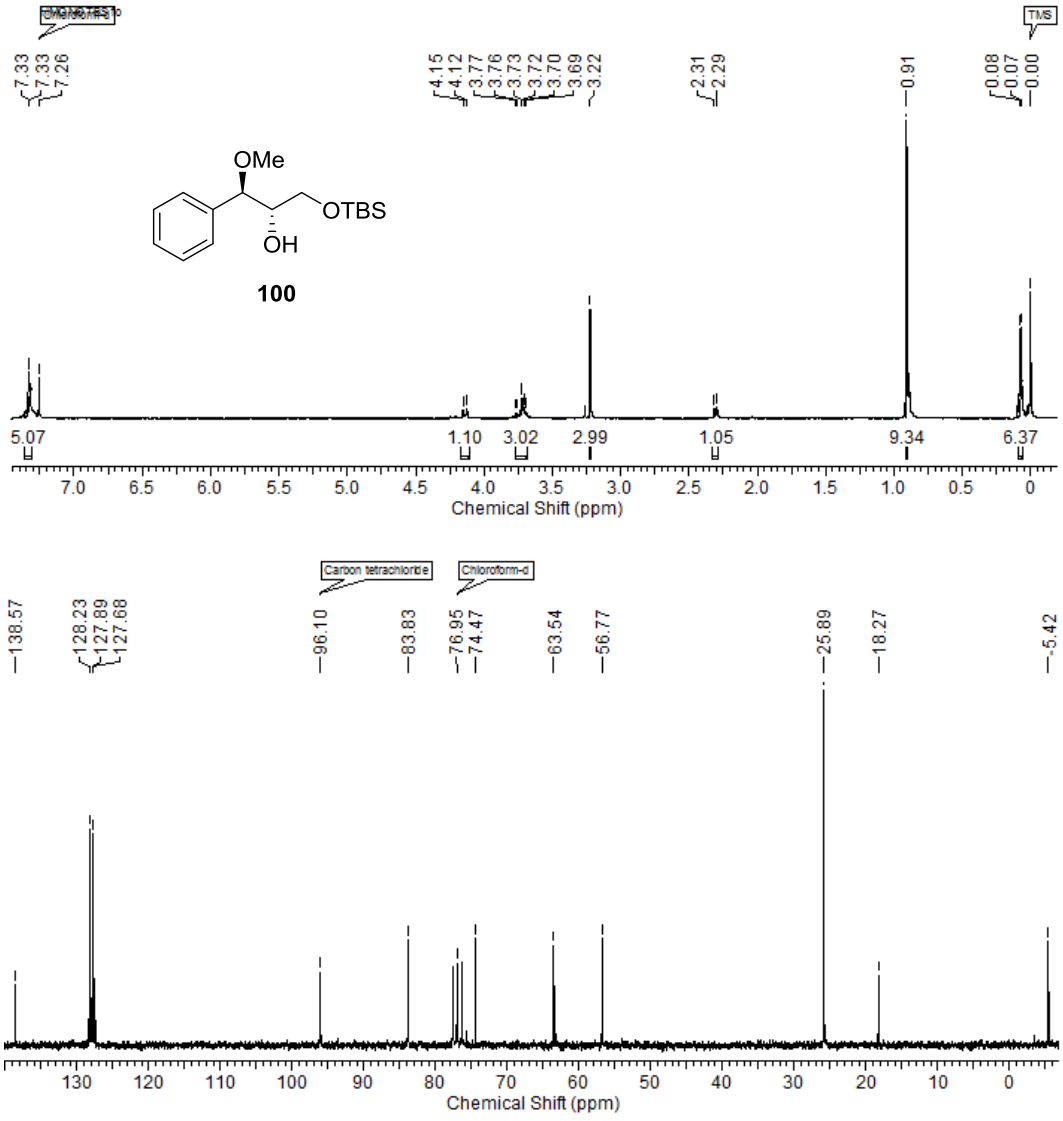


Fig. 7: ^{1}H and ^{13}C NMR spectra of silyl ether **100**

Its ^{13}C NMR spectrum showed characteristic carbon signals at δ -5.4 and 25.9 corresponding to methyl and quaternary carbons of silyl group respectively (**Fig. 7**). Protection of secondary alcohol in **100** as benzyl ether (BnBr, NaH) was then carried out to produce the protected ether **101**. Formation of **101** was confirmed by its ^{1}H NMR spectrum, which showed a characteristic singlet at δ 4.43 due to benzylic proton while its ^{13}C NMR spectrum showed a typical carbon signal at δ 73.7 for benzylic carbon (**Fig. 8**).

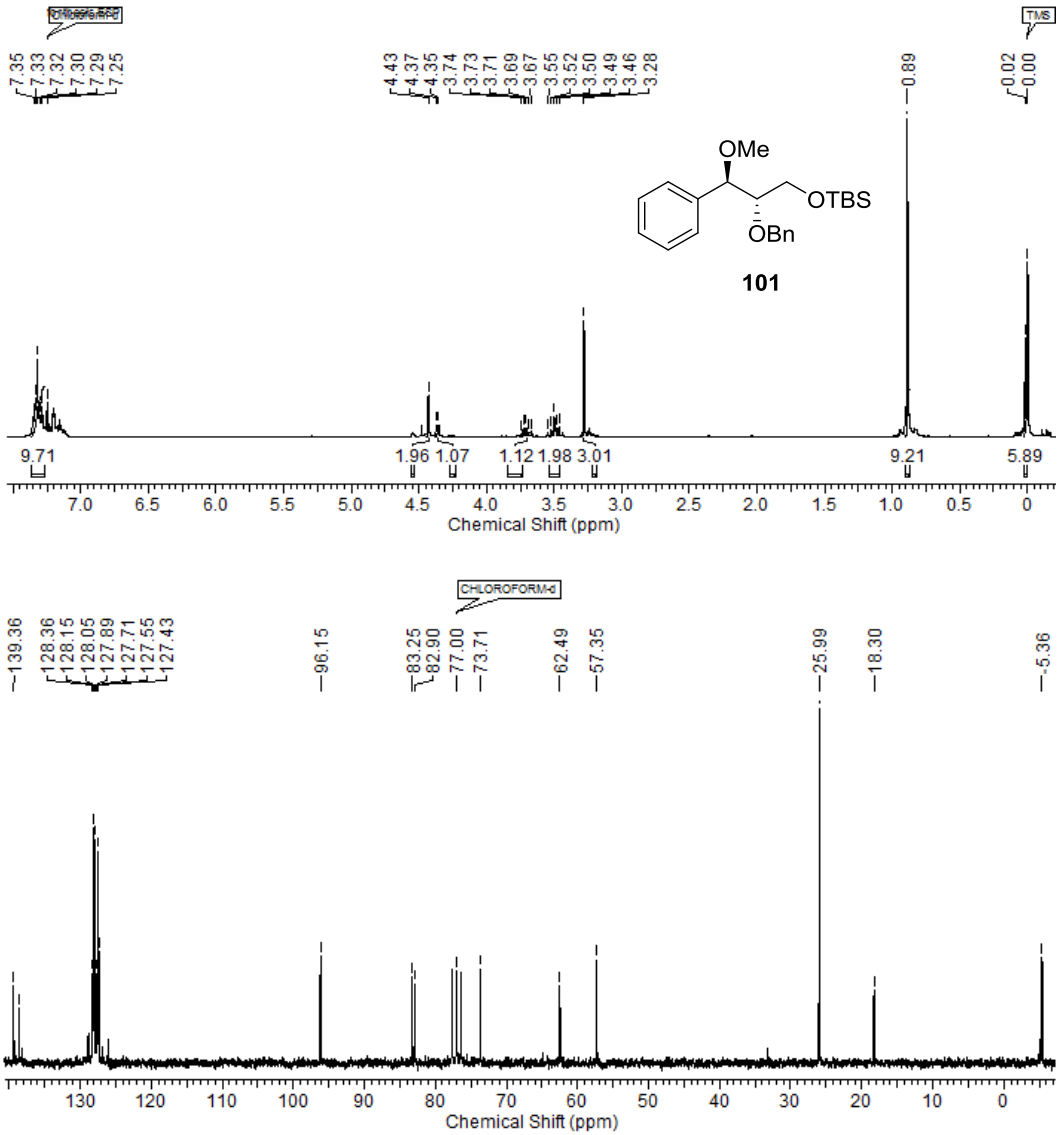


Fig. 8: ^{1}H and ^{13}C NMR spectra of benzyl ether **101**

The selective deprotection of TBS group was achieved using tetrabutylammonium fluoride to give the primary alcohol **102** in 91% yield. The disappearance of proton signals at δ 0.9 and 0.02 in the ^{1}H NMR spectrum of **102** due to the TBS group confirmed the deprotection of silyl ether (**Fig. 9**).

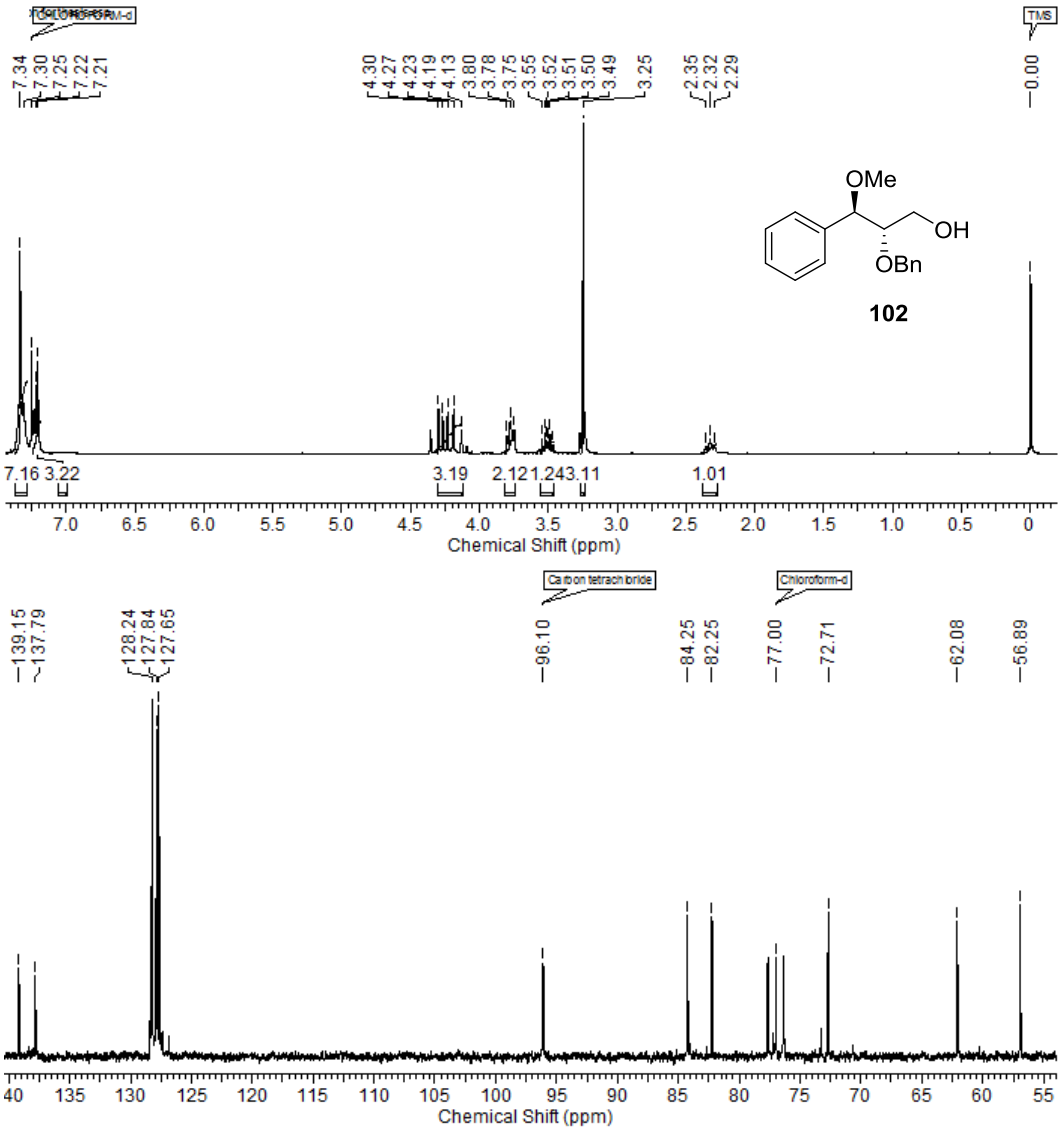


Fig. 9: ^{1}H and ^{13}C NMR spectra of alcohol **102**

The smooth IBX oxidation of alcohol **102** at 25 ^{o}C gave the corresponding crude aldehyde, which was found to be quite unstable on exposure both to moisture as well as air. Hence, the crude aldehyde was immediately subjected to Ti-mediated

diastereoselective allylation ($TiCl_4$, tri-*n*-butyl allyl stannane, CH_2Cl_2, -78 ^oC) to furnish the key intermediate homoallylic alcohol **103** in 73% yield over two steps as a single diastereomer as determined from its ^1H NMR spectrum of the crude product.[33]

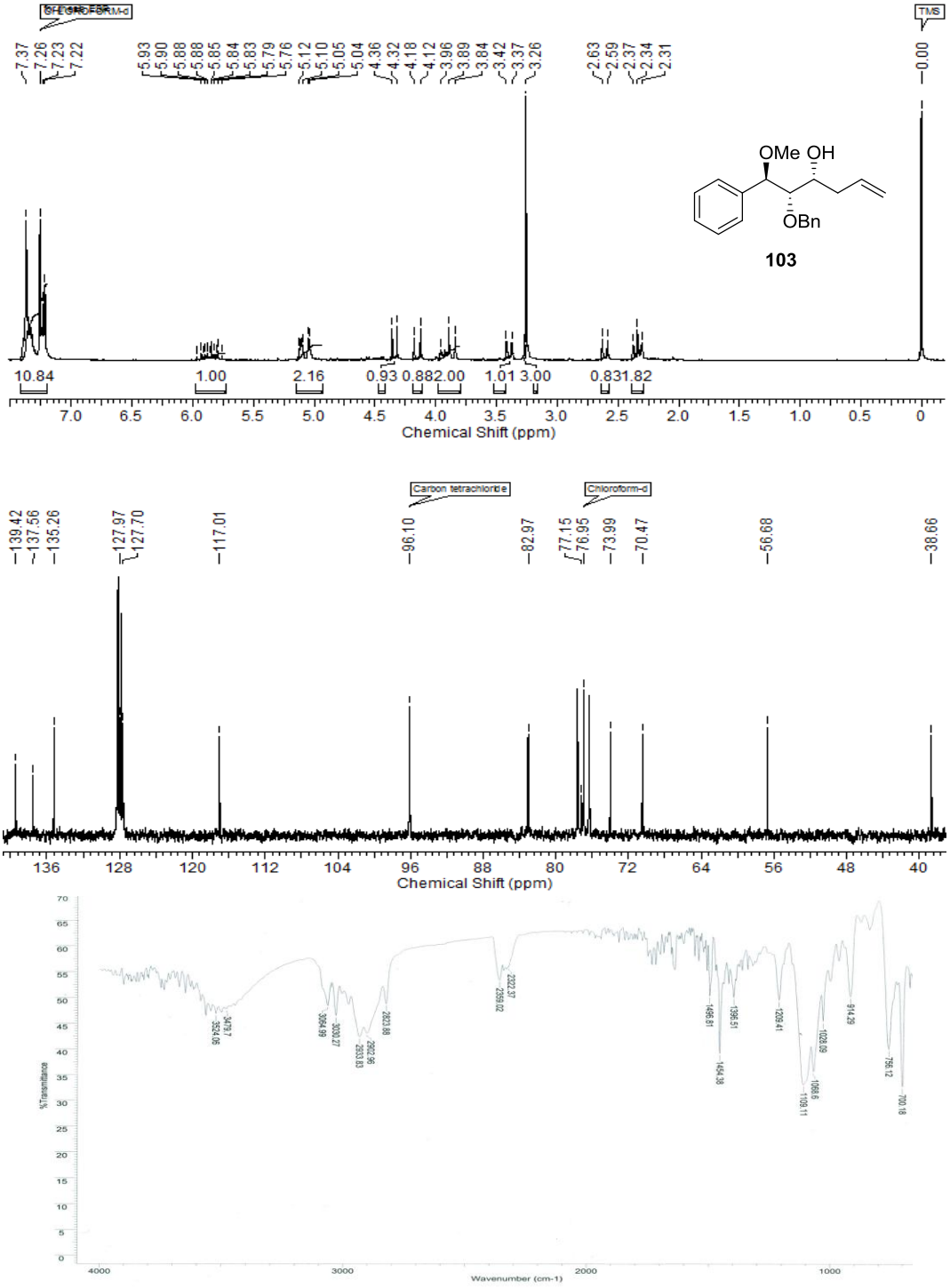


Fig. 10: ^1H, ^{13}C NMR and IR spectra of homoallylic alcohol **103**

Its ^{1}H NMR spectrum showed two typical multiplets at δ 5.03-5.10 (m, 2H) and 5.76-5.93 (m, 1H) corresponding to olefinic protons. It was further substantiated from its ^{13}C NMR spectrum, by the appearance of characteristic olefinic carbon signals at δ 117.0 and 135.3 confirming the formation of homoallylic alcohol **103**. Its IR spectrum displayed a characteristic broad absorption band at 3479 cm^{-1} indicating the presence of OH functional group (**Fig. 10**).

Esterification of alcohol **103** with (*E*)-cinnamoyl chloride in the presence of pyridine and catalytic amount of DMAP in CH_2Cl_2 at 25 ^{o}C gave the corresponding ester **104** in 64% yield.[11]

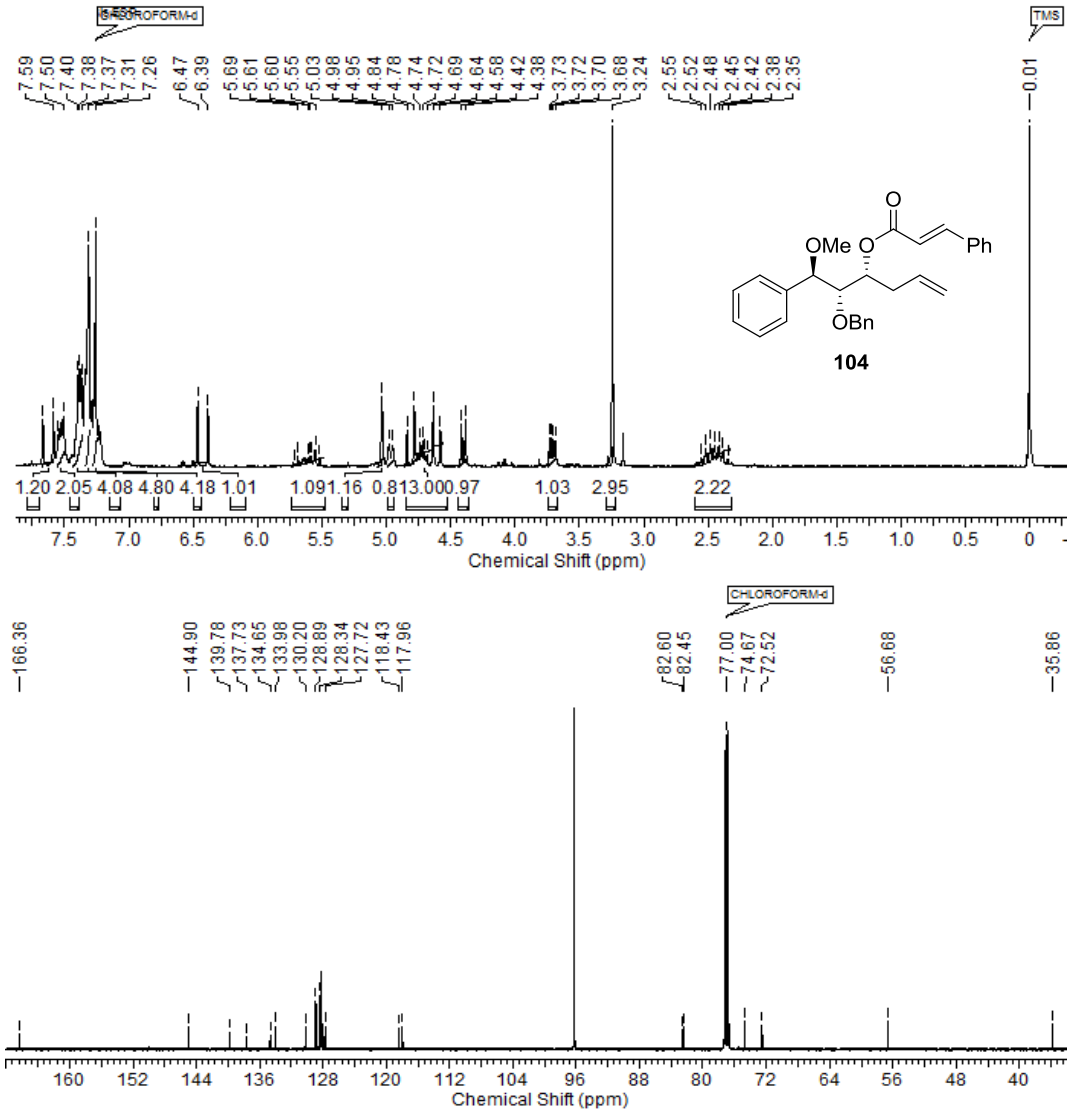


Fig. 11: ^{1}H and ^{13}C NMR of ester **104**

The ^{1}H NMR spectrum of **104** showed two doublets at δ 6.43 (d, *J* = 16.0 Hz, 1H) and 7.63 (d, *J* = 16.0 Hz, 1H) establishing the presence of α- and β- CH proton of COC**H**=C**H**Ph. This was further ascertained by the presence of carbon signals at δ 117.9 and 144.9 corresponding to α- and β- carbon respectively of CO**C**H=**C**HPh in its ^{13}C NMR spectrum. Its IR spectrum displayed a strong absorption band at 1714 cm^{-1} indicating the presence of ester carbonyl group (**Fig. 11**).

Ring closing metathesis of cinnamate ester **104** with Grubbs' second generation catalyst led to the isolation of α-pyrone **105** in 76% yield.

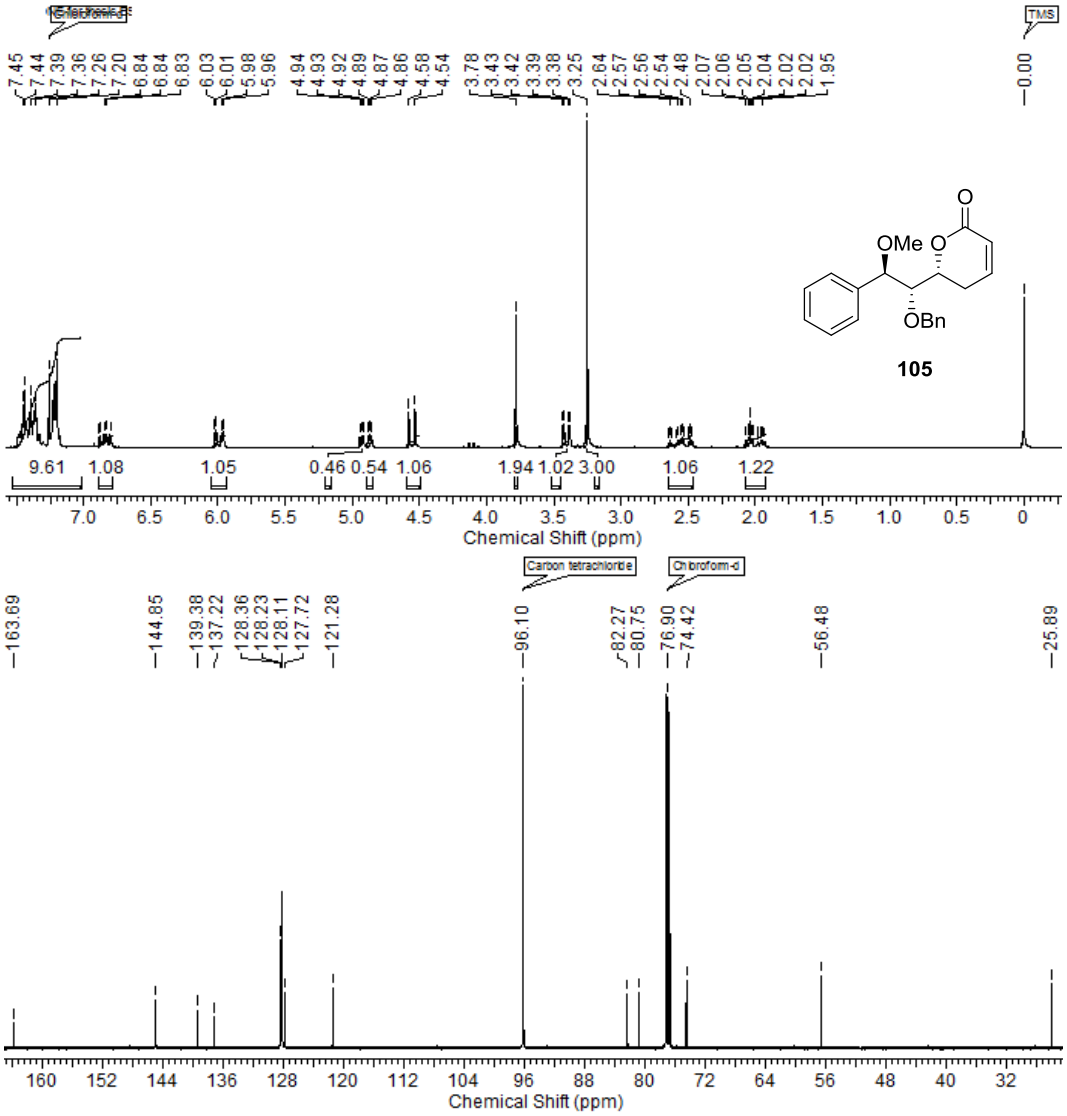


Fig. 12: ^{1}H and ^{13}C NMR spectra of α-pyrone **105**

The ^{1}H NMR spectrum of **105** showed two typical multiplets at δ 5.99 and 6.84 due to olefinic protons. Its ^{13}C NMR spectrum displayed a typical carbon signal at δ 163.7 due to lactone carbonyl carbon, confirming the formation of α-pyrone **105** (**Fig. 12**). Its IR spectrum showed a strong absorption band at 1720 cm^{-1} due to carbonyl of lactone moiety.

Finally, simultaneous demethylation and debenzylation of **105** were achieved successfully with BBr_3 (CH_2Cl_2, -78 °C, 6 h) to afford (+)-goniodiol (**1**) in 71% yield.[34]

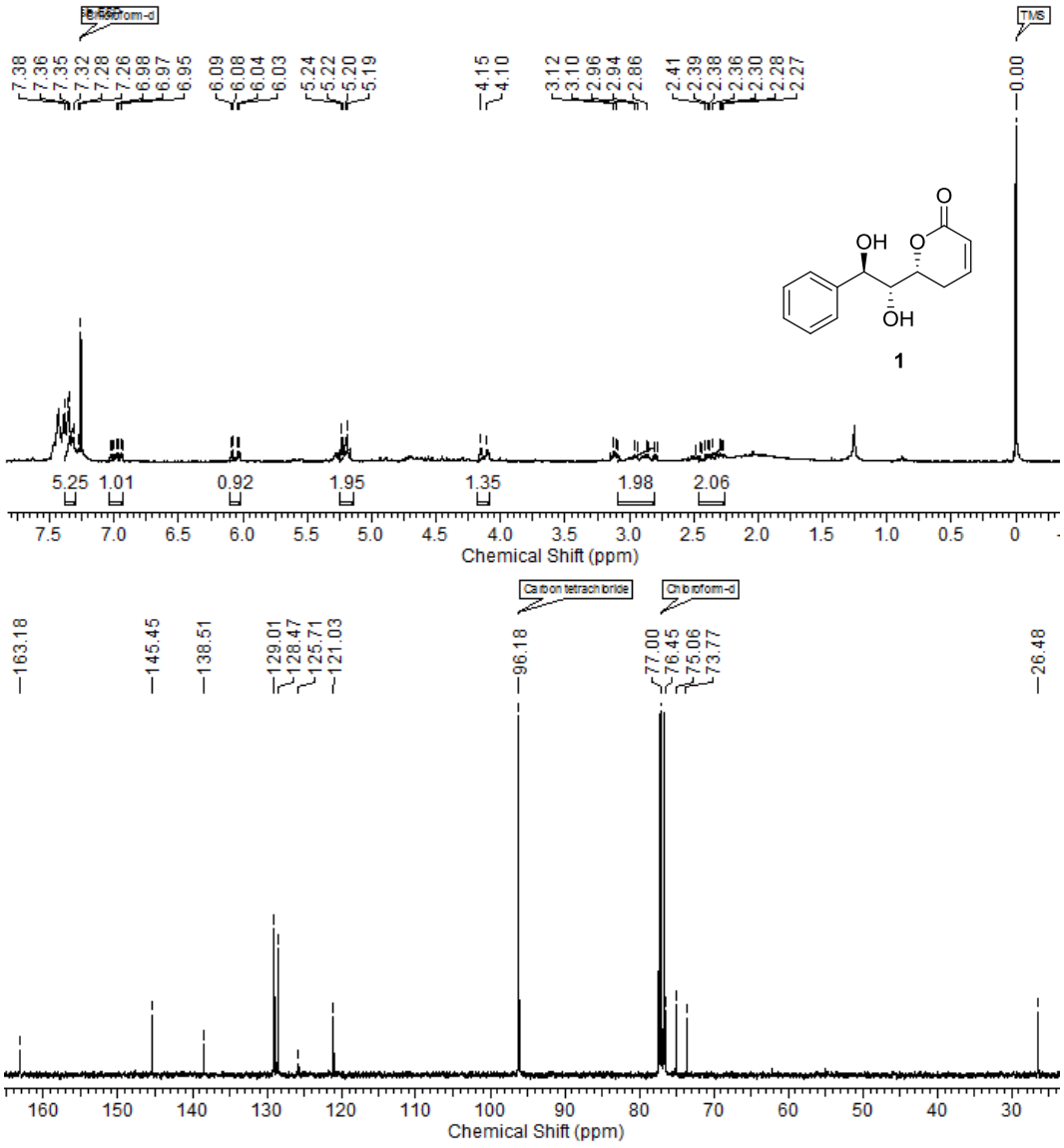


Fig. 13: ^{1}H and ^{13}C NMR spectra of (+)-goniodiol (**1**)

The ^{1}H NMR spectrum of (+)-goniodiol (**1**) showed typical proton signals at δ 6.06 (dd, *J* = 3.6, 7.2 Hz, 1H) and 6.98 (ddd, *J* = 2.9, 6.4, 8.1 Hz, 1H), accounting for two olefinic protons. The other signal at δ 2.27-2.40 (m, 2H) was attributed to methylene protons C**H**$_2$CH=CH. Its ^{13}C NMR spectrum showed characteristic carbonyl resonance at δ 163.2, while two olefinic carbons displayed signals at δ 121.0 and 145.5 (**Fig. 13**). The ee of (+)-goniodiol (**1**) was found to be 98% based on comparison of its optical rotation with the reported value {$[\alpha]^{D}_{25}$ + 73.77 (*c* 0.24, $CHCl_3$**)**; lit.[6] $[\alpha]^{D}_{25}$ +74.4 (c 0.3, $CHCl_3$)}. The spectral data of (+)-goniodiol (**1**) were in complete agreement with the reported values.[6, 11]

1.1.6 Conclusion

In conclusion, an efficient and straight-forward enantioselective synthesis of (+)-goniodiol (**1**) has been achieved with an overall yield of 5.9% and 98% ee. The approach involved a two-stereocentred Co-catalyzed HKR of racemic epoxide and Lewis acid-mediated diastereoselective allylation of aldehyde as the key chiral inducing steps. This methodology is also amenable for a viable synthesis of other diastereomers (**3-5)** of styryllactone family by suitably employing (*R*, *R*)-salen Co(OAc) complex for HKR and $BF_3.OEt_2$ for Lewis acid-mediated diastereoselective allylation respectively.

1.1.7 Experimental section

(3-Phenyloxiran-2-yl)methanol (95)

To a stirred solution of cinnamyl alcohol **62** (1.8 g, 13.415 mmol) in CH_2Cl_2 at 0 °C was added *m*-chloroperoxybenzoic acid (5.0 g, 28.973 mmol) in portions. After being stirred for 14 h at 0 ^{o}C, the mixture was quenched with $NaHSO_3$. The aqueous layer

was extracted with CH_2Cl_2 (3x75 mL) and washed with $NaHCO_3$. The combined organic extracts were dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to get the crude epoxy alcohol, which was purified by column chromatography on silica gel with pet. ether:EtOAc (85:15) gave the pure epoxy alcohol **95** (1.77 g, 88%).

Yield: 88%; colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 669, 757, 929, 1025, 1069, 1216, 1384, 2927, 3019, 3435; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.98 (dd, *J* = 5.3, 7.8 Hz, 1H), 3.19-3.23 (m, 1H), 3.74-3.86 (m, 1H), 3.92 (d, *J* = 2.2 Hz, 1H), 4.00-4.10 (m, 1H), 7.24-7.36 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 55.6, 61.2, 62.5, 125.7, 128.3, 128.4, 136.6; **Analysis** for $C_9H_{10}O_2$ requires: C, 71.98; H, 6.71%; found: C, 71.94; H, 6.69%.

3-Methoxy-3-phenylpropane-1,2-diol (96)

To a stirred solution of epoxy alcohol **95** (2.1 g, 13.984 mmol) in MeOH (75 mL) at 25 ^oC was added camphor sulfonic acid (0.32 g, 1.39 mmol) and the mixture was stirred for 1 h. After completion of the reaction as monitored by TLC, solvent was disltilled off. The crude residue was dissolved in EtOAc, washed with water, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to get the crude diol. The crude diol was then purified by column chromatography over silica gel with pet. ether:EtOAc (60:40) to give methoxy diol **96** (2.45 g, 96%).

Yield: 96%; colorless gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 720, 845, 1065, 1125, 1654, 2985, 3085, 3465; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.32 (br s, 1H), 3.30 (s, 3H), 3.63-3.75 (m, 3H), 4.32 (d, *J* = 5.1 Hz, 1H), 7.33-7.36 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 56.6, 62.2, 75.7, 84.5, 127.5, 128.2, 128.4, 137.9; **Analysis** for $C_{10}H_{14}O_3$ requires: C, 65.91; H, 7.74; found: C, 65.88; H, 7.64%.

(2*SR*, 3*RS*)-3-Methoxy-3-phenyl-1,2-epoxypropane (97)

To a stirred solution of diol **96** (4 g, 21.951 mmol) in dry CH_2Cl_2 (100 mL) were added Bu_2SnO (107 mg, 0.43 mmol) and *p*-toluenesulfonyl chloride (4.61 g, 24.2 mmol) followed by triethylamine (6.11 mL, 43.902 mmol) and 4-dimethylaminopyridine (0.268 g, 2.19 mmol) at 0 °C. The reaction mixture was slowly warmed to 25 ^oC and stirred for 1.5 h. After completion of the reaction as monitored by TLC, it was diluted with CH_2Cl_2 (3x75 mL) and extracted. The combined organic phases were washed with water, brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to get the crude product. The crude tosylate was dissolved in methanol (100 mL) and anhyd. K_2CO_3 (4 g, 28.941 mmol) was added to it and the entire contents were stirred for 30 min at 0 °C. The reaction mass was concentrated and the crude residue dissolved in EtOAc, washed with water, brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to get the crude epoxide, which was then purified by column chromatography over silica gel with pet. ether:EtOAc (85:15) to give the racemic methoxy epoxide **97** (2.739 g, 76% over two steps).

Yield: 76% for two steps; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 685, 757, 1035, 1215, 1620, 2978, 3018, 3069; **^{1}H NMR** (200 MHz, $CHCl_3$): δ 2.59 (dd, *J* = 2.6, 4.8 Hz, 1H), 2.73 (t, *J* = 4.2 Hz, 1H), 3.14-3.21 (m, 1H), 3.37 (s, 3H), 3.86 (d, *J* = 6.6 Hz, 1H), 7.31-7.42 (m, 5H); **^{13}C NMR** (50 MHz, $CHCl_3$): δ 43.8, 55.0, 55.8, 85.0, 127.4, 128.1, 128.4, 137.8; **Analysis** for $C_{10}H_{12}O_2$ requires: C, 73.15; H, 7.37; found: C, 73.09; H, 7.31%.

(2*R*, 3*S*)-3-Methoxy-3-phenyl-1,2-epoxypropane (98)

To a solution of (*S*, *S*)-salenCo(II) complex (purchased from Aldrich, USA.) (0.043 g, 0.07 mmol) in toluene (2.0 mL) was added gl. AcOH (0.04 g, 7.3 mmol). It was

allowed to stir at 25 °C in air for 30 min over which time the color was changed from orange-red to a dark brown. It was then concentrated *in vaccuo* to get (salen)Co(III)(OAc) complex as brown colored solid. To a stirred solution of (salen)Co(III)(OAc) complex (0.004 g, 0.5 mol%) and racemic methoxy epoxide **97** (1.41 mmol) in THF (0.5 mL) at 0 °C was added H_2O (0.012 g, 0.7 mmol) drop-wise over 5 min. The reaction mixture was allowed to warm to 25 °C and stirred for 14 h. After completion of reaction (monitored by TLC), solvent was removed *in vaccuo*. The crude product was purified by column chromatography over silica gel to give (2*R*, 3*S*)-3-methoxy-3-phenyl-1,2-epoxypropane (**98)** on eluting with pet. ether:EtOAc (85:15) and (2*S*, 3*R*)-3-methoxy-3-phenylpropane-1,2-diol **(99)** with pet. ether:EtOAc (60:40) in high enantiomeric excess.

The chiral methoxy epoxide **98** was obtained as a colorless liquid (48% and 96% ee); [%ee was determined by transforming epoxide **98** to the corresponding diol, (0.5M NaOH, *tert*-BuOH-H_2O (3:1), 75 °C, 8 h) and comparing its specific rotation with its antipode **99**]; **Yield**: 48%; colorless liquid; $[\alpha]^{D}_{25}$ - 111.34 (*c* 1.02, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 685, 757, 1035, 1215, 1620, 2978, 3018, 3069; **^{1}H NMR** (200 MHz, $CHCl_3$): δ 2.59 (dd, *J* = 2.6, 4.8 Hz, 1H), 2.73 (t, *J* = 4.2 Hz, 1H), 3.14-3.21 (m, 1H), 3.37 (s, 3H), 3.86 (d, *J* = 6.6 Hz, 1H), 7.31-7.42 (m, 5H); **^{13}C NMR** (50 MHz, $CHCl_3$): δ 43.8, 55.0, 55.8, 85.0, 127.4, 128.1, 128.4, 137.8; **Analysis** for $C_{10}H_{12}O_2$ requires: C, 73.15; H, 7.37; found: C, 73.09; H, 7.31%.

(2*S*, 3*R*)-3-Methoxy-3-phenylpropane-1,2-diol (99)

Yield: 47%; colorless gum; $[\alpha]^{D}_{25}$ + 113.95 (*c* 1.16, $CHCl_3$); lit.[35] $[\alpha]^{D}_{25}$ +113.97 (*c* 1.016, $CHCl_3$); 98% ee by chiral HPLC analysis (Chiralcel OJ-H, *n*-hexane/ ^{i}PrOH,

86:14, 0.5 mL/min) retention time 24.16 (1.08%) and 25.50 (98.92%); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 720, 845, 1065, 1125, 1654, 2985, 3085, 3465; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.32 (br s, 1H), 3.30 (s, 3H), 3.63-3.75 (m, 3H), 4.32 (d, *J* = 5.1 Hz, 1H), 7.33-7.36 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 56.6, 62.2, 75.7, 84.5, 127.5, 128.2, 128.4, 137.9; **HRMS** (ESI) *m/z* calcd for $C_{10}H_{14}O_3$ $[M + Na]^+$: 205.8811, found: 205.8670; **Analysis** for $C_{10}H_{14}O_3$ requires: C, 65.91; H, 7.74; found: C, 65.88; H, 7.64%.

(1*R*, 2*S*)- 3-*tert*-Butyldiphenylsilyloxyl-1-methoxyphenylpropan-2-ol (100)

To a stirred solution of diol **99** (4 g, 21.951 mmol) in dry CH_2Cl_2 (110 mL) was added imidazole (2.24 g, 32.926 mmol) at 0 ^oC. After stirring for 10 min, TBSCl (3.97 g, 30.91 mmol) was added and the reaction mixture was stirred at 25 ^oC for 1 h. After completion of the reaction as monitored by TLC, it was poured into water and extracted with CH_2Cl_2 (3x40 mL). The combined organic phases were washed with brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to get the crude product. The crude product was then purified by column chromatography over silica gel with pet. ether:EtOAc (95:5) to give the silyl ether **100** (5.86 g, 90%).

Yield: 90%; viscous liquid; $[\alpha]^D_{25}$ +59.62 (*c* 1.88, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 710, 815, 1042, 1145, 1257, 2985, 3077, 3455; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.07 (d, *J* = 2.5 Hz, 6H), 0.9 (s, 9H), 2.30 (d, *J* = 4.4 Hz, 1H), 3.22 (s, 3H), 3.69-3.76 (m, 3H), 4.13 (d, *J* = 6.1 Hz, 1H), 7.33-7.36 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.4, 18.3, 25.9, 56.8, 63.5, 74.5, 83.8, 127.7, 128.0, 128.2, 138.6; **LCMS** calcd for $C_{16}H_{28}O_3Si$ $[M + Na]^+$: 319.1709, found: 319.1713; **Analysis** for $C_{16}H_{28}O_3Si$ requires: C, 64.82; H, 9.52; found: C, 64.79; H, 9.44%.

(1*R*, 2*S*)-2-Benzyloxy-3-*tert*-butyldiphenylsilyloxy-1-methoxy-1-phenylpropane (101)

To a stirred solution of alcohol **100** (6 g, 20.237 mmol) in dry DMF was slowly added 60% NaH in oil suspension (1.13 g, 28.331 mmol) followed by the addition of benzyl bromide (3.46 g, 20.237 mmol). The reaction mixture was stirred at 25 ^{o}C for 2 h, quenched with cold water and extracted with ether (3x100 mL). The combined organic layers were washed with brine, dried over anhyd. Na_2SO_4 and concentrated to give the crude material, which was then purified by column chromatography over silica gel with pet. ether:EtOAc (97:3) to give the protected ether **101** (7.43 g, 95%).

Yield: 95%; colorless viscous liquid; $[\alpha]^{D}_{25}$ +27.4 (*c* 1.6, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 695, 990, 1045, 1210, 1268, 1343, 1425, 2860, 3048; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.02 (d, *J* = 3.5 Hz, 6H), 0.90 (s, 9H), 3.28 (s, 3H), 3.46-3.55 (m, 2H), 3.67-3.74 (m, 1H), 4.36 (d, *J* = 4.1 Hz, 1H), 4.43, (s, 2H), 7.33-7.38 (m, 10H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.4, 18.3, 26.0, 57.3, 62.5, 73.7, 82.9, 83.2, 127.3, 128.7, 138.6, 139.4; **Analysis** for $C_{23}H_{34}O_3Si$ requires: C, 71.46; H, 8.86; found: C, 71.42; H, 8.83%.

(1*R*, 2*S*)-2-(Benzyloxy)-1-methoxy-1-phenylpropan-1-ol (102)

To a stirred solution of protected ether **101** (6 g, 15.519 mmol) in dry THF (100 mL) was added tetra-*n*-butylammonium fluoride (6.08 g, 23.28 mmol) at 25 ^{o}C. The reaction mixture was stirred for 8 h and then diluted with water and extracted with EtOAc (3x100 mL). The organic layer was washed with brine, dried over anhyd. Na_2SO_4 and concentrated to give the crude material, which was then purified by column chromatography over silica gel with pet. ether:EtOAc (8:2) to give the alcohol **102** (3.85 g, 91%).

Yield: 91%; colorless liquid; $[\alpha]^{D}_{25}$ +42.32 (*c* 1.62, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 690, 773, 837, 1101, 1255, 1471, 2359, 2823, 2856, 2930, 2955, 3495; **^{1}H NMR** (200

MHz, $CDCl_3$): δ 2.32 (t, *J* = 6.2 Hz, 1H), 3.26 (s, 3H), 3.46-3.55 (m, 1H), 3.78 (t, *J* = 6.1 Hz, 2H), 4.13-4.35 (m, 3H), 7.21-7.24 (m, 3H), 7.30-7.35 (m, 7H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 56.9, 62.1, 72.7, 82.2, 84.2, 127.6, 127.8, 128.2, 137.8, 139.1; **Analysis** for $C_{17}H_{20}O_3$ requires: C, 74.97; H, 7.40; found: C, 74.93; H, 7.38%.

(1*R*, 2*S*, 3*R*)-2-(Benzyloxy)-1-methoxy-1-phenyl-hex-5-en-3-ol (103)

To a stirred solution of alcohol **102** (3.5 g, 12.851 mmol) in dry DMSO (100 mL) was slowly added 2-iodoxybenzoic acid (4.32 g, 15.421 mmol). The reaction mixture was stirred for 2 h at 25 ^oC and quenched with cold water. It was filtered and the filtrate was then extracted with ether (3x100 mL). The combined organic layers were washed with brine, dried over anhyd. Na_2SO_4 and concentrated to give the crude aldehyde, which was directly used for the next step without purification. To a stirred crude aldehyde solution in dry CH_2Cl_2 (100 mL) was added $TiCl_4$ (4.01 mL, 1M solution in CH_2Cl_2) at -78 ^oC. After stirring for 10 min, tributyl allyl stannane (8.15 g) was added. The reaction mixture was stirred at -78 ^oC for 30 min, quenched with $NaHCO_3$, extracted with CH_2Cl_2 (3x100 mL). The combined organic layers were washed with brine, dried over anhyd. Na_2SO_4 and concentrated to give the crude material, which was then purified by column chromatography over silica gel with pet. ether:EtOAc (85:15) to give the alcohol **103** (2.93 g, 73%).

Yield: 73%; colorless liquid; $[\alpha]^D_{25}$ +18.21 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 700, 756, 1109, 1209, 1396, 1496, 1650, 1980, 3020, 3063, 3479; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.34 (t, *J* = 6.1 Hz, 2H), 2.60 (d, *J* = 8.7 Hz, 1H), 3.25 (s, 3H), 3.37-3.42 (m, 1H), 3.84-3.95 (m, 2H), 4.15 (d, *J* = 10.9 Hz, 1H), 4.33 (d, *J* = 7.8 Hz, 1H), 5.03-5.10 (m, 2H), 5.76-5.93 (m, 1H), 7.23-7.37 (m, 10H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 38.7, 56.7, 70.5, 74.0, 77.1, 83.0, 117.0, 127.7, 128.0, 135.3, 137.6, 139.4; **Analysis** for $C_{20}H_{24}O_3$ requires: C, 76.89; H, 7.74; found: C, 76.86; H, 7.71%.

[(1*R*, 2*S*, 3*R*)-2-(Benzyloxy)-3-(methoxy)-3-phenyl-1-(prop-2-enyl)propyl] prop-2 enoate (104)

A stirred solution of alcohol **103** (1 g, 3.2 mmol) in dry CH_2Cl_2 (20 mL) was cooled to 0 ^oC followed by addition of cinnamoyl chloride (2.13 g, 12.8 mmol), dry pyridine (1.03 mL, 12.80 mmol) and 4-dimethylaminopyridine (0.12 g, 1.0 mmol). The entire reaction mixture was then warmed to 25 ^oC and stirred for 12 h. The resulting mixture was filtered through a short pad of silica to remove solid pyridinium hydrochloride and washed thoroughly with ether. Solvent was removed under vacuum to give the crude product, which was then purified by column chromatography over silica gel with pet. ether:EtOAc (95:5) to give cinnamate ester **104** (0.906 g, 64%).

Yield: 64%; colorless liquid; $[\alpha]^D_{25}$ +72.39 (*c* 1.2, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 700, 767, 1118, 1203, 1309, 1454, 1637, 1714, 2885, 3030, 3063; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.35- 2.55 (m, 2H), 3.24 (s, 3H), 3.68-3.73 (m, 1H), 4.39 (d, *J* = 6.6 Hz, 2H), 4.58-4.84 (m, 3H), 4.96 (d, *J* = 6.6 Hz, 2H) 5.03 (br s, 1H), 5.52-.5.71 (m, 1H), 6.43 (d, *J* = 16.0 Hz, 1H), 7.30-7.42 (m, 15H), 7.63 (d, *J* = 16.0 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 35.9, 56.7, 72.5, 74.7, 82.4, 82.6, 118.0, 118.4, 127.7, 128.3, 128.9, 130.1, 133.9, 137.7, 139.8, 144.9, 166.3; **LCMS** calcd for $C_{29}H_{30}O_4$ [M + Na]$^+$: 465.2042, found: 465.2961; **Analysis** for $C_{29}H_{30}O_4$requires: C, 78.71; H, 6.83; found: C, 78.62; H, 6.80%.

(6*R*)-6-[(1*S*, 2*R*)-1-(Benzyloxy)-2-(methoxy)-2-phenylethyl]-5,6-dihydropyran-2-one (105)

A solution of Grubbs' II generation catalyst [$RuCl_2$(=CHPh)(PCy_3)(*bis*mesitylimidazo -lidinylidene)] (0.115 g, 10 mol%) in dry CH_2Cl_2 (10 mL) was added dropwise to a refluxing solution of cinnamoyl ester **104** (0.6 g, 1.356 mmol) in CH_2Cl_2 (30 mL). Heating to reflux was continued for 8 h till starting material was consumed completely (TLC). Solvent was distilled off under reduced pressure and the crude

product was then purified by column chromatography over silica gel with pet. ether:EtOAc (75:25) to give lactone **105** (0.348 g, 76%).

Yield: 76%; colorless liquid; $[\alpha]^{D}_{25}$ +84.31 (*c* 0.8, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 700, 754, 815, 960, 1066, 1120, 1240, 1382, 1456, 1720, 2330, 2823, 2899, 2933, 3030, 3063; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.93-2.07 (m, 1H), 2.47-2.65 (m, 1H), 3.25 (s, 3H), 3.40 (dd, *J* = 2.2, 8.9 Hz, 1H), 3.78 (s, 2H), 4.55 (d, *J* = 8.9 Hz, 1H), 4.85-4.94 (m, 1H), 5.96-6.02 (m, 1H), 6.79-6.88 (m, 1H), 7.24-7.45 (m, 10H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 25.9, 56.5, 74.4, 80.7, 82.3, 121.3, 127.7, 128.1, 137.2, 139.4, 163.7; **Analysis** for $C_{21}H_{22}O_4$ requires: C, 74.54; H, 6.55; found: C, 74.48; H, 6.52%.

(6*R*)-6-[(1*S*, 2*R*)-1,2-Dihydroxy-2-phenylethyl]-5,6-dihydropyran-2-one: [(+)-Goniodiol] (1)

To a stirred and cooled (-78 ^{o}C) solution of α-pyrone **105** (68 mg, 0.201 mmol) in dry CH_2Cl_2 (3 mL), was added BBr_3 (0.6 mL, 1M solution in CH_2Cl_2). After stirring for 6 h at -78 ^{o}C, it was quenched with an aq. solution of $NaHCO_3$. The reaction mixture was allowed to warm to 20 ^{o}C and was extracted with EtOAc (2x30 mL). The combined organic layers were dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to get the crude product. The crude product was then purified by column chromatography over silica gel with pet. ether:EtOAc (20:80) to give (+)-goniodiol (**1)** (0.034 g, 71%).

Yield: 71%; colorless liquid; $[\alpha]^{D}_{25}$ +73.77 (*c* 0.24, $CHCl_3$); lit.[15] $[\alpha]^{D}_{25}$ +74.4 (*c* 0.3, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1035, 1259, 1380, 1690, 3390; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.27-2.40 (m, 2H) 2.78 - 3.12 (m, 2H), 4.10 (t, *J* = 7.8 Hz, 1H), 5.18 - 5.24 (m, 2H), 6.06 (dd, *J* = 3.6, 7.2 Hz, 1H), 6.98 (ddd, *J* = 2.9, 6.4, 8.1 Hz, 1H) 7.27-7.38 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 26.5, 73.8, 75.1, 76.4, 121.03, 125.8, 128.4,

129.0, 138.5, 145.4, 163.2; **Analysis** for $C_{13}H_{14}O_4$ requires: C, 66.66; H, 6.02; found: C, 66.62; H, 6.01%.

Section II:

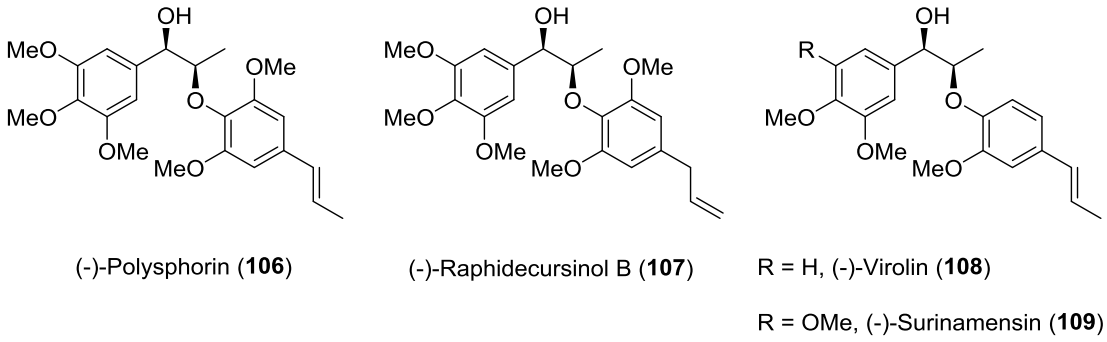
Enantioselective Synthesis of (-)-Polysphorin Analog *via* Co-Catalyzed Hydrolytic Kinetic Resolution of *syn*-(2*SR*, 3*SR*)-3-(Methoxymethyl)oxy-3-(3,4,5-trimethoxyphenyl)-1,2-epoxy propane

1.2.1 Introduction

Malaria is by far the most important tropical parasitic disease that kills more people than any other communicable diseases except for tuberculosis. In many developing countries, especially in Africa and Asia, malaria exacts an enormous toll in lives, in medical costs, and in days of labor lost. *Plasmodium falciparum* accounts for the majority of infections and is found to be the most lethal.[36] However, malaria is a curable disease if promptly diagnosed and adequately treated. Although several research programs are focused on various strategies to control malaria, drug discovery is one of the main areas of concentrated effort.[37] In humans, malaria develops *via* two phases: an hepatic phase and an erythrocytic phase. Most of the research programs were focused on the erythrocytic stage of *Plasmodium falciparum*. However, the development of drugs able to inhibit the parasite during the hepatic phase is of very high importance as they could act against relapse and constitute a radical cure of the parasite. Today, only two drugs, primaquine and tafenoquine, are active during the hepatic phase of parasite development. However, these drugs have a hematologic toxicity. Accordingly, there is a strong need of antimalarial drugs active during the hepatic phase of parasite development, and without any toxicity.

Polysphorin (**106**), a neolignan was isolated from *Piper polysphorum C* in China,[38] and from the leaves and stems of *Rhaphidopora decursiva* in Vietnam (**Fig. 14**).[39] The structure and relative configuration of polysphorin (**106**) were established by synthetic

studies and X-ray crystallography.[40] Biological screening has since shown polysphorin (**106**) to possess *in vitro* antimalarial activity (IC_{50} 400ng/ml).[39] Several other members of this family of neolignans have also been shown to display interesting biological properties: rhaphidecursinol B (**107**) shows activity against *Plasmodium falciparum*, the parasite responsible for the most severe forms of malaria,[41] but is ten times less active than polysphorin (**106**);[39] neolignans virolin (**108**) and surinamensin (**109**) both displayed interesting and varied biological properties spanning from antimalarial to antifungal,[42] antileishmanial, antioxidant, and antischistosomial activities.[43]

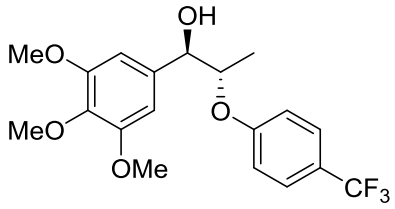


(-)-Polysphorin (**106**) (-)-Raphidecursinol B (**107**) R = H, (-)-Virolin (**108**)

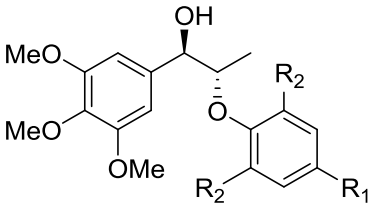
R = OMe, (-)-Surinamensin (**109**)

Fig. 14: Structures of bioactive neolignans

The pharmaceutically important biological profiles coupled with the scarce availability from natural sources make them ideal targets for testing new synthetic methodology and prompted many groups to attempt the laboratory synthesis of this class of compounds.[40, 44-46] Synthetic methods also provide the opportunity to expand the diversity by generating non natural analogs. Recently, Choppin *et al*, synthesized new polysphorin analogs (**110a-x**), and it was found that both the *syn*- and *anti*-diastereomers are highly effective in the hepatic phase (**Fig. 15**).[45]



Polysphorin analog (**110a**)



Polysphorin analogs (**110b-x**)

R_1 = OMe, Cl, CN, NH_2, etc

R_2 = OMe, OCF_3, CH_3, H, etc

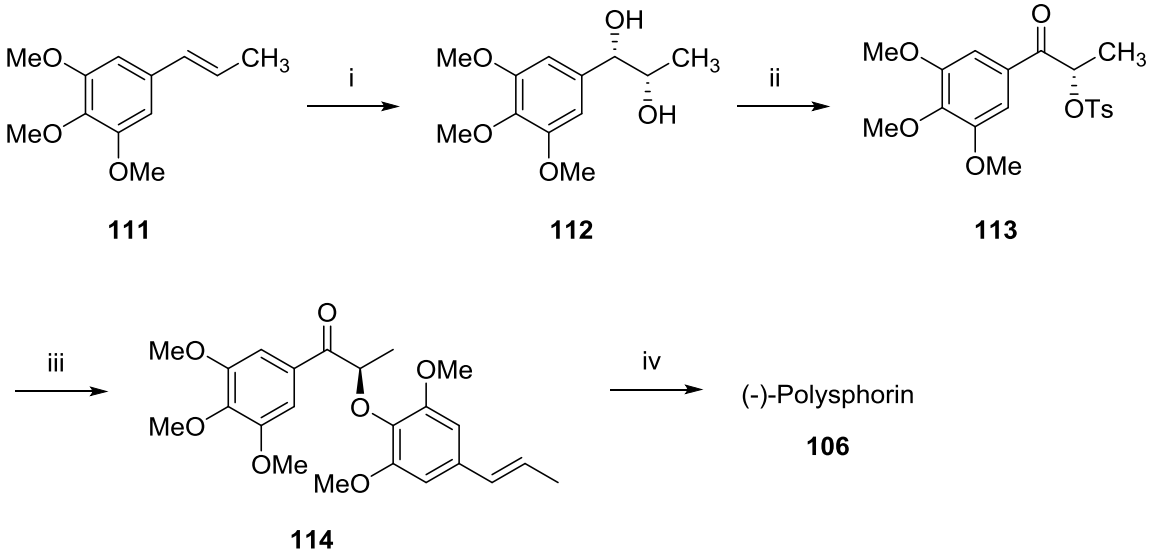
Fig. 15: Structures of bioactive polysphorin analogs

1.2.2 Review of Literature

Literature search reveals that there are only three reports on the asymmetric synthesis and one report on the racemic synthesis of polysphorin (**106**) and its analogs (**110a-x**) available. A short description of all the four reported methods is presented below.

Ley's approach (2003)[40]

Ley *et al.* have reported the synthesis of polysphorin (**106**) by employing Sharpless asymmetric dihydroxylation as the key reaction. Thus, 1,2,3-trimethoxy-5-(*E*)-(propenyl)-benzene **111** was subjected to Sharpless asymmetric dihydroxylation using AD-mix-α, followed by purification under Frechet's protocol (polymer supported boronic acid) resulted in diol **112** in 96% ee and 92% yield. Tosylated α-hydroxy ketone **113** was prepared efficiently in two steps *via* selective benzylic oxidation of diol **112** using DDQ, followed by tosylation of α-hydroxy ketone. The S_N2 coupling of tosylate **113** with (*E*)-2,6-dimethoxy-4-(propenyl)-phenol using polymer-supported phosphazene base gave phenolic ether **114**. Finally, polymer-supported diastereoselective borohydride reduction of ketone **114** afforded (-)-polysphorin (**106**) (dr = 32 : 1) (**Scheme 18**).



111 **112** **113**

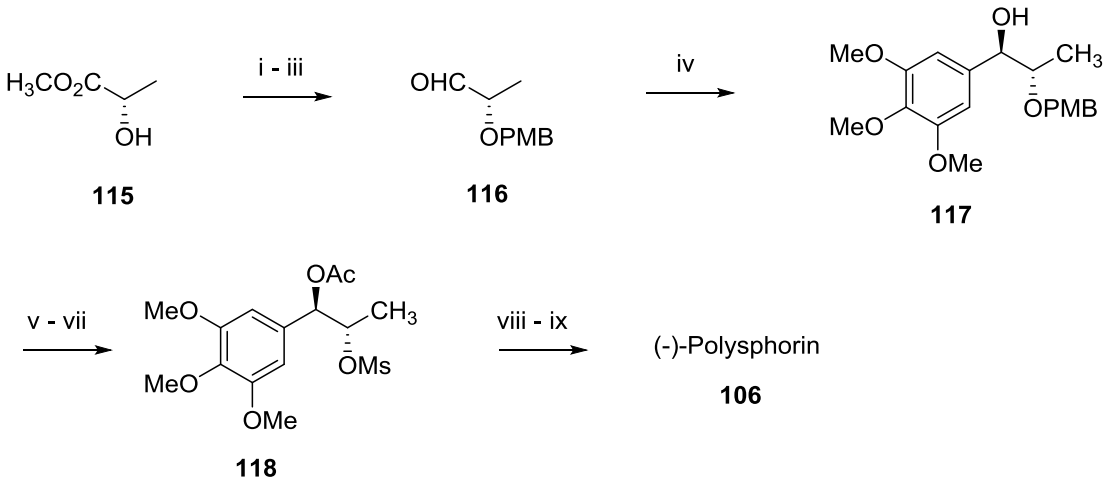
106

114

Scheme 18: (i) AD-mix-α, $CH_3SO_2NH_2$, *tert*-BuOH:H_2O (1:1), 0 °C to 25 °C, 16 h, polymer-supported boronic acid, toluene reflux, 24 h, 83%; (ii) (a) DDQ, dioxane, 60 °C, 12 h, polymer-supported ascorbate, 25 °C, 16 h, 89%; (b) *p*-toluene sulfonic anhydride, pyridine, 0 °C, 1 h, 94%; (iii) (*E*)-2,6-dimethoxy-4-(propenyl)phenol, polymer-supported phosphazene base, CH_3CN, 25 °C, 15 h, 100%; (iv) polymer-supported borohydride, CH_3OH, 25 °C, 16 h, 96%, dr = 32:1.

Casiraghi's approach (2006)[44]

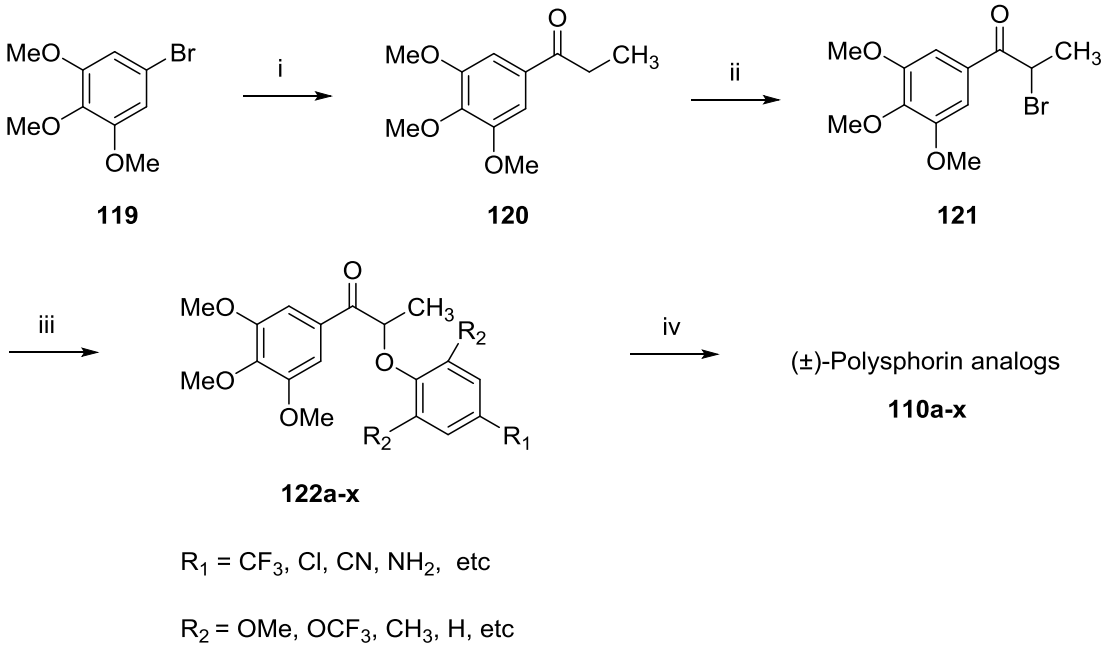
Casiraghi *et al.* have achieved the synthesis of (-)-polysphorin (**106**) using a chiral pool approach commencing from (*S*)-methyl lactate **115**. The hydroxy group of **115** was protected as its PMB ether, followed by reduction of ester group and oxidation of the resulting alcohol under Swern condition gave aldehyde **116** in 91% yield. Arylation of aldehyde **116** with lithium derivative of 5-bromo-1,2,3-trimethoxy benzene afforded the *anti*-configured compound **117** in 80% yield (*anti*:*syn* = 83:17). Benzylic alcohol **117** was converted to mesylate **118** using simple standard transformations. The S_N2 displacement of mesylate **118** with (*E*)-2,6-dimethoxy-4-(propenyl)-phenol under microwave irradiation and subsequent deacetylation afforded (-)-polysphorin (**106**) in 40% overall yield and 97% ee (**Scheme 19**).



Scheme 19: (i) $PMBOC(CCl_3)=NH$, $Sc(OTf)_3$, toluene; (ii) $LiAlH_4$, THF; (iii) $(COCl)_2$, DMSO, CH_2Cl_2, -80 °C, then Et_3N, 91%, (over three steps); (iv) 5-bromo-1,2,3 trimethoxy benzene, *tert*-BuLi, THF, -85 °C, 1 h, 80%, dr = 83:17; (v) Ac_2O, Et_3N, DMAP, CH_3CN, 25 °C, 1 h; (vi) DDQ, CH_2Cl_2, 25 °C, 3 h; (vii) MsCl, Et_3N, 25 °C, 3 h, 80% (over three steps); (viii) Cs_2CO_3, 18-crown-6, (*E*)- 2,6-dimethoxy-4-(propenyl) phenol, DMF, MW 200 W, 2 bar, 120 °C, 10 min, 70%; (ix) NaOMe, CH_3OH, 25 °C, 1 h, 98%.

Choppin's approach (2010)[45]

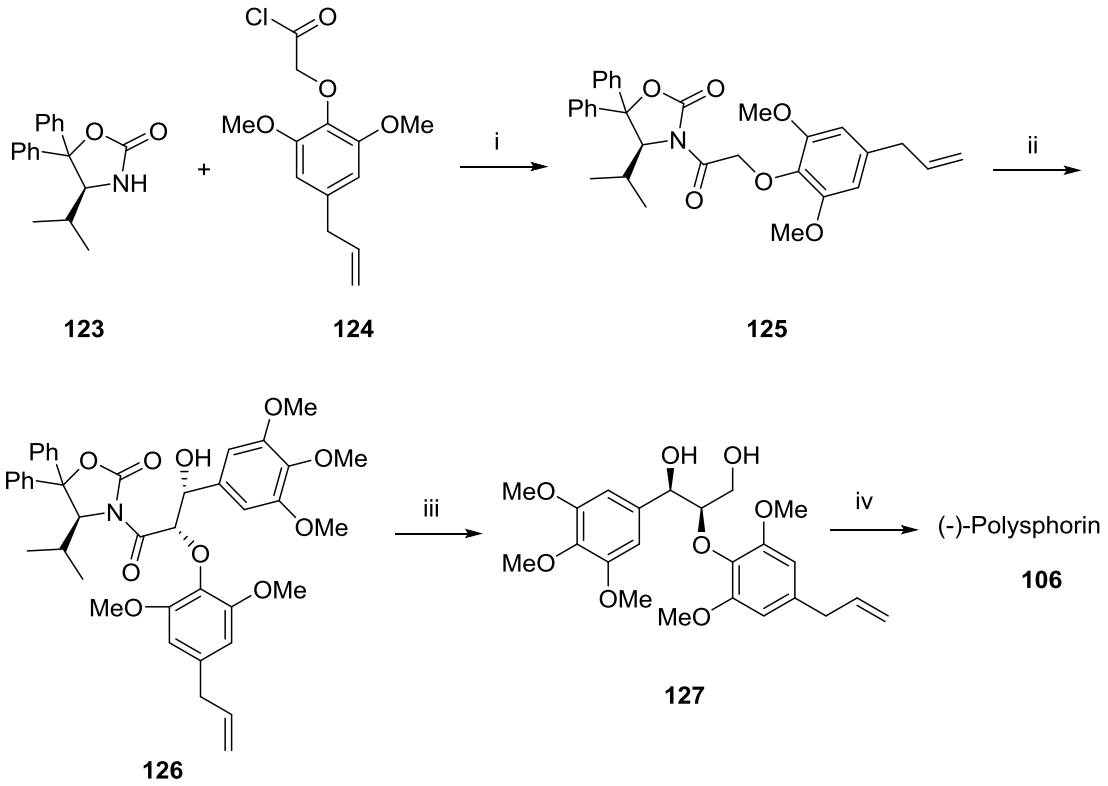
Choppin *et al.* have developed a useful synthetic method for the racemic synthesis of *syn*-(±)-polysphorin analogs (**110a-x**). Reaction of 5-bromo-1,2,3-trimethoxy benzene **119** with *N*,*N*-dimethylpropionamide in the presence of *tert*-BuLi afforded aryl ketone **120** in 49% yield. α-Bromination of ketone **120** gave bromo compound **121**, which on substitution with different phenols resulted in aryl keto ethers **122a-x**. Finally, diastereoselective reduction of ketones **122a-x** using $ZnCl_2$ and $NaBH_4$ afforded (±)-polysphorin analogs (**110a-x**) with diastereomeric ratio of *anti:syn* in 69:31 to 85:15 (**Scheme 20**).



Scheme 20: (i) *tert*-BuLi, THF, -78 °C, *N*, *N*-dimethylpropionamide, 1 h, 49%; (ii) Br_2, toluene, 25 °C, 1 h, 98%; (iii) substituted phenol, K_2CO_3, butan-2-one, reflux, 16 h, 59-90%; (iv) $ZnCl_2$, $NaBH_4$, Et_2O, 0 °C, 2 h, 84-90%, *anti:syn* = 69:31 to 85:15.

Gawali's approach (2012)[46]

Gawali *et al*. have utilized valine-based chiral oxazolidinone **123** for the introduction of chirality in (-)-polysphorin (**106**) synthesis. Chiral oxazolidinone **123** was thus attached to aryloxyacid chloride derivative **124** under basic conditions to afford *N*-acylimidazolidinone derivative **125**. Aldol reaction between boron enolate of imidazolinone **125** with 3,4,5-trimethoxybenzaldehyde afforded *syn*-aldol product **126** in 86% yield and as a single diastereomer. The reductive removal of the chiral auxiliary afforded the diol **127**. Further, deoxygenation of the primary alcohol in **127** followed by olefin isomerization delivered (-)-polysphorin (**106**) (**Scheme 21**).



Scheme 21: (i) *n*-BuLi, THF, 0 °C to 25 °C, 92%; (ii) *n*-Bu_2BOTf, $^{i}Pr_2NEt$, CH_2Cl_2, 0 °C to 25 °C, 3,4,5-trimethoxybenzaldehyde, -78 °C to 25 °C, 86%; (iii) $LiAlH_4$, Et_2O, 25 °C, 4 h, 87%; (iv) (a) *p*-TsCl, cat. DMAP, Et_3N, CH_2Cl_2, 0 °C to 25 °C, 3 h; (b) $LiAlH_4$, Et_2O, 25 °C, 2 h, 98%; (c) $PdCl_2$, CH_3OH, 25 °C, 6 h, 97%.

1.2.3 Present Work

1.2.3.1 Objective

From the above discussions, it is obvious that only a few reports are available for the synthesis of polysphorin (**106**) and its analogs (**110a-x**); Notably, some of the reported methods suffer from certain limitations such as use of chiral starting material, chiral auxiliary, expensive reagents, lack of selectivity, etc. Hence, a catalytic method that introduces chirality into the molecule, along with a flexibility to obtain all the four diastereoisomers is desirable. This section describes an elegant

synthetic route to the synthesis of (-)-polysphorin analog (**110a**) using a late-stage two-stereocentered Co-catalyzed HKR of racemic *syn*-epoxide **136** as the key step.

Retrosynthetic analysis of (-)-polysphorin analog (**110a**) reveals that alcohol **139** could be visualized as the key intermediate. The alcohol **139** could be obtained by means of the regioselective opening of chiral epoxide **138**. The chiral epoxide **138** could in turn be obtained by performing Co-catalyzed two-stereocentered HKR of the corresponding racemic *syn*-alkoxy epoxide **136**. The required racemic *syn*-alkoxy epoxide **136** could be prepared from *syn*-diol **130,** which in turn could be readily prepared from aldehyde **128** (**Fig. 16**).

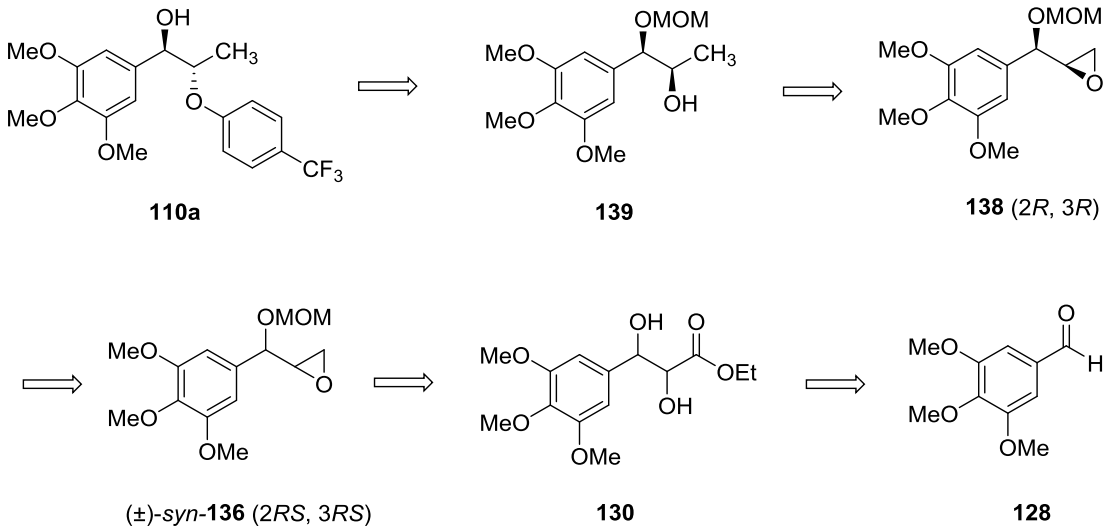
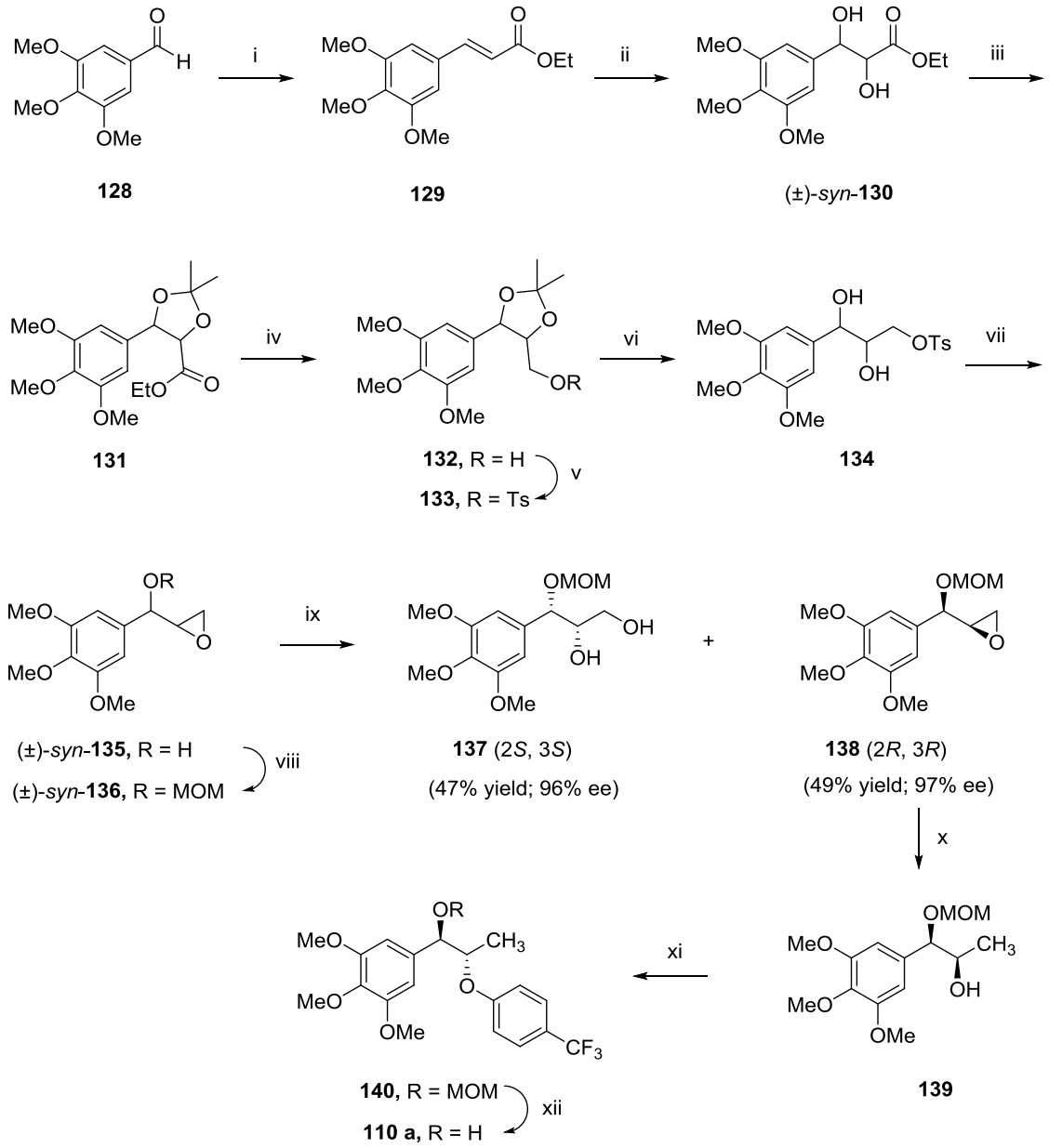


Fig. 16: Retrosynthetic analysis of (-)-polysphorin analog (**110 a**)

1.2.4 Results and Discussion

The complete synthetic sequence for (-)-polysphorin analog (**110a**) is shown in **Scheme 22**, wherein late-stage two-stereocentered Co-catalyzed HKR of racemic *syn*-epoxide constitutes a key step for the introduction of chirality in the molecule.



Scheme 22: (i) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, 25 °C, 5 h, 96%; (ii) $K_2OsO_4.2H_2O$ (2 mol%), NMO, acetone:H_2O (4:1), 0 to 25 °C, 20 h, 93%; (iii) 2,2-dimethoxypropane, camphor sulfonic acid (10 mol %), CH_2Cl_2, 25 °C, 6 h, 98%; (iv) $LiAlH_4$, THF, 0 to 25 °C, 1 h, 92%; (v) *p*-TsCl, Et_3N, DMAP (10 mol%), CH_2Cl_2, 25 °C, 4 h, 94%; (vi) camphor sulfonic acid (10 mol %), CH_3OH, 40 °C, 1 h, 96%; (vii) K_2CO_3, CH_3OH, 25 °C, 3 h, 88%; (viii) MOMCl, $^{i}Pr_2NEt$, CH_2Cl_2, 25 °C, 8 h, 92%; (ix) (*S*, *S*)-Co(salen)OAc (0.5 mol%), H_2O (0.5 equiv), 0 °C, 14 h; (x) $LiAlH_4$, THF, 0 to 25 °C, 4 h, 96%; (xi) PPh_3, $^{i}PrO_2C\text{-}N{=}N\text{-}CO_2Pr^{i}$, 4-(trifluoromethyl)phenol, THF, 70 °C, 12 h, 74%; (xii) conc. HCl, CH_3OH, 25 °C, 4 h, 86%.

The present synthesis of (-)-polysphorin analog (**110a**) started from commercially available 3,4,5-trimethoxybenzaldehyde **128**, which on Wittig olefination (CH_2Cl_2, $Ph_3P{=}CHCO_2Et$) gave the cinnamate ester **129** in 96% yield. The formation of cinnamate ester **129** was confirmed from its ^{1}H NMR spectrum, which showed two doublets at δ 6.31 (d, *J* = 16 Hz, 1H) and 7.57 (d, *J* = 16 Hz, 1H) establishing the presence of α- and β- CH olefin protons of -C**H**=C**H**CO_2Et. This was further ascertained by the presence of characteristic carbon signals at δ 117.3 and 144.3 corresponding to α- and β- carbon signal of -**C**H=**C**HCO_2Et in its ^{13}C NMR spectrum (**Fig. 17**).

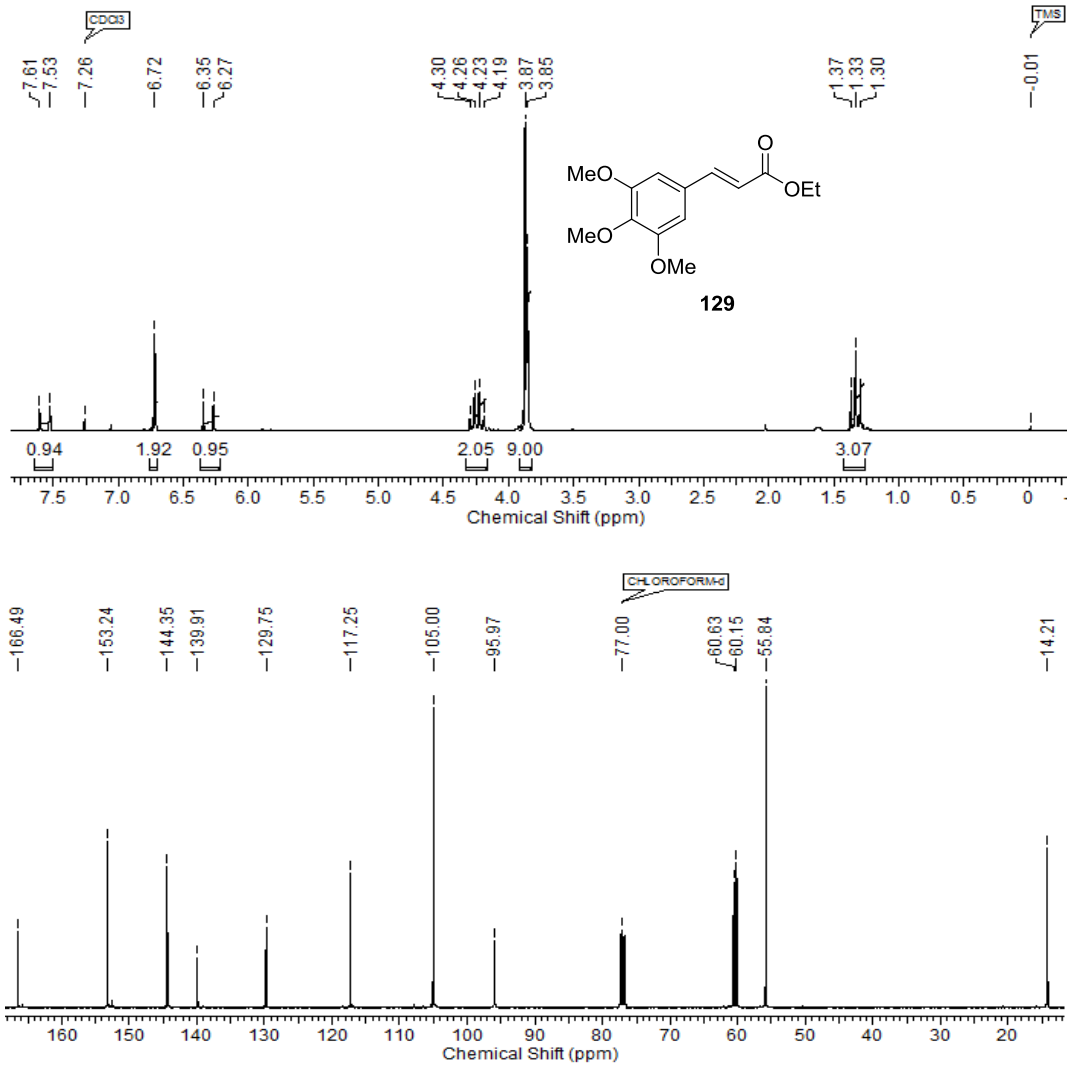


Fig. 17: ^{1}H and ^{13}C NMR spectra of cinnamate ester **129**

The Upjohn dihydroxylation of cinnamate ester **129** with catalytic amount of $K_2OsO_4.2H_2O$ and NMO gave racemic *syn*-diol **130** in 93% yield.[47] The formation of diol **130** was confirmed from its ^{1}H NMR spectrum, which showed characteristic multiplets at δ 4.34-4.36 (m, 1H) and 4.93-4.96 (m, 1H), corresponding to methine (-C**H**(OH)-C**H**(OH)-) protons, while its ^{13}C NMR spectrum showed characteristic carbon signals at δ 74.8 and 77.2 due to methine carbons attached to hydroxyl groups (**Fig. 18**).

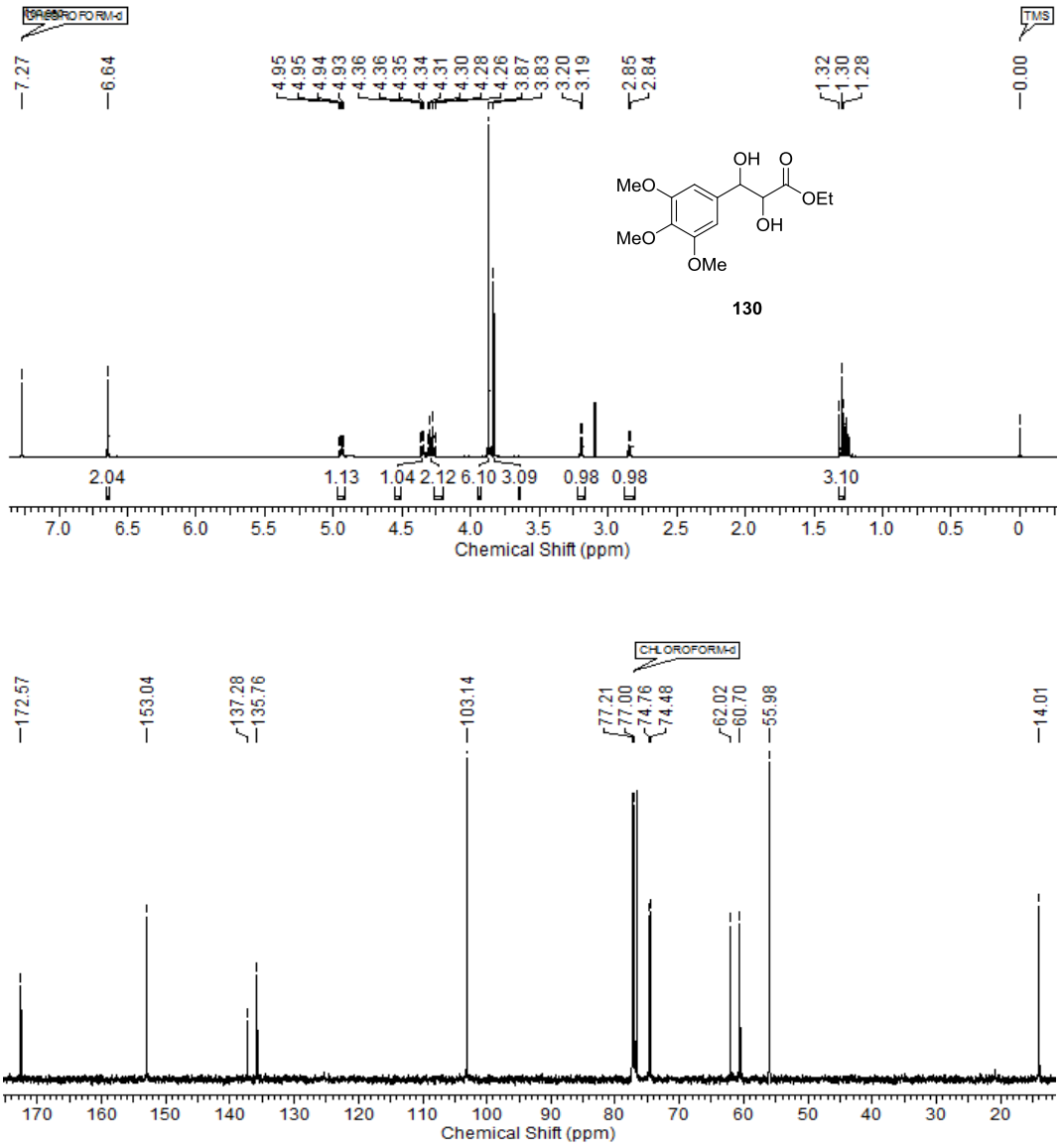


Fig. 18: ^{1}H and ^{13}C NMR spectra of racemic *syn*-diol **130**

The racemic *syn*-diol **130** was then protected as its acetonide **131** on treatment with 2, 2-dimethoxypropane in the presence of catalytic amount of camphor sulfonic acid.[48] Acetonide **131** was confirmed from its ^{1}H NMR spectrum, which showed two characteristic singlets at δ 1.55 (s, 3H) and 1.61 (s, 3H) corresponding to the methyl protons of isopropylidene group, while its ^{13}C NMR spectrum showed characteristic carbon signals at δ 25.7 and 26.9 due to methyl carbon of isopropylidene group (**Fig. 19**).

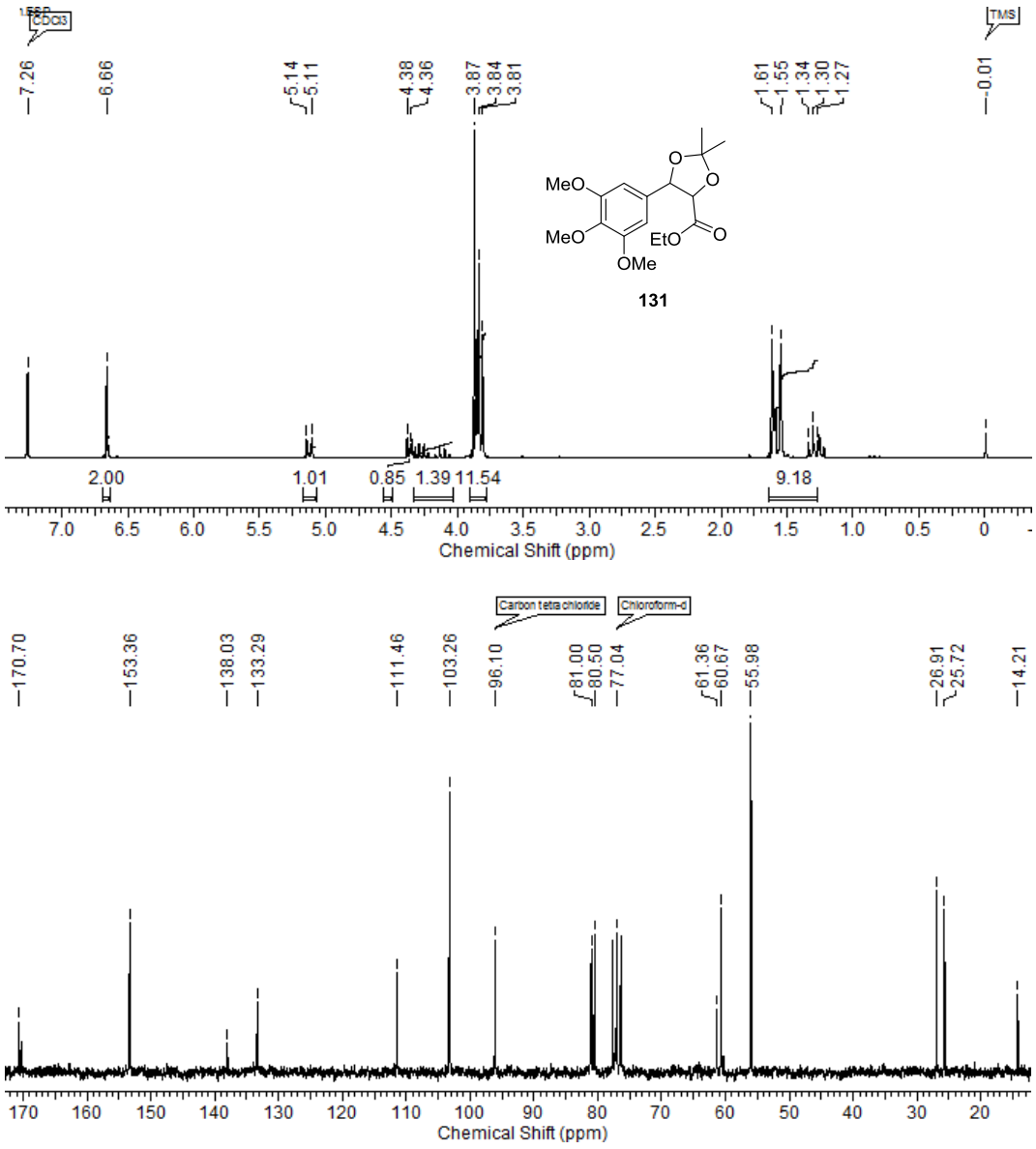


Fig. 19: ^{1}H and ^{13}C NMR spectra of acetonide **131**

The reduction of the ester function in **131** was achieved on its treatment with $LiAlH_4$ in THF at room temperature to afford the corresponding alcohol **132** in 92% yield. Its ^{1}H NMR spectrum showed a characteristic multiplet at δ 3.79-3.82 (m, 2H) for methylene (-C**H**$_2$-OH) protons, while its ^{13}C NMR spectrum showed a typical carbon signal at δ 60.1 due to methylene carbon (-**C**H_2-OH) attached to hydroxyl group, which confirmed the formation of alcohol **132** (**Fig. 20**).

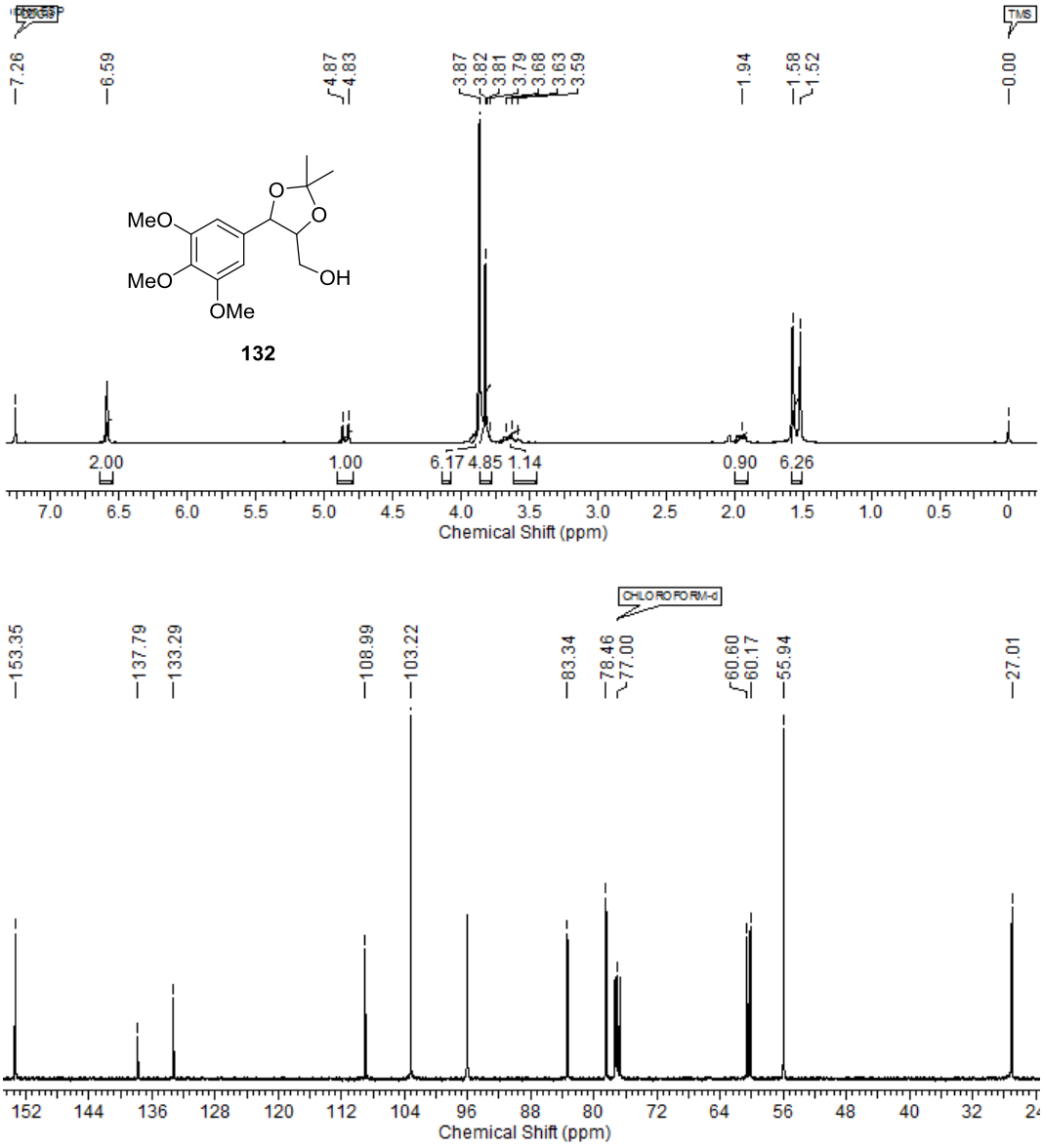


Fig. 20: ^{1}H and ^{13}C NMR spectra of alcohol **132**

The primary hydroxyl function in **132** was duly protected [*p*-TsCl, Et_3N, DMAP (10 mol%), CH_2Cl_2] as the tosylate **133**. Formation of tosylate **133** was confirmed by its ^1H NMR spectrum, which showed a characteristic singlet at δ 2.45 (s, 3H) and two doublets at δ 7.33 (d, J = 8.2 Hz, 2H) and 7.76 (d, J = 8.3 Hz, 2H) due to methyl and aromatic protons of tosyl group respectively, while its ^{13}C NMR spectrum showed a typical carbon signal at δ 21.6 for methyl carbon of tosyl group (**Fig. 21**).

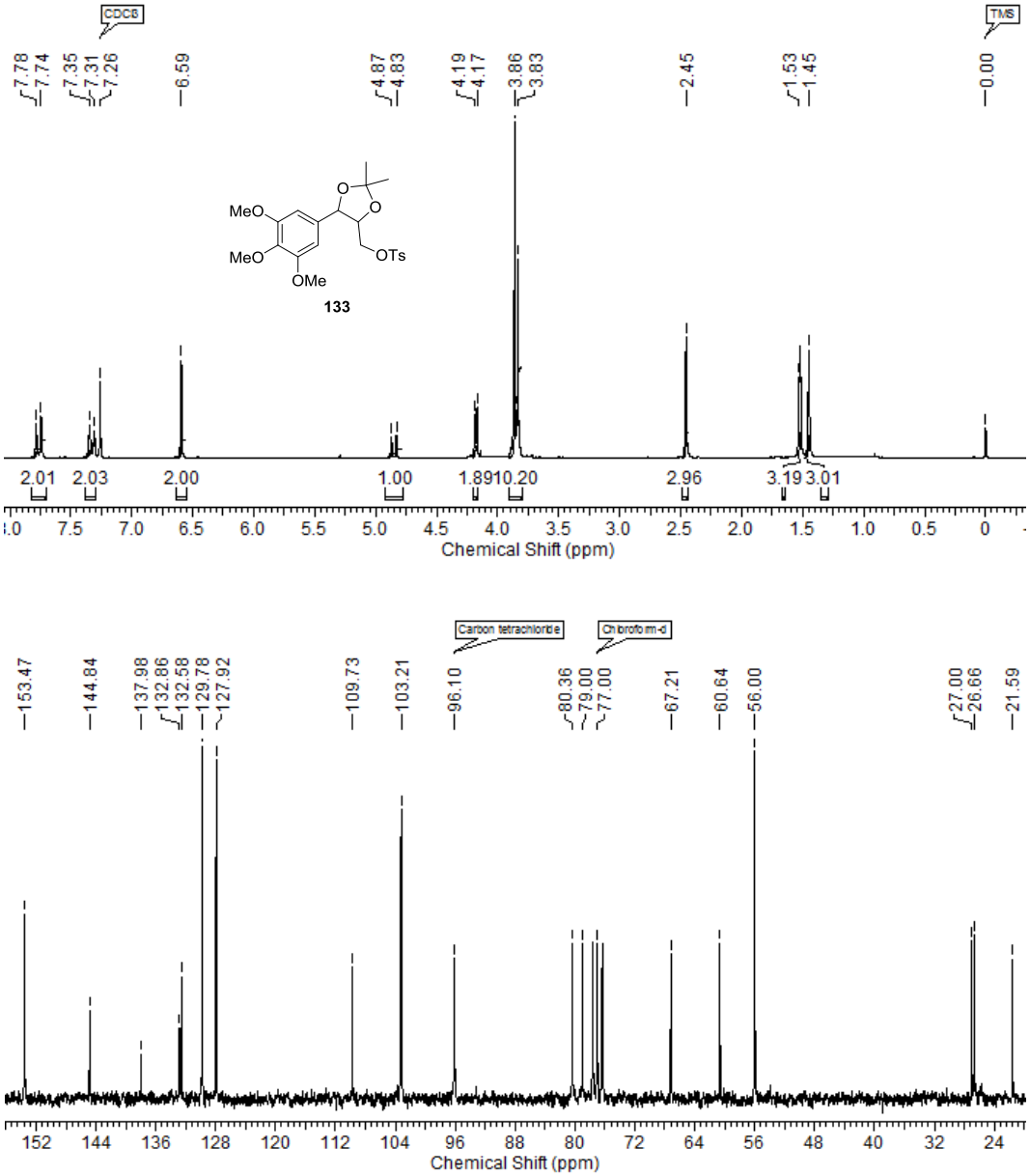


Fig. 21: ^1H and ^{13}C NMR spectra of tosylate **133**

The selective deprotection of acetonide group was achieved using catalytic amount of camphor sulfonic acid in methanol to afford diol **134** in 96% yield.[49] The disappearance of proton singlets at δ 1.45 (s, 3H) and 1.53 (s, 3H) in the ^{1}H NMR spectrum of **134** corresponding to the methyl protons of isopropylidene group confirmed the removal of acetonide group (**Fig. 22**).

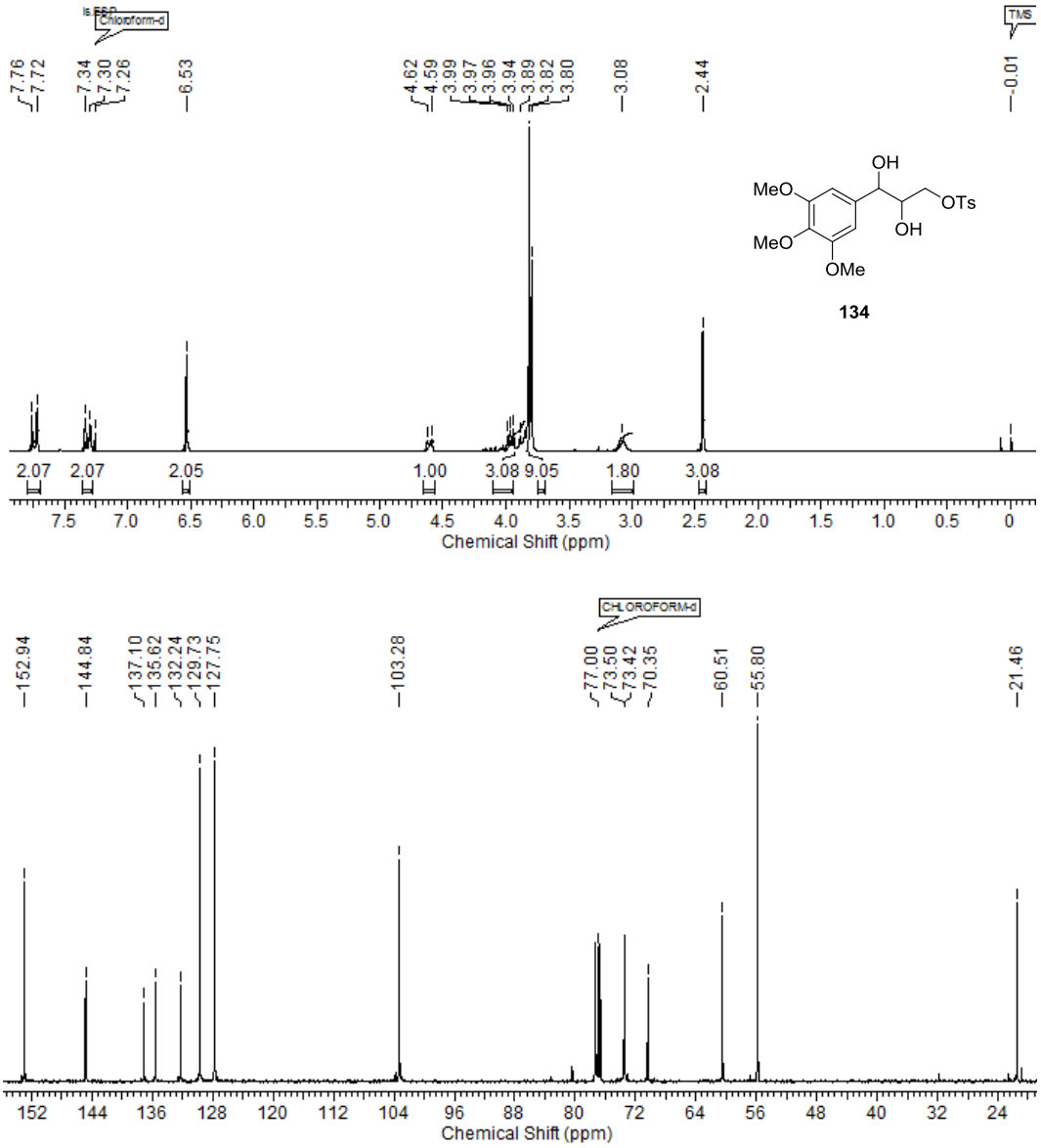


Fig. 22: ^{1}H and ^{13}C NMR spectra of diol **134**

Racemic *syn*-diol **134** was further converted to racemic *syn*-epoxide **135** in 88% yield, when carried out under basic conditions (K_2CO_3, CH_3OH). The formation of racemic

syn-epoxide **135** was confirmed from its ^{1}H NMR spectrum, which showed typical proton signals at δ 2.48-252 (m, 1H) and 2.84 (t, *J* = 4.4 Hz, 2H), corresponding to methylene and methine protons of epoxide respectively. Its ^{13}C NMR spectrum showed two characteristic carbon signals at δ 45.1 and 55.9 corresponding to methylene and methine carbons of the epoxide moiety respectively (**Fig. 23**).

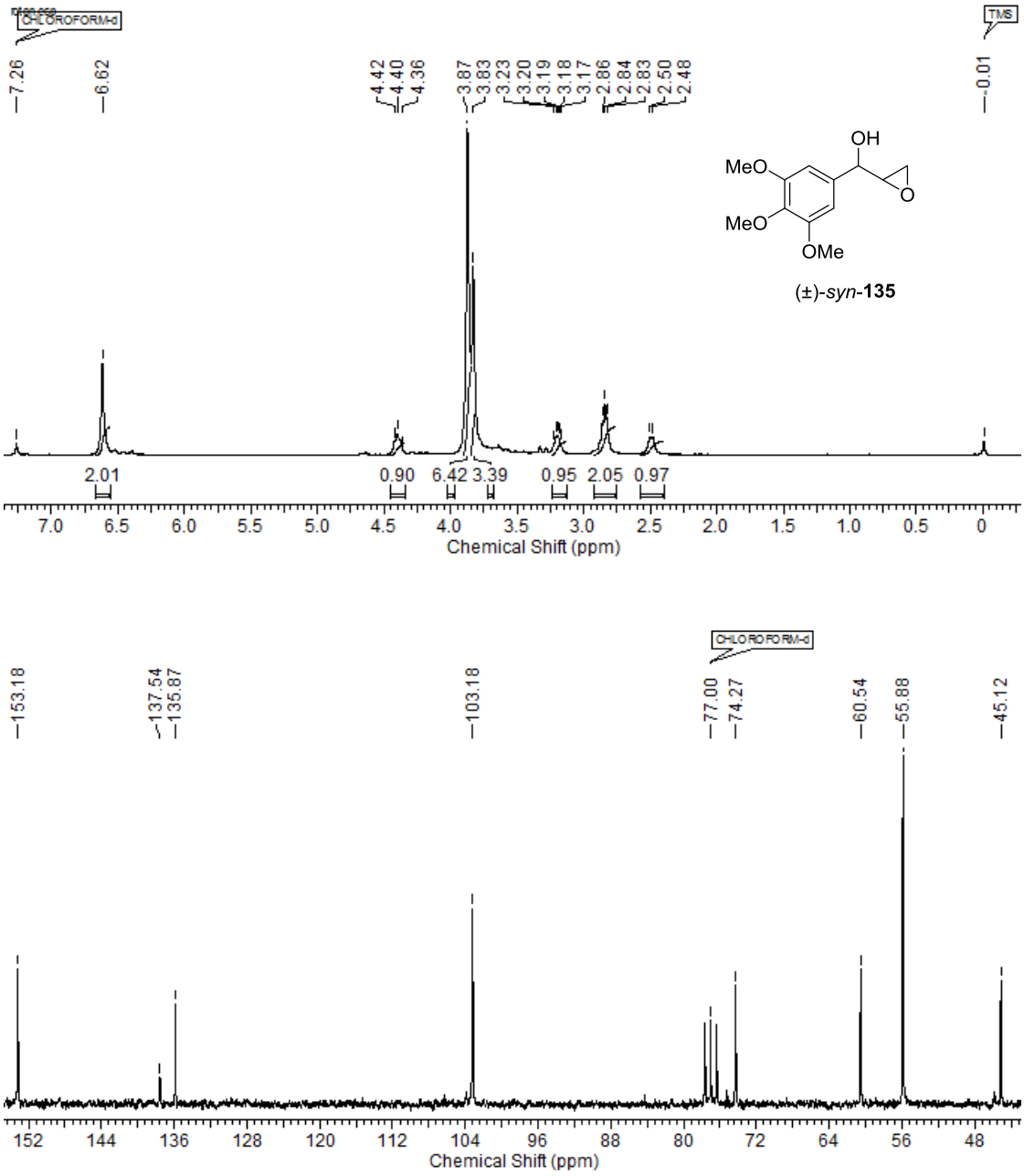


Fig. 23: ^{1}H and ^{13}C NMR spectra of (±)-*syn*-epoxide **135**

The benzylic hydroxyl group in **135** was then protected as its MOM ether **136** in 92% yield (MOMCl and diisopropylethylamine).[50] MOM protection in racemic *syn*-epoxide **136** was confirmed from its ^{1}H NMR spectrum, which showed typical proton signals at δ 4.59-4.71 (m, 2H) corresponding to the methylene protons of the MOM group, while its methyl protons appeared as a singlet at δ 3.39 (s, 3H). It was further confirmed by the appearance of carbon signals at δ 55.5 and 94.2 corresponding to the methyl and methylene carbons respectively of the MOM group in its ^{13}C NMR spectrum (**Fig. 24**).

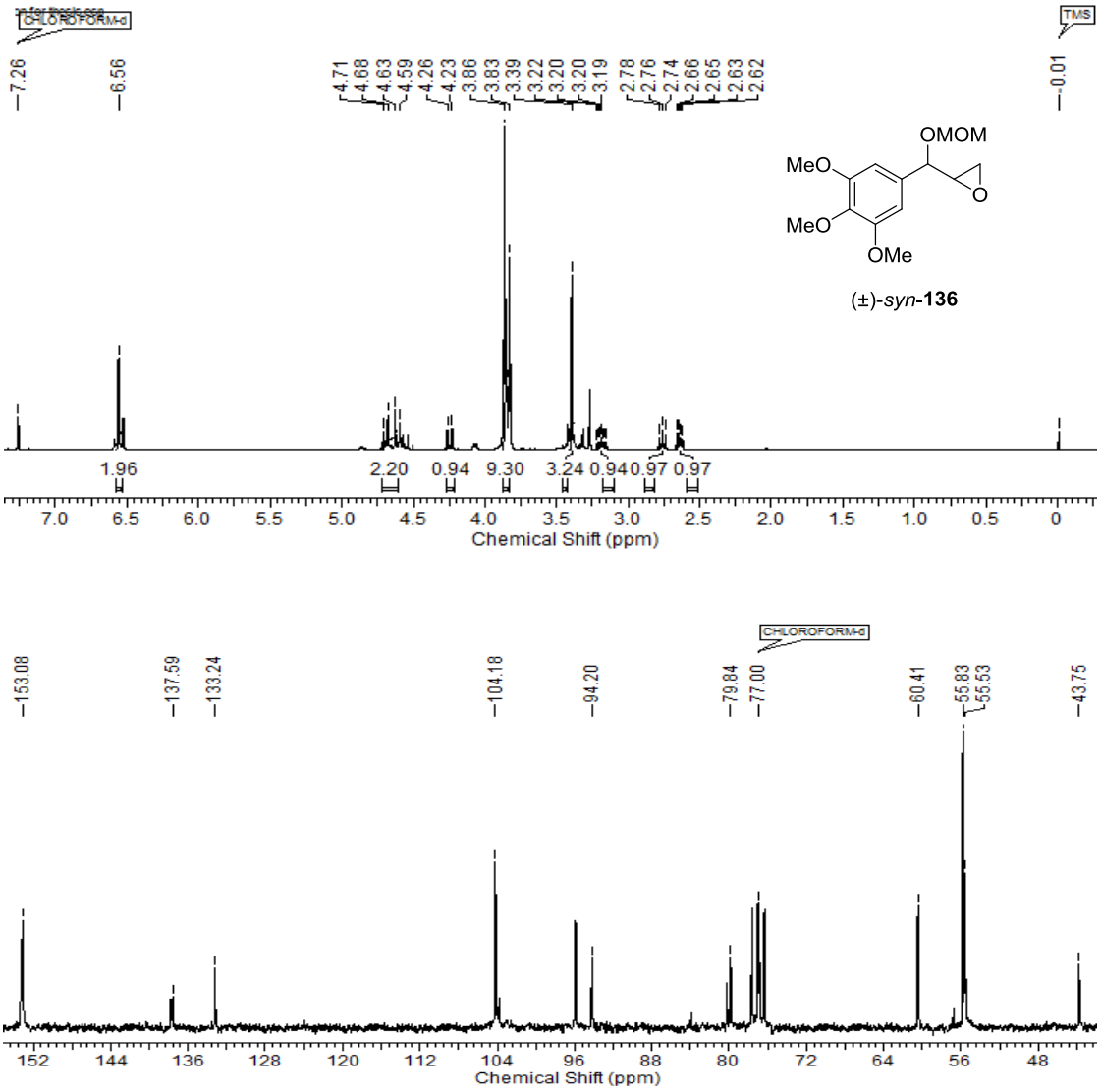
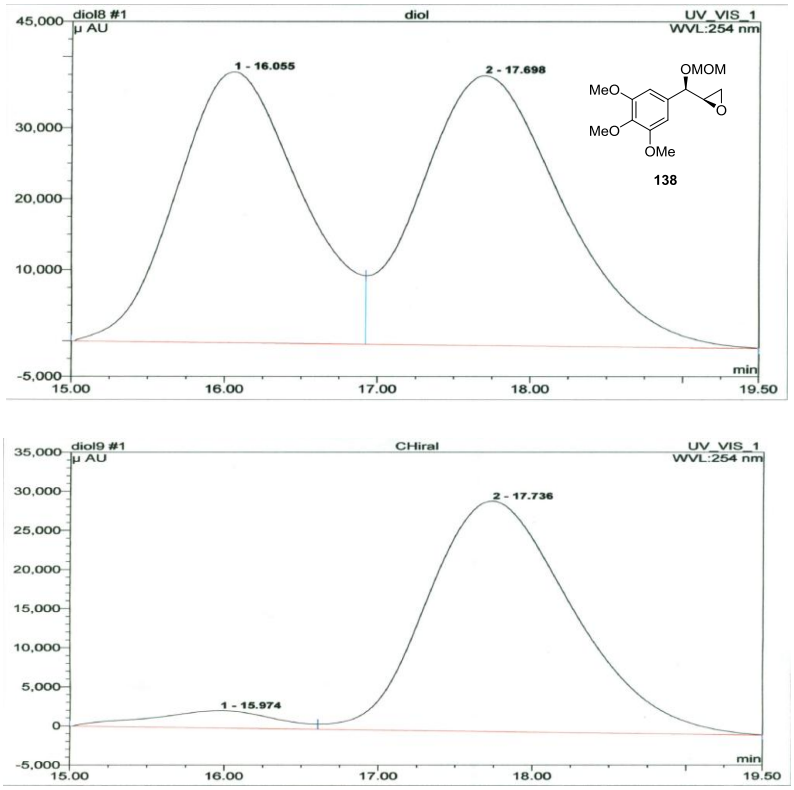


Fig. 24: ^{1}H and ^{13}C NMR spectra of (±)-*syn*-epoxide **136**

Then, *syn*-3-(methoxymethyl)oxy-3-(3,4,5-trimethoxyphenyl)-1,2-epoxypropane **136** was subjected to two-stereocentered HKR with (*S, S*)-salen Co(OAc) complex[20a,b] (0.5 mol%) and H_2O (0.5 equiv), which produced the corresponding chiral diol **137** (47%, 96% ee) and chiral *syn*-epoxide **138** (49%, 97% ee) in high optical purity. The chiral *syn*-epoxide **138** was readily separated from diol **137** by the column chromatographic purification. The optical purity of chiral *syn*-epoxide **138** was determined to be 97% ee from chiral HPLC analysis (Chiralcel OJ-H, *n*-hexane/ ^{i}PrOH, 90:10, 0.5 mL/min) retention time 15.97 (1.50%) and 17.73 (98.50%) (**Fig**. **25**).



No	Ret. Time min	Height µ AU	Area µ AU* min	Rel. Area %
1	15.97	560.800	512.360	1.50
2	17.73	36825.916	33644.986	98.50

Fig. 25: HPLC chromatogram of *syn*-epoxide **138**

The regioselective reductive ring opening of chiral *syn*-epoxide **138** with $LiAlH_4$[51] in THF furnished the secondary alcohol **139** in 96% yield. The ^1H and ^{13}C NMR spectra were in accordance with the proposed structure of **139**. In its ^1H NMR spectrum the newly generated methyl protons resonated at δ 1.54 as a doublet, while its typical carbon signal appeared at δ 18.4 in its ^{13}C NMR spectrum (**Fig. 26**). The IR spectrum of **139** displayed a characteristic strong absorption band at 3452 cm^{-1} indicating the presence of hydroxyl group.

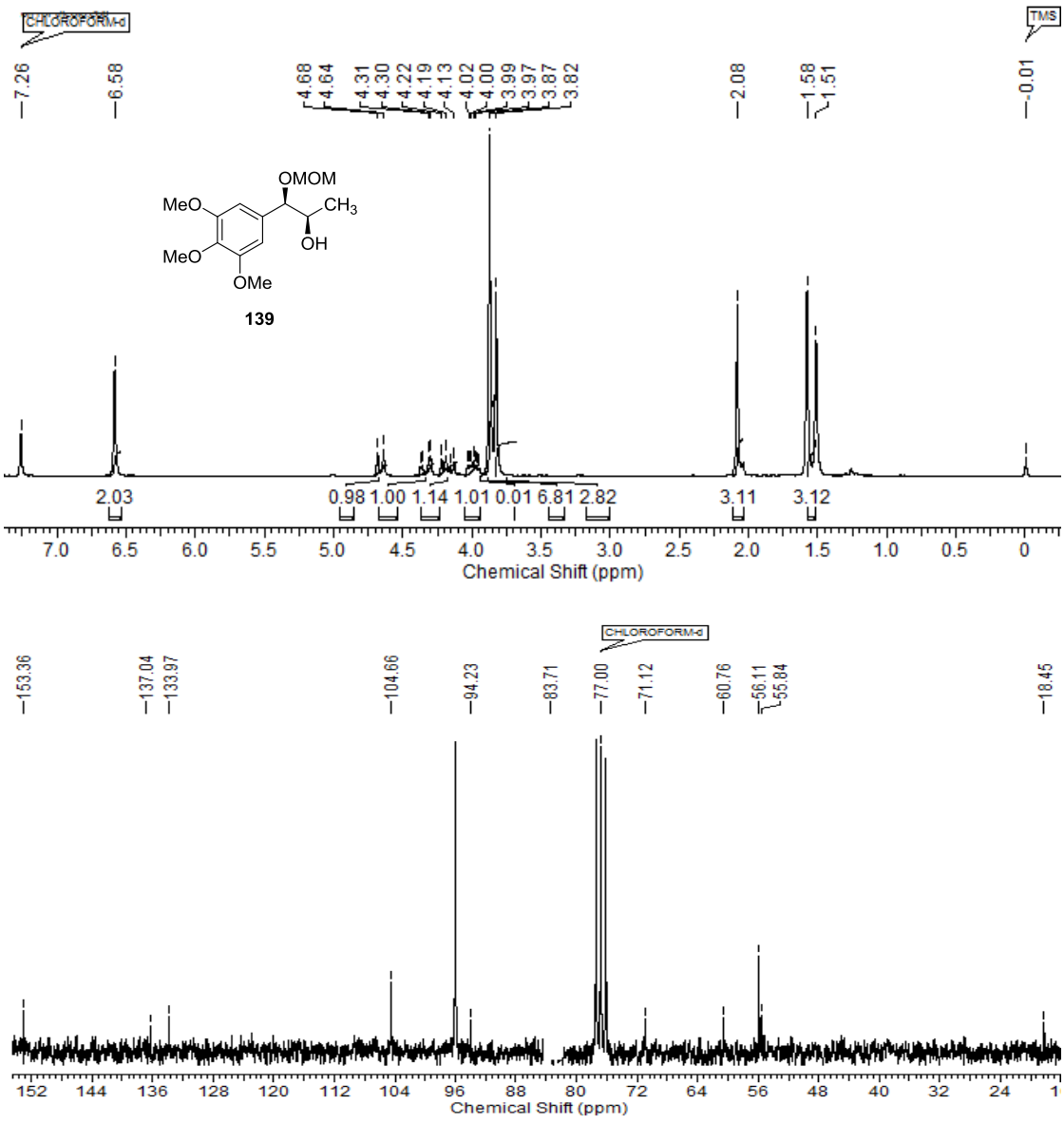


Fig. 26: ^1H and ^{13}C NMR spectra of alcohol **139**

Mitsunobu reaction of alcohol **139** with 4-(trifluoromethyl)phenol in the presence of PPh_3 and diisopropyl azodicarboxylate (DIAD) in THF at 70 °C afforded aryloxy ether **140** in 74% yield; $[\alpha]^{25}_D$ -46.20 (*c* 1.0, $CHCl_3$). The ^1H NMR spectrum of the aryloxy ether **140** showed characteristic proton signal as doublets at δ 6.87 (d, *J* = 8.6 Hz, 2H) and 7.48 (d, *J* = 8.6 Hz, 2H) corresponding to the aromatic protons of 4-(trifluoromethyl)ether moiety. Its ^{13}C NMR spectrum showed characteristic carbon signals at δ 122.9 (q, *J* = 32.3 Hz) and 124.3 (d, *J* = 271.2 Hz) corresponding to the -**C**-CF_3 and -C-**C**F_3 carbons respectively (**Fig. 27**).

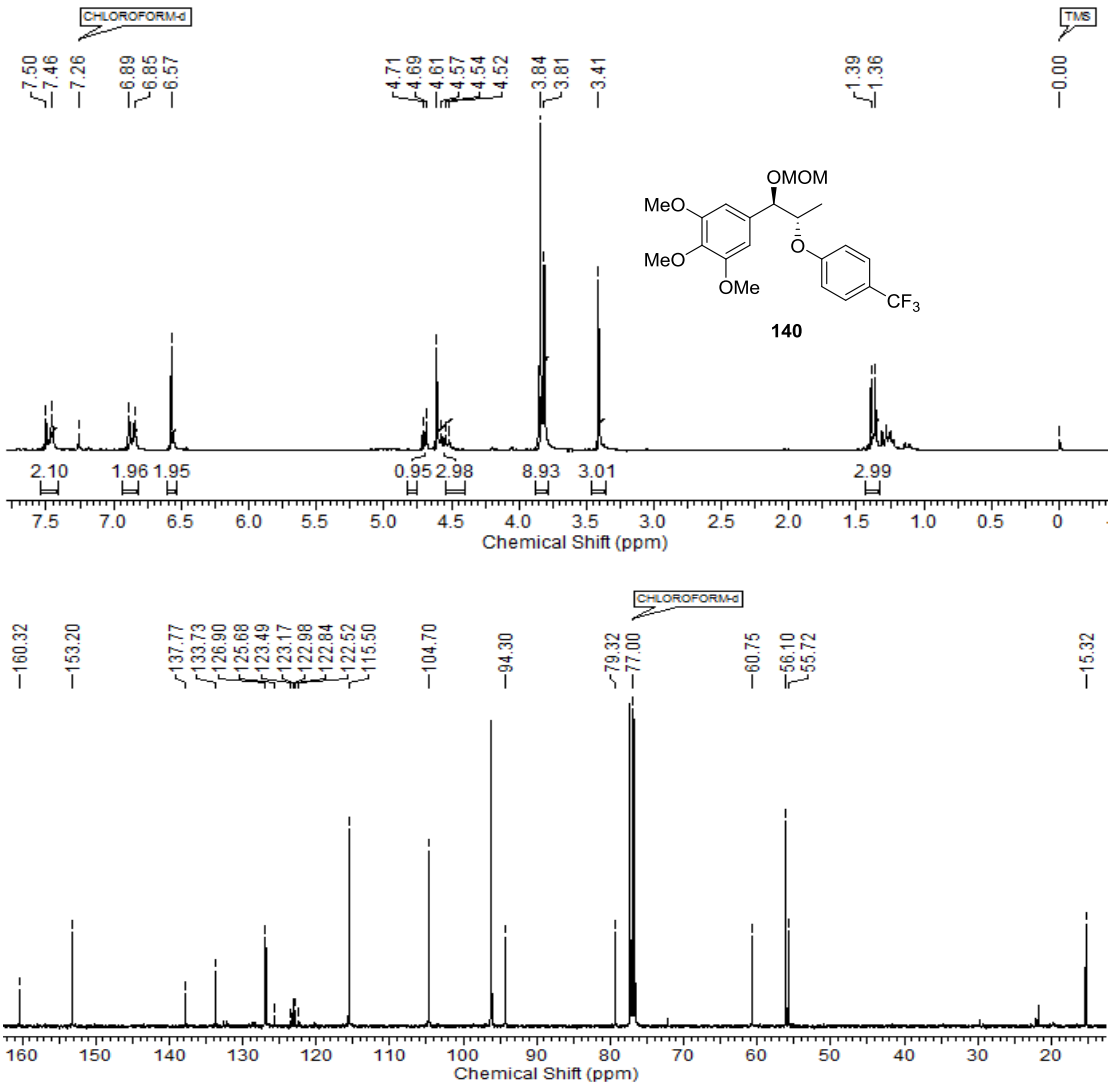


Fig. 27: ^1H and ^{13}C NMR spectra of ether **140**

Finally, deprotection of the MOM protecting group with con. HCl in methanol furnished (-)-polysphorin analog (**110a**) in 86% yield and 97% ee; $[\alpha]^{25}_{D}$ -126.30 (*c* 1.0, $CHCl_3$). The ^{1}H NMR spectrum of **110a** showed typical proton signals at δ 1.25 (d, *J* = 6.3 Hz, 3H) and 2.64 (br s, 1H), which accounted for methyl and hydroxyl group protons respectively.

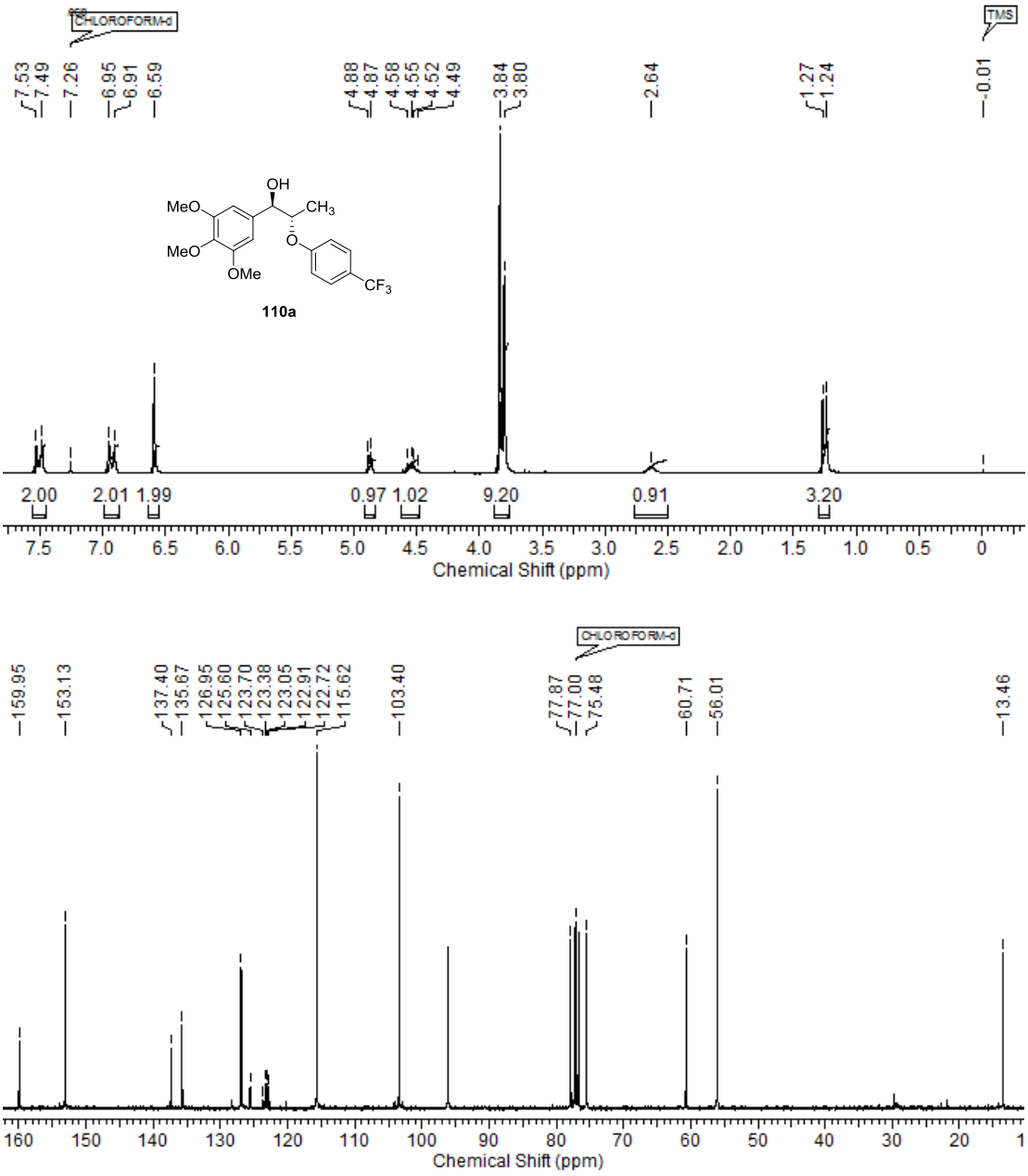


Fig. 28: ^{1}H and ^{13}C NMR spectra of (-)-polysphorin analog (**110a**)

The other signals at δ 6.93 (d, *J* = 8.6 Hz, 2H) and 7.51 (d, *J* = 8.6 Hz, 2H) were attributed to aromatic protons of 4-(trifluoromethyl)ether moiety. Its ^{13}C NMR spectrum showed characteristic carbon signals at δ 56.0, 60.7, 75.5, 77.8, 137.4, 153.1 and 159.9 for the carbons attached to oxygen atom (**Fig. 28**). The spectral data of (-)-polysphorin analog (**110a**) were in complete agreement with the reported values.[45]

1.2.5 Conclusion

In conclusion, we have achieved the asymmetric synthesis of (-)-polysphorin analog (**110a**) (overall yield 18%, 97% ee) *via* late- stage two-stereocentered HKR of racemic *syn*-epoxide as the key step. The high enantiomeric excess obtained in this method render our approach a good alternative to the known methods. The present protocol provides for all four diastereomers of polysphorin analogs with a large diversity of aromatic units by suitably employing (*R*, *R*)-salen Co(OAc) complex for HKR and with various aromatic phenols for Mitsunobu reaction.

1.2.6 Experimental Section

Ethyl (*E*)-3-(3,4,5-trimethoxyphenyl)acrylate (129)

To a stirred solution of 3,4,5-trimethoxybenzaldehyde **128** (9.81 g, 50 mmol) in CH_2Cl_2 (100 mL), $Ph_3P{=}CHCO_2Et$ (19.25 g, 55 mmol) was added. It was then allowed to stir for 5 h under N_2 atmosphere. After the completion of reaction, CH_2Cl_2 was distilled out to give the crude product. Chromatographic purification of the crude product over silica gel with pet. ether:EtOAc (90:10) as eluent, afforded cinnamate ester **129** (12.78 g).

Yield: 96%**,** colorless solid; **mp:** 68-70 °C, (lit.[52] **mp:** 67 °C); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 768, 980, 1039, 1176, 1203, 1270, 1312, 1367, 1450, 1639, 1705, 3063; **^{1}H NMR**

(200 MHz, $CDCl_3$): δ 1.33 (t, *J* = 7.2 Hz, 3H), 3.85 (s, 3H), 3.87 (s, 6H), 4.25 (q, *J* = 7.2 Hz, 2H), 6.31 (d, *J* = 16 Hz, 1H), 6.72 (s, 2H), 7.57 (d, *J* = 16 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.2, 55.8, 60.1, 60.6, 105.0, 117.3, 129.8, 139.9, 144.3, 153.2, 166.5; **Analysis**: $C_{14}H_{18}O_5$ requires C, 63.15; H, 6.81; found: C, 63.02; H, 6.71%.

Ethyl 2,3-dihydroxy-3-(3,4,5-trimethoxyphenyl)propanoate (130)

Potassium osmate (0.16g, 0.45 mmol) and 50% aqueous *N*-methylmorpholine *N*-oxide (10.4 mL, 44.5 mmol) were added to a solution of cinnamate ester **129** (6 g, 22.5 mmol) in acetone (41.6 mL) at 0 °C. After continuous stirring for 20 h at 25 °C, the reaction mixture was diluted with CH_2Cl_2 (40 mL), and dried over anhyd. Na_2SO_4 and concentrated to give the crude diol, which was purified by column chromatography over silica gel using pet. ether:EtOAc (40:60) as eluent, afforded diol **130** (6.34 g).

Yield: 93%; colorless gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 670, 762, 1039, 1182, 1217, 1326, 1732, 2362, 3020, 3451; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.30 (t, *J* = 7.3 Hz, 3H), 2.84 (br s, 1H), 3.18-3.20 (m, 1H), 3.83 (s, 3H), 3.87 (s, 6H), 4.29 (q, *J* = 7.3 Hz, 2H), 4.34-4.36 (m, 1H), 4.93-4.96 (m, 1H), 6.64 (s, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.0, 56.0, 60.7, 62.0, 74.5, 74.8, 77.2, 103.2, 135.7, 137.3, 153.0, 172.6; **Analysis:** $C_{14}H_{20}O_7$ requires C, 55.99; H, 6.71; found: C, 55.87; H, 6.60%.

Ethyl 2,2-dimethyl-5-(3,4,5-trimethoxyphenyl)-1,3-dioxolane-4-carboxylate (131)

To a solution of diol **130** (2 g, 6.6 mmol) in dry CH_2Cl_2 was added 2,2-dimethoxy propane (8 mL) and camphor sulfonic acid (0.152 g, 0.3 mmol). The reaction mixture was stirred at 25 °C for 6 h. The reaction mixture was diluted with water, extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic phases were dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to afford the crude product, which was then purified by column chromatography over silica gel using pet. ether:EtOAc (85:15) to furnish **131** (2.3 g).

Yield: 98%; colorless solid; **mp:** 57-59 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 682, 721, 834, 1006, 1132, 1235, 1381, 1462, 1595, 1753, 2990; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.30 (t, *J* = 7.2 Hz, 3H), 1.55 (s, 3H), 1.61 (s, 3H), 3.84 (s, 3H), 3.87 (s, 8H), 4.36-4.38 (m, 1H), 5.13 (d, *J* = 7.5 Hz, 1H), 6.66 (s, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.2, 25.7, 26.9, 56.0, 60.7, 61.4, 80.5, 81.0, 103.3, 111.5, 133.3, 138.0, 153.4, 170.7; **Analysis**: $C_{17}H_{24}O_7$ requires C, 59.99; H, 7.11; found: C, 59.45; H, 6.99%.

(2,2-Dimethyl-5-(3,4,5-trimethoxyphenyl)-1,3-dioxolan-4-yl)methanol (132)

A solution of ester **131** (2 g, 5.8 mmol) in THF (10 mL) was added to a stirred slurry of lithium aluminium hydride (0.23 g, 5.8 mmol) in THF (30 mL). After being stirred for 1 h at 25 °C, the reaction was carefully quenched with EtOAc and water. The reaction mixture was then extracted with EtOAc (2 × 100 mL) and the combined organic phases were dried over anhyd. Na_2SO_4 and concentrated to give the crude product, which was then purified by column chromatography using pet. ether:EtOAc (70:30) to give the alcohol **132** (1.62 g).

Yield: 92%; colorless gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 670, 763, 1128, 1217, 1461, 1595, 2362, 3019, 3422; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.52 (s, 3H), 1.58 (s, 3H), 1.94 (br s, 1H), 3.59-3.68 (m, 1H), 3.79-3.82 (m, 5H), 3.87 (s, 6H), 4.85 (d, *J* = 8.4 Hz, 1 H), 6.59 (s, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 27.0, 27.1, 55.9, 60.1, 60.6, 78.4, 83.4, 103.2, 109.0, 133.3, 137.8, 153.3; **Analysis**: $C_{15}H_{22}O_6$ requires C, 60.39; H, 7.43; found: C, 60.22; H, 7.28%.

(2,2-Dimethyl-5-(3,4,5-trimethoxyphenyl)-1,3-dioxolan-4-yl)methyl4-methyl benzenesulfonate (133)

A solution of alcohol **132** (2 g, 6.7 mmol) in dry CH_2Cl_2 (50 mL) was treated with *p*-toluene sulfonyl chloride (1.39 g, 7.3 mmol), DMAP (0.081 g, 0.67 mmol) and Et_3N (2.3 mL, 16.7 mmol) at 25 °C. After being stirred for 4 h, the mixture was extracted with CH_2Cl_2 (3 × 50 mL), washed with water and the combined organic phases were

dried over anhyd. Na_2SO_4 and concentrated to give the crude tosylate, which was then purified by column chromatography over silica gel using pet. ether:EtOAc (80:20) to give the tosylate **133** (2.84 g).

Yield: 94%; colorless gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 690, 762, 1129, 1224, 1631, 2371, 3019; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.45 (s, 3H), 1.53 (s, 3H), 2.45 (s, 3H), 3.83 (s, 3H), 3.86 (s, 6H), 4.06-4.19 (m, 3H); 4.85 (d, *J* = 8.3 Hz, 1H), 6.59 (s, 2H), 7.33 (d, *J* = 8.2 Hz, 2H), 7.76 (d, *J* = 8.3 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.6, 26.7, 27.0, 56.0, 60.6, 67.2, 79.0, 80.4, 103.2, 109.7, 127.9, 129.8, 132.6, 132.9, 138.0, 144.9, 153.5; **Analysis**: $C_{22}H_{28}O_8S$ requires C, 58.39; H, 6.24; found: C, 58.31; H, 6.04%.

2,3-Dihydroxy-3-(3,4,5-trimethoxyphenyl)propyl-4-methylbenzenesulfonate (134)

To a solution of tosylate **133** (2.84 g, 6.27 mmol) in CH_3OH (40 mL) was added camphor sulfonic acid (0.317 g, 0.62 mmol).and stirred for 1 h at 40 °C. Solvent was evaporated and the residue extracted with EtOAc (3 × 30 mL) and the combined organic phases were dried over anhyd. Na_2SO_4 and concentrated to give the crude product, which was then purified by column chromatography over silica gel using pet. ether:EtOAc (50:50) to give diol **134** (2.48 g).

Yield: 96%; colourless gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 688, 771, 1130, 1216, 1470, 1631, 2368, 3028, 3432; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.44 (s, 3H), 3.08 (brs, 1H), 3.80 (s, 3H), 3.82 (s, 6H), 3.88-3.89 (m, 3H); 4.61 (d, *J* = 6.2 Hz, 1H), 6.53 (s, 2H), 7.32 (d, *J* = 8.3 Hz, 2H), 7.74 (d, *J* = 8.3 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.5, 55.8, 60.5, 70.3, 73.4, 73.5, 103.3, 127.7, 129.7, 132.2, 135.6, 137.1, 144.8, 152.9; **Analysis**: $C_{19}H_{24}O_8S$ requires C, 55.33; H, 5.87; found: C, 55.16; H, 5.72%.

Oxiran-2-yl (3,4,5-trimethoxyphenyl)methanol (135)

To a stirred solution of **134** (2.48 g, 6.02 mmol) in CH_3OH (30 mL) was added anhydrous K_2CO_3 (1.62 g, 12.04 mmol) at 0 °C. The mixture was then warmed up and stirred at 25 °C. After the reaction was complete (monitored by TLC), 50 mL of aq. $NaHCO_3$ was added and the reaction mixture was extracted with EtOAc (3 × 60 mL). The combined organic phases were dried over anhyd. Na_2SO_4 and concentrated to give the crude product, which was then purified by flash column chromatography using pet. ether:EtOAc (65:35) to give epoxy alcohol, **135** (1.27 g).

Yield: 88%; colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 690, 748, 1109, 1690, 2408, 2945, 3040, 3420; **^{1}H NMR** (200 MHz, $CHCl_3$): δ 2.48-252 (m, 1H), 2.84 (t, *J* = 4.4 Hz, 2H), 3.17-3.23 (m, 1H), 3.83 (s, 3H), 3.86 (s, 6H), 4.36-4.42 (m, 1H), 6.62 (s, 2H); **^{13}C NMR** (50 MHz, $CHCl_3$): δ 45.1, 55.9, 60.5, 74.3, 103.2, 135.9, 137.5, 153.2; **Analysis**: $C_{12}H_{16}O_5$ requires C, 59.99; H, 6.71; found: C, 59.86; H, 6.64%.

2-[(Methoxymethoxy)(3,4,5-trimethoxyphenyl)methyl]oxirane (136)

To a solution of the epoxy alcohol **135** (1.00 g, 4.1 mmol) and diisopropylethylamine (3.60 mL, 20.8 mmol) in dry CH_2Cl_2 (20 mL) was added methoxymethyl chloride (0.80 mL, 10.2 mmol) under nitrogen over 5 min at 0 °C, and the mixture was allowed to warm to 25 °C and stirred for 8 h. After cooling to 0 °C, the reaction mixture was quenched with water and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with water (3 × 50 mL) and brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. Silica gel column chromatographic purification of the crude product using pet. ether:EtOAc (70:30) gave *syn*-epoxide **136** (1.15 g).

Yield: 92%; colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 672, 760, 1102, 1209, 1677, 2361, 2930, 3026, 3633; **^{1}H NMR** (200 MHz, $CHCl_3$): δ 2.64 (dd, *J* = 2.6, 4.9 Hz, 1H),

2.76 (t, *J* = 4.4 Hz, 1H), 3.15-3.22 (m, 1H), 3.39 (s, 3H), 3.83 (s, 3H), 3.86 (s, 6H), 4.24 (d, *J* = 6.3 Hz, 1H), 4.59-4.71 (m, 2H), 6.56 (s, 2H); **^{13}C NMR** (50 MHz, $CHCl_3$): δ 43.7, 55.5, 55.8, 60.4, 79.8, 94.2, 104.2, 133.2, 137.6, 153.1; **Analysis**: $C_{14}H_{20}O_6$ requires C, 59.15; H, 7.09; found: C, 59.04; H, 7.16%.

(2*S*, 3*S*)-3-(Methoxymethoxy)-3-(3,4,5-trimethoxyphenyl)propane-1,2-diol (137)

To a solution of (*S, S*)-salen Co(II) complex (purchased from Aldrich, USA.) (0.043 g, 0.07 mmol) in toluene (2.0 mL) was added gl. AcOH (0.04 g, 7.3 mmol). It was allowed to stir at 25 °C in air for 30 min over which time the color was changed from orange- red to a dark brown. It was then concentrated *in vaccuo* to get (salen)Co(III)(OAc) complex as brown colored solid. To a stirred solution of (salen)Co(III)(OAc) complex (0.004 g, 0.5 mol%) and racemic *syn*-epoxide **136** (1.41 mmol) in THF (0.5 mL) at 0 °C was added H_2O (0.012 g, 0.7 mmol) drop-wise over 5 min. The reaction mixture was allowed to warm to 25 °C and stirred for 14 h. After completion of reaction (monitored by TLC), solvent was removed *in vaccuo*. The crude product was purified by column chromatography over silica gel to (2*R*, 3*R*)-3-(methoxymethoxy)-3-(3,4,5-trimethoxy phenyl-1,2 epoxy propane (**138**) on eluting with pet. ether:EtOAc (70:30) and (2*S*, 3*S*)-3-(methoxymethoxy)-3-(3,4,5-trimethoxyphenyl)propane-1,2-diol (**137**) with pet. ether:EtOAc (55:45) in high enantiomeric excess.

The chiral diol **137** was obtained as a colorless liquid (47% and 96% ee); [%ee was determined by transforming diol **137** to the corresponding *syn*-epoxide, [(i) TsCl, Bu_2SnO (2 mol%), Et_3N, DMAP (10 mol%), CH_2Cl_2, 3 h; (ii) K_2CO_3, MeOH, 1 h, 83% (over two steps) and comparing its specific rotation with its antipode **138**];

Yield: 47%; colorless liquid; $[\alpha]^{D}_{25}$ +71.55 (*c* 1, CH_3OH); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 670, 748, 840, 1075, 1275, 1278, 1385, 1494, 1644, 2920, 3018, 3088, 3458; **^{1}H**

NMR (200 MHz, $CHCl_3$): δ 2.64 (dd, *J* = 2.6, 4.9 Hz, 1H), 2.76 (t, *J* = 4.4 Hz, 1H), 3.15-3.22 (m, 1H), 3.39 (s, 3H), 3.83 (s, 3H), 3.86(s, 6H), 4.24 (d, *J* = 6.3 Hz, 1H), 4.59-4.71 (m, 2H), 6.56 (s, 2H); **^{13}C NMR** (50 MHz, $CHCl_3$): δ 55.5, 55.8, 60.4, 64.0, 65.1, 85.2, 94.4, 103.8, 133.6, 137.2, 153.3; **Analysis** for $C_{14}H_{22}O_7$ requires: C, 55.62; H, 7.34; found: C, 55.51; H, 7.21%.

(2*R*, 3*R*)-3-(Methoxymethoxy)-3-(3,4,5-trimethoxyphenyl-1,2-epoxypropane (138)

Yield: 49%; colorless oil; $[\alpha]^{D}_{25}$ -72.30 (*c* 1.16, CH_3OH); 97% ee by chiral HPLC analysis (Chiralcel OJ-H, *n*-hexane/ ^{i}PrOH, 90:10, 0.5 mL/min) retention time 15.97 (1.50%) and 17.73 (98.50%); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 672, 760, 1102, 1209, 1677, 2361, 2930, 3026, 3633; **^{1}H NMR** (200 MHz, $CHCl_3$): δ 2.64 (dd, *J* = 2.6, 4.9 Hz, 1H), 2.76 (t, *J* = 4.4 Hz, 1H), 3.15-3.22 (m, 1H), 3.39 (s, 3H), 3.83 (s, 3H), 3.86 (s, 6H), 4.24 (d, *J* = 6.3 Hz, 1H), 4.59-4.71 (m, 2H), 6.56 (s, 2H); **^{13}C NMR** (50 MHz, $CHCl_3$): δ 43.7, 55.5, 55.8, 60.4, 79.8, 94.2, 104.2, 133.2, 137.6, 153.1; **Analysis**: $C_{14}H_{20}O_6$ requires C, 59.15; H, 7.09; found: C, 59.06; H, 7.02%.

(1*R*, 2*R*)-1-(Methoxymethoxy)-1-(3,4,5-trimethoxyphenyl)propan-2-ol (139)

A solution of epoxide **138** (1.00 g, 3.5 mmol) in THF (30 mL) was added to a stirred slurry of lithium aluminium hydride (0.167 g, 4.4 mmol). After being stirred for 4 h at 25 °C, the reaction was carefully quenched with water. It was then extracted with EtOAc (3 × 50 mL) and the combined organic phases were dried over anhyd. Na_2SO_4 and concentrated to give the crude product, which was then purified by flash column chromatography using pet. ether:EtOAc (60:40) to give the alcohol **139** (0.967 g).

Yield: 96%; colorless oil; $[\alpha]^{25}_{D}$ -116.42 (*c* 1.1, CH_3OH); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 690, 762, 1031, 1129, 1217, 1461, 1593, 2363, 3019, 3452; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.54 (d, *J* = 13.2 Hz, 3H), 2.08 (s, 3H), 3.82 (s, 3H), 3.87 (s, 7H), 3.97-4.03 (m, 1H), 4.13-4.22 (m, 1H), 4.30-4.37 (m, 1H), 4.66 (d, *J* = 8.6 Hz, 1H), 6.58 (s, 2H); **^{13}C**

NMR (50 MHz, $CDCl_3$): δ 18.4, 55.8, 56.1, 60.8, 71.1, 83.7, 94.2, 104.7, 134.0, 137.0, 153.4; **Analysis**: $C_{14}H_{22}O_6$ requires C, 58.73; H, 7.74; found: C, 58.62; H, 7.61%.

1,2,3-Trimethoxy-5-[(1*R*, 2*S*)-1-(methoxymethoxy)-2-(4-(trifluoromethyl) phenoxy)propyl)benzene (140)

To a stirred solution of chiral alcohol **139** (0.100 g, 0.35 mmol), PPh_3 (0.183 g, 0.7 mmol) and diisopropylazodicarboxylate (0.120 g, 0.6 mmol) in THF (5 mL) at 0 ºC was added 4-(trifluoromethyl)phenol (0.113 g, 0.7 mmol). The resulting solution was stirred for 12 h at 70 °C and then concentrated *in vaccuo*. The crude compound was purified by column chromatography using pet. ether:EtOAc (80:20) to afford the aryloxy ether **140** (0.112 g).

Yield: 74%; gum; $[\alpha]^{25}_D$ -46.20 (*c* 1.0, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 756, 891, 1052, 1097, 1130, 1190, 1325, 1374, 1485, 1629, 1765, 2928, 3015; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.37 (d, *J* = 6.2 Hz, 3H), 3.41 (s, 3H), 3.81 (s, 3H), 3.84 (s, 6H), 4.52-4.69 (m, 3H), 4.70 (d, *J* = 4.8 Hz, 1H), 6.57 (s, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 7.48 (d, *J* = 8.6 Hz, 2H) ; **^{13}C NMR** (50 MHz, $CDCl_3$): δ 15.3, 55.7, 56.1, 60.7, 79.3, 94.3, 104.7, 115.5, 122.9 (q, *J* = 32.3 Hz), 124.3 (d, *J* = 271.2 Hz), 126.9, 133.7, 137.8, 153.2, 160.3; **Analysis**: $C_{21}H_{25}F_3O_6$ requires C, 58.60; H, 5.85; found: C, 58.48; H, 5.73%.

(1*R*, 2*S*)-2-(4-(Trifluoromethyl)phenoxy)-1-(3,4,5-trimethoxyphenyl)propan-1-ol: [(-)-Polysphorin analog] (110a)

To a stirred solution of the aryloxy ether **140** (0.100 g, 0.23 mmol) in CH_3OH (5 mL) was added con. HCl (2 mL) and stirred for 4 h and then extracted with EtOAc (3 × 10 mL), washed with brine, dried over anhyd. Na_2SO_4 and concentrated under reduced

pressure. Silica gel column chromatographic purification of the crude product using petroleum ether:EtOAc (60:40) gave (-)-polysphorin analog **110a** (76 mg).

Yield: 86%; gum; $[\alpha]^{25}_{D}$ -126.30 (*c* 1.0, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 775, 865, 1019, 1068, 1327, 1413, 1440, 2957, 3471; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.25 (d, *J* = 6.3 Hz, 3H), 2.64 (br s, 1H), 3.80 (s, 3H), 3.84 (s, 6H), 4.49-4.58 (m, 1H), 4.87 (d, *J* = 3.9 Hz, 1H), 6.59 (s, 2H), 6.93 (d, *J* = 8.6 Hz, 2H), 7.51 (d, *J* = 8.6 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.5, 56.0, 60.7, 75.5, 77.8, 103.4, 115.6, 123.2 (q, *J* = 32.6 Hz), 123.8 (d, *J* = 270.3 Hz), 126.9, 135.7, 137.4, 153.1, 159.9; **Analysis**: $C_{19}H_{21}F_3O_5$ requires C, 59.07; H, 5.48; found: C, 59.14; H, 5.29%.

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CHAPTER 2

CN-Assisted Oxidative Cyclization of Cyano Cinnamates and Styrene Derivatives: A Facile Entry to 3-Substituted Chiral Phthalides and its Application to the Synthesis of (-)-Matteucen C and Butylphthalide

Section I:

CN-Assisted Oxidative Cyclization of Cyano Cinnamates and Styrene Derivatives: a Facile Entry to 3-Substituted Chiral Phthalides

2.1.1 Introduction

Chiral phthalides [isobenzofuran-1(3H)-ones] comprising of 5-membered lactones are found in a large number of plant products displaying broad and potent biological activities.[1] Some representative examples are shown in **Fig. 1**. 3-Butylphthalide (**1**), a component in the Chinese folk medicine extracted from celery seed oil,[2a] is in phase II clinical trials in China and potentially can be used for the treatment of stroke.[2b] Moreover, it is employed for seasoning and flavoring purposes, shows anticonvulsant action,[2c] increases the duration of anesthesia,[2d] and exhibits cerebral antiischemic action.[2e]

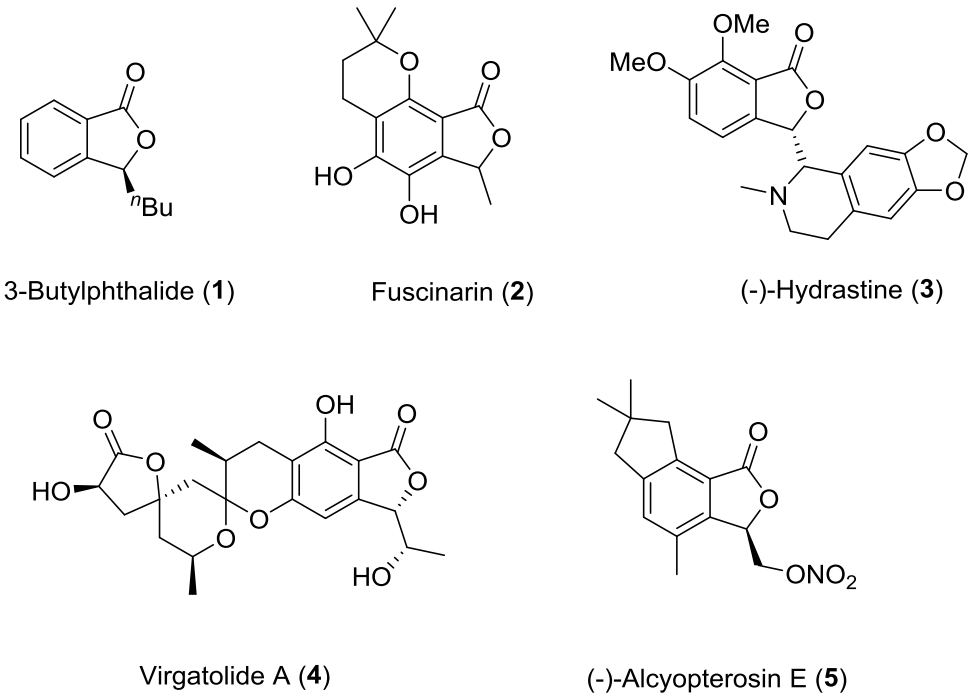


Fig. 1: Some of the examples of chiral phthalides

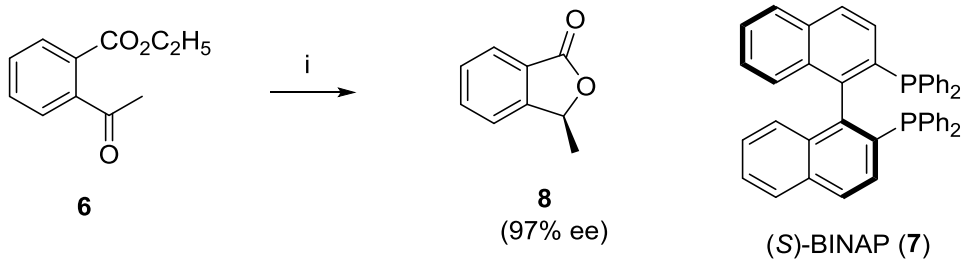
Fuscinarin (**2**) is a potent human CCR5 antagonist, used effectively for blocking HIV entry into host cells.[3] (-)-Hydrastine (**3**) is active at the opioid receptor.[4] In addition, it possesses antipaclitaxel-resistant human ovarian cancer activity through c-Jun kinasemediated apoptosis and is in phase I clinical trials.[5] Both Virgatolide A (**4**) and (-)-Alcyopterosin E (**5**) show cytotoxic activity against HeLa cells.[6] Due to the biological importance of 3-substituted phthalides **1-5** (**Fig. 1**), their molecular architectures have become a platform for new synthetic methodology development.[7]

2.1.2 Review of Literature

Literature search revealed that there are various methods available for the synthesis of 3-substituted phthalide derivatives, which are described below.

Noyori's approach (1990)[8]

Noyori *et al*. have described the synthesis of chiral phthalide ((*S*)-3-methyl isobenzo furan-1(3H)-one) **8** *via* asymmetric hydrogenation of ethyl o-acetylbenzoate **6** in ethanol with 0.4 mol% of the (*S*)-BINAP(**7**)-Ru catalyst at 100 atm H_2 pressure in 97% ee and 97% yield (**Scheme 1**).



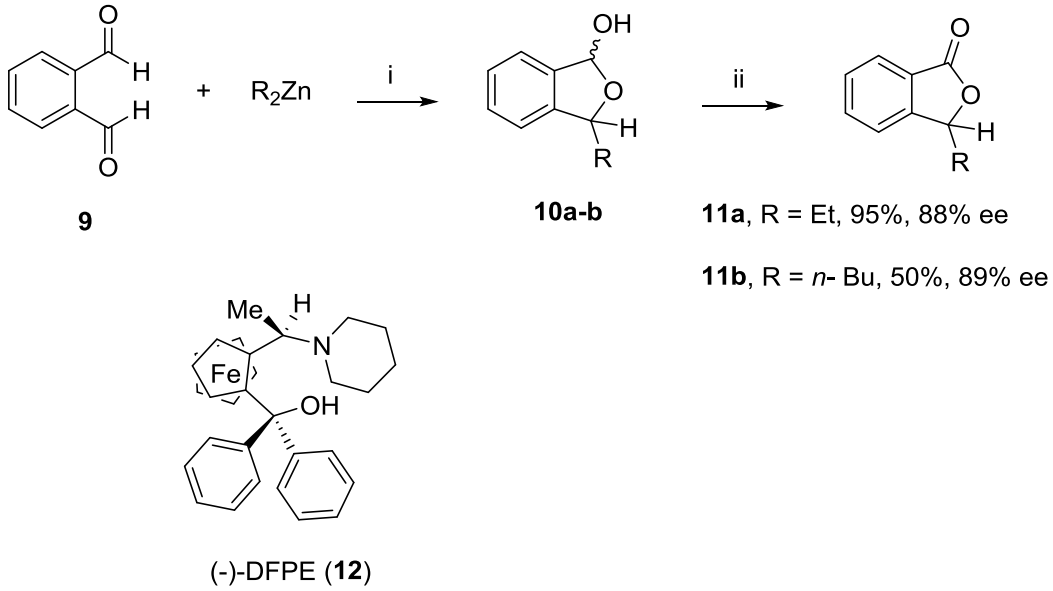
6 **8** (97% ee) (*S*)-BINAP (**7**)

Scheme 1: (i) $Ru(OCOCH_3)_2$[(*S*)-BINAP] (0.4 mol%), H_2 (100 atm), EtOH, 0.5N HCl, 35 °C, 165 h, 97%.

Butsugan's approach (1992)[9]

Butsugan *et al.* have reported the synthesis of optically active 3-ethyl- and 3-*n*-butylphthalides using enantioselective addition of dialkylzinc reagents. Thus, *o*-phthalaldehyde **9** was subjected to asymmetric addition of dialkyl reagents, catalyzed

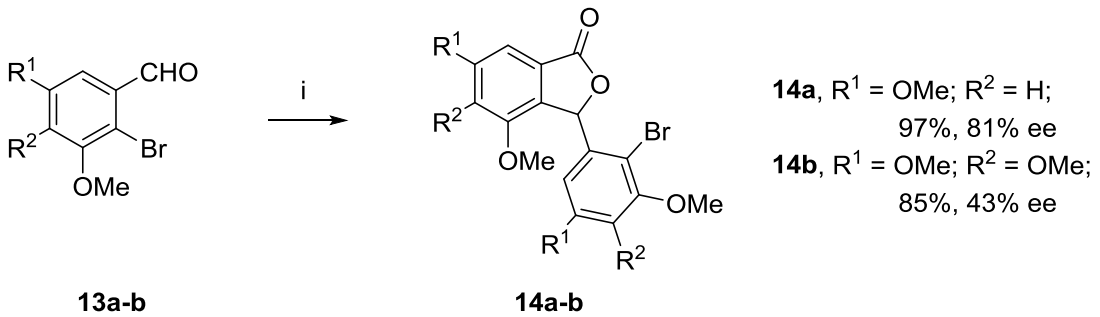
by chiral 1,2-disubstituted ferrocenyl amino alcohol **12**, followed by oxidation of the resulting lactols **10a-b** to provide phthalides **11a-b** in 88-89% ee (**Scheme 2**).



Scheme 2: (i) (-)-DFPE (**12**) (5 mol%), 25 °C, 1-3 h, (ii) Ag_2O, 0 °C.

Lin's approach (2002)[10]

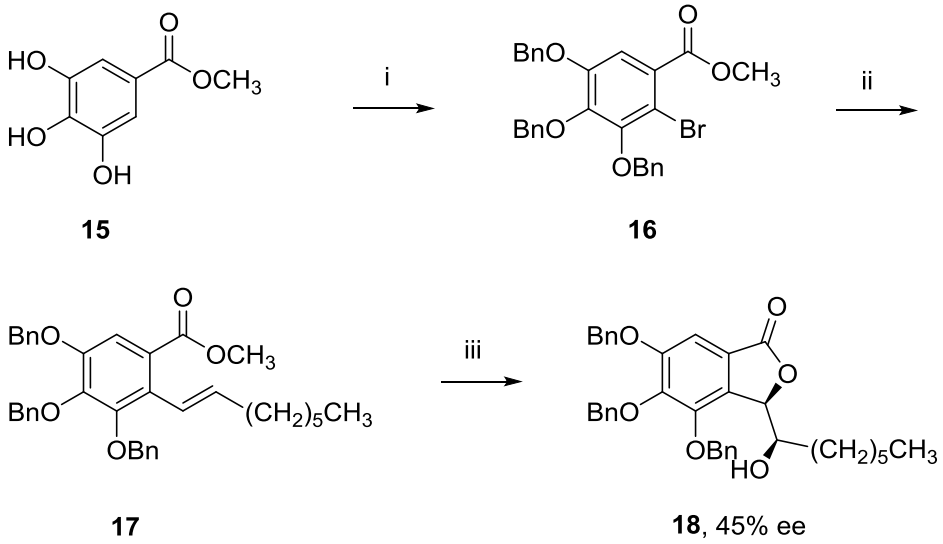
Ni-catalyzed tandem homo addition of *o*-bromoaldehydes **13a-b** *via in situ* cyclization was developed in presence of (*S*)-BINAP (**7**) and Zn that provided optically pure phthalides **14a-b** in good yields with moderate enantiomeric excess (**Scheme 3**).



Scheme 3: (i) $NiCl_2(PPh_3)_2$ (0.2 equiv). (*S*)-BINAP (**7**), Zn, toluene, 90 °C.

Mori's approach (2003)[11]

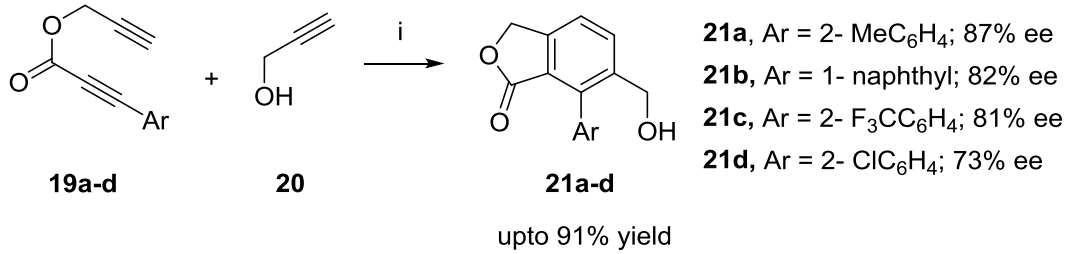
Mori *et al.* have used Sharpless asymmetric dihydroxylation as the key reaction. Thus, commercially available methyl 3,4,5-trihydroxybenzoate **15** was benzylated completely and subjected to bromination with NBS to afford bromo compound **16** in 96% yield. The bromo compound **16** was subjected to Miyaura-Suzuki coupling with (*E*)-1-octeneboronic acid to give olefin **17.** Asymmetric dihydroxylation of olefin **17** with AD-mix-β proceeded to furnish phthalide **18** in 54% yield with 45% ee (**Scheme 4**).



Scheme 4: (i) (a) BnBr, K_2CO_3, 96%; (b) NBS, DMF, 96%; (ii) (*E*)-$CH_3(CH_2)_5CH{=}CHB(OH)_2$, $Pd(PPh_3)_4$, K_2CO_3, C_6H_6:EtOH (5:1), 71%; (iii) AD-mix-β, $CH_3SO_2NH_2$, *tert*-BuOH:H_2O (1:1), 54%.

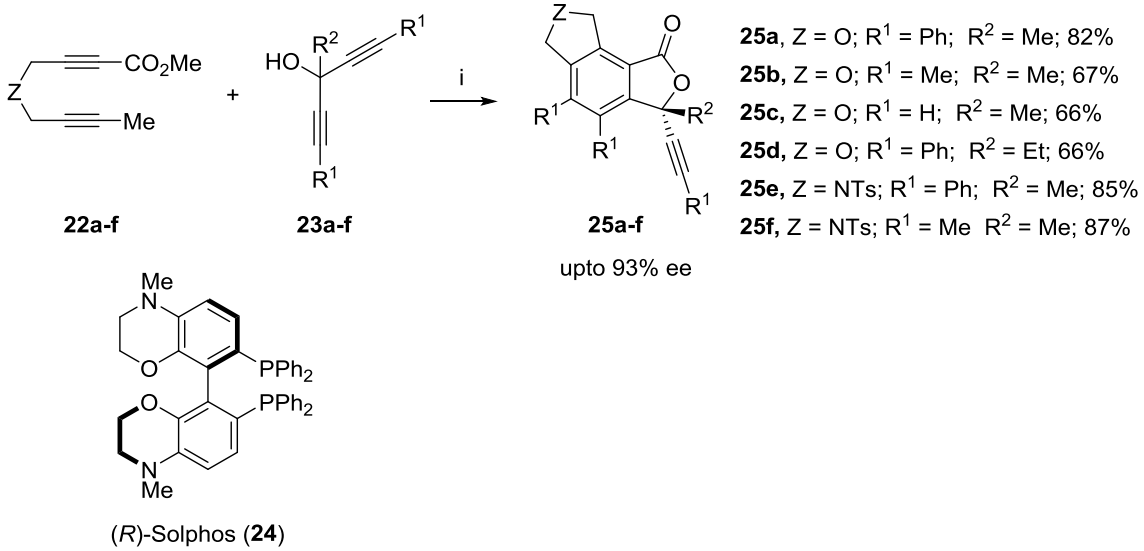
Tanaka's approach (2004)[12]

Tanaka *et al.* have described the enantioselective synthesis of axially chiral phthalides by the cationic [$Rh^I(H_8$-BINAP)] complex-catalyzed alkyne cyclotrimerization. The reaction of aryl-substituted 1,6-diyne **19a-d** with terminal monoyne **20** in the presence of the cationic complex [$Rh^I(H_8$-BINAP)] provided axially chiral phthalides **21a-d** in high yields with moderate enantioselectivity (**Scheme 5**).



Scheme 5: (i) 5% [Rh{(*S*)-H_8-BINAP}]BF_4 (1 mol%), CH_2Cl_2, 25 °C, 3 h.

Same authors have developed a cationic rhodium(I)/Solphos (**24**) complex-catalyzed asymmetric one-pot transesterification followed by [2+2+2] cycloaddition of 1,6-diyne esters **22a-f** with tertiary propargylic alcohols **23a-f** leading to enantioenriched tricyclic 3,3-disubstituted phthalides **25a-f** in good yields (66-87%) with moderate enantioselectivity (**Scheme 6**).

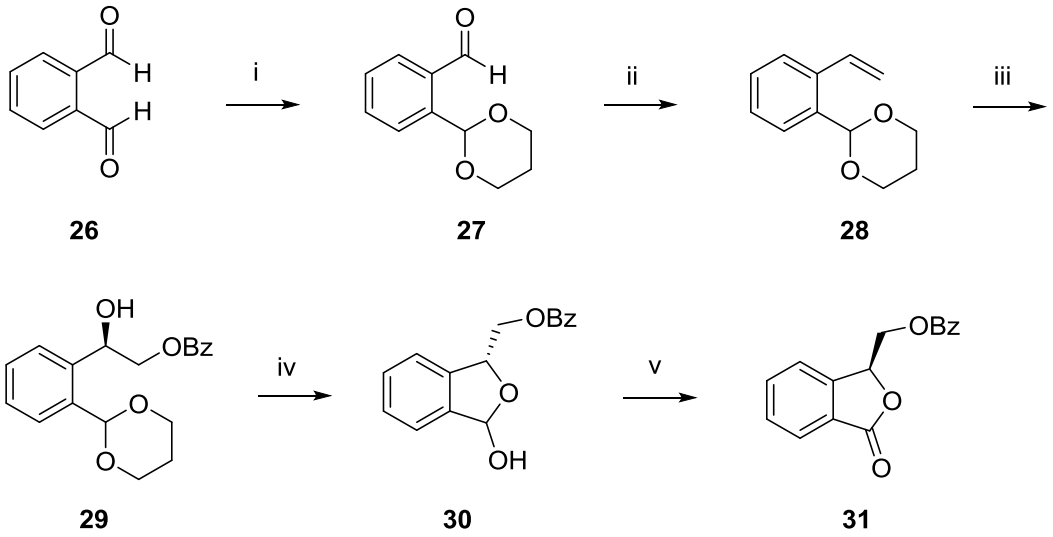


Scheme 6: (i) 5% [Rh(cod)$_2$]BF_4/(*R*)-Solphos (**24**) (1 mol%), CH_2Cl_2, 25 °C, 1-3 h.

Vaccher's approach (2005)[13]

Vaccher *et al*. have reported the synthesis of 3-benzoyloxy methylisobenzofuranone **30** using Sharpless asymmetric dihydroxylation as the key step. Thus, phthalaldehyde **26** was firstly protected using propane-1,3-diol to give the benzaldehyde derivative

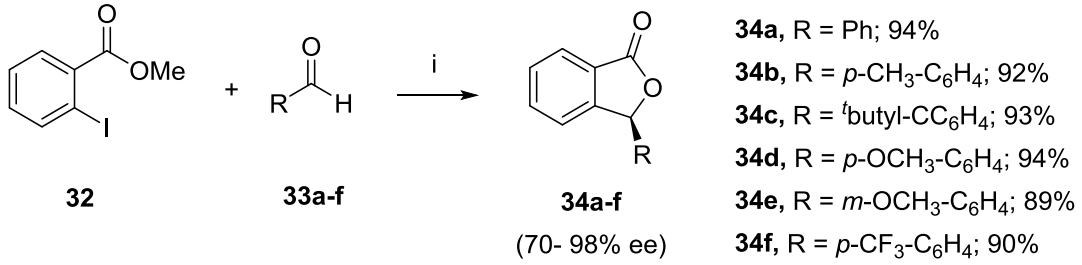
27, which was subjected to Wittig reaction to afford the styrene derivative **28**. Asymmetric dihydroxylation using AD-mix-β gave diol, which was selectively protected with benzoyl chloride to afford compound **29** with a free secondary hydroxyl group. Removal of the acetal from **29** in acidic medium gave benzo[c]furan **30,** which was converted to phthalide **31** in 50% yield using $RuCl_3$-$NaIO_4$ combination as oxidant (**Scheme 7**).



Scheme 7: (i) *p*-TSA, propan-1,3-diol, toluene, 5 h, 82%; (ii) *tert*-BuOK, $CH_3(C_6H_5)_3PBr$, toluene, 3 h, 78%; (iii) (a) AD-mix-β, *tert*-BuOH: H_2O (1:1), 12 h, 72%; (b) BzCl, $(C_2H_5)_3N$, toluene, 5 h, 78%; (iv) *p*-TSA, acetone, H_2O, 1 h, 82%; (v) $NaIO_4$, $RuCl_3$, CH_3CN, EtOAc, H_2O, 50%.

Cheng's approach (2007)[14]

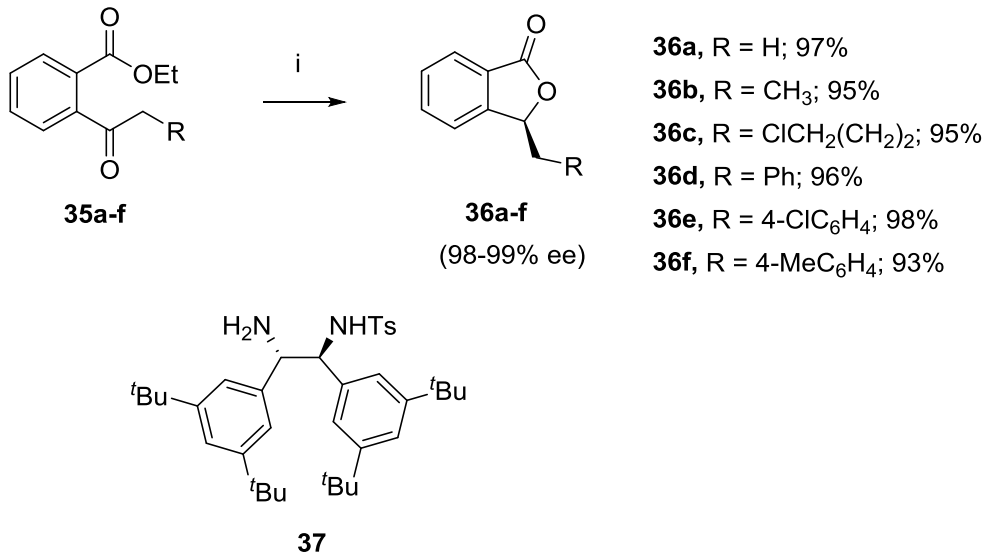
Cheng *et al.* have reported Co-bidentate phosphine complex-catalyzed synthesis of phthalides **34a-f**. Thus, methyl 2-iodobenzoates **32** underwent cyclization reactions with various aromatic aldehydes **33a–f** in the presence of [CoI_2(dppe)] (5 mol%) and Zn powder in dry THF at 75 ºC for 24 h to give the corresponding phthalide derivatives **34a-f** in 89-94% yields with 70-98% ee (**Scheme 8**).



Scheme 8: (i) $[CoI_2(dppe)]$ (5 mol%), Zn, THF, 75 °C, 24 h.

Xu's approach (2009)[15]

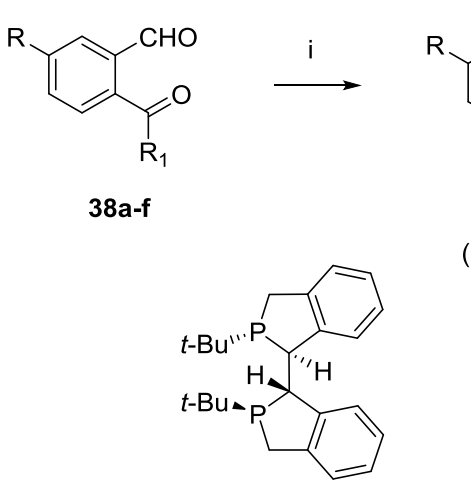
Xu *et al.* have reported a new diamine ligand **37** for asymmetric transfer hydrogenation (ATH) to synthesize 3-substituted phthalides. The reductive cyclization of 2-acylaryl carboxylates **35a-f** *via* the new $[RuCl_2(p\text{-cymene})]_2$/**37**-catalyzed ATH and subsequent *in situ* lactonization under aqueous conditions proceeded to give a variety of 3-substituted phthalides **36a-f** in high yields (93-97%) with high ee (98-99%) (**Scheme 9**).



Scheme 9: (i) $[RuCl_2(p\text{-cymene})]_2$/ligand **37** (1 mol%), HCO_2Na, H_2O/CH_2Cl_2, 40 °C, 24 h.

Dong's approach (2009)[16]

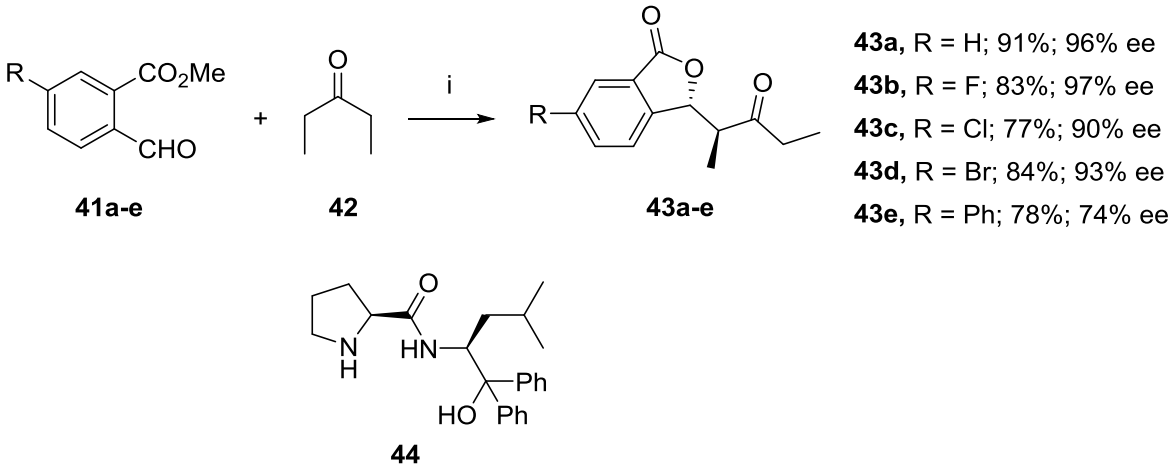
Dong *et al.* have employed $[Rh(cod)Cl]_2$-catalyzed hydroacylation of ketones **38a-f** in presence of duanphos **40** (10 mol%), and $AgNO_3$ (10 mol%) to give chiral phthalides **39a-f** in 81-94% yields with 92-98% ee (**Scheme 10**).



Scheme 10: (i) $[Rh(cod)Cl]_2$ (10 mol%), Duanphos (**40**) (10 mol%), $AgNO_3$ (10 mol%), toluene, 90 °C, 3-3.5 h.

Wang's approach (2010)[17]

Wang *et al*. have described the synthesis of chiral phthalides **43a-e** by employing organocatalytic asymmetric aldol-lactonization as the key reaction.

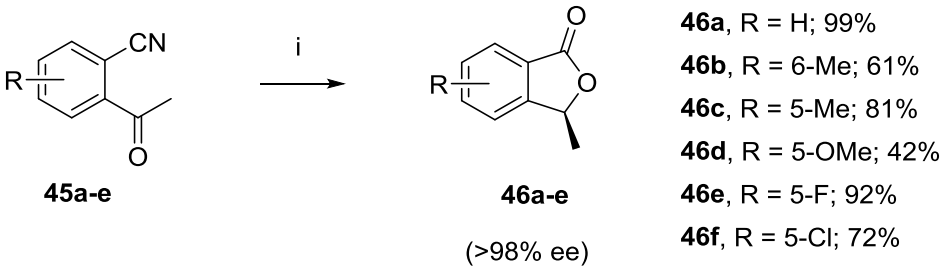


Scheme 11: (i) (a) *L*-prolinamide alcohol **44** (2.5 mol%), $PhCO_2H$ (2.5 mol%), -40 °C, 12-24 h; (b) K_2CO_3, acetone:methanol (10:1), 15 min.

Thus, 2-formylbenzoic esters **41a-e** and ketone **42** were subjected to aldol reaction using *L*-prolinamide alcohol **44** as catalyst and $PhCO_2H$ as an additive to give 3-substituted phthalides **43a-e** in 77-91% yield with 74-97% ee (**Scheme 11**).

Gotor's approach (2012)[18]

Gotor *et al.* have described Baker's yeast-catalyzed bioreduction of 2-acetylbenzo nitriles **45a-e** followed by aqueous HCl that provided access to enantiopure (*S*)-3-methylphthalides **46a-e** in moderate to excellent yields (42-99%) with >98% ee (**Scheme 12**).



Scheme 12: (i) (a) Baker's yeast, glucose, H_2O, 25 °C, 16-72 h; (b) HCl 1M, 25 °C, 48 h.

2.1.3 Present Work

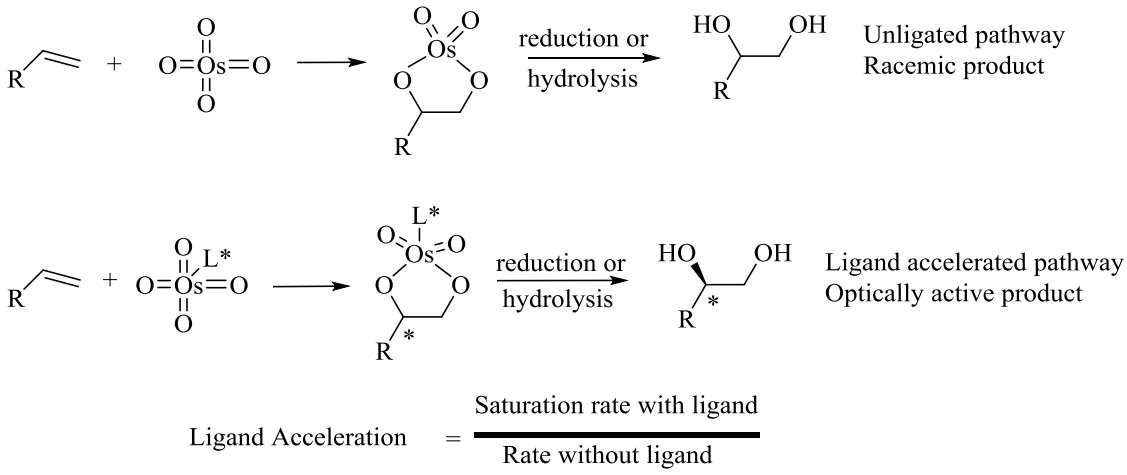
2.1.3.1 Objective

As can be seen from the above discussion, the reported methods for the synthesis of 3-substituted phthalides employ either chiral auxiliaries or expensive organometallic reagents in stoichiometric amounts and often lack in broad substrate scope and higher reaction stereoselectivity; only a few are atom economical. In this context, a more practical and efficient synthesis of functionalized 3-substituted phthalide derivatives is highly desirable. In this section, we present a single-step oxidative cyclization of cyanocinnamates and styrenic substrates that affords 3-substituted phthalides in high yields *via* synergetic acceleration of CN and osmate ester groups present in proximity

positions. Since the method involves asymmetric dihydroxylation (ADH) as the key chiral inducing reaction, a brief account of ADH is described below.

2.1.3.2 Asymmetric Dihydroxylation (ADH)

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).[19] Among all these reactions, Sharpless catalytic Asymmetric Dihydroxylation (ADH) 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*-*syn*-diols from activated as well as unactivated olefins.[20] In 1936, Criegee *et al.*[21] found that addition of pyridine or any other tertiary amine to osmylation of olefins, accelerated the rate of reaction considerably. A major breakthrough had occurred in the field of asymmetric oxidation when Sharpless *et al*.[20b] demonstrated that asymmetric induction could be achieved when chiral amines were added to OsO_4-mediated asymmetric oxidation of olefins.



Scheme 13: Mechanism of OsO_4-catalyzed dihydroxylation of olefin

Among the various ligands screened best results were obtained with ligands which were representatives of the cinchona alkaloid family, namely dihydroquinidine (DHQD) and dihydroquinine (DHQ) (**Scheme** 13).[22]

To improve the %ee of the chiral diol, the second catalytic cycle of ADH should be avoided and this was achieved by employing the $K_3Fe(CN)_6$ as reoxidant and using biphasic conditions **(Fig. 2)**.

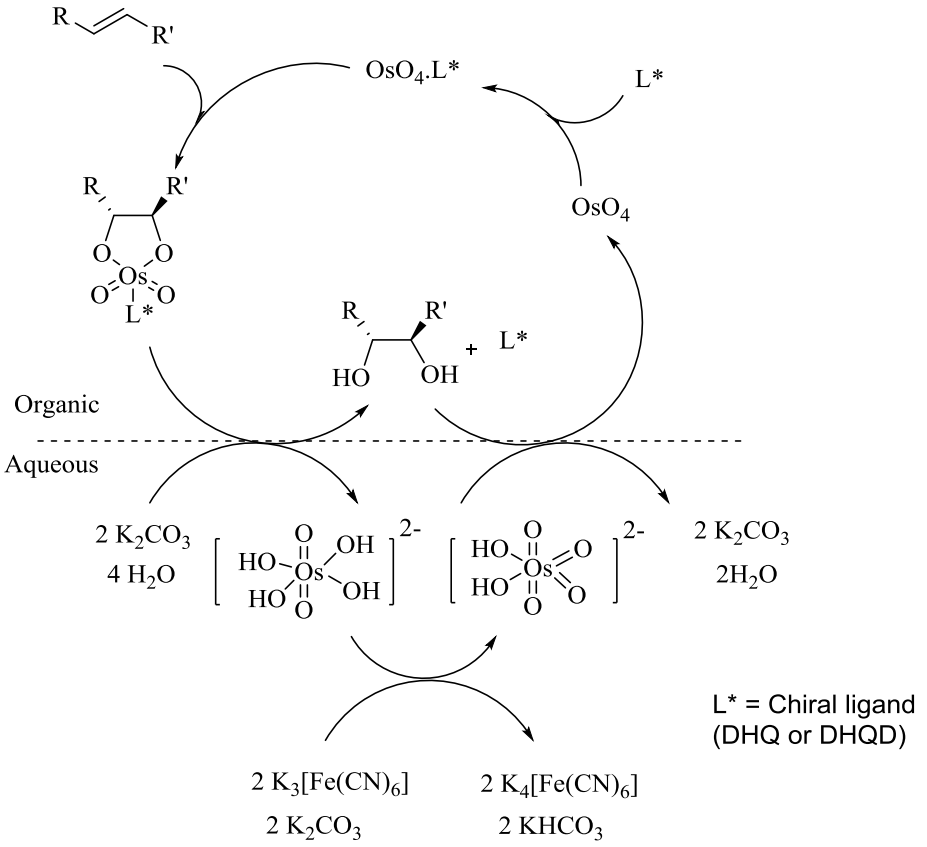


Fig. 2: Catalytic cycle for ADH using $K_3Fe(CN)_6$ as co-oxidant

These conditions helped in protecting the organic osmate-(VI) monoglycolate ester 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) reoxidized and recycled into the catalytic cycle. Further improvement in the ADH was realized by the addition of methyl sulfonamide ($MeSO_2NH_2$) to the

reaction mixture. It also helps to accelerate the hydrolysis, 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 ADH reaction, Sharpless and coworkers 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 or DHQD ethers of phthalazine-1,4-diol have proven to be the best for obtaining high enantioselective diols[23] **(Fig. 3)**.

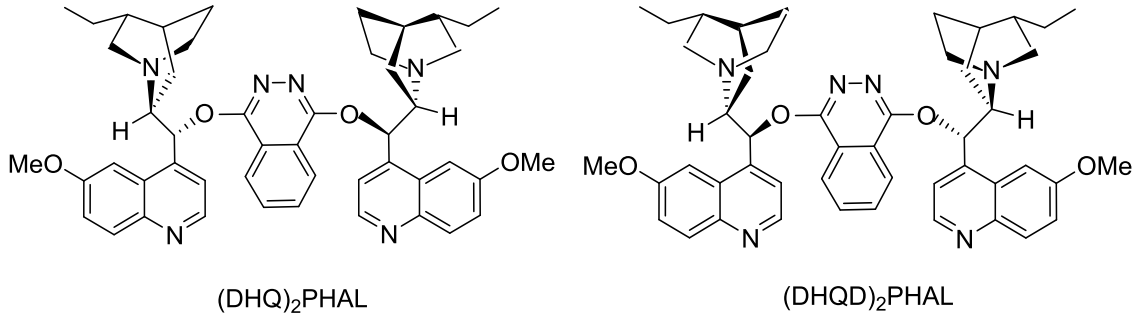


Fig. 3: Ligands for asymmetric dihydroxylation reaction

Studies have demonstrated the importance of enzyme-like binding pocket of the dimeric cinchona alkaloid for high enantioselectivity of the chiral diols.[24] Sharpless *et al*.[20] have shown that the facial selectivity for both ligands $(DHQ)_2PHAL$ and $(DHQD)_2PHAL$ 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.

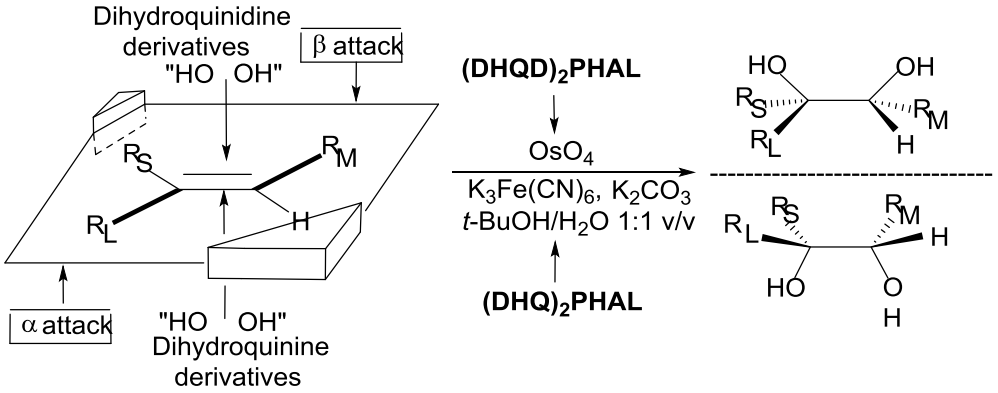
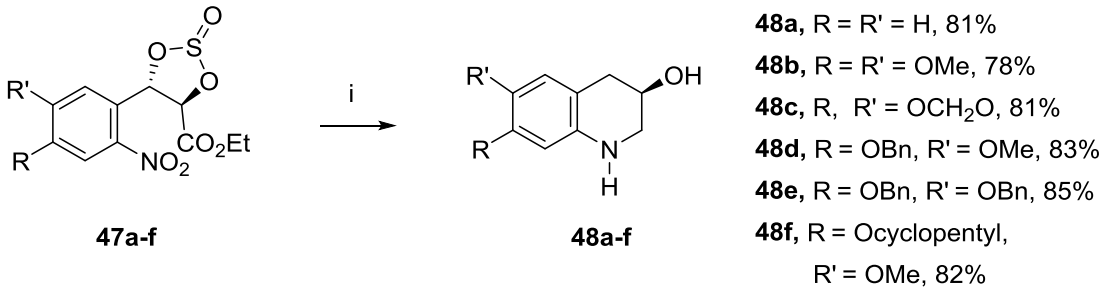


Fig. 4: Enantioselectivity mnemonic scheme

2.1.4 Results and Discussion

Recently, Sudalai *et al.* have developed a novel protocol of ADH process followed by Co-catalyzed "one-pot" reductive cyclization ($CoCl_2$-$NaBH_4$) of *nitro* cyclic sulfites **47a-f** that led to the construction of 3-substituted tetrahydroquinolin-3-ols **48a-f** (**Scheme 14**).[25]



47a-f **48a-f**

48a, R = R' = H, 81%
48b, R = R' = OMe, 78%
48c, R, R' = OCH_2O, 81%
48d, R = OBn, R' = OMe, 83%
48e, R = OBn, R' = OBn, 85%
48f, R = Ocyclopentyl, R' = OMe, 82%

Scheme 14: (i) $CoCl_2 \cdot 6H_2O$ (1 mol%), $NaBH_4$ (4 equiv), EtOH, 0 to 25 °C.

In analogy with this, we reasoned that subjecting *cyano* cyclic sulfites to the same reaction conditions should afford synthetically useful benzazepines.[26] In order to synthesize cyano cyclic sulfite, we visualized a strategy in which cyano diol **52** could

serve as a starting material to *cyano* cyclic sulfite. Accordingly, *o*-cyanobenzaldehyde **49** was subjected to Wittig olefination to afford (*E*)-α,β- unsaturated ester **50a** in 88% yield (**Scheme 15**). The formation of cinnamate ester **50a** was confirmed from its ^{1}H NMR spectrum, which showed two doublets at δ 6.60 (d, *J* = 16 Hz, 1H) and 7.96 (d, *J* = 16 Hz, 1H) confirming the presence of α- and β- CH olefin protons of -C**H**=C**H**CO_2Et. This was further ascertained by the presence of characteristic carbon signals at δ 122.9 and 139.0 corresponding to α- and β- carbon signal of olefinic ester -**C**H=**C**HCO_2Et in its ^{13}C NMR spectrum (**Fig. 5**).

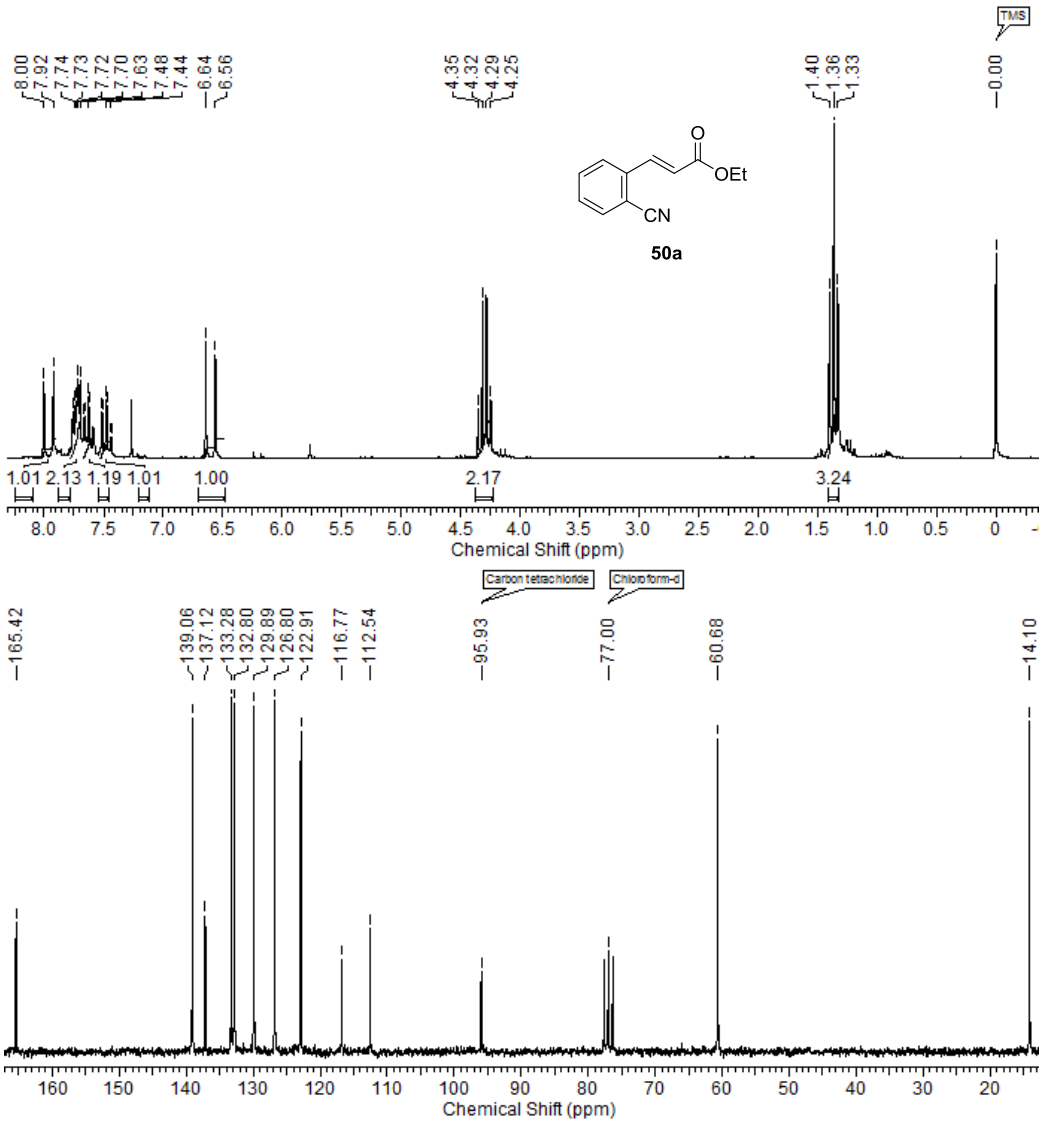
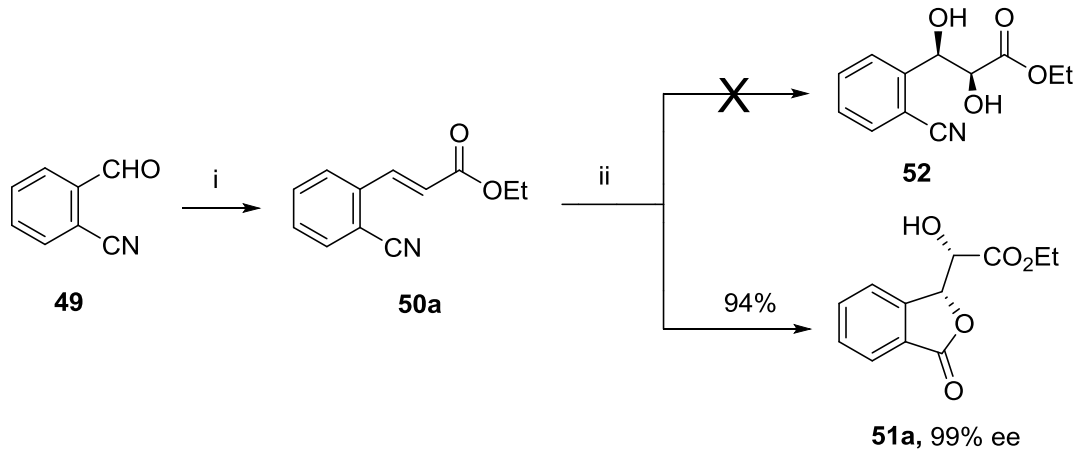


Fig. 5: ^{1}H and ^{13}C NMR spectra of *o*-cyanocinnamate **50a**

In order to validate our hypothesis, ethyl 2-cyanocinnamate **50a** was subjected to Sharpless asymmetric dihydroxylation using $(DHQD)_2PHAL$ as the chiral ligand, with THF as co-solvent for better solubility. Surprisingly, the reaction took altogether a different course to give the cyclized chiral phthalide **51a** exclusively with 99% ee in a single step, instead of the expected cyano diol **52** (**Scheme 15**). This unexpected transformation is characterized by high rate, excellent yield and enantioselectivity, which is attributed to coordination assistance provided by the neighboring CN group to osmate ester, leading to faster hydrolysis of osmate ester in the catalytic cycle. Incidentally, the rate of ADH process for electron-deficient *o*- substituted cinnamates is generally reported to be sluggish (48 h to 7 days) giving products invariably with moderate enantioselectivity (88% ee).[27]



Scheme 15: (i) $Ph_3P{=}CHCO_2Et$, benzene, reflux,12 h, 88%; (ii) $K_2[OsO_2(OH)_4]$ (0.1 mol%), $(DHQD)_2PHAL$ (0.5 mol%), $K_3Fe(CN)_6$ (3 equiv), K_2CO_3 (3 equiv), *tert*-BuOH:THF:H_2O (1:1:2), 25 °C, 7 h.

The formation of chiral phthalide **51a** was confirmed by the presence of a doublet of doublet at δ 4.66 (dd, J = 2.1, 5.8 Hz) integrating for one methine proton (-C**H**-OH) and a doublet at δ 5.79 (d, J = 2.1 Hz, 1H) integrating for benzylic proton (-C**H**-O-CO-) in its ^{1}H NMR spectrum. It was further substantiated by the carbon signals displaying at δ 70.3 and 80.3 in its ^{13}C NMR spectrum, corresponding to carbons

attached to hydroxyl and lactone groups respectively (**Fig. 6**). The IR spectrum of phthalide **51a** displayed two strong absorption bands at 1720 and 1768 cm^{-1} due to the presence of ester and γ-lactone carbonyl groups respectively.

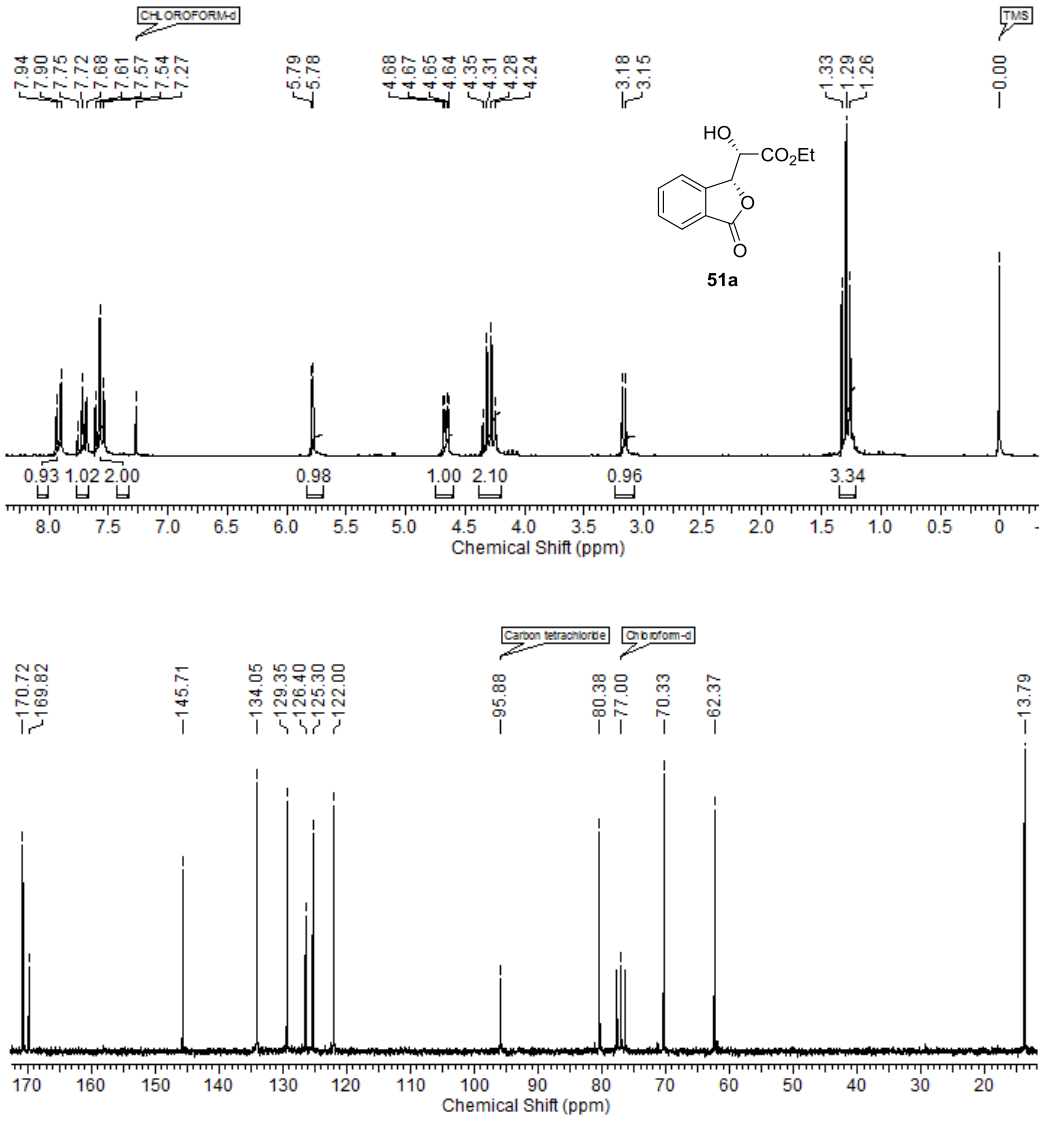


Fig. 6: ^{1}H and ^{13}C NMR spectra of phthalide **51a**

Further, the formation of chiral phthalide **51a** was confirmed by COSY and mass spectra (**Fig. 7**).

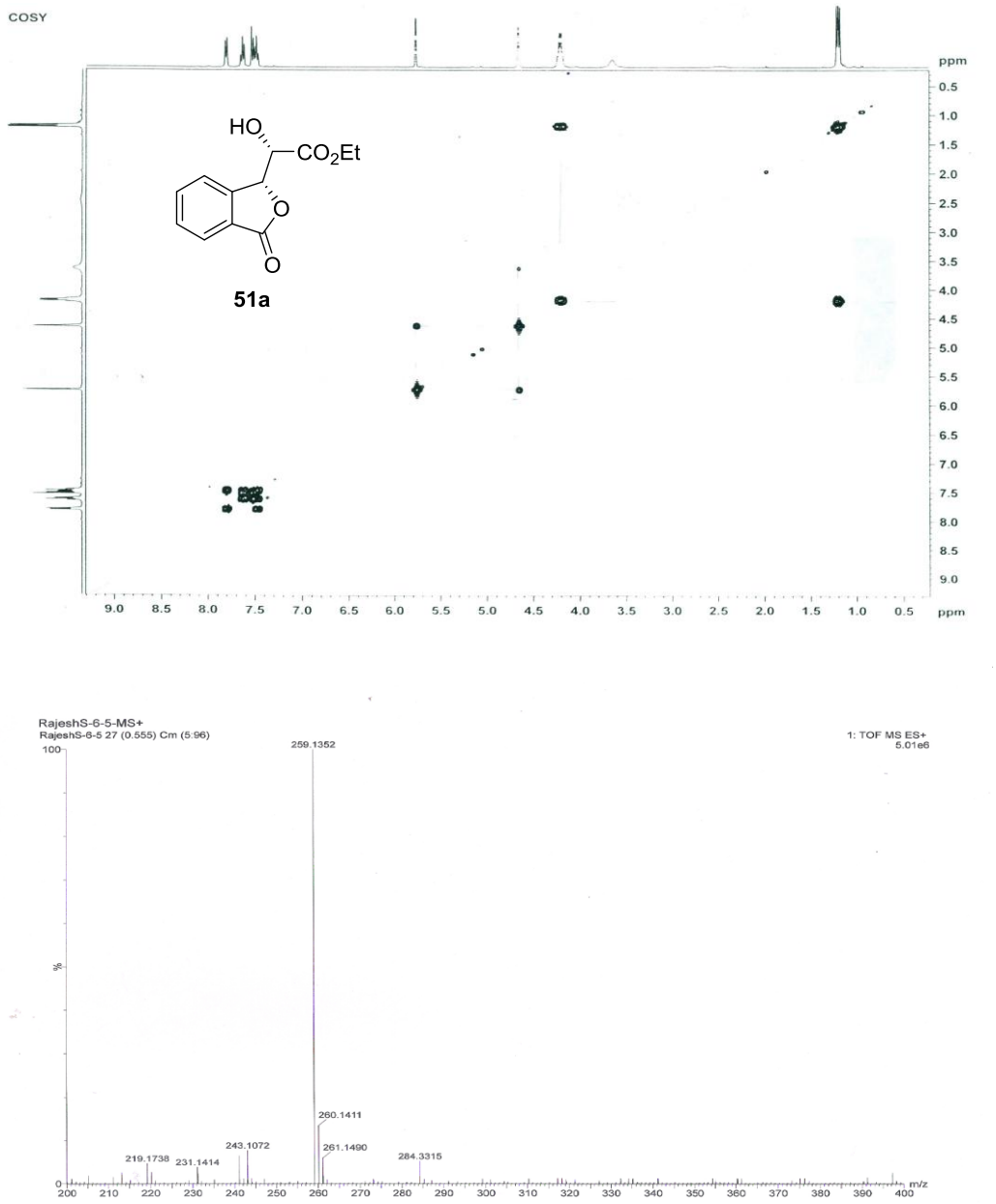
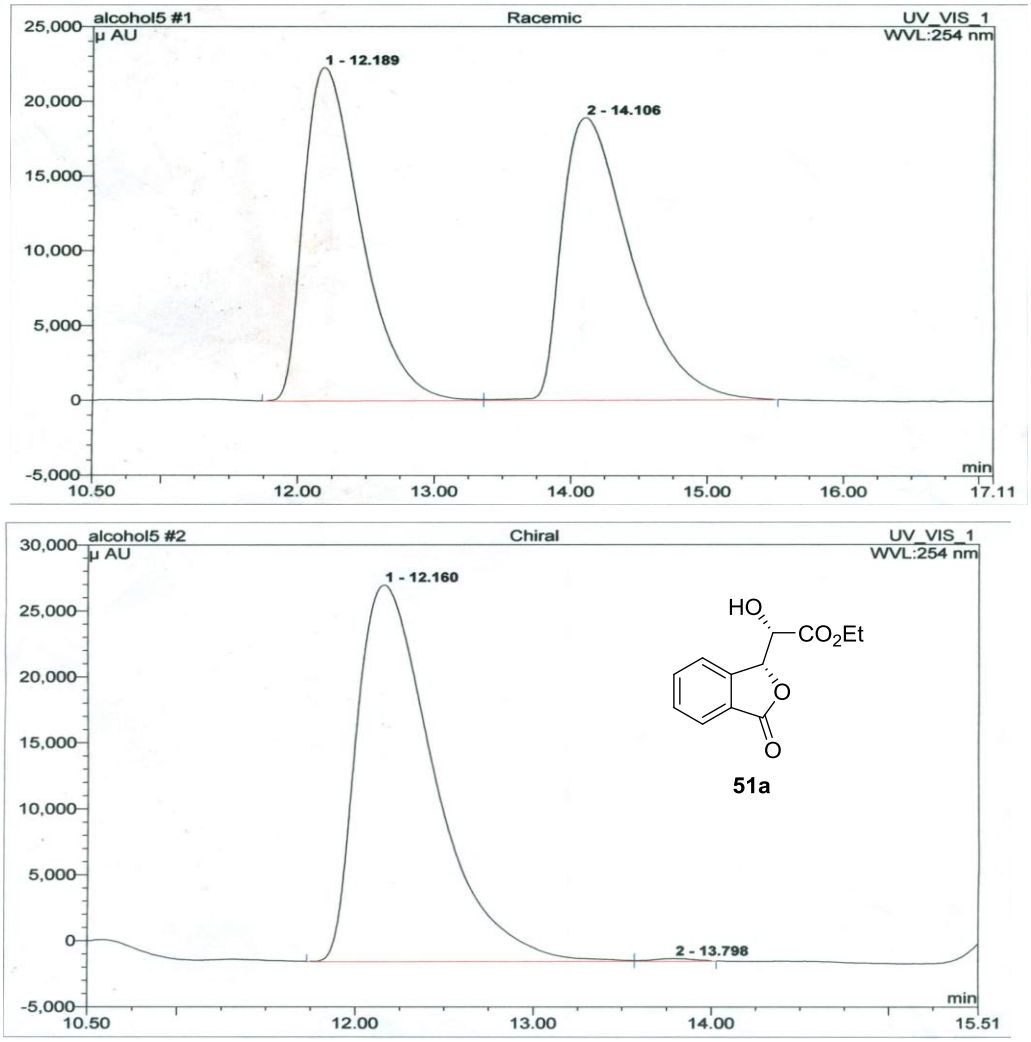


Fig. 7: COSY and mass spectra of phthalide **51a**

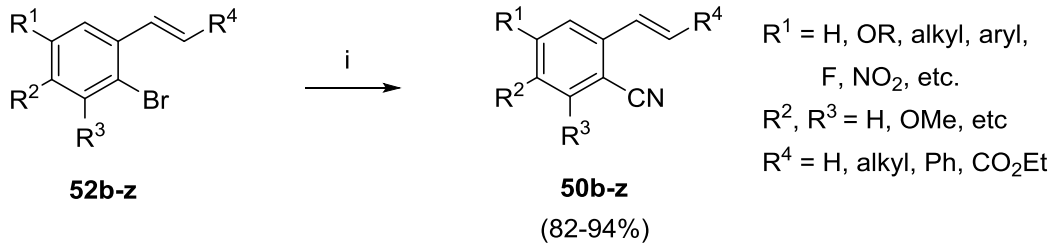
The enantiomeric excess (99% ee) of chiral phthalide **51a** was determined from chiral HPLC analysis (Chiracel OJ-H, *n*-hexane/*i*PrOH, 90:10, 0.5 mL/min) retention time 12.16 (99.65%) and 13.80 (0.35%) (**Fig. 8**).



No	Ret. Time min	Height µ AU	Area µ AU* min	Rel. Area %	Amount	Type
1	12.16	28495.075	14410.126	99.65	n. a.	BMB
2	13.80	189.662	50.523	0.35	n. a.	BMB

Fig. 8: HPLC chromatogram of phtalide **51a**

Encouraged by the result, we became interested in the scope of the reaction by subjecting other *o*-cyanoalkenes **50b-z**. *o*-Cyanoalkenes **50b-z** were prepared in 76-84% yield, in a single step, starting from the corresponding *o*-bromo alkene derivatives **52b-z** *via* Rosenmund-von Braun reaction with CuCN (3 equiv) and DMF as solvent at 150 °C (**Scheme 16**). *o*-Bromo alkene derivatives **52b-z** were in turn prepared in high yields *via* Wittig or Julia olefination of the respective benzaldehydes by following the literature procedures.[28]

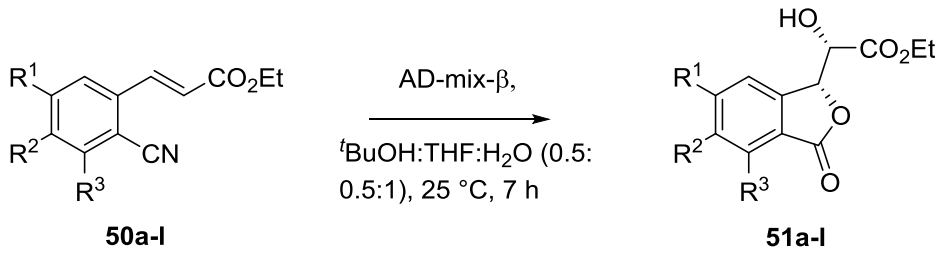


Scheme 16: (i) CuCN (3 equiv), DMF reflux, 18 h.

When subjected to Os-catalyzed asymmetric dihydroxylation (ADH) using $(DHQD)_2PHAL$ as the chiral ligand, *o*-cyano *α*,*β*-unsaturated esters **50b-l** gave the corresponding chiral phthalide derivatives **51b-l** in 92-95% yields with excellent enantioselectivities (98-99% ee). Results of such studies are presented in **Table 1**. As can be seen, in every case, the reaction proceeded rapidly within 7 h giving the desired phthalides **51b-l** in excellent yields and ees (up to 99%) at ambient conditions. For instance, substrates having halogen (entry i), highly electron-rich (entry f) or electron-deficient (entry j) groups on the aromatic nucleus including 2-naphthyl system (entry l) underwent this oxidative cyclization smoothly affording the corresponding phthalides **51b-l** with excellent yields in one step.

Subsequently, we extended our study to include other styrene derivatives **50m-z** bearing different functionalities on the aromatic nucleus as well as on the *β*-position of the styrene derivative side chain (R^4) (**Table 2**). It was again found that this ADH process displayed a wide substrate scope tolerating alkyl, aryl, alkoxy, fluoro or tosyl groups. Excellent yields of phthalide derivatives **51m-z** (93-95%) and enantio-selectivities (97-99%ee) were indeed realized in all the cases studied. The stereochemistry of the cyclized products was assigned according to the previously established absolute configuration of phthalides as well as in accordance with ADH rules.[29]

Table 1: CN-assisted Os-catalyzed oxidative cyclization of cyano ethyl cinnamates

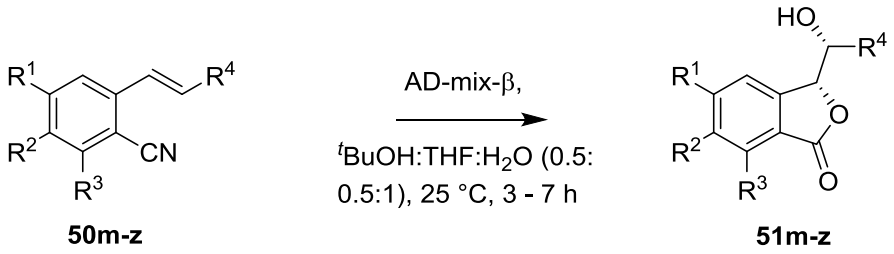


50a-l **51a-l**

entry	R^1	R^2	R^3	yield (%)[a]	ee (%)[b,c]
a	H	H	H	94	99
b	OMe	H	H	95	99
c	OMe	OMe	H	94	99
d	H	OMe	OMe	94	99
e	OMe	H	OMe	94	99
f	OMe	OMe	OMe	92	99
g	OTs	OMe	H	93	99
h	OBn	OMe	H	94	99
i	F	H	H	94	99
j	NO_2	H	H	93	99
k	-O-CH_2-O-		H	95	98
l	(*E*)-ethyl 3-(1-cyanonaphthalen-2-yl)acrylate			94	98

[a] Isolated yield after column chromatographic purification. [b]ee determined by chiral HPLC analysis. [c]ee determined by Mosher's ester analysis for entries h, i & l.

Table 2: CN-assisted Os-catalyzed oxidative cyclization of cyano styrene derivatives



50m-z **51m-z**

entry	R^1	R^2	R^3	R^4	yield (%)[a]	ee (%)[b,c,d]
m	H	H	H	H	95	99
n	OMe	H	H	H	95	99
o	OMe	OMe	H	H	93	99
p	H	OMe	OMe	H	94	99
q	OMe	H	OMe	H	94	99
r	OMe	OMe	OMe	H	92	99
s	OTs	OMe	H	H	93	99
t	OBn	OMe	H	H	94	99
u	F	H	H	H	94	99
v	-O-CH_2-O-		H	H	93	99
w	H	H	H	C_3H_7	93	97
x	OMe	OMe	H	CH_2OTBS	94	97
y	OMe	OMe	H	Ph	94	97
z	OMe	OMe	H	*n*-C_6H_{13}	92	98

[a] Isolated yield after column chromatographic purification. [b]ee determined by chiral HPLC analysis. [c]ee determined by Mosher's ester analysis for entries t, u, w-z.[d]reaction completed in 3 h for m-v.

The formation of phthalide derivatives **51m-z** were confirmed by ^1H and ^{13}C NMR spectroscopy. For example: The formation of phthalide **51m** was confirmed by the

appearance of typical signals at δ 3.90 (d, *J* = 11.8 Hz, 1H), 4.14 (d, *J* = 11.8 Hz, 1H) and 5.54-5.59 (m, 1H) due to diastereotopic methylene protons and benzylic proton respectively, in its ^{1}H NMR spectrum. Further, its ^{13}C NMR spectrum showed characteristic signals at δ 61.7, 81.5 and 170.6 corresponding to carbons attached to oxygen atoms and carbonyl carbon of lactone respectively (**Fig. 9**). Its IR spectrum displayed a strong absorption at 1756 cm^{-1} indicating the presence of lactone carbonyl group.

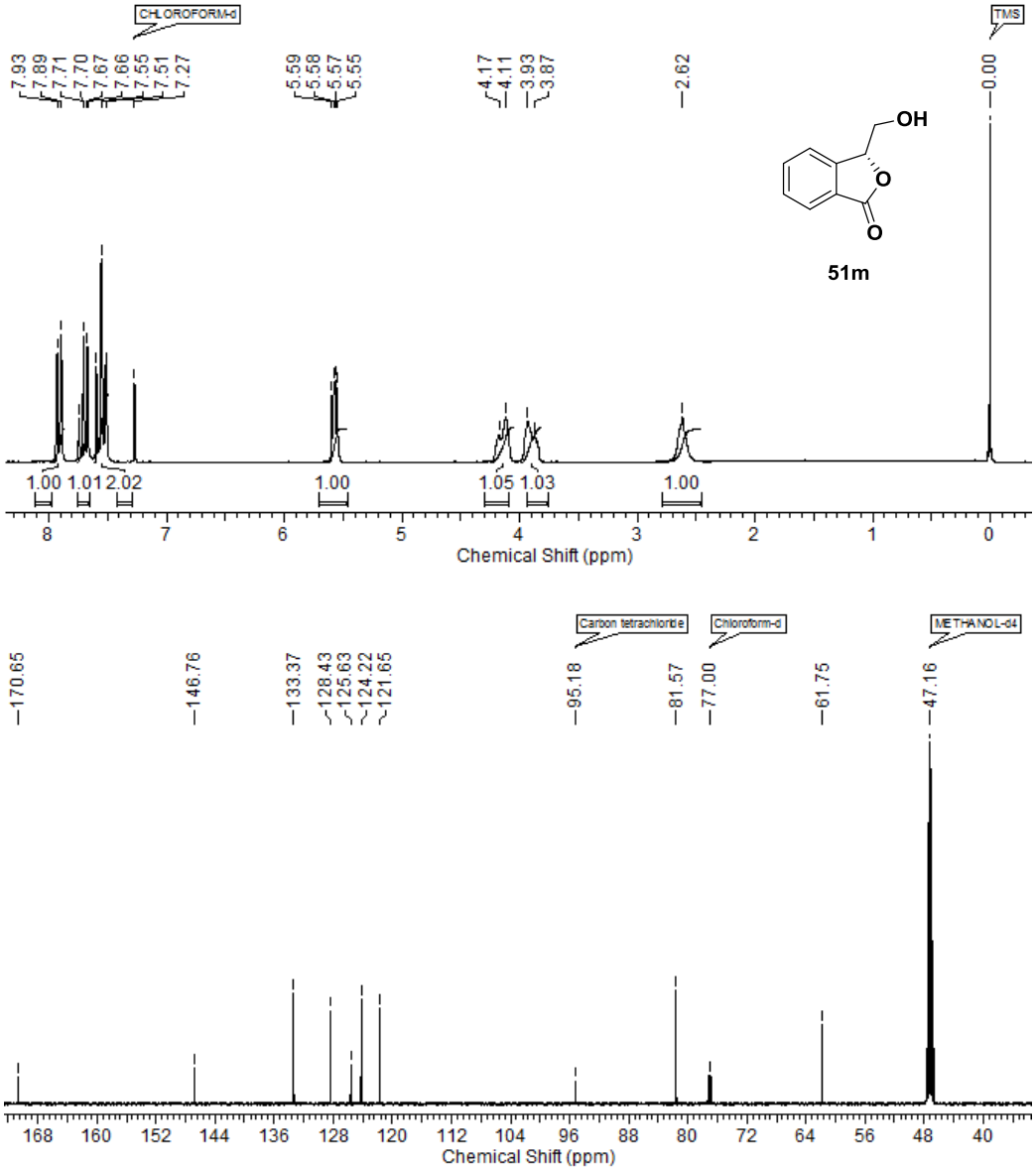
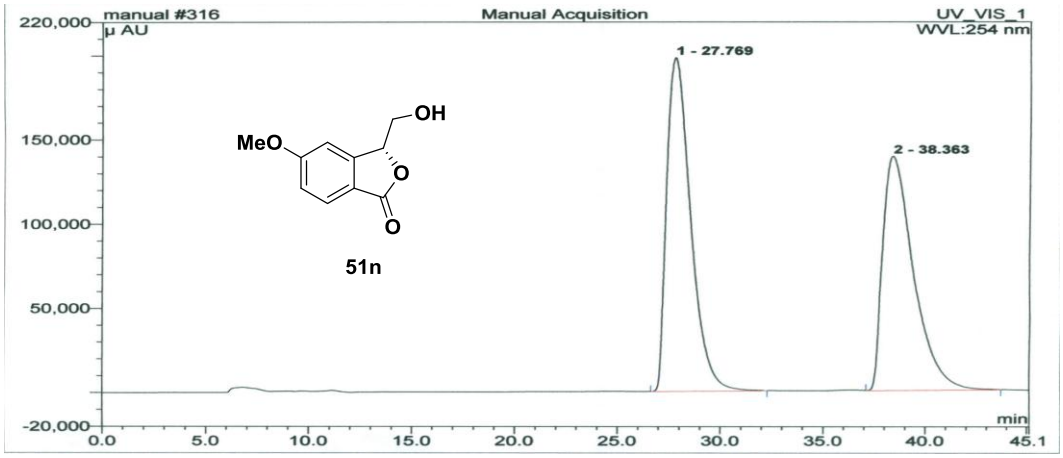
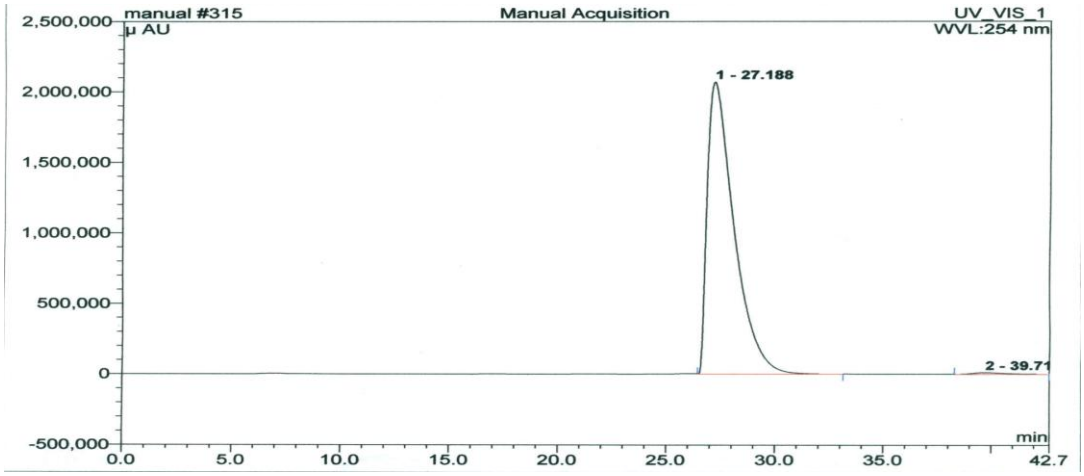


Fig. 9: ^{1}H and ^{13}C NMR spectra of phthalide **51m**

The enantiomeric excess of chiral phthalides **51m-z** was determined by chiral HPLC analysis and also by Mosher's ester analysis. For example: The enantiomeric excess of chiral phthalide **51n** was determined as 99% from chiral HPLC analysis (Chiracel OJ-H, *n*-hexane/*i*PrOH, 90:10, 1 mL/min) retention time 27.19 min (99.36%) and 39.72 min (0.64%) (**Fig. 10**).





No	Ret. Time min	Height µ AU	Area µ AU* min	Rel. Area %	Amount	Type
1	27.19	2066521.172	26133.285	99.36	n. a.	BMB
2	39.72	10209.799	168.309	0.64	n. a.	BMB

Fig. 10: HPLC chromatogram of phtalide **51n**

The higher reactivity of cyano substituted cinnamates and styrenes **50a-z** were substantiated by carrying out several competitive experiments involving 1:1 molar

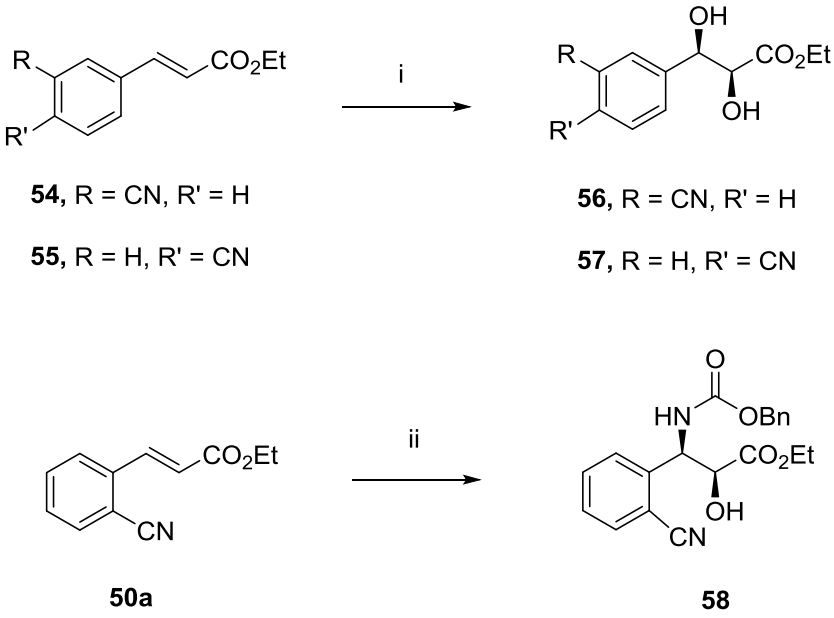
equivalents of aromatic substrates with or without cyano substitution; the results of which are presented in **Table 3**. The results clearly showed that cyano substituted substrates reacted almost 10-12 times faster than the one without cyano substitution, giving excellent yields of phthalides (92-94%).

Table 3: Competitive experiments[a]

entry	substrates	product	yield (%)[b,c]
1	**50a** + ethyl cinnamate	**51a**	92
2	**50e** + 3,5-dimethoxyethyl cinnamate	**51e**	93
3	**50m** + styrene	**51m**	94
4	**50o** + 3,5-dimethoxystyrene	**51o**	92
5	**50r** + 3,4,5-trimethoxystyrene	**51r**	92

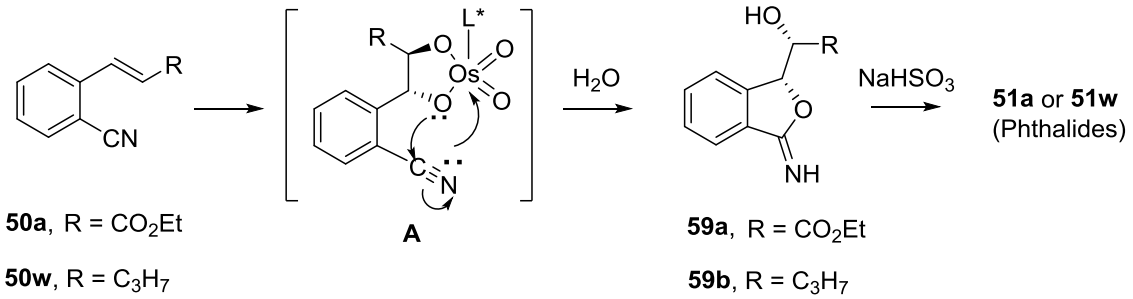
[a]1:1 molar equivalents of aromatics substrates with and without cyano substitution (1 mmol each) AD-mix-β (0.5 mol%), *tert*-BuOH:THF:H_2O (0.5: 0.5:1), 25 °C, 3 h for entries 3-5 and 7 h for entries 1 and 2. [b]Isolated yields after column chromatographic purification. [c]5-8 % of 1, 2-diol from the corresponding substrates without cyano substitution was indeed isolated.

In order to account for the mechanistic course of the reaction, the following experiments (**Scheme 17**) were conducted: (i) AD-mix-β of substrates **54** & **55** for 36 h gave the corresponding cyanodiols **56** & **57** respectively, indicating that both CN and C=C groups must be positioned in proximity for CN coordination assistance to take place; (ii) asymmetric *aminohydroxylation*[30] of **50a** gave the expected amino alcohol **58** (64%) with no phthalide formation, suggesting that coordination of CN onto imino osmate ester is thermodynamically less favorable, due to its reduced Lewis acid character;[31] (iii) in addition, imino intermediates **59a-b** were indeed isolated in 20% yield during the AD-mix-β of substrates **50a** and **50 w**.



Scheme 17: (i) $K_2[OsO_2(OH)_4]$ (0.1 mol%), $(DHQD)_2PHAL$ (0.5 mol%), $K_3Fe(CN)_6$ (3 equiv), K_2CO_3 (3 equiv), *tert*-BuOH:THF:H_2O (1:1:2), 36 h, 94-95%; (ii) $BnOCONH_2$, aq. NaOH, $K_2[OsO_2(OH)_4]$, $(DHQD)_2PHAL$, *tert*-BuOCl, ^nPrOH:H_2O, 3 h, 64%, dr = 6:1.

This study clearly excludes the hydrolysis of CN to CO_2H followed by cyclization route, (iv) addition of benzonitrile as an external source of CN-assistance resulted in no rate enhancement for the ADH process.



Scheme 18: Mechanism of CN-assisted Os-catalyzed oxidative cyclization

On the basis of these results, a mechanistic model is presented in species **A** in which a synergism involving co-ordination of CN to Os(VI) and concurrent attack of osmate ester onto electropositive carbon of CN is shown that probably helps to accelerate the hydrolysis of osmate ester. These results indicate the 5-*exo*-*dig* type cyclization[32] to

afford iminoesters **59a-b**, which finally lead to the formation of phthalides **51a** or **51w** (**Scheme 18).** The formation of iminoester **59b** was clearly demonstrated by IR data of the nonsubstituted imidate C=NH band (at 1687 cm^{-1}) and the phthalide (**51w**) C=O band (at 1752 cm^{-1}) (**Fig. 11**).

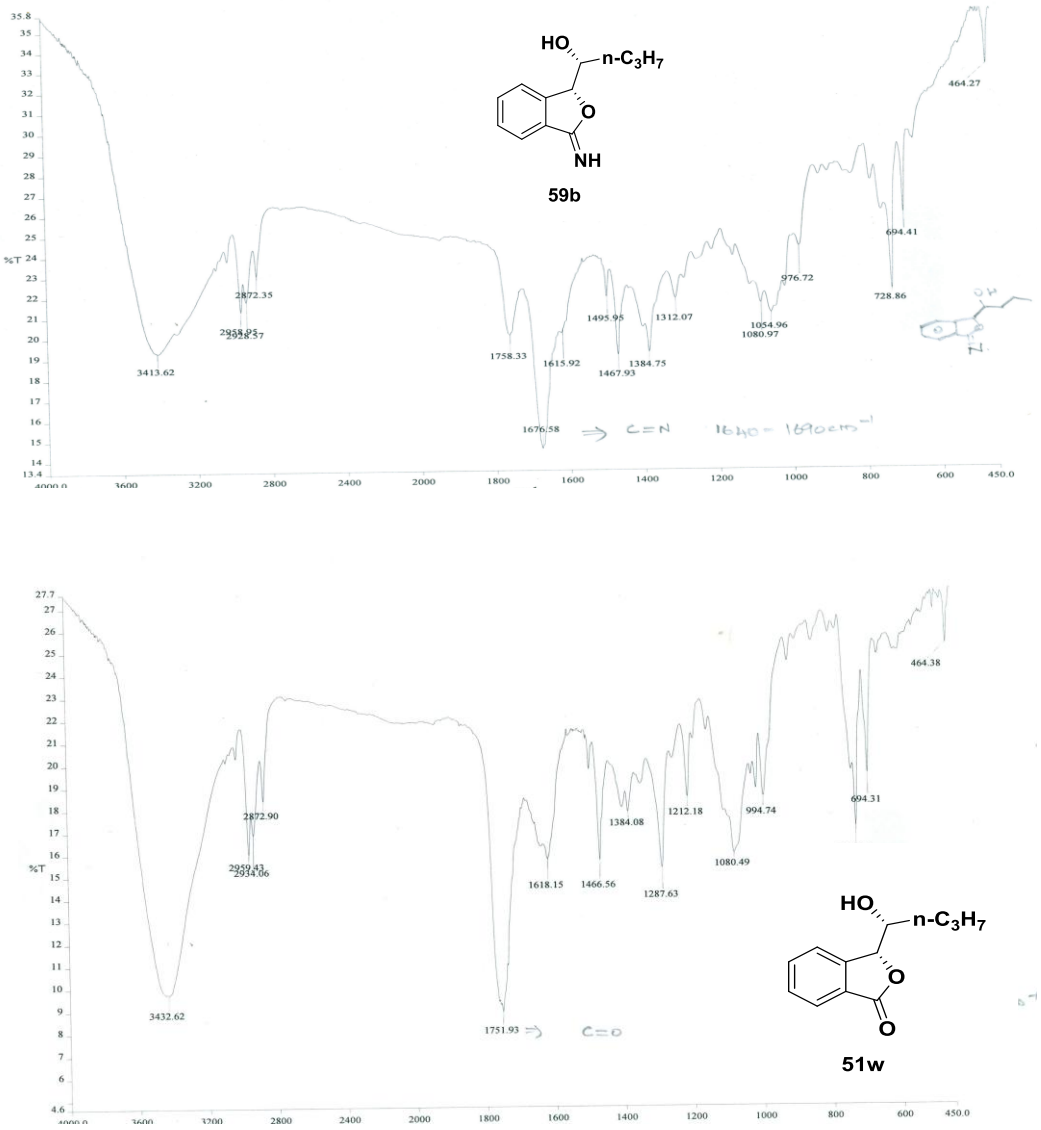


Fig. 11: IR spectra of iminoester **59b** and phthalide **51w**

2.1.5 Conclusion

A novel CN-assisted oxidative cyclization for the synthesis of a wide variety of 3-substituted phthalides and their structural analogues *via* ADH process of cyano cinnamates and styrene derivatives has been demonstrated. This reaction is highly practical in the sense that the products were obtained in excellent yields and optical purities (97-99% ee) and shows broad substrate scope and good functional group tolerance. The synergism shown by CN and osmate groups in proximity helps to enhance the rate of this reaction. We believe that this oxidative intramolecular cyclization ADH strategy should find wide applications in the total synthesis of other bioactive phthalide frameworks.

2.1.6 Experimental Section

Typical experimental procedure for the preparation of (*E*)-Ethyl 3-(2-cyano phenyl)acrylate (50a)

To a stirred solution of 2-cyanobenzaldehyde **49** (2 g, 7.9 mmol) in benzene (40 mL), $Ph_3P{=}CHCO_2Et$ (3.1 g, 8.6 mmol) was added. It was then refluxed for 12 h under N_2 atmosphere. After the completion of reaction, benzene was distilled out to give the crude product. Chromatographic purification of crude product [silica gel (230-400 mesh) and pet. ether:EtOAC (90:10) as eluent] afforded the cyano cinnamate **50a** (1.4 g).

Yield: 88%**,** colorless solid; **mp:** 60-62 ºC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 765, 784, 1031, 1184, 1318, 1447, 1480, 1594, 1640, 1712, 2225, 2938, 2983; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.36 (t, *J* = 7.3 Hz, 3H), 4.31 (q, *J* = 7.3 Hz, 2H), 6.60 (d, *J* = 16 Hz, 1H), 7.47 (td, *J* = 1.4, 7.5 Hz, 1H), 7.62 (td, *J* = 1.4, 7.5 Hz, 1H), 7.70-7.76 (m, 2H), 7.96 (d, *J* = 16 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.1, 60.7, 112.5, 116.8, 122.9, 126.8, 129.9, 132.8, 133.3, 137.1, 139.1, 165.4; **Analysis**: $C_{12}H_{11}NO_2$ requires C, 71.63; H, 5.51; N, 6.96; found: C, 71.59; H, 5.56; N, 6.93%.

Typical experimental procedure for the preparation of (*S*)-Ethyl 2-((*R*)-1,3-di hydro-1-oxoisobenzofuran-3-yl)-2-hydroxyacetate (51a)

A 50 mL RB flask was charged with $K_3Fe(CN)_6$ (1 g, 3 mmol), K_2CO_3 (414 mg, 3 mmol), *tert*-BuOH (2.5 mL), THF (2.5 mL) and H_2O (5 mL) and stirred for 10 min. Subsequently, $(DHQD)_2PHAL$ (8 mg, 1 mol%) and $K_2OsO_4{\cdot}2H_2O$ (2 mg, 0.5 mol%) were added and the stirring continued for additional 30 min. To this reaction mixture, (*E*)-ethyl 3-(2-cyanophenyl)acrylate (**50a**) (200 mg, 1 mmol) was added and allowed to stir for 7 h at 25 ºC. After completion of reaction (as monitored by TLC), sodium bisulphite (1 g) was added slowly at 0 ºC. The organic layer was separated, aqueous layer extracted with ethyl acetate (3 x 10 ml) and the combined organic layers washed with brine (15 mL), dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to yield the crude product. Flash column chromatographic purification [silica gel (230-400 mesh) and pet. ether:EtOAc (7:3) as an eluent] gave **51a** (221 mg).

Yield: 94%; colorless solid; **mp:** 146-148 ºC; $[\alpha]^{D}_{25}$ -95.65 (*c* 1.24, $CHCl_3$); 99% ee from chiral HPLC analysis (Chiracel OJ-H, *n*-hexane/*i*PrOH, 90:10, 0.5 mL/min) retention time 12.16 (99.65%) and 13.80 (0.35%); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 762, 856, 968, 1027, 1068, 1078, 1210, 1298, 1349, 1467, 1611, 1652, 1720, 1768, 2924, 3014, 3440; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.29 (t, *J* = 7.1 Hz, 3H), 3.16 (d, *J* = 5.7 Hz, 1H), 4.30 (q, *J* = 7.1 Hz, 2H), 4.66 (dd, *J* = 2.1, 5.8 Hz, 1H), 5.79 (d, *J* = 2.1 Hz, 1H), 7.57 (t, *J* = 7.0 Hz, 2H), 7.68-7.75 (m, 1H), 7.90-7.93 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.7, 62.3, 70.3, 80.3, 122.0, 125.3, 126.4, 129.3, 134.0, 145.7, 169.8, 170.7; **HRMS** (ESI) *m/z* calcd for $C_{12}H_{12}O_5$ $[M + Na]^+$: 259.1357, found: 259.1352; **Analysis**: $C_{12}H_{12}O_5$ requires C, 61.01; H, 5.12; found: C, 60.96; H, 5.07%.

General experimental procedure for the preparation of *o*-cyanoalkenes (50b-z)

o-Bromo alkenes **52b-z** (1 mmol) were taken in dry DMF (10 mL) and CuCN (3 mmol) was added and the mixture refluxed under N_2 for 18 h (monitored by TLC). It was then cooled to 25 ºC, and then diluted with water (30 mL) and EtOAc (25 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine and dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give crude products which were purified by column chromatography [silica gel (230-400 mesh) and pet. ether:EtOAc (7:3) as an eluent] to give *o*-cyanoalkenes **50b-z** in 76-84% yield.

(*E*)-Ethyl 3-(2-cyano-5-methoxyphenyl)acrylate (50b)

Yield: 86%**,** colorless solid; **mp:** 130-132 ºC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 728, 868, 1026, 1256, 1490, 1594, 1607, 1640, 1712, 2228, 2853, 2923 3023; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.36 (t, *J* = 7 Hz, 3H), 3.90 (s, 3H), 4.29 (q, *J* = 7 Hz, 2H), 6.56 (d, *J* = 16 Hz, 1H), 6.97 (dd, *J* = 2.5, 8.7 Hz, 1H), 7.15 (d, *J* = 2.5 Hz, 1H), 7.63 (d, *J* = 8.7 Hz, 1H), 7.90 (d, *J* = 16 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.2, 55.6, 60.8, 104.6, 112.1, 116.0, 117.3, 123.1, 135.0, 139.4, 162.7, 165.5; **Analysis**: $C_{13}H_{13}NO_3$ requires C, 67.52; H, 5.67; N, 6.06; found: C, 67.49; H, 5.61; N, 6.01%.

(*E*)-Ethyl 3-(2-cyano-4,5-dimethoxyphenyl)acrylate (50c)

Yield: 87%, colorless solid; **mp:** 159-161 ºC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 761, 848, 1094, 1149, 1204, 1326, 1462, 1571, 1594, 1709, 2222, 2984, 3018; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.36 (t, *J* = 7.3 Hz, 3H), 3.94 (s, 3H), 3.97 (s, 3H), 4.29 (q, *J* = 7.3 Hz, 2H), 6.47 (d, *J* = 16 Hz, 1H), 7.07 (s, 1H), 7.11 (s, 1H), 7.89 (d, *J* = 16 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.2, 55.9, 56.2, 60.7, 105.2, 108.2, 114.2, 117.1, 120.7, 131.5, 139.2, 150.5, 152.6, 165.8; **Analysis**: $C_{14}H_{15}NO_4$ requires C, 64.36; H, 5.79; N, 5.36; found: C, 64.32; H, 5.71; N, 5.34%.

(*E*)-Ethyl 3-(2-cyano-3,4-dimethoxyphenyl)acrylate (50d)

Yield: 88%**,** colorless solid; **mp:** 145-147 ºC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 758, 894, 1078, 1138, 1208, 1318, 1326, 1462, 1571, 1594, 1608, 1710, 2222, 2984, 3018; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.35 (t, *J* = 7.0 Hz, 3H), 3.93 (s, 3H), 4.03 (s, 3H), 4.27 (q, *J* = 7.0 Hz, 2H), 6.48 (d, *J* = 16 Hz, 1H), 7.10 (d, *J* = 8.6 Hz, 1H), 7.40 (d, *J* = 8.6 Hz, 1H), 7.83 (d, *J* = 16 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.3, 56.1, 60.6, 61.6, 107.9, 114.1, 116.4, 120.7, 122.9, 129.7, 139.2, 152.1, 153.5, 165.9; **Analysis**: $C_{14}H_{15}NO_4$ requires C, 64.36; H, 5.79; N, 5.36; found: C, 64.34; H, 5.71; N, 5.32%.

(*E*)-Ethyl 3-(2-cyano-3,5-dimethoxyphenyl)acrylate (50e)

Yield: 87%**,** colorless solid; **mp:** 119-122 ºC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 734, 876, 1069, 1128, 1208, 1326, 1326, 1478, 1568, 1594, 1608, 1712, 2228, 2958, 3082; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.36 (t, *J* = 7.1 Hz, 3H), 3.89 (s, 3H), 3.93 (s, 3H), 4.29 (q, *J* = 7.1 Hz, 2H), 6.47 (d, *J* = 2.1 Hz, 1H), 6.55 (d, *J* = 16 Hz, 1H), 6.73 (d, *J* = 2.1 Hz, 1H), 7.86 (d, *J* = 16 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.3, 55.7, 56.1, 60.8, 94.9, 96.1 99.4, 103.4, 114.8, 123.3, 139.6, 140.1, 163.4, 163.9, 165.6; **Analysis**: $C_{14}H_{15}NO_4$ requires C, 64.36; H, 5.79; N, 5.36; found: C, 64.32; H, 5.71; N, 5.34%.

(*E*)-Ethyl 3-(2-cyano-3,4,5-trimethoxyphenyl)acrylate (50f)

Yield: 88%**,** colorless solid; **mp:** 150-152 ºC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 669, 703, 749, 940, 1260, 1311, 1573, 1607, 1640, 1708, 2210, 2979, 3016; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.36 (t, *J* = 7.1 Hz, 3H), 3.90 (s, 3H), 3.96 (s, 3H), 4.06 (s, 3H), 4.28 (q, *J* = 7.1 Hz, 2H), 6.50 (d, *J* = 16 Hz, 1H), 6.91 (s, 1H), 7.84 (d, *J* = 16 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.3, 55.8, 60.3, 109.1, 115.4, 117.0, 118.5, 126.2, 142.5, 148.5, 151.1, 161.2; **Analysis**: $C_{15}H_{17}NO_5$ requires C, 61.85; H, 5.88; N, 4.81; found: C, 61.82; H, 5.79; N, 4.75%.

5-((*E*)-2-(Ethoxycarbonyl)vinyl)-4-cyano-2-methoxyphenyl 4-methylbenzene sulfonate (50g)

Yield: 87%, colorless solid; **mp:** 150-151 ºC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 742, 865, 1030, 1128, 1232, 1318, 1329, 1478, 1571, 1594, 1608, 1708, 2225, 2982, 3025; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.35 (t, *J* = 6.9 Hz, 3H), 2.48 (s, 3H), 3.73 (s, 3H), 4.30 (q, *J* = 6.9 Hz, 2H), 6.54 (d, *J* = 16 Hz, 1H), 7.09 (s, 1H), 7.35 (d, *J* = 8.5 Hz, 2H), 7.39 (s, 1H), 7.77 (d, *J* = 8.5 Hz, 2H), 7.91 (d, *J* = 16 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.2, 21.7, 56.0, 61.0, 104.5, 110.3, 116.0, 123.8, 128.3, 129.7, 132.6, 137.9, 138.4, 139.1, 145.8, 155.6, 165.2; **Analysis**: $C_{20}H_{19}NO_6S$ requires C, 59.84; H, 4.77; N, 3.49; found: C, 59.78; H, 4.69; N, 3.42%.

(*E*)-Ethyl 3-(5-(benzyloxy)-2-cyano-4-methoxyphenyl)acrylate (50h)

Yield: 86%**,** colorless solid; **mp:** 146-148 ºC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 738, 825, 1031, 1098, 1234, 1334, 1380, 1467, 1568, 1575, 1608, 1710, 2228, 2982, 3034; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.35 (t, *J* = 7.2 Hz, 3H), 3.93 (s, 3H), 4.28 (q, *J* = 7.3 Hz, 2H), 5.20 (s, 2H), 6.34 (d, *J* = 15.4 Hz, 1H), 7.08 (s, 2H), 7.34-7.43 (m, 5H), 7.84 (d, *J* = 15.4 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.3, 56.2, 60.8, 71.0, 105.5, 110.5, 114.7, 117.2, 120.9, 127.3, 128.8, 131.5, 135.4, 139.3, 151.1, 151.8, 165.9; **Analysis**: $C_{20}H_{19}NO_4$ requires C, 71.20; H, 5.68; N, 4.15; found: C, 71.14; H, 5.61; N, 4.09%.

(*E*)-Ethyl 3-(2-cyano-5-fluorophenyl)acrylate (50i)

Yield: 85%**,** colorless solid; **mp:** 72-74 ºC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 756, 828, 866, 981, 1030, 1186, 1226, 1276, 1325, 1370, 1480, 1574, 1603, 1640, 1693, 2984, 3012; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.36 (t, *J* = 7.2 Hz, 3H), 4.31 (q, *J* = 7.2 Hz, 2H), 6.58 (d, *J* = 15.9 Hz, 1H), 7.19 (td, *J* = 2.8, 8.4 Hz, 1H), 7.41 (dd, *J* = 2.6, 9.1 Hz, 1H), 7.74 (dd, *J* = 5.4, 8.4 Hz, 1H), 7.91 (d, *J* = 15.9 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.1, 60.9, 108.8, 133.9 (d, *J* = 23.6 Hz), 116.0, 117.6 (d, *J* = 23.6 Hz), 124.2, 135.7

(d, *J* = 9.8 Hz), 140.2 (d, *J* = 8.8 Hz), 164.5 (d, *J* = 257.7 Hz), 164.9; **Analysis**: $C_{12}H_{10}FNO_2$ requires C, 65.75; H, 4.60; N, 6.39; found: C, 65.68; H, 4.56; N, 6.36%.

(*E*)-Ethyl 3-(2-cyano-5-nitrophenyl)acrylate (50j)

Yield: 87%**,** colorless solid; **mp:** 105-107 ºC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 739, 830, 968, 1032, 1106, 1346, 1540, 1708, 2233, 2980, 3087; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.38 (t, *J* = 7.0 Hz, 3H), 4.33 (q, *J* = 7.0 Hz, 2H), 6.78 (d, *J* = 15.8 Hz, 1H), 7.95 (d, *J* = 2.0 Hz, 1H), 7.98 (d, *J* = 15.8 Hz, 1H), 8.33 (dd, *J* = 2.0, 8.4 Hz, 1H) 8.59 (d, *J* = 2.0 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 14.2, 61.3, 115.2, 117.8, 121.7, 124.1, 125.9, 134.7, 136.9, 139.5, 150.2, 164.8; **Analysis**: $C_{12}H_{10}N2O_4$ requires C, 58.54; H, 4.09; N, 11.38; found: C, 58.48; H, 4.02; N, 11.31%.

(*E*)-Ethyl 3-(5-cyanobenzo[d][1,3]dioxol-6-yl)acrylate (50k)

Yield: 86%, colorless solid; **mp:** 148-149 ºC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 728, 878, 1042, 1134, 1256, 1366, 1382, 1478, 1568, 1594, 1608, 1712, 2218, 2958, 3082; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.35 (t, *J* = 7 Hz, 3H), 4.28 (q, *J* = 7 Hz, 2H), 6.12 (s, 2H), 6.41 (d, *J* = 15.8 Hz, 1H), 7.05 (s, 1H), 7.13 (s, 1H), 7.90 (d, *J* = 15.8 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.3, 60.8, 102.8, 105.9, 106.8, 111.8, 116.9, 121.4, 133.9, 138.9, 149.2, 151.9, 165.7; **Analysis**: $C_{13}H_{11}NO_4$ requires C, 63.67; H, 4.52; N, 5.71; found: C, 63.59; H, 4.48; N, 5.65%.

(*E*)-Ethyl 3-(1-cyanonaphthalen-2-yl)acrylate (50l)

Yield: 88%**,** colorless solid; **mp:** 118-119 ºC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 784, 865, 989, 1030, 1106, 1210, 1275, 1291, 1319, 1368, 1573, 1607, 1712, 2218, 2978, 3084; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.35 (t, *J* = 7.0 Hz, 3H), 4.32 (q, *J* = 7.0 Hz, 2H), 6.68 (d, *J* = 16 Hz, 1H), 7.59-7.78 (m, 3H), 7.90 (d, *J* = 7.7 Hz, 1H), 8.04 (d, *J* = 8.7 Hz, 1H), 8.19 (d, *J* = 16 Hz, 1H), 8.28 (d, *J* = 8.7 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.2, 60.8, 110.8, 115.5, 122.1, 123.5, 125.8, 128.3, 129.1, 132.5, 132.9, 137.0, 139.5,

165.5; **Analysis**: $C_{16}H_{13}NO_2$ requires C, 76.48; H, 5.21; N, 5.57; found: C, 76.42; H, 5.19; N, 5.52%.

2-Vinylbenzonitrile (50m)

Yield: 86%, colorless gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 752, 839, 962, 1014, 1072, 1118, 1202, 1308, 1347, 1368, 1444, 1573, 1607, 1625, 1675, 2215, 2889, 2923, 3012; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 5.54 (d, *J* = 10.6 Hz, 1H), 5.95 (d, *J* = 17.8 Hz, 1H), 7.08 (dd, *J* = 10.6, 17.8 Hz, 1H), 7.34 (td, *J* = 1.2, 7.5 Hz, 1H), 7.51-7.70 (m, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 111.0, 117.4, 118.7, 125.2, 127.8, 132.5, 132.7, 140.4; **Analysis**: C_9H_7N requires C, 83.69; H, 5.46; N, 10.84; found: C, 83.62; H, 5.41; N, 10.78%.

4-Methoxy-2-vinylbenzonitrile (50n)

Yield: 84%**,** colorless gum, **IR** ($CHCl_3$, cm^{-1}): υ_{max} 752, 839, 1030, 1083, 1119, 1256, 1308, 1347, 1368, 1456, 1573, 1607, 1625, 1668, 2208, 2923, 3081; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.88 (s, 3H), 5.53 (d, *J* = 11.1 Hz, 1H), 5.92 (d, *J* = 17.7 Hz, 1H), 6.85 (dd, *J* = 2.3, 8.5 Hz, 1H), 7.03 (dd, *J* = 11.1, 17.7 Hz, 1H), 7.11 (s, 1H), 7.55 (d, *J* = 8.5 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 55.4, 103.2, 110.4, 114.1, 117.9, 118.7, 132.9, 134.4, 142.5, 162.7; **Analysis**: $C_{10}H_9NO$ requires C, 75.45; H, 5.70; N, 8.80; found: C, 75.41; H, 5.67; N, 8.73%.

4,5-Dimethoxy-2-vinylbenzonitrile (50o)

Yield: 88%**,** colorless solid; **mp:** 106-107 ºC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 752, 839, 936, 1031, 1086, 1119, 1256, 1308, 1378, 1389, 1456, 1575, 1612, 1628, 1656, 2210, 2923, 3052; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.91 (s, 3H), 3.97 (s, 3H), 5.45 (d, *J* = 11.0 Hz, 1H), 5.80 (d, *J* = 17.2 Hz, 1H), 6.94-7.08 (m, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 55.7, 55.9, 102.7, 106.9, 113.5, 116.5, 117.7, 132.5, 134.9, 148.7, 152.5;

Analysis: $C_{11}H_{11}NO_2$ requires C, 69.83; H, 5.86; N, 7.40; found: C, 69.75; H, 5.75; N, 7.39%.

2,3-Dimethoxy-6-vinylbenzonitrile (50p)

Yield: 86%, colorless solid; **mp:** 108-110 ºC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 748, 840, 936, 1028, 1086, 1119, 1256, 1308, 1378, 1389, 1456, 1575, 1612, 1628, 1656, 2202, 2981, 3029; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.88 (s, 3H), 3.90 (s, 3H), 5.53 (d, *J* = 10.9 Hz, 1H), 5.90 (d, *J* = 17.3 Hz, 1H), 6.37 (d, *J* = 2.2 Hz, 1H), 6.69 (d, *J* = 2.2 Hz, 1H), 7.01 (dd, *J* = 10.9, 17.3 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 56.1, 61.5, 106.7, 114.7, 116.7, 120.8, 132.4, 133.4, 151.5, 151.7; **Analysis**: $C_{11}H_{11}NO_2$ requires C, 69.83; H, 5.86; N, 7.40; found: C, 69.73; H, 5.78; N, 7.39%.

2,4-Dimethoxy-6-vinylbenzonitrile (50q)

Yield: 83%**,** colorless solid; **mp:** 76-79 ºC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 724, 867, 968, 1030, 1086, 1119, 1259, 1308, 1386, 1389, 1456, 1578, 1612, 1636, 1656, 2212, 2985, 3029; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.90 (s, 3H), 4.00 (s, 3H), 5.40 (d, *J* = 10.8 Hz, 1H), 5.79 (d, *J* = 17.6 Hz, 1H), 6.94 (dd, *J* = 10.8, 17.6 Hz, 1H), 7.07 (d, *J* = 8.5 Hz, 1H), 7.32 (d, *J* = 8.5 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 55.5, 55.9, 93.6, 97.5, 101.7, 115.5, 118.9, 133.1, 143.4, 163.0, 163.8; **Analysis**: $C_{11}H_{11}NO_2$ requires C, 69.83; H, 5.86; N, 7.40; found: C, 69.79; H, 5.78; N, 7.39%.

2,3,4-Trimethoxy-6-vinylbenzonitrile (50 r)

Yield: 87%, colorless solid; **mp:** 102-103 ºC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 771, 867, 1051, 1105, 1204, 1238, 1257, 1580, 1609, 1753, 2228, 2979, 3013; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.86 (s, 3H), 3.95 (s, 3H), 4.04 (s, 3H), 5.48 (d, *J* = 11.2 Hz, 1H), 5.83 (d, *J* = 17.3 Hz, 1H), 6.85 (s, 1H), 6.97 (dd, *J* = 11.2, 17.3 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 55.9, 60.8, 61.5, 98.7, 103.4, 114.8, 117.8, 132.6, 137.2, 141.1, 155.4,

157.2; **Analysis**: $C_{12}H_{13}NO_3$ requires C, 65.74; H, 5.98; N, 6.39; found: C, 65.72; H, 5.91; N, 6.37%.

4-Cyano-2-methoxy-5-vinylphenyl 4-methylbenzenesulfonate (50s)

Yield: 82%, colorless solid; **mp:** 149-150 ºC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 746, 845, 938, 1034, 1086, 1119, 1256, 1308, 1378, 1389, 1456, 1575, 1612, 1628, 1656, 2220, 2978, 3075; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.48 (s, 3H), 3.74 (s, 3H), 5.57 (d, *J* = 10.9 Hz, 1H), 5.86 (d, *J* = 17.6 Hz, 1H), 6.93-7.08 (m, 2H), 7.28 (s, 1H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.77 (d, *J* = 8.2 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.7, 55.8, 102.9, 108.9, 116.6, 119.7, 127.7, 128.5, 129.6, 132.3, 132.7, 137.7, 141.4, 145.6, 155.5; **Analysis**: $C_{17}H_{15}NO_4S$ requires C, 61.99; H, 4.59; N, 4.25; found: C, 61.89; H, 4.53; N, 4.23%.

4-(Benzyloxy)-5-methoxy-2-vinylbenzonitrile (50t)

Yield: 84%**,** colorless solid; **mp:** 111-113 ºC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 747, 858, 934, 1028, 1065, 1119, 1232, 1308, 1394, 1389, 1456, 1574, 1612, 1631, 1656, 2220, 2988, 3086; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.90 (s, 3H), 5.21 (s, 2H), 5.39 (d, *J* = 11.1 Hz, 1H), 5.66 (d, *J* = 17.4 Hz, 1H), 6.89-7.04 (m, 2H), 7.10 (s, 1H), 7.32-7.47 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 56.0, 70.8, 103.1, 109.2, 114.0, 116.6, 117.8, 127.2, 128.2, 128.6, 132.6, 134.9, 135.7, 149.3, 151.8; **Analysis**: $C_{17}H_{15}NO_2$ requires C, 76.96; H, 5.70; N, 5.28; found: C, 76.91; H, 5.67; N, 5.27%.

4-Fluoro-2-vinylbenzonitrile (50u)

Yield: 86%**,** colorless solid; **mp:** 105-107 ºC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 752, 839, 962, 1014, 1072, 1118, 1202, 1308, 1347, 1368, 1444, 1573, 1607, 1625, 1675, 2853, 2923, 3012; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 5.62 (d, *J* = 11.0 Hz, 1H), 5.96 (d, *J* = 17.3 Hz, 1H), 7.02-7.08 (m, 2H), 7.34 (dd, *J* = 2.2, 9.4 Hz, 1H), 7.64 (dd, *J* = 5.5, 8.5 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 107.6, 112.6 (d, *J* = 23.7 Hz), 115.8 (d, *J* =

23.7 Hz), 116.8, 120.2, 132.2, 143.8 (d, *J* = 9.5 Hz), 165.1 (d, *J* = 243.8 Hz); **Analysis**: C_9H_6FN requires C, 73.46; H, 4.11; N, 9.52; found: C, 73.44; H, 4.08; N, 9.49%.

6-Vinylbenzo[*d*][1,3]dioxole-5-carbonitrile (50v)

Yield: 88%, colorless solid; **mp:** 88-91 ºC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 756, 868, 930, 1038, 1162, 1263, 1359, 1486, 1505, 1604, 1615, 2219, 2916, 3018; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 5.44 (d, *J* = 11.1 Hz, 1H), 5.77 (d, *J* = 17.3 Hz, 1H), 6.07 (s, 2H), 6.95-7.04 (m, 2H), 7.09 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 102.3, 104.0, 104.8, 110.9, 117.2, 117.7, 132.5, 137.5, 147.4, 151.8; **Analysis**: $C_{10}H_7NO_2$ requires C, 69.36; H, 4.07; N, 8.09; found: C, 69.34; H, 4.02; N, 7.99%.

2-((*E*)-Pent-1-enyl)benzonitrile (50w)

Yield: 87%, colorless solid; **mp:** 126-128 ºC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 756, 857, 974, 1037, 1095, 1184, 1202, 1216, 1251, 1275, 1291, 1319, 1347, 1368, 1393, 1444, 1477, 1573, 1607, 1640, 1716, 2219, 2984, 3023; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.98 (t, *J* = 7.3 Hz, 3H), 1.45-1.63 (m, 2H), 2.22-2.33 (m, 2H), 6.43 (dt, *J* = 15.3, 6.8 Hz, 1H), 6.74 (d, *J* = 15.3 Hz, 1H), 7.25 (dd, *J* = 15.3, 1.4 Hz, 1H), 7.45-7.62 (m, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.7, 22.2, 35.2, 110.5, 117.9, 125.2, 126.0, 126.8, 132.5, 132.7, 136.4, 141.1; **Analysis**: $C_{12}H_{13}N$ requires C, 84.17; H, 7.65; N, 8.18; found: C, 84.14; H, 7.61; N, 8.15%.

4,5-Dimethoxy-2-((*E*)-3-*tert*-butyldimethylsilyloxyprop-1-enyl)benzonitrile (50x)

Yield: 85%**,** colorless gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 748, 876, 932, 1032, 1098, 1276, 1339, 1486, 1505, 1604, 1615, 2220, 2989, 3054; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.12 (s, 6H), 0.94 (s, 9H), 3.88 (s, 3H), 3.94 (s, 3H), 4.39 (dd, *J* = 1.7, 4.7 Hz, 2H), 6.27-6.39 (m, 1H), 6.89 (d, *J* = 15.5 Hz, 1H), 6.98 (s, 1H), 7.00 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.3, 18.3, 25.9, 55.8, 55.9, 63.3, 102.6, 107.4, 113.7, 117.9, 124.9,

132.4, 134.8, 148.4, 152.5; **Analysis**: $C_{18}H_{27}NO_3Si$ requires C, 64.83; H, 8.16; N, 4.20; found: C, 64.79; H, 8.09; N, 4.13%.

4,5-Dimethoxy-2-styrylbenzonitrile (50y)

Yield: 83%, colorless solid; **mp:** 158-159 ºC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 696, 761, 1149, 1204, 1326, 1462, 1571, 1594, 2215, 2984, 3023; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.91 (s, 3H), 4.01 (s, 3H), 7.01-7.17 (m, 3H), 7.26-7.42 (m, 4H), 7.54 (d, *J* = 6.9 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 55.9, 102.9, 106.8, 113.6, 118.0, 123.8, 126.7, 128.7, 128.6, 131.2, 134.9, 136.1, 148.5, 152.6; **Analysis**: $C_{17}H_{15}NO_2$ requires C, 76.96; H, 5.70; N, 5.28; found: C, 76.89; H, 5.57; N, 5.19%.

2,3,4-Trimethoxy-6-((*E*)-oct-1-enyl)benzonitrile (50z)

Yield: 86%**,** colorless solid; **mp:** 172-174 ºC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 694, 755, 878, 969, 989, 1097, 1216, 1271, 1452, 1464, 1513, 1600, 2220, 2970, 3025, 3059; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.87-0.93 (m, 3H), 1.26-1.46 (m, 8H), 2.21-2.31 (m, 2H), 3.85 (s, 3H), 3.94 (s, 3H), 4.03 (s, 3H), 6.23-6.36 (m, 1H), 6.63 (d, *J* = 15.6 Hz, 1H), 6.78 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.1, 22.6, 28.9, 29.0, 31.6, 33.1, 56.0, 61.1, 61.6, 98.3, 103.3, 115.4, 125.8, 135.9, 138.1, 140.5, 155.6, 157.2; **Analysis**: $C_{18}H_{25}NO_3$ requires C, 71.26; H, 8.31; N, 4.62; found: C, 71.22; H, 8.28; N, 4.58%.

(*E*)-Ethyl 3-(3-cyanophenyl)acrylate (54)

Yield: 93%; colorless solid; **mp:** 62-65 ºC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 710, 765, 977, 1032, 1185, 1278, 1318, 1447, 1480, 1640, 1712, 2225, 2938, 2983; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.35 (d, *J* = 7 Hz, 3H), 4.28 (d, *J* = 7 Hz, 2H), 6.48 (d, *J* = 16.1 Hz, 1H), 7.48-7.80 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.1, 60.5, 113.2, 117.8, 120.8, 129.6, 131.1, 131.6, 132.8, 135.5, 141.5, 165.7; **Analysis**: $C_{12}H_{11}NO_2$ requires C, 71.63; H, 5.51; N, 6.96; found: C, 71.59; H, 5.45; N, 6.85%.

(*E*)-Ethyl 3-(4-cyanophenyl)acrylate (55)

Yield: 93%; colorless solid; **mp:** 68-70 ºC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 730, 795, 955, 1065, 1194, 1268, 1375, 1445, 1495, 1652, 1721, 2226, 2983; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.35 (d, *J* = 7.1 Hz, 3H), 4.28 (d, *J* = 7.1 Hz, 2H), 6.51 (d, *J* = 15.8 Hz, 1H), 7.59-7.71 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.1, 60.6, 113.2, 117.9, 121.6, 128.2, 132.4, 138.5, 141.8, 165.7; **Analysis**: $C_{12}H_{11}NO_2$ requires C, 71.63; H, 5.51; N, 6.96; found: C, 71.58; H, 5.48; N, 6.88%.

General experimental procedure for the preparation of chiral phthalides (51b-z)

A 50 mL RB flask was charged with $K_3Fe(CN)_6$ (3 mmol), K_2CO_3 (3 mmol), *tert*-BuOH (2.5 mL), THF (2.5 mL) and H_2O (5 mL) and stirred for 10 min. Subsequently, $(DHQD)_2PHAL$ (1 mol%) and $K_2OsO_4{\cdot}2H_2O$ (0.5 mol%) were added and the stirring continued for additional 30 min. To this reaction mixture, *o*-cyanoalkenes **50b-z** (1 mmol) was added and allowed to stir for 3-7 h at 25 ºC. After completion of reaction (as monitored by TLC), sodium bisulphite (1 g) was added slowly at 0 ºC. The organic layer was separated, aqueous layer extracted with ethyl acetate (3 x 10 ml) and the combined organic layers washed with brine (15 mL), dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to yield the crude product. Flash column chromatographic purification [silica gel (230-400 mesh) and pet. ether:EtOAc (7:3) as an eluent] gave phthalides **51b-z** in 92-95% yield.

(*S*)-Ethyl 2-((*R*)-1,3-dihydro-5-methoxy-1-oxoisobenzofuran-3-yl)-2-hydroxylacetate (51b)

Yield: 95%; colorless solid; **mp:** 121-122 ºC; $[\alpha]^{D}_{25}$ -94.49 (*c* 1.15, $CHCl_3$); 99% ee from chiral HPLC analysis (Chiracel OJ-H, *n*-hexane/*i*PrOH, 90:10, 1 mL/min) retention time 25.80 min (99.55%) and 30.33 min (0.45%); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 724, 876, 1031, 1084, 1191, 1212, 1278, 1295, 1357, 1398, 1445, 1486, 1578, 1607, 1721, 1765, 2984, 3023, 3415; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.29 (t, *J* = 7.2 Hz,

3H), 3.14 (br s, 3H), 3.91 (s, 3H), 4.29 (q, *J* = 7.2 Hz, 2H), 4.63 (d, *J* = 1.7 Hz, 1H), 5.69 (d, *J* = 2.2 Hz, 1H), 6.96 (d, *J* = 2.1 Hz, 1H), 7.05 (dd, *J* = 2.1, 8.6 Hz, 1H), 7.80 (d, *J* = 8.6 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.0, 55.7, 62.6, 70.5, 79.6, 106.0, 116.9, 118.9, 127.0, 148.5, 164.7, 169.5, 170.8; **Analysis**: $C_{13}H_{14}O_6$ requires C, 58.64; H, 5.30; found: C, 58.62; H, 5.19%.

(*S*)-Ethyl 2-((*R*)-1,3-dihydro-5,6-dimethoxy-1-oxoisobenzofuran-3-yl)-2-hydroxylacetate (51c)

Yield: 94%; colorless solid; **mp:** 144-146 ºC; $[\alpha]^{D}_{25}$ -95.12 (*c* 1.12, $CHCl_3$); 99% ee from chiral HPLC analysis (Chiracel OJ-H, *n*-hexane/*i*PrOH, 90:10, 0.5 mL/min) retention time 23.18 min (99.36%) and 27.60 min (0.64%); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 758, 945, 1125, 1297, 1507, 1722, 1764, 2925, 3010, 3341; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.30 (t, *J* = 7.2 Hz, 3H), 3.20 (d, *J* = 6.2 Hz, 1H), 3.94 (s, 3H), 3.98 (s, 3H), 4.29 (q, *J* = 7.2 Hz, 2H), 4.62 (dd, *J* = 2.4, 6.1 Hz, 1H), 5.66 (d, *J* = 2.2 Hz, 1H), 6.93 (s, 1H), 7.27 (s, 1H); **^{13}C NMR** (50 MHz, DMSO-d_6): δ 14.3, 56.1, 56.3, 61.1, 70.1, 81.1, 105.2, 105.7, 118.2, 141.6, 150.4, 154.7, 170.2, 171.3; **Analysis**: $C_{14}H_{16}O_7$ requires C, 64.36; H, 5.79; N, 5.36; found: C, 64.32; H, 5.71; N, 5.34%.

(*S*)-Ethyl 2-((*R*)-1,3-dihydro-6,7-dimethoxy-1-oxoisobenzofuran-3-yl)-2-hydroxyacetate (41d)

Yield: 94%**,** colorless solid; **mp:** 110-112 ºC; $[\alpha]^{D}_{25}$ -95.28 (*c* 1.0, $CHCl_3$); 99% ee from chiral HPLC analysis (Chiracel OJ-H, *n*-hexane/*i*PrOH, 90:10, 0.5 mL/min) retention time 23.90 min (99.44%) and 27.87 min (0.56%); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 762, 946, 1132, 1298, 1518, 1728, 1764, 2985, 3034, 3425; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.30 (t, *J* = 7.1 Hz, 3H), 3.19 (br s, 1H), 3.91 (s, 3H), 4.10 (s, 3H), 4.29 (q, *J* = 7.1 Hz, 2H), 4.57 (s, 1H), 5.65 (d, J = 2.0 Hz, 1H), 7.13 (d, *J* = 8.1 Hz, 1H), 7.23 (d, *J* = 8.1 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.0, 56.6, 62.2, 62.6, 70.7, 79.0,

116.4, 118.7, 119.2, 138.5, 148.3, 152.9, 167.2, 170.9; **Analysis**: $C_{14}H_{16}O_7$ requires C, 64.36; H, 5.79; found: C, 64.34; H, 5.71%.

(*S*)-Ethyl 2-((*R*)-1,3-dihydro-5,7-dimethoxy-1-oxoisobenzofuran-3-yl)-2-hydroxyacetate (51e)

Yield: 94%**,** colorless solid; **mp:** 154-156 ºC; $[\alpha]^{D}_{25}$ -96.29 (*c* 1.15, $CHCl_3$); 99% ee from chiral HPLC analysis (Chiracel OJ-H, *n*-hexane/*i*PrOH, 90:10, 0.5 mL/min) retention time 18.37 min (99.60%) and 21.74 min (0.40%); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 746, 985, 1130, 1287, 1514, 1723, 1762, 2954, 3085, 3414; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.32 (t, *J* = 7.2 Hz, 3H), 3.37 (br s, 1H), 3.91 (s, 3H), 3.94 (s, 3H), 4.30 (q, *J* = 7.2 Hz, 2H), 4.61 (s, 1H), 5.67 (s, 1H), 6.47 (s, 1H), 6.59 (s, 1H); **^{13}C NMR** (50 MHz, CD_3OD): δ 14.5, 56.5, 56.8, 62.9, 71.9, 82.1, 99.8, 100.2, 108.0, 153.0, 160.9, 168.9, 170.6, 172.4; **Analysis**: $C_{14}H_{16}O_7$ requires C, 64.36; H, 5.79; found: C, 64.34; H, 5.76%.

(*S*)-Ethyl 2-((*R*)-1,3-dihydro-5,6,7-trimethoxy-1-oxoisobenzofuran-3-yl)-2-hydroxyacetate (51f)

Yield: 92%**,** colorless solid; **mp:** 111-112 ºC; $[\alpha]^{D}_{25}$ -94.65 (*c* 1.23, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1012, 1094, 1140, 1254, 1350, 1475, 1602, 1765, 2954, 3085, 3408 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.31 (t, *J* = 7.2 Hz, 3H), 3.09 (s,1H), 3.86 (s, 3H), 3.96 (s, 3H), 4.13 (s, 3H), 4.31 (q, *J* = 7.2 Hz, 2H), 4.58 (d, *J* = 2.1 Hz, 1H), 5.58 (d, *J* = 2.1 Hz, 1H), 6.70 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.9, 56.3, 61.1, 62.0, 62.4, 79.1, 99.5, 111.0, 141.9, 143.5, 152.1, 159.6, 167.3, 176.7; **Analysis**: $C_{15}H_{18}O_8$ requires C, 55.21; H, 5.56; found: C, 55.18; H, 5.53%.

(*S*)-Ethyl 2-((*R*)-5-(*p*-toluenesulfonoyloxy)-1,3-dihydro-6-methoxy-1-oxoisobenzofuran-3-yl)-2-hydroxyacetate (51g)

Yield: 93%**,** colorless solid; **mp:** 107-108 ºC; $[\alpha]^{D}_{25}$ -94.89 (*c* 1.15, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 768, 819, 1025, 1050, 1120, 1180, 1190, 1330, 1374, 1494, 1614, 1767, 2924, 3012, 3371; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.27 (t, *J* = 7.2 Hz, 3H), 2.48

(s, 3H), 3.07 (s, 1H), 3.78 (s, 3H), 4.26 (q, *J* = 7.2 Hz, 2H), 4.63 (d, *J* = 2.1 Hz, 1H), 5.67 (d, *J* = 2.1 Hz, 1H), 6.99 (s, 1H), 7.35 (d, *J* = 8.1 Hz, 2H), 7.49 (s, 1H), 7.76 (d, *J* = 8.1 Hz, 2H); **^{13}C NMR** (50 MHz, DMSO-d_6): δ 14.4, 21.7, 56.6, 61.4, 70.3, 71.6, 81.3, 107.3, 118.6, 119.7, 128.6, 130.0, 132.5, 139.5, 145.9, 147.9, 156.9, 168.8, 170.9; **Analysis**: $C_{20}H_{20}O_9S$ requires C, 55.04; H, 4.62; found: C, 55.01; H, 4.59%.

(*S*)-Ethyl 2-((*R*)-5-(benzyloxy)-1,3-dihydro-6-methoxy-1-oxoisobenzofuran-3-yl)-2-hydroxyacetate (51h)

Yield: 94%**,** colorless solid; **mp:** 138-140 ºC; $[\alpha]^{D}_{25}$ -96.04 (*c* 1.21, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 738, 856, 1025, 1078, 1130, 1184, 1195, 1336, 1395, 1494, 1645, 1765, 2942, 3035, 3413; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.28 (t, *J* = 7.0 Hz, 3H), 3.04 (d, *J* = 5.9 Hz, 1H), 3.94 (s, 3H), 4.27 (q, *J* = 7.0 Hz, 2H), 4.55 (dd, *J* = 2.5, 5.9 Hz, 1H), 5.22 (d, *J* = 3.5 Hz, 2H), 5.61 (d, *J* = 2.0 Hz, 1H), 6.94 (s, 1H), 7.26 (s, 1H), 7.29-7.45 (m, 5H); **^{13}C NMR** (50 MHz, DMSO-d_6): δ 13.7, 55.7, 61.4, 70.3, 70.6, 79.9, 105.2, 105.8, 118.5, 127.0, 127.8, 128.2, 135.3, 139.9, 150.7, 153.5, 169.6, 170.4; **Analysis**: $C_{20}H_{20}O_7$ requires C, 64.51; H, 5.41; found: C, 64.39; H, 5.36%.

(*S*)-Ethyl 2-((*R*)-5-fluoro-1,3-dihydro-1-oxoisobenzofuran-3-yl)-2-hydroxy acetate (50i)

Yield: 94%**,** colorless solid; **mp:** 108-109 ºC; $[\alpha]^{D}_{25}$ -95.41 (*c* 1.15, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 756, 891, 1052, 1097, 1130, 1190, 1325, 1374, 1485, 1629, 1765, 2928, 3015, 3351; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.30 (t, *J* = 7.2 Hz, 3H), 3.17 (d, *J* = 6.7 Hz, 1H), 4.31 (q, *J* = 7.2 Hz, 2H), 4.62 (dd, *J* = 2.2, 5.8 Hz, 1H), 5.74 (d, *J* = 7.2 Hz, 1H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.91 (dd, *J* = 5.8, 8.3 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.9, 62.2, 70.2, 79.7, 109.5 (d, *J* = 24.6 Hz), 117.6 (d, *J* = 24.6 Hz), 122.7, 127.7, 148.6 (d, *J* = 10.3 Hz), 166.3 (d, *J* = 256.3 Hz), 168.5, 170.5; **Analysis**: $C_{12}H_{11}FO_5$ requires C, 56.70; H, 4.36; found: C, 56.67; H 4.33%.

(*S*)-Ethyl 2-((*R*)-1,3-dihydro-5-nitro-1-oxoisobenzofuran-3-yl)-2-hydroxy acetate (51j)

Yield: 93%**,** colorless solid; **mp:** 146-148 ºC; $[\alpha]^{D}_{25}$ -95.28 (*c* 1.0, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 738, 829, 967, 1037, 1106, 1346, 1540, 1740, 1779, 2853, 2918, 3009, 3444; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.35 (t, *J* = 7.2 Hz, 3H), 3.21 (d, *J* = 6.1 Hz, 1H), 4.36 (q, *J* = 7.2 Hz, 2H), 4.71 (d, *J* = 3.6 Hz, 1H), 5.90 (s, 1H), 8.09 (d, *J* = 8.2 Hz, 1H), 8.42-8.46 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 14.1, 63.2, 70.1, 80.1, 117.8, 125.3, 127.0, 131.8, 146.8, 151.7, 167.3, 170.2; **Analysis**: $C_{12}H_{11}NO_7$ requires C, 51.25; H, 3.94; N, 4.98; found: C, 51.24; H, 3.85; N, 4.93%.

(*S*)-Ethyl 2-((*R*)-5-1,3-dihydro-5,6-dioxomethyl-1-oxoisobenzofuran-3-yl)-2-hydroxyacetate (51k)

Yield: 95%**,** colorless solid; **mp:** 150-153 ºC; $[\alpha]^{D}_{25}$ -95.74 (*c* 1.0, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 786, 891, 1015, 1054, 1122, 1183, 1196, 1356, 1395, 1489, 1618, 1755, 2942, 3021, 3410; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.31 (t, *J* = 7.1 Hz, 3H), 3.10 (br s, 1H), 4.30 (qd, *J* = 1.4, 7.1 Hz, 2H), 4.56 (s, 1H), 5.62 (d, *J* = 2.1 Hz, 1H), 6.14 (dd, *J* = 1.4, 4.4 Hz, 2H), 6.89 (s, 1H), 7.20 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.0, 62.6, 70.4, 79.6, 101.8, 102.7, 104.2, 120.4, 142.2, 149.6, 153.7, 169.2, 170.8; **Analysis**: $C_{13}H_{12}O_7$ requires C, 55.72; H, 4.32; found: C, 55.65; H, 4.29%.

(*S*)-Ethyl 2-((*R*)-1,3-dihydro-1-oxonaphtho[2, 1-c]furan-3-yl)-2-hydroxyacetate (51l)

Yield: 94%**,** colorless solid; **mp:** 107-109 ºC; $[\alpha]^{D}_{25}$ -95.69 (*c* 1.15, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 784, 865, 989, 1010, 1106, 1210, 1275, 1291, 1319, 1368, 1573, 1607, 1750, 2978, 3084, 3457; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.28 (t, *J* = 7.4 Hz, 3H), 3.14 (d, *J* = 6.0 Hz, 1H), 4.31 (q, *J* = 7.4 Hz, 2H), 4.74 (dd, *J* = 2.1, 6.0 Hz, 1H), 5.85 (d, *J* = 2.1 Hz, 1H), 7.58 (d, *J* = 8.5 Hz, 1H), 7.63-7.78 (m, 2H), 7.97 (d, *J* = 8.5 Hz, 1H), 8.16 (d, *J* = 8.5 Hz, 1H) 8.97 (d, *J* = 8.5 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$+ CD_3OD): δ 13.2, 61.4, 69.8, 80.3, 118.1, 118.6, 120.2, 122.4, 126.7, 128.0,

128.3, 133.0, 135.2, 147.6, 170.3; **Analysis**: $C_{16}H_{14}O_5$ requires C, 67.13; H, 4.93; found: C, 67.11; H, 4.89%.

(*R*)-3-(Hydroxymethyl)isobenzofuran-1(3*H*)-one (51m)

Yield: 95%**,** colorless solid; **mp:** 101-104 ºC; $[\alpha]^{D}_{25}$ -78.12 (*c* 1.23, $CHCl_3$); 99% ee from chiral HPLC analysis (Chiracel OJ-H, *n*-hexane/*i*PrOH, 90:10, 0.5 mL/min) retention time 8.03 (99.36%) and 9.24 (0.64%); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 744, 847, 968, 1025, 1067, 1089, 1211, 1288, 1349, 1467, 1607, 1640, 1756, 2924, 3012, 3440; **^{1}H NMR** (200 MHz, $CDCl_3$): 2.61 (s, 1H), 3.90 (d, *J* = 11.8 Hz, 1H), 4.14 (d, *J* = 11.8 Hz, 1H), 5.54-5.59 (m, 1H), 7.55 (t, *J* = 7.7 Hz, 2H), 7.70 (td, *J* = 1.1, 7.4 Hz, 1H), 7.89 (d, *J* = 7.4 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$+CD_3OD): δ 61.7, 81.5, 121.6, 124.2, 125.6, 128.4, 133.3, 146.7, 170.6; **Analysis**: $C_9H_8O_3$ requires C, 65.85; H, 4.91; found: C, 65.83; H, 4.85%.

(*R*)-3-(Hydroxymethyl)-5-methoxyisobenzofuran-1(3*H*)-one (51n)

Yield: 95%**,** colorless solid; **mp**: 137-140 ºC; $[\alpha]^{D}_{25}$ -78.36 (*c* 1.12, $CHCl_3$); 99% ee from chiral HPLC analysis (Chiracel OJ-H, *n*-hexane/*i*PrOH, 90:10, 1 mL/min) retention time 27.19 min (99.36%) and 39.72 min (0.64%); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 728, 868, 1026, 1256, 1490, 1607, 1640, 1749, 2853, 2923, 3440; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.31 (br s, 1H), 3.84-3.91 (m, 4H), 4.06-4.14 (m, 1H), 5.46 (t, *J* = 5.3 Hz, 1H), 6.94 (d, *J* = 2.0 Hz, 1H), 7.04 (dd, *J* = 2.0, 8.6 Hz, 1H), 7.80 (d, *J* = 8.6 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$+CD_3OD): δ 54.8, 62.1, 81.0, 105.5, 116.3, 117.7, 126.0, 149.8, 164.5, 170.8; **Analysis**: $C_{10}H_{10}O_4$ requires C, 61.85; H, 5.19; found: C, 61.79; H, 5.12%.

(*R*)-3-(Hydroxymethyl)-5,6-dimethoxyisobenzofuran-1(3*H*)-one (51o)

Yield: 93%**,** colorless solid; **mp:** 165-167 ºC; $[\alpha]^{D}_{25}$ -77.89 (*c* 1, $CHCl_3$); 99% ee from chiral HPLC analysis (Chiracel OJ-H, *n*-hexane/*i*PrOH, 90:10, 0.5 mL/min)

retention time 23.18 min (99.36%) and 27.60 min (0.64%); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 698, 828, 956, 1027, 1056, 1225, 1266, 1309, 1335, 1474, 1508, 1612, 1752, 2922, 3023, 3358; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.71 (t, *J* = 6.4 Hz, 1H), 3.81-3.90 (m, 1H), 3.93 (s, 3H), 3.99 (s, 3H), 4.04-4.15 (m, 1H), 5.42-5.47 (m, 1H), 6.93 (s, 1H), 7.25 (s, 1H); **^{13}C NMR** (50 MHz, DMSO-d_6): δ 56.1, 56.3, 62.4, 81.6, 105.0, 105.8, 117.9, 142.4, 150.3, 154.6, 170.5; **Analysis**: $C_{11}H_{12}O_5$ requires C, 58.93; H, 5.39; found: C, 58.85; H, 5.37%.

(*R*)-3-(Hydroxymethyl)-6,7-dimethoxyisobenzofuran-1(3*H*)-one (51p)

Yield: 94%**,** colorless solid; **mp:** 85-88 ºC; $[\alpha]^D_{25}$ -78.21 (*c* 1, $CHCl_3$); 99% ee from chiral HPLC analysis (Chiracel OJ-H, *n*-hexane/*i*PrOH, 90:10, 0.5 mL/min) retention time 18.35 min (99.35%) and 20.85 min (0.56%); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 698, 798, 956, 1030, 1067, 1220, 1328, 1339, 1458, 1605, 1745, 2976, 3012, 3457; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.24 (br s, 1H), 3.79-3.85 (m, 1H), 3.90 (s, 3H), 3.95 (s, 3H), 4.03-4.09 (m, 1H), 5.35-5.39 (m, 1H), 6.42 (s, 1H), 6.48(s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 56.6, 62.0, 63.7, 80.7, 116.8, 118.4, 119.4, 139.6, 148.0, 152.5, 168.2; **Analysis**: $C_{11}H_{12}O_5$ requires C, 58.93; H, 5.39; found: C, 58.83; H, 5.36%.

(*R*)-3-(Hydroxymethyl)-5,7-dimethoxyisobenzofuran-1(3*H*)-one (51q)

Yield: 94%**,** colorless solid; **mp:** 152-153 ºC; $[\alpha]^D_{25}$ -78.1, $CHCl_3$); 99% ee from chiral HPLC analysis (Chiracel OJ-H, *n*-hexane/*i*PrOH, 90:10, 0.5 mL/min) retention time 18.27 min (99.36%) and 20.40 min (0.64%); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 695, 765, 950, 1030, 1058, 1232, 1331, 1365, 1463, 1615, 1751, 2982, 3010, 3443; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.53 (br s, 1H), 3.77-3.88 (m, 3H), 3.91 (s, 3H), 3.99-4.04 (m, 3H), 4.10 (s, 1H), 5.40-5.45 (m, 1H), 7.09 (dd, *J* = 8.4, 8.2 Hz, 1H), 7.22 (d, *J* = 8.2 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 54.6, 54.9, 62.2, 80.4, 97.6, 98.2, 105.8,

151.7, 158.9, 166.6, 168.9; **Analysis**: $C_{11}H_{12}O_5$ requires C, 58.93; H, 5.39; found: C, 58.89; H, 5.37%.

(*R*)-3-(Hydroxymethyl)-5,6,7-trimethoxyisobenzofuran-1(3H)-one (51r)

Yield: 93%**,** colorless solid; **mp:** 178-180 ºC; $[\alpha]^{D}_{25}$ -78.05 (*c* 1.15, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1014, 1097, 1254, 1345, 1483, 1600, 1754, 2947, 3017, 3444; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.62 (br s, 1H), 3.84-3.90 (m, 4H), 3.96 (s, 3H), 4.03-4.09 (m, 1H), 4.13 (s, 3H), 5.35-5.39 (m, 1H), 6.69 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$+ CD_3OD): δ 56.3, 61.1, 62.0, 63.7, 80.6, 99.9, 110.6, 141.8, 144.8, 152.1, 159.7, 168.3; **Analysis**: $C_{12}H_{14}O_6$ requires C, 56.09; H, 5.55; found: C, 56.05; H, 5.53%.

(*R*)-1,3-Dihydro-1-(hydroxymethyl)-5-methoxy-3-oxoisobenzofuran-6-yl 4-methylbenzenesulfonate (51s)

Yield: 95%**,** colorless solid; **mp:** 152-154 ºC; $[\alpha]^{D}_{25}$ -77.79 (*c* 1.18, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 734, 849, 973, 103, 1053, 1178, 1345, 1372, 1494, 1614, 1755, 2919, 3018, 3437; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.24 (br s, 1H), 2.48 (s, 3H), 3.80 (s, 3H), 3.92 (dd, *J* = 4.6, 12.3 Hz, 1H), 4.03 (dd, *J* = 4.7, 12.3 Hz, 1H), 5.44 (t, *J* = 4.6 Hz, 1H), 6.97 (s, 1H), 7.35 (d, *J* = 8.2 Hz, 2H), 7.48 (s, 1H), 7.78 (d, *J* = 8.2 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$+CD_3OD): δ 20.0, 55.0, 61.4, 80.9, 105.3, 117.4, 119.3, 127.6, 128.8, 131.9, 138.9, 145.1, 147.7, 156.6, 169.5; **Analysis**: $C_{17}H_{16}O_7S$ requires C, 56.04; H, 4.43; found: C, 55.97; H, 4.37%.

(*R*)-5-(Benzyloxy)-3-(hydroxymethyl)-6-methoxyisobenzofuran-1(3*H*)-one (51t)

Yield: 94%**,** colorless solid; **mp:** 126-128 ºC; $[\alpha]^{D}_{25}$ -78.22 (*c* 1.10, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 689, 825, 975, 1025, 1076, 1223, 1268, 1312, 1334, 1494, 1528, 1621, 1752, 2924, 3032, 3385; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.31 (br s, 1H), 3.75-3.85 (m, 1H), 3.92 (s, 3H), 3.98-4.06 (m, 1H), 5.22 (s, 2H), 5.36-5.41 (m, 1H), 6.92 (s, 1H), 7.28 (s, 1H), 7.32-7.45 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 56.2, 64.1,

71.1, 81.0, 105.4, 106.6, 118.6, 127.3, 128.3, 128.7, 135.6, 140.9, 151.2, 154.0, 170.5; **Analysis**: $C_{17}H_{16}O_5$ requires C, 67.99; H, 5.37; found: C, 67.91; H, 5.35%.

(*R*)-5-Fluoro-3-(hydroxymethyl)isobenzofuran-1(3*H*)-one (51u)

Yield: 93%**,** colorless gum; $[\alpha]^{D}_{25}$ -77.21 (*c* 1.2, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 689, 825, 975, 1025, 1076, 1223, 1268, 1312, 1334, 1494, 1528, 1621, 1752, 2924, 3032, 3385; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 2.87 (br s, 1H), 3.93 (dd, *J* = 4.0, 12.5 Hz, 1H), 4.11 (dd, *J* = 4.0, 12.5 Hz, 1H), 5.51-5.53 (t, *J* = 4.0 Hz, 1H), 7.21-7.27 (m, 2H), 7.88-7.91 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 63.4, 80.9, 109.7 (d, *J* = 24.6 Hz), 117.7 (d, *J* = 24.6 Hz), 122.6, 128.2 (d, *J* = 9.4 Hz), 149.7 (d, *J* = 9.4 Hz), 167.3 (d, *J* = 398.5 Hz), 167.9; **Analysis**: $C_9H_7FO_3$ requires C, 59.35; H, 3.87; found: C, 73.44, H, 4.08%.

(*R*)-3 (Hydroxymethyl)-5,6-dioxomethylisobenzofuran-1(3*H*)-one (51v)

Yield: 94%**,** colorless solid; **mp:** 144-145 ºC; $[\alpha]^{D}_{25}$ -78.11 (*c* 1.2, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 698, 852, 957, 1024, 1067, 1232, 1286, 1319, 1343, 1484, 1582, 1612, 1766, 2942, 3054, 3389; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.40 (br s, 1H), 3.84 (dd, *J* = 4.0, 12.4 Hz, 1H), 4.06 (dd, *J* = 4.0, 12.4 Hz, 1H), 5.41 (m, 1H), 6.13 (d, *J* = 2.3 Hz, 2H), 6.87 (s, 1H), 7.20 (s, 1H); **^{13}C NMR** (50 MHz, DMSO-d_6): δ 62.1, 81.3, 102.8, 103.3, 119.7, 144.5, 149.0, 153.2, 169.6; **Analysis**: $C_{10}H_8O_5$ requires C, 57.70; H, 3.87; found: C, 57.68; H, 3.85%.

(*R*)-3-((*R*)-1-Hydroxybutyl)isobenzofuran-1(3*H*)-one (51w)

Yield: 93%; colorless solid; **mp:** 103-109 ºC; $[\alpha]^{D}_{25}$ -76.89 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 694, 728, 1080, 1212, 1287, 1467, 1618, 1752, 2873, 2959, 3433; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.93 (t, *J* = 6.8 Hz, 3H), 1.44-1.72 (m, 4H), 1.97 (br s, 1H), 3.99 (br s, 1H), 5.40 (d, *J* = 3.6 Hz, 1H), 7.51-7.57 (m, 2H), 7.65-7.73 (m, 1H), 7.87-7.92 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.9, 18.8, 34.9, 71.9, 83.2, 122.4,

125.6, 126.6, 129.2, 134.0, 147.2, 170.5; **Analysis**: $C_{12}H_{14}O_3$ requires C, 69.88; H, 6.84; found: C, 69.82; H, 6.81%.

(*R*)-3-((*R*)-1-Hydroxy-2-tertiarybutyldimethylsilylethyl)-5,6-dimethoxyisobenzofuran-1(3*H*)-one (51x)

Yield: 94%**,** colorless solid; **mp:** 166-168 ºC; $[\alpha]^{D}_{25}$ -79.24 (*c* 1.1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 775, 837, 1060, 1137, 1471, 1503, 1740, 2855, 2926, 3406; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.08 (d, *J* = 5.4 Hz, 6H), 0.90 (s, 9H), 2.30 (d, *J* = 5.5 Hz, 1H), 3.62-3.82 (m, 2H), 3.94 (s, 3H), 3.98 (s, 3H), 4.05-4.12 (m, 1H), 5.51 (d, *J* = 3.4 Hz, 1H), 6.98 (s, 1H), 7.28 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.0, -4.5, 17.8, 25.5, 56.2, 63.1, 73.3, 80.1, 104.2, 106.0, 118.9, 141.5, 150.6, 154.6, 170.6; **Analysis**: $C_{18}H_{28}O_6Si$ requires C, 58.67; H, 7.66; found: C, 58.65; H, 7.56%.

(*R*)-3-(Hydroxy(phenyl)methyl)-5,6-dimethoxyisobenzofuran-1(3*H*)-one (51y)

Yield: 94%**,** colorless solid; **mp:** 113-115 ºC; $[\alpha]^{D}_{25}$ -79.23 (*c* 1.15, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 756, 857, 974, 1026, 1064, 1158, 1216, 1334, 1604, 1743, 2858, 2928, 3430 ; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.05 (br s, 1H), 3.64 (s, 3H), 3.90 (s, 3H), 4.69 (d, *J* = 7.4 Hz, 1H), 5.47 (d, *J* = 7.4 Hz, 1H), 5.85 (s, 1H), 7.20 (s, 1H), 7.34-7.41 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$+CD_3OD): δ 54.7, 74.3, 83.0, 104.3, 117.4, 126.6, 127.4, 138.1, 140.6, 149.8, 153.5, 170.6; **Analysis**: $C_{17}H_{16}O_5$ requires C, 67.99; H, 5.37; found: C, 67.92; H, 5.29%.

(*R*)-3-((*R*)-1-Hydroxyheptyl)-5,6,7-trimethoxyisobenzofuran-1(3*H*)-one (51z)

Yield: 92%**,** colorless solid; **mp:** 113-115 ºC; $[\alpha]^{D}_{25}$ -78.36 (*c* 1.08, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 796, 1089, 1130, 1254, 1326, 1465, 1543, 1749, 2898, 2974, 3988 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.87-0.93 (m, 3H), 1.26-1.37 (m, 8H), 1.64-1.78 (m, 2H), 3.87 (s, 3H), 3.94-3.96 (m, 4H), 4.13 (s, 3H), 5.23 (d, *J* = 3.0 Hz, 1H), 6.68 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.0, 22.5, 25.7, 29.1, 31.7, 32.8, 56.3, 61.2,

62.1, 72.1, 81.7, 99.8, 111.1, 141.8, 145.3, 152.2, 159.6, 168.1; **Analysis**: $C_{18}H_{26}O_6$ requires C, 63.89; H, 7.74; found: C, 63.81; H, 7.68%.

(2*S*, 3*R*)-Ethyl 3-(3-cyanophenyl)-2,3-dihydroxypropanoate (56)

Yield: 93%; colorless gum; $[\alpha]^{D}_{25}$ -36.06 (*c* 1.2, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 680, 725, 954, 1057, 1118, 1214, 1291, 1734, 2229, 2985, 3443; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.30 (d, *J* = 7.1 Hz, 3H), 3.26 (d, *J* = 7.5 Hz, 1H), 3.43 (d, *J* = 5.8 Hz, 1H), 4.24-4.34 (m, 3H), 5.02 (dd, *J* = 2.3, 7.5 Hz, 1H), 7.49 (d, *J* = 7.5 Hz, 1H), 7.57-7.67 (m, 2H), 7.72 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.1, 62.3, 73.5, 74.5, 112.2, 118.6, 129.0, 130.2, 130.9, 131.3, 141.9, 172.3; **Analysis**: $C_{12}H_{13}NO_4$ requires C, 61.27; H, 5.57; N, 5.95; found: C, 61.26; H, 5.54; N, 5.89.

(2*S*, 3*R*)-Ethyl 3-(4-cyanophenyl)-2,3-dihydroxypropanoate (57)

Yield: 93%; colorless solid; **mp:** 102-103 ºC; $[\alpha]^{D}_{25}$ -36.42 (*c* 1.1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 685, 765, 1017, 1050, 1105, 1204, 1257, 1752, 2228, 2978, 3332; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.31 (d, *J* = 7.0 Hz, 3H), 3.03 (d, *J* = 7.6 Hz, 1H), 3.27 (d, *J* = 5.3 Hz, 1H), 4.24-4.35 (m, 3H), 5.05 (dd, *J* = 2.3, 7.5 Hz, 1H), 7.49 (d, *J* = 7.5 Hz, 1H), 7.57-7.67 (m, 2H), 7.72 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$+CD_3OD): δ 12.9, 60.6, 73.2, 74.2, 110.0, 117.9, 126.7, 131.0, 146.2, 171.4; **Analysis**: $C_{12}H_{13}NO_4$ requires C, 61.27; H, 5.57; N, 5.95; found: C, 61.23; H, 5.52; N, 5.84%.

Benzyl(1*R*,2*S*)-2-(ethoxycarbonyl)-1-(2-cyanophenyl)-2-hydroxyethylcarbamate (58)

Sodium hydroxide (60 mg, 1.5 mmol) was dissolved in water (4 mL), and 0.5 mL of this NaOH solution was transferred to a small vial containing $K_2OsO_2(OH)_4$ (0.02 mmol for 4 mol %) for later use. To the remainder of the NaOH solution were added the carbamate (1.55 mmol) and *n*-PrOH (2 mL). The mixture was stirred for 2-3 min and placed in a water bath before *tert*-butylhypochlorite (175 μL, 1.52 mmol) was slowly added with vigorous stirring. Then, the resulting solution was sequentially

treated with a solution of $(DHQD)_2PHAL$ (0.025 mmol for 5 mol %) in *n*-PrOH (1 mL), the *o*-cyano ethylcinnamate (0.50 mmol), the previously prepared solution of $K_2OsO_2(OH)_4$, and *n*-PrOH (1 mL). The reaction mixture was monitored by TLC to establish completion, quenched by the addition of saturated aqueous sodium sulfite (4 mL) while being cooled in an ice-water bath, and stirred for an additional 30 min. The separated aqueous phase was extracted with EtOAc (3 X 5 mL), and the combined organic extracts were washed with water (3 mL) followed by brine (5 mL), dried over anhyd.Na_2SO_4, and concentrated under reduced pressure to give the crude products which were purified by column chromatography [silica gel (230-400 mesh) and pet. ether:EtOAc (60:40) as an eluent] to give product **58** in 64% yield with dr 6:1.

Yield: 64%; colorless gum; $[\alpha]^{D}_{25}$ -36.06 (*c* 1.1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 756, 857, 974, 1037, 1095, 1184, 1202, 1275, 1291, 1319, 1347, 1368, 1393, 1477, 1573, 1607, 1640, 1716, 2219, 2984, 3023, 3415; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.28 (t, *J* = 7.1 Hz, 3H), 3.34 (d, *J* = 7.5 Hz, 1H), 4.29 (q, *J* = 7.1 Hz, 2H), 4.50 (s, 1H), 5.06 (dd, *J* = 2.3, 7.5 Hz, 1H), 5.62 (d, *J* = 8.9 Hz, 1H), 5.85 (d, *J* = 8.9 Hz, 1H), 7.32-7.36 (m, 5H), 7.39-7.56 (m, 3H), 7.66-7.77 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.2, 55.3, 60.3, 62.8, 72.5, 111.1, 117.0, 122.0, 128.4, 132.8, 133.2, 142.9, 145.8, 155.3, 172.0; **Analysis**: $C_{12}H_{13}NO_4$ requires C, 61.27; H, 5.57; N, 5.95; found: C, 61.26; H, 5.54; N, 5.89.

Section II:

First Enantioselective Synthesis of (-)-Matteucen C and Facile Synthesis of antiIschemic Stroke Drug, 3-Butylphthalide

2.2.1 Introduction

3-Alkylated phthalide frameworks are present in a large number of natural products and biologically active compounds.[1] In recent years such chiral phthalide systems have attracted considerable attention as they play a pivotal role in modern drug discovery. Among them (-)-matteucen C (**62**) and 3-butylphthalide (**1**) are of particular interest due to their biological activities. *Matteuccia orientalis* (HOOK.) TREV (Onocleaceae), mainly distributed in Southern China, is a Chinese medicinal herb used for the treatment of hemostatics and reliving ostalgia.[33] Search for new bioactive constituents from the rhizomes of this plant led to the isolation of new isocourmarin derivatives, such as matteucen A (**60**), *racemic*-matteucen B (**61**) and new phthalide derivative, (-)-matteucen C (**62**) (**Fig. 12**).[34]

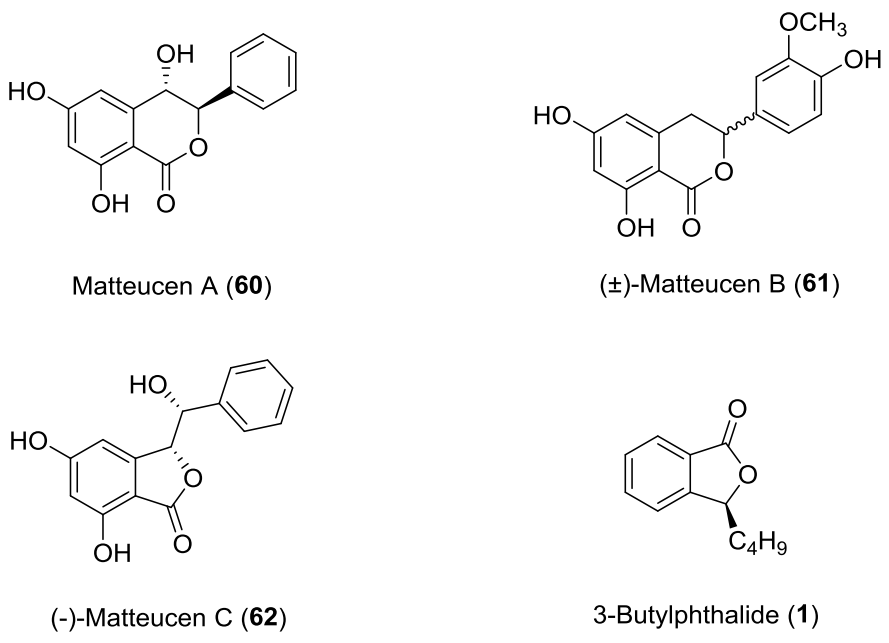


Fig. 12: Structures of matteucen A-C and 3-butylphthalide

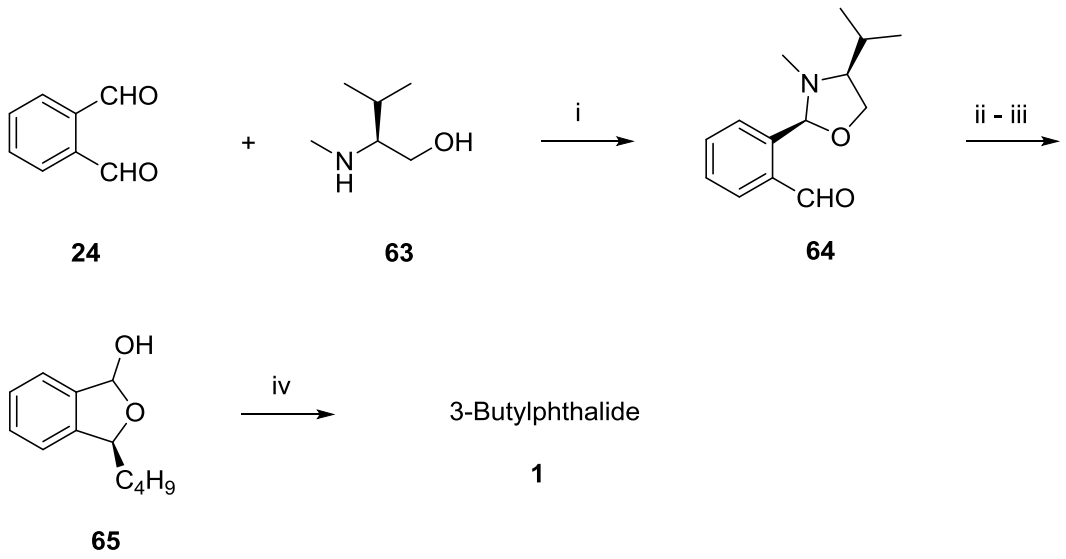
Worldwide ischemic stroke is the second leading cause of human morbidity and mortality.[35] Currently, ischemic stroke approximately causes loss of 5 million people each year, and the mortality rate of stroke is increasing.[36] Studies have suggested that the pathogenesis of ischemic stroke is attributed to the interaction of multiple factors, including genetic high risk, thrombosis, and chronic inflammatory diseases such as hypertension, diabetes, and etc.[37] During the process of ischemic stroke, the platelet aggregation related thrombosis limits sufficient blood flow in the special region of the brain and leads to ischemic inflammation and brain damage.[38] Although few drugs are available for the intervention of ischemic stroke, the efficacy of these drugs are not satisfactory and need to be used in combinations with other active drugs. For centuries in China, seeds of *Apium graveolens Linn*, Chinese celery have been employed against ischemic stroke and 3-butylphthalide (**1**) has been reported as the active ingredient in the seed oil of *Apium graveolens Linn* celery.[2a] 3-Butylphthalide (**1**) (**Fig. 12**), was approved as antiischemic drug by the State Food and Drug Administration (SFDA) of China in 2002. It intervents ischemic stroke through multiple mechanism for example, by improving energy metabolism, reducing oxidative damage,[39] improving micro circulation in arterioles,[40] decreasing neuronal apoptosis,[41] improving mitochondrial function and inhibiting inflammation.[42] Moreover, it showed promising preclinical potential as a multi-target drug for the prevention and treatment of Alzheimer's disease and vascular dementia.[43] It is noteworthy that Alzheimer's disease is the most common form of senile dementia, characterized by progressive memory loss and vascular dementia, the second most common cause of dementia especially in the Asian population.[44] Currently, there is no specific drug available to prevent or cure vascular dementia.

2.2.2 Review of Literature

Literature search revealed that there is no report available for the synthesis of (-)-matteucen C (**62**), where as there are six reports for the synthesis of 3-butylphthalide. [45-50] A short description of all the six methods are presented below.

Takahashi's approach (1991)[45]

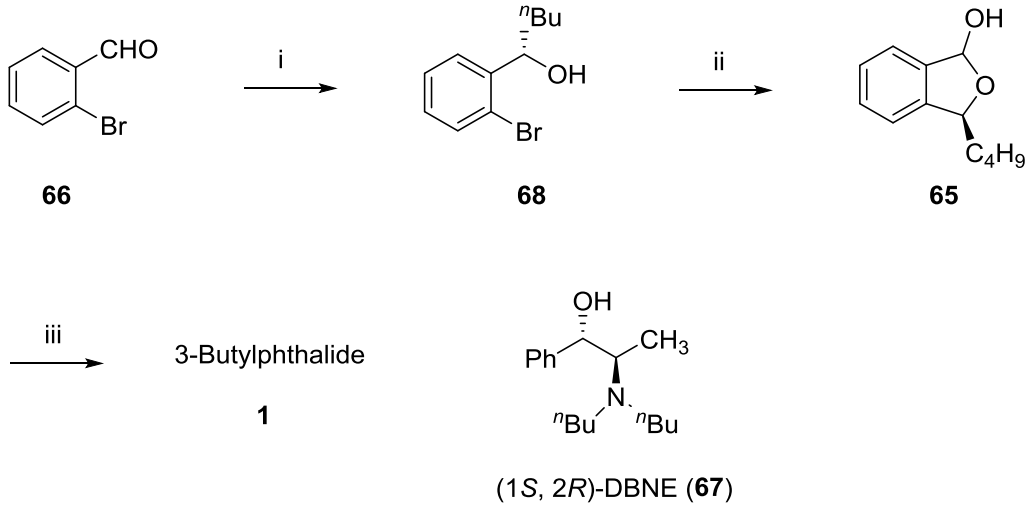
Takahashi *et al.* have utilized valine-based chiral auxiliary for the introduction of chirality in 3-butylphthalide (**1**) synthesis. Thus, chiral oxazolidine **64** was prepared by condensation of phthalaldehyde **24** with (*S*)-N-methyl valinol **63** in 56% yield (dr = 93:7). Diastereoselective addition of dibutylcupriolithium onto oxazolidine **64** followed by subsequent hydrolysis under acidic condition afforded lactol **65** in 85% ee. Further, oxidation of lactol **65** with PCC gave 3-butylphthalide (**1**) (**Scheme 19**).



Scheme 19: (i) anhyd. Na_2SO_4, CH_2C1_2, 25 °C, 16 h, 56%; (ii) $(^nBu)_2CuLi$, Et_2Zn, ^{n}BuMgCl, THF, -50 °C, 24 h; (iii) *p*-TSA, THF:H_2O (5:1), reflux, 1 h, 86% (over 2 steps); (iv) PCC, CH_2Cl_2, 25 °C, 30 min, 41%.

Soai's approach (1991)[46]

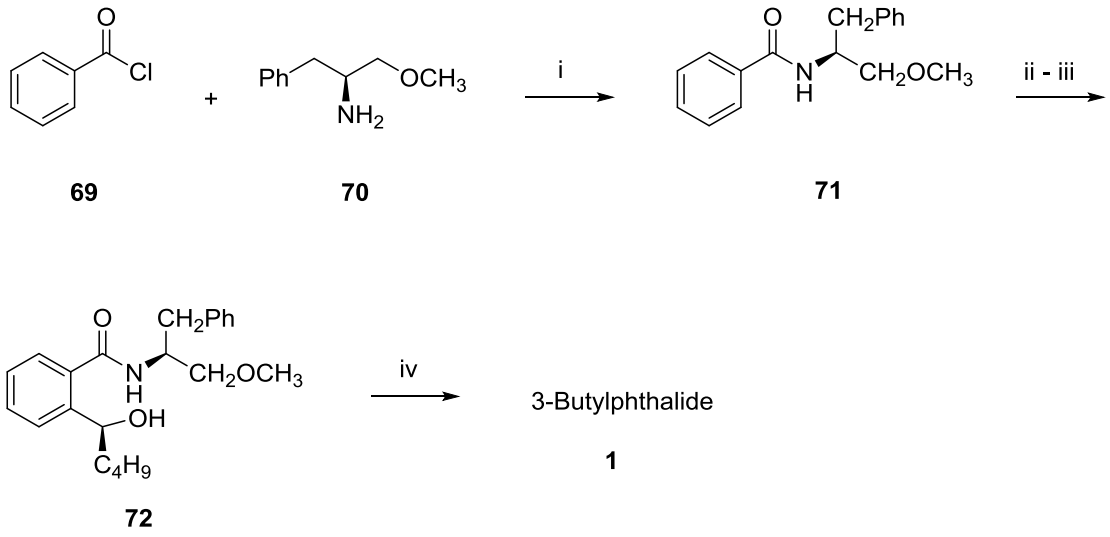
Soai *et al*. have described the synthesis of 3-butylphthalide (**1**) using enantioselective addition of dibutylzinc reagent as key step. Thus, *o*-bromobenzaldehyde **66** was subjected to asymmetric addition of dibutylzinc reagent catalyzed by chiral N,N-dibutylnorephedrine (**67**) to give alcohol **68** in 94% yield and 90% ee. Treatment of alcohol **68** with *n*-BuLi followed by quenching with DMF afforded lactol **65** in 82% yield, which was finally transformed to 3-butylphthalide (**1**) using Ag_2O oxidation (**Scheme 20**).



Scheme 20: (i) (1*S*, 2*R*)-DBNE (**67**), *n*-Bu_2Zn, hexane, 25 °C, 17 h, 94%; (ii) *n*-BuLi, DMF, 82%; (iii) Ag_2O, 25 °C, 76%.

Matsui's approach (1993)[47]

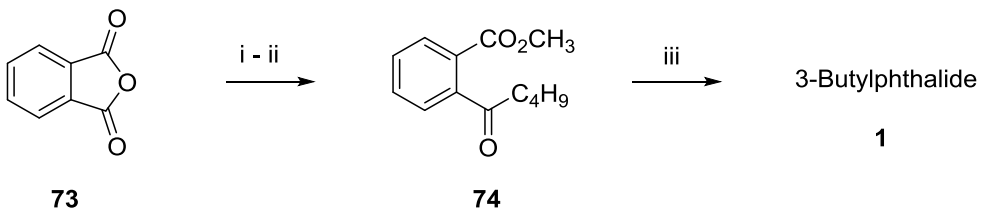
Matsui *et al*. have commenced their synthesis from commercially available benzoyl chloride **69**. The chiral benzamide **71** was obtained in 90% yield by treating benzoyl chloride **69** with chiral amine **70.** *ortho*-Lithiation of chiral benzamide **71** followed by diastereoselective addition onto *n*-pentanal afforded alcohol **72** in 57% yield (dr = 90:10). Finally, cyclization under acidic condition provided 3-butylphthalide (**1**) (**Scheme 21**).



Scheme 21: (i) Et_3N, THF, 25 °C, 16 h, 90%; (ii) *n*-BuLi, TMEDA, THF, -78 °C to 0 °C, (iii) C_4H_9CHO, THF, -78 °C, 4 h, 57% (over two steps); (iv) 5% HCl, dioxane, reflux, 4 h, 95%.

Kitayama's approach (2002)[48]

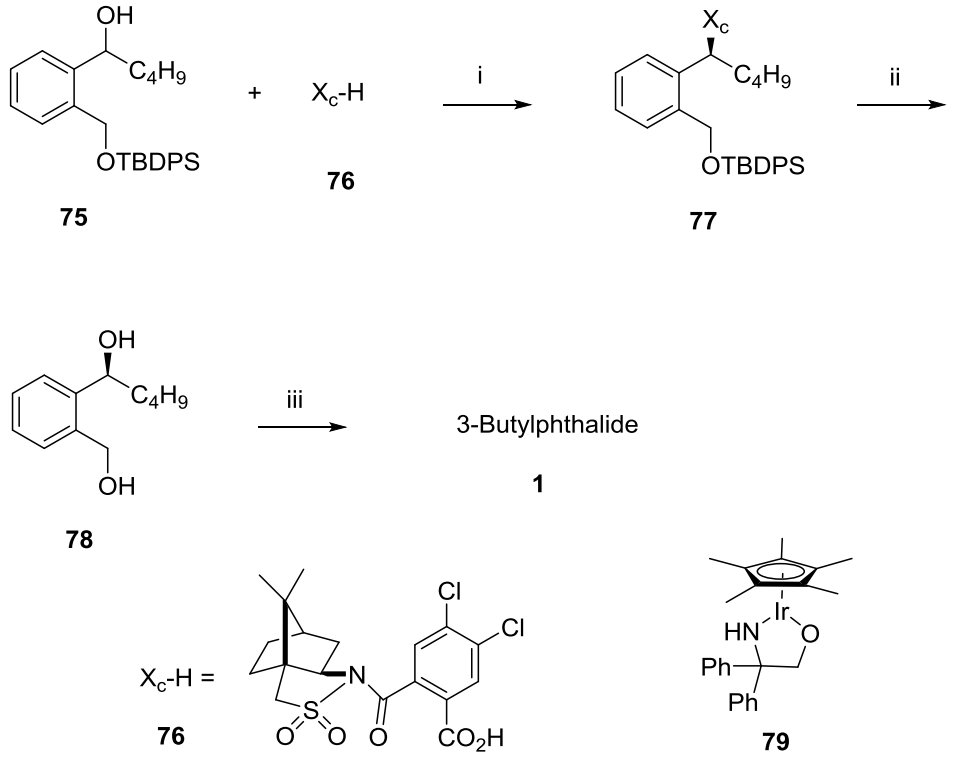
Kitayama have reported the synthesis of 3-butylphthalide (**1**) by employing enzymatic reduction as the key reaction. Methyl 2-pentanoyl benzoate (**74**) was prepared from phthalic anhydride **73** by reacting with dibutylcadmium, followed by esterification in acidic methanol. Methyl 2-pentanoylbenzoate (**74**) was subjected to enzymatic reduction with *Pseudomonas putida* ATCC to give 3-butylphthalide (**1**) in 80% yield and 99% ee (**Scheme 22**).



Scheme 22: (i) $CdCl_2$, *n*-BuBr, Mg, THF, reflux, 30 min, 64%; (ii) 97% H_2SO_4, CH_3OH, reflux, 30 min, 64%; (iii) *Pseudomonas putida* ATCC 12633, H_2O, 0 °C, 24 h, 80%.

Kosaka's approach (2002)[49]

Kosaka *et al.* have utilized camphorsultam dichlorophthalic acid (**76**) for enantio-resolution of racemic alcohol as key step in 3-butylphthalide (**1**) synthesis. Thus, racemic alcohol **75** was esterified with chiral auxiliary **76** to give diastereomeric mixture of esters, which were separated by HPLC to provide optically pure ester **77** in 49% yield. Enantiopure diol **78** was obtained by treating ester **77** with methanolic KOH. Selective oxidation of primary alcohol in **78** followed by lactol formation in a single step was achieved with Ir catalyst **79** to afford 3-butylphthalide (**1**) in 99% ee (**Scheme 23**).

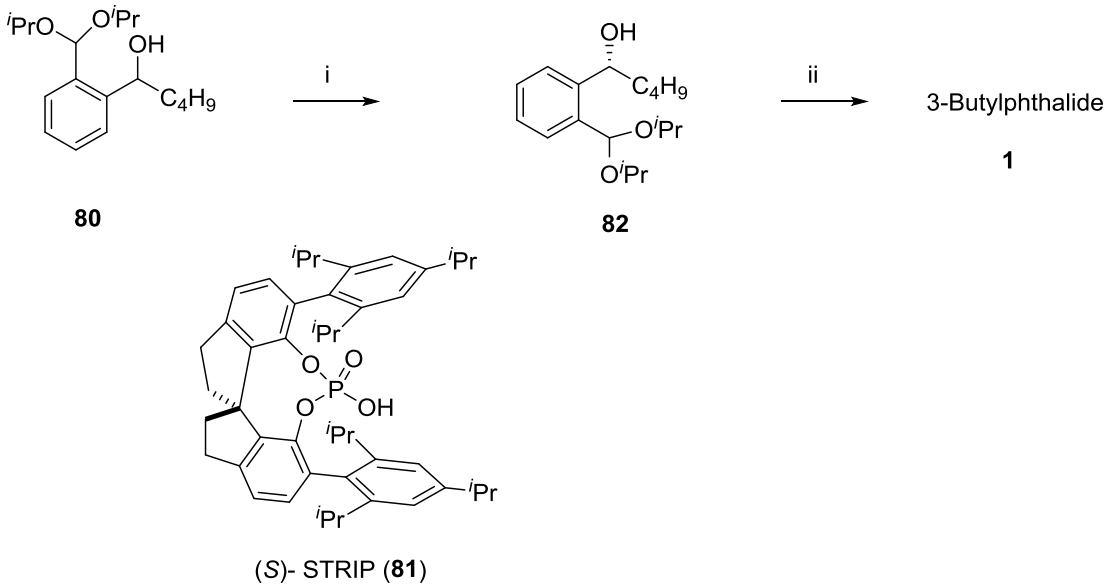


Scheme 23: (i) DCC, DMAP, CH_2Cl_2, 25 °C, 18 h, HPLC separation, 49%; (ii) KOH, CH_3OH, 16 h, 99%; (iii) Ir catalyst **79**, acetone, 25 °C to 50 °C, 48 h, 84%.

List's approach (2010)[50]

List *et al.* have achieved the synthesis of 3-butylphthalide (**1**) by employing kinetic resolution as the key reaction. These authors have developed a new spirocyclic

phosphoric acid catalyst [(*S*)-STRIP (**81**)], for kinetic resolution of homoaldol **80** to afford chiral alcohol **82** in 34% yield and 95% ee. Jones oxidation of chiral alcohol **82** provided access to 3-butylphthalide (**1**) in 85% yield (**Scheme 24**).



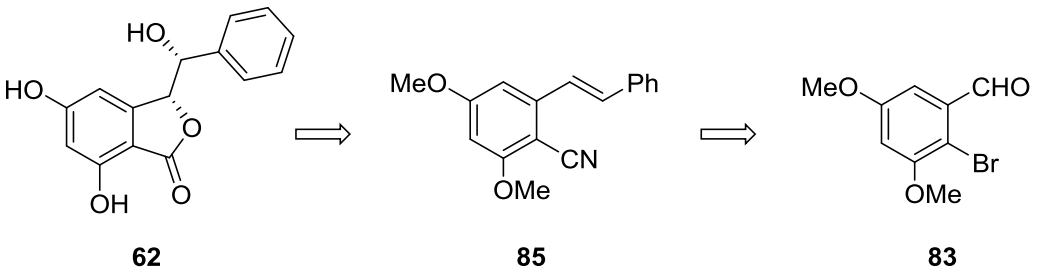
Scheme 24: (i) (*S*)-STRIP (**81**), CH_2Cl_2, 4 A° MS, 25 °C, 6 h, 34%; (ii) CrO_3, conc. H_2SO_4, acetone:water (3:1), 0 °C, 1 h, 85%.

2.2.3 Present Work

2.2.3.1 Objective

Even though few methods have been reported for the synthesis of 3-butylphthalide (**1**),[45-50] they suffer from certain limitations such as use of chiral auxiliary, expensive and exotic reagents, low overall yields, etc. In this context, a more practical method for the synthesis of 3-butylphthalide (**1**) is highly desirable. In Section I of this Chapter, we have described an elegant method for the synthesis of 3-substituted chiral phthalide derivatives **51a-z**. In continuation of the work on Os-catalyzed oxidative cyclization of *o*-cyano alkenes, a short synthesis of two natural products namely (-)-matteucen C (**62**) and 3-butylphthalide (**1**) is described in this section.[51]

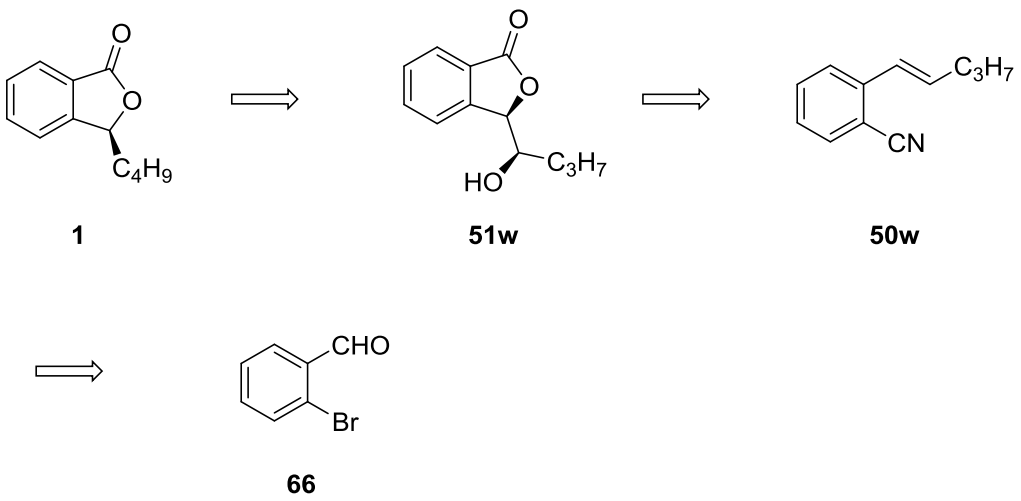
Retrosynthetic analysis of (-)-matteucen C (**62**) reveals that *o*-cyanostilbene derivative (**85**) could serve as the key intermediate for the oxidative cyclization leading to the synthesis of (-)-matteucen C (**62**). *o*-Cyanostilbene dervative (**85**) can in turn be obtained from *o*-bromobenzaldehyde (**83**) (**Fig. 13**).



62 **85** **83**

Fig. 13: Retrosynthetic analysis of (-)-matteucen C (**62**)

Similarly, we envisaged that 3-butylphthalide (**1**) could be obtained by means of Barton-McCombie deoxygenation of phthalide **51w.** The required phthalide **51w** could be prepared by means of oxidative cyclization of *o*-cyanostyrene **50w**. The *o*-cyanostyrene **50w** could in turn be obtained from *o*-bromobenzaldehyde (**66**) (**Fig. 14**).



1 **51w** **50w**

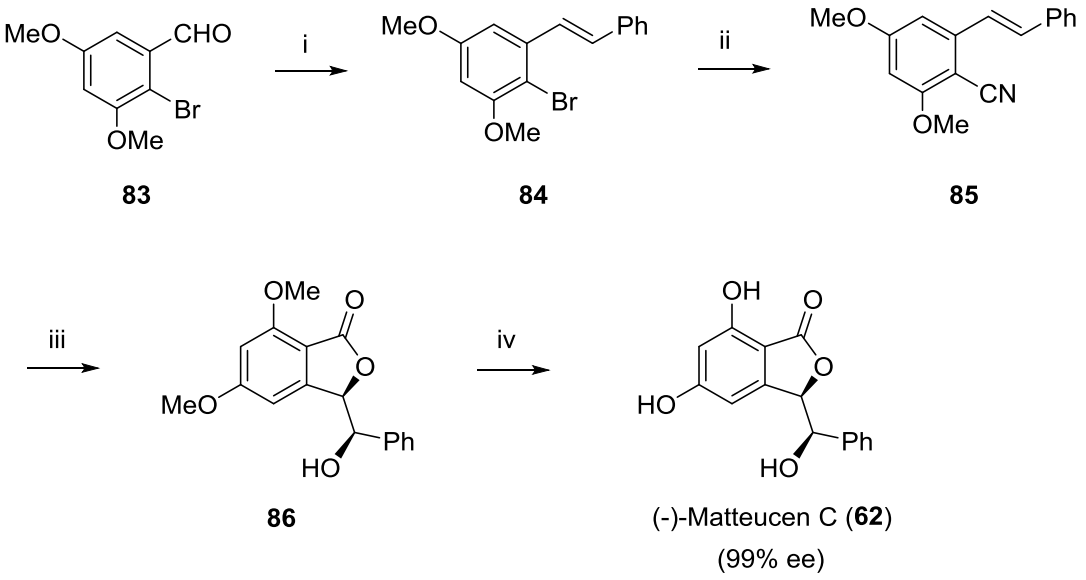
66

Fig. 14: Retrosynthetic analysis of 3-butylphthalide (**1**)

2.2.4 Results and Discussion

(a) First Enantioselective Synthesis of (-)-Matteucen C (62)

The complete synthetic sequence for (-)-matteucen C (**62**), wherein Os-catalyzed CN-assisted oxidative cyclization of *o*-cyanostilbene derivative (**85**) constitutes a key step for the introduction of chirality, is presented in **Scheme 25**.



83 **84** **85** **86**

(-)-Matteucen C (**62**)
(99% ee)

Scheme 25: (i) $PhCH_2Ph_3P^+I^-$, *n*-BuLi, THF, 0 to 25 °C, 3 h, 82%; (ii) CuCN (3.5 equiv), DMF, reflux, 14 h, 83%; (iii) AD-mix-β, *tert*-BuOH:THF:H_2O (0.5:0.5:1), 25 °C, 7 h, 93%; (iv) BBr_3, CH_2Cl_2, 25 °C, 12 h, 69%.

Accordingly, the synthesis of (-)-matteucen C (**62**) was undertaken starting from *o*-bromobenzaldehyde derivative **83**, which on subjecting to Wittig olefination [$PhCH_2Ph_3P^+I^-$, *n*-BuLi, THF] gave (*E*)-*o*-bromostilbene derivative **84** in 82% yield. Two doublets at δ 6.99 (d, *J* = 16.1 Hz, 1H) and 7.52 (d, *J* = 16.1 Hz, 1H) integrating for one proton each in the ^{1}H NMR spectrum of **84** accounted for olefinic protons. It was further supported by the typical olefinic carbon signals at δ 127.9 and 128.6 in its ^{13}C NMR spectrum (**Fig. 15**).

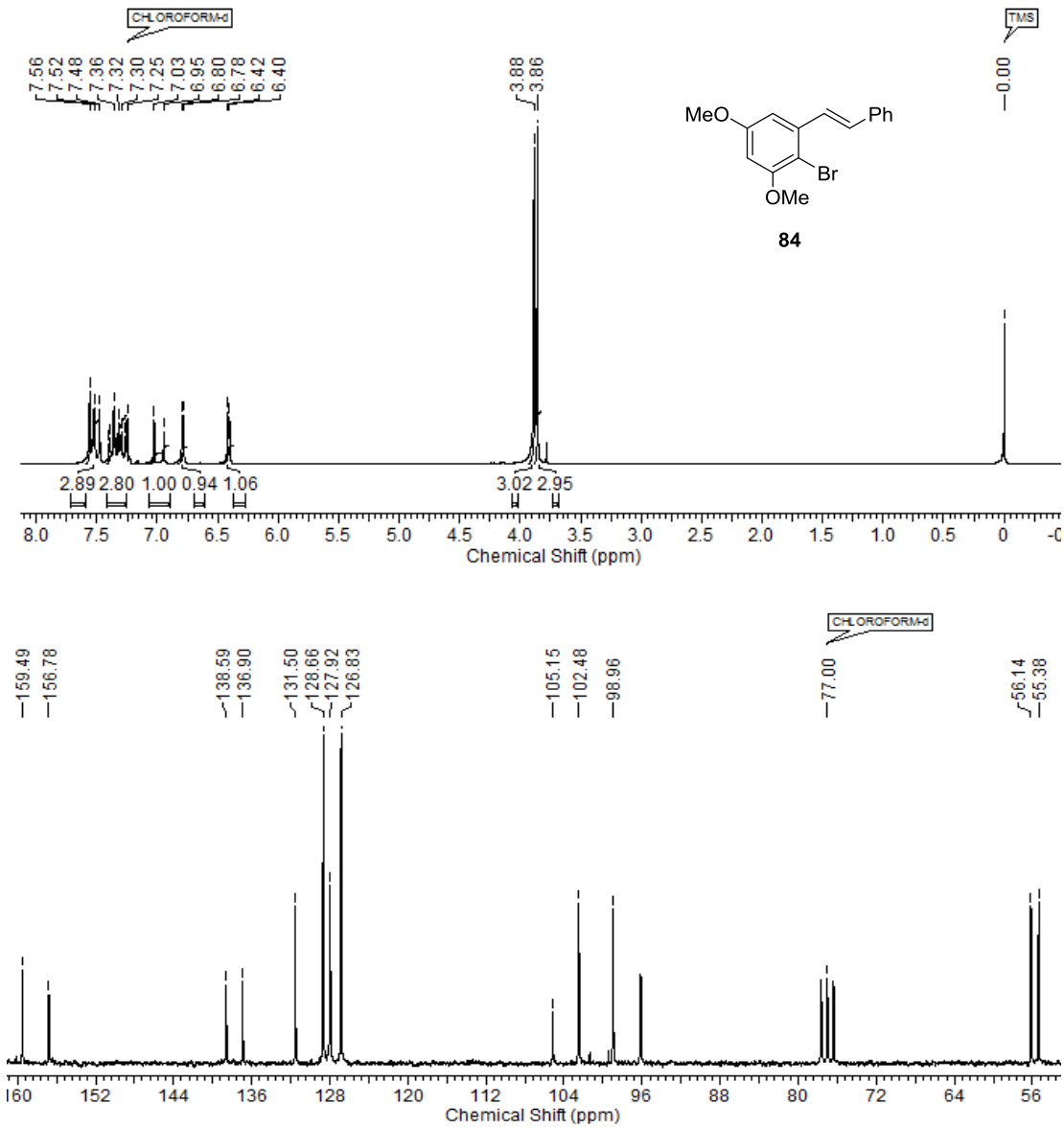


Fig. 15: ^{1}H and ^{13}C NMR spectra of *o*-bromostilbene derivative **84**

o-Bromostilbene derivative **84** was then converted to *o*-cyanostilbene derivative **85** using Rosenmund-von Braun reaction [CuCN, DMF, reflux, 83%]. The formation of the *o*-cyanostilbene derivative **85** was confirmed by the appearance of CN carbon at δ 115.7 in its ^{13}C NMR spectrum. Its IR spectrum displayed a sharp CN stretching vibrational frequency at 2216 cm^{-1} (**Fig. 16**).

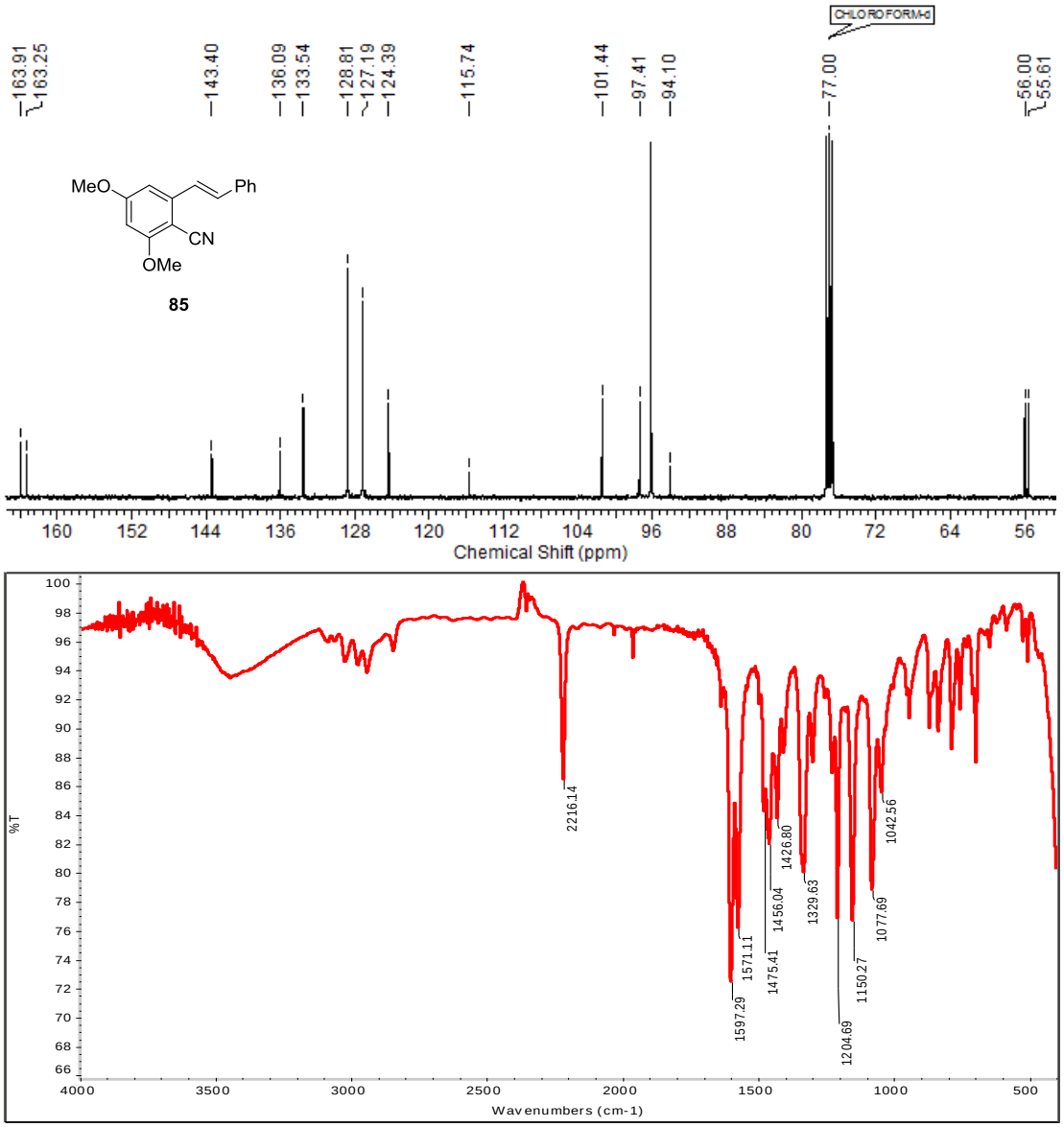
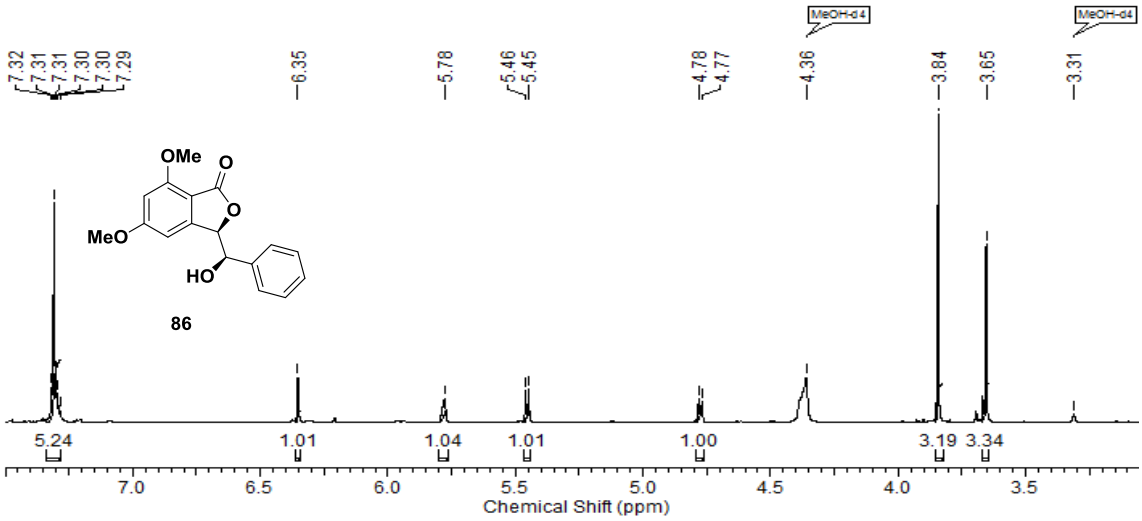
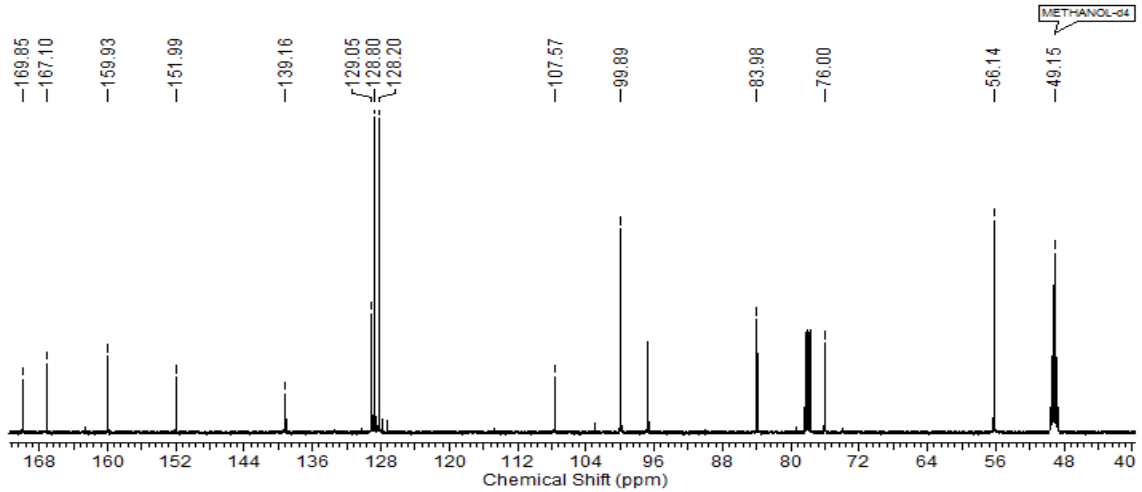
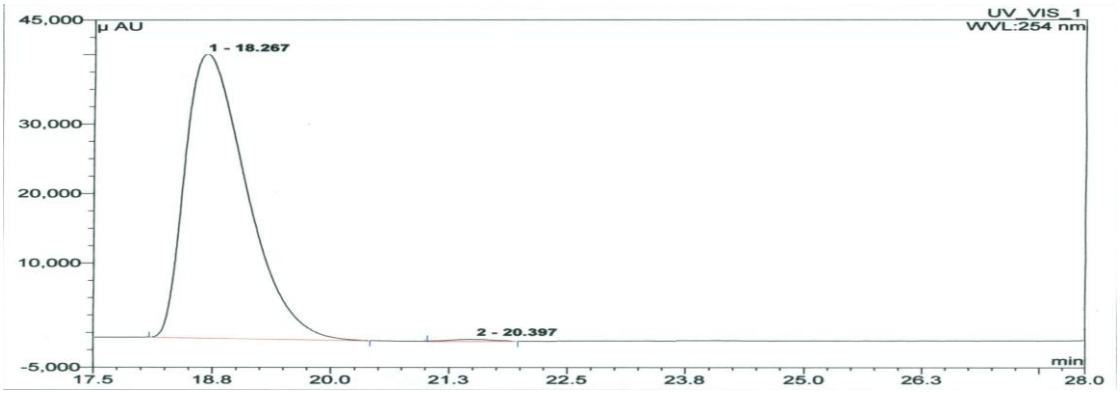


Fig. 16: ^{13}C NMR and IR spectra of *o*-cyanostilbene derivative **85**

o-Cyanostilbene derivative **85** was then subjected to CN-assisted one-pot oxidative cyclization using AD-mix-β process to give chiral phthalide **86** in 93% yield and 99% ee. The ^{1}H, ^{13}C NMR and IR spectra of **86** confirmed the formation of phthalide (**Fig. 17**). Thus, the methine protons attached to lactone moiety and hydroxyl group resonated at δ 4.77 (d, *J* = 6.4 Hz, 1H) and 5.45 (d, *J* = 6.4 Hz, 1H) respectively in its ^{1}H NMR spectrum. It was further substantiated by the appearance of carbonyl carbon [-(**C**=O)-O-] signal at δ 169.8 in its ^{13}C NMR spectrum. Its IR spectrum also exhibited a characteristic lactone carbonyl absorption band at 1752 cm^{-1}.







No	Ret. Time min	Height μ AU	Area μ AU* min	Rel. Area %	Amount	Type
1	18.27	40895.238	30456.124	99.36	n. a.	BMB
2	20.40	2196.930	195.138	0.64	n. a.	BMB

Fig. 17: ^{1}H, ^{13}C NMR spectra and HPLC chromatogram of phthalide **86**

The enantiomeric excess of chiral phthalide **86** was determined to be 99% ee from chiral HPLC analysis (Chiracel OJ-H, *n*-hexane/*i*PrOH, 90:10, 0.5 mL/min) retention time 18.27 min (99.36%) and 20.40 min (0.64%) (**Fig. 17**).

Finally, demethylation of chiral phthalide **66** was achieved with BBr_3 in CH_2Cl_2 that afforded (-)-matteucen C (**62**) in 69% yield with 99% ee. The optical rotation of the target molecule was found to be $[\alpha]^{D}_{25}$ -54.16 (*c* 1.0, CH_3OH). The formation of (-)-matteucen C (**62**) was confirmed by the appearance of two doublets at δ 4.94 (t, *J* = 4.8 Hz, 1H) and 5.45 (d, *J* = 4.0 Hz, 1H) in its ^{1}H NMR spectrum corresponding to the methine protons attached to benzylic hydroxyl group and lactone moiety respectively (**Fig. 18**). The corresponding methine carbons resonated at δ 72.6 and 81.7 in its ^{13}C NMR spectrum. The spectral data of (-)-matteucen C (**62**) were in complete agreement with the reported values.[34]

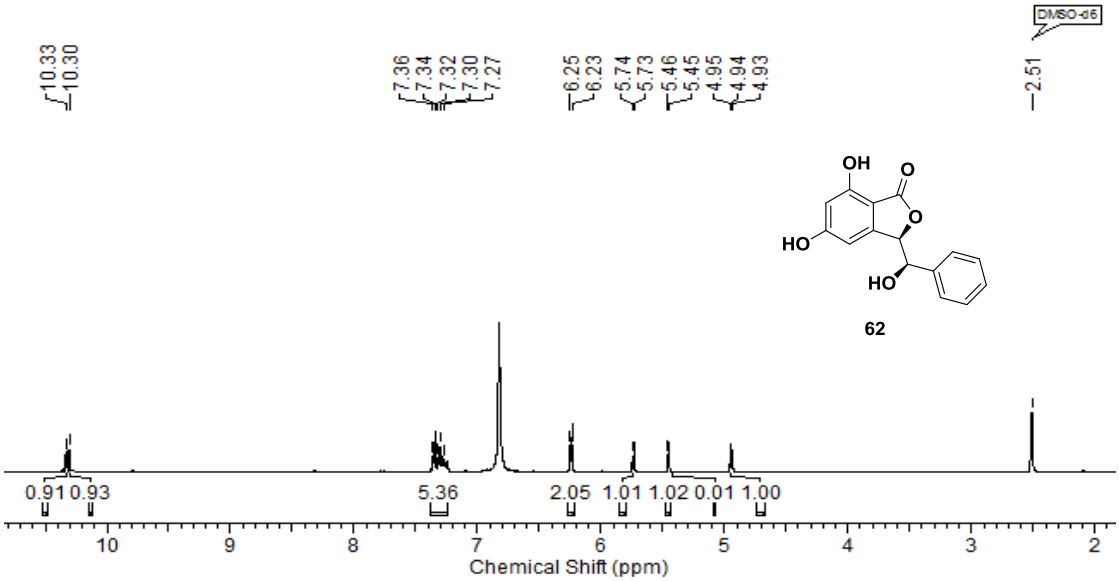
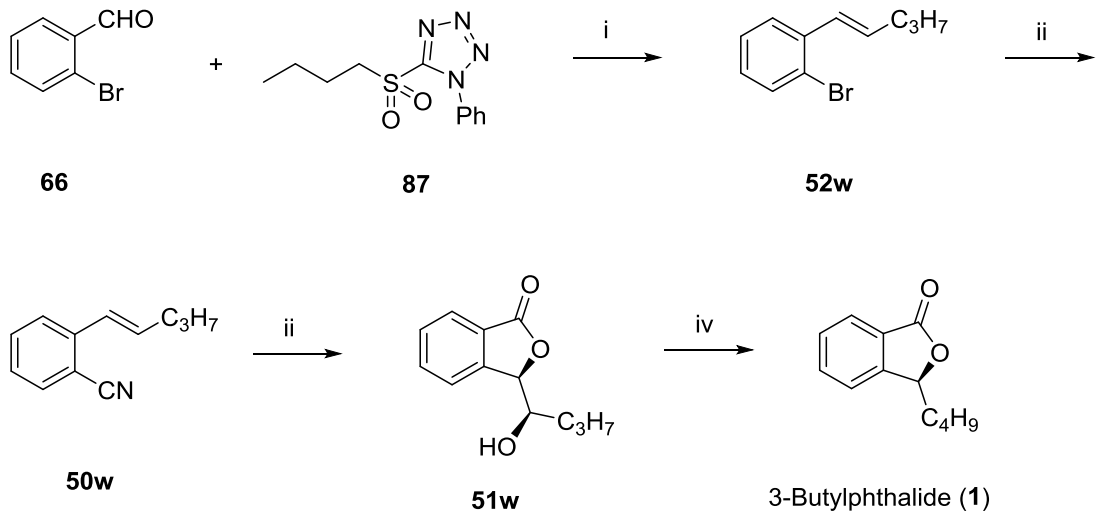


Fig. 18: ^{1}H NMR spectrum of (-)-matteucen C (**62**)

(b) Facile Enantioselective Synthesis of 3-Butylphthalide (1)

The synthetic scheme for 3-butylphthalide (**1**), wherein Os-catalyzed CN-assisted oxidative cyclization of *o*-cyanostyrene **50w** constitutes a key step for the introduction of chirality, is shown in **Scheme 26**.



Scheme 26: (i) NaHMDS, THF, -78 ^{o}C to 25 ^{o}C, 14 h, 82%; (ii) CuCN (3.5 equiv), dry DMF, reflux, 14 h, 87%; (iii) AD-mix-β, *tert*-BuOH:THF:H_2O (0.5:0.5:1), 25 ^{o}C, 7 h, 93%; (iv) (a) 1,1-thiocarbonyldiimidazole, DMAP (10 mol%), CH_2Cl_2, 18 h; (b) AIBN (10 mol%), Bu_3SnH, toluene, reflux, 15 min, 86%.

The present synthesis of 3-butylphthalide (**1**) commenced from commercially available *o*-bromobenzaldehyde (**66**), which on subjecting to Julia-Kocienski olefination[52] with butyl sulfone **87** gave (*E*)-2-bromoalkene **52w** in 82% yield. The formation of (*E*)-2-bromoalkene **52w** was confirmed from its ^{1}H NMR spectrum, which showed a doublet at δ 6.69 (d, *J* = 15.6 Hz, 1H) and a triplet of doublet at δ 6.15 (td, *J* = 6.9, 15.6 Hz, 1H) corresponding to *trans*-olefinic protons of alkene **52w**; It was further confirmed by its ^{13}C NMR spectrum, which displayed typical carbon signals at δ 127.4 and 128.8 corresponding to olefinic carbons (**Fig. 19**).

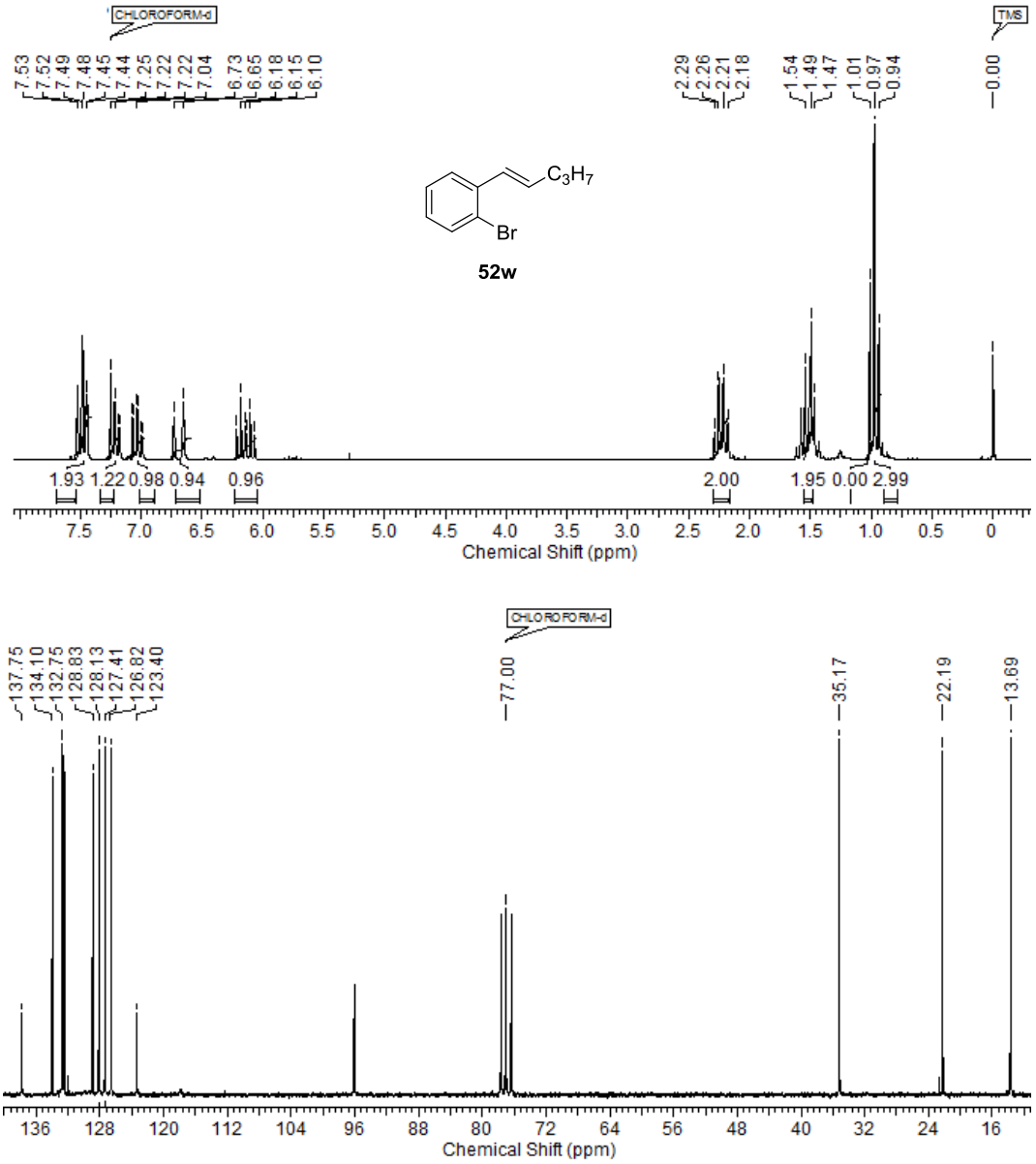


Fig. 19: ^{1}H and ^{13}C NMR spectra of (*E*)-2-bromoalkene **52w**

(*E*)-2-Bromoalkene **52w** was then converted to *o*-cyanoalkene derivative **50w** using Rosenmund-von Braun reaction [CuCN, DMF, reflux, 87%]. Its ^{1}H NMR spectrum showed characteristic doublet at δ 6.74 (d, *J* = 15.3 Hz, 1H) and a triplet of doublet at δ 6.43 (dt, *J* = 6.8, 15.3 Hz, 1H), corresponding to *trans*-olefinic protons of alkene **50w.** Its ^{13}C NMR spectrum showed a characteristic carbon signal for CN carbon at δ 117.9 confirming the formation of *o*-cyanoalkene **50w** (**Fig. 20**). Its IR spectrum displayed a sharp CN stretching vibrational frequency at 2219 cm^{-1}.

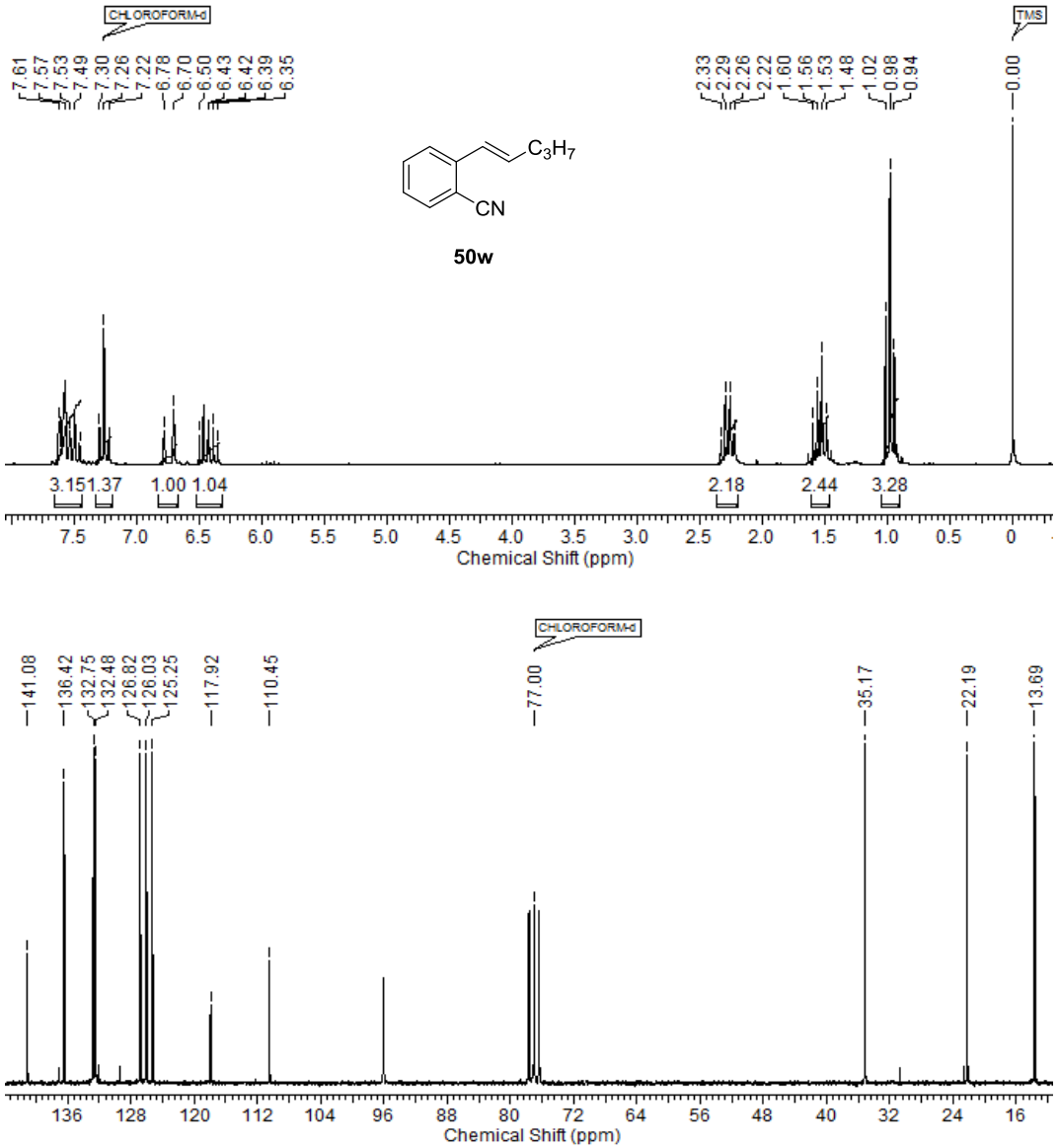


Fig. 20: ^{1}H and ^{13}C NMR spectra of *o*-cyanoalkene **50w**

o-Cyanoalkene **50w** was then subjected to CN-assisted one-pot oxidative cyclization using AD-mix-β process to give chiral phthalide **51w** in 93% yield and 97% ee. The ^{1}H, ^{13}C NMR and IR spectra of **51w** confirmed the formation of phthalide **51w** (**Fig. 21**). The methine proton attached to lactone moiety resonated at δ 5.40 (d, J = 3.6 Hz, 1H) in its ^{1}H NMR spectrum. It was further substantiated by the appearance of carbonyl carbon [-(**C**=O)-O-] signal at δ 170.5 in its ^{13}C NMR spectrum. Its IR spectrum exhibited a characteristic lactone carbonyl absorption band at 1752 cm^{-1}.

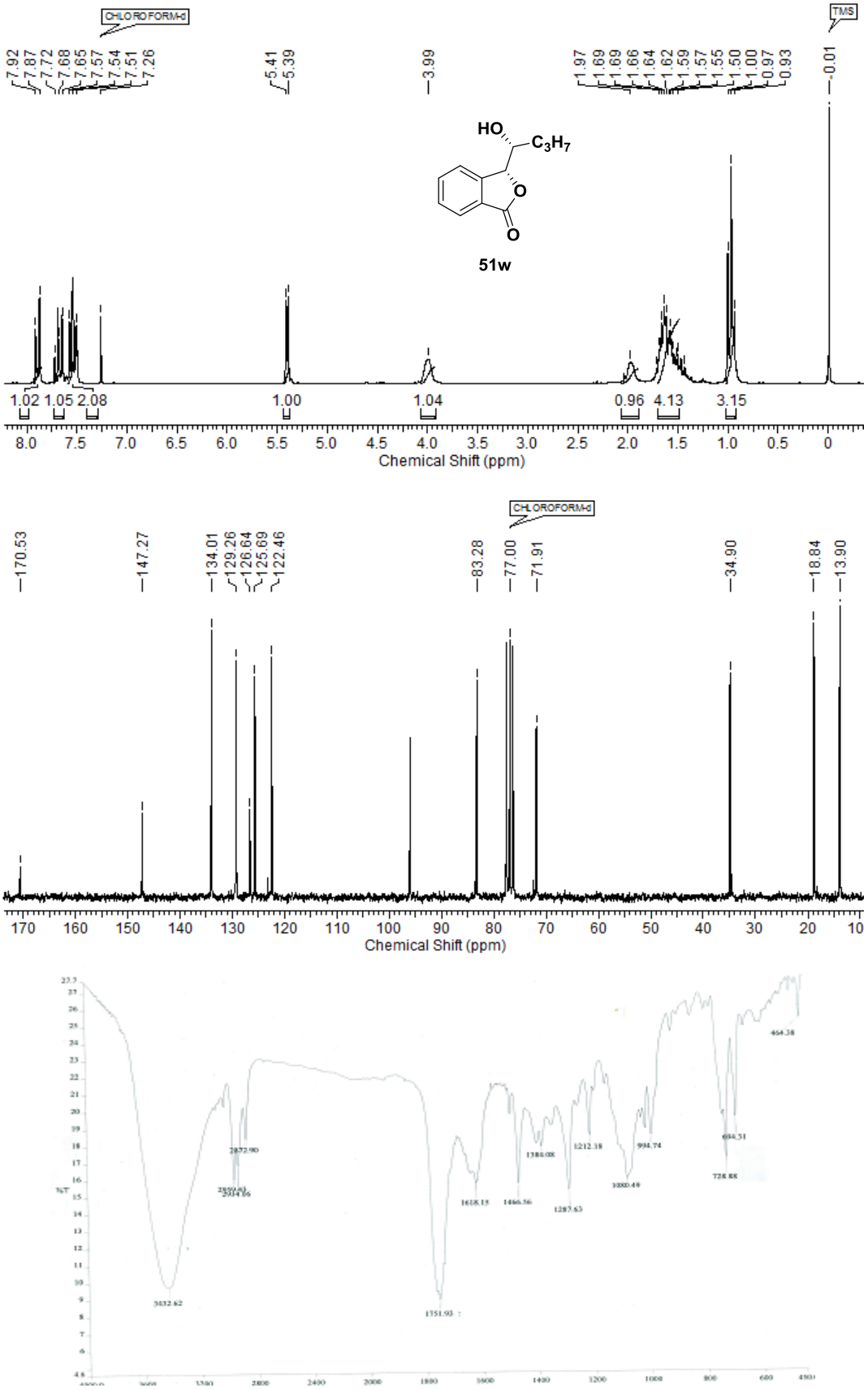


Fig. 21: ^{1}H, ^{13}C NMR and IR spectra of phthalide **51w**

The optical purity of chiral phthalide **51w** was determined to be 97% ee from ^{1}H NMR analysis of the corresponding Mosher's ester **88** (**Fig**. **22**) (see experimental section for details).

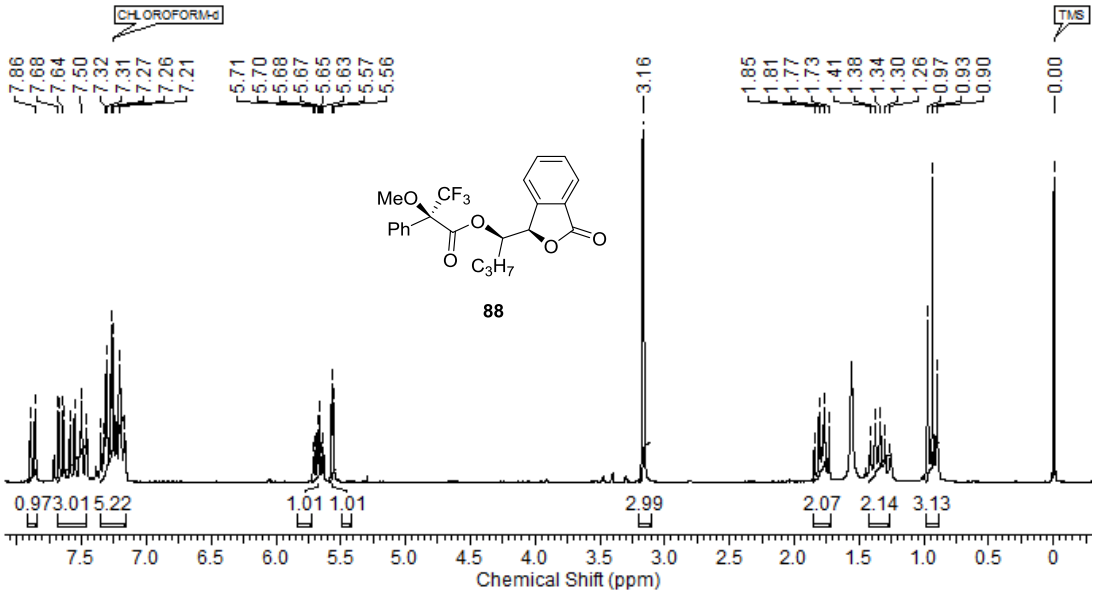


Fig. 22: ^{1}H NMR spectrum of Mosher's ester **88**

Finally, Barton-McCombie protocol[53] was utilized for deoxygenation of alcohol **51w**, in a two-step reaction sequence: (i) xanthate formation of alcohol **51w** (1,1-thiocarbonyldiimidazole, DMAP); (ii) followed by reduction of formed xanthate (Bu_3SnH, AIBN) afforded 3-butylphthalide (**1**) in 86% yield. The ^{1}H NMR spectrum of 3-butylphthalide (**1**) showed typical proton signals at δ 5.46 (dd, *J* = 4.3, 7.9 Hz, 1H), 1.68-1.86 (m, 1H) and 1.97-2.07 (m, 1H) corresponding to the methine proton attached to lactone moiety and homobenzylic protons respectively. Its ^{13}C NMR spectrum showed a characteristic carbonyl resonance of lactone [-(**C**=O)-O-] at δ 170.3 (**Fig. 23**). The ee of 3-butylphthalide (**1**) was found to be 97% based on comparison of its optical rotation with the reported value {$[\alpha]^{D}_{25}$ -67.0 (*c* 1.15,

$CHCl_3$); lit.[49] $[\alpha]^{D}_{25}$ -64.7 (c 1.06, $CHCl_3$)}. The spectral data of 3-butylphthalide (**1**) were in complete agreement with the reported values.[46-51]

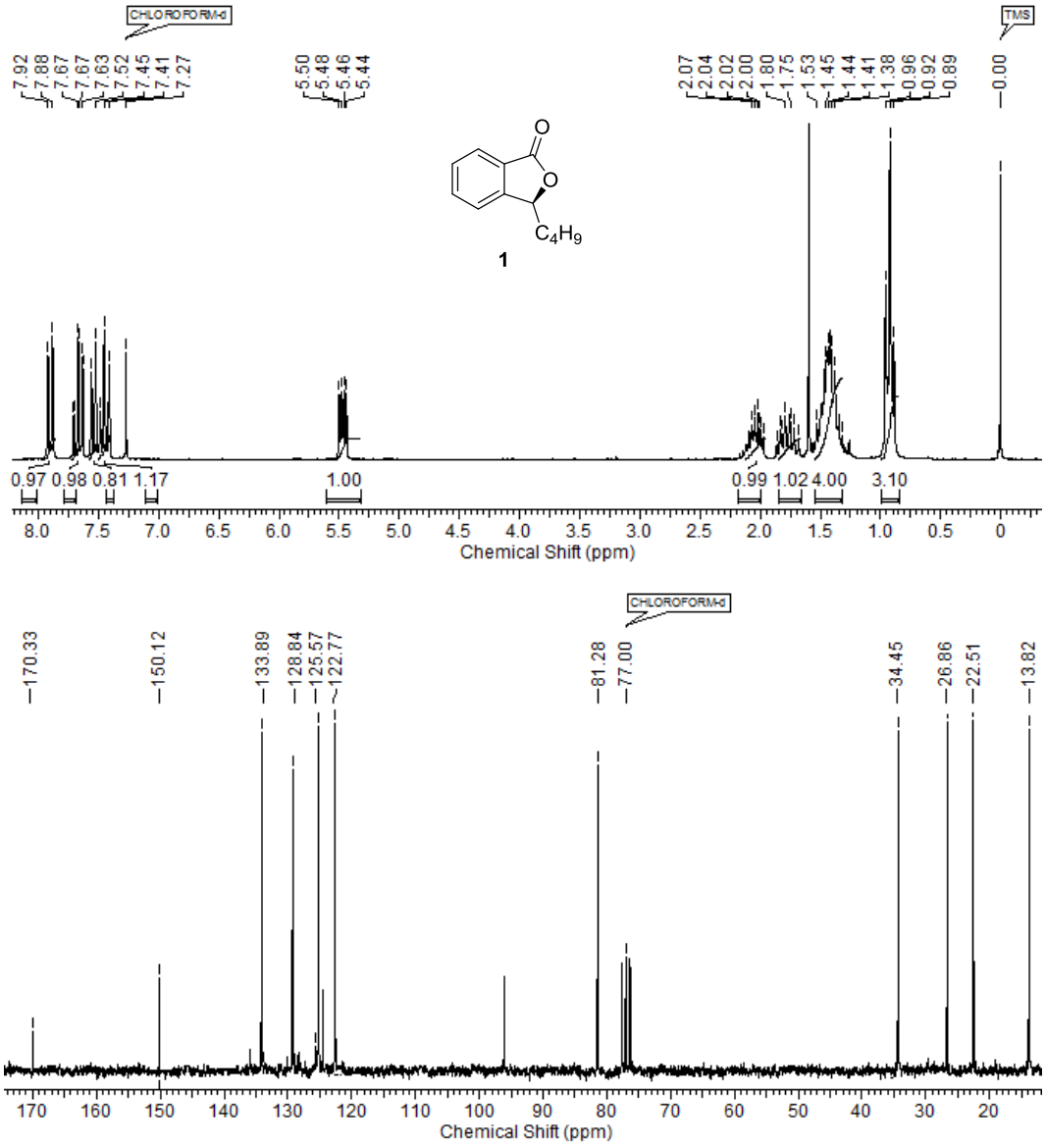


Fig. 23: ^{1}H and ^{13}C NMR spectra of 3-butylphthalide (**1**)

2.2.5 Conclusion

A short and an efficient enantioselective synthesis of (-)-matteucen C (**62**) and 3-butylphthalide (**1**) has been achieved in four linear steps (44 % overall yield, 99% ee and 57% overall yield, 97% ee respectively). Synthesis of (-)-matteucen C (**62**) was achieved for the first time, thereby confirming its structural and stereochemical

assignments. The CN-assisted one-pot oxidative cyclization of *o*-cyanoalkene derivatives **85** and **50w** was used as the key reaction, which proceeded to give high enantioselectivity.

2.2.6 Experimental Section

(*E*)-2-Bromo-1, 5-dimethoxy-3-styrylbenzene (84)

To a stirred solution of benzyltriphenylphosphonium iodide (2.1 g, 4.5 mmol) in THF was added *n*-butyllithium in hexane (2.8 mL, 4.5 mmol). The solution was stirred for 30 min at 0 °C followed by the addition of 2-bromobenzaldehyde (**83**) (1 g, 4.1 mmol) in THF dropwise *via* syringe at the same temperature and the reaction mixture was allowed to stir for 90 min at 25 °C (monitored by TLC). It was then cooled to 0 °C, diluted with sat. NH_4Cl (25 mL) and EtOAc (25 mL). The organic layer was separated and the aqueous layer extracted with EtOAc (2 x 20 mL). The combined organic extracts were washed with brine and dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give crude product, which was purified by column chromatography [silica gel (230-400 mesh) and pet. ether:EtOAc (90:10) as an eluent] affording (*E*)-2-bromostyrene derivative **84** (1.12 g) as a gum.

Yield: 86%; colorless gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 669, 769, 1216, 1384, 1468, 1580, 2098, 3020; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.86 (s, 3H), 3.89 (s, 3H), 6.42 (d, *J* = 2.7 Hz, 1H), 6.99 (d, *J* = 16.1 Hz, 1H), 7.26-7.40 (m, 3H), 7.52 (d, *J* = 16.1 Hz, 1H), 7.53-7.55 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 55.3, 56.1, 98.9, 102.4, 105.1, 126.8, 127.9, 128.0, 128.6, 131.5, 136.9, 138.5, 156.7, 159.4; **Analysis:** $C_{16}H_{15}BrO_2$ requires C, 60.21; H, 4.74; found: C, 60.08; H, 4.59%.

2, 4-Dimethoxy-6-styrylbenzonitrile (85)

o-Bromostilbene derivative **84** (1 g, 3.1mmol) was taken up in dry DMF (10 mL) and CuCN (0.83 g, 9.3 mmol) was added and the mixture refluxed under N_2 for 18 h (monitored by TLC). The reaction mixture was then cooled to 25 ºC and then diluted with water (30 mL) and EtOAc (25 mL). The organic layer was separated and the aqueous layer extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine and dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give crude product, which was purified by column chromatography [silica gel (230-400 mesh) and pet. ether:EtOAc (7:3) as an eluent] to give *o*-cyanostilbene derivative **85** (0.7 g).

Yield: 83%; colorless solid; **mp:** 147-148 ºC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 694, 831, 953, 1045, 1073, 1150, 1203, 1326, 1460, 1570, 1595, 2216; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.90 (s, 6H), 6.34 (d, *J* = 2.3 Hz, 1H), 6.80 (d, *J* = 2.3 Hz, 1H), 7.20 (d, *J* = 16.4 Hz, 1H), 7.26-7.30 (m, 1H), 7.32-7.38 (m, 3H), 7.55 (d, *J* = 7.4 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 55.6, 56.0, 94.1, 97.4, 101.4, 115.7, 124.4, 127.2, 128.8, 133.5, 136.1, 143.4, 163.2, 163.9; **Analysis**: $C_{17}H_{15}NO_2$ requires C, 76.96; H, 5.70; N, 5.28; found: C, 76.92; H, 5.68; N, 5.24%.

(*R*)-3-((*R*)-Hydroxy(phenyl)methyl)-5,7-dimethoxyisobenzofuran-1-(3*H*)-one (86)

A 50 mL RB flask was charged with $K_3Fe(CN)_6$ (1 g, 3 mmol), K_2CO_3 (414 mg, 3 mmol), *tert*-BuOH (2.5 mL), THF (2.5 mL) and H_2O (5 mL) and stirred for 10 min. Subsequently, $(DHQD)_2PHAL$ (8 mg, 1 mol%) and $K_2OsO_4{\cdot}2H_2O$ (2 mg, 0.5 mol%) were added and the stirring continued for additional 30 min. To this reaction mixture, *o*-cyanostilbene derivative **85** (265 mg, 1 mmol) was added and allowed to stir for 7 h at 25 ºC. After completion of reaction (as monitored by TLC), sodium bisulphite (1 g) was added slowly at 0 ºC. The organic layer was separated, aqueous layer extracted

with ethyl acetate (3 x 10 ml) and the combined organic layers washed with brine (15 mL), dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to yield the crude product. Flash column chromatographic purification [silica gel (230-400 mesh) and pet. ether:EtOAc (7:3) as an eluent] gave **86** (221 mg).

Yield: 93%; colorless solid; **mp:** 170-172 ºC; $[\alpha]^{D}_{25}$ -77.56 (*c* 1.15, $CHCl_3$); 99% ee from chiral HPLC analysis (Chiracel OJ-H, *n*-hexane/*i*PrOH, 90:10, 0.5 mL/min) retention time 18.27 min (99.36%) and 20.40 min (0.64%); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 698, 759, 947, 1041, 1077, 1204, 1336, 1461, 1625, 1754, 2981, 3018, 3444; **^{1}H NMR** (500 MHz, CD_3OD): δ 3.61 (s, 3H), 3.84 (s, 3H), 4.77 (d, *J* = 6.4 Hz, 1H), 5.45 (d, *J* = 6.4 Hz, 1H), 5.78 (d, *J* = 1.7 Hz, 1H), 6.35 (d, *J* = 1.7 Hz, 1H), 7.29-7.32 (m, 5H); **^{13}C NMR** (125 MHz, $CDCl_3$+CD_3OD): δ 56.1, 76.0, 83.9, 99.9, 102.9, 107.6, 128.2, 128.8, 129.0, 139.2, 152.0, 159.9, 167.1, 169.8; **HRMS** (ESI) *m/z* calcd for $C_{17}H_{16}O_5$ $[M + Na]^+$: 323.0890, found: 323.0850; **Analysis**: $C_{17}H_{16}O_5$ requires C, 67.99; H, 5.37; found: C, 67.85; H, 5.29%.

(*R*)-5, 7-Dihydroxy-3-((*R*)-hydroxy(phenyl)methyl)isobenzofuran-1(3H)-one: [(-)-Matteucen C] (62)

To a solution of phthalide **86** (0.17 mmol, 50 mg) in CH_2Cl_2 (5 mL) at - 78 ^{o} C was added BBr_3 (1.36 mL, 1.36 mmol, 1 M in CH_2Cl_2) over 10 min. The reaction mixure was allowed to warm to 25 °C and then stirred for 24 h. It was quenched with sat. aq. $NaHCO_3$ (5 mL). The aqueous layer washed with CH_2Cl_2 and extracted with ethyl acetate (3 x10 mL). The combined organic layers were washed with brine (10 mL) and dried over anhyd. Na_2SO_4. After concentration, the crude product was purified by silica gel column chromatography to give **62** (31 mg).

Yield: 68%; colorless powder; **mp:** 135-147 ºC; $[\alpha]^{D}_{25}$ -54.16 (*c* 1.0, CH_3OH); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 691, 710, 1169, 1615, 1684, 1725, 3364; **^{1}H NMR** (500 MHz,

DMSO-d_6): δ 4.94 (t, *J* = 4.8 Hz, 1H), 5.44 (d, *J* = 4.0 Hz, 1H), 5.73 (d, *J* = 4.8 Hz, 1H), 6.23 (d, *J* = 1.8 Hz, 1H), 6.25 (d, *J* = 1.8 Hz, 1H), 7.27-7.36 (m, 5H), 10.30 (s, 1H), 10.33 (s, 1H); **^{13}C NMR** (125 MHz, DMSO-d_6): δ 72.6, 81.7, 101.1, 102.3, 104.2, 126.9, 127.3, 127.6, 140.7, 151.5, 157.6, 163.9, 167.7; **Analysis**: $C_{15}H_{12}O_5$ requires C, 66.17; H, 4.44; found: C, 66.09; H, 4.39%.

(*E*)-1-Bromo-2-(pent-1-enyl)benzene (52w)

To a stirred solution of sulfone **87** (1 g, 3.78 mmol) in dry THF (20 mL) at - 78 ^{o}C under N_2 atmosphere was added drop-wise NaHMDS (4.15 mL, 4.15 mmol), the mixture was stirred for 30 min followed by addition of neat *o*-bromobenzaldehyde (**66**) (0.3 mL, 5.6 mmol). After being stirred for 3 h at - 78 ^{o}C, the mixture was allowed to warm slowly to 25 ^{o}C and stirred for 10 h, finally quenched with H_2O. The aqueous layer was extracted with EtOAc (3x25 mL). The combined organic extracts were dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to get the crude alkene, which was purified by column chromatography on silica gel with pet. ether:EtOAc (95:5) to give pure (*E*)-*o*-bromoalkene **52w** (0.700 g, 82%).

Yield: 82%; colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 671, 757, 929, 1025, 1216, 1435, 1465, 1588, 1647, 2870, 2929; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.97 (t, *J* = 7.3 Hz, 3H), 1.47-1.54 (m, 2H), 2.18-2.29 (m, 2H), 6.15 (td, *J* = 6.9, 15.6 Hz, 1H), 6.69 (d, *J* = 15.6, 1H), 7.04 (dt, *J* = 1.8, 7.6 Hz, 1H), 7.22 (t, *J* = 7.6 Hz, 1H), 7.44-7.53 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.7, 22.2, 35.2, 123.4,126.8, 127.4, 128.1, 128.8, 132.8, 134.1, 137.7; **Analysis** for $C_{11}H_{13}Br$ requires: C, 58.69; H, 5.82%; found: C, 58.47; H, 5.69%.

(*E*)-2-(Pent-1-en-1-yl)benzonitrile (50w)

o-Bromoalkene **52w** (0.7 g, 3.1 mmol) was taken up in dry DMF (10 mL) and CuCN (0.83 g, 9.3 mmol) was added and the mixture refluxed under N_2 for 14 h (monitored

by TLC). The reaction mixture was then cooled to 25 ºC and then diluted with water (30 mL) and EtOAc (25 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to get the crude *o*-cyanoalkene, which was purified by column chromatography on silica gel with pet. ether:EtOAc (80:20) to give pure *o*-cyanoalkene **50w** (0.461 g, 87%).

Yield: 87%, colorless solid; **mp:** 126-128 ºC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 756, 857, 974, 1037, 1095, 1184, 1202, 1216, 1251, 1275, 1291, 1319, 1347, 1368, 1393, 1444, 1477, 1573, 1607, 1640, 1716, 2219, 2984, 3023; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.98 (t, *J* = 7.3 Hz, 3H), 1.48-1.60 (m, 2H), 2.22-2.33 (m, 2H), 6.43 (dt, *J* = 6.8, 15.3 Hz, 1H), 6.74 (d, *J* = 15.3 Hz, 1H), 7.25 (dd, *J* = 15.3, 1.4 Hz, 1H), 7.45-7.62 (m, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.7, 22.2, 35.2, 110.5, 117.9, 125.2, 126.0, 126.8, 132.5, 132.7, 136.4, 141.1; **Analysis**: $C_{12}H_{13}N$ requires C, 84.17; H, 7.65; N, 8.18; found: C, 84.14; H, 7.61; N, 8.15%.

(*R*)-3-((*R*)-1-Hydroxybutyl)isobenzofuran-1(3*H*)-one (51w)

A 50 mL RB flask was charged with $K_3Fe(CN)_6$ (1 g, 3 mmol), K_2CO_3 (414 mg, 3 mmol), *tert*-BuOH (2.5 mL), THF (2.5 mL) and H_2O (5 mL) and stirred for 10 min. Subsequently, $(DHQD)_2PHAL$ (8 mg, 1 mol%) and $K_2OsO_4{\cdot}2H_2O$ (2 mg, 0.5 mol%) were added and the stirring continued for additional 30 min. To this reaction mixture, *o*-cyanoalkene **50w** (172 mg, 1 mmol) was added and allowed to stir for 7 h at 25 ºC. After completion of reaction (as monitored by TLC), sodium bisulphite (1 g) was added slowly at 0 ºC. The organic layer was separated, aqueous layer extracted with ethyl acetate (3 x 10 ml) and the combined organic layers washed with brine (15 mL), dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to yield the crude

product. Flash column chromatographic purification [silica gel (230-400 mesh) and pet. ether:EtOAc (75:25) as an eluent] gave phthalide 5**1w** (0.191 g, 93%).

Yield: 93%; colorless solid; **mp:** 103-109 ºC; $[\alpha]^{D}_{25}$ -76.89 (*c* 1, $CHCl_3$); 97% ee by Mosher's ester analysis**; IR** ($CHCl_3$, cm^{-1}): υ_{max} 694, 728, 1080, 1212, 1287, 1467, 1618, 1752, 2873, 2959, 3433; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.93 (t, *J* = 6.8 Hz, 3H), 1.44-1.72 (m, 4H), 1.97 (br s, 1H), 3.99 (br s, 1H), 5.40 (d, *J* = 3.6 Hz, 1H), 7.51-7.57 (m, 2H), 7.65-7.73 (m, 1H), 7.87-7.92 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.9, 18.8, 34.9, 71.9, 83.2, 122.4, 125.6, 126.6, 129.2, 134.0, 147.2, 170.5; **Analysis**: $C_{12}H_{14}O_3$ requires C, 69.88; H, 6.84; found: C, 69.82; H 6.81%.

Mosher's ester of (*R*)-3-((*R*)-1-Hydroxybutyl)isobenzofuran-1(3*H*)-one (88)

A two-neck 10 mL flask with septum was charged with (38 mg, 0.18 mmol) *N*,*N*'-dicyclohexylcarbodiimide (DCC), catalytic amount of 4-dimethylaminopyridine (DMAP) and CH_2Cl_2 (2 mL) under argon atmosphere. The flask was allowed to cool at 0 ºC for 10 min and a solution of alcohol **51w** (34 mg, 0.16 mmol) in CH_2Cl_2 (2 mL) was introduced through a syringe. It was allowed to stir for additional 10 min, followed by dropwise addition of (*R*)-α-methoxy-α-trifluoromethylphenyl acetic acid (42 mg, 0.176 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was then stirred at 0 ºC for additional one hour and then at room temperature for overnight. The reaction mixture was diluted with CH_2Cl_2 (50 mL), washed with saturated $NaHCO_3$ solution (50 mL), dried over anhyd. Na_2SO_4 and then concentrated under reduced pressure to get Mosher's ester **88** (53 mg, 80%) as a thick syrup.

Yield: 80%; **$[\alpha]^{25}_{D}$** -42.5 (*c* 0.4, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 650, 737, 1016, 1154, 1243, 1410, 1496, 1644, 1754, 2255, 2851, 2930, 2951,3069, 3156; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.93 (t, *J* = 6.8 Hz, 3H), 1.26-1.41 (m, 2H), 1.73-1.85 (m, 2H), 3.16 (s, 3H), 5.56 (d, *J* = 3.6 Hz, 1H), 5.63-5.71 (m, 1H), 7.17-7.35 (m, 5H), 7.46-7.52 (m,

2H), 7.67 (td, *J* = 1.13, 7.4 Hz, 1H), 7.89 (d, *J* = 7.6 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.1, 19.3, 33.8, 37.5, 49.9, 55.2, 80.1, 92.8 (d, *J* = 36.3 Hz), 123.8 (d, *J* = 271.4 Hz), 125.8, 127.5, 128.1, 129.1, 131.9, 137.2, 148.1, 165.2, 170.6; **Analysis:** **$C_{23}H_{23}F_3O_4$** requires C, 65.71; H, 5.51; found: C, 65.62; H, 5.34%.

(*S*)-3-Butylisobenzofuran-1(3H)-one: [3-Butylphthalide] (1)

Under a nitrogen atmosphere, 1,1-thiocarbonyldiimidazole (233 mg, 1.818 mmol) was added to a solution of **51w** (250 mg, 1.212 mmol) and DMAP (22 mg, 0.121mmol) in CH_2Cl_2 (10 mL). After stirring for 18 h at room temperature, solvent was removed *in vacuo*. To this were added AIBN (20 mg, 0.121 mmol) and tributyltin hydride (1.6 ml, 6.06 mmol) in toluene (15 mL) and the mixture was refluxed for 15 min. It was then diluted with ethyl acetate and successively washed with water and brine. The organic layer was dried with anhyd. Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed twice on silica gel (pet. ether:EtOAc 80:20) to give butylphthalide (163 mg, 86%).

Yield: 86%; colourless oil; $[\alpha]^{D}_{25}$ -67.0 (*c* 1.15, $CHCl_3$); lit.[49] $[\alpha]^{D}_{25}$ -64.7 (*c* 1.06, $CHCl_3$); **IR** ($CHCl_3$): 780, 1346, 1465, 1526, 1716, 2932 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.88-0.95 (m, 3H), 1.32-1.53 (m, 4H), 1.68-1.86 (m, 1H), 1.97-2.07 (m, 1H), 5.46 (dd, *J* = 4.3, 7.9 Hz, 1H), 7.42 (dd, *J* = 1.13, 7.6 Hz, 1H), 7.52 (t, *J* = 7.4 Hz, 1H), 7.66 (td, *J* = 1.13, 7.4 Hz, 1H), 7.90 (d, *J* = 7.6 Hz, 1H); **^{13}C NMR** ($CDCl_3$): δ 13.8, 22.5, 26.9, 34.4, 81.3, 121.8, 125.5, 128.9, 133.9, 150.1, 170.3; **Analysis**: $C_{12}H_{14}O_2$ requires C, 75.76; H, 7.42; found: C, 75.72; H, 7.39%.

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CHAPTER 3

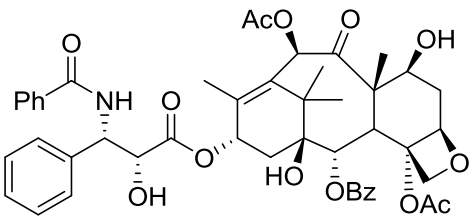
A New Concise Method for the Synthesis of Chiral 3-Amino-1,2-Diols, (+)-*epi*-Cytoxazone and Formal Synthesis of *N*-Thiolated-2-Oxazolidinone *via* Proline-Catalyzed α-Amino oxylation of β-Aminoaldehydes

Section I:

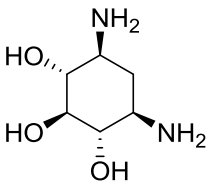
Proline-Catalyzed α-Aminooxylation of β-Aminoaldehydes: A Highly Stereoselective Synthesis of 3-Amino-1,2-Alkane Diols

3.1.1 Introduction

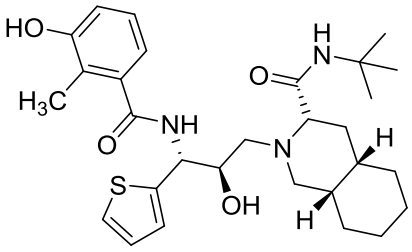
The enantiomerically pure *syn*- and *anti*-3-amino-1,2-alkane diols are ubiquitous substructures associated with biologically active natural products.[1] They are important and versatile 'building blocks' for asymmetric synthesis of bioactive pharmaceuticals and complex bioactive molecules. Some representative examples of biologically active and pharmacologically relevant therapeutic agents, wherein 3-amino-1,2-alkane diols play a vital role as key intermediates in their synthesis are shown in **Fig. 1**. For example, taxol (**1**) is a mitotic inhibitor drug used in cancer chemotherapy and AIDS-related Kaposi's sarcoma.[2]



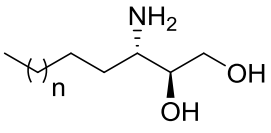
Taxol (**1**)



2-Deoxystreptamine (**2**)



Nelfinavir Analogue (**3**)



n = 11; Amino Diol (**4a**)
n = 15; Amino Diol (**4b**)

Fig. 1: Structures of bioactive 3-amino-1,2-alkane diols

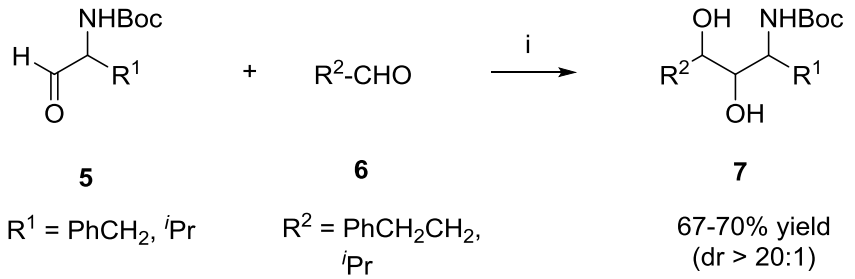
2-Deoxystreptamine (**2**) is a key structural fragment of aminoglycoside antibiotics, which have broad antibacterial spectrum and proven efficacy in the treatment of serious infections.[3] Nelfinavir analogue (**3**) showed inhibitory activity against wildtype HIV PR with a IC_{50} value of 30μM.[4] Also, long chain 3-amino-1,2-alkane diols (**4a** and **4b**) showed *in vitro* cytotoxicity against six solid tumor cell lines (A2780, H322, LL, WiDr, C26-10 and UMSCC-22B).[5] The wide interest in amino alcohol functionality, as found in chiral auxiliaries, ligands, and in various bioactive compounds has resulted in numerous synthetic strategies for this important class of compounds.[6-17]

3.1.2 Review of Literature

Literature search revealed that there are various methods available for the synthesis of 3-amino-1,2-alkane diols derivatives, some of which are described below.

Pederson's approach (1990)[6]

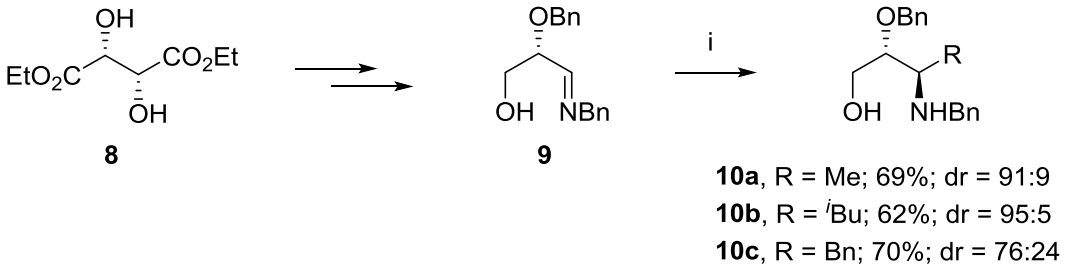
Pederson *et al*. have described the synthesis of *syn*,*syn*-3-amino-1,2-alkane diols **7** *via* chelation-controlled pinacol cross coupling reaction between N-Boc-α-amino aldehydes **5** and aliphatic aldehydes **6** using vanadium(II) reagent {$[V_2C1_3(THF)_6]_2$ $[Zn_2C1_6]$} in 67-70% yield (dr > 20:1) (**Scheme 1**).



Scheme 1: (i) $[V_2C1_3(THF)_6]_2[Zn_2C1_6]$, CH_2Cl_2, 1 h, 10 % aq. sodium tartrate.

Jagers's approach (1994)[7a]

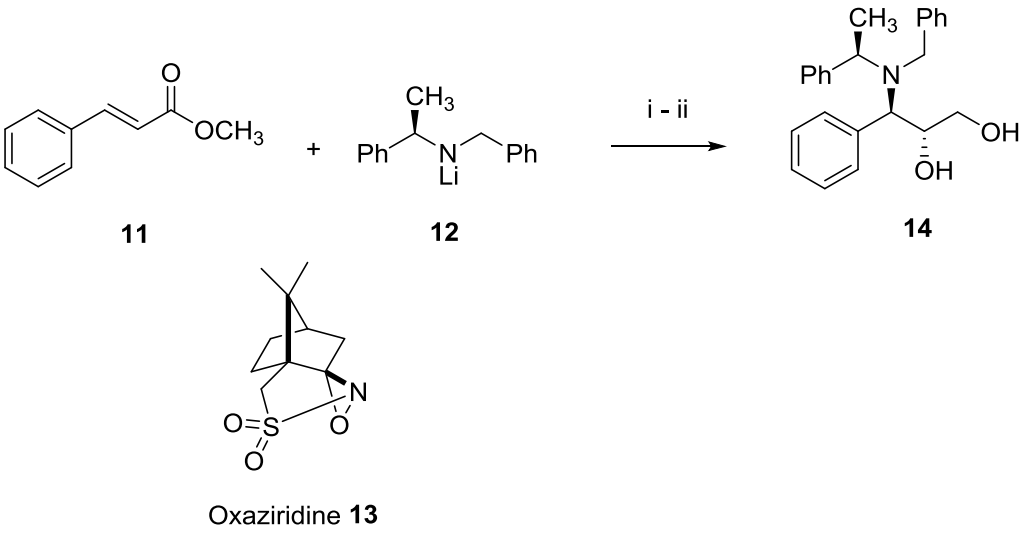
Jagers *et al.* have achieved the synthesis of optically active 3-amino-1,2-alkane diols **10a-c** using a chiral pool approach commencing from (+)-diethyl tartrate (**8**), which was converted to glycerinealdimine **9** using simple standard transformations.[7b] Stereoselective Grignard addition of alkyl magnesium halides onto glycerinealdimine **9** in the presence of $CeCl_3$ provided *anti*-amino diols **10a-c** as major diastereomers (de = 52-90%) in 62-70% yield (**Scheme 2**).



Scheme 2: (i) RMgX, $CeCl_3$, THF, 0 °C to 25 °C, 12 h.

Bunnage's approach (1994)[8]

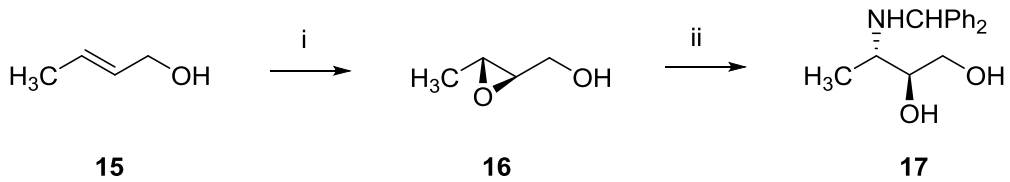
Bunnage *et al*. have reported a useful method for the synthesis of 3-amino1,2-alkane diol **14** using diastereoselective conjugate addition of amine source with enoate acceptor **11** as key step. Thus, tandem diastereoselective conjugate addition of lithium N-benzylamide **12** with methyl cinnamate **11**, followed by the electrophilic hydroxylation of the resultant β-amino enolates with camphorsulfonyl oxaziridine **13** resulted in β-amino-α-hydroxyester. Subsequent reduction of ester with $LiAlH_4$ provided *anti*-amino diol **14** with good diastereoselectivity (> 90% d.e.) and moderate yield (**Scheme 3**).



Scheme 3: (i) THF, -78 °C, 2 h then oxaziridine (**13**), -78 °C to 0 °C, 1 h, 43%; (ii) $LiAlH_4$, THF, 0 ºC to 25 ºC, 2 h, 72%.

Riera's approach (1995)[9]

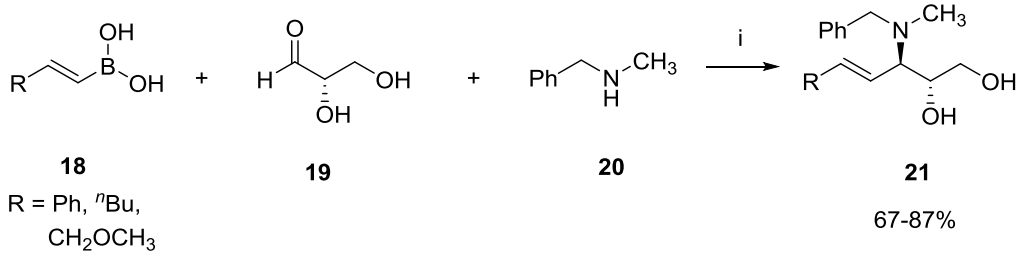
Riera *et al.* have used Sharpless asymmetric epoxidation as the key reaction for the introduction of chirality. Thus, commercially available (*E*)-crotyl alcohol **15** was subjected to Sharpless asymmetric epoxidation with D-(-)-DIPT to give epoxy alcohol **16**. $Ti(O^iPr)_4$ mediated regioselective ring opening of chiral epoxy alcohol **16** by primary amine provided (2*S*, 3*S*)-3-benzhydrylamino-1,2-butanediol (**17**) in 68% yield with 92% ee (**Scheme 4**). Regioselective opening of chiral epoxides with amine source have been extensively used for many bioactive molecule syntheses, especially antiHIV Protease inhibitors.



Scheme 4: (i) D-(-)-DIPT, $Ti(O^iPr)_4$, *tert*-BuOOH, CH_2Cl_2, -25 °C; (ii) Ph_2CHNH_2, $Ti(O^iPr)_4$, CH_2Cl_2, 25 °C, 24 h, 68% (over two steps).

Petasis's approach (1998)[10]

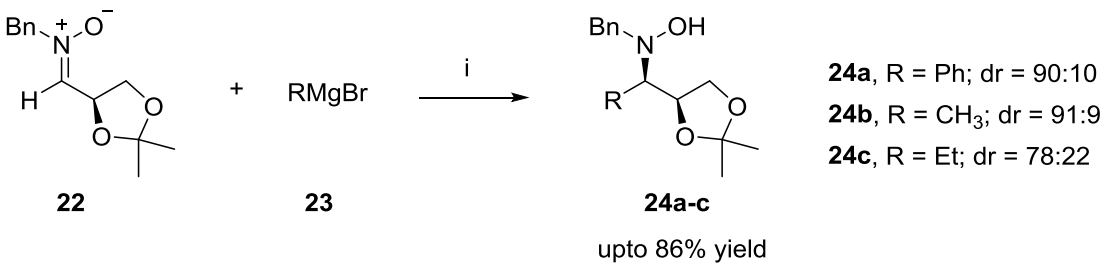
Petasis *et al.* have described the enantioselective synthesis of 3-amino-1,2-alkane diols using chiral pool approach. This method involves one-step three component variant of Mannich reaction involving organoboronic acids **18**, α-hydroxy aldehyde **19** and an amine **20** under milder reaction conditions that gave directly the corresponding *anti*-3-amino-1,2-alkane diols **21** in 99% de and ee (**Scheme 5**).



Scheme 5: (i) EtOH, sealed tube, 25 °C, 24 h.

Merino's approach (1998)[11]

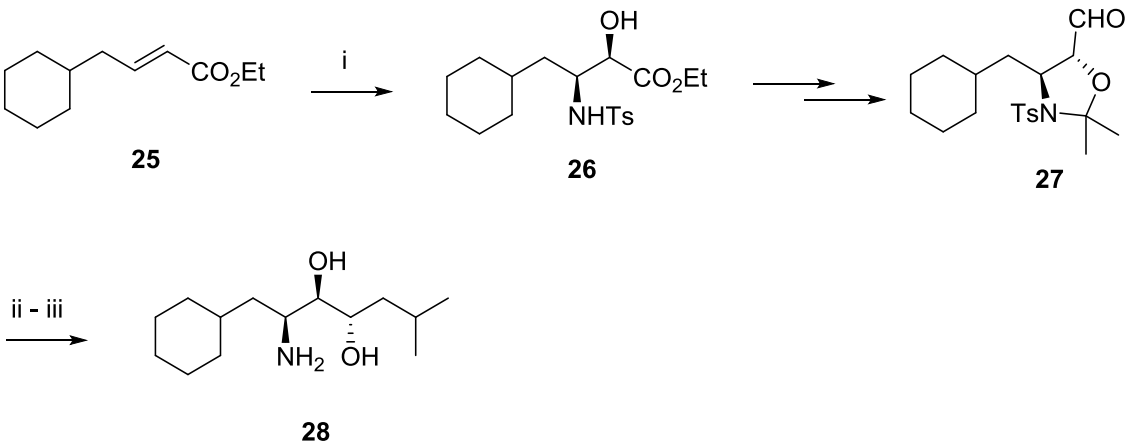
Merino *et al*. have reported the synthesis of *syn*-3-amino-1,2-alkane diols **24** using a chiral pool approach commencing from glyceraldehyde nitrone **22**, which was derived from D-glyceraldehyde by condensation with N-benzyl hydroxylamine. Stereoselective Grignard addition of alkyl magnesium halides **23** onto glyceraldehyde nitrone **22** in the presence of $ZnBr_2$ provided *syn*-amino diols **24a-c** as major diastereomer (de = 66-82%) in 72-86% yield (**Scheme 6**).



Scheme 6: (i) $ZnBr_2$, Et_2O, -60 ºC, 6 h.

Chandrasekhar's approach (1999)[12]

Chandrasekhar *et al.* have reported the synthesis of Abbott amino diol **28** using Sharpless asymmetric aminohydroxylation as the key step. Thus, α,β-unsaturated ester **25** was subjected to asymmetric aminohydroxylation using catalytic amount of quinine derived ligand $(DHQ)_2PHAL$, $K_2OsO_2(OH)_4$ and commercially available Chloramine-T to provide amino alcohol **26** in 65% yield and 89% ee. Acetonide protection of amino alcohol **26** followed by reduction of ester afforded aldehyde **27**, which on reaction with ^{i}BuMgBr followed by deprotection of acetonide with HCl gave *syn,anti*-amino diol **28** as major diastereomer (dr = 80:20) (**Scheme 7**). Sharpless asymmetric aminohydroxylation has been extensively used for the introduction of chiral amino alcohols in the synthesis of many bioactive molecules. But the major drawback with this method is the poor regioselectivity of the newly introduced amino alcohol functionality.

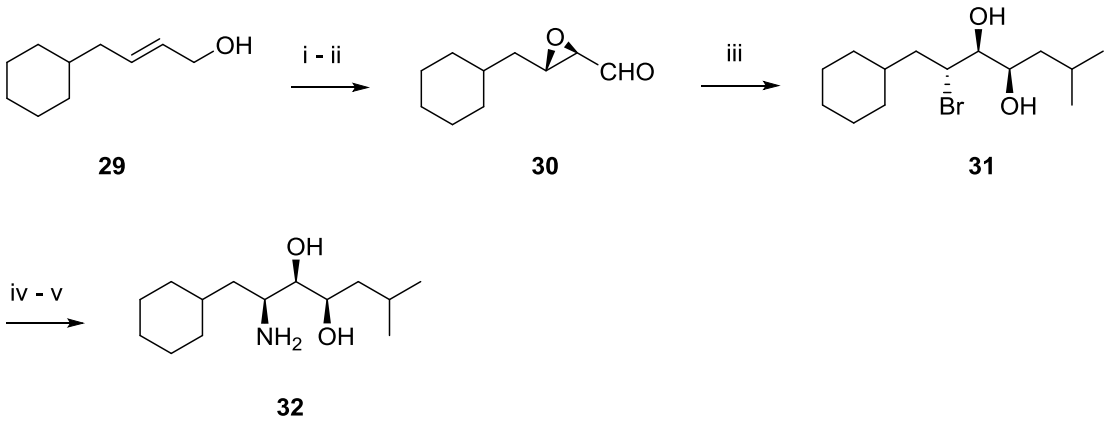


25 **26** **27** **28**

Scheme 7: (i) chloroamine-T, $K_2[OsO_2(OH)_4]$, $(DHQ)_2PHAL$, *tert*-BuOH:H_2O (1:1), 12 h, 25 ºC, 65%; (ii) ^{i}BuMgBr, THF, 0 °C to 25 °C, 6 h, 72%; (iii) 6 N HCl, CH_3OH, 25 °C, 4 h, 52%.

Righi's approach (2000)[13]

Righi *et al.* have used Sharpless asymmetric epoxidation as the key reaction for the synthesis of 3-amino-1,2-alkane diol **32**. Thus, allyl alcohol **29** was subjected to Sharpless asymmetric epoxidation using L-(+)-DET to give epoxy alcohol, which on subsequent oxidation provided epoxy aldehyde **30** in 68% yield with 93% ee. One-pot ring opening/organometallic addition of α,β-epoxy aldehyde **30** with ^{i}BuMgBr in the presence of $MgBr_2.Et_2O$ afforded *syn*-diol **31** in stereocontrolled manner**.** Subsequent substitution of the bromine with azide, followed by catalytic hydrogenation to the amino group, led to *syn,syn*-3-amino-1,2-alkane diol **32** in 63% yield (over two steps) (**Scheme 8**).

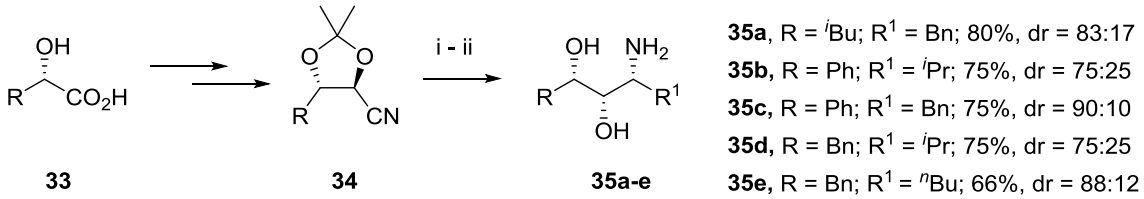


Scheme 8: (i) L-(+)-DET, $Ti(O^{i}Pr)_4$, *tert*-BuOOH, CH_2Cl_2, -25 °C, 24 h; (ii) TEMPO, $PhI(OAc)_2$, dry CH_2Cl_2, 25 ºC, 1 h, 72% (over two steps); (iii) $MgBr_2.Et_2O$, CH_2Cl_2, ^{i}BuMgBr, THF, -50 °C, 24 h, 65%; (iv) NaN_3, DMF, 40 ºC, 24 h, 71%; (v) 10% Pd/C, H_2 (50 psi), EtOAc, 24 h, 89%.

Larcheveque's approach (2000)[14a]

Larcheveque *et al.* have reported the synthesis of *syn,syn*-3-amino-1,2-alkane diols **35a-e** using a chiral pool approach commencing from acetonide protected *syn*-2,3-dihydroxynitriles **34**, which were derived from optically active 2-hydroxy acids **33**

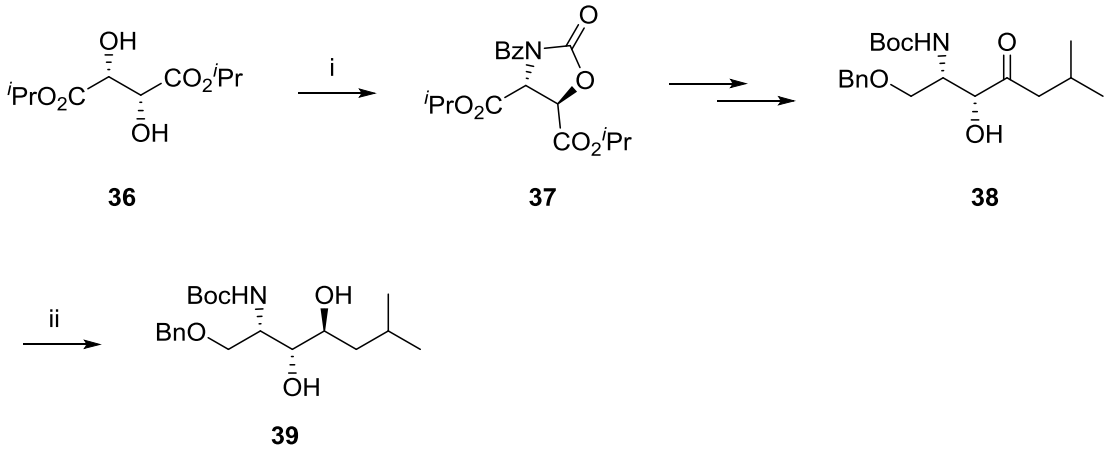
using simple standard transformation.[14b] Stereoselective Grignard addition of alkyl magnesium bromide onto dihydroxynitriles **34,** followed by $NaBH_4$ reduction of the resulting imine, afforded the corresponding *syn*-amino diols **35a-e** as major diastereomer (de = 50-80%) in 66-80% yield (**Scheme 9**).



Scheme 9: (i) R^1MgBr, Et_2O, -15 ºC, 6 h then $NaBH_4$, CH_3OH, 25 ºC, 14 h; (ii) 2 N HCl, CH_3OH, H_2O, 25 °C, 3 h.

Ko's approach (2003)[15]

Ko *et al*. have reported the synthesis of *syn,anti*-3-amino-1,2-alkane diol **39** using a chiral pool approach.



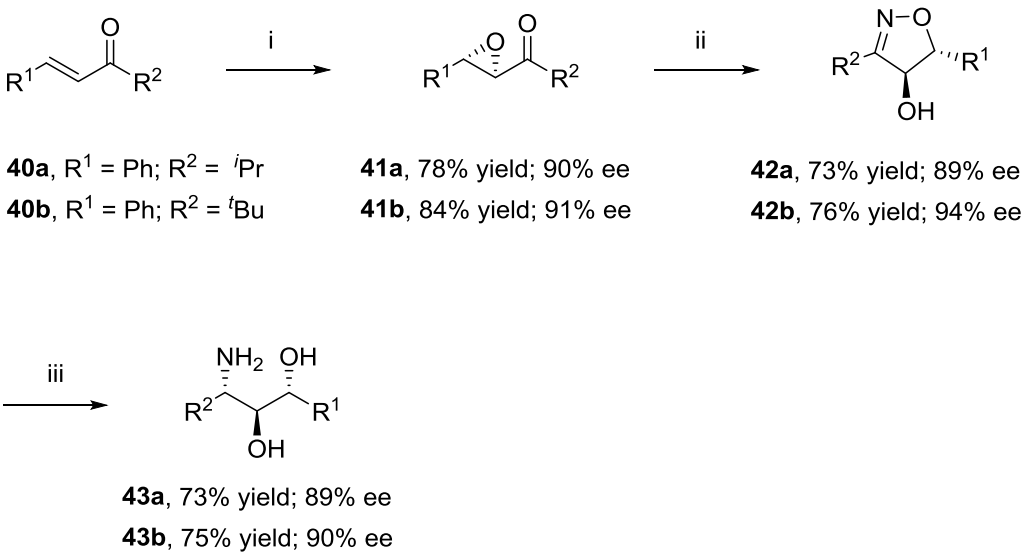
Scheme 10: (i) Bu_2SnO, CH_2Cl_2, reflux, Dean-Stark, 4 h, then BzNCS, Et_3N, Bu_4NBr, reflux, 2 h, 76%; (ii) $NaBH(OAc)_3$, CH_3CN:*n*-hexane (1.2:1), 3 h, 84%.

(+)-Diisopropyl tartrate **36** was converted to protected amino alcohol **37** in 76% yield using a three-step reaction sequence in one pot: (i) activation of diol **36** *via* tin

ketalization; (ii) iminocarbonate formation by treatment of tinketal with BzNCS; (iii) rearrangement of iminocarbonate under nucleophilic condition. Protected amino alcohol **37** was then converted to ketone **38** using simple standard transformations, where regioselective reduction of ester and Weinreb's amide formation served as key steps. Diastereoselective reduction of the carbonyl group **38** with $NaBH(OAc)_3$ afforded *syn,anti*-3-amino-1,2-alkane diol **39** in 8.5:1 diastereoselectivity and 84% yield (**Scheme 10**).

Bickley's approach (2003)[16]

Bickley *et al.* have used L-leucine-based chiral epoxidation as the key reaction for synthesis of *anti,anti*-3-amino-1,2-alkane diols **43a-b**.



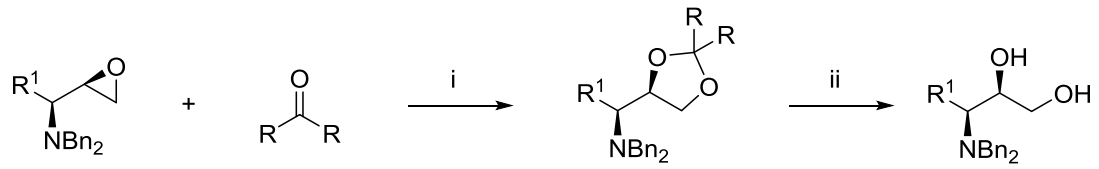
Scheme 11: (i) poly-*L*-leucine, THF, $NH_2CONH_2.H_2O_2$, DBU, 25 ºC, 24 h; (ii) NH_2OH. HCl, EtOH, pyridine, reflux, 14 h; (iii) $LiAlH_4$, THF, 0 ºC to 25 ºC, 2 h.

Thus, enones **40a-b** were epoxidised using urea-hydrogen peroxide complex in the presence of poly-L-leucine supported on silica to yield epoxides **41a-b** in 90% ee. Dihydroisoxazoles **42a-b** were obtained in good yields by treatment of epoxides **41a-**

b with hydroxylamine. Subsequent diastereoselective reduction of dihydroisoxazoles **42a-b** with $LiAlH_4$ afforded *anti,anti*-3-amino-1,2-alkane diols **43a-b** in good yields (73-75%) with 90% ee (**Scheme 11**).

Concellon's approach (2005)[17]

Concellon *et al.* have reported the synthesis of *syn*-3-amino-1,2-alkane diol **47** using a chiral pool approach commencing from enantiopure *syn*-2-(1-aminoalkyl)epoxides **44**. Thus, epoxides **44** were treated with different ketones **45** in the presence of $BF_3.Et_2O$ to provide the corresponding 4-(1-aminoalkyl)-1,3-dioxolanes **46** in high yields and without epimerization. Finally, deprotection of 1,3-dioxolanes **46** with HCl afforded *syn*-3-amino-1,2-alkane diol **47** (**Scheme 12**).



44 **45** **46** **47**

R^1 = Bn, Me, ^{i}Bu R = Me, Et 85-91% 83-95%

Scheme 12: (i) $BF_3.Et_2O$, CH_2Cl_2, 0 °C, 1 h; (ii) 1N HCl, CH_3CN, reflux, 1 h.

3.1.3 Present Work

3.1.3.1 Objective

As can be seen from the above discussion, the reported methods are quite effective. However, there are certain serious short-comings associated with them such as: (i) dependence on chiral pool resources; (ii) expensive chiral ligands, catalysts and reagents; (iii) multi-step reaction sequences; (iv) lack of broader substrate scope; (v) lack of higher enantio- and diastereoselectivity and (vi) use of protection and

deprotection of various functional groups involved in the synthesis limiting the overall yield of the process, particularly unsuitable for atom economic synthesis. In this regard, a simple metal-free procedure to obtain chiral 3-amino-1,2-alkane diol derivatives in high enantio- and diastereoselectivity is highly desirable. In this section, a highly stereoselective, one-pot procedure for obtaining chiral 3-amino-1,2-alkane diols using proline-catalyzed α-aminooxylation of β-aminoaldehydes is decribed. Since the method involves organocatalysis, especially proline-catalysed (i) Mannich reaction of acetaldehyde[18] and (ii) α-aminooxylation of aldehydes[19] for introducing stereogenicity into the prochiral molecule, a brief account of each of them is described below.

3.1.3.2 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.[20] This rediscovery has initiated an explosive growth of research activities in organocatalysis both in industry and in academia. 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. In particular, L-proline (**48**) has been defined as a "universal catalyst" because of its high utility in a 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).

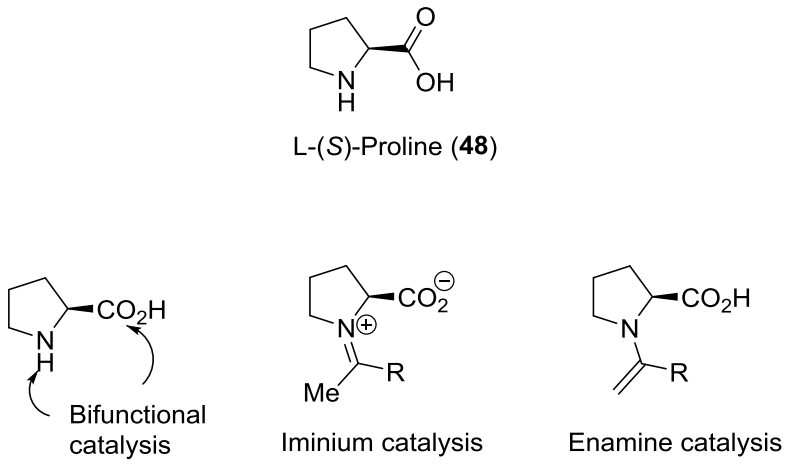


Fig. 2: Modes of proline catalysis

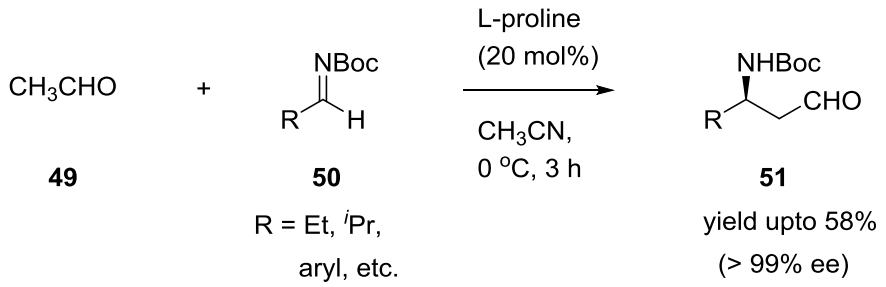
It can be regarded as a bifunctional catalyst as the secondary amine acts as Lewis base and the acid group acts as Bronsted acid (**Fig. 2**). The high stereoselectivity in the proline-catalyzed reactions is possibly due to its formation of organized transition states with many hydrogen bonding frameworks. Proline is not the only molecule to promote catalysis, but it still seems to be one of the best in the diversity of

transformations. It is known to catalyze aldol,[21] Diels-Alder,[22] Michael addition,[23] Mannich[18] and α-functionalization[24] among many other organic transformations.[25]

3.1.3.3 Proline-catalyzed Mannich reaction of acetaldehyde

Mannich reaction is enormously useful for the construction of nitrogenous molecules.[26] The increasing popularity of the Mannich reaction has been fueled by the ubiquitous nature of nitrogen in drugs and natural products as well as by the potential of this multi-component reaction to generate diversity. Only a handful of catalytic asymmetric Mannich reactions have been reported.[27] The proline-catalysed Mannich reaction has evolved into a broadly useful transformation that has been applied to the synthesis of natural products, pharmaceuticals, and several classes of chiral amino acids.[28] Very recently, N-Boc-imines **50** have been introduced to the proline-catalysed Mannich reaction,[29] significantly widening the already large substrate scope and utility of this process. However, acetaldehyde, which would be a particularly useful nucleophile in this reaction, was not used under proline-catalysed Mannich reactions conditions till recent years due to several problems associated with the potential use of acetaldehyde, such as: (i) acetaldehyde rapidly reacting with itself *via* aldol condensation, forming coloured oligomers and polymers if treated with proline and (ii) hypothetical acetaldehyde Mannich products, themselves α-unbranched aldehydes, may undergo further reaction with an additional imine equivalent or eliminate to form the corresponding unsaturated aldehydes. It was recently found that these potential side reactions can be suppressed if a higher excess of acetaldehyde (5-10 equivalents) is used.[18] Thus, when N-Boc-imines **50** were treated with acetaldehyde **49** in the presence of L-proline (20 mol%) in CH_3CN at 0 ºC the desired β-aminoaldehydes **51** were obtained in extremely high enantioselectivities (> 99%) and reasonable yields (**Scheme 13**). The β-amino aldehyde products **51** formed with very high

enantioselectivity are highly attractive precursors of chiral β-amino acids, which play a key role in investigations of β-peptides and pharmaceuticals.[30]

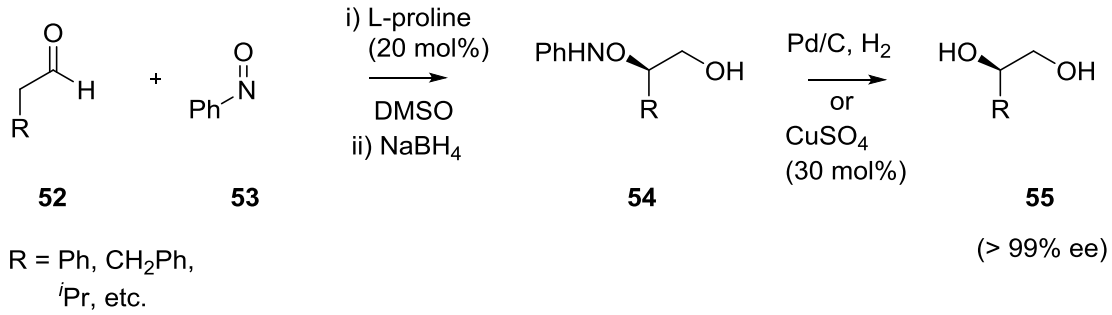


Scheme 13: Mannich reaction of acetaldehyde

3.1.3.4 Proline-catalyzed α-Aminooxylation of Aldehydes

Optically active α-hydroxy aldehydes and ketones are important intermediates in organic synthesis as they are the 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-oxygenations include the use of Davis oxaziridine,[31a] Sharpless dihydroxylation of enol ethers,[31b] manganese-salen epoxidation of enol ethers,[31c] and Shi' epoxidation of enol ethers.[31d] It is only rather recently that direct catalytic, asymmetric variants have been reported.[32] Most of these methods, however, require multiple manipulations and there is no direct method, nor catalytic asymmetric version for their synthesis from the corresponding aldehyde.

Proline is equally efficient for α-functionalization[24] of aldehydes and ketones. When an aldehyde **52** without substitution at α-position was reacted with nitrosobenzene **53** in presence of L-proline in DMSO at ambient temperature, aminooxylation of the aldehyde takes place at α-position. The aminooxyl moiety **54** undergoes hydrogenolysis with Pd/C, H_2 or $CuSO_4$ to give the corresponding diols **55** in very high enantioselectivities (**Scheme 14**).



Scheme 14: α-aminooxylation of aldehydes

The mechanism of the α-aminooxylation reaction is shown in **Fig. 3**. The observed enantioselectivitiy of the catalytic α-aminooxylation of aldehydes can be rationalized by invoking an enamine mechanism operating through a chair like transition state, wherein 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.

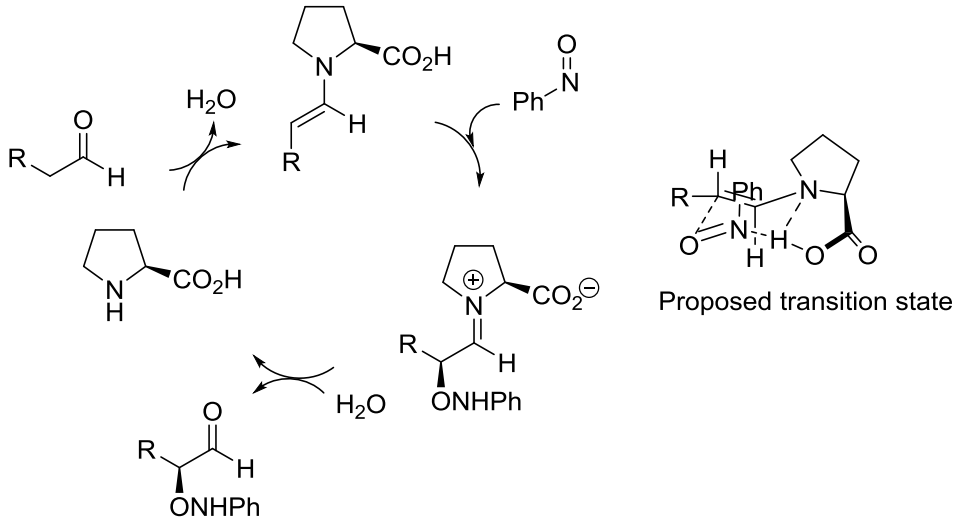
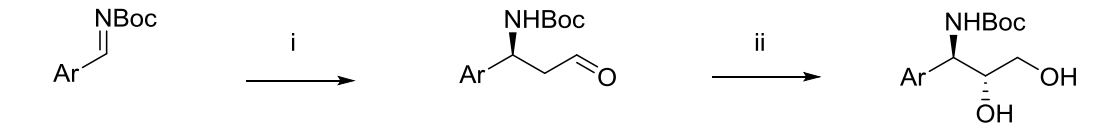


Fig. 3: Proposed mechanism of the α-aminooxylation reaction

3.1.4 Results and Discussion

Considering the high biological importance of chiral 3-amino-1,2-diols, which are also key intermediates in many drugs, we became interested in synthesizing them in one-pot reaction. Based on the literature knowledge of proline-catalyzed Mannich reaction (**Scheme 13**) and α-functionalization of aldehydes (**Scheme 14**), we hypothesized that one pot-synthesis of 3-amino-1,2-alkanediol **56** should be possible through sequential Mannich reaction of Boc-protected benzaldimine **50** with acetaldehyde **49** *via* List's protocol using L-proline providing β-aminoaldehyde **51** *in situ* followed by addition of PhNO and reduction with $NaBH_4$ in the same pot. Accordingly, we performed several experiments to identify a suitable reaction condition for this sequential α-aminooxylation reaction in one-pot, such as the variation of solvents (CH_3CN, DMSO), temperature, oxygen source (PhNO, benzoyl peroxide) and so on. Unfortunately, we ended up with complex reaction mixtures, often achieving a maximum yield of only 12% of the required product. We then reasoned that low yields may be due to unwanted side reaction of PhNO with the undesired products formed in the Mannich reaction of the first step. To overcome this, we decided to separate pure β-aminoaldehydes **51** after Mannich reaction and then subject it to α-aminooxylation process subsequently (**Scheme 15**).



50a-f

Ar = Ph, 4-OMe-Ph, 2-Cl-Ph, 4-Me Ph, 1-naphthyl, 2-furfuryl

51a-f

39-58% yield
96-98% ee

56a-f

55-68% yield
(90-99% ee)

Scheme 15: (i) CH_3CHO, L-proline (20 mol%), CH_3CN, 0 ^oC, 3 h; (ii) (a) PhNO (0.8 equiv), L-proline (20 mol%), CH_3CN, -10 ^oC, 20 h then $NaBH_4$ CH_3OH, 10 min; (b) $Cu(OAc)_2.H_2O$ (15 mol%), CH_3OH, 25 ^oC, 10 h.

Thus, pure β-aminoaldehydes **51a-f**, the starting materials for α-aminooxylation were efficiently prepared from the corresponding Boc-protected arylaldimines **50a-f** following literature protocol (L-proline, CH_3CN, 0 ºC). The formation of β-aminoaldehydes **51a-f** was confirmed by ^{1}H and ^{13}C NMR spectroscopy as follows.

Example 1: The ^{1}H NMR spectrum of β-aminoaldehyde **51e** showed a typical triplet at δ 9.81 (t, *J* = 2.2 Hz, 1H) and a doublet at δ 3.09 (d, *J* = 6.5 Hz, 2H) corresponding to aldehydic and homobenzylic methylene protons respectively. Its ^{13}C NMR spectrum showed two characteristic carbon signals at δ 195.4 and 200.2 due to carbamate and aldehydic carbonyl carbons respectively (**Fig. 4**).

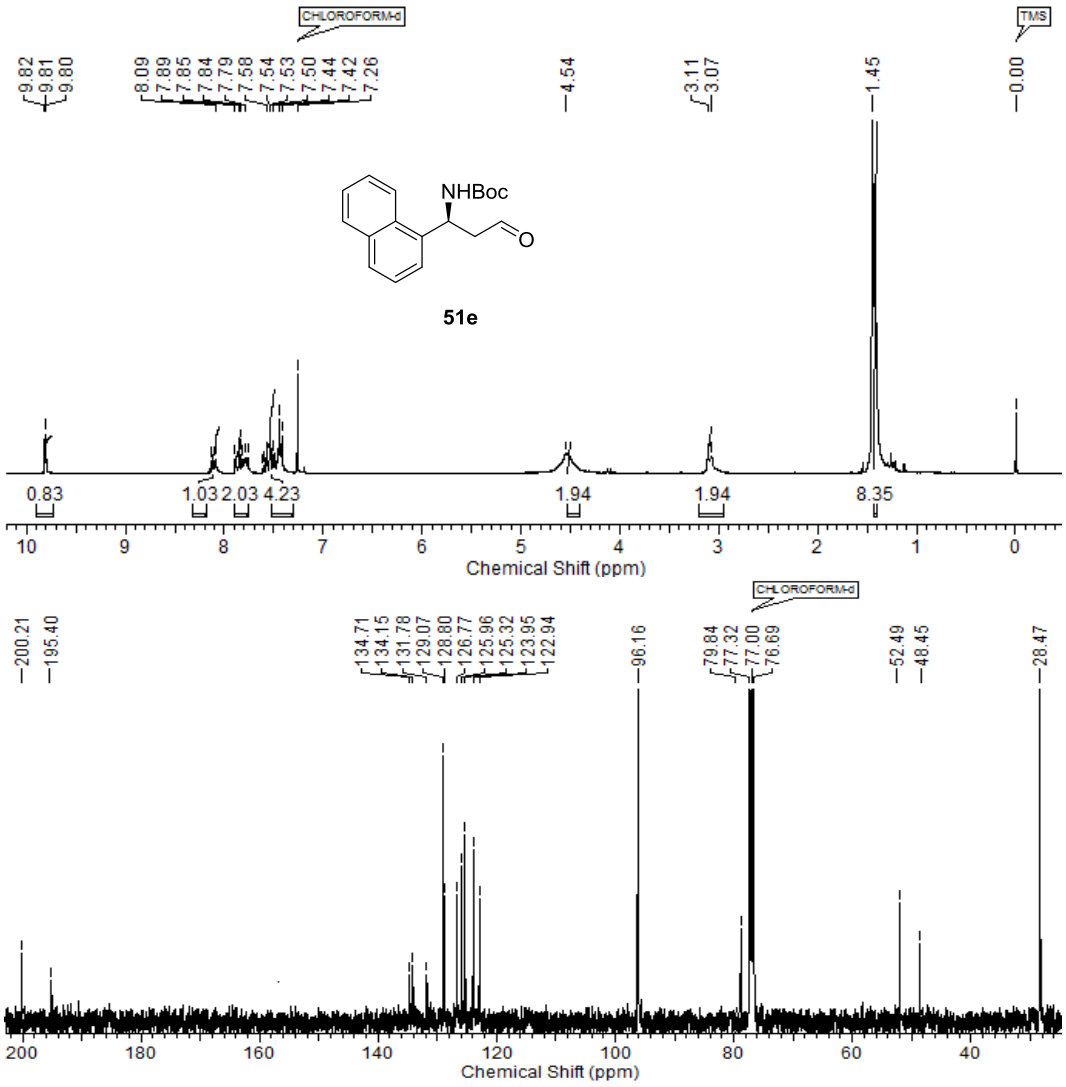


Fig. 4: ^{1}H and ^{13}C NMR spectra of β-aminoaldehyde **51e**

Example 2: The ^{1}H NMR spectrum of β-aminoaldehyde **51a** showed typical proton signals at δ 9.73 (t, *J* = 1.7 Hz, 1H) and δ 2.83-2.96 (m, 2H) corresponding to aldehydic and homobenzylic methylene protons respectively. Its ^{13}C NMR showed two characteristic carbon signals at δ 199.8 and 193.3 corresponding to carbamate and aldehyde carbonyl carbons respectively. Its IR spectrum also exhibited a characteristic strong C=O absorption band at 1692 cm^{-1} due to carbamate and aldehydic carbonyl group (**Fig. 5**).

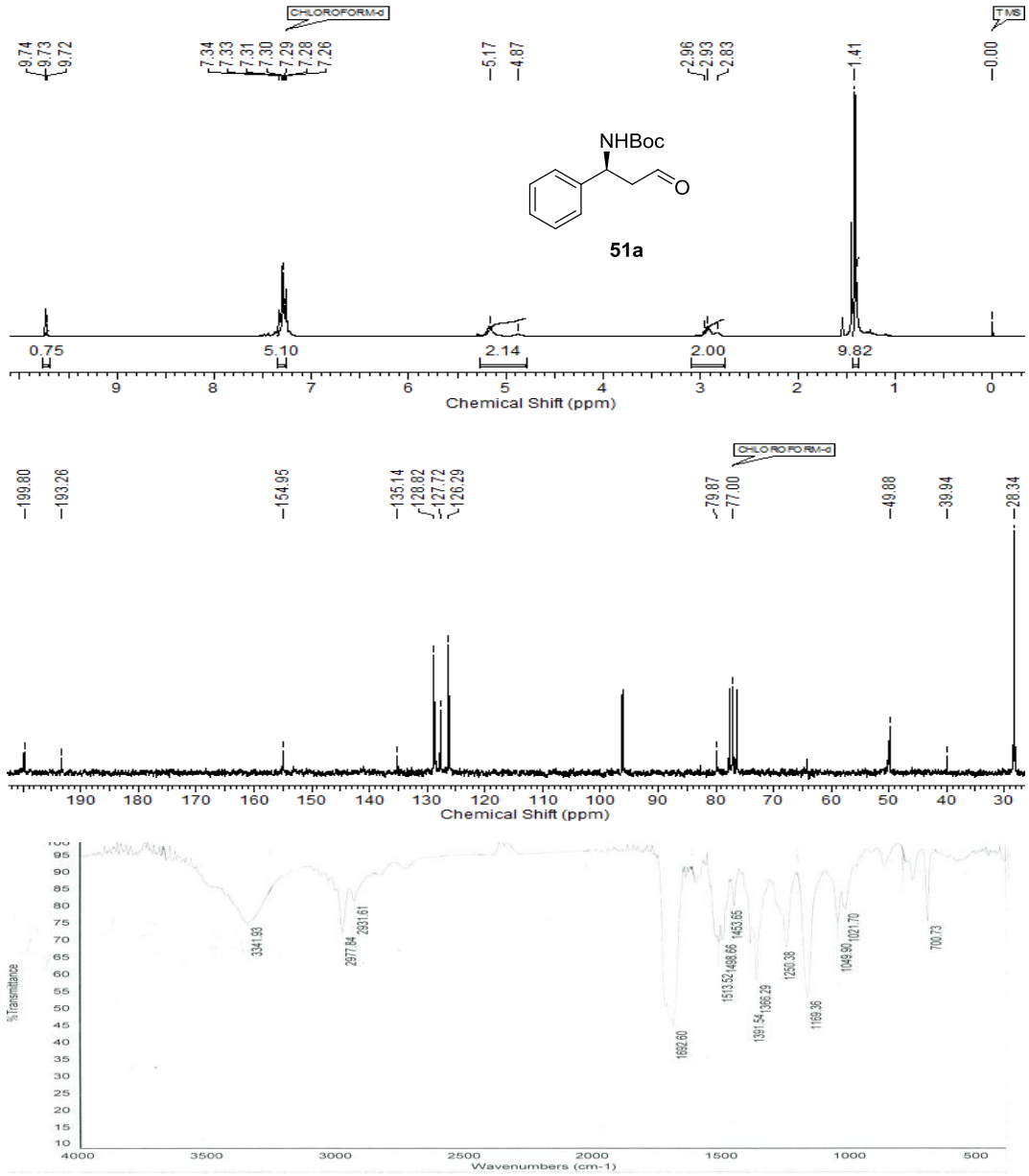


Fig. 5: ^{1}H, ^{13}C NMR and IR spectra of β-aminoaldehyde **51a**

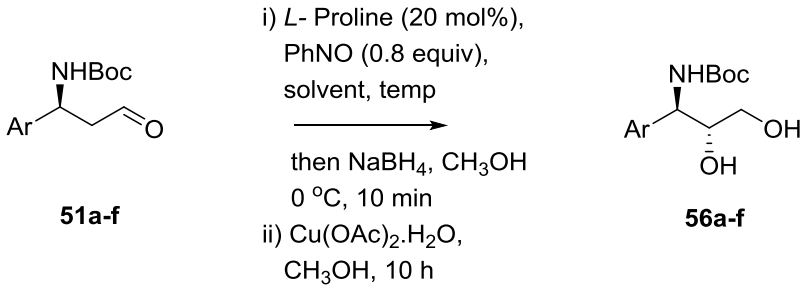
We observed a drastic improvement in the yield of **56a**, when pure β-aminoaldehyde **51a** was subjected to α-aminooxylation separately. The reaction proceeded through α-aminoxy aldehyde, which was *in situ* reduced with $NaBH_4$. This was followed by subsequent reduction of the crude aminoxy product with $Cu(OAc)_2.H_2O$ providing a single diastereomer of *anti*-3-amino-1,2-diol **56a** in 50% yield and 98% ee (**Table 1, Entry 1**).

Encouraged by the result, we became interested to improve the yield further by optimizing the reaction conditions such as variation of solvents and temperatures for the α-aminooxylation step using β-aminoaldehyde **51a** as the model substrate. Among the solvents screened, CH_3CN was found to give a maximum yield as compared to DMSO, $CHCl_3$, CH_2Cl_2 and THF. When the temperature was maintained at -10 ^oC, high yields and high enantiomeric excess were obtained (**Table 1, Entry 2**). However, further increase or decrease in the temperature to either 0 ^oC or -20 ^oC had a deleterious effect on the yield.

To determine the scope and generality of the reaction, a variety of β-amino aldehydes **51a-f** were subjected to α-aminooxylation process. In every case, the reaction proceeded smoothly to give a single diastereomer of *anti*-3-amino-1,2-diols **56a-f**, yields ranging from 55-68% with the intact of excellent enantioselectivity. For instance, substrates having electron-rich (entry 9) or electron-deficient (entry 11) substituent on the aromatic ring including 1-naphthyl ring system (entry 12) and heteroaryl (entry 13) gave the desired *anti*-3-amino-1,2-diols in excellent stereoselectivity.

A major advantage of this strategy is that all the four stereoisomers of 3-amino-1,2-diols can be prepared by choosing a suitable L or D-proline for Mannich and subsequent aminooxylation reactions.

Table 1: L-proline-catalyzed α-aminooxylation of β-aminoaldehydes: studies on optimization and substrate scope



entry	substrates **51a-f** (Ar)	solvent	temp (^oC)	time (h)	products **56a-f**	yield (%)[a]	dr (%)[b]	% ee
1	Ph	CH_3CN	-20	22	56a	50	>99	93[d]
2	**Ph**	**CH_3CN**	**-10**	**15**	**56a**	**68**	**>99**	**93**[d]
3	Ph	CH_3CN	0	15	56a	53	>99	90[d]
4	Ph	DMSO	25	0.5	56a	55	>99	93[d]
5	Ph	DMF	25	1	56a	17	>99	nd
6	Ph	$CHCl_3$	25	24	56a	30	>99	nd
7	Ph	CH_2Cl_2	25	20	56a	40	>99	91[d]
8	Ph	THF	25	24	56a	16	>99	nd
9	4-OMe-Ph	CH_3CN	-10	15	56b	65	>99	92[d]
10	4-Me-Ph	CH_3CN	-10	15	56c	63	>99	95[c]
11	2-Cl-Ph	CH_3CN	-10	15	56d	55	>99	>99[c]
12	1-naphthyl	CH_3CN	-10	15	56e	62	>99	92[c]
13	2-furfuryl	CH_3CN	-10	15	56f	58	>99	90[c]

[a]Isolated yield after column chromatographic purification. [b]determined based on ^{1} HNMR spectrum. [c]determined from HPLC analysis. [d] by comparing with specific rotation reported in the literature.

The formation of all *anti*-3-amino-1,2-diols **56a-f** was established unambiguously from their corresponding ^{1}H & ^{13}C NMR, IR and HRMS spectral data. Their optical purity was established from their chiral HPLC analyses.

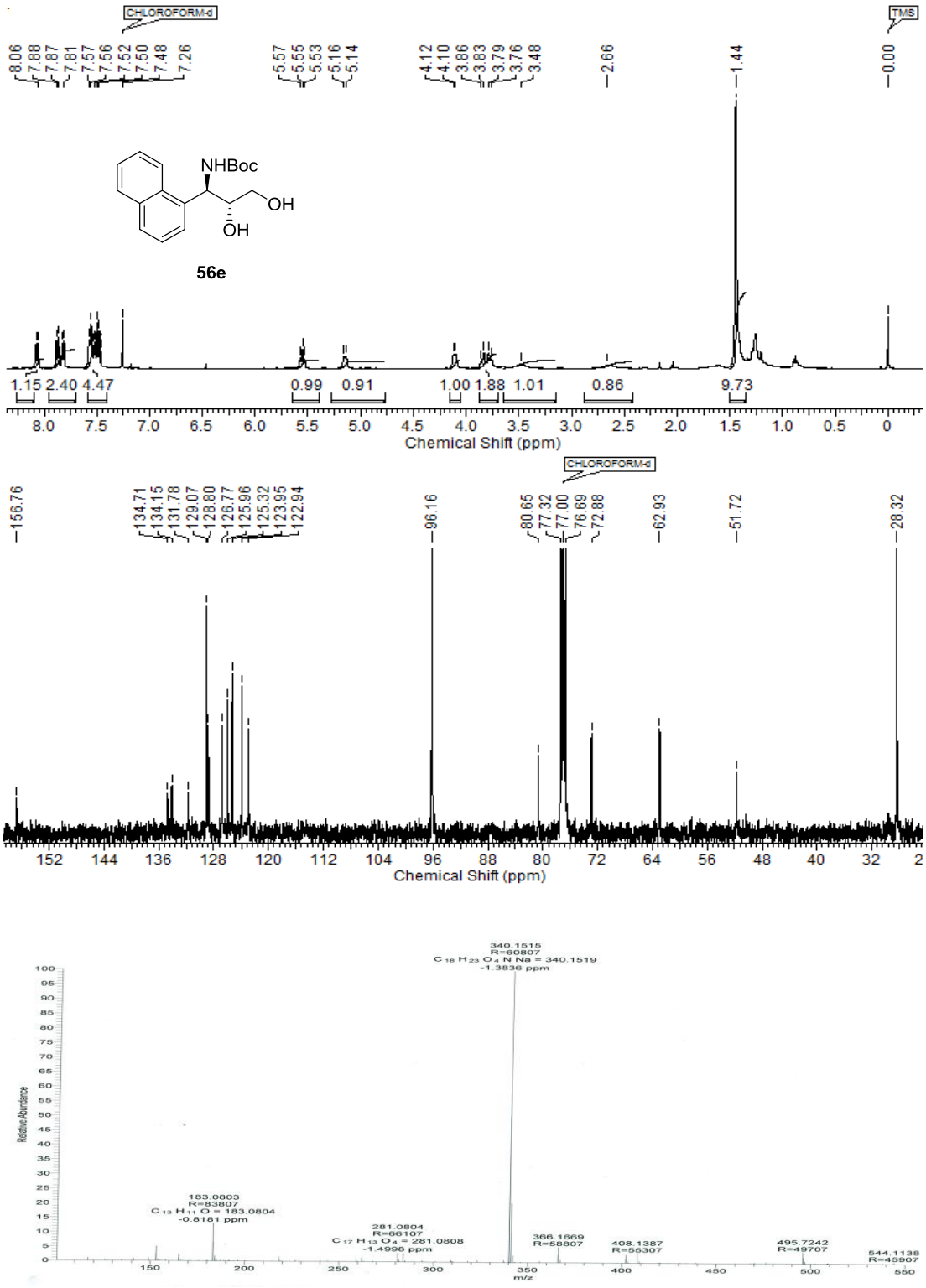
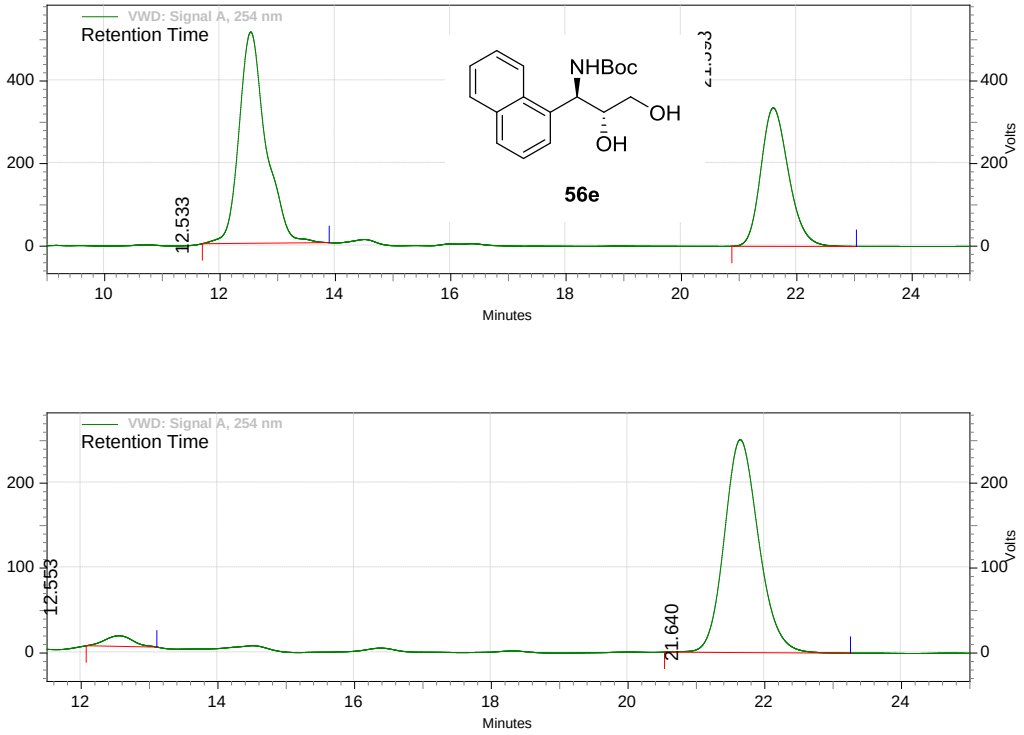


Fig. 6: ^{1}H, ^{13}C NMR and mass spectra of *anti*-3-amino-1,2-diol **56e**

Example 1: The ^{1}H NMR spectrum of *anti*-3-amino-1,2-diol **56e** showed two typical signals at δ 2.66 (br s, 1H) and 3.48 (br s, 1H) corresponding to hydroxyl protons while the other signal at δ 3.81 (dd, *J* = 11.8, 28.9 Hz, 2H) for methylene (-CH_2-OH) protons; Its ^{13}C NMR spectrum showed two characteristic carbon signals at δ 62.9 and 72.9 attributed to methylene and methine carbons attached to hydroxyl groups respectively. The mass spectrum also confirmed the formation of *anti*-3-amino-1,2-diols **56e** (**Fig. 6**).



Retention Time	Area	Area %	Height	Height %
12.553	5989186	3.92	209816	4.75
21.640	146796171	96.08	4207363	95.25

Fig. 7: HPLC chromatogram of *anti*-3-amino-1,2-diol **56e**

The optical purity of *anti*-3-amino-1,2-diol **56e** was determined to be 92% ee from chiral HPLC analysis (Chiracel AD-H, *n*-hexane/*i*PrOH, 90:10, 0.5 mL/min) retention time 12.55 min (3.92%) and 21.64 min (96.1%) (**Fig.7**).

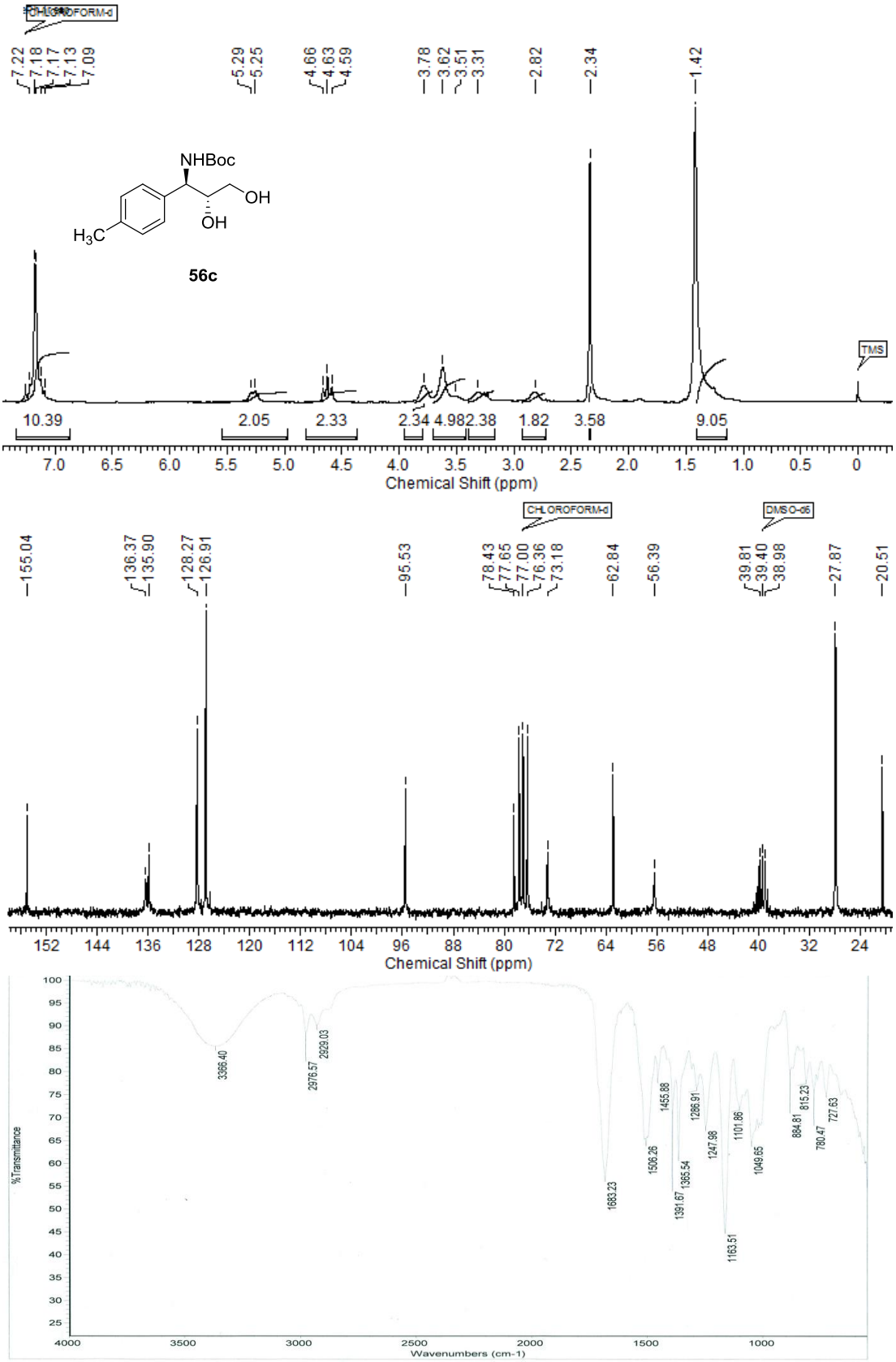


Fig. 8: ^{1}H, ^{13}C NMR and mass spectra of *anti*-3-amino-1,2-diol **56c**

Example 2: The ^{1}H NMR spectrum of *anti*-3-amino-1,2-diol **56c** showed two typical signals at δ 2.82 (br s, 1H) and 3.31 (br s, 1H) corresponding to hydroxyl protons while the other signal at δ 2.31 (s, 3H) for methyl protons attached to aromatic ring. Its ^{13}C NMR spectrum showed two characteristic carbon signals at δ 62.8 and 73.2 due to methylene and methine carbons attached to hydroxyl groups respectively. Its IR spectrum displayed a characteristic broad absorption band at 3366 cm^{-1} indicating the presence of OH functional group (**Fig. 8**).

The absolute configuration of the newly generated chiral center was assigned on the basis of the previously established configuration of α-aminoxylation of aldehydes.[19] The *anti*-stereochemistry in *anti*-3-amino-1,2-diol **56c** is, however, unambiguously proven from X-ray crystallographic analysis (**Fig. 9**).

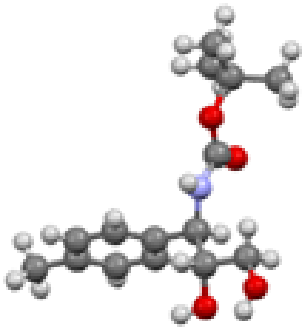


Fig. 9: ORTEP diagram of *anti*-3-amino-1,2-diol **56c**

3.1.5 Conclusion

A highly stereoselective route to 3-amino-1,2-diols using proline as catalyst in a single transformation starting from β-aminoaldehydes has been developed. This reaction is also practical in the sense that (i) all the four stereoisomers of 3-amino-1,2-diols can be prepared by choosing a suitable proline as catalyst for Mannich and subsequent aminooxylation reactions; (ii) products were obtained in high optical purities (single diastereomer with 90-99% ee) and moderate yields; (iii) showed broad

substrate scope and good functional group tolerance. We believe that this strategy will find applications in the field of asymmetric synthesis of bioactive molecules owing to the flexible nature of the synthesis and the ready availability of proline catalysts in both enantiomeric forms.

3.1.6 Experimental Section

General experimental procedure for the preparation of β-aminoaldehydes (51a-f)

To a stirred solution of aryl N-Boc-imine **50a-f** (1.4 mmol) and redistilled acetaldehyde **49** (0.39 mL, 7 mmol) in CH_3CN (15 mL) at 0 ^oC was added L-proline (0.032 g, 20 mol%) and the mixture stirred further at 0 ^oC for 3 h. After the completion of reaction (monitored by TLC), it was quenched with water and extracted with Et_2O (3 x 50 mL). The combined organic layers were washed with brine, dried over anhyd. Na_2SO_4, filtered and concentrated under reduced pressure to give the crude aldehyde. Flash column chromatographic purification [silica gel (230-400 mesh) and pet. ether:EtOAc as an eluent] gave β-aminoaldehydes **51a-f**.

(*S*)-*tert*-Butyl (3-oxo-1-phenylpropyl)carbamate (51a)

Yield: 55%; pale yellow solid; **mp**: 91-94 ºC, (lit.[33] **mp**: 92-93.5 ºC); $[\alpha]^D_{25}$ -30.10 (*c* 1.15, $CHCl_3$); lit.[33] $[\alpha]^D_{25}$ +29.0 (*c* 1.4, $CHCl_3$) for its antipode; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 700, 1021, 1049, 1169, 1250, 1369, 1391, 1498, 1513, 1692, 2977, 3341; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.41 (s, 9H), 2.83-2.96 (m, 2H), 4.87 (br s, 1H), 5.17 (br s, 1H), 7.26-7.34 (m, 5H), 9.73 (t, *J* = 1.7 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 28.3, 39.9, 49.9, 79.9, 126.3, 127.7, 128.8, 135.2, 155.0, 193.3, 199.8; **Analysis**: $C_{14}H_{19}NO_3$ requires C, 67.45; H, 7.68; N, 5.62; found: C, 67.32; H, 7.41; N, 5.46%.

(*S*)-*tert*-Butyl (1-(4-methoxyphenyl)-3-oxopropyl)carbamate (51b)

Yield: 56%; pale yellow liquid; $[\alpha]^D_{25}$ -32.90 (*c* 1.1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 690, 1021, 1050, 1170, 1246, 1378, 1387, 1463, 1520, 1689, 2850, 2924, 2978, 3346;

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.41 (s, 9H), 2.80-2.94 (m, 2H), 3.78 (s, 3H), 4.90 (br s, 1H), 5.13 (br s, 1H), 6.85 (d, *J* = 8.6 Hz, 2H), 7.21 (d, *J* = 8.6 Hz, 2H), 9.72 (t, *J* = 1.6 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 28.3, 39.8, 49.8, 55.1, 79.6, 114.1, 127.5, 134.9, 154.9, 159.0, 193.4, 200.0; **Analysis**: $C_{15}H_{21}NO_4$ requires C, 64.50; H, 7.58; N, 5.01; found: C, 64.32; H, 7.38; N, 5.06%.

(*S*)-*tert*-Butyl (3-oxo-1-(p-tolyl)propyl)carbamate (51c)

Yield: 58%; pale yellow liquid; $[\alpha]^D_{25}$ -36.28 (*c* 1.0, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 700, 1026, 1054, 1172, 1242, 1384, 1467, 1518, 1692, 2900, 2982, 3341; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.41 (s, 9H), 2.33 (s, 3H), 2.83-2.96 (m, 2H), 5.15 (br s, 1H), 5.17 (br s, 1H), 7.13-7.26 (m, 4H), 9.73 (t, *J* = 1.7 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.3, 28.4, 50.8, 53.1, 79.6, 125.1, 128.8, 136.9, 140.5, 193.4, 202.2; **Analysis**: $C_{15}H_{21}NO_3$ requires C, 68.42; H, 8.04; N, 5.32; found: C, 68.26; H, 8.01; N, 5.26%.

(*S*)-*tert*-Butyl (1-(2-chlorophenyl)-3-oxopropyl)carbamate (51d)

Yield: 49%; yellow liquid; $[\alpha]^D_{25}$ -12.32 (*c* 1.6, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 696, 1032, 1061, 1168, 1256, 1376, 1459, 1522, 1698, 2851, 2868, 3347; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.45 (s, 9H), 2.86-2.98 (m, 2H), 4.54 (br s, 2H), 5.26 (br s, 1H), 7.21-7.28 (m, 2H), 7.32-7.40 (m, 2H), 9.73 (t, *J* = 1.5 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 28.4, 46.4, 51.5, 79.4, 126.6, 128.3, 132.2, 136.5, 193.4, 199.7; **Analysis**: $C_{14}H_{18}ClNO_3$ requires C, 59.26; H, 6.39; N, 4.94; found: C, 59.12; H, 6.19; N, 4.82%.

(*S*)-*tert*-Butyl (1-(naphthalen-1-yl)-3-oxopropyl)carbamate (51e)

Yield: 44%; yellow liquid; $[\alpha]^D_{25}$ -18.71 (*c* 1.9, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 700, 1024, 1053, 1174, 1259, 1398, 1481, 1501, 1626, 2979, 3412; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.45 (s, 9H), 3.09 (d, *J* = 6.5 Hz, 2H), 4.54 (br s, 2H), 7.42-7.61 (m, 4H), 7.76-7.89 (m, 2H), 8.11 (d, *J* = 8.1 Hz, 1H), 9.81 (t, *J* = 2.2 Hz, 1H); **^{13}C NMR** (50

MHz, $CDCl_3$): δ 28.4, 48.4, 52.5, 79.8, 122.9, 123.9, 125.3, 125.9, 126.7, 128.8, 129.1, 131.8, 134.2, 134.7, 195.4, 200.2; **Analysis**: $C_{18}H_{21}NO_3$ requires C, 72.22; H, 7.07; N, 4.68; found: C, 72.12; H, 7.03; N, 4.47%.

(*S*)-*tert*-Butyl (1-(furan-2-yl)-3-oxopropyl)carbamate (51f)

Yield: 39%; yellow liquid; $[\alpha]^{D}_{25}$ -18.71 (*c* 1.9, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 690, 1084, 1062, 1174, 1259, 1391, 1467, 1501, 1683, 2824, 2841, 3421; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.44 (s, 9H), 2.91-3.02 (m, 2H), 5.11 (br s, 1H), 5.27 (br s, 1H), 6.30-6.34 (m, 2H), 7.36 (br s, 2H), 9.77 (t, *J* = 2.1 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 28.4, 50.1, 51.5, 79.4, 108.3, 110.6, 142.3, 151.8, 193.6, 200.7; **Analysis**: $C_{12}H_{14}NO_4$ requires C, 60.24; H, 7.16; N, 5.85; found: C, 60.12; H, 7.03; N, 5.76%.

General experimental procedure for the preparation of 3-amino-1,2-alkane diols (56a-f)

To a stirred precooled (-10 °C) acetonitrile (25 mL) solution of β-aminoaldehydes **51a-f** (17 mmol) and nitrosobenzene (1.45 g, 13.6 mmol) was added L-proline (0.039 g, 20 mol%). The reaction mixture was allowed to stir at the same temperature for 20 h followed by the addition of MeOH (10 mL) and $NaBH_4$ (0.97 g, 25 mmol) to the reaction mixture, which was stirred for further 10 min. After addition of phosphate buffer, the resulting mixture was extracted with EtOAc (3 × 30 mL) and the combined organic phases were dried over anhyd. Na_2SO_4 and concentrated to give the crude aminooxy alcohol, which was directly taken up for the next step without purification. To a MeOH (25 mL) solution of the above crude aminooxyalcohol was added $Cu(OAc)_2.H_2O$ (0.501 g, 2.6 mmol) at 25 °C and the reaction mixture was allowed to stir for 10 h at that temperature. After addition of phosphate buffer, the resulting mixture was extracted with $CHCl_3$ (3 × 30 mL) and the combined organic phases were dried over anhyd. Na_2SO_4 and concentrated to give the crude product, which was then

purified by column chromatography over silica gel using pet. ether:EtOAc to give 3-amino-1,2-alkane diols **56a-f**.

(2*R*, 3*R*)-3-(*tert*-Butoxycarbonylamino)-3-phenyl-1,2-propanediol (56a)

Yield: 68%; colourless solid; **mp**: 106-109 ºC,(lit.[34] **mp**: 107-108 ºC); $[\alpha]^{D}_{25}$ -40.96 (*c* 1.32, $CHCl_3$); lit.[34] $[\alpha]^{D}_{25}$ +42.90 (*c* 1.4, $CHCl_3$) for its antipode; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 790, 1025, 1056, 1124, 1161, 1369, 1400, 1495, 1696, 2930, 2986, 3370; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.43 (s, 9H), 2.81 (br s, 1H), 3.28 (br s, 1H), 3.64 (br s, 2H), 3.82 (br s, 1H), 4.66-4.71 (m, 1H), 5.29 (br s, 1H), 7.28-7.38 (m, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 28.3, 56.7, 63.2, 73.9, 80.1, 127.4, 127.7, 128.6, 139.0, 156.1; **HRMS** (ESI) *m/z* calcd for $C_{14}H_{21}NO_4$ $[M + Na]^+$: 290.1368, found: 290.1377; **Analysis**: $C_{14}H_{21}NO_4$ requires C, 62.90; H, 7.92; N, 5.24; found: C, 62.78; H, 7.81; N, 5.12%.

(2*R*, 3*R*)-3-(*tert*-Butoxycarbonylamino)-3-(*p*-methoxyphenyl)-1,2-propanediol (56b)

Yield: 65%; colorless solid; **mp:** 114-116 ºC, (lit.[35] **mp**: 116-118 ºC); $[\alpha]^{D}_{25}$ -49.43 (*c* 1.0, $CHCl_3$); lit.[35] $[\alpha]^{D}_{25}$ -50.2 (*c* 0.5, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 669, 757, 831, 927, 1035, 1167, 1216, 1368, 1585, 1612, 1701, 2400, 2839, 2981, 3019, 3438, 3682; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.34 (s, 9H), 3.11 (br s, 2H), 3.54 (br s, 2H), 3.71 (br s, 4H), 4.55 (br s, 1H), 5.29 (br s, 1H), 6.78 (d, *J* = 6.71 Hz, 2H), 7.14 (d, *J* = 6.71 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 28.3, 55.2, 56.1, 63.2, 74.1, 80.1, 114.7, 128.5, 131.1, 156.2, 159.2; **HRMS** (ESI) *m/z* calcd for $C_{15}H_{23}NO_5$ $[M + Na]^+$: 320.1473, found: 320.1469; **Analysis**: $C_{15}H_{23}NO_5$ requires C, 60.59; H, 7.80; N, 4.71; found: C, 60.29; H, 7.62; N, 4.69%.

(2*R*, 3*R*)-3-(*tert*-Butoxycarbonylamino)-3-(*p*-tolyl)-1,2-propanediol (56c)

Yield: 63%; colorless solid recrystallized from $CHCl_3$; **mp:** 126-129 ºC; $[\alpha]^{D}_{25}$ -57.87 (*c* 2.7, $CHCl_3$); 95% ee from chiral HPLC analysis (Chiracel AD-H, *n*-hexane/*i*PrOH,

90:10, 0.5 mL/min) retention time 21.6 min (97%) and 27.1 min (2%); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 727, 780, 815, 884, 1049, 1101, 1163, 1247, 1287, 1365, 1391, 1506, 1683, 2929, 2976, 3366; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.42 (s, 9H), 2.31(s, 3H), 2.82 (br s, 1H), 3.31 (br s, 1H), 3.51-3.62 (m, 2H), 3.78 (br s, 1H), 4.59-4.66 (m, 1H), 5.27 (d, *J* = 6.7 Hz, 1H), 7.09-7.22 (m, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$+DMSO-d_6): δ 20.5, 27.9, 56.4, 62.8, 73.2, 78.4, 127.0, 128.3, 135.9, 136.4, 155.0; **HRMS** (ESI) *m/z* calcd for $C_{15}H_{23}NO_4$ $[M + Na]^+$: 304.1519, found: 304.1514; **Analysis**: $C_{15}H_{23}NO_4$ requires C, 64.04; H, 8.24; N, 4.98; found: C, 63.91; H, 8.12; N, 4.93%.

(2*R*, 3*R*)-3-(*tert*-Butoxycarbonylamino)-3-(*o*-chlorophenyl)-1,2-propanediol (56d)

Yield: 55%; colorless gum; $[\alpha]^{D}_{25}$ -7.50 (*c* 0.32, $CHCl_3$); 99% ee from chiral HPLC analysis (Chiracel AS-H, *n*-hexane/*i*PrOH, 95:05, 0.5 mL/min) retention time 25.9 min (0.5%) and 28.8 min (99.5%); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 702, 704, 1036, 1164, 1264, 1367, 1393, 1498, 1694, 2928, 3420; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.43 (s, 9H), 2.97 (br s, 1H), 3.39 (br s, 1H), 3.64-3.79 (m, 2H), 3.98-3.99 (m, 1H), 5.13-5.17 (m, 1H), 5.56 (br s, 1H), 7.20-7.29 (m, 2H), 7.34-7.42 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 28.3, 54.1, 62.8, 72.2, 80.4, 127.1, 128.7, 129.0, 130.1, 133.8, 136.6, 156.3; **HRMS** (ESI) *m/z* calcd for $C_{14}H_{20}ClNO_4$ $[M + Na]^+$: 324.0973, found: 324.0970; **Analysis**: $C_{14}H_{20}ClNO_4$ requires C, 55.72; H, 6.68; N, 4.64; found: C, 55.56; H, 6.48; N, 4.47%.

(2*R*, 3*R*)-3-(*tert*-Butoxycarbonylamino)-3-(1-naphthyl)-1,2-propanediol (56e)

Yield: 62%; colorless gum; $[\alpha]^{D}_{25}$ -13.00 (*c* 0.2, $CHCl_3$); 92% ee from chiral HPLC analysis (Chiracel AD-H, *n*-hexane/*i*PrOH, 90:10, 0.5 mL/min) retention time 12.55 min (3.92%) and 21.64 min (96.1%); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 774, 1019, 1038, 1121, 1159, 1351, 1408, 1499, 1687, 2921, 2991, 3382; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.44 (s, 9H), 2.66 (br s, 1H), 3.48 (br s, 1H), 3.81 (dd, *J* = 11.8, 28.9 Hz, 2H), 4.24 (d, *J* =

8.3 Hz, 1H), 5.15 (d, *J* = 8.3 Hz, 1H), 5.53-5.57 (m, 1H), 7.46-7.57 (m, 4H), 7.82 (d, *J* = 8.1 Hz, 1H), 7.88 (d, *J* = 7.8 Hz, 1H), 8.07 (d, *J* = 8.3 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 28.3, 51.7, 62.9, 72.9, 80.6, 122.9, 123.9, 125.3, 125.9, 126.8, 128.8, 129.1, 131.8, 134.2, 134.7, 156.8; **HRMS** (ESI) *m/z* calcd for $C_{18}H_{23}NO_4$ $[M + Na]^+$: 340.1519, found: 340.1515; **Analysis**: $C_{18}H_{23}NO_4$ requires C, 68.12; H, 7.30; N, 4.41; found: C, 67.93; H, 7.12; N, 4.31%.

(2*R*, 3*R*)-3-(*tert*-Butoxycarbonylamino)-3-(furfuryl)-1,2-propanediol (56f)

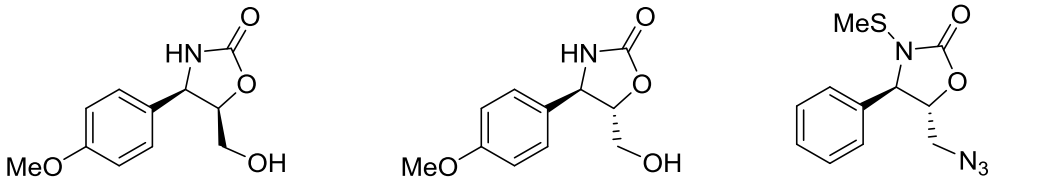
Yield: 58%; colorless gum; $[\alpha]^{D}_{25}$ -44.32 (*c* 0.46, $CHCl_3$); 90% ee from chiral HPLC analysis (Chiracel AS-H, *n*-hexane/*i*PrOH, 90:10, 0.5 mL/min) retention time 13.68 min (4.98%) and 14.84 min (95.02%); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 784, 1089, 1066, 1178, 1263, 1398, 1469, 1508, 1699, 2824, 2841, 3384, 3421; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.44 (s, 9H), 2.98 (br s, 2H), 3.67 (s, 1H), 3.81 (br s, 1.02), 4.76-4.79 (m, 1H), 5.29 (br s, 1H), 6.32-6.34 (m, 2H), 7.37 (br s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 28.3, 50.7, 62.8, 73.1, 80.6, 108.1, 110.5, 142.2, 151.7, 156.2; **HRMS** (ESI) *m/z* calcd for $C_{12}H_{19}NO_5$ $[M + Na]^+$: 280.1169, found: 280.1177; **Analysis**: $C_{12}H_{19}NO_5$ requires C, 56.02; H, 7.44; N, 5.44; found: C, 56.07; H, 7.36; N, 5.32%.

Section II:

Enantioselective Synthesis of Cytokine Modulator (+)-*epi*-Cytoxazone and Formal Synthesis of Antibacterial *N*-Thiolated -2-Oxazolidinone

3.2.1 Introduction

In 1998, Osada had reported the isolation of (4*R*, 5*R*)-5-(hydroxylmethyl)-4-(4-methoxyphenyl)-1,3-oxazolidine-2-one [(-)-**57**, generic name cytoxazone],[36] which was shown to possess high cytokine modulator activity by acting on the Th2 cells.[37] Its *trans*-diastereoisomer namely (+)-*epi*-cytoxazone (**58**) showed highly potential biological activity to allergens. Because of these biological properties, several total syntheses of (+)-*epi*-cytoxazone (**58**) and its epimer have been reported.[38] Prompted by the first positive biological results, many researchers have also reported the preparation of *cis*- and *trans*-isocytoxazones which are structural isomers of cytoxazone (**57**) and its *trans*-epimer **58** (**Fig 10**).[39]



(-)-Cytoxazone (**57**) (+)-*epi*-Cytoxazone (**58**) N-Thiolated 2-oxazolidinone (**59**)

Fig. 10: Structures of cytoxazone epimers (**57** & **58**) and *N*-thiolated 2-oxazolidinone (**59**)

The problem of bacterial drug resistance has reached a crisis level such that successful treatment of antibiotic-resistant infections in hospitals and health care centers can no longer be taken for granted. Infections caused by methicillin-resistant *Staphylococcus*

aureus (MRSA) are becoming particularly difficult to treat with conventional antibiotics such as penicillin, leading to a sharp rise in clinical complications and deaths. The need for new antibacterial agents and protocols for treating MRSA infections is becoming extremely serious. Oxazolidinones have already been recognized for their favorable pharmacological properties and are the only new class of antibacterial drugs introduced into clinical use in the last three decades.[40] Recent studies have shown that *N*-thiolated-2-oxazolidinone (**59**) possesses antibacterial activity against methicillin-resistant *Staphylococcus aureus* and *Bacillus anthracis*.[41]

3.2.2.1 Pharmacology of Cytoxazone Epimers

It is well established that the induction of humoral or cellular response is influenced by the development of distinct subsets of $CD4^+$ T cells.[42] The Th1 cell subset produces predominantly IL-2, GM-CSF, INF-γ, and TNF-β, (type 1 cytokines) and is involved in delayed-type hypersensitivity reactions, whereas the Th2 cell subset secretes IL-4, IL-5, IL-6, IL-10, and IL-13 (type 2 cytokines), which are important factors for β cell growth and differentiation to Ig secretion. The imbalance of cytokine production by $CD4^+$ T cells leads to a wide variety of immunological disorders, *i.e.* allergy, progressive lymphoproliferation, and severe immunodeficiency.[43] Skin and lung biopsies from allergic patients indicate that the pivotal cells in the allergic site are the Th2 cells.[44] Treatments effectively suppressing the function or the differentiation of these allergen-specific Th2 cells will most likely provide efficient ways to intervene in Ig-mediated allergic diseases. In the course of screening for chemical immunomodulators that inhibit the type 2 cytokine productions in Th2 cells, it was found that cytoxazone containing a 2-oxazolidinone ring, which is rare in microbial metabolites, as a novel cytokine modulator produced by *Streptomyces sp*.

Cytoxazones show a cytokine-modulating activity by inhibiting the signaling pathway of Th2 cells, but not Th1 cells.

3.2.2.2 Pharmacology of *N*-Thiolated-2-oxazolidinone

N-Thiolated-2-oxazolidinone (**59**), like their β-lactam counterparts,[45] react covalently with their biological target through transfer of the organothio side chain as shown in **Fig 11**. Further studies to assess the mode of action of this antiMRSA, antiBacillus compound, and to identify their cellular targets, are of current interest.

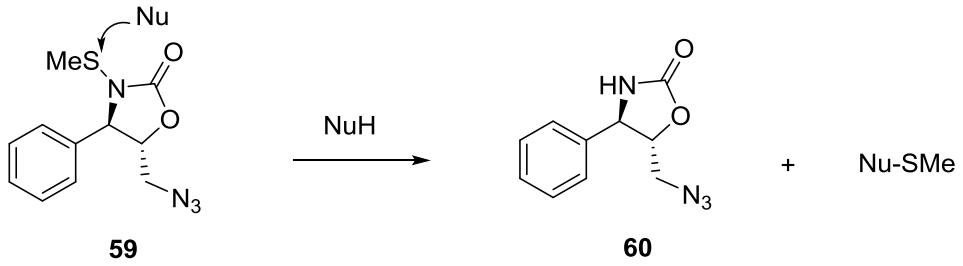


Fig 11: Pharmacology of *N*-thiolated-2-oxazolidinone (**59**)

3.2.3 Review of Literature

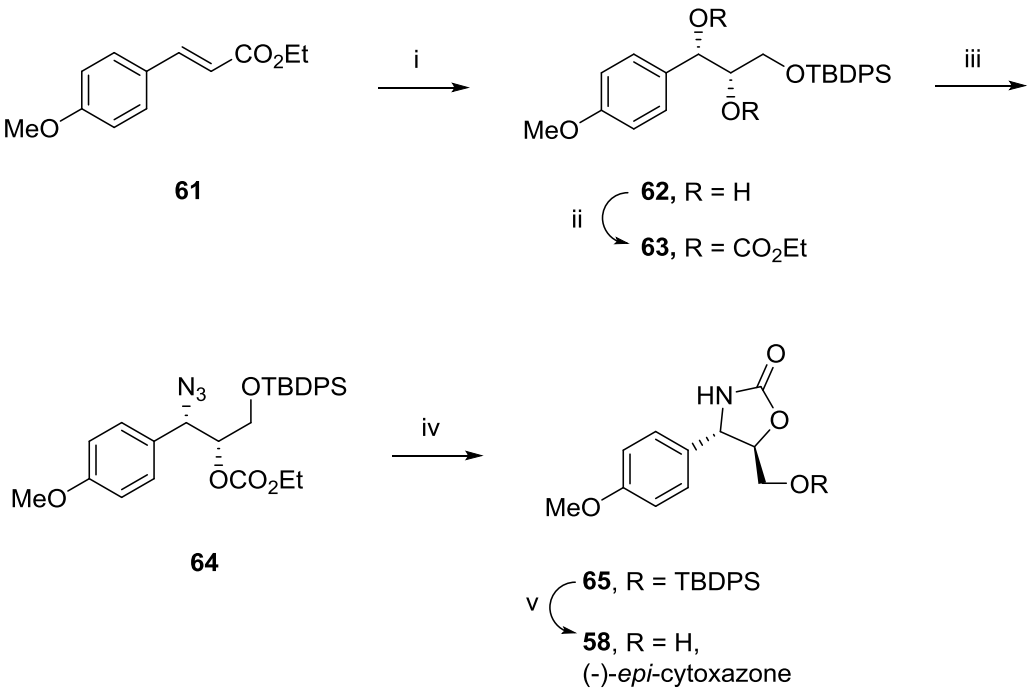
(a) Review of Literature for (+)-*epi*-Cytoxazone (58)

Literature search revealed that there are several reports available for the synthesis of (+)-*epi*-cytoxazone (**58**), which are described below.

Nakata's approach (1999)[46]

Nakata *et al.* have achieved the synthesis of (-)-*epi*-cytoxazone (**58**) using Sharpless asymmetric dihydroxylation as the key step. Thus, *p*-methoxycinnamate **61** was subjected to Sharpless asymmetric dihydroxylation to give chiral diol **62** in 93% yield and 99% ee. (4*S*, 5*S*)-Diethylcarbonate **63**, prepared from diol **62**, was treated with $TMSN_3$ (6 equiv) for achieving stereoselective azidation in the presence of TMSOTf that afforded the desired α-azide **64** (dr = 6:1). The α-azide **64** was then treated under Staudinger reaction condition (PPh_3, THF, H_20, 50 °C) to give 2-oxazolidinone **65**,

which was converted to *4-epi*-cytoxazone (**58**) in 99% yield on reaction with tetrabutylammonium fluoride (**Scheme 16**).

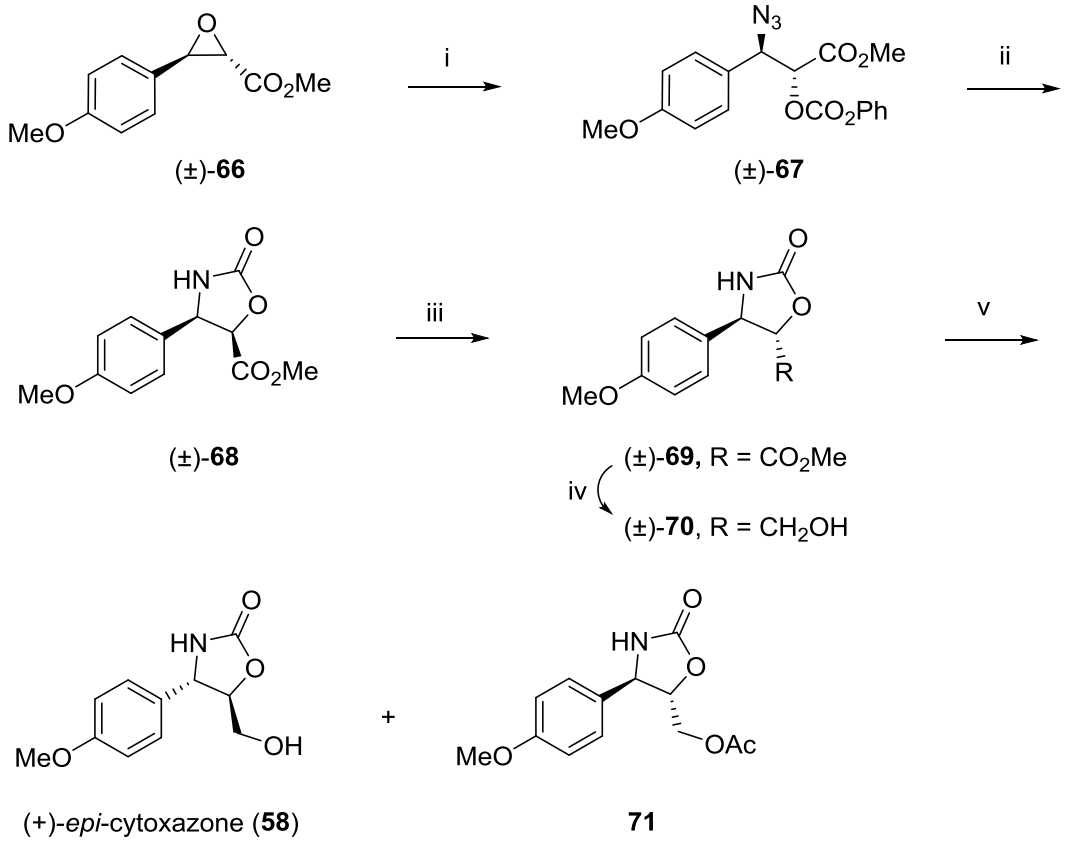


Scheme 16: (i) (a) AD-mix-α, *tert*-BuOH: H_2O (1:1), 25 °C, 93 %, 99% ee; (b) $NaBH_4$, THF, 0 °C, 66%; (c) TBDPSCl, imid., DMF, 0 °C, 99%; (ii) $ClCO_2Et$, pyridine, CH_2Cl_2, 0 °C, 92%; (iii) $TMSN_3$, TMSOTf, CH_3CN, -43 °C, 99%; (iv) PPh_3, THF, H_2O, 50 °C, 100%; (v) $^nBu_4NF$, THF, 0 °C, 99%.

Sunjic's approach (2001)[47]

Sunjic *et al.* have reported the synthesis of (-)-*epi*-cytoxazone (**58**) by employing the enzymatic kinetic resolution as the key reaction, starting from the glycidic ester (±)-**66**. Nucleophilic ring opening of epoxide (±)-**66** with NaN_3, followed by protection of the alcohol coupled with intramolecular cyclization gave the ester (±)-**68.** Epimerization at C(5) in oxazolidinone (±)-**68** using potassium hydroxide followed by esterification with methyl iodide gave ester (±)-**69**. Reduction of ester (±)-**69** with $NaBH_4$ in the presence of $CaCl_2$ and the subsequent kinetic resolution using lipase

from *Candida antarctica* in SOL-Gel-AK afforded (+)-*epi*-cytoxazone (**58**) in 49% yield and 87.3% ee (**Scheme 17**).

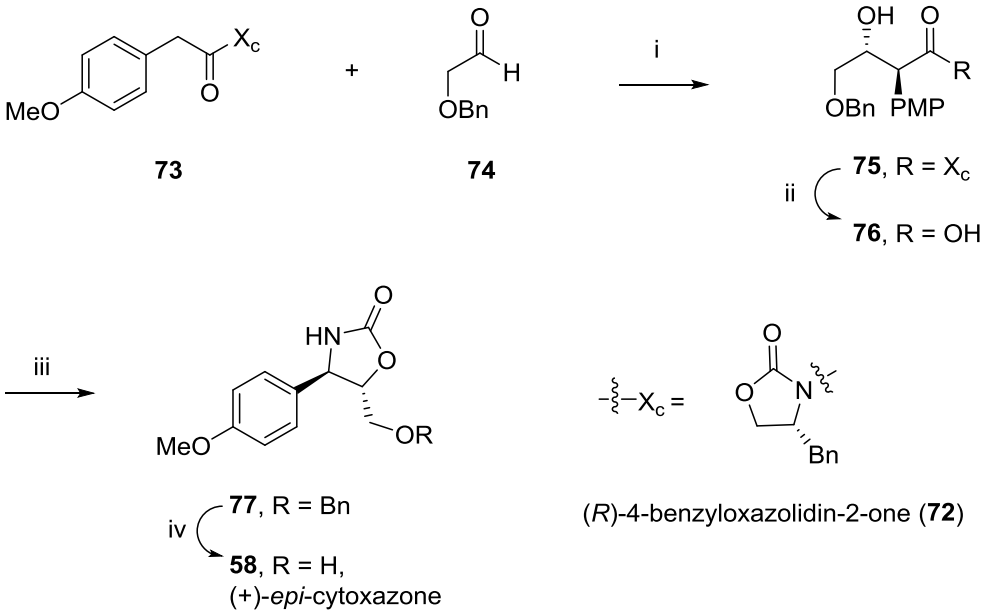


Scheme 17: (i) aq. NaN_3, dioxane, 50 °C, 3 h, 56%; (ii) $ClCO_2Ph$, CH_2Cl_2, -5 °C, 1 h, 100%; (iii) (a) KOH, EtOH, reflux, 1 h; (b) MeI, K_2CO_3, DMF, 25 ºC, 16 h, 46%; (iv) $NaBH_4$, $CaCl_2$, absolute EtOH, 25 °C, 20 min, 82%; (v) CAL in SOL-Gel-AK, vinyl acetate, 30 °C, 49%.

Carter's approach (2003)[48]

Carter *et al*. have made use of the Evans' *anti*-selective aldol approach as the key reaction for the synthesis of (+)-*epi*-cytoxazone (**58**). Thus, acylation of the commercially available (*R*)-oxazolidin-2-one **72** with 4-methoxyphenylacetic acid afforded imide **73**. The reaction of dibutylboryl enolate of **73** with pre-complexed solution of benzyloxyacetaldehyde **74** and 0.5 equiv of $SnCl_4$ provided the *anti*-aldol

75 (dr = 3:1). Removal of the chiral auxiliary from **75** provided the corresponding acid **76**, which was transformed into the oxazolidinone **77** in a one-pot 3 step procedure: (i) acyl azide formation, (ii) Curtius rearrangement and (iii) isocyanate trapping. Oxazolidinone **77** was debenzylated using Pearlman's catalyst to provide (+)-*epi*-cytoxazone (**58**) (**Scheme 18**).

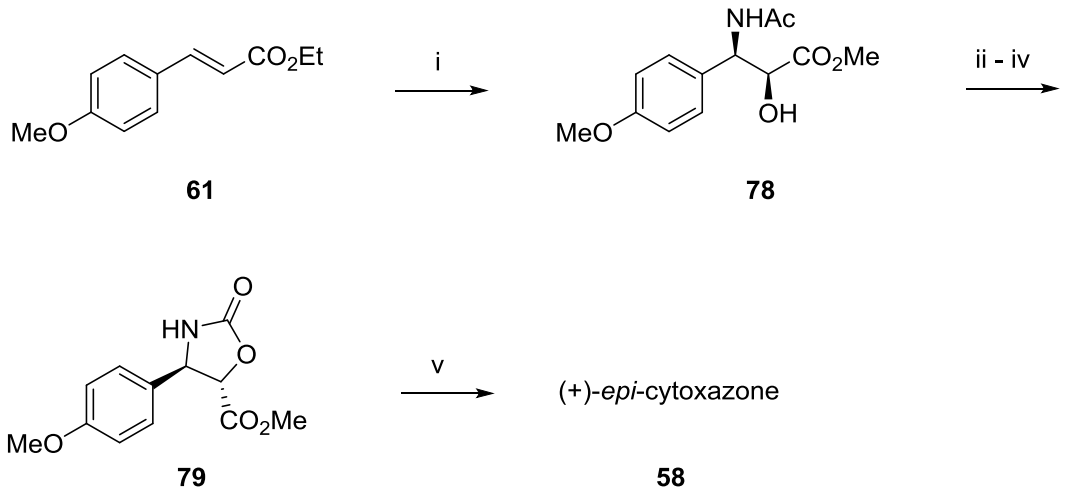


Scheme 18: (i) Bu_2BOTf, $^iPr_2EtN$, 0 °C, 30 min, then $BnOCH_2CHO$ precomplexed with 0.5 equiv $SnCl_4$, -78 °C, 3 h, 64%; (ii) H_2O_2, LiOH, THF:H_2O (4:1), 0 °C, 1 h, 99%; (iii) $(PhO)_2PON_3$, CH_2Cl_2, 23 °C, 40 min, 45 °C, 12 h, 61%; (iv) H_2 (1 atm), $Pd(OH)_2$, CH_3OH, 23 °C, 24 h, 84%.

Saicic's approach (2004)[49]

Saicic's approach was based on the Sharpless' asymmetric aminohydroxylation reaction, starting from methyl *p*-methoxycinnamate **61** in five steps with 36% overall yield. *p*-Methoxycinnamate **61** was thus subjected to Sharpless aminohydroxylation with catalytic amount of $K_2OsO_2(OH)_4$, $(DHQD)_2PHAL$ and BrNHAc as amine source to provide *syn*-amino alcohol **78** in 72% yield and 98% ee. Hydrolysis of aminoalcohol **78** under acidic medium gave hydroxy amino acid, which on

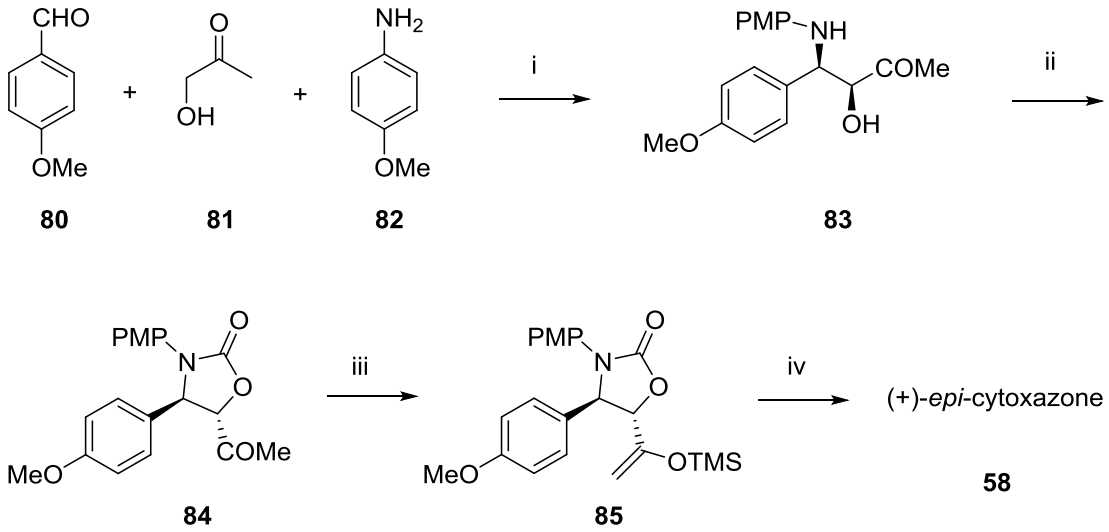
subsequent treatment with diphosgene, followed by esterification with diazomethane provided ester **79**. Reduction of ester **79** with sodium borohydride gave (+)-*epi*-cytoxazone (**58**) in 80% yield (**Scheme 19**).



Scheme 19: (i) $K_2[OsO_2(OH)_4]$ (4 mol %), BrNHAc, $(DHQD)_2PHAL$ (1 mol%), LiOH, H_2O, *tert*-BuOH, 4 °C, 20 h, 72%; (ii) 10% HCl, reflux, 4 h; (iii) $ClCO_2CCl_3$, NaOH, H_2O, 0 °C; (iv) CH_2N_2, THF, 63%; (v) $NaBH_4$, THF, 0 °C, 80%.

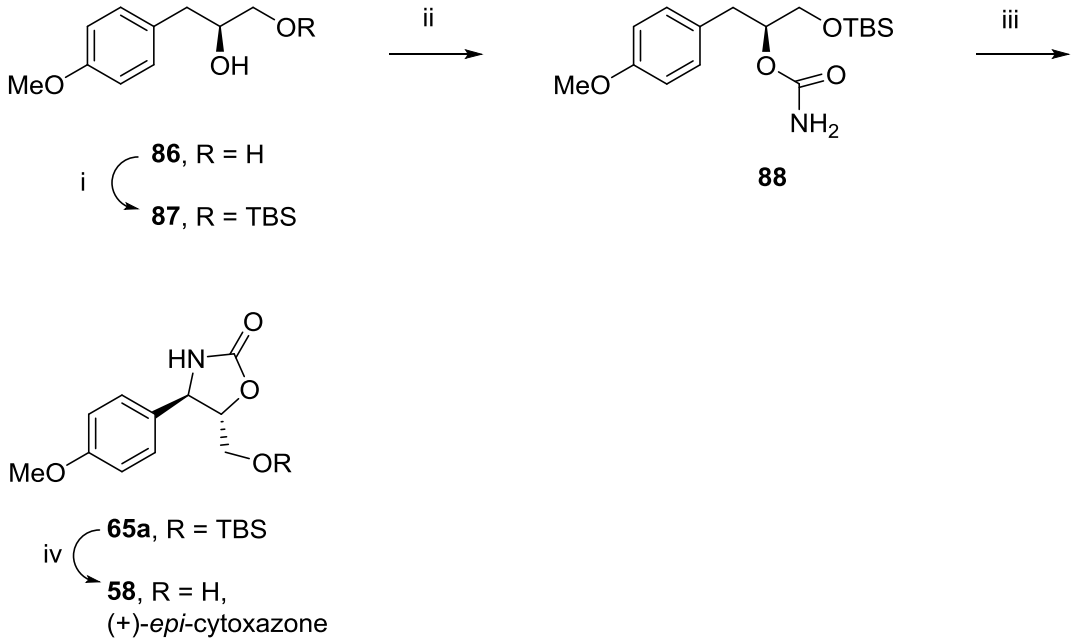
Sudalai's approach (2006), (2007) and (2010)[50,51,52]

Sudalai *et al*. have developed a simple method for the enantioselective synthesis of (+)-*epi*-cytoxazone (**58**) using L-proline-catalyzed asymmetric Mannich reaction. Thus, the key intermediate *syn*-amino alcohol **83** was obtained from L-proline-catalyzed asymmetric Mannich reaction of 4-methoxybenzaldehyde (**80**), hydroxyacetone **81**and *p*-anisidine **82** in 76% yield with *syn*/*anti* ratio (2:1). Amino alcohol **83** was then protected with triphosgene to give oxazolidinone **84** in 82% yield. The *in situ* generated silyl enol ether **85** was then subjected to ozonolysis without purification. Reductive work up of ozonide and PMP deprotection with CAN provided (+)-*epi*-cytoxazone (**58**) in 59% yield and 81% ee (**Scheme 20**).



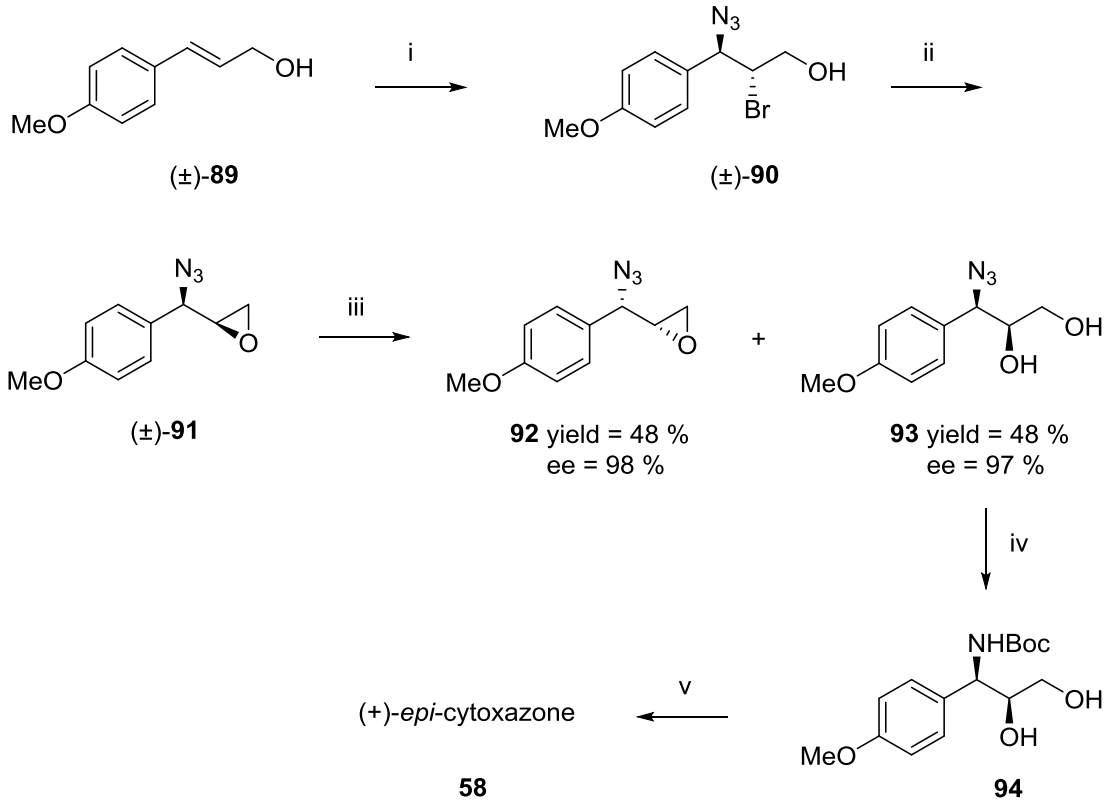
Scheme 20: (i) L-proline, DMSO, 25 °C, 24 h, 76%; (ii) triphosgene, Et_3N, CH_2Cl_2, -10 to 25 °C, 82%; (iii) LiHMDS, TMSCl, THF, -78 °C; (iv) (a) O_3, PPh_3, CH_2Cl_2, -78 °C; (b) $NaBH_4$, CH_3OH, 25 °C; (c) CAN, CH_3CN, 5 h, 59% (in three steps), 81% ee.

Sudalai *et al*. have also developed another useful route for the enantioselective synthesis of (+)-*epi*-cytoxazone (**58**) commencing from the diol **86,** which was obtained by two different routes: (i) hydrolytic kinetic resolution and (ii) proline-catalyzed α-aminooxylation. Primary alcohol of diol **86** was selectively protected with TBSCl to give the secondary alcohol **87**, which was then converted to carbamate **88** in 92% yield using reported conditions (trichloroacetyl isocyanate, CH_2Cl_2, then K_2CO_3, MeOH, H_2O). Carbamate **88** underwent C-H insertion on treatment with catalytic amount of $Rh_2(OAc)_4$ (2 mol%), $PhI(OAc)_2$ and MgO in CH_2Cl_2 at 40 °C to afford the corresponding oxazolidinone **65a** with *syn* diastereoselectivity (5.5:1) in 87% combined yield. The *syn*-diastereomer, namely oxazolidinone **65a**, was readily separated by column chromatography. Finally, deprotection of the TBS group using TBAF in THF furnished (+)-*epi*-cytoxazone (**58**) in 92% yield (**Scheme 21**).



Scheme 21: (i) TBSCl, imid., CH_2Cl_2, 25 °C, 98%; (ii) trichloroacetyl isocyanate, CH_2Cl_2, 0 °C to 25 °C, 2 h, then K_2CO_3, CH_3OH, H_2O, 0 °C to 25 °C, 12 h, 92%; (iii) $Rh_2(OAc)_4$ (2 mol%), $PhI(OAc)_2$, MgO, CH_2Cl_2, 40 °C, 87%, *syn*:*anti* (5.5:1); (iv) TBAF, THF, 92%.

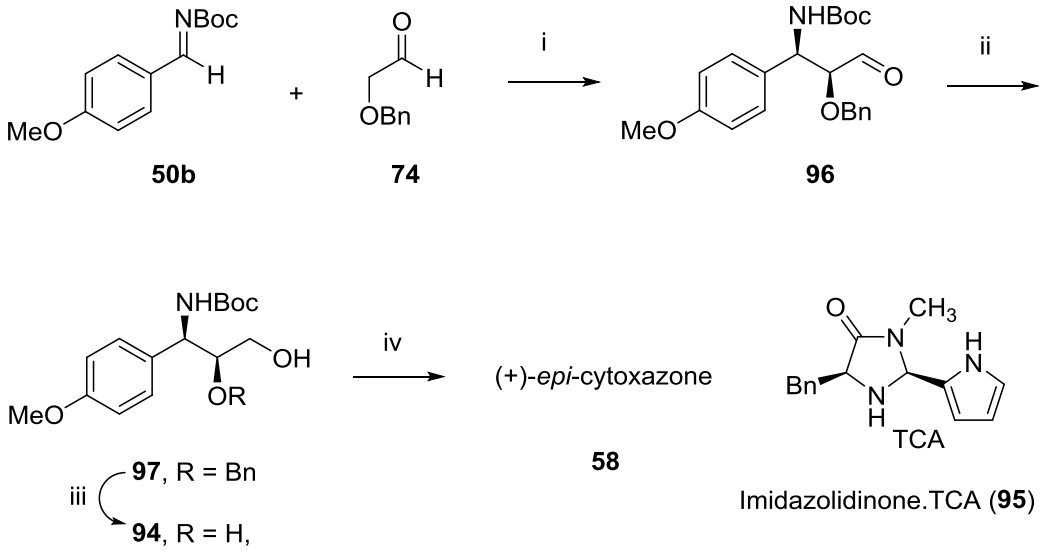
In yet another approach Sudalai *et al*. have employed two stereo-centered hydrolytic kinetic resolution of *syn*-azido epoxide **91** as the key step. Here, the synthesis commenced from 4-methoxycinnamyl alcohol **89**, which on azidobromination with NBS and NaN_3 afforded (±)-*anti*-bromo azide **90**. (±)-*syn*-Azido epoxide **91** was obtained from (±)-*anti*-bromo azide **90** under basic conditions and subjected to two stereo-centered hydrolytic kinetic resolution to give chiral *syn*-azido epoxide **92** and the corresponding diol **93**. Chiral azido diol **93** was then subjected to one pot azide reduction followed by Boc protection to give N-Boc amino diol **94**. Regioselective intramolecular cyclization of amino diol **94** with NaH gave (+)-*epi*-cytoxazone (**58**) in 43% yield and 97% ee (**Scheme 22**).



Scheme 22: (i) NBS, NaN_3, $CH_3CN:H_2O$ (4:1), 0 °C, 75%; (ii) LiOH, $THF:H_2O$ (4:1), 0 °C to 25 °C, 3 h, 76%; (iii) (*R*, *R*)-Co(salen)OAc (0.5 mol%), THF, H_2O (0.5 equiv), 0 °C, 12 h; (iv) polymethylhydro siloxane (PMHS), 10 % Pd/C, $(Boc)_2O$, EtOH, 25 °C, 4 h, 95 %; (v) NaH, THF, 25 °C, 3 h, 96%.

Kim's approach (2008)[53]

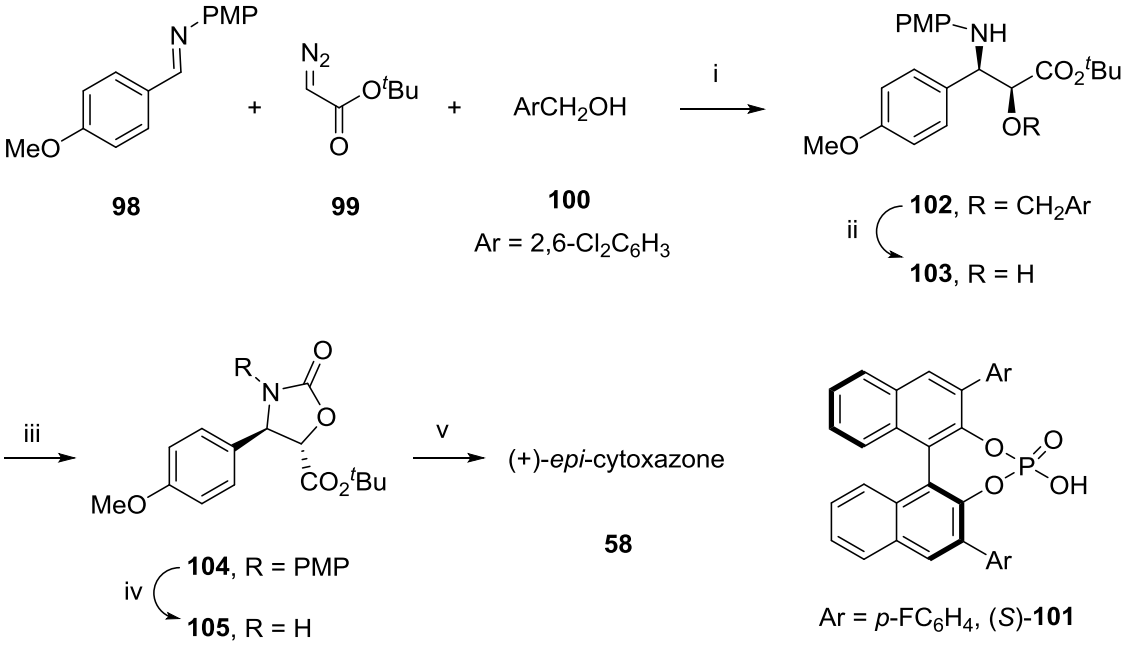
Kim *et al* have reported the synthesis of (+)-*epi*-cytoxazone (**58**) by employing Mannich reaction as the key step. Thus, N-Boc-imine **50b** was treated with benzyloxy acetaldehyde **74** in the presence of a newly developed catalyst namely 2-pyrrole-derived imidazolidinone.TCA salt **95** to afford the corresponding β-aminoaldehyde **96** in 78% yield with a diastereomeric excess of 70% for the *syn*-isomer. Aldehyde **96** was then reduced with $NaBH_4$ to afford β-aminoalcohol **97** in 98% yield. Deprotection of **97** by hydrogenolysis of the benzyl group afforded the desired diol **94** in 91% yield. Finally, treatment of compound **94** with sodium hydride in THF gave (+)-*epi*-cytoxazone (**58**) in 85% yield (**Scheme 23**).



Scheme 23: (i) imidazolidinone.TCA (**95**) (20 mol%), $CHCl_3$, -30 °C, 78%; (ii) $NaBH_4$, CH_3OH, 0 °C to 25 °C, 98%; (iii) 10% Pd/C, H_2 (1 atm), EtOH, 91%; (iv) NaH, THF, 85%.

Qian's approach (2010)[54]

Qian *et al* have reported the synthesis of (+)-*epi*-cytoxazone (**58**) utilizing chiral Bronsted acid and Rh(II)-catalyzed three component reaction as the key step. Key intermediate *i.e.* amino alcohol **102** was obtained in 68% yield with 80% ee (*syn* : *anti* = 57:43) from $Rh_2(OAc)_4$ catalyzed three-component reaction of imine **98**, ethyl diazoacetate (**99**) and 2,6-dichlorophenylmethanol (**100**) in the presence of chiral (*S*)-phosphoric acid **101** as cocatalyst. Deprotection of **102** by hydrogenolysis of the benzyl group provided the alcohol **103**, which was then protected with triphosgene to give oxazolidinone **104** in 87% yield. Subsequent PMP deprotection with CAN followed by reduction of ester with superhydride resulted in the formation of (+)-*epi*-cytoxazone (**58**) (**Scheme 24**).



Scheme 24: (i) $Rh_2(OAc)_4$ (2 mol %), phosphoric acid **101**(5 mol %), 4 A^o MS, CH_2Cl_2, 2 h, 68%; (ii) 10% Pd/C (1 atm), CH_3OH, 35 °C, 2 h, 84%; (iii) triphosgene, $^iPr_2EtN$, CH_2Cl_2, 0 °C, 2.5 h, 87%; (iv) CAN, CH_3CN:H_2O, 0 °C, 1 h, 62%; (v) $LiEt_3BH$, THF, 0 °C, 4 h, 62%.

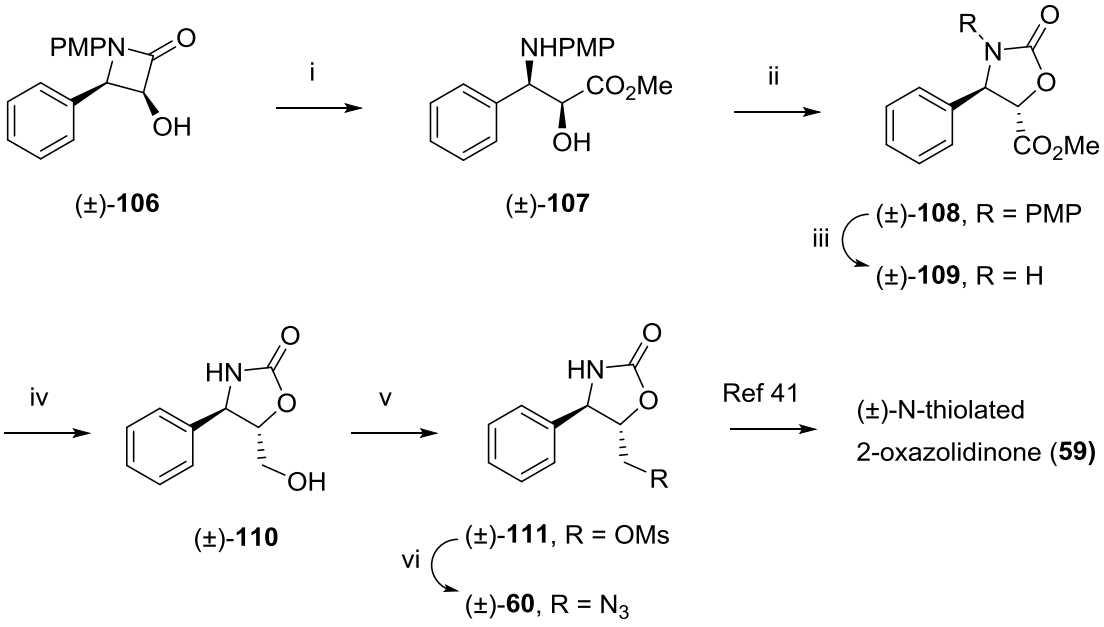
(b) Review of Literature for *N*-Thiolated-2-oxazolidinone (59)

Literature search revealed that there is only one report available for the racemic synthesis of antiMRSA *N*-thiolated-2-oxazolidinone (**59**) and its precursor 2-oxazolidinone (**60**), which is presented below.

Turos's approach (2007)[55]

Turos *et al.* have reported the synthesis of (±)-*N*-thiolated-2-oxazolidinone (**59**), starting from lactam (±)-**106**. This was hydrolyzed with Me_3SiCl in refluxing methanol to afford the *syn*-aminol (±)-**107** in 95% yield. Treatment of (±)-**107** with triphosgene and Hunig's base in CH_2Cl_2 led to the isolation of oxazolidinone (±)-**108** (80% yield). The *N*-methoxyphenyl moiety on the oxazolidinone ring was then cleaved (CAN, CH_3CN and H_2O) to give the *N*-protio oxazolidinone (±)-**109** in 70% yield. The ester functionality of oxazolidinone (±)-**109** was selectively reduced

($NaBH_4$, aq. THF) to furnish the alcohol (±)-**110** in 92% yield. The conversion of the hydroxyl group into an azide group proceeded through mesylate (±)-**111**; It gave the azide (±)-**60** in 72% yield after treatment with sodium azide in DMF (**Scheme 25**).



Scheme 25: (i) Me_3SiCl, CH_3OH, reflux, 95 %; (ii) triphosgene, $^{i}Pr_2EtN$, CH_2Cl_2, 0 °C to 23 °C, 80%; (iii) $(NH_4)_2Ce(NO_3)_6$, CH_3CN:H_2O, 0 °C to 23 °C, 70%; (iv) $NaBH_4$, aq. THF, CH_2Cl_2, 0°C to 25 °C, 92%; (v) MsCl, Et_3N, CH_2Cl_2, 0°C to 25 °C, 98 %; (vi) NaN_3, DMF, reflux, 12 h, 72%.

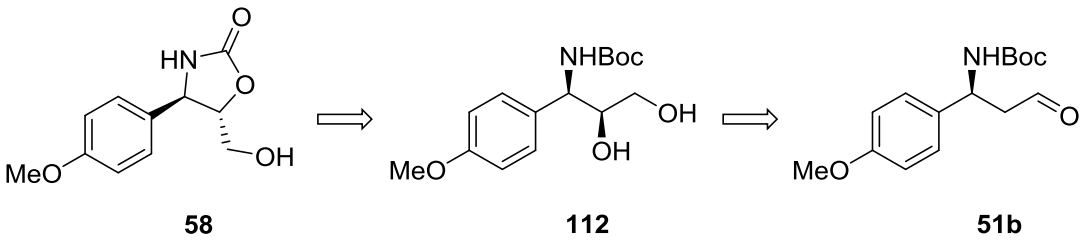
3.2.4 Present Work:

3.2.4.1 Objective

Literature search revealed that several methods such as chemo-enzymatic and metal-catalyzed enantioselective synthesis have been reported for (+)-*epi*-cytoxazone (**58**). However, these methods suffer from disadvantages such as low overall yields, the use of expensive chiral reagents, usage of protecting groups, especially the need for separation of diastereomers. The synthetic precursors of (+)-*epi*-cytoxazone (**58**) and *N*-thiolated 2-oxazolidinone (**59**) are found to be *syn*-amino diols, which have been the subject of thorough synthetic efforts in recent years. We became interested in providing, a more practical method for the synthesis of (+)-*epi*-cytoxazone (**58**) and

N-thiolated 2-oxazolidinone (**59**). In this section, we describe a concise protecting group-free enantioselective synthesis of (+)-*epi*-cytoxazone (**58**) and 2-oxazolidinone **60** using α-aminooxylation of β-aminoaldehydes as the key reaction.

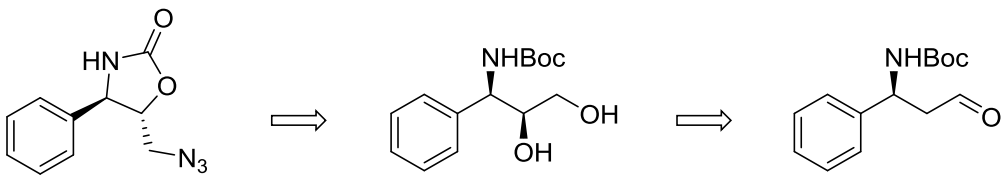
Retrosynthetic analysis of (+)-*epi*-cytoxazone (**58**) revealed that *syn*-amino diol **112** could be visualized as the key intermediate, which in turn can be obtained using α-aminooxylation of β-aminoaldehyde **51b** (**Fig. 12**).



58 **112** **51b**

Fig. 12: Retrosynthetic analysis of (+)-*epi*-cytoxazone (**58**)

Similarly, we envisaged that 2-oxazolidinone (**60**) could be obtained from *syn*-amino diol **113** through cyclization followed by azide displacement of hydroxyl group. The required *syn*-amino diol **113** could be prepared by means of α-aminooxylation of the corresponding β-aminoaldehyde **51a** (**Fig. 13**).



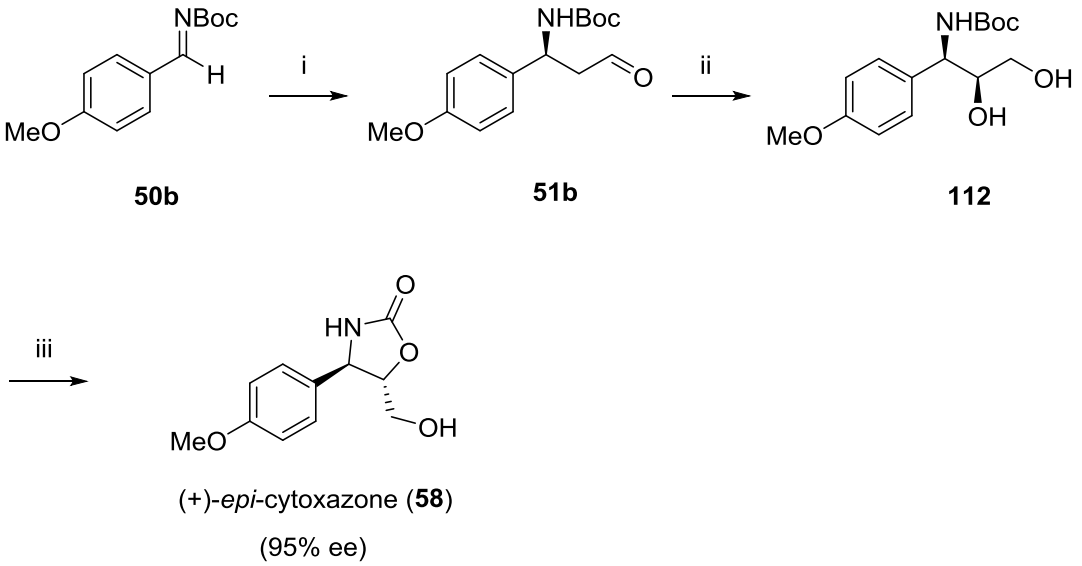
60 **113** **51a**

Fig. 13: Retrosynthetic analysis of 2-oxazolidinone (**60**)

3.2.5 Results and Discussion

(a) Concise Enantioselective Synthesis of (+)-*epi*-Cytoxazone (58)

The complete synthetic sequence for (+)-*epi*-cytoxazone (**58**), wherein α-amino oxylation of β-aminoaldehyde **51b** constitutes a key step, is presented in **Scheme 26**.



Scheme 26: (i) CH_3CHO, L-proline (20 mol%), CH_3CN, 0 °C, 3 h, 56%; (ii) (a) PhNO (0.8 equiv), D-proline (20 mol%), CH_3CN, -10 °C, 18 h; then $NaBH_4$, CH_3OH, 0 °C, 10 min; (b) $Cu(OAc)_2.H_2O$, CH_3OH, 25 °C, 16 h, 68% (over two steps); (iii) NaH, dry THF, 25 °C, 3 h, 90%.

Accordingly, the synthesis of (+)-*epi*-cytoxazone (**58**) was undertaken commencing from arylaldimine **50b**, which on subjecting to Mannich reaction with acetaldehyde [L-proline, CH_3CN, 0 °C, 3 h] gave β-aminoaldehyde **51b** in 56% yield. Compound **51b** was confirmed from its ^1H and ^{13}C NMR spectroscopy. The ^1H NMR spectrum of **51b** showed a typical triplet at δ 9.72 (t, J = 1.6 Hz, 1H) and a multiplet at δ 2.80-2.94 (m, 2H) corresponding to aldehydic and homobenzylic protons respectively. Its ^{13}C NMR spectrum showed two characteristic carbon signals at δ 193.4 and 200.0 due to carbamate and aldehydic carbonyl carbons respectively (**Fig. 14**).

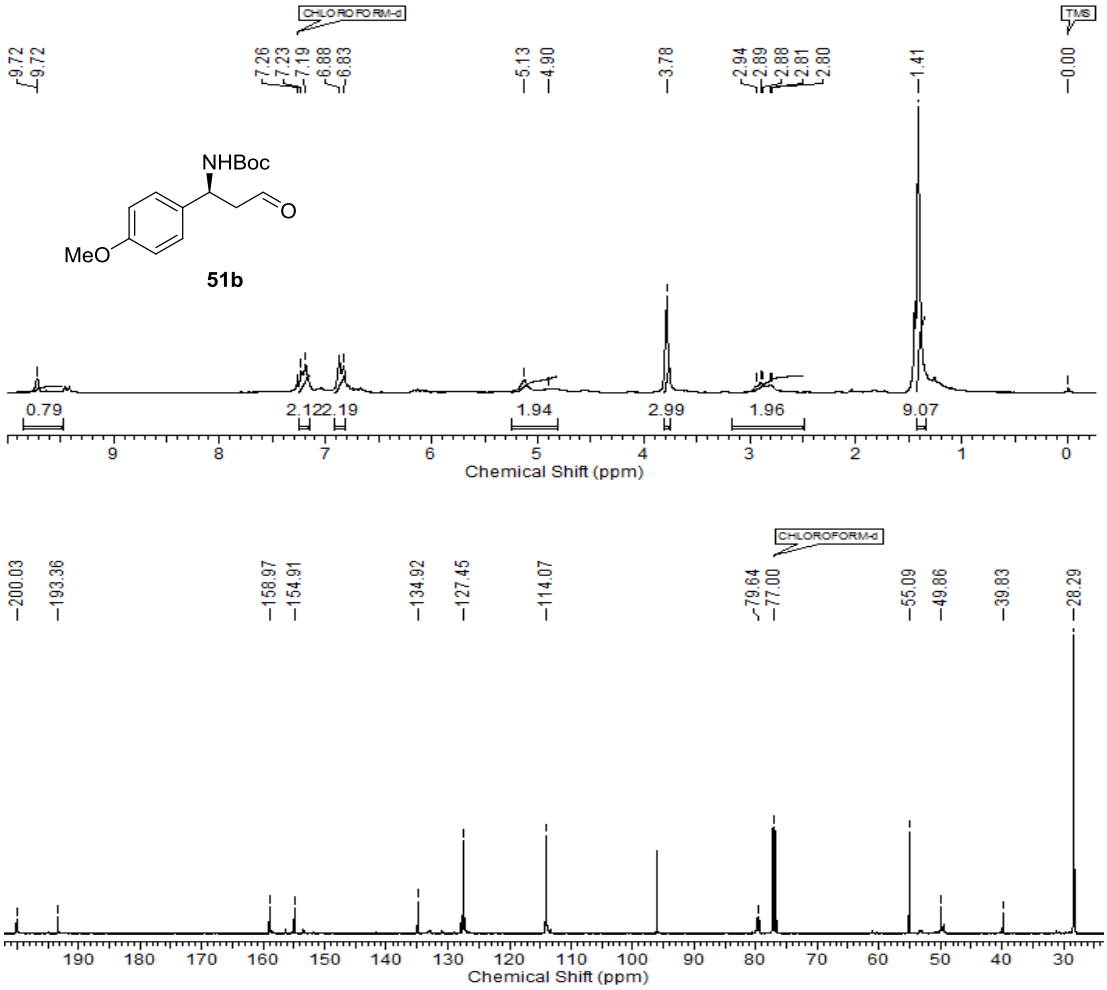


Fig. 14: ^{1}H and ^{13}C NMR spectra of β-aminoaldehyde **51b**

β-Aminoaldehyde **51b** was subjected to α-aminooxylation [D-proline, PhNO] to give α-aminoxyaldehyde, which was *in situ* reduced with $NaBH_4$. It was then followed by subsequent reduction of the crude aminoxy product with $Cu(OAc)_2.H_2O$ that provided a single diastereomer of *syn*-3-amino-1,2-diol **112** in 68% yield and 95% ee. The formation of *syn*-3-amino-1,2-diol **112** was confirmed from its ^{1}H NMR spectrum, which showed a characteristic multiplet at δ 3.42-3.56 (m, 2H) due to methylene (-CH_2-OH) protons. Its ^{13}C NMR spectrum showed two characteristic carbon signals at δ 63.1 and 74.1 attributed to methylene and methine carbons attached to hydroxyl groups respectively. The mass spectrum also confirmed the formation of *syn*-3-amino-1,2-diol **112** (**Fig. 15**).

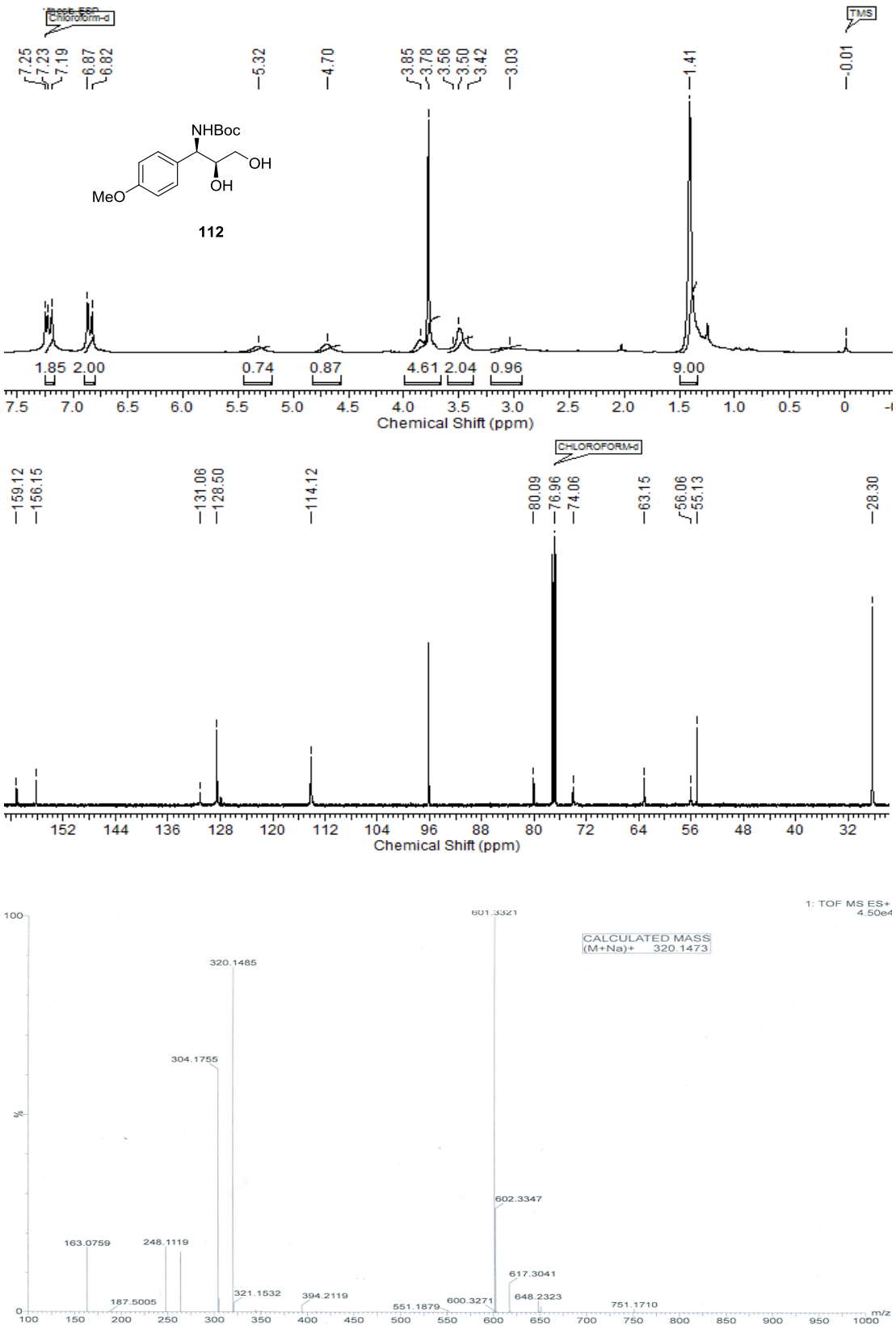


Fig. 15: ^{1}H, ^{13}C NMR and mass spectra of *syn*-3-amino-1,2-diol **112**

Finally, the regioselective intramolecular cyclization of **112** using NaH in THF gave (+)-*epi*-cytoxazone (**58**) in 90 % yield and 95% ee.

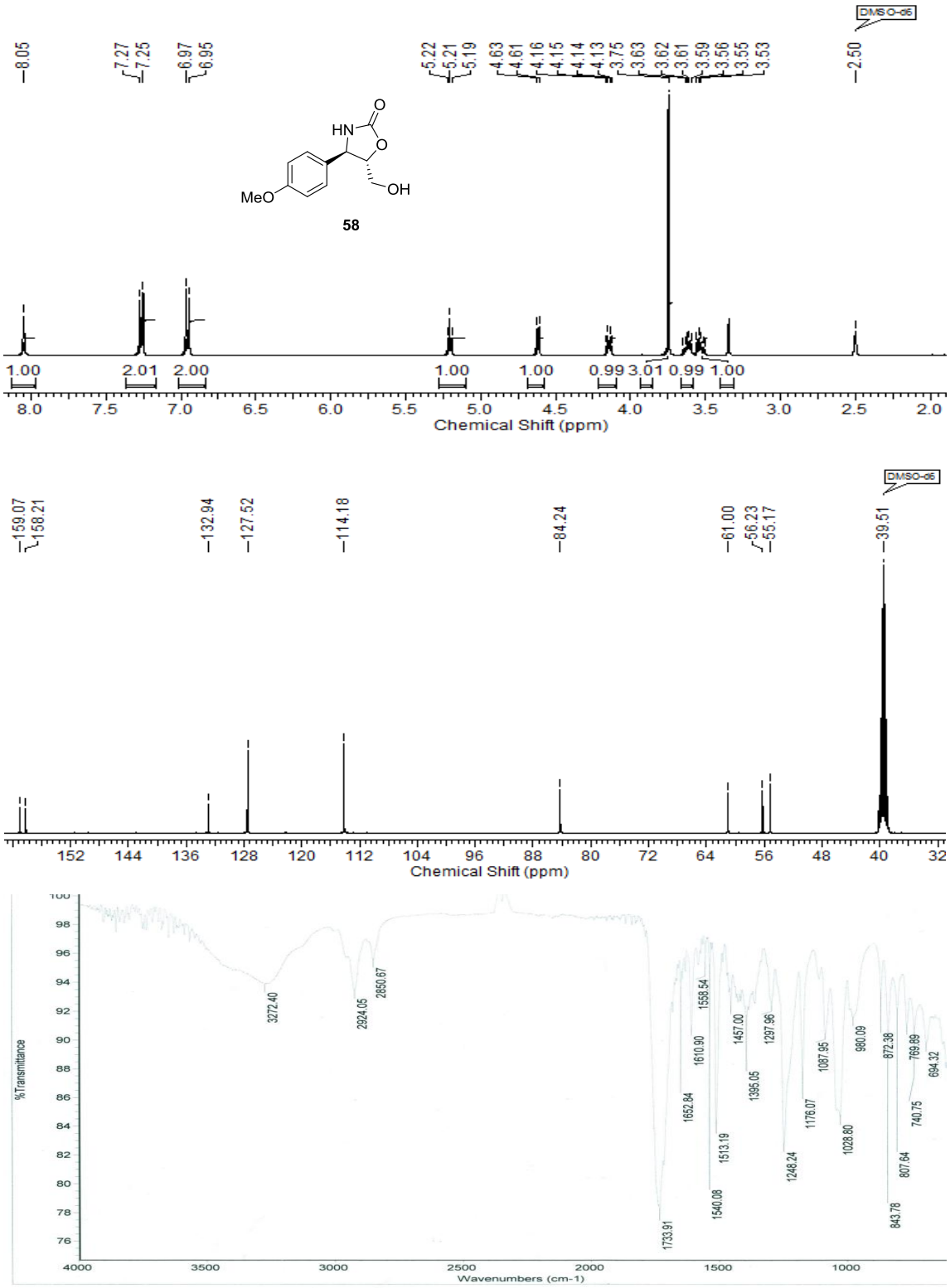
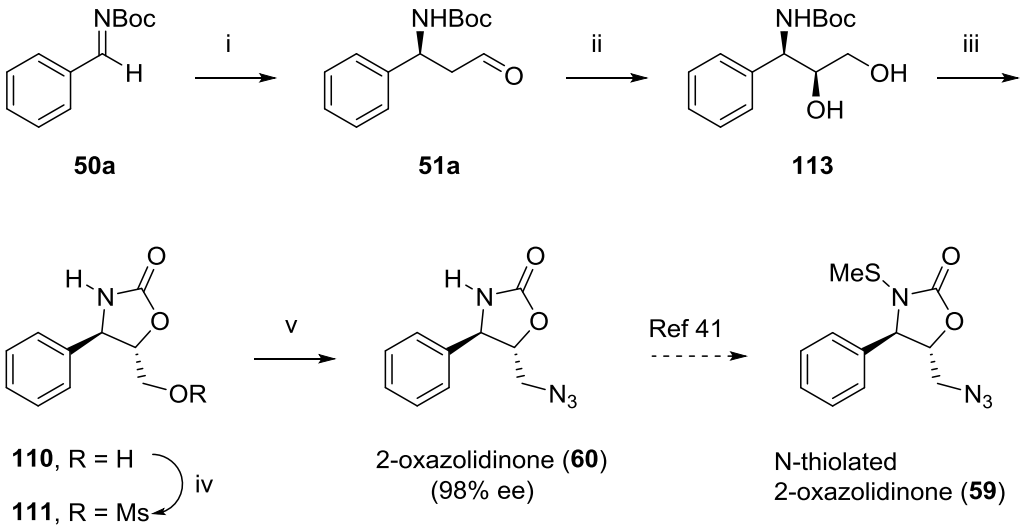


Fig. 16: ^{1}H, ^{13}C NMR and IR spectra of (+)-*epi*-cytoxazone (**58**)

The ^{1}H, ^{13}C NMR and IR spectra of **58** confirmed the formation of (+)-*epi*-cytoxazone (**Fig. 16**). The ^{1}H NMR spectrum of (+)-*epi*-cytoxazone (**58**) showed a typical signal at δ 8.05 (s, 1H) for N-H proton of oxazolidinone ring. Its ^{13}C NMR spectrum showed a characteristic signal at δ 159.1 due to the carbonyl carbon in oxazolidinone ring. Its IR spectrum exhibited a characteristic oxazolidinone carbonyl absorption frequency at 1733 cm^{-1}. The spectral data of (+)-*epi*-cytoxazone (**58**) were in complete agreement with the reported values.[51]

(b) Facile Enantioselective Synthesis of 2-Oxazolidinone (60)

The synthetic scheme for 2-oxazolidinone (**60**), wherein α-aminooxylation of β-amino aldehyde **51a** constitutes a key step, is presented in **Scheme 27**.



Scheme 27: (i) CH_3CHO, L-proline (20 mol%), CH_3CN, 0 °C, 3 h, 55%; (ii) (a) PhNO (0.8 equiv), D-proline (20 mol%), CH_3CN, -10 °C, 18 h; then $NaBH_4$, CH_3OH, 0 °C, 10 min; (b) $Cu(OAc)_2.H_2O$, CH_3OH, 25 °C, 16 h, 64% (over two steps); (iii) NaH, dry THF, 25 °C, 3 h, 94%; (iv) MsCl, Et_3N, CH_2Cl_2, 0 °C, 1 h; (v) NaN_3, DMF, 60 °C, 12 h, 82% (over two steps).

The present synthesis of 2-oxazolidinone **60** commenced from benzaldimine **50a**, which on subjecting to Mannich reaction with acetaldehyde [L-proline, CH_3CN, 0 °C, 3 h] gave β-aminoaldehyde **51a** in 55% yield. β-Aminoaldehyde **51a** on susbjecting to α-aminooxylation [D-proline, PhNO] provided α-aminoxyaldehyde, which was *in situ* reduced with $NaBH_4$. It was then followed by immediate reduction of the crude aminoxy product with $Cu(OAc)_2.H_2O$ that provided a single diastereomer of *syn*-3-amino-1,2-diol **113** in 64% yield and 98% ee.

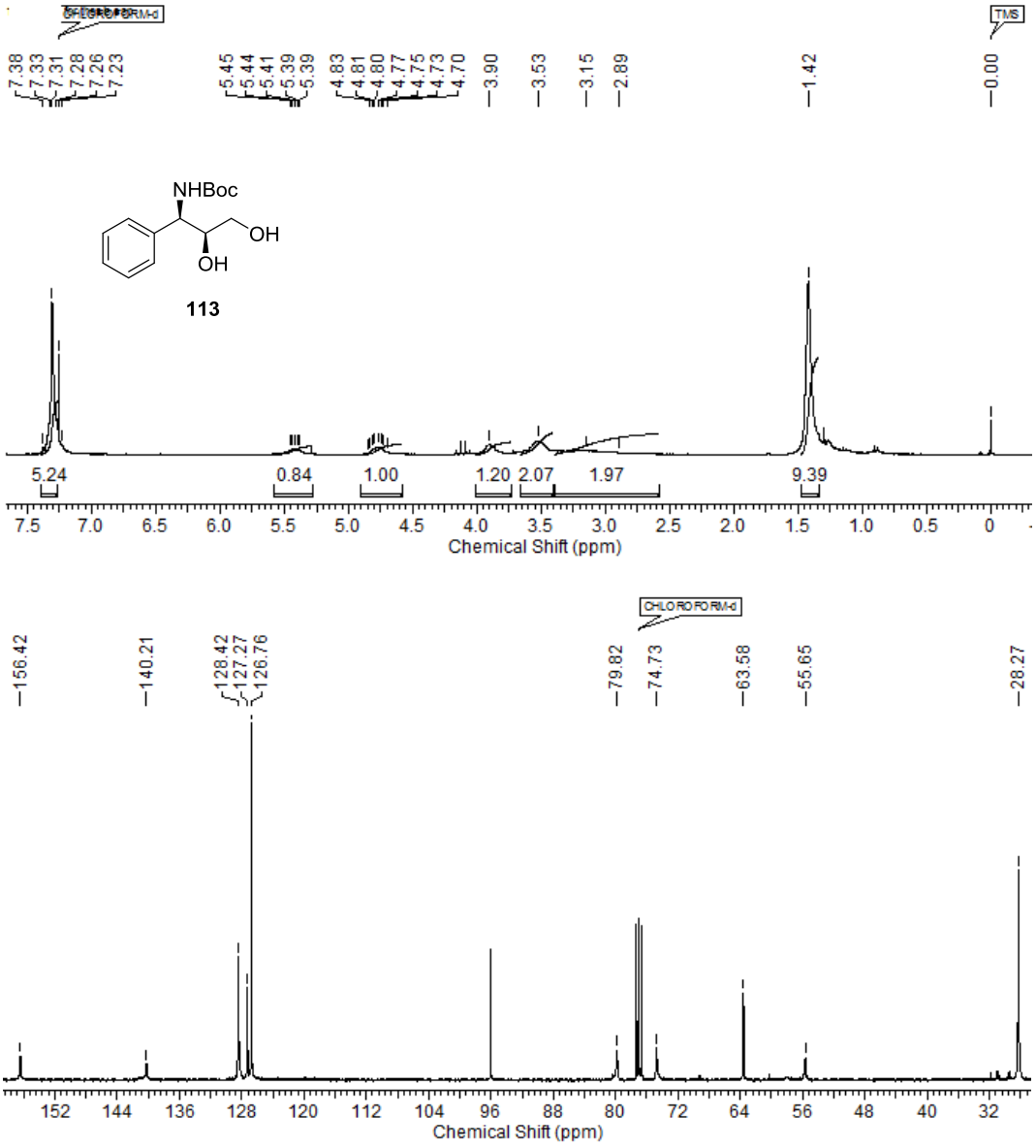
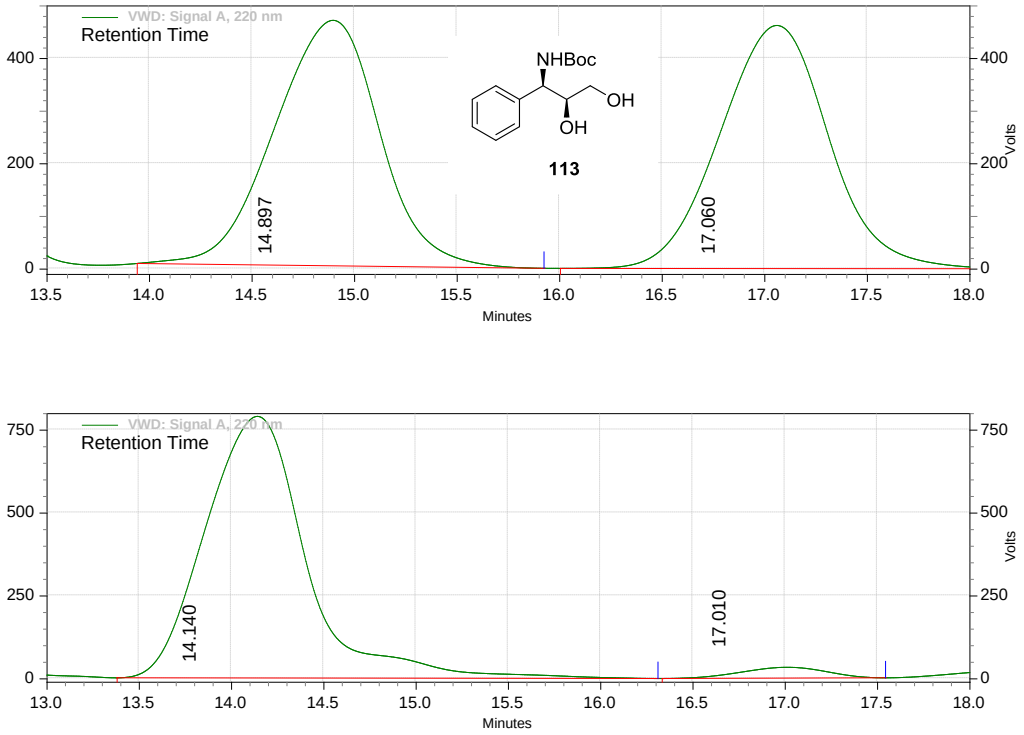


Fig. 17: ^{1}H and ^{13}C NMR spectra of *syn*-3-amino-1,2-diol **113**

The formation of *syn*-3-amino-1,2-diol **113** was confirmed from its ^{1}H NMR spectrum, which showed a characteristic broad singlet at δ 3.53 (br s, 2H) for methylene (-CH_2-OH) protons. Its ^{13}C NMR spectrum also showed two characteristic carbon signals at δ 63.6 and 74.7 attributed to methylene and methine carbons attached to hydroxyl groups respectively (**Fig. 17**).



Retention Time	Area	Area %	Height	Height %
14.140	151226434	98.86	43203378	98.62
17.010	1743861	1.14	604549	1.38

Fig. 18: HPLC chromatogram of *syn*-3-amino-1,2-diol **113**

The optical purity of *syn*-3-amino-1,2-diol **113** was determined to be 98% ee from chiral HPLC analysis (Chiracel AD-H, *n*-hexane/*i*PrOH, 85:15, 0.5 mL/min) retention time 14.14 min (98.86%) and 17.01 min (1.14%) (**Fig**.**18**).

The regioselective intramolecular cyclization of *syn*-3-amino-1,2-diol **113** with NaH in THF gave oxazolidinone **110** (**mp**: 106-108 ºC; lit.[55] **mp**: 105-107 ºC) in 94% yield. The formation of oxazolidinone **110** was confirmed from its ^{1}H and ^{13}C NMR spectra. The ^{1}H NMR spectrum of oxazolidinone **110** showed a typical singlet at δ 8.14 (s, 1H) corresponding to the N-H proton of oxazolidinone ring. Its ^{13}C NMR spectrum showed a characteristic signal at δ 158.1 due to the carbonyl carbon of oxazolidinone ring (**Fig. 19**).

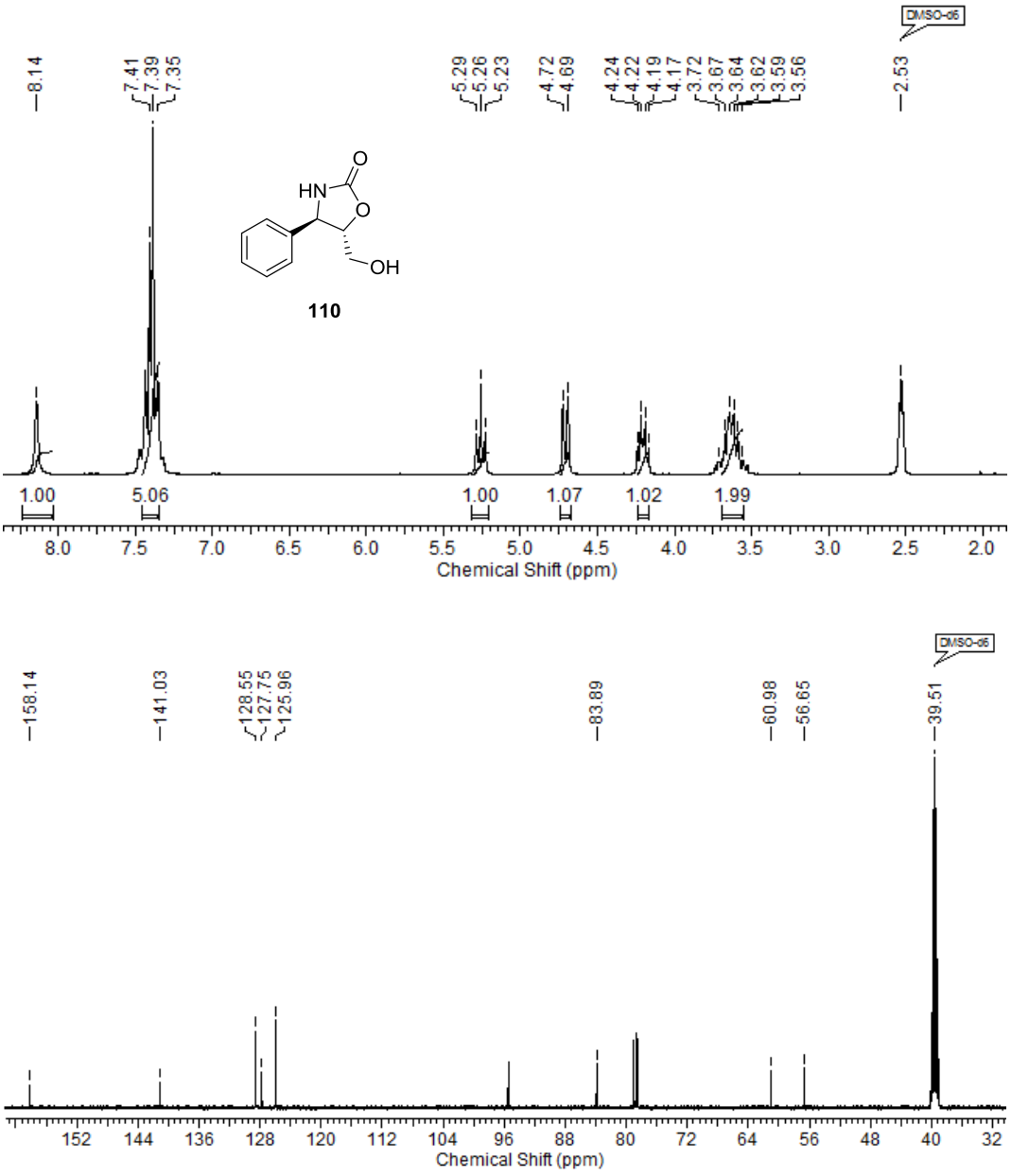


Fig. 19: ^{1}H and ^{13}C NMR spectra of oxazolidinone **110**

Finally, mesylation of primary alcohol in oxazolidinone **110** gave the mesylate, which on subsequent displacement with NaN_3 in DMF at 60 °C afforded (+)-2-oxazolidinone azide (**60**) in 82% yield.

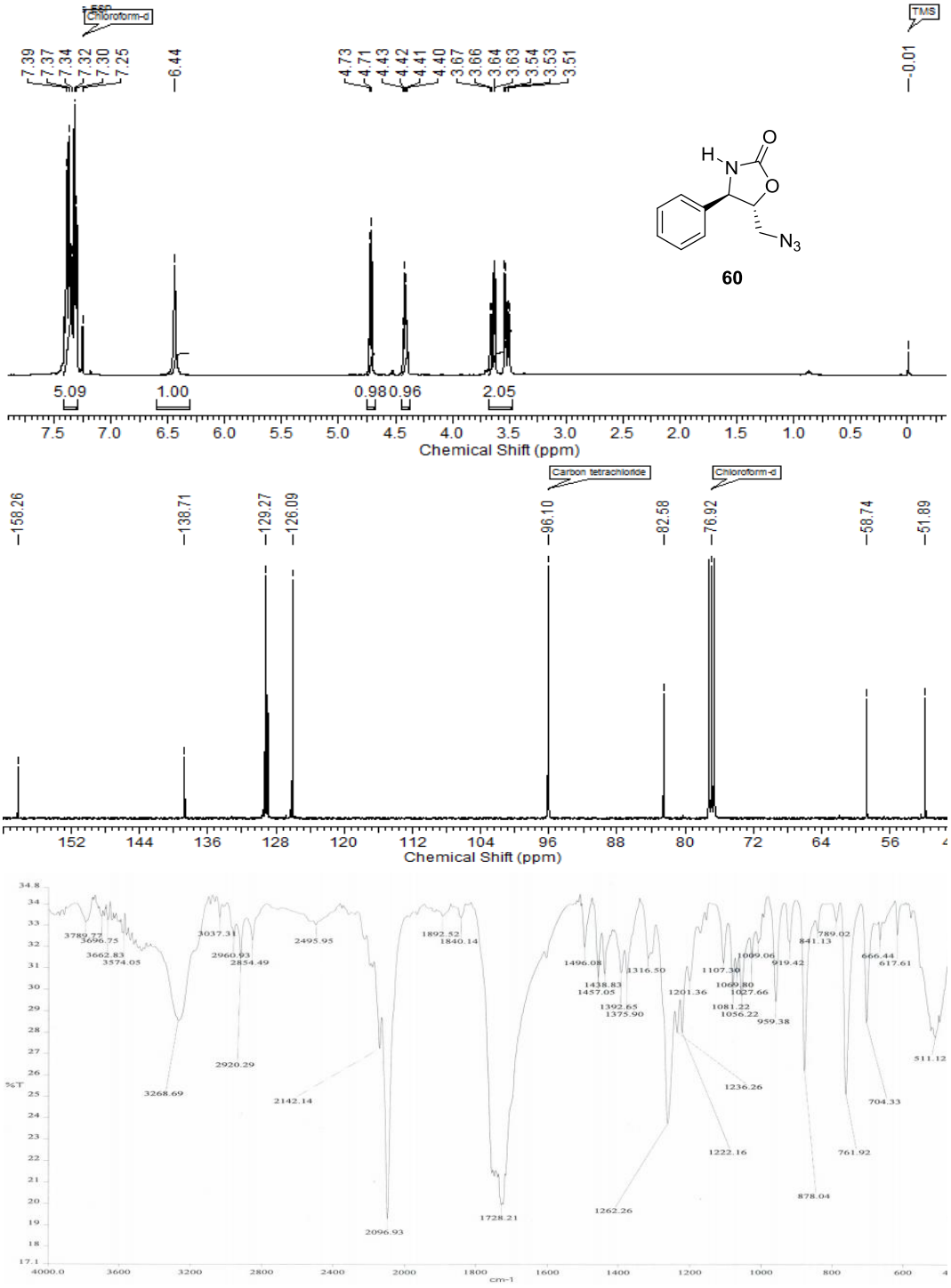


Fig. 20: ^{1}H, ^{13}C NMR and IR spectra of (+)-2-oxazolidinone **60**

The formation of (+)-2-oxazolidinone **60** was confirmed from its ^{1}H, ^{13}C NMR and IR spectra. The methylene proton attached to azide moiety resonated at δ 3.60 (dddd, *J* = 4.5, 13.6 Hz, 2H) in its ^{1}H NMR spectrum. It was further substantiated by the appearance of a carbon signal at δ 51.9 corresponding to carbon attached to azide group in its ^{13}C NMR spectrum. Its IR spectrum exhibited a characteristic strong absorption bands at 1728 cm^{-1} and 2096 cm^{-1} for oxazolidinone carbonyl and azide function respectively (**Fig. 20**). The conversion of (+)-2-oxazolidinone **60** to *N*-thiolated-2-oxazolidinone **59** has already been reported in the literature.[41]

3.2.6 Conclusion

A short and protecting group-free synthesis of (+)-*epi*-cytoxazone (**58**) and (+)-2-oxazolidinone **60** has been achieved. D-Proline-catalyzed α-aminooxylation of β-aminoaldehydes was used as the key reaction, which proceeded to give high enantioselectivity. This methodology can be used for a viable synthesis of other diastereomers of (+)-*epi*-cytoxazone (**58**) family by suitably employing L-proline as catalyst for α-aminooxylation of β-aminoaldehydes.

3.2.7 Experimental Section

Vide supra on section I of the same chapter for experimental procedure and spectral details of compounds **51a** and **51b**.

(2*S*, 3*R*)-3-(*tert*-Butoxycarbonylamino)-3-(4-methoxyphenyl)-1,2-propanediol (112)

To a stirred, precooled (-10 °C) acetonitrile (25 mL) solution of β-aminoaldehyde **51b** (4.78 g, 17 mmol) and nitrosobenzene (1.45 g, 13.6 mmol) was added D-proline (0.039 g, 20 mol%). The reaction mixture was allowed to stir at the same temperature for 18 h followed by the addition of CH_3OH (10 mL) and $NaBH_4$ (0.97 g, 25 mmol)

to the reaction mixture. It was stirred for another 10 min. After addition of phosphate buffer, the resulting mixture was extracted with EtOAc (3 × 30 mL) and the combined organic phases were dried over anhyd. Na_2SO_4 and concentrated to give the crude aminooxy alcohol, which was directly taken up for the next step without purification.

To a CH_3OH (25 mL) solution of the above crude aminooxy alcohol was added $Cu(OAc)_2.H_2O$ (0.501 g, 2.6 mmol) at 25 °C and the reaction mixture was allowed to stir for 16 h at that temperature. After addition of phosphate buffer, the resulting mixture was extracted with $CHCl_3$ (3 × 30 mL) and the combined organic phases were dried over anhyd. Na_2SO_4 and concentrated to give the crude product, which was then purified by column chromatography over silica gel using pet. ether:EtOAc (30:70) as an eluent to give *syn*-amino diol **112** (2.74 g) as a colorless solid.

Yield: 68%; colorless solid; **mp**: 140-143 °C, (lit.[53] **mp**: 141-142 °C); $[\alpha]^{25}_D$ -36.5 (*c* 1.0, $CHCl_3$); lit.[53] $[\alpha]^{25}_D$ -36.1 (*c* 1.0, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 720, 832, 1070, 1250, 1512, 1688, 2934, 3384; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.41 (s, 9H), 3.03 (br s, 1H), 3.42-3.56 (m, 2H), 3.78 (s, 3H), 3.85 (br s, 2H), 4.70 (br s, 1H), 5.32 (br s, 1H), 6.84 (d, *J* = 8.5 Hz, 2H), 7.21 (d, *J* = 8.5 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 28.3, 55.1, 56.1, 63.1, 74.1, 80.1, 114.1, 128.5, 131.1, 156.1, 159.1; **HRMS** (ESI) *m/z* calcd for $C_{15}H_{23}NO_5$ $[M + Na]^+$: 320.1473, found: 320.1485; **Analysis**: $C_{15}H_{23}NO_5$ requires C, 60.59; H, 7.80; N, 4.71; found: C, 60.36; H, 7.63; N 4.62%.

(4*S*, 5*S*)-5-(Hydroxymethyl)-4-(4-methoxyphenyl)oxazolidin-2-one: [(+)-*epi*-cytoxazone] (58)

To a solution of *syn*-3-amino-1,2-diol **112** (0.3 g, 1.0 mmol) in dry THF (10 mL) was added NaH (0.05 g, 60% w/w, 2.0 mmol) at 25 °C, and the mixture was stirred under nitrogen atmosphere for 3 h. The reaction mixture was concentrated and the resulting mixture was extracted with EtOAc (3 x 10 mL), washed with saturated aq. NH_4Cl (5

mL) and brine solution (5 mL). The organic layers were separated, dried over anhyd. Na_2SO_4, and concentrated to give the crude product, which was then purified by column chromatography over silica gel using pet. ether:EtOAc (60:40) as an eluent to give **58** (0.20 g) as a colorless solid.

Yield: 90%; colorless solid, **mp:** 158-160 °C, (lit.[53] **mp**: 161-162 °C); $[\alpha]^{25}_{D}$ +31.90 (*c* 1, MeOH); lit.[53] $[\alpha]^{25}_{D}$ +32.8 (*c* 0.6, MeOH); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 769, 843, 1028, 1248, 1395, 1513, 1610, 1733, 2580, 2924, 3272; **^{1}H NMR** (400 MHz, DMSO-d_6): δ 3.50-3.53 (m, 1H), 3.59-3.65 (m, 1H), 3.75 (s, 3H), 4.13-4.16 (m, 1H), 4.62 (d, *J* = 6.3 Hz, 1H), 5.21 (t, *J* = 5.8 Hz, 1H), 6.96 (d, *J* = 8.6 Hz, 2H), 7.26 (d, *J* = 8.6 Hz, 2H), 8.05 (s, 1H); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 55.2, 56.2, 61.0, 84.2, 114.2, 127.5, 132.9, 158.2, 159.1; **Analysis:** $C_{11}H_{13}NO_4$ requires C, 59.19; H, 5.87; N, 6.27; found: C, 59.01; H, 5.69; N, 6.13%.

(2*S*, 3*R*)-3-(*tert*-Butoxycarbonylamino)-3-phenyl-1,2-propanediol (113)

To a stirred, precooled (-10 °C) acetonitrile (25 mL) solution of β-aminoaldehyde **51a** (4.23 g, 17 mmol) and nitrosobenzene (1.45 g, 13.6 mmol) was added D-proline (0.039 g, 20 mol%). The reaction mixture was allowed to stir at the same temperature for 18 h followed by the addition of CH_3OH (10 mL) and $NaBH_4$ (0.97 g, 25 mmol) to the reaction mixture. It was stirred for further 10 min. After addition of phosphate buffer, the resulting mixture was extracted with EtOAc (3 × 30 mL) and the combined organic phases were dried over anhyd. Na_2SO_4 and concentrated to give the crude aminooxy alcohol, which was directly taken up for the next step without purification.

To a CH_3OH (25 mL) solution of the above crude aminooxy alcohol was added $Cu(OAc)_2.H_2O$ (0.501 g, 2.6 mmol) at 25 °C and the reaction mixture was allowed to stir for 16 h at that temperature. After addition of phosphate buffer, the resulting mixture was extracted with $CHCl_3$ (3 × 30 mL) and the combined organic phases were

dried over anhyd. Na_2SO_4 and concentrated to give the crude product, which was then purified by column chromatography over silica gel using pet. ether:EtOAc (35:65) as an eluent to give *syn*-amino diol **113** (2.32 g) as a colorless gum.

Yield: 64%; colorless gum; $[\alpha]^{25}_D$ -28.0 (*c* 0.7, $CHCl_3$); 98% ee from chiral HPLC analysis (Chiracel AD-H, *n*-hexane/*i*PrOH, 85:15, 0.5 mL/min) retention time 14.1 min (98.9%) and 17.0 min (1.1%); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 832, 1035, 1070, 1250, 1512, 1699, 2934, 3363; **^{1}H NMR** (200MHz, $CDCl_3$): δ 1.42 (s, 9H), 3.15 (br s, 2H), 3.53 (br S, 2H), 3.90 (br s, 1H), 4.70-4.85 (m, 1H), 5.39-5.45 (d, *J* = 5.0 Hz, 1H), 7.23-7.38 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 28.3, 55.6, 63.6, 74.7, 79.8, 126.8, 127.3, 128.4, 140.2, 156.4; **Analysis:** $C_{14}H_{21}NO_4$ requires C, 62.90; H, 7.92; N, 5.24; found: C, 62.69; H, 7.76; N, 5.10%.

(4*S*, 5*S*)-5-Hydroxymethyl-4-phenyloxazolidin-2-one (110)

To a stirred solution of *syn*-3-amino-1,2-diol **113** (0.267g, 1.0 mmol) in dry THF (10 mL) was added NaH (0.05 g, 60% w/w, 2.0 mmol) at 25 °C and the mixture was stirred under nitrogen atmosphere for 3 h. The reaction mixture was concentrated and the resulting mixture was extracted with EtOAc (3 x 10 mL), washed with saturated aq. NH_4Cl (5 mL) and brine solution (5 mL). The organic layers were separated, dried over anhyd. Na_2SO_4, and concentrated to give the crude product, which was then purified by column chromatography over silica gel using pet. ether:EtOAc (70:30) as an eluent to give **110** (0.181 g) as a colorless solid.

Yield: 94%; colorless solid, **mp:** 106-108 °C, (lit.[55] **mp**: 105-107 °C); $[\alpha]^{25}_D$ +26.7 (*c* 1, MeOH); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 772, 832, 1104, 1252, 1395, 1522, 1570, 1610, 1724, 2580, 2924, 3244; **^{1}H NMR** (200 MHz, DMSO-d_6): δ 3.56-3.72 (m, 2H), 4.17-4.24 (m, 1H), 4.70 (d, *J* = 6.2 Hz, 1H), 5.26 (d, *J* = 5.9 Hz, 1H), 7.35-7.41 (m, 5H), 8.14 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$+DMSO-d_6) δ: 56.6, 60.9, 83.9, 125.9, 127.7,

128.5, 141.0, 158.1; **Analysis:** $C_{10}H_{11}NO_3$ requires C, 62.17; H, 5.74; N, 7.25; found: C, 62.03; H, 5.47; N, 7.13%.

(4*S*, 5*S*)-5-Azidomethyl-4-phenyloxazolidin-2-one (60)

To a stirred solution of alcohol **110** (0.791 g, 4.1 mmol) in CH_2Cl_2 (5 mL) was added Et_3N (0.82 g, 8.2 mmol) at 0 ^oC. After 5 min of stirring, methane sulfonyl chloride (0.47 g, 4.1 mmol) was added drop-wise over a period of 5 min. The reaction mixture was then stirred for another 1 h at 0 ^oC. After the completion of the reaction, as monitored by TLC, it was extracted with CH_2Cl_2 (3 x 20 mL) washed with water, brine and dried over anhyd. Na_2SO_4. The combined organic layers were concentrated under reduced pressure to give crude methane sulfonate ester **111** in almost quantitative yield. To a solution of the crude mesylate **111** in DMF (10 mL) was added NaN_3 (0.53 g, 8.2 mmol) and the reaction mixture was heated at 60 ^oC for 12 h. After the completion of the reaction, as monitored by TLC, it was extracted with EtOAc (3 x 20 mL) washed with water, brine and dried over anhyd. Na_2SO_4. The combined organic layers were concentrated under reduced pressure to give the crude 2-oxazolidinone **60**, which was purified by column chromatography using pet. ether:EtOAc (85:15) to give **60** (0.732 g) as colorless solid.

Yield: 82%; colorless solid, **mp:** 80-83 °C, (lit.[55] **mp**: 82-84 °C); $[\alpha]^{25}_D$ +30.4 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 761, 878, 1222, 1262, 1457, 1728, 2096, 2142, 2920, 3268; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.60 (dddd, *J* = 4.5, 13.6 Hz, 2H), 4.40-4.43 (m, 1H), 4.72 (d, *J* = 6.5 Hz, 1H), 6.44 (s, 1H), 7.30-7.39 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 51.9, 58.7, 82.6, 126.1, 129.0, 129.3, 138.7, 158.3; **Analysis:** $C_{10}H_{10}N_4O_2$ requires C, 55.04; H, 4.62; N, 25.68; found: C, 55.09; H, 4.48; N, 25.48%.

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CHAPTER 4

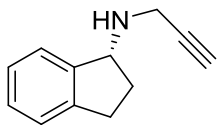
Asymmetric Synthesis of Rasagiline and NHC-catalyzed Esterification of Aromatic Aldehydes

Section I:

Enantioselective Synthesis of Rasagiline an anti-Parkinson Drug

4.1.1 Introduction and Pharmacology

Neurodegenerative diseases are the third cause of death among aged population all over the world. Parkinson's disease (PD) named after the English doctor James Parkinson is the most common neurodegenerative disorder and manifests as rigidity, resting tremor and posture instability.[1] PD is a degenerative disorder of the central nervous system, resulting from the death of cells that use dopamine to transmit their signals, resulting in decreased synaptic signal strength and concomitant symptomology.[2] It is generally characterized by insufficient formation and activity of dopamine produced within substantia nigra, a region of the midbrain. Modern treatments are effective at managing the early stages of the disease, mainly through the use of dopamine agonists.[3] As the disease progresses and dopaminergic neurons continue to be lost, these drugs eventually become ineffective at treating the symptoms and at the same time produce a complication called dyskinesia, marked by involuntary writhing movements.[4]



Rasagiline (**1**)

Fig. 1: Structure of anti-Parkinson drug, rasagiline (**1**)

The existing therapies are still well-below the expectations for the advanced stages of the disease. Therefore, there is a need for novel therapeutic drug to ameliorate the

pathophysiological process of the disease. It is well-established that human cells contain two forms of monoamine oxidase (MAO) type A and type B. In the brain, MAO type B is far more prevalent and is responsible for the breakdown of dopamine after its release into the synapse.[5] Since PD is generally regarded as a dopamine deficiency-disorder, there is a need for drugs, which can correct dopamine deficiency. In this regard, rasagiline (**1**) (**Fig. 1**) (Azilect®, Teva Pharmaceutical Industries Ltd., Israel), an irreversible MAO B inhibitor, was approved first in Israel (January 2005), followed by European agency (February 2005) and by US federal drug administration (May 2006) for the treatment of idiopathic PD as monotherapy or as adjunct therapy with L-dopa in advanced cases.[6] Rasagiline (**1**) presents a very significant and selective activity concerning monoamine oxidase B inhibition.[7] It is selective for MAO B over MAO A by a factor of fourteen.[8] By inhibiting the breakdown of dopamine in the synapse, rasagiline (**1**) permits the signaling neurons to re-absorb more of dopamine.[9] Structure activity studies show that its neuroprotective efficacy is strongly related to the propargylamino group.[10] Very recently studies have revealed that rasagiline salts decrease human melanoma tumor growth *in vivo*, proving its potential as multi-target drug candidature for melanoma and PD.[10e]

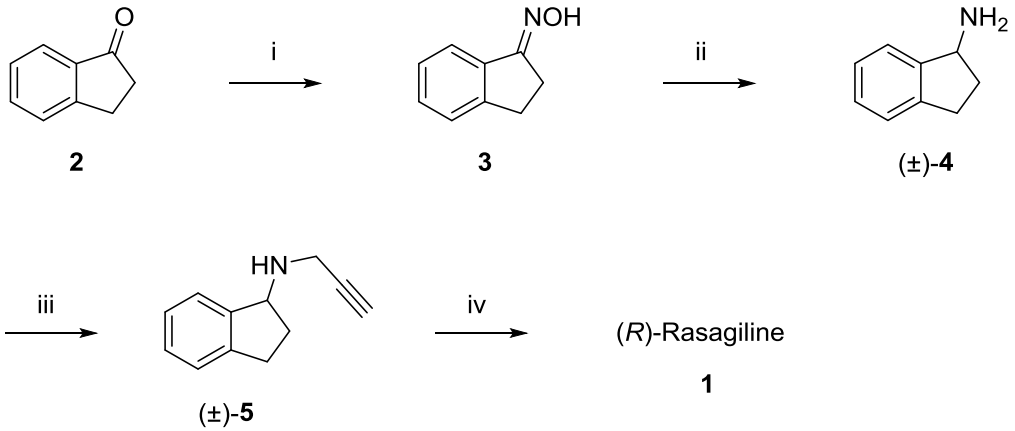
4.1.2 Review of Literature

Literature search revealed that there are only few reports available on the synthesis of rasagiline (**1**)[11-16] and its analogs.[17] A short description on the reported synthesis of rasagiline (**1**) is presented below.

Moussa's approach (1991)[11,12]

Moussa *et al.* have reported the synthesis of rasagiline (**1**) by using high-performance liquid chromatography for the separation of racemic mixture as the key technique.

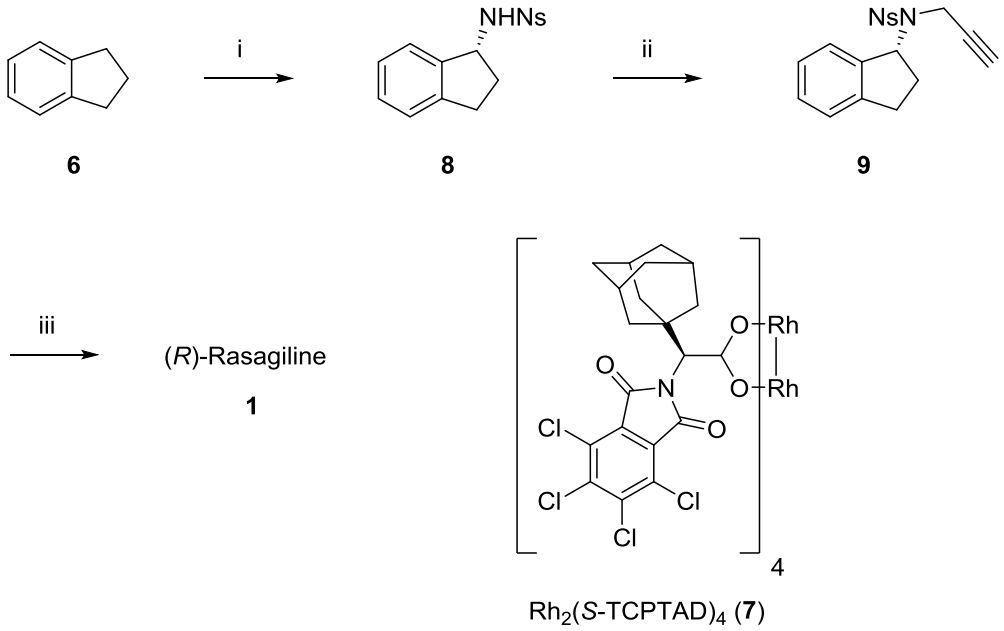
Thus, indanone **2** was treated with hydroxyl amine under basic condition to provide 1-indanone oxime **3**. Hydrogenation of oxime **3** using Raney Ni afforded racemic mixture of primary amine (±)-**4** in 87% yield. Propargylation of amine (±)-**4** gave racemic mixture of rasagiline (±)-**5,** from which (+)-rasagiline (**1**) was isolated by resolving the racemic mixture on a Chiracel OJ (cellulose tris[*p*-methylbenzoate]) preparative HPLC column (**Scheme 1**).



Scheme 1: (i) $NH_2OH.HCl$, H_2O, 50% aq. NaOH, C_2H_5OH, reflux, 15 min, 98%; (ii) Raney Ni, H_2 (80 psi), 16% aq. NH_3, CH_3OH, 25 °C, 25 h, 87%; (iii) K_2CO_3, propargyl chloride, CH_3CN, 60 °C, 16 h, 56%; (iv) Chiral HPLC separation.

Davies' approach (2006)[13]

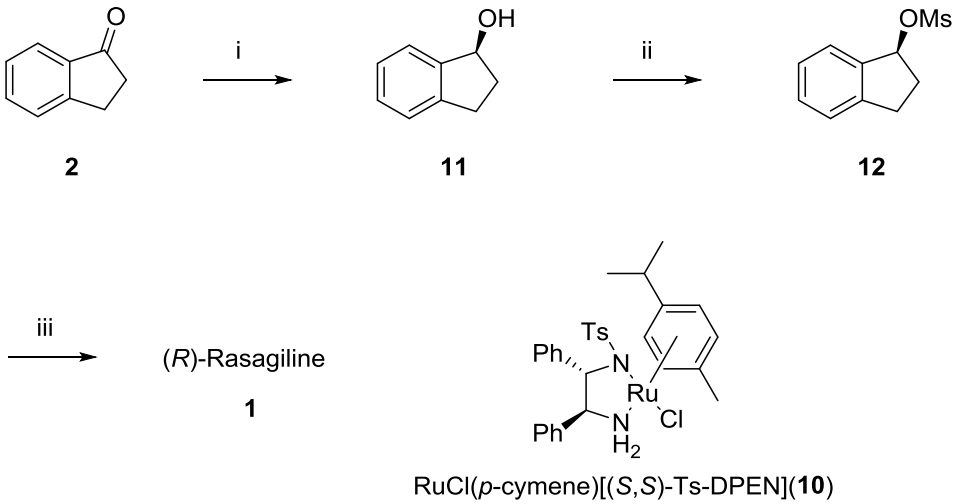
Davies *et al.* have achieved the synthesis of (+)-rasagiline (**1**) using catalytic enantio-selective C-H amination as the key step. Thus, sulfonamide **8** was obtained *via* enantioselective amination of indane **6** in trifluorotoluene with newly developed catalyst *i.e.* Rh_2(*S*-TCPTAD)$_4$ (**7**) (2 mol%), $PhI(OAc)_2$, MgO and $NsNH_2$ as amine source in 95% yield and 94% ee. Alkylation of sulfonamide **8** with propargyl bromide forming nosyl protected rasagiline **9**, followed by the removal of nosyl group under Fukuyama's protocol, afforded rasagiline (**1**) (**Scheme 2**).



Scheme 2: (i) Rh_2(*S*-TCPTAD)$_4$ (**7**), $PhI(OAc)_2$, trifluorotoluene, $NsNH_2$, MgO, 23 °C, 3 h, 95%; (ii) propargyl bromide, K_2CO_3, CH_3CN, 60 °C, 16 h, 75%; (iii) $HSCH_2CH_2OH$, DBU, DMF, 25 °C, 1 h, 64%.

Boulton's approach (2009)[14]

Boulton *et al.* have developed a useful synthetic method for the synthesis of (+)-rasagiline (**1**) using chiral ketone reduction as the key step.

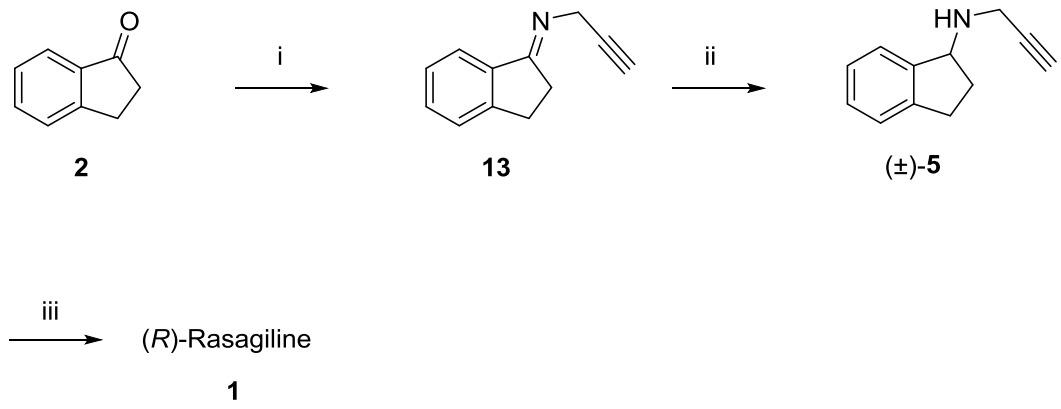


Scheme 3: (i) RuCl(*p*-cymene)[(*S*,*S*)-Ts-DPEN](**10**), HCOOH, Et_3N, CH_2Cl_2, 30 °C, 21 h, 96%; (ii) $(CH_3SO_2)O$, Et_3N, CH_2Cl_2, -20 °C, 45 min; (iii) propargyl amine, CH_2Cl_2, 25 °C, 12 h, 68% (over two steps).

Thus, chiral reduction of l-indanone **2** in the presence of an optically active Ru-catalyst *i.e.* RuCl(*p*-cymene)[(*S,S*)-Ts-DPEN](**10**) gave the corresponding (*S*)-indanol **11** in 96% yield with 98% ee. Mesylation of the hydroxyl moiety of indanol **11** provided mesylate **12**, which on subsequent benzylic SN_2 substitution with propargyl amine afforded rasagiline (**1**) (**Scheme 3**).

Praveen's approach (2010)[15]

Praveen *et al*. have reported the synthesis of rasagiline (**1**) by employing classical resolution, for the separation of racemic mixture as the key step. Indanone **2** was thus condensed with propargyl amine to afford indanylimine **13**. Reduction of imine **13** with $NaBH_4$ afforded racemic mixture of rasagiline (±)-**5,** from which (+)-rasagiline (**1**) was isolated by resolving the racemic mixture in the presence of tartaric acid as the chiral resolving agent (**Scheme 4**).

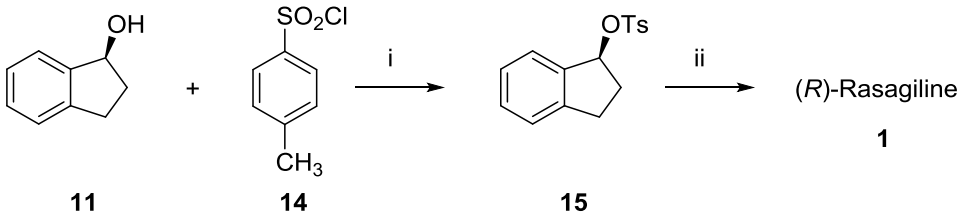


Scheme 4: (i) propargyl amine, CH_3OH, 30 °C, 20 h; (ii) $NaBH_4$, CH_3OH, 0 °C to 25 °C, 6 h, 47% (over two steps); (iii) (a) tartaric acid, ^{i}PrOH, 60 °C, 8 h, 77%; (b) NaOH, H_2O, 35 °C, 4 h, 41%.

Tatendra's approach (2011)[16]

Tatendra *et al.* have developed a useful synthetic method for the synthesis of rasagiline (**1**) commencing from chiral starting material. Reaction of (*S*)-indanol **11** with *p*-TsCl (**14**) in presence of triethylbenzylammonium chloride (TEBA) as PTC

and NaOH afforded tosylate **15**, in 92% yield, which on treatment with propargyl amine in presence of TEBA under reflux conditions gave rasagiline (**1**) (**Scheme 5**).



Scheme 5: (i) TEBA, NaOH, H_2O, toluene, 25 °C, 2 h, 92%; (ii) propargyl amine, toluene, TEBAC, ^{i}PrOH, H_2O, reflux, 20 h, 79%.

4.1.3 Present work

4.1.3.1 Objective

From the above discussion, it is evident that only few reports are available for the synthesis of rasagiline (**1**). However, some of the reported methods suffer from certain drawbacks such as use of chiral starting materials, chiral resolving agents, expensive separation methods, exotic reagents, etc. Significant commercial interest in the synthesis of rasagiline (**1**) is evident from the large number of patents filed for its synthesis. In this context, a more practical method that introduces chirality into the molecule using organocatalyst is highly desirable. This section describes an elegant synthetic route to the synthesis of rasagiline (**1**) using proline-catalyzed Mannich reaction of acetaldehyde as the key step.

Retrosynthetic analysis of rasagiline (**1**) reveals that amine **20** could be visualized as the key intermediate. The amino derivative **20** could be obtained by means of the Wolff-Kishner reduction of indanone **19**, which could in turn be obtained by performing Friedel-Crafts acylation of the β-amino acid **18**. The required β-amino acid **18** could be readily prepared from imine **16** (**Fig. 2**).

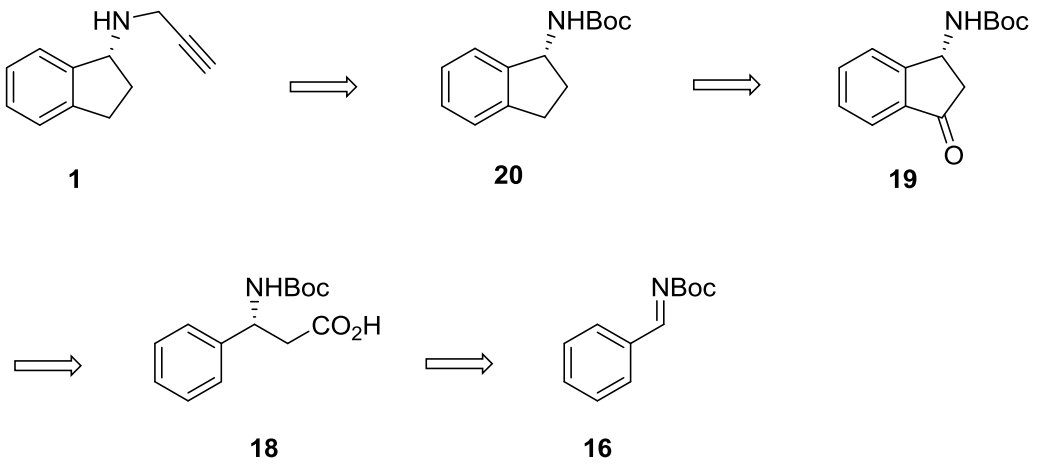
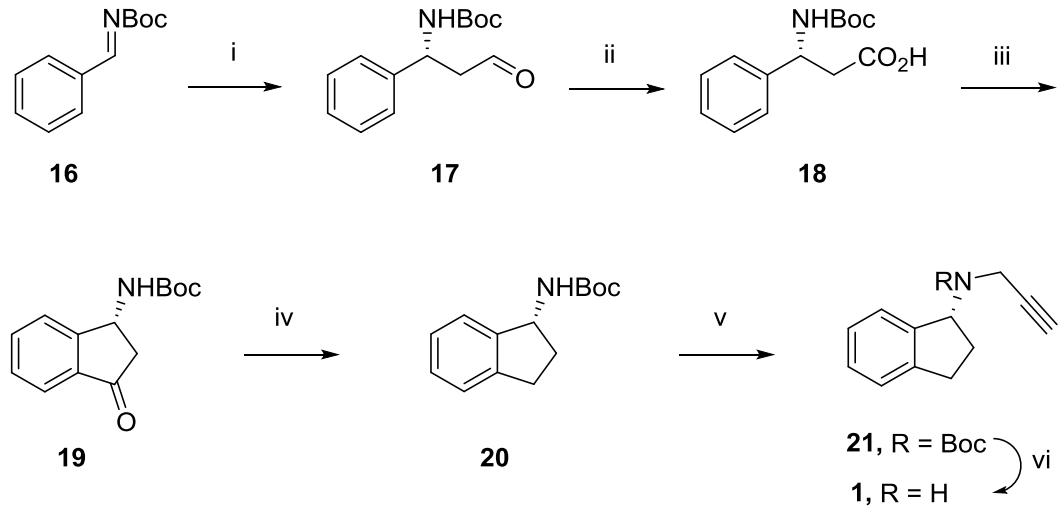


Fig. 2: Retrosynthetic analysis of rasagiline (**1**)

4.1.4 Results and Discussion

The complete synthetic sequence for rasagiline (**1**) is shown in **Scheme 6**, wherein proline-catalyzed Mannich reaction of acetaldehyde constitutes a key step for the introduction of chirality in the molecule.



Scheme 6: (i) CH_3CHO, D-proline (20 mol%), CH_3CN, 0 ^oC, 3 h, 62%; (ii) $NaClO_2$, NaH_2PO_4, *tert*-BuOH:H_2O (5:1), 25 ^oC, 30 min, 93%; (iii) $ClSO_3H$, CH_2Cl_2, 25 ^oC, 2 h, then $(Boc)_2O$, Et_3N, cat. DMAP, CH_2Cl_2, 25 ^oC, 3 h, 83%; (iv) $NH_2NH_2.H_2O$, KOH, diethylene glycol, reflux, 4 h, 88%; (v) NaH, propargyl bromide, DMF, 25 ^oC, 4 h, 81%; (vi) 37% aq. HCl, dioxane, 25 ^oC, 30 min, 97%.

The present synthesis of rasagiline (**1**) started from Boc-protected benzaldimine **16**, which on Mannich reaction with acetaldehyde (D-proline, CH_3CN, 0 ºC)[18] afforded β-aminoaldehyde **17** in 62% yield and 98% ee. The formation of β-aminoaldehyde **17** was confirmed from its ^{1}H NMR spectrum, which showed typical proton signals at δ 9.73 (t, *J* = 1.7 Hz, 1H) and δ 2.83-2.96 (m, 2H) corresponding to aldehydic and homo benzylic methylene protons respectively. This was further ascertained by the presence of two characteristic carbon signals at δ 199.8 and 193.3 in its ^{13}C NMR spectrum corresponding to carbamate and aldehydic carbonyl carbons respectively (**Fig. 3**).

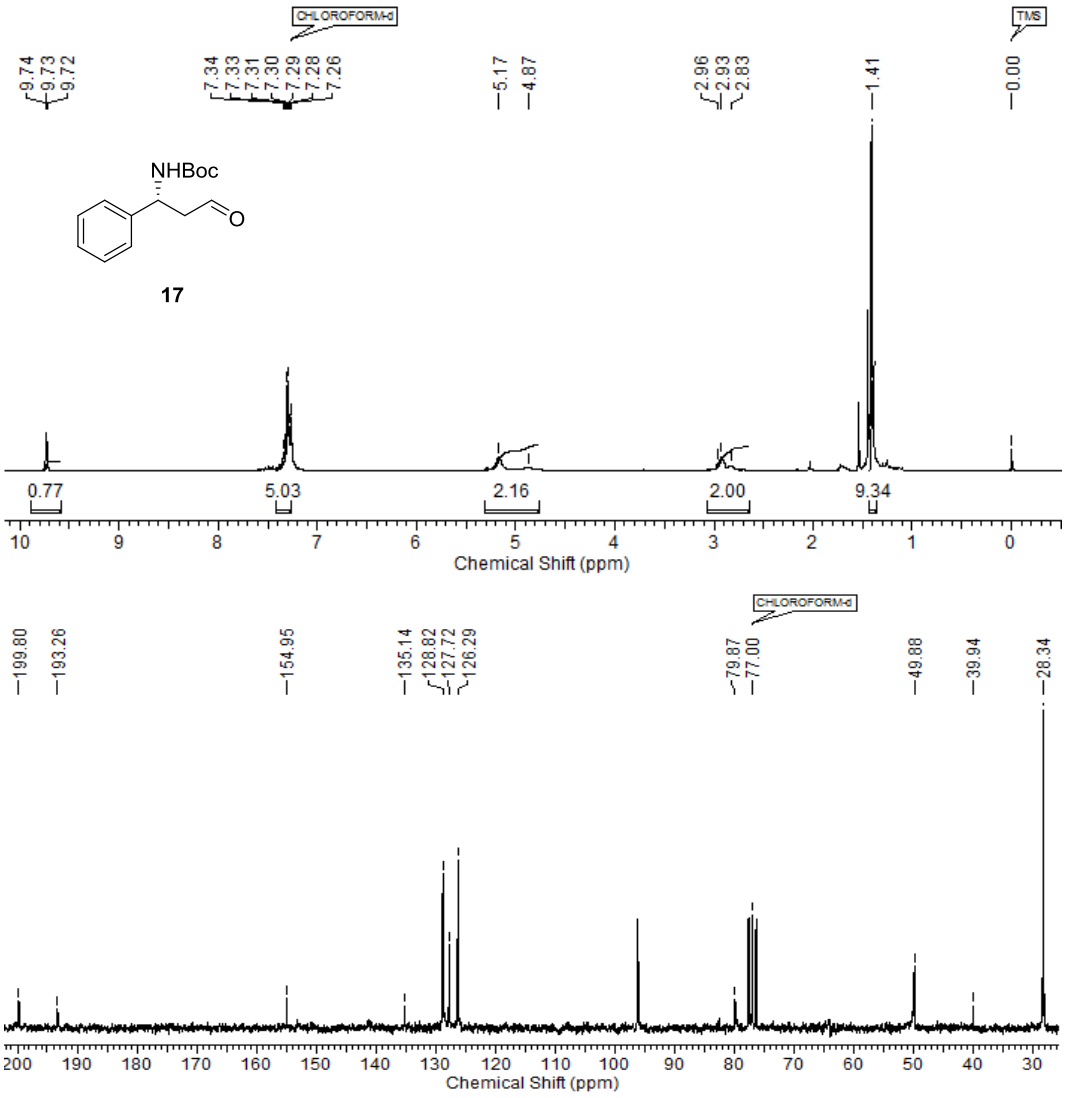


Fig. 3: ^{1}H and ^{13}C NMR spectra of β-aminoaldehyde **17**

The Pinnick oxidation of β-aminoaldehyde **17** with $NaClO_2$ and NaH_2PO_4 gave the corresponding β-aminocarboxylic acid **18** in 93% yield.[19] The formation of carboxylic acid **18** was confirmed from its ^{1}H NMR spectrum, which showed two characteristic proton signals at δ 2.67 (br s, 1H) and 2.86 (br s, 1H) corresponding to homo benzylic methylene protons, while its ^{13}C NMR spectrum showed a typical carbon signal at δ 170.1 due to the presence of carboxylic acid carbonyl carbon (**Fig. 4**). Its IR spectrum displayed a characteristic strong absorption band at 1707 cm^{-1} indicating the presence of carboxylic acid group.

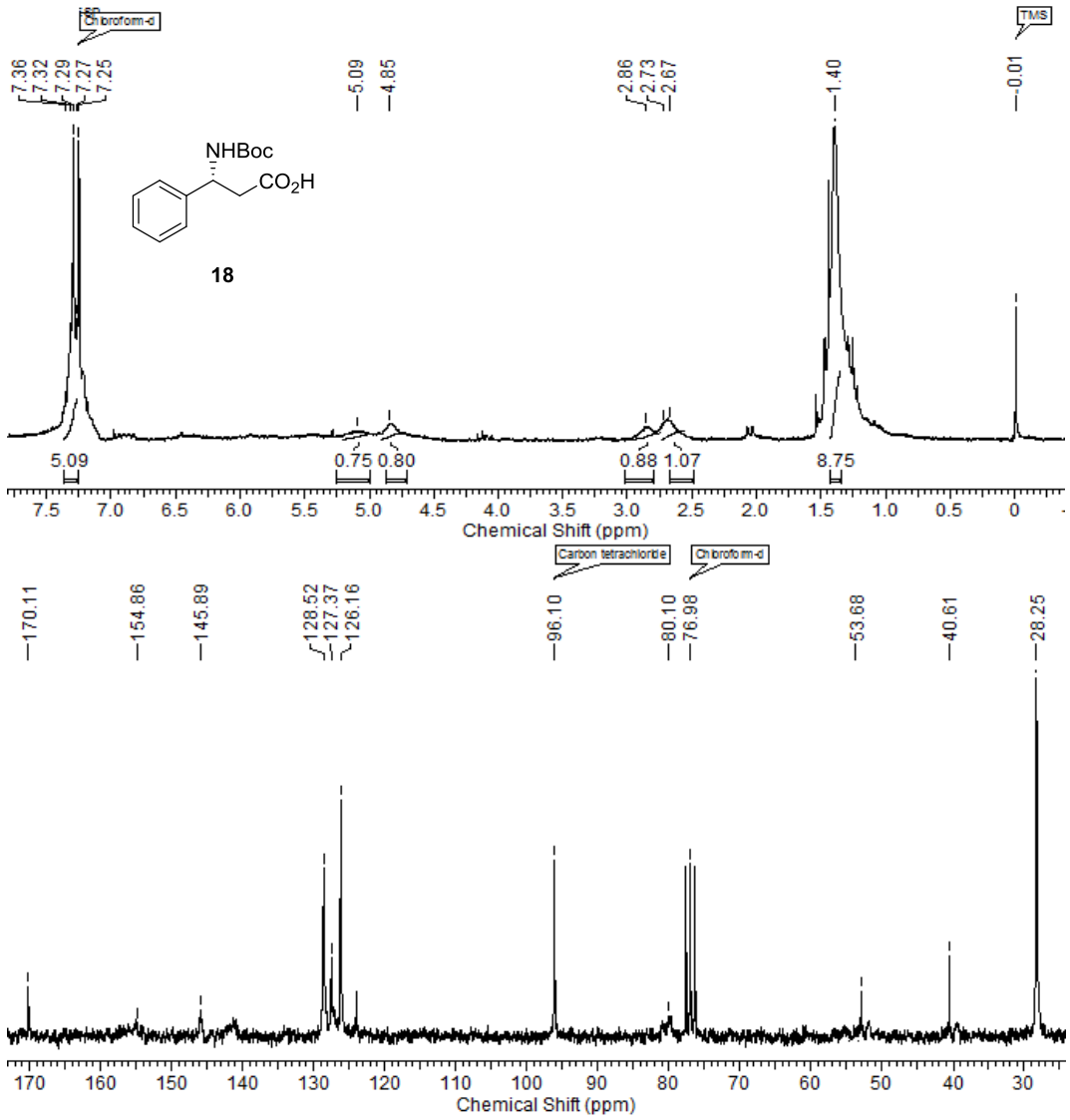


Fig. 4: ^{1}H and ^{13}C NMR spectra of carboxylic acid **18**

The indanone **19** was obtained by the Friedel-Crafts' intramolecular acylation[20] of β-amino acid **18** on reaction with $ClSO_3H$, followed by the protection of primary amine [$(Boc)_2O$, Et_3N, cat. DMAP]. Indanone **19** was confirmed from its ^1H NMR spectrum, which showed two characteristic doublet of doublets at δ 2.45 (dd, J = 3.2, 19.2 Hz, 1H) and 3.16 (dd, J = 7.6, 19.2 Hz, 1H), corresponding to the diastereotopic methylene protons, while its ^{13}C NMR spectrum showed a characteristic carbon signal at δ 202.9 due to ketone carbonyl carbon (**Fig. 5**).

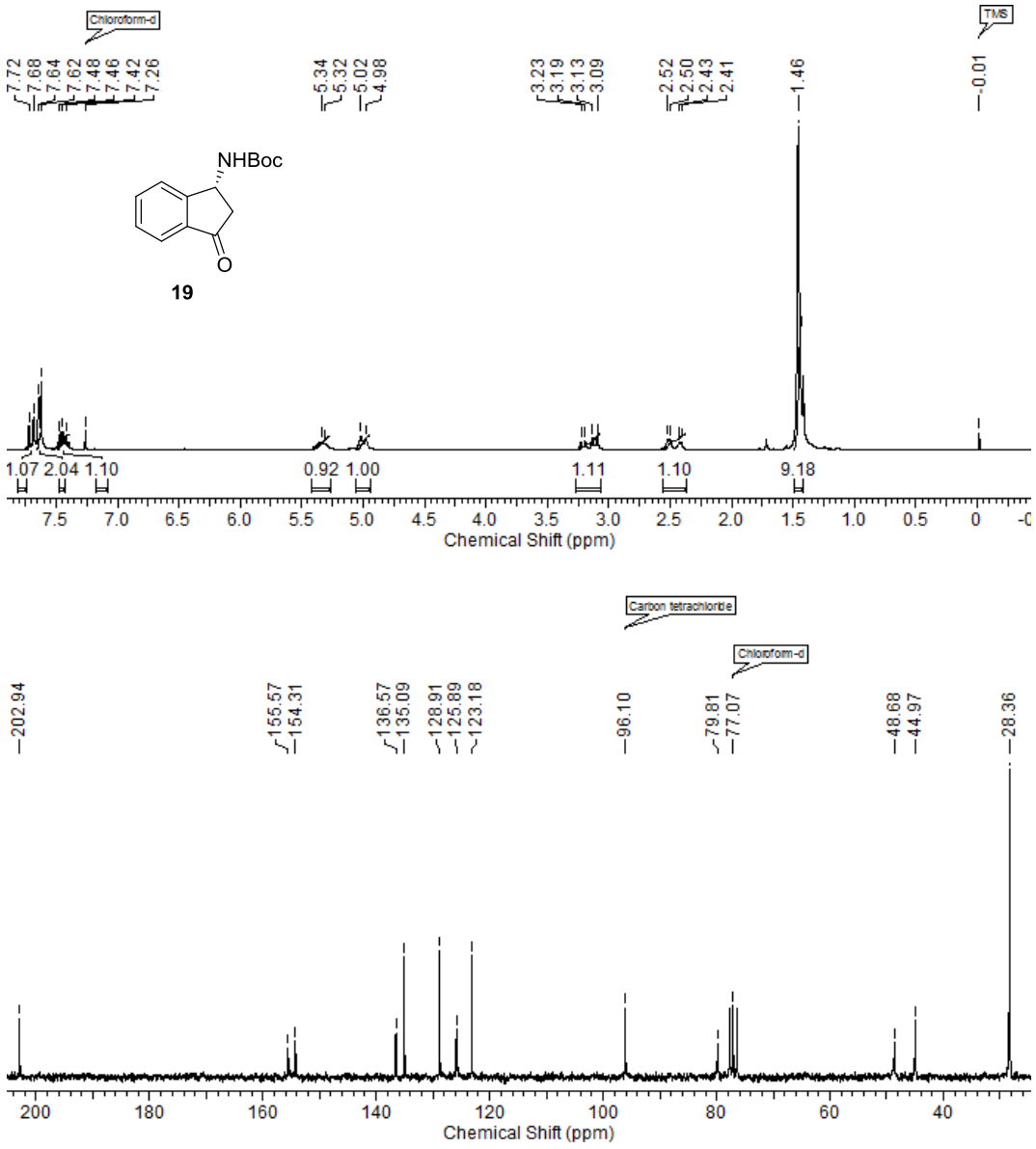
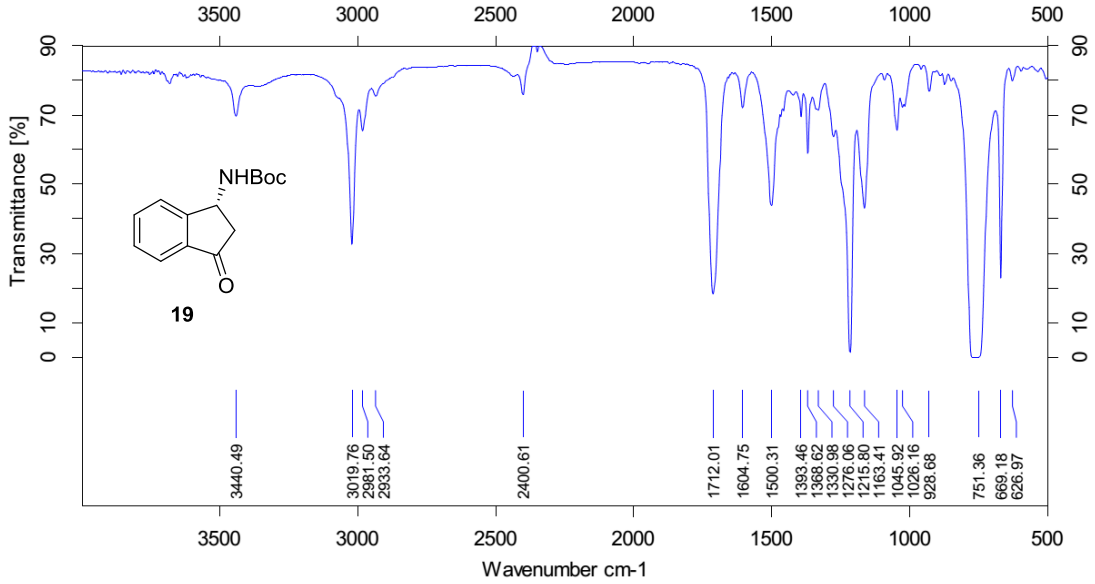
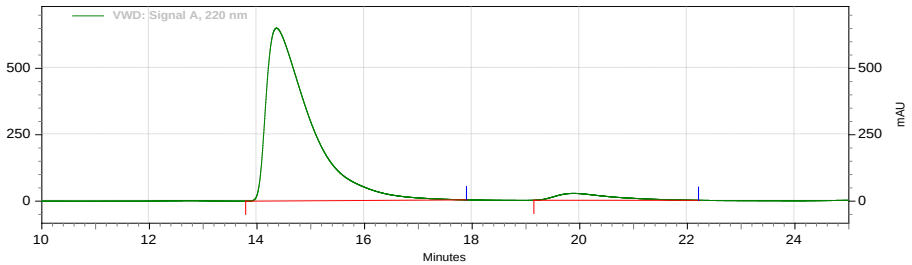


Fig. 5: ^1H and ^{13}C NMR spectra of indanone **19**

The formation of indanone **19** was also confirmed from its IR spectrum, which displayed a strong absorption band at 1712 cm^{-1} indicating the presence of ketone functional group. The optical purity of **19** was determined to be 98% ee from chiral HPLC analysis (Chiralcel AD-H, *n*-hexane/ ^{i}PrOH, 90:10, 0.5 mL/min) retention time 14.36 (99.08%) and 19.88 (0.92%) (**Fig**.**6**).





Ret. time	Area	Area %	Height	Height %
14.363	641328648	99.08	11318224	99.70
19.887	5955009	0.92	34057	0.30

Fig. 6: IR spectrum and HPLC chromatogram of indanone **19**

Wolff-Kishner reduction of indanone **19** with $NH_2NH_2.H_2O$ and KOH afforded carbamate **20** in 88% yield.[21] The formation of carbamate **20** was established from its ^{1}H NMR spectrum, which showed two characteristic proton signals at δ 2.74-3.03 (m, 2H) and 5.17 (d, *J* = 7.7 Hz, 1H) due to benzylic protons, while its ^{13}C NMR spectrum displayed the disappearance of carbon signal at δ 202.9 corresponding to the ketone carbonyl carbon, confirming the reduction of ketone group (**Fig**.**7**).

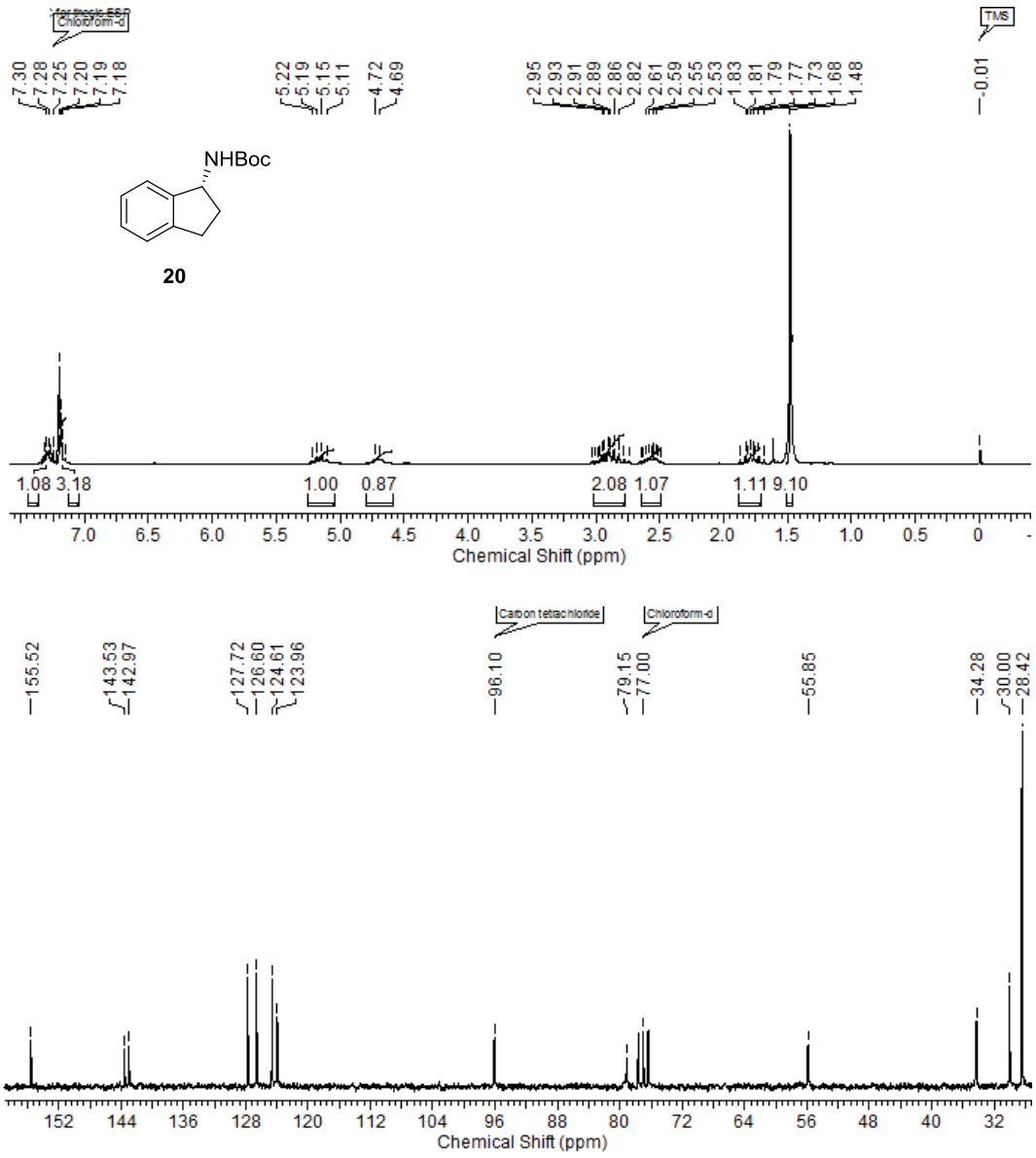


Fig. 7: ^{1}H and ^{13}C NMR spectra of carbamate **20**

Alkylation of carbamate **20** was achieved with propargyl bromide under basic conditions to afford the protected rasagiline **21** in 81% yield.[22] The formation of protected rasagiline **21** was confirmed from its ^{1}H NMR spectrum, which showed three typical proton signals at δ 2.96-3.10 (m, 1H), 3.32-3.63 (m, 1H) and 3.82-4.16 (m, 1H) corresponding to terminal alkyne and diastereotopic methylene protons attached to alkyne respectively. Its ^{13}C NMR spectrum showed two characteristic carbon signals at δ 61.1 and 69.6 corresponding to alkyne carbons (**Fig. 8**).

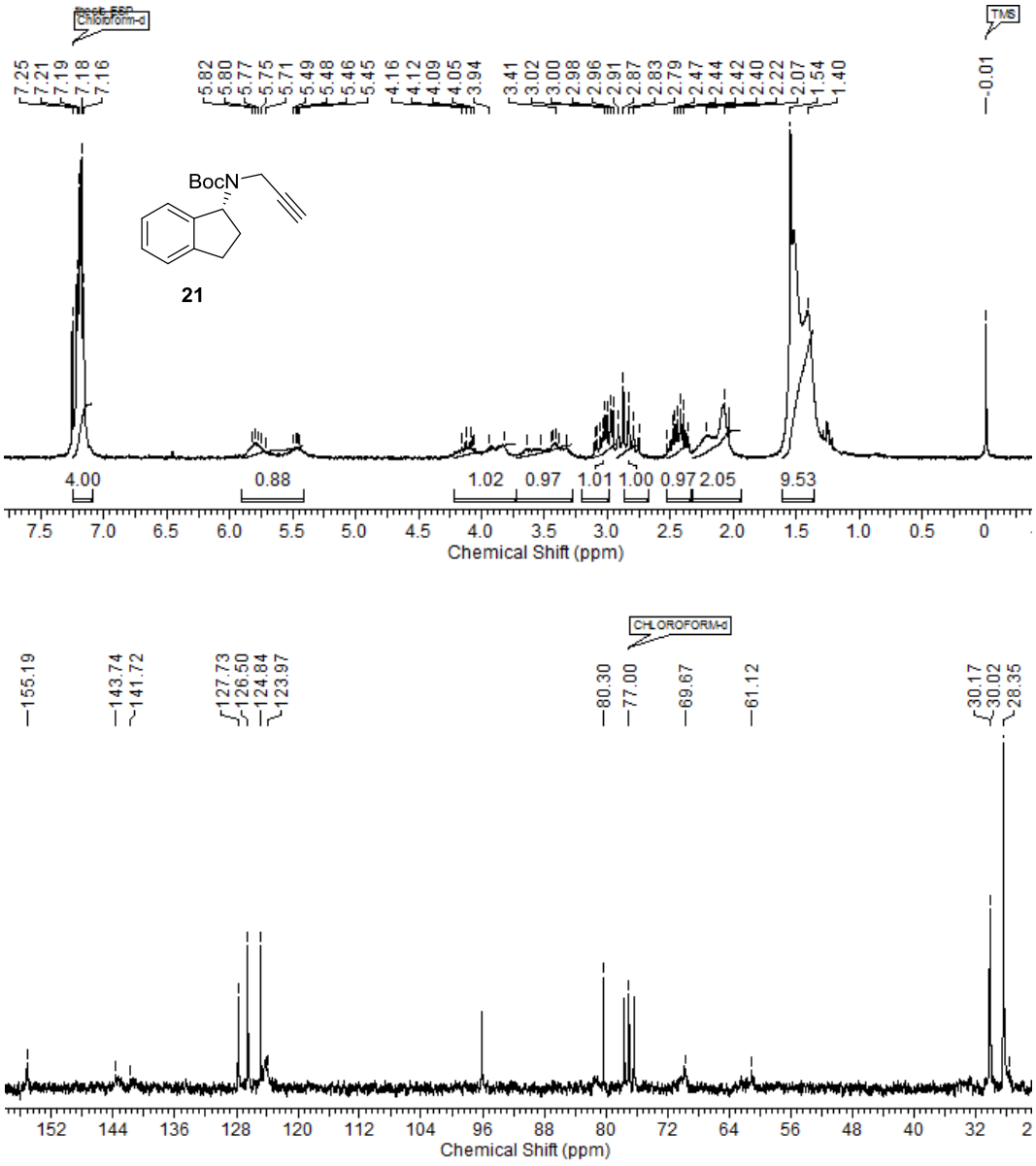


Fig. 8: ^{1}H and ^{13}C NMR spectra of protected rasagiline **21**

Finally, deprotection of the Boc protecting group with 37% aq. HCl in dioxane furnished rasagiline (**1**) in 97% yield and 98% ee, $[\alpha]^{D}_{25}$ +19.4 (*c* 0.5, $CHCl_3$) [lit.[13] $[\alpha]^{D}_{25}$ +18.8 (*c* 1.7, $CHCl_3$)]. The ^{1}H NMR spectrum of rasagiline (**1**) showed two typical proton signals at δ 2.23 (t, *J* = 2.4 Hz, 1H) and 3.52 (t, *J* = 2.4 Hz, 2H) corresponding to benzylic methine and diastereotopic methylene protons attached to alkyne respectively.

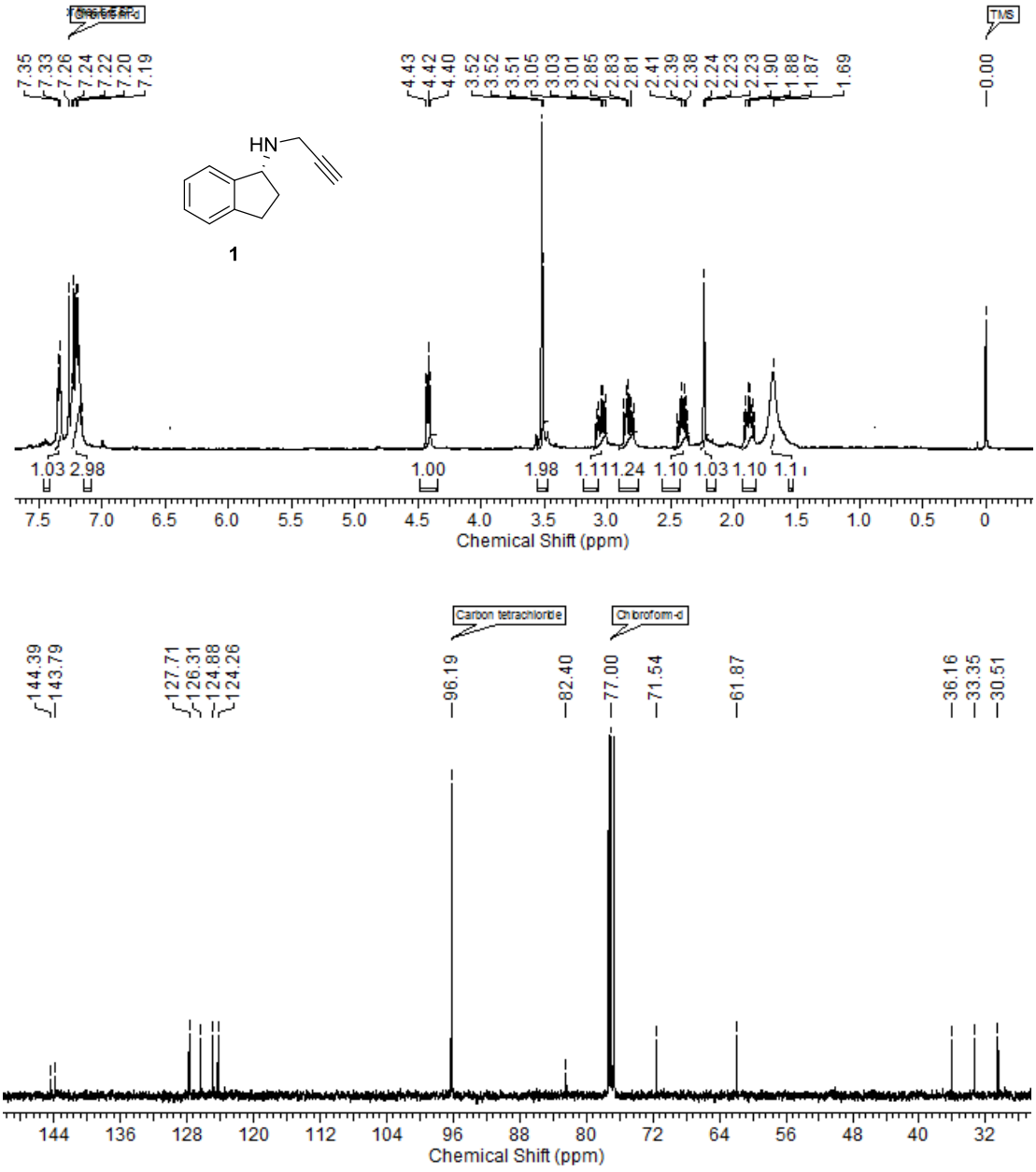


Fig. 9: ^{1}H and ^{13}C NMR spectra of rasagiline (**1**)

Its ^{13}C NMR spectrum showed characteristic carbon signals at δ 61.8, 71.5 and 82.4 corresponding to benzylic methine and alkyne carbons respectively (**Fig. 9**). The spectral data of rasagiline (**1**) were in complete agreement with the reported values.[22]

4.1.5 Conclusion

In conclusion, we have achieved the asymmetric synthesis of rasagiline (**1**) (33% overall yield, 98% ee) using proline-catalyzed Mannich reaction, Friedel-Crafts acylation and Wolff–Kishner reduction as the key steps. The utilization of organocatalyst for introduction of chirality into the molecule and the high enantiomeric excess obtained in this method render our approach a good alternative to the known methods.

4.1.6 Experimental Section

(*R*)-*tert*-Butyl (3-oxo-1-phenylpropyl)carbamate (17)

To a stirred solution of benzaldehyde-derived N-Boc-imine **16** (2.870 g, 14 mmol) and redistilled acetaldehyde (3.9 mL, 70 mmol) in CH_3CN (150 mL) at 0 ^oC was added D-proline (0.320 g, 20 mol%) and the mixture was stirred further at 0 ^oC for 3 h. After the completion of reaction (monitored by TLC), it was quenched with water and extracted with Et_2O (3 x 100 mL). The combined organic layers were washed with brine, dried over anhyd. Na_2SO_4, filtered and concentrated under reduced pressure to give the crude aldehyde, which was purified by column chromatography over silica gel using pet. ether:EtOAc (85:15) as eluent, to afford β-amino aldehyde **17** (2.16 g).

Yield: 62%; yellow solid; **mp**: 90-93 ºC, (lit.[23] **mp**: 92-93.5 ºC); $[\alpha]^D_{25}$ +29.6 (*c* 1.7, $CHCl_3$); lit. [23] $[\alpha]^D_{25}$ +29.0 (*c* 1.4, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 720, 1024, 1052,

1258, 1371, 1394, 1479, 1513, 1692, 2979, 3346; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.41 (s, 9H), 2.83-2.96 (m, 2H), 4.87 (br s, 1H), 5.17 (br s, 1H), 7.26-7.34 (m, 5H), 9.73 (t, *J* = 1.7 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 28.3, 39.9, 49.9, 79.9, 126.3, 127.7, 128.8, 135.2, 155.0, 193.3, 199.8; **Analysis**: $C_{14}H_{19}NO_3$ requires C, 67.45; H, 7.68; N, 5.62; found: C, 67.26; H, 7.53; N, 5.49%.

(*R*)-3-((*tert*-Butoxycarbonyl)amino)-3-phenylpropanoic acid (18)

NaH_2PO_4 (3.37 g, 24.4 mmol) and $NaClO_2$ (1.502 g, 24.4 mmol) were added to a solution of β-amino aldehyde **17** (2.02 g, 8.14 mmol) in *tert*-BuOH:H_2O (45:9 mL) at 25 °C and the mixture allowed to stir for 30 min. After TLC showed the complete disappearance of starting material, it was diluted with EtOAc (100 mL) and dried over anhyd. Na_2SO_4 and concentrated to give the crude acid, which was purified by column chromatography over silica gel using pet. ether:EtOAc (60:40) as eluent, to afford carboxylic acid **18** (2.01 g).

Yield: 93%; colorless solid; **mp**: 126-129 ºC; $[\alpha]^{D}_{25}$ +40.1 (*c* 1.2, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 758, 1029, 1046, 1215, 1420, 1507, 1707, 2400, 2980, 3019; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.40 (s, 9H), 2.67 (br s, 1H), 2.86 (br s, 1H), 4.85 (br s, 1H), 5.09 (br s, 1H), 7.27-7.36 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 28.2, 40.6, 53.7, 80.1, 126.2, 127.4, 128.5, 145.9, 154.8, 170.1; **Analysis:** $C_{14}H_{19}NO_4$ requires C, 63.38; H, 7.22; N, 5.28; found: C, 63.16; H, 7.11; N, 5.21%.

(*R*)-*tert*-Butyl (3-oxo-2,3-dihydro-1H-indenyl)carbamate (19)

To a solution of carboxylic acid **18** (2 g, 7.5 mmol) in dry CH_2Cl_2 (40 mL) was added $ClSO_3H$ (2.5 mL, 37.5 mmol). The reaction mixture was stirred at 25 °C for 2 h, and quenched with saturated solution of $NaHCO_3$, extracted with Et_2O (3 × 50 mL). The combined organic phases were dried over anhyd. Na_2SO_4 and concentrated under

reduced pressure to afford the crude product, which was directly used for the next step without purification.

To a stirred solution of crude amine in CH_2Cl_2 (40 mL) and Et_3N (3.2 mL, 22.5 mmol) was added catalytic amount of DMAP (0.091 g, 0.75 mmol). After stirring for 5 min at 0 ^oC, $(Boc)_2O$ (3.27 g, 15.0 mmol) was added drop-wise and the reaction mixture was allowed to stir for another 3 h. After the completion of the reaction, it was extracted with Et_2O (3 × 50 mL), washed with water, brine and dried over anhyd. Na_2SO_4 and concentrated to give the crude ketone, which was then purified by column chromatography over silica gel using pet. ether:EtOAc (85:15) to furnish indanone **19** (1.54 g).

Yield: 83%; colorless solid; **mp:** 104-106 °C; $[\alpha]^D_{25}$ -14.6 (*c* 0.8, $CHCl_3$); 98% ee from chiral HPLC analysis (Chiralcel AD-H, *n*-hexane/ ^{i}PrOH, 90:10, 0.5 mL/min) retention time 14.36 (99.08%) and 19.88 (0.92%); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 751, 1045, 1163, 1276, 1393, 1500, 1604, 1712, 2400, 2933, 2981, 2981, 3019, 3440; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.46 (s, 9H), 2.45 (dd, *J* = 3.2, 19.2 Hz, 1H), 3.16 (dd, *J* = 7.6, 19.2 Hz, 1H), 5.00 (d, *J* = 8.4 Hz, 1H), 5.34 (br s, 1H), 7.41-7.48 (m, 1H), 7.63 (d, *J* = 3.8 Hz, 2H), 7.70 (d, *J* = 7.6 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 28.4, 44.9, 48.7, 79.8, 123.2, 125.9, 128.9, 135.1, 136.6, 154.3, 155.6, 202.9; **Analysis**: $C_{14}H_{17}NO_3$ requires C, 68.00; H, 6.93; N, 5.66; found: C, 67.94; H, 6.73; N, 5.46%.

(*R*)-*tert*-Butyl (2,3-dihydro-1H-indenyl)carbamate (20)

To a stirred solution of indanone **19** (1.632 g, 6.6 mmol) and $NH_2NH_2.H_2O$ (1.668 g, 33 mmol) in diethylene glycol (40 mL) was added KOH pellets (1.847 g, 33 mmol). The resulting solution was refluxed for 4 h. After TLC showed the complete disappearance of starting material, the reaction mixture was diluted with H_2O, extracted with EtOAc (3 x 50 mL) and dried over anhyd. Na_2SO_4 and concentrated to

give the crude carbamate, which was purified by column chromatography over silica gel using pet. ether:EtOAc (85:15) as eluent, to afford carbamate **20** (1.355 g).

Yield: 88%; colorless gum; $[\alpha]^{D}_{25}$ +24.3 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 768, 849, 928, 1024, 1050, 1168, 1215, 1421, 1505, 1706, 2400, 2979, 3019; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.48 (s, 9H), 1.68-1.87 (m, 1H), 2.49-2.65 (m, 1H), 2.74-3.03 (m, 2H), 4.70 (d, *J* = 7.3 Hz, 1H), 5.17 (d, *J* = 7.7 Hz, 1H), 7.15-7.20 (m, 3H), 7.27-7.32 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 28.4, 30.0, 34.3, 55.1, 79.1, 123.9, 124.6, 126.6, 127.7, 142.9, 143.5, 155.5; **Analysis**: $C_{14}H_{19}NO_2$ requires C, 72.07; H, 8.21; N, 6.00; found: C, 72.01; H, 8.14; N, 5.87%.

(*R*)-*tert*-Butyl (2,3-dihydro-1H-indenyl)(prop-2-yn-1-yl)carbamate (21)

To a stirred solution of carbamate **21** (0.500 g, 2.14 mmol) and NaH (0.098 g, 60% w/w, 2.35 mmol) in dry DMF (5 mL) was added propargyl bromide (80% solution in toluene, 286 µL, 2.57 mmol) at 25 °C and the mixture was stirred under nitrogen atmosphere for 4 h. The reaction was quenched with H_2O and the resulting mixture was extracted with EtOAc (3 x 10 mL), washed with saturated aq. NH_4Cl (5 mL) and brine solution (5 mL). The organic layers were separated, dried over anhyd. Na_2SO_4, and concentrated to give the crude product, which was then purified by column chromatography over silica gel using pet. ether:EtOAc (95:05) as an eluent to give protected rasagiline **21** (0.470 g).

Yield: 81%; yellow oil; $[\alpha]^{D}_{25}$ -14.4 (*c* 0.7, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 669, 761, 929, 1159, 1215, 1330, 1405, 1439, 1456, 1477, 1521, 1687, 2126, 2400, 2935, 2980, 3019, 3308; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.50 (br s, 9H), 2.07 (br s, 1H), 2.22 (br s, 1H), 2.36-2.52 (m, 1H), 2.75-2.91 (m, 1H), 2.96-3.10 (m, 1H); 3.32-3.63 (m, 1H), 3.82-4.16 (m, 1H), 5.45-5.82 (m, 1H), 7.16-7.21 (m, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 27.6, 28.3, 30.0, 30.1, 61.1, 69.6, 80.3, 123.9, 124.8, 126.5, 127.7, 141.7,

143.7, 155.2; **Analysis**: $C_{17}H_{21}NO_2$ requires C, 75.25; H, 7.80; N, 5.26; found: C, 75.03; H, 7.56, N, 5.14%.

(*R*)-Indanyl-prop-2-ynyl-amine [rasagiline] (1)

To a solution of protected rasagiline **21** (0.300 g, 1.1 mmol) in dioxane (5 mL) was added 37% aq. HCl in H_2O (0.5 mL) and the mixture stirred for 30 min at 25 °C. The reaction mixture was quenched with sat. $NaHCO_3$. Dioxane was evaporated and the residue was extracted with EtOAc (3 × 10 mL) and the combined organic phases were dried over anhyd. Na_2SO_4 and concentrated to give the crude product, which was then purified by column chromatography over silica gel using pet. ether:EtOAc (70:30) to give rasagiline **1** (0.182 g).

Yield: 97%; yellow solid; **mp:** 146-149 °C, (lit.[13] **mp**: 148 ºC); $[\alpha]^{D}_{25}$ +19.4 (*c* 0.5, $CHCl_3$); lit.[13] $[\alpha]^{D}_{25}$ +18.8 (*c* 1.7, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 649, 1088, 1161, 1215, 1349, 1456, 2400, 2848, 2929, 3281; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.69 (br s, 1H), 1.84-1.92 (m, 1H), 2.23 (t, *J* = 2.4 Hz, 1H), 2.36-2.45 (m, 1H), 2.79-2.87 (m, 1H), 3.01-3.09 (m, 1H); 3.52 (t, *J* = 2.4 Hz, 2H), 4.42 (t, *J* = 6.2 Hz, 1H), 7.16-7.24 (m, 3H), 7.34 (d, *J* = 5.9 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 30.5, 33.3, 36.1, 61.8, 71.5, 82.4, 124.3, 124.9, 126.3, 127.7, 143.8, 144.4; **Analysis**: $C_{12}H_{13}N$ requires C, 84.17; H, 7.65; N, 8.18; found: C, 84.13; H, 7.57; N, 8.12%.

Section II:

N-Heterocyclic Carbene-Catalyzed Esterification of Aromatic Aldehydes with Alcohols under Aerobic Condition

4.2.1 Introduction

The direct transformation of aldehydes to the corresponding esters[24] with alcohols under mild conditions is often required in organic synthesis, especially in the synthesis of natural products.[25] For example: Lee *et al.* have utilized intramolecular oxidative esterification of ω-hydroxy aldehyde **22** as the key step in their synthesis of cytotoxic (+)-dactylolide (**24**) (**Fig. 10**).[25e]

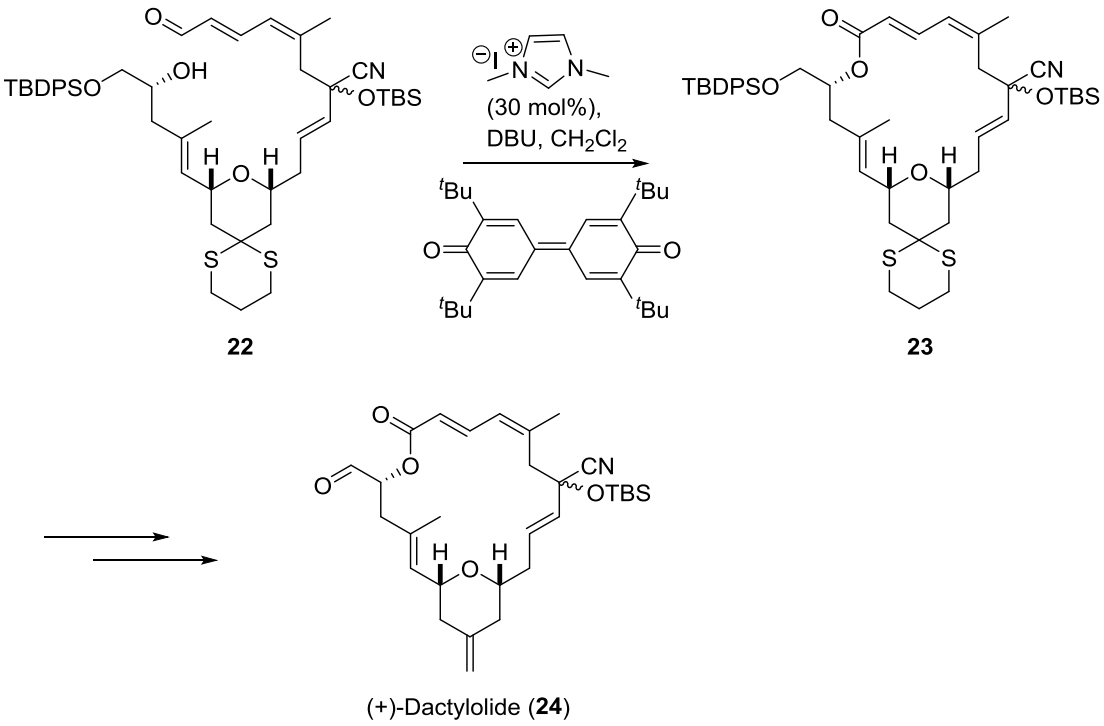


Fig. 10: Oxidative esterification of aldehyde in the synthesis of (+)-dactylolide (**24**)

Further esterification processes are widespread in the industrial synthesis of a variety of end-products such as fragrances, monomers, plasticizers, etc, many of which are

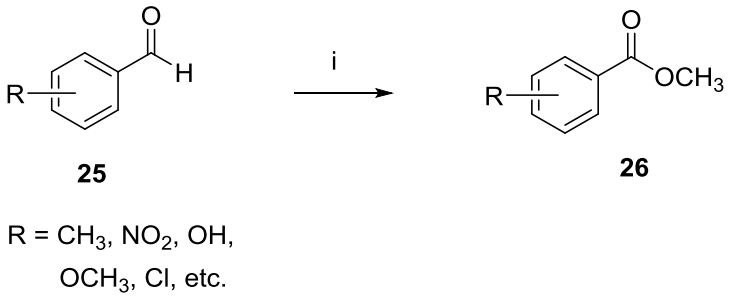
classified as high production volume (HPV) chemicals. In addition, applications to lower volume, high-value pharmaceutical and fine chemicals targets are prominent, and often require more stringent coupling protocols to achieve the desired chemo- and stereoselectivity. Aromatic esters are also important and useful structural elements finding tremendous applications in wide range of fields encompassing solvents, lubricants, plasticizing agents, perfumes, pharmaceuticals, agrochemicals, etc.[26] The conventional methods for the synthesis of carboxylic esters from aldehydes involve oxidation of aldehydes to carboxylic acids followed by esterification with alcohols catalyzed by acids. In contrast, the direct method of conversion of aldehydes to carboxylic esters holds considerable promise in organic synthesis as it minimizes the number of steps.

4.2.2 Review of Literature

Literature search revealed that there are several methods available for the direct transformation of aldehydes into the corresponding esters. Direct transformation of aldehydes into esters has been achieved using a variety of reagents such as V_2O_5/H_2O_2,[27] oxone®,[28] pyridinium hydrobromide perbromide,[29] acetone cyano hydrins,[30] $(NaIO_4)$/LiBr,[31] I_2,[32] TBHP,[33] and electrochemical methods.[34] Recently, *N*-Heterocyclic carbenes (NHCs)-catalyzed oxidative esterification of aldehydes with alcohols,[35] alkyl halides[36] and boronic acids[37] has also been reported. Some of the recent developments on this transformation are discussed below.

Gopinath's approach (2000)[27]

In Gopinath's approach, aldehydes **25**, in the presence of methanol, undergo oxidative transformation to the corresponding esters **26** upon treatment with catalytic amounts of V_2O_5 in combination with 30% aq. H_2O_2 as oxidant (**Scheme 7**).



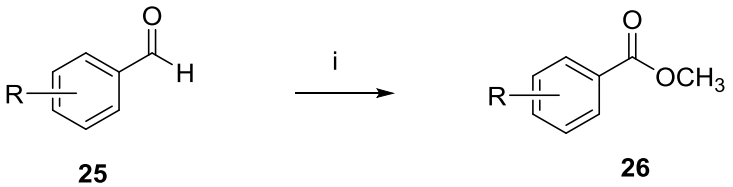
25 **26**

R = CH_3, NO_2, OH, OCH_3, Cl, etc.

Scheme 7: (i) V_2O_5 (cat.), 30% aq. H_2O_2, CH_3OH, 80 ^oC, 0.5-6 h, 83-100%.

Traivs' approach (2003)[28]

Travis *et al*. have developed a highly efficient, mild, and simple protocol for the oxidation of aldehydes **25** to the corresponding carboxylic acids utilizing oxone as the sole oxidant. Direct conversion of aldehydes **25** in alcoholic solvents to their corresponding ester products **26** has also been reported. These reactions may prove to be valuable alternatives to traditional metal-mediated oxidations, however, it uses more than stoichiometric amounts of oxone (**Scheme 8**).



25 **26**

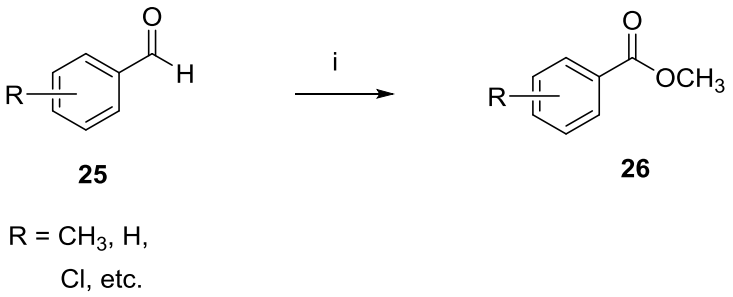
R = CN, NO_2, OH, CH_3, H, etc.

Scheme 8: (i) Oxone, CH_3OH, 18 h, 25 ^oC, 9-98%.

Onami's approach (2004)[29]

In this approach, the direct esterification of aldehydes with alcohols was carried out with pyridinium hydrobromide perbromide (PHPB) in water at 25 ^oC. A variety of aldehydes **25** were converted to their corresponding esters **26**. Further, a variety of

aliphatic alcohols were also converted to the corresponding Tishchenko-like dimeric esters in good yields under the same reaction conditions (**Scheme 9**).



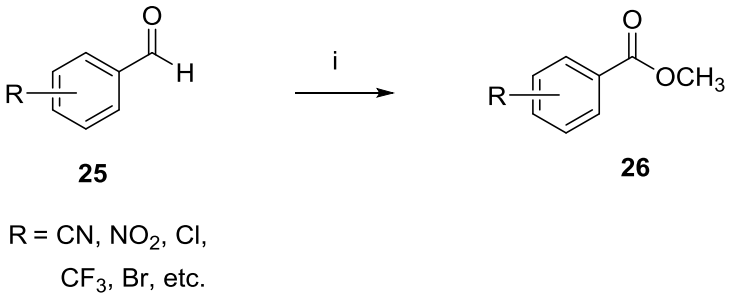
25 **26**

R = CH_3, H, Cl, etc.

Scheme 9: PHPB, CH_3OH, H_2O, 25 ^oC, 40-87 h, 70-94%.

Sudalai's approach (2005), (2007)[30, 31]

Sudalai *et al.* have described a simple procedure for the conversion of electron-deficient aldehydes **25** into the corresponding esters **26** on reaction with methanol in excellent yields mediated by acetone cyanohydrin and base (**Scheme 10**).

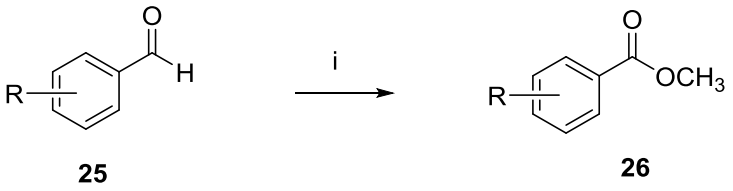


25 **26**

R = CN, NO_2, Cl, CF_3, Br, etc.

Scheme 10: (i) acetone cyanohydrin (5 mmol), Et_3N, CH_3OH, 25 ^oC, 2 h, 60-92%.

In yet another approach, these authors have converted aromatic aldehydes **25** directly to the corresponding aromatic esters **26** in high yields on treatment with CH_3OH using sodium metaperiodate ($NaIO_4$)/LiBr as oxidant under acidic medium (**Scheme 11**).



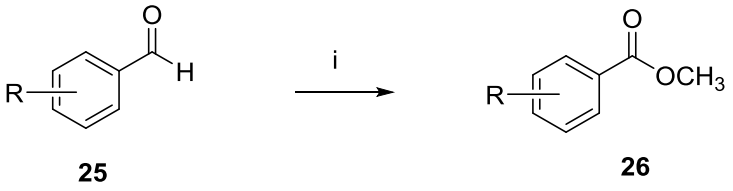
25 **26**

R = CN, NO_2, OH, CH_3, H, etc.

Scheme 11: (i) LiBr, $NaIO_4$, conc. H_2SO_4, CH_3OH, 25 ^oC, 18 h, 78-98%.

Budhewar's approach (2006)[32]

Budhewar *et al.* have developed a simple and mild procedure for the facile, direct oxidative methyl esterification of aldehydes **25** using molecular I_2 in combination with $PhI(OAc)_2$ in methanol (**Scheme 12**).



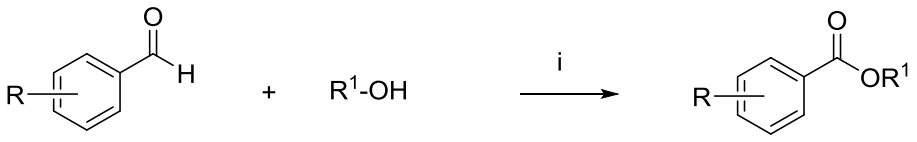
25 **26**

R = CH_3, NO_2, OH, OCH_3, Cl, etc.

Scheme 12: (i) I_2, $PhI(OAc)_2$, CH_3OH, 25 ^oC, 10-14h, 67-89%.

Li's approach (2007)[33]

Li *et al.* have developed an oxidative esterification reaction between aldehydes **25** and alcohols **27** catalyzed by a combination of $Cu(ClO_4)_2.6H_2O$ and $InBr_3$ using TBHP as an oxidant (**Scheme 13**).



25 **27** **26**

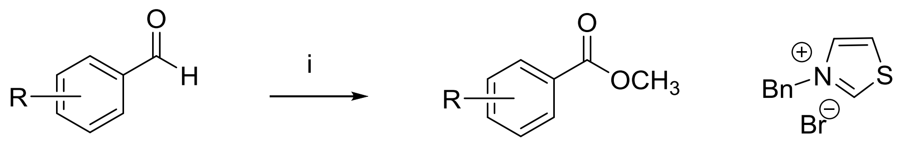
R = Cl, CH_3, CN, H

R^1 = Me, Et, ^nBu, ^iPr

Scheme 13: (i) $Cu(ClO_4)_2.6H_2O$, $InBr_3$, TBHP, 100 ^oC, 16 h, 42-91%.

Connon's approach (2008)[35e]

Connon *et al.* have developed a novel method of direct esterification of aldehydes with methnol using thiazolium NHC (**28**) as a catalyst and azobenzene as an oxidant in THF. Aromatic aldehydes **25** were thus converted to their corresponding esters **26** in moderate to good yields (**Scheme 14**).



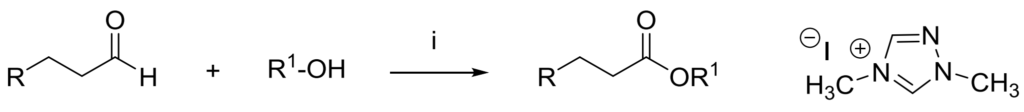
25 **26** NHC (**28**)

R = OCH_3, CH_3, Cl, H, etc.

Scheme 14: (i) NHC (**28**) (5 mol%), PhN=NPh, CH_3OH, THF, Et_3N, 25 to 60 ^{o}C, 24-48 h, 16-97%.

Scheidt's approach (2008)[35f]

Scheidt *et al.* have described NHC-catalyzed oxidation of unactivated aldehydes to the corresponding carboxylic esters. Thus the reaction of unactivated aldehydes **29** with alcohols **27** in the presence of triazolium NHC catalyst (**30**) and oxidant MnO_2 provided esters **31** in high yields (**Scheme 15**).



29 **27** **31** NHC (**30**)

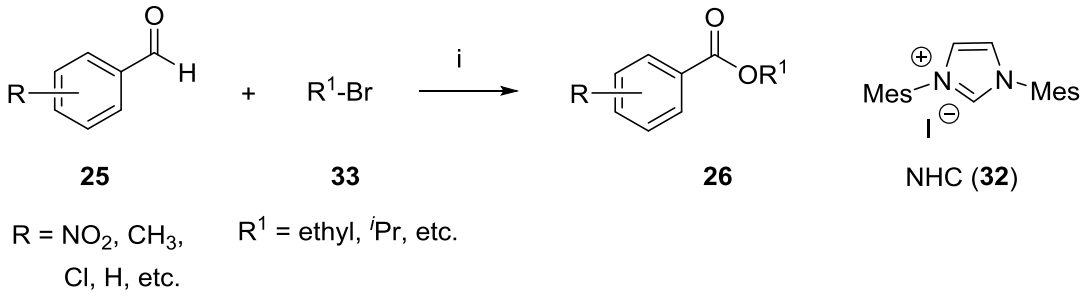
R = aryl, alkyl, heteroaryl

R^1 = CH_3, ^{i}Pr, etc.

Scheme 15: (i) NHC (**30**) (10 mol%), DBU, MnO_2, CH_2Cl_2, 25 ^{o}C, 0.5-3 h, 56-98%.

Xin's approach (2011)[36a]

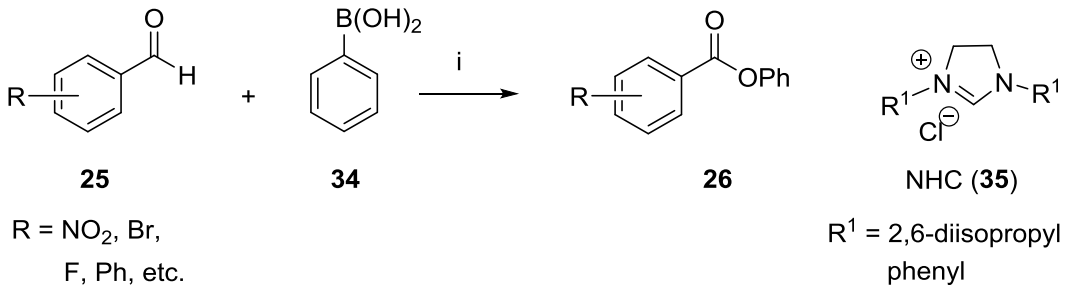
Xin *et al.* have developed an oxidative esterification reaction between aldehydes **25** and alkyl halides **33** catalyzed by imidazolium NHC (**32**) and molecular oxygen as an oxidant in THF at 50 ^{o}C that gave carboxylic esters in good yields (**Scheme 16**).



Scheme 16: (i) NHC (**32**) (10 mol%), DBU, O_2, THF, 50 ^{o}C, 24-72 h, 25-90%.

Arde's approach (2011)[37a]

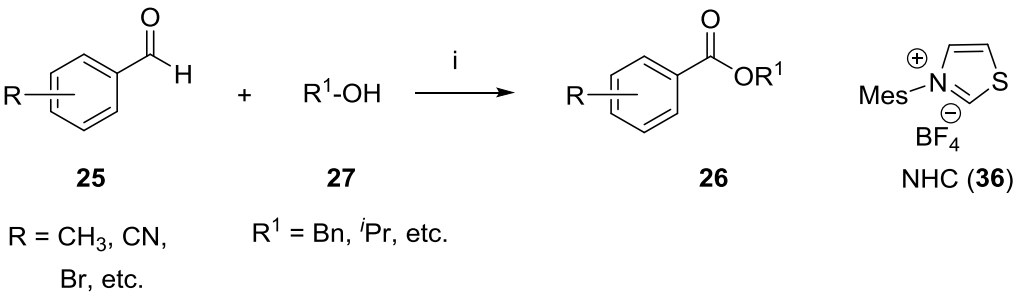
Arde *et al.* have developed an useful method of imidazolidine NHC (**35**) catalyzed aerobic oxidation of aromatic aldehydes **25** with boronic acids **34**. Aromatic aldehydes **25** were thus converted into their corresponding esters **26** in good yields (**Scheme 17**).



Scheme 17: (i) NHC (**35**) (10 mol%), Cs_2CO_3, O_2, toluene, 25 ^{o}C, 3-48 h, 25-99%.

Boydston's approach (2012)[34]

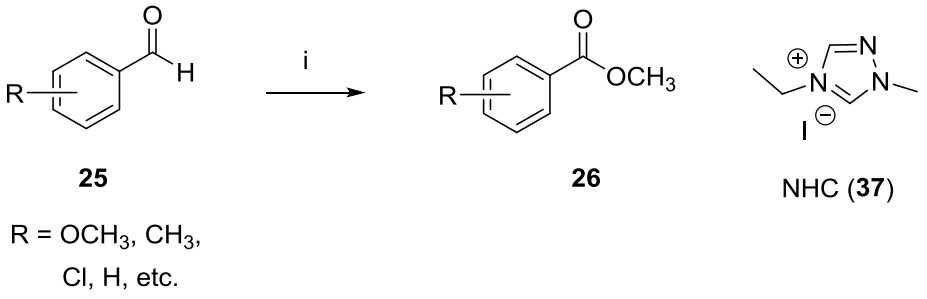
This methodology involves thiazolium NHC (**36**) catalyzed anodic oxidation of aldehydes **25** to the corresponding carboxylic esters **26** on reaction with alcohols **27** (**Scheme 18**). The electrochemical approach assumes the formation of electroactive intermediates that react with alcohol to provide esters.



Scheme 18: (i) NHC (**36**) (10 mol%), DBU, TBAB, CH_3CN, graphite anode, Pt cathode, +0.1V vs. $Ag/AgNO_3$, 2-56 h, 45-98%.

Delany's approach (2013)[35j]

This methodology employs an additive-free mild protocol for triazolium NHC (**37**)-catalyzed direct esterification of aldehydes **25** with CH_3OH using O_2 as oxidant. No other stoichiometric oxidants or catalysts for O_2 activation were required (**Scheme 19**).



Scheme 19: (i) NHC (**37**) (15 mol%), DBU, THF:CH_3OH (1:1), O_2, 25 ^oC, 12-92 h, 15-94%.

4.2.3 Present Work

4.2.3.1 Objective

Although several reports for transformation of aldehydes to the corresponding esters in the presence of alcohols has been reported, there are certain drawbacks associated with them such as (i) heavy metals (Pd, Mn, Fe, etc) as oxidants; (ii) harsh reaction conditions; (iii) excess use of bases and alcohols/halides; (iv) use of more than stoichiometric amounts of oxidants and (v) effective for a limited range of substrates. In this regard, an organocatalytic additive-free mild protocol for oxidative esterification of aldehydes is highly desirable. This section describes NHC-catalyzed direct esterification of aromatic aldehydes with a variety of alcohols under aerobic condition using catalytic amount of DBU. On a similar line Delany *et al.* have reported,[35j] entitled "NHC-catalysed aerobic aldehyde esterifications with alcohols: no additives or cocatalysts required" (see **Scheme 19**) using triazolium NHC (**37**) as a new catalyst several months after our publication. Since the method involves NHC as catalyst, a brief account of NHC catalyst is described below.

4.2.3.2 *N*-Heterocyclic Carbene Catalysis

Proline, a naturally available amino acid, has been studied extensively as organo catalyst for reactions occurring through enamine as well as iminium ion as intermediates.[38] In the last two decades, *N*-heterocyclic carbenes (NHC) have emerged as an important and powerful class of organocatalysts with tremendous applications in a variety of synthetic transformations and are receiving much attention as proline, because of their unique electronic properties. **Fig. 11** shows the presence of a carbene moiety stabilized by two adjacent π-donating atoms in NHC. The unsaturation in the backbone makes this an aromatic system, so that the carbene p-orbital is available to act as a π-acid. The ability of NHCs to act as both electron

donors and acceptors permits them to serve as organocatalysts in a variety of coupling reactions. [39]

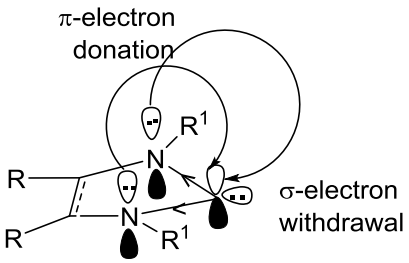


Fig. 11: Stabilization of *N*-heterocyclic carbenes

NHC can provide catalytic access to acyl anion equivalents, an umpolung strategy in which organic molecules react in an inverse manner compared to their innate polarity-driven reactivity.[40]

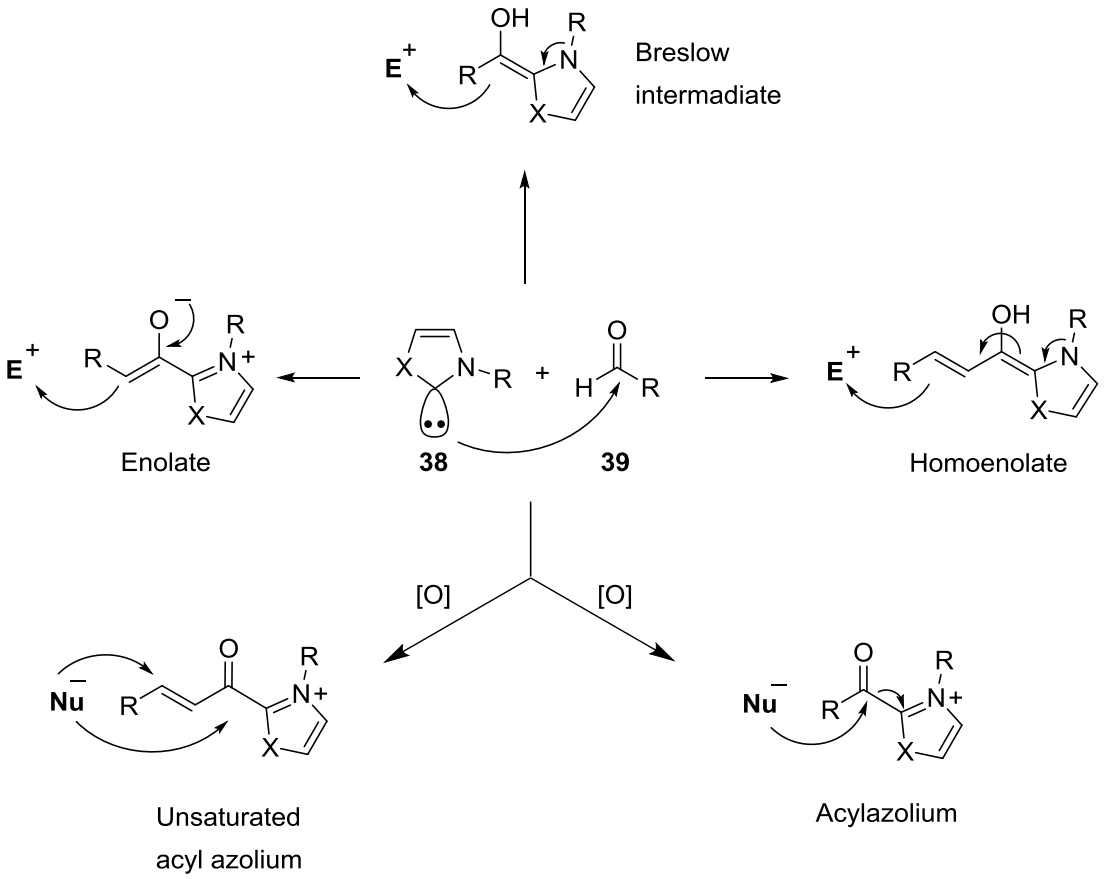


Fig. 12: Intermediates in NHC-organocatalysis

The majority of organocatalyzed transformations that are proceeding through umpolung are mediated by NHC. They have a number of modes of activation for a given substrate, like (i) acyl anion,[41] (ii) hydroacylation,[42] (iii) homoenolate,[43] and (iv) rebound catalysis,[44] in which it forms four important intermediates namely (i) Breslow intermediate, (ii) enolate, (iii) homoenolate and (iv) acylazolium and α,β-unsaturated acylazolium (**Fig. 12**). The most prominent intermediate in NHC catalysis is Breslow intermediate. It is assumed that the azolium precatalyst is deprotonated in the reaction mixture to afford a nucleophilic carbene **38**. Addition to an aldehyde **39** followed by proton transfers affords an enamine type intermediate, referred to as the Breslow intermediate,[45] in which the originally electrophilic carbon atom of the aldehyde has gained nucleophilic character. It can then attack a second molecule of aldehyde to furnish the benzoin product[46] or a Michael acceptor to afford a Stetter product.[47]

Breslow intermediates also occur in biosynthesis; for example, 2-oxoacid dehydro genases[48] such as pyruvate dehydrogenase, use thiamine pyrophosphate (TPP) as a carbene cofactor (**Fig. 13**). Decarboxylation is achieved by the reaction of carbene **40** with pyruvate to give **41**, that after CO_2 elimination provides Breslow intermediate **42**. Under aerobic conditions, enaminol **42** opens the dithiolane ring of a lipoyl group in a nucleophilic reaction to give an acetyl lipoamide thioester, which on transacylation with coenzyme A (CoASH) using enzymes eventually provides acetyl coenzyme A (CoASAc). Importantly, most published NHC-catalyzed processes mimic the reactivity of the naturally-occurring enaminol **42** of 2-oxoacid dehydrogenases and react *via* umpoled aldehydes. For anaerobic condition nature has developed an alternative reaction pathway for formation of CoASAc. Pyruvate ferredoxin oxidoreductase (PFOR), catalyses the decarboxylation of pyruvate to form

CoASAc *via* Breslow intermediate **42,** which reacts as a single electron-transfer reductant and the two electrons obtained during the turnover are transferred to ferredoxine. Electron transfer from the electron-rich enaminol **42** to a $[Fe_4S_4]^{2+}$ cluster leads to radical cation **43**. Renewed electron transfer in the presence of CoASH eventually provides CoASAc.

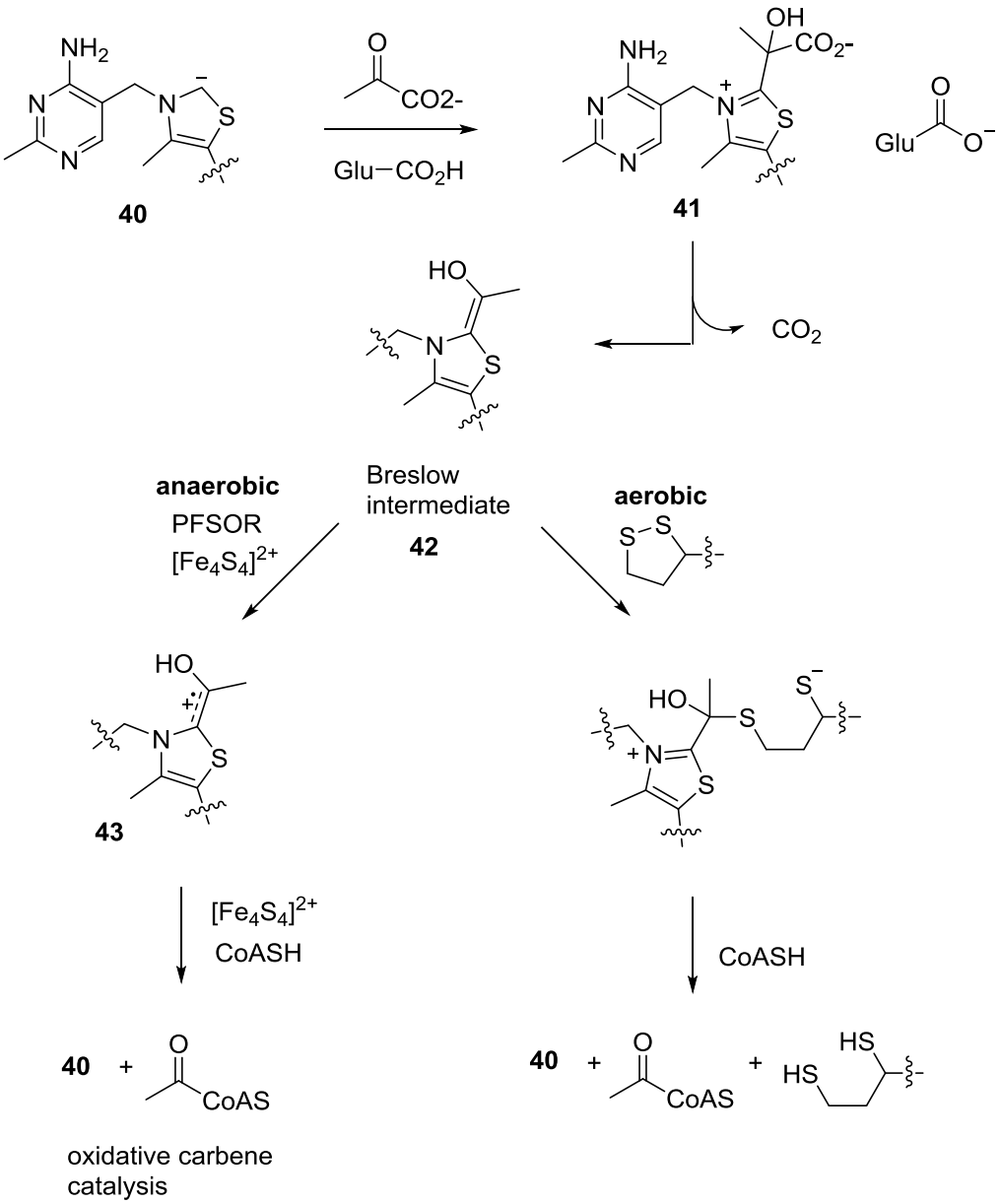


Fig. 13: TPP-mediated enzymatic transformation of pyruvate to CoASAc

4.2.4 Results and Discussion

The fact that Breslow intermediates can behave as single electron transfer reagents[48] inspired us to develop catalytic processes for oxidative esterification of aldehydes, that proceeds *via* oxidation of enaminol intermediates. The major challenge in the oxidation of aldehydes using NHC is the identification of mild oxidant, with the following characteristics (i) it is compatible with the carbene catalyst; (ii) avoids the formation of carboxylic acid by-products and (iii) shows high functional group compatibility. We envisaged that molecular O_2 should be an ideal oxidant for this purpose based on its nature of reactivity, low cost, and environment-friendly characteristics. **Fig. 14** shows some of the NHC precatalysts[49] **44**-**49** that were examined for the oxidative esterification of aldehydes using molecular O_2 as oxidant.

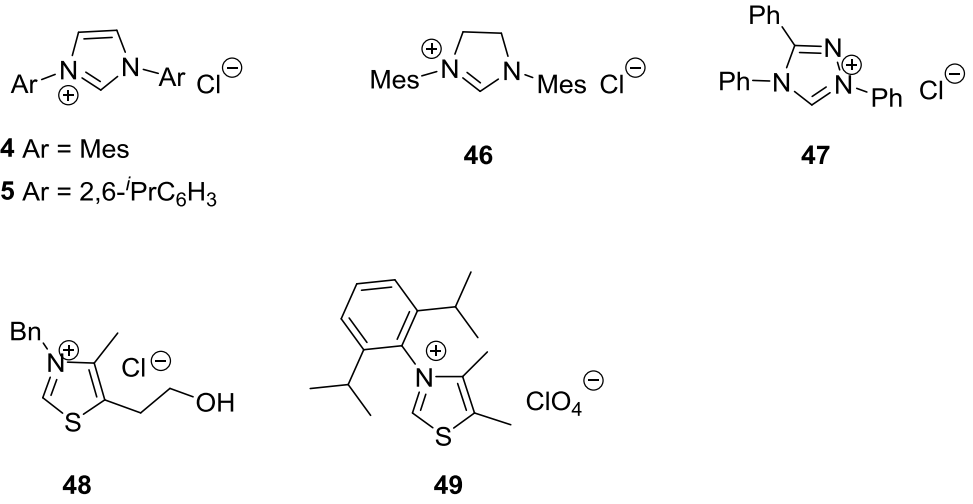
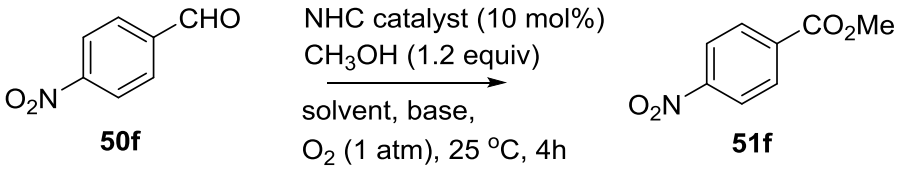


Fig. 14: *N*-Heterocyclic carbene precatalysts screened for the oxidative esterification of aromatic aldehydes

In a preliminary study, when 4-nitrobenzaldehyde **50f** was subjected to oxidative esterification with MeOH (1 equiv) in the presence of NHC **44** (10 mol%) and DBU (20 mol%) as base in THF under N_2 atmosphere at 25 ^{o}C, no trace of ester **51f** was

formed. When the same experiment was conducted in open air, **51f** was indeed isolated in low yields (45%). However, a dramatic increase in yield (70%) was realized when the experiment was carried out under O_2 atmosphere (O_2 balloon, 1 atm). Out of several NHC catalysts screened, imidazolium salt **44** showed higher catalytic activity,[50] providing the desired product **51f** in 70% yield.

Table 1: Oxidative esterification of 4-nitrobenzaldehyde: optimization studies[a]



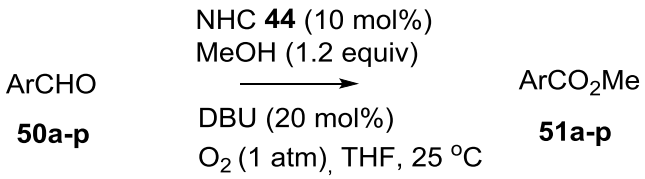
entry	NHC catalysts (10 mol%)	base (20 mol%)	solvent	yield of **51f** (%)[b]
1	No catalyst	DBU	THF	-
2	**1a**	DBU	THF	76 (45)[c]
		DBU	CH_2Cl_2	60
		DBU	CH_3CN	58
		DBU	DMSO	27
		DBU	toluene	60
3	**1a**	K_2CO_3	THF	56
		Et_3N	THF	40
		^nBuLi	THF	16
		K^tOBu	THF	12
4	**1b**	DBU	THF	36
5	**1c**	DBU	THF	54
6	**1d**	DBU	THF	14
7	**1e**	DBU	THF	27
8	**1f**	DBU	THF	26

[a]Reaction conditions: 4-nitrobenzaldehyde (5 mmol), methanol (6 mmol), NHC catalyst (10 mol%), base (20 mol%), 25 °C, O_2 (1 atm), 4h. [b]isolated yield after column chromatographic purification. [c]under open air.

When NHC catalyst loading was increased from 10 mol% up to 20 mol%, there was neither improvement in the yield of ester formed nor reduction in the time required for completion of the reaction. Additionally, increasing the temperature from 25 ^{o}C to 50 °C had deleterious effect in the yield, which may be due to the formation of unwanted acid by- product. Surprisingly, increasing the amount of alcohol from 1 equiv to 1.2 equiv resulted in improved yield (76%) of the ester formed. However, a further systematic increase in the amount of alcohol (from 1.2 up to 3 equiv) had no effect on yield improvement. Among several solvents and bases screened for the reaction, THF and DBU were found to be the effective solvent and base (**Table 1**).

With the optimized conditions (aldehyde (1 equiv), MeOH (1.2 equiv), NHC **44** (10 mol%), DBU (20 mol%), O_2, and THF at 25 ^{o}C) in hand, we then turned our attention to a variety of aromatic aldehydes **50a-p** as substrates having both electron-donating and -withdrawing groups in order to gauge the scope and generality of the reaction. The results of such studies are presented in **Table 2**. As can be seen, several aromatic aldehydes underwent oxidative esterification with methanol smoothly under mild conditions in moderate to good yields. Remarkably, substrates with electron-withdrawing groups showed higher reactivity as compared to electron-releasing substituents. Heteroaromatic aldehydes such as 3-pyridine carboxaldehyde **50o** also gave the corresponding ester in 76% yield, which are otherwise difficult to obtain under acid-catalysed esterifications due to salt formation of aldehyde **50o**. It is noteworthy that, 4-(methylthio)benzaldehyde **50e**, was not over-oxidized under our reaction condition. In the case of cinnamaldehyde, an inseparable mixture of saturated and unsaturated methyl esters were obtained,[51] while aliphatic aldehydes failed to undergo this reaction, which may be a limitation.

Table 2: Oxidative esterification of aryl aldehydes: substrate scope [a]



entry	substrates, Ar (**50a-p**)	time (h)	yield of **51a-p** (%)[b]
a	*m*-tolualdehyde	10	78
b	4-OMe-benzaldehyde	30	72
c	3,4-$(OMe)_2$-benzaldehyde	36	70
d	3,4,5-$(OMe)_3$-benzaldehyde	36	65
e	4-SMe-benzaldehyde	28	68
f	4-NO_2-benzaldehyde	4	76
g	3- NO_2-benzaldehyde	10	82
h	4-Br-benzaldehyde	14	78
i	3- Br-benzaldehyde	18	72
j	4-Cl-benzaldehyde	18	79
k	3-Cl-benzaldehyde	14	70
l	4-F-benzaldehyde	10	76
m	4-CF_3-benzaldehyde	7	69
n	4-CN-benzaldehyde	6	72
o	3-pyridinecarboxaldehyde	20	76
p	furfural	24	63

[a]Reaction conditions: aldehyde (5 mmol), methanol (6 mmol), NHC **44** (10 mol%), DBU (20 mol%), 25 °C, O_2 (1 atm). [b]isolated yield after column chromatographic purification.

A wide range of alcohols were then examined for oxidative esterification with 4-nitrobenzaldehyde as the substrate; the results are summarized in **Table 3**. Both primary and secondary alcohols including allylic, propargylic and benzylic alcohols underwent this reaction to give the corresponding esters in excellent yields.

Table 3: Oxidative esterification of 4-nitrobenzaldehyde: alcohol scope [a]

entry	alcohol components	time (h)	yield of ester %[b]
1	ethanol	4	80
2	2-propanol	7	76
3	benzyl alcohol	4	80
4	allyl alcohol	4	76
5	propargyl alcohol	5	82
6	(*S*)-tetrahydrofuran-3-ol[c]	16	66 (99% ee)

[a]Reaction conditions: 4-nitrobenzaldehyde (5 mmol), alcohol (6 mmol), NHC **44** (10 mol%), DBU (20 mol%), 25 ^{o}C, O_2 (1 atm). [b]isolated yield after column chromatographic purification; [c] the (*R*)-isomer gave the corresponding ester in 64% yields and 99% ee.

The formation of all ester products were confirmed unambiguously from their corresponding ^{1}H, ^{13}C NMR and IR spectral data.

Example 1: The ^{1}H NMR spectrum of methyl 4-cyanobenzoate (**51n**) showed a typical singlet at δ 3.96 (s, 3H) corresponding to methoxyl protons (-OC**H$_3$**), while other signals at δ 7.75 (d, *J* = 8.6 Hz, 2H) and 8.14 (d, *J* = 8.6 Hz, 2H) correspond to aromatic protons. Its ^{13}C NMR spectrum showed two characteristic carbon signals at δ 52.6 and 165.1 attributed to methoxyl carbon (-O**C**H$_3$) and ester carbonyl carbon

(**C**=O) respectively. Its IR spectrum displayed two characteristic strong absorption frequencies at 1727 and 2229 cm^{-1} indicating the presence of ester carbonyl and cyano functional groups respectively (**Fig. 15**).

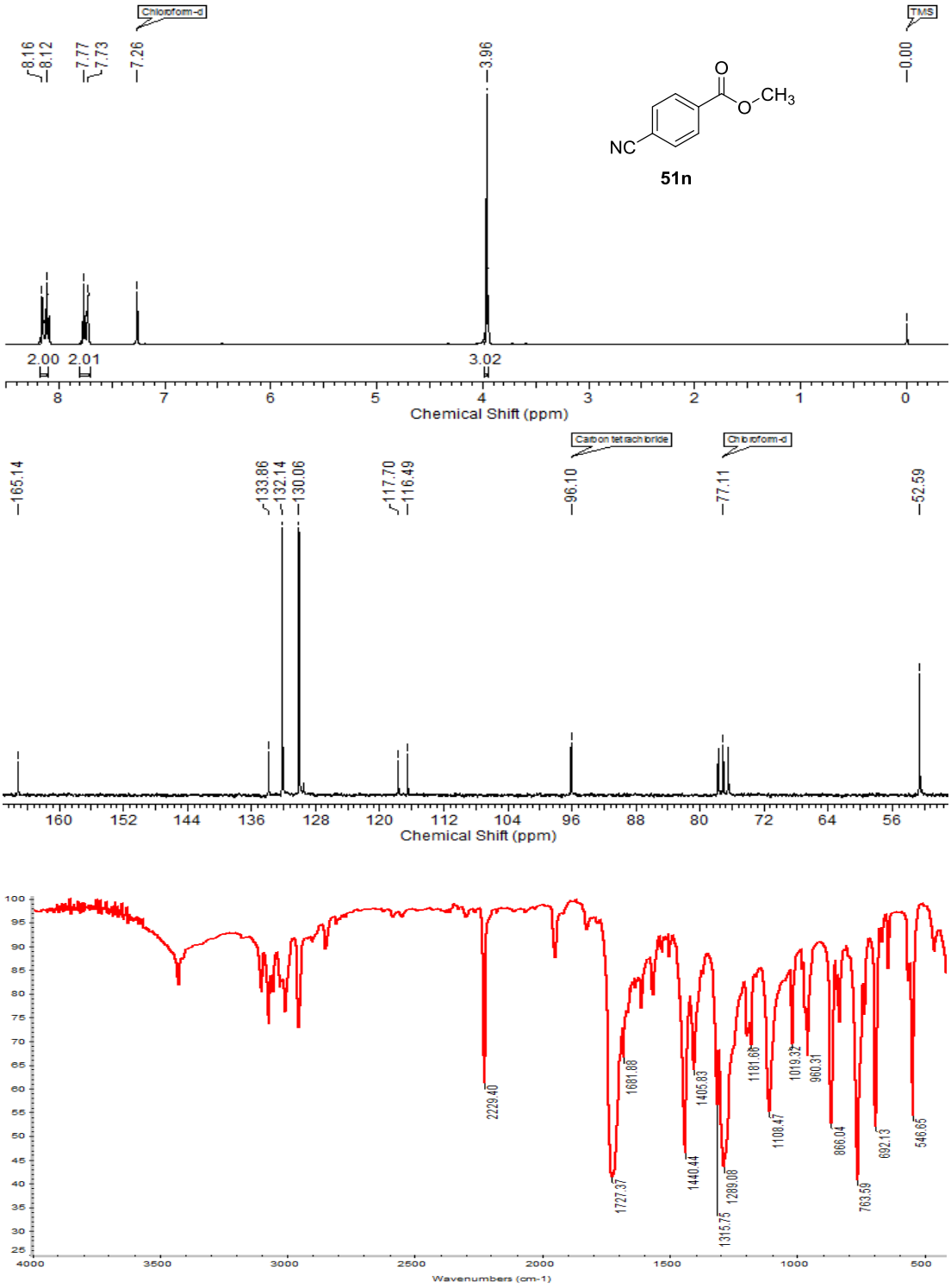


Fig. 15: ^{1}H, ^{13}C NMR and IR spectra of methyl 4-cyanobenzoate (**51n**)

Example 2: The ^{1}H NMR spectrum of allyl 4-nitrobenzoate (**51t**) showed two typical proton signals at δ 4.86 (d, *J* = 5.8 Hz, 2H) and 5.31-5.46 (m, 2H) corresponding to allylic methylene and terminal olefinic protons respectively, while its ^{13}C NMR spectrum showed characteristic carbon signals at δ 119.0, 131.6 and 164.1 corresponding to olefinic and ester carbonyl carbons respectively (**Fig. 16**).

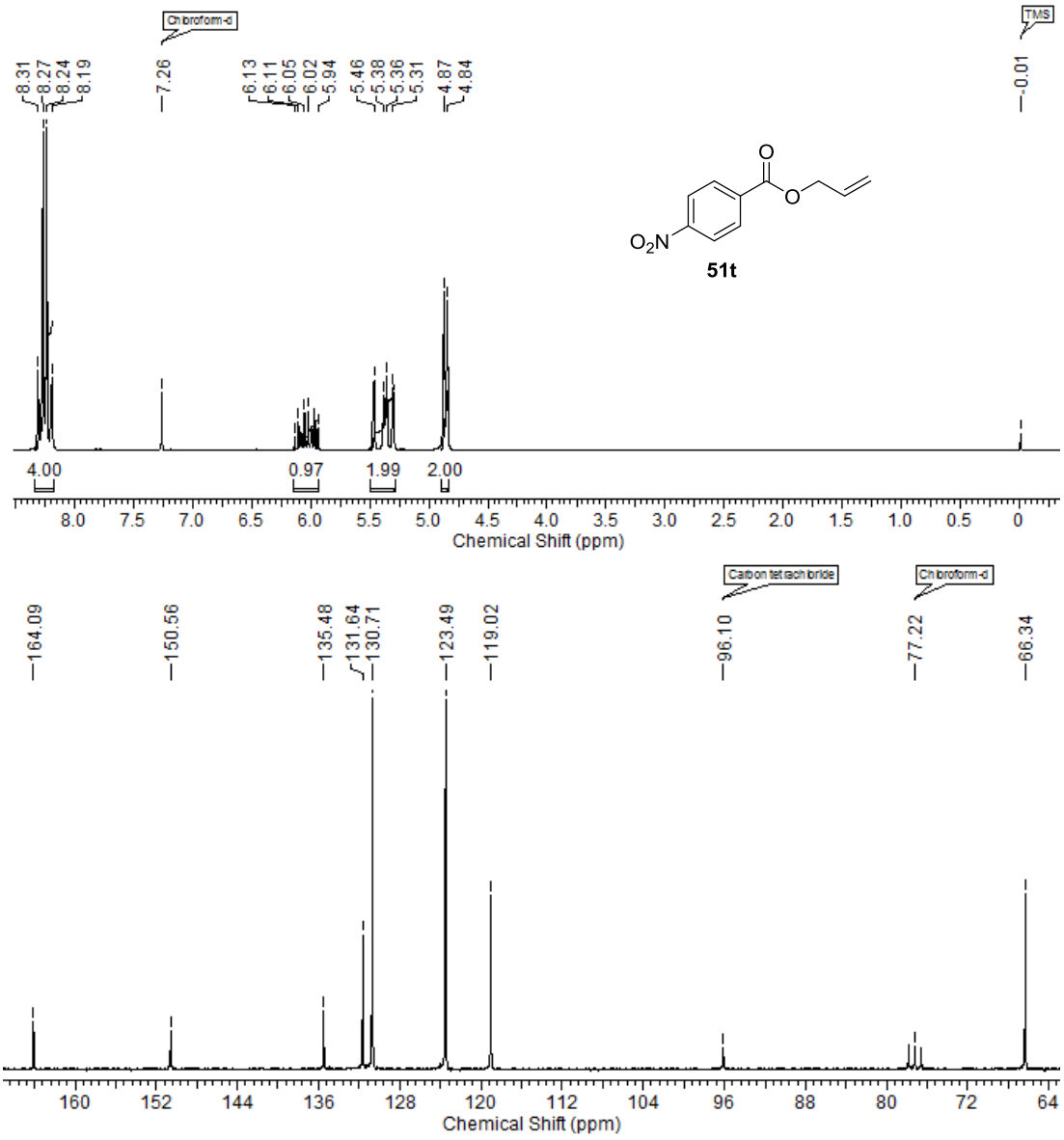
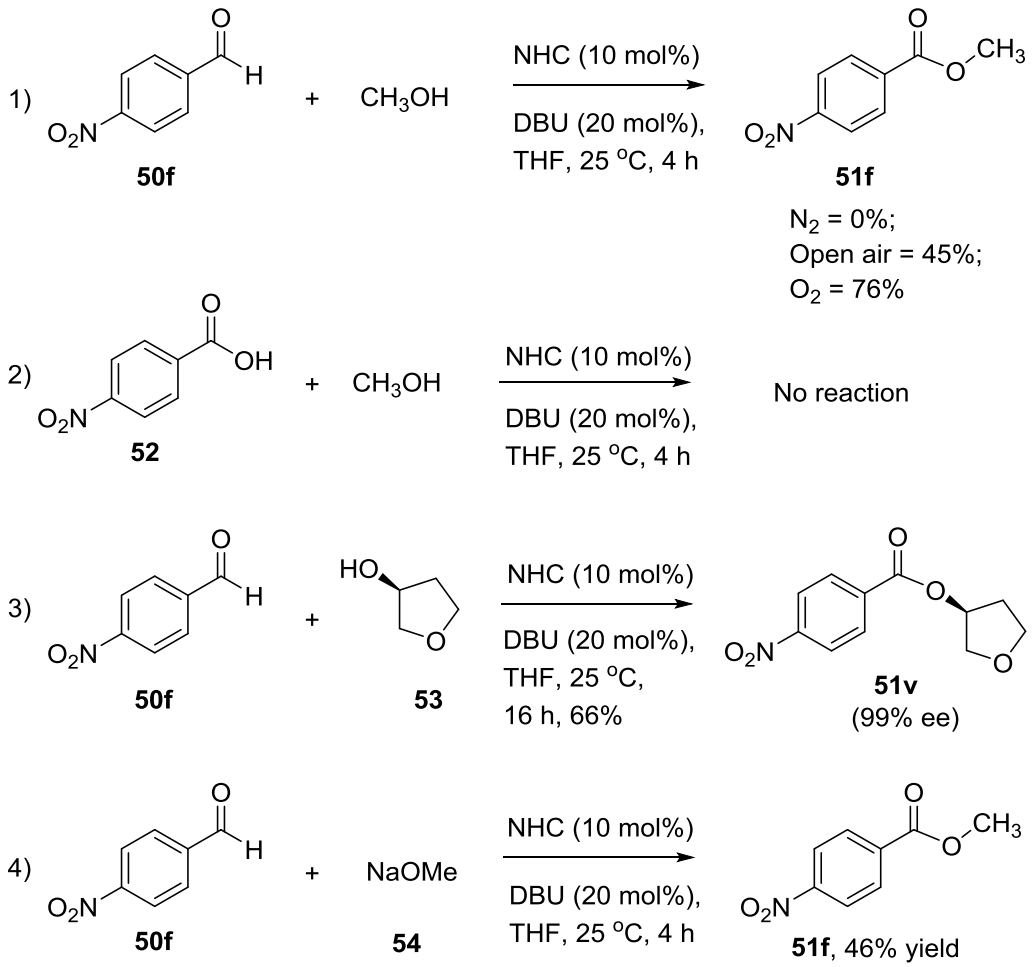


Fig. 16: ^{1}H and ^{13}C NMR spectra of allyl 4-nitrobenzoate (**51t**)

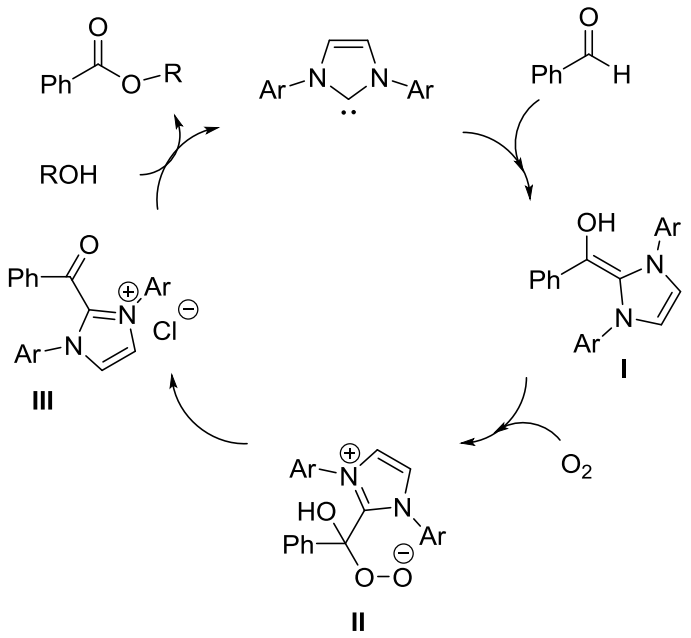
In order to gain insight into the mechanistic details of the reaction, the following experiments (see **Scheme 20**) were conducted: (i) for aldehyde **50f,** no esterification

took place under N_2 atmosphere, while at the same time low yield (45%) was obtained under open air conditions, suggesting the necessity of O_2 for realizing higher yields; (ii) the esterification reaction between *p*-nitrobenzoic acid (**52**) and methanol did not proceed under the reaction conditions, suggesting the absence of carboxylic acid as the intermediate; (iii) when (*S*)-tetrahydrofuran-3-ol **53** was used as alcohol partner, retention of configuration was indeed obtained in ester **51v**, thereby confirming the incorporation of alcohol oxygen into ester moiety; (iv) when 1 equivalent of sodium methoxide (**54**) was used as alcohol component, the corresponding methyl ester **51f** was obtained in 46% yield, suggesting the possibility of alkoxide anion formation as the intermediate (**Scheme 20**).



Scheme 20: A series of control experiments for mechanistic details

Based on the above results and literature precedents,[37, 50] we have proposed a catalytic cycle in which peroxy anion **II**,[37] formed from reaction between Breslow intermediate **I** and O_2, has been depicted as the key intermediate in the esterification process. This on decomposition results in the formation of acyl intermediate **III**.[37b] Subsequently, alkoxide ion[50] formed from alcohol reacts with **III** to give the corresponding ester with the liberation of NHC (**Scheme 21**).



Scheme 21: Probable mechanistic pathway for the oxidative esterification of aromatic aldehydes

4.2.5 Conclusion

A simple organocatalytic procedure for the direct oxidative esterification of aromatic aldehydes with alcohols employing NHC as catalyst and oxygen as oxidant at ambient conditions has been developed. The reaction is simple to carry out and the products are obtained in high yields and purity from stoichiometric amount of alcohol and catalytic amount of organic base.

4.2.6 Experimental Section

General experimental procedure for esterification of aromatic aldehydes

To a flame-dried round bottom flask equipped with a magnetic stir bar was added imidazolium salt **44** (0.170 g, 10 mol%), DBU (0.15 mL, 20 mol%) and THF (10 mL) in that order. The contents were evacuated and covered with molecular O_2 in balloon. The resultant reaction mixture was kept stirring at 25 °C for 45 min. To this mixture was added aromatic aldehydes **50a-p** (5 mmol) and alcohol (6 mmol) successively. It was allowed to stir at 25 °C. After completion of the reaction (monitored by TLC), THF was evaporated, H_2O (50 mL) added and the mixture extracted with EtOAc (3 x 50 ml). The combined organic layers were dried over anhyd. Na_2SO_4 concentrated to give crude ester, which was purified by silica gel-packed column chromatography to obtain pure esters, **51a-w**.

Methyl 3-methylbenzoate (51a)

Yield: 78%; colorless gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 684, 815, 897, 976, 1043, 1166, 1239, 1381, 1607, 1682, 1722, 1873, 2496; ^{1}**H NMR** (200 MHz, $CDCl_3$): δ 2.41 (s, 3H), 3.91 (s, 3H), 7.30-7.34 (m, 2H), 7.81-7.85 (m, 2H); ^{13}C **NMR** (50 MHz, $CDCl_3$): δ 21.2, 51.8, 126.7, 128.1, 130.0, 133.5, 137.9, 166.9; **Analysis**: $C_9H_{10}O_2$ requires C, 71.98; H, 6.71; found: C, 71.83; H, 6.59%.

Methyl 4-methoxybenzoate (51b)

Yield: 72%; colorless solid; **mp:** 49-51 ºC, (lit.[32] **mp:** 49 ºC); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 770, 848, 1029, 1103, 1168, 1256, 1280, 1317, 1434, 1458, 1606, 1716, 2953; ^{1}**H NMR** (200 MHz, $CDCl_3$): δ 3.86 (s, 3H), 3.88 (s, 3H), 6.90 (d, *J* = 8.9 Hz, 2H), 7.98 (d, *J* = 8.9 Hz, 2H); ^{13}C **NMR** (50 MHz, $CDCl_3$): δ 51.7, 55.2, 113.5, 122.6, 131.5, 163.2, 166.5; **Analysis**: $C_9H_{10}O_3$ requires C, 65.05; H, 6.07; found: C, 64.91; H, 5.93%.

Methyl 3,4-dimethoxybenzoate (51c)

Yield: 70%; colorless solid; **mp:** 59-61 ºC, (lit.[32] **mp:** 60 ºC); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 764, 1133, 1271, 1294, 1434, 1514, 1600, 1714; ^{1}**H NMR** (200 MHz, $CDCl_3$): δ 3.89 (s, 3H), 3.93 (s, 6H), 6.87 (d, *J* = 8.4 Hz, 1H), 7.53 (d, *J* = 1.9 Hz, 1H), 7.66 (dd, *J* = 1.9, 8.4 Hz, 1H); ^{13}C **NMR** (50 MHz, $CDCl_3$): δ 51.8, 55.8, 110.2, 111.9, 122.6, 123.5, 148.6, 152.9, 166.6; **Analysis**: $C_{10}H_{12}O_4$ requires C, 61.22; H, 6.16; found: C, 61.09; H, 6.12%.

Methyl 3,4,5-trimethoxybenzoate (51d)

Yield: 65%; colorless solid; **mp:** 82-85 ºC, (lit.[32] **mp:** 82 ºC); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 761, 1132, 1229, 1342, 1413, 1465, 1591, 1719; ^{1}**H NMR** (200 MHz, $CDCl_3$): δ 3.90 (s, 3H), 3.91 (s, 9H), 7.28 (s, 2H); ^{13}C **NMR** (50 MHz, $CDCl_3$): δ 52.1, 56.1, 60.7, 106.7, 125.0, 142.1, 152.9, 166.4; **Analysis**: $C_{11}H_{14}O_5$ requires C, 58.40; H, 6.24; found: C, 58.31; H, 6.12%.

Methyl 4-(methylthio)benzoate (51e)

Yield: 68%; colorless gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 759, 1116, 1302, 1281, 1402, 1708; ^{1}**H NMR** (200 MHz, $CDCl_3$): δ 2.51 (s, 3H), 3.89 (s, 3H), 7.23 (d, *J* = 8.6 Hz, 2H), 7.91 (d, *J* = 8.6 Hz, 2H); ^{13}C **NMR** (50 MHz, $CDCl_3$): δ 14.7, 51.8, 124.8, 126.3, 129.8, 145.3, 166.5; **Analysis**: $C_9H_{10}O_2S$ requires C, 59.32; H, 5.53; found: C, 59.18; H, 5.41%.

Methyl 4-nitrobenzoate (51f)

Yield: 76%; colorless solid; **mp:** 94-96 ºC, (lit.[32] **mp:** 96 ºC); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 722, 818, 1076, 1104, 1136, 1262, 1298, 1338, 1536, 1618, 1719; ^{1}**H NMR** (200 MHz, $CDCl_3$): δ 3.98 (s, 3H), 8.21 (d, *J* = 8.6 Hz, 2H), 8.30 (d, *J* = 8.6 Hz, 2H); ^{13}C **NMR** (50 MHz, $CDCl_3$): δ 52.7, 123.5, 130.7, 135.4, 150.5, 165.0; **Analysis**: $C_8H_7NO_4$ requires C, 53.04; H, 3.89; N, 7.73; found: C, 52.92; H, 3.76; N, 7.62%.

Methyl 3-nitrobenzoate (51g)

Yield: 82%; colorless solid; **mp:** 78-80 ºC, (lit.[32] **mp:** 78 ºC); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 719, 823, 1072, 1100, 1133, 1266, 1292, 1350, 1528, 1615, 1722; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.99 (s, 3H), 7.61-7.69 (m, 1H), 8.34-8.44 (m, 2H), 8.81-8.87 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 52.6, 124.4, 127.2, 129.5, 131.8, 135.1, 148.2, 164.6; **Analysis**: $C_8H_7NO_4$ requires C, 53.04; H, 3.89; N, 7.73; found: C, 52.96; H, 3.81; N, 7.67%.

Methyl 4-bromobenzoate (51h)

Yield: 78%; colorless solid; **mp:** 77-80 ºC, (lit.[32] **mp:** 79 ºC); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 758, 847, 1157, 1276, 1397, 1590, 1716; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.92 (s, 3H), 7.57 (d, *J* = 10 Hz, 2H), 7.89 (d, *J* = 10 Hz, 2H); ^{13}C **NMR** (50 MHz, $CDCl_3$): δ 52.1, 127.9, 129.0, 131.0, 131.6, 166.0; **Analysis**: $C_8H_7BrO_2$ requires C, 44.68; H, 3.28; found: C, 44.59; H, 3.12%.

Methyl 3-bromobenzoate (51i)

Yield: 72%; colorless gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 718, 746, 1067, 1121, 1260, 1293, 1436, 1571, 1727; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.92 (s, 3H), 7.26-7.35 (m, 1H), 7.63-7.71 (m, 1H), 7.93-7.99 (m, 1H), 8.12-8.18 (m, 1H); ^{13}C **NMR** (50 MHz, $CDCl_3$): δ 52.2, 122.4, 128.0, 129.8, 132.0, 132.6, 135.7, 165.4; **Analysis**: $C_8H_7BrO_2$ requires C, 44.68; H, 3.28; found: C, 44.53; H, 3.11%.

Methyl 4-chlorobenzoate (51j)

Yield: 79%; colorless gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 760, 1015, 1091, 1115, 1434, 1488, 1596, 1725; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.92 (s, 3H), 7.41 (d, *J* = 8.6 Hz, 2H), 7.97 (d, *J* = 8.6 Hz, 2H); ^{13}C **NMR** (50 MHz, $CDCl_3$): δ 52.1, 128.6, 131.0, 139.3, 165.9; **Analysis**: $C_8H_7ClO_2$ requires C, 56.32; H, 4.14; found: C, 56.21; H, 4.03%.

Methyl 3-chlorobenzoate (51k)

Yield: 70%; colorless gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 748, 1126, 1259, 1283, 1295, 1437, 1728; ^{1}**H NMR** (200 MHz, $CDCl_3$): δ 3.92 (s, 3H), 7.32-7.40 (m, 1H), 7.48-7.54 (m, 1H), 7.88-7.94 (m, 1H), 7.97-8.02 (m, 1H); ^{13}C **NMR** (50 MHz, $CDCl_3$): δ 52.2, 127.6, 129.5, 131.8, 132.8, 134.5, 165.5; **Analysis**: $C_8H_7ClO_2$ requires C, 56.32; H, 4.14; found: C, 56.23; H, 4.06%.

Methyl 4-flurobenzoate (51l)

Yield: 76%; colorless gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 607, 767, 854, 1092, 1113, 1154, 1280, 1436, 1508, 1601, 1727; ^{1}**H NMR** (200 MHz, $CDCl_3$): δ 3.90 (s, 3H), 7.04-7.13 (m, 2H), 7.99-8.09 (m, 2H); ^{13}C **NMR** (50 MHz, $CDCl_3$): δ 52.1, 115.4, 128.6, 131.0, 165.1, 166.1; **Analysis**: $C_8H_7FO_2$ requires C, 62.34; H, 4.58; found: C, 62.23; H, 4.39%.

Methyl 4-(trifluromethyl)benzoate (51m)

Yield: 69%; pale yellow liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 775, 865, 1019, 1068, 1327, 1413, 1440, 1730, 2957; ^{1}**H NMR** (200 MHz, $CDCl_3$): δ 3.92 (s, 3H), 7.70 (d, *J* = 8.2 Hz, 2H), 8.14 (d, *J* = 8.2 Hz, 2H); ^{13}C **NMR** (50 MHz, $CDCl_3$): δ 52.3, 120.9, 125.2-125.4 (m), 126.3, 128.1, 129.9, 132.5-135.7 (m), 165.5; $C_9H_7F_3O_2$ requires C, 52.95; H, 3.46; found: C, 52.76; H, 3.33%.

Methyl 4-cyanobenzoate (51n)

Yield: 72%; colorless gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 763, 866, 960, 1019, 1108, 1181, 1289, 1315, 1440, 1727, 2229; ^{1}**H NMR** (200 MHz, $CDCl_3$): δ 3.96 (s, 3H), 7.75 (d, *J* = 8.6 Hz, 2H), 8.14 (d, *J* = 8.6 Hz, 2H); ^{13}C **NMR** (50 MHz, $CDCl_3$): δ 52.6, 116.5, 117.7, 130.1, 132.1, 133.9, 165.1; **Analysis**: $C_9H_7NO_2$ requires C, 67.07; H, 4.38; N, 8.69; found: C, 66.91; H, 4.26; N, 8.52%.

Methyl nicotinate (51o)

Yield: 76%; colorless liquid; IR ($CHCl_3$, cm^{-1}): υ_{max} 824, 959, 1072, 1292, 1350, 1436, 1528, 1615, 1722, 3045; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.93 (s, 3H), 7.33-7.40 (m, 1H), 8.23-8.29 (m, 1H), 8.71-8.76 (m, 1H), 9.16-9.19 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 52.3, 123.2, 126.0, 136.9, 150.8, 153.3, 165.5; **Analysis**: $C_7H_7NO_2$ requires C, 61.31; H, 5.14; N, 10.21; found: C, 61.26; H, 5.06; N, 10.12%.

Methyl furan-2-carboxylate (51p)

Yield: 63%; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 797, 1121, 1177, 1197, 1306, 1479, 1731, 3127, 3144; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.90 (s, 3H), 6.50 (d, *J* = 3.8 HZ, 1H), 7.17 (d, *J* = 3.8 Hz, 1H), 7.57 (s, 1H); ^{13}C **NMR** (50 MHz, $CDCl_3$): δ 52.0, 111.9, 118.0, 144.8, 146.5, 159.2; **Analysis**: $C_6H_6O_3$ requires C, 57.14; H, 4.80; found: C, 57.02; H, 4.69%.

Ethyl 4-nitrobenzoate (51q)

Yield: 80%; colorless solid; **mp:** 97-99 ºC, (lit.[37a] **mp:** 97-98 ºC); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 757, 872, 1103, 1277, 1320, 1352, 1528, 1724; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.44 (t, *J* = 7.4 Hz, 3H), 4.43 (q, *J* = 7.4 Hz, 2H), 8.21 (d, *J* = 8.9 Hz, 2H), 8.30 (d, *J* = 8.9 Hz, 2H); ^{13}C **NMR** (50 MHz, $CDCl_3$): δ 14.2, 61.9, 123.5, 130.6, 135.8, 150.5, 164.4; **Analysis**: $C_9H_9NO_4$ requires C, 55.39; H, 4.65; N, 7.18; found: C, 55.21; H, 4.52; N, 7.01%.

Isopropyl 4-nitrobenzoate (51r)

Yield: 76%; colorless solid; **mp:** 105-108 ºC, (lit.[37a] **mp:** 105-106 ºC); **IR** ($CHCl_3$, cm^{-1}): 717, 874, 1103, 1287, 1322, 1349, 1375, 1525, 1607, 1713; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.39 (d, *J* = 6.4 HZ, 6H), 5.24-5.31 (m, 1H), 8.19 (d, *J* = 8.4 Hz, 2H), 8.27 (d, *J* = 8.4 Hz, 2H); ^{13}C **NMR** (50 MHz, $CDCl_3$): δ 21.8, 69.7, 123.4, 130.6,

136.2, 150.4, 164.1; **Analysis**: $C_{10}H_{11}NO_4$ requires C, 57.41; H, 5.30; N, 6.70; found: C, 57.30; H, 5.19; N, 6.54%.

Benzyl 4-nitrobenzoate (51s)

Yield: 80%; colorless solid; **mp:** 82-84 ºC, (lit.[37a] **mp:** 81-82 ºC); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 743, 1103, 1286, 1348, 1523, 1713; ^{1}**H NMR** (200 MHz, $CDCl_3$): δ 5.40 (s, 2H), 7.37-7.46 (m, 5H), 8.21-8.31 (m, 4H); ^{13}C **NMR** (50 MHz, $CDCl_3$): δ 67.5, 123.5, 128.4, 128.6, 128.7, 130.7, 135.2, 135.4, 150.5, 164.3; **Analysis**: $C_{14}H_{11}NO_4$ requires C, 65.37; H, 4.31; N, 5.44; found: C, 65.23; H, 4.21; N, 5.31%.

Allyl 4-nitrobenzoate (51t)

Yield: 76%; colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 720, 855, 933, 995, 1014, 1048, 1102, 1271, 1319, 1348, 1526, 1608, 1727; ^{1}**H NMR** (200 MHz, $CDCl_3$): δ 4.86 (d, *J* = 5.8 Hz, 2H), 5.31-5.46 (m, 2H), 5.94-6.13 (m, 1H), 8.21 (d, *J* = 8.9 Hz, 2H), 8.29 (d, *J* = 8.9 Hz, 2H); ^{13}C **NMR** (50 MHz, $CDCl_3$): δ 66.3, 119.0, 123.5, 130.7, 131.6, 135.5, 150.6, 164.1; **Analysis**: $C_{10}H_9NO_4$ requires C, 57.97; H, 4.38; N, 6.76; found C, 57.78; H, 4.19; N, 6.59%.

Prop-2-ynyl 4-nitrobenzoate (51u)

Yield: 82%; yellow gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 715, 875, 1124, 1286, 1322, 1350, 1527, 1608, 1728, 3290; ^{1}**H NMR** (200 MHz, $CDCl_3$): δ 2.55 (t, *J* = 2.5 Hz, 1H), 4.94 (d, *J* = 2.5 Hz, 2H), 8.24 (d, *J* = 8.4 Hz, 2H), 8.32 (d, *J* = 8.4 Hz, 2H); ^{13}C **NMR** (50 MHz, $CDCl_3$): δ 53.2, 75.8, 123.6, 130.9, 134.7, 150.8, 163.8; **Analysis**: $C_{10}H_7NO_4$ requires C, 58.54; H, 3.44; N, 6.83; found: C, 58.42; H, 3.29; N, 6.74%.

(*S*)-Tetrahydrofuran-3-yl 4-nitrobenzoate (51v)

Yield: 66%**,** colorless gum; $[\alpha]^D_{25}$ -31.24 (*c* 1.2, CH_2Cl_2); lit[37a] $[\alpha]^D_{25}$ +31.26 (*c* 1.0, CH_2Cl_2) for the corresponding (*R*)-enantiomer; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 720, 878, 1086, 1106, 1120, 1529, 1604, 1718, 2877, 2933, 3076; **^{1}H NMR** (200 MHz, $CDCl_3$):

δ 2.14-2.21 (m, 1H), 2.29-2.43 (m, 1H), 3.91-4.07 (m, 4H), 5.57-5.60 (m, 1H), 8.21 (d, *J* = 8.8 Hz, 2H), 8.30 (d, *J* = 8.8 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 32.8, 66.9, 72.9, 76.4, 123.5, 130.7, 135.2, 150.7, 164.1; **Analysis:** $C_{11}H_{11}NO_5$ requires C, 55.70; H, 4.67; N, 5.90; found: C, 55.62; H, 4.51; N, 5.79%.

(*R*)-Tetrahydrofuran-3-yl 4-nitrobenzoate (51w)

Yield: 64%; colorless gum; $[\alpha]^D_{25}$ +31.24 (*c* 1.2, CH_2Cl_2); lit[37aa] $[\alpha]^D_{25}$ +31.26 (*c* 1.0, CH_2Cl_2); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 721, 879, 1084, 1105, 1122, 1528, 1604, 1718, 2877, 2933, 3076; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.14-2.20 (m, 1H), 2.30-2.35 (m, 1H), 3.91-3.93 (m, 1H), 3.98-4.03 (m, 3H), 5.55-5.58 (m, 1H), 8.20 (d, *J* = 8.8 Hz, 2H), 8.29 (d, *J* = 8.8 Hz, 2H); ^{13}C **NMR** (50 MHz, $CDCl_3$): δ 32.8, 66.9, 72.9, 76.4, 123.5, 130.7, 135.2, 150.7, 164.1; **Analysis:** $C_{11}H_{11}NO_5$ requires C, 55.70; H, 4.67; N, 5.90; found: C, 55.60; H, 4.49; N, 5.76%.

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LIST OF PUBLICATIONS

1. A concise enantioselective synthesis of (+)-goniodiol and (+)-8-methoxygoniodiol *via* Co-catalyzed HKR of *anti*-(2*SR*, 3*RS*)-3-methoxy-3-phenyl-1,2-epoxypropane; **Kiran, I. N. C.**; Reddy, R. S.; Suryavanshi, G.; Sudalai, A. *Tetrahedron Lett.* **2011**, *52*, 438.
2. CN-assisted oxidative cyclization of cyano cinnamates and styrene derivatives: a facile entry to 3-substituted chiral phthalides; Reddy, R. S.; **Kiran, I. N. C.**; Sudalai, A. *Org. Biomol. Chem.* **2012**, *10*, 3655.
3. *N*-Heterocyclic carbene catalyzed esterification of aromatic aldehydes with alcohols under aerobic conditions; **Kiran, I. N. C.**; Lalwani, K.; Sudalai, A. *RSC Adv.* **2013**, *3*, 1695.
4. Enantioselective synthesis of (-)-polysphorin analog *via* Co-catalyzed HKR of *syn*-(2*SR*, 3*SR*)-3-(methoxymethyl)oxy-3-(3,4,5-trimethoxyphenyl)-1,2-epoxypropane; **Kiran, I. N. C**.; Lalwani, K.; Sudalai, A. (*to be communicated*).
5. First enantioselective synthesis of new antitumour and antiinflammatory neolignan, surinamensinol B; Lalwani, K.; **Kiran, I. N. C**.; Sudalai, A. (*manuscript under preparation*).
6. Highly stereoselective synthesis of chiral 3-amino-1,2-diols *via* proline-catalyzed α-aminooxylation of β-aminoaldehydes; Venkataramasubramanian, V.; **Kiran, I. N. C.**; Sudalai, A. (Patent filed, *to be communicated*).
7. Enantioselective synthesis of cytoxazone epimers, taxol side chain and formal synthesis of *N*-thiolated-2-oxazolidinone; **Kiran, I. N. C.**; Venkataramasubramanian, V.; Sudalai, A. (Patent filed, *to be communicated*).
8. Organocatalytic enantioselective synthesis of rasagiline an anti-Parkinson drug; **Kiran, I. N. C**.; Sudalai, A. (*manuscript under preparation*).
9. A new process for the production of 3-substituted phthalides; Reddy, R. S.; **Kiran, I. N. C.**; Sudalai, A. *WO056340*/**2012**.
10. *N*-Heterocyclic carbene catalyzed esterification of aromatic aldehydes with alcohols under aerobic conditions; **Kiran, I. N. C.**; Lalwani, K.; Sudalai, A. *IN Ap. No 1685/DEL/***2012**: 6/1/2012.
11. Cu-mediated annulation strategy for the effective synthesis of 3-substituted phthalides; Reddy, R. S.; Prasad, K. P.; **Kiran, I. N. C.**; Sudalai, A. *WOPCT /IN/0000051*/**2013**.
12. A single step enantioselective process for the preparation of 3-substituted chiral phthalides; Reddy, R. S.; **Kiran, I. N. C.**; Sudalai, A. *WO072830*/**2013**.