Asymmetric Synthesis of Bioactive Molecules and Formation of C-N, C-Br and C-I Bonds *via* Olefin Functionalization

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In Chemical Sciences

By

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UNDER THE GUIDANCE OF

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CERTIFICATE

This is to certify that the work incorporated in the thesis entitled ***"Asymmetric Synthesis of Bioactive Molecules and Formation of C-N, C-Br and C-I Bonds via Olefin Functionalization"*** which is being submitted to the ***AcSIR*** for the award of ***Doctor of Philosophy*** in ***Chemical Sciences*** by ***Ms. Karabal Pratibha Uttam*** was carried out by her 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.

April 2014 **Dr. A. Sudalai**

Pune (Research Guide)

CSIR-NATIONAL CHEMICAL LABORATORY

DECLARATION

I hereby declare that the thesis entitled ***"Asymmetric Synthesis of Bioactive Molecules and Formation of C-N, C-Br and C-I Bonds via Olefin Functionalization"*** submitted to AcSIR for the award of degree of Doctor of Philosophy in Chemical Sciences, 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.

April 2014
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DEDICATED TO

MY

BELOVED FAMILY MEMBERS

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Though, many have not been mentioned, none is forgotten.

Pratibha U. Karabal

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ABBREVATIONS

Ac	Acetyl
Ar	Aryl
Bn	Benzyl
Boc	*N-tert*-Butoxycarbonyl
$(Boc)_2O$	Ditert-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]undecene-7
DIBAL-H	Diisobutyl alulinum 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
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 dichromatel
$Pd(OH)_2$	Palladium hydroxide
Ph	Phenyl
p-TSA	*p*-Toluene sulfonic acid
PhNO	Nitrosobenzene
Py	Pyridine
TBS	*tert*-Butyldimethylsilyl
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TBAF	Tetrabutylammonium fluoride
TBDMSCl	*tert*-Butyldimethylsilyl chloride
TBDPSCl	*tert*-Butyldiphenylsilyl chloride
TFA	Trifluoroacetic acid
Ts	Tosyl
CBS	Corey-Bakshi Shibata

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 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

Asymmetric Synthesis of Bioactive Molecules and Formation of C-N, C-Br and C-I Bonds *via* Olefin Functionalization

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Date of Synopsis submission: 17/02/2014

The thesis entitled "**Asymmetric Synthesis of Bioactive Molecules and Formation of C-N, C-Br and C-I Bonds *via* Olefin Functionalization**" is divided into four chapters.

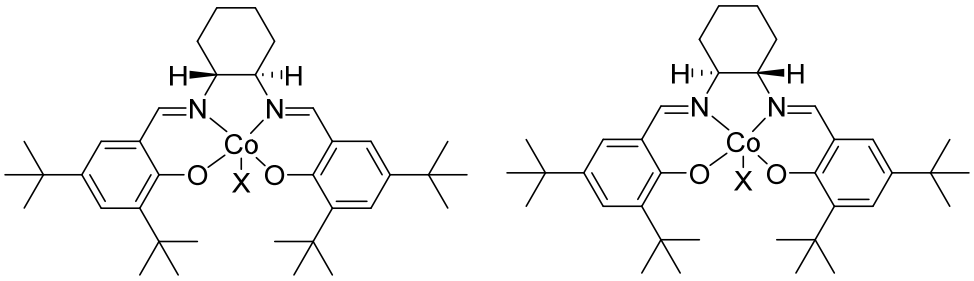
The title of the thesis clearly reflects the objective, which is to synthesize enantiomerically pure bioactive molecules and to develop useful synthetic methodologies**. Chapter 1** deals with phenolic kinetic resolution of azido epoxides and its application in the synthesis of ICI-118,551, an *anti*-hypertensive agent. **Chapter 2** describes the synthesis of optically pure γ-butyrolactones and epoxy esters *via* two-stereocentered hydrolytic kinetic resolution of 3-substitued epoxy esters and their application in the formal synthesis of Ro 67-8867. **Chapter 3** deals with enantioselective synthesis of 1,4-dideoxy-1,4-imino-D-allitol, (*S*)-3-hydroxy piperidine using HKR and enantioselective synthesis of (*R*)-coniine *via* asymmetrc reduction of ketone using CBS reagent. **Chapter 4** describes the formation of C-N, C-Br and C-I bonds *via* catalytic olefin functionalization.

CHAPTER 1

Cobalt-Catalyzed Phenolic Kinetic Resolution of Azido Epoxides and its Application in the Synthesis of ICI-118,551, an a*nti*-Hypertensive Agent

Phenolic kinetic resolution (PKR), in which phenol is used as nucleophile to react with racemic epoxides, has emerged as a powerful tool to obtain terminal epoxides as well as their corresponding α-aryloxy alcohols in enantiomerically pure form.[1] These compounds are important intermediates for the synthesis of several bioactive molecules. The enantiomerically pure α-aryloxy alcohols are also valuable synthetic

intermediates in a variety of pharmaceutically important compounds.[2] This chapter is divided into two sections. **Section I** deals with the development of a novel catalytic method in which PKR of *syn*/*anti*- azido epoxides catalyzed by chiral (salen) Co[$OC(CF_3)_3$].H_2O **1a** complex was employed to produce chiral α-aryloxy-α'-azido alcohols while **Section II** presents its application in the synthesis of ICI-118,551, an *anti*-hypertensive drug. The catalyst Co(III)salen **1a** was readily prepared from the commercially available (salen)Co(III) complex[1] (**Fig.1**).



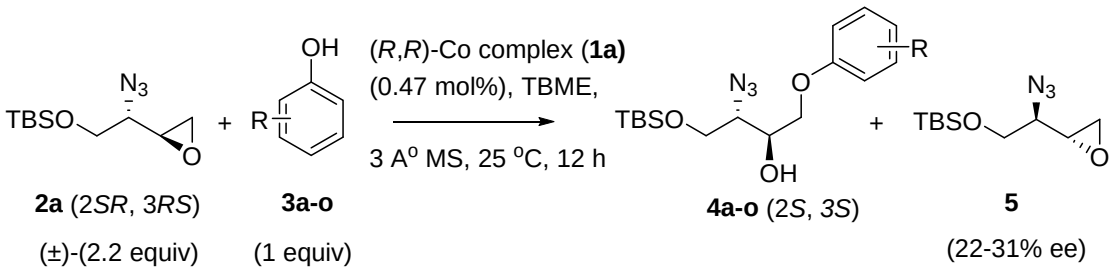
(*R, R*)-**1a**, X = O-$C(CF_3)_3$.H_2O
(*R, R*)**1b**, X = OAc

(*S, S*)-**1c**, X = OAc

Fig 1: Structure of Co(III)-salen complex

SECTION I: Phenolic Kinetic Resolution of Azido Epoxides: A new Synthesis of Enantiomerically Pure α-Aryloxy-α'-Azido Alcohols

The enantiomerically pure α-azido alcohols **4a-o** are versatile synthetic intermediates. To begin with, the racemic *anti*- and *syn*- azido epoxides **2a-b**, substrates for PKR, were efficiently prepared in a highly diastereoselective fashion from *cis*-2-butenediol and *trans*-cinnamyl alcohol respectively, essentially involving a two-step reaction sequence of NBS-bromination in the presence of sodium azide, followed by its treatment with base.[3] When racemic *anti*-azido epoxide **2a** was subjected to PKR with several differently substituted phenols **3a-o** using (salen)Co[$OC(CF_3)_3$].H_2O (**1a**) as catalyst, the corresponding optically pure *anti*-1-aryloxy-3-azido-2-alcohols (**4a-o)** were obtained with complete regiocontrol in excellent yields (35-92%) and ees (68-99%) (**Scheme 1**). The results of such a study are presented in **Table 1**.



2a (2*SR*, 3*RS*) (±)-(2.2 equiv) **3a-o** (1 equiv) **4a-o** (2*S*, *3S*) **5** (22-31% ee)

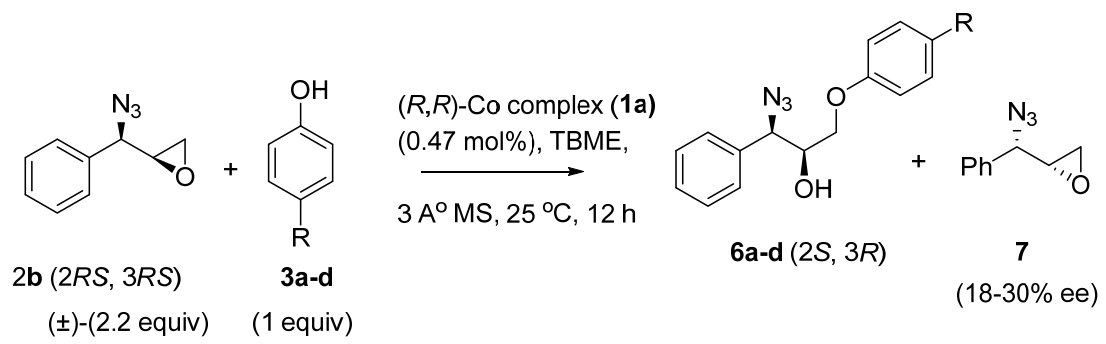
Scheme 1: PKR of *anti*-azido epoxides with phenols as nucleophile

Table 1: Co-catalyzed PKR of *anti*-azido epoxide **2a** with phenols (**3a-o**)

		anti-azido alcohols (**4a-o**)	
entry	R (**3a-o**)	yield (%)[a]	ee (%)[b]
a	H	65	92
b	2-CH_3	72	94
c	3-CH_3	70	95
d	4-CH_3	35	99
e	4-Bu^t	76	99
f	3-OMe	60	93
g	4-CN	87	98
h	4-F	72	68
i	4-Cl	90	97
j	4-Br	86	97
k	2, 5-Cl_2	89	95
l	4-$COCH_3$	88	98
m	4-CO_2Me	81	94
n	4-NO_2	92	96
o	7-Me-4-indanol	75	99

[a]Isolated yield after column chromatographic purification *w.r.t.* phenol; [b] determined f chiral HPLC analysis.

Similarly, racemic *syn*- azido epoxide **2b**, when subjected to (salen)Co[$OC(CF_3)_3$].H_2O, (**1a**) -catalyzed PKR under identical conditions, gave the corresponding enantiopure *syn*-products **6a-d** in high yields (88-96%) and ees (93-94%) (**Scheme 2**). The results of such a study are presented in **Table 2**.



Scheme 2: PKR of *syn*-azido epoxide with phenol as nucleophile

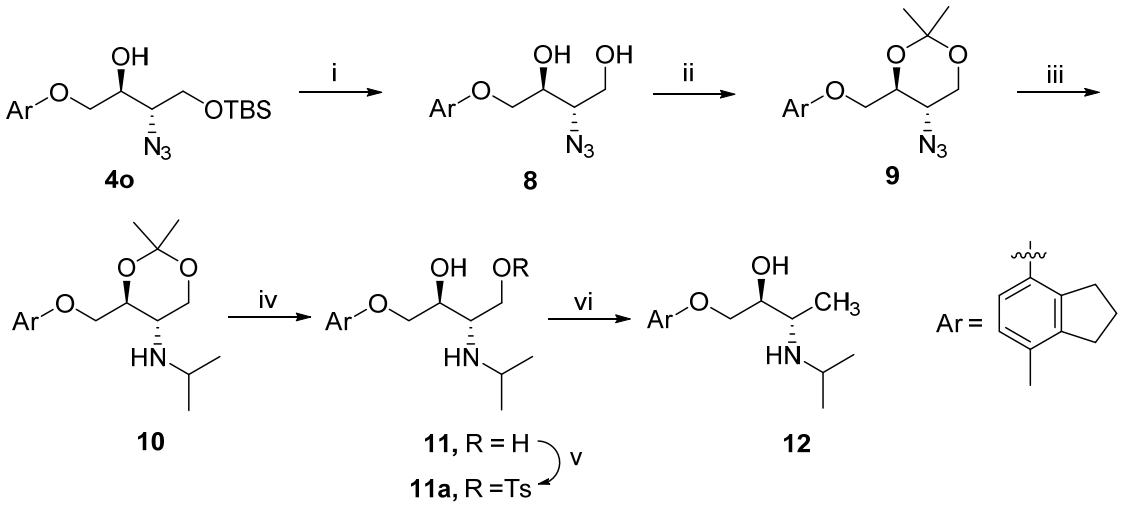
Table 2: Co-catalyzed PKR of *syn*-azido epoxide **2b** with phenols (**3a-d**)

		syn- azido alcohols (**6a-d**)	
entry	R **3(a-d)**	yield (%)[a]	ee (%)[b]
a	$COCH_3$ (**3a**)	88	93
b	CO_2Me (**3b**)	96	93
c	NO_2 (**3c**)	90	94
d	Bu^t (**3d**)	89	94

[a]Isolated yield after column chromatographic purification *w.r.t.* phenol; [b] determined by chiral HPLC analysis.

SECTION II: Asymmetric Synthesis of ICI 118,551, an *anti*-Hypertensive Agent *via* Phenolic Kinetic Resolution

ICI-118,551 (**12**),[4] the most potent and selective β_2 AR antagonist, is used in the treatment of a wide range of diseases including heart failure,[5] ischemic heart disease[6] and hypertension.[7] This section describes an efficient synthesis of **12**, which commences from optically pure azido alcohol **4o** (entry o, T**able 1**). The acid-catalyzed silyl deprotection of **4o** gave the diol **8**, which was protected with 2,2-dimethoxypropane to give acetonide **9** in 89% yield over two steps. The catalytic hydrogenation of azide **9** gave the crude amine, which was smoothly *N*-alkylated[8] with 2-bromopropane under basic conditions to give the *N*-isopropyl derivative **10**. The acid-catalyzed acetonide deprotection gave diol **11** in 65% yields. Selective monotosylation of diol **11** gave the crude tosylate **11a**, which on reduction with $LiAlH_4$ afforded **12** in 21% overall yield and 99% ee (**Scheme 3**).



Scheme 3: (i) TBAF, THF, 0 °C, 1 h, 90%; (ii) 2,2-dimethoxypropane, cat. camphorsulphonic acid, CH_2Cl_2, 1 h, 89%; (iii) (a) 5% Pd/C, H_2 (1 atm), MeOH, 6 h; (b) KOH/18-crown-6, 4 A^0 MS, isopropyl bromide, DMF, 20 h, 65%; (iv) TFA, CH_2Cl_2, 65%; (v) *p*-TsCl, Et_3N, CH_2Cl_2, 0 °C, 1 h, 57%; (vi) $LiAlH_4$, THF, reflux, 62%, 90% ee.

CHAPTER 2

Synthesis of Optically Pure γ-Butyrolactones and Epoxy Esters *via* Two-Stereocentered HKR of 3-Substituted Epoxy Esters: A Formal Synthesis of Ro 67-8867

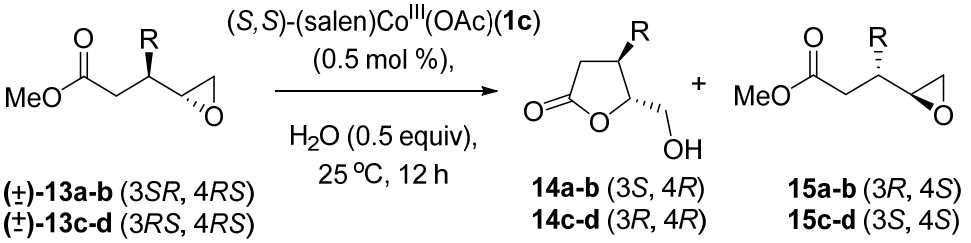
Hydrolytic Kinetic Resolution (HKR) of racemic terminal epoxides developed by Jacobsen *et al.* has emerged as a powerful tool to obtain terminal epoxides, as well as their corresponding diols in enantiomerically pure form.[9] These compounds are key intermediates in the synthesis of various bioactive molecules.[10] The enantiomerically pure γ-butyrolactone and epoxy esters are also valuable 'building blocks' for the asymmetric synthesis of bioactive natural products.[11, 12] This chapter deals with the development of a novel method in which HKR of 3-substituted epoxides catalyzed by chiral (*S, S*)-(salen)Co(III)OAc complex (**1c**) produces chiral substituted γ-butyrolactones and epoxy esters; its application in the asymmetric synthesis of Ro 67-8867. This chapter is thus divided into two sections. **Section I** deals with the synthesis of optically pure γ-butyrolactones and epoxy esters *via* two-stereocentered HKR of 3-substituted epoxy esters while **Section II** describes the formal synthesis of Ro 67-8867 *via* HKR strategy.

<u>SECTION I:</u> Synthesis of Optically Pure γ-Butyrolactones and Epoxy Esters *via* Two-Stereocentered HKR of 3-Substitued Epoxy Esters

For the first time, HKR of racemic *anti*- or *syn*-3-substituted aryl or alkyl epoxy esters derivatives (**13** & **16**) was carried out. In this strategy, the relative stereochemistry between aryl/alkyl epoxide functions is established prior to the HKR step and thus a single asymmetric reaction is employed to form products with two asymmetric centers. The racemic *anti*- and *syn*-3-substituted epoxy esters (**13** & **16**), the substrates for HKR, were efficiently prepared in a highly diastereoselective manner from the corresponding allylic alcohol by essentially following a three-step procedure:[13] (i) Johnson-Claisen rearrangement (ii) diastereoselective iodolactonization; (iii) methanolysis to form the corresponding racemic epoxides. In this section, a flexible, novel method is described that employs HKR of racemic 3-substituted (aryl or alkyl) epoxy esters **13** with two stereocentres to produce substituted γ-butyrolactones **14** and epoxy esters **15** in high optical purities in a single step (**Table 3**).

For instance when HKR of racemic *anti*-3-substituted epoxy ester **13a** was carried out with (*S, S*)-(salen)Co(III)OAc complex (**1c**) (0.5 mol %) and H_2O (0.5 equiv) as the nucleophile, the corresponding *trans*- 3,4-disubstituted γ-butyrolactone **14a** (45% yield, 98% ee) and 3-substituted epoxy ester **15a** (48% yield, 98% ee) were isolated in high yields and optical purity.

Table 3. Co-catalyzed HKR of racemic 3-substituted *anti*-epoxy esters (**13 a-d**)



(±)-13a-b (3*SR*, 4*RS*)
(±)-13c-d (3*RS*, 4*RS*)

14a-b (3*S*, 4*R*)
14c-d (3*R*, 4*R*)

15a-b (3*R*, 4*S*)
15c-d (3*S*, 4*S*)

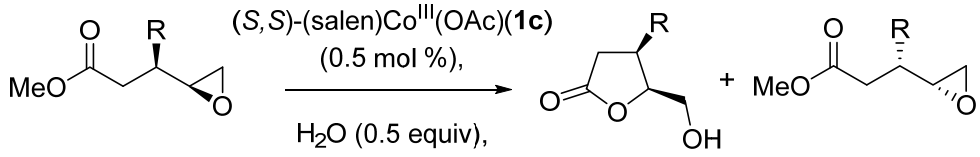
entry	substrates (R) (±)-**13a-d**	lactones **14a-d**		epoxides **15a-d**	
		yield (%)[a]	ee (%)[b]	yield (%)[a]	ee (%)[b]
1	4-chlorophenyl (**13a**)	45	98	48	98

2	4-bromophenyl (**13b**)	46	96	48	96
3	benzyl (**13c**)	47	99	48	97
4	3-phenylpropyl (**13d**)	48	96	48	96

[a] Isolated yield after column chromatographic purification; [b] ee determined from chiral HPLC analysis.

We have examined its scope by subjecting other racemic *anti*-3-substituted epoxy esters **13b-d** to HKR, which proceeded smoothly, with complete regiocontrol, to give the respective enantioenriched *trans*-3,4-disubstituted γ-butyrolactones **14b-d** and *anti*-epoxy esters **15b-d** in high yields (45-48%) with excellent ees (96 to 99% ee). Similarly, when *syn*-3-substituted epoxy esters **16a-b** were subjected to HKR under identical reaction conditions, the corresponding chiral *cis*-3,4-disubstituted γ-butyrolactones **17a-b** and *syn*-epoxy esters **18a-b** were obtained in high yields and ees upto 99%. The results of this study are presented in **Table 4**.

Table 4. Co-catalyzed HKR of racemic 3-substituted *syn*-epoxy esters (**16a-b**)



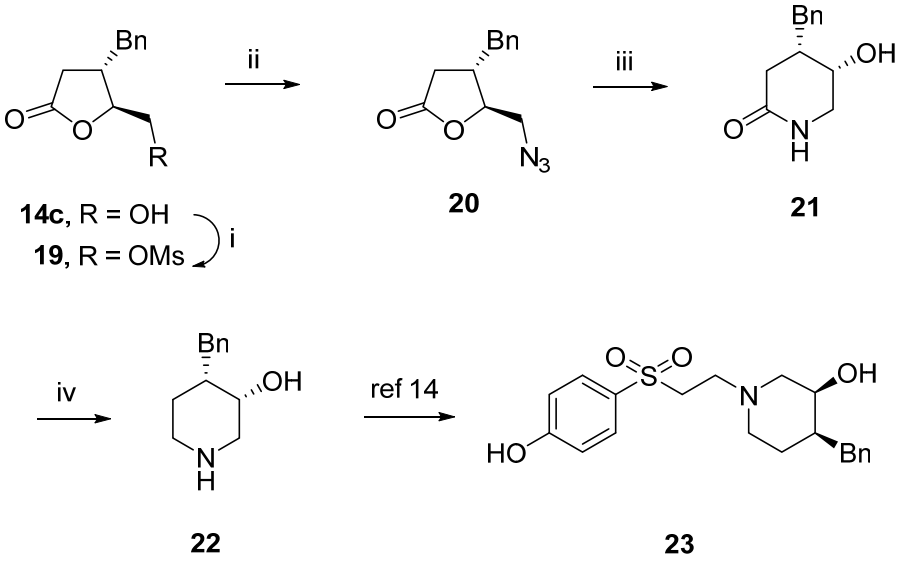
(±)-16a-b (3*SR*, 4*SR*) **17a-b** (3*S*, 4*S*) **18a-b** (3*R*, 4*R*)

entry	substrates (R) (±)-**16a-b**	lactones **17a-b**		epoxides **18a-b**	
		yield (%)[a]	ee (%)[b]	yield (%)[a]	ee (%)[b]
a	4-fluorophenyl (1**6a**)	46	98	48	98
d	4-chlorophenyl (**16b**)	47	99	46	97

[a] Isolated yield after column chromatographic purification; [b] ee determined from chiral HPLC analysis.

SECTION II: A Formal Synthesis of Ro 67-8867 *via* HKR Strategy

Ro 67-8867 (**23**), a *trans*-3,4-disubstitued piperidine derivative and a selective antagonist of the *N*-methyl-D-aspartate (NMDA) receptor, has been reported to selectively block an NMDA receptor subtype in brain regions.[14] This section describes a concise enantioselective synthesis of Ro 67-8867 using HKR of racemic 3-substituted epoxides. The synthesis of **23** commences from γ-butyrolactone **14c** (obtained from HKR of **13c** with (*R, R*)-(salen)Co(III)(OAc) complex as catalyst; see Section I). Mesylation of **14c** gave the mesylate **19**, which was readily converted to the corresponding azide **20** (NaN_3, DMF, 80 ^oC) in 95% yield. Azide **20** was then subjected to intramolecular reductive cyclization over 5% $Pd(OH)_2/H_2$ (1 atm) to afford *cis*-3,4-disubstituted piperidinone core **21** in 98% yield. Reduction of imide carbonyl in **21** was achieved with $BH_3.SMe_2$ to give *cis*-piperidine derivative **22**[15] in 85% yield (overall yield: 17% from **14c**), thus constituting a formal synthesis of Ro 67-8867 (**23)** (**Scheme 4**).



Scheme 4: (i) MsCl, Et_3N, CH_2Cl_2, 0 ^oC, 1 h, 93%; (ii) NaN_3, DMF, 80 ^oC, 3 h, 95%; (iii) $Pd(OH)_2$, H_2 (1 atm), MeOH, 12 h, 25 ^oC, 98%; (iv) $BH_3.SMe_2$, THF, reflux, 12 h, 85%.

CHAPTER 3

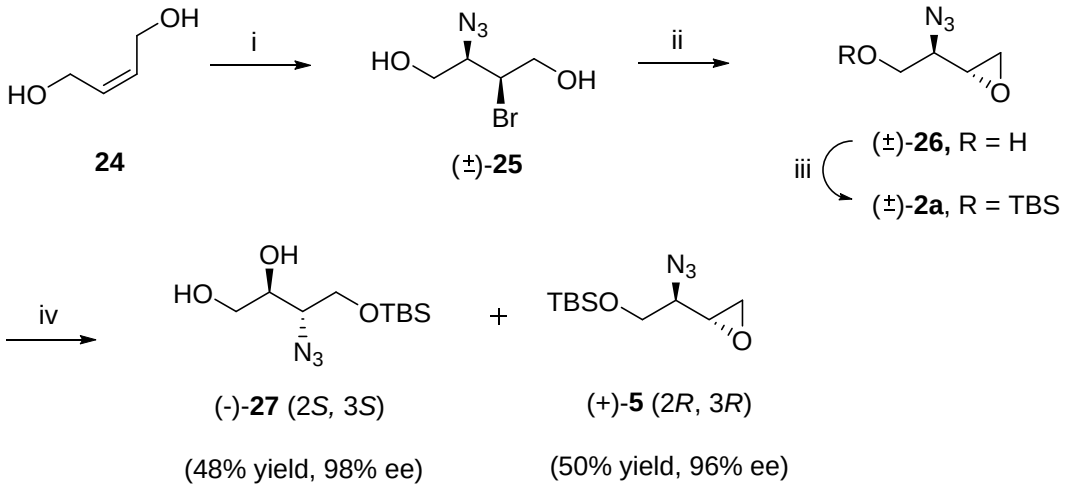
Chapter 3 is divided into three sections. **Section I** deals with the formal synthesis of 1,4-dideoxy-1,4-imino-D-allitol *via* HKR of azido epoxide. **Section II** describes the enantioselective synthesis of (*S*)-3-hydroxypiperidine *via* HKR of epoxy ester while

Section III deals with the synthesis of (*R*)-coniine *via* enantioselective CBS-reduction of ketone.

SECTION I: A Formal Synthesis of 1,4-Dideoxy-1,4-Imino-D-Allitol

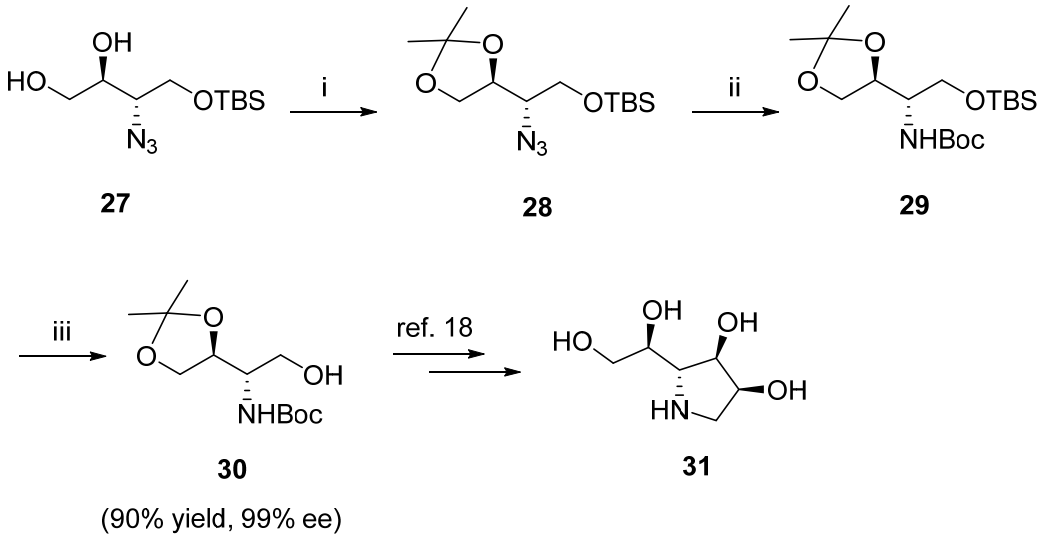
Azasugars such as 1,4-dideoxy-1,4-imino hexitols **31**, belonging to a family of polyhydroxylated pyrrolidines, are potent glycosidase inhibitors. Many pyranoses and furanoses with the ring oxygen replaced by an imino group are natural products that are useful as potent glycosidase inhibitors.[16] They have been found to be chemotherapeutic agents as well for the treatment of diseases such as diabetes, cancer, inflammation and viral infections including AIDS.[17]

This section presents the formal synthesis of **31** starting from commercially available *cis*-2-butene-1,4-diol **24**, which on treatment with NBS in the presence of NaN_3, gave the bromo azido diol **25** in 89% yield. The bromo azido diol **25** was readily transformed into racemic *anti*- azido epoxide **26** (NaOH, dry THF, 0 ^oC, 84%). The protection of primary hydroxyl group in **26** as TBS ether (TBSCl, imidazole, CH_2Cl_2, 0 ^oC) was achieved to give the protected racemic azido epoxide **2a** in 94% yield. Azido epoxide **2a** was then subjected to HKR with (*R*, *R*)-(salen)Co(III)(OAc) complex (**1b**) (0.5 mol %) and H_2O (0.49 equiv) as nucleophile, which produced the corresponding chiral azido diol **27** (48% yield, 98% ee) and chiral azido epoxide **5** (50% yield, 96% ee) in high optical purity (**Scheme 5**).[3]



Scheme 5: (i) NBS (1.2 equiv), NaN_3 (2 equiv), CH_3CN/H_2O (3:1), 0 ^oC, 3 h, 89%; (ii) NaOH, THF, 0 ^oC, 3 h, 84%; (iii) TBSCl, imid., CH_2Cl_2, 0 ^oC, 1 h, 94%; (iv) (*R, R*)-Co^{III}(salen) complex (**1b**) (0.5 mol %), H_2O (0.49 equiv), 0 to 25 ^oC, 12 h.

Both the free hydroxyl groups in diol **27** were then protected as acetonide **28** (2,2-dimethoxypropane, cat. CSA, CH_2Cl_2). The azide **28** was reduced over catalytic hydrogenation [(5% Pd/C, H_2 (1 atm)], in MeOH and the crude amine was further selectively protected as its Boc derivative to give mono Boc protected amine **29**. Deprotection of silyl group in **29** was achieved using TBAF in THF at 0 ^oC to afford the known intermediate **30** (overall yield: 16% from **24**); thus constituting a formal synthesis of 1,4-dideoxy-1,4-imino-D-allitol **31** (**Scheme 6**). The conversion of **30** to 1,4-dideoxy-1,4-imino-D-allitol **31** has been reported in the literature.[18]

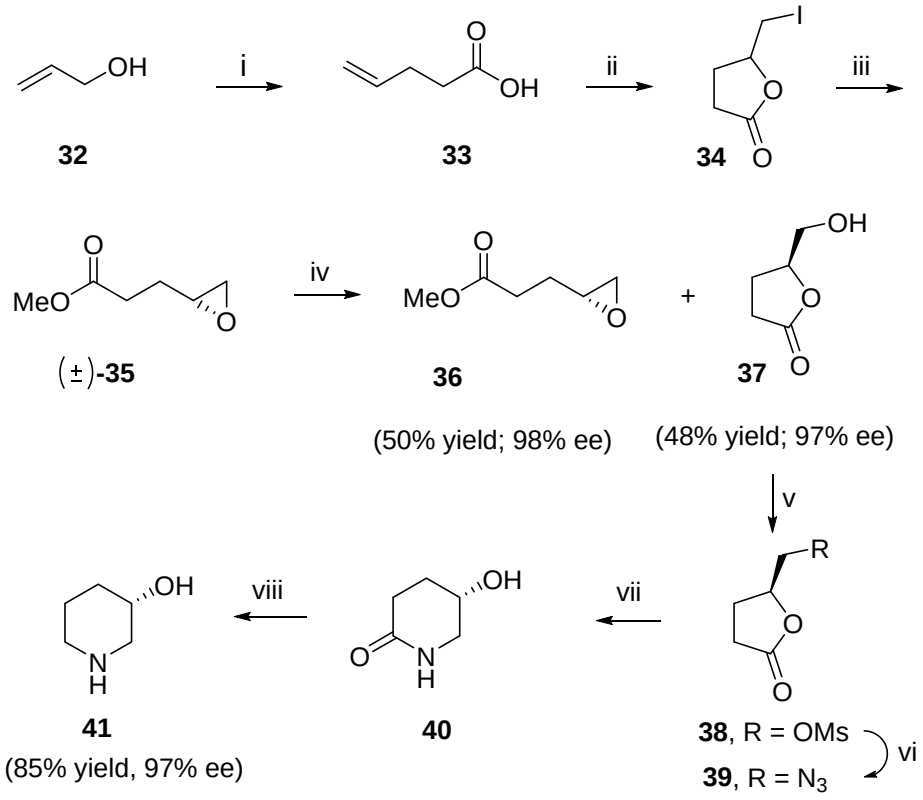


Scheme 6: (i) 2,2-dimethoxypropane, cat. CSA, CH_2Cl_2, 2 h, 89%; (ii) (a) 5% Pd/C, H_2 (1 atm), MeOH; (b) $(Boc)_2O$, DMAP (10 mol%), Et_3N, CH_2Cl_2, 25 ^oC, 6 h, 75% (for two steps); (iii) TBAF, THF, 0 ^oC, 3 h, 90%.

SECTION II: Asymmetric Synthesis of (*S*)-3-Hydroxypiperidine Skeleton: A Key Element in Natural Product Synthesis

3-Hydroxypiperidine (**41**) motif which is present in a variety of natural products.[19] In addition medicinally important drugs containing 3-piperidinol fragments include cholinotoxic agents, antihypertensives and calcium antagonists, 2,3-oxydosqualene cyclase inhibitors, 5-HT4 agonists, nootropics or antiarrhythmic agents. This section presents the synthesis of **41** commencing from commercially available allylic alcohol **32.** Johnson–Claisen rearrangement of allylic alcohol 3**2** [$MeC(OEt)_3$, hexanoic acid (cat.), 80–150 °C] gave the unsaturated olefinic acid **33** in 80% yield. Iodolactonization of **33** led to isolation of iodolactone **34** (I_2, CH_3CN, 0 °C, 24 h),

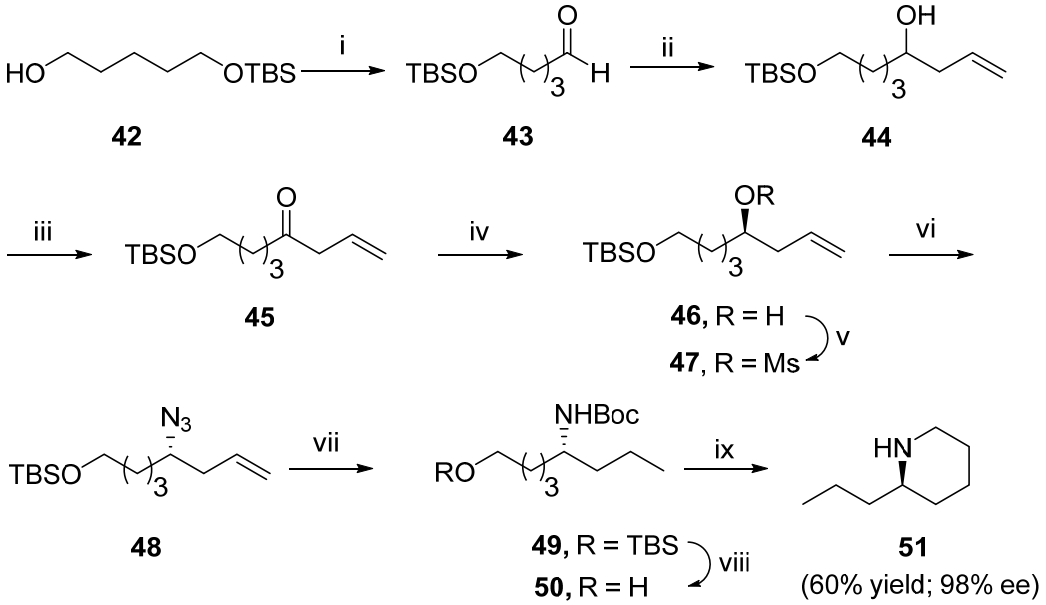
followed by its methanolysis under basic conditions produced the required racemic epoxy ester **35.** The racemic epoxy ester **35** was then subjected to HKR using (*S, S*)-(salen)Co(III)OAc complex (**1c**) as a catalyst to furnish γ-butyrolactone **37** in 48% yield and 97% ee (its optical purity was determined from ^{1}H NMR analysis of the corresponding Mosher's ester). Mesylation of **37** gave the mesylate **38**, which was readily converted to the corresponding azide **39** (NaN_3, DMF, 80 ^oC) in 95% yield via S_N2 displacement. Azide **39** was then subjected to intramolecular catalytic reductive cyclization over $Pd(OH)_2/H_2$ (1 atm) to afford piperidinone core **40** in 98% yield. Reduction of imide carbonyl in **40** with $BH_3.SMe_2$ produced (*S*)-3-hydroxypiperidine **41** in 85% (17% overall yield and 97% ee) (**Scheme 7**).



Scheme 7: (i) $MeC(OEt)_3$, hexanoic acid, 80-150 ^oC, 3 h, 80%; (ii) I_2, CH_3CN, 0 ^oC, 24 h, 85%; (iii) MeOH, Na_2CO_3, reflux, 3 h, 70%; (iv) (*S, S*)-Co^{III}(salen) complex (**1c**) (0.5 mol %), H_2O (0.49 equiv), 0 to 25 ^oC, 12 h. (v) MsCl, Et_3N, CH_2Cl_2, 0 ^oC, 1 h, 92%; (vi) NaN_3, DMF, 80 ^oC, 3 h, 95%; (vii) 5% $Pd(OH)_2$, H_2 (1 atm), MeOH, 12 h, 25 ^oC, 98%; (viii) $BH_3.SMe_2$, THF, reflux, 12 h, 85%.

<u>SECTION III</u>: Enantioselective Synthesis of (*R*)-Coniine *via* Reduction of Ketone with CBS Reagent

Coniine **51**, an alkaloid found in the poisonous hemlock plant *Conium maculatum L.*, has been considered as an excellent target for its anaesthetic property.[20] This section presents the synthesis of (*R)*-coniine **51** starting from mono protected 1,5-pentanediol **42.** Alcohol **42** on Swern oxidation gave aldehyde **43** in 90% yield. The aldehyde **43** was then subjected to Barbier allylation with allyl bromide to give allylic alcohol **44** in 85% yield, which was subsequently oxidized under IBX DMSO conditions to provide the corresponding ketone **45** in 82% yield. Ketone **45** was then subjected to asymmetric reduction [(*R*)-CBS reagent conditions, BH_3.THF, -30 ^oC] [21] to furnish the chiral allylic alcohol **46** in 75% yield and 98% ee (its optical purity was determined from ^1H NMR analysis of the corresponding Mosher's ester).



<u>Scheme 8</u>: (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 ^oC, 1 h, 90%; (ii) Zn, THF/H_2O, NH_4Cl, allyl bromide, 0 ^oC to 25 ^oC, 85%; (iii) IBX, dry DMSO, 25 ^oC, 1 h, 82%; (iv) (*R*)-CBS reagent, BH_3.THF, -30 ^oC, 75%; (v) MsCl, Et_3N, CH_2Cl_2, 0 ^oC, 85%; (vi) NaN_3, DMF, 80 ^oC, 5 h, 68% (over two steps); (vii) (a) 5% Pd/C, H_2 (1 atm), MeOH; (b) $(Boc)_2O$, DMAP (10 mol%), Et_3N, CH_2Cl_2, 25 ^oC, 6 h, 85% (over two steps) ; (viii) TBAF, THF, 0 ^oC, 90%; (ix) (a) MsCl, Et_3N, CH_2Cl_2; (b) NaH, DMF, -30 °C, (c) HCl-methanol,60% (for three steps).

Mesylation of **46** gave the mesylate **47**, which underwent S_N2 displacement with azide to give the corresponding azide **48** (NaN_3, DMF, 80 ^oC) in 68% yield with complete

stereochemical inversion. Then azide **48** was reduced to amino group under catalytic hydrogenation conditions (10% Pd/C, H_2 1 atm) followed by *in situ* protection of the corresponding amine as its carbamate derivative **49** (85%). Desilylation of **49** with TBAF in THF furnished alcohol **50** in 90% yield. Finally, mesylation of alcohol **51** gave the mesylate which was treated with base that afforded the target molecule **51** in 14% overall yield and 98% ee (**Scheme 8**).

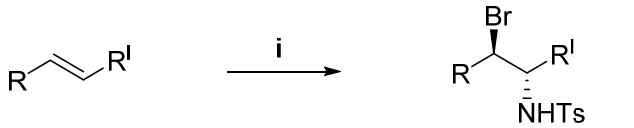
CHAPTER 4

Synthetic Methodologies Involving Formation of C-N, C-Br and C-I Bonds *via* Olefin Functionalization

Chapter 4 is divided into three sections. **Section I** presents aminobromination of olefins using Titanium Superoxide as heterogeneous catalyst. **Section II** deals with $NaIO_4$-mediated synthetic transformation involving regioselective azido iodination of olefins and **Section III** describes $NaIO_4$-mediated aziridination of olefins using chloramine-T as amine source.

SECTION I: Titanium Superoxide: A Heterogeneous Catalyst for Aminobromination of Alkenes

The haloamination of olefins by the addition of two different functional groups in a single step is an important transformation (for e.g. aminohydroxylation, haloamination, etc.). Among all these, haloamination is one of the most useful reactions[22] as the halogens can be replaced by a variety of nucleophiles such as N_3, CN, OAc etc. to give a new class of intermediates in organic synthesis. The vicinal haloamine functionality represents a useful structural moiety as well as versatile building blocks in organic and medicinal chemistry.



52
R = aryl, alkyl
R^1 = H, alkyl, CO_2R''

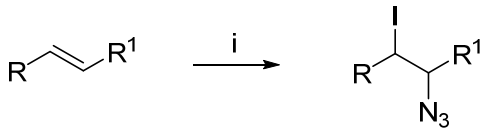
53
anti : *syn* > 99:1
Yield = 20-81%
16 examples

Scheme 9: (i) olefin (3 mmol), *p*-$TsNH_2$ (3.3 mmol), NBS (3 mmol), titanium superoxide (10 wt%), CH_2Cl_2 (20 mL), 25 ^oC, 14 h.

This section describes a new heterogeneous catalytic method for the regiospecific bromoamination of olefins **52** catalyzed by titanium superoxide using NBS (N-bromosuccinimide) as bromine source and *p*-toluene sulfonamide as the nitrogen source, occurring truly under heterogeneous conditions (**Scheme 9**). The present method has been demonstrated for several olefins (aliphatic and aromatic) with electron-donating and -withdrawing groups that underwent bromoamination in high yields and diastereoselectivity (>99:1). Bromoamination of α,β-unsaturated (R = CO_2Et, COPh, etc.) compounds were also carried out using titanium superoxide as catalyst in good to excellent yields (20-68%) in highly regiospecific and stereoselective manner. The protocol makes use of stable, reusable and readily accessible titanium superoxide as solid catalyst, which could be recovered by simple filtration.

SECTION II: $NaIO_4$–KI-NaN_3–Mediated Regioselective Azidoiodination of Alkenes

Azido iodination of alkenes constitutes an important method for introducing nitrogen functionality into a carbon skeleton leading to vinyl azides, amines and heterocycles, particularly aziridines.[23] The conventional method for synthesis of azido iodides involves the use of iodine azide reagent, which is prepared *in situ* from sodium azide and iodine chloride in polar solvent. During the course of our study on $NaIO_4$-mediated oxidative halogenations, [24] we noticed that $NaIO_4$-KI-NaN_3 combination was found to be excellent for regiospecific azidoiodination of styrene in acetic acid as solvent. This prompted us to explore the effectiveness of the $NaIO_4$-KI-NaN_3 combination in the azidoiodination of alkenes. Several alkenes **54a-l** (aliphatic, styrenic, allylic and disubstituted) underwent azidoiodinations to give the corresponding β-iodoazides **55a-l** in excellent yields (**Scheme 10**). It is interesting to note that the regiochemistry of the addition, for all the cases examined, proceeded in an *anti*-Markovnikov fashion, indicating a possible radical pathway. Internal olefins such as β-methylstyrene, cyclohexene and cinnamyl alcohol have proceeded to give products in excellent yields with diastereoselectivities reaching up to 1:4 as confirmed by their ^{1}H-NMR spectra. Terminal functionalized olefin such as allyl acetate also underwent regiospecific azidoiodination in 92% yield. However, no reactions took place in the case of conjugated alkenes with electron-withdrawing groups, which may be a limitation of this method.



54a-l **55a-l**

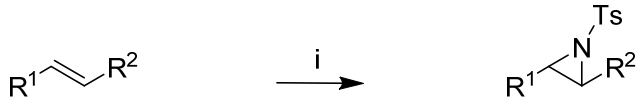
R = aryl, alkyl
R^1 = H, alkyl, CH_2OH
CH_2OAc

Yield = 70-96%
12 examples

Scheme 10: (i) alkenes (1 equiv), KI (1 equiv), $NaIO_4$ (1 equiv), NaN_3 (3 equiv), glacial AcOH, 25 °C, 2 h.

SECTION III: $NaIO_4$/LiBr-Mediated Aziridination of Olefins Using Chloramine-T

The aziridine ring is a versatile building block for organic synthesis, not only because the ring opening of aziridines provides a convenient entry to the stereoselective preparation of functionalized amino compounds but also because the exocyclic N–substituent modulates the properties and reactivity of the three membered ring.[25] Many biologically active compounds such as amino acids, β-lactam antibiotics and alkaloids have been derived from aziridines. This section describes aziridination of a variety of alkenes **56a-o** using anhydrous chloramine–T as the nitrogen nucleophile in the 1,2-aminobromination of alkenes mediated by $NaIO_4$–LiBr combination. It is a milder method that involves a reaction of $NaIO_4$/LiBr/H^+/chloramine-T combination with olefins, thus affording aziridines **57a-o** in good yields. Both electron rich and electron-deficient olefins underwent aziridination in moderate to good yields (**Scheme 11**).



56a-o **57a-o**

R^1 = aryl, alkyl, H
R^2 = alkyl, aryl, CH_2Br

Yield = 52- 81%
15 examples

Scheme 11: (i) $NaIO_4$ (30 mol%), olefin : LiBr : chloramine-T = 1:1: 2 (equiv), conc. H_2SO_4 (30 mol%), CH_3CN, 25 °C, 12 h.

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Chapter I

Cobalt-Catalyzed Phenolic Kinetic Resolution of Azido Epoxides and its Application in the Synthesis of ICI-118,551, an anti-Hypertensive Agent

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1. "Co(III)(salen)-catalyzed PKR of two stereocentered benzyloxy and azido epoxides: its application in the synthesis of ICI-118,551, an *anti*-hypertensive agent" **Karabal, P. U**.; Kamble, D. A.; Sudalai, A. *Org. Biomol. Chem*., **2014**, 12, 2349.

Section I:

Phenolic Kinetic Resolution of Racemic Azido Epoxides: A new Synthesis of Enantiomerically Pure α-Aryloxy-α'-Azido Alcohols

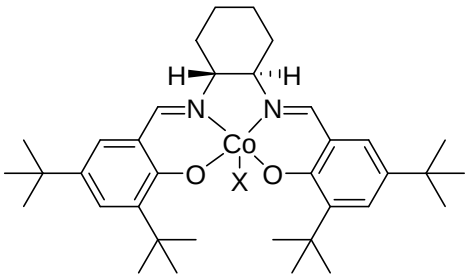
1.1.1 Introduction

The enantiomerically pure *syn*- or *anti*-1-aryloxy-3-azido 2-alcohols are valuable 'building blocks' for asymmetric synthesis of bioactive pharmaceuticals.[1] These structural units are present in numerous bioactive compounds such as erythritol,[2] an antidiabetic C4 polyol, *β*-adrenolytic drugs,[3] and broussonetine family of naturally occurring iminosugars,[4] which show potent glucosidase inhibitory activities with enormous therapeutic potential as *anti*-tumor and *anti*-HIV agents. In addition, these aryloxy azido alcohols are the direct precursors of amino alcohols and simple aziridines,[5] which are versatile intermediates in the synthesis of bioactive molecules.[6]

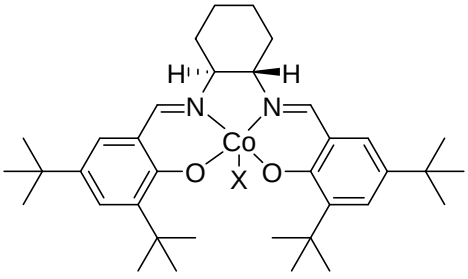
1.1.2 Phenolic Kinetic Resolution (PKR)

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[7] but more so because the ring opening of epoxides allows straight forward elaboration to useful new functionality, often with generation of new carbon-oxygen bonds. No catalytic methods have been devised for phenolic opening of terminal epoxides[8] and forcing conditions are often required for the uncatalyzed reaction, such as heating epoxide in the presence of a phenoxide salt to high temperatures in a polar solvent. These thermal methods are generally low-yielding and are particularly unsuitable for sensitive substrates. Epoxides are versatile building blocks for organic synthesis. The enantioselective ring opening of achiral epoxides by nucleophilic addition is an attractive method, which is invaluable in asymmetric synthesis. In principle, access to

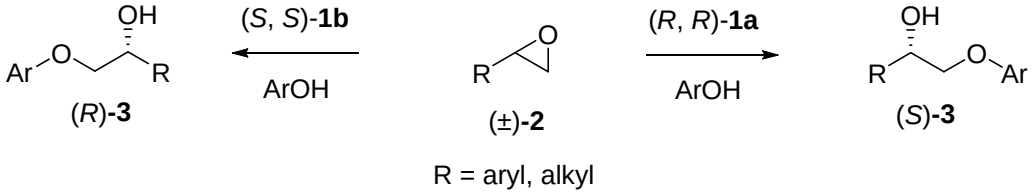
these building blocks may be provided by multi steps, including asymmetric reduction of aryloxy ketones[9] or the ring opening of enantiopure terminal epoxides with phenols and other tedious methods. Terminal epoxides are available very inexpensively as racemic mixtures and phenolic kinetic resolution is an attractive strategy for the production of optically active α-aryloxy alcohols **3**, given an economical and operationally simple method. Readily accessible synthetic catalysts (chiral cobalt-salen complexes)[10] have been used for the efficient asymmetric synthesis of α-aryloxy alcohols. This process uses phenol as the only reagent and low loadings of catalyst (0.44 mol%), and it affords highly valuable α-aryloxy alcohols in high yields with high enantiomeric enrichment. With a specific interest in devising a practical method for obtaining highly enantioenriched α-aryloxy alcohols, the following criteria must be met in order for a phenolic kinetic resolution approach to be viable: (1) The racemic epoxides must be inexpensive or easily accessible from inexpensive commercial starting materials; (2) The catalyst for the resolution must be readily available in both enantiomeric forms. In the optimal case, the catalyst would be used in small quantities in the resolution and would be recyclable; (3) The nucleophile used for the ring opening should be inexpensive and easily handled; (4) The ring-opened products must be obtained in good yield and very high enantiopurity and must be easily separated from the resolved epoxides.



(*R, R*)-**1a**, X = O-C(CF$_3$)$_3$



(*S, S*)-**1b**, X = O-C(CF$_3$)$_3$



Scheme 1: Phenolic kinetic resolution (PKR) of terminal racemic epoxide

The (salen)Co complex **1** catalyzes the efficient phenolic kinetic resolution (PKR) of a variety of terminal epoxides having one chiral centre (**Scheme 1**).[10] This new method appears to hold considerable promise with regard to meeting all of the criteria outlined above. First, racemic epoxides are generally available directly from commercial suppliers at low cost. Second, the ligands for catalyst **1** had previously been commercialized.[10] The cobalt analogues (*R*, *R*)-**1a** and (*S*, *S*)-**1b** proved equally accessible, and these are also now available in bulk. Third, phenol 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 phenol to the epoxide-catalyst mixture. Fourth, for those examples that were

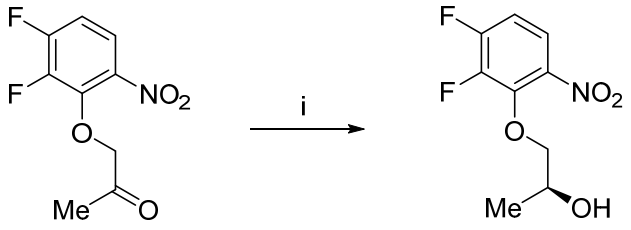
described in the preliminary report, highly enantioenriched α-aryloxy alcohols were recovered from the PKR. Finally, the PKR provided useful enantioenriched α-aryloxy alcohols including many that are otherwise not readily accessible using existing asymmetric reduction of aryloxy ketones.[9] A general mechanistic pattern has begun to emerge for asymmetric epoxide ring-opening reactions, wherein the catalyst can serve a dual role of Lewis acid activator of the epoxide and counterion for nucleophile delivery[11].

1.1.4 Review of Literature

In the literature, a few reports on the synthesis of enantiomerically pure aryloxy-3-azido-2-alcohols are available, which are described as follows.

Youseung Kim's approach (1996)[12]

Youseung Kim *et al.* have reported a new method of synthesis of chiral (*S*)-1-(2,3-difluoro-6-nitrophenoxy)propan-2-ol (**5**) directly from (2,3-difluoro-6-nitrophenoxy)-2-propanone (**4**) *via* of Bakers' Yeast reduction in MeOH/H_2O at 35 °C for 6 h that afforded **5** in 91% yield and >99% ee (**Scheme 2**).

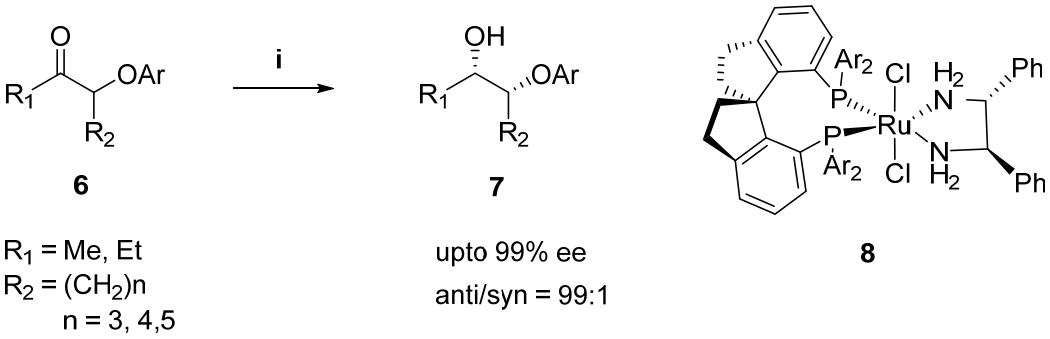


4 **5**

Scheme 2: (i) Baker's Yeast, MeOH/H_2O, 35 ^oC, 91%, >99% ee%.

Zhou's approach (2009)[13]

Zhou *et al.* have developed a highly efficient method for the synthesis of chiral β-aryloxy alcohols **7** with two adjacent stereogenic centers by chiral $RuCl_2$-SDPs/DPEN (**8**) catalyzed asymmetric hydrogenation of racemic α-aryloxydialkyl ketones **6** *via* DKR (**Scheme 3**).



6 **7** **8**

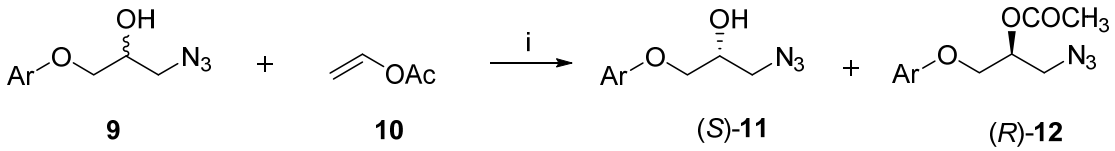
R_1 = Me, Et
R_2 = $(CH_2)n$
n = 3, 4,5

upto 99% ee
anti/syn = 99:1

Scheme 3: (i) H_2, (10 atm), [$RuCl_2$-(*S*)-SDP/(*R, R*)-DEN] (0.002 mmol), *t*-BuOK, ^{i}PrOH, 99%.

Pchelka's approach (2000)[14]

Pchelka *et al.* have reported kinetic resolution of racemic 1-azido-3-aryloxy-2-propanols **9**, which was performed using supported lipase of *Candida antarctica-B* (Novozym SP 435) in toluene at 22 ^oC with isopropenyl acetate **10** as the acyl donor to afford the optically active (*S*)-alcohols **11** and their corresponding (*R*)-acetates **12** with ee values ranging from 56 to 72% (**Scheme 4**).

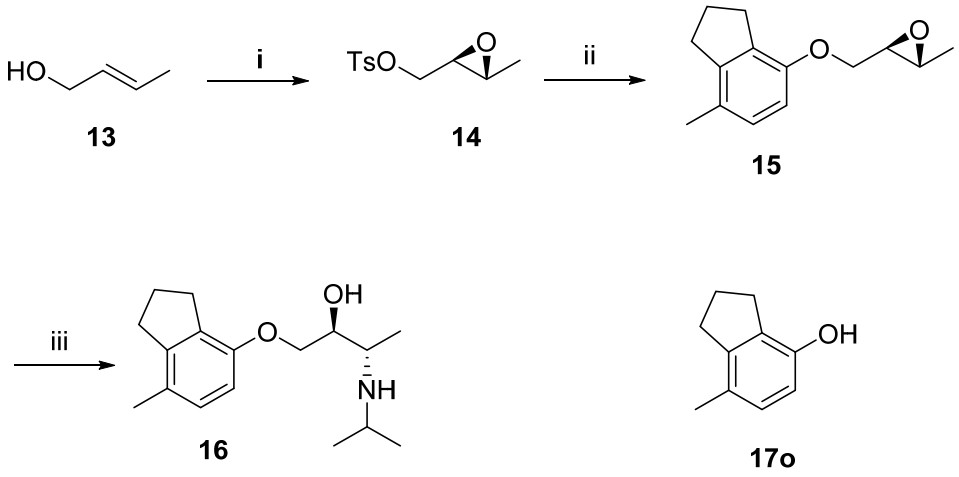


9 **10** (*S*)-**11** (*R*)-**12**

Scheme 4: (i) Navozyn SP 435, toluene, 22^oC, 17-41%.

Caddick's approach (2010)[15]

Caddick *et al*. have developed a highly efficient method for the synthesis of chiral amino aryloxy alcohol from epoxide **14**, which was prepared *via* a known one-pot Sharpless asymmetric epoxidation followed by tosylation of *trans* crotyl alcohol **13**.[16] Displacement of the tosylate **14** with the commercially available phenol derivatives **17o** using caesium carbonate as the base led to the protection of epoxide **15** in high yield with >95% ee. Ring-opening of the epoxide **15** with isopropylamine gave (2*S*, 3*S*)-ICI 118,551 in 35% yield (**16**) (**Scheme 5**).



Scheme 5: (i) (a) $Ti(O^iPr)_4$, D-(-)-DIPT, 5.5 M TBHP in decane, -20 ^oC, 24 h, CH_2Cl_2, (b) *p*-TsCl, Et_3N, cat. DMAP, CH_2Cl_2, -10 ^oC, 18 h, 50% (for two step); (ii) **17o**, Cs_2CO_3, DMF, 50 ^oC, 2.5 h, 92%; (iii) isopropylamine, MeOH, reflux, 18 h, then 6 M HCl, 35%.

1.14 Present Work

1.1.4.1 Objective

As can be seen from the above discussion, the literature methods suffer from certain limitations such as use of expensive catalysts, chiral pool resources, multiple steps or

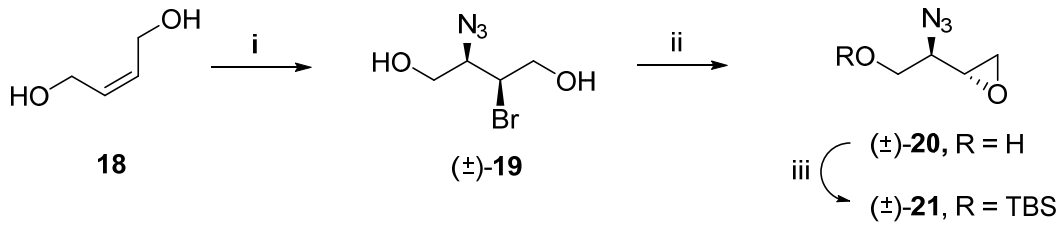
products obtained in low yields. Despite achievements, PKR has only been applied to the resolution of simple terminal epoxides with one stereocentre.[10] To the best our knowledge, study related to PKR of functionalized epoxides with two stereocentres is rare.[10]

1.1.5 Results and Discussion

In the present section, we have thus extended the scope of the applicable substrates for PKR to cover multi-functionalized molecules with two stereocentres. The aim of such an investigation is to access enantiomerically enriched *anti*- or *syn*- 1-aryloxy-3-azido-2-alcohols **25a-o** and **27a-d** (**Scheme 4** and **5**) by a direct and simple method from the respective racemic materials; thus complementing the other tedious routes. Due to their importance as 'building-blocks' for the synthesis of highly functionalized molecules, racemic azido epoxides are chosen for the study and subjected to PKR with chiral Co-catalysts. In this section, we have described a flexible, novel method that employs PKR of racemic azido epoxides to generate *anti*- or *syn*- 1-aryloxy-3-azido-2-alcohols **25a-o** and **27a-d** with two stereocentres of high optical purities in a single step.

1.1.5.1 Synthesis of racemic azido epoxides

The racemic *anti*- azido epoxides **21,** the substrates for PKR, were efficiently prepared in a three-step reaction sequence, in highly diastereoselective manner[16] from the corresponding (*Z*)-allylic alcohols **18**. Thus, *cis*-2-butene 1,4 diol **18**, was subjected to azidobromination in presence of NBS and NaN_3 to give *anti*-azido bromides, (±)-**19** in 89% yields (**Schemes 6**).



Scheme 6: (i) NBS, NaN_3, CH_3CN: water (4: 1), 0 to 25 °C, 3 h, 89%; (ii) NaOH powder, THF, 2 h, 84%; (iii) TBSCl, imid., CH_2Cl_2, 25 °C, 2.5 h, 76%.

The formation of azido bromide, (±)-**19** was confirmed from ^1H and ^{13}C NMR spectroscopy. The ^1H NMR spectrum of **19** showed a typical signal at δ 4.12-4.20 (m, 1H) for methine (-CH-N_3) proton.

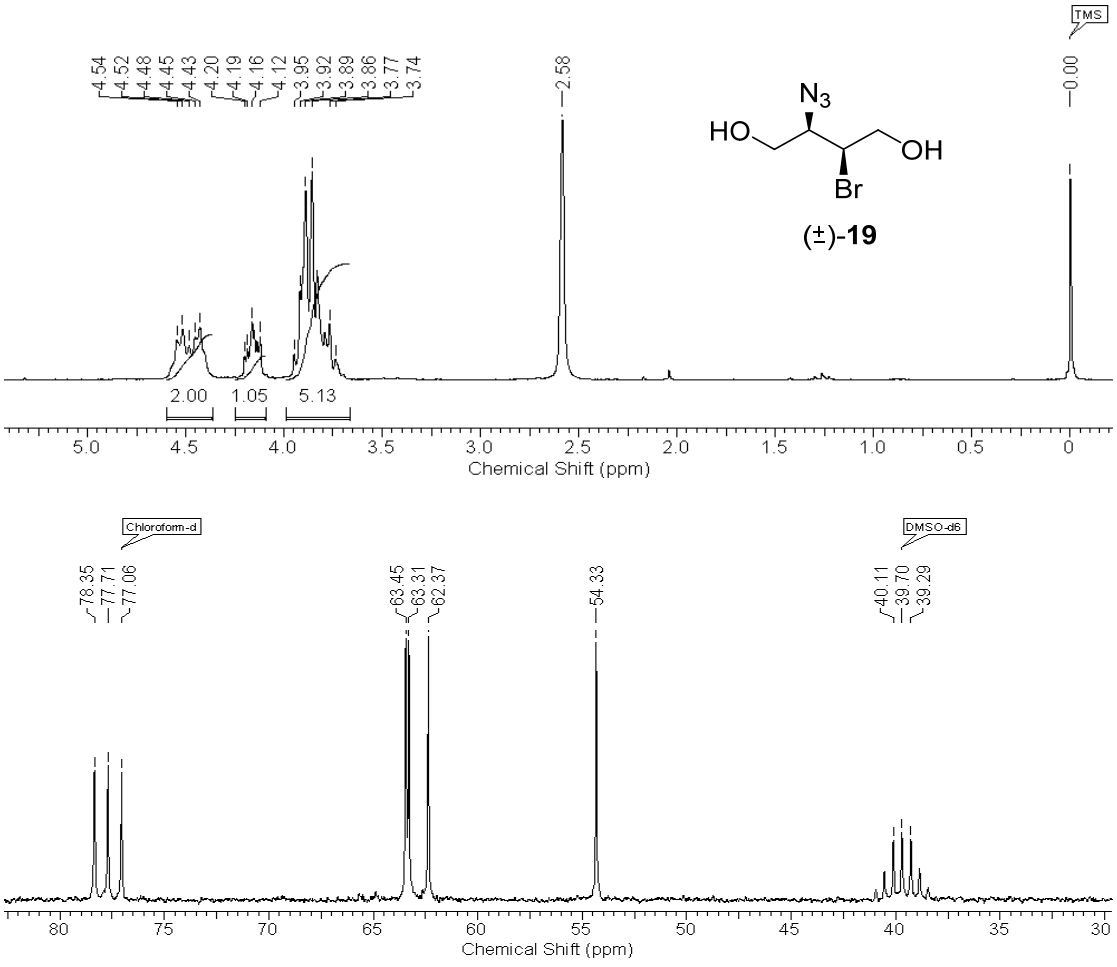


Fig. 1: ^1H and ^{13}C NMR spectra of *anti*-azido bromide (±)-**19**

Its ^{13}C NMR showed a typical carbon signal at δ 54.3 due to carbon attached to bromo group (**Fig. 1**).

The bromo azide **19** was readily transformed into racemic *anti*-azido epoxide (±)-**20** (84% yield) on treatment with base (NaOH, dry THF, 0 ^{o}C). The formation of epoxide was confirmed by ^{1}H and ^{13}C NMR spectroscopy. The ^{1}H NMR spectrum of **20** showed proton signals at δ 2.82-2.90 (m, 2H) and 3.47-3.49 (m, 1H) corresponding to methylene and methine protons of epoxide ring respectively. Its ^{13}C NMR showed two typical carbon signals at δ 44.8 and 50.6 due to carbons of epoxide ring (**Fig. 2**).

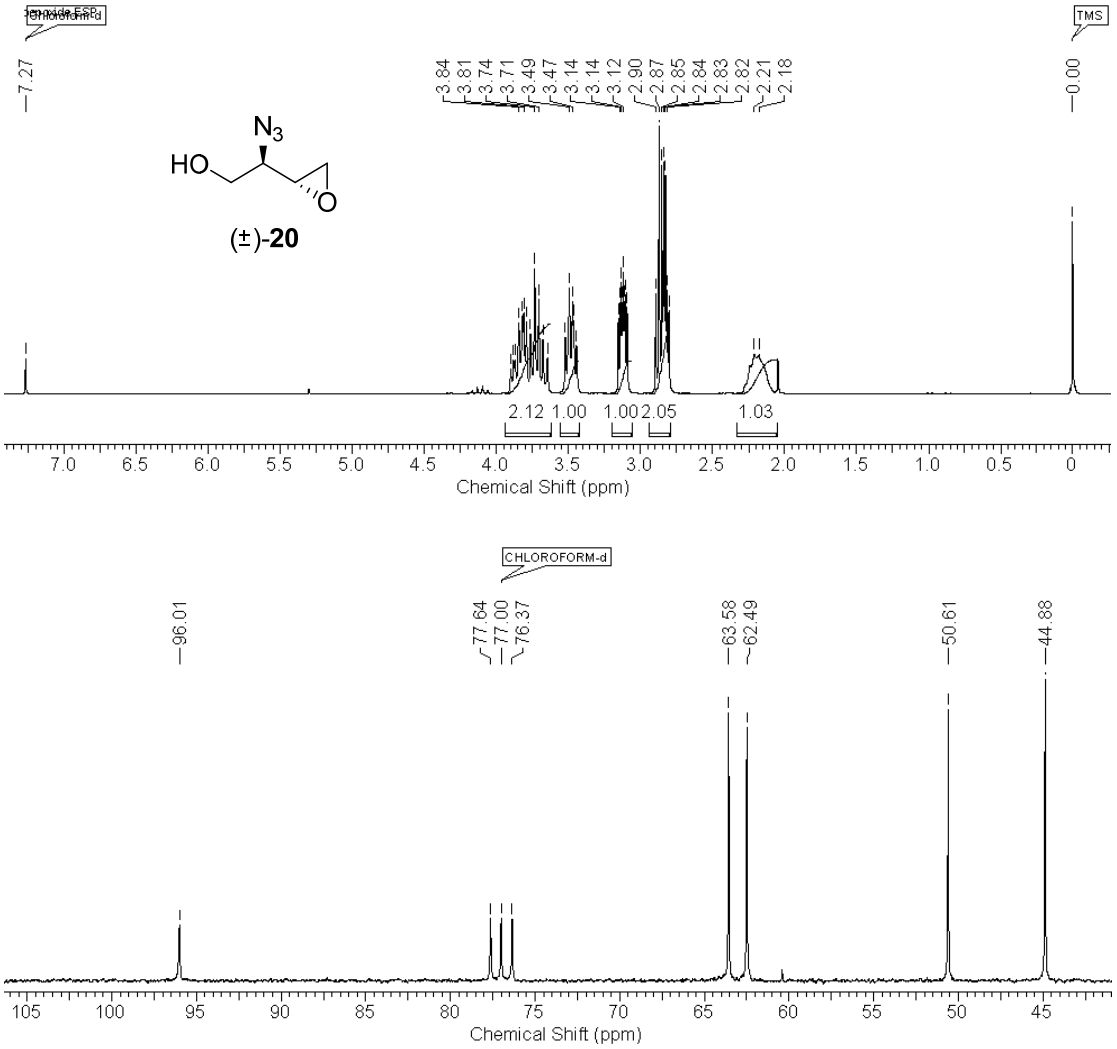


Fig. 2: ^{1}H and ^{13}C NMR spectra of *anti*-azido epoxide (±)-**20**

The protection of primary alcohol (±)**-20** with TBS ether was carried out to give TBS protected *anti*-azido epoxide, (±)-**21** in 76% yield. The ^{1}H NMR spectrum of (±)-**21** showed two siglets at δ 0.10 (s, 6H) and 0.96 (s, 9H) due to methyl protons (Si**Me$_2$** and Si**Me$_3$**) of OTBS group. Its ^{13}C NMR showed two typical signals at δ -5.5 and 25.7 due to methyl carbons of OTBS group (Si**Me$_2$** and Si**Me$_3$**) respectively (**Fig. 3**).

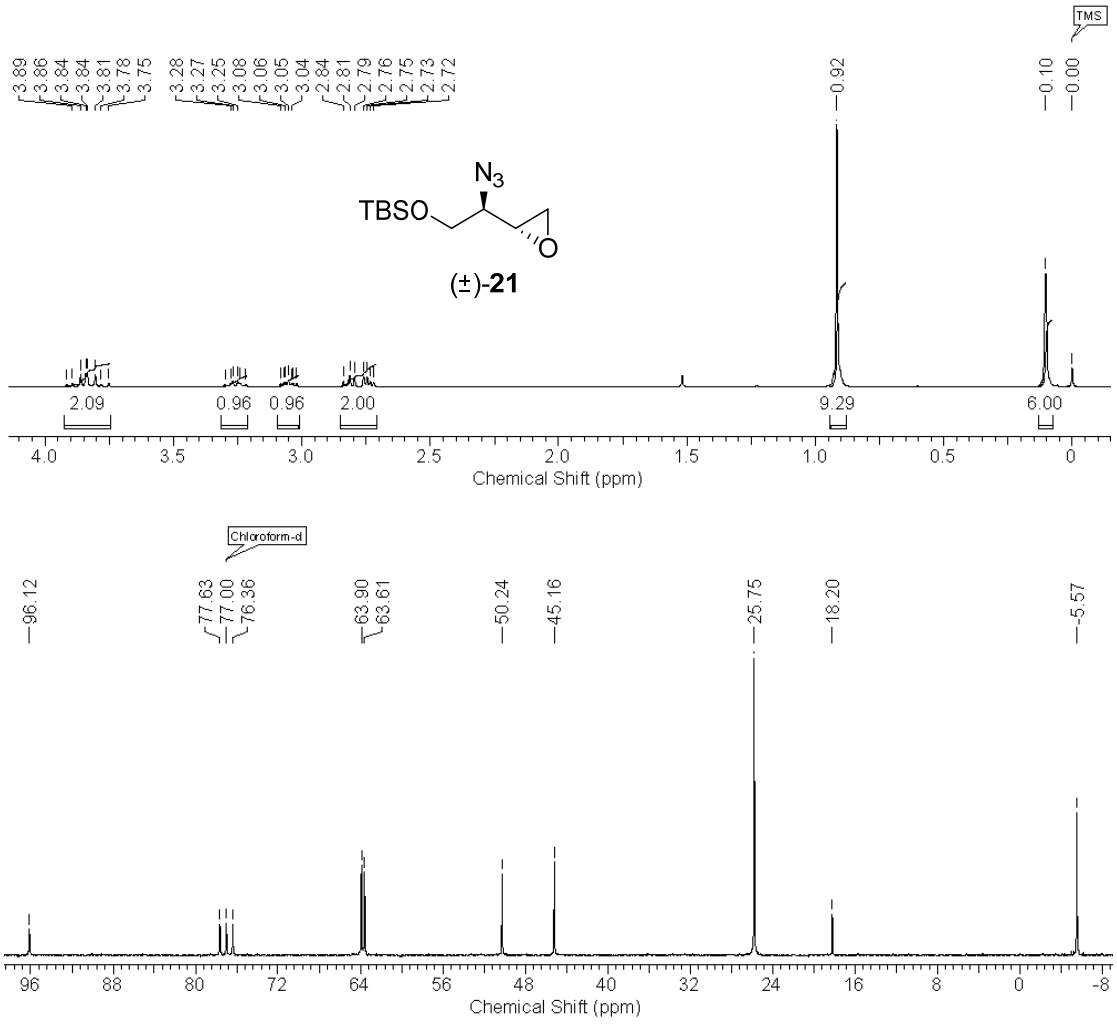
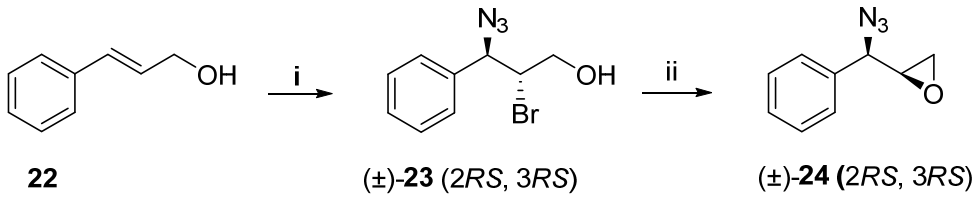


Fig. 3: ^{1}H and ^{13}C NMR spectra of TBS protected *anti*-azido epoxide (±)-**21**

Similarly, racemic *syn*-azido epoxide **24**, the substrates for PKR, was efficiently prepared in a two-step reaction sequence, in highly diastereoselective manner[16] from the corresponding (*E*)-allylic alcohol **22**. Thus, cinnamyl alcohol **22** was subjected to azidobromination in presence of NBS and NaN_3 to give *anti*-azido bromide, (±)-**23** in 70% yield (**Scheme 7**).



22 (±)-**23** (2*RS*, 3*RS*) (±)-**24** (2*RS*, 3*RS*)

Scheme 7: (i) NBS, NaN_3, CH_3CN:water (4:1), 0-25 °C, 3 h, 70%;
(ii) LiOH, THF:water (4:1), 0 25 °C, 3 h 75%.

The formation of azido bromide, (±)-**23** was confirmed from ^1H and ^{13}C NMR spectroscopy. The ^1H NMR spectrum of (±)-**23** showed typical signals at δ 4.19-4.26 (m, 1H) and 4.87 (d, J = 8.5 Hz, 1H) for bromo methine (-C**H**-Br) and azido methine (Ar-C**H**-N_3) protons respectively. Its ^{13}C NMR showed a typical signal at δ 66.8 due to benzylic carbon attached to azide group (**Fig. 4**).

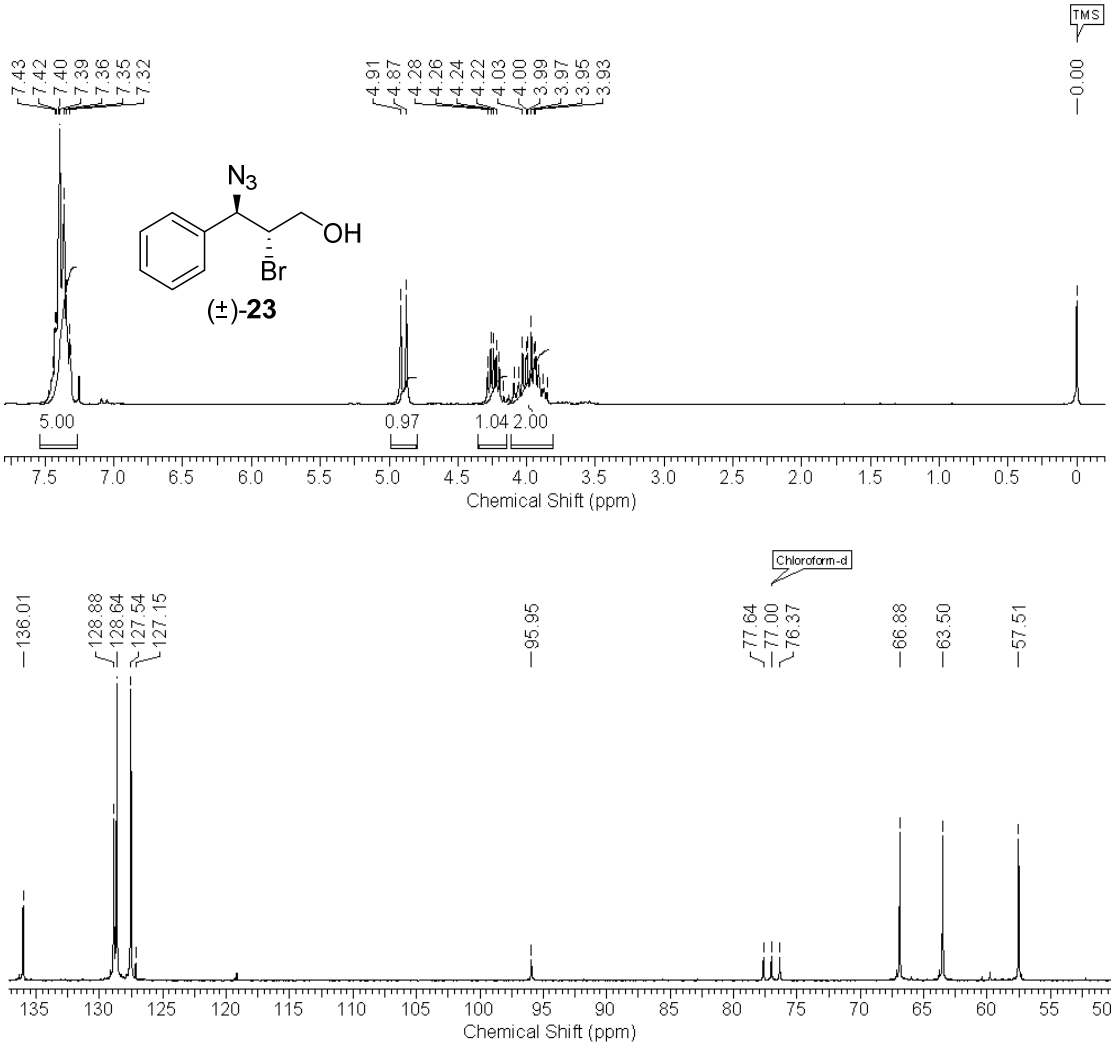


Fig. 4: ^{1}H and ^{13}C NMR spectra of azido bromide (±)-**23**

Azido bromide, (±)-**23** was then subjected to base treatment [LiOH, THF: water (4:1)] to give *syn*-azido epoxide, (±)-**24** in 75% yield. The formation of *syn*-azido epoxides, (±)-**24** was confirmed from ^{1}H and ^{13}C NMR spectroscopy. The ^{1}H NMR spectrum of *syn*-azido epoxide, (±)-**24** showed typical proton signals at δ 2.73-2.83 (m, 2H) and 3.25-3.28 (m, 1H) indicating methylene and methine protons respectively. Its ^{13}C NMR showed two characteristic carbon resonance signals at δ 44.6 and 54.6 due to carbons of the epoxide ring (**Fig. 5**).

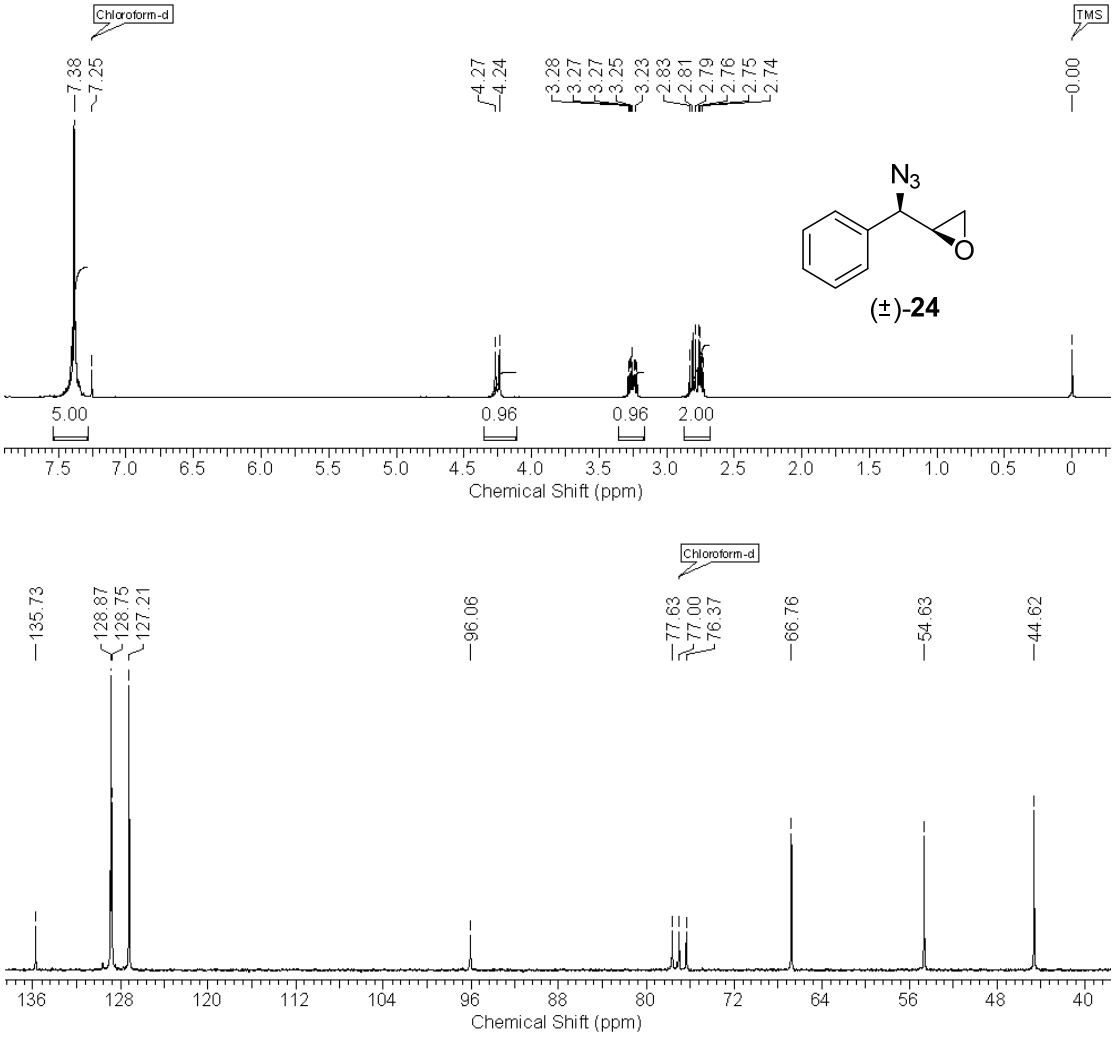
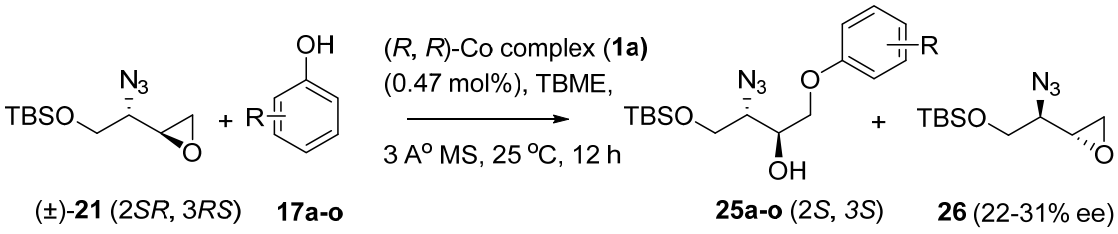


Fig. 5: ^{1}H and ^{13}C NMR spectra of *syn*-azido epoxide (±)-**24**

1.1.5.2 PKR of racemic azido epoxides

The relative stereochemistry of azido and epoxide groups is established prior to the PKR step itself and in this way a simple asymmetric reaction can be used to obtain the key enantiomerically pure *anti*-1-aryloxy-3-azido-2-alcohols **25a-o**. When the PKR of racemic *anti*- azido epoxide **21** was performed with (*R*, *R*)- Co(III)-salen complex **1a** (0.044 equiv) and phenol (1 equiv) in *tert*-butyl methyl ether (TBME), the corresponding *anti*-1-aryloxy-3-azido-2-alcohol **25a** was isolated in 65% yield and 92% ee (entry a, **Table 1**). The PKR can be conducted at low temperatures (-20 ^{o}C),

although yields obtained were found to be low. Further, the stereoselectivities in the PKR displayed a strong epoxide concentration dependence, requiring at least 2.2 equivalents of epoxide to realize excellent enantioselectivity (**Scheme 8**).



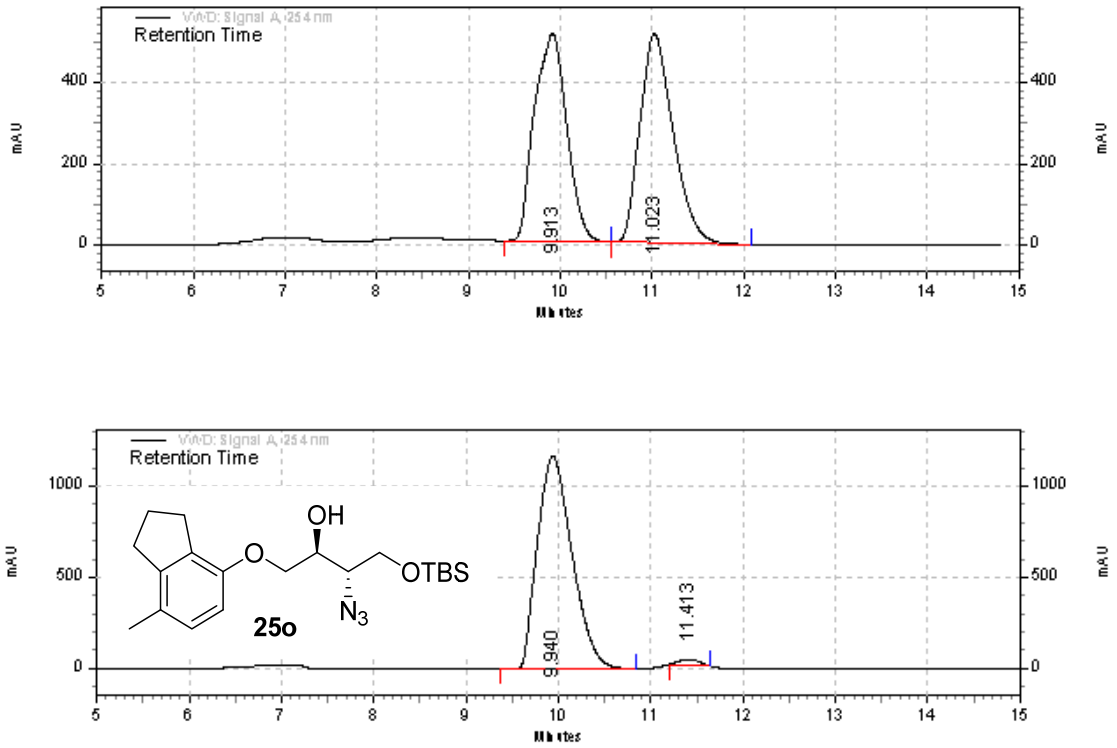
Scheme 8: PKR of *anti*-azido epoxides with phenols as nucleophile

Encouraged by this result, a variety of phenolic substrates were then screened for the PKR process that led to the isolation of **25a-o** with complete regiocontrol. The results of such a study are shown in **Table 1**. In the case of azido epoxides, a wide range of substituted phenols bearing both electron-donating and electron-withdrawing groups reacted efficiently, delivering the corresponding aryloxy alcohols **25a-o** in good to excellent yields and enantioselectivity (entries a-o), Additionally, *ortho* substituted phenol displayed poor reactivity (entry d), while 1-naphthol failed to undergo reaction. The enantiomeric excess of *anti*-1-aryloxy-3-azido-2-alcohol **25a-o** were determined from chiral HPLC analysis (**Fig. 6**).

Table 1: Co-catalyzed PKR of *anti*-azido epoxide **21** with phenols **17a-o**

	Phenols	*anti*-azido alcohols (**25a-o)**	
entry	R **17a-o**	yield (%)[a]	ee (%)[b]
a	H	65	92
b	2-CH_3	35	94
c	3-CH_3	70	95
d	4-CH_3	72	99
e	4-Bu^t	76	99
f	3-OMe	60	93
g	4-CN	87	98
h	4-F	72	68
i	4-Cl	90	97
j	4-Br	86	97
k	2, 5-Cl_2	89	95
l	4-$COCH_3$	88	98
m	4-CO_2Me	81	94
n	4-NO_2	92	96
o	7-Me-4-indanol	75	99

[a]Isolated yield after column chromatographic purification *w.r.t.* phenol; [b] determined f chiral HPLC analysis.



Retention Time	Area	Area %	Height	Height %
9.940	514024562	99.35	99588723	99.40
11.413	3102764	0.65	522812	0.60
Totals	517127326	100.00	20111535	100.00

Column: Chiracel OD-H (4.6X250 nm), Mobile Phase :IPA: n-Hexane (5:95)
Wavelength: 254 nm, Flow rate : 0.5 ml/min

Fig. 6: HPLC chromatogram of azido alcohol **25o**

The formation of *anti*-1-aryloxy-3-azido-2-alcohols **25a-o** was confirmed from ^{1}H and ^{13}C NMR spectroscopy. For example, the ^{1}H NMR spectrum of **25i** exhibited characteristic multiplets at δ 6.78-6.82 (m, 2H) and 7.36-7.41 (m, 2H) due to aromatic protons. Its ^{13}C NMR spectrum also showed two typical carbon signals at δ 113.6 and 157.3 indicating the presence of carbon attached to bromine group and phenolic carbon respectively (**Fig. 7**).

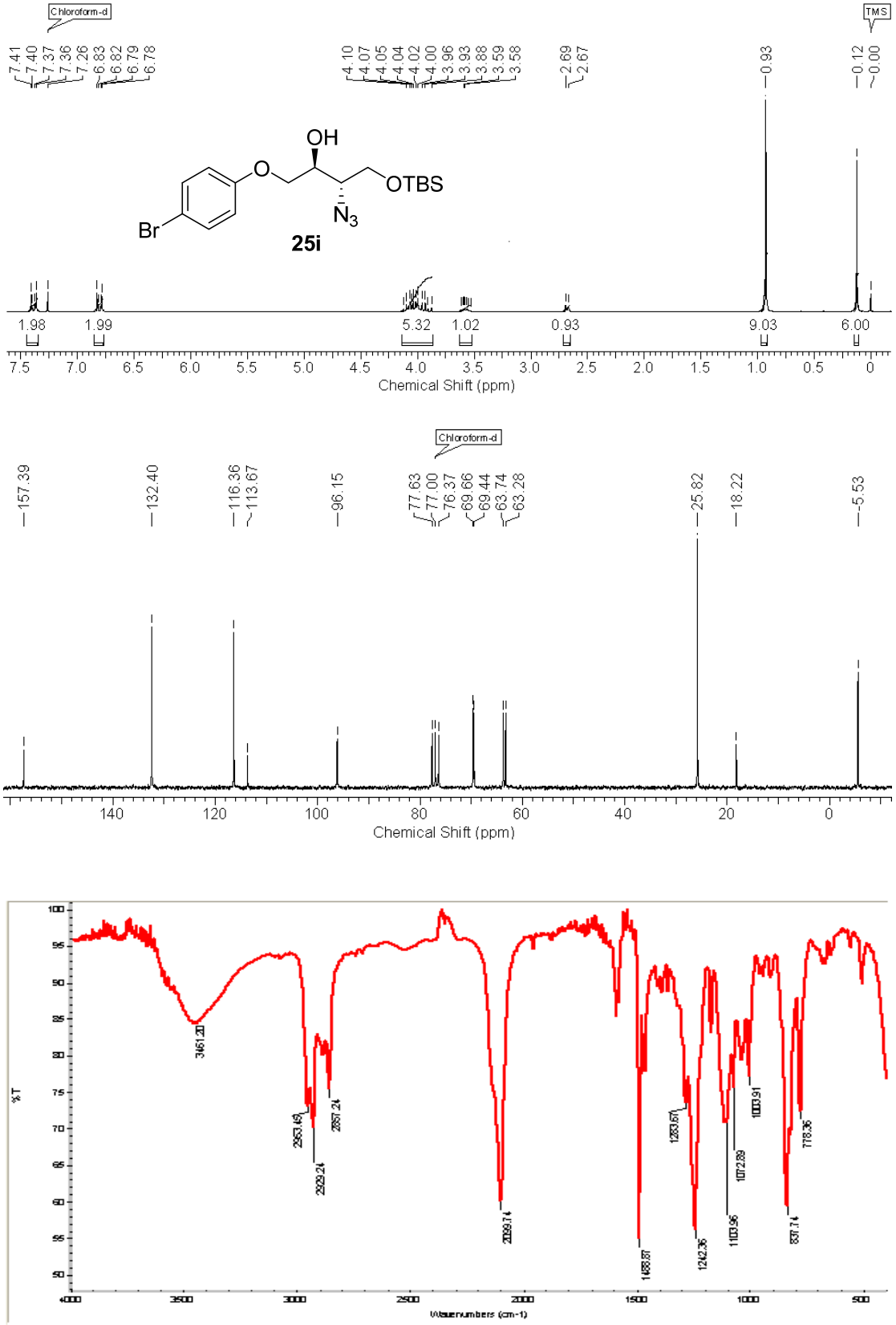
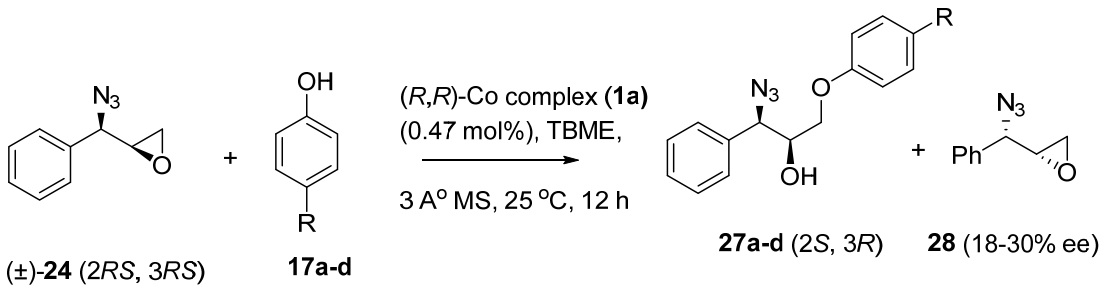


Fig. 7: ^{1}H , ^{13}C NMR and IR spectra of *anti*-1-aryloxy-3-azido-2-alcohol **25i**

Azide functionality in 1-aryloxy-3-azido-2-alcohol (**25i**) was further confirmed from the IR spectrum, which showed a characteristic strong absorption band at υ_{max} 2099 cm^{-1} (**Fig. 7**).

Similarly, the racemic *syn*- azido epoxide **24** was subjected to PKR under identical reaction conditions that produced the corresponding enantiopure *syn*- products **27a-d** in high isolated yields and ees (**Scheme 9**). The results of this study are presented in **Table 2**.



Scheme 9: PKR of *syn*-azido epoxide with phenol as nucleophile

Table 2: Co-catalyzed PKR of *syn*-azido epoxide **24** with phenols **17a-d**

	Phenols	*syn*- azido alcohols **27a-d**	
entry	R **17a-d**	yield (%)[a]	ee (%)[b]
a	$COCH_3$	88	93
b	CO_2Me	96	93
c	NO_2	90	94
d	Bu^t	89	94

[a]Isolated yield after column chromatographic purification *w.r.t.* phenol; [b] determined by chiral HPLC analysis.

The formation of *cis*-1-aryloxy-3-azido-2-alcohols (**27a-d**) was confirmed from ^{1}H and ^{13}C NMR spectroscopy. For example, the ^{1}H NMR spectrum of **27c** showed typical multiplets at δ 6.88-6.92 (m, 2H) and 8.16-8.21 (m, 2H) due to aromatic protons *ortho* to oxygen and bromine atoms respectively. Its ^{13}C NMR spectrum showed characteristic two signals at δ 141.8 and 163.1 due to carbons attached to nitro group and phenolic carbon respectively (**Fig. 8**).

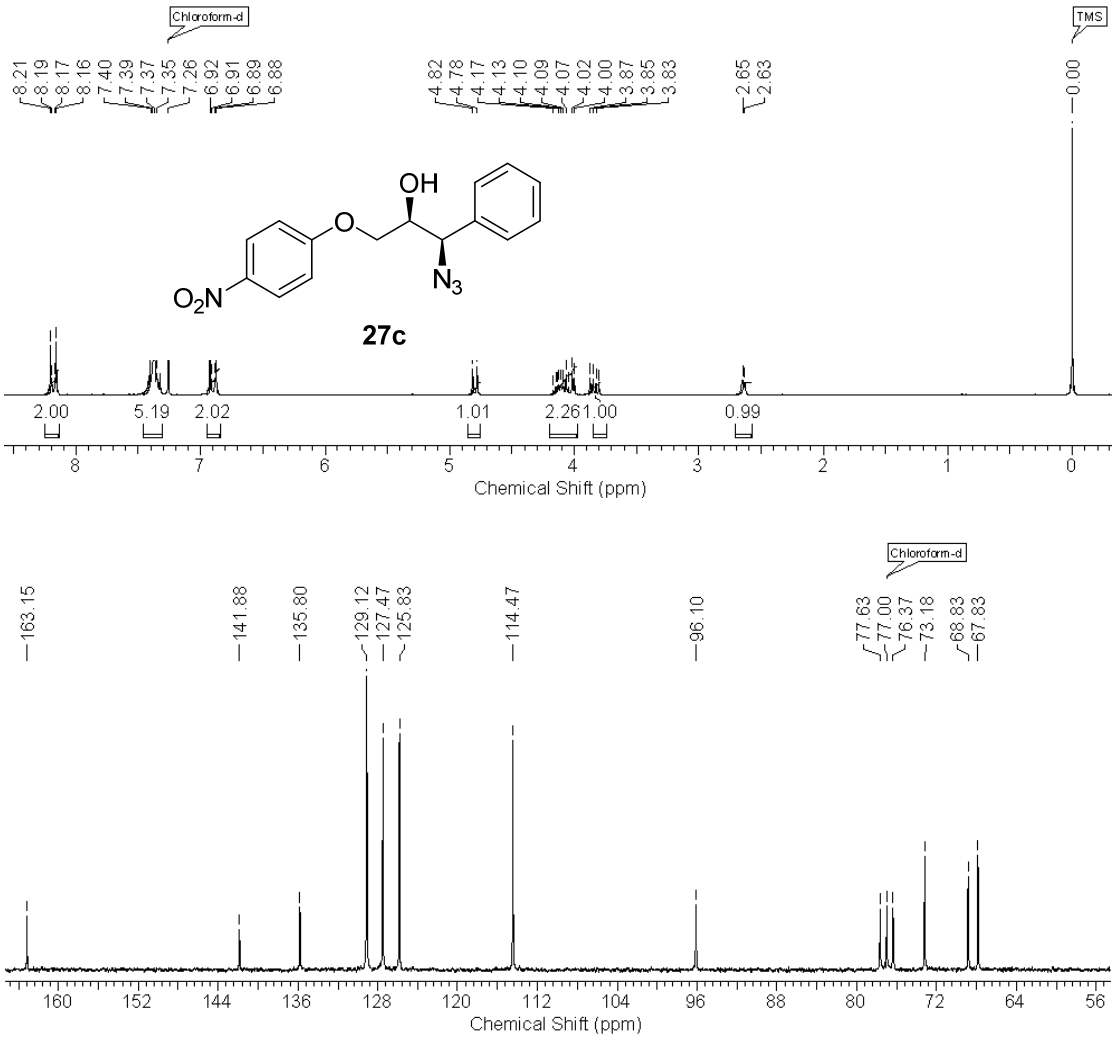


Fig. 8: ^{1}H and ^{13}C NMR spectra of *cis*-1-aryloxy-3-azido-2-alcohol **27c**

1.1.6 Conclusion

In conclusion, the (salen) Co(III)-catalyzed PKR of racemic azido epoxides provides a highy practical route to enantiopure *anti*- or *syn* - α-aryloxy α'-azido alcohols (**25a-o** and **27a-d**) in a single step. The reaction is convenient to carry out under mild conditions. We believe that this PKR strategy will find applications in the field of asymmetric synthesis of bioactive molecules owing to the flexible nature of synthesis of racemic azido epoxides and the ready availability of cobalt salen catalysts in both enantiomeric forms.

1.1.7 Experimental Section

A general experimental procedure for the preparation of racemic azido bromides (19 and **23):**

A mixture of allylic alcohols **18** or **22** (13 mmol) and NaN_3 (1.6 g, 26 mmol) was taken in CH_3CN:H_2O (30:10 mL) and NBS (2.3 g, 15.6 mmol) was added slowly to it *via* solid addition funnel, with stirring at 0 °C and the progress of the reaction was monitored by TLC. After completion of the reaction, it was diluted with EtOAc (30 mL) and washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude product, which was purified by column chromatography [silica gel (60-120 mesh) and petroleum ether: EtOAc (90:10) as an eluent] to afford pure products.

2-Azido-3-bromobutane-1, 4-diol (19)

Yield: 89%, colorless solid, **mp:** 52 °C; **IR:** (neat, cm^{-1}): υ_{max} 1035, 1267, 2104, 3361; **^{1}H NMR** (200 MHz, $CDCl_3$ + DMSO-d_6): δ 3.74-3.95 (m, 5H), 4.12-4.20 (m, 1H), 4.43-4.54 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$ + DMSO-d_6): δ 54.3, 62.3, 63.3, 63.4; **Anal**. Calcd for $C_4H_8BrN_3O_2$ requires C, 22.87; H, 3.84; N, 20.01; found: C, 22.80; H, 3.82; N, 20.06%.

3-Azido-2-bromo-3-phenylpropane-1-ol (23):

Yield: 70%; yellow thick liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 740, 1109, 1265, 1471, 2103, 2931, 3390; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.16 (brs, 1H), 3.98-4.10 (m, 2H), 4.20-4.29 (m, 1H), 4.68 (d, *J* = 8.5 Hz, 2H), 7.32-7.48 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 57.7, 63.1, 67.1, 127.5, 128.7, 129.0, 131.6; **Anal.** Calcd for $C_9H_{10}BrN_3O$ requires C, 42.21; H, 3.94; N, 16.41; found: C, 42.30; H, 3.92; N, 16.43%.

2-Azido-2-(oxiran-2-yl)ethanol (20)

Azido bromide **19** (10 mmol) was taken up in THF (20 mL) and NaOH powder (0.4 g, 10 mmol) was added slowly to it with stirring at 0 °C for 2 h (monitored by TLC). The reaction mixture was diluted with EtOAc (25 mL) and water (30 mL). The organic layer was separated and the aq. layer was 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 purified by column chromatography [silica gel (60-120 mesh) and petroleum ether:EtOAc (90:10) as an eluent] to give **20** in 84% yield.

Yield: 84%, colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1264, 2104, 2931, 3383; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.18 (br s, 1H), 2.80-2.90 (m, 2H), 3.09-3.15 (m, 1H), 3.44-3.52 (m, 1H), 3.65-3.90 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 44.2, 49.9, 61.8, 62.9; **Anal**. Calcd for $C_4H_7N_3O_2$ requires C, 37.21; H, 5.46; N, 32.54; found: C, 37.28; H, 5.56; N, 32.46%.

2-(Azidophenylmethyl)-oxirane (24):

Azido bromide **23** (13 mmol) was taken up in THF:H_2O (20:5 mL) and LiOH powder (375 mg, 15.6 mmol) was added slowly to it with stirring at 0 °C for 2 h (monitored by TLC). The reaction mixture was diluted with EtOAc (25 mL) and water (30 mL). The organic layer was separated and the aq. layer was 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 (60-120 mesh) and petroleum ether:EtOAc (90:10) as an eluent] to give *syn*-azido epoxide **24** in 75% yields.

Yield: 75%; yellow viscous liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 758, 860, 1125, 1250, 1460, 1493, 1602, 2105, 2932, 3025; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.73-2.84 (m, 2H), 3.23-3.29 (m, 1H), 4.25 (d, *J* = 6.1 Hz, 1H), 7.35-7.47 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 44.6, 54.6, 66.8, 127.2, 128.8, 128.9, 135.7; **Anal.** Calcd for $C_9H_9N_3O$ requires C, 61.70; H, 5.18; N, 23.99; found: C, 61.79; H, 5.14; N, 23.90%.

2-Azido-2-(oxiran-2-yl)ethoxy)(*tert*-butyl)dimethylsilane (21)

Azido epoxide **19** (8 g, 62.01mmol) was taken up in dry CH_2Cl_2 (80 mL) followed by the addition of imidazole (5.07 g, 74.41 mmol) and *tert*-butyl dimethyl silyl chloride (11.21 g, 74.41 mmol). It was stirred for 0.5 h and quenched with aq. $NaHCO_3$ solution (20 mL). The aq. layer was extracted with CH_2Cl_2 (2 × 30 mL), dried over anhyd. Na_2SO_4 and concentrated *in vacuo* to give the crude product, which was purified by column purified by column chromatography [silica gel (60-120 mesh) and petroleum ether:EtOAc (80:20) as an eluent] to give the product **21** as thick liquid in pure form.

Yield: 76%; yellow liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 740, 839, 1127, 1250, 1463, 1493, 1602, 2106, 2932, 3025; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.09 (s, 6H), 0.90 (s, 9H), 2.73 (dd, *J* = 5.0, 2.6 Hz, 1H), 2.80 (dd, *J* = 5.0, 3.6 Hz, 1H), 3.01-3.07 (m, 1H), 3.21-3.29 (m, 1H), 3.74-3.90 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.5, 18.2, 25.7, 45.2, 50.2, 63.5, 63.9; **Anal.** Calcd for $C_{10}H_21N_3O_2Si$ requires C, 49.35; H, 8.70; N, 17.27; found: C, 49.20; H, 8.75; N, 17.30%.

General procedure for the phenolic kinetic resolutions of *anti*- and *syn*- aryloxy azidoalcohols (see **Schemes 8 and 9)**

Preparation of (salen)Co[OC(CF$_3$)$_3$] (1)

Solid (salen)Co(II) complex (0.0302 g, 0.5 mmol) was added in one portion to a stirred solution of perfluoro *tert*-butyl alcohol (1.18 g, 5 mmol) in CH_2Cl_2 (5 mL). The resulting black solution was stirred for 45 min, and the solution was concentrated *in vacuo* to afford a black powder.

To a stirred solution of (*R*, *R*)-(salen) Co[OC(CF$_3$)$_3$](H$_2$O) (**1a**) (86 mg, 0.1 mmol), molecular sieve (100 mg, 3 A^o) and racemic *anti*- or *syn*- azido epoxide (**21** or **24**) (5 mmol), in *tert*-butyl methyl ether (0.15 mL), phenol (2.25 mmol) (**17**) was added at 25 ^{o}C. The reaction was stirred for 6-15 h until all the phenol was converted (as monitored by TLC). Solvent was removed under reduced pressure. The crude product was purified by column chromatography over silica gel (eluting with pet. ether/EtOAc) to give optically pure *anti*- or *syn*-1-aryloxy-3-azido or benzyloxy-2-alcohols in pure form. The enantiomeric purity was determined by chiral HPLC analysis.

(2*S*, 3*S*)-3-Azido-4-(*tert*-butyldimethylsiloxy)-1-phenoxybutan-2-ol (25a)

Yield: 65%; gum; **[α]$_D^{25}$** +16 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 690, 752, 837, 1042, 1108, 1243, 1497, 1599, 2099, 2857, 2929, 2953, 3460; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.12 (s, 6H), 0.93 (s, 9H), 2.7 (d, *J* = 5.0 Hz, 1H), 3.88-4.17 (m, 5H), 6.89-7.00 (m, 3H), 7.29-7.33 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.5, 18.2, 25.8, 63.4, 63.7, 69.0, 69.6, 114.5, 121.4, 129.5, 158.2; **Optical purity**: 92% ee determined by HPLC analysis (Chiral OD-H column, *n*-hexane/ 2-propanol (95:5), 0.5 mL/min, 254 nm) Retention time: t $_{major}$ = 14.36 and t $_{minor}$ = 19.88 min.; **HRMS** (ESI) m/z Calcd $C_{16}H_{27}N_3O_3NaSi$ $[M + Na]^+$: 360.1714; found: 360.1713.

(2*S*, 3*S*)-1-(*o*-tolyloxy)-3-azido-4-(*tert*-butyl-dimethyl siloxy)butan-2-ol (25b)

Yield: 35%; gum; $[\alpha]_D^{25}$ +15 (*c* 1.0, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 774, 838, 1109, 1172, 1258, 1289, 1462, 1500, 1603, 2098, 2857, 2884, 2929, 2953, 3451; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.12 (s, 6H), 0.93 (s, 9H), 2.24 (s, 3H), 2.63-2.65 (d, *J* = 5.4 Hz, 1H), 3.57-3.65 (m, 1H), 3.88-4.15 (m, 5H), 6.81-6.91 (m, 2H), 7.11-7.15 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.5, 16.3, 18.2, 25.8, 29.7, 63.6, 63.9, 69.0, 69.8, 111.3, 121.1, 126.6, 126.9, 130.8, 156.3; **Optical purity**: 94% ee determined by HPLC analysis (Chiral OJ-H column, *n*-hexane/ 2-propanol (95:5), 0.5 mL/min, 210 nm) Retention time: t_{minor} = 20.71 and t_{major} = 24.23 min.; **HRMS** (ESI) m/z Calcd $C_{17}H_{29}N_3O_3NaSi$ $[M + Na]^+$: 374.1870; found: 374.1865.

(2*S*, 3*S*)-1-(*m*-tolyloxy)-3-azido-4-(*tert*-butyl-dimethyl siloxy)butan-2-ol (25c)

Yield: 70%; gum; $[\alpha]_D^{25}$ +16 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 774, 838, 1109, 1172, 1258, 1289, 1462, 1500, 1603, 2098, 2857, 2884, 2929, 2953, 3451; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.12 (s, 6H), 0.93 (s, 9H), 2.33 (s, 3H), 2.65-2.68 (d, *J* = 4.84 Hz, 1H), 3.56-3.62 (m, 1H), 3.67-4.15 (m, 5H), 6.69-6.80 (m, 3H), 7.12-7.20 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.5, 18.2, 21.5, 25.8, 63.5, 63.80, 69.0, 69.6, 111.5, 115.4, 122.2, 129.3, 139.5, 158.3; **Optical purity**: 95% ee determined by HPLC analysis (Chiral OJ-H column, *n*-hexane/ 2-propanol (95:5), 0.5 mL/min, 210 nm) Retention time: t_{minor} = 22.71 and t_{major} = 28.23 min; **HRMS** (ESI) m/z Calcd $C_{17}H_{29}N_3O_3NaSi$ $[M + Na]^+$: 374.1870; found: 374.1868.

(2*S*, 3*S*)-1-(*p*-Tolyloxy)-3-azido-4-(*tert*-butyldimethylsiloxy)butan-2-ol (25d)

Yield: 72%; gum; $[\alpha]_D^{25}$ +28 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 777, 838, 1047, 1109, 1172, 1258, 1289, 1462, 1490, 1586, 1603, 2098, 2857, 2284, 2929, 2953, 3451; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.12 (s, 6H), 0.92 (s, 9H), 2.29 (s, 3H), 2.67 (d, *J* = 4.9 Hz, 1H) 3.55-3.60 (m, 1H), 3.86-4.08 (m, 5H), 6.8 (d, *J* = 8.5 Hz, 2H), 7.05-

7.09 (d, *J* = 8.4 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.5, 18.2, 20.5, 25.8, 63.5, 63.8, 69.2, 69.6, 114.4, 130.0, 130.5, 156.2; **Optical purity**: 99% ee determined by HPLC analysis (Chiral OJ-H column, *n*-hexane/ 2-propanol (95:5), 0.5 mL/min, 210 nm) Retention time: t_{minor} = 23.71 and t_{major} = 25.23 min.; **HRMS** (ESI) m/z Calcd $C_{17}H_{29}N_3O_3NaSi$ $[M + Na]^+$: 374.1870; found: 374.1874.

(2*S*, 3*S*)-1-(4-*tert*-Butylphenoxy)-3-azido-4-(*tert*-butyldimethylsiloxy)butan-2-ol (25e)

Yield: 76%; gum; **$[\alpha]_D^{25}$** +12 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 777, 836, 1113, 1243, 1513, 2095, 2858, 2929, 2956, 3460; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.12 (s, 6H), 0.92 (s, 9H), 1.30 (s, 9H), 2.64 (d, *J* = 5.2 Hz, 1H), 3.53-3.62 (m, 1H), 3.87-4.13 (m, 5H), 6.82-6.86 (m, 2H), 7.27-7.31 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.4, 18.2, 25.8, 31.6, 34.1, 63.5, 63.8, 69.1, 69.6, 114.1, 126.3, 144.1, 156.0; **Optical purity**: 99% ee determined by HPLC analysis (Chiral OJ-H column, *n*-hexane/ 2-propanol (95:5), 0.5 mL/min, 210 nm) Retention time: t_{major} = 21.61 and t_{minor} = 29.29 min.; **HRMS** (ESI) m/z Calcd $C_{20}H_{35}N_3O_3SiNa$ $[M + Na]^+$: 416.2340; found: 416.2346.

(2*S*, 3*S*)-1-(3-Methoxyphenoxy)-3-azido-4-(*tert*-butyldimethylsiloxy)butan-2-ol (25f)

Yield: 60%; gum; **$[\alpha]_D^{25}$** +18 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 771, 839, 1112, 1170, 1254, 1283, 1436, 1511, 1606, 1716, 2099, 2857, 2930, 3471; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.12 (s, 6H), 0.93 (s, 9H), 2.7 (d, *J* = 3.1 Hz, 1H), 3.56-3.59 (m, 1H), 3.78 (s, 3H), 3.90-3.93 (m, 1H), 4.03 (br s, 1H), 4.02-4.12 (m, 3H), 6.46-6.53 (m, 3H), 7.19 (t, *J* = 8.31, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.4, 18.3, 25.8, 55.2, 63.5, 63.8, 69.2, 69.7, 101.2, 106.7, 107.1, 130.0, 159.5, 160.9; **Optical purity**: 93% ee determined by HPLC analysis (Chiral OJ-H column, *n*-hexane/ 2-propanol (95:5), 0.5

mL/min, 210 nm) Retention time: t_{major} = 14.45 and t_{minor} = 20.25 min.; **HRMS** (ESI) m/z Calcd $C_{17}H_{29}N_3O_4NaSi$ $[M + Na]^+$: 390.1820; found: 390.1815.

4-(2*S*, 3*S*)-[3-Azido-4-(*tert*-butyldimethylsiloxy)-2-hydroxybutoxy]benzonitrile (25g)

Yield: 87%; gum; $[\alpha]_D^{25}$ +70 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 778, 836, 1031, 1111, 1172, 1257, 1463, 1471, 1509, 1609, 2099, 2226, 2857, 2929, 2953, 2445; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.13 (s, 6H), 0.93 (s, 9H), 2.71 (d, *J* = 4.9 Hz, 1H), 3.54-3.62 (m, 1H), 3.94-4.23 (m, 5H), 6.9 (d, *J* = 9.1 Hz, 2H), 7.6 (d, *J* = 8.7 Hz , 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.5, 18.1, 25.7, 63.1, 63.6, 69.5, 69.6, 104.7, 115.3, 133.9, 161.6; **Optical purity**: 98% ee determined by HPLC analysis (Chiral OD-H column, *n*-hexane/2-propanol (80:20), 0.5 mL/min, 210 nm) Retention time: t_{major} = 10.35 and t_{minor} = 11.80 min.; **HRMS** (ESI) m/z Calcd $C_{17}H_{26}N_4O_3NaSi$ $[M + Na]^+$: 385.1666; found: 385.1656.

(2*S*, 3*S*)-1-(4-Fluorophenoxy)-3-azido-4-(*tert*-butyldimethylsiloxy)butan-2-ol (25h)

Yield: 72%; gum; $[\alpha]_D^{25}$ +26 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 778, 836, 1098, 1220, 1252, 1507, 2100, 2858, 2930, 2953, 3440; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.12 (s, 6H), 0.93 (s, 9H), 2.68 (d, *J* = 5.0 Hz, 1H), 3.53-3.62 (m, 1H), 3.88-4.14 (m, 5H), 6.82-6.89 (m, 2H), 6.94-7.03 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.5, 18.2, 25.8, 63.3, 63.7, 69.6, 69.8, 115.5, 115.7, 116.2, 154.3, 154.4, 155.2, 155.9; **Optical purity**: 68% ee determined by HPLC analysis (Chiral OD-H column, *n*-hexane/ 2-propanol (95:5), 0.5 mL/min, 210 nm) Retention time: t_{major} = 15.53 and t_{minor} = 17.74 min.; **HRMS** (ESI) m/z Calcd for $C_{16}H_{26}FN_3O_3NaSi$ $[M + Na]^+$: 378.1620; found: 378.1624.

(2*S*, 3*S*)-1-(4-Chlorophenoxy)-3-azido-4-(*tert*-butyldimethylsiloxy)butan-2-ol (25i)

Yield: 90%; gum; $[\alpha]_D^{25}$ -6.5 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 778, 837, 1095, 1243, 1492, 2100, 2858, 2929, 2953, 3446; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.12 (s, 6H), 0.93 (s, 9H), 2.66 (d, *J* = 4.6 Hz, 1H), 3.57-3.62 (m, 1H), 3.91-4.12 (m, 5H), 6.85 (d, *J* = 8.9 Hz, 2H), 7.25 (d, *J* = 8.8 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.5, 18.2, 25.8, 63.3, 63.7, 69.5, 69.6, 115.8, 126.4, 129.4, 156.9; **Optical purity**: 97% ee determined by HPLC analysis (OD-H column, *n*-hexane/ 2-propanol (10:90), 0.5 mL/min, 254 nm) Retention time: t_{major} = 12.33 and t_{minor} = 13.14 min.; **HRMS** (ESI) m/z Calcd for $C_{16}H_{26}ClN_3O_3NaSi$ $[M + Na]^+$: 394.1324; found: 394.1320.

(2*S*, 3*S*)-1-(4-Bromophenoxy)-3-azido-4-(*tert*-butyldimethylsiloxy)butan-2-ol (25j)

Yield: 86%; gum; $[\alpha]_D^{25}$ +20 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 778, 837, 1003, 1072, 1103, 1242, 1488, 2099, 2857, 2929, 2953, 3461; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.12 (s, 6H), 0.93 (s, 9H), 2.68 (d, *J* = 4.7 Hz, 1H), 3.53-3.61 (m, 1H), 3.87-4.12 (m, 5H), 6.78-6.82 (m, 2H), 7.36-7.41 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.5, 18.2, 25.8, 63.2, 63.7, 69.4, 69.6, 113.6, 116.3, 132.4, 157.3; **Optical purity**: 97% ee determined by (OD-H column, *n*-hexane/ 2-propanol (10:90), 0.5 mL/min, 254 nm) Retention time: t_{major} = 10.99 and t_{minor} = 12.08 min.; **HRMS** (ESI) m/z Calcd for $C_{16}H_{26}BrN_3O_3NaSi$ $[M + Na]^+$: 438.0819; found: 438.0821.

(2*S*, 3*S*)-1-(3, 5-Dichlorophenoxy)-3-azido-4-*tert*-butyl-dimethylsiloxy)butan-2-ol (25k)

Yield: 89%; gum; $[\alpha]_D^{25}$ +12 (*c* 1.0, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 771, 839, 1112, 1170, 1254, 1283, 1436, 1511, 1606, 1716, 2099, 2857, 2930, 3471; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.12 (s, 6H), 0.93 (s, 9H), 2.73-2.76 (d, *J* = 5.56 Hz, 1H), 3.58-3.67

(m, 1H), 3.88-4.21 (m, 5H), 6.86-6.91 (d, *J* = 8.82 Hz, 1H), 7.17-7.22 (dd, *J* = 2.53, 8.8 Hz, 1H), 7.37-7.38 (d, *J* = 2.53, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.4, 18.2, 25.8, 63.4, 63.8, 69.4, 70.8, 114.6, 124.0, 126.7, 127.7 130.1, 152.7; **Optical purity**: 95% ee determined by HPLC analysis (OD-H column, *n*-hexane/ 2-propanol (90:10), 0.5 mL/min, 254 nm) Retention time: t_{minor} = 10.20 and t_{major} = 11.50 min.; **HRMS** (ESI) m/z Calcd for $C_{16}H_{25}Cl_2N_3O_3NaSi$ $[M + Na]^+$: 428.0934; found: 428.0936.

(2*S*, 3*S*)-1-(4-(3-Azido-4-(*tert*-butyldimethylsiloxy)-2-hydroxybutoxy)phenyl)-ethanone (25l)

Yield: 88%; gum; **$[\alpha]_D^{25}$** +6 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 777, 836, 1033, 1114, 1173, 1256, 1307, 1600, 2098, 2857, 2929, 2953, 3440; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.13 (s, 6H), 0.93 (s, 9H), 2.56 (s, 3H), 2.74 (d, *J* = 4.9 Hz, 1H), 3.55-3.67 (m, 1H), 3.89-4.25 (m, 5H), 6.95 (d, *J* = 8.8 Hz, 2H), 7.93 (d, *J* = 8.9 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.5, 18.1, 25.7, 26.2, 63.4, 63.6, 69.4, 114.2, 130.6, 162.2, 196.6; **Optical purity**: 98% ee determined by HPLC analysis (Chiral OD-H column, *n*-hexane/ 2-propanol (70:30), 0.5 mL/min, 254 nm) Retention time: t_{major} = 10.15 and t_{minor} = 11.35 min.; **HRMS** (ESI) m/z Calcd for for $C_{18}H_{29}N_3O_4NaSi$ $[M + Na]^+$: 402.1820; found: 402.1823.

(2*S*, 3*S*)-(Methyl-4-(3-azido-4-(*tert*-butyldimethylsiloxy)-2-hydroxybutoxy)benzoate (25m)

Yield: 81%; gum; **$[\alpha]_D^2$** +14 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 771, 839, 1112, 1170, 1254, 1283, 1436, 1511, 1606, 1716, 2099, 2857, 2930, 3471; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.13 (s, 6H), 0.93 (s, 9H), 2.73 (d, *J* = 5.1 Hz, 1H), 3.55-3.64 (m, 1H), 3.89 (s, 3H), 3.94-4.23 (m, 5H), 6.94 (d, *J* = 9.0 Hz, 2H), 7.99 (d, *J* = 9.0 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.5, 18.2, 25.7, 51.8, 63.2, 63.7, 69.3, 69.6, 114.1, 123.1, 131.6, 162.0, 166.6; **Optical purity**: 94% ee determined by HPLC

analysis (OD-H column, *n*-hexane/ 2-propanol (30:70), 0.5 mL/min, 254 nm) Retention time: t_{minor} = 12.56 and t_{major} = 13.31 min.; **HRMS** (ESI) m/z Calcd for for $C_{18}H_{29}N_3O_5NaSi$ $[M + Na]^+$: 418.1769; found: 418.1765.

(2*S*, 3*S*)-1-(4-Nitrophenoxy)-3-azido-4-(*tert*-butyldimethylsiloxy)butan-2-ol (25n)

Yield: 92%; gum; $[\alpha]_D^{25}$ +18 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 779, 840, 862, 1111, 1260, 1298, 1343, 1498, 1514, 1593, 1608, 2100, 2857, 2929, 2954, 3461; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.13 (s, 6H), 0.93 (s, 9H), 2.74 (d, *J* = 4.8 Hz, 1H), 3.59-3.65 (m, 1H), 3.91-4.28 (m, 5H), 7.1 (d, *J* = 9.3 Hz, 2H), 8.22 (d, *J* = 9.3 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.6, 18.1, 25.7, 63.0, 63.5, 69.6, 70.0, 114.5, 125.8, 141.8, 163.2; **Optical purity**: 96% ee determined by HPLC analysis (OJ-H column, *n*-hexane/ 2-propanol 40:60), 0.5 mL/min, 254 nm) Retention time: t_{major} = 10.51 and t_{minor} = 13.84 min.; **HRMS** (ESI) m/z Calcd for for $C_{16}H_{26}N_4O_5NaSi$ $[M + Na]^+$: 405.1565; found: 405.1558.

(2*S*, 3*S*)-3-Azido-4-((*tert*-butyldimethylsilyl)oxy)-1-[(7-methyl-2,3-dihydro-1*H*-inden-4-yl)oxy]butan-2-ol (25o)

Yield: 75%; gum; $[\alpha]_D^{25}$ -6.7 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 770, 1170, 1112, 1253, 1284, 1510, 1605, 1715, 2104, 3550; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.12 (s, 6H), 0.93 (s, 9H), 2.08 (app. quintet, *J* = 7.4 Hz, 2H), 2.20 (s, 3H), 2.66 (d, *J* = 5.4 Hz, 1H), 2.86 (q, *J* = 7.7 Hz, 4H), 3.54-3.63 (m, 1H), 3.80-4.11 (m, 5H), 6.59 (d, *J* = 8.2 Hz, 1H), 6.9 (d, *J* = 7.9 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.5, 18.2, 18.4, 24.4, 25.8, 29.7, 31.8, 63.7, 63.8, 69.1, 69.6, 109.6, 126.6, 127.9, 131.4, 144.9, 152.7; **Optical purity**: 99% ee determined by HPLC analysis (Chiral OD-H column, *n*-hexane/ 2-propanol (95:5), 0.5 mL/min, 254 nm) Retention time: t_{major} = 9.94 and t

$_{minor}$ = 11.41 min.; **HRMS** (ESI) m/z Calcd for $C_{20}H_{33}N_3O_3NaSi$ $[M + Na]^+$: 414.2183; found: 414.2188.

(2*S*, 3*R*)-1-(4-(3-Azido-2-hydroxy-3-phenylpropoxy)phenyl)ethanone (27a)

Yield: 88%; gum; $[\alpha]_D^{25}$ +16 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 775, 845, 1110, 1173, 1254, 1359, 1599, 1671, 2104, 3426; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.54 (s, 3H), 2.65-2.67 (d, *J* = 4.6 Hz, 1H), 3.77-3.84 (dd, *J* = 4.8 , 9.7 Hz, 1H), 3.96-4.15 (m, 2H), 4.81 (d, *J* = 7.3 Hz, 1H), 6.86 (d, *J* = 8.6 Hz, 2H), 7.32-7.41 (m, 5H), 7.89 (d, *J* = 8.6 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 26.1, 67.7, 68.3, 73.1, 114.0, 127.4, 128.7, 128.8, 130.4, 136.0, 162.0, 196.6; **Optical purity**: 93% ee determined by HPLC analysis (Chiral OJ-H column, *n*-hexane/ 2-propanol (70:30), 0.5 mL/min, 214 nm) Retention time: t $_{minor}$ = 11.21 and t $_{major}$ = 11.64 min.; **HRMS** (ESI) m/z Calcd for $C_{17}H_{17}N_3O_3Na$ $[M + Na]^+$: 334.1162; found: 334.1169.

(2*S*, 3*R*)-Methyl-4-(3-azido-2-hydroxy-3-phenylpropoxy)benzoate (27b)

Yield: 96%; gum; $[\alpha]_D^{25}$ +18 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 770, 1170, 1112, 1253, 1284, 1510, 1605, 1715, 2104, 3550; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.69 (br s, 1H), 3.73-3.80 (dd, *J* = 4.9 and 9.7 Hz, 1H), 3.85 (s, 3H), 3.92-3.99 (dd, *J* = 3.6, 9.7 Hz, 1H), 4.09-4.11 (m, 1H), 4.79 (d, *J* = 7.0 Hz, 1H), 6.82-6.84 (m, 2H), 7.35-7.37 (m, 5H), 7.94-7.96 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 51.8, 67.9, 68.2, 73.4, 114.1, 123.2, 127.5, 129.0, 129.1, 131.6, 136.0, 161.9, 166.5; **Optical purity**: 93% ee determined by HPLC analysis (Chiral OJ-H column, *n*-hexane/ 2-propanol (70:30), 0.5 mL/min, 254 nm) Retention time: t $_{minor}$ = 13.35 and t $_{major}$ = 14.48 min.; **HRMS** (ESI) m/z Calcd for $C_{17}H_{17}N_3O_4Na$ $[M + Na]^+$: 350.1111; found: 350.1118.

(1*R*, 2*S*)-3-(4-Nitrophenoxy)-1-azido-1-phenylpropan-2-ol (27c)

Yield: 90%; gum; $[\alpha]_D^{25}$ +21.56 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 702, 752, 845, 1111, 1167, 1260, 1342, 1510, 1592, 2105, 3481; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.64

(d, J = 4.2 Hz, 1H), 3.83-3.87 (dd, J = 4.8, 9.8 Hz, 1H), 4.00-4.17 (m, 2H), 4.80 (d, J = 7.3 Hz, 1H), 6.88-6.92 (m, 2H), 7.32-7.40 (m, 5H), 8.16-8.21 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 67.8, 68.8, 73.1, 114.4, 125.8, 127.4, 129.1, 135.8, 141.8, 163.1; **Optical purity**: 94% ee determined by HPLC analysis (Chiral OJ-H column, *n*-hexane/ 2-propanol (70:30), 0.5 mL/min, 254 nm) Retention time: minor = 13.27 and t_{major} = 14.03 min.; **HRMS** (ESI) m/z Calcd for $C_{15}H_{14}N_4O_4Na$ $[M + Na]^+$: 337.0907; found: 337.0898.

(1*R*, 2*S*)-3-(4-*tert*-butylphenoxy)-1-azido-1-phenylpropan-2-ol (27d)

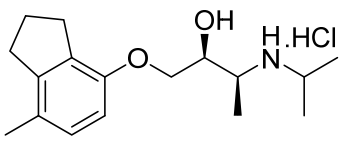
Yield: 89%; gum; **$[\alpha]_D^{25}$** +20.4 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 702, 752, 845, 1113, 2095, 2956, 3481; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.34 (s, 9H), 2.65-2.2.67 (d, J = 4.5 Hz, 1H), 3.77-3.85 (dd, J = 4.8, 9.6 Hz, 1H), 4.05-4.17 (m, 2H), 4.78 (d, J = 7.3 Hz, 1H), 6.83-6.90 (m, 2H), 7.30-7.39 (m, 5H), 8.10-8.18 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 31.6, 34.1, 67.9, 68.5, 73.2, 114.2, 125.8, 127.6, 129.2, 136.1, 142.8, 156.2; **Optical purity**: 89% ee determined by HPLC analysis (Chiral OJ-H column, *n*-hexane/ 2-propanol (70:30), 0.5 mL/min, 254 nm) Retention time: minor = 13.30 and t_{major} = 14.30 min.; **HRMS** (ESI) m/z Calcd for $C_{19}H_{22}N_3O_2Na$ $[M + Na]^+$: 348.1682; found: 348.1685.

Section II

Asymmetric Synthesis of ICI-118,551, an *anti*-Hypertensive Agent *via* Phenolic Kinetic Resolution

1.2.1 Introduction and Pharmacology

The β-adrenergic receptors (βARs) are G-protein-coupled receptors (GPRCs) that exist as three subtypes, namely β_1, β_2 and β_3. Most clinically used β-blockers are either selective for the β_1AR subtype or nonselective for the β_1AR and β_2AR. However, β_2AR-selective antagonism is useful as a pharmacological tool to probe the receptor and could potentially represent an important pharmacotherapy in its own right. By far the most potent and selective β_2AR antagonist currently known is the experimental compound namely ICI-118,551.[17–19] ICI 118,551 (**16**) has been reported to have 550 times higher affinity for β_2AR over β_1AR[18] as well as has a higher affinity for the uterine β-2-receptor than did propranolol but a lower affinity for the atrial β- 1-receptor. Additionally, ICI-118,551 (**16**), the most potent and selective β_2 AR antagonist, is used in the treatment of a wide range of diseases including heart failure,[20] ischemic heart disease[21] and hypertension.[22] Its structure consists of an indane core with a pendant propanolamine side chain incorporating an a-methyl substituent (**Fig. 9**).



16

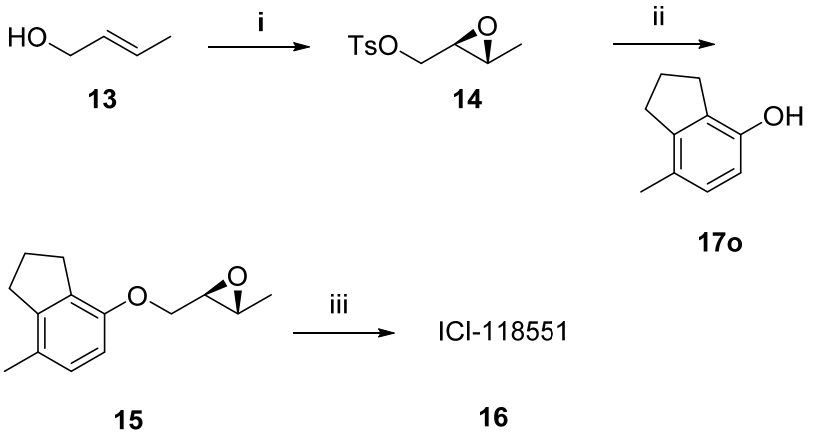
Fig 9: Structures of ICI-118,551 (**16**)

1.2.2 Review of Literature

So far only one synthetic route has been documented in the literature, which is described below.

Caddick's approach (2010)[15]

Caddick *et al*. have developed a highly efficient asymmetric synthesis of ICI 118,551 from epoxide **14** which was prepared *via* a known[23]one-pot Sharpless asymmetric epoxidation of *trans*-crotyl alcohol **13** followed by on-*in situ* tosylation. Displacement of the tosylate **14** with the commercially available phenol **17o** using caesium carbonate as the base led to epoxide **15** in high yield with >95% ee. Ring-opening of the chiral epoxide **15** with isopropylamine produced (2*S*, 3*S*)-ICI 118,551 (**16**).



Scheme 10: (i) (a) $Ti(O^iPr)_4$, D-(-)-DIPT, 5.5 M TBHP in decane, -20 ^oC, 24 h, CH_2Cl_2, (b) *p*-TsCl, Et_3N, cat. DMAP, CH_2Cl_2, -10 ^oC, 18 h, 50% (for two step); (ii) **17o**, Cs_2CO_3, DMF, 50 ^oC, 2.5 h, 92%; (iii) isopropylamine, MeOH, reflux, 18 h, then 6 M HCl, 35%.

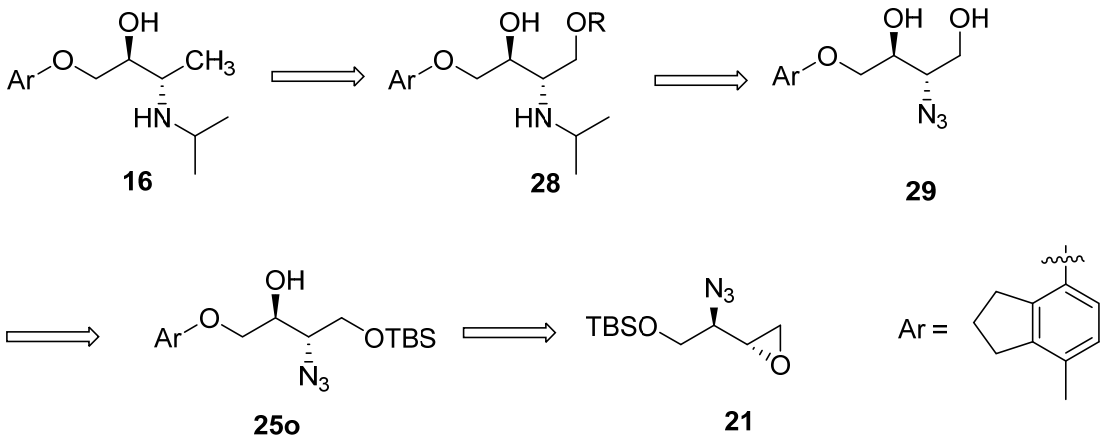
1.2.3 Present Work

1.2.3.1 Objective

Literature search revealed that only one method has been reported for the synthesis of ICI 118, 551 (**16**)**.** The drawbacks of, this method include disadvantages such as low

overall yields, low enantiomeric excess and the use of expensive chiral reagents. In this section, a concise enantioselective synthesis of ICI-118,551 (**16**) using PKR of racemic azido epoxides as the chiral inducing step is described.

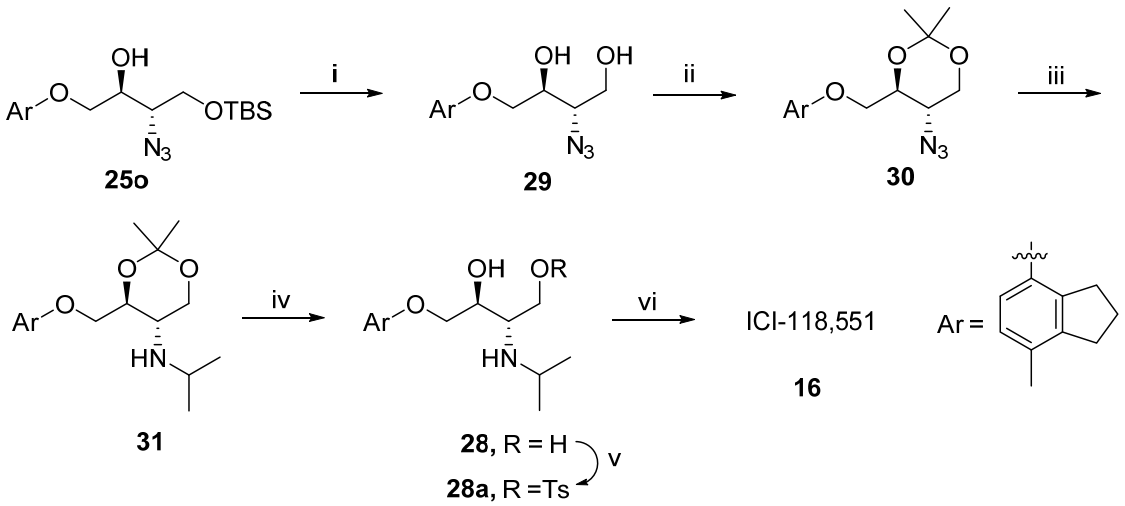
Retrosynthetic analysis of ICI-118,551 (**16**) reveals that *anti*-amino alcohol **28** could be visualized as the key intermediate for the synthesis of ICI-118,551 (**16**). The *anti*-amino diol **28** could be obtained from *anti*-1-aryloxy-3-azido- 2-alcohol **25o** which in turn can be prepared by the Co-catalyzed phenolic kinetic resolution of *racemic* azido epoxide (±)**-21** (see **Section I**) (**Scheme 11**).



Scheme 11: Retrosynthetic analysis of ICI-118, 551(**16**)

1.2.3.2 Results and Discussion

This section describes an efficient synthesis of ICI-118,551 (**16**) commencing from optically pure azido alcohol **25o**, readily obtained by the Co-catalyzed phenolic kinetic resolution of *racemic* azido epoxide (±)**-21**, as described in the previous section **(Section I, Table 1)**. The synthetic sequences for ICI-118,551 are shown in **Scheme 12**.



Scheme 12: (i) TBAF, THF, 0 ^{o}C, 1 h, 90%; (ii) 2,2-dimethoxypropane, cat. camphor sulphonic acid, CH_2Cl_2, 1 h, 89%; (iii) (a) 5% Pd/C, H_2 (1 atm), MeOH, 6 h; (b) KOH/18-crown-6, 4 A^0 MS, isopropyl bromide, DMF, 20 h, 65%; (iv) TFA, CH_2Cl_2, 65%; (v) *p*-TsCl, Et_3N, CH_2Cl_2, 0 ^{o}C, 1 h, 57%; (vi) $LiAlH_4$, THF, reflux, 62%, 90% ee.

The first step involved the acid-catalyzed silyl deprotection of TBS ether **25o** (TBAF, THF) that afforded diol **29** in 90% yield. The formation of diol **29** was confirmed from its ^{1}H NMR spectrum, which displayed signals at δ 2.69 (d, *J* = 5.2 Hz, 1H) and 3.68 (m, 1H) corresponding to the methine and methylene protons (-C**H**-N_3 and –C**H$_2$**OH) respectively. This was further confirmed from its ^{13}C NMR spectrum, which showed two typical carbon signals at δ 63.8 and 62.7 corresponding to the methine and methylene carbons (-**C**H-N_3 and –**C**H_2OH) respectively (**Fig. 10**).

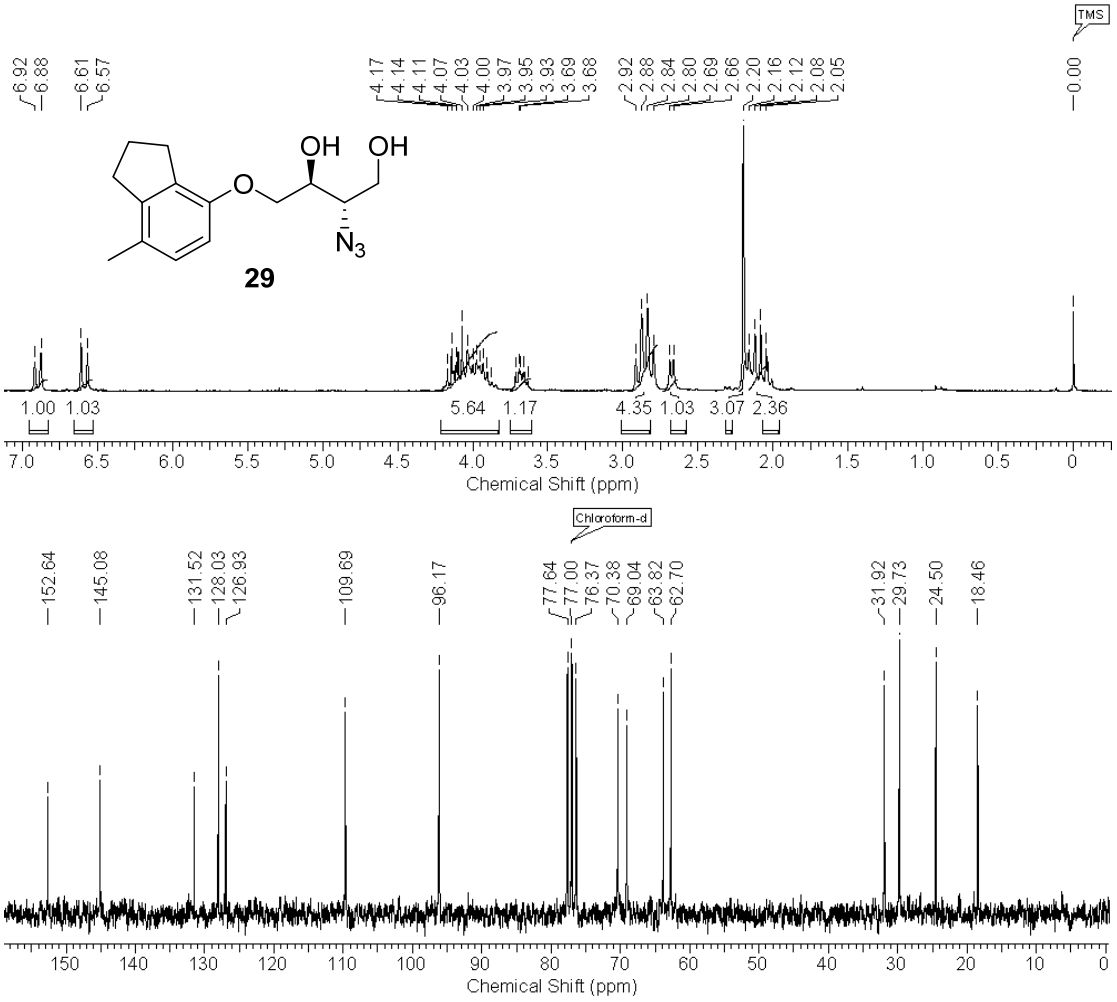


Fig. 10: ^{1}H and ^{13}C NMR spectra of azido diol **29**

The azido diol **29** was readily protected as its acetonide **30** (2,2-dimethoxypropane, cat. CSA). The formation of azido acetonide derivative **30** was confirmed by its IR spectrum, which showed a strong absorption band at υ_{max} 2100 cm^{-1} typically for azide functionality. Its ^{1}H NMR spectrum showed two singlets at δ 1.41 (s, 3H) and 1.47 (s, 3H) integrating for three protons each confirming the formation of acetonide. Its ^{13}C NMR spectrum also displayed typical signals at δ 19.2, 28.3 and 99.1 attributable to methyl and quaternary carbons of isopropylidene group respectively (**Fig. 11**).

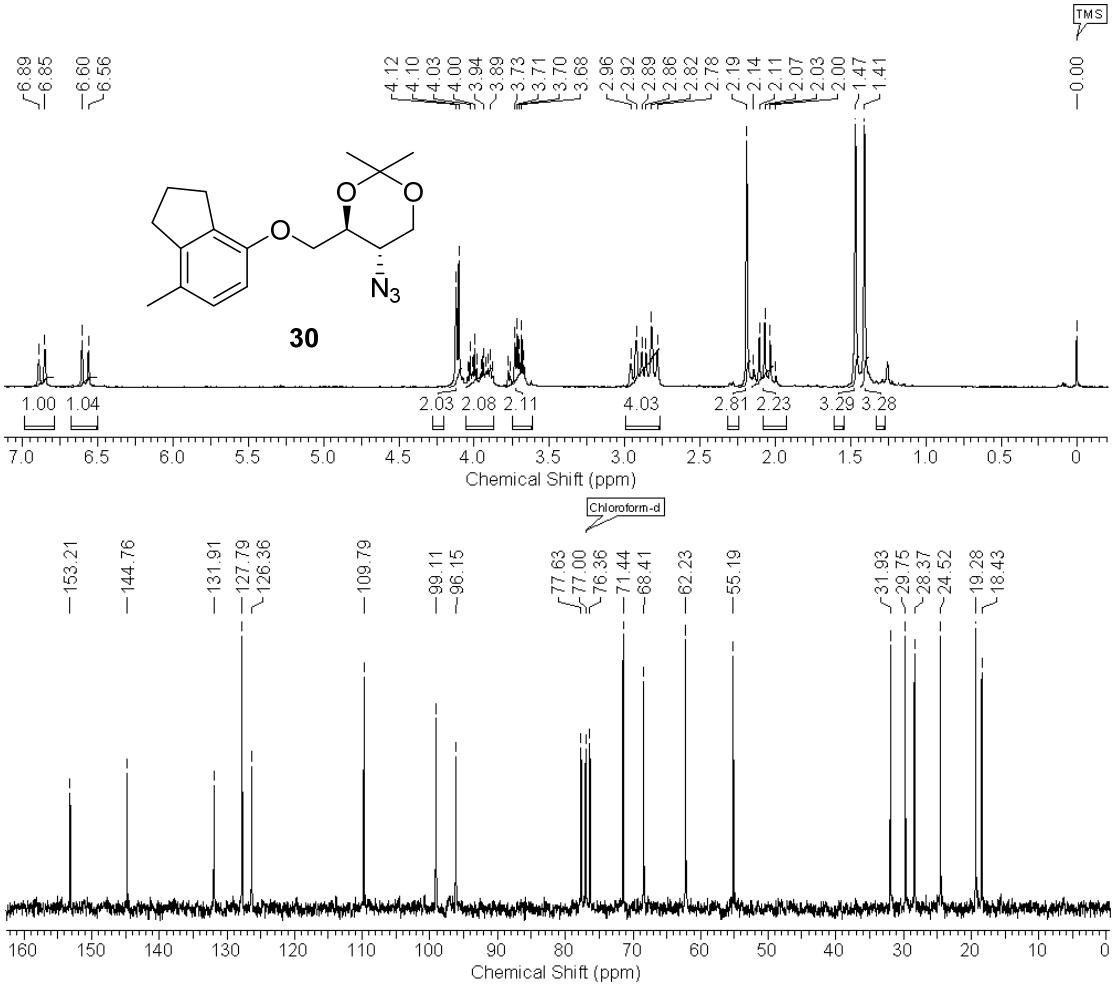


Fig. 11: ^{1}H and ^{13}C NMR spectra of acetonide **30**

The reduction of azide **30** under catalytic hydrogenation [H_2 (1 atm), 10% Pd/C] at ambient conditions produced the corresponding amine. The *N*-alkylation of crude amine with isopropyl bromide (KOH/18-Crown-6, DMF, 25 ^{o}C)[24] afforded the *N*-isopropyl derivative **31** in 65%. The formation of **31** was confirmed from its ^{1}H NMR spectrum, which displayed multiplets at δ 1.54 (m, 6H) and 2.99 (m, 1H) corresponding to the isopropyl methyl and methine protons (CH-(C**H**$_3$)$_2$ and –C**H**-(CH_3)$_2$) respectively. This was further confirmed from its ^{13}C NMR spectrum which showed carbon signals at δ 19.5 and 48.5 corresponding to the methyl and methine carbons (CH-(**C**H_3)$_2$ and –**C**H-(CH_3)$_2$ respectively (**Fig. 12**).

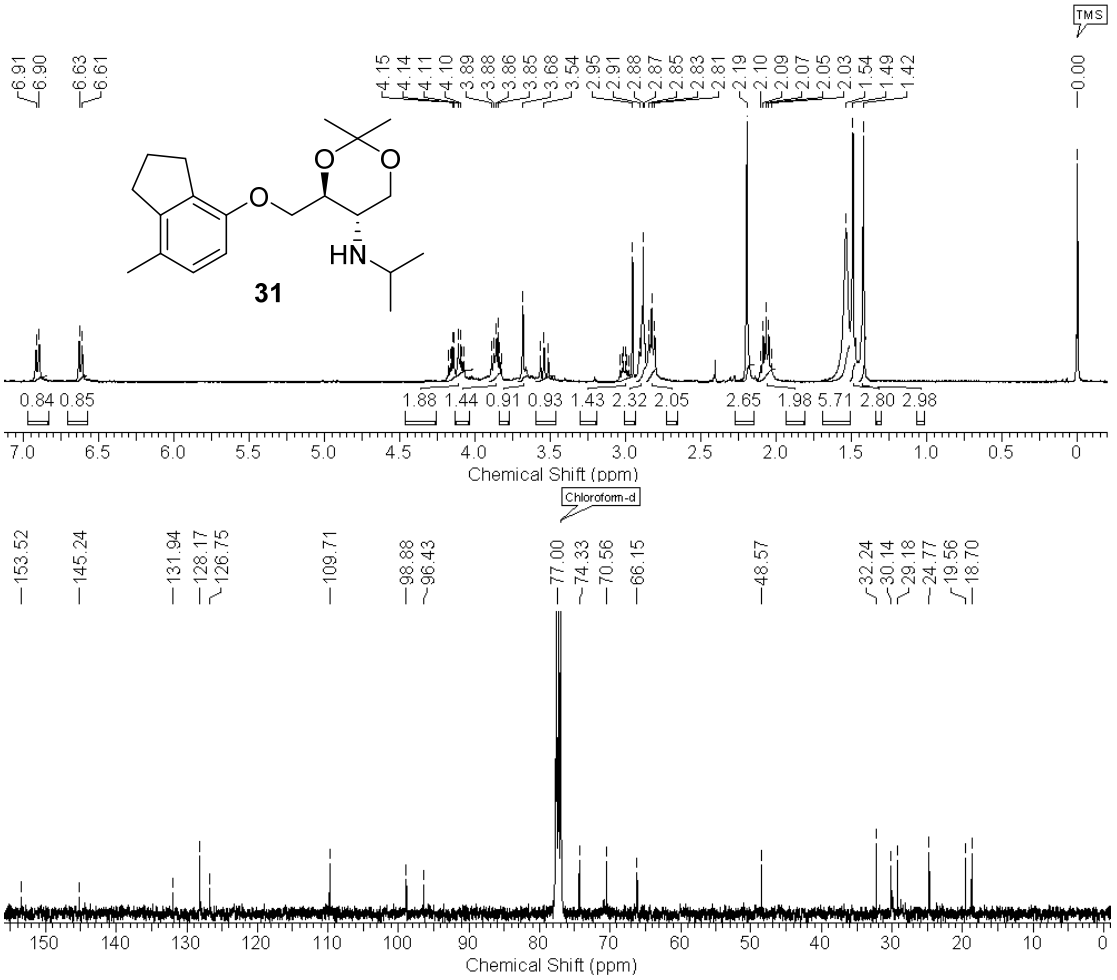


Fig. 12: ^{1}H and ^{13}C NMR spectra of *N*-isopropyl derivatives **31**

Next, the acid-catalyzed acetonide deprotection of *N*-isopropyl derivative **31** was carried out to give amino diol **28** in 65% yield. The formation of **28** was confirmed from its ^{1}H NMR spectrum, which displayed signals at δ 3.45 (m, 2H) and 4.96 (m, 2H) corresponding to the methylene protons attached to -C**H**$_2$OH and -C**H**$_2$O groups respectively. This was further confirmed by its ^{13}C NMR spectrum, which showed two typical carbon signals at δ 63.8 and 69.9 corresponding to the methylene carbons attached to -**C**H$_2$OH and -**C**H$_2$O groups respectively (**Fig. 13**).

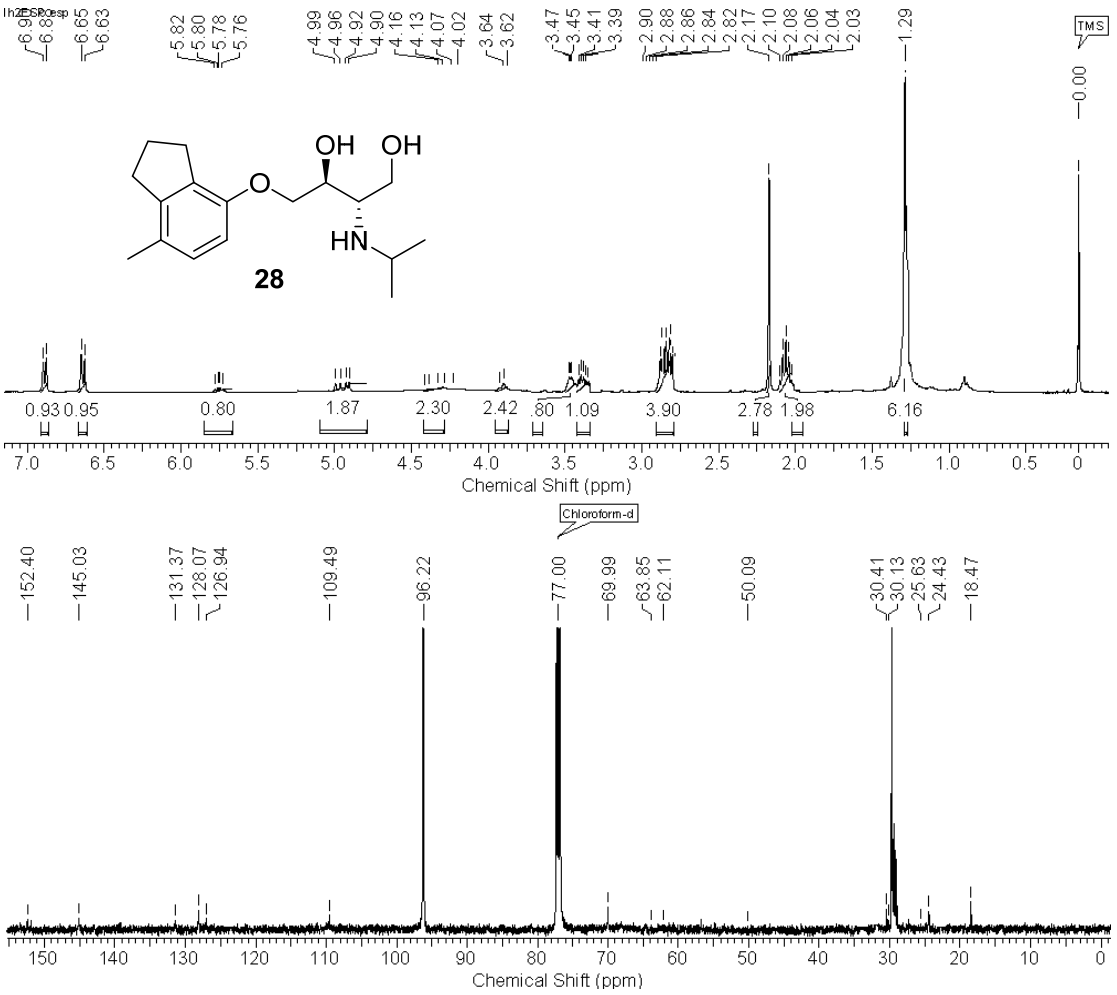


Fig. 13: ^{1}H and ^{13}C NMR spectra of amino diol **28**

The selective monotosylation of diol **28** was achieved to give the crude tosylate **28a**, which on reduction with $LiAlH_4$ afforded the target molecule ICI-118,551 (**16**) in 21% overall yield and 99% ee. The formation of ICI-118,551 **16** was confirmed from its ^{1}H NMR spectrum, which displayed typical multiplet at δ 1.27 (m, 9H) and 3.48 (m, 1H) corresponding to the methyl and methine protons (-CH-**CH_3**, -NHCH(**CH_3**)$_2$ and -C**H**CH_3) respectively. This was also confirmed from its ^{13}C NMR spectrum, which showed two typical carbon signals at δ 11.9 and 53.7 corresponding to methyl and methine carbons (-**C**H-**CH_3** and –**CH**CH_3) respectively (**Fig. 14**).

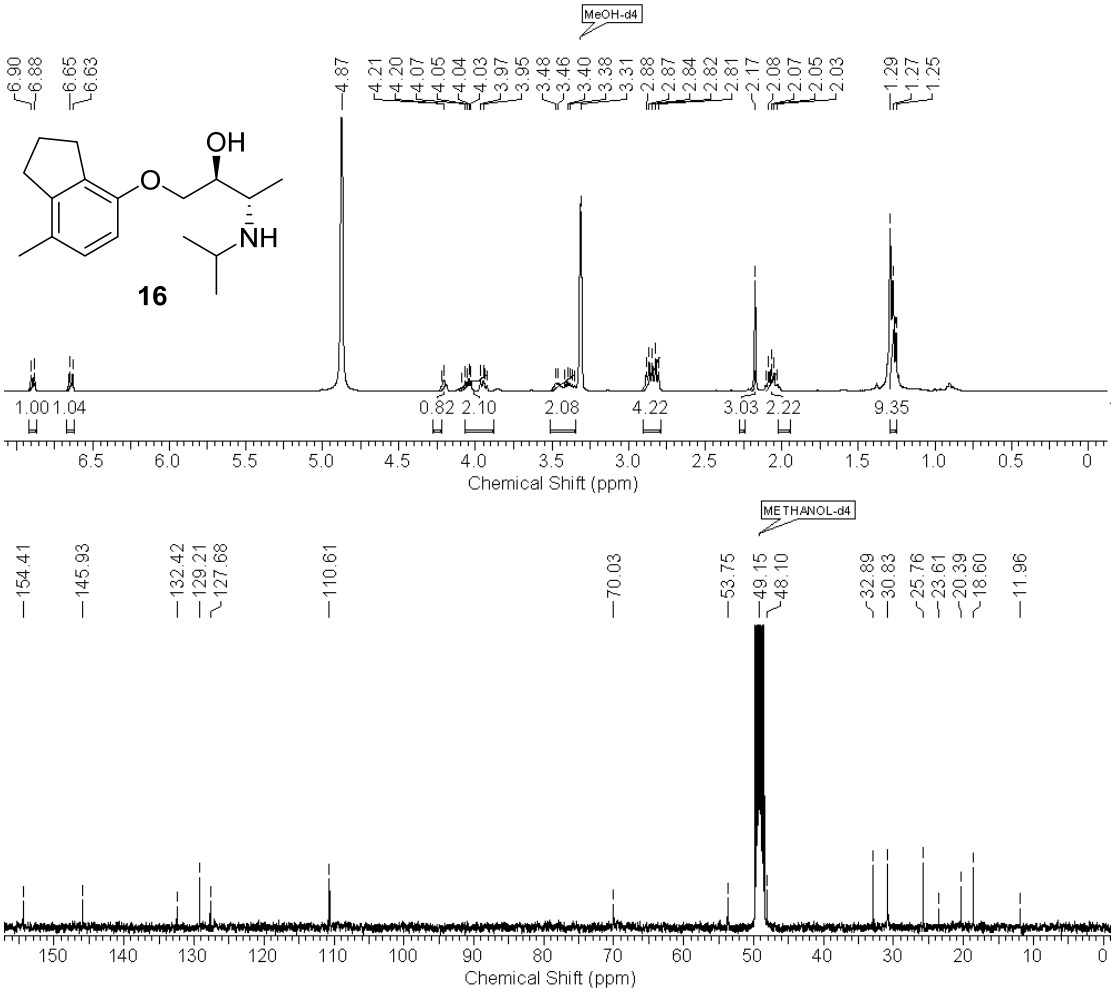


Fig. 14: ^{1}H and ^{13}C NMR spectra of ICI-118,551 (**16**)

1.2.4 Conclusion

This section has described an elegant route to an enantioselective synthesis of ICI-118,551, an *anti*-hypertensive agent efficient, (**16**) *via* two-stereocentred PKR of *racemic* azido epoxide as a key step. The high enantiomeric excess obtained in this method renders the present protocol a good alternative to the known method.

1.2.5 Experimental Section

(4*S*, 5*S*)-5-Azido-2,2-dimethyl-4-[(7-methylindan-4-yloxy)methyl]-1,3-dioxane (29)

To a stirred solution of silyl ether **25o** (1.8 g, 4.6 mmol) in THF (20 mL) was added TBAF (10 mL, 1 M solution in THF) at 0 ^{o}C. The reaction mixture was stirred for 1 h at the same temperature and then quenched with water. It was extracted with ethyl acetate and the combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain the crude azido diol, which was purified by column chromatography using pet. ether:ethyl acetate (70:30) to obtain pure azido diol **29** (1.15 g, 90 %).

Yield: 90%, gum; $\mathbf{[\alpha]_D^{25}}$ +12 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 778, 837, 1095, 1243, 1492, 2100, 2858, 2929, 2953, 3446; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.01-2.16 (appt. quintet, *J* = 7.9 Hz, 2H), 2.20 (s, 3H), 2.68 (d, *J* = 5.2 Hz, 1H), 2.85 (q, *J* = 8.0 Hz, 4H), 3.63-3.71 (m, 1H), 3.87-4.17 (m, 5H), 6.59 (d, *J* = 8.0 Hz, 1H), 6.89 (d, *J* = 8.2 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 18.4, 24.5, 29.7, 31.9, 62.7, 63.8, 69.0, 70.3, 109.6, 126.9, 128.0, 131.5, 145.0, 152.6; **HRMS** (ESI): m/z Calcd for $C_{14}H_{19}N_3O_3Na$ $[M + Na]^+$: 300.1319; found: 300.1314.

(4S,5S)-5-azido-2,2-dimethyl-4-(((7-methyl-2,3-dihydro-1H-inden-4-yl)oxy)methyl)-1,3-dioxane (30)

To a stirred mixture of the above azido diol **29** (1 g, 3.6 mmol), 2,2-dimethoxypropane (1.8 mL, 14.4 mmol) in dry CH_2Cl_2 (25 mL) was added camphor sulfonic acid (0.080 g, 10 mol %). The reaction mixture was stirred at 25 ^{o}C for 12 h. After completion of the reaction (as monitored by TLC), it was neutralized with triethylamine, concentrated and the crude was purified by column chromatography

using pet. ether/EtOAc (9:1) as eluent to produce protected azide **30** as gum (1 g, 89%).

Yield: 89% gum; $[\alpha]_D^{25}$ +15 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 778, 837, 1095, 1243, 1492, 2100, 2858, 2929, 2953, 3446; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.41 (s, 3H), 1.47 (s, 3H), 2.00-2.14 (appt. quintet, *J* = 7.9 Hz, 2H), 2.19 (s, 3H), 2.82 (t, *J* = 7.4 Hz, 2H), 2.92 (t, *J* = 7.4 Hz, 2H), 3.67-3.77 (m, 2H), 3.88-3.96 (m, 1H), 3.98-4.04 (m, 1H), 4.11 (d, *J* = 3.5 Hz, 2H), 6.58 (d, *J* = 8.2 Hz, 1H), 6.87 (d, *J* = 8.1 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 18.4, 19.2, 24.5, 28.3, 29.7, 31.9, 55.1, 62.2, 68.4, 71.4, 99.1, 109.7, 126.3, 127.7, 131.9, 144.7, 153.2; **HRMS** (ESI): m/z Calcd for $C_{17}H_{23}N_3O_3Na$ $[M + Na]^+$: 340.1632; found: 340.1630.

(4*S*, 5*S*)-*N*-Isopropyl-2,2-dimethyl-4-[(7-methylindan-4-yloxy)methyl]-1,3-dioxan-5-amine (31)

To a stirred solution of acetonide **30** (0.5 g, 1.5 mmol) in methanol (5 mL), was added 10% Pd/C (10 mg) at 25 ^oC. The reaction mixture was stirred under H_2 atmosphere (60 psi) for 20 h. After completion of reaction (as monitored by TLC), it was filtered through a Celite pad and washed with EtOAc (3 x 20 mL). The combined organic phase was concentrated under reduced pressure to give the crude amino compound, which was taken up for next step without purification.

To a stirred suspension containing activated powdered 4 Å molecular sieves (1.6 g) in anhydrous DMF (30 mL), KOH powder (63 mg, 1.14 mmol) and 18-Crown-6 (300 mg, 1.14 mmol) was added, and the mixture was vigorously stirred for 10 min. The crude amine compound (332 mg, 1.14 mmol) obtained above was added and the mixture was stirred for an additional 30 min followed by the addition of 2-bromopropane (0.12 mL, 1.34 mmol). The whole reaction mixture was allowed to stir at room temperature for 20 h. It was filtered to remove insoluble solids and the

residue washed several times with ethyl acetate. The filtrate was concentrated, the residue basified with 1 N NaOH, and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and evaporated. The resulting crude mixture was purified by column chromatography using ethyl acetate/methanol (9:1 v/v) as the eluting solvent to afford the *N*-alkylated acetonide **31** as a colorless oil (0.204 g, 65%).

Yield: 65%, gum; $[\alpha]_D^{25}$ +25 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 778, 837, 1095, 1243, 1492, 2100, 2858, 2929, 2953, 3446; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.42 (s, 3H), 1.49 (s, 3H), 1.54 (s, 6H), 2.03-2.10 (appt. quintet, *J* = 7.6 Hz, 2H), 2.19 (s, 3H), 2.83 (t, *J* = 7.2 Hz, 2H), 2.89 (t, *J* = 7.4 Hz, 2H), 2.95-3.04 (m, 2H), 3.51-3.57 (m, 1H), 3.66-3.68 (m, 1H), 3.82-3.89 (m, 1H), 4.07-4.18 (m, 2H), 6.62 (d, *J* = 8.0 Hz, 1H), 6.91 (d, *J* = 7.9 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 18.7, 19.5, 24.7, 29.1, 30.1, 32.2, 48.5, 66.1, 70.5, 74.3, 98.8, 109.7, 126.7, 128.1, 131.9, 145.2, 153.5; **HRMS** (ESI): m/z Calcd for $C_{20}H_{31}NO_3Na$ $[M + Na]^+$: 356.2196; found: 356.2190.

(2*S*, 3*S*)-3-Isopropylamino-1-(7-methylindan-4-yloxy)-butan-1,3-diol (28)

To a stirred solution of acetonide **31** (0.18 g, 0.54 mmol) in CH_2Cl_2 (6 mL), was added trifluoroacetic acid (0.162 mL, 2.12 mmol). The reaction mixture was stirred at 25 ^oC (monitored by TLC). The organic layer was washed with saturated aq. $NaHCO_3$ followed by brine and dried over anhyd. Na_2SO_4 and concentrated to give the crude product **28**, which was then purified by column chromatography over silica gel using pet. ether/EtOAc (20:80) as an eluent to give colorless oil (0.102 g, 65%).

Yield: 65%, gum; $[\alpha]_D^{25}$ +35 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 785, 1160, 1125, 1250, 1280, 1513, 1605, 2915, 3358, 3556; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.41 (s, 6H), 2.03-2.10 (m, 2H), 2.17 (s, 3H), 2.82-2.90 (m, 4H), 3.39-3.41 (m, 1H), 3.45-3.47 (m, 1H), 3.62-3.69 (m, 2H), 4.02-4.16 (m, 2H), 4.90-4.99 (dd, *J* = 10.1 and 16.8 Hz,

2H) 5.76-5.82 (m, 1H), 6.58 (d, *J* = 8.1 Hz, 1H), 6.87 (d, *J* = 7.8 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 18.4, 24.4, 25.6, 30.1, 30.4, 50.0, 62.1, 63.5, 69.9, 109.4, 126.9, 128.0, 131.3, 145.0, 152.4; **HRMS** (ESI): m/z Calcd $C_{17}H_{27}NO_3Na$ $[M + Na]^+$: 316.1883; found: 316.1880.

(2*S*, 3*S*)-3-Isopropylamino-1-(7-methylindan-4-yloxy)-butan-2-ol (16)

To a stirred solution of amino diol **28** (50 mg, 0.17 mmol) in CH_2Cl_2 (5 mL) at 0 °C were added dry Et_3N (0.45 mL, 0.18 mmol) and *p*-toluenesulfonyl chloride (36 mg, 0.187 mmol). The reaction mixture was stirred at 0 °C for 1 h. After complete conversion, (monitored by TLC), it was quenched with 10% aq. $NaHCO_3$ solution and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated under reduced pressure to give the crude tosylate **28a**, which was directly taken up for the next step.

A solution of the above tosylate **28a** (76 mg, 0.17 mmol) in THF (5 mL) was added drop-wise to a stirred suspension of $LiAlH_4$ (20 mg, 0.53 mmol) in THF (10 mL) at 0 ^oC. It was then refluxed for 4 h and then cooled to 0 °C. The excess $LiAlH_4$ was quenched with EtOAc (2 mL). Then it was treated with aq. 20% NaOH (0.5 mL), the formed white precipitate was filtered off and the residue was washed with EtOAc (3 x 10 mL). The combined ethyl acetate layers were dried over anhyd. Na_2SO_4, and solvent concentrated under reduced pressure. The crude product was purified by column chromatography using ethyl acetate/methanol (9:1) to obtain pure **16** as gummy liquid (0.058 g, 62% yield over two steps).

Yield: 62% gum; **$[\alpha]_D^{25}$** +38.4 (*c* 1, MeOH); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 778, 837, 1095, 1243, 1492, 2932, 2953, 3343, 3446; **^{1}H NMR** (200 MHz, MeOH-d_4): δ 1.24-1.30 (m, 9H), 1.98-2.14 (appt. quintet, *J* = 7.9 Hz, 2H), 2.17 (s, 3H), 2.85 (q, *J* = 8.0 Hz, 4H), 3.37-3.50 (m, 2H), 3.90-4.11 (m, 2H), 4.01-4.25 (m, 1H), 6.62-6.66 (d, *J* = 8.0

Hz, 1H) 6.89 (d, *J* = 8.2 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 11.9, 18.6, 20.3, 23.6, 25.7, 30.8, 32.8, 48.1, 53.7, 69.4, 70.0, 110.6, 127.6, 129.2, 132.4, 145.9, 154.4; **HRMS** (ESI): m/z Calcd $C_{17}H_{27}NO_2Na$ $[M + Na]^+$: 300.1934; found: 300.1940.

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Chapter II

Synthesis of Optically Pure γ-Butyrolactones and Epoxy Esters via Two-Stereocentered HKR of 3-Substituted Epoxy Esters: A Formal Synthesis of R067-8867

1. "Optically pure γ-butyrolactones and epoxy esters *via* two stereocentered HKR of 3-substituted epoxy ester" Devalankar, D. A.; **Karabal, P. U**.; Sudalai, A. *Org. Biomol. Chem.*, **2013**, *11*, 1280.

Section I

Synthesis of Optically Pure γ-Butyrolactones and Epoxy Esters *via* Two-Stereocentered HKR of Racemic 3-Substitued Epoxy Esters

2.1.1 Introduction

The γ-butyrolactone skeleton represents an important core structure in many biologically active natural products.[1] In particular, certain functionalized chiral γ-butyrolactones are sex attractant pheromones[2] and some utilized as flavoring components.[3] The enantiomerically pure epoxy esters are also valuable 'building blocks' for the asymmetric synthesis of bioactive natural products.[4] Due to their interesting biological activity in medicinal chemistry, an efficient catalytic method for the synthesis of substituted γ-butyrolactones and epoxy esters from commercially available materials is of current interest.[5]

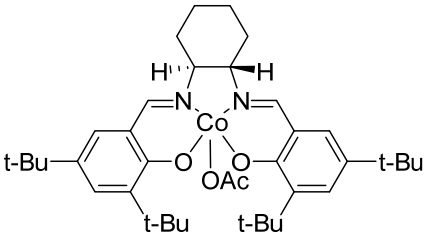
Jacobsen's Hydrolytic Kinetic Resolution (HKR) that uses readily accessible Co(III)-based chiral salen complexes as catalyst and water as the only reagent to afford chiral epoxides and diols of high ee in excellent yields, has been comprehensively studied in recent years to reveal its mechanistic and synthetic aspects.[6] In the present section, we have described a flexible, novel single-step method that employs Co-catalyzed HKR of racemic 3-substituted (aryl or alkyl) epoxy esters with *two stereocentres* to produce substituted γ-butyrolactones and epoxy esters in high optical purities.

2.1.2 Hydrolytic kinetic resolution (HKR)

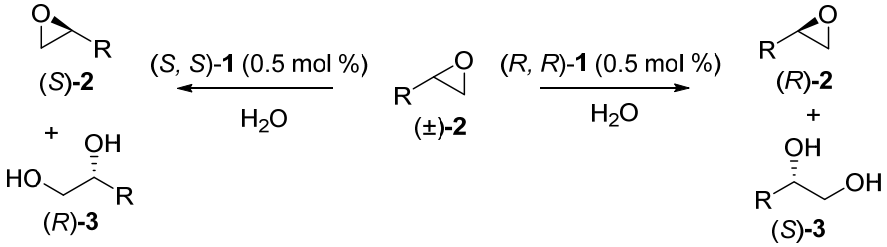
The importance of epoxides in organic synthesis arises partly from the occurrence of the strained three-membered ring unit in a number of interesting natural products[7] but more so because the ring opening of epoxides allows straightforward elaboration to useful new functionality, often with generation 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.[8] 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 inexpensively as racemic mixtures, and kinetic resolution is an attractive strategy for the production of optically active epoxides, given an economical and operationally simple method. Readily accessible synthetic catalysts (chiral cobalt-salen complexes)[9] have been used for the efficient asymmetric hydrolysis of terminal epoxides. This process uses water as the only reagent, no added solvent, and low loadings of a recyclable catalyst (0.5 mol%), and it affords highly valuable terminal epoxides and 1,2-diols in high yields with high enantiomeric enrichment. One of the most attractive features of kinetic resolution processes in general is the fact that the enantiomeric composition of unreacted substrate can be controlled by adjusting the degree of conversion, and virtually enantiopure material can be obtained at appropriately high conversions. This is an important consideration in the present case, since low-molecular weight terminal epoxides are typically liquids at room temperature and are not readily derivatized as salts, and therefore it is not a straightforward matter to upgrade their enantiomeric composition by crystallization. However, in the absence of straightforward substrate racemization protocols, kinetic resolutions have the significant disadvantage of a 50% maximum yield of substrate recovery. With a specific interest in devising a practical method for obtaining highly enantioenriched terminal epoxides, the following criteria must be met in order for a kinetic resolution approach to be viable.[10] (1) The racemic epoxides must be inexpensive or easily accessible from inexpensive commercial starting materials. (2) The catalyst for the resolution must be readily available in both

enantiomeric forms. In the optimal case, the catalyst would be used in small quantities in the resolution and would be recyclable. (3) The nucleophile used for the ring opening should be inexpensive and easily handled. (4) The resolved epoxides must be obtained in good yield and very high enantiopurity and must be easily separated from the ring-opened products. (5) Ideally, although not necessarily, the ring-opened byproducts should also be valuable chiral building blocks and be obtainable in high enantiomeric excess.



(*S*, *S*)-(salen)Co(III)(OAc) complex (**1**)



Scheme 1: Hydrolytic Kinetic Resolution (HKR) of racemic terminal epoxide

The (salen)Co complex **1** catalyzes the efficient hydrolytic kinetic resolution (HKR) of a variety of terminal epoxides (**Scheme 1**).[11] This new method appears to hold considerable promise with regard to meeting all of the criteria outlined above. First, racemic 1,2-epoxides are generally available directly from commercial suppliers at low cost or are obtainable in one step from inexpensive olefins or aldehydes. In fact, certain racemic epoxides, such as propylene oxide, epichlorohydrin, styrene oxide, and butadiene monoepoxide, are commodity chemicals and are no more expensive

than common organic solvents. Second, the ligands for catalyst **1** had previously been commercialized and manufactured on a ton scale in the context of (salen)Mn epoxidation catalysts.[12]

The cobalt analogues (*R*, *R*)-**1** and (*S*, *S*)-**1** 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 provides useful enantioenriched 1,2-diols, including many that are otherwise not readily accessible using existing asymmetric dihydroxylation methods.[13]

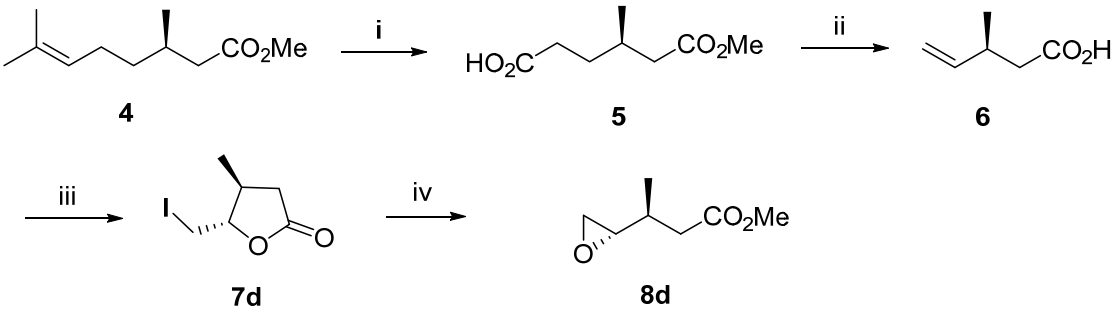
Two useful methods for the generation of complex **1**.OAc have been developed. Method A involves isolation of **1.**OAc as a crude solid prior to the HKR. Thus, the Co(II) complex **1** is dissolved in toluene to generate ~ 1 M solution, and acetic acid (2 equiv) is added. The resulting solution is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

2.1.3. Review of Literature

Various syntheses of enantiomerically pure *syn*- or *anti*-3,4-disubstituted γ-butyrolactones and epoxy esters have been documented in the literature. Some of the recent and important synthetic routes are described below.

Umemura's approach (1982)[4f]

Umemura *et al.* have synthesized *anti* 3-substituted epoxy esters **8d** by using chiral pool staring material namely methyl (*R*)-(+)-citronellate **4**. Ozonolysis of **4**, followed by its oxidative work up gave half ester **5**. Compound **5** was oxidatively



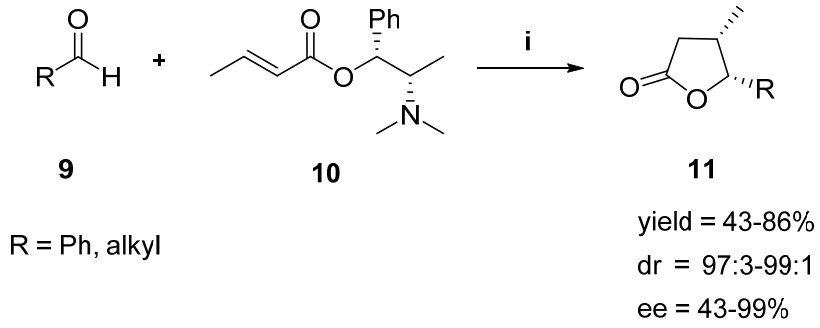
Scheme 2: (i) (a) O_3, CH_2Cl_2, -78 ^oC, 1 h, 80%; (b) CrO_3, aq. H_2SO_4, acetone, 1 h, 25 ^oC, 90 %; (ii) (a) $Pb(OAc)_4$, $Cu(OAc)_2$, benzene, refluxed, 6 h, 85%;(b) aq. 10% KOH, H_2O, refluxed, 2 h, 82%; (iii) I_2, CH_3CN, 0 ^oC, 24 h, 80%; (iv) K_2CO_3, MeOH, reflux, 1 h, 93%.

decarboxylated and the resulting ester was hydrolyzed to give olefinic acid **6**. Thermodynamic iodolactonization of **6** yielded iodolactone product **7d**. Finally, iodolactone **7d** was converted into epoxy ester **8d** by methanolysis reaction with an overall yield of 37% (**Scheme 2**).

Fukuzawa's approach (1997)[14]

Fukuzawa, *et al.* have reported SmI_2-mediated asymmetric synthesis of *cis*-3,4-disubstituted-γ-butyrolactones **11** by reductive coupling of aldehydes **9** with crotonates **10** possessing *N*-methylephedrine as chiral auxiliary. The *cis* isomer of the 3,4-disubstituted-γ-butyrolactone **11** was produced predominantly (97:3 to 99:1) with enantioselectivity 43 to 99% ee and chemical yield up to 86%. The mechanism of the reaction includes the ketyl radical and alkene coupling reaction where chelation

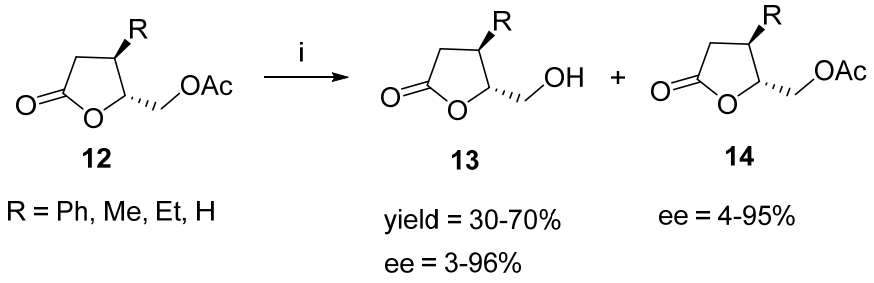
control by Sm atom would play an important role in the asymmetric induction and diastereoselectivity (**Scheme 3**).



Scheme 3: (i) SmI_2, *t*-BuOH, THF, -78 to 0 ^oC, 5-6 h.

Hyun-Joon Ha's approach (1998)[15]

Hyun-Joon Ha *et al.* have described a new method of synthesis of chiral *γ*-butyrolactones by resolution of the *β*-substituted *γ*-((acetyloxy)methyl)-*γ*-butyrolactones **12** by using lipase PS (LPS). A mixed solvent system made up of buffer

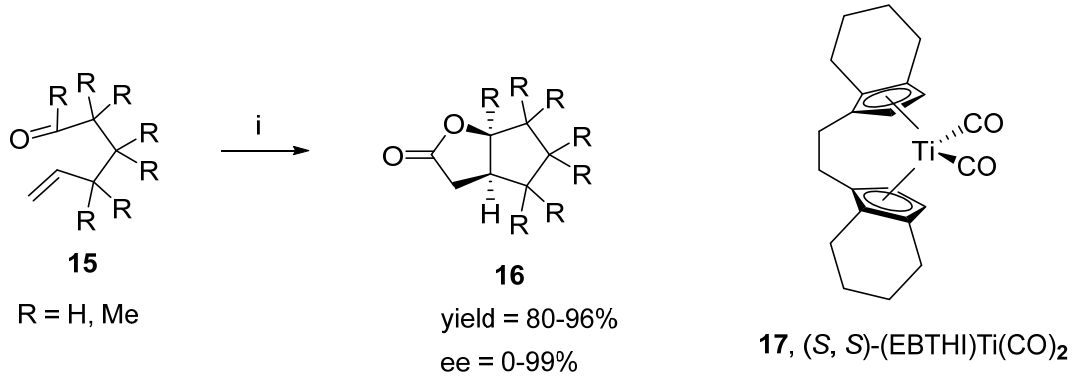


Scheme 4: (i) Lipase PS (3.0 mass equiv), pH=7.2, acetone, 35 ^oC, 0.5 to 58 h.

and acetone (97:3) was used as the reaction medium. Under this reaction medium, resolution of *trans*- and *cis*-*β*- substituted-*γ*-((acetyloxy)methyl)-*γ*-butyrolactones **7** was achieved up to 70% conversion to give lactone **13** along with unreacted ester **14** (**Scheme 4**).

Crowe's approach (2001)[16]

Crowe *et al*. have reported a new route for the synthesis of *γ*-butyrolactones by intramolecular Hetero-Pauson-Khand cyclization. In this method, intramolecular cyclocarbonylation between enals and enones of substrate **15** was achieved using a chiral titanocene catalyst **17** in toluene at 100 °C, which gave fused γ-butyrolactones **16** with yield up to 96% (**Scheme 5**).



15

R = H, Me

16

yield = 80-96%

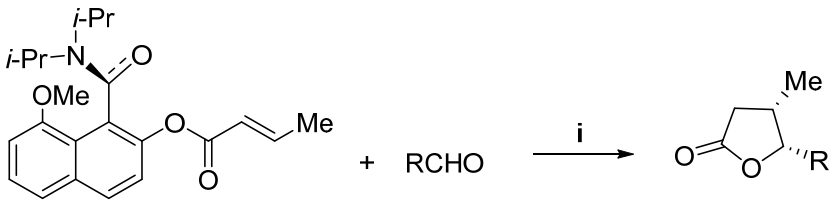
ee = 0-99%

17, (*S*, *S*)-(EBTHI)Ti(CO)$_2$

Scheme 5: (i) ligand **12** (10-20 mol%), PMe_3 (30-80 mol%), CO (50 psi), toluene, 36-40 h, 100 ^oC.

Dai's approach (2005)[17]

Dai *et al*. have reported reductive coupling of aldehydes **19** with chiral crotonates possessing 2-hydroxy-8 methoxy-1-naphthamide **18** as chiral auxiliary that afforded



18

R = alkyl

19

20

80-99% ee

Scheme 6: (i) SmI_2 (3 equiv), *t*-BuOH (1.3 equiv), THF, -20 to -15 ^oC, 6 h, 58-90%.

the *cis*-γ-butyrolactones **20** in 90% yield and up to 99% ee with a *cis*/*trans* ratio of 90:10 (**Scheme 6**).

2.1.4 Present Work

2.1.4.1 Objective

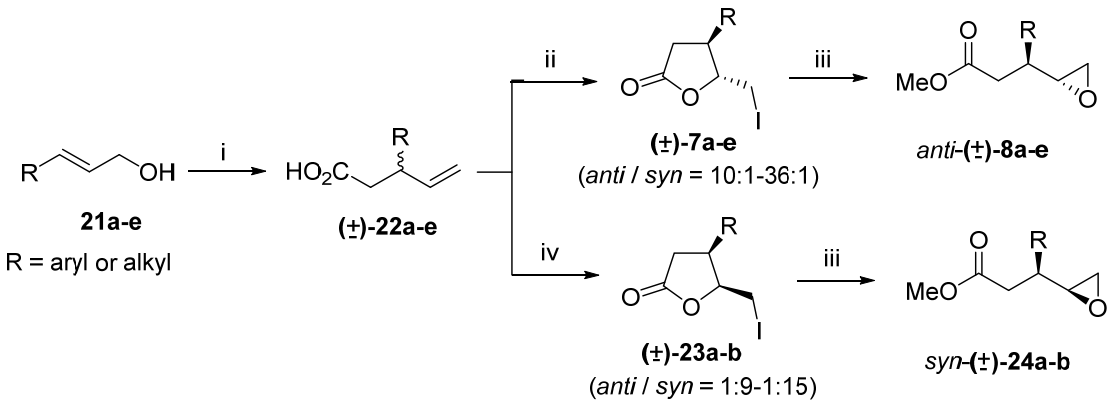
As can be seen from the above discussion, the literature methods for the synthesis of enantiomerically pure 3,4-disubstituted γ-butyrolactones **13** and **25** and 3-substituted epoxy esters **8** and **24** suffer from certain limitations such as use of expensive catalysts, chiral pool resources, multiple steps or products obtained in low optical purity. Despite enormous applications, HKR has only been applied to the resolution of simple terminal epoxides with one stereocentre.[18] To the best our knowledge, study related to HKR of functionalized epoxides with two stereocentres is rather rare.[19]

2.1.4.2 Results and Discussion

In the present work, we have extended the scope of the applicable substrates for HKR to cover multi-functionalized molecules with *two stereocentres*. The aim of such an investigation is to access enantiomerically enriched 3,4-disubstituted γ-butyrolactones **13** and **25** and 3-substituted epoxy esters **8** and **24** by a direct and simple method from the respective racemic materials; thus complementing the other tedious routes. Due to their importance as 'building-blocks' for the synthesis of highly functionalized molecules, racemic 3-substituted epoxy esters (±)-**8** and (±)-**24** were chosen for the study and subjected to HKR with chiral Co-catalysts. In this section, we have described a flexible, novel method that employs HKR of racemic 3-substituted epoxy esters (±)-**8** and (±)-**24** to generate 3,4-disubstituted γ-butyrolactones **13** and **25** and 3-substituted epoxy ester **8** and **24** with two stereocentres of high optical purities in a single step (**Table 1**).

Preparation of racemic *anti*- and *syn*-3-substituted epoxy esters

The racemic *anti* and *syn*-3-substituted epoxy esters **8** and **24**, the substrates for HKR, were efficiently prepared[20] in a highly diastereoselective manner from the corresponding allylic alcohols **21a-e** Thus, allylic alcohols **21a-e** were subjected to Johnson-Claisen rearrangement in the presence of $MeC(OEt)_3$, hexanoic acid (catalytic) to give acyclic olefinic acids **22a-e** in 78-92% yields (**Scheme 7**).



Scheme 7: (i) $MeC(OEt)_3$, hexanoic acid, 80-150 ^oC, 3 h, 78-92%; (ii) I_2, CH_3CN, 0 ^oC, 24 h, 80-89%; (iii) MeOH, Na_2CO_3, reflux, 3 h, 88-95%; (iv) I_2, $NaHCO_3$, $CHCl_3$, 0 ^oC, 6 h, 71-80%.

The formation of olefinic acids, (±)-**22a-e**, was confirmed from ^1H and ^{13}C NMR spectroscopy. For example, the ^1H NMR spectrum of (±)-**22a** showed typical signals at δ 5.01-5.12 (m, 2H) and δ 5.84-6.01 (m, 1H) due to olefinic protons and at δ 3.82 (q, 1H) due to benzylic protons. Its ^{13}C NMR spectrum showed a typical carbon signal at δ 178.0 corresponding to carbonyl carbon group (**Fig. 1**).

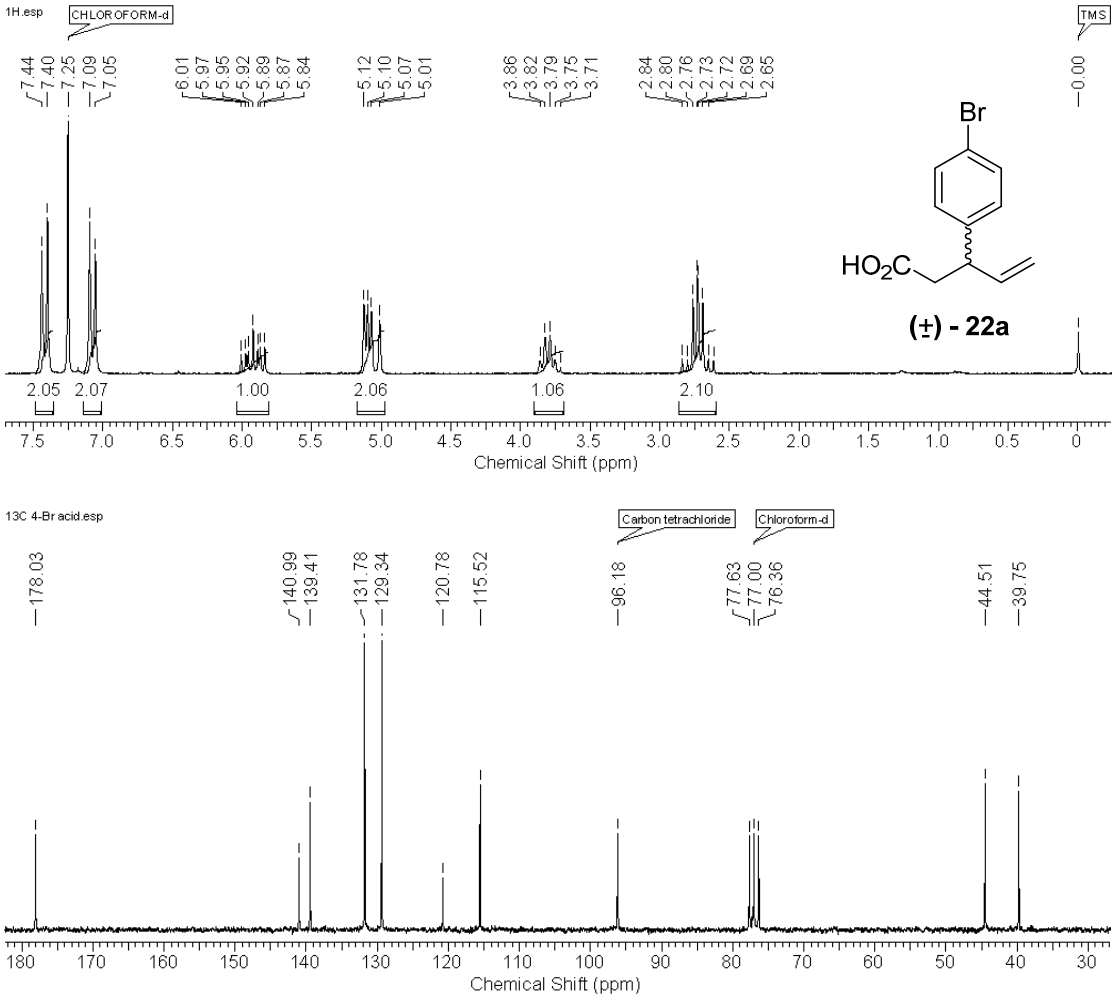


Fig. 1: ^{1}H and ^{13}C NMR spectra of olefinic acid (±)-**22a**

Acyclic olefinic acids **22a-e** were then subjected to diastereoselective iodolactonization (for *trans*: I_2, CH_3CN, 0 ^{o}C, 24 h; for *cis*: I_2, $NaHCO_3$, $CHCl_3$, 0 ^{o}C, 6 h) to give *trans* or *cis*-iodolactones (**19** or **23**) in 71-89% yields.

The formation of *trans* iodolactone (±)-**7** was confirmed from ^{1}H and ^{13}C NMR spectroscopy. For example, the ^{1}H NMR spectrum of iodolactone (±)-**7a** showed two doublet of doublet at δ 2. 80 (dd, J = 9.1 and 17.9 Hz, 1H) and δ 3.05 (dd, J = 9.1 and 17.8 Hz, 1H) for the protons attached to α-carbon atom. Its ^{13}C NMR spectrum

showed a typical carbon signal at δ 6.2 due to carbon attached to iodo group and a characteristic signal at δ 173.7 for carbonyl carbon group (**Fig. 2**).

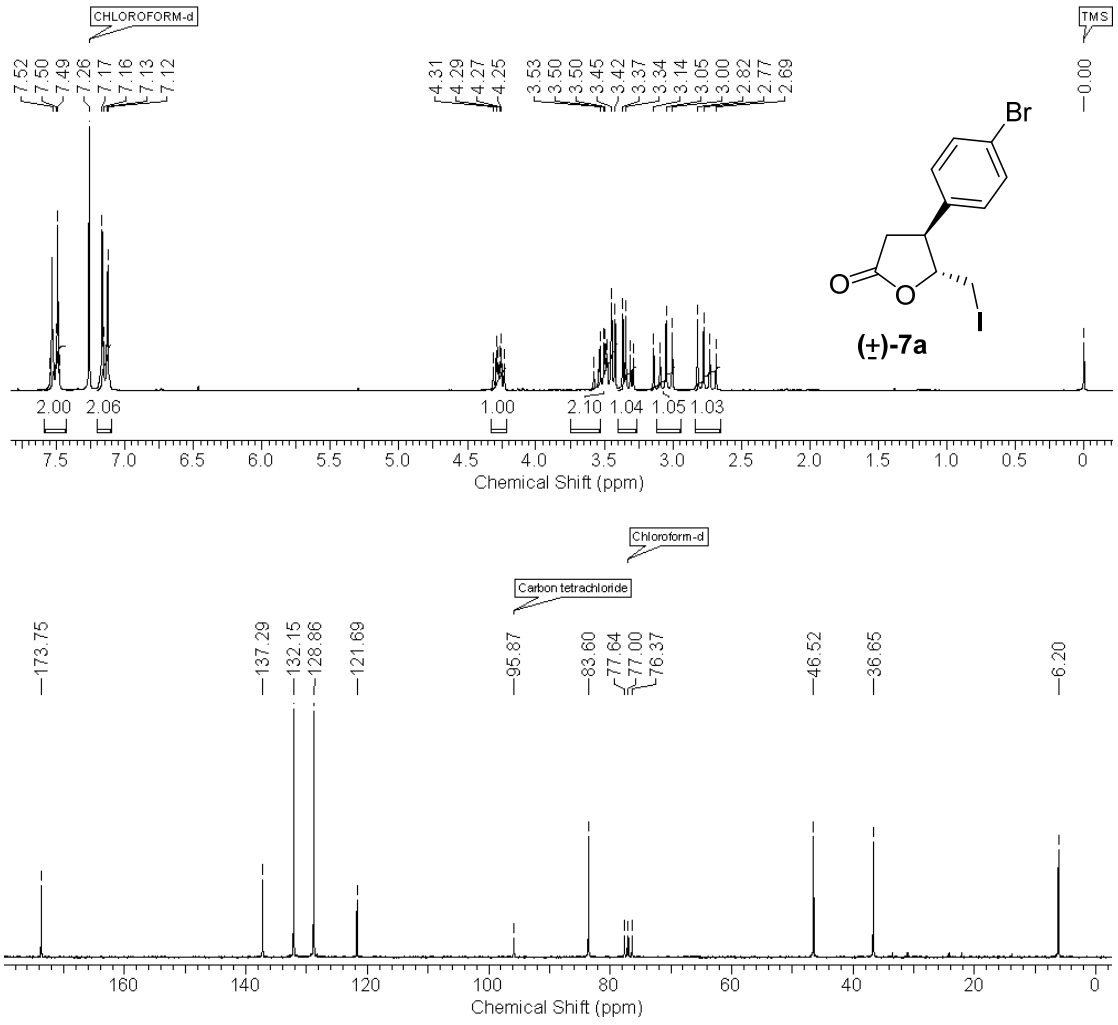


Fig. 2: ^{1}H and ^{13}C NMR spectra of *anti*-iodolactone (±)-**7a**

Similarly, the formation of racemic *cis*-iodolactone (±)-**23** was confirmed from ^{1}H and ^{13}C NMR spectroscopy. The ^{1}H NMR spectrum of *syn*-iodolactone (±)-**23a** showed typical signal at δ 3.87 (m, 1H) for methine protons at benzylic position and a multiplet at δ 4.94 (m, 1H) due to methine protons attached to adjacent oxygen atom. Its ^{13}C NMR spectrum showed two characteristic signals at δ 1.1 and 175.1 due to carbons attached to iodo and carbonyl carbon groups respectively (**Fig. 3**).

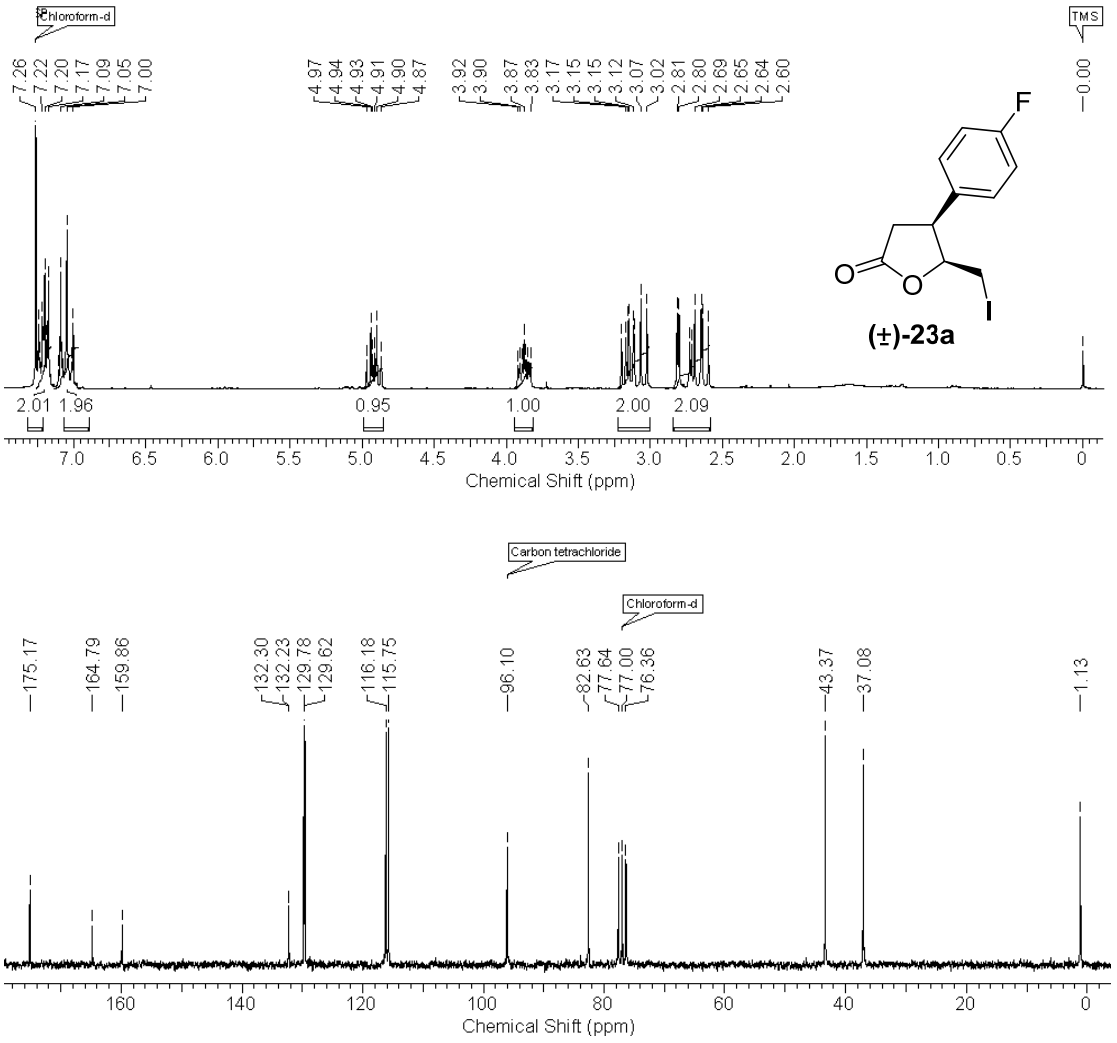


Fig. 3: ^{1}H and ^{13}C NMR spectra of *syn*-iodolactone (±)-**23a**

Methanolysis of iodolactones (±)-**7** or (±)-**23** under basic conditions produced the required racemic *anti*- or *syn*- 3- substituted epoxy esters (±)-**8** or (±)-**24** (**Scheme 7**). For example, the ^{1}H NMR spectrum of *anti*-3-substituted epoxy ester (±)-**8a** showed a typical singlet at δ 3.60 (s, 3H) corresponding to methoxy protons. Its ^{13}C NMR spectrum showed characteristic signals at δ 46.5 and δ 54.7 due to carbons of the epoxide moiety and δ 171.4 for carbonyl carbon group (**Fig. 4**).

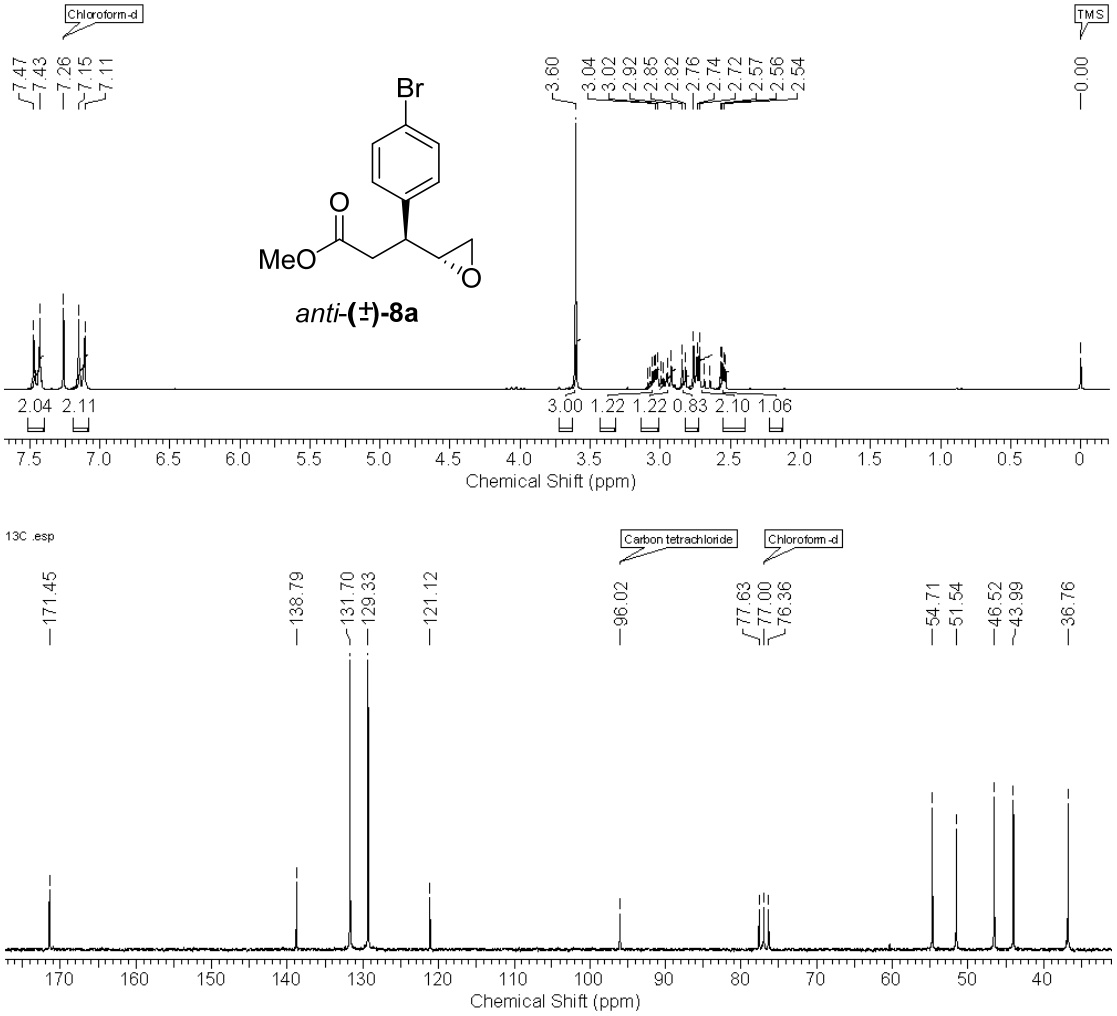


Fig. 4: ^{1}H and ^{13}C NMR spectra of *anti*-epoxy ester (±)-**8a**

Similarly, the formation of *syn*-3- substituted epoxy ester (±)-**24** was confirmed from ^{1}H and ^{13}C NMR spectroscopy. The ^{1}H NMR spectrum of (±)-**24a** showed a typical singlet at δ 3.63 (s, 3H) for methoxy protons. Its ^{13}C NMR showed characteristic carbon signals at δ 45.6 and 54.3 due to carbons of the epoxide ring and δ 171.6 for carbonyl carbon group (**Fig. 5**).

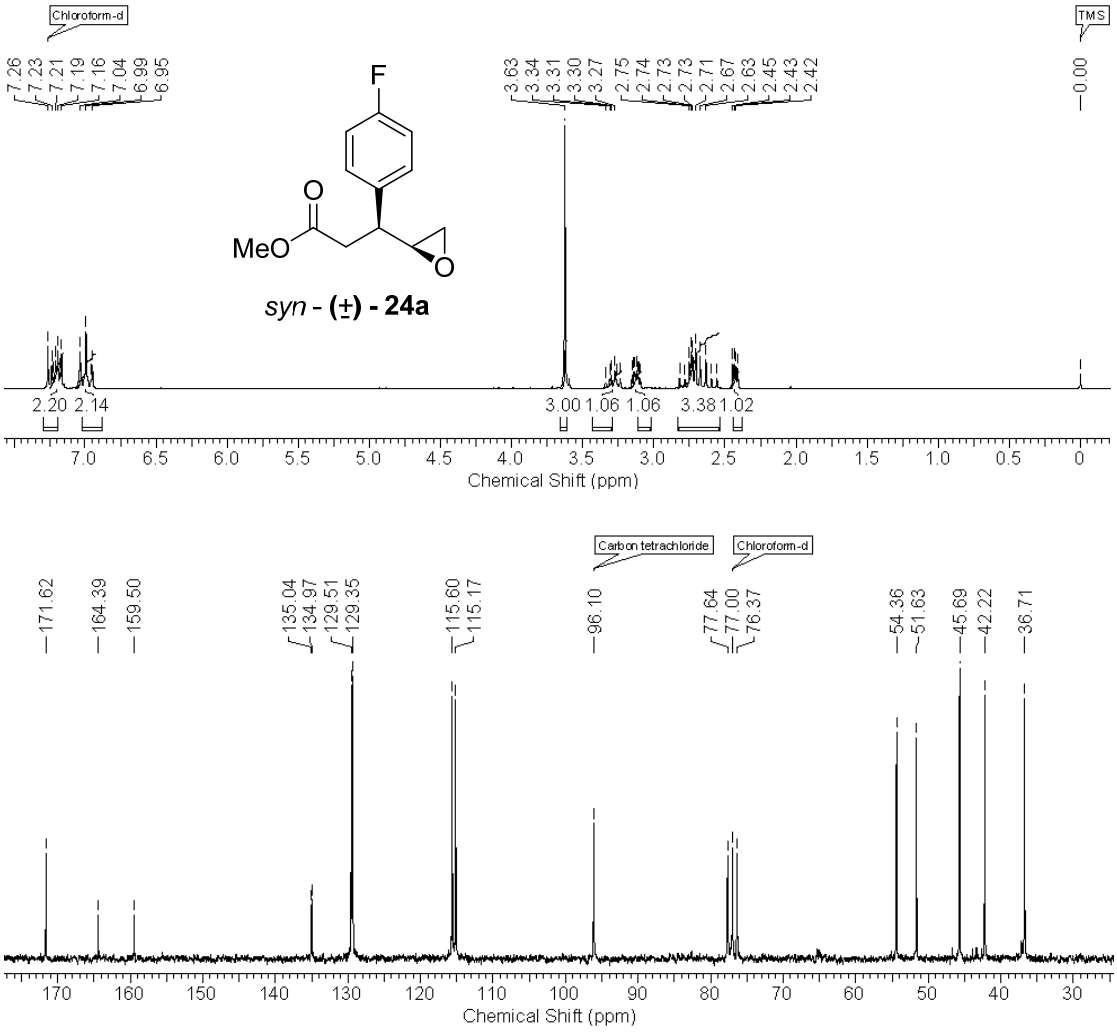


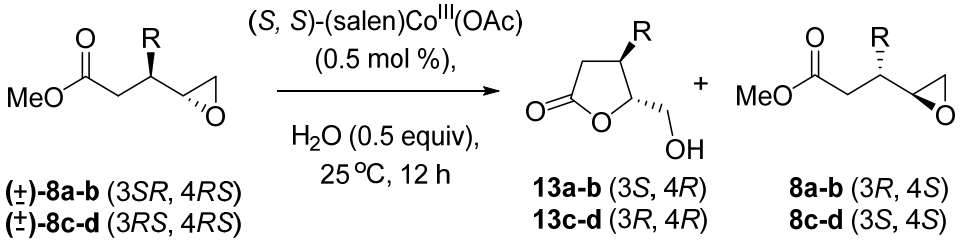
Fig. 5: ^{1}H and ^{13}C NMR spectra of *syn*-epoxy ester (±)-**24a**

HKR of racemic azido epoxides

Initially, when HKR of racemic *anti*- 3-substituted epoxy ester **8a** was carried out with (*S, S*)-(salen)Co(OAc) complex **1** (0.5 mol %) and H_2O (0.5 equiv), the corresponding *trans*-3,4-disubstituted γ-butyrolactone **13a** (45%) and 3-substituted epoxy ester **8a** (48%) were obtained in high yields and optical purity [**13a** (96% ee) and **8a** (96% ee)]. The formation of γ-butyrolactone **13a** can be explained on the basis of intramolecular cyclization of the chiral diol formed *in situ* with ester carbonyl functionality. Encouraged by this result, we have examined its scope by subjecting

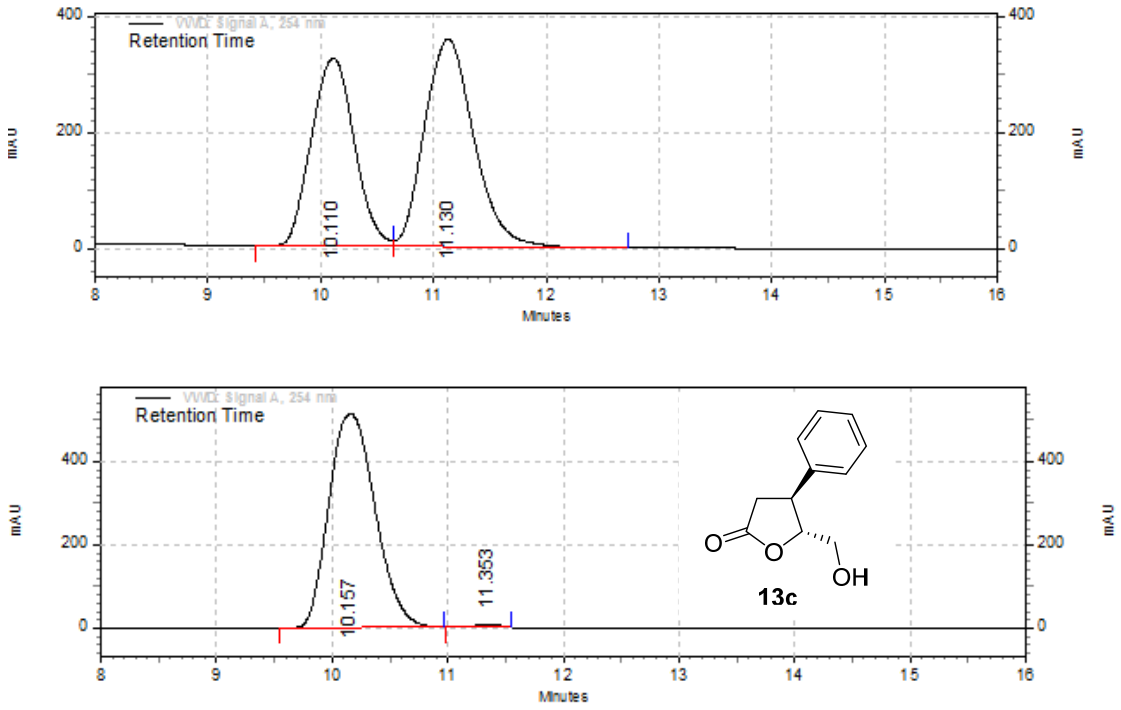
several racemic *anti*-3-substituted epoxy esters **8a-e** to HKR, which proceeded smoothly, with complete regiocontrol, to give the respective enantioenriched *trans*-3,4-disubstituted γ-butyrolactones **13a-e** and *anti*- epoxy esters **8a-e** in excellent ees (96 to 99% ee) and high yields (45 to 49%). The ees of *trans*-3,4-disubstituted γ-butyrolactone **13a-e** and *anti*- epoxy esters **8a-e** were determined from chiral HPLC analysis (**Fig. 6**). The results of such a study are shown in **Table 1**. The reaction thus exhibited good generality with respect to the degree of functionalization of epoxides.

Table 1. Co-catalyzed HKR of racemic 3-substituted *anti*-epoxy esters



entry	substrates (R)	lactones **13a-e**		epoxy ester **8a-e**	
	(±)-**8a-e**	yield (%)[a]	ee (%)[b]	yield (%)[a]	ee (%)[b]
a	4-bromophenyl	46	96	48	96
b	4-chlorophenyl	45	98	48	98
c	phenyl	45	99	48	97
d	benzyl	47	99	48	97
e	3-phenylpropyl	48	96	48	96

[a] Isolated yield after column chromatographic purification; [b] ee determined by chiral HPLC.



Retention Time	Area	Area %	Height	Height %
10.157	239861276	99.56	8617320	99.39
11.353	1070458	0.44	52774	0.61
Totals	240931734	100.00	8670094	100.00

Column :Chiracel OD-H (4.6X250 nm), Mobile Phase :IPA:n-Hexane (50:50) Wavelength :254 nm, Flow rate :0.5 ml/min

Fig. 6: HPLC chromatogram of lactone **13c**

The formation of *trans*-3,4-disubstituted γ-butyrolactone **13a** was confirmed from ^{1}H and ^{13}C NMR spectroscopy. For example, the ^{1}H NMR spectrum of **13a** exhibited characteristic doublet of doublets at δ 2.72 (dd, J = 9.6 and 17.8 Hz, 1H) and δ 3.03 (dd, J = 9.1 and 17.8 Hz, 1H) due to the protons attached to α-carbon atom. Its ^{13}C NMR spectrum also showed typical carbon signals at δ 61.4 and 176.1 due to carbon attached to hydroxyl group and carbonyl carbon group respectively **(Fig.7)**.

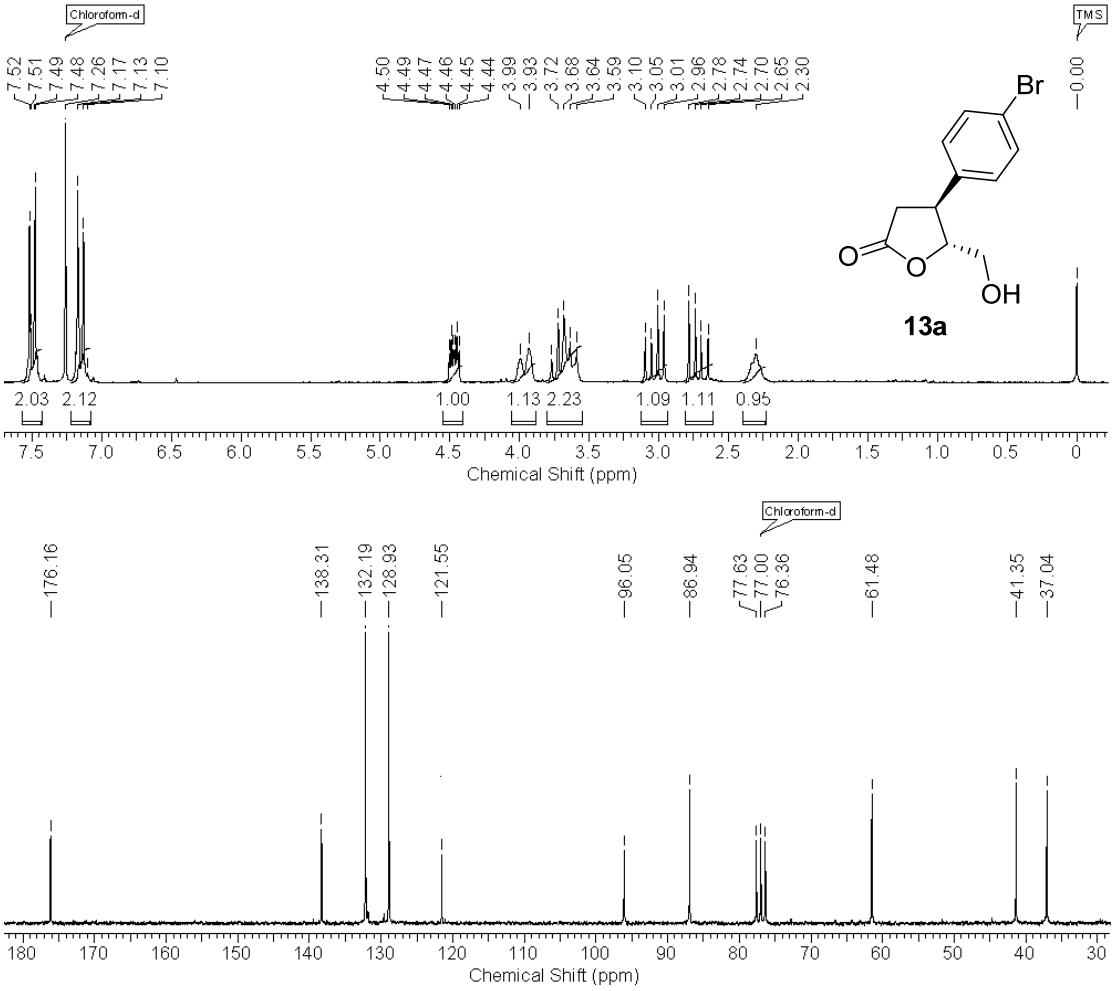


Fig. 7: ^{1}H and ^{13}C NMR spectra of *trans*-lactone **13a**

Lactone functionality in **13a** was further confirmed from its IR spectrum, which showed a characteristic strong absorption band at υ_{max} 1775 cm^{-1}.

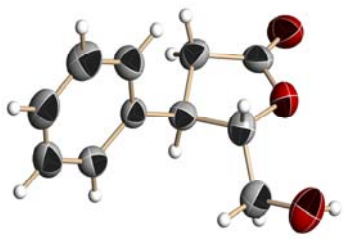
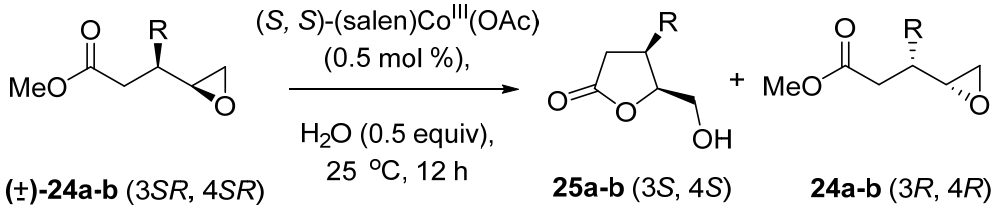


Fig. 8: ORTEP diagram for lactone **13c**

The *trans*-stereochemistry of γ-butyrolactone **13c** was further confirmed by single crystal X-ray crystallographic study **(Fig. 8)**.

Similarly, when *syn*- 3-substituted epoxy esters **24a-b** were subjected to HKR under identical reaction conditions, the corresponding chiral *cis*-3,4-disubstituted γ-butyrolactones **25a-b** and *syn*-epoxy esters **24a-b** were obtained in high yields and ees upto 99%. The enantiomeric excess of *cis*-3,4-disubstituted γ-butyrolactones **25a-b** was determined from chiral HPLC analysis. The results of this study are presented in Table 2.

Table 2. Co-catalyzed HKR of racemic 3-substituted *syn*-epoxy esters



(±)-24a-b (3*SR*, 4*SR*) **25a-b** (3*S*, 4*S*) **24a-b** (3*R*, 4*R*)

entry	substrates (R)	lactones **25a-b**		Epoxy ester **24a-b**	
	(±)-**24a-b**	yield (%)[a]	ee (%)[b]	yield (%)[a]	ee (%)[b]
a	4-fluorophenyl	46	98	48	98
b	4-chlorophenyl	47	99	46	97

[a] Isolated yield after column chromatographic purification; [b] ee determined by chiral HPLC chromatogram.

The formation of *cis*-3,4-disubstituted γ-butyrolactones **25a-b** was confirmed from ^{1}H and ^{13}C NMR spectroscopy. For example, the ^{1}H NMR spectrum of **25a** showed a typical quartet at δ 3.88 (q, J = 8.6 Hz, 1H) for methine protons at benzylic position

and a multiplet at δ 4.74 (m, 1H) for methine protons adjacent to oxygen atom. Its ^{13}C NMR showed characteristic signals at δ 61.9 and 176.3 due to carbons attached to hydroxy and carbonyl carbon groups respectively (**Fig. 9**). The absolute configuration of both 3,4-disubstituted γ-butyrolactones (**13** and **25**) and 3-substituted epoxy esters (**8** and **24**) was further ascertained by comparing their optical rotations with those reported in the literature.[4d, 15]

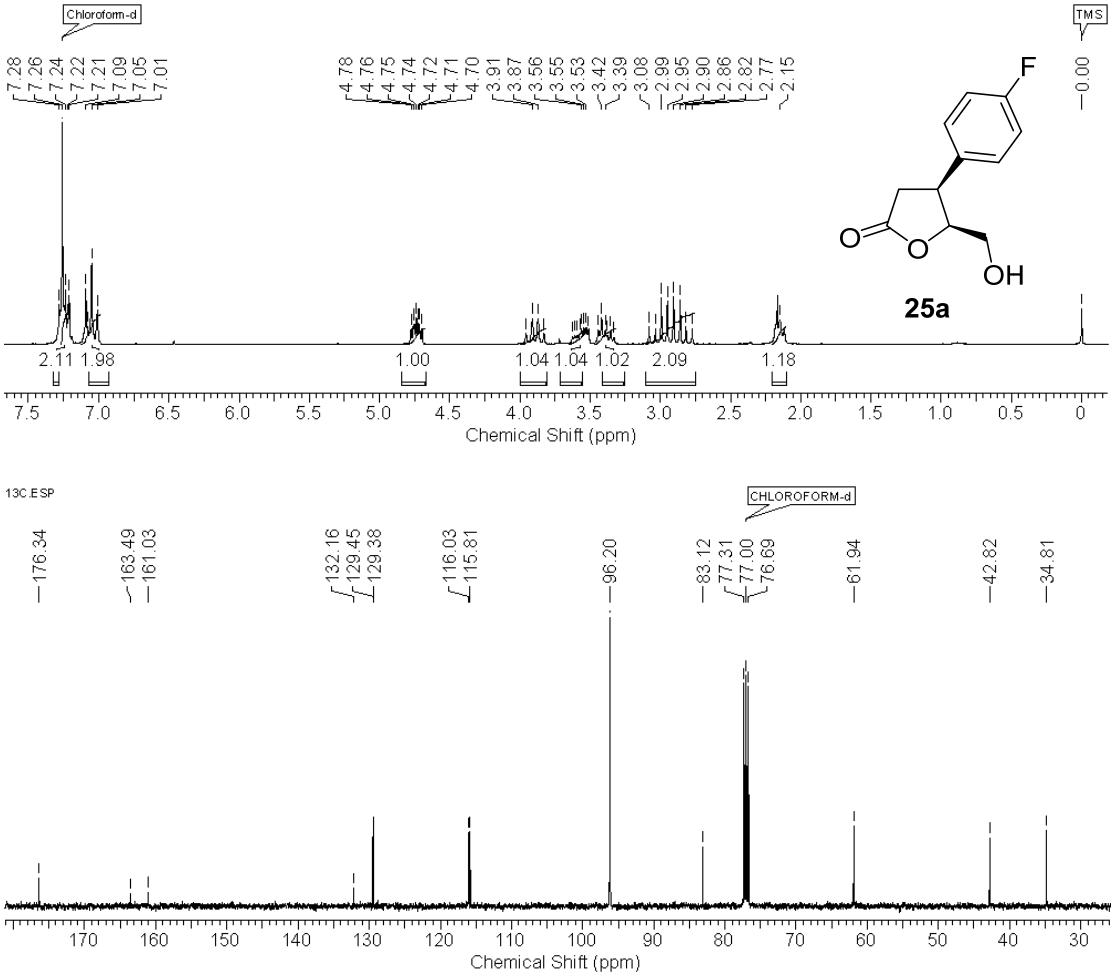


Fig. 9: ^{1}H and ^{13}C NMR spectra of *syn*-lactone **25a**

2.1.5 Conclusion

In conclusion, the (salen)Co(III)-catalyzed HKR of racemic *anti*- or *syn*- 3-substituted epoxy esters provides a highly practical route to the synthesis of substituted enantioenriched γ-butyrolactones **13a-e** and **25a-b** and 3-substituted epoxy esters **8a-e** and **24a-b** in a single step. The reaction is convenient to carry out under mild conditions. We believe that this HKR strategy will find applications in the field of asymmetric synthesis of bioactive molecules owing to the flexible nature of synthesis of racemic 3-substituted epoxy ester and the commercial availability of Co-salen catalysts in both enantiomeric forms.

2.1.6 Experimental Section

General procedure for the synthesis of acyclic olefinic carboxylic acids (22a-e)

A mixture of allylic alcohol **21** (37.31 mmol), triethyl orthoacetate (37.31 mmol) and hexanoic acid (0.23 mL, 1.85 mmol) was placed in a round-bottomed flask equipped with thermometer, Claisen head and condenser. The solution was heated with distillation of ethanol (upto 70-150 ^{o}C). After 3 h distillation of ethanol slowed and another 0.1-mL portion of hexanoic acid was added. Additional portions (0.1 mL) of hexanoic acid were added again after 3 and 4 h followed by continued heating for the next 6 h. It was allowed to cool and aq. solution of KOH (2.9 g, 52.2 mmol, 20 ml) in MeOH (60 mL) was added. The resulting mixture was refluxed for 4 h and then allowed to cool to room temperature. After that the resulting solution was washed with diethyl ether and acidified with dil. HCl. The acidic solution was extracted with diethyl ether and the organic layer dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude product **22**. The crude material can be used as such for the next reaction without any further purification.

3-(4-Bromophenyl)pent-4-enoic acid (22a)

Yield: 84%, colorless solid **mp**: 108 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1124, 1420, 1509, 1706, 2912, 2987, 3044, 3076; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.70 (dd, *J* = 7.7, 15.8 Hz, 1H), 2.81 (dd, *J* = 7.6, 15.8 Hz, 1H), 3.79 (q, *J* = 7.6 Hz, 1H), 5.02-5.13 (m, 2H), 5.84- 6.01 (m, 1H), 7.08 (d, *J* = 8.3 Hz, 2H), 7.42 (d, *J* = 8.3 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 39.7, 44.5, 115.5, 120.7, 129.3, 131.7, 139.4, 140.9, 178.0; **Anal**. Calcd for $C_{11}H_{11}O_2Br$ requires C, 51.79; H, 4.35; found: C, 51.68; H, 4.32%.

3-(4-Chlorophenyl)pent-4-enoic acid (22b)

Yield: 85%, colorless solid **mp**: 100 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1496, 1707, 2610, 2905; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.70 (dd, *J* = 7.7, 15.8 Hz, 1H), 2.81 (dd, *J* = 7.6, 14.4 Hz, 1H), 3.83 (q, *J* = 7.3 Hz, 1H), 5.02-5.13 (m, 2H), 5.85-6.02 (m, 1H), 7.13 (d, *J* = 8.5 Hz, 2H), 7.27 (d, *J* = 8.5 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 39.8, 44.4, 115.4, 128.8, 128.9, 139.5, 140.4, 178.0; **Anal**. Calcd for $C_{11}H_{11}O_2Cl$ requires C, 62.72; H, 5.26; found: C, 62.65; H, 5.18%.

3-Phenylpent-4-enoic acid (22c)

Yield: 90%, colorless solid, **mp:** 48 ^oC; **IR** ($CHCl_3$, cm^{-1}): υ_{max}732, 1026, 1638, 1708, 3028; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.69 (dd, *J* = 7.5, 15.7 Hz, 1H), 2.82 (dd, *J* = 7.9, 15.7 Hz, 1H), 3.83 (q, *J* = 7.3 Hz, 1H), 5.03 (d, *J* = 5.5 Hz, 1H), 5.11 (s, 1H), 5.89-6.06 (m, 1H), 7.18-7.33 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 40.0, 45.1, 115.0, 126.8, 127.5, 128.6, 139.9, 142.0, 178.3; **Anal**. Calcd for $C_{11}H_{12}O_2$ requires C, 74.98; H, 6.86; found: C, 74.70; H, 6.80%.

3-Benzylpent-4-enoic acid (22d)

Yield: 92%, colorless viscous liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1011, 1495, 1641, 1693, 2675, 3071; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.33 (dd, *J* = 8.2, 15.5 Hz, 1H), 2.41 (dd, *J* = 5.7, 15.4 Hz, 1H), 2.67-2.95 (m, 3H), 4.96-5.05 (m, 2H), 5.64-5.82 (m, 1H), 7.12-

7.31 (m, 5H) ; **^{13}C NMR** (50 MHz, $CDCl_3$): δ 38.5, 40.8, 41.3, 115.4, 126.2, 128.3, 129.2, 139.1, 139.9, 179.1; **Anal**. Calcd for $C_{12}H_{14}O_2$ requires C, 75.76; H, 7.42; found: C, 75.72; H, 7.50%.

3-Phenethylpent-4-enoic acid (22e)

Yield: 85%, colorless liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1044, 1260, 1603, 1641, 1708, 3025; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.64-1.80 (m, 2H), 2.34-2.43 (m, 2H), 2.51-2.68 (m, 3H), 5.07 (s, 1H), 5.15 (d, *J* = 3.9 Hz, 1H), 5.60-5.74 (m, 1H), 7.13-7.30 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 33.3, 36.1, 39.8, 39.9, 116.0, 125.8, 128.3, 140.2, 141.8, 178.9; **Anal**. Calcd for $C_{13}H_{16}O_2$ requires C, 76.44; H, 7.90; found: C, 76.45; H, 7.95%.

General procedure for the synthesis of *anti*-iodolactones product (7)

To a solution of olefinic acid **22** (5.68 mmol) in acetonitrile (20 mL), solid I_2 (4.6 g, 18.17 mmol) was added at 0 ^oC under N_2 atmosphere. The reaction mixture was protected from light and stirred for 24 h. After the completion of the reaction (monitored by TLC), it was quenched with the addition of saturated solution of aq. $NaHCO_3$ followed by extraction with diethyl ether. Organic layer was separated and washed with 20% aq. $Na_2S_2O_3$ until colorless, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude products **7**. Column chromatographic purification with silica gel using petroleum ether: ethyl acetate (8:2) as eluent gave **7** in pure form as given below.

***anti*-(±)-4-(4-Bromophenyl)-5-(iodomethyl)dihydrofuran-2(3*H*)-one (7a)**

Yield: 82%, colorless gummy liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 945, 1126, 1782, 2812; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.75 (dd, *J* = 9.1, 17.8 Hz, 1H), 3.07 (dd, *J* = 9.1, 17.8 Hz, 1H), 3.29-3.58 (m, 3H), 4.28 (m, 1H), 7.15 (d, *J* = 8.5 Hz, 2H), 7.51 (d, *J* = 8.5 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 6.2, 36.6, 46.5, 83.6, 121.6, 128.8, 132.1,

137.2, 173.7; **Anal**. Calcd for $C_{11}H_{10}BrO_2I$ requires C, 34.68; H, 2.65; found: C, 34.70; H, 2.68%.

***anti*-(±)-4-(4-Chlorophenyl)-5-(iodomethyl)dihydrofuran-2(3*H*)-one (7b)**

Yield: 80%, colorless gummy liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1056, 1230, 1789, 2833, 2963; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.75 (dd, *J* = 9.1, 17.8 Hz, 1H), 3.07 (dd, *J* = 9.2, 17.9 Hz, 1H), 3.29-3.59 (m, 3H), 4.28 (m, 1H), 7.20 (d, *J* = 8.5 Hz, 2H), 7.36 (d, *J* = 8.6 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 5.9, 36.8, 46.6, 83.8, 128.5, 129.5, 134.0, 137.1, 173.7; **Anal**. Calcd for $C_{11}H_{10}ClO_2I$ requires C, 39.26; H, 2.99; found: C, 39.28; H, 3.02%.

***anti*-(±)-5-(Iodomethyl)-4-phenyldihydrofuran-2(3*H*)-one (7c)**

Yield: 89%, colorless thick liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1420, 1506, 1780, 2839, 2913; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.80 (dd, *J* = 9.6, 17.9 Hz, 1H), 3.05 (dd, *J* = 9.1, 17.8 Hz, 1H), 3.34 (dd, *J* = 4.4, 11.2 Hz, 1H), 3.45-3.59 (m, 2H), 4.31 (m, 1H), 7.24-7.42 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 6.3, 36.8, 47.1, 83.9, 127.1, 128.0, 129.2, 138.3, 174.0; **Anal**. Calcd for $C_{11}H_{11}O_2I$ requires C, 43.73; H, 3.67; found: C, 43.72; H, 3.70%.

***anti*-(±)-4-Benzyl-5-(iodomethyl)dihydrofuran-2(3*H*)-one(7d)**

Yield: 85%, colorless solid, **mp**: 62 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 749, 826, 1782, 2913; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.31-2.44 (m, 1H), 2.64-2.89 (m, 4H), 3.08 (dd, *J* = 4.4, 10.9 Hz, 1H), 3.27 (dd, *J* = 5.4, 10.9 Hz, 1H), 4.17 (q, *J* = 5.2 Hz, 1H), 7.15-7.38 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 7.2, 34.4, 39.2, 42.1, 82.2, 126.8, 128.6, 128.7, 137.5, 174.5; **Anal**. Calcd for $C_{12}H_{13}O_2I$ requires C, 45.59; H, 4.14; found: C, 45.62; H, 4.20%.

***anti*-(±)-5-(Iodomethyl)-4-phenethyldihydrofuran-2(3*H*)-one (7e)**

Yield: 82%, colorless gummy liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 748, 1130, 1778, 2812; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.64-2.07 (m, 2H), 2.23-2.41 (m, 2H), 2.55-2.88 (m, 3H), 3.26-3.42 (m, 2H), 4.15 (q, *J* = 5.3 Hz, 1H), 7.13-7.33 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 7.2, 34.4, 39.2, 42.1, 82.2, 126.8, 128.6, 128.7, 137.5, 174.5; **Anal**. Calcd for $C_{13}H_{15}O_2I$ requires C, 47.29; H, 4.58; found: C, 47.22; H, 4.50%.

General procedure for the synthesis of *syn*-iodolatone product (23)

To a stirred solution of olefinic acid **22** (5.68 mmol) in $CHCl_3$ (20 mL), aq. $NaHCO_3$ (0.95 g, 11.36 mmol) in 20 mL of water and solid I_2 (2.88 g, 11.36 mmol) were added at 0 ^oC under N_2 atmosphere. The reaction mixture was protected from light and stirring continued for 6 h. After the completion of the reaction (monitored by TLC), organic layer was separated and washed with 20% aq. $Na_2S_2O_3$ until it become colorless, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude product **23**. Column chromatographic purification with silica gel using petroleum ether: ethyl acetate (9:1) as eluent gave **23** in pure form as given below.

***syn*-(±)-4-(4-Fluorophenyl)-5-(iodomethyl)dihydrofuran-2(3*H*)-one (23a)**

Yield: 76%, colorless solid, **mp**: 99 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1052, 1132, 1785, 2906; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.60-2.81 (m, 2H), 3.02-3.20 (m, 2H), 3.88 (m, 1H), 4.92 (m, 1H), 7.00-7.10 (m, 2H), 7.17-7.26 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 1.1, 37.0, 43.3, 86.6, 115.7 (d, *J* = 21.6 Hz), 129.7 (d, *J* = 8.1 Hz), 132.2 (d, *J* = 3.3 Hz), 162.3 (d, *J* = 248.1 Hz), 175.1; **Anal**. Calcd for $C_{11}H_{10}O_2FI$ requires C, 41.27; H, 3.15; found: C, 41.18; H, 3.27%.

***syn*-(±)-4-(4-Chlorophenyl)-5-(iodomethyl)dihydrofuran-2(3*H*)-one (23b)**

Yield: 75%, colorless gummy liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1207, 1420, 1780; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.60-2.81 (m, 2H), 3.02-3.21 (m, 2H), 3.86 (m, 1H), 4.92

(m, 1H), 7.17 (d, *J* = 8.5 Hz, 2H), 7.34 (d, *J* = 8.6 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 1.0, 36.9, 43.5, 82.4, 129.1, 129.4, 134.1, 134.9, 175.0; **Anal**. Calcd for $C_{11}H_{10}ClO_2I$ requires C, 39.26; H, 2.99; found: C, 3.28; H, 2.84%.

General procedure for the synthesis of *anti*- and *syn*-epoxy esters (8a-e &24a-b)

To a solution of iodolactone **7** or **23** (3.3 mmol) in MeOH (15 mL) finely powdered anhydrous Na_2CO_3 (0.38 g, 3.63 mmol) was added and the reaction mixture refluxed for 8 h under N_2 atmosphere. After the completion of the reaction (monitored by TLC), the resulting reaction mixture was concentrated under reduced pressure and partitioned between 50 mL water and 50 mL diethyl ether. The organic layer was dried over anhydrous Na_2SO_4 andconcentrated under reduced pressure to give the corresponding crude product **8** or **24**. Column chromatographic purification with silica gel using petroleum ether:ethyl acetate (9:1) as eluent gave **8** or **24** pure in form as given below.

Methyl 3-(4-bromophenyl)-3-(oxiran-2-yl)propanoate (8a)

Yield: 95%, colorless liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 760, 823, 1224, 1734; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.55 (dd, *J* = 2.3, 4.7 Hz, 1H), 2.65-3.09 (m, 5H), 3.60 (s, 3H), 7.13 (d, *J* = 8.5 Hz, 2H), 7.45 (d, *J* = 8.3 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 36.7, 43.9, 46.5, 51.5, 54.7, 121.1, 129.3, 131.7, 138.7, 171.4; **HRMS** (*m/z*): calculated $[M+H]^+$ for $C_{12}H_{14}BrO_3$: 285.0121; found: 285.0121.

Methyl 3-(4-chlorophenyl)-3-(oxiran-2-yl)propanoate (8b)

Yield: 90%, colorless thick liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1520, 1736, 2851, 2940; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.56 (dd, *J* = 2.4, 4.7 Hz, 1H), 2.65-3.09 (m, 5H), 3.60 (s, 3H), 7.16 (m, 2H), 7.30 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 36.9, 44.0, 46.6, 51.6, 54.8, 128.8, 129.0, 133.1, 138.2, 171.5; **HRMS** (*m/z*): calculated $[M+H]^+$ for $C_{12}H_{14}ClO_3$: 241.0626; found: 241.0626.

Methyl 3-(oxiran-2-yl)-3-phenylpropanoate (8c)

Yield: 88%, colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1044, 1426, 1736; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.55 (dd, *J* = 2.6, 4.8 Hz, 1H), 2.72-3.12 (m, 5H), 3.60 (s, 3H), 7.20-7.34 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 37.3, 44.9, 46.9, 51.6, 55.2, 127.3, 127.6, 128.7, 139.8, 171.8; **HRMS (*m/z*)**: calculated $[M+H]^+$ for $C_{12}H_{15}O_3$: 207.1016; found: 207.1014.

Methyl 3-(oxiran-2-yl)-4-phenylbutanoate (8d)

Yield: 95%, colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1220, 1523, 1737, 2480; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.01 (m, 1H), 2.26 (dd, *J* = 2.7, 4.8 Hz, 1H), 2.32-2.56 (m, 2H), 2.60-2.89 (m, 4H), 3.67 (s, 3H), 7.14-7.31 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 35.8, 37.5, 40.4, 47.0, 51.4, 54.2, 126.2, 128.3, 129.0, 138.8, 172.3; **HRMS** (*m/z*): calculated $[M+H]^+$ for $C_{13}H_{17}O_3$: 221.1172; found: 221.1172.

Methyl 3-(oxiran-2-yl)-5-phenylpentanoate (8e)

Yield: 91%, colorless liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 732, 950, 1022, 1743; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.77 (m, 3H), 2.34-2.87 (m, 7H), 3.68 (s, 3H), 7.14-7.30 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 33.0, 33.2, 36.4, 38.1, 47.1, 51.42, 54.5, 125.9, 128.1, 128.3, 141.4, 172.4; **HRMS** (*m/z*): calculated $[M+H]^+$ for $C_{14}H_{19}O_3$: 235.1329; found: 235.1329.

Methyl 3-(4-fluorophenyl)-3-(oxiran-2-yl)propanoate (24a)

Yield: 90%, colorless liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 731, 950, 1022, 1736; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.43 (dd, *J* = 2.5, 4.8 Hz, 1H), 2.56-2.82 (m, 3H), 3.09-3.15 (m, 1H), 3.24-3.34 (m, 1H), 3.63 (s, 3H), 6.95-7.04 (m, 2H), 7.16-7.26 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 36.7, 42.2, 45.6, 51.6, 54.3, 115.6 (d, *J* = 21.2 Hz), 129.5 (d, *J* = 8.1 Hz), 135.0 (d, *J* = 3.3 Hz), 162.0 (d, *J* = 245.9 Hz), 171.6; **HRMS** (*m/z*): calculated $[M+H]^+$ for $C_{12}H_{14}FO_3$: 225.0921; found: 225.0921.

Methyl 3-(4-chlorophenyl)-3-(oxiran-2-yl)propanoate (24b)

Yield: 90%, colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 842, 1039, 1207, 1736; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.44 (dd, *J* = 2.6, 4.8 Hz, 1H), 2.57-2.83 (m, 3H), 3.10-3.16 (m, 1H), 3.23-3.33 (m, 1H), 3.63 (s, 3H), 7.17 (d, *J* = 8.5 Hz, 2H), 7.29 (d, *J* = 8.6 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 36.5, 42.4, 45.7, 51.7, 54.2, 128.7, 129.3, 133.1, 137.7, 171.5; **HRMS** (*m/z*): calculated $[M+H]^+$ for $C_{12}H_{14}ClO_3$: 241.0626; found: 241.0626.

A general experimental procedure for Hydrolytic Kinetic Resolution (HKR) of 3-substituted epoxy esters (8a-d & 24a-b):

To a solution of (*R*, *R*)- or (*S*, *S*)-(salen)Co(II)complex (0.024 mmol, 0.5 mol %) in toluene (1 mL), AcOH (0.014 g, 0.24 mmol) was added. It was allowed to stir at 25 °C in open air for 30 min during which time the color changed from orange-red to a dark brown and it was then concentrated under reduced pressure to get the Co(III)-salen complex-**1** as brown colored solid. To this, racemic 3-substituted epoxy esters (±)-**8/24** (4.85 mmol) and H_2O (0.043 g, 2.42 mmol) was added at 0 °C. The reaction was allowed to warm to 25 °C and stirred for 12 h. After completion of reaction (monitored by TLC), the crude product was purified by column chromatography over silica gel to give chiral epoxy esters **8a-e** and **24a-b** [solvent system; petroleum ether: ethyl acetate (9:1)] and chiral γ-butyrolactones **13a-e** and **25a-b** [solvent system; petroleum ether:ethyl acetate (1:1)] in pure form.

(4*S*, 5*R*)-4-(4-Bromophenyl)-5-(hydroxymethyl)dihydrofuran-2(3*H*)-one (13a)

Yield: 46%, colorless gummy liquid; **$[\alpha]_D^{25}$** = -21.2 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1010, 1073, 1197, 1775, 3440; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.30 (br s, 1H), 2.72 (dd, *J* = 9.6, 17.8 Hz, 1H), 3.03 (dd, *J* = 9.1, 17.7 Hz, 1H), 3.59-3.77 (m, 2H), 3.93-3.99 (m, 1H), 4.48 (m, 1H), 7.15 (d, *J* = 8.5 Hz, 2H), 7.50 (d, *J* = 8.5 Hz, 2H);

^{13}C NMR (50 MHz, $CDCl_3$): δ 37.0, 41.3, 61.4, 86.9, 121.5, 128.9, 132.1, 138.3, 176.1; **HRMS** (*m/z*): calculated $[M+H]^+$ for $C_{11}H_{12}BrO_3$: 270.9964; found: 270.9965; **Optical purity**: 99% ee determined by HPLC analysis (Chiral OJ-H column, *n*-hexane/ 2-propanol (50:50), 0.5 mL/min, 254 nm) Retention time: t_{minor} = 11.91 and t_{major} = 12.47 min.

(*R*)-Methyl 3-(4-bromophenyl)-3-((*S*)-oxiran-2-yl)propanoate (8a)

Yield: 48%, colorless gummy liquid; **$[\alpha]_D^{25}$** -8.8 (*c* 1, $CHCl_3$); **Optical purity**: 99% ee determined by HPLC analysis (OD-H column, *n*-hexane/ 2-propanol (90:10), 0.5 mL/min, 254 nm) Retention time: t_{minor} = 13.54 and t_{major} = 14.33 min.

(4*S*, 5*R*)-4-(4-Chlorophenyl)-5-(hydroxymethyl)dihydrofuran-2(3*H*)-one (13b)

Yield: 45%, colorless gummy liquid; **$[\alpha]_D^{25}$** -26.6 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1051, 1153, 1494, 1777, 3438; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.35 (br s, 1H), 2.72 (dd, *J* = 9.6, 17.7 Hz, 1H), 3.03 (dd, *J* = 9.1, 17.7 Hz, 1H), 3.60-3.78 (m, 2H), 3.92-4.00 (m, 1H), 4.48 (m, 1H), 7.21 (d, *J* = 8.5 Hz, 2H), 7.35 (d, *J* = 8.6 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 37.1, 41.3, 61.6, 86.9, 128.5, 129.3, 133.7, 137.8, 175.8; **HRMS** (*m/z*): calculated $[M+H]^+$ for $C_{11}H_{12}ClO_3$: 227.0469; found: 227.0470; **Optical purity**: 99% ee determined by HPLC analysis (Chiral OJ-H column, *n*-hexane/ 2-propanol (50:50), 0.5 mL/min, 254 nm) Retention time: t_{minor} = 11.21 and t_{major} = 11.64 min.

(*R*)-Methyl 3-(4-chlorophenyl)-3-((*S*)-oxiran-2-yl)propanoate (8b)

Yield: 48%, colorless gummy liquid; **$[\alpha]_D^{25}$** -11.8 (*c* 1, $CHCl_3$); **Optical purity**: 98% ee determined from HPLC analysis (OD-H column, *n*-hexane/ 2-propanol (90:10), 0.5 mL/min, 254 nm) Retention time: t_{minor} = 12.56 and t_{major} = 13.31 min.

(4*S*, 5*R*)-5-(Hydroxymethyl)-4-phenyldihydrofuran-2(3*H*)-one (13c)

Yield: 45%, colorless solid, **mp:** 82 °C; **$[\alpha]_D^{25}$** = -25.4 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}):

υ_{max} 1015, 1177, 1778, 3443; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.04 (br s, 1H), 2.80 (dd, *J* = 9.9, 17.8 Hz, 1H), 3.09 (dd, *J* = 9.1, 17.8 Hz, 1H), 3.63-3.77 (m, 2H), 3.93-3.99 (m, 1H), 4.53 (m, 1H), 7.24-7.40 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 37.2, 41.9, 61.7, 87.2, 127.1, 127.6, 129.1, 139.3, 176.3; **HRMS (*m/z*):** calculated $[M+H]^+$ for $C_{11}H_{13}O_3$: 193.0859; found: 193.0859; **Optical purity**: 99% ee determined from HPLC analysis (Chiral OD-H column, *n*-hexane/ 2-propanol (50:50), 0.5 mL/min, 254 nm) Retention time: t_{major} = 10.15 and t_{minor} = 11.35 min.

(*R*)-Methyl 3-((*S*)-oxiran-2-yl)-3-phenylpropanoate (8c)

Yield: 48%, colorless oil; **$[\alpha]_D^{25}$** -12.7 (*c* 1, $CHCl_3$); **Optical purity**: 97% ee determined from HPLC analysis (OD-H column, *n*-hexane/ 2-propanol (90:10), 0.5 mL/min, 254 nm) Retention time: t_{minor} = 10.28 and t_{major} = 11.24 min.

(4*R*, 5*R*)-4-Benzyl-5-(hydroxymethyl)dihydrofuran-2(3*H*)-one (13d)

Yield: 47%, colorless gummy liquid; **$[\alpha]_D^{25}$** -38.0 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1041, 1217, 1773, 3421; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.12 (t, *J* = 6.6 Hz, 1H), 2.26-2.42 (m, 1H), 2.64-2.86 (m, 4H), 3.40-3.52 (m, 1H), 3.72-3.83 (m, 1H), 4.28 (m, 1H), 7.13-7.18 (m, 2H), 7.23-7.36 (m, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 34.9, 37.5, 39.1, 62.8, 85.3, 126.7, 128.6, 138.1, 176.8; **HRMS** (*m/z*): calculated $[M+H]^+$ for $C_{12}H_{15}O_3$: 207.1016; found: 207.1014; **Optical purity**: 98% ee determined from HPLC analysis (Chiral OD-H column, *n*-hexane/ 2-propanol (50:50), 0.5 mL/min, 254 nm) Retention time: t_{major} = 9.94 and t_{minor} = 11.41 min.

(*S*)-Methyl 3-((*S*)-oxiran-2-yl)-4-phenylbutanoate (8d)

Yield: 48%, colorless liquid; **$[\alpha]_D^{25}$** -3.0 (*c* 1, $CHCl_3$); **Optical purity**: 97% ee determined from HPLC analysis (OD-H column, *n*-hexane/ 2-propanol (90:10), 0.5 mL/min, 254 nm) Retention time: t_{minor} = 13.01 and $_{major}$ = 13.50 min.

(4*R*, 5*R*)-5-(hydroxymethyl)-4-phenethyldihydrofuran-2(3*H*)-one (13e)

Yield: 48%, colorless gummy liquid; $[\alpha]_D^{25}$ -54.8 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1044, 1215, 1772, 3440; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.69-2.00 (m, 2H), 2.19-2.31 (m, 2H), 2.36-2.54 (m, 1H), 2.62-2.81 (m, 3H), 3.57-3.68 (m, 1H), 3.86-3.93 (m, 1H), 4.23 (m, 1H), 7.12-7.33 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 33.7, 35.1, 35.2, 35.8, 62.8, 85.9, 126.2, 128.1, 128.5, 140.6, 176.7; **HRMS** (*m/z*): calculated $[M+H]^+$ for $C_{13}H_{17}O_3$: 221.1172; found: 221.1169; **Optical purity**: 99% ee determined by HPLC analysis (Chiral OD-H column, *n*-hexane/ 2-propanol (50:50), 0.5 mL/min, 254 nm) Retention time: t_{major} = 13.35 and t_{minor} = 14.48 min.

(*S*)-Methyl 3-((*S*)-oxiran-2-yl)-5-phenylpentanoate (8e)

Yield: 48%, colorless liquid; $[\alpha]_D^{25}$ -5.9 (*c* 1, $CHCl_3$); **Optical purity**: 97% ee determined by HPLC analysis (OD-H column, *n*-hexane/ 2-propanol (90:10), 0.5 mL/min, 254 nm) Retention time: t_{minor} = 14.94 and t_{major} = 15.53 min.

(4*S*, 5*S*)-4-(4-Fluorophenyl)-5-(hydroxymethyl)dihydrofuran-2(3*H*)-one (25a)

Yield: 46%, colorless solid, **mp**: 113 °C; $[\alpha]_D^{25}$ = -156.12 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1225, 1513, 1774, 3415; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.15 (br s, 1H), 2.84 (dd, *J* = 9.1, 17.3 Hz, 1H), 3.01 (dd, *J* = 8.7, 17.3 Hz, 1H), 3.33-3.44 (m, 1H), 3.51-3.62 (m, 1H), 3.88 (q, *J* = 8.6 Hz, 1H), 4.74 (m, 1H), 7.01-7.09 (m, 2H), 7.21-7.28 (m, 2H); ^{13}C **NMR** (50 MHz, $CDCl_3$): δ 34.8, 42.8, 61.9, 83.1, 115.8 (d, *J* = 21.6 Hz), 129.3 (d, *J* = 7.7 Hz), 132.1 (d, *J* = 3.1 Hz), 162.2 (d, *J* = 247.4 Hz), 176.3; **HRMS** (*m/z*): calculated $[M+H]^+$ for $C_{11}H_{12}FO_3$: 211.0765; found: 211.0766; **Optical purity**: 99% ee determined by HPLC (OJ-H column, *n*-hexane/ 2-propanol (50:50), 0.5 mL/min, 254 nm) Retention time: t_{major} = 10.83 and t_{minor} = 18.58 min.

(*R*)-Methyl 3-(4-fluorophenyl)-3-((*R*)-oxiran-2-yl)propanoate (24a)

Yield: 48%, colorless liquid; **$[\alpha]_D^{25}$** +10.4 (*c* 1, $CHCl_3$); **Optical purity**: 98% ee determined by HPLC analysis (OD-H column, *n*-hexane/ 2-propanol (90:10), 0.5 mL/min, 254 nm) Retention time: t_{minor} = 12.77 and t_{major} = 13.11 min.

(4*S*, 5*S*)-4-(4-Chlorophenyl)-5-(hydroxymethyl)dihydrofuran-2(3*H*)-one (25b)

Yield: 47%, colorless solid, **mp**: 108 °C; **$[\alpha]_D^{25}$** -110.11 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1042, 1493, 1775, 3436; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.29 (t, *J* = 6.3 Hz, 1H), 2.86 (dd, *J* = 9.1, 17.3 Hz, 1H), 3.00 (dd, *J* = 8.7, 17.3 Hz, 1H), 3.36 (m, 1H), 3.57 (m, 1H), 3.87 (q, *J* = 8.6 Hz, 1H), 4.75 (m, 1H), 7.19 (d, *J* = 8.5 Hz, 2H), 7.32 (d, *J* = 8.6 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 34.5, 42.7, 61.6, 83.2, 128.9, 129.1, 133.5, 134.9, 176.8; **HRMS** (*m/z*): calculated $[M+H]^+$ for $C_{11}H_{12}ClO_3$: 227.0469; found: 227.0470; **Optical purity**: 99% ee determined by (OJ-H column, *n*-hexane/ 2-propanol (50:50), 0.5 mL/min, 254 nm) Retention time: t_{major} = 10.99 and t_{minor} = 12.08 min.

(*R*)-Methyl 3-(4-chlorophenyl)-3-((*R*)-oxiran-2-yl)propanoate (24b)

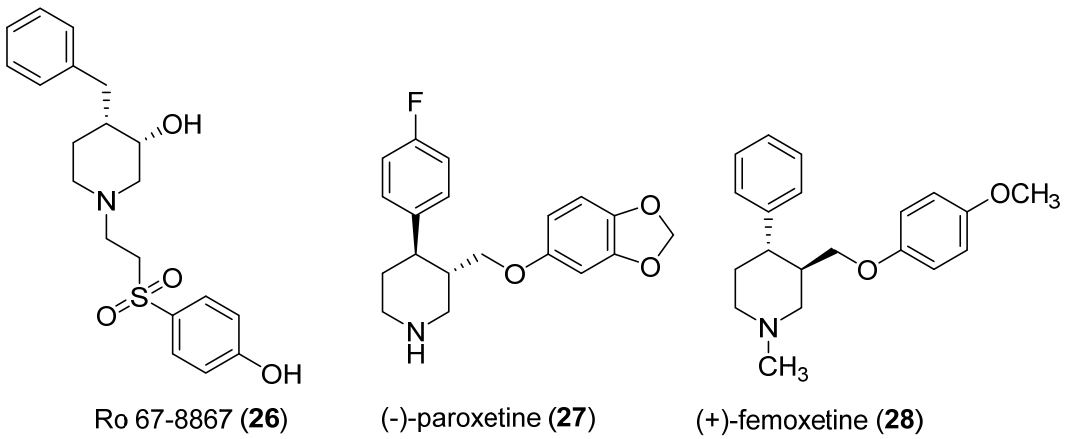
Yield: 46%, colorless liquid; **$[\alpha]_D^{25}$** + 9.4 (*c* 1, $CHCl_3$); **Optical purity** : 98% ee determined by HPLC analysis (OD-H column, *n*-hexane/ 2-propanol (90:10), 0.5 mL/min, 254 nm) Retention time: t_{minor} = 13.15 and t_{major} = 13.54 min.

Section II

A Formal Synthesis of Ro 67-8867, NMDA Receptor *via* HKR Strategy

2.2.1 Introduction and Pharmacology

The class of compounds containing 3,4-disubstituted piperidine ring as a core structure is of substantial medicinal use. Many biological compounds, which consist of the piperidine core have wide range of biological activities.[21] The biological activity of these classes of compounds depends on the position and substitution at the piperidine ring. The three important molecules belonging to the 3,4-disubstituted piperidine class are Ro 67-8867 (**26**), paroxetine (**27**) and femoxetine (**28**) (**Fig. 10**). Ro 67-8867 is a high affinity, selective, and activity-dependent antagonist of the N-ethyl-D-aspartate (NMDA) receptor. NMDA receptor subtypes with different pharmacological properties are formed by heteromeric assembly of different subunits. It is proposed that by selectively blocking a NMDA receptor subtype in brain regions vulnerable to ischemic damage, neuroprotection will be achieved without the unwanted side effects of non-selective NMDA receptor antagonist.[22]



Ro 67-8867 (**26**) (-)-paroxetine (**27**) (+)-femoxetine (**28**)

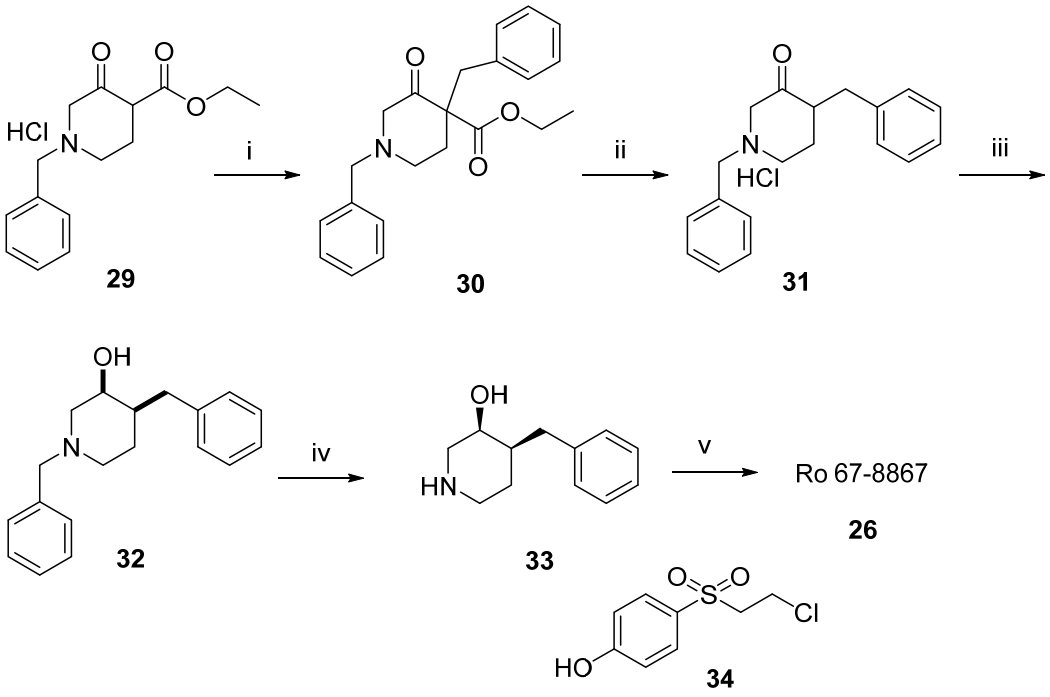
Fig 10: Structures of 3, 4-disubstituted piperidine class molecules

2.2.2 Review of Literature

Till date two synthetic routes have been documented in the literatures which are described below.

Waldmeier's approach (2003)[23]

Waldmeier *et al*. have reorted the asymmetric synthesis of Ro 67-8867 (**26**) in 9 steps starting from α-keto ester **29**. Alkylation of **29** with benzyl bromide gave ester **30**, which was then hydrolyzed and decarboxylated in a mixture HCl and EtOH to provide a stable hydrochloride piperidinone **31**.



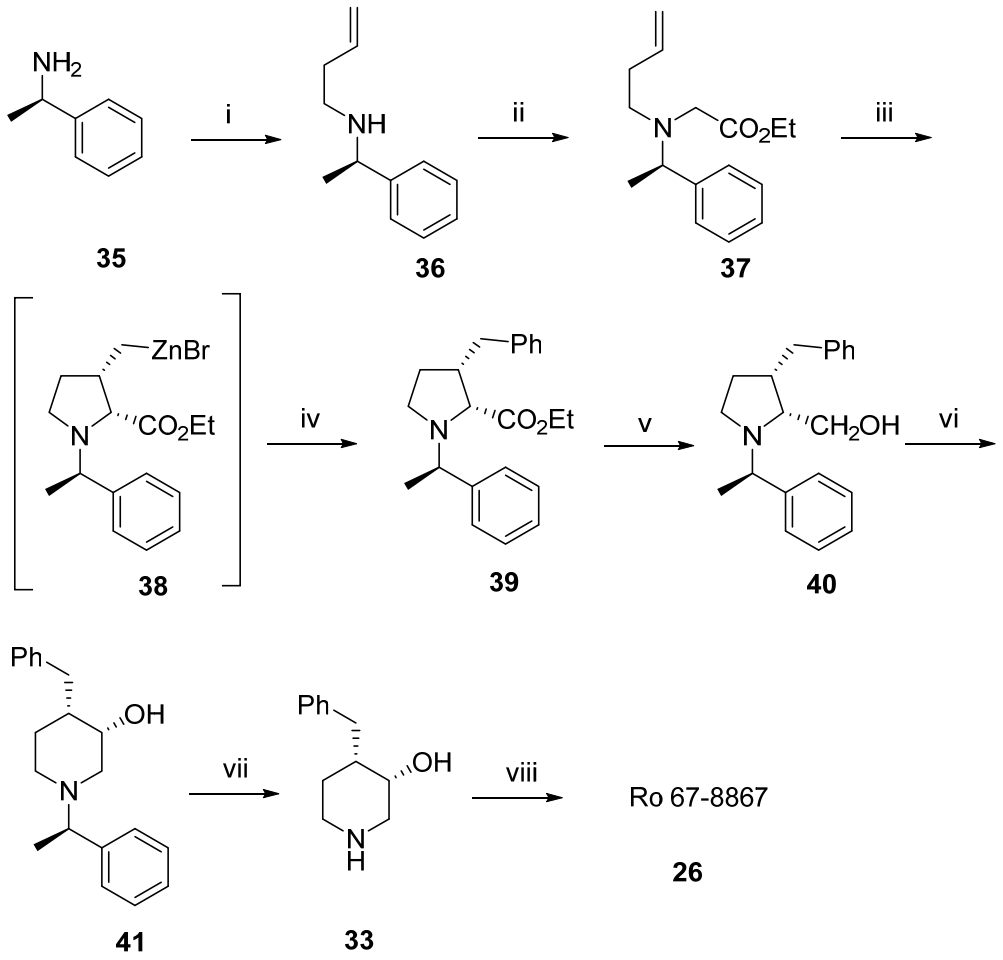
Scheme 8: (i) benzyl bromide, ^{t}BuOK, THF, 25 ^{o}C, 4 h, 75%; (ii) aq. HCl (37%), EtOH, reflux, 40 h, 78%; (iii) [$RuCl_2${(*S*)-3,5-$_i$Pr-MeOBIPHEP}, {(*R,R*)-DPEN}, ^{t}BuOK, S/C = 10^5, 25 ^{o}C, 40 bar H_2, 20 h, THF, 74%; (iv) H_2, Pd/C (10%), EtOH, 55 ^{o}C, 81% (over two step); (v) **34**, NEt_3, CH_2Cl_2, 25 ^{o}C, 6 h, 85%.

The synthesis of the amino alcohol (*S, S*)-**32** was achieved by the highly selective asymmetric hydrogenation[24] of the piperidinone **31***HCl proceeding with concomitant dynamic kinetic resolution to (*S, S*)-**32** with 74% yield. Subsequent debenzylation of

(*S, S*)-**32** afforded the enantiomerically pure amino alcohol (*S, S*)-**33** with only 81% yield over two steps. Finally treatment of amino alcohol **33** with sulfone **34** afforded Ro 67-8867 (**26**) after workup and crystallization from MeOH/toluene, in 85% yield (**Scheme 8**).

Cossy's approach (2005)[25]

Cossy *et al*. have reported a formal enantioselective synthesis of Ro 67-8867 (**26**) in 7 steps starting from commercially available (*R*)-phenylethylamine **35**. The treatment of 1-bromobut-3-ene in the presence of K_2CO_3 gave the secondary amine **36** in 79% yield. The alkylation of amine **36** with ethyl 2-bromoethanoate in the presence base led to the desired amino ester **37**. The key reaction in the synthesis is enantioselective amino-zinc-ene-enolate cyclization[26] of amino ester **37** to give pyrrolidinoester **39** in 43% yield with an excellent diastereoselectivity. Reduction of pyrrolidinoester **39** to prolinol **40** with $LiAlH_4$ followed by its enantioselective ring expansion on treatement with trifluoroacetic anhydride (TFAA) in THF, coupled with triethylamine /NaOH addition gave 3-hydroxypiperidine **41** in 70% yield. The hydrogenolysis of piperidine **41** over Pd/C in EtOH to give desired 3-hydroxypiperidine **33** in 94% yield. The preparation of compound **33** represents a formal synthesis as its transformation to Ro 67-8867 (**26**) was achieved in a single step by treatment with sulfone **34** (**Scheme 9**).



Scheme 9: (i) 1-bromobut-3-ene, K_2CO_3, NaI, DMF, 100 °C, 79%; (ii) ethyl 2-bromoethanoate, K_2CO_3, DMF, 25 °C, 79%; (iii) (a) LDA, -78°C, THF; (b) $ZnBr_2$; (iv) Pd_2dba_3, P(*o*-tolyl)$_3$, PhI, 43%; (v) $LiAlH_4$, THF, 95%; (vi) (a) TFAA, THF; (b) Et_3N; (c) NaOH, THF, 70%; (vii) H_2 (1 atm), Pd/C (10%), EtOH, 94%; (viii) **34**, NEt_3, CH_2Cl_2, 25 °C, 15 h, 66%.

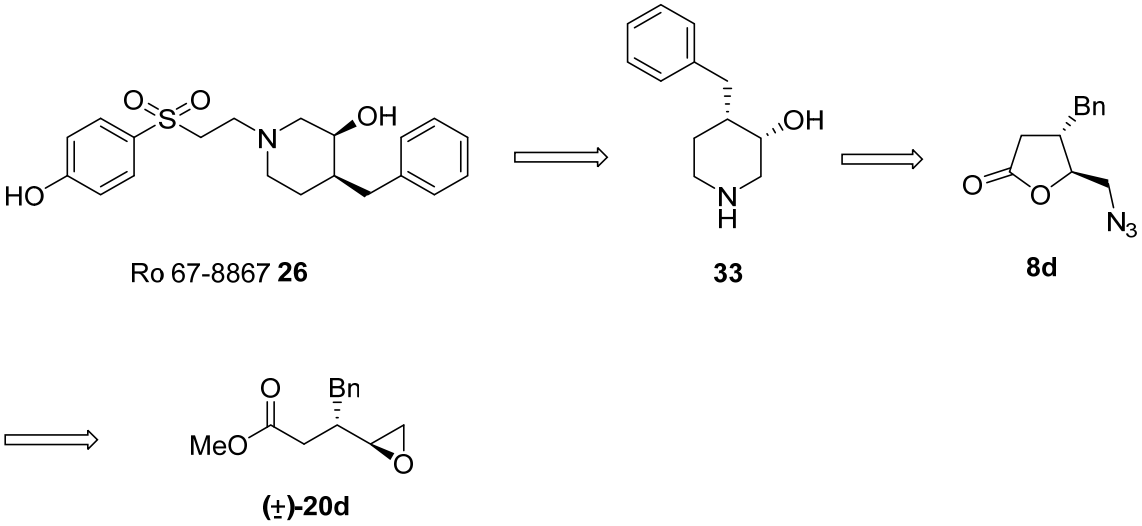
2.2.3 Present Work

2.2.3.1 Objective

Literature search revealed that two strategies such as dynamic kinetic resolution and amino-zinc-ene-enolate cyclization have been reported for the synthesis of Ro 67-8867 (**26**). However, these methods suffer broadly from disadvantages such as low overall yields, the need for separation of diastereomers and use of expensive reagents.

In this section, a concise, formal enantioselective synthesis of Ro 67-8867 (**26**) using HKR of 3-substituted epoxides as the chiral inducing step is described.

Retrosynthetic analysis of Ro 67-8867 (**26**) reveals that *cis*-3,4-disubstituted piperidinone core **33** could be visualized as the key intermediate for the synthesis of Ro 67-8867 (**26**). The *cis*-isomer **33** could be obtained from γ-butyrolactone **8d**, which in turn can be prepared by the Co-catalyzed hydrolytic kinetic resolution of *racemic* 3-substituted epoxy ester (±)-**20d** (see **Section I**) (**Scheme 10**).

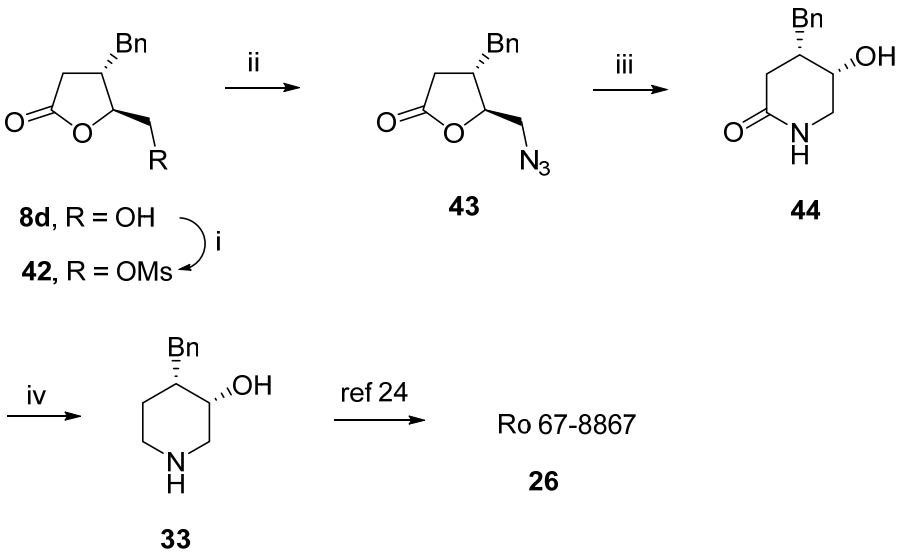


Scheme 10: Retrosynthetic analysis of Ro 67-8867 (**26**)

2.2.3.2 Results and Discussion

Formal synthesis of Ro 67-8867 (26)

The synthesis of Ro 67-8867 (**26**) commenced from γ-butyrolactone **8d**, obtained by the Co-catalyzed hydrolytic kinetic resolution of *racemic* 3-substituted epoxy ester (±)-**20d** {[(*R, R*)-(salen)Co(III)(OAc)]complex was used as catalyst} as described in the previous section **(Section I**, **Table 1)**.



Scheme 11: (i) MsCl, Et_3N, CH_2Cl_2, 0 ^oC, 1 h, 93%; (ii) NaN_3, DMF, 80 ^oC, 3 h, 95%; (iii) 20% $Pd(OH)_2$, H_2 (1 atm), MeOH, 12 h, 25 ^oC, 98%; (iv) $BH_3.SMe_2$, THF, reflux, 12 h, 85%.

Thus, mesylation of **8d** gave the mesylate **42** in 93% yield (**Scheme 11**). The formation of mesylate **42** was confirmed by ^1H and ^{13}C NMR spectroscopy. The ^1H NMR spectrum of **42** showed a singlet at δ 2.99 (s, 3H) for methyl protons. Its ^{13}C NMR showed a typical carbon signal at δ 37.4 for methyl carbon, which confirmed the formation of mesylate **42** (**Fig. 11**).

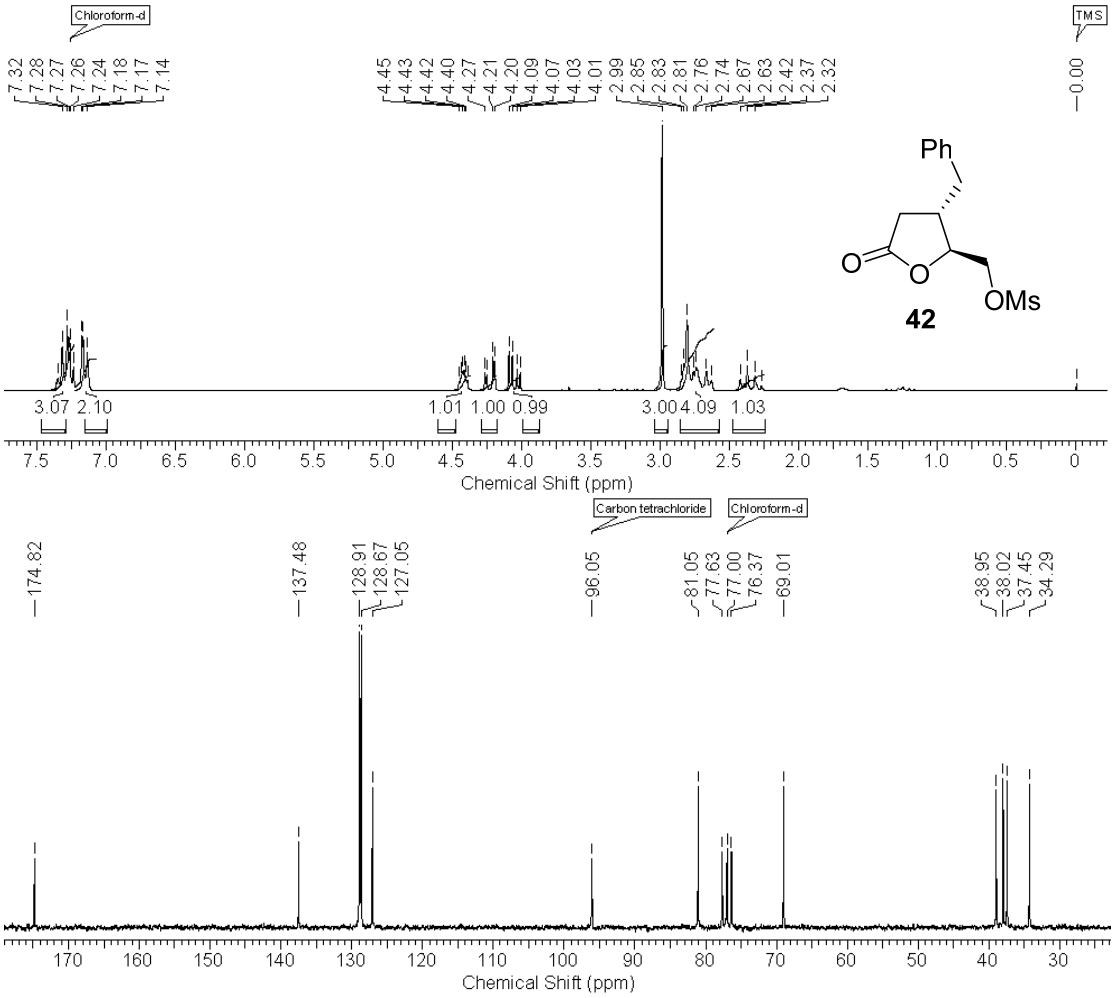


Fig. 11: ^{1}H and ^{13}C NMR spectra of mesylate **42**

Mesylate **42** was then converted into the corresponding azide **43** (NaN_3, DMF, 80 ^{o}C) in 95% yield. The formation of azido derivative **43** was confirmed by its IR spectrum, which showed a strong absorption band at υ_{max} 2104 cm^{-1} typically for azide functionality. Its ^{1}H NMR spectrum showed a multiplet at δ 4.28-4.35 (m, 1H) corresponding to methine proton (-**CH**-O). Its structure was further confirmed by its ^{13}C NMR spectrum, which showed a typical methine carbon (-**CH**-O) appearing at δ 82.4 (**Fig. 12**).

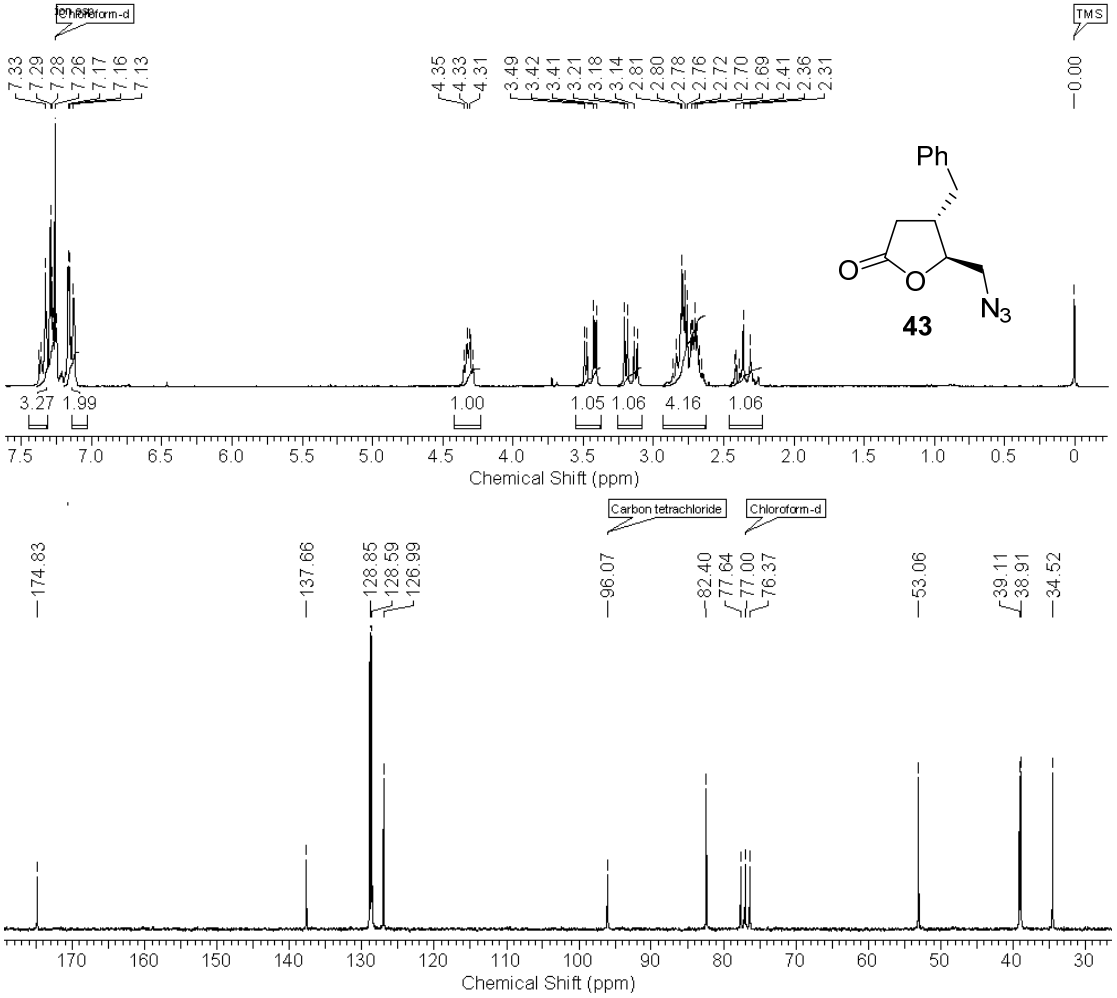


Fig. 12: ^{1}H and ^{13}C NMR spectra of azide **43**

Azide **43** was subjected to intramolecular reductive cyclization over $Pd(OH)_2/H_2$ (1 atm) to afford *cis*-3,4-disubstituted piperidinone core **44** in 98% yield. The ^{1}H NMR spectrum of the lactam **44** showed a typical singlet at δ 3.75 (s, 1H) corresponding to the methine protons attached C**H**-OH and a multiplet at δ 2.08 (m, 3H) corresponding to α and β methylene and methine protons attached to C**H**-C**H₂**-CO of lactam. Its ^{13}C NMR spectrum showed a typical carbon signal at δ 174.6 for amide carbonyl carbon. The formation of cylclic lactam was further confirmed by its IR spectrum, which

showed a strong absorption band at υ_{max} 1642 cm^{-1} typically for amide carbonyl functionality (**Fig. 13**).

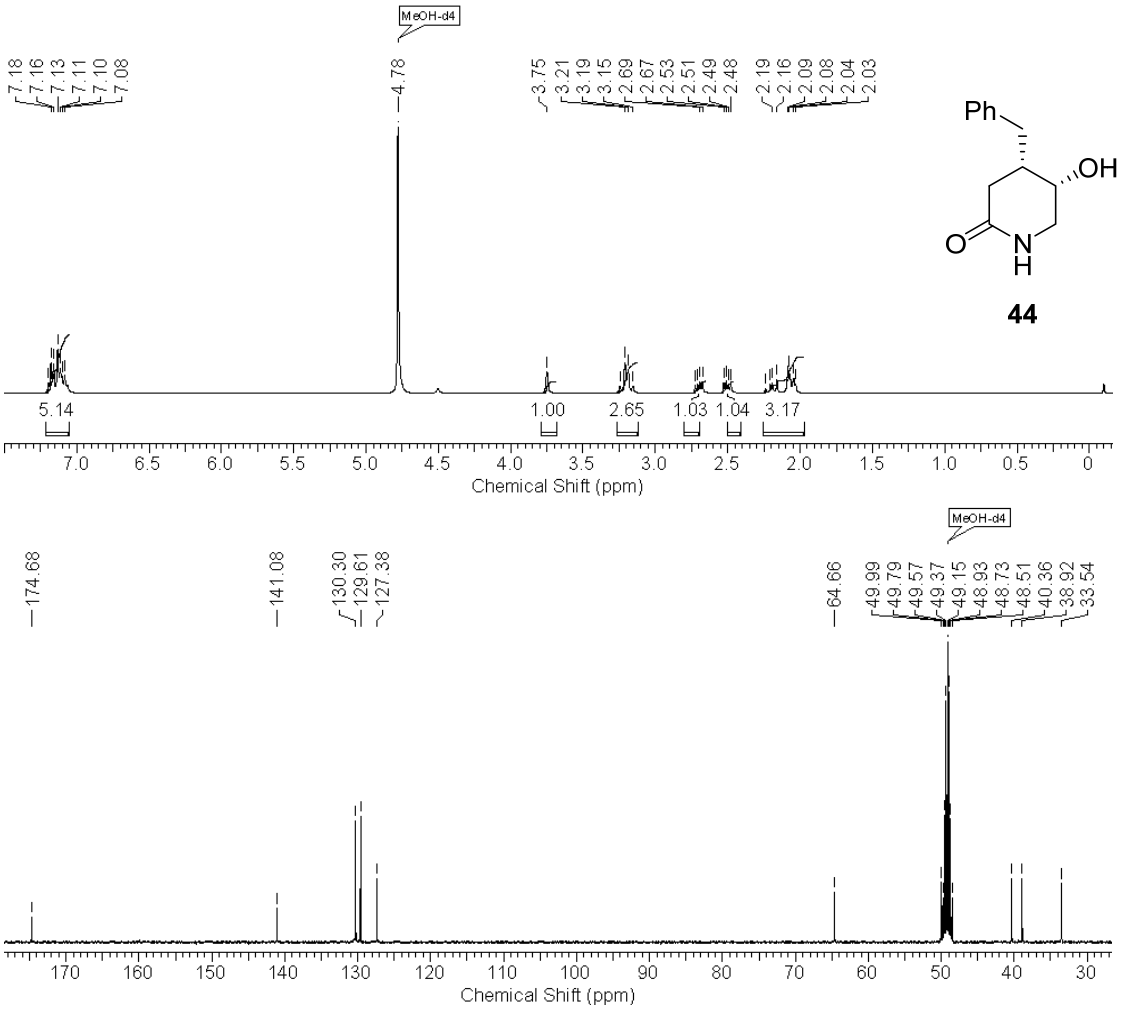


Fig. 13: ^{1}H and ^{13}C NMR spectra of lactam **44**

The reduction of amide carbonyl in **44** with $BH_3{\cdot}SMe_2$ gave *cis*-piperidine core **33** in 85% yield (overall yield: 17% from **8d**), thus constituting a formal synthesis of Ro 67-8867 (**26**). The formation of **33** was confirmed by its ^{1}H NMR spectrum, which showed typical signals at δ 2.97 (m, 2H) corresponding to methylene protons attached to **CH_2**NH and δ 3.54 (s, 1H) for methine proton (-**C**H-O). This was further confirmed by its ^{13}C NMR spectrum, which showed characteristic carbon signals at δ

38.6 and 66.3 for benzylic methylene and methine carbons attached to hydroxyl group respectively (**Fig. 14**).

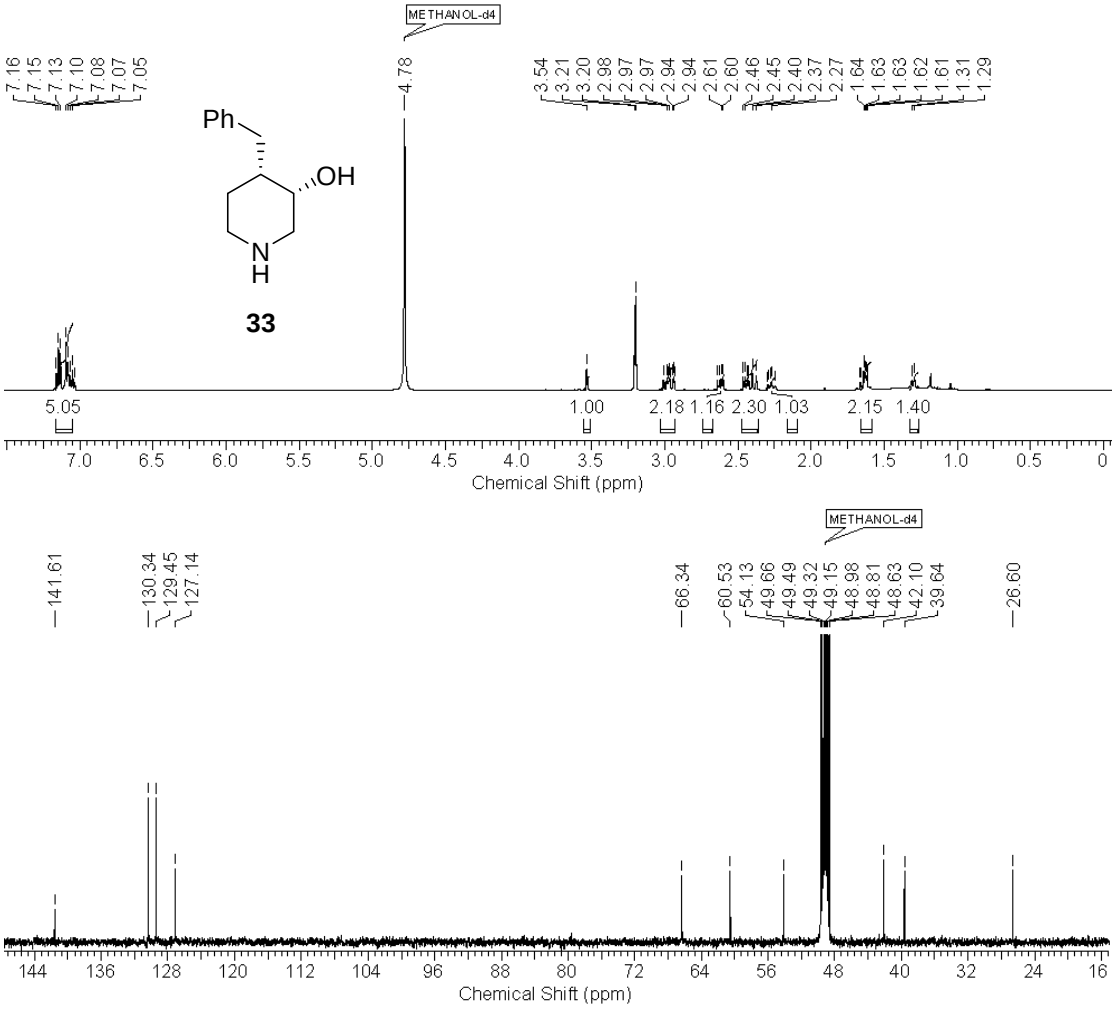


Fig. 14: ^{1}H and ^{13}C NMR spectra of *cis*- piperidine core **33**

2.2.4 Conclusion

In conclusion, we have successfully demonstrated an efficient, formal synthesis of R0 67-8867 (**26**) *via* two-stereocentred HKR of *racemic* 3-substituted epoxy esters as a key step. The high enantiomeric excess obtained in this method render the present protocol a good alternative to the known methods.

2.2.5 Experimental Section

((2*S*, 3*S*)-3-Benzyl-5-oxotetrahydrofuran-2-yl)methylmethanesulfonate (42)

To a stirred solution of lactone **8d** (3.88 mmol) in CH_2Cl_2 (15 mL) and triethylamine (0.81 mL, 5.82 mmol), mesyl chloride (0.36 mL, 4.65 mmol) was added at 0 ^oC under N_2 atmosphere. The resulting solution was stirred at the same temperature for 1 h. After the completion of the reaction (monitored by TLC), it was quenched with water and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude product **42**. Column chromatographic purification with silica gel using petroleum ether:ethyl acetate (7:3) as eluent gave **42** in pure form (1 g, 93%).

Yield: 93%, colorless solid **mp**: 78 °C; $[\alpha]_D^{25}$ +26.0 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1148, 1442, 1782, 2839; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.27-2.42 (m, 1H), 2.63-2.85 (m, 4H), 2.99 (s, 3H), 4.05 (dd, *J* = 4.7, 11.7 Hz, 1H), 4.23 (dd, *J* = 2.7, 11.7 Hz, 1H), 4.43 (m, 1H), 7.14-7.35 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 34.2, 37.4, 38.0, 38.9, 69.0, 81.0, 127.0, 128.6, 128.9, 137.4, 174.8; **HRMS (*m/z*)**: calculated $[M+H]^+$ for $C_{13}H_{17}O_5S$: 285.0791; found: 285.0790.

(4*S*, 5*S*)-5-(Azidomethyl)-4-benzyldihydrofuran-2(3*H*)-one (43)

To a stirred mixture of crude **42** (3.16 mmol) in DMF (10 mL), sodium azide (0.24 g, 3.8 mmol) was added. Reaction mixture was stirred for 8 h at 80 ^oC. After the completion of the reaction (monitored by TLC), it was extracted with EtOAc (3 x 10 mL), washed with water, brine and dried over anhydrous Na_2SO_4. The combined organic layer was concentrated under reduced pressure to give the crude azido lactone **43**, which was purified by column chromatography with silica gel using petroleum ether: ethyl acetate (8:2) as eluent to give pure **43** as colorless oil (0.695 g, 95%).

Yield: 95%, colorless liquid; $[\alpha]_D^{25}$ +78.5 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1065, 1217, 1781, 2104; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.26-2.42 (m, 1H), 2.66-2.86 (m, 4H), 3.16 (dd, *J* = 4.6, 13.4 Hz, 1H), 3.45 (dd, *J* = 3.4, 13.3 Hz, 1H), 4.33 (m, 1H), 7.13-7.17 (m, 2H), 7.25-7.37 (m, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 34.5, 38.9, 39.1, 53.0, 82.4, 126.9, 128.5, 128.8, 137.6, 174.8; **HRMS (*m/z*)**: calculated $[M+H]^+$ for $C_{12}H_{14}N_3O_2$: 232.1081; found: 232.1080.

(4*S*, 5*S*)-4-Benzyl-5-hydroxypiperidin-2-one (44)

To a solution of **43** (2.59 mmol) in dry MeOH, 20% $Pd(OH)_2$ (0.09 g) was added and the reaction mixture was stirred under an atmosphere of H_2 (1 atm) for 24 h at 25 ^oC. After the completion of the reaction (monitored by TLC), the catalyst was filtered over Celite and the filtrate concentrated under reduced pressure to provide amide **44**, which was purified by column chromatography using ethyl acetate:methanol (9:1) to obtain pure **44** (0.521 g, 98%).

Yield: 98%, colorless solid **mp**.: 213 °C; $[\alpha]_D^{25}$ +7.3 (*c* 1, MeOH); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1130, 1642, 2912, 3440; **^{1}H NMR** (200 MHz, MeOH-d_4 + $CDCl_3$): δ 2.03-2.24 (m, 3H), 2.51 (dd, *J* = 6.8, 13.1 Hz, 1H), 2.71 (dd, *J* = 7.0, 13.0 Hz, 1H), 3.21 (m, 2H), 3.75 (s, 1H), 7.08-7.20 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 33.5, 38.9, 40.3, 49.9, 64.6, 127.3, 129.6, 130.3, 141.0, 174.6; **HRMS (*m/z*)**: calculated $[M+H]^+$ for $C_{12}H_{16}NO_2$: 206.1176; found: 206.1177.

(3*S*, 4*S*)-4-Benzylpiperidin-3-ol (33)

To a solution of lactam **44** (0.49 g, 2.39 mmol) in dry THF (10 mL), $BH_3{\cdot}SMe_2$ (0.45 mL, 4.78 mmol) was added dropwise at 0 ^oC under N_2 atmosphere and the mixture was then refluxed for 6 h. After the completion of the reaction (monitored by TLC), the solvent (THF) was removed under reduced pressure to give the crude product **33**,

which was purified by column chromatography with silica gel using petroleum ether: ethyl acetate (6:4) as eluent gave pure **33** as colorless solid (0.388 g, 85%).

Yield: 85%, colorless solid **mp**: 95.5 °C; $\mathbf{[\alpha]_D^{25}}$ -34.8 (*c* 1, $CHCl_3$) {lit.$^{25}[\alpha]_D$ -36.6 (*c* 1, $CHCl_3$)}; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1123, 1217, 2923, 3441; **^{1}H NMR** (200 MHz, MeOH-d_4): δ 1.29 (m, 1H), 1.64 (m, 2H), 2.27 (d, *J* = 13.43 Hz, 1H), 2.45 (m, 2H), 2.61 (dd, *J* = 7.02, 13.12 Hz, 1H), 2.94-3.01 (m, 2H), 3.53 (s, 1H), 7.05-7.10 (m, 3H), 7.13-7.16 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 26.6, 39.6, 42.1, 54.13, 60.5, 66.3, 127.1, 129.4, 130.3, 141.6; **HRMS (*m/z*)**: calculated $[M+H]^+$ for $C_{12}H_{18}NO$: 192.1383; found: 192.1384.

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Chapter III

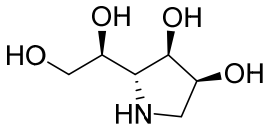
Asymmetric Synthesis of 1,4-dideoxy 1,4-Imino-D-Allitol, (S)-3-Hydroxypiperidine and (R)-Coniine

Section I

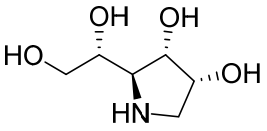
A Formal Synthesis of 1,4-Dideoxy-1,4-Imino-D-Allitol *via* Co(III)(salen)-Catalyzed Two-Stereocentered HKR of Racemic Azido Epoxides

3.1.1 Introduction and Pharmacology

Many natural and unnatural polyhydroxylated pyrrolidines and polyhydroxylated piperidines commonly referred to as azasugars or iminocyclitols are potent glycosidase inhibitors.[1] These azasugars represent many important class of transition state analogue inhibitors of glycosidase and glycotransferases and they have been found to be chemotherapeutic agents for the treatment of diseases such as diabetes, cancer, inflammation and viral infections including AIDS (**Fig. 1**).[2]



1, 4-dideoxy-1, 4-imino-D-allitol (**1**)



1, 4-dideoxy-1, 4-imino-L-allitol **(2)**

Fig. 1: 1,4-dideoxy-1,4-imino-D-allitols (**1**) and 1,4-dideoxy-1,4-imino-L-allitols (**2**)

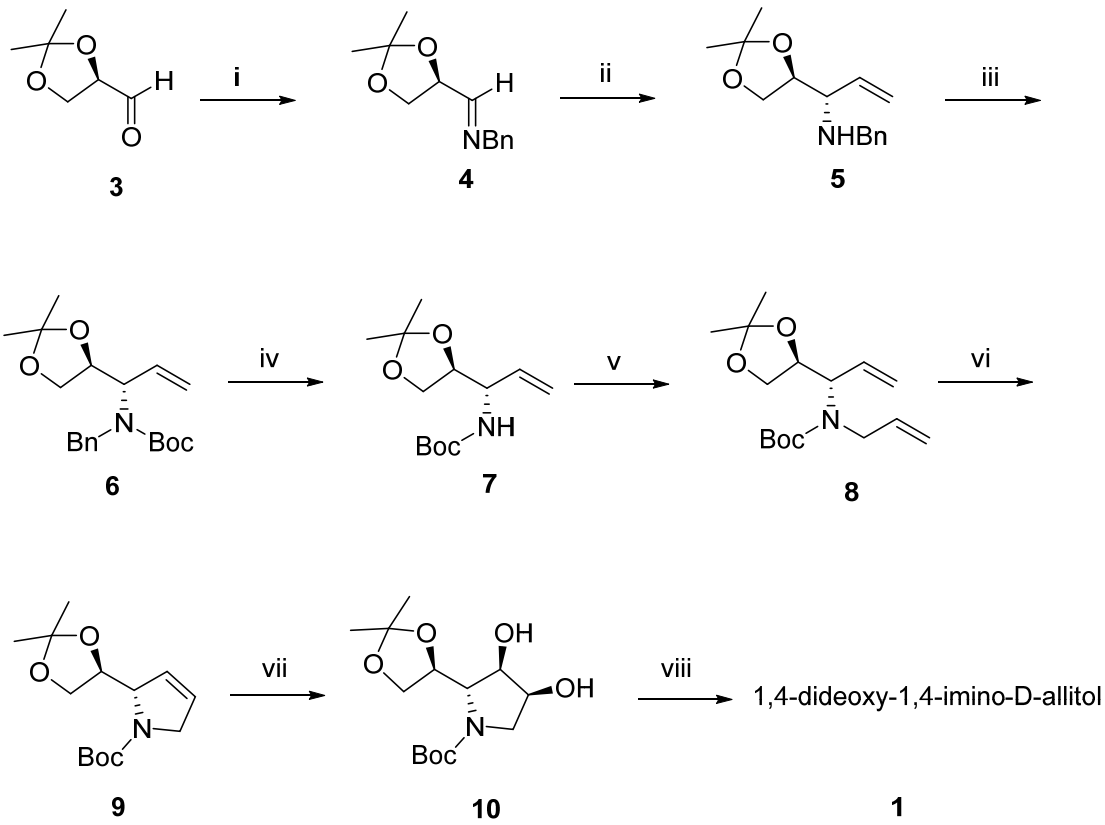
The asymmetric inducing properties of hydroxylated pyrrolidine derivatives as chiral auxiliaries in alkylation, [3] acylation[4] and aldolisation[5] have also been demonstrated. Among these azasugars, iminofuranoses, *i.e*. 1,4-dideoxy-1,4-imino-D-allitols (**1**) have attracted considerable attention because of their potential biological activity and structural features. Several syntheses of these compounds have been developed mostly based on transformation of sugar derivatives.[6]

3.1.2 Review of Literature

The wide applicability and occurrence of this scaffold attracted attention of many organic chemists towards its synthesis. The reported routes for the synthesis of **1** and its enantiomer are broadly divided into two groups; (a) synthesis using chiral pool approach; (b) synthesis using asymmetric induction. Till date, three synthetic routes have been documented in the literatures which are described below.

Rao's approach (2003)[7]:

Rao *et al*. have reported a stereoselective synthesis of 1,4-dideoxy-1,4-imino-D-allitol (**1**) *via* the addition of vinyl magnesium bromide to the benzylimine **4** derived from (*R*)-2,3-*O*-isopropylidene glyceraldehyde **3**, as a single diastereomer of **5** in 76% yield. Compound **5**, on treatment with $(Boc)_2O$ afforded **6**, which on reduction with Li/liq. NH_3/THF conditions gave compound **7** with 81 % yield. Further treatment of **7** with allyl bromide in presence of base resulted in diene **8** with 75% yield. Diene **8** was then subjected to ring closing metathesis (RCM) using Grubbs' first generation catalyst to give pyrroline **9** in 75% yield. Dihydroxylation of **9** with catalytic amount of OsO_4 yielded compound **10**, as a single isomer. Compound **10** on hydrolysis with MeOH–HCl finally afforded the target molecule **1** (**Scheme 1**).

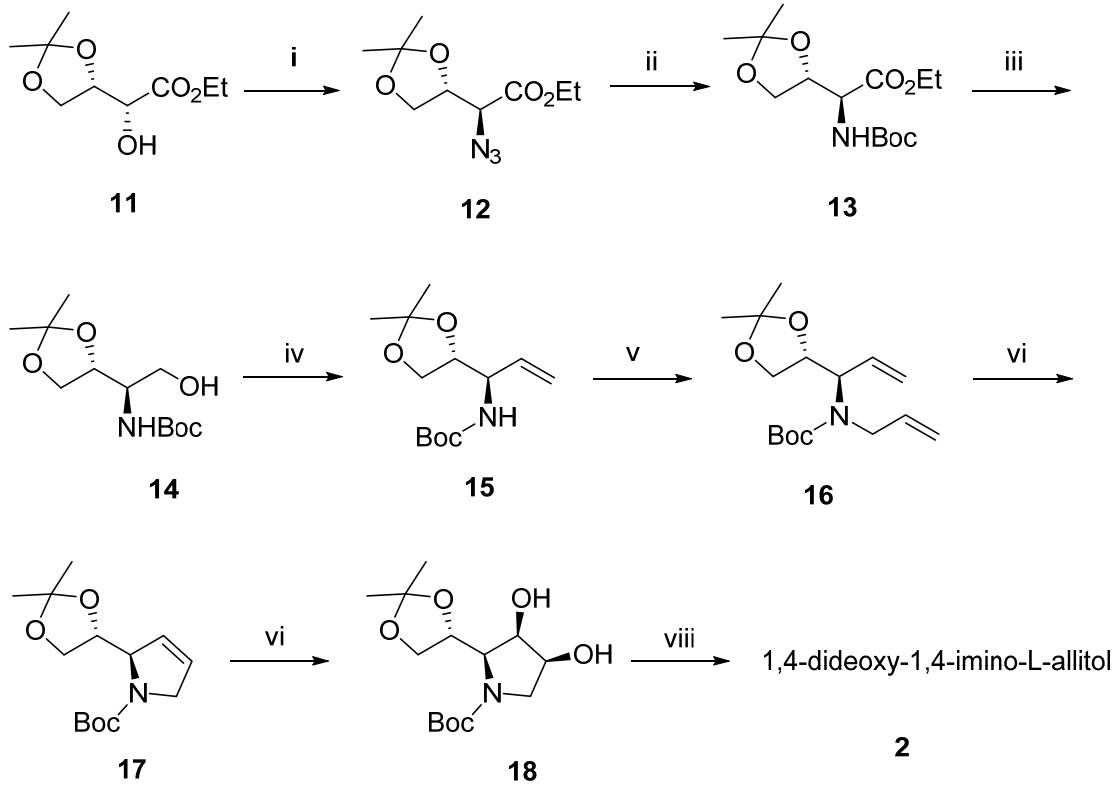


Scheme 1: (i) $BnNH_2$, anhy. $MgSO_4$, dry ether, 0-25 ^oC, 2 h; (ii) CH_2=CH-MgBr, dry ether, 0-25 °C, 15h, 76% (overall yield for two steps); (iii) $(Boc)_2O$, Et_3N, dry CH_2Cl_2, 0-25 °C, 24 h, 72%; (iv) Li, liq NH_3, THF, -50 °C, 1 h, 81%; (v) allyl bromide, NaH (60%), DMF, 0-25 °C, 12 h, 75%; (vi) 10 mol% Grubbs' catalyst *i.e.* $[Cl_2(Pcy_3)_2Ru\text{-}CHPh]$, CH_2Cl_2, 25 ^oC, 12 h, 75%; (vii) OsO_4 (10 mol%), NMO monohydrate, acetone:H_2O (3:1), 12 h, 80%; (viii) methanol-HCl, 25 ^oC, 10 h, 82%.

Rao's approach (2007)[8]:

In yet another approach, Rao *et al*. have the reported synthesis of 1,4-dideoxy-1,4-imino-L-allitol **2** starting from ethyl 3,4-*O*-methylidine D-erythronate **11**, prepared from D-isoascorbic acid. The triflate derivative of **11**, (Tf_2O, 2,6-lutidine, in CH_2Cl_2 at -20 to 0 ^oC) was subjected to nucleophilic displacement with azide to give azide **12** in 80% yield. Reduction of azide **12** under Staudinger reaction condition gave amino derivative which was protected as its NHBoc derivative **13** in quantitative yield. Reduction of ester **13** to its NHBoc protected amino alcohol **14** was achieved using

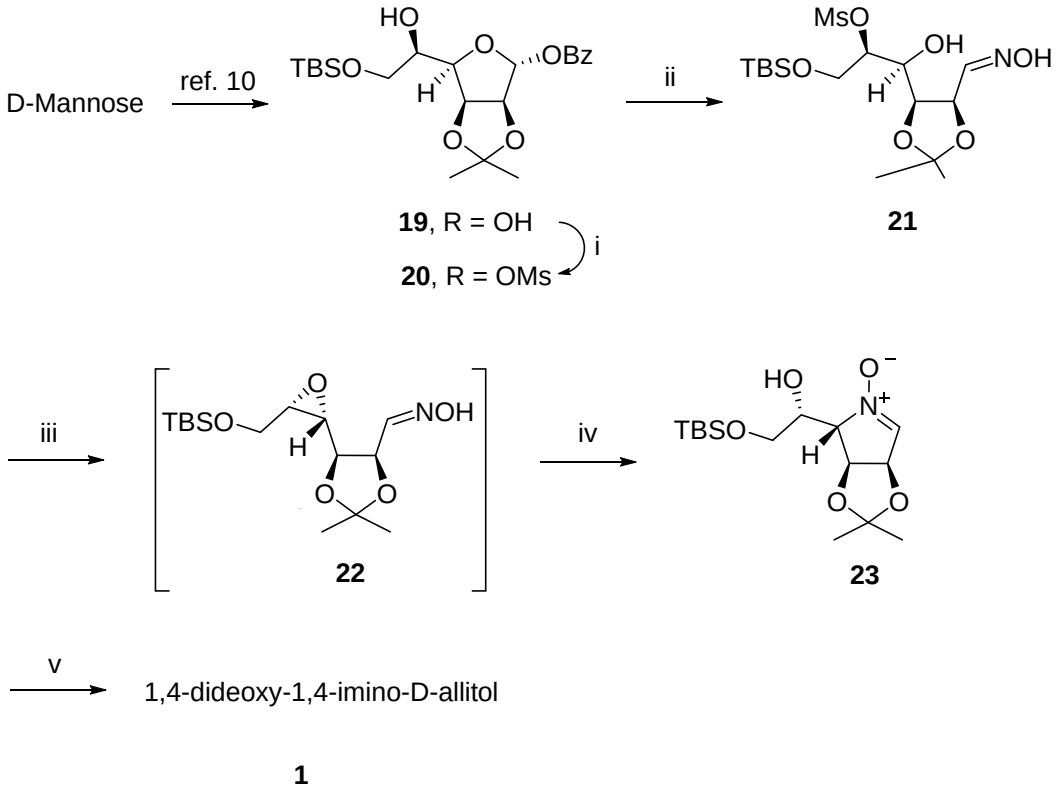
$LiAlH_4$. Dess-Martin periodinane oxidation of the primary alcohol **14** led to aldehyde, which on methylenation under Takai-Nozaki reaction condition gave the corresponding olefin **15** in 60% overall yield (for two steps). *N*-allylation of **15** followed by ring closing metathesis afforded pyrroline **17** in 75% yield. Dihydroxylation of **17** with OsO_4 yielded diol **18**, as a single isomer. Compound **18** on treatment with MeOH-HCl finally afforded the target molecule **2** (**Scheme 2**).



Scheme 2: (i) (a) Tf_2O, 2,6-lutidine, CH_2Cl_2, -20 to 0 °C, 45 min; (b) LiN_3, DMF, rt, 3 h; (ii) PPh_3, THF/H_2O, 60 °C, 3 h then NEt_3, $(Boc)_2O$, 0-25 °C, 12 h; (iii) $LiAlH_4$, THF, 0-25 °C, 30 min.; (iv) Li, liq NH_3, THF, -50 °C, 1 h, 81%; (v) allyl bromide, NaH, DMF, 0 to 25 °C , 12 h, 75%; (vi) 10 mol% Grubbs' catalyst $[Cl_2(Pcy_3)_2Ru\text{-}CHPh]$, CH_2Cl_2, 25 °C, 12 h, 75%; (vii) OsO_4 (10 mol%), NMO monohydrate, acetone:H_2O (3:1), 12 h, 80%; (viii) methanol-HCl, 25 °C, 10 h, 82%.

Dhavale's approach (2009)[9]:

Dhavale *et al*. have developed an elegant stereo-controlled approach to 1,4-dideoxy-1,4-imino-D-allitol (**1**) using a D-mannose-derived cyclic nitrone. The compound **19** was obtained from benzoyl 2,3-*O*-isopropylidene-α-D-mannofuranoside which was



Scheme 3: (i) MsCl, Et_3N, CH_2Cl_2, 3 h, 98%; (ii)(a) K_2CO_3, MeOH, 25 ^{0}C, 0.5 h, 98%, (b) hydroxylamine hydrochloride, $NaHCO_3$, MeOH–H_2O, 25 ^{o}C for 3 h, 90%; (iii) hydroxylamine hydrochloride, $NaHCO_3$, MeOH–H_2O, reflux for 12 h, 80% in the 2:8 ratio; (iv) (a) H_2, Pd/C, 12 h, (b) TFA, H_2O, (9:1), 0–25 ^{0}C, 6 h, 75%; (v) MeOH, HCl, 25 ^{0}C, 2 h. 98%.

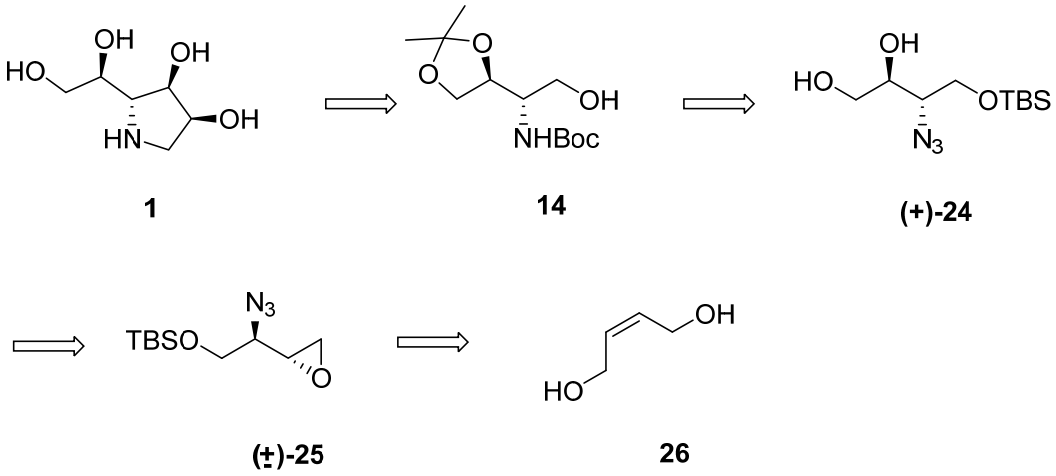
selectively silylated at the more reactive 6-hydroxyl and then the secondary hydroxyl was protected as its methyl ether. [10] Treatment of **19** with mesyl chloride to afforded Debenzoylation of **20** with base afforded a mixture of hemiacetals which on treatment with hydroxylamine hydrochloride and base in methanol–water afforded a mixture of oxime **21**, which on treatment with hydroxylamine hydrochloride and sodium

bicarbonate in methanol-water afforded five-membered cyclic nitrones **23**, reductive cleavage of N-O bond by hydrogenation followed by global deprotection of TBS ether and acetonide function gave 1,4-dideoxy-1,4-imino-D-allitol (**1**) in 98% yield (**Scheme 3**).

3.1.3. Present Work:

3.1.3.1 Objective

As can be seen from the above discussion, the reported methods of synthesis 1,4-dideoxy-1,4-imino-D-allitol (**1**) suffer from certain limitations such as the use of chiral building blocks, exotic reagents, involvement of longer reaction sequences, low overall yields, etc. We have recently reported a flexible method that employs Co-catalyzed Hydrolytic Kinetic Resolution (HKR) of racemic *anti*-azido epoxides with two-stereocenters to generate the corresponding diols and epoxides in high optical purity (97-99% ee) in a single step.[11] This section describes an formal synthesis 1,4-dideoxy-1,4-imino-D-allitol (**1**) by employing two-stereocentered HKR of racemic azido epoxides as the key chiral-inducing step.

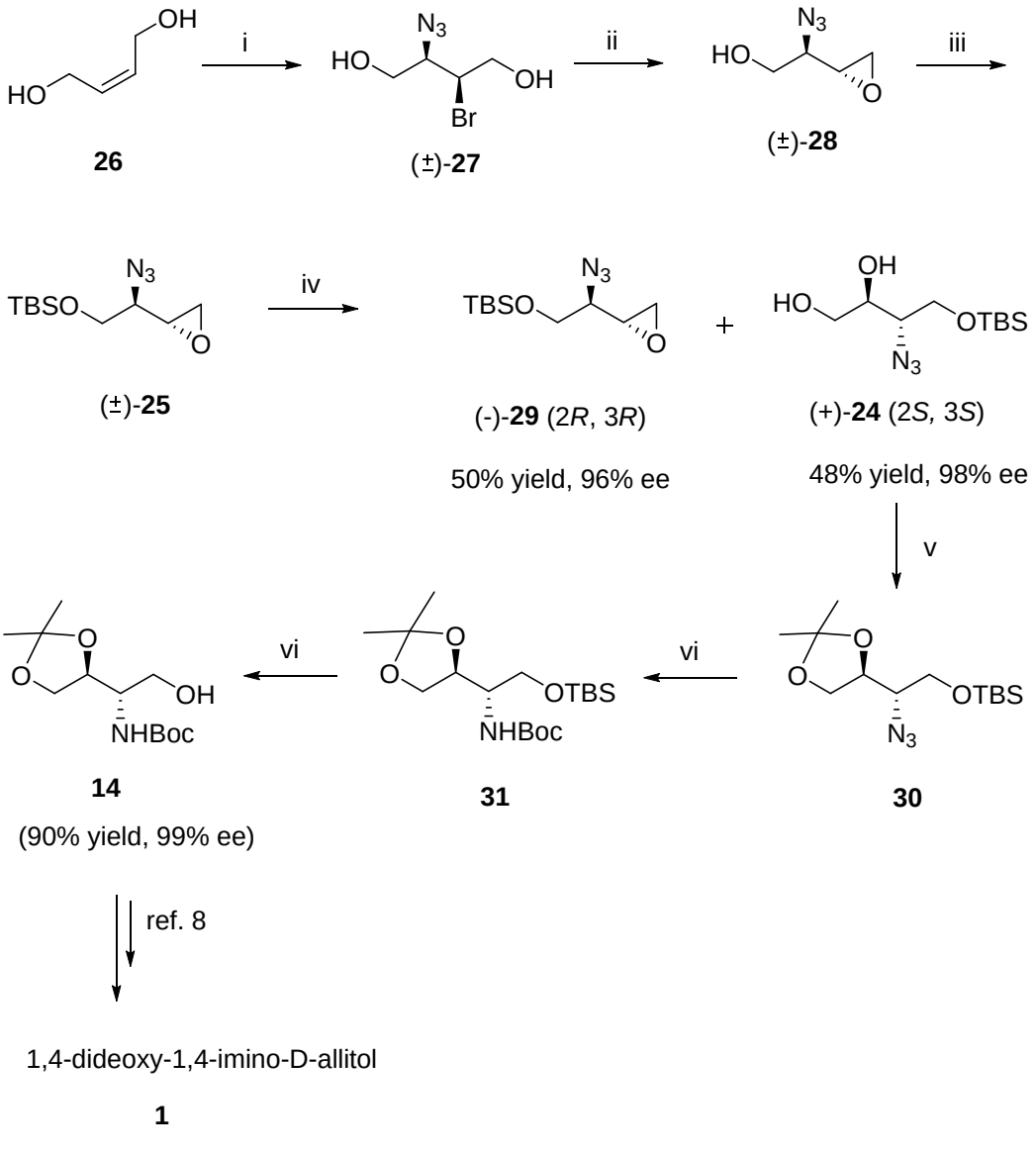


Scheme 4: Retrosynthetic analysis of 1,4-dideoxy-1, 4-imino-D-allitol (**1**)

As can be seen from the retrosynthetic analysis of **1** (**Scheme 4**), the *N*-Boc-amino alcohol **14** could be visualized as an important intermediate for the synthesis of target molecule **1.** Compound **14** can be prepared from *anti*-azido diol (+)-**24**, which inturn by means of cobalt-catalyzed Hydrolytic Kinetic Resolution of racemic azido epoxide (±)-**25**. The racemic azido epoxide can be prepared in two steps from *cis*-butene 1,4-diol **26.**

3.1.3.2 Results and Discussion

Accordingly, the synthesis of 1,4-dideoxy-1,4-imino-D-allitol (**1**) has commenced starting from commercially available *cis*-2-butene-1,4-diol (**26**), which on treatment with NBS in the presence of NaN_3, gave the racemic bromo azido diol **27** in 89% yield. The bromo azido diol (±)-**27** was readily transformed into racemic *anti*- azido epoxide (±)-**28** under basic conditions (NaOH, dry THF, 0 ^oC, 84%). The protection of primary hydroxyl group in **28** as TBS ether (TBSCl, imidazole, CH_2Cl_2, 0 ^oC) was achieved to give the protected racemic azido epoxide (±)-**25** in 94% yield (see Chapter 1; Section I in **Scheme 6** for details).



Scheme 5: i) NBS, NaN_3, CH_3CN:water (4: 1), 0 to 25 °C, 3 h, 89%; (ii) NaOH powder, THF, 2 h, 84%; (iii) TBSCl, imid., CH_2Cl_2, 25 °C, 2.5 h, 76%. (iv) (*R, R*)-Co^{III}(salen) complex (0.5 mol %), H_2O (0.49 equiv), 0 to 25 ^oC, 12 h. (v) 2,2-dimethoxypropane, cat. CSA, CH_2Cl_2, 2 h, 89%; (vi) (a) 5% Pd/C, H_2 (1 atm), MeOH; (b) $(Boc)_2O$, DMAP (10 mol%), Et_3N, CH_2Cl_2, 25 ^oC, 6 h, 75% (for two steps); (vii) TBAF, THF, 0 ^oC, 3 h, 90%.

The racemic azido epoxide **25** was subjected to HKR using (*R, R*)-Co(III)salen-OAc complex (0.5 mol %) and H_2O (0.5 equiv), which produced the corresponding chiral azido diol (+)-**24** in (48% yield, 98% ee) and chiral azido epoxide **25** (50%, 96% ee)

in high optical purity (**Scheme 5**). The formation of azido diol **24** was confirmed by its IR spectrum, which showed a strong absorption band at υ_{max} 2109 cm^{-1} typically for azide functionality. The formation of (+)-**24** was further confirmed by ^{1}H and ^{13}C NMR spectroscopy. The ^{1}H NMR spectrum of *anti*-azido diol **24** showed typical signals at δ 3.04 (d, J = 4.6 Hz, 1H) and 3.45 (m, 2H) for methine and methylene protons (-**CH**-N_3, -**CH_2**-OH) respectively.

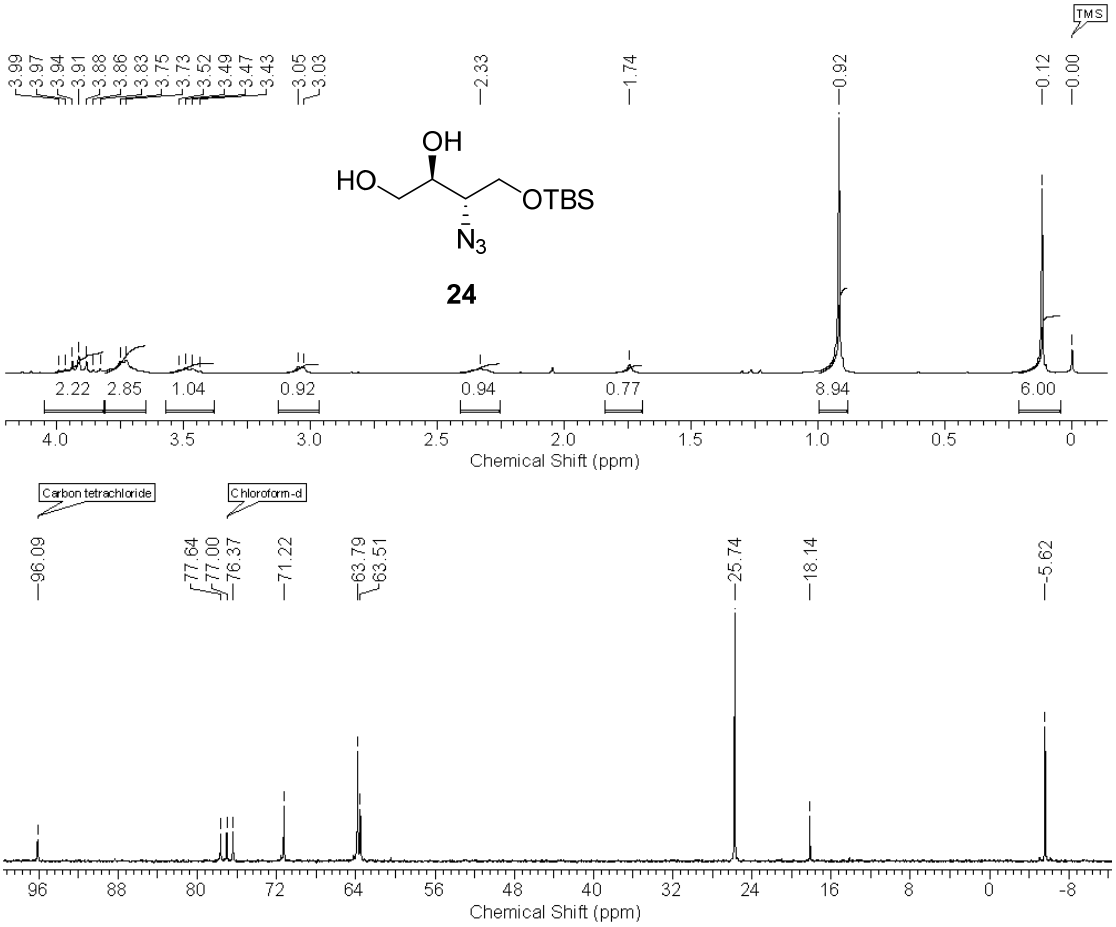


Fig. 2: ^{1}H and ^{13}C NMR spectra of azidodiol (+)-**24**

Its ^{13}C NMR spectrum showed two characteristic carbon signal at δ 63.5 and 71.2 corresponding to the methine carbons attached to azide and hydroxyl group respectively (**Fig. 2**).

The azido diol **(**+)-**24** was readily protected as its acetonide **30** (2,2-dimethoxypropane, cat. CSA) in 89% yield. The ^{1}H NMR spectrum of **30** showed two singlets at δ 1.33 (s, 3H) and 1.43 (s, 3H) integrating for three protons each confirming the formation of acetonide moiety. Its ^{13}C NMR spectrum also displayed typical carbon resonance signals at δ 25.3, 26.6 and 109.6 corresponding to the *gem*-dimethyl and quaternary carbons of isopropylidene group respectively (**Fig 3**).

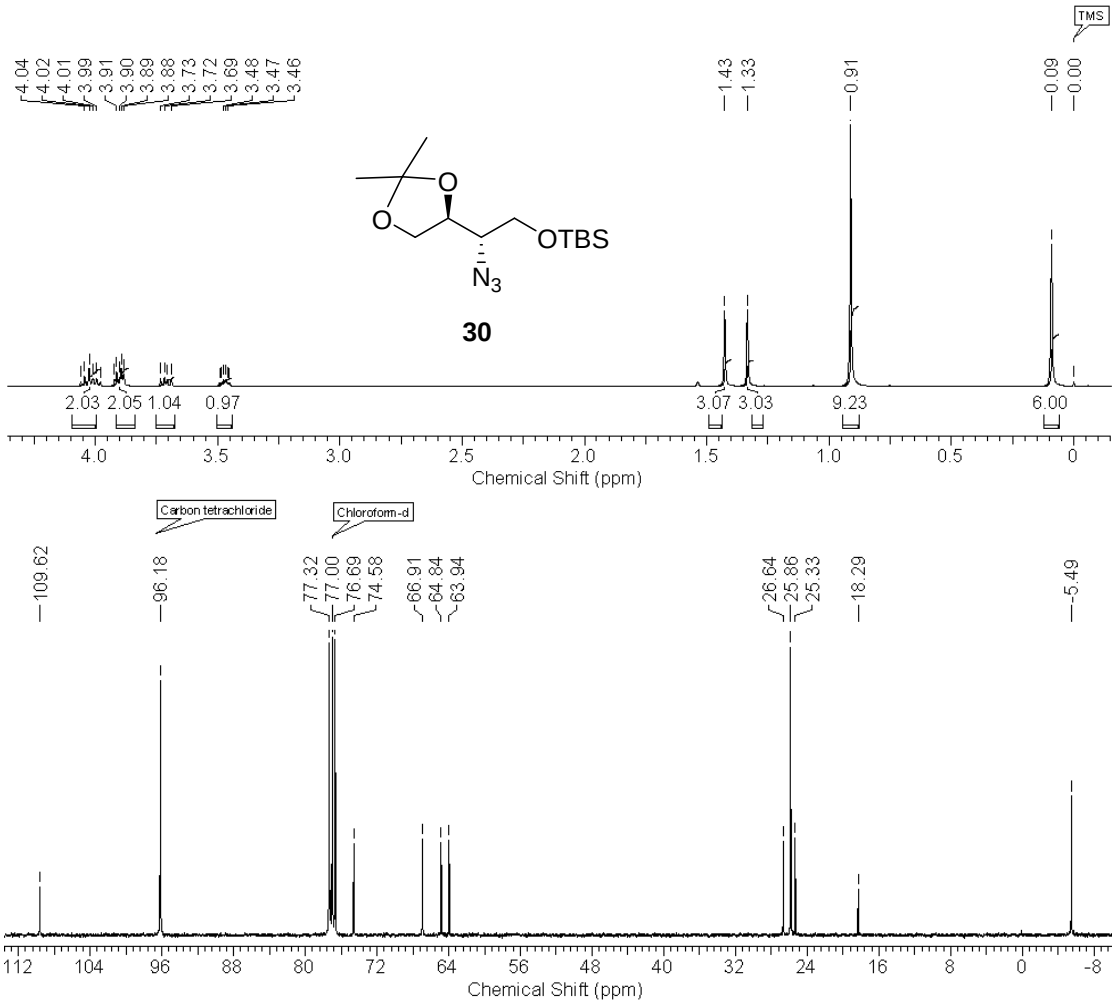


Fig. 3: ^{1}H and ^{13}C NMR spectra of acetonide **30**

The azido diol **30** was reduced under catalytic hydrogenation [H_2 (1 atm), 10% Pd/C, in methanol] at ambient conditions to produce the corresponding amine. Further, the

crude amine was selectively protected as its Boc derivative *in situ* [$(Boc)_2O$, DMAP, Et_3N, CH_2Cl_2] to give *tert*-butyl carbamate **31** in 75% yield. The ^1H NMR spectrum of **31** indicated the presence of Boc methyl protons [NH-($\mathbf{CH_3}$)$_3$] at δ 1.45 (s, 9H) as a singlet. The display of a broad singlet at δ 4.87 further indicated the presence of NH proton (-**NH**-Boc). Its ^{13}C NMR spectrum showed two typical signals at δ 79.3 and 155.4 indicating the presence of *tert*-butyl (Me_3**C**-O) and Boc carbonyl (-N**C**O-) carbons respectively (**Fig 4**).

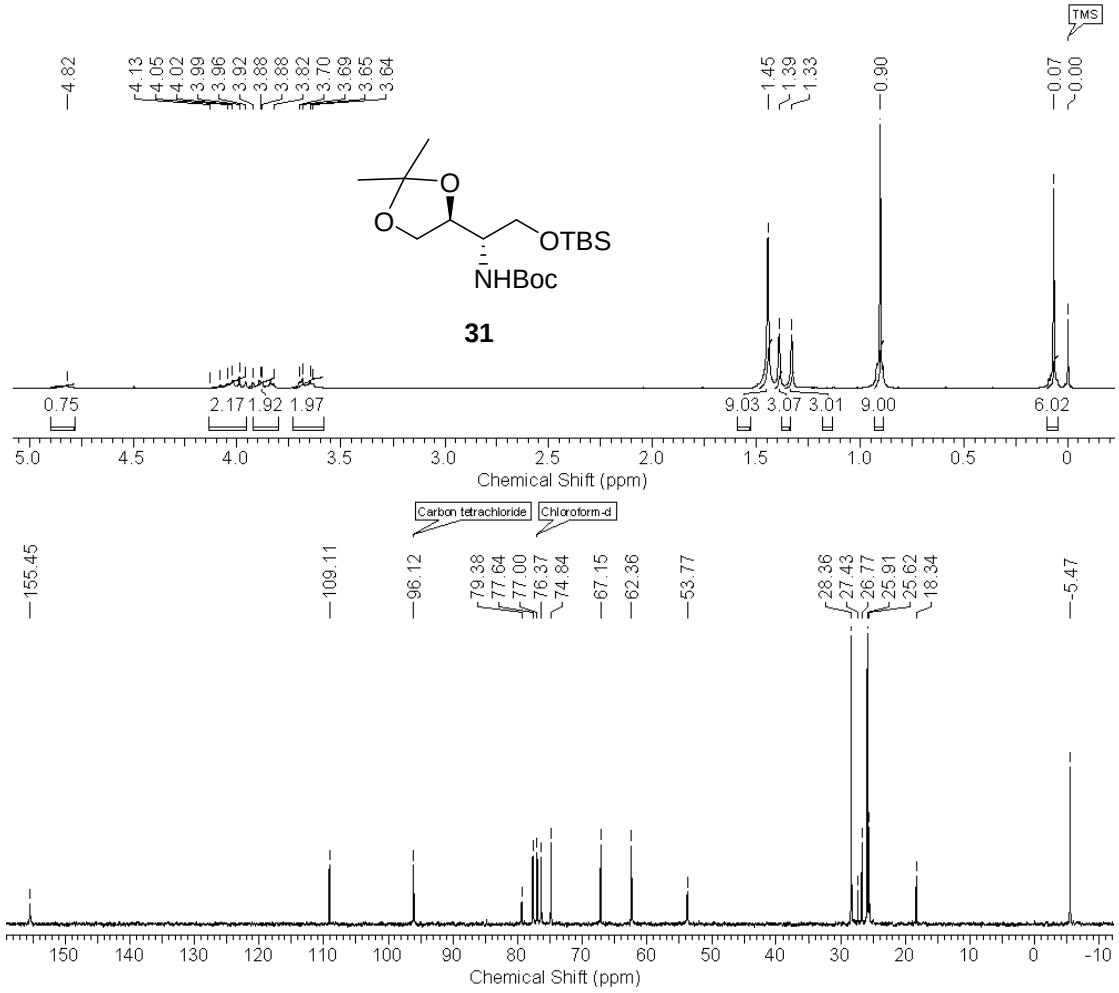


Fig. 4: ^1H and ^{13}C NMR spectra of carbamate **31**

The silyl deprotection of TBS ether group in **31** (TBAF, THF) was achieved to give

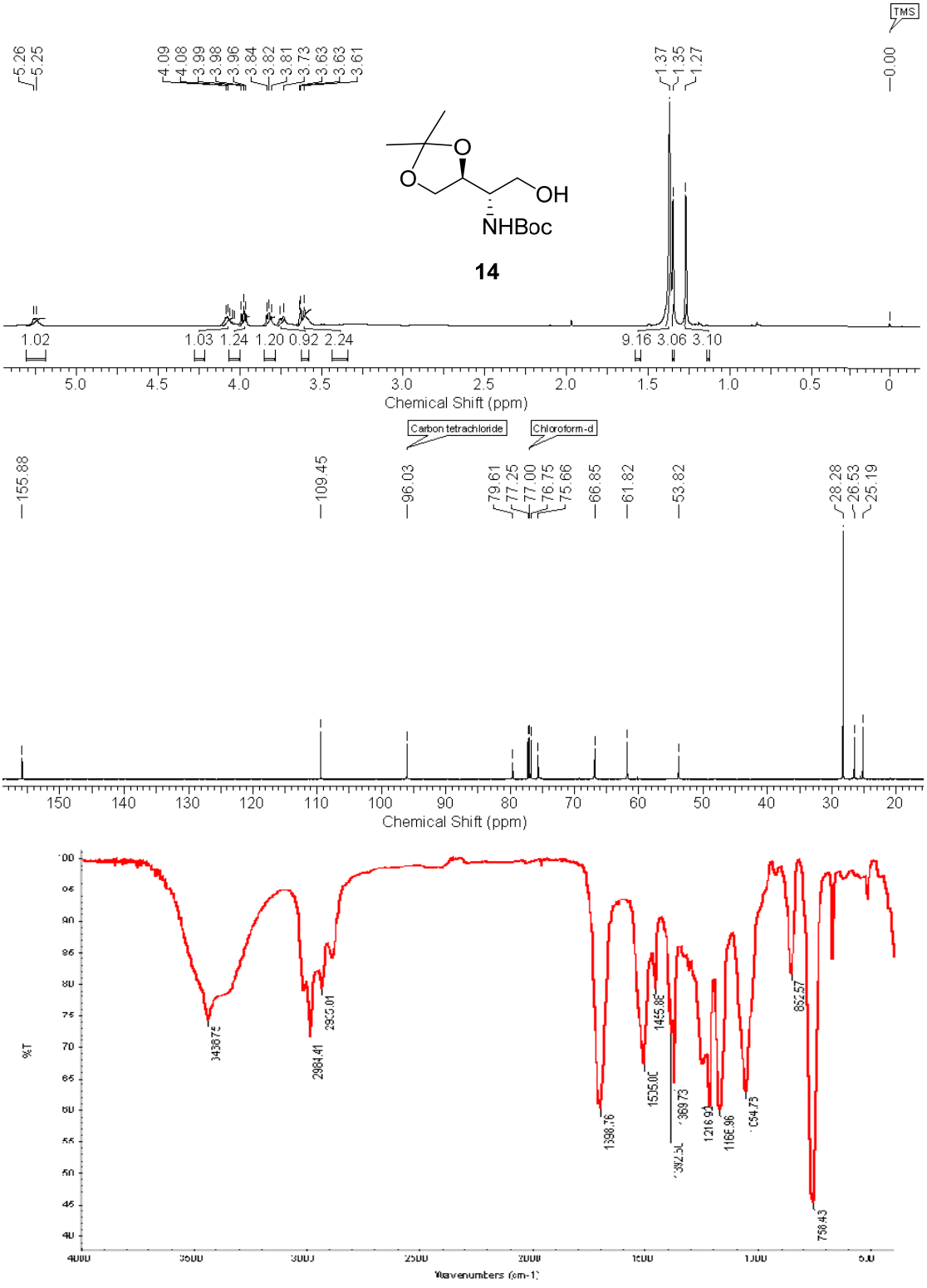


Fig. 5: ^{1}H, ^{13}C NMR and IR spectra of *N*-Boc-amino alcohol **14**

the corresponding known intermediate namely *N*-Boc-amino alcohol **14** (overall yield: 16% from **26**); thus constituting a formal synthesis of 1,4-dideoxy-1,4-imino-D-allitol (**1**). The formation of *N*-Boc-amino alcohol **14** was confirmed by its IR spectrum, which showed a strong absorption band at υ_{max} 1698 cm^{-1} typically for C=O functionality of -NHBoc group. The formation of amino diol **14** was further confirmed from ^{1}H NMR spectrum, which displayed two typical signals at δ 3.63 and 3.99 corresponding to methylene and methine protons (-C**H**$_2$-O and (-C**H**-O) respectively. Its ^{13}C NMR spectrum showed a characteristic signal at δ 61.8 corresponding to methylene carbon attached to hydroxyl group (**C**H_2OH) (**Fig 5**).

3.1.4 Conclusion:

In conclusion, this section has presented a novel route for formal syntheses of 1, 4-dideoxy-1,4-imino-D-allitol with good overall yield and high optical purity (ee up to 99%). The key reaction employed was a two-stereocentered Co-catalyzed HKR of racemic azido epoxides (±)-**25.**

3.1.5 Experimental Section

Hydrolytic Kinetic Resolution (HKR) of racemic azido epoxides(±)-25

To a solution of (*R, R*)-salen Co^{III}(OAc) complex or (*R, R*)-salen Co(OAc) (0.043 g, 0.07 mmol) in toluene (2.0 mL) was added acetic acid (0.04 g, 7.3 mmol). It was allowed to stir at 25 °C in open air for 30 min over which time the color has changed from orange-red to a dark brown. It was then concentrated in *vaccuo* to get the Co^{III}-salen complex as brown colored solid.

To a solution of the above Co-salen complex (0.004 g, 0.5 mol %) and racemic azido epoxide **25** (6.5 g, 26.7 mmol) in THF (0.5 mL) at 0 °C was added H_2O (0.24 g, 13.35

mmol) dropwise over 5 min. The reaction 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 residue was purified by column chromatography over silica gel to give chiral azido epoxide **29**, (solvent system; pet ether:EtOAc = 90:10) and chiral azido diol **24** (solvent system; pet ether: EtOAc = 60:40) in pure form.

(2*S*, 3*S*)-3-Azido-4-(*tert*-butyldimethylsilyloxy)butane-1,2-diol ((+)-24)

Yield: 48%; yellow liquid; $[\alpha]^{25}_{D}$ +29 (*c* 1, $CHCl_3$) {lit.[11] $[\alpha]_D$ -29 (*c* 1, $CHCl_3$)}; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 740, 839, 1109, 1265, 1471, 2100, 2931, 3390; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.12 (s, 6H), 0.90 (s, 9H), 1.74 (br s, 1H), 2.33 (br s, 1H), 3.04 (d, *J* = 4.6 Hz, 1H), 3.39-3.48 (m, 2H), 3.61-3.81 (m, 3H), 3.81-3.97 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.6, 18.1, 25.7, 63.5, 63.7, 71.6; **Anal.** Calcd for $C_{10}H_{23}N_3O_3Si$ requires C, 45.95; H, 8.87; N, 16.08; found: C, 45.90; H, 8.92; N, 16.13%.

(2*R*, 3*R*)-3-Azido-4-*tert*-butyldimethylsilyloxy-1,2-epoxybutane (29):

Yield: 50%; yellow viscous liquid; $[\alpha]^{25}_{D}$ -26 (*c* 1, $CHCl_3$) {lit.[11] $[\alpha]_D$ -26 (*c* 1, $CHCl_3$)}; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 740, 839, 1127, 1250, 1463, 1493, 1602, 2106, 2932, 3025; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.09 (s, 6H), 0.90 (s, 9H), 2.73 (dd, *J* = 5.0, 2.6 Hz, 1H), 2.80 (dd, *J* = 5.0, 3.6 Hz, 1H), 3.01-3.07 (m, 1H), 3.21-3.29 (m, 1H), 3.74-3.90 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.5, 18.2, 25.7, 45.2, 50.2, 63.5, 63.9; **Anal.** Calcd for $C_{10}H_{21}N_3O_2Si$ requires C, 49.35; H, 8.70; N, 17.27; found: C, 49.32; H, 8.74; N, 17.30%.

((*S*)-2-Azido-2-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)ethoxy)(*tert*-butyl)dimethylsilane (30)

To a mixture of azido diol **(+)-24** (2.5 g, 9.56 mmol), 2,2-dimethoxypropane (3.5 mL, 28.68 mmol) in dry CH_2Cl_2 (25 mL) was added catalytic amount of CSA (0.22 g, 10 mol%). The reaction mixture was stirred at 25 ^oC for 12 h. After completion of the

reaction as monitored over TLC, it was neutralized with triethylamine, concentrated and purified by silica gel chromatography using pet. ether:EtOAc (9:2) as eluent to yield **30** as an oil (2.56 g, 89%).

Yield: 89%; yellow viscous liquid; $[\alpha]^{25}_{D}$ +13.52 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 740, 839, 1109, 1265, 1471, 2100; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.09 (s, 6H), 0.91 (s, 9H), 1.33 (s, 3H), 1.43 (s, 3H), 3.45-3.49 (m, 1H), 3.69-3.73 (m, 1H), 3.88-3.92 (m, 2H), 3.99-4.04 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.4, 18.2, 25.2, 25.8, 26.6, 63.9, 64.8, 66.9, 74.5, 109.6; **Anal**. Calcd for $C_{13}H_{27}N_3O_3Si$ requires C, 51.80; H, 9.03; N, 13.94; found: C, 51.76; H, 9.00; N, 13.95.

***tert*-butyl ((*S*)-2-((*tert*-Butyldimethylsilyl)oxy)-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)ethyl)carbamate (31)**

To a stirred solution of acetonide **30** (2 g, 6.63 mmol) in methanol (5 mL), was added 10% Pd/C (10 mg) at 25 ^oC. The reaction mixture was stirred under H_2 atmosphere (60 psi) at 25 ^oC for 20 h. After completion of reaction (monitored by TLC), it was filtered through a Celite pad and washed with EtOAc (3 x 20 mL). The combined organic phase was concentrated under reduced pressure to give the crude amino compound, which was taken up for next step without purification.

To a solution of the above crude amine (2 g, 7.26 mmol) in dry CH_2Cl_2 (20 mL) were added dry Et_3N (2.1 mL, 8.71 mmol), $(Boc)_2O$ (1.5 mL, 10.89 mmol) and DMAP (0.088 g, 10 mol%), and the reaction mixture stirred for 10 h. After completion of the reaction as monitored by TLC, it was extracted with CH_2Cl_2 (3 x 60 mL), washed with brine and dried over anhyd. Na_2SO_4 and concentrated to give the crude product, which was then purified by column chromatography over silica gel using petroleum ether:EtOAc (7:3) to give carbamate **31** as a colorless gummy liquid (1.86 g, 75%).

Yield: 75%; colorless gummy liquid; **[α]** $^{25}_{D}$ +12.25 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 740, 839, 1053, 1167, 1692, 2981; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.07 (s, 6H), 0.9 (s, 9H), 1.33 (s, 3H), 1.39 (s, 3H), 1.45 (s, 9H), 3.64-3.70 (m, 2H), 3.82-3.88 (m, 2H), 3.96-4.13 (m, 2H), 4.82 (br s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.47, 18.34, 25.62, 25.91, 26.77, 27.43, 28.36, 53.77, 62.36, 67.15, 74.84, 76.37, 79.38, 109.11, 155.45; **Anal**. Calcd for $C_{18}H_{37}NO_5Si$ requires C, 57.56; H, 9.93; N, 3.73; found: C, 57.53; H, 9.95; N, 3.75.

***tert*-Butyl ((*S*)-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-hydroxyethyl)carbamate (14)**

The silyl ether **31** (1.5 g, 3.99 mmol) was dissolved in THF (20 mL) and to this mixture TBAF (10 mL of 1 M solution in THF) was added at 0 ^{o}C. The reaction mixture was stirred for 1 h at the same temperature and then quenched with water. It was extracted with ethyl acetate and the combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain the crude product, which was then purified by column chromatography using pet ether:ethyl acetate (90:10) to obtain pure alcohol **14** (0.936 g, 90%).

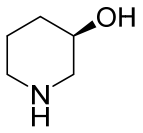
Yield: 90%; colorless solid, **mp**: 55 ^{o}C; **[α]$^{25}_{D}$** -5.25 (*c* 1, $CHCl_3$) {lit.[8] $[\alpha]_D$ -4.14 (*c* 0.725, $CHCl_3$)}; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 740, 839, 1054, 1166, 1392, 1698, 2984, 3438; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.27 (s, 3H), 1.35 (s, 3H), 1.37 (s, 3H), 3.61-3.63 (m, 2H), 3.73-3.75 (m, 1H), 3.81-3.84 (m, 1H), 3.96-3.99 (m, 1H), 4.03-4.09 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 25.19, 26.53, 28.28, 53.82, 61.82, 66.85, 75.66, 79.61, 109.45, 133.88; **Anal.** Calcd for $C_{12}H_{23}NO_5$ requires C, 55.16; H, 8.87; N, 5.36; found: C, 55.20; H, 8.90; N, 5.40%.

Section II

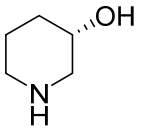
Asymmetric Synthesis of (*S*)-3-Hydroxypiperidine Skeleton: A Key Element in Natural Product Synthesis

3.2.1 Introduction and Pharmacology

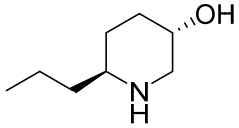
Natural products often provide an inspiration for synthetic organic chemists, because of their biological properties and structural design. In majority of natural products, so the so called privileged skeletal fragments can be identified such as the benzodiazepinone and quinazoline structures. Another scaffold in nature is the 3-hydroxypiperidine motif, which is present in the variety of natural products such as Bao Gong Teng A,[12] Pseudoconhydrine,[13] Cassine[14] and Deoxocassine.[15] Thus, functionalized piperidines are among the most ubiquitous heterocyclic building blocks of natural and synthetic compounds with important biological activities. In particular, 3-hydroxypiperidines (**32** and **33**) is an attractive target because of their widespread occurrence in natural products (**Fig. 1**).



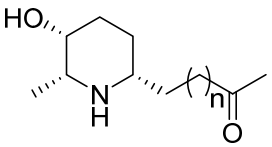
(*R*)-3-Hydroxypiperidine (**32**)



(*S*)-3-Hydroxypiperidine (**33**)

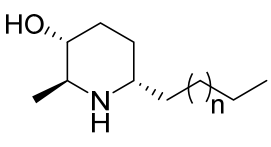


Pseudoconhydrine (**34**)



n = 9

Cassine (**35**)



n = 10

Deoxocassine (**36**)

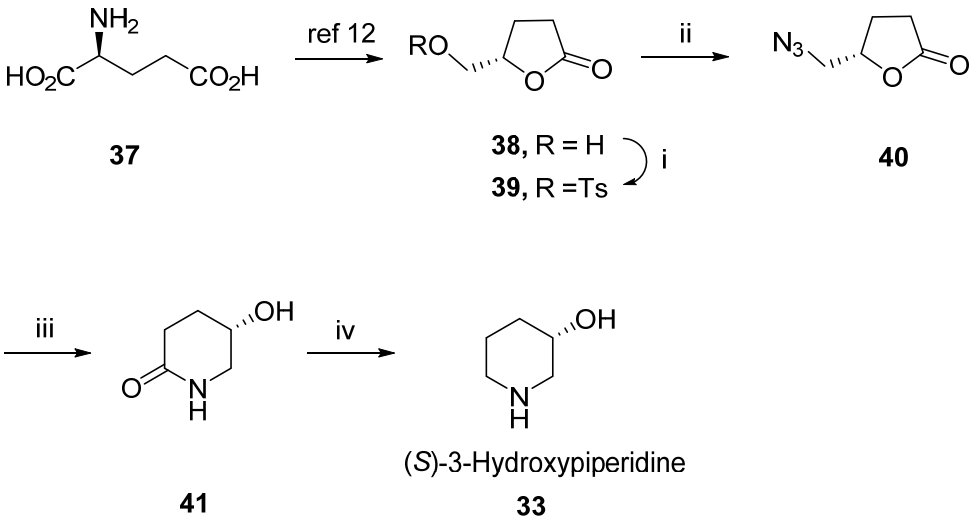
Fig. 6: Some of the structures of 3-hydroxypiperidine containing alkaloids

Medicinally important examples containing 3-piperidinol fragments include cholinotoxic agents,[16] antihypertensives and calcium antagonists,[17] 2,3-oxydosqualene cyclase inhibitors,[18] 5-HT4 agonists,[19] nootropics[20] or antiarrhythmic agents.[21]

3.2.2 Review of Literature

Olsen's approach (1985)[22]

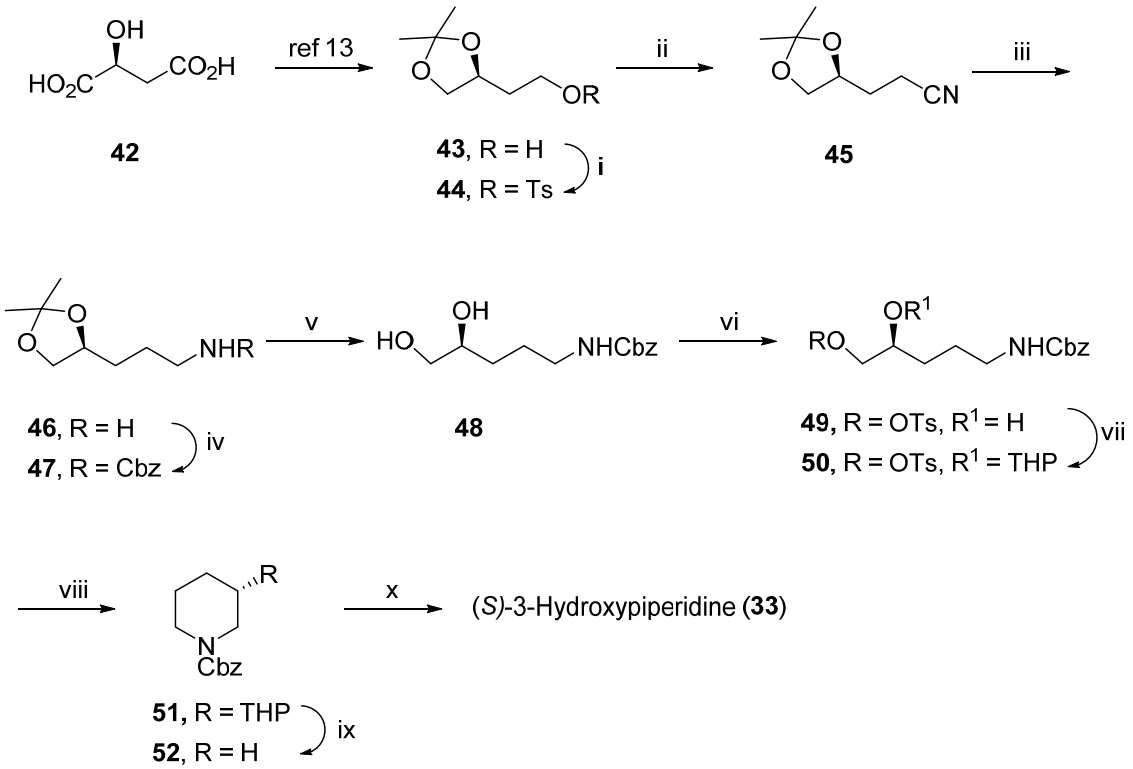
Olsen *et al*. have reported the synthesis of (*S*)-3-hydroxypiperidine (**33**) from L-(+)-glutamic acid **37**, which was converted into (*S*)-(+)-5-hydroxy-4-pentanolide **38**. The tosylation of primary hydroxyl in **38** gave its tosylate **39** in 94% yield. Nucleophilic displacement of tosylate **39** with sodium azide resulted in 5-azido-4-pentanolide **40** in 87% yield. The catalytic reduction of the azide in **40** to give hydroxy lactam namely *(S)*-5-hydroxy-2-piperidinone **41**. Finally, reduction of the lactam function in **41** with $BH_3.SMe_2$ afforded (*S*)-3-piperidinol (**33**) in 68% yield (**Scheme 6**).



Scheme 6: (i) TsCl, pyridine, 94%; (ii) NaN_3, DMF, 87%; (iii) H_2, Pd/C, 67%; (iv) BH_3.THF, 68%.

Olsen's approach (1985)[22]

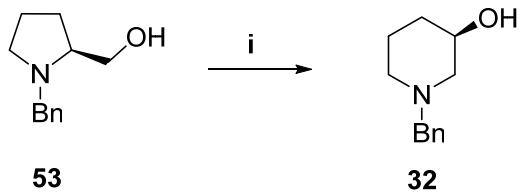
In yet another approach, Olsen *et al*. have reported the synthesis of (*S*)-3-hydroxypiperidine (**33**) from (*S*)-(-)-malic acid **42**. Reduction of acid **42** and protection of the formed diol with 2,2-dimethoxy propane afforded acetonide **43**.[23] The formed acetonide **43** was transformed to the known[23] intermediate acetonide **46** *via* tosylation of **43**, displacement of tosylate **44** with cynide and reduction of CN with $LiAlH_4$. Selective activation and protection of the primary and secondary alcohol functions afforded **50** in quantitative yield. Cyclization of **50** gave the protected 3-piperidinol **51** in 62% yield. Deprotection of **51** furnished (*S*)-3-hydroxypiperidine **33**, with an overall yield of 10% starting from acetonide diol **43** (**Scheme 7**).



Scheme 7: (i) TsCl, pyridine, 92%; (ii) NaCN, DMF, 82%; (iii) $LiAlH_4$, Et_2O, 70%; (iv) CbzCl, MgO, H_2O, 93%; (v) 90% TFA, 60%; (vi) TsC1, pyridine, 80%; (vii) DHP, TsOH, Et_2O, 100%; (viii) NaH, THF, 37-62%; (ix) $AcOH/H_2O/THF$, 70%; (x) H_2, Pd/C, 100%.

Cossy's approach (1995)[24]

Cossy *et al.* have reported the synthesis of (*R*)-3-hydroxypiperidine **32** starting from 2-hydroxymethyl-*N*-benzylpyrrolidine **53** *via* the treatment of trifluoroacetic anhydride in THF followed by the addition of triethylamine and then sodium hydroxide that led directly to the formation of (*R*)-3-hydroxypiperidine **32** in 66% yield (**Scheme 8**).

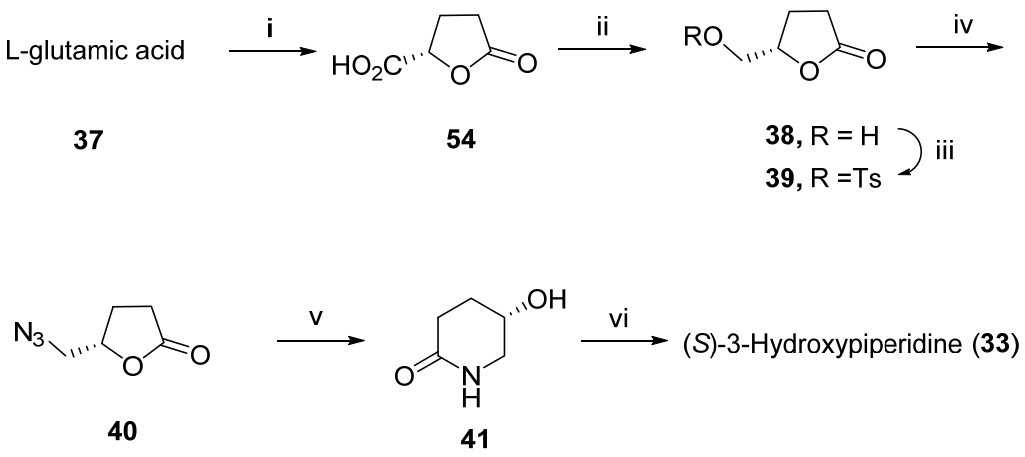


53 **32**

Scheme 8: (i) (a) $(CF_3CO)_2O$, THF, reflux; (b) Et_3N; (c) aq. 10% NaOH, 66%, >97% ee.

Thompson's approach (1995)[25]

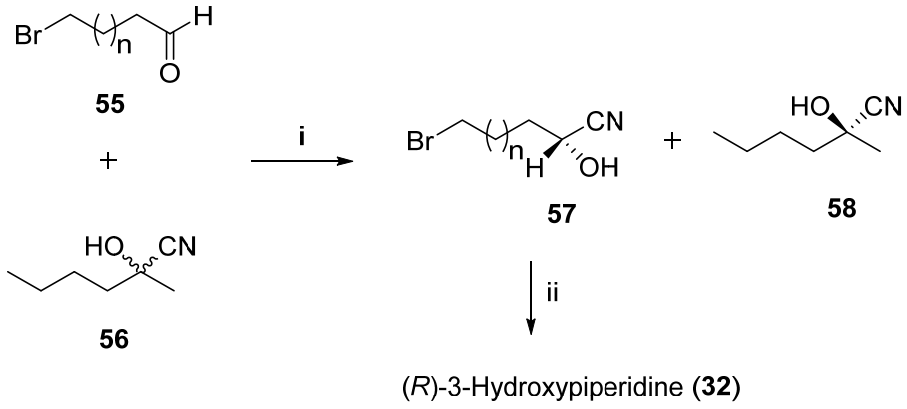
Thompson *et al.* have reported the synthesis of (*S*)-3-hydroxypiperidine **33** from L-glutamic acid **37**, which was converted to (*S*)-5-oxo-2-tetrahydrofuran carboxylic acid **54** in 91% yield. The carboxylic acid **54** was reduced with borane-methyl sulfide complex to the corresponding primary alcohol **38** with in 90% yield. The primary alcohol was protected as its tosylate **39** in 93% yield using pyridine/CH_2Cl_2 as co-solvents. The tosylate **39** was then displaced with azide in DMF to give **40** in 93% yield. Reduction of **40** by catalytic hydrogenation (H_2, Pd/C) led to the amine, which underwent ring expansion to form the lactam, namely (*S*)-5-hydroxypiperidin-2-one **41** in 96% yield. The lactam carbonyl was finally reduced using BH_3.THF to give (*S*)-3-hydroxypiperidine (**33**) in 50% (**Scheme 9**).



Scheme 9: (i) $NaNO_2$, H^+, 91%; (ii) $BH_3.SMe_2$, 90%; (iii) TsCl, pyridine, 93%; (iv) NaN_3, DMF, 93%; (v) H_2 (1 atm), 5% Pd/C, 96%; (vi) BH_3.THF, 50%.

Gotor's approach (1999)[26]

Gotor *et al*. have reported a new enantioselective route to (*R*)-3-hydroxypiperidine **32**. The (*R*)-oxynitrilase-catalyzed transcyanation of bromoaldehyde **55** with (±)-2-methyl-2-hydroxyhexanenitrile **56** as the hydrogen cyanide donor gave the longer chain bromocyanohydrin **57** in moderate yields. The reduction of bromocyanohydrin **57** with $BH_3.SMe_2$ afforded (*R*)-3-hydroxypiperidine in good yields (**Scheme 10**).



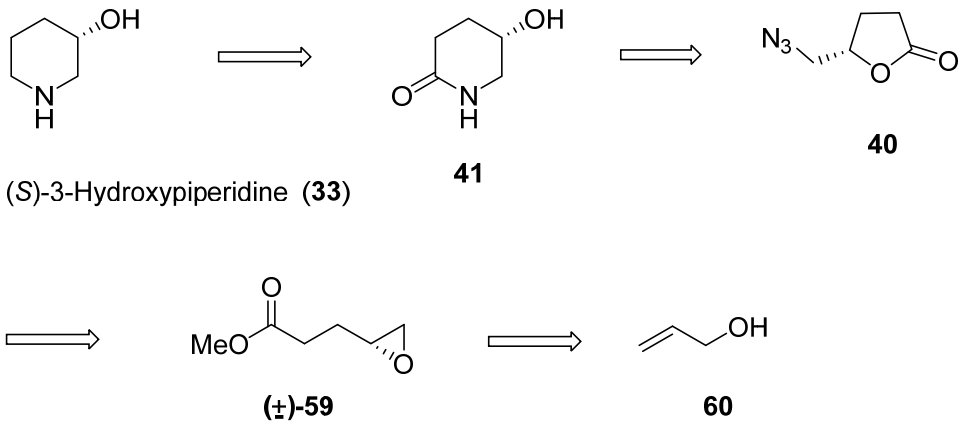
Scheme 10: (i) (*R*)-oxynitrilase, 65%; (ii) BH_3-SMe_2, THF, 0 °C, 96%.

3.2.3 Present Work

3.2.3.1 Objective

As can be seen from the above discussion, the reported methods of synthesis of (*S*)-3-hydroxypiperidine **33** suffer from certain limitations such as the use of chiral building blocks, low overall yields, etc. Jacobsen *et al*. have reported a flexible method that employs Co-catalyzed Hydrolytic Kinetic Resolution (HKR) of racemic terminal epoxides to generate the corresponding diols and epoxides in high optical purity (97-99% ee) in a single step.[27] This section describes an efficient synthesis of (*S*)-3-hydroxypiperidine (**33**) by employing HKR of racemic epoxides as the key chiral-inducing step.

Retrosynthetic analysis of (*S*)-3-hydroxypiperidine (**33**) reveals that piperidinone core **41** could be visualized as the key intermediate. The 3-substituted piperidinone **41** could be obtained from γ-butyrolactone **40**, which in turn can be prepared by the Co-catalyzed hydrolytic kinetic resolution of *racemic* epoxy ester (±)**-59** (**Scheme 11**).

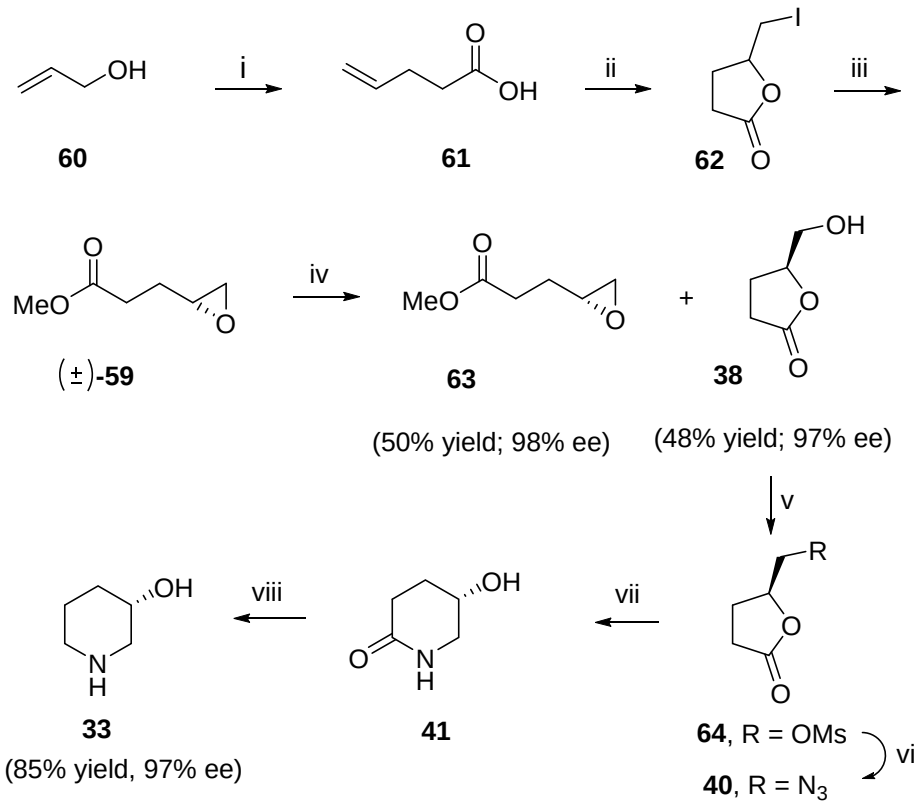


Scheme 11: Retrosynthetic analysis of (*S*)-3-hydroxypiperidine (**33**)

3.2.3.2 Results and Discussion

Synthesis of (*S*)-3-hydroxypiperidine (33) *via* HKR

The complete synthetic scheme for (*S*)-3-hydroxypiperidine (**33**) is shown in **Scheme 12**. Thus, the commercially available allylic alcohol **60** was subjected to Johnson-Claisen rearrangement[28] with triethyl orthoacetate in the presence of catalytic amount of hexanoic acid to give acyclic olefinic acid **61** in 80% yield (**Scheme 12**).



Scheme 12: (i) $MeC(OEt)_3$, hexanoic acid, 80-150 ^oC, 3 h, 80%; (ii) I_2, CH_3CN, 0 ^oC, 24 h, 85%; (iii) MeOH, Na_2CO_3, reflux, 3 h, 70%; (iv) (*S, S*)-Co^{III}(salen) complex (0.5 mol %), H_2O (0.49 equiv), 0 to 25 ^oC, 12 h. (v) MsCl, Et_3N, CH_2Cl_2, 0 ^oC, 1 h, 92%; (vi) NaN_3, DMF, 80 ^oC, 3 h, 95%; (vii) 20% $Pd(OH)_2$, H_2 (1 atm), MeOH, 12 h, 25 ^oC, 98%; (viii) $BH_3.SMe_2$, THF, reflux, 12 h, 85%.

The formation of olefinic acid, **60** was confirmed from ^1H and ^{13}C NMR spectroscopy. The ^1H NMR spectrum of **60** showed two typical proton signals at δ

5.00-5.12 (m, 2H) and δ 5.76-5.93 (m, 1H) due to olefinic protons. Its ^{13}C NMR spectrum showed a typical carbon signal at δ 179.7 corresponding to carbonyl carbon group (**Fig.7**).

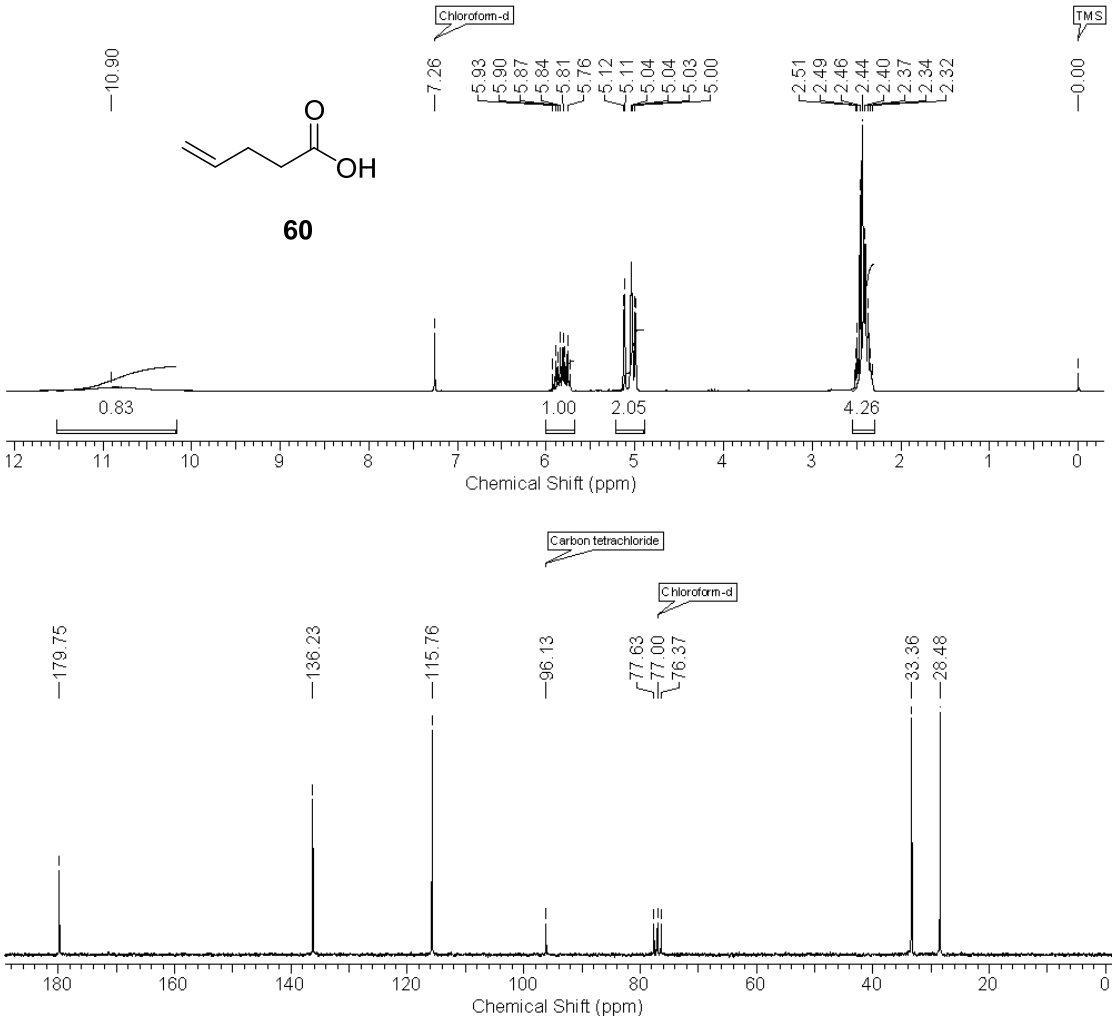


Fig.7: ^{1}H and ^{13}C NMR spectra of olefinic acid **60**

Acyclic olefinic acid **60** was then subjected to iodolactonization (I_2, CH_3CN, 0 ^{o}C, 24 h) to give iodolactone **61** in 85% yield. The formation of iodolactone **61** was confirmed from ^{1}H and ^{13}C NMR spectroscopy. The ^{1}H NMR spectrum of iodolactone **61** showed two typical proton signals at δ 3.25-3.41 (m, 2H) and δ 4.49-4.65 (m, 1H) corresponding to methine and methylene protons (-**CH**-O and **CH_2**-I) respectively. Its ^{13}C NMR spectrum showed two characteristic typical carbon signals

at δ 7.70 and 175.7 due to carbon attached to iodo and carbonyl carbon groups respectively (**Fig. 8**).

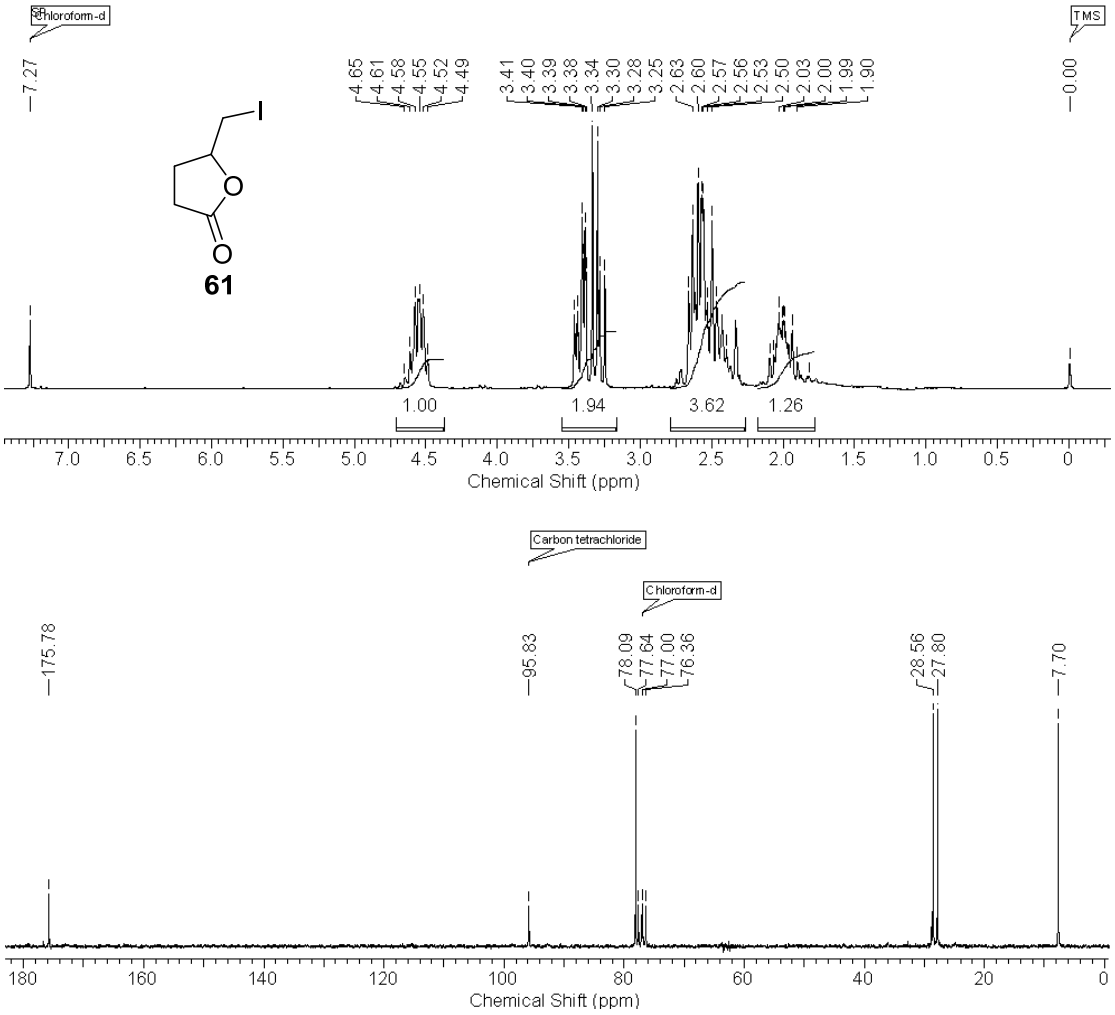


Fig. 8: ^{1}H and ^{13}C NMR spectra of iodolactone **61**

Methanolysis of iodolactone **61** under basic conditions produced the required racemic epoxy ester (±)**-59** in 70% yield. The ^{1}H NMR spectrum of epoxy ester (±)**-59** showed a typical singlet at δ 3.70 (s, 3H) corresponding to methoxy protons. Its ^{13}C NMR spectrum showed two characteristic signals at δ 46.9 and δ 51.6 due to carbons of the epoxide moiety and a carbon signal at δ 173.2 for carbonyl carbon group (**Fig. 9**).

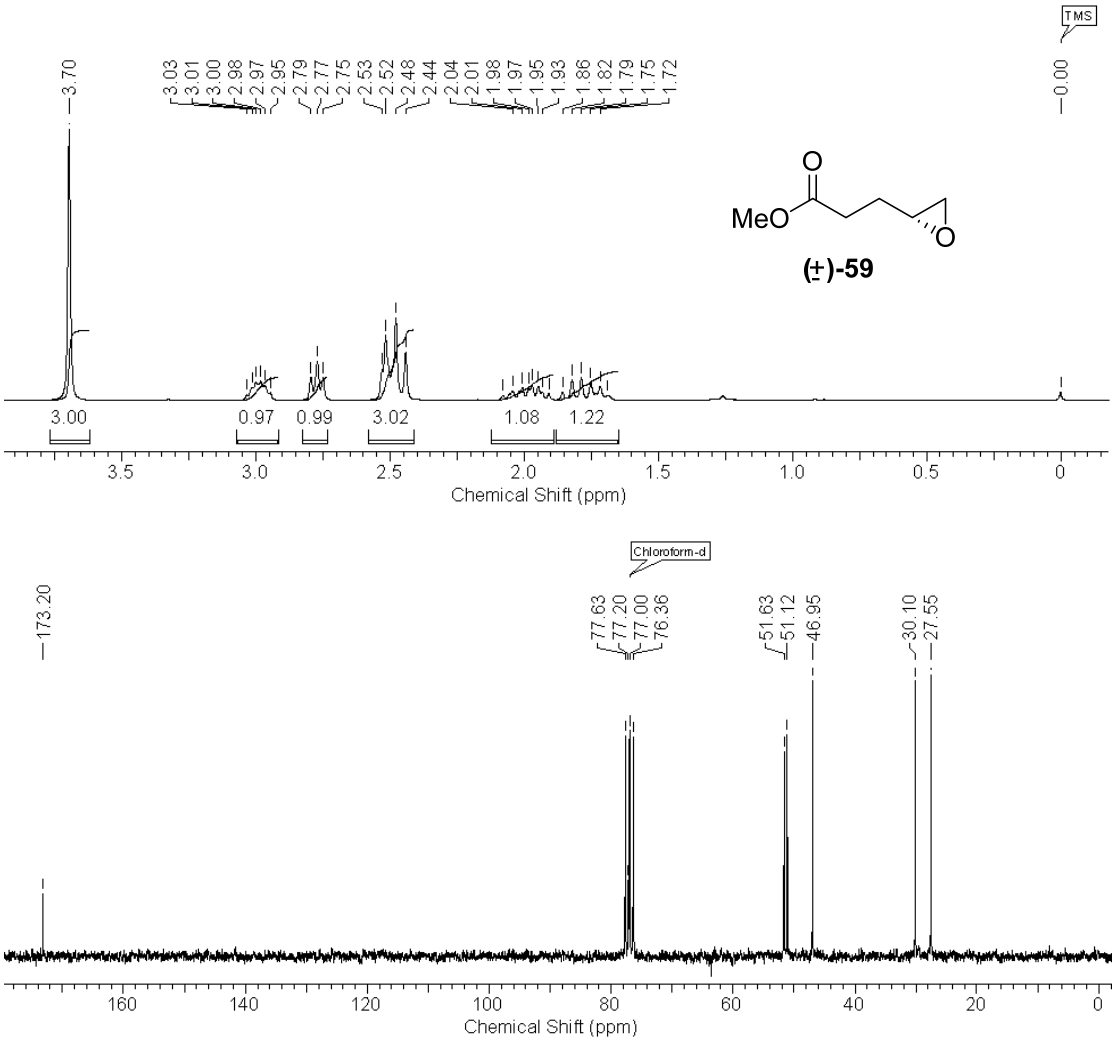


Fig. 9: ^{1}H and ^{13}C NMR spectra of epoxy ester (±)-**59**

Epoxy ester (±)-**59** was then subjected to HKR with (*S*, *S*)-salenCo(III)OAc complex (0.5 mol %) and H_2O (0.49 equiv), which produced the corresponding chiral γ-butyrolactone **38** (48%, 97% ee) and chiral epoxide **63** (50%, 98% ee) in high optical purity. The γ-butyrolactone (+)-**38** was readily separated from epoxide (-)-**63** by a simple flash column chromatographic purification over silica gel. The formation of γ-butyrolactone **38** was confirmed by its IR spectrum, which showed two strong absorption bands at υ_{max} 1620 and 3438 cm^{-1} typically for lactone carbonyl and hydroxyl functionality respectively. The ^{1}H NMR spectrum of **38** showed a typical proton signal at δ 4.59-4.66 (m, 1H) due to the methine proton (-**CH**-O). Its ^{13}C NMR

spectrum also showed two typical carbon signals at δ 63.7 and δ 177.9 due to carbon attached to hydroxyl and carbonyl carbon groups respectively (**Fig. 10**).

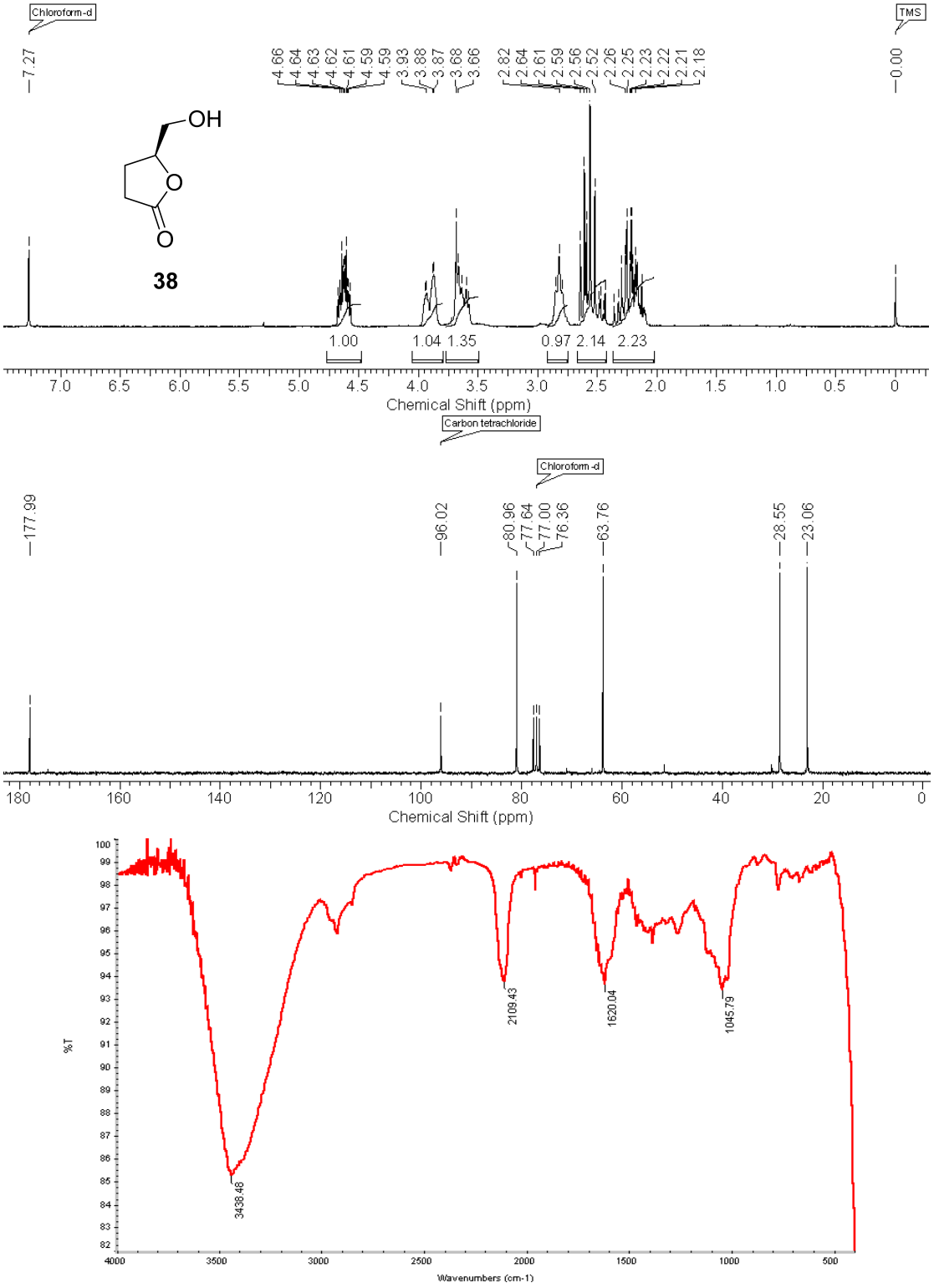


Fig. 10: ^{1}H, ^{13}C NMR and IR spectra of lactone **38**

The optical purity of lactone **38** was found to be 97% ee, based on comparison of its specific rotation with the reported value $[\alpha]_D^{25}$ +46.7 (*c* 1, $CHCl_3$){lit.[29] $[\alpha]_D^{25}$ +48.2 (*c* 1.03, $CHCl_3$)}.

The subsequent mesylation of lactone alcohol **38** gave the mesylate **64** in 92% yield. The formation of mesylate **64** was confirmed by ^1H and ^{13}C NMR spectroscopy. The ^1H NMR spectrum of **64** showed a singlet at δ 3.08 (s, 3H) for methyl protons. Its ^{13}C NMR showed a typical carbon signal at δ 37.4 for methyl carbon, which confirmed the formation of mesylate **64** (**Fig. 11**).

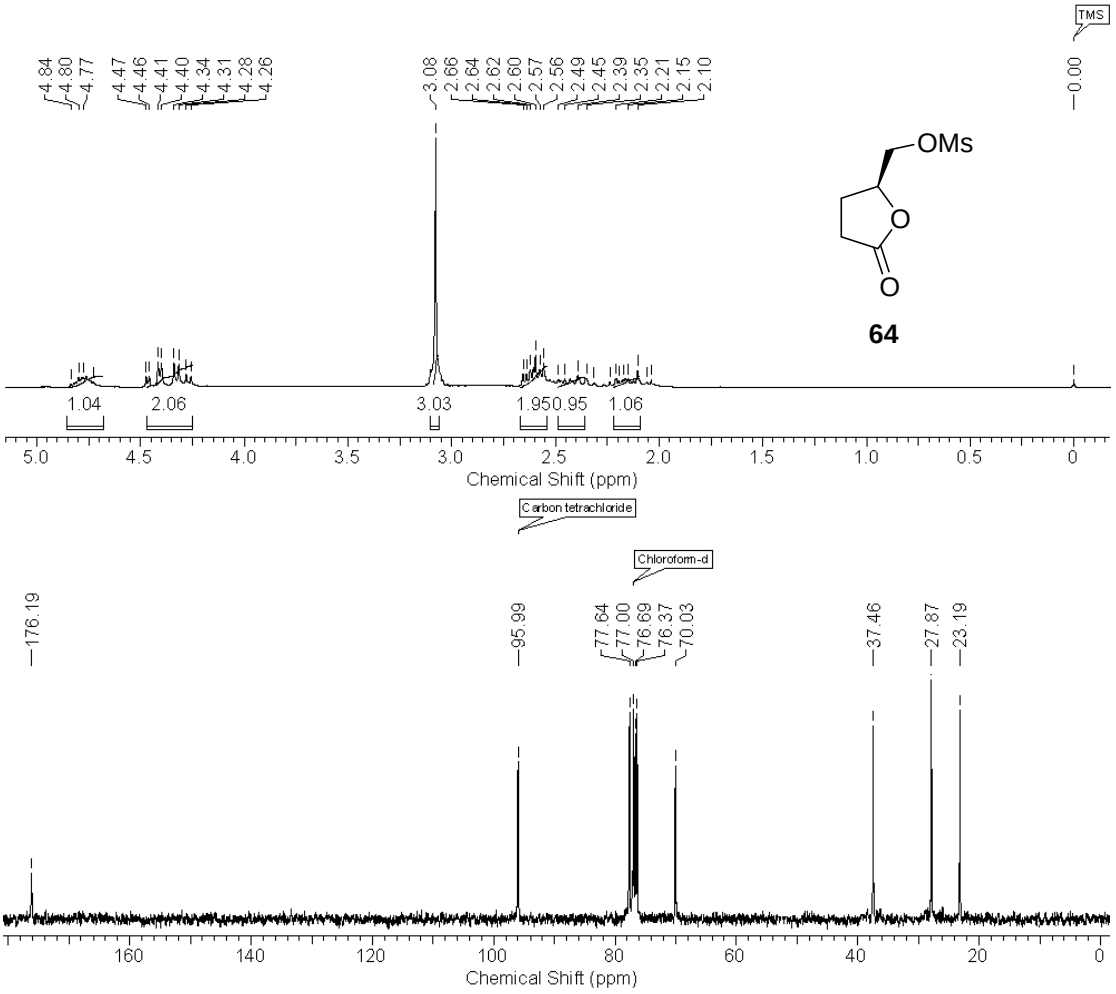


Fig. 11: ^1H and ^{13}C NMR spectra of mesylate **64**

The S_N2 displacement of mesylate **64** with azide ion produced the corresponding azide **40** (NaN_3, DMF, 80 ^oC) in 95% yield. The formation of azido derivative **40** was confirmed by its IR spectrum, which showed a strong vibrational band at υ_{max} 2105 cm^{-1} due to azide functionality. Its ^1H NMR spectrum showed a multiplet at δ 4.63-4.69 (m, 1H) corresponding to methine proton (-**CH**-O). Its structure was further confirmed from ^{13}C NMR spectrum, which showed a typical methine carbon (-**CH**-O) appearing at δ 77.83 (**Fig. 12**).

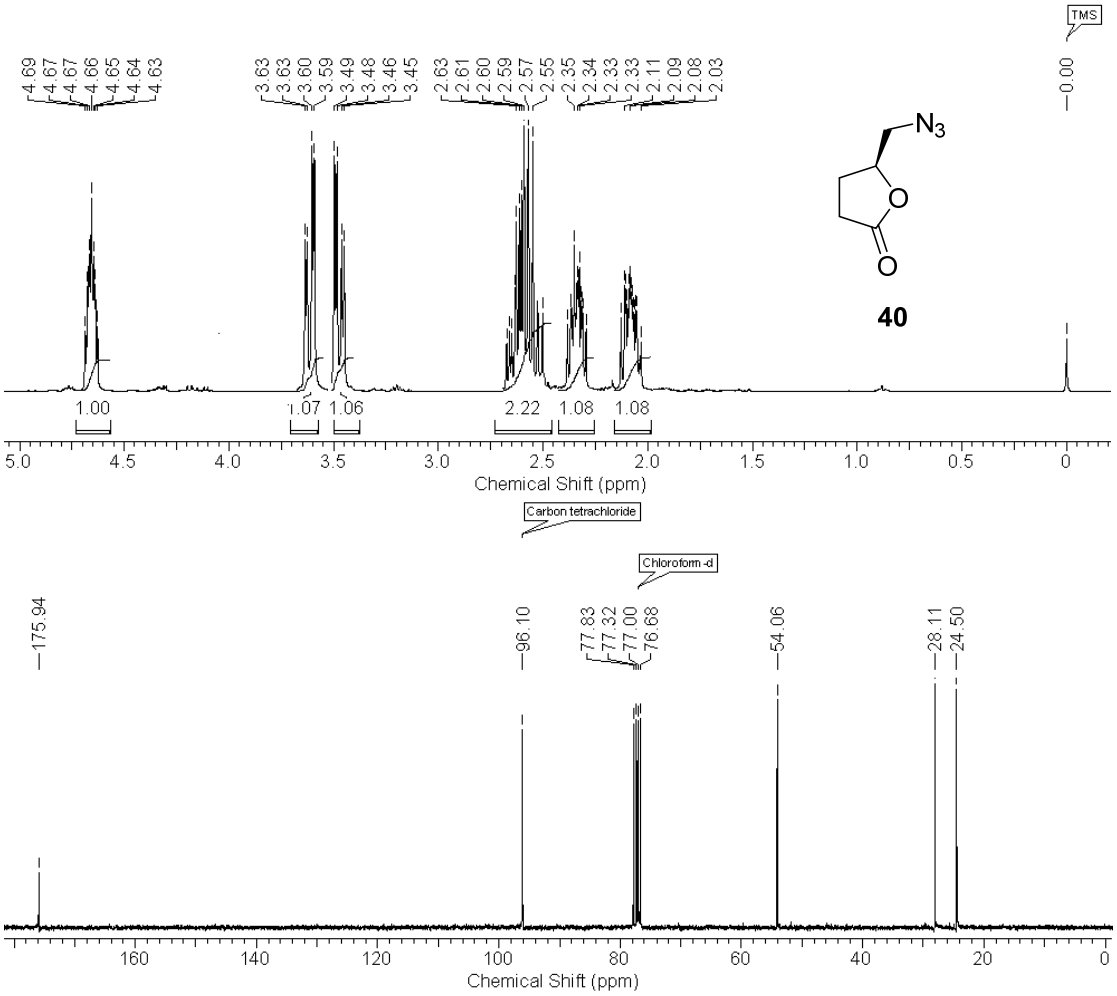


Fig. 12: ^1H and ^{13}C NMR spectra of azide **40**

Azide **40** was then subjected to intramolecular reductive cyclization over $Pd(OH)_2/H_2$ (1 atm) to afford piperidinone core **41** in 98% yield. The ^1H NMR spectrum of the lactam **41** showed a typical multiplet at δ 3.92-4.01 (m, 1H) corresponding to the methine proton attached to C**H**-OH. Its ^{13}C NMR spectrum showed a typical carbon signal at δ 174.5 for amide carbonyl carbon. The formation of cylclic lactam was further confirmed by its IR spectrum, which showed a strong vibrational frequency at υ_{max} 1652 cm^{-1} typically for amide carbonyl functionality (**Fig. 13**).

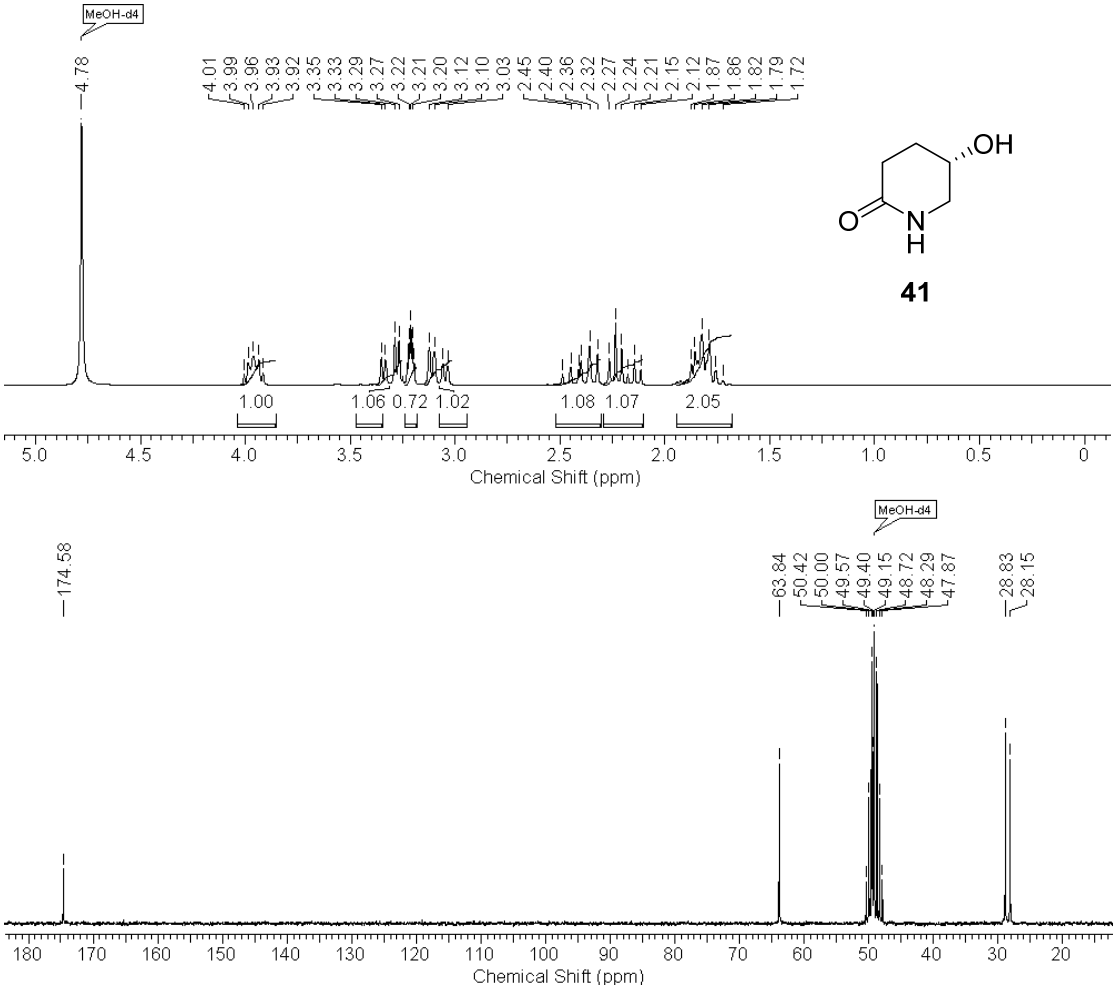


Fig. 13: ^1H and ^{13}C NMR spectra of lactam **41**

The reduction of amide carbonyl in **41** was carried out with $BH_3{\cdot}SMe_2$ to give (*S*)-3-hydroxypiperidine **33** in 85% yield (overall yield: 17% from **60**). The formation of **33** was confirmed by its ^{1}H NMR spectrum, which showed two typical proton signals at δ 3.07 (m, 2H) corresponding to methylene protons attached to **C$\mathbf{H_2}$**NH and δ 3.67 (m, 1H) for methine proton (-**CH**-O). This finally further confirmed from its ^{13}C NMR spectrum, which showed a characteristic carbon signal at δ 66.2 for methine carbons attached to hydroxyl group (**Fig. 14**).

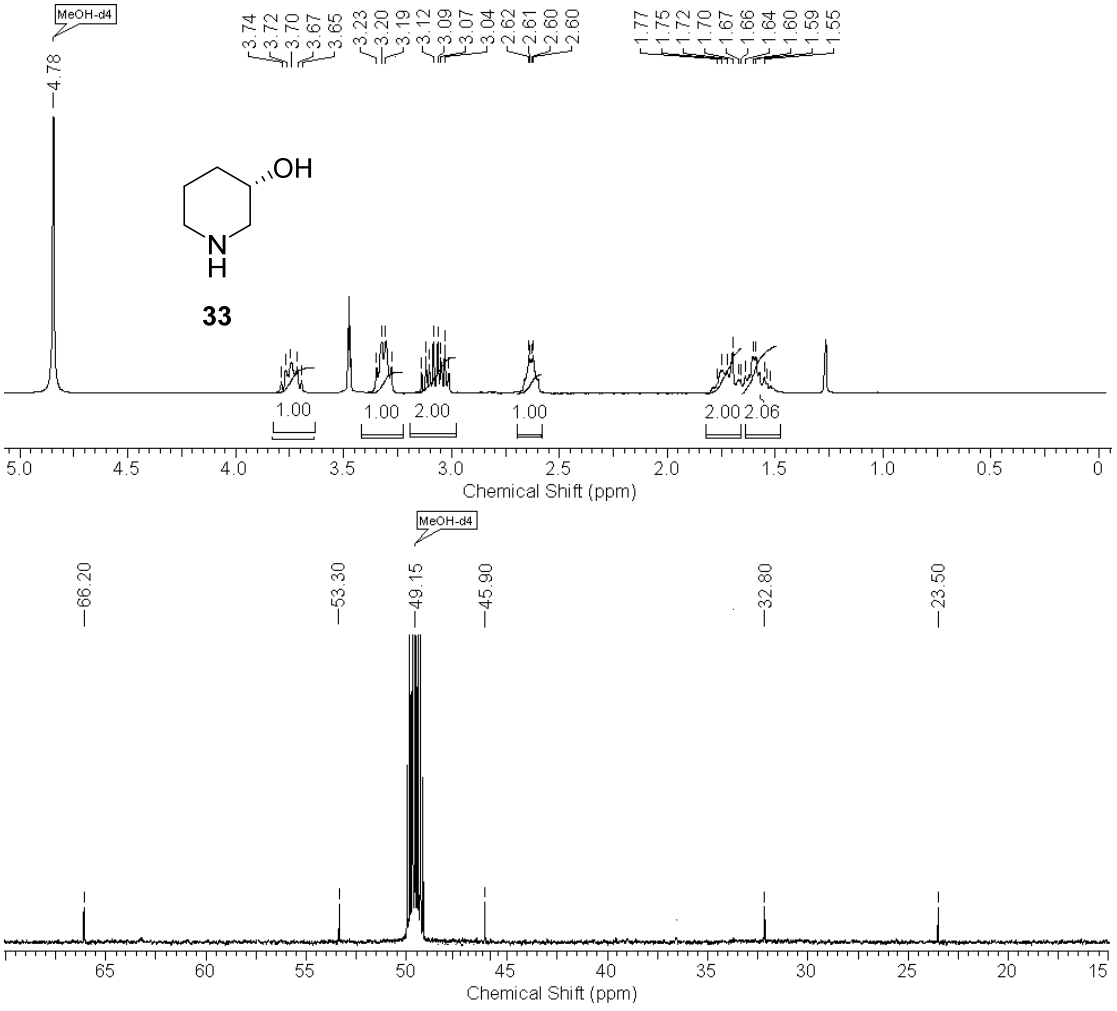


Fig. 14: ^{1}H and ^{13}C NMR spectra of 3-hydroxypiperidine (**33**)

3.2.4 Conclusion

This section has presented an elegant route to an enantioselective synthesis of (*S*)-3-hydroxypiperidine (**33**), a key structural unit present in several natural products, *via* HKR of *racemic* epoxy ester as a key step. The operationally simple reaction sequences include Johnson-Claisen rearrangement and intramolecular reductive cyclization. This strategy is expected to find wide scope for the synthesis of other similar multifunctionalized piperidine alkaloids.

3.2.5 Experimental Section

Pent-4-enoic acid (61)

A mixture of allylic alcohol **60** (10 g, 58.13 mmol), triethyl orthoacetate (29 mL, 58.13 mmol) and hexanoic acid (0.363 mL, 1.85 mmol) was placed in a round-bottomed flask equipped with thermometer, Claisen head and condenser. The solution was heated simultaneous with distillation of ethanol (upto 70-150 ^{o}C). After 3 h, distillation of ethanol slowed and another 0.1 mL portion of hexanoic acid was added. Additional portions (0.1 mL) of hexanoic acid were added again after 3 and 4 h, followed by continued heating for the next 6 h. It was allowed to cool to RT and aq. solution of KOH (6.5 g, 116.32 mmol, 20 mL) in MeOH (80 mL) was added. The resulting mixture was refluxed for 4 h and then allowed to cool to room temperature. The resulting solution was then washed with diethyl ether and acidified with aq. dil. HCl. The acidic solution was extracted with diethyl ether and the organic layer dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude product **61** (13.79 g, 80%). The crude material can be used as such for the next reaction without any further purification.

Yield: 80%; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1291, 1711, 2932, 2967, 3083; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.34-2.51 (m, 4H), 4.99-5.12 (m, 2H), 5.73-5.93 (m, 1H), 10.84 (br s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 28.4, 33.3, 115.1, 136.2, 179.9; **Anal**. Calcd for $C_5H_8O_2$ requires C, 59.98; H, 8.05; found: C, 59.95; H, 8.03%.

5-(Iodomethyl)dihydrofuran-2(3H)-one (62)

To a solution of olefinic acid **61** (13 g, 130 mmol) in acetonitrile (20 mL), solid I_2 (22 g, 416 mmol) was added at 0 ^oC under N_2 atmosphere. The reaction mixture was protected from light and stirred for 24 h. After the completion of the reaction (monitored by TLC), it was quenched with the addition of saturated solution of aq. $NaHCO_3$ followed by extraction with diethyl ether. Organic layer was separated and washed with 20% aq. $Na_2S_2O_3$ until colorless, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude product **57**. Column chromatographic purification with silica gel using petroleum ether:ethyl acetate (8:2) as eluent gave **62** in pure form (24.97 g, 85%).

Yield: 85%; gm; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 938, 989, 1086, 1254, 1346, 1417, 1559, 1778; **^{1}H NMR** (200 MHz, MeOH-d_4): δ 1.29 (m, 1H), 1.64 (m, 2H), 2.27 (d, *J* = 13.4 Hz, 1H), 2.45 (m, 2H), 2.61 (dd, *J* = 7.0 and 13.1 Hz, 1H), 2.94-3.01 (m, 2H), 3.53 (s, 1H); **^{13}C NMR** (50 MHz, MeOH-d_4): δ 7.7, 27.8, 28.5, 78.0, 175.7; **Anal.** Calcd for $C_5H_7IO_2$ requires C, 26.57; H, 3.12; found: C, 26.56; H, 3.10%.

Methyl -3-(oxiran-2-yl)propanoate (59)

To a solution of iodolactone **62** (23 g, 110.6 mmol) in MeOH (50 mL), finely powdered anhydrous Na_2CO_3 (11.86 g, 111.8 mmol) was added and the reaction mixture refluxed for 8 h under N_2 atmosphere. After the completion of the reaction (monitored by TLC), the resulting reaction mixture was concentrated under reduced pressure and partitioned between 50 mL water and 50 mL diethyl ether. The organic

layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the corresponding crude product **59**. Column chromatographic purification with silica gel using petroleum ether:ethyl acetate (9:1) as eluent gave **59** in pure form (9.26 g, 70%).

Yield: 70%; colorless liquid; (**IR** ($CHCl_3$, cm^{-1}): υ_{max} 920, 1290, 1737, 1963; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.69-1.86 (m, 1H), 1.91-2.08 (m, 1H), 2.44-2.53 (m, 3H), 2.75-2.79 (t, *J* = 4.2 Hz, 1H), 2.95-3.03 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 27.5, 30.1, 46.9, 51.1, 51.6, 173.2; **Anal.** Calcd for $C_6H_{10}O_3$ requires C, 55.37; H, 7.75; found: C, 55.35; H, 7.71%.

Hydrolytic Kinetic Resolutionof 3-substituted epoxy ester 59

To a solution of (*S*, *S*)-(salen)Co(II)complex (0.024 mmol, 0.5 mol %) in toluene (1 mL), AcOH (0.014 g, 0.24 mmol) was added. It was allowed to stir at 25 °C in open air for 30 min during which time the color changed from orange-red to a dark brown. It was then concentrated under reduced pressure to get the (*S*, *S*)-(salen)Co(III)-salen complex as brown colored solid. To this, racemic epoxy ester (±)-**59** (7 g, 60.3 mmol) and H_2O (0.543 g, 30.2 mmol) were added at 0 °C. The reaction mixture was allowed to warm to 25 °C and stirred for 12 h. After completion of reaction (monitored by TLC), the crude product was extracted purified by column chromatography over silica gel to give chiral epoxy ester **63** [solvent system; petroleum ether:ethyl acetate (9:1)] and chiral γ-butyrolactone **38** [solvent system; petroleum ether:ethyl acetate (1:1)] in pure form.

methyl (*R*)-3-(oxiran-2-yl)propanoate (63)

Yield: 50%; colorless liquid; **$[\alpha]_D^{25}$**-17.5 (*c* 1, $CHCl_3$){lit.[29] $[\alpha]_D^{25}$-17.9 (*c* 7, $CHCl_3$)}; **Optical purity**: The optical purity of epoxide **63** was found to 98%, based on comparison of its specific rotation with the reported value.

(*S*)-5-(Hydroxymethyl)dihydrofuran-2-(3H)-one (38)

Yield: 48%; colorless liquid; **$[\alpha]_D^{25}$** +47.5 (*c* 1, $CHCl_3$) {lit.[29] $[\alpha]_D^{25}$ +46.7 (*c* 1.03, $CHCl_3$)}; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1045, 1620, 2934, 2109, 3438; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.13-2.36 (m, 1H), 2.43-2.64 (m, 2H), 2.79-2.85 (t, *J* = 5.8 Hz, 1H), 3.58-3.68 (m, 1H), 3.87-3.94 (m, 1H) 4.57-4.68 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 23.0, 28.5, 63.7, 177.9; **Anal**. Calcd for $C_5H_8O_3$ requires C, 51.72; H, 6.94; found: C, 51.75; H, 6.93%.

(*S*)-(5-Oxotetrahydrofuran-2-yl)methyl methanesulfonate (64)

To a stirred solution of lactone **38** (3 g, 25.86 mmol) and triethylamine (5.4 mL, 38.79 mmol) in CH_2Cl_2 (20 mL), mesyl chloride (2.4 mL, 31.03 mmol) was added at 0 ^oC under N_2 atmosphere. The resulting solution was stirred at the same temperature for 1 h. After completion of the reaction (monitored by TLC), it was quenched with water and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude mesylate **64**. Column chromatographic purification with silica gel using petroleum ether:ethyl acetate (7:3) as eluent gave **64** in pure form (4.7 g, 92%).

Yield: 92%; colorless liquid; **$[\alpha]_D^{25}$** +33.5 (*c* 1, $CHCl_3$) {lit.[29] $[\alpha]_D^{25}$+33.7 (*c* 1, $CHCl_3$)}; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 938, 1035, 1090, 1150, 1789; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.10-2.21 (m, 1H), 2.31-2.49 (m, 1H), 2.56-2.66 (m, 2H), 3.08 (s, 3H), 4.26-4.47 (m, 2H) 4.73-4.84 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 23.1, 27.8, 37.4, 70.0, 77.6, 176.1; **Anal.** Calcd for $C_6H_{10}O_5S$ requires C, 37.11; H, 5.19; found: C, 37.10; H, 5.13%.

(*S*)-5-(Azidomethyl)dihydrofuran-2-(3H)-one (40)

To a stirred mixture of mesylate **64** (3 g, 15.44 mmol) in DMF (15 mL), sodium azide (1.25 g, 18.52 mmol) was added. The reaction mixture was stirred for 8 h at 80 ^oC.

After completion of the reaction (monitored by TLC), it was extracted with EtOAc (3 x 10 mL), washed with water, brine and dried over anhydrous Na_2SO_4. The combined organic layer was concentrated under reduced pressure to give the crude azido lactone **40**, which was purified by column chromatography with silica gel using petroleum ether:ethyl acetate (8:2) as eluent to give pure azide **40** as colorless oil (2 g, 95%).

Yield: 95%; pale yellow oil; $\mathbf{[\alpha]_D^{25}}$ +91.7 (*c* 1, $CHCl_3$) {lit.[29] $[\alpha]_D^{25}$ +92.9 (*c* 2.15, $CHCl_3$)}; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 930, 1040, 1291, 1789, 2105; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.03-2.11 (m, 1H), 2.31-2.37 (m, 1H), 2.55-2.63 (m, 2H), 3.45-3.49 (dd, *J* = 4.8 and 12.9 Hz, 1H), 3.59-3.63 (dd, *J* = 3.9 and 13.1 Hz, 1H), 4.63-4.69 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 24.5, 28.1, 54.0, 77.8, 175.9; **Anal.** Calcd for $C_5H_7N_3O$ requires C, 42.55; H, 5.00; found: C, 42.53; H, 5.03%.

(*S*)-5-Hydroxypiperidin-2-one (41)

To a solution of azide **40** (1.5 g, 10.62 mmol) in dry MeOH was added 20% $Pd(OH)_2$ (0.037 g, 0.53 mmol) and the reaction mixture was stirred under an atmosphere of H_2 (1 atm) for 24 h at 25 ^oC. After completion of the reaction (monitored by TLC), the catalyst was filtered over Celite and the filtrate concentrated under reduced pressure to provide hydroxylactam **41**, which was purified by column chromatography using ethyl acetate:methanol (9:1) as eluent to obtain pure hydroxyl lactam **41** (1.17 g, 98%).

Yield: 98%; colorless solid, **mp**: 120-121 °C; $\mathbf{[\alpha]_D^{25}}$ -13.8 (*c* 1, MeOH) {lit.[16] $[\alpha]_D^{25}$-12.4 (*c* 0.5, MeOH)}; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1636, 1652, 3439; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.72-1.87 (m, 2H), 2.12-2.27 (m, 1H), 2.32-2.49 (m, 1H), 3.03-3.12 (dd, *J* = 4.8 and 12.7 Hz, 1H), 3.20-3.22 (m, 1H), 3.27-3.35 (dd, *J* = 3.9 and 12.7 Hz, 1H), 3.92-4.01 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 28.1, 28.8,49.4, 63.8, 174.5; **Anal.** Calcd for $C_5H_9NO_2$ requires C, 52.16; H, 7.88; found: C, 52.15; H, 7.85%.

(*S*)-Piperidin-3-ol (33)

To a solution of lactam **41** (1.2 g, 10.43 mmol) in dry THF (20 mL), $BH_3.SMe_2$ (0.95 mL, 8.68 mmol) was added dropwise at 0 ^oC under N_2 atmosphere and the mixture was then refluxed for 6 h. After the reduction was complete (monitored by TLC). THF was removed under reduced pressure to give the crude product **33**, which was purified by column chromatography with silica gel using petroleum ether:ethyl acetate (6:4) as eluent to give pure **33** as colorless viscous liquid (0.373 g, 85%).

Yield: 85%; viscous liquid; $\mathbf{[\alpha]_D^{25}}$ -7.8 (*c* 1.3, MeOH)}, {lit.[16] $[\alpha]_D^{25}$ -7.5 (*c* 2, $CHCl_3$)}; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1636, 1652, 3439; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.55-1.64 (m, 2H), 1.67-1.77 (m, 2H), 2.60-2.62 (m, 1H), 3.04-3.12 (m, 2H), 3.19-3.23 (m, 1H), 3.65-3.74(m, 1H); **^{13}C NMR**(50 MHz, $CDCl_3$): δ 23.5, 32.8, 45.9, 53.3, 66.2; **Anal.** Calcd for $C_5H_{10}NO$ requires C, 59.37; H, 10.96; found: C, 59.33; H, 10.91%

Section III

Enantioselective Synthesis of (*R*)-Coniine *via* Reduction of Ketone with (*R*)-CBS Reagent

3.3.1 Introduction and Pharmacology

The substituted piperidines and ring-fused piperidines such as indolizidines are among the most ubiquitous heterocyclic building blocks in both natural products and synthetic compounds with important biological activities.[30] The interest in the piperidine and indolizidine alkaloids is well displayed by the wealth of published materials detailing their sources and biological activities and their structure diversity makes them interesting targets for organic chemists **Fig. 15** shows the structures of some of these bioactive molecules (**65-72**).

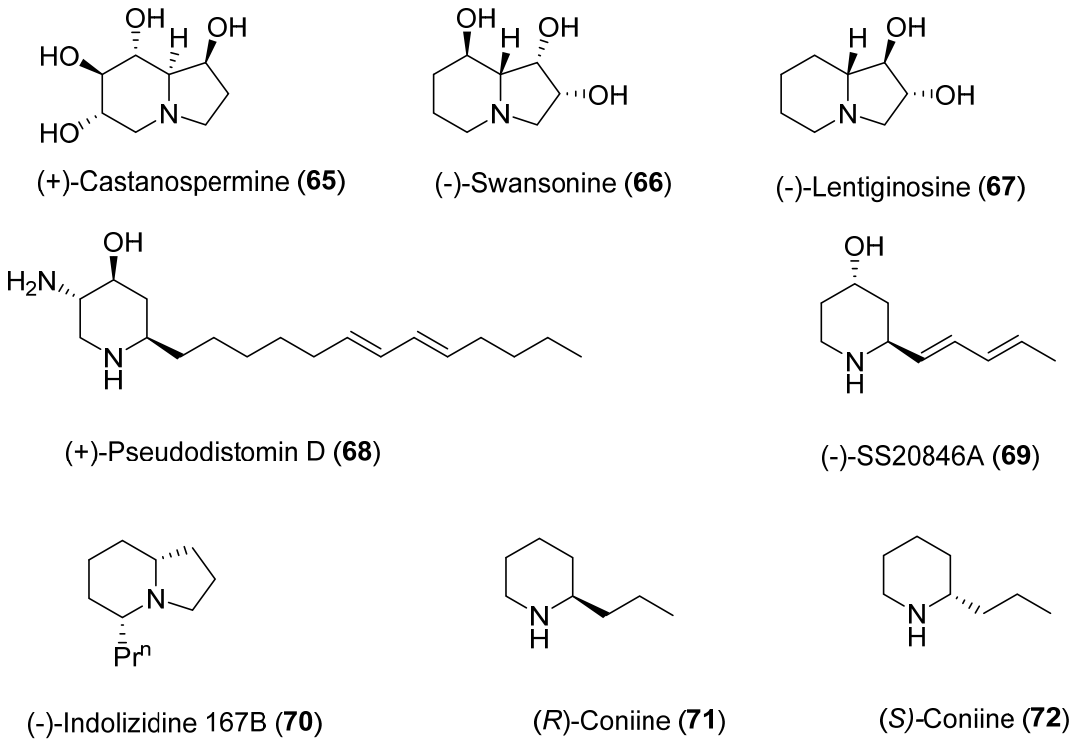


Fig. 15: Some of the important piperidine and indolizidine-containing natural products and bioactive molecules

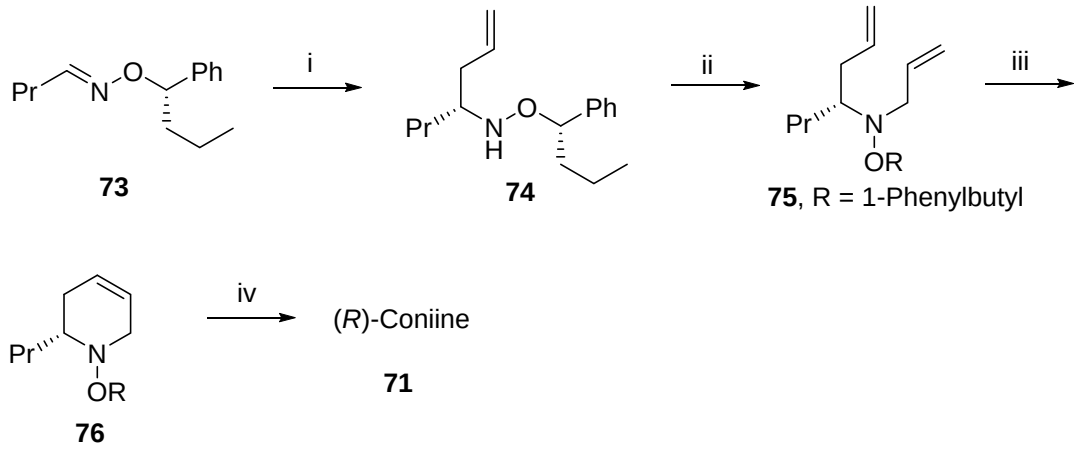
Therefore considerable efforts have been directed towards synthesizing them[31] in stereo- and enantioselective manner[32] and the interest in their chemistry remains unabated. (*R*)-Coniine, the simplest members of piperidine, have attracted great interest from chemists as an representative targets demonstrating the viability of the synthetic routs to piperidine derivatives and there are numerous successful asymmetric synthesis of these molecules.[33] (*S*)-2-Propylpiperidine alkaloid (*R*)-coniine (**71**) is popular target for the demonstration of chiral methodology in the piperidine field. It is a poisonous hemlock alkaloid extracted from the plant *Conium maculatum* and from other tropical subspecies.

3.3.2 Review of literature

Several approaches have been reported in the literature for the synthesis of racemic as well as optically active coniine. A few interesting and recent syntheses of (*R)*-coniine (**71**) and (*S*)-coniine (**72**) are described below.

Moody's approach (2000)[34]

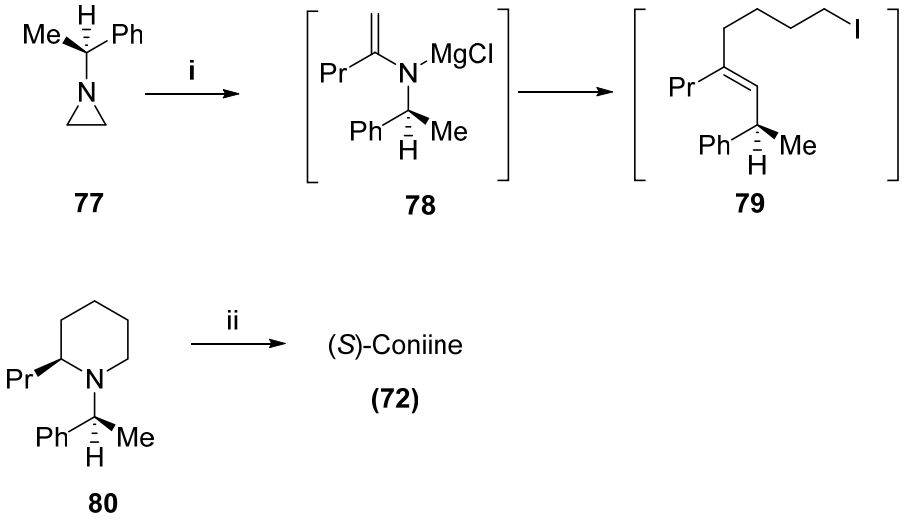
Moody *et al*. have accomplished the synthesis of (*R*)-coniine (**71**) by the addition of an alkene containing organometallic reagent to the aldoxime ether **73** to give hydroxylamine **74** in 87% yield. *N*-alkylation of hydroxyl amine **74** under basic condition afforded the corresponding diene **75** in 90% yield. The ring closing metathesis (RCM) reaction was carried out by heating the diene **75** in dichloromethane in the presence of Grubbs' catalyst furnishing the compound **76** in 91% yield, which was hydrogenated over Pd/C to give (*R*)-coniine (**71**) in 76% yield (**Scheme 13**).



Scheme 13: (i) allylMgBr, $BF_3.Et_2O$, 87%; (ii) K_2CO_3, allyl bromide, acetonitrile, 90%; (ii) Grubbs' catalyst, CH_2Cl_2, 91%; (iv) H_2 (1 atm), 5% Pd/C, MeOH, HCl in Et_2O, 76%.

Shipman's approach (2001)[35]

Shipman *et al*. have synthesized (*S*)-coniine (**72**) by making use of multi-component coupling reaction of 2-methyleneaziridine **77**. Thus, ring opening of **77** with EtMgCl in presence of CuI) iodide furnished metalloenamine **78** in a regiocontrolled fashion, which was treated with 1,3-diiodopropane, and sodium triacetoxyborohydride to afford piperidine **79** as a single diastereomer (97% dr).

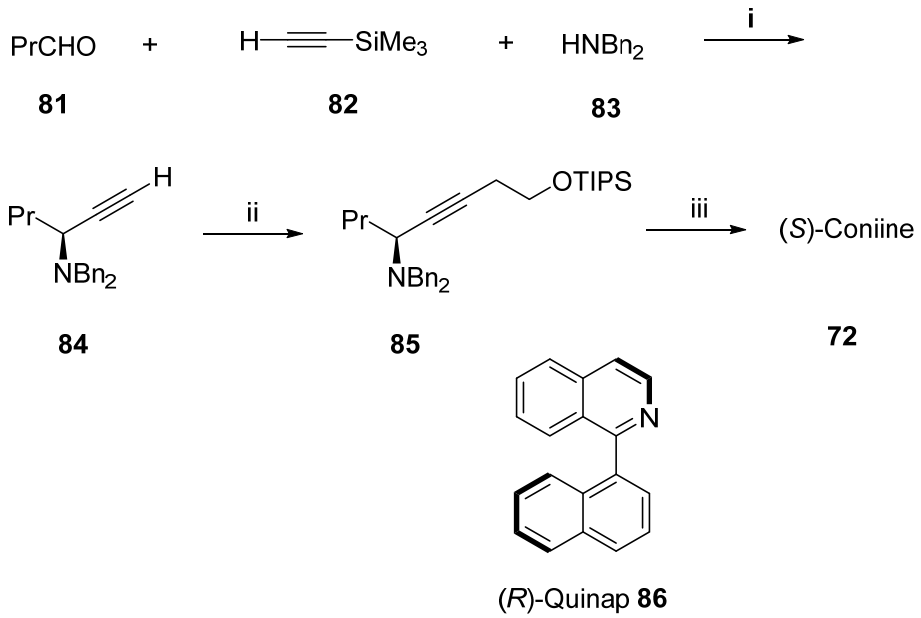


Scheme 14: (i) (a) EtMgCl, CuI, THF, -30 to 25 ^oC; (b) $ICH_2CH_2CH_2I$, 40 °C; (b) $NaBH(OAc)_3$, 42 % (over two step); (ii) cat. $Pd(OH)_2$, H_2 (1 atm), HCl, EtOH, 93%.

Finally, hydrogenolysis of **80** furnished (*S*)-coniine (**72**) hydrochloride in 93% yield (**Scheme 14**).

Knochel's approach (2004)[36]

Knochel *et al*. have developed a short enantioselective route for the synthesis of (*S*)-coniine (**72**) using one-pot three-component addition reaction of aldehydes **81**, trimethylsilylacetylene **82** and dibenzylamine **83** in presence of CuBr/Quinap **86** as catalyst, to furnish enantiomerically enriched propargylamine **84** in good yield and excellent enantiomeric excess. The formed chiral propargylamine **84** was alkylated with ethylene oxide followed by protection with TIPSCl to afford **85** in 70% yield for two steps.



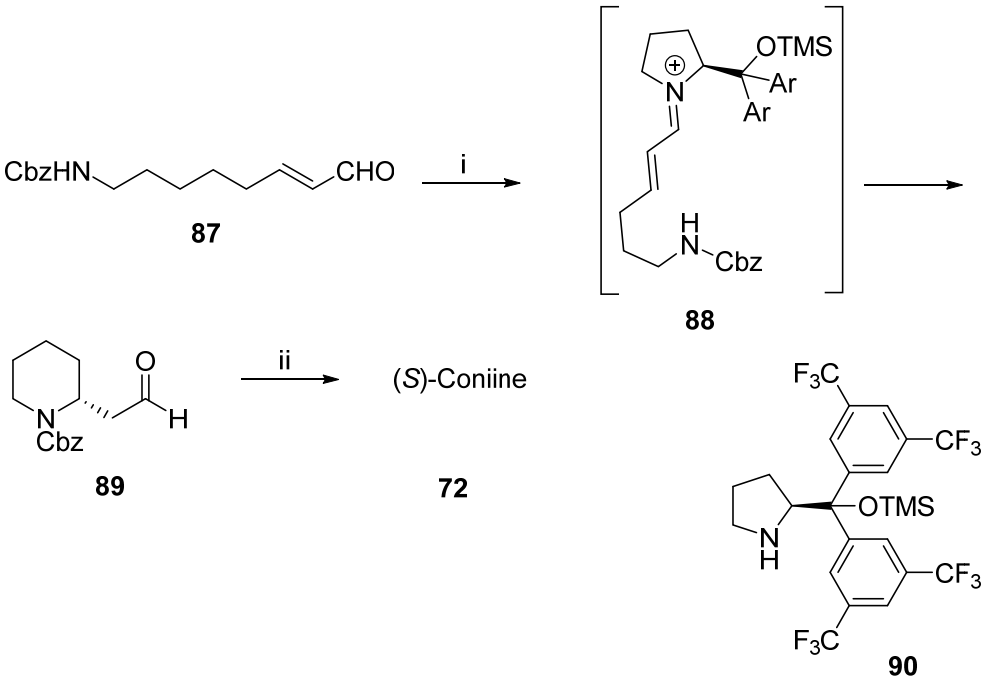
Scheme 15: (i) (a) CuBr (5 mol%), (*R*)-Quinap **86** (5.5 mol%), toluene, 25 °C, 6 d; (b)Bu_4NF; (ii) (a) *n*-BuLi, -78 °C; (b) ethylene oxide, $BF_3.OEt_2$; (c) TIPSCl, imid., DMAP (cat.), 0 to 25 °C, overnight, DMF, 93%; (iii) (a) H_2 (1 atm), 5% Pd/C, MeOH, 3 d, 99%; (b) TBAF, THF, 0 to 25 °C, overnight; (c) PPh_3, DEAD, THF, -10 to 25 °C, overnight, 70% (for two steps).

The hydrogenolysis of benzyl groups and the reduction of the triple bond was achieved by hydrogenation of **85** in methanol leading to an intermediate primary

amine which was desilylated with Bu_4NF and subjected to an intramolecular Mitsunobu reaction to afford (*S*)-coniine (**72**) in 5 steps with 41% overall yield (**Scheme 15**).

Fustero's approach (2007)[37]

Fustero *et al*. have reported an intramolecular aza-Michael reaction approach for the synthesis of (*S*)-coniine (**72**). Thus, intramolecular aza-Michael reaction (IMAMR) of carbamate **87** bearing remote α,β-unsaturated aldehyde as Michael acceptor in presence of organo catalyst **90** and phenyl acetic acid as additive furnished aldehyde **89** in 80% yield, which was subsequently transformed into (*S*)-coiinine (**72**) by Wittig homologation followed by hydrogenation of the double bond (**Scheme 16**).

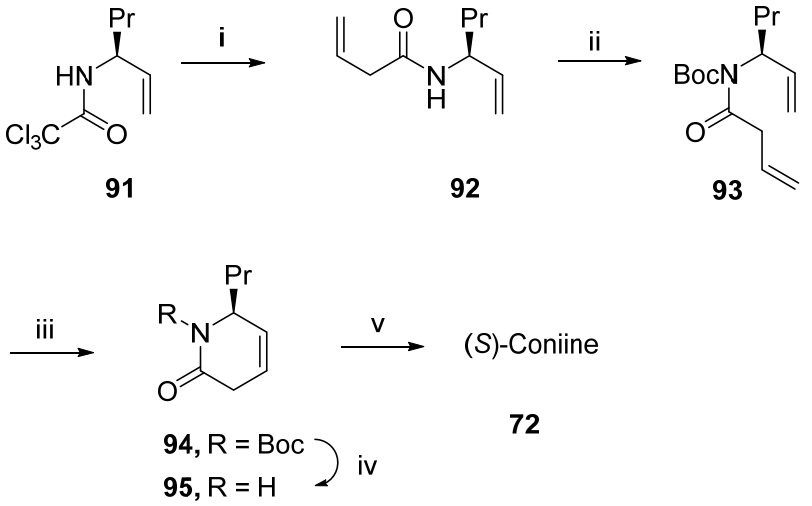


Scheme 16: (i) (a) Catalyst **90** (20 mol%), $PhCO_2H$, $CHCl_3$, -50 to -30 °C, 80%; (b) (i) PPh_3MeBr, ^tBuOK, THF; (ii) H_2 (1 atm), 10% Pd/C, EtOH, 25 ^oC, 12 h.

Richard's approach (2009)[38]

Richard *et al*. have reported the synthesis of (*S*)-coniine (**72**) from hydrolysis of trichloroacetamide (*S*)-**91**, was followed by DCC-mediated acylation with but-3-enoic

acid to give (*S*)-**91**. Protection of amine **92** as NBoc was achieve to give (*S*)-**93** carbamate in 56% yield. Ring closing metathesis (RCM) of carbamate **93** with 2.7 mol % Grubbs' II catalyst gave NBoc protected lactam **94** in 81% yield. Further, TFA-mediated deprotection of NBoc **94** afforded lactam **95** in 74% yield. Alkene **7** hydrogenation and reduction of amide group of a known intermediate **95** produced (*S*)-coniine **72** in 80% yield (**Scheme 17**).

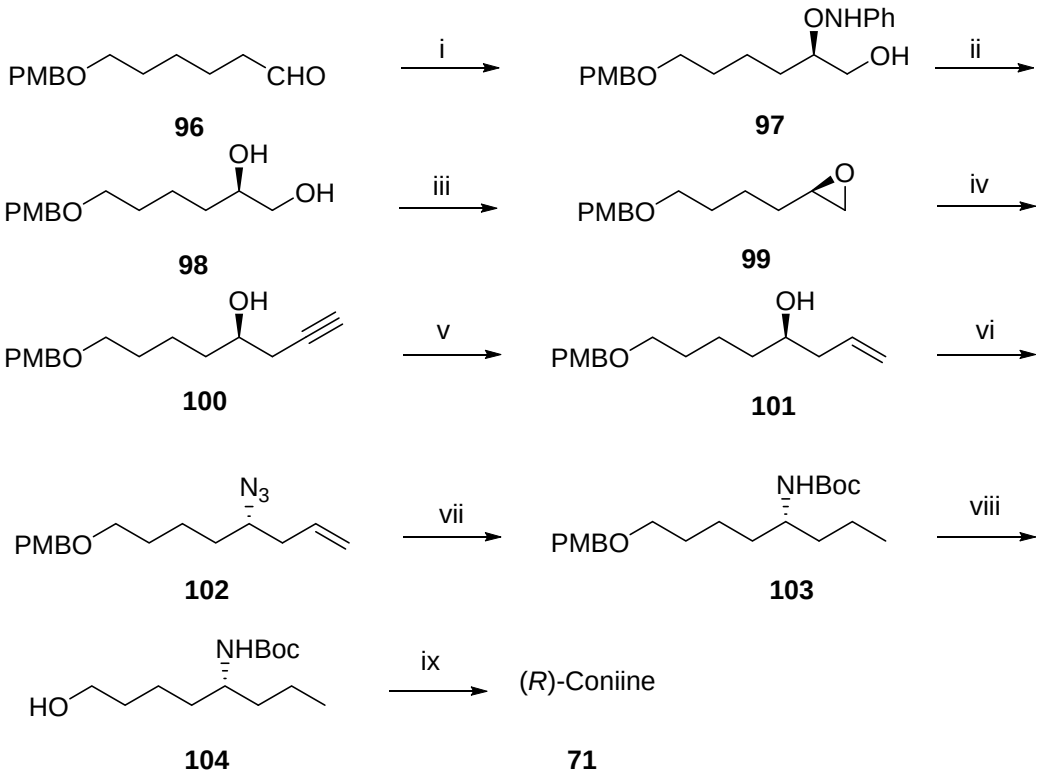


Scheme 17: (i) (a) NaOH, MeOH, 50 ^{o}C, 12 h; (b) but-3-enoic acid, DCC, CH_2Cl_2, 25 ^{o}C, 12 h, 81%; (ii) (a) NaH, THF; (b) $(Boc)_2O$, 50 ^{o}C, 20 h, 56%; (iii) 2.7 mol% Grubbs' II cat. CH_2Cl_2, 25 ^{o}C, 12 h, 81%; (iv) TFA, CH_2Cl_2, -5 ^{o}C, 12 h, 74%; (v) (a) H_2 (1 atm), 5% Pd/C, MeOH, 25 ^{o}C, 12 h; $LiAlH_4$, Et_2O, reflux, 16 h, (c) HCl, 80%.

Kumar's approach (2010)[39]

Kumar *et al*. have developed an organocatalytic approach for the synthesis of (*R*)-coniine (**71**) starting from aldehyde **95**, which on aminoxylation, $NaBH_4$ reduction and reductive hydrogenation gave the diol **98** in 71% yield and >95% ee. Monotosylation of diol **98** followed by treatment with base gave the epoxide **99** in 79% yield. Epoxide **99** on opening with lithium acetylide followed by partial reduction gave the alcohol **100**. Alcohol **100** was then treated sequentially with MsCl

and sodium azide to give azide **102**, which was converted into amine, *in situ* protected as *tert*-butyl carbamate **103**. Finally, PMB deprotection with DDQ gave amino alcohol **104**, which was subjected to mesylation and base treatement affording the target molecule *i.e*. (*R*)-Coniine **71** (**Scheme 18**).

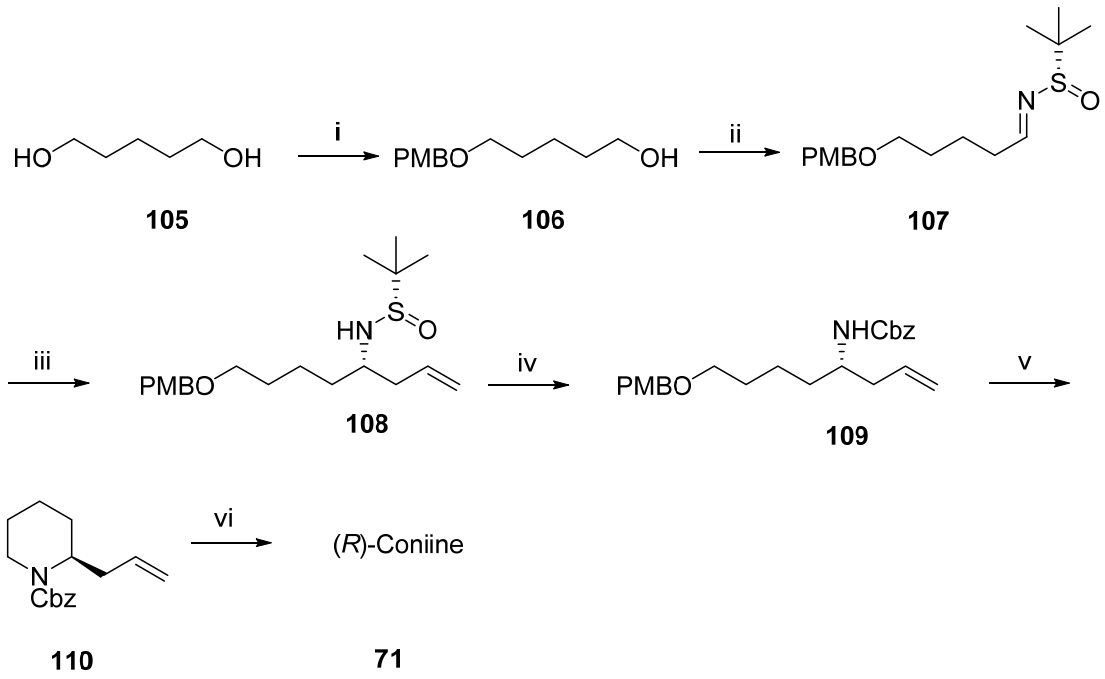


Scheme 18: (i) (a) L-proline, nitrosobenzene, DMSO; (b) $NaBH_4$, MeOH, 71% (over two steps); (ii) H_2/Pd-C, EtOAc, 85%; (iii) (a) TsCl, Bu_2SnO, Et_3N; (b) K_2CO_3, MeOH, 79% (over two steps); (iv) HC≡CLi, DMSO, 82%; (v) H_2, Lindlar's catalyst, EtOAc, 90%; (vi) (a) MsCl, Et_3N, CH_2Cl_2; (b) NaN_3, DMF, 68% (over two steps); (vii) (a) H_2 (1 atm), 5% Pd/C, $(Boc)_2O$, EtOAc; (b) DDQ, $NaHCO_3$,CH_2Cl_2, H_2O, 80% (over two steps); (viii) MsCl, Et_3N, 85%; (ix) NaH, -78 °C, HCl in methanol, 90%.

Das's approach (2011)[40]

Das *et al*. have developed a useful synthetic route to piperidine alkaloid namely (*R*)-coniine. Its synthesis was initiated by converting pentane-1,5-diol **105** into its mono (*p*-methoxybenzyl) ether **106**. The ether **106** underwent oxidation with pyridinium chlorochromate (PCC), followed by anhydrous Cu(II) sulfate-mediated condensation

with (*S*)-*N*-*tert*-butanesulfinamide to give the corresponding (*S*)-(*N*-*tert*-butanesulfinyl)imine **107** in 88% yield.



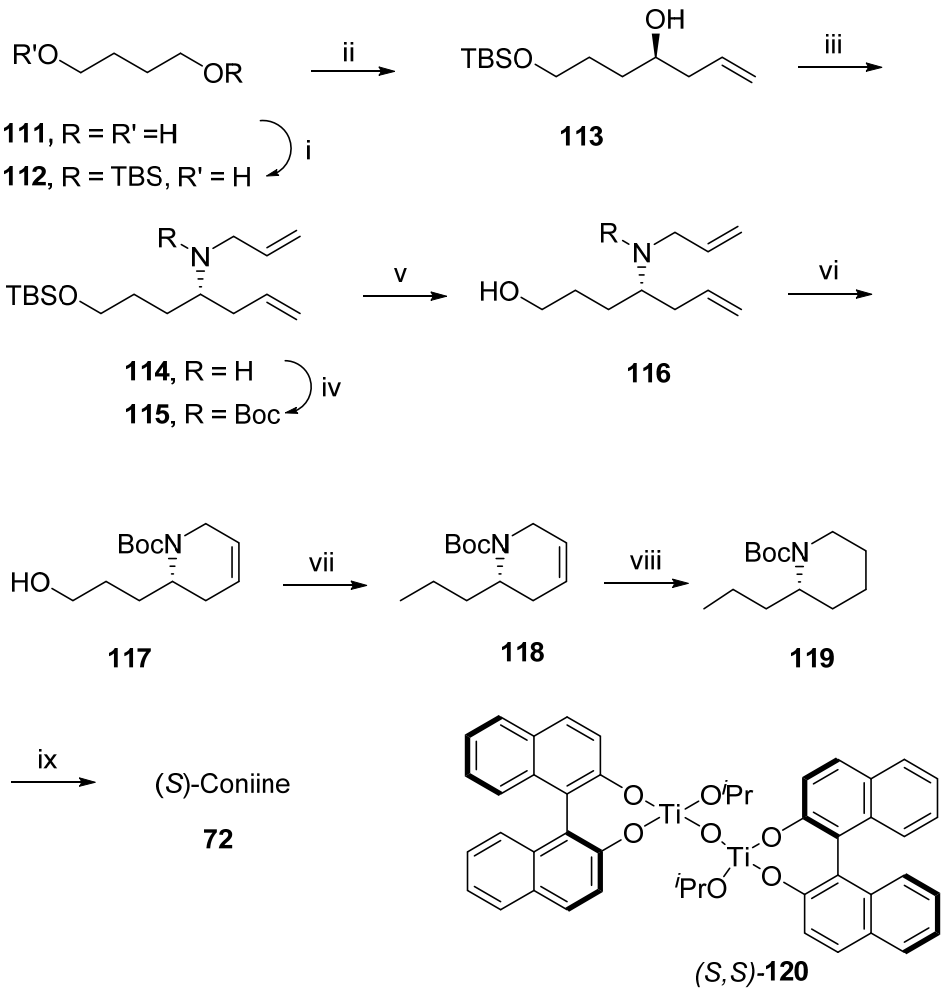
Scheme 19: (i) PMBBr, NaH, THF, 0 to 25 ^{o}C, 8 h, 79%; (ii) (a) PCC, CH_2Cl_2, 25 ^{o}C, 2 h, 90%; ii) (*S*)-*t*-$BuSONH_2$, $CuSO_4$ (anhyd), CH_2Cl_2, 25 ^{o}C, 24 h, 88%; (iii) CH_2=$CHCH_2Br$, In, THF, 66 °C, 4 h, 85%; (iv) (a) 4 M HCl/dioxane, MeOH, 25 ^{o}C, 45 min; (b) CbzCl, K_2CO_3, THF-H_2O (1:1), 24 h, 64% (two steps); (v) (a) MsCl, Et_3N, CH_2Cl_2, 0 °C, 1 h; (b) *t*-BuOK, THF, 0 °C to 25 ^{o}C, 3 h, 93% (two steps); (vi) (a) H_2 (1 atm), 10% Pd/C, EtOAc, 25 ^{o}C., 24 h; (b) HCl, Et_2O, 25 ^{o}C, 10 min, 80% (two steps).

The sulfinimine **107** was then subjected to indium-mediated allylation under Barbier conditions to give the corresponding *N*-*tert*-butanesulfinyl homoallylamine **108** was obtained in 85% yield with excellent diastereoselectivity. Removal of the sulfinyl group in **108**, selective *N*-protection with benzyloxycarbonyl chloride gave the hydroxyhomoallylamine **109** in moderate yield. Amine **109** was then mesylated and the crude product was subjected to ring closer by the treatment of base to give 2-allylpiperidine **110** in 93% yield over the two steps. Compound **110** was subjected to

reduction of the olefinic double bond followed by deprotection of the benzyloxycarbonyl group to give a 2-propylpiperidine whose hydrochloride salt showed identical analytical data to those reported for (*R*)-coniine **71** (**Scheme 19**).

Das's approach (2011)[41]

In yet another approach Das *et al*. have achieved the synthesis of (*S*)-coniine from the butane-1,4-diol **111**, which was converted into mono-silylated ether **112** on by treatment with TBSCl and imidazole. The silylated ether **112** on oxidation with PCC followed by Maruoka allylation with allyltributylstannane in the presence of the (*S*,*S*)-Binol Ti-complex **120** to produce the chiral homoallylic alcohol **113** (96% ee). Mesylation followed by nucleophilic displacement by a S_N2 process with allylamine in DMF at 50 ^oC afforded the amine derivative **114** (92% ee). Amine **114** was treated with $(Boc)_2O$ to form Boc derivative **115** followed by the deprotection of TBS ether gave the compound **116** The resulting compound **116** was subjected to a ring-closing metathesis (RCM) reaction using a Grubbs' second generation catalyst to give the cyclic tetrahydropyridine derivative **117**. Compound **117** was treated with I_2 and imidazole to form the corresponding iodide derivative, which was reduced with Zn/AcOH to produce (S)-coniine derivative **118**. The reduction of the olefinic double bond in **118** with H_2/Pd-C followed by treatment with aqueous HCl and washing with NaOH solution afforded (*S*)-coniine **72** (**Scheme 20**).



Scheme 20: (i) TBSCl, imidazole, CH_2Cl_2, 0 to 25 °C, 0.5 h, 90%; (ii) (a) PCC, CH_2Cl_2, 0 to 25 °C, 0.5 h, 90%, (b) (*S*,*S*)-**120**, CH_2=$CHCH_2SnBu_3$, CH_2Cl_2, -15 to 0 °C, 72 h, 85%; (iii) (a) MsCl, Et_3N, DMAP, CH_2Cl_2, 0 to 25 °C, 1 h, (b) allylamine, DMF, H_2O, 50 °C, 30 h, 78% (over two steps); (iv) $(Boc)_2O$, Et_3N, CH_2Cl_2, 25 °C, 3 h, 92%; (v) *p*-TSA, THF/H_2O (3:1), 25 °C, 0.5 h; 89%; (vi) Grubbs' II catalyst (10 mol %), CH_2Cl_2, reflux at 50 °C, 4 h, 90%; (vii) (a) I_2, TPP, imidazole, CH_3CN/ether (1:3), 0 to 25 °C, 15 min; (b) Zn, CH_2Cl_2, 25 °C, 30 min, then AcOH, 0 to 25 °C, 0.5 h, 80% (over two steps); (viii) H_2 (1 atm), 10% Pd/C, EtOAc, 25 °C, 2 h, 91%; (ix) 5 M HCl, THF, 25 °C, 89%.

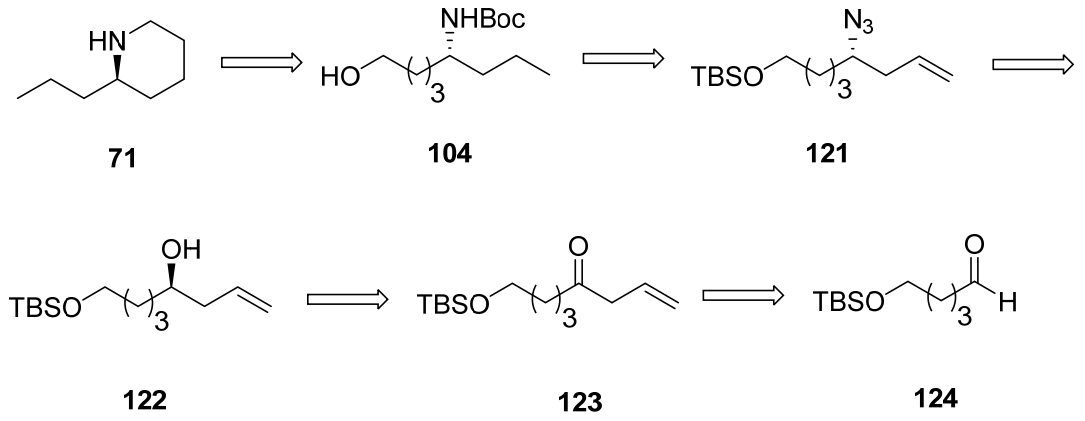
3.3.3 Present Work

3.3.3.1 Objective

As can be seen from the above synthetic studies, the literature methods in the synthesis of (*R*)-coniine (**71**) employ either chiral starting materials or expensive

reagents involving longer reaction sequences, often resulting in poor product selectivities. The enantioselective synthesis of (*R*)-coniine (**71**) is thus undertaken to overcome some of the disadvantages associated with the reported methods. This section describes an enantioselective synthesis of (*R*)-coniine (**71**) *via* reduction of ketone with chiral (*R*)-Me-CBS reagent as key step.[42]

The retrosynthetic analysis of (*R*)-coniine **71** reveals that (*R*)-amino alcohol **104** could be visualized as the key intermediate for the asymmetric synthesis of (*R*)-coniine **71**. The (*R*)-amino alcohol **104** moiety could be obtained from the corresponding azide **121** after reduction of the C=C bond and azide function. The azide **121** can be prepared from homoallylic alcohol **122**, which could be achieved by means of reduction of ketone **122** with chiral CBS reagent. Ketone **123** could be prepared from the corresponding aldehyde **124 (Scheme 21**).

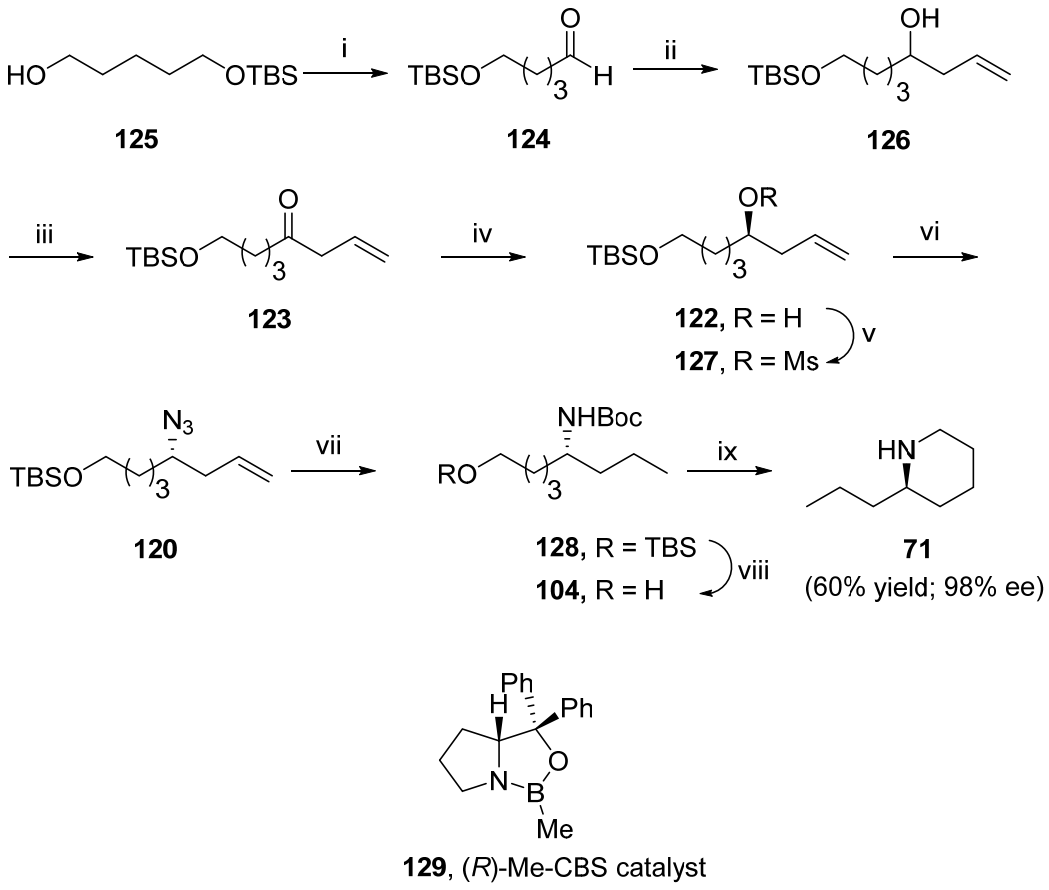


Scheme 21 : Retrosynthetic analysis of (*R)*-coniine **71**

3.3.3.2 Results and Discussion

The complete synthetic sequence for (*R*)-coniine (**71**) wherein the CBS reduction of ketone constitutes a key step for the introduction of chirality, is presented in **Scheme 22**. The synthesis of (*R*)-coniine **71** started from mono protected 1,5-pentanediol **124**.

The primary alcohol function in **125** was then oxidized under Swern conditions to provide the corresponding aldehyde **124** in 90% yield (**Scheme 22**).



Scheme 22: (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 ^oC, 1 h, 90%; (ii) Zn, THF/H_2O, NH_4Cl, allyl bromide, 0 to 25 ^oC, 85%; (iii) IBX, dry DMSO, 25 ^oC, 1 h, 82%; (iv) (*R*)-Me CBS reagent **129**, BH_3.THF, -30 ^oC, 75%; (v) MsCl, Et_3N, CH_2Cl_2, 0 ^oC, 85%; (vi) NaN_3, DMF, 80 ^oC, 5 h, 68% (over two steps); (vii) (a) 5% Pd/C, H_2 (1 atm), MeOH; (b) $(Boc)_2O$, DMAP (10 mol%), Et_3N, CH_2Cl_2, 25 ^oC, 6 h, 85% (over two steps) ; (viii) TBAF, THF, 0 ^oC, 90%; (ix) (a) MsCl, Et_3N, CH_2Cl_2; (b) NaH, DMF, -30 °C, (c) HCl-methanol, 60% (for three steps).

The formation of aldehyde **124** was confirmed by its IR spectrum which showed a strong stretching vibrational frequency at 1725 cm^{-1} for the carbonyl function. Its ^1H NMR spectrum showed a typical singlet at δ 9.86 (s, 1H) corresponding to aldehydic

proton. Its ^{13}C NMR spectrum showed a typical carbon signal at δ 201.9 due to carbonyl carbon of aldehyde group (**Fig. 16**).

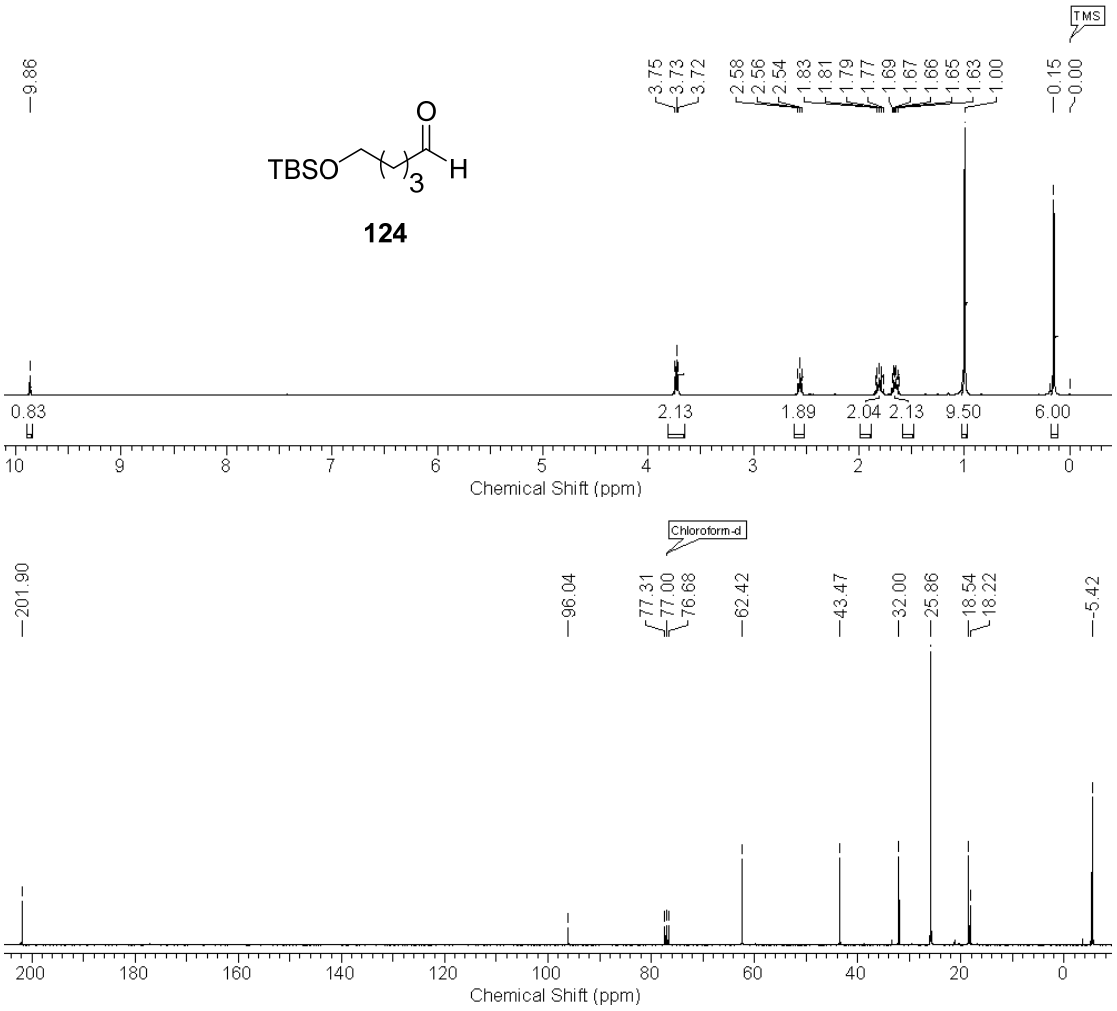


Fig. 16: ^{1}H and ^{13}C NMR spectra of aldehyde **124**

Barbier allylation of aldehyde **124** with allyl bromide (Zn, aq. NH_4Cl) provided the corresponding precursor homoallylic alcohol **126** in 85% yield. The formation of homoallylic alcohol **126** was confirmed from its ^{1}H NMR spectrum, which showed typical signals at δ 5.09-5.17 (m, 2H) and 5.75-5.85 (m, 1H) due to olefinic protons (-C**H**$_2$ and -C**H**). Its ^{13}C NMR spectrum showed two typical carbon signals at δ 117.8 and 134.8 corresponding to terminal and internal olefinic carbons (-**C**H_2 and -**C**H) respectively (**Fig. 17**).

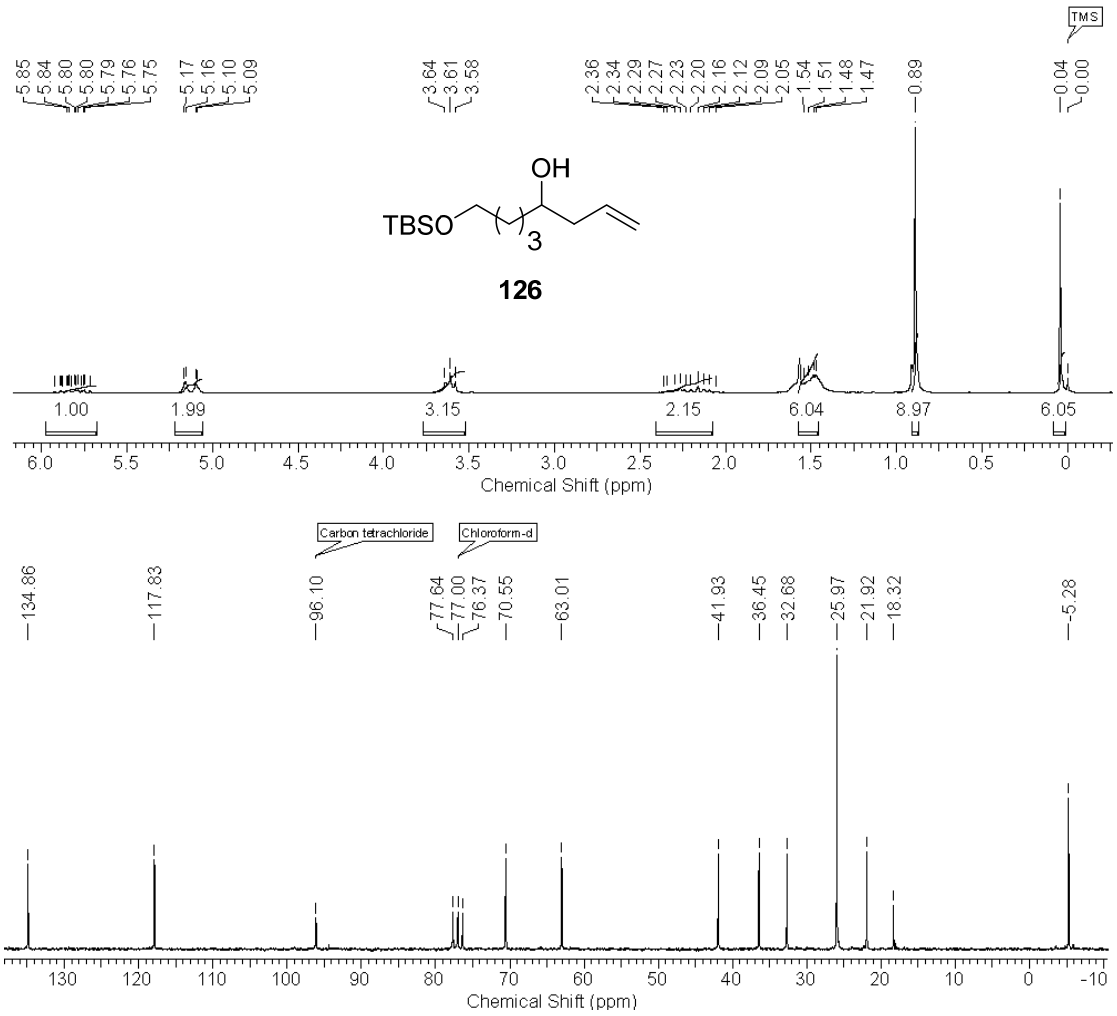


Fig. 17: ^{1}H and ^{13}C NMR spectra of homoallylic alcohol **126**

Next, the oxidation of homoallylic alcohol **126** was carried out using IBX (IBX, DMSO, 25 ^{o}C) that gave the corresponding ketone **123** in 82% yield. The formation of ketone **123** was confirmed by its IR spectrum, which showed a strong absorption band at υ_{max} 1722 cm^{-1} typically for ketone functionality. Its ^{1}H NMR spectrum showed two triplets at δ 2.46 (t, *J* = 7.4 Hz, 2H) and 3.7 (t, *J* = 6.2 Hz, 2H) corresponding to methylene protons {(-CH_2-C**H₂**-CO-) and (Si-C**H₂**-CH_2-)}. Its ^{13}C NMR spectrum showed a typical signal at δ 208.0 due to carbonyl carbon of ketone (**Fig. 18**).

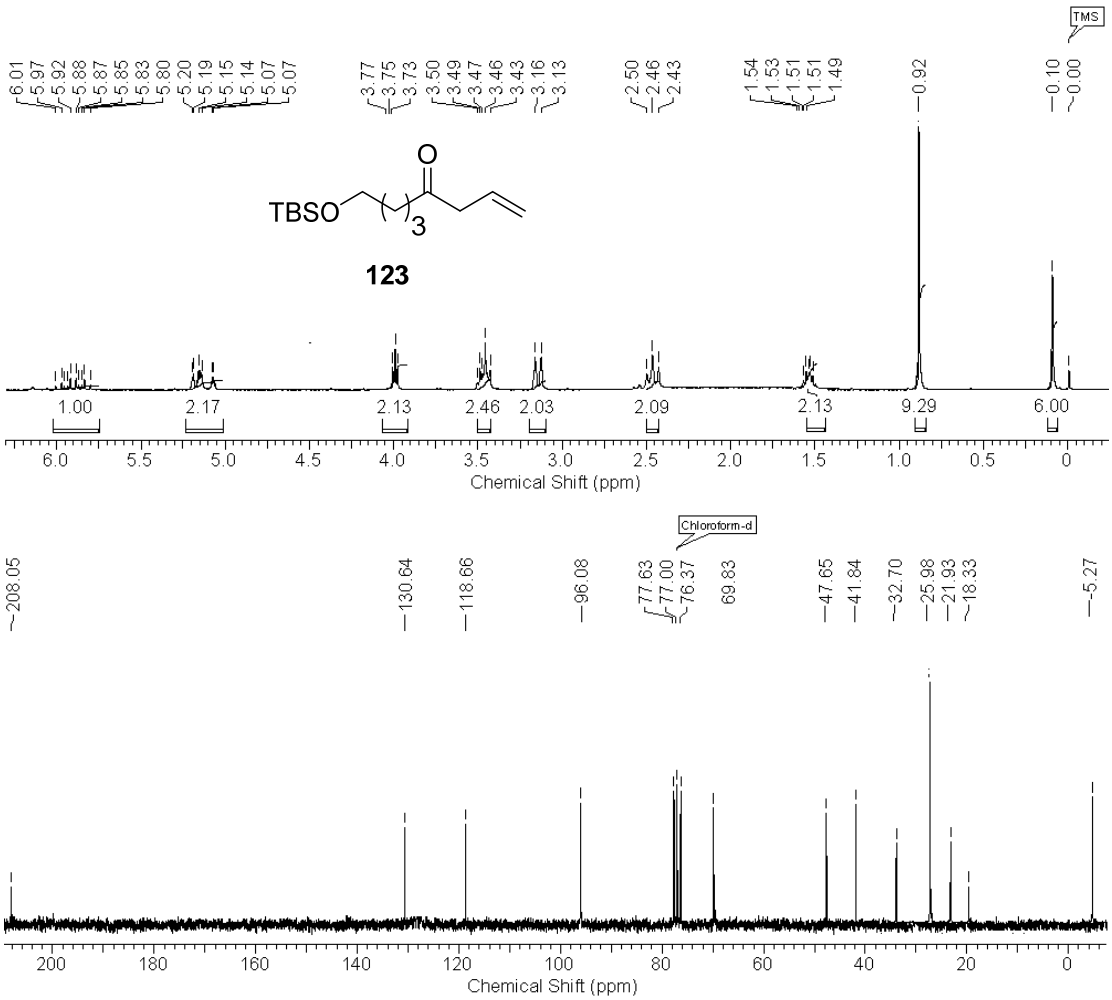


Fig. 18: ^{1}H and ^{13}C NMR spectra of ketone **123**

The enantioselective reduction of ketone **123** with chiral (*R*)-Me-CBS/(BH_3.SMe_2) **129** reagent afforded the corresponding (*S*)-homoallylic alcohol **122** in 75% yield and >97% ee (determined from ^{1}H NMR analysis of the corresponding Mosher's ester **130** (**Fig. 19**), (see experimental section); $[\alpha]_D^{25}$ +4.9 (*c* 1, $CHCl_3$). The formation of the allylic alcohol **122** was confirmed by ^{1}H NMR spectrum, which showed the presence of a multiplet at δ 3.61 (m, 3H) due to methine and methylene protons (-C**H**OH-, and -C**H**$_2$O-$SiMe_3$) respectively (**Fig. 19**). Its ^{13}C NMR spectrum showed a typical signal at δ 70.5 corresponding to the carbon attached to oxygen atoms.

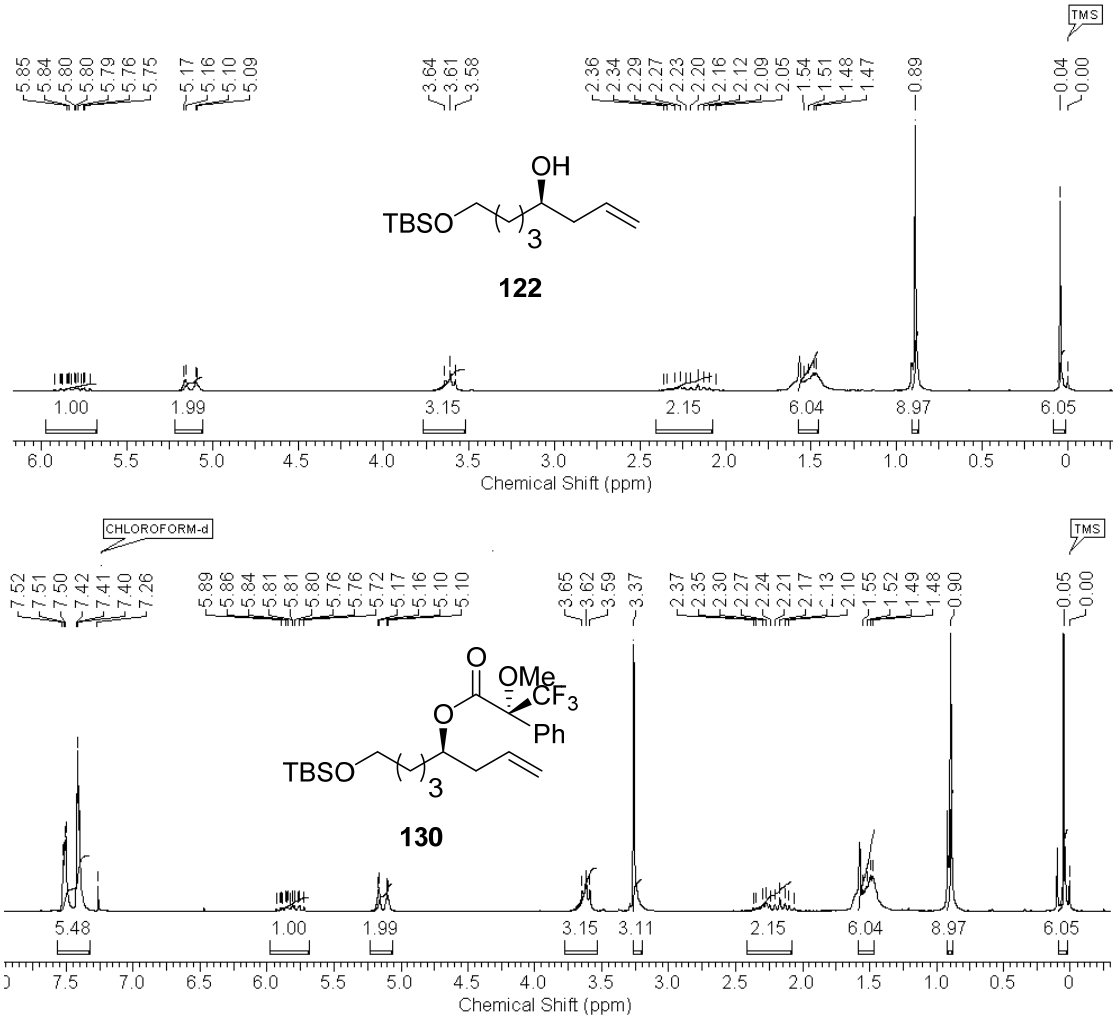


Fig. 19: ^{1}H NMR spectra of homoallylic alcohol **122** and its Mosher's ester **130**

The subsequent mesylation of homoallylic alcohol **122** gave the corresponding mesylate **127** in 85% yield. The formation of mesylate **127** was confirmed by ^{1}H and ^{13}C NMR spectroscopy. The ^{1}H NMR spectrum of **127** showed a singlet at δ 2.98 (s, 3H) for methyl protons. Its ^{13}C NMR showed a typical carbon signal at δ 38.6 for methyl carbon, which confirmed the formation of mesylate **127** (**Fig. 20**).

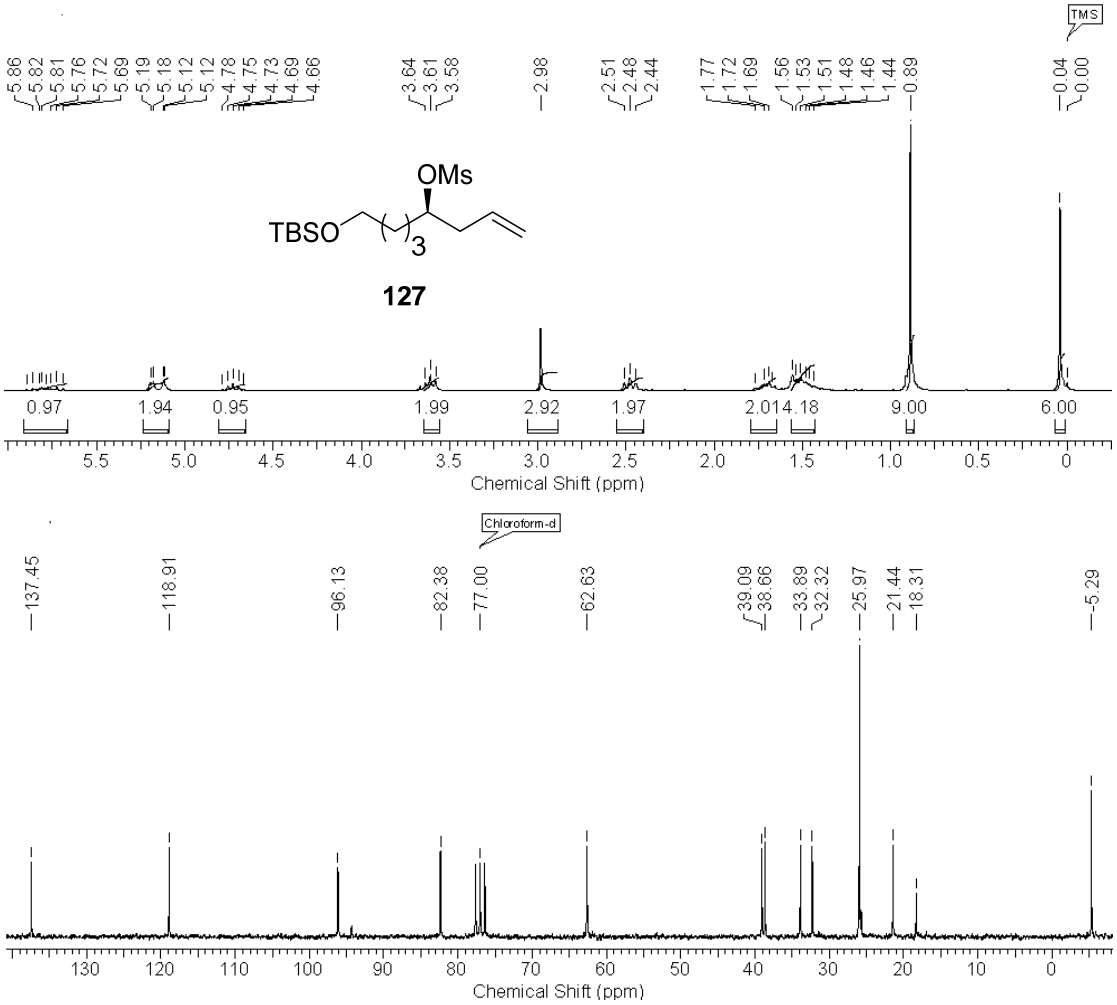


Fig. 20: ^{1}H and ^{13}C NMR spectra of mesylate **127**

Mesylate **127** was converted into the corresponding azide **120** (NaN_3, DMF, 80 ^{o}C) in 68% yield. The formation of azido derivative **120** was evidenced by its IR spectrum, which showed a strong absorption band at υ_{max} 2105 cm^{-1} typically for azide functionality. Its ^{1}H NMR spectrum showed a triplet at δ 3.61 (t, J = 4.5 Hz, 1H) corresponding to methine proton (-**C**H-N_3). Its structure was further confirmed by its ^{13}C NMR spectrum, which showed a typical methine carbon (-**C**H-N_3) appearing at δ 51.1 (**Fig. 21**).

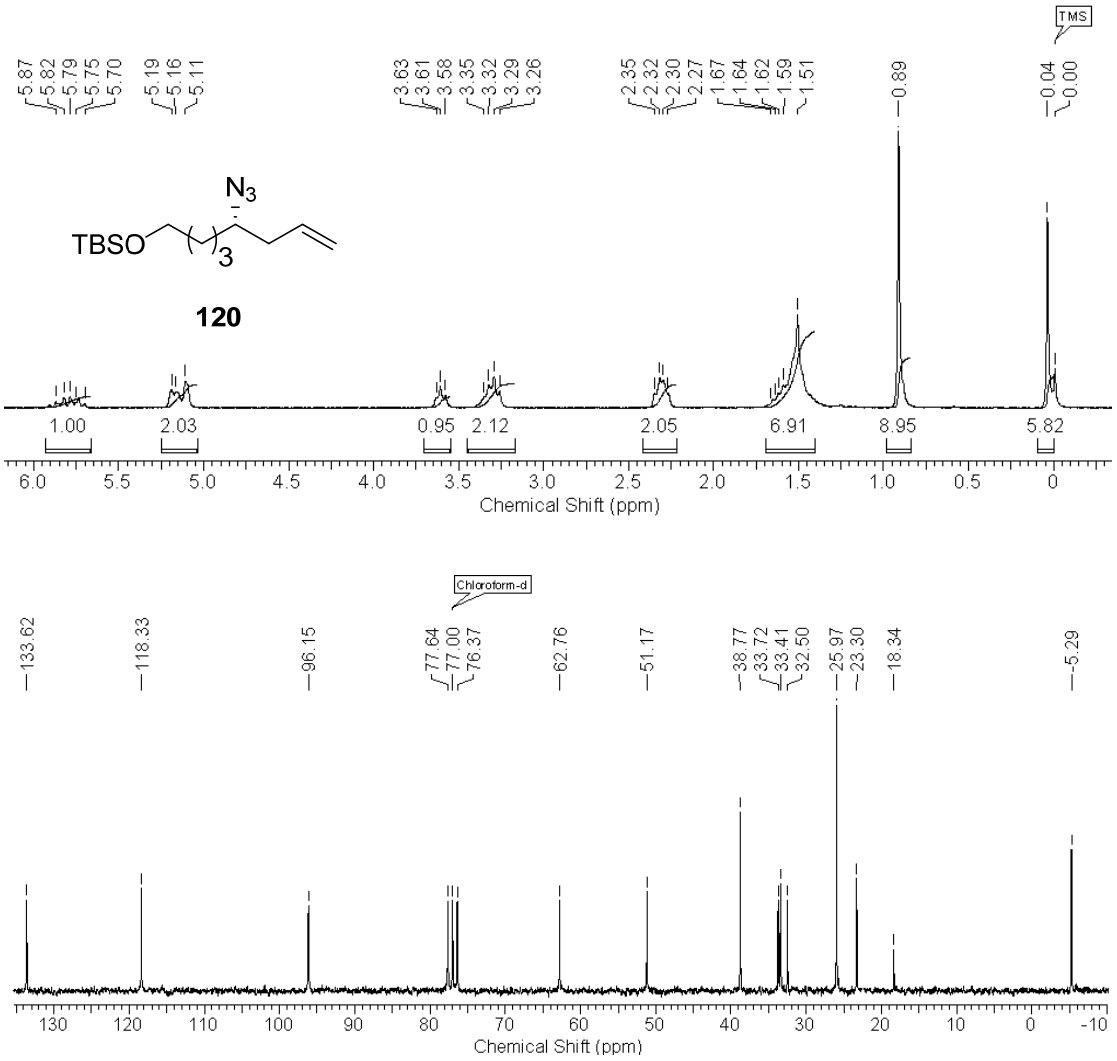


Fig. 21: ^{1}H and ^{13}C NMR spectra of azide **120**

The formed azide **120** was reduced under catalytic hydrogenation [H_2 (1 atm), 10% Pd/C, in methanol] along with the reduction of double bond at ambient conditions to produce the corresponding saturated amine. Further, the crude amine was selectively protected as its Boc derivative *in situ* [$(Boc)_2O$, DMAP, Et_3N, CH_2Cl_2] to give its *tert*-butyl carbamate derivative **128** in 85% yield. The ^{1}H NMR spectrum of **128** indicated the presence of Boc methyl protons [NH-($\mathbf{CH_3)_3}$] at δ 1.53 (s, 9H) as a singlet. Its ^{13}C NMR spectrum showed two typical carbon signals at δ 84.8 and 146.7

indicating the presence of *tert*-butyl (Me_3**C**-O) and Boc carbonyl (-N**C**O-) carbons respectively (**Fig. 22**).

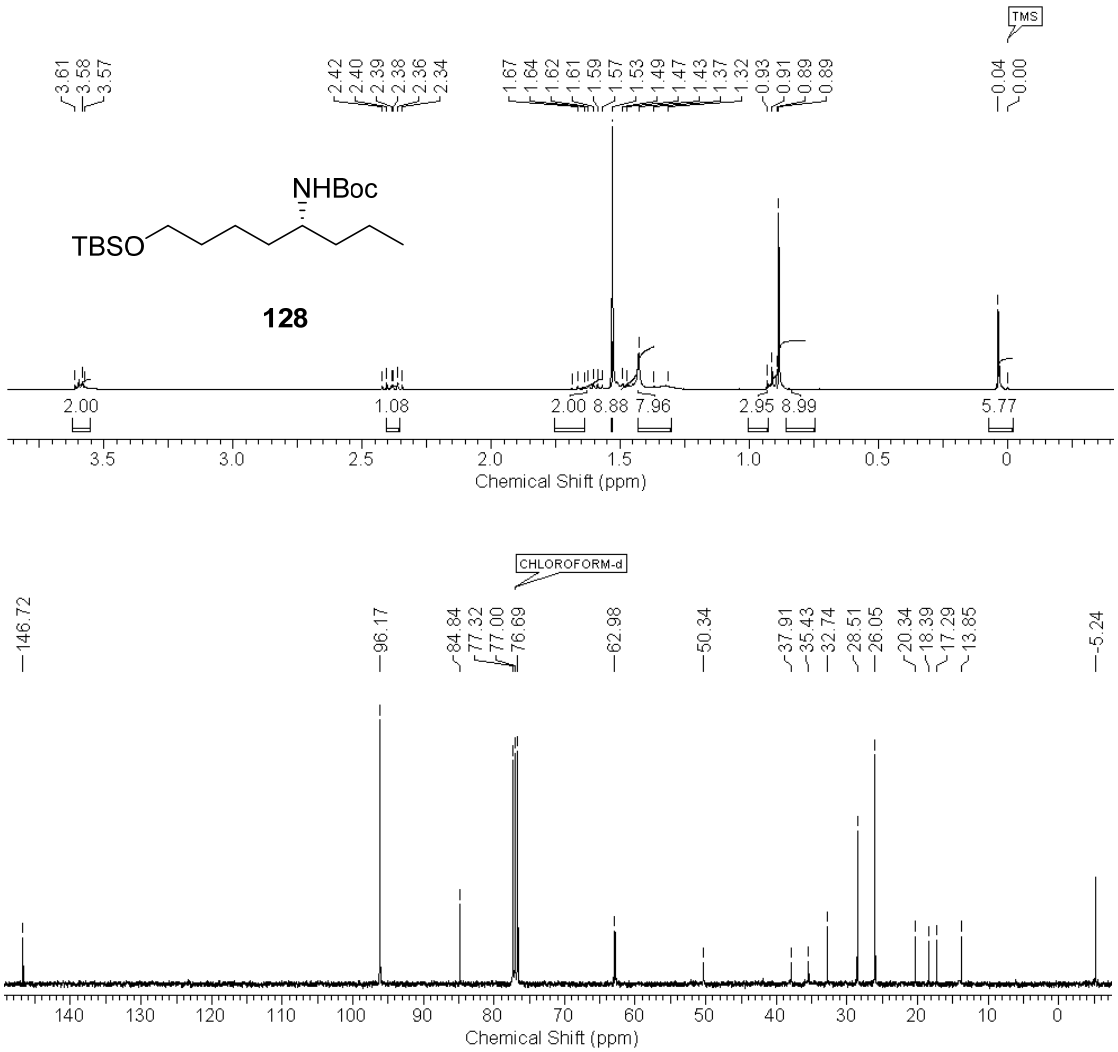


Fig. 22: ^{1}H and ^{13}C NMR spectra of carbamate **128**

The silyl deprotection of TBS ether group in **128** (TBAF, THF) was achieved to give the corresponding known intermediate namely *N*-Boc-amino alcohol **104** in 90% yield. The formation of *N*-Boc-amino alcohol **104** was confirmed by its IR spectrum, which showed a strong absorption band at υ_{max} 1698 cm^{-1} typically for C=O functionality of -NHBoc group. The formation of amino alcohol **115** was further confirmed from ^{1}H NMR spectrum, which displayed a typical signal at δ 3.59-3.65

(m, 2H) corresponding to methylene protons (-C**H**$_2$-O). Its ^{13}C NMR spectrum showed a characteristic signal at δ 62.6 corresponding to methylene carbon attached to hydroxyl group (**C**H$_2$OH) (**Fig. 23**).

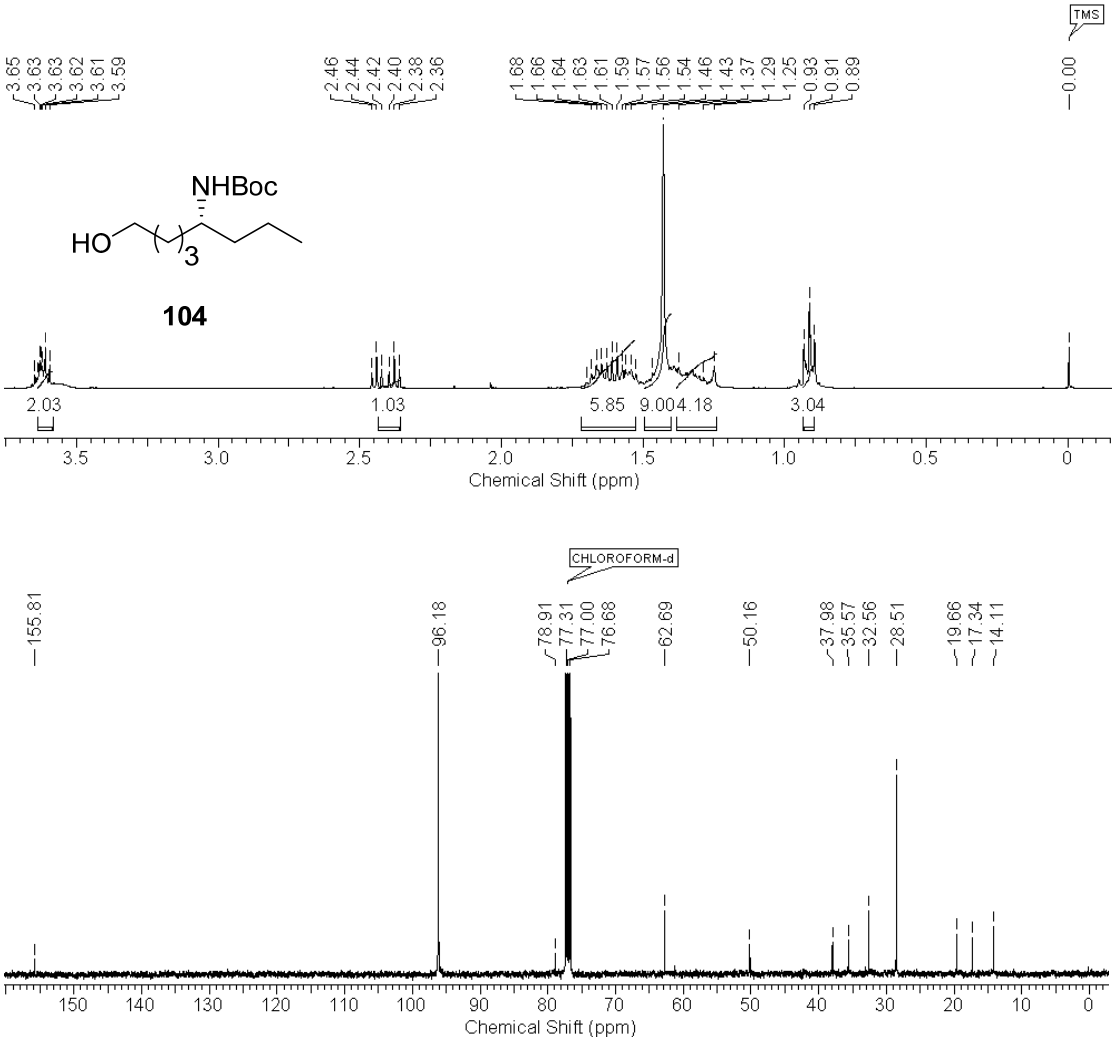


Fig. 23: ^{1}H and ^{13}C NMR spectra of amino alcohol **104**

Finally, the free hydroxyl group of **104**, protected as its mesylate (MsCl, Et_3N, CH_2Cl_2) without purification, was subjected to intramolecular cyclization under the suspension of NaH in THF, followed by acidic work-up, to produce (*R*)-piperidine alcohol **71** in 60% yield.

The formation of (*R*)-coniine (**71)** was confirmed from ^{1}H NMR spectrum, which displayed a triplet signal at δ 0.92 (t, *J* = 7.2 Hz, 3H) corresponding to methyl protons (-C**H**$_3$-CH$_2$-). Further it showed multiplet at δ 2.34-2.49 (m, 3H) due to methylene and methine protons attached to ring nitrogen (C**H**$_2$-NH-C**H**-). Its ^{13}C NMR spectrum showed two characteristic signals at δ 44.8 and 56.5 corresponding to methylene and methine carbons attached to ring nitrogen (**C**H$_2$-NH-**C**H-) respectively (**Fig. 24**).

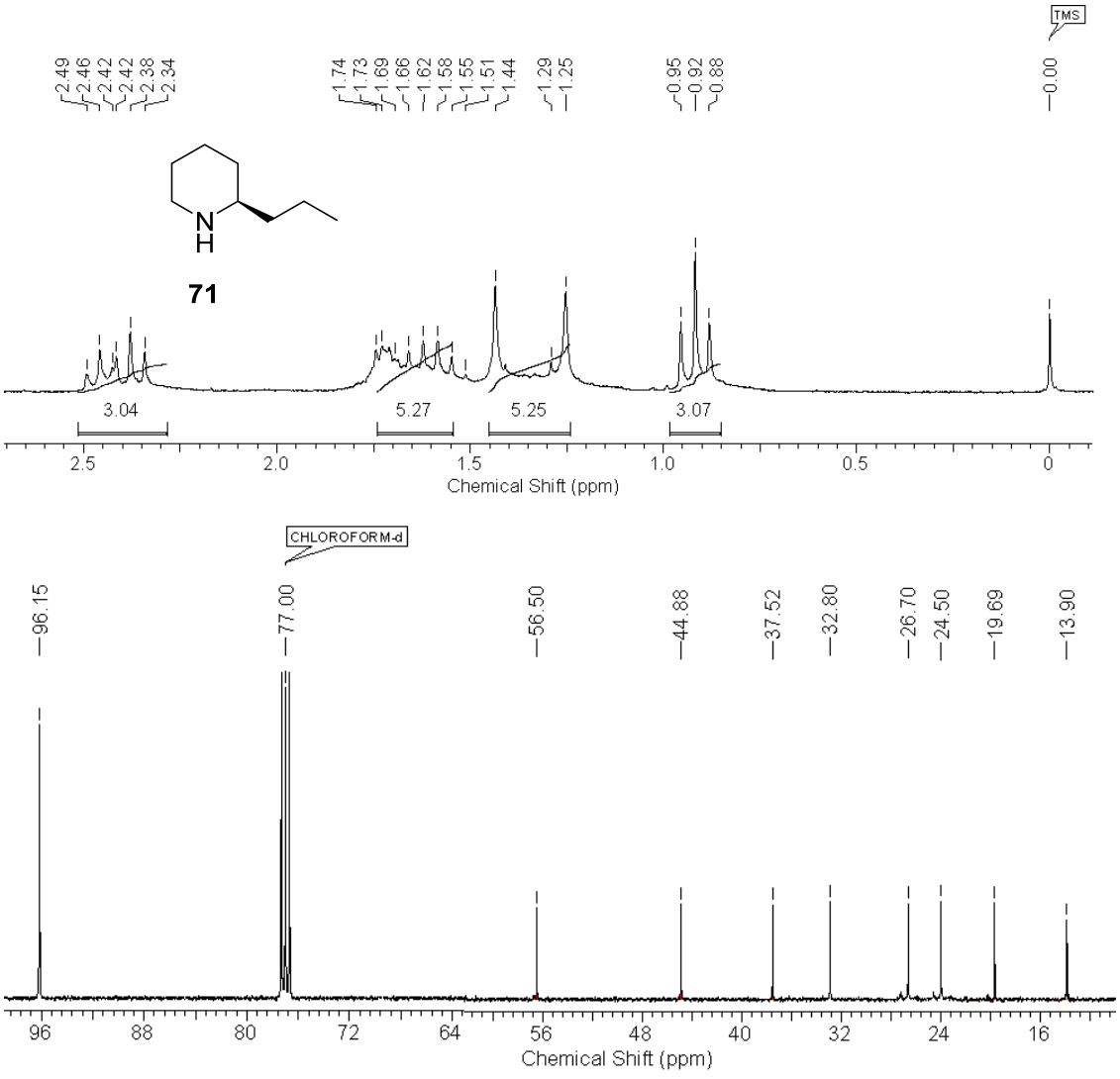


Fig. 24: ^{1}H and ^{13}C NMR spectra of (*R*)-coniine (**71**)

3.3.4 Conclusion

In conclusion, we have described an elegant, high yielding method of synthesis of (*R*)-coniine **71** with an overall yield of 14% and 98% ee, that are achieved *via* enantioselective reduction of ketone using (*R*)-Me-CBS regent as key reaction.

3.3.5 Experimental Section

5-((*tert*-Butyldimethylsilyl)oxy)pentanal (124)

To a stirred solution of oxalyl chloride (6.5 mL, 91.56 mmol) in CH_2Cl_2 (50 mL) at -78 ^oC, was added a solution of DMSO (9.7 mL, 137.34 mmol). The reaction mixture was stirred for 20 min, followed by the addition of a solution of mono protected 1,5-pentanediol **125** (10 g, 45.78 mmol) in CH_2Cl_2 (30 mL). After stirring for 1 h at -78 ^oC, the reaction mixture was quenched by the addition of Et_3N (25 mL, 183.12 mmol). The reaction mixture was then stirred for 20 min, followed by the addition of water (20 mL). The organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (3 x 30 mL), dried over anhyd. Na_2SO_4 and concentrated to give the corresponding crude aldehyde **124**, which upon column chromatographic purification with silica gel using petroleum ether:ethyl acetate (8:2) as eluent gave pure **124** as colorless liquid (8.91 g, 90%).

Yield: 90%, colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 699, 823, 874, 1190, 1275, 1549, 1620, 1725, 2948; **^{1}H NMR** (200 MHz, $CDCl_3$): δ .01 (s, 6H), 1.00 (s, 9H), 1.66 (m, 2H), 1.81 (m, 2H), 2.56 (t, *J* = 7.0 Hz, 1H), 9.86 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.4, 18.2, 18.5, 25.8, 32.0, 43.4, 62.4, 201.9; **Anal. Calcd** for $C_{11}H_{24}O_2Si$ requires C, 61.06; H, 11.18; found: C, 61.09; H, 11.14%.

8-((*tert*-Butyldimethylsilyl)oxy)oct-1-en-4-ol (126)

To a stirred solution of the aldehyde **124** (8 g, 36.97 mmol) in THF (50 mL), allyl bromide (6.4 mL, 73.94 mmol) and zinc powder (4.8 g, 73.94 mmol) were added. The mixture of a saturated aqueous ammonium chloride solution which was added equal amount of THF. The reaction mixture was stirred at 0 to 25 ^{o}C for 12 h. After completion of reaction (monitored by TLC), it was diluted with water and the organic phase was separated and the aqueous phase extracted twice with EtOAc. The combined organic layers were washed with brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give crude product **126**, which upon column chromatographic purification with silica gel using petroleum ether:ethyl acetate (8:2) as eluent gave pure **126** as colorless oil (8 g, 85%).

Yield: 85%, colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1243, 1670, 2930, 3010, 3415; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.04 (s, 6H), 0.89 (s, 9H), 1.47-1.54 (m, 6H), 2.05-2.36 (m, 2H), 3.61 (t, *J* = 6.0 Hz, 3H), 5.09-5.17 9 (m, 2H), 5.75-5.85 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.2, 18.3, 21.9, 25.9, 32.6, 36.4, 41.9, 63.0, 70.5, 117.8, 134.8; **Anal.** Calcd for $C_{14}H_{30}O_2si$ requires C, 65.06; H, 11.70; found: C, 65.08; H, 11.75%.

8-((*tert*-Butyldimethylsilyl)oxy)oct-1-en-4-one (123)

To a solution of the homoallylic alcohol **126** (7 g, 27 mmol) in DMSO (100 mL) was slowly added IBX (8.3 g, 29.7 mmol). The reaction mixture was stirred for 2 h at 25 °C followed by quenching with cold water. The reaction mixture was filtered and the filtrate was then extracted with diethyl ether (3 × 100 mL) and the combined organic layers were washed with brine, dried over anhyd. Na_2SO4 and concentrated to give the crude aldehyde which was then purified by column chromatography over silica gel using petroleum ether/EtOAc (9:1) to give ketone **123** as a colorless oil (5.65 g, 82%).

Yield: 82%, colorless oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 749, 850, 1011, 1236, 1462, 1722, 2844, 3456; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.1 (s, 6H), 0.92 (s, 9H), 1.49-1.54 (m, 2H), 2.46 (t, *J* = 6.8 Hz, 2H), 3.14 (d, *J* = 7.0 Hz, 2H), 3.43-3.50 (m, 2H), 3.75 (t, *J* = 6.5 Hz, 2H), 5.07-5.20 (m, 2H), 5.80-6.01 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.2, 18.3, 21.9, 25.9, 32.7, 41.8, 47.6, 69.5, 118.6, 130.6, 208.0; **Anal.** Calcd for $C_{14}H_{28}O_2Si$ requires C, 65.57; H, 11.01; found: C, 65.60; H, 11.06%.

(*R*)-8-((*tert*-Butyldimethylsilyl)oxy)oct-1-en-4-ol (122)

To a solution of (*R*)-Me-CBS **129** (0.540 g, 19.51 mmol) in THF (5 ml) was added 1 M BH_3-THF solution (19.51 ml, 19.51 mmol) and the mixture was stirred under N_2 atmosphere at -30 ^oC for 5 min. A solution of ketone **123** (5 g, 19.51 mmol) in THF (5 ml) was added dropwise. The reaction mixture was stirred until the ketone had disappeared on a TLC (10 min). The reaction mixture was quenched with 2N HCl (4 ml), extracted with ether, dried over Na_2SO_4 and concentrated under reduced pressure to give crude product **122**, which upon column chromatographic purification with silica gel using petroleum ether:ethyl acetate (8:2) as eluent gave pure **122** as colorless oil (3.7 g, 75%).

Yield: 75%, colorless oil; **$[\alpha]_D^{25}$** +4.9 (*c* 0.5, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1245, 1671, 2932, 3011, 3417; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.04 (s, 6H), 0.89 (s, 9H), 1.47-1.54 (m, 6H), 2.05-2.36 (m, 2H), 3.61 (t, *J* = 6.0 Hz, 3H), 5.09-5.17 9 (m, 2H), 5.75-5.85 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.3, 18.3, 22.0, 26.0, 32.7, 36.5, 41.9, 63.1, 70.6, 117.9, 134.9; **Anal.** Calcd for $C_{14}H_{30}O_2si$ requires C, 65.06; H, 11.70; found: C, 65.08; H, 11.75%.

Mosher's ester of (*R*)-8-((*tert*-butyldimethylsilyl)oxy)oct-1-en-4-ol (130)

A two-necked 10 mL flask equipped with septum was charged with (*N*,*N*'-dicyclohexylcarbodiimide (DCC) 39 mg, 0.2 mmol), catalytic amount of 4-

dimethylaminopyridine (DMAP) and CH_2Cl_2 (2 mL) under argon atmosphere. The flask was allowed to cool to 0 ºC for 10 min and a solution of alcohol **122** (50 mg, 0.2 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 (51 mg, 0.22 mmol) in CH_2Cl_2 (2 mL). This reaction mixture was then stirred at 0 ºC for additional 1 h and then at room temperature overnight. The reaction mixture was diluted with CH_2Cl_2 (50 mL), washed with saturated sodium bicarbonate solution (50 mL), dried over anhyd. Na_2SO_4 and then concentrated under reduced pressure to give Mosher's ester **124** (64 mg, 75%) as a thick syrup.

Yield: 75%; $\mathbf{[\alpha]_D^{25}}$ +20.5 (*c* 0.5, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 668, 928, 1021, 1106, 1171, 1266, 1363, 1453, 1496, 1749, 2401, 2856, 3019, 3484; **^{1}H NMR** (400 MHz, CDCl3): δ 0.04 (s, 6H), 0.89 (s, 9H), 1.47-1.54 (m, 6H), 2.05-2.36 (m, 2H), 3.61 (t, *J* = 6.0 Hz, 3H), 3.37 (s, 3H) 5.09-5.17 9 (m, 2H), 5.75-5.85 (m, 1H), 7.40-7.52 (m, 5H); **^{19}F NMR** (400 MHz, $CDCl_3$+CF_3COOH) δ -72.17 (minor diasteromer, integral = 1%), -72.27 (major diastereomer, integral = 58.46%) [Ratio of diasteromer major : minor, 98.32 : 1.68]; **Analysis:** $C_{22}H_{33}F_3O_5$ requires C, 59.17, H, 7.45; Found: C, 59.16, H, 7.40%.

(*R*)-8-((*tert*-butyldimethylsilyl)oxy)oct-1-en-4-yl methanesulfonate (127)

To a stirred solution of homoallylic alcohol **122** (3 g, 11.6 mmol) and triethylamine (2.4 mL, 17.4 mmol) in CH_2Cl_2 (20 mL), mesyl chloride (1.1 mL, 13.4 mmol) was added at 0 ^oC under N_2 atmosphere. The resulting solution was stirred at the same temperature for 1 h. After completion of the reaction (monitored by TLC), it was quenched with water and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated

under reduced pressure to give the crude mesylate **127**. Column chromatographic purification with silica gel using petroleum ether:ethyl acetate (8:2) as eluent gave **127** in pure form (3.3 g, 85%).

Yield: 85%; colorless liquid; $[\alpha]_D^{25}$ +12.6 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 938, 1035, 1090, 1150, 1789; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.04 (s, 6H), 0.89 (s, 9H), 1.44-1.54 (m, 4H), 1.69-1.77 (m, 2H), 2.48 (t, *J* = 6.3 Hz, 2H), 2.98 (s, 3H), 3.61 (t, *J* = 5.7 Hz, 2H), 4.66-4.78 (m, 1H), 5.12-5.19 (m, 2H), 5.69-5.86 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.2, 18.3, 21.4, 25.9, 32.3, 33.8, 38.6, 39.0, 62.6, 82.3, 118.9, 137.4; **Anal.** Calcd for: $C_{15}H_{32}O_4SSi$ requires C, 53.53; H, 9.58; found: C, 53.50; H, 9.55%.

(*S*)-((5-Azidooct-7-en-1-yl)oxy)(*tert*-butyl)dimethylsilane (120)

To a stirred mixture of mesylate **127** (3 g, 8.91 mmol) in DMF (15 mL), sodium azide (0.694g, 10.69 mmol) was added. The reaction mixture was stirred for 5 h at 80 ^oC. After completion of the reaction (monitored by TLC), it was extracted with EtOAc (3 x 10 mL), washed with water, brine and dried over anhydrous Na_2SO_4. The combined organic layer was concentrated under reduced pressure to give the crude azide **120**, which was purified by column chromatography with silica gel using petroleum ether:ethyl acetate (9:1) as eluent to give pure azide **120** as pale yellow oil (1.7 g, 68%).

Yield: 68%; pale yellow oil; $[\alpha]_D^{25}$ +20.4 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 930, 1040, 1291, 1789, 2105; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.04 (s, 6H), 0.89 (s, 9H), 1.57-1.67 (m, 6H), 2.27-2.35 (m, 2H), 3.26-3.35 (m, 2H), 2.61 (t, *J* = 4.5 Hz, 1H), 5.11-5.19 (m, 2H), 5.70-5.87 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 24.5, 28.1, 54.0, 77.8, 175.9; **Anal.** Calcd for $C_{14}H_{29}N_3OSi$ requires C, 59.32; H, 10.31; N; 14.82; found: C, 59.36; H, 10.35; N, 14.80%.

***tert*-Butyl (*R*)-(8-((tert-butyldimethylsilyl)oxy)octan-4-yl)carbamate (128)**

To a stirred solution of azide **120** (1.5 g, 5.82 mmol) in methanol (5 mL), was added 10% Pd/C (10 mg) at 25 ^{o}C. The reaction mixture was stirred under H_2 atmosphere (60 psi) at 25 ^{o}C for 10 h. After completion of reaction (monitored by TLC), it was filtered through a Celite pad and washed with EtOAc (3 x 20 mL). The combined organic phase was concentrated under reduced pressure to give the crude amino compound, which was taken up for the next step without purification.

To a solution of the above crude amine (1.5 g, 5.82 mmol) in dry CH_2Cl_2 (20 mL) were added dry Et_3N (0.97 mL, 6.98 mmol), $(Boc)_2O$ (2.1 mL, 8.73 mmol) and DMAP (0.07 g, 10 mol%), and the reaction mixture stirred for 6 h. After completion of the reaction as monitored by TLC, it was extracted with CH_2Cl_2 (3 x 60 mL), washed with brine and dried over anhyd. Na_2SO_4 and concentrated to give the crude product, which was then purified by column chromatography over silica gel using petroleum ether:EtOAc (8:2) to give carbamate **128** as a colorless gummy liquid (1.61 g, 85%).

Yield: 85%; colorless viscous liquid; **[α]** $^{25}_{D}$ +8.23 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1243, 1465, 1478, 1518, 1740, 2256, 2984, 3464; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.04 (s, 6H), 0.89 (s, 9H), 0.91 (t, *J* = 7.3 Hz, 3H), 1.32-1.47 (m, 8H), 1.53 (s, 9H), 1.57-1.69 (m, 2H), 2.32-2.42 (m, 1H), 3.57-3.61(m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.2, 13.8, 17.2, 18.3, 20.3, 26.0, 28.5, 32.7, 35.4, 37.9, 50.3, 62.9, 84.8, 146.7; **Anal**. Calcd for $C_{19}H_{41}NO_3Si$ requires C, 63.46; H, 11.49; N, 3.89; found: C, 63.48; H, 11.45; N, 3.85%.

***tert*-Butyl (*R*)-(8-hydroxyoctan-4-yl)carbamate (104)**

The silyl ether **128** (1 g, 2.78 mmol) was dissolved in THF (20 mL) and to this mixture TBAF (10 mL of 1 M solution in THF) was added at 0 ^{o}C. The reaction

mixture was stirred for 1 h at the same temperature and then quenched with water. It was extracted with ethyl acetate and the combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain the crude product, which was then purified by column chromatography using pet ether:ethyl acetate (90:10) to obtain pure alcohol **104** (0.613 g, 90%).

Yield: 90%; colorless viscous liquid; **[α]** $^{25}_{D}$ +4.29 (c 1, $CHCl_3$) {lit. $^{39}[\alpha]_D$ + 4.32 (*c* 1.72, $CHCl_3$)}; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 740, 839, 1054, 1166, 1392, 1698, 2984, 3438; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.91 (t, *J* = 7.3 Hz, 3H), 1.43 (s, 9H), 1.25-1.37 (m, 4H), 1.54-1.68 (m, 6H), 2.36-2.46 (m, 1H), 3.59-3.65 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.1, 17.3, 19.6, 28.5, 32.5, 35.5, 37.9, 50.1, 62.6, 78.9, 155.8; **Anal.** Calcd for $C_{13}H_{27}NO_3$ requires C, 63.64; H, 11.09; N, 5.71; found: C, 63.60; H, 11.12; N, 5.67%.

(*R*)-2-Propylpiperidine (71)

To a stirred solution of amino alcohol **104** (0.5 g, 2.03 mmol) and Et_3N (0.3 mL, 2.22 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added methanesulfonyl chloride (0.15 mL, 2.22 mmol) dropwise using a syringe. After stirring at 0 °C for 0.5 h, the mixture was poured into ice-water (30 mL), washed with aqueous $NaHCO_3$, brine and dried over anhyd. Na_2SO_4. Solvent was distilled off under reduced pressure to give the crude mesylate (0.6 g). To a stirred solution of this crude mesylate (0.6 g, 1.85 mmol) at -30 ^oC in THF (25 mL) was added a suspension of NaH (74 mg, 1.85 mmol in THF (10 mL) over a period of 15 min. After stirring for 1 h at that temperature, the mixture was warmed to 50 ^oC and stirred for another 2 h. It was then quenched by the addition of saturated NH_4Cl and the aqueous phase was extracted with brine, dried over anhyd. Na_2SO_4 and concentrated *in vacuo*. The residue was stirred in 3N HCl in MeOH for 2 h at 25 ^oC, then quenched with cold water (5 mL) and the aqueous layer was extracted

with EtOAc (2 x 50 mL). The combined organic layer was washed with saturated $NaHCO_3$, brine and dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel using pet.ether:EtOAc (1:1) to afford pure (*R*)-coniine **71** (0.187 g, 60%).

Yield: 60%; colorless viscous liquid, $\mathbf{[\alpha]^{25}_D}$ +4.35 (c 1, $CHCl_3$) {lit.[36] $[\alpha]_D$ +4.0 (*c* 0.85, $CHCl_3$)}; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 740, 839, 1054, 1166, 1215, 2962, 3020; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.92 (t, *J* = 7.2 Hz, 3H), 1.25-1.44 (m, 5H), 1.51-1.74 (m, 5H), 2.34-2.49 (m, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.9, 19.6, 24.5, 26.7, 32.8, 37.5, 44.8, 56.5; **Anal.** Calcd for $C_8H_{17}N$ requires C, 75.52; H, 13.47; N, 11.01; found: C, 75.57; H, 13.45; N, 11.04%.

3.3.6 References

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Chapter IV

Synthetic Methodologies Involving Formation of C-N, C-Br and C-I Bonds via Olefin Functionalization

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1. "Titanium Superoxide: A Heterogeneous Catalyst for anti-Markovnikov aminobromination of olefins" Shaikh, T. M**.**; **Karabal, P. U**.; Suryavanshi, G.; Sudalai, A, *Tetrahedron Lett.* **2009**, *50*, 2815.
2. "Regiospecific Azidoiodination of Alkenes with Sodium Periodate, Potassium Iodide, and Sodium Azide: A High-Yield Synthesis of β-Iodoazides" Chouthaiwale, P. V.; **Karabal, P. U**.; Suryavanshi, G.; Sudalai, A. *Synthesis,* **2010**, *22,* 3879.
3. "$NaIO_4$/LiBr-mediated aziridination of olefins using chloramine-T" **Karabal, P. U.**; Chouthaiwale, P. V.; Shaikh, T. M. S.; Suryavanshi, G.; Sudalai, A. *Tetrahedron Lett.,* **2010**, *51,* 6460.

Section I

Titanium Superoxide: A Heterogeneous Catalyst for *anti*-Markovnikov Aminobromination of Olefins

4.1.1 Introduction

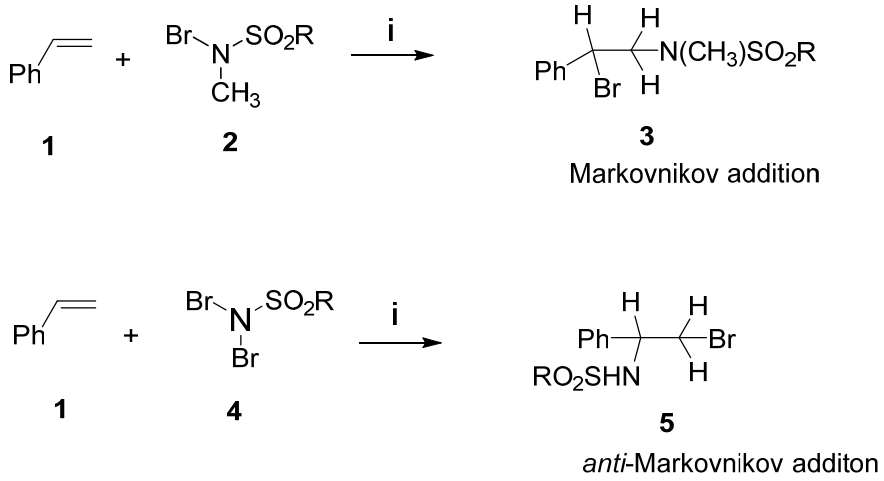
The fuctionalization of olefins by the addition of two different functional groups in a single step provides access to wide range of functional group manipulation in organic synthesis. Variety of reactions such as aminohydroxylation, halohydration, haloazidation, azidohydroxylation and haloamination are some of the examples of this kind of synthetic transformation. Further, the vicinal haloamine functionality presents a very useful structural moiety in synthetic organic chemistry as the halo functionality can be replaced by a variety of nucleophiles such as azido (N_3), cyano (CN), acetate (OAc), alkoxy (OR), amino (NHR), thio (SR), *etc*. thereby providing a new class of functionalized reactive intermediates in organic synthesis. On treatment with base the vicinal haloamines can be converted to the corresponding aziridines, which are important building blocks in organic synthesis. Thus, the vicinal haloamines represents a very useful class of compounds in organic synthesis.[1]

4.1.2 Review of Literature

Literature search revealed that even though the initial work has been started in the late thirties, the progress on direct haloamination of olefins has been quite tardy. Most of these methods, which involve use of *N, N*-dihalo sulfonamides or carbamates as halogen and amine sources, are described below.

Kharasch's approach (1939)[2]

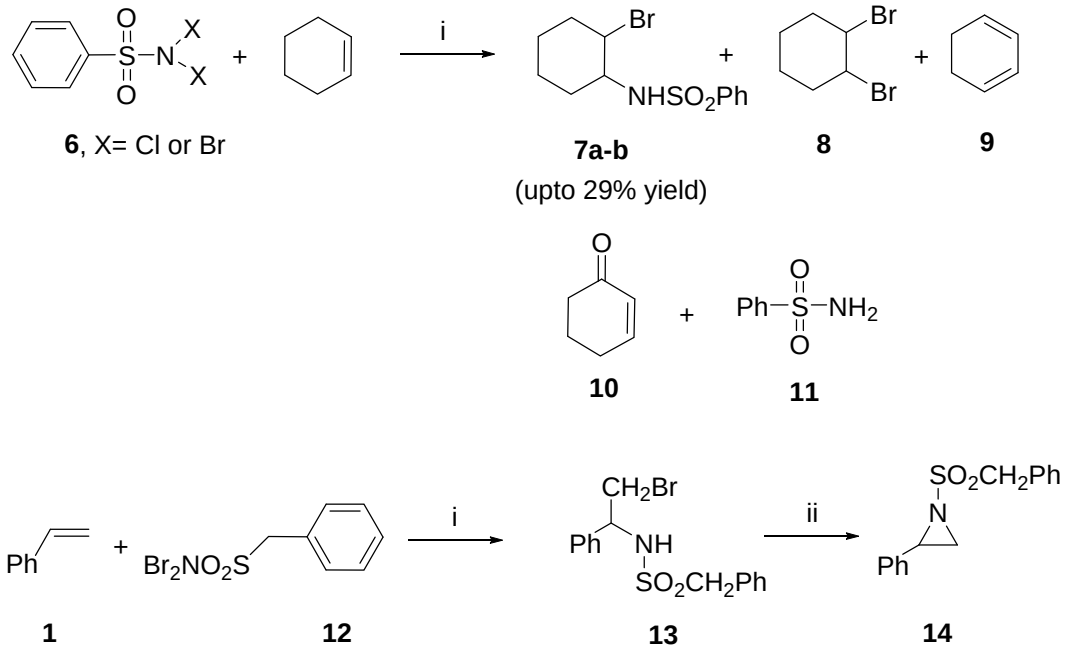
Kharasch *et al*. have studied the addition of N-bromo sulfonamides **2** and **4** to styrene to give the corresponding bromoamine **3** and **5** (**Scheme 1**).



Scheme 1: (i) 25 °C, stirring.

Terauchi's approach (1967)[3]

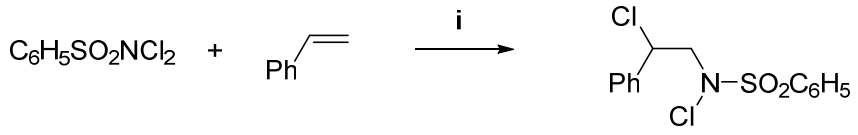
Terauchi *et al*. have studied the reaction between *N, N*-dihalosulfonamide with cyclohexene and styrene; cyclohexene gave many addition products such as *cis* and *trans*-2-halo-1-benzenesulfonamidocyclohexanes **7a-b**, *trans*-1,2-dihalocyclohexane **8**, 1,3-cyclohexadiene **9**, 1-cyclohexene-3-one **10** and benzene sulfonamide **11** (**Scheme 2**).



Scheme 2: (i) reflux, 10 min. then 50 °C for 30 min; (ii) 5% NaOH.

Danither's approach (1968)[4]

Danithes *et al.* have found that, addition of *N,N*-dichlorosulfonamides to olefins and conjugated dienes has been examined. The reaction of these reagents with propylene and styrene gave high yields of *N*-chloro-*N*-(*β*-chloroalkyl)sulfonamides **15**, which are predominantly *anti*-Markovnikov product in 85% yield (**Scheme 3**).

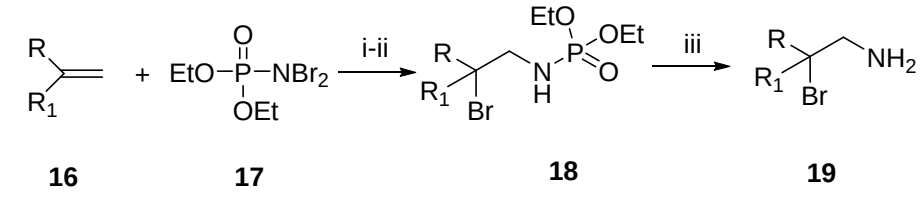


1 **6** **15**

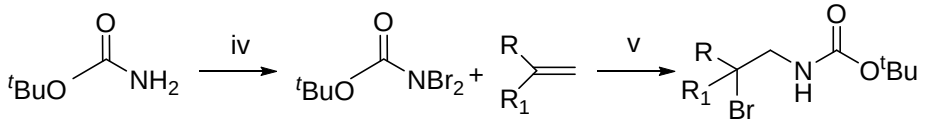
Scheme 3: (i) CH_2Cl_2, 0-25 °C, 85%.

Zwierzak's approach (1981)[5]

Zwierzak *et al.* have described, diethyl *N, N*-dibromophosphoramidate (DBPA, **17**) and *ter*-butyl *N,N*-dibromocarbamate (**21**), prepared from *ter*-butyl carbamate, was added to phenyl ethylenes and terminal olefins to give *N*-bromo adducts, which were.



16 **17** **18** **19**



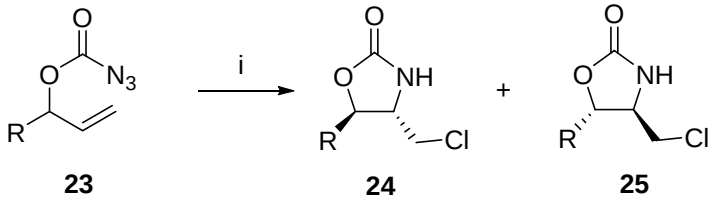
20 **21** **16** **22**

Scheme 4: (i) CH_2Cl_2, reflux; (ii) 12% aq. Na_2SO_3, 5-10 °C; (iii) HCl, benzene; (iv) Br_2 (2 equiv), K_2CO_3, H_2O, 25 °C, 90%; (v) CH_2Cl_2, reflux.

reduced *in situ* (Na_2SO_3) to give diethyl-*N*-(β-bromoalkyl)phosphoramidates **18** and β-bromo-*N*-Boc-amines **19** respectively (**Scheme 4**). The addition followed *anti*-Markovnikov fashion.

Bach's approach (2000)[6]

Bach *et al.* have reported that 2-alkenyloxycarbonyl azides **23** underwent an efficient intermolecular aminochlorination with TMSCl catalyzed by $FeCl_2$ to furnish the corresponding 4-(chloromethyl)-oxazolidinones **24-25** in 60-84% yield (**Scheme 5**).

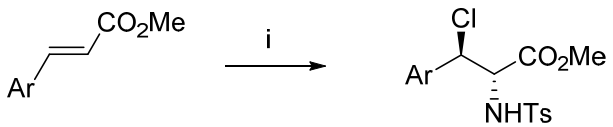


23 **24** **25**

Scheme 5: (i) $FeCl_2$, TMSCl, EtOH, 0 to 25 °C, 60-84%.

Li's approach (2001)[7]

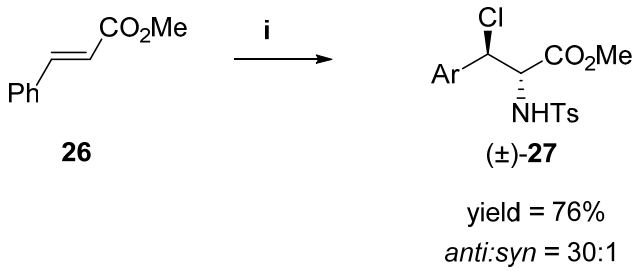
Li *et al*. have recently reported a new method of Cu or Zn-catalyzed aminochlorination of cinnamic esters **26** that produced vicinal haloamine derivatives **27** in 52-85% yields and >95% regio-and stereoselectivities.[7a] *N*,*N*-Dichloro-*p*-toluenesulfonamide was used as chlorine as well as nitrogen source (**Scheme 6**).



26 **27**

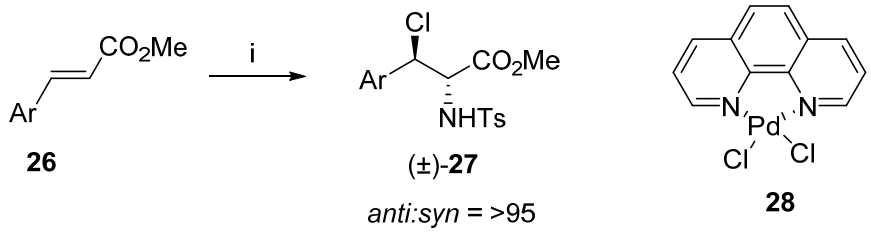
Scheme 6: (i) (a) $TsNCl_2$, 4 Å MS, CuOTf or $ZnCl_2$ (8 mol%), CH_3CN, 25 °C; (b) Na_2SO_3, 52-85%.

Another approach from Li *et al.* that comprised of a new regio- and stereoselective aminohalogenation of cinnamic esters **26** using the combination of 2-$NsNCl_2$/2-NsNHNa (Ns = nitrobenzenesulfonyl) as the nitrogen and chlorine sources respectively and CuOTf as catalyst affording upto 76% yield (**Scheme 7**).[7b]



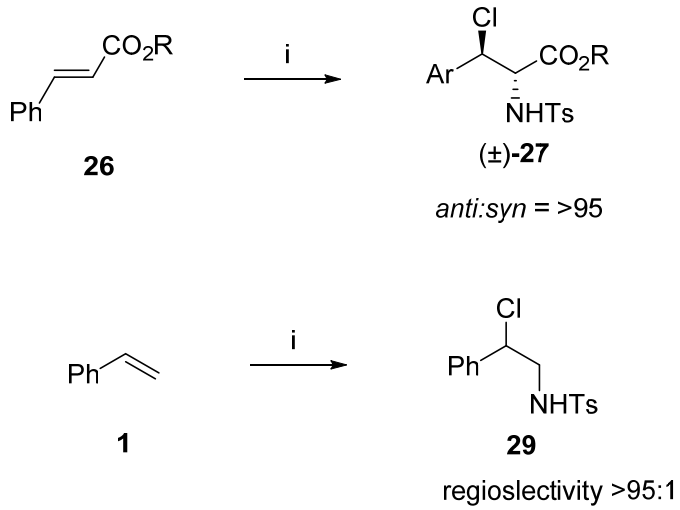
Scheme 7: (i) (a) 2-$NsNCl_2$/2-NsNHNa, CuOTf (10 mol%), CH_3CN, 25 °C; (b) aq. Na_2SO_3.

In yet another finding, Li *et al.*[7c] have reported a useful method of Pd-complex **28** catalyzed aminohalogenation of cinnamic esters using *p*-$TsNCl_2$ as the nitrogen and chlorine sources that produced chloramine **27** in 62-92% yield (**Scheme 8**).



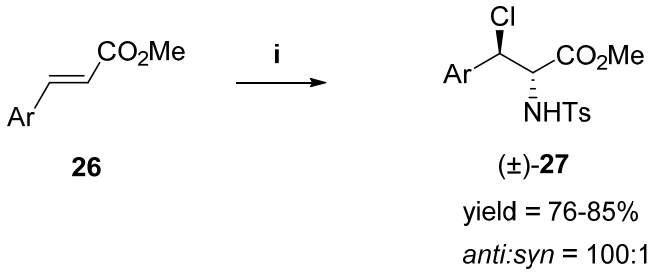
Scheme 8: (i) (a) $TsNCl_2$, Pd-catalyst (8 mol%) **28**, CH_3CN; (b) aq. Na_2SO_3.

N-Chloro-*N*-sodium-sulfonamide was also found to react with olefins in the presence of copper catalyst to give vicinal haloamine derivatives in upto 74% yield (**Scheme 9**).[7d]



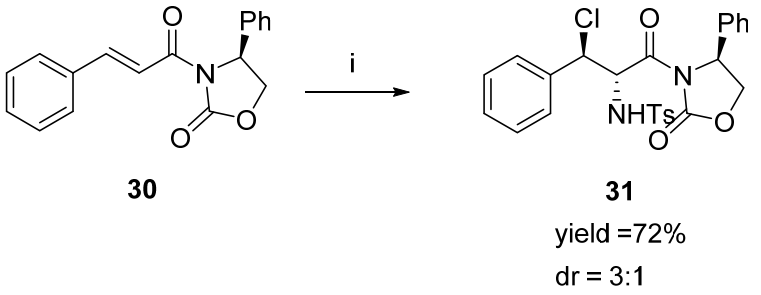
Scheme 9: (i) (a) *o*-NsNClNa, CuOTf (10 mol%), CH_3CN; (b) aq. Na_2SO_3.

Li *et al.*[7e] have also used ionic liquid butylmethylimidazolium tetrafluoroborate [bmim][BF_4] to reduce the amount of catalyst loading (6 mol% of CuOTf) and enhance the rate of the aminohalogenation of cinnamic esters **26** using *p*-$TsNCl_2$ as the nitrogen and chlorine sources giving **27** upto 85% yield (**Scheme 10**).



Scheme 10: (i) (a) $TsNCl_2$, CuOTf (6 mol%), [Bmim][BF_4], CH_3CN, 25 °C; (b) aq. Na_2SO_3.

Li *et al.*[7f] have also developed the asymmetric aminohalogentation of chiral auxilliary attached α,β-unsaturated *N*-acyl 4-alkyloxazolidinones **30** with $TsNCl_2$ and CuOTf as the catalyst in ionic liquid [bmim][BF_4] to give the corresponding chiral aminohalogens **31** in up to 72% yield and 75% diastereomeric ratio (**Scheme 11**).



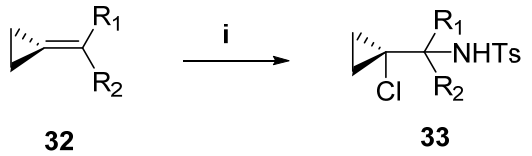
30 **31**

yield =72%

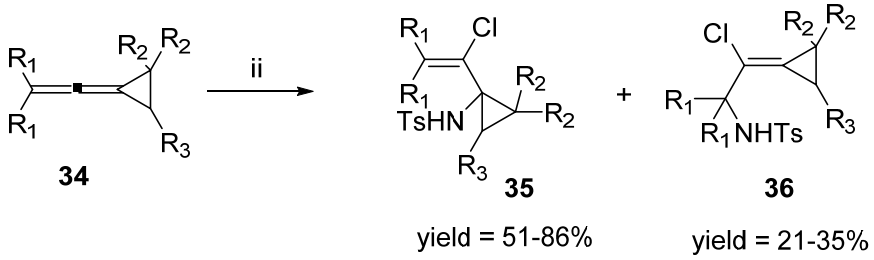
dr = 3:1

Scheme 11: (i) (a) 4 Å MS, CuOTf (8 mol%), $TsNCl_2$, $[Bmim][BF_4]$; (b) aq. Na_2SO_3.

The same group have recently developed the aminochlorination of arylmethylene cyclopropanes **32** and arylvinylidine cyclopropanes **34** using $FeCl_3$ as the catalyst and $TsNCl_2$ as the nitrogen and chlorine sources respectively (**Scheme 12**).[7g]



32 **33**



34 **35** **36**

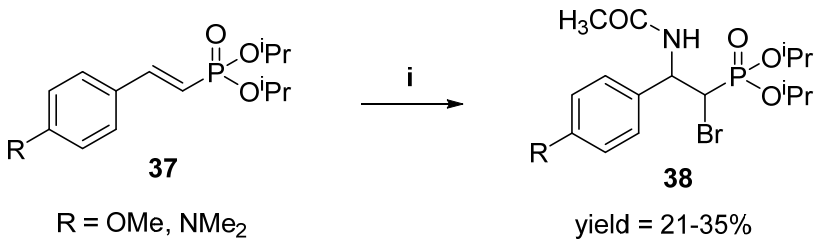
yield = 51-86% yield = 21-35%

Scheme 12: (i) $TsNCl_2$, $FeCl_3$ (20 mol%), CH_3CN, 25 °C; (ii) $TsNCl_2$, $FeCl_3$ (20 mol%), CH_3CN, -15 °C.

Yoon's approach (2003)[8]

Yoon *et al.* have developed a new catalytic regiosective method of *syn*-β-amino-α-bromination of unsaturated phosphonates **37** under typical Sharpless asymmetric

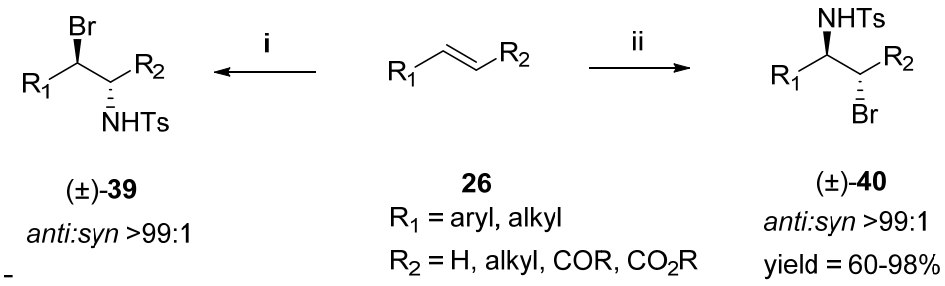
aminohydroxylation conditions using Os-catalyst, $(DHQD)_2$-PHAL as the ligand and excess *N*-bromoacetamide which produced bromaamines in low yields (**Scheme 13**).



Scheme 13: (i) $BrNHCOCH_3$, 4 % $K_2OsO_2(OH)_4$, 5 % $(DHQD)_2$-PHAL, LiOH, CH_3CN-H_2O, 0-4 °C, upto 35%.

Sudalai's approach (2003)[9]

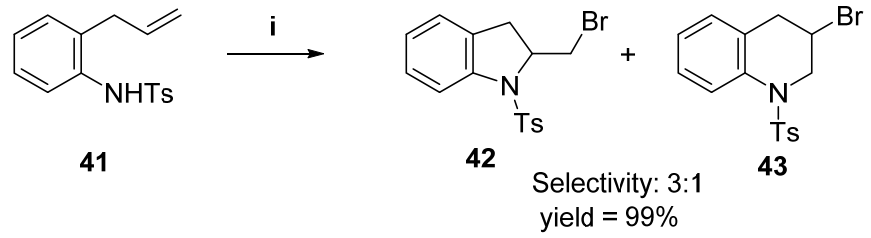
Sudalai *et al.* has reported recently a new synthetic procedure for aminohalogenation of olefins leading to the preparation of vicinal haloamine derivatives **39** and **40** in high yields employing Cu, Mn or V catalysts with *p*-toluenesulfonamide ($TsNH_2$) and *N*-bromosuccinimide (NBS) as nitrogen and bromine sources respectively. Unprecedented regio- and stereoselectivity (*anti:syn* > 99:1) towards the aminohalogenation process was observed for olefinic substrates as well as for transition metal catalysts (**Scheme 14**).



Scheme 14: (i) $TsNH_2$, NBS, Mn(II) salen, CH_2Cl_2, 25 ^oC, 65-97%; (ii) $TsNH_2$, NBS, CuI, $MnSO_4$ or V_2O_5, CH_2Cl_2, 25 ^oC, 60-98%.

Chemler's approach (2004)[10]

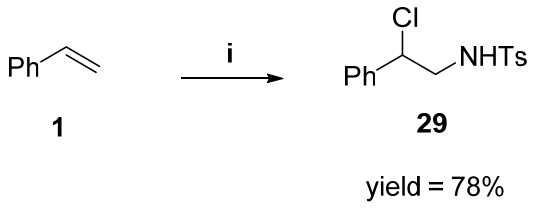
Chemler *et al*. have used intramolecular aminobromination of olefins **41** catalyzed by Pd(II) salts using Cu (II) halides as the halogen source has been reported (**Scheme 15**).



Scheme 15: (i) $Pd(OCOCF_3)_2$ (10 mol%), $CuBr_2$, K_2CO_3, THF, 0-25 °C, 99%.

Minakata's approach (2006)[11]

Minakata *et al*. have developed a new synthetic procedure for the aminochlorination of olefins **1** for the synthesis of vicinal chloroamine derivatives **29** using a combination of chloramine-T and carbon dioxide (10 atm) (**Scheme 16**).

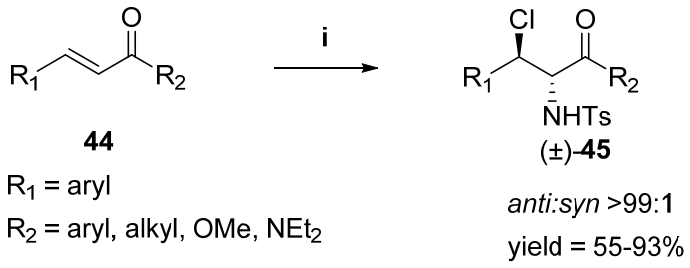


Scheme 16: (i) (a) TsN(Cl)Na, CO (10 atm.), PhH, 25 °C; (b) Na_2SO_3 (aq.), up to78%.

Wang's approach (2007)[12]

Wang *et al.* have developed a practical and scalable process for the regio- and diastereoselective synthesis of vicinal chloramines from **45** electron-deficient olefins and Chloramine-T promoted include by Bronsted acids in water. The novel features of

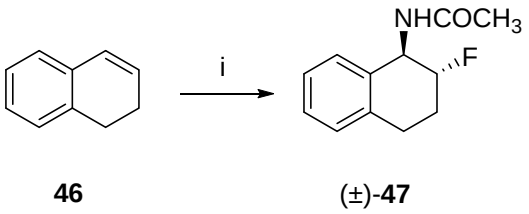
this protocol: the use of water as a solvent, reaction conditions are mild, ecofriendly, and broadly applicable for the aminochlorination of various electron-deficient olefins including α,β-unsaturated ketones, cinnamates and amides (**Scheme 17**).



Scheme 17: (i) H_2SO_4, triethylbenzylammonium chloride, H_2O, 25 ^oC

Yadav's approach (2009)[13]

A variety of alkenes are converted into the corresponding α-fluoroamides in high yields by Selectfluor^{TM} in the presence of 10 mol % of InF_3 in CH_3CN as solvent. However α -bromoamides are obtained with NBS in the presence of 10 mol% of $InBr_3$ under similar conditions (**Scheme 18**).



Scheme 18: (i) InF_3, Selectfluor^{TM}, CH_3CN, 25 ^oC, upto 83%.

4.1.3 Present Work

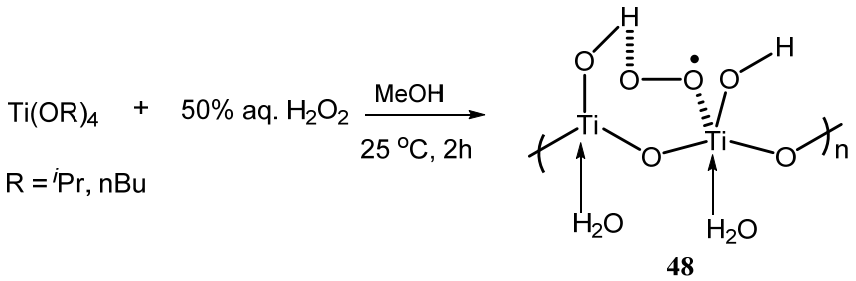
4.1.3.1 Objective

Although there are many direct methods available in the literature for haloamination of olefins, they suffer from certain drawbacks like low yields, multi-step reaction

sequences, cumbersome experimental procedures and the use of *N*,*N*-dihalo sulfonamides or carbamates as the nitrogen as well as bromine sources. Our aim was to develop a catalytic, mild and efficient method for the aminobromination of olefins using a heterogeneous catalyst and *N*-bromosuccinnimide (NBS) and *p*-toluenesulfanamide ($TsNH_2$) as the bromo and amine sources respectively.

4.1.4 Results and discussion

Recently, in our laboratory, we have reported a simple procedure for the preparation of titanium superoxide (**48**) by treating aq. H_2O_2 with titanium tetraisopropoxide ($Ti(O^iPr)_4$ in dry methanol.[14] Titanium superoxide **48** was filtered as an yellow-colored solid and its structure was proposed to have polymeric Ti oxide matrix as shown in **Fig. 1**.



48

Fig. 1: Preparation of titanium superoxide (**48**)

We have thoroughly characterized the structure of superoxide species **48** on the hydrated titanium matrix by various spectroscopic techniques such as FTIR, Raman spectroscopy, XRD, ESR, TG/DTA, and chemical analysis as follows. Its IR spectrum showed characteristic absorption bands at 3720 (w), 3665 (w), and 3450 (s) cm^{-1} indicating the presence of vibrational modes of coordinated water molecules at Ti^{4+} site and of surface Ti-OH groups. The other IR absorption bands at 1027 (s) and 1157 (m) indicated the presence of superoxide radical ion in the solid material. It also had IR absorption bands in the range of 900-538 (m) cm^{-1} corresponding to the presence

of Ti-O-Ti linkages. An intense line at 900 cm^{-1} in the Raman spectrum of the catalyst **48** further confirmed the presence of Ti-O-Ti linkages. The other weak Raman lines observed in the range of 1025-1119 cm^{-1} has been assigned for the $O_2^{\cdot}$ species. A sample of **48** dried at 25 ^oC (3 mm Hg) showed characteristic ESR signals at g_1 = 2.024, g_2 = 2.009 and g_3 = 2.003 (**Fig. 2**), which strongly suggested the presence of unpaired electrons of the stable superoxide radical anion generated by the decomposition of H_2O_2 over Ti-matrix. However, the characteristic ESR signals disappeared when its ESR was recorded at 90 ^oC.

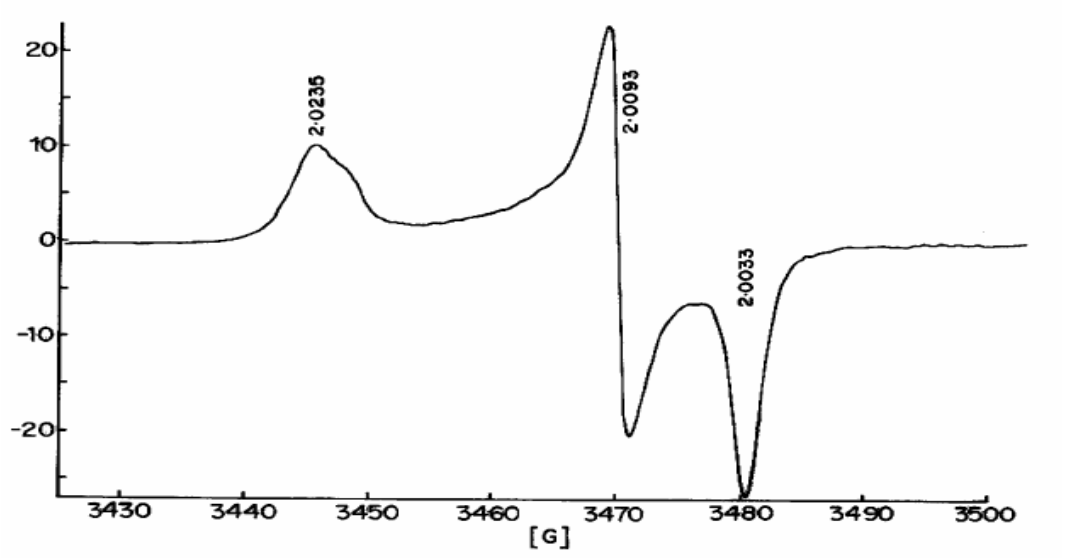
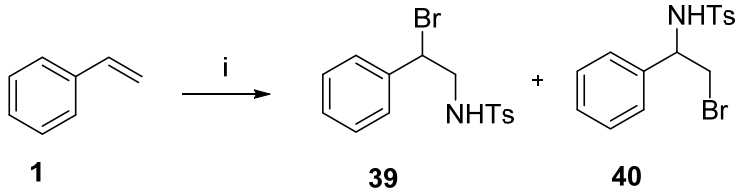


Fig. 2: ESR spectrum of titanium superoxide **48** at 298 K.

During the course of our study on further application of titanium superoxide in organic synthesis,[14] we have now found that olefins can be regiospecifically aminobrominated using *p*-$TsNH_2$ and NBS as nitrogen and bromine sources under ambient conditions. For instance, when styrene **1** was subjected to bromoamination, the corresponding *anti*-Markovnikov product, **39** was formed in 81% yield; whereas

the commercially available TiO_2, under similar conditions, gave the expected Markovnikov product, (**40**) in 30% yield (**Scheme 19**).



TiO_2	--	30%
titanium superoxide	81%	--

Scheme 19: titanium catalyst (10 wt%), *p*-$TsNH_2$ (1.1 equiv), NBS (1 equiv), CH_2Cl_2, 25 ^oC, 14 h.

Encouraged by this result, it was of interest to screen several other titanium salts such as titanium silicalite (a zeolite), $TiCl_4$ and titanium isopropoxide under similar reaction conditions; the results of which are presented in **Table 1**.

Table 1: Titanium-catalyzed regiospecific aminobromination of styrene[a]

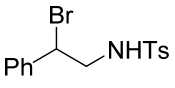
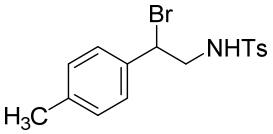
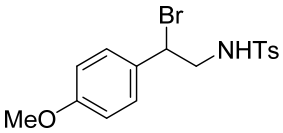
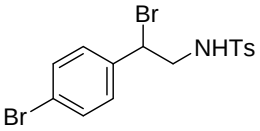
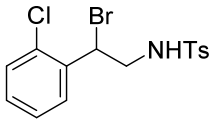
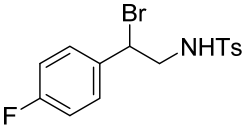
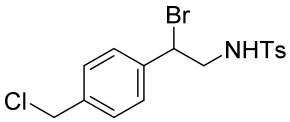
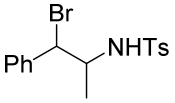
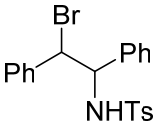
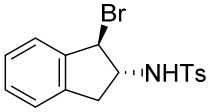
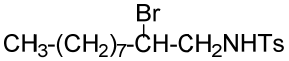
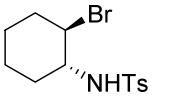
No.	Catalyst	Solvent	Yield (%)[b]	
			39	**40**
1	no catalyst	CH_2Cl_2	-	17
2	TiO_2	CH_2Cl_2	-	38
3	titanium silicate	CH_2Cl_2	-	23
4	$Ti(O^iPr)_4$	CH_2Cl_2	-	24
5	titanium superoxide	CH_2Cl_2	81	-
6	titanium superoxide	$CHCl_3$	61	-
7	titanium superoxide	EDC	58	-

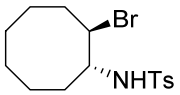
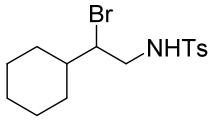
Reaction conditions: [a]olefin (3 mmol), *p*-$TsNH_2$ (3.3 mmol), *N*-bromosuccinimide (3 mmol), titanium catalyst (10 wt%), CH_2Cl_2 (20 mL), 25 ^oC, 14 h; [b]isolated yield after chromatographic purification.

Remarkably, titanium superoxide gave the *anti*-Markovnikov product **39** exclusively in 81% yield, whereas all other titanium salts furnished the expected Markovnikov product, **40** with low yields. Among several solvents screened, CH_2Cl_2 was found to be more suitable for titanium superoxide-catalyzed aminobromination of olefins. Thus, the optimal condition for the aminobromination of olefins turned out to be: olefin (3 mmol), *p*-$TsNH_2$ (3.3 mmol), NBS (3 mmol) and titanium superoxide (10 wt %) in CH_2Cl_2 at ambient conditions.

In order to establish its scope, various olefins were subjected to aminobromination; the results of which are presented in **Table 2**. It is evident that several styrenic substrates including indene underwent the aminobromination regiospecifically to produce the corresponding *anti*-Markovnikov products. No trace of Markovnikov products was, however, observed in the crude product sample (as confirmed by ^1H, ^{13}C NMR and GC analysis). Interestingly, electron-rich olefins gave relatively higher yields of products as compared to electron-deficient olefins. This may be ascribed to the benzylic radical, which abruptly increases its reactivity, thereby resulting in high yields of the aminobrominated product. Also aliphatic olefins underwent aminobromination smoothly to give 1,2-bromoamines in good yields. After the reaction was complete, solid titanium superoxide was recovered by simple filtration, which on subsequent reuse with styrene as substrate was found to catalyze the aminobromination process with moderate yield (58%). Notably, substrates like indene, cyclohexene and cyclooctene gave the corresponding aminobrominated products with high *anti*-selectivity > 99:1 (**Table 2**, entries j, l & m).

Table 2: Titanium superoxide-catalyzed aminobromination of olefins[a]

entry	Olefins (**1a-n**)	Product[b] (**39**)	Yield (%)[c]	*anti : syn*
a	styrene		81 (58)[d]	
b	4-methylstyrene		86	
c	4-methoxystyrene		67	
d	4-bromostyrene		69	
e	2-chlorostyrene		68	
f	4-fluorostyrene		78	
g	4-chloromethylstyrene		67	
h	β-methylstyrene		30	
i	*trans*-stilbene		61	
j	indene		80	>99 : 1
k	1-dodecene		66	
l	cyclohexene		65	>99 : 1

m	cyclooctene		72	>99 : 1
n	vinylcyclohexane		63	

Reaction conditions: [a] olefin (3 mmol), *p*-$TsNH_2$ (3.3 mmol), *N*-bromosuccinimide (3 mmol), titanium superoxide (10 wt%), CH_2Cl_2 (20 mL), 25 °C, 14 h; [b]products were characterized by m.p., IR, ^1H and ^{13}C NMR and elemental analysis; [c]isolated yield after chromatographic purification; [d] Yield in parenthesis refers to use of recovered catalyst.

The structures of regioisomers **39** were confirmed by ^1H and ^{13}C NMR spectroscopy. For example, the ^1H NMR spectrum of compound **39b** showed two typical singlets at δ 2.31 (s, 3H) and 2.41 (s, 3H) for methyl protons; multiplets at δ 3.50-3.65 (m, 2H) for homobenzylic protons; and a doublet of doublet at δ 4.48 (dd, J = 6.3 and 12.5 Hz, 1H) for benzylic protons. Further, a doublet at δ 5.28 (d, J = 6.8 Hz, 1H) is due to N-H proton. Its ^{13}C NMR spectrum showed two typical carbon signals at δ 36.4 and 58.0 for the homobenzylic and benzylic carbons respectively (**Fig. 3**).

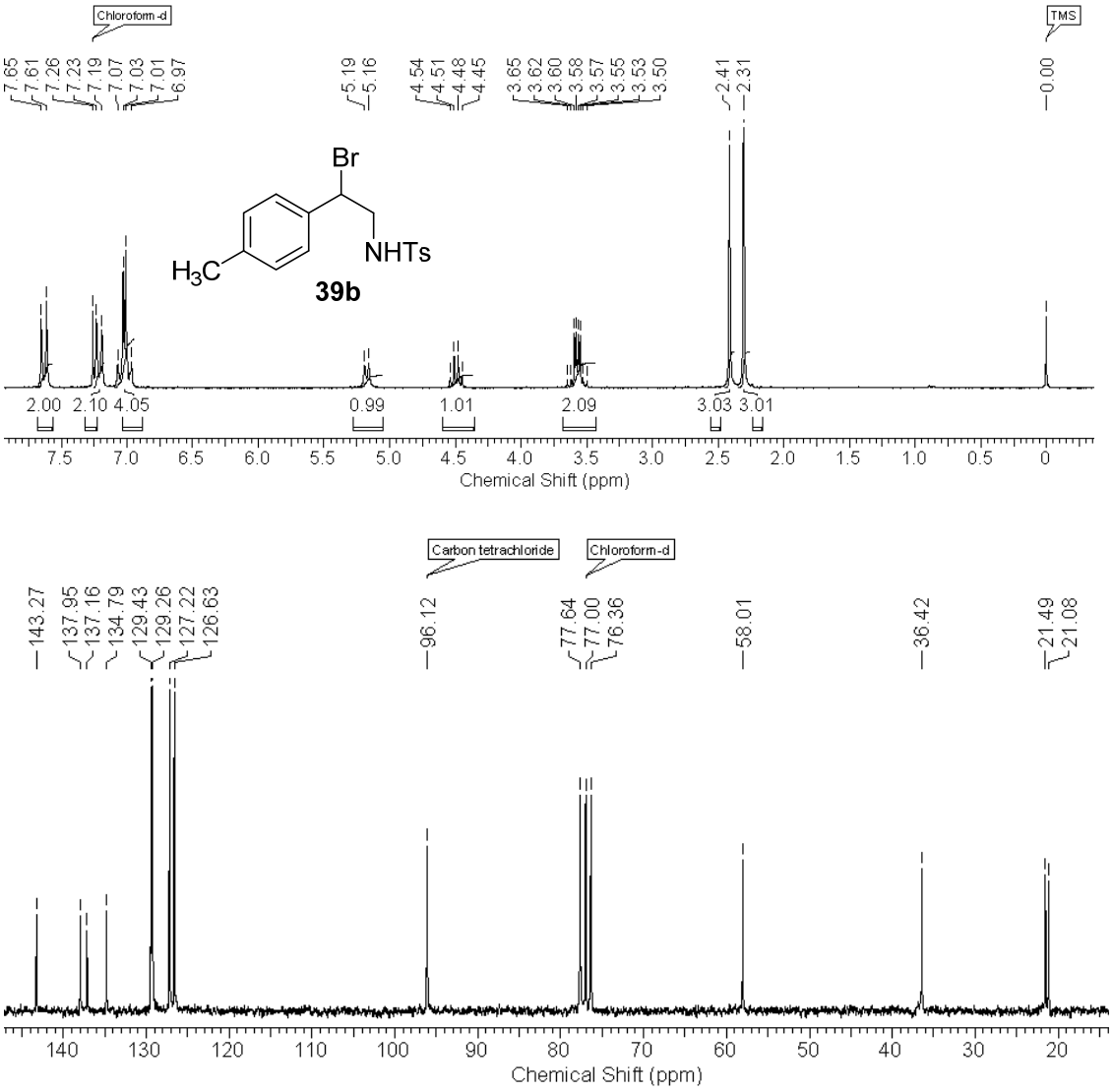
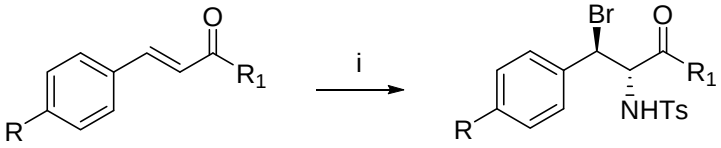


Fig. 3: ^{1}H and ^{13}C NMR spectra of bromoamine **39b**

Having established the aminobromination of simple olefins, we turned our attention to α,β-unsaturated carbonyl compounds **44a-c** as substrates; the results of which are presented in **Table 3**. For α,β-unsaturated esters or ketones, the reaction was found to be relatively slow and gave poor yields of the expected bromoaminated products **45a–c** (**Table 3**, entries a and b). However, use of *p*-$TsNBr_2$ resulted in the formation of bromoamino ester **45c** in good yield (**Scheme 20**).



44 (±)-**45**

R = H, Cl

R^1 = OMe, Ph

Scheme 20: (i) titanium superoxide catalyst (10 wt%), *p*-$TsNH_2$ (1.1 equiv), NBS (1 equiv), CH_2Cl_2, 25 °C, 14 h.

Table 3: Titanium superoxide-catalyzed regiospecific aminobromination of α,β-unsaturated carbonyl compounds.[a]

entry	R	R^1	Amine Source	Yield (%)[b] **45**
a	H	OMe	p-$TsNH_2$	20
b	Cl	Ph	p-$TsNH_2$	21
c	Cl	Ph	p-$TsNBr_2$	68

[a]Products were characterized by m.p., IR, ^{1}H and ^{13}C NMR, and elemental analysis.

[b]Isolated yield after chromatographic purification.

The structures of regioisomers **45a-c** were confirmed by ^{1}H and ^{13}C NMR spectroscopy. For example, the ^{1}H NMR spectrum of compound **49c** showed two doublets at δ 4.99-5.03 (d, *J* = 8.0 Hz, 1H) and 5.56-5.71 (d, *J* = 9.7 Hz, 1H) for methine proton attached to tosyl amine and bromine groups with respectively. Its ^{13}C NMR showed two typical carbon signal at δ 59.4 and 54.9 for carbons attached to tosyl amine and bromine groups respectively (**Fig. 4**).

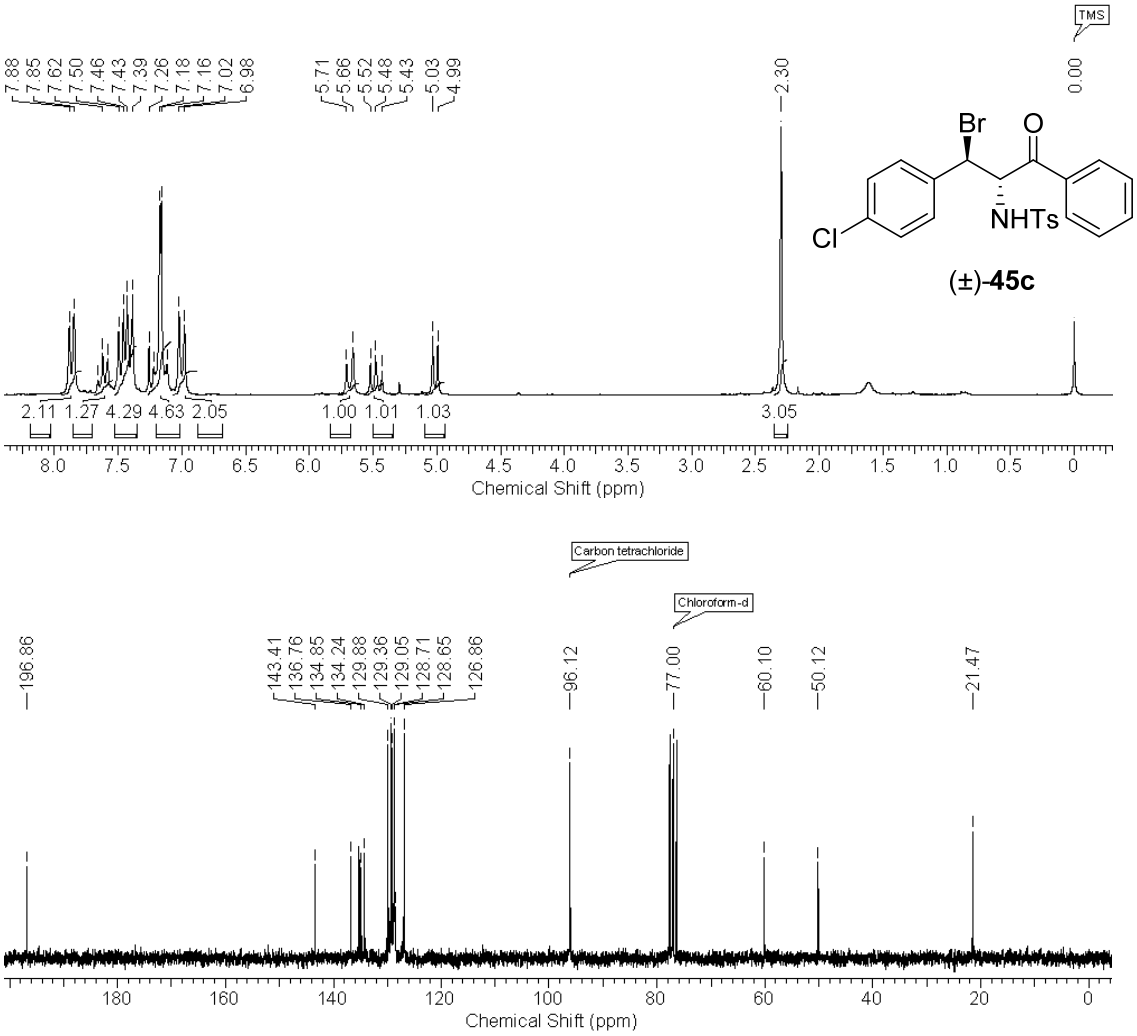


Fig. 4: ^{1}H and ^{13}C NMR spectra of bromoamine (±)-**45c**

4.1.4.1 Mechanism

A plausible mechanistic pathway is outlined in **Fig. 5** to explain the formation of *anti*-Markovnikov product. Firstly, *p*-toluenesulfonamide reacts with NBS to form *p*-TsNH-Br[3] followed by its interaction with titanium superoxide which facilitates the polarization of the NH-Br bond homolytically. Since the catalyst possesses a stable radical, interaction of which with *p*-Ts-NHBr probably generates *p*-TsNH• radical, which in turn adds on to styrene regiospecifically at the homobenzylic position to

form benzylic radical **49**. The recombination of this radical with Br• radical leads to *anti*-Markovnikov product **39**. The radical pathway proposed here has been supported by the trapping experiment with TEMPO,[15,16] which failed to produce the corresponding haloamine. In the case of other titanium salts, the formation of Markovnikov product **40** can be reasoned on the basis of the formation of bromonium ion followed by its preferential opening at the benzylic position with *p*-toluenesulfonamide.

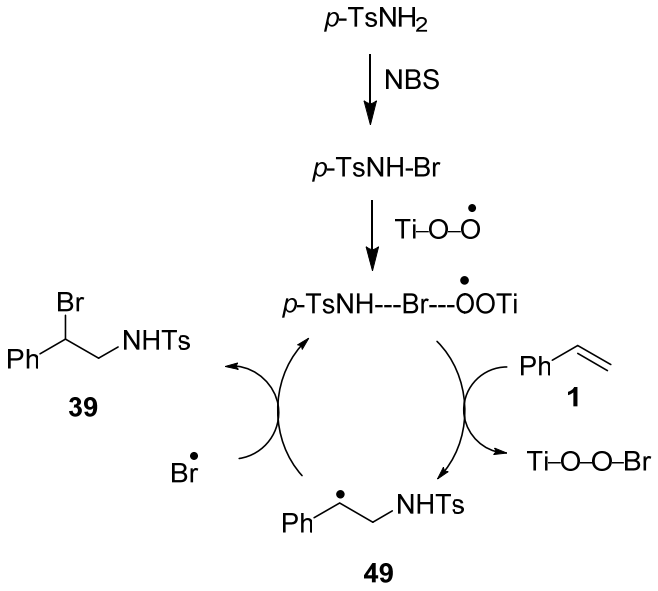


Fig 5: Titanium superoxide catalytic cycle for bromoamination process

4.1.5 Conclusion

In conclusion, we have described a titanium superoxide-catalyzed regiospecific aminobromination of olefins to give exclusively *anti*-Markovnikov products in high yields using *p*-$TsNH_2$ and NBS as amine and bromine sources respectively under ambient conditions. The protocol makes use of stable and readily accessible titanium superoxide as solid catalyst for the aminobromination process.

4.1.6 Experimental Section

Preparation of titanium superoxide (48)

Aqueous 50% H_2O_2 (5.98 g, 0.175 mol) was added slowly to a solution of titanium isopropoxide (5.0 g, 0.0175 mol) in anhydrous MeOH (50 ml) over 40 min under N_2 with stirring at room temperature. The yellow precipitate formed was collected by filtration on a sintered funnel, washed with anhydrous methanol and dried at room temperature. **Yield**: 3.94 g (98 %).

Typical experimental procedure for aminobromination of styrene (39a)

To a stirred solution of styrene **1** (0.312 g, 3.0 mmol), titanium superoxide **48** (0.030 g, 10 wt %) and *p*-$TsNH_2$ (0.564 g, 3.3 mmol) in 25 mL of dry dichloromethane was added NBS (0.534 g, 3.0 mmol) slowly using a solid addition funnel. The reaction mixture was stirred further at 25 ^oC for 14 h. When TLC showed the completion of the reaction, catalyst was filtered off and the filtrate was diluted with water, extracted with CH_2Cl_2 (20 x 3 mL) and washed with brine. The organic layer was dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give the crude product, which was purified by column chromatography packed with silica gel using pet ether and EtOAc as eluents to afford the pure bromoaminated product **39**.

2-Bromo-2-phenyl-*N*-tosylethanamine (39a)

Yield: 81%; **mp**: 113-114 ^oC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 662, 710, 1086, 1153, 1461, 1593, 1655, 2930, 2985, 3252; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.43 (s, 3H), 3.50-3.58 (m, 2H), 4.85-4.99 (m, simplifies to triplet with J = 7.1 Hz, 2H), 7.24-7.33 (m, 7H), 7.71 (d, J = 8.4 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.4, 49.8, 52.4, 126.8, 127.5, 128.7, 129.7, 136.6, 138.0, 143.6; **Anal.** Calcd for $C_{15}H_{16}BrNO_2S$ requires C, 50.86; H, 4.55; N, 3.95; found: C, 50.83; H, 4.50; N, 3.91%.

2-Bromo-2-*p*-tolyl-*N*-tosylethanamine (39b)

Yield: 86%; colorless gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 669, 759, 1161, 1215, 1460, 1597, 2851, 2922, 2954, 3268; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.30 (s, 3H), 2.41 (s, 3H), 3.49-3.64 (m, 2H), 4.49 (dd, *J* = 6.3, 12.5 Hz, 1H), 5.28 (d, *J* = 6.8 Hz, 1H), 6.96-7.06 (m, 4H), 7.21 (d, *J* = 8.2 Hz, 2H), 7.63 (dd, *J* = 1.7 and 6.6 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.0, 21.4, 36.4, 58.0, 126.6, 127.2, 129.2, 129.4, 134.7, 137.1, 137.9, 143.2; **Anal.** Calcd for $C_{16}H_{18}BrNO_2S$ requires C, 52.18; H, 4.93; N, 3.80; found: C, 52.19; H, 4.96; N, 3.77%.

2-Bromo-2-(4-methoxyphenyl)-*N*-tosylethanamine (39c)

Yield: 67%; colorless gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 676, 812, 1027, 1091, 1163, 1336, 1461, 2854, 2923, 3246; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.41 (s, 3H), 3.55 (q, *J* = 2.8 and 6.0 Hz, 2H), 3.76 (s, 3H), 4.48 (q, *J* = 6.1 and 12.1 Hz, 1H), 5.24 (d, *J* = 6.4 Hz, 1H), 6.74 (d, *J* = 8.7 Hz, 2H), 7.02 (dd, *J* = 1.8, 6.6 Hz, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.62 (dd, *J* = 1.7 and 6.7 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.5, 36.4, 55.1, 57.7, 113.9, 127.2, 127.9, 129.4, 129.7, 137.0, 143.2, 159.4; **Anal.** Calcd for $C_{16}H_{18}BrNO_3S$ requires C, 50.01; H, 4.72; N, 3.64; found: C, 49.99; H, 4.76; N, 3.71%.

2-Bromo-2-(4-bromophenyl)-*N*-tosylethanamine (25d)

Yield: 69%; colorless gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 565, 765, 825, 1091, 1151, 1319, 1458, 1596, 2854, 2923, 2954, 3253; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.46 (s, 3H), 3.47-3.56 (m, 2H), 4.88 (t, *J* = 7.4 Hz, 1H), 7.14-7.46 (m, 6H), 7.64 (dd, *J* = 1.5, 8.5 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.6, 49.5, 51.2, 123.0, 127.0, 128.5, 129.3, 129.8, 131.6, 132.0, 136.8, 137.3, 143.7; **Anal.** Calcd for $C_{15}H_{15}Br_2NO_2S$ requires C, 41.59; H, 3.49; N, 3.23; found: C, 41.61; H, 3.71; N, 2.99%.

2-Bromo-2-(2-chlorophenyl)-*N*-tosylethanamine (39e)

Yield: 68%; colorless gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 549, 669, 757, 1093, 1161, 1215, 1334, 1419, 1598, 2854, 2925, 3018, 3284; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.45 (s, 3H), 3.51-3.68 (m, 2H), 4.92 (t, *J* = 6.4 Hz, 1H), 5.29-5.40 (m, 1H), 7.22-7.37 (m, 5H), 7.43-7.48 (m, 1H), 7.74 (d, *J* = 8.2 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.4, 47.7, 48.6, 126.9, 127.4, 128.8, 129.7, 129.8, 133.1, 136.9, 143.4; **Anal.** Calcd for $C_{15}H_{15}BrClNO_2S$ requires C, 46.35; H, 3.89; N, 3.60; found: C, 46.41; H, 3.92; N, 3.57%.

2-Bromo-2-(4-fluorophenyl)-*N*-tosylethanamine (39f)

Yield: 78%; colorless gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 545, 670, 759, 1091, 1160, 1214, 1336, 1418, 1598, 2853, 2927, 3017, 3282; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.41 (s, 3H), 3.54 (d, *J* = 6.1 Hz, 2H), 4.56 (q, *J* = 6.1, 12.3 Hz, 1H), 5.42 (d, *J* = 6.4 Hz, 1H), 6.86-6.96 (m, 2H), 7.06-7.13 (m, 2H), 7.21 (d, *J* = 8.1 Hz, 2H), 7.61 (d, *J* = 8.4 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.5, 36.3, 57.5, 115.3, 115.7, 127.2, 128.4, 128.6, 129.5, 133.6, 137.0, 143.6; **Anal.** Calcd for $C_{15}H_{15}BrFNO_2S$ requires C, 48.40; H, 4.06; N, 3.76; found: C, 48.44; H, 3.99; N, 3.78%.

1-(4-Chloromethylphenyl)-1-bromo-2-(*p*-toluenesulfonamido)ethane (39g)

Yield: 67%; **mp**: 111-112 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 549, 669, 757, 1093, 1161, 1215, 1334, 1419, 1456, 1598, 2854, 2925, 3018, 3284; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.43 (s, 3H), 3.51- 3.62 (m, 2H), 4.55 (s, 2H), 4.83 (t, *J* = 7.2 Hz, 1H), 4.92 (t, *J* = 7.2 Hz, 1H), 7.25-7.40 (m, 6H), 7.72 (d, *J* = 8.4 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.4, 45.3, 49.7, 51.7, 126.8, 127.9, 128.9, 129.7, 136.6, 138.1, 138.8, 143.7; **Anal.** Calcd for $C_{16}H_{17}BrClNO_2S$ requires C, 47.72; H, 4.25; N, 3.48; found: C, 47.69; H, 4.19; N, 3.51%.

(±)-*trans*-1-Phenyl-1-(*p*-toluenesulfonamido)-2-bromopropane (39h)

Yield: 30%; colorless gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 662, 759, 1161, 1215, 1377, 1460, 1598, 2854, 2925, 2954, 3269; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.52-1.55 (d, *J* = 6.5 Hz, 2H), 2.35 (s, 3H), 4.36-4.48 (m, 2H), 5.36-5.40 (d, *J* = 7.8Hz, 1H), 7.07-7.19 (m, 7H), 7.49-7.54 (d, *J* = 8.3 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.3, 22.1, 53.1, 62.7, 127.0, 127.6, 127.7, 127.9, 128.2, 128.4, 129.1, 129.6, 136.5, 137.2, 142.8; **Anal.** Calcd for $C_{16}H_{18}BrNO_2S$ requires C, 52.18; H, 4.93; N, 3.80; found: C, 52.20; H, 4.98; N, 3.77%.

2-Bromo-1,2-diphenyl-*N*-tosylethanamine (39i)

Yield: 61%; colorless gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 662, 710, 1086, 1153, 1340, 1461, 1590, 1593, 1655, 2930, 2985, 3252; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.34 (s, 3H), 4.72-4.80 (m, 1H), 5.21 (dd, *J* = 6.0. 21.7 Hz, 1H), 5.57 (d, *J* = 5.8 Hz, 1H), 6.84-6.90 (m, 2H), 7.01-7.26 (m, 10H), 7.43 (dd, *J* = 3.4 and 8.6 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.4, 58.1, 63.1, 127.0, 127.1, 127.6, 127.7, 127.8, 127.9, 128.0, 128.2, 128.3, 128.4, 128.6, 129.1, 136.4, 137.0, 137.1, 142.9; **Anal.** Calcd for $C_{21}H_{20}BrNO_2S$ requires C, 58.61; H, 4.68; N, 3.25; found: C, 58.64; H, 4.65; N, 3.30%.

1-Bromo-2,3-dihydro-*N*-tosyl-1H-inden-2-amine (39j)

Yield: 80%; **mp**: 136-137 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 667, 752, 767, 1093, 1161, 1215, 1340, 1429, 1598, 3020, 3274; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.47 (s, 3H), 2.74-2.87 (dd, *J* = 16.1 and 10.2 Hz, 1H), 2.93-23.04 (dd, *J* = 6.1, 16.1 Hz, 1H), 3.90-3.99 (m, 1H), 5.13 (d, *J* = 5.5 Hz, 1H), 5.34-5.36 (d, *J* = 10.2 Hz, 1H), 7.19-7.37 (m, 6H), 7.81-7.84 (d, *J* = 8.4 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.5, 36.4, 56.3, 59.5, 125.0, 127.1, 127.6, 129.7, 137.4, 139.4, 140.5, 143.7; **Anal.** Calcd for

$C_{16}H_{16}BrNO_2S$ requires C, 52.47; H, 4.40; N, 3.82; found: C, 52.50; H, 4.42; N, 3.81%.

***N*-(1-bromoundecan-2-yl)-4-methylbenzenesulfonamide (39k)**

Yield: 66%; colorless gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 667, 752, 767, 1093, 1161, 1215, 1340, 1429, 1598, 3020, 3274; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.85-0.92 9 (t, *J* = 6.0 Hz, 3H), 1.15-1.35 (m, 12H), 1.71-1.82 (q, *J* = 7.2 and 14.7 Hz, 2H), 2.44 (s, 3H), 3.08-3.22 (m, 2H), 3.30-3.43 (m, 1H), 3.90-4.02 (m, 1H), 4.85-4.91 (m, 1H), 7.30-7.34 (d, *J* = 8.2, 2H), 7.72-7.76 (d, *J* = 8.1 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.1, 21.4, 22.6, 27.1, 28.8, 29.2, 29.3, 29.5, 31.8, 49.5, 55.1, 127.0, 129.7, 137.1, 143.4; **Anal.** Calcd for $C_{18}H_{30}BrNO_2S$ requires C, 53.46; H, 7.48; N, 3.46; found: C, 53.41; H, 7.52; N, 3.46%.

(±)-*trans*-1-(*p*-Toluenesulfonamido)-2-bromocyclohexane (39l)

Yield: 65%; **mp:** 116-117 ^oC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 661, 813, 1093, 1159, 1321, 1446, 1596, 2862, 2926, 3276; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.19-1.39 (m, 3H), 1.64-1.88 (m, 3H), 2.25-2.34 (m, 2H), 2.44 (s, 3H), 3.09-3.23 (m, 1H), 3.85 (dd, *J* = 4.2 and 9.6 Hz, 1H), 5.08 (d, *J* = 5.5 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.78 (d, *J* = 8.1 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.5, 23.1, 24.8, 32.2, 35.2, 54.6, 58.1, 127.2, 129.4, 137.3, 143.1; **Anal.** Calcd for $C_{13}H_{18}BrNO_2S$ requires C, 46.99; H, 5.46; N, 4.22; found: C, 47.01; H, 5.50; N, 4.29%.

(±)-*trans*-1-(*p*-Toluenesulfonamido)-2-bromocyclooctane (39m)

Yield: 72%; **mp:** 99-98 ^oC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 669, 757, 1091, 1159, 1215, 1328, 1444, 1598, 2860, 2929, 3020, 3280; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.27-1.83 (m, 10H), 1.92-2.34 (m, 4H), 2.45 (s, 3H), 3.38-3.50 (m, 1H), 3.99-4.08 (m, 1H), 4.81 (d, *J* = 4.2 Hz, 1H), 7.31 (d, *J* = 8.1 Hz, 2H), 7.77 (d, *J* = 8.3 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.5, 24.9, 25.3, 25.6, 31.8, 32.0, 59.3, 60.9, 127.5, 129.4, 136.8,

143.2; **Anal.** Calcd for $C_{15}H_{22}BrNO_2S$ requires C, 50.00; H, 6.15; N, 3.89; found: C, 49.98; H, 6.20; N, 3.75%.

2-Bromo-2-cyclohexyl-N-tosylethanamine (39n)

Yield: 63%; colorless gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1080, 1162, 1220, 1321, 1434, 1596, 2858, 2922, 3010, 3275; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.96-1.20 (m, 4H), 1.58-1.78 (m, 5H), 2.44 (s, 3H), 3.12-3.26 (m, 1H), 3.32-3.48 (m, 1H), 3.83-3.92 (m, 1H), 4.69 (d, *J* = 8.8 Hz, 1H), 7.30 (dd, *J* = 3.7 and 8.0 Hz, 2H), 7.74 (dd, *J* = 2.8 and 8.3 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.5, 25.6, 25.8, 25.9, 29.2, 29.6, 30.6, 41.4, 47.3, 62.1, 127.0, 129.6, 129.7, 136.8, 143.4; **Anal.** Calcd for $C_{15}H_{22}BrNO_2S$ requires C, 50.00; H, 6.15; N, 3.89; found: C, 49.98; H, 6.1; N, 3.85%.

(±)-*trans*-Methyl 3-bromo-2-(p-toluenesulfonamido)-3-phenylpropionate (45a):

Yield: 20%; **mp**: 136-137 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 696, 754, 904, 1091, 1159, 1215,1346, 1367, 1454, 1494, 1596, 1730, 2854, 2923, 3280; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.41 (s, 3H), 3.52 (s, 3H), 4.44-4.52 (m, 1H), 5.11 (d, *J* = 7.23 Hz, 1H), 5.27 (d, *J* = 8.4 Hz, 1H), 7.22-7.29 (m, 7H), 7.63 (d, *J* = 9.1 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.3, 51.2, 52.4, 61.6, 126.9, 127.1, 128.1, 128.5, 128.8, 129.4, 136.2, 143.6, 169.3; **Anal.** Calcd for $C_{17}H_{18}BrNO_4S$ requires C, 49.52; H, 4.40; Br, 19.38; N, 3.40%; found: C, 49.42; H, 4.33; Br, 19.24; N, 3.41%.

(±)-*trans*-4-(4-Chlorophenyl)-4-bromo-3-(p-toluenesulfonamido)2-butanone (45c):

Yield: 68%; **mp**: 168-170 °C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 667, 757, 1091, 1159, 1215, 1336, 1492, 1596, 1691, 3020, 3278; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.30 (s, 3H), 4.99-5.03 (d, *J* = 8.0 Hz, 1H), 5.43-5.52 (m, 1H), 5.56-5.71 (d, *J* = 9.7 Hz, 1H), 6.98-7.02 (d, *J* = 8.0 Hz, 2H), 7.12-7.26 (m, 4H), 7.39-7.50 (m, 4H), 7.58-7.66 (m, 1H), 7.85-7.88 (d, *J* = 8.4 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.4, 50.1, 60.1, 126.8,

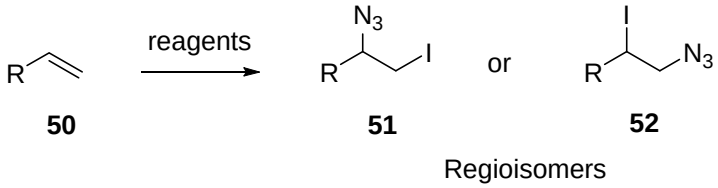
128.4, 128.6, 128.7, 129.0, 129.3, 129.8, 134.2, 134.8, 136.7, 143.4, 196.8; **Anal.** Calcd for $C_{17}H_{17}BrClNO_3S$ requires C, 47.48; H, 3.98; N, 3.25%; found: C, 47.42; H, 3.90; N, 3.21%.

Section II

$NaIO_4$-KI-NaN_3-Mediated Regioselective Azidoiodination of Alkenes

4.2.1 Introduction

The 1,2-functionalization of olefins by the selective addition of two different functional groups in a single step provides access to wide range of functional group manipulation in organic synthesis. Variety of reactions such as aminohydroxylation, halohydration, haloamination, azidohydroxylation, and haloazidation are some of the examples of this class of synthetic transformation. Among these, the vicinal azidoiodination of alkenes in particular is an important organic transformation for simultaneous introduction of iodo and azido functionalities into a carbon skeleton (**Scheme 21**).



Scheme 21: Azidoiodination of olefins

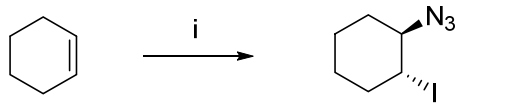
The resulting azidoiodides can be subjected to further synthetic manipulations to achieve a variety of compounds such as vinyl azide,[17] amines,[18] aziridines[19] and tetrazoles.[20] Since the pioneering work of Hassner *et al*.,[21] azidoiodination of alkenes involves the use of iodine azide reagent, which is generated *in situ* from sodium azide and iodine chloride in polar solvents. However, its explosive character is regarded to be a major disadvantage.

4.2.2 Review of literature

Literature survey revealed that there are various methods available for the azidoiodination of alkenes, using a variety of reagents such as I_2/NaN_3/Adogen,[22] $PhI(OAc)_2/Et_4NI/TMSN_3$, $CAN/NaI/NaN_3$, $IPy_2BF_4/TMS\text{-}N_3$ and Oxone/wet $Al_2O_3/KI/NaN_3$ reagent combination. Some of the recent developments on this reaction are discussed in the following section.

Hassner's approach (1965)[23]

Hassner *et al*. have reported *in situ* preparation of $I\text{-}N_3$ from reaction of I-Cl with NaN_3 in polar solvent followed by the addition of this onto alkenes **54f** to give the corresponding azidoiodides **55f** (**Scheme 22**).

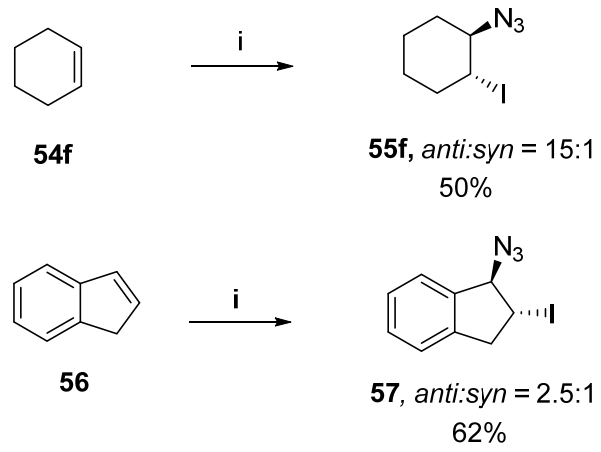


54f **55f**, yield = 76%

Scheme 22: (i) ICl, NaN_3, CH_3CN, 25 °C.

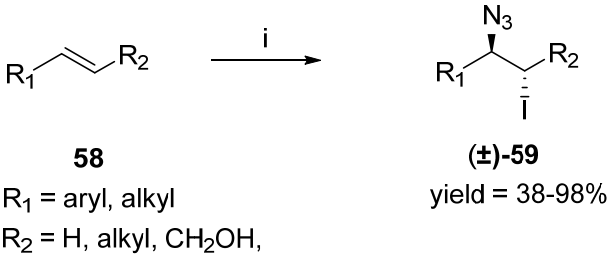
Krisching's approach (1999)[24, 25]

Krisching *et al*. have developed a new reagent system consisting of reagents such as $PhI(OAc)_2$, tetraalkylammonium halide and $TMSN_3$. This reagent system is equivalent to $I\text{-}N_3$ system. The treatment of these reagents with indene **56** and cyclohexene **54f** gave the corresponding azidoiodides 62% and 50% yields respectively (**Scheme 23**).



Scheme 23: (i) $PhI(OAc)_2$, $TMSN_3$, Et_4NI, CH_2Cl_2, 25 °C .

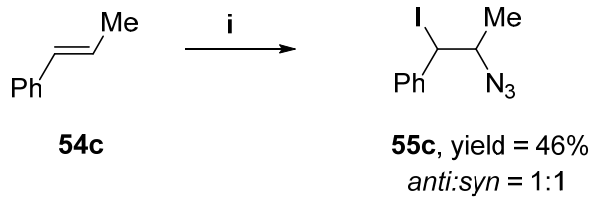
The same authors have also developed a new polymer-supported azide source, which was employed for the azidoiodination of alkenes **58** to give the corresponding vicinal azidoiodides **59** in 38-98% yield (**Scheme 24**).



Scheme 24: (i) polystyrene-NMe_3I, $PhI(OAc)_2$, $TMSN_3$, CH_2Cl_2, 25 °C.

Nair's approach (2000)[26]

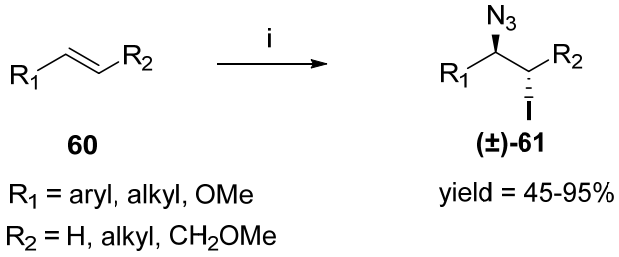
In this approach, NaN_3/NaI/CAN (3 equiv) reagent combination was employed for the azidoiodination of alkenes. The addition followed *anti*-Markovnikov fashion (**Scheme 25**).



Scheme 25: (i) CAN (2.1 equiv), NaN_3, NaI, MeOH, 0 °C.

Barluenga's approach (2001)[27]

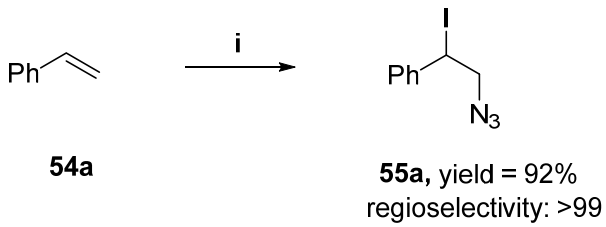
Barluenga *et al*. have used IPy_2BF_4 and Me_3SiN_3 reagent combination for the azidoiodination of alkenes **60** in the presence of $BF_3.OEt_2$ to furnish the corresponding azidoiodides **61** in 45-95% yield (**Scheme 26**).



Scheme 26: (i) IPy_2BF_4, $TMSN_3$, $BF_3.OEt_2$, CH_2Cl_2, 0 °C, 3h.

Marcolullio's approach (2002)[28]

In this approach, NaN_3/KI/Oxone® supported on wet alumina was used for the azidoiodination of alkenes **54a**. Here again the addition followed an *anti*-Markovnikov fashion with excellent yields (**Scheme 27**).



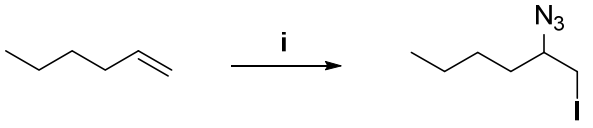
54a

55a, yield = 92%
regioselectivity: >99

Scheme 27: (i) Oxone-wet (5 equiv), Al_2O_3, KI (5 equiv), NaN_3, $CHCl_3$, 25 °C.

Terent'ev's approach (2008)[29]

Terent'ev *et al*. have reported a new synthesis of vicinal azidoiodides in 62-77% yields by the reaction of sodium azide and iodine with unsaturated olefinic compounds in aqueous methanol solvent system (**Scheme 28**).



54h

55h, yield = 74%

Scheme 28: (i) I_2, NaN_3, $MeOH/H_2O$, 25 °C, 62-77%.

4.2.3 Present Work

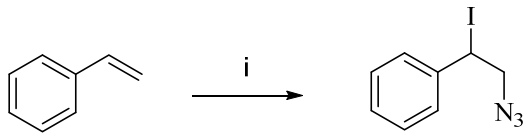
4.2.3.1 Objective

From the above discussion, it is clear that most of the reported methods suffer from certain drawbacks such as use of expensive reagents and large excess of oxidants or halide sources. Hence, a practical method that involves less toxic yet readily available reagents is of paramount importance. This section describes one such process, in which an excellent regiospecific azidoiodination of alkenes takes place using $NaIO_4$ as the

stoichiometric oxidizing agent and NaN_3 and KI as the azide and iodine sources respectively, in acetic acid as solvent.

4.2.4 Results and Discussion

In connection with our interest on $NaIO_4$-mediated oxidative functionalization of alkenes,[30] we thought of providing a cheaper method of azidoiodination of alkenes using $NaIO_4$-KI-NaN_3 combination. We realized that $NaIO_4$-KI-NaN_3 combination was found to be an excellent system for the regiospecific azidoiodination of styrene in acetic acid as solvent. This prompted us to explore the effectiveness of the $NaIO_4$-KI-NaN_3 combination in the azidoiodination of alkenes. Thus, when styrene **54a** was treated initially with $NaIO_4$, KI and NaN_3 (all equimolar) in acetic acid at 25 °C, the corresponding 2-azido-1-iodo-ethylbenzene **55a** was obtained in 33% yield. However, this yield could be increased to 95% when stoichiometry of NaN_3 was altered to increase to 3 equiv (**Scheme 29**). This prompted us to explore the effectiveness of the $NaIO_4$-KI-NaN_3 system in the 1,2- azidoiodination of several alkenes. This new azidoiodination procedure was indeed found to be quite general for a variety of olefins; the results of this study are summarized in **Table 4**.

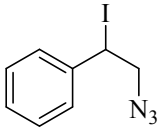
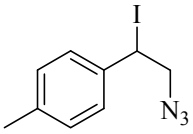
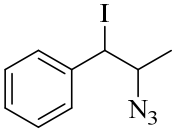
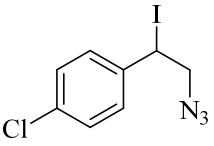


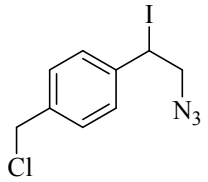
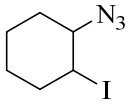
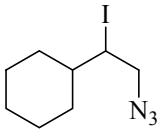
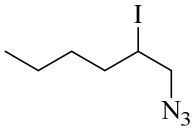
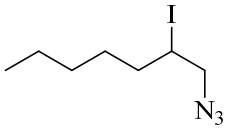
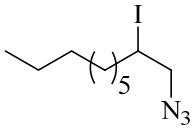
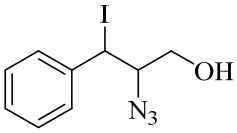
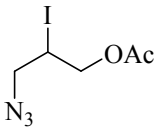
54a **55a,** 95%

Scheme 29: (i)styrene (1 equiv), KI (1 equiv), $NaIO_4$ (1 equiv), NaN_3 (3 equiv), glacial AcOH, 25 °C, 2 h.

As can be seen from **Table 4**, a variety of alkenes **54a-l** (aliphatic, styrenic, allylic and disubstituted) underwent azidoiodinations to give the corresponding β-iodoazides **55a-l** in excellent yields. It is interesting to note that the regiochemistry of the addition, for all the cases examined, proceeded in an *anti*-Markovnikov fashion, indicating a possible radical pathway. Internal olefins such as β-methylstyrene, cyclohexene and cinnamyl alcohol have proceeded to give products in excellent yields with diastereoselectivities reaching up to 1:4 (**55c**, **55f** and **55k**) as confirmed by their ^{1}H NMR spectra. Terminal functionalized olefin such as allyl acetate also underwent regiospecific azidoiodination in 92% yield. However, no reaction took place in the case of conjugated alkenes with electron-withdrawing groups, which may be a limitation of this method.

Table 4: $NaIO_4$-mediated azidoiodination of alkenes.[a]

entry	Alkenes (54a-l)	Products (55a-l)	Yield (%)[b]
a	styrene		95
b	4-methylstyrene		70
c	β-methylstyrene		95[c]
d	4-chlorostyrene		92

e	4-chloromethylstyrene		85
f	cyclohexene		93[d]
g	vinylcyclohexane		88
h	1-hexene		93
i	1-heptene		94
j	1-decene		90
k	*trans*-cinnamyl alcohol		90[c]
l	allyl acetate		92

[a] Reaction conditions: alkene (5 mmol), KI (5 mmol), $NaIO_4$ (5 mmol), NaN_3 (15 mmol), glacial AcOH (15 mL), 25 °C, 2 h; [b]isolated yield. [c]*syn*:*anti* = 1:1; [d] *syn*:*anti* = 1:4.

The formation of azidoiodides **55a-l** was confirmed by ^1H and ^{13}C NMR spectroscopy. For example, the ^1H NMR spectrum of 2-azido-1-iodoethylbenzene (**55a**) showed a doublet at δ 3.92 and a triplet at δ 5.12 due to -C**H**$_2$N$_3$ and -C**H**I protons respectively. Its

^{13}C NMR spectrum showed two typical carbon signals at δ 26.8 and 58.5 for carbons attached to iodo and azido groups respectively (**Fig. 6**).

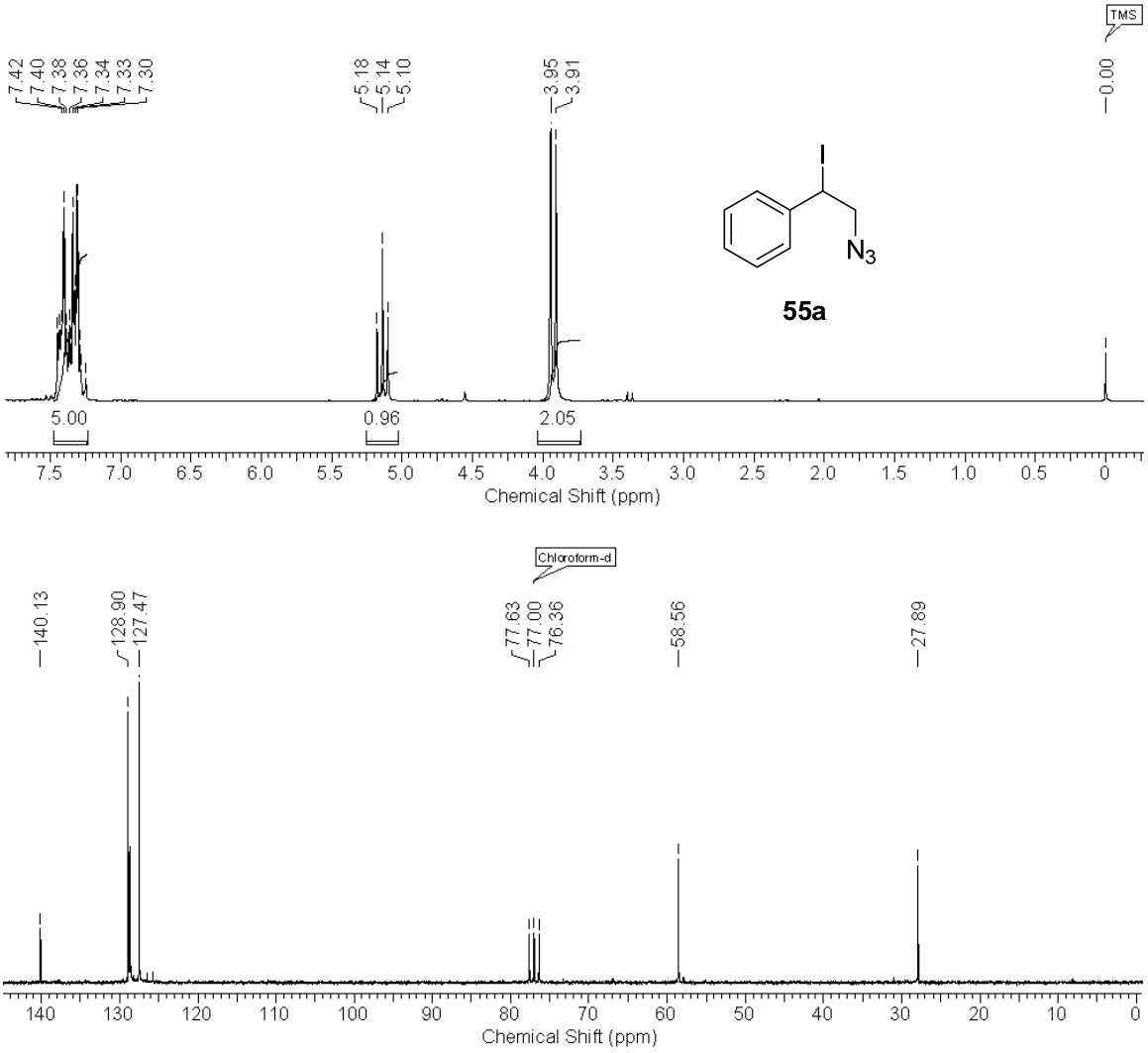


Fig. 6: ^{1}H and ^{13}C NMR spectra of azidoiodide **55a**

Another example: The ^{1}H NMR spectrum of 3-azido-2-iodopropylacetate (**55l**) showed multiplets at δ 3.78 (m, 2H) and 4.20 (m, 1H) due to methylene and methine protons (-C**H**$_2$N$_3$ and –C**H**I) respectively. Its ^{13}C NMR spectrum showed two typical carbon

signals at δ 23.8 and 55.3 for carbons attached to iodo and azido groups respectively (**Fig. 7**).

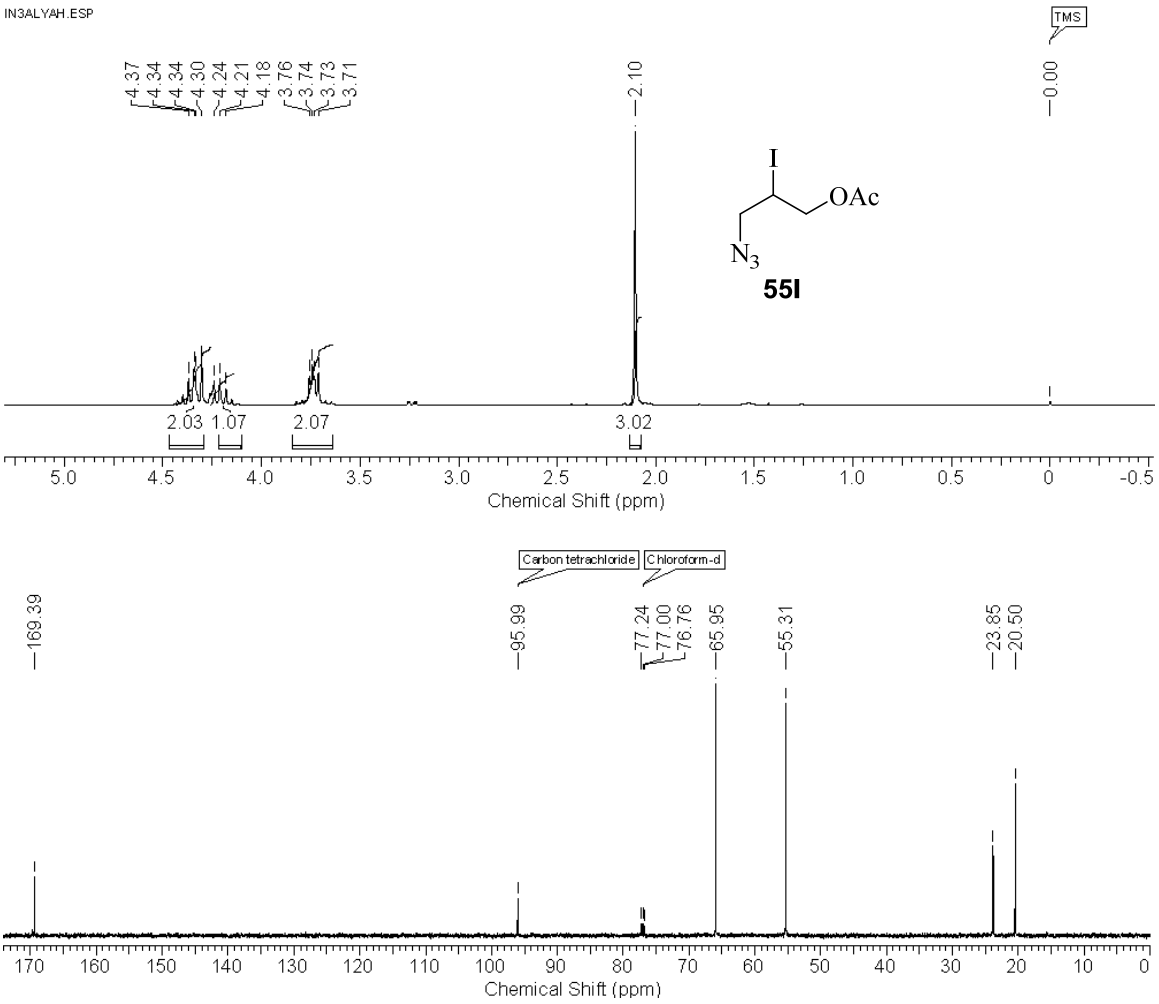
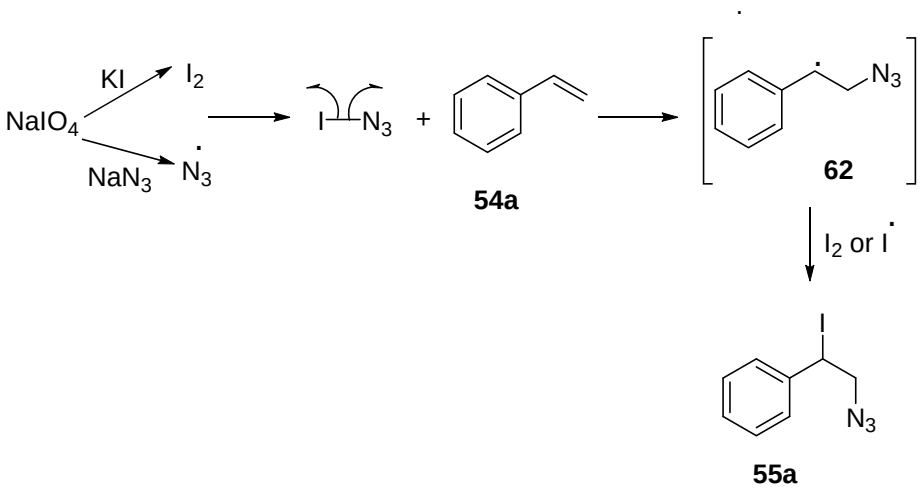


Fig. 7: ^{1}H and ^{13}C NMR spectra of azidoiodide **55l**

4.2.4.1 Mechanism

Mechanistically, we have proved that $NaIO_4$ oxidizes both KI and NaN_3 simultaneously to liberate I_2[31] and an azide radical[32] respectively; combination of which probably results in the formation of IN_3.[33] Homolysis of IN_3[34] provides an azide radical, which then adds

onto alkenes to produce a more stable alkyl radical species **62**, thus controlling the regiochemistry of the process. The combination of alkyl radical either I_2 or iodine radical results in the formation of β-iodoazides **55a-l** (**Scheme 30**).



Scheme 30: Proposed radical pathway for the azidoiodination of alkenes

4.2.5 Conclusion

In conclusion, we have developed a simple procedure with $NaIO_4$-KI-NaN_3 as a new combination for the 1, 2- azidoiodination of alkenes that provides a mild, efficient entry to vicinal azidoiodoalkanes in high yields (70-95%) under ambient conditions. The azidoiodination reaction proceeds to give β-iodoazides **55a-l** in a regiospecific manner.

4.2.6 Experimental Section

General experimental procedure for azidoiodination of alkenes:

To a suspension of NaN_3 (0.975 g, 15 mmol) and KI (0.830 g, 5 mmol) in AcOH (20 mL) at 25 °C was added $NaIO_4$ (1.069 g, 5 mmol) and the reaction mixture was stirred for 5

min. when a dark brown color was observed. This was followed by the addition of alkenes **54a-l** (5 mmol) and the entire reaction mixture was stirred at the same temperature for 2 h. After the reaction was complete as monitored by TLC, it was poured into water (100 mL) and extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were washed with a saturated solution of $NaHCO_3$ (50 mL), washed with aq. $Na_2S_2O_3$ (5%, 50 mL), dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give the crude product, which was then purified by column chromatography (packed with silica gel 60-120 mesh) using pet. ether as eluents to afford the pure products **55a-l**.

2-Azido-1-iodoethylbenzene (55a)

Yield: 95%; pale yellow oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 693, 1257, 1446, 1605, 2100, 2921, 3027; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.94 (d, *J* = 7.7 Hz, 2H), 5.14 (t, *J* = 7.7 Hz, 1H), 7.30-7.45 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 27.8, 58.5, 127.4, 128.7, 128.9, 140.1; **Anal.** Calcd for $C_8H_8IN_3$ requires C, 35.19; H, 2.95; N, 15.39; found: C, 35.10; H, 2.90; N, 15.44%.

2-Azido-1-iodoethyl-4-methylbenzene (55b)

Yield: 70%; pale yellow oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1257, 1446, 2101, 2920, 3027; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.30 (s, 3H), 3.87 (d, *J* = 7.7 Hz, 2H), 5.09 (t, *J* = 7.7 Hz, 1H), 7.10 (d, *J* = 7.8 Hz, 2H), 7.27 (d, *J* = 7.8 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.2, 28.1, 58.6, 127.3, 129.5, 137.2, 138.5; **Anal**. Calcd for $C_9H_{10}IN_3$ requires C, 37.65; H, 3.51; N, 14.64; found: C, 37.70; H, 3.48; N, 14.60%.

2-Azido-1-iodopropylbenzene (55c)

Yield: 95%; pale yellow oil; mixture of *anti:syn* (1:1); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1258, 1605, 1458, 2101, 2990; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.23 (d, *J* = 6.4 Hz, 3H), 1.52 (d, *J* = 6.4 Hz, 3H), 3.74-3.99 (m, 2H), 4.91 (d, *J* = 7.0 Hz, 1H), 4.96 (d, *J* = 8.0 Hz, 1H), 7.26-7.40 (m, 10H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.2, 28.1, 58.6, 127.3, 129.5, 137.2, 138.5; **Anal**. Cald for $C_9H_{10}IN_3$ requires C, 37.65; H, 3.51; N, 14.64; found: C, 37.70; H, 3.48; N, 14.62%.

2-Azido-1-iodoethyl-4-chlorobenzene (55d)

Yield: 92%; pale yellow oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 693, 1257, 1489, 1589, 2100; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.88-3.94 (m, 2H), 5.10 (dd, *J* = 8.2 and 7.0 Hz, 1H), 7.30-7.40 (m, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 26.0, 58.5, 128.8, 129.1, 134.4, 138.7; **Anal.** Calcd for $C_8H_7ClIN_3$ requires C, 31.25; H, 2.29; N, 13.66; found: C, 31.30; H, 2.25; N, 13.68%.

2-Azido-1-iodoethyl-4-chloromethylbenzene (55e)

Yield: 85%; pale yellow oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1257, 1489, 2101, 2920, 3027; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.92 (d, *J* = 6.9 Hz, 2H), 4.55 (s, 2H), 5.12 (t, *J* = 7.2 Hz, 1H), 7.32 -7.43 (m, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 26.8, 45.3, 58.5, 127.9, 129.0, 137.9, 140.4; **Anal.** Calcd for $C_9H_9ClIN_3$ requires C, 33.62; H, 2.82; N, 13.07; found: C, 33.55; H, 2.85; N, 13.01%.

1-Azido-2-iodocyclohexane (55f)

Yield; 93%; pale yellow oil; mixture of *anti:syn* (4:1); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 669, 769, 923, 1217, 1257, 1448, 2100, 2860, 2939; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.31-1.57 (m,

4H), 1.99-2.50 (m, 4H), 3.46-3.58 (m, 1H), 3.90-4.03 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 23.7, 26.9, 31.8, 33.2, 38.3, 67.1; **Anal**. Calcd for $C_6H_{10}IN_3$ requires C, 28.70; H, 4.01, N, 16.74; found: C, 28.64; H, 4.10, N, 16.78%.

2-Azido-1-iodoethylcyclohexane (55g)

Yield: 88%; pale yellow oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 669, 769, 923, 1217, 1257, 1448, 2102, 2860, 2939; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.02-1.45 (m, 6H), 1.63-1.93 (m, 5H), 3.63-3.82 (m, 2H), 4.07-4.15 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 25.6, 25.8, 26.0, 30.5, 32.8, 41.0, 42.1, 56.5; **Anal**. Calcd for $C_6H_{14}IN_3$ requires C, 34.42; H, 5.06, N, 15.05; found: C, 34.50; H, 5.01, N, 14.98%.

1-Azido-2-iodohexane (55h)

Yield: 93%; pale yellow oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 667, 769, 925, 1258, 1446, 2103, 2939; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.9 (t, J = 6.9 Hz, 3H), 1.27-1.52 (m, 4H), 1.73 1.84 (m, 2H), 3.60-3.83 (m, 2H), 4.04-4.17 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.8, 22.3, 28.4, 31.5, 37.1, 58.9; **Anal.** Calcd for: $C_6H_{12}IN_3$ requires C, 28.47; H, 4.78, N, 16.60; found: C, 28.50; H, 4.69, N, 16.65%.

1-Azido-2-iodoheptane (55i)

Yield: 94%; pale yellow oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 669, 769, 923, 1257, 1448, 2102, 2939; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.9 (t, J = 6.6 Hz, 3H), 1.27-1.50 (m, 6H), 1.69 1.84 (m, 2H), 3.57-3.80 (m, 2H), 4.04-4.17 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.9, 22.3, 28.8, 30.7, 32.2, 37.0, 58.9; **Anal.** Calcd for: $C_7H_{14}IN_3$ requires C, 31.48; H, 5.28, N, 15.73; found: C, 31.40; H, 5.33, N, 15.65%.

1-Azido-2-iododacane (55j)

Yield: 90%; pale yellow oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 668, 770, 923, 1257, 1448, 2103, 2939; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.9 (t, *J* = 6.1 Hz, 3H), 1.28-1.51 (m, 12H), 1.72 1.82 (m, 2H), 3.59-3.80 (m, 2H), 4.01-4.11 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.1, 22.6, 25.8, 28.7, 29.2, 29.3, 31.8, 32.0, 37.1, 59.0; **Anal.** Calcd for $C_{10}H_{20}IN_3$ requires C, 38.85; H, 6.52, N, 13.59; found: C, 38.75; H, 6.60, N, 13.65 %.

2-Azido-3-iodo-3-phenylpropan-1-ol (55k)

Yield: 90%; pale yellow oil; mixture of *anti:syn* (1:1); **IR** ($CHCl_3$, cm^{-1}): υ_{max} 757, 1153, 1217, 1258, 1458, 2096, 2927, 3004, 3330; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.36 (br s, 2H), 3.40-3.49 (m, 1H), 3.59-3.66 (m, 1H), 3.75-3.94 (m, 2H), 4.02-4.17 (m, 2H), 5.13 (d, *J* = 8.5 Hz, 1H), 5.16 (d, *J* = 9.2 Hz, 1H), 7.28-7.48 (m, 10H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 28.9, 32.1, 63.1, 64.8, 68.6, 70.0, 127.8, 128.2, 128.6, 128.9, 129.0, 140.1, 140.2; **Anal.** Calcd for $C_9H_{10}ION_3$ requires C, 35.66; H, 3.33; N, 13.86; found: C, 35.70; H, 3.30; N, 13.85%.

3-Azido-2-iodopropylacetate (55l)

Yield: 92%; pale yellow oil; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 669, 769, 923, 1257, 1448, 1735, 2101, 2940; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.10 (s, 3H), 3.74-3.82 (m, 2H), 4.15-4.24 (m, 1H), 4.30-4.37 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 20.5, 23.8, 55.3, 65.9, 169.3; **Anal.** Calcd for $C_5H_8IN_3O_2$ requires C, 22.32; H, 3.0; N, 15.62; found: C, 22.38; H, 2.98; N, 15.73%.

Section III

$NaIO_4$/LiBr-Mediated Aziridination of Olefins using Chloramine-T

4.3.1 Introduction

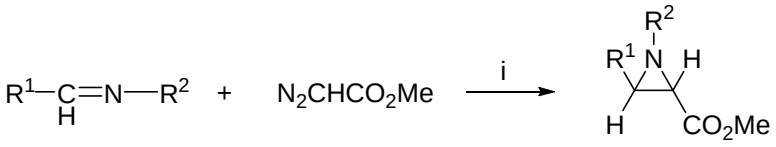
Aziridines and azirines can be regarded as representatives of the first and most simple of all heterocyclic systems, which are characterized by the presence of two carbon atoms and one nitrogen atom in a three-membered ring. Interest in these nitrogen containing small rings is due to the general influence of ring strain upon chemical reactivity. The stabilities and overall profiles of chemical reactivity of these heterocycles are attributable not only to the combined effects of bond shortening and angle compression but also to the presence of the electron rich nitrogen atom.[35] The chemistry of aziridines has been a very active area of research. Synthetic approaches to the aziridine ring, modifications of functionalized aziridines and the reactions of aziridines have received particular attention The aziridine ring is a versatile building block for organic synthesis, not only because the ring opening of aziridines provides a convenient entry to the stereoselective preparation of functionalized amino compounds but also because the exocyclic *N*-substituent controls the properties and reactivity of the three membered ring. Many biologically active compounds such as amino acids, β-lactam antibiotics and alkaloids have been derived from aziridines.[36] Aziridines with a strained ring are of paramount importance in organic synthesis since they are valuable precursors of amino sugars, alkaloids, substituted α–amino acids[37] or present in natural products such as mitomycins[38] and azinomycins[39] that exhibit potent biological activity.

4.3.2 Review of Literature

Literature search revealed that there are various catalytic as well as non-catalytic approaches available for the synthesis of aziridines.

Sudalai's approach (1997)[40]

Sudalai *et al*. have reported a heterogeneous catalytic method for the preparation of *trans*-aziridines **65** from imines **63** and methyl diazoacetate **64** using Rh^{III} and Mn^{III}-exchanged montmorillonite K10 clays as catalysts (**Scheme 31**).



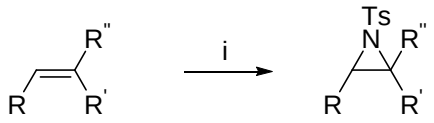
63 **64** **65**

yield = 90%

Scheme 31: (i) Rh-clay (10% m/m), benzene, reflux.

Sharpless's approach (1998)[41]

Aziridination of olefins and allylic alcohols **66** by chloramine-T or N-chloramine-T salt of *tert*-butylsulfonamide was carried out using PTAB (phenyltrimethylammonium tribromide, $PhNMe_3^+ Br_3^-$) as catalyst (**Scheme 32**).



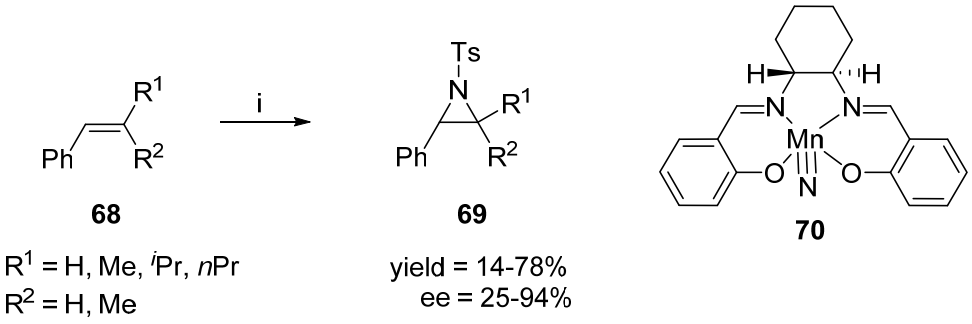
66 **67**

R''= alkyl or CH_2OH yield = 30-94%

Scheme 32: (i) PTAB (10 mol%), anhydrous Chloramine-T, or *tert*-butylsulfonamide, CH_3CN, 25 ^oC.

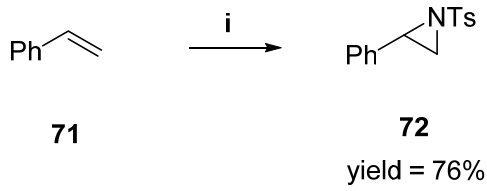
Komatsu's approach (1998)[42]

Komastu *et al.*[42a] have developed new catalytic asymmetric method for aziridination of styrenes **68** using chiral nitridomanganese complex **70** to afford *N*-tosylaziridines in good to excellent ee. Additive like Ts_2O (*p*-toluenesulfonic anhydride) was found to be effective for the activation of the complex **70** (**Scheme 33**).



Scheme 33: (i) cat. **70** (0.5 mmol), pyridine, Ts_2O, pyridine *N*-oxide, CH_2Cl_2, 0 °C, 3 h.

Komatsu *et al.*[42b] have also reported a simple and efficient method for the aziridination of various alkenes **71** utilizing Chloramine-T and a catalytic amount of iodine. The aziridination of both conjugated alkenes with an aryl group and non-conjugated compounds proceeded with good yields, by altering the solvent or the amount of iodine.

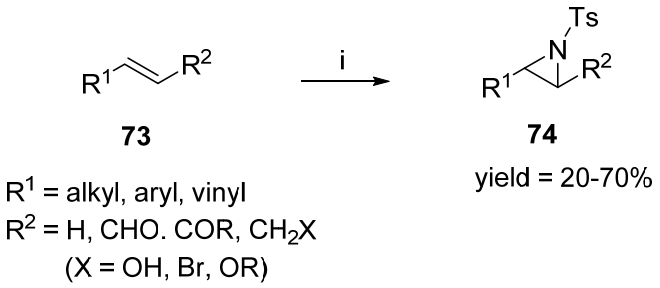


Scheme 34: (i) Chloramine-T, I_2 (10 mol%), MS 5A°, CH_3CN, 25 °C, 24 h.

It was also found an electron-releasing p-substituent on styrene accelerated the aziridination of the substituted styrene derivatives (**Scheme 34**).

Sudalai's approach (1999)[43]

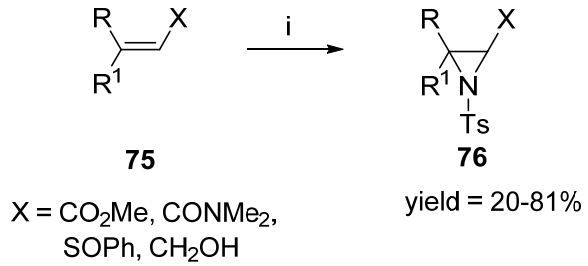
In this approach, pyridinium hydrobromide perbromide ($Py.HBr_3$) catalyzes effectively the aziridination of electron-deficient as well as electron-rich olefins **73** using Chloramine-T (*N*-chloro-*N*-sodio-*p*-toluenesulfonamide) as a nitrogen source to afford the corresponding aziridines **74** in moderate to good yields (**Scheme 35**).



Scheme 35: (i) $Py.HBr_3$ (10 mol %), anhydrous Chloramine-T, CH_3CN, 25 ^oC, 12 h.

Antunes's approach (2001)[44]

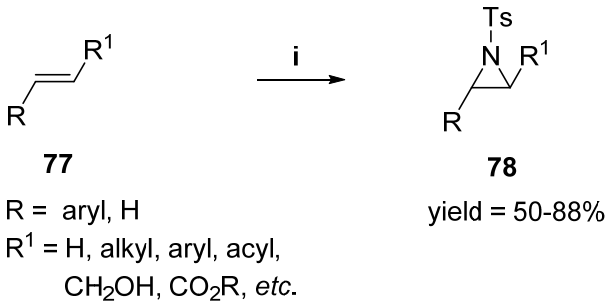
Antunes *et al.* have developed a Pd(II)-promoted reaction of a variety of olefins **75** and bromamine T, as the nitrogen atom transfer reagent, provided *N*-tosyl-2-substituted aziridines **75** under mild condition (**Scheme 36**).



Scheme 36: (i) $PdCl_2$ (20 mol%), Bromamine-T (1.2 equiv), CH_3CN, 25 ^oC.

Sudalai's approach (2003)[45]

In yet another approach, these authors demonstrated that *N*-bromoamides is a versatile catalyst for the aziridination of electron-deficient as well as electron-rich olefins **77** using chloramine-T (*N*-chloro-*N*-sodio-*p*-toluenesulfonamide) as a nitrogen source under ambient conditions to afford the corresponding aziridines **78** in good to excellent yields (**Scheme 37**).

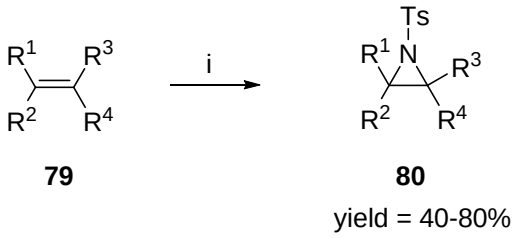


Scheme 37: (i) NBS or *N*-bromoacetamide (20 mol%), anhydrous chloramine-T (1 equiv), CH_3CN, 25 °C.

Sain's approach (2003)[46]

Sain *et al.* for the first time reported that use of *N*-iodo-*N*-potassio-p-toluenesulphononamide (TsN.KI) as a convenient nitrene precursor for Cu-catalyzed

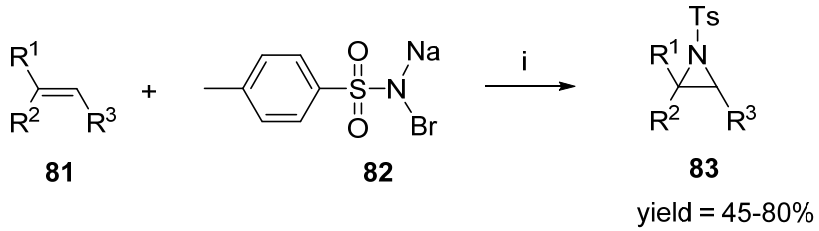
aziridination of alkenes. The simple and cost effective preparation of *N*-iodo-*N*-potassio-*p*-toluenesulphononamide (TsN.KI) and better yields of aziridines **80** as compared to those obtained using chloramine-T and bromamine-T make this procedure useful and attractive for aziridination of variety of alkenes (**Scheme 38**).



Scheme 38: (i) TsN.KI, CH_3CN, MS 3A°, Cu-catalyst (5 mol %), 25 °C.

Zhang's approach (2004)[47]

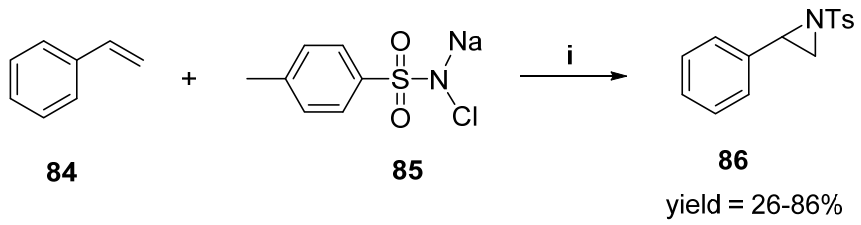
Zang *et al*. have reported that a new Fe(TPP)Cl/bromamine-T catalytic aziridination system can be operated under mild and practical conditions with alkenes **81** as limiting reagents. The catalytic reaction is general and suitable for a wide range of alkene substrates, forming the desired aziridines **83** in good yields, although the stereospecificity is only moderate to low for 1,2-disubstituted olefins (**Scheme 39**). It is suitable for aromatic, aliphatic, cyclic and acyclic alkenes as well as α,β-unsaturated esters.



Scheme 39: (i) [Fe(Por)Cl] (10 mol%), CH_3CN, 25 °C.

Yang's approach (2005)[48]

Yang *et al.* have reported that tetrabutylammonium iodide was found to be a mild and efficient catalyst for aziridinaton of olefins **84** with chloramines-T **85** under environment benign conditions (**Scheme 40**).



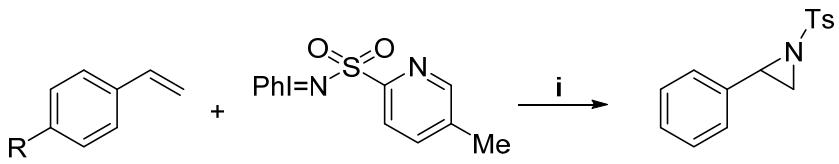
84 **85** **86**

yield = 26-86%

Scheme 40: (i) tetrabutylammonium iodide (5 mol%), H_2O, 25 ^oC, 48 h.

Bolm's approach (2008)[49]

Bolm *et al.* have developed a catalytic system for the aziridination of olefins **84** using ligand-modified $Fe(OTf)_2$ as the catalyst and a preformed iminoiodinane with a pyridine backbone **87** as the nitrene source. Remarkable features are the substrate-to-iminoiodinane ratio of 1:1 and the pronounced additive effect (**Scheme 41**).



84

R = Me, Cl, NO_2, CF_3, OAc

87 **86**

yield = 36-95%

Scheme 41: (i) $Fe(OTf)_2$ (5 mol%), ligand **87** (5 mol%), emim BTA, CH_3CN, 4 A^o MS, 85 ^oC.

4.3.3 Present Work

4.3.3.1 Objective

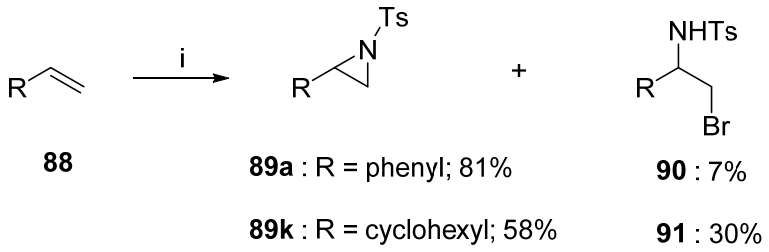
As can be seen a variety of catalytic as well as non-catalytic routes have been reported for the direct aziridination of alkenes. Recent studies have proven the use of several halogenated compounds in the aziridination of olefins with chloramine-T as the nitrogen source. However, these methods suffer from certain drawbacks: (i) the use of heavy transition metals as catalysts, (ii) low yields possibly due to competing C-H abstraction and insertion processes, (iii) the expense and inconvenience of PhI=NTs as a nitrene source and (iv) formation of significant amounts of allylic amination products in the case of cyclohexene.

During the course of our study on $NaIO_4$-mediated oxidative transformations of alkenes, we have reported the regiospecific halohydroxylation[50] and iodoazidation[51] of olefins in the presence of water or NaN_3, respectively. This prompted us to explore the possibility of employing chloramine-T[52] as the nitrogen nucleophile in the 1,2-aminobromination of alkenes mediated by $NaIO_4$-LiBr combination. In this section, we describe a novel milder method that involves a reaction of $NaIO_4$/LiBr/H^+/chloramine-T combination with olefins to produce aziridines **89** in good yields (**Scheme 42**).

4.3.4 Results and Discussion

Using styrene as a test substrate, the reaction conditions were optimized to determine the optimal condition for aziridination (**Table 5**). Thus, when styrene was treated with $NaIO_4$, LiBr and chloramine-T (all 1 equiv) in CH_3CN at 25 ^oC, the corresponding *N*-tosylaziridine (**89a**) was obtained in 20% yield; however, the yield could be significantly improved to 65% when 2 equiv of chloramine-T was used. Interestingly, lowering the

molar ratio of $NaIO_4$ (30 mol%) resulted in a dramatic improvement in yield of **89a** (81%) along with the formation of **90** as a minor product. However, further lowering the concentration of either H_2SO_4 or LiBr had a deleterious effect on the yield (entries 4 and 7). In general, higher chloramine-T concentration (2 equiv) gave better yields.



Scheme 42: (i) $NaIO_4$ (30 mol%); olefin : LiBr:chloramine-T = 1:1: 2 (equiv), conc. H_2SO_4 (30 mol%), CH_3CN, 25 ^oC, 12 h.

After several experimentation, it was finally found that a combination of $NaIO_4$ (30 mol%); olefin : LiBr : chloramine-T (1:1:2 equiv) and conc. H_2SO_4 (30 mol%), in CH_3CN, 25 ^oC, 12 h turned out to be the best reaction condition in achieving a good conversion of alkenes with excellent product selectivity. The reaction mixture became homogeneous as it proceeded. In the absence of either $NaIO_4$ or LiBr, no reaction occurred; also reaction failed when other amine sources such as *p*-$TsNH_2$ and *p*-$TsNCl_2$ were used. A brief comparison of solvents demonstrated that CH_3CN was the most suitable solvent for aziridination as other solvents like CH_2Cl_2, $CHCl_3$, THF and Et_2O were found to be ineffective (**Table 5**).

Table 5: $NaIO_4$-mediated aziridination of styrene with chloramine-T and LiBr[a]

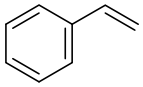
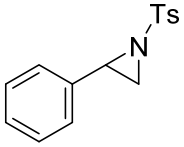
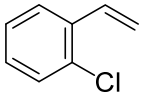
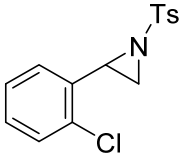
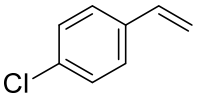
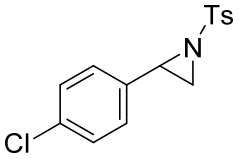
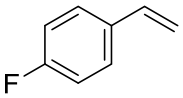
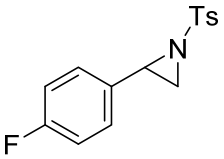
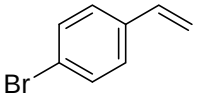
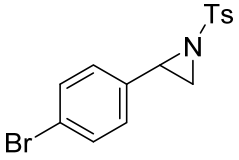
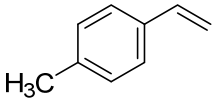
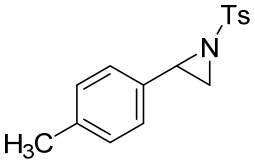
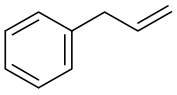
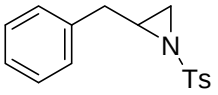
entry	$NaIO_4$ (equiv)	LiBr (equiv)	chloramine-T [b] (equiv)	conc. H_2SO_4 (mol%)	yield **89** (%)[c]
1	1	1	1.1	30	20
2	1	1	2	30	65
3	0.3	1	1.1	30	40
4	0.3	1	1.1	10	25
5	0.3	1	2	30	81[d]
6	0.5	1	2	30	62
7	1	0.3	2	30	35

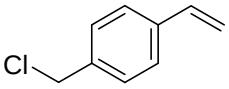
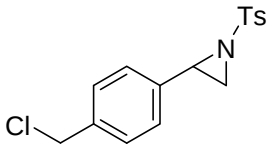
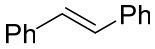
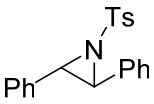
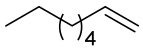
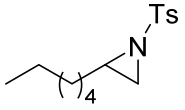
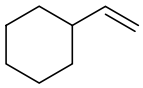
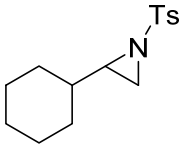
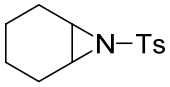
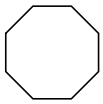
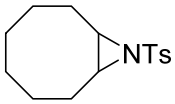
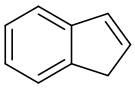
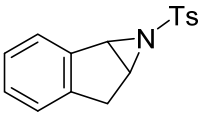
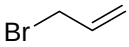
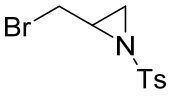
Reaction conditions: [a]experiments were conducted with styrene (1 equiv as substrate) in dry CH_3CN as solvent; temp = 25 °C; time = 12 h; [b]anhydrous chloramine-T was used;[14] [c]isolated yield after column chromatographic purification; [d]7% of 1-phenyl-1-(*p*-toluenesulfonamido)-2-bromoethane **90** was isolated.

Encouraged by these results, substrate scope of $NaIO_4$-mediated aziridination was next examined using the conditions optimized for the aziridination of styrene. As can be seen from **Table 6**, a wide array of aromatic, cyclic and acyclic olefins afforded the corresponding aziridines, **89a-o** in good isolated yields.[52] With styrene derivatives, the reaction proceeded well giving aziridines **89a-i** in moderate to good yields. The better results, however, were achieved with allylbenzene (80%) and unsubstituted styrene (81%). Monosubstituted terminal olefins, one of the most challenging substrates, such as 1-octene produced a reasonably good yield (60%) of the corresponding *N*-tosyl aziridine. Allyl bromide also reacted very well (60%) under the reaction conditions without allylic amination. Notably, cyclic alkenes were also transformed to the corresponding aziridines **89l-m** in moderate yields. In contrast, electron-deficient olefins such as α,β- unsaturated esters and ketones exhibited only low reactivity and yielded their aziridine derivatives in

only 10-20% yield. No byproduct other than *p*-tosamide was detected by TLC or NMR in all the substrates examined.

Table 6: Scope of the aziridination reaction mediated by $NaIO_4$-LiBr-chloramine-T combination[a]

entry	Olefins **(88)**	Product[b] **(89)**	yield[c] (%)	m.p. (°C)
a			81	92-94
b			79	gum
c			77	115-116
d			75	136-138
e			72	127-129
f			40	130-131
g			80	gum

h			65	101-103
i			64	140-142
j			60	gum
k			58[d]	94-95
l			60	55-57
m			48	122-123
n			52	164-166
o			60	75-78

Reaction conditions: [a]alkenes (3 mmol), LiBr (3 mmol), chloramine-T (6 mmol), $NaIO_4$ (30 mol%), H_2SO_4 (30 mol%), 25 ^oC, 12 h; [b]products were characterized by m.p., IR, ^1H and ^{13}C NMR and elemental analysis; [c]Isolated yield after chromatographic purification; [d]30% of aminobrominated product (**91**) was formed.

The formation of aziridines **89a-o** was confirmed by ^{1}H and ^{13}C NMR spectroscopy. For example, The ^{1}H NMR spectrum of compound **89c** showed two doublets at δ 2.32 (d, J = 4.4 Hz, 1H) and 2.97 (d, J = 7.0 Hz, 1H) corresponding to two ring (methylene) protons and a singlet observed at δ 2.45 corresponding to methyl of *N*-tosyl group. Further it has dispyed a signal at δ 3.76 (dd, J = 4.4 and 7.2 Hz, 1H) for benzylic protons. Its ^{13}C NMR spectrum showed two typical carbon signals at δ 35.9 and 40.1 due to homobenzylic and benzylic carbons respectively (**Fig. 8**).

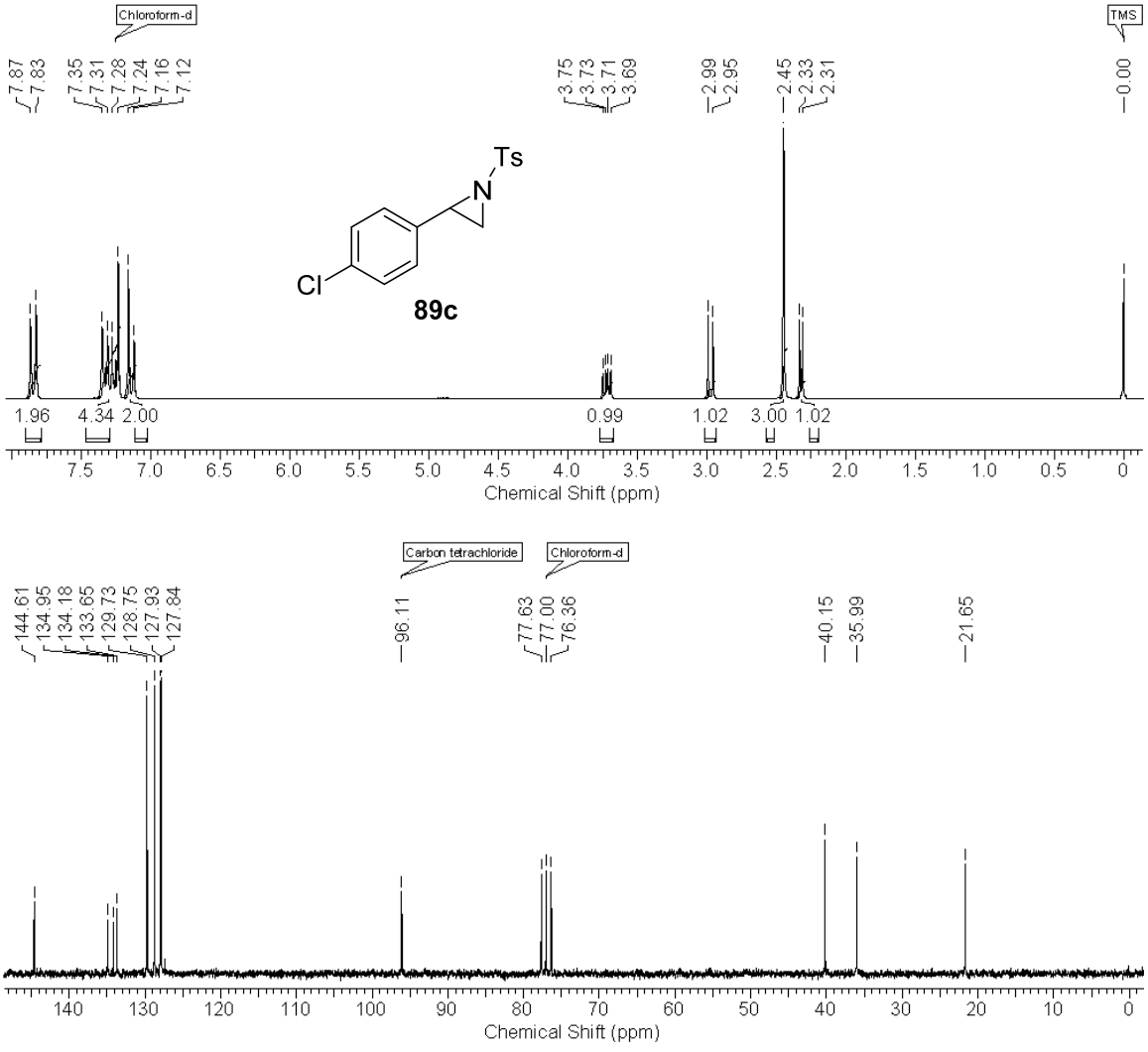


Fig. 8: ^{1}H and ^{13}C NMR spectra of aziridine **89c**

Another example: The ^{1}H NMR spectrum of compound **89k** showed signals at δ 2.8 (d, *J* = 4.2 Hz, 1H) and 2.59 (m, 2H) corresponding to methine and methylene protons (-C**H**-N and C**H$_2$**-N-) and a singlet observed at δ 2.46 corresponding to methyl of *N*-tosyl group.

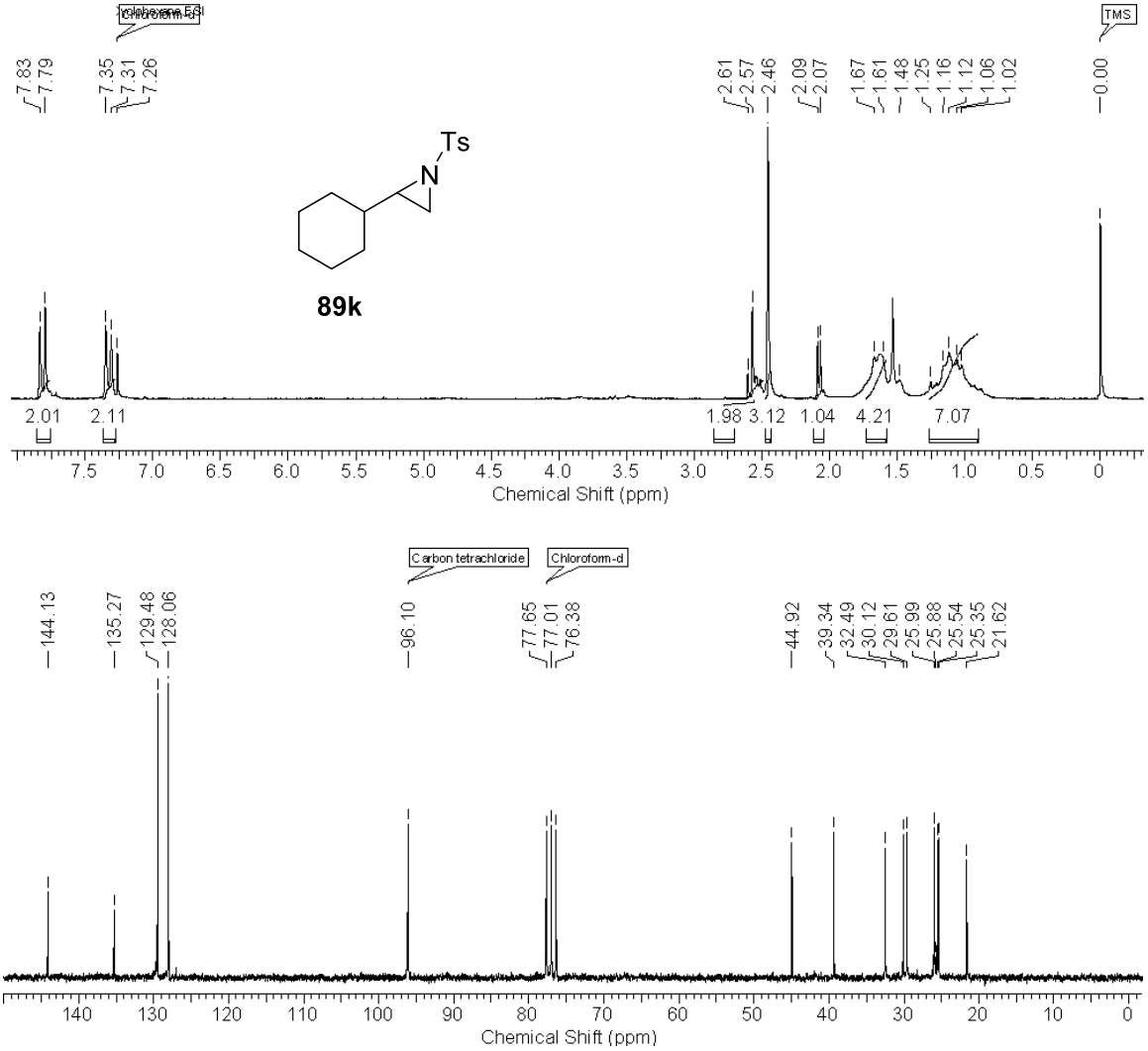
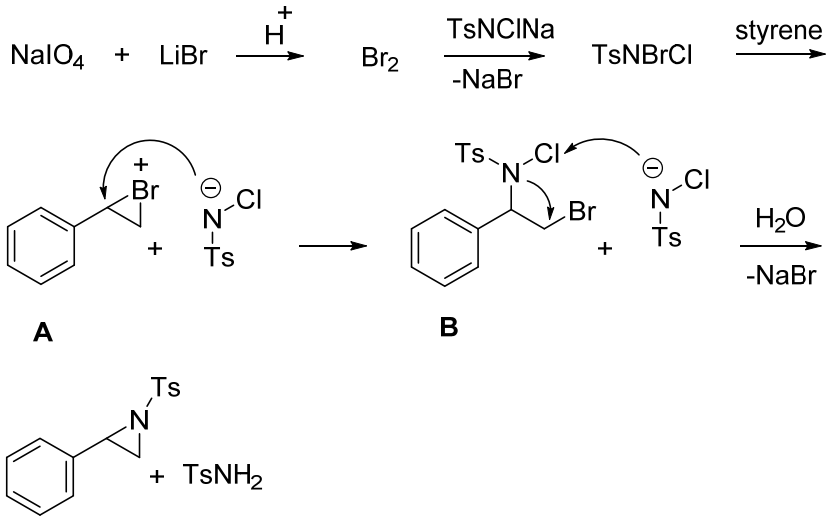


Fig. 9: ^{1}H and ^{13}C NMR spectra of aziridine **89k**

Its ^{13}C NMR spectrum showed two typical carbon signals at δ 32.4 and 39.3 due to homobenzylic and benzylic carbons respectively (**Fig. 9**)

4.3.4.1 Mechanism

Although the exact nature of the species involved in the reaction is not yet known, our earlier studies[50] had shown that 1 equiv of $NaIO_4$ was sufficient to oxidize 8 equiv of Br^- ions, ($IO_4^- + 8H^+ + 8e^- \rightarrow 4H_2O + I^-$). Hence, only 30 mol % of $NaIO_4$ was required to bring about 100% conversions. From the above facts and the evidence provided by the cyclic voltammetry study, it is believed that Br_2, generated by the $NaIO_4$-mediated oxidation of LiBr in acidic condition, reacts with chloramine-T to give the reactive species TsNBrCl, which then subsequently adds onto styrene to form bromonium ion **A**. The stereospecific opening of **A** with $TsNCl^-$ at the benzylic position occurs to give β-bromo-*N*-chloro-*N*-toluenesulfonamide (**B**).



Scheme 43: Plausible mechanistic pathway for $NaIO_4$-mediated aziridination

Finally, cyclization of **B** with another molecule of chloramine-T results in the formation of aziridine, along with the generation of 1 mole of $TsNCl_2$; the hydrolysis of which leads to isolation of $TsNH_2$ as the by product (**Scheme 43)**.

4.3.5 Conclusion

In conclusion, a mild one-pot procedure for the preparation of *N*-tosyl-2-substituted aziridines has been reported. The method employs catalytic amount of $NaIO_4$ as an oxidant and LiBr and chloramine-T as the bromine and nitrogen sources respectively.

4.3.6 Experimental Section

General experimental procedure for aziridination of olefins:

To a stirred solution of olefins **88** (3 mmol) in dry CH_3CN (25 mL), anhydrous chloramine-T (1.365 g, 6 mmol), LiBr (0.257g, 3 mmol), $NaIO_4$ (0.192 g 30 mol %), and conc. H_2SO_4 (0.088 g, 30 mol %) were added at 25 ^oC. The resulting reaction mixture was stirred at 25 ^oC (monitored by TLC). After completion, the reaction mixture was diluted with EtOAc (15 mL) and washed with water followed by aq. saturated $Na_2S_2O_3$ (2 x 15 mL) solution. The organic layer was dried over anhyd. Na_2SO_4 concentrated under pressure to afford crude product, which was purified by column chromatography on silica gel using pet. Ether:EtOAc (10:1) as eluent to afford pure aziridines **89a-o**.

***N*-(*p*-Toluenesulfonyl)-2-phenylaziridine (89a):**

Yield: 81%; **mp:** 92-94ºC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 911, 1160, 1187, 1219, 1324, 1455, 1528, 2926, 3025, 3203, 3321, 3933; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.35-2.37 (d, *J* = 4.5 Hz, 1H), 2.44 (s, 3H), 2.96-2.2.99 (d, *J* = 7.2 Hz, 1H), 3.73-3.79 (dd, *J* = 4.4 and 7.2 Hz, 1H), 7.18-7.36 (m, 7H), 7.84-7.88 (d, *J* = 8.3 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.6, 35.8, 40.9, 125.9, 126.5, 127.9, 128.2, 128.5, 128.6, 129.6, 135.1, 135.2, 144.4;

Anal. Calcd for $C_{15}H_{15}NO_2S$ requires C, 65.91; H, 5.53; N, 5.12; found: C, 65.89; H, 5.52; N, 5.11%.

***N*-(*p*-Tolylsulfonyl)-2-(*o*-chlorophenyl)aziridines (89b)**

Yield: 79%; **mp:** 94-96 ºC; **IR** $CHCl_3$, cm^{-1}): υ_{max} 914, 1091, 1325, 1454, 1527, 1695, 2928, 2954, 3024, 3121, 3935; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.26-2.28 (d, *J* = 4.3 Hz, 1H), 2.45 (s, 3H), 3.01-3.04 (d, *J* = 7.2 Hz, 1H), 3.99-4.05 (dd, *J* = 4.2 and 7.2 Hz, 1H), 7.17-7.37 (m, 7H), 7.87-7.91 (d, *J* = 8.3 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.5, 35.4, 38.7, 126.9, 127.3, 127.4, 128.0, 129.1, 129.1, 129.6, 133.0, 133.6, 134.7, 144.5; **Anal.** Calcd for $C_{15}H_{14}ClNO_2S$ requires C, 58.53; H, 4.58; N, 4.55; found: C, 58.51; H, 4.54; N, 4.54%.

***N*-(*p*-Tolylsulfonyl)-2-(*p*-chlorophenyl)aziridines (89c)**

Yield: 77%; **mp:** 115-116 ºC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 910, 1095, 1162, 1185, 1220, 1325, 1457, 1530, 1698, 2927, 2955, 3029, 3132, 3324, 3936; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.31-2.33 (d, *J* = 4.3 Hz, 1H), 2.45 (s, 3H), 2.95-2.99 (d, *J* = 7.1 Hz, 1H), 3.69-2.75 (dd, *J* = 4.4 and 7.2 Hz, 1H), 7.12-7.35 (m, 2H), 7.24-7.35 (m, 4H), 7.87-7.83 (d, *J* = 8.3 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.6, 35.9, 40.1, 127.8, 127.9, 128.7, 129.7, 133.6, 134.2, 134.9, 144.6; **Anal.** Calcd for $C_{15}H_{14}ClNO_2S$ requires C, 58.53; H, 4.58; N, 4.55; found: C, 58.53; H, 4.56; N, 4.56%.

***N*-(*p*-Tolylsulfonyl)-2-(*p*-fluorophenyl)aziridines (89d)**

Yield: 75%; **mp:** 136-138 ºC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 915, 1096, 1165, 1189, 1220, 1330, 1400, 1456, 1530, 1698, 2930, 2960, 3024, 3126, 3320, 3932; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.32-2.34 (d, *J* = 4.3 Hz, 1H), 2.45 (s, 3H), 2.97 (d, *J* = 7.1 Hz, 1H), 3.71-3.77 (dd, *J* = 4.4 and 7.2 Hz, 1H), 6.93-7.14 (m, 2H), 7.15-7.35 (m, 4H), 7.83-7.87 (d, *J* = 8.3

Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.6, 35.9, 40.1, 127.8, 127.9, 128.7, 129.7, 133.6, 134.2, 134.9, 144.6; **Anal.** Calcd for $C_{15}H_{14}FNO_2S$ requires C, 61.84; H, 4.84; N, 4.81; found: C, 61.85; H, 4.86; N, 4.80%.

***N*-(*p*-Tolylsulfonyl)-2-(*p*-bromophenyl)aziridines (89e)**

Yield: 72%; **mp:** 127-129 ºC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 912, 1091, 1162, 1184, 1220, 1328, 1457, 1530, 1697, 2930, 2960, 3025, 3130, 3321, 3936; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.30-2.32 (d, *J* = 4.3 Hz, 1H), 2.44 (s, 3H), 2.95-2.98 (d, *J* = 7.2 Hz, 1H), 3.67-3.73 (dd, *J* = 4.1 and 7.4 Hz, 1H), 7.05-7.11 (m, 2H), 7.27-7.46 (m, 5H), 7.81-7.86 (d, *J* = 8.2 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.6, 35.9, 40.2, 122.3, 127.7, 127.9, 128.1, 129.72, 131.6, 134.2, 134.9, 144.6; **Anal.** Calcd for $C_{15}H_{14}BrNO_2S$ requires C, 51.15; H, 4.01; N, 3.98; found: C, 51.16; H, 4.06; N, 4.01%.

***N*-(*p*-Tolylsulfonyl)-2-(*p*-methylphenyl)aziridines (89f)**

Yield: 40%; **mp:** 130-131 ºC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 909, 1095, 1160, 1186, 1219, 1324, 1455, 1528, 1696, 2930, 2956, 3025, 3132, 3321, 3936; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.31 (s, 3H), 2.34-2.36 (d, *J* = 4.5 Hz, 1H), 2.44 (s, 3H), 2.94-2.98 (d, *J* = 7.1 Hz, 1H), 3.69-3.75 (dd, *J* = 4.4 and 7.2 Hz, 1H), 7.08 (m, 4H), 7.29-7.33 (d, *J* = 8.1 Hz, 2H), 7.83-7.87 (d, *J* = 8.4 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.1, 21.5, 35.6, 40.9, 126.4, 127.8, 129.1, 129.6, 132.0, 135.2, 137.9, 144.3; **Anal.** Calcd for $C_{16}H_{17}NO_2S$ requires C, 66.87; H, 5.96; N, 4.87; found: C, 66.90; H, 5.98; N, 4.86%.

***N*-(*p*-Toluenesulfonyl)-2-benzylaziridine (89g)**

Yield: 80%; gum; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 675, 770, 840, 915, 1090, 1130, 1250, 1355, 1370, 1400, 1480, 2880, 2910, 2980, 3280; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.12-2.14 (d, *J* = 4.5 Hz, 1H), 2.42 (s, 3H), 2.65-2.72 (m, 2H), 2.75-2.78 (d, *J* = 5.1 Hz, 1H), 2.82-2.93

(m, 1H), 7.01-7.04 (m, 2H), 7.12-7.22 (m, 5H), 7.65-7.69 (d, *J* = 8.4 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.3, 21.4, 32.5, 37.2, 40.9, 41.9, 126.2, 127.7, 128.2, 128.5, 129.36, 134.6, 136.7, 143.9; **Anal**. Calcd for $C_{16}H_{17}NO_2S$ requires C, 66.87; H, 5.96; N, 4.87; found: C, 66.80; H, 6.01; N, 4.90%.

N-(*p*-Tolylsulfonyl)-2-(4-chloromethylphenyl)aziridine (89h):

Yield: 65%; **mp**: 101-103 ^{o}C; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 574, 667, 754, 813, 912, 1093, 1161, 1215, 1325, 1450, 1515, 1595, 2925, 2964, 3020; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.33-2.36 (d, *J* = 4.4 Hz, 1H), 2.45 (s, 3H), 2.96-3.00 (d, *J* = 7.1 Hz, 1H), 3.72-3.78 (dd, *J* = 4.4 and 7.2 Hz, 1H), 4.49 (s, 2H), 7.16-7.39 (m, 6H), 7.83-7.88 (d, *J* = 8.2 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.5, 35.9, 39.8, 40.1, 115.2, 115.70, 127.7, 126.9, 128.1, 128.3, 129.6, 130.8, 130.8, 134.9, 144.5, 160.12, 165.0; **Anal.** Calcd for $C_{16}H_{16}ClNO_2S$ requires C, 59.72; H, 5.01; N, 4.35 found: C, 59.62; H, 5.10; N, 4.41%.

***trans*-*N*-(*p*-Toluenesulfonyl)-2-3-biphenylaziridine (89i):**

Yield: 64%; **mp**: 140-142 ºC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 980, 1020, 1180, 1240, 1380, 1450, 2650, 2800, 3000; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.40 (s, 3H), 4.25 (s, 2H), 7.05-7.70 (m, 12H), 7.85 (d, *J* = 8.2 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.5, 47.3, 127.6, 127.8, 129.7, 131.9, 134.7, 144.6; **Anal.** Calcd for $C_{21}H_{19}NSO_2$ requires C, 72.18; H, 5.48; N, 4.01; found: C, 72.20; H, 5.41; N, 3.98 %.

***N*-(*p*-Toluenesulfonyl)-2-hexylaziridine (89j)**

Yield: 60%; gum, **IR** ($CHCl_3$, cm^{-1}): υ_{max} 980, 1020, 1180, 1240, 1380, 1450, 2650, 2800, 3000; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.82-0.89 (t, *J* = 6.2 Hz, 3H), 1.20-1.32 (m, 9H), 1.50-1.56 (m, 2H), 2.03-2.05 (d, *J* = 4.4 Hz, 1H), 4.25 (s, 3H), 2.60-2.71 (m, 2H), 7.31-7.35 (d, *J* = 8.2 Hz, 2H), 7.80-7.84 (d, *J* = 8.3 Hz, 2H); **^{13}C NMR** (50 MHz,

$CDCl_3$): δ 14.0, 21.5, 22.4, 26.7, 28.8, 31.2, 31.5, 33.6, 40.2, 127.9, 129.4, 135.3, 144.1; **Anal.** Calcd for $C_{15}H_{21}NSO_2$ requires C, 64.02; H, 8.24; N, 4.98; found: C, 64.05; H, 8.26; N, 4.98 %.

***N*-(*p*-Toluenesulfonyl)-2-cyclohexylaziridine (89k)**

Yield: 58%; **mp**: 94-95 ºC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 980, 1020, 1180, 1240, 1380, 1450, 2650, 2800, 3000; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.88-0.16 (m, 7H), 1.48-1.67 (m, 4H), 2.07-2.09 (d, *J* = 4.2 Hz, 1H), 4.26 (s, 3H), 2.51-2.57 (m, 2H), 7.31-7.35 (d, *J* = 8.1 Hz, 2H), 7.79-7.83 (d, *J* = 8.2 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.6, 25.3, 25.5, 25.9, 29.6, 30.1, 32.4, 39.3, 44.9, 128.0, 129.4, 135.2, 144.1; **Anal.** Calcd for $C_{15}H_{21}NSO_2$ requires C, 64.48; H, 7.58; N, 5.01; found: C, 64.45; H, 7.60; N, 4.98 %.

7-[Methyl-7-(phenylsulfonyl) 7-azabicyclo[4.1.0] heptane (89l):

Yield: 60%; **mp:** 55-57 ºC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 920, 964, 1091, 1156, 1184, 1238, 1320, 1400, 1439, 1597, 2862, 2937; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.12-1.47 (m, 4H), 1.65-1.80 (m, 4H), 2.45 (s, 3H), 2.95-2.98 (t, *J* = 1.3 Hz, 2H), 7.30-7.34 (d, *J* = 8.2 Hz, 2H), 7.79-7.83 (d, *J* = 8.4 Hz, 2H); **^{13}C NMR** (200 MHz, $CDCl_3$): δ 19.3, 21.5, 22.7, 39.5, 127.5, 129.4, 137.9, 143.7; **Anal.** Calcd for $C_{13}H_{17}NSO_2$ requires C, 62.12; H, 6.82; N, 5.57; found: C, 62.08; H, 6.81; N, 5.54%.

9-[Methyl-7-(phenylsulfonyl) 9-azabicyclo[6.1.0]nonane (89m):

Yield: 48%; **mp**: 122-123 ºC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 964, 1091, 1159, 1184, 1237, 1320, 1403, 1442, 1597, 2860, 2940; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.25-1.60 (m, 10H), 1.98-2.05 (m, 2H), 2.45 (s, 3H), 2.70-2.82 (m, 2H), 7.29-7.33 (d, *J* = 8.0 Hz, 2H), 7.87-7.82 (d, *J* = 8.3 Hz, 2H); **^{13}C NMR** (200 MHz, $CDCl_3$): δ 21.5, 25.1, 26.0, 26.3, 43.6, 127.5,

129.44, 135.9, 143.7; **Anal.** Calcd for $C_{15}H_{21}NSO_2$ requires C, 64.48; H, 7.58; N, 5.01; found: C, 64.52; H, 7.59; N, 5.01%.

***N*-(*p*-Toluenesulfonyl)-indeneaziridine (89n):**

Yield: 52%; **mp**: 164-166ºC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 675, 750, 770, 840, 915, 1090, 1130, 1158, 1250, 1323, 1355, 1370, 1400, 1480, 2980, 2910. 3280; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.40 (d, *J* = 6.4 Hz, 1H), 2.47 (s, 3H), 3.12-3.23 (dd, *J* = 5.3 and 7.0 Hz, 1H), 3.52-3.63 (dd, *J* = 6.5 and 17.8 Hz, 1H), 4.25-4.31 (m, 1H), 4.48-4.96 (m, 2H), 7.09-7.27 (m, 4H), 7.32-7.37 (d, *J* = 8.1 Hz, 2H), 7.81-7.869 (d, *J* = 8.3 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.6, 41.1, 51.6, 67.1, 124.6, 124.7, 127.4, 127.8, 129.2, 129.7, 137.4, 139.3, 140.4, 143.7; **Anal.** Calcd for $C_{16}H_{15}NSO_2$ requires C, 67.34; H, 5.30; N, 4.91; found: C, 67.30; H, 5.27; N, 4.91%.

***N*-(*p*-Toluenesulfonyl)-2-bromomethylaziridine (89o)**

Yield: 60%; **mp**: 75-78 ^oC; **IR** ($CHCl_3$, cm^{-1}): υ_{max} 1093, 1119, 1292, 1328, 1403, 1597, 2926, 2981, 3029, 3132, 3150, 3175, 3200, 3277; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.45 (s, 3H), 3.50-3.65 (m, 1H), 3.75-3.80 (m, 1H), 4.10-4.30 (m, 1H), 5.01-5.25 (m, 1H), 7.35 (d, *J* = 8.2 Hz, 2H), 7.85 (d, *J* = 8.2 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.3, 32.8, 47.2, 49.9, 126.9, 129.7, 136.7, 143.7; **Anal.** Calcd for $C_{10}H_{12}BrNO_2S$ requires C, 41.39; H, 4.17; N, 4.83; found: C, 41.35; H, 4.19; N, 4.80%.

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LIST OF PUBLICATIONS

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