ENANTIOSELECTIVE SYNTHESIS OF BIOACTIVE MOLECULES USING ASYMMETRIC OXIDATIONS AND SYNTHETIC METHODOLOGIES INVOLVING FORMATION OF C-N, C-O AND C-Br BONDS

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CERTIFICATE

Certified that the work incorporated in the thesis entitled "**Enantioselective Synthesis of Bioactive Molecules Using Asymmetric Oxidations and Synthetic Methodologies Involving Formation of C-N, C-O and C-Br Bonds**" was carried out by the candidate under my supervision. Such material as had been obtained from other sources has been duly acknowledged in the thesis.

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DECLARATION

I here by declare that the thesis entitled **"Enantioselective Synthesis of Bioactive Molecules Using Asymmetric Oxidations and Synthetic Methodologies Involving Formation of C-N, C-O and C-Br Bonds"** submitted for the degree of Doctor of Philosophy in Chemistry to the University of Pune, has not been submitted by me to any other university or institution. This work was carried out at the National Chemical Laboratory, Pune, India.

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ABBREVATIONS

AD	Asymmetric Dihydroxylation
Ac	Acetyl
Ar	Aryl
bp	Boiling Point
Bn	Benzyl
Boc	N-*tert*-Butoxycarbonyl
$(Boc)_2O$	Ditert-butyl dicarbonate
n-BuLi	n-Butyl Lithium
Cbz	Benzyloxy carbonyl
CH_2Cl_2	Methylene chloride
$CHCl_3$	Chloroform
CH_3CN	Acetonitrile
$CuSO_4$	Copper(II) sulfate
DHQ	Dihydoquinine
DHQD	Dihydroquinidine
DIBAL-H	Diisobutyl alulinum hydride
DMF	Dimethyl formamide
DMSO	Dimethyl sulphoxide
ee	Enantiomeric excess
Et	Ethyl
Et_3N	Triethylamine
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
EtOH	Ethyl alcohol
g	Grams
h	Hours
HCl	Hydrochloric acid
HPLC	High pressure liquid chromatography
H_2SO_4	Sulfuric acid
IR	Infra red
K_2CO_3	Potassium carbonate
KF	Potassium fluoride
KOH	Potassium hydroxide
$LiAlH_4$	Lithium aluminum hydride
M+	Molecular ion
Me	Methyl
MeOH	Methyl alcohol
min	Minutes
mL	Milliliter
mp	Melting point
MS	Mass spectrum
$NaBH_4$	Sodium borohydride
$NaHCO_3$	Sodium bicarbonate
NaOH	Sodium hydroxide
Na_2SO_4	Sodium sulfate
NH_4Cl	Ammonium chloride
NH_4OH	Ammonium hydroxide
NMR	Nuclear Magnetic Resonance

NBS	*N*-Bromosuccinimide
Pd/C	Palladium on activated charcoal
Pet. ether	Petroleum ether
Ph	Phenyl
p-TSA	*p*-Toluene sulfonic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TBAF	Tetrabutylammonium fluoride
TBDMSCl	*tert*-Butyldimethylsilyl chloride

GENERAL REMARKS

1. All solvents were distilled and dried before use.

2. Petroleum ether refers to the fraction collected in the boiling range 60-80 °C.

3. Organic layers after every extraction were dried over anhydrous sodium sulfate.

4. Column Chromatography was performed over silica gel (60-120 mesh).

5. TLC analyses were performed over aluminum plates coated with silica gel (5-25 m) containing UV active G-254 additive.

6. IR spectra were recorded on a Perkin-Elmer model 683 B or 1605 FT-IR and absorptions were expressed in cm^{-1}.

7. ^{1}H and ^{13}C NMR spectra were recorded on Brucker FT AC-200 and MSL-300 MHz instruments using TMS as an internal standard. The following abbreviations were used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br s = broad singlet, and dd = doublet of doublet.

8. Mass spectra (MS) were recorded on an automated finnigan MAT 1020C mass spectrometer using ionization energy of 70eV.

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

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

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

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

13. The ligands $(DHQD)_2$-PHAL, $(DHQ)_2$-PHAL, $(DHQD)_2$-AQN were purchased from Aldrich

ABSTRACT

The thesis entitled "**Enantioselective synthesis of bioactive molecules using asymmetric oxidations and synthetic methodologies involving formation of C-N, C-O and C-Br bonds**" is divided into four chapters.

The title of the thesis clearly reflects the objective, which is to synthesize enantiomerically pure bioactive molecules and to interface synthetic organic chemistry for the development of synthetic methodologies. **Chapter 1** describes the asymmetric synthesis of (+)-hygroline (**10**) using proline catalyzed α-aminooxylation reaction. This chapter also describes the enantioselective synthesis of (*R*)-selegiline (**20**) using proline catalyzed α-aminooxylation and α-amination. **Chapter 2** deals with the asymmetric synthesis of novel antidepressant, (*S,S*)-reboxetine (**37**) using chiral-borane reduction of ketones as well as Sharpless asymmetric dihydroxylation of olefins as the chiral induction steps. This chapter also presents the synthesis of (*S*)-toliprolol (**44**) using proline catalyzed α-aminooxylation of aldehydes and Co-Salen catalyzed asymmetric kinetic resolution of (±)-epichlorohydrin. **Chapter 3** deals with the first enantioselective synthesis of (*S*)-latifine (**55**), a tetrahydroisoquinoline alkaloid, using Sharpless asymmetric dihydroxylation of olefins. This chapter also deals with the asymmetric synthesis of (*1R,2S*)-cispentacin (**62**) using Sharpless asymmetric dihydroxylation. **Chapter 4** deals with development of new synthetic methodologies such as 1,2-Aminobromination, Hydroamination of activated styrenes and Michael addition of carbamates and sulfonamides onto enones.

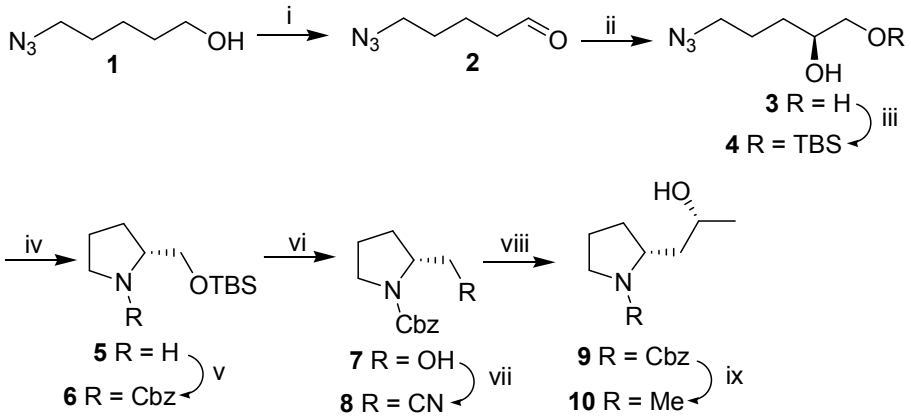
CHAPTER 1

Asymmetric Synthesis of (+)-Hygroline and (*R*)-Selegiline using Proline-catalyzed α-Functionalization of Aldehydes

Organocatalytic asymmetric synthesis has provided several new methods for obtaining chiral compounds in an environmentally benign manner.[1] Particularly, proline, an abundant, inexpensive amino acid available in both enantiomeric forms, has emerged as arguably the most practical and versatile organocatalyst for α-functionalization of carbonyl compounds.[2] In this chapter we exploit these reactions for the asymmetric synthesis of bioactive molecules, (+)-hygroline (**10**) and (*R*)-selegiline (**20**). This chapter is divided into two sections.

SECTION 1: Asymmetric Synthesis of (+)-Hygroline using D-proline-catalyzed Asymmetric Aminooxylation.

(+)-Hygroline (**10**) is a biosynthetic precursor to a range of homologous alkaloids and was first identified in *Erythoxylum* coca.[3] The synthetic route for (+)-hygroline (**10**) is presented in **Scheme 1**.



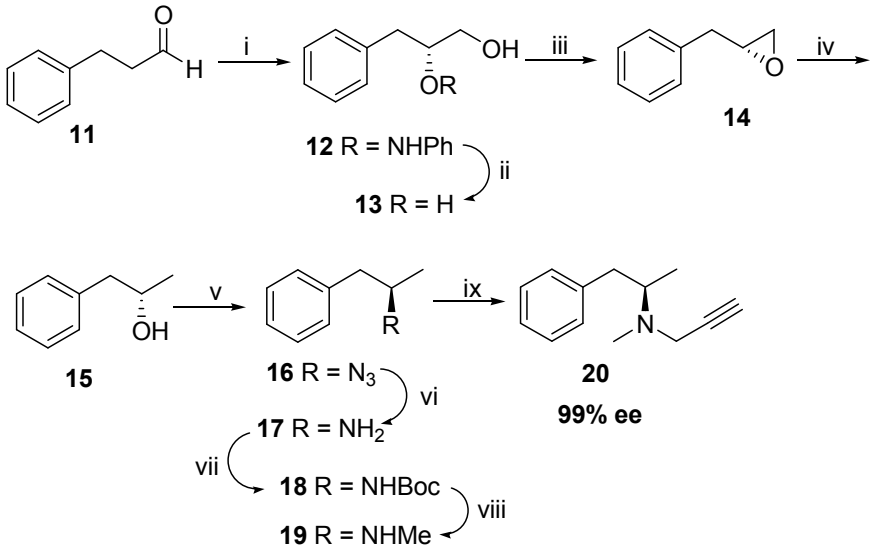
Scheme 1: (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C, 0.5 h, (ii) (a) 20 mol% D-Proline, PhNO, CH_3CN, -20 °C, 24 h, then $NaBH_4$, EtOH, 0.5h, (b) 30 mol% $CuSO_4$, MeOH, 24 h, 61% for 3 steps; (iii) TBDMSCl, Imidazole, CH_2Cl_2, 0 °C, 1 h, 95%; (iv) (a) MsCl, Et_3N, CH_2Cl_2, 0 °C, 0.5 h, (b) Pd/C, H_2, MeOH, 2 h, 80% for 2 steps; (v) CbzCl, dioxane, H_2O, $NaHCO_3$, 0 °C, 12 h, 99%; (vi) TBAF, THF, 0 °C, 1 h, 90%; (vii) (a) MsCl, Et_3N, CH_2Cl_2, 0 °C, 0.5 h, (b) NaCN, DMF, 50 °C, 12 h, 82% for 2 steps; (viii) (a) DIBAL-H, CH_2Cl_2, -78 °C, 1 h, (b) MeMgBr, THF, 0 °C, 85% for 2 steps; (ix) $LiAlH_4$, THF, reflux, 4 h, 50%.

5-Azido-pentan-1-ol (**1**) was subjected to Swern oxidation to obtain aldehyde **2** which was converted to the azidodiol **3** in 2-steps of (i) D-proline catalyzed asymmetric α-aminooxylation followed by reduction of the aldehyde with $NaBH_4$ and (ii) cleavage of aminooxy moiety with $CuSO_4$. Protection of the primary hydroxyl group in diol **3** as *tert*-butyldimethylsilyl ether followed by mesylation of the secondary hydroxyl gave azidomesylate *in situ* which underwent reduction (Pd/C and H_2) to give chiral pyrrolidine **5** in 80% yield. Pyrrolidine **5** was converted to nitrile **8** using standard sequence of reactions. The nitrile **8** was reduced *in situ* to the aldehyde using DIBAL-H which was then treated with MeMgBr to give alcohol **9** in 85% yield. Reduction of alcohol **9** using $LiAlH_4$ gave (+)-hygroline (**10**) in 50% yield and 92% ee.

SECTION 2: Asymmetric Synthesis of (*R*)-Seligiline using Proline-catalyzed Asymmetric α-Aminooxylation and α-Amination Reactions.

Selegiline (**20**), commonly referred to in the clinical and pharmacological literature as L-deprenyl, a selective, irreversible inhibitor of monoamineoxidase-B, is widely used

in the treatment of Parkinson's disease and Alzheimer's disease.[4] The synthesis of (*R*)-Selegiline (**20**) using proline-catalyzed *α-aminooxylation* is shown in **Scheme 2**.

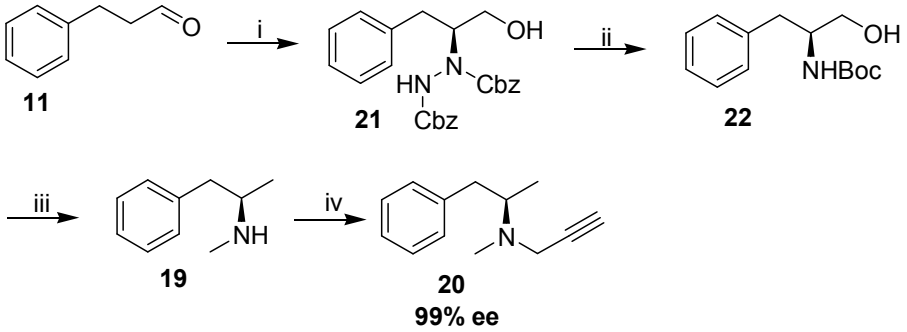


Scheme 2: (i) (a) PhNO, L-proline (10 mol %), DMSO, 25 °C, 20 min. then MeOH, $NaBH_4$, 86%; (ii) H_2 (1atm.), 10% Pd/C, MeOH, 12 h, 88%; (iii) (a) *p*-TsCl, Et_3N, CH_2Cl_2, 0 °C , 1 h, (b) NaH, DMF, 0 °C, 0.5 h, 81% for 2 steps; (iv) $LiAlH_4$, THF, reflux, 2 h, 92%; (v) (a) MsCl, Et_3N, CH_2Cl_2, 0 °C, 0.5 h, (b) NaN_3, DMF, 80 °C, 12 h, 76% for 2 steps; (vi) H_2 (1atm.), 10% Pd/C, MeOH, 2 h, 98%; (vii) $(Boc)_2O$, Et_3N, 0 °C, 1 h, 95%; (viii) $LiAlH_4$, THF, reflux, 4 h, 90%; (ix) propargyl bromide, anhyd. K_2CO_3, CH_3CN, 12 h, 72%, 99% ee.

α-Aminooxylation of 3-phenylpropanaldehyde (**11**) furnished aminooxy aldehyde *in situ* which on reduction with $NaBH_4$ afforded the α-aminooxy alcohol **12** in 86% yield. The alcohol **12** was converted to the diol **13** (H_2, Pd/C) which was then transformed into the corresponding epoxide **14** *via* the primary tosylate. The epoxide **14** was then opened regioselectively with $LiAlH_4$ to give the secondary alcohol **15** in 92% yield and 99% ee (determined by ^1H NMR analysis of its Mosher's ester), which was protected as its tosylate followed by its displacement with azide gave the compound **16** in 80% yield. The amine **19** was obtained in 3 steps of azide reduction with Pd/C, H_2 *N*-Boc protection, followed by $LiAlH_4$ reduction. *N*-Propargylation of amine **19** furnished (*R*)-Selegiline (**20**) in 72% yield and 99% ee.

The synthesis of (*R*)-Selegiline (**20**) *via* proline-catalyzed *α-amination* of aldehyde **11** involving lesser number of steps is presented in **Scheme 3**. 3-Phenylpropanaldehyde (**11**) was subjected to D-proline catalyzed α-amination and reduction to give the aminoalcohol **21** in 95% yield. The aminoalcohol **21** was then hydrogenated to give the deprotected amino alcohol *in situ*, which was protected as carbamate **22**. The

primary alcohol was then tosylated and reduced with $LiAlH_4$ to yield the methyl amine **19**, which on *N*-propargylation afforded (*R*)-Selegiline **20** in 72% yield.



Scheme 3: (i) Dibenzyl azodicarboxylate , D-Proline (10 mol%), 0-20 °C, 3 h then $NaBH_4$, EtOH, 95%; (ii) (a) H_2 (60 psi), Raney Ni, MeOH, AcOH, 16 h, (b) $(Boc)_2O$, Et_3N, 0 °C, 1 h, 66% for 2 steps; (iii) (a) *p*-TsCl, Et_3N, CH_2Cl_2, 0 °C, 1 h, (b) $LiAlH_4$, THF, reflux, 4 h, 81% for 2 steps; (iv) propargylbromide, K_2CO_3, CH_3CN, 12 h, 72%.

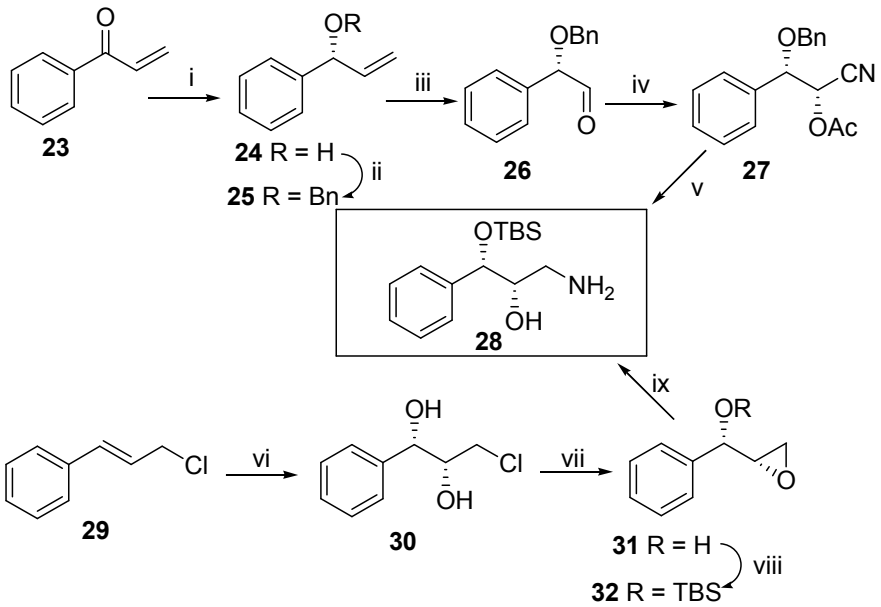
CHAPTER 2

Asymmetric Synthesis of (*S,S*)-Reboxetine and (*S*)-Toliprolol

This chapter is divided into two sections. First section deals with synthesis of (*S,S*)-Reboxetine (**37**) and the second section describes the synthesis of (*S*)-Toliprolol (**44**).

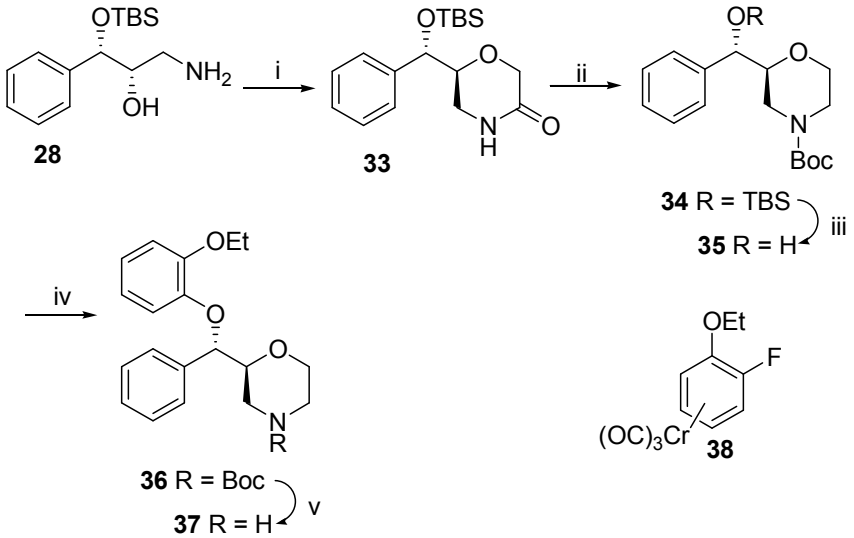
SECTION 1: Asymmetric Synthesis of (*S,S*)-Reboxetine

Reboxetine, 2-[α-(2-ethoxyphenoxy) phenylmethyl]morpholine (**37**) is a specific norepinephrine reuptake inhibitor (NRI) widely studied for its pharmacological properties.[5] The intermediate **28** was synthesized *via* two routes: (i) asymmetric reduction of ketone **23** using Brown's reduction conditions[6] and (ii) Sharpless asymmetric dihydroxylation of cinnamyl chloride **29** (**Scheme 4**). Ketone **23** was subjected to asymmetric reduction to give the corresponding allylalcohol **24** in 70% yield, which was protected as benzyl ether **25**. The olefin moiety was cleaved oxidatively to give the α-bezyloxy aldehyde **26**, which on diastereoselective hydrocyanation (Ward's protocol)[7] gave the corresponding cyanohydrin *in situ* which was then protected as its acetate **27**. The acetate **27** was then converted to the amino alcohol **28** in 3 steps using standard conditions. In the second route, cinnamyl chloride **29** was subjected to Sharpless buffered AD conditions[8] to give the diol **30** in 80% yield, which was converted to the corresponding epoxy-alcohol **31** in 88% yield and 97% ee. Protection of hydroxyl group in **31** and opening of epoxide with 30% NH_3 gave aminoalcohol **28** in 80% yield.



Scheme 4: (i) (-)-Ipc_2BCl, THF, -25 °C, 10 h, then $NH(CH_2CH_2OH)_2$ 70%; (ii) NaH, BnBr, DMF, 0 °C, 1 h, 95%; (iii) OsO_4, $NaIO_4$, 2,6-lutidine, dioxane, H_2O, 2 h, 90%; (iv) (a) TMSCN, $MgBr_2.OEt_2$, CH_2Cl_2, 0 °C, 1.5 h, (b) Ac_2O, py, CH_2Cl_2, -78 to 0 °C, 80% for 2 steps; (v) (a) Pd/C, H_2, MeOH, 25 °C, 2 h, (b) TBDMSCl, imidazole, CH_2Cl_2, 0 °C, 1 h, (c) DIBAL-H, CH_2Cl_2, -78 °C, 72% for 3 steps; (vi) $(DHQ)_2$-PHAL, $K_2OsO_2(OH)_4$, $CH_3SO_2NH_2$, $K_3Fe(CN)_6$, K_2CO_3, $NaHCO_3$, *t*-BuOH:H_2O (1:1), 24 h, 0 °C, 80%; (vii) NaOH, THF, 0 °C, 0.5 h, 88%; (viii) TBDMSCl, imidazole, CH_2Cl_2, 0 °C, 1 h, 92%; (ix) 30% NH_4OH, MeOH, 25 °C, 12 h, 80%.

The completion of synthesis of (*S,S*)-Reboxetine **37** from aminoalcohol **28** is presented in **Scheme 5**.

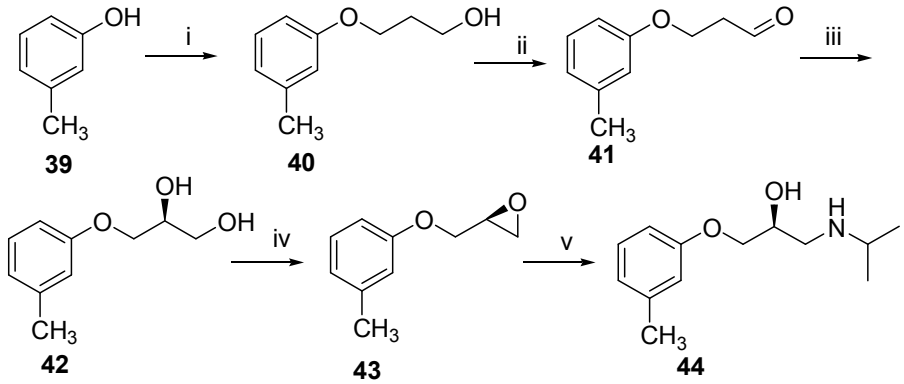


Scheme 5: (i) (a) $ClCH_2CO_2Cl$, Et_3N, CH_2Cl_2, -10 °C, (b) KO^{t}Bu, *t*-BuOH, 3 h, 72% for 2 steps; (iii) (a) Red-Al, dry toluene, 25 °C, then 2N NaOH, (b) $(Boc)_2O$, Et_3N, CH_2Cl_2, 0 °C, 1 h, 75% for 2 steps; (iv) TBAF, THF, 0 °C, 1 h, 93%; (v) (a) arene-chromium complex **38**, NaH, DMF, 25 °C, 2h, (b) I_2 in THF, 0 °C to 25 °C, 1 h, 85%; (v) TFA, CH_2Cl_2, 0 °C, 1 h, 96%.

Aminoalcohol **28** was converted to **33** in 2-steps of acylation and chloride displacement. Compound **33** was reduced to the morpholine derivative *in situ* which was protected as carbamate **34** in 92% yield using $(Boc)_2O$. Removal of silyl protection in **34** gave the alcohol **35** in 93% yield. The transformation of **35** to (*S,S*)-Reboxetine (**37**) in 97% ee was achieved in 2-steps of (i) nucleophilic displacement of the fluoride in arylchromium **38** by sodium alkoxide of alcohol **35** in DMF followed by oxidative dechromination with iodine and (ii) deprotection of *N*-Boc with trifluoroacetic acid.

SECTION 2: Asymmetric Synthesis of (*S*)-Toliprolol

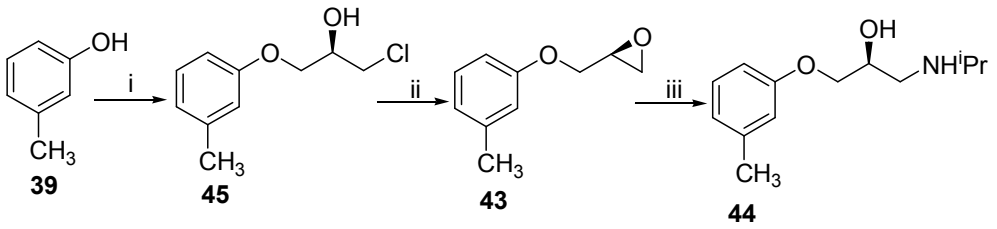
β-Adrenergic blocking agents (β-blockers) are important drugs widely used for the treatment of hypertension and angina pectoris.[9]



Scheme 5: (i) $Br(CH_2)_3OH$, K_2CO_3, acetone, 50 °C, 12 h, 92%; (ii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C, 0.5 h, 90%; (iii) (a) 20 mol% D-Proline, PhNO, CH_3CN, -20 °C, 24 h, then $NaBH_4$, EtOH, 0.5 h, (b) Pd/C, H_2, MeOH, 12 h 70% for 2 steps; (iv) (a) *p*-TsCl, pyridine, CH_2Cl_2, 0 °C, 1 h, (b) NaH, THF, 0 °C, 0.5 h, 84% for 2 steps; (v) *i*-$PrNH_2$, H_2O (cat.), reflux, 2 h, 99%.

The synthesis of (*S*)-Toliprolol **44**, a β-blocker, using proline-catalyzed α-aminooxylation is presented in **Scheme 5**. Aldehyde **41** derived from *m*-cresol **39** in two steps of bromide displacement and Swern oxidation, was subjected to D-proline catalyzed α-aminooxylation reaction gave aminooxy aldehyde *in situ* and the subsequent reduction of aldehyde ($NaBH_4$) and aminooxy moieties (H_2, Pd/C) gave diol **41** in 60% yield. Diol **41** was protected as it tosylate and the subsequent reaction with NaH gave the epoxide **43** in 90% yield, which on opening with isoproryl amine gave (*S*)-Toliprolol **44** in 99% yield and 99% ee.

The synthesis of **44** using proline-catalyzed α-aminooxylation is presented in **Scheme 6**.



Scheme 6: (i) Epichlorohydrin, (R,R)-Co-Salen, 12 h, 78%; (ii) KO^{t}Bu, *t*-BuOH, 0 °C, 1 h, 91%; (iii) *i*-PrNH$_2$, H$_2$O (cat.), reflux, 2 h, 99%.

Co-salen catalyzed asymmetric ring opening[10] of epichlorohydrin with m-cresol gave chloro alcohol **45** which on reaction with KO^{t}Bu gave epoxide **43**. Opening of epoxide **43** with isoprorylamine gave (*S*)-Toliprolol **44** in 99% yield and 97% ee.

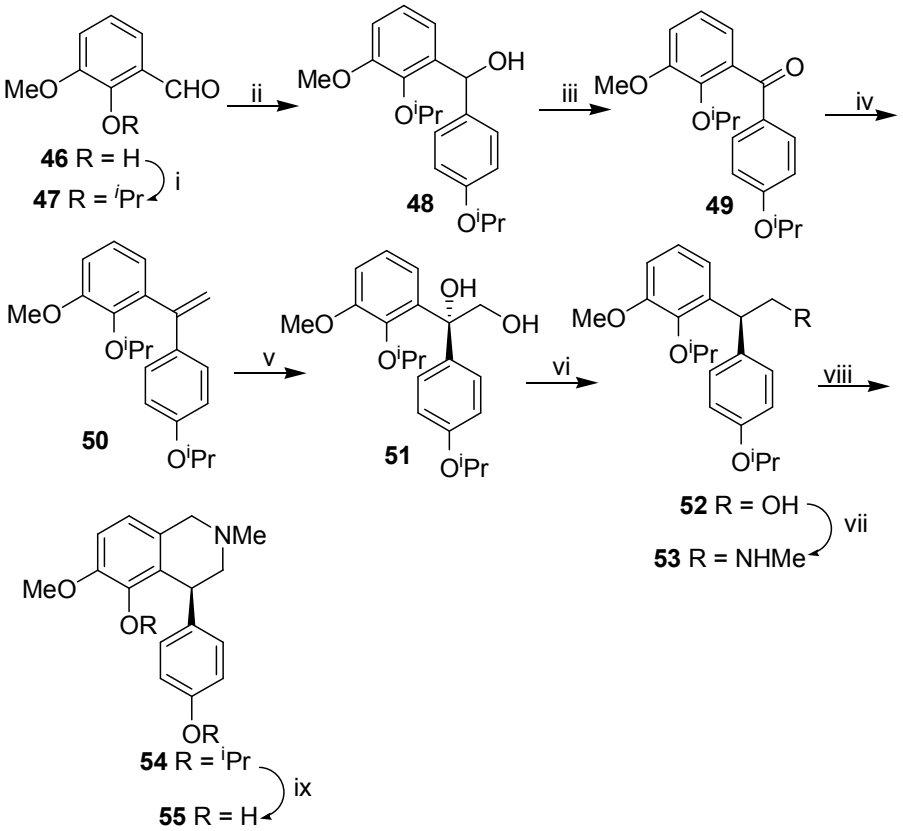
CHAPTER 3

Total Synthesis of (*S*)-Latifine and (1*R*,2*S*)-Cispentacin using Sharpless Asymmetric Dihydroxylation

SECTION 1: Asymmetric Synthesis of (*S*)-Latifine

Latifine **55**, a 1,2,3,4-tetrahydroisoquinoline alkaloid, was isolated from *Crinum latifolium*, a plant used as rubefaciant and tonic[11] and is reported to be a possible anabolic or catabolic metabolite of *O,N*-dimethylnorbelladine. The synthetic sequence for (*S*)-Latifine (**55**) is presented in **Scheme 7**.

Reaction of 4-isoproyloxyphenylmagnesium bromide with protected *o*-vanillin (2-isopropoxy-3-methoxybenzaldehyde) **47** gave the corresponding addition product **48** in 86% yield. The secondary alcohol **48** was then oxidized to the corresponding benzophenone **49** using standard oxidation conditions (PDC, CH_2Cl_2). 1-carbon Wittig olefination of the benzophenone **49** at -40 °C using n-BuLi and methyltriphenylphosphonium iodide gave the olefin **50** in 78% yield. Olefin **50** was the subjected to Os-catalyzed Sharpless AD reaction[12] to give diol **51** in 88% yield which underwent hydrogenolysis with Raney-Ni and ethanol to give alcohol **52** in 80% yield. Alcohol **52** was protected as its mesylate and subjected to nucleophilic displacement with methyl amine to give secondary amine **53**. The secondary amine **53** was *N*-formylated with acetic formic anhydride and subjected to Bischler-Napieralski conditions ($POCl_3$, C_6H_6, reflux, 45 min., then $NaBH_4$, MeOH, H_2O) to give tertiary amine **54**. Deprotection of isopropyl groups with BCl_3 gave (*S*)-Latifine **55** in 90% yield and 89% ee.

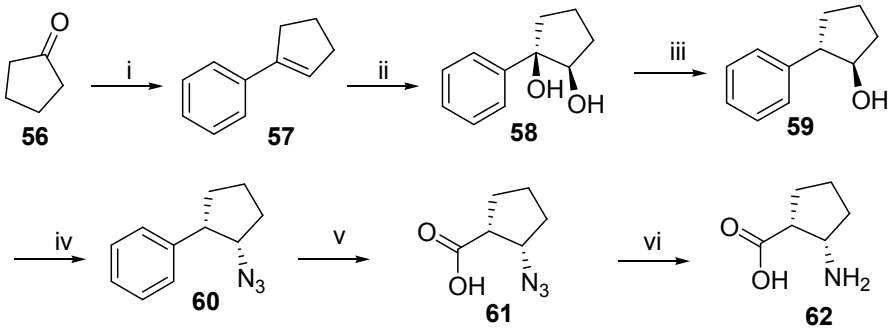


Scheme 7: (i) $(CH_3)_2CHBr$, K_2CO_3, DMF, 140 °C, 10 h, 68%; (ii) 4-$[(CH_3)_2CHO]$-C_6H_4MgBr, THF, -78 °C, 1 h, 86%; (iii) PDC, CH_2Cl_2, 10 h, 90%; (iv) CH_3PPh_3I, n-BuLi, THF, -40 °C, 1 h, 78%; (v) $(DHQD)_2$-AQN, $K_2OsO_2(OH)_4$, $CH_3SO_2NH_2$, $K_3Fe(CN)_6$, K_2CO_3, $NaHCO_3$, *t*-BuOH:H_2O (1:1), 72 h, 22 °C, 88%; (vi) Raney-Ni, EtOH, reflux, 1 h, 80%; (vii) (a) MsCl, Et_3N, cat. DMAP, CH_2Cl_2, 0 °C, 1 h; (b) $MeNH_2$ in MeOH, 70 °C, 4 h, 70% for 2 steps; (viii) (a) HCO_2COCH_3, pyirdine, CH_2Cl_2, 0 °C, 1 h, (b) $POCl_3$, C_6H_6, reflux, 45 min., then $NaBH_4$, MeOH, H_2O, 0 °C, 0.5 h, 46% for 2 steps; (x) BCl_3, CH_2Cl_2, -10-0 °C, 2 h, 90%, 89.2% ee.

SECTION 2: Asymmetric Synthesis of (*1R,2S*)-Cispentacin

(*1R,2S*)-2-Aminocyclopentanecarboxylic acid (Cispentacin **62)**, a cyclic β-amino acid (also known as FR109615), was isolated from *Bacillus cereus* and reported in 1989 as an antifungal agent.[13] The synthesis of Cispentacin (**62**) is presented in **Scheme 8**. The olefin **57** obtained from commercially available cyclopentanone **56** *via* Grignard reaction with PhMgBr followed by dehydration with *p*-TSA, was subjected to Sharpless AD reaction gave the chiral diol **58** in 97% ee. Hydrogenolysis of diol **58** with Raney-Ni and ethanol furnished the alcohol **59** in 80% yield and 95% ee (determined by ^1H NMR analysis of its Mosher's ester). The alcohol **59** was protected as its mesylate and the subsequent treatment with NaN_3 gave the azide **60** in 80% yield. Ru-catalyzed oxidative cleavage of C-C bond of the phenyl ring in **60** led to the

isolation of azido carboxylic acid **61** in 60% yield which was reduced with H_2, Pd/C to afford Cispentacin (**62**) in 92% yield 93.4% ee.



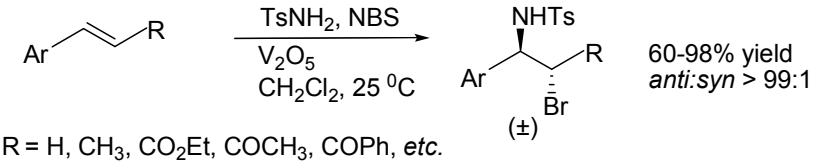
Scheme 8: (i) (a) PhMgBr, Et_2O, 0 °C, 1 h, 90%; (b) *p*-TSA, C_6H_6, reflux (Dean-Stark), 10 h, 92%; (ii) $(DHQD)_2PHAL$, $K_2OsO_2(OH)_4$, $MeSO_2NH_2$, $K_3[Fe(CN)_6]$, K_2CO_3, *t*-BuOH-H_2O, 0 °C, 12 h, 76%; (iii) Raney-Ni, EtOH, reflux, 2 h, 80%; (iv) (a) MsCl, Et_3N, CH_2Cl_2, 0 °C, 1 h, 94 %; (b) NaN_3, DMF, 80 °C, 6 h, 80% for 2 steps; (v) 20 mol% $RuCl_3$, $NaIO_4$, EtOAc, CH_3CN, H_2O, 18 h, 60 %; (vi) 5% Pd/C, H_2 (1 atm.), MeOH, 1 h, 92%.

CHAPTER 4

Synthetic Methodologies Involving Formation of C-N, C-O and C-Br Bonds

SECTION 1: V_2O_5-catalyzed 1,2-Aminobromination of Olefins

The functionalization of olefins by addition of the 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[14] 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. This section describes regiospecific and stereoselective bromoamination of olefins catalyzed by V_2O_5 using NBS (N-bromosuccinimide) as the bromine source and *p*-toluene sulfonamide as the nitrogen source (**Scheme 9**).[15] Bromoamination of α,β-unsaturated (R= CO_2Et, COPh, *etc.*) compounds were also carried out using V_2O_5 in good to excellent yields (60-98%) in highly regiospecific and stereoselective manner.



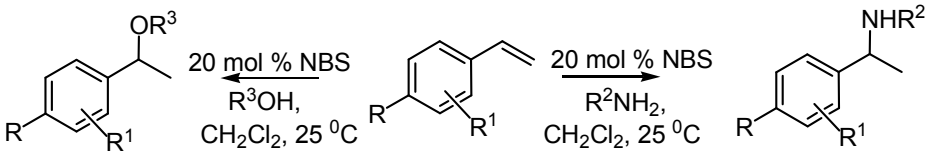
R = H, CH_3, CO_2Et, $COCH_3$, COPh, *etc.*

Ar = Ph, 4-ClC_6H_4, 4-$ClCH_2C_6H_4$, *etc.*

Scheme 9: (i) olefin (2 mmol), $TsNH_2$ (2 mmol), *N*-bromosuccinimide (2.2 mmol), catalyst (5 mol%), CH_2Cl_2, 25 °C.

SECTION 2: NBS-catalyzed Hydroamination and Hydroalkoxylation of Activated Styrenes

The catalytic addition of organic amines and their derivatives to alkenes or alkynes (hydroamination) to produce nitrogen- containing organic molecules is of great importance for synthetic chemists in basic research as well as for the chemical industry.[16] This section describes *N*-bromosuccinimide catalyzed hydroamination and hydroalkoxylation of activated styrenes using tosylamides, carbamates and alcohols as the nucleophiles, to afford amino and ether derivatives respectively **(Scheme 10)**.



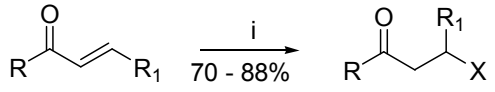
R = OMe, SMe, OEt, OBn, R^1 = H, Me, Cl R^2 = Tosyl, Cbz, CO_2Me
R^3 = alkyl, benzyl, allyl, propargyl.

Scheme 10:

Both the processes give good to excellent yields of the products with 100 % regioselectivity (Markovnikov fashion).[17]

SECTION 3: $BF_3.OEt_2$ Catalyzed aza-Michael Addition of Sulfonamides and Carbamates as the Nucleophiles onto α, β- unsaturated Enones

The β-amino carbonyl compounds are versatile functional groups for the synthesis of nitrogen-containing compounds such as 1,3–amino alcohols, β-amino ketones, β-amino acids and β-lactams.[18] This section describes a systematic study involving aza-Michael reaction of enones using sulfonamides and carbamates using $BF_3.OEt_2$ as the catalyst (**Scheme 11**). Aliphatic enones as well as enones with varied functional groups on the aromatic ring were subjected to the Aza-Michael reaction using *p*-toluenesulfonamide and benzyl carbamate as the nucleophiles.



1, X = NHTs
2, X = NHCbz

R = CH_3, ph, 4-$OMeC_6H_4$, cyclopentyl, *etc.*
R_1 = H, CH_3, alkyl *etc.*

Scheme 11: (i) enone (5 mmol), *p*-toluene sulfonamide or benzyl carbamate (5 mmol), $BF_3.OEt_2$ (15 mol%), CH_2Cl_2, 25 °C.

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There is an unparalleled opportunity for the application of chemical synthesis to medical and biological problems at fundamental level

- Elias J. Corey

Chapter I

Asymmetric Synthesis of (+)-Hygroline and (R)-Selegiline using Proline Catalyzed α-Functionalization of Aldehydes

Section I

Asymmetric Synthesis of (+)-Hygroline using D-proline-catalyzed Asymmetric Aminooxylation

1.1.1 Introduction

The alkaloids are organic nitrogenous bases found mainly in plants, but also to a lesser extent in microorganisms and animals. Alkaloids are often classified according to the nature of nitrogen-containing structure e.g. pyrrolidine, piperidine, quinoline, isoquinoline, indole, etc, though the structural complexity of some of alkaloids rapidly expands the number of subdivisions.

1.1.2 Pharmacology of tropane alkaloids and Hygroline

L-Ornithine is a non-protein amino acid forming part of the urea cycle in animals, where it is produced from L-arginine in a reaction catalyzed by enzyme arginase. It supplies a C_4N building block to the alkaloid, principally as a pyrrolidine ring system, but also part of the tropane alkaloids. The tropane alkaloids, which have the 8-azabicyclo[3.2.1]octane nucleus, are commonly found in plants of three families, the *Solanaceae*, *Erythroxylaceae*, and *Convolvulaceae* families. Plants containing these alkaloids have been used throughout recorded history as poisons, but many of the alkaloids do have valuable pharmaceutical properties. The *Solanaceae* alkaloids derived from these plants, while very toxic, are often important medicinal agents. This can be a major problem since the plants produce very attractive berries which are tempting to small children. As few as three berries of henbane (*Hyoscyamus niger*) or deadly nightshade (*Atropa belladonna*) can cause death in infants. In fact, the juice of the berries of *Atropa belladonna* was used during the Renaissance by ladies of the Italian courts to exaggerate the size of their eyes by dilating the pupils. (The rough translation of *belladonna* from Italian is beautiful

lady). Tropane alkaloids have also found use as CNS stimulants and are useful in treating poisoning cases, particularly anticholinesterase poisoning induced by organophosphorous insecticides and nerve gas and poisoning induced by the toxic principles of the mushroom *Amanita muscaria*. Cocaine **1**, from *Erythroxylum coca*, is closely related in structure, is also a CNS stimulant, and has been used as a topical anesthetic in ophthalmology. It is also a drug of abuse. Cocaine **1** was found in very small amounts in the original Coca-Cola formula, but was not the main concern of the USDA at the time. It is well-established that hygrine **2** is a precursor of the tropane alkaloids.[1,2] The mechanism of this reaction is thought to involve an intra-molecular Mannich reaction between the quaternary Schiff's base on the pyrrolidine ring C-5 carbon and the C-3' carbon of the side chain, giving tropinone **3** (**Fig. 1**).[3]

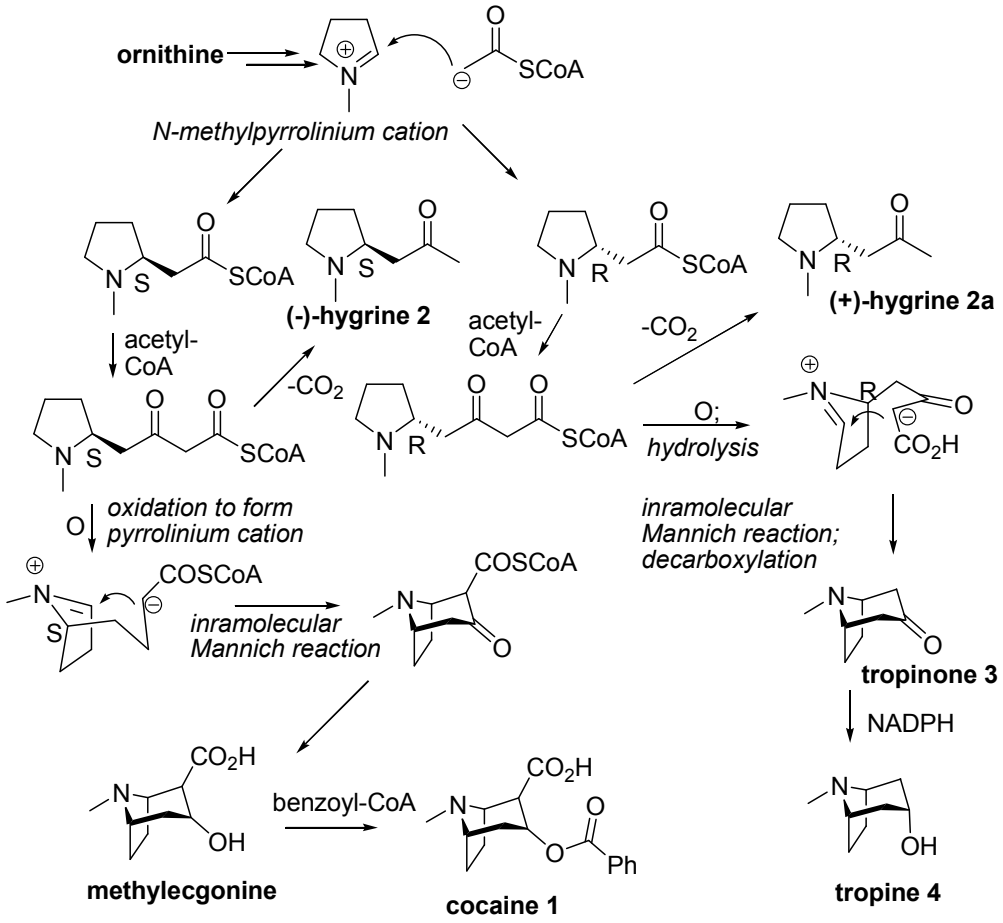
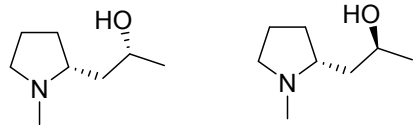


Fig. 1: Biosynthesis of tropane alkaloids

The tropinone **3** undergoes stereospecific reduction[4] yielding tropine **4** which can then be esterified to give the various tropane ester alkaloids commonly found in *Datum***.**[3,5,6] Other routes from hygrine **2** to the tropane alkaloids have been postulated (**Fig. 1**).[7] Literature also reveals that hygroline **5** may be the more immediate precursor of tropine **4**. Possible support for this view has been lent by the identification of hygroline **5** from *Cochlearia artica* (Cruciferae)[8] and *Erythroxylon coca* (Erythroxylaceae).[9] Recently,[10] hygroline **5** and pseudohygroline **6** have been found to be natural components of *Schizanthus hookeri* (Solanaceae) (**Fig. 2**).



(+)-Hygroline 5 **(+)-Pseudohygroline 6**

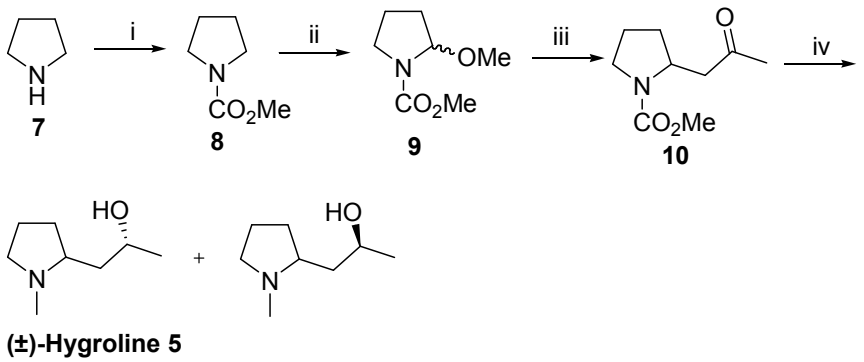
Fig. 2

(+)-Hygroline **5**, a biosynthetic precursor to a range of homologous alkaloids, was first identified in *Erythoxylum coca.*[9] During this study, pseudohygroline **6** was first synthesized as part of the structural proof of hygroline **5**. Despite the fact that synthetic studies on hygroline **5** and pseudohygroline **6** have attracted much attention, methods for the elaboration of this biologically important alkaloid lack flexibility and universality.

1.1.3 Review of Literature

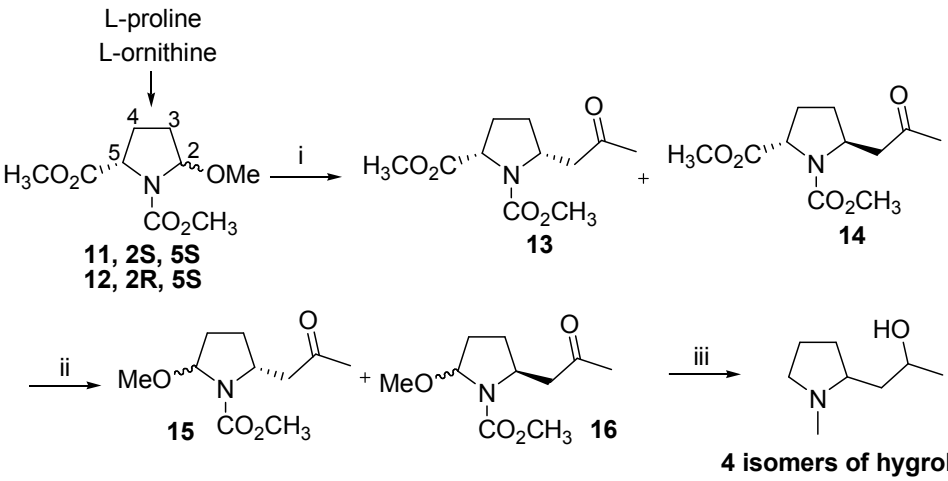
Shono's approach (1981)[11]

This approach involves the anodic oxidation of pyrrolidine at α-position to get the corresponding methoxylated pyrrolidine **9**, which on treatment with prop-1-en-2-yl acetate resulted in the formation of protected hygrine **10** (**Scheme 1**). $LiAlH_4$ reduction of the ketone moiety as well as carbamate yielded (±)-hygroline **5** in 88% yield as a mixture along with other isomer.



Scheme 1: (i) $ClCO_2CH_3$, base, 90%; (ii) tetraethylammonium *p*-toluenesulfonate, MeOH, e^-, 78%; (iii) $CH_2C(OAc)CH_3$; (iv) $LiAlH_4$, THF, 88%.

In this approach,[12] Shono *et al*, have prepared starting compounds **11** and **12** from L-ornithine or L-proline by using anodic oxidation at α-position. Treatment of **11** with isopropenyl acetate in the presence of $TiC1_4$ gave a mixture of stereoisomers **13** and **14** in a ratio of 7:3 (85% yield). A similar mixture of **13** and **14** was also obtained by the reaction of **12** with isopropenyl acetate under similar conditions (**Scheme 2**).

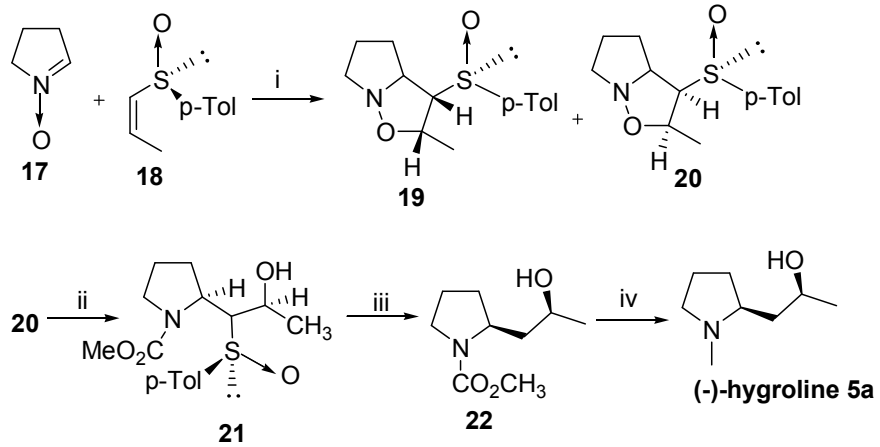


Scheme 2: (i) $CH_2C(OAc)CH_3$, $TiCl_4$, 85%; (ii) (a) KOH; (b) -2e, MeOH, CH_3ONa, 52%; (iii) $LiAlH_4$, 81%.

A mixture of **15** and **16** was obtained by alkaline hydrolysis of a mixture of **13** and **14** followed by anodic oxidation. Subsequent reduction of **15** and **16** with $LiAlH_4$ yielded a mixture of hygroline **(+)-5** and **(-)-5** and its diastereoisomers pseudohygroline **(+)-6** and **(-)-6** in a ration of 2:3.

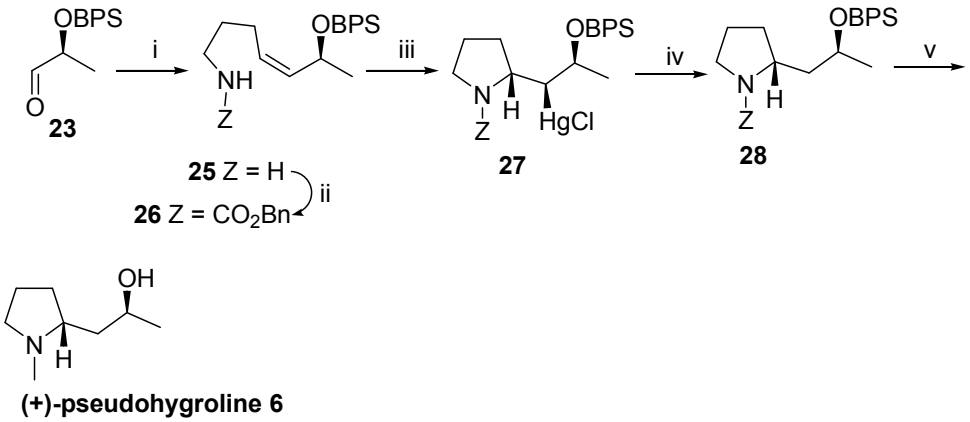
Hootelé's approach (1997)[13]

This approach describes the synthesis of (-)-hygroline **5a** using nitrone-vinyl sulfone cycloaddtion. Reaction of cyclic nitrone **17** with *Z*-vinyl sulfone **18** in ether yielded the cycloadducts **19** and **20** in the ratio 87:13. The major cycloadduct **20** was treated with Ni/Al alloy to give the amino alcohol in 85% yield which was protected as carbamate **21**. W6 Raney nickel reduction gave carbamate **22** which was reduced with $LiAlH_4$ reduction to give (-)-hygroline **5a** in 83% yield (**Scheme 3**).



Scheme 3: (i) Et_2O, 25 °C, 17 d, 72%; (ii) (a) Ni/Al (3x weight), aq. KOH 1M/MeOH, 25 °C, 2 h, 85%; (b) $C1CO_2CH_3$ (10 equiv.), aq. K_2CO_3, 25 °C, 12 h, 95%; (iii) W6 Raney Nickel/H_2, MeOH, 6 h, 75%; (iv) $LiAlH_4$, THF, reflux, 40 min., 83%.

Perlmutter's Approach (1998)[14]

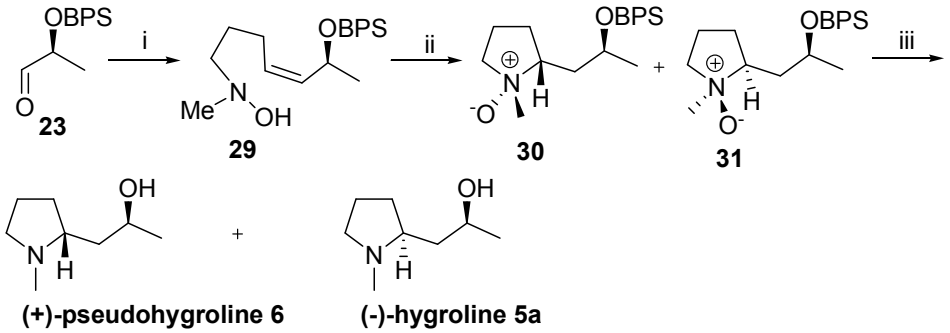


Scheme 4: (i) (a) $Ph_3P{=}CH(CH_2)_2CN$ (**24**), THF, 0 °C, 64%; (b) $LiAlH_4$, Et_2O, reflux, l h; (c) H_2O, 91%; (ii) (a) $ClCO_2Bn$, toluene, 25 °C, 24 h; (b) Aq. $NaHCO_3$, 87%; (iii) (a) $Hg(OAc)_2$, CH_2Cl_2, 25 °C, 72 h; (b) Aq. NaCl, 84%; (iv) Bu_3SnH, AIBN, toluene, 92%; (v) (a) $LiAlH_4$, 68%; (b) NH_4F, MeOH, 25 °C, 70%.

This approach describes the synthesis of (+)-pseudohygroline **6** using mercuric acetate ($Hg(OAc)_2$) catalyzed ring closing as the key step. Wittig reaction of the known protected lactaldehyde **23** with the ylide **24**, followed by nitrile reduction gave amine **25** as a single alkene stereoisomer which was converted into the corresponding carbamate **26**. Treatment of **26** with $Hg(OAc)_2$ in CH_2Cl_2 provided the ring closed product **27** as a single diastereomer in 84% yield. Demercuration of **27** then provided the intermediate **28** which on treatment with $LiAlH_4$, followed by fluorodesilylation using ammonium fluoride in methanol, gave pure (+)-pseudohygroline **6** (**Scheme 4**).

Knight's approach (1999)[15]

This approach by Knight *et al.* describes the synthesis of (-)-hygroline **5a** and pseudohygroline **6** using reverse Cope-elimination. The (Z)-precursor **25** was obtained from (S)-lactataldehyde **23** using: (i) Wittig reaction with ylide derived from triphenyl phosphine salt of ethyl 4-bromobutanoate to give the (Z)-alkenoate (ii) DIBAL-H reduction (iii) and reaction with *N*-methyl hydroxylamine (iv) reduction using sodium cyanoborohydride (**Scheme 5**).



Scheme 5: (i) (a) $EtO_2C(CH_2)_3PPh_3Br$, $NaN(TMS)_2$, 0 °C, THF, 90%; (b) DIBAL-H, 90%; (c) MeNHOH.HCl, K_2CO_3, CH_2Cl_2, 0 °C, 100%; (d) $NaBH_3CN$, pH 4, MeOH, 100%; (ii) $CHCl_3$, 60 °C, 100%; (iii) (a) H_2, 5% Pd/C, 20 °C, EtOH, 99%; (b) NH_4F, MeOH, 20 °C, 70%.

Upon heating in $CHCl_3$ the compound **29** underwent reverse-Cope cyclization to give the mixture of **30** and **31** in 3:1 ratio. Completion of the syntheses of (-)-hygroline **5a**

and (+)-pseudohygroline **6** was done by reduction of the mixed *N*-oxides **30** and **31**, separation of the resulting pyrrolidines and desilylation.

1.1.4 Present Work

1.1.4.1 Objective

Even though few methods are reported for the synthesis of hygroline (**5**), most of these methods suffer from the fact that they make use of chiral starting materials, expensive reagents and also mixtures of products were obtained in many cases. Hence, the synthesis of hygroline (**5**), starting from prochiral substrates using catalytic enantioselective reactions, is highly desirable. The use of catalytic enantioselective reactions are advantageous in the sense that both the stereoisomers can be synthesized from the same prochiral substrate. Hence we have decided to synthesize (+)-hygroline (**5**) using proline-catalyzed α-aminooxylation reaction. The Retrosynthetic analysis for the synthesis of (+)-hygroline (**5**) is shown in **Figure 3**.

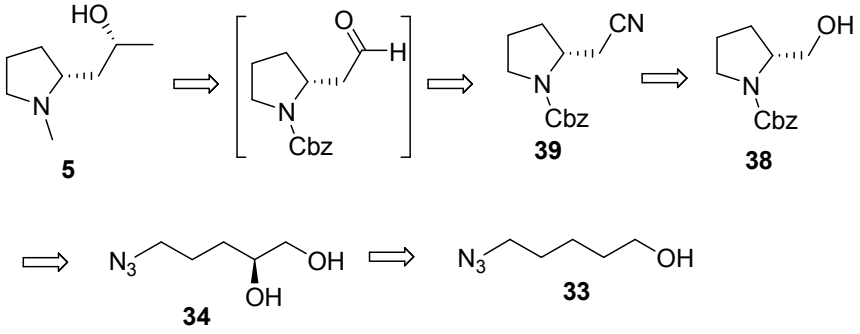


Figure 3: Retrosynthetic analysis

The secondary alcohol moiety in (+)-hygroline (**5**) can be obtained by the addition of methylmagnesium bromide on to the aldehyde derived from the nitrile **39** using DIBAL-H reduction. The nitrile **39** can be obtained from the corresponding alcohol **38**. The prolinol **38** can in turn be obtained from the corresponding azido diol **34** using simple organic reactions. The diol **34** can be obtained from 5-azidopentanol **33** *via* (i) Swern oxidation and (ii) D-proline catalyzed α-aminooxylation. Since this

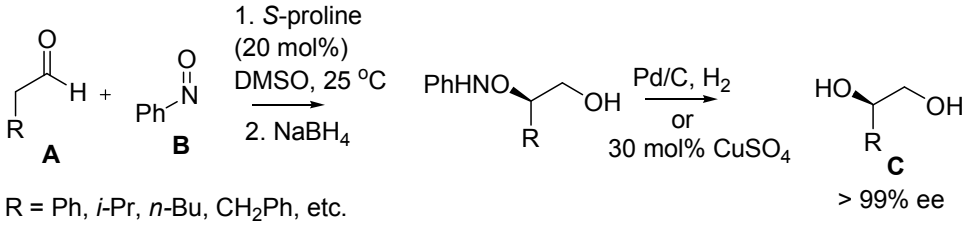
section deals with a highly important and attractive asymmetric reaction (proline-catalyzed *α-aminooxylation*), which introduces stereogenicity into the prochiral molecule, a brief account of proline-catalyzed *α-aminooxylation* of carbonyl compounds is described.

1.1.4.2 Proline-catalyzed α-Aminooxylation

Optically active α-hydroxy carbonyl moieties are commonly found in numerous important natural products and are highly versatile functional synthons. This has led to extensive research into finding new diastereoselective and enantioselective routes for their syntheses.[16] One way of preparing these compounds is asymmetric a-hydroxylation of enolates.[17] In addition, nucleophilic additions to chiral glyoxal derivatives and chiral hydrazones have also been successfully employed.[18] However, these methods are indirect and most of them require multiple manipulations for the desired α-hydroxy product to be obtained.

Asymmetric reactions catalyzed by metal-free organic catalysts have experienced a renaissance in recent years.[19] Interestingly, since the discovery of amino acid catalyzed stereoselective Robinson annulations in the early 1970s,[20] there was no intensive research on this concept for other C-C bond-forming reactions for several decades, even though the reaction is frequently used in the preparation of building blocks for the total synthesis of natural products.[21] The field of asymmetric organocatalysis is rapidly developing and attracts an increasing number of research groups around the world. In particular, organocatalytic asymmetric synthesis have provided several new methods for obtaining chiral compounds in an environmentally benign manner.[22] In this connection, proline, an abundant, inexpensive amino acid available in both enantiomeric forms, has emerged as arguably the most practical and versatile organocatalyst.[23] Proline has also been found to be an excellent asymmetric

catalyst for α-functionalization[24,25] of carbonyl compounds. When an aldehyde **A** without substitution at α-position was reacted with nitrosobenzene **B** in presence of L-proline in DMSO at ambient temperature, aminooxylation of the aldehyde takes place at α-position. The aminooxyl moiety undergoes hydrogenolysis with Pd/C, H_2 or $CuSO_4$ to give the corresponding diols **C** in very high ee s (**Scheme 6**).



Scheme 6: α-aminooxylation of aldehydes

The mechanism of the α-aminooxylation reaction is given in **Fig. 4**.

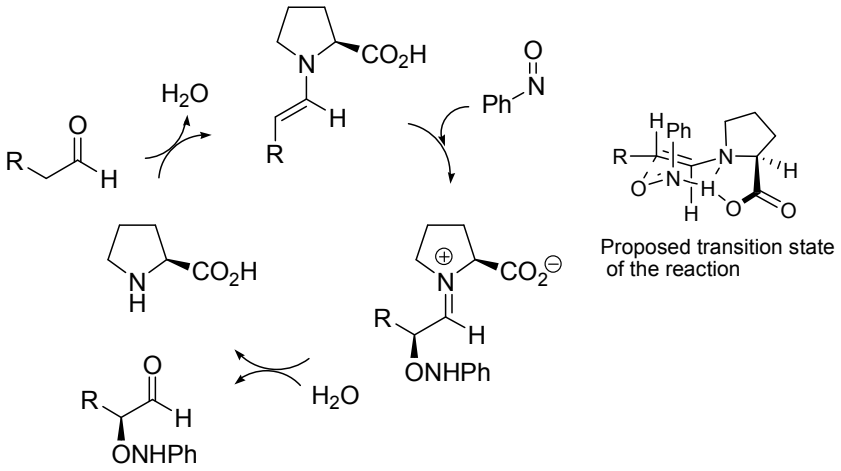


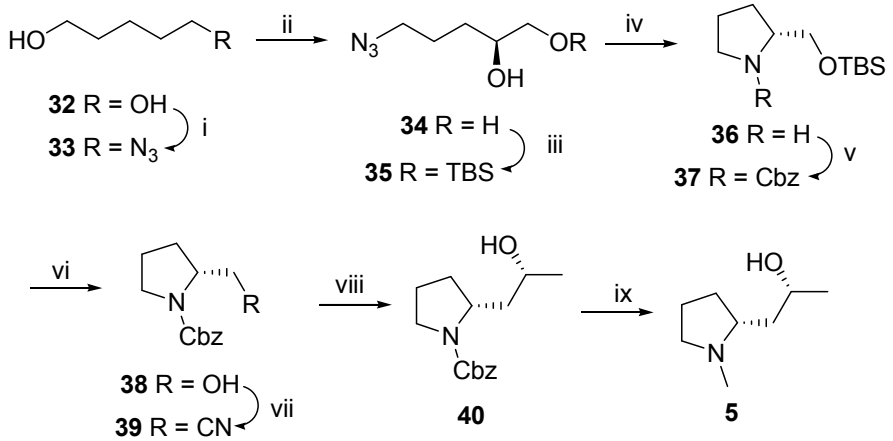
Fig. 4: Proposed mechanism of the α-aminooxylation reaction

The observed enantioselectivitiy of the catalytic α-aminoxylation of aldehydes can be rationalized by invoking an enamine mechanism operating through a chair transition state where the *Si* face of an *E*-enamine formed from the aldehyde and L-proline approaches the less-hindered oxygen atom of nitrosobenzene to provide a chiral α-aminoxyaldehyde with *R* configuration (**Fig. 4**). Since proline is commercially available in both enantiopure forms, a one-pot sequence-catalytic α-aminooxylation of

aldehydes followed by in situ reduction with $NaBH_4$ affords *R*- or *S*- configured 1,2-diol units (the secondary alcohol "protected" by an O-amino group) with excellent enantioselectivities and in good yields.

1.1.5 Results and Discussion

The synthesis of (+)-hygroline (**5**), wherein D-proline-catalyzed α-aminooxylation reaction constitutes a key step for the introduction of chirality, is presented in S**cheme 7**.



Scheme 7: (i) (a) *p*-TsCl, Et_3N, CH_2Cl_2, 0 °C, 1 h, (b) NaN_3, DMF, 80 °C, 6 h, 80% for 2 steps; (ii) (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C, 0.5 h, (b) 20 mol% D-Proline, PhNO, CH_3CN, -20 °C, 24 h, then 0 °C $NaBH_4$, EtOH, 0.5 h, (c) 30 mol% $CuSO_4$, MeOH, 24 h, 61% for 3 steps; (iii) TBDMSCl, imidazole, CH_2Cl_2, 0 °C, 1 h, 95%; (iv) (a) MsCl, Et_3N, CH_2Cl_2, 0 °C, 0.5 h, (b) Pd/C, H_2, Et_3N, MeOH, 2 h, 80% for 2 steps; (v) CbzCl, dioxane, H_2O, $NaHCO_3$, 0 °C, 12 h, 99%; (vi) TBAF, THF, 0 °C, 1 h, 90%; (vii) (a) MsCl, Et_3N, CH_2Cl_2, 0 °C, 0.5 h, (b) NaCN, DMF, 50 °C, 12 h, 82% for 2 steps; (viii) (a) DIBAL-H, CH_2Cl_2, -78 °C, 1 h, (b) MeMgBr, THF, -78 °C, 0.5 h, 85% for 2 steps; (ix) $LiAlH_4$, THF, reflux, 4 h, 50%.

5-Azido-pentan-1-ol (**33**), obtained from 1,5-pentanediol **32** in two steps using simple organic transformations, was subjected to Swern oxidation conditions to obtain the corresponding aldehyde *in situ*, which was converted to the azidodiol **34** in 61% yield using a 2-step reaction sequence: (i) D-proline catalyzed asymmetric α-aminooxylation using nitrosobenzene as the oxygen source followed by reduction of the aldehyde with $NaBH_4$ and (ii) cleavage of aminooxy moiety (N-O bond) with

$CuSO_4$; $[\alpha]^{25}_D$: +12 (*c* 1.0, $CHCl_3$). The ^1H NMR spectrum of the diol **34** showed signals at δ 1.40-1.53 (m) and 1.60-1.85 (m) corresponding to the aliphatic methylene groups. Also signals at δ 1.94 (br s) and 3.33 (t) correspond to the hydroxyl and methylene group ($C\mathbf{H_2}N_3$) protons respectively. Its ^{13}C NMR spectrum showed peaks at δ 66.15 and 71.50 corresponding to the carbons present in diol moiety and δ 51.24 for CH_2N_3 moiety.

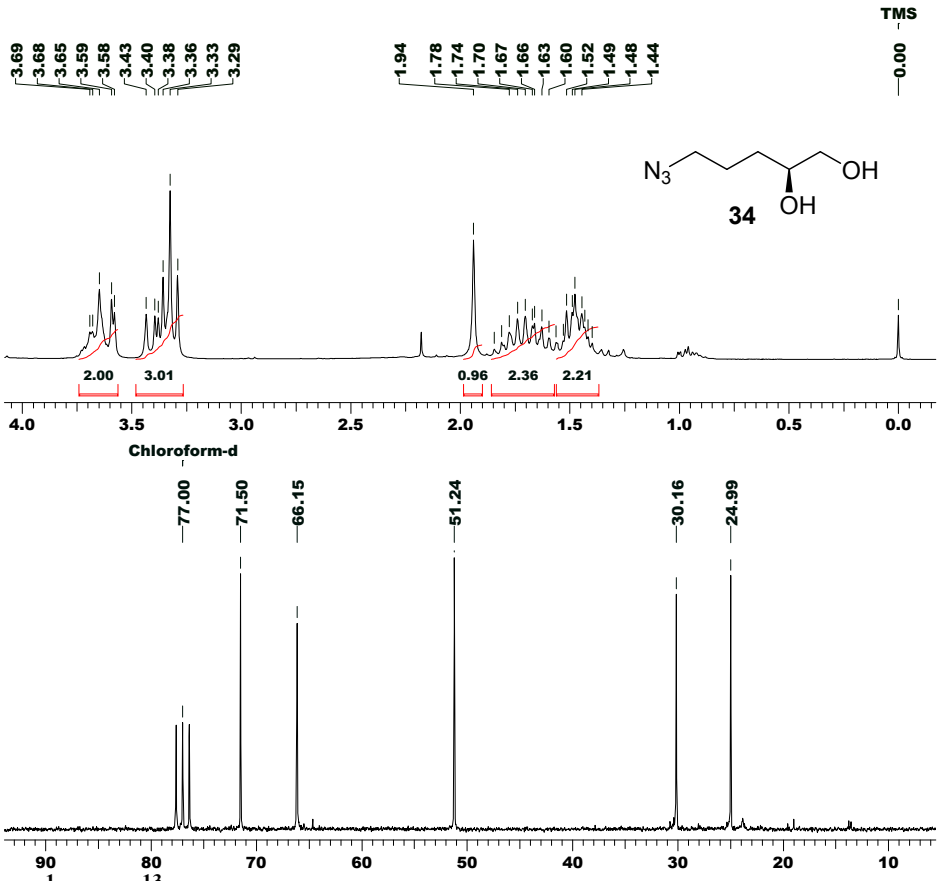


Fig. 5: ^1H and ^{13}C NMR spectra of (*S*)-5-azidopentane-1,2-diol (34)

The primary hydroxyl group in diol **34** was then protected selectively as *tert*-butyldimethylsilyl ether **35** using TBDMSCl and imidazole as base; $[\alpha]^{25}_D$: +49.04 (*c* 1.0, $CHCl_3$). The ^1H NMR spectrum of silyl ether **35** showed two singlets at δ 0.03 (6H) and 0.87 (9H) corresponding to the dimethyl and *tert*-butyl protons respectively.

Its ^{13}C NMR spectrum showed carbon signals at δ -5.7 and 25.8 corresponding to the methyl and *tert*-butyl carbons in the silyl protecting group.

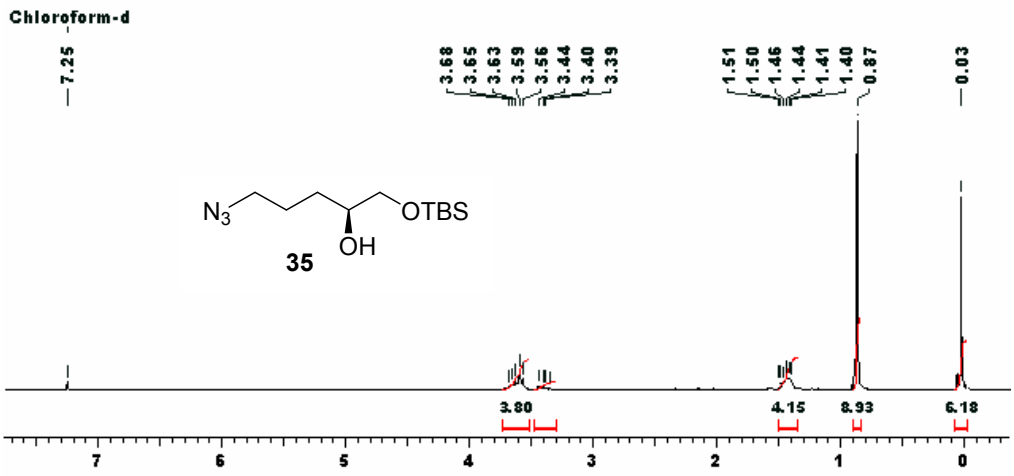


Fig. 6: ^{1}H NMR spectrum of silylether 35

Mesylation of the secondary hydroxyl in **35** using methanesulfonyl chloride and Et_3N gave the corresponding mesylate *in situ* which underwent reduction (Pd/C and H_2) to give chiral pyrrolidine **36** in 80% yield; $[\alpha]^{25}_{D}$: +48.49 (*c* 0.6, MeOH). The ^{1}H NMR spectrum of pyrrolidine **36** showed peaks at δ 1.33-1.45 (m), 1.60-1.77 (m) and 2.66-3.12 (m) corresponding to the methylene protons in the pyrrolidine ring. Other peaks at δ 2.35 (br s) and 3.5 (dd) are due to the NH and the exocyclic methylene protons respectively (**Fig. 7**).

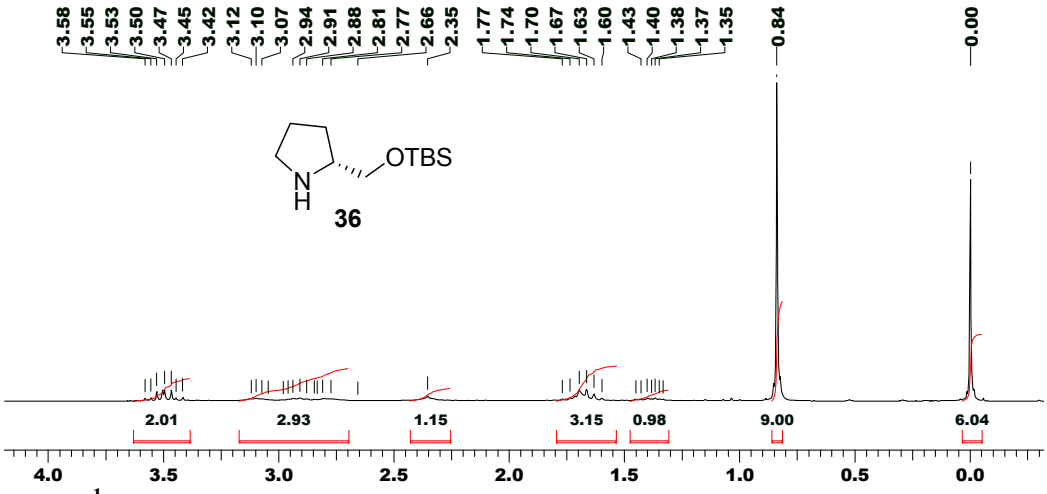


Fig. 7: ^{1}H NMR spectrum of pyrrolidine 36

Its ^{13}C NMR spectrum displayed peaks at δ 68.54 and 60.91 due to the exocylic methylene carbon and the tertiary carbon (-**C**(H)-NH) respectively.

The secondary amine moiety in pyrrolidine **36** was then protected as its carbamate using CbzCl and $NaHCO_3$ to give the corresponding carbamate **37** in 99% yield; $[\alpha]^{25}_D$: +42.54 (*c* 0.9, $CHCl_3$). The appearance of signals at δ 5.16 (s) (**CH_2**Ph) and 7.33 (s) (CH_2**C$_6$H$_5$**) in the ^1H NMR spectrum of the **37** confirms the presence of the carbamate moiety. Its ^{13}C NMR spectrum displayed carbon signals at δ 66.72 and 154.84 due to the benzylic and carbonyl carbons respectively.

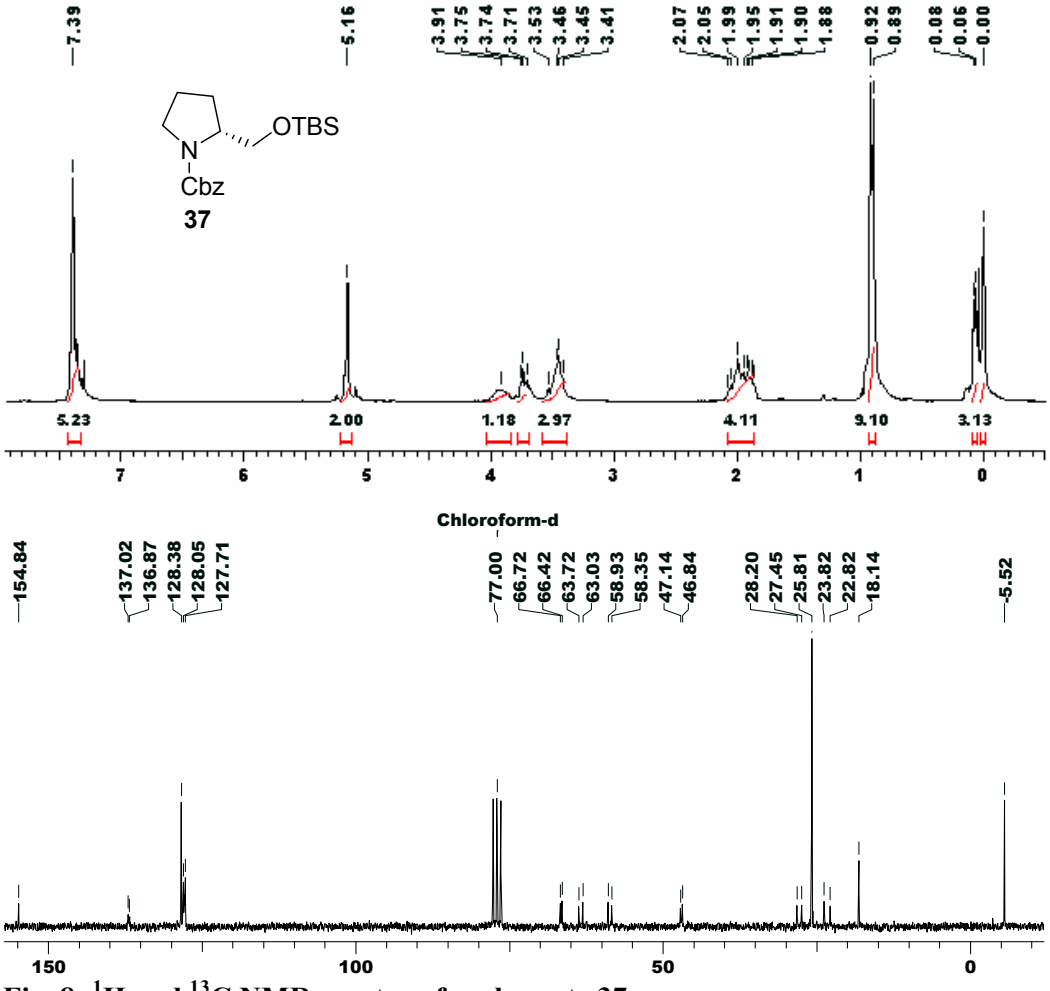


Fig. 8: ^1H and ^{13}C NMR spectra of carbamate 37

The silyl protection in carbamate **37** was then removed using TBAF in THF to give prolinol **38** in 90% yield; $[\alpha]^{25}_D$: -39.9 (*c* 1.0, CH_2Cl_2) {lit.[26] $[\alpha]_D$: -40 (*c* 1, EtOH)}.

The disappearance of signals at δ 0.06-0.8 (m) and 0.91 (d) in the ^{1}H NMR spectrum of the prolinol **38** confirmed the deprotection of the silyl group. Its ^{13}C NMR spectrum displayed characteristic carbon signals at δ 23.76, 28.24 and 47.07 corresponding to the methylene carbons present in the pyrrolidine ring.

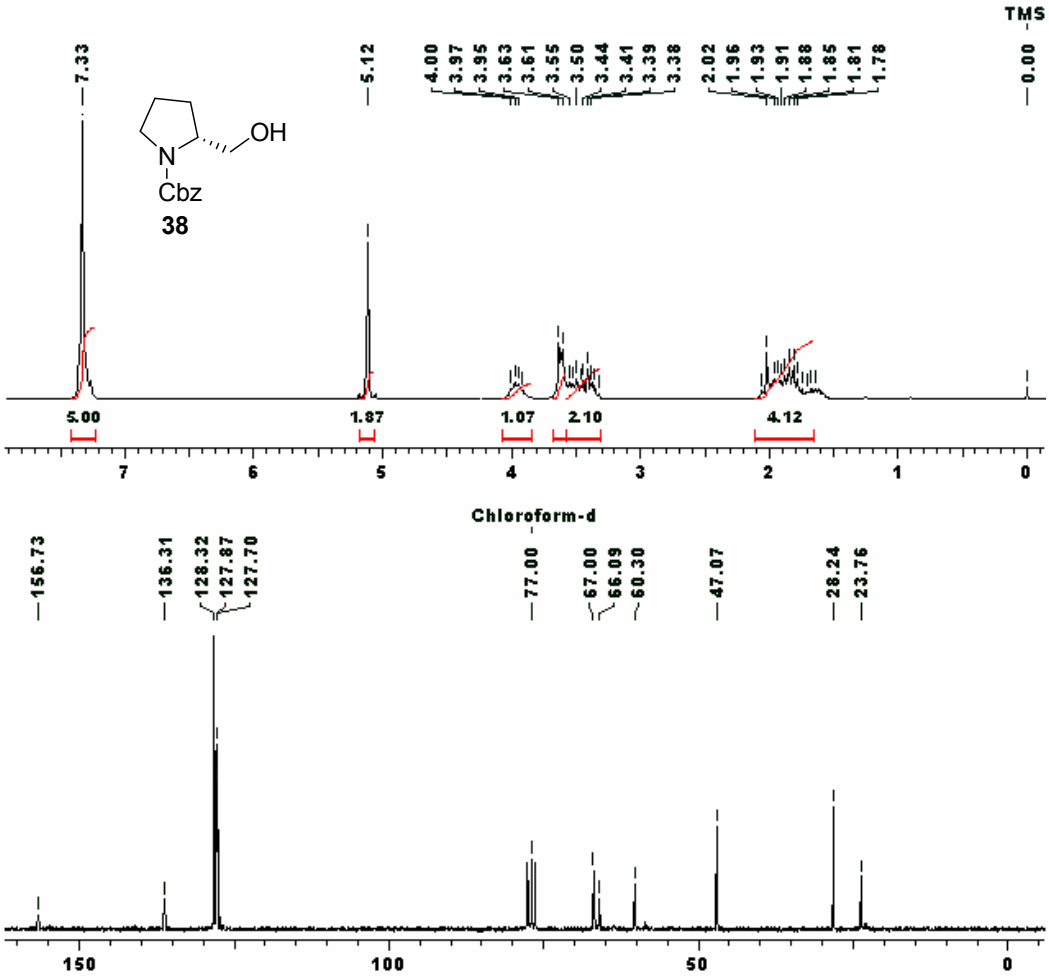


Fig. 9: ^{1}H and ^{13}C NMR spectra of prolinol 38

The primary alcohol in the prolinol **38** was then protected as its mesylate using methanesulfonyl chloride and Et_3N as the base which was then treated with sodium cyanide in DMF to give the corresponding nitrile **39** in 82% yield; $[\alpha]^{25}_{D}$: +104.61 (*c* 1.0, $CHCl_3$). The characteristic carbon signal at δ 117.35 (-**C**≡N) in the ^{13}C NMR spectrum of the nitrile **39** confirmed the presence of the nitrile group. Also, its IR

spectrum displayed characteristic bands at 1701 and 2257 cm^{-1} corresponding to the carbonyl and the nitrile group stretching frequencies.

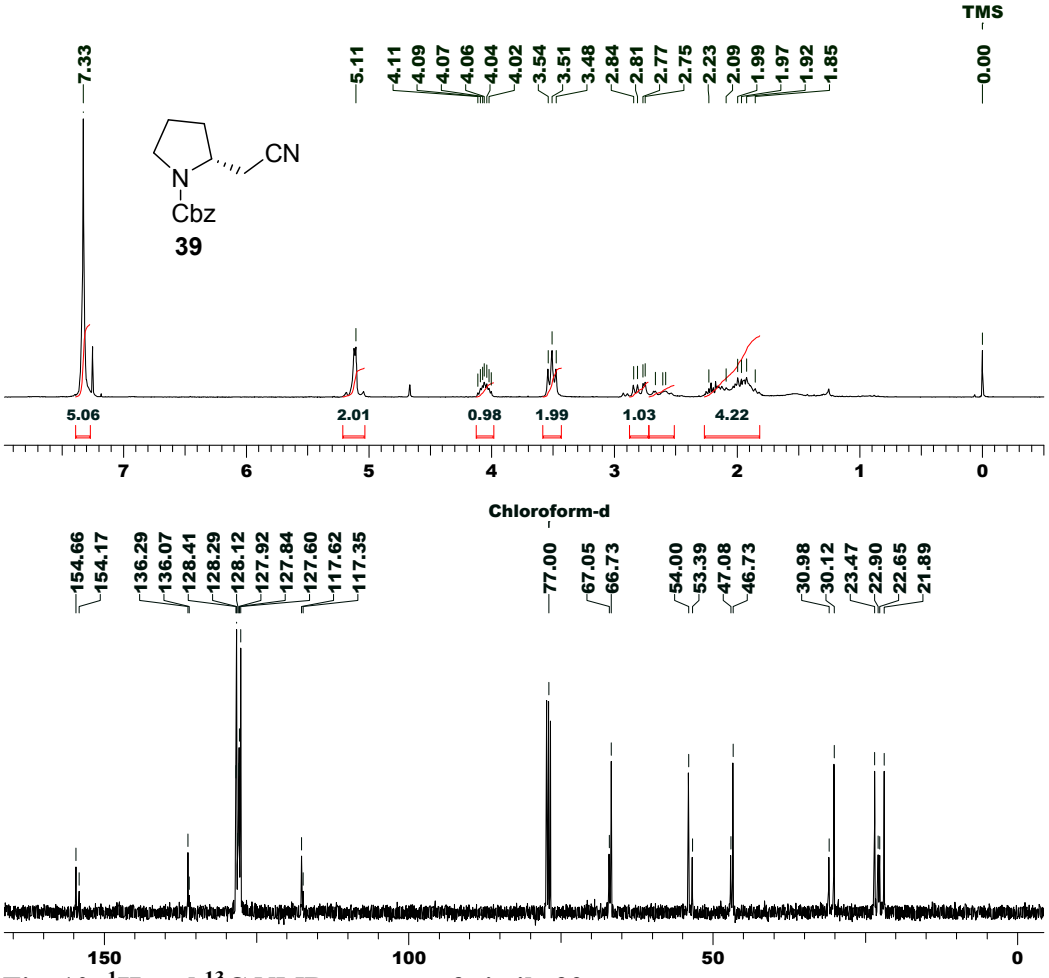


Fig. 10: ^{1}H and ^{13}C NMR spectra of nitrile 39

The next step involved the reduction of the nitrile **39** in to the corresponding aldehyde followed by the addition of methylmagnesium bromide (MeMgBr). Subsequently, when nitrile **39** was reduced with DIBAL-H at -78 °C in CH_2Cl_2 to the corresponding aldehyde *in situ* and then treated with MeMgBr, the addition product **40** was obtained in 85% yield (dr = 10:1, determined by ^{13}C NMR spectrum); $[\alpha]^{25}_{D}$: -12.7 (*c* 0.32, $CHCl_3$). The ^{1}H NMR spectrum of the alcohol **40** showed signals at δ 1.18 (d) and 4.20-4.31 (m) corresponding to the methyl protons and the proton on the carbon attached to the hydroxyl group respectively. Its ^{13}C NMR spectrum showed

carbon signals at δ 23.66, 31.22 and 67.2 corresponding to the methyl, exocyclic methylene carbons and methine carbon attached to the hydroxyl group respectively.

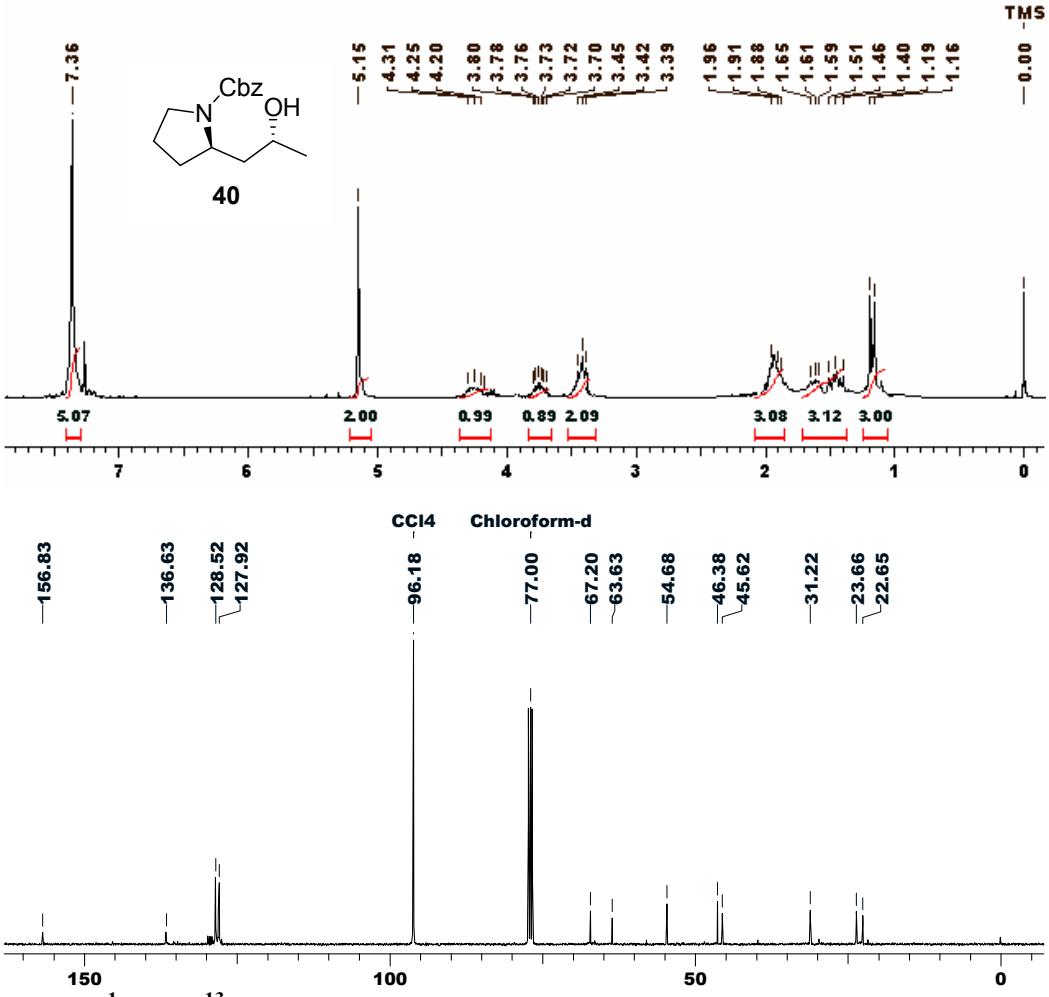


Fig. 11: ^{1}H and ^{13}C NMR spectra of alcohol 40

To confirm the stereochemistry (*anti*/*syn*) of the alcohol **40** (by comparing the spectral and optical data with known silylether **28**[14]), it was converted to its corresponding *tert*-butyldiphenylsilyl ether (TBDPS) **40a**; $[\alpha]^{25}_{D}$: -62.4 (*c* 1.8, $CHCl_3$). The spectral data and optical rotation of the silyl ether **40a** were found to be not matching with the data reported for *syn* aminoalcohol **28**, thereby confirming the formation of *anti*-aminoalcohol **40**.

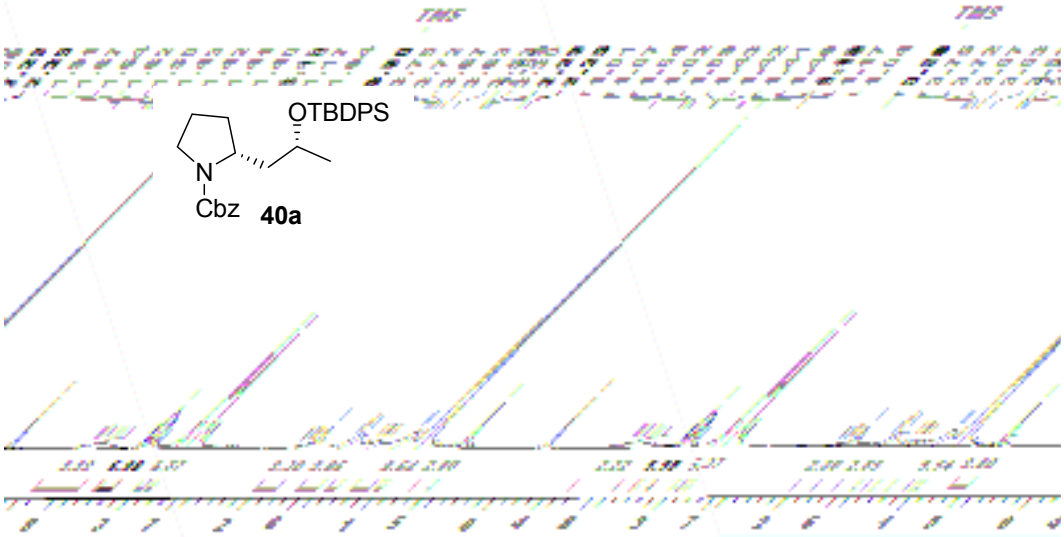


Fig. 12: ^{1}H NMR spectrum of silylether 40a

Finally, reduction of the Cbz group in the alcohol **40** with $LiAlH_4$ gave (+)-hygroline (**5**) in 50% yield and 92% ee based on comparison of its optical rotation with that of reported value; $[\alpha]^{25}_{D}$: +46.64 (*c* 0.8, EtOH); {lit.[15] $[\alpha]^{24}_{D}$: +50.7 (*c* 1, EtOH)}. The ^{1}H NMR spectrum of (+)-hygroline (**5**) showed signals at δ 1.13 (d) and 2.34 (s) corresponding to the terminal methyl and *N*-methyl protons respectively. Its ^{13}C NMR spectrum showed carbon signals at δ 65.28 and 65.71 corresponding to the methine carbons attached to the hydroxyl and NMe moieties respectively. The spectral data obtained for (+)-hygroline (**5**) were in full agreement with the values reported in the literature.[13]

1.1.6 Conclusion:

In conclusion, we have successfully applied proline-catalyzed α-aminooxylation and α-amination strategies for the enantioselective synthesis of (+)-hygroline (**5**), which was obtained in 92% ee. The reactions are rapid, and require a relatively low amount of an inexpensive and nontoxic proline catalyst that is available in both enantiomeric forms. The high yields and less number of steps render our approach a good alternative to the known methods.

1.1.7 Experimental Section:

5-Azidopentan-1-ol (33)

To a stirred solution of 1,5-pentanediol (5.2 g, 50 mmol) and Et_3N (7 mL, 50 mmol) in CH_2Cl_2 (200 mL), at 0 °C was added *p*-toluenesulfonyl chloride (8.6 g, 45 mmol). After stirring for 1 h at 0 °C, the reaction mixture was poured into ice water (150 mL), washed with aqueous H_2SO_4 (20 %), saturated aqueous $NaHCO_3$, and brine, dried over anhyd. Na_2SO_4 and the solvent was distilled off under reduced pressure to give the crude product which was then dissolved in DMF (100 mL) followed by the addition sodium azide (3.3g, 50 mmol). The reaction mixture was then heated at 80 °C for 6 h followed by quenching it by the addition of water. The aqueous layer was extracted with Et_2O (3 x 100 mL) and the combined organic layers were dried over anhyd. Na_2SO_4, solvent distilled off under reduced pressure and the crude product purified by column chromatography over silica gel using EtOAc/Pet. ether (10:90) as eluent to yield pure azidoalcohol 33 in 80% yield.

Yield: 4.6 g (80% for 2 steps); colorless liquid; **IR** ($CHCl_3$, cm^{-1}): 780, 930, 1038, 1117, 1224, 1338, 1456, 2103, 3227; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.23-1.43 (m, 4H), 1.46-1.54 (m, 2H), 1.94 (br s, 1H), 3.21 (t, *J*=6.7 Hz, 2H), 3.31-3.43 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 22.74, 30.16, 32.24, 51.15, 62.22; **Analysis:** **$C_5H_{11}N_3O$** requires C, 46.50; H, 8.58; N, 32.53%; found C, 46.62; H, 8.51; N, 32.59%.

(*S*)-5-Azidopentane-1,2-diol (34)

Swern oxidation: To a stirred solution of oxalyl chloride $(COCl)_2$ (6.35 g, 50 mmol) in CH_2Cl_2 (30 mL) at -78 °C, was added a solution of DMSO (5.3 mL, 75 mmol). The reaction mixture was stirred for 20 min. followed by the addition of a solution of 5-azidopentan-1-ol (**33**) (3.23 g, 25 mmol) in CH_2Cl_2 (20 mL). After stirring for 0.5 h at

-78 °C, the reaction was quenched by the addition of Et_3N (13.9 mL, 100 mmol). The reaction mixture was then stirred for 10 min. followed by the addition of water (100 mL). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 60 mL). The combined organic layer was washed with water (3 x 30 mL), dried over anhyd. Na_2SO_4 and concentrated to give the corresponding crude aldehyde.

α-Aminooxylation: without purification the aldehyde was dissolved in CH_3CN (100 mL). The solution was cooled to -20 °C followed by the addition of nitrosobenzene (2.25 g, 21 mmol) and L-proline (483 mg, 4.2 mmol, 20 mol%). After 24 h, the reaction mixture was warmed to 0 °C, followed by dilution with anhyd. MeOH (20 mL) and careful addition of excess $NaBH_4$ (1.44 g, 38 mmol). The reaction was quenched after 10 min. by pouring of the reaction mixture into a vigorously stirred biphasic solution of Et_2O and aqueous HCl (1M). The organic layer was separated, and the aqueous phase was extracted with EtOAc (3 x 100 mL). The combined organic phases were dried over anhyd. Na_2SO_4 and concentrated to give the crude product which was dissolved in MeOH (40 mL) followed by the addition of $CuSO_4$ (g, 7.5 mmol). After stirring for 24 h at 25 °C, the reaction mixture was quenched by the addition of a solution saturated aqueous NH_4Cl (40 mL). The organic layer was separated and the aqueous phase was extracted with EtOAc (3 x 30 mL). The combined organic phases were dried over anhyd. Na_2SO_4 and concentrated to give the crude product which was purified by column chromatography over silica gel using EtOAc/Pet. ether (40:60) as eluent to give pure diol **34** in 61% yield.

Yield: 2.2 g (61% for 3 steps); gum; **$[\alpha]^{25}_D$:** +12 (*c* 1.0, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 669, 770, 930, 1038, 1124, 1215, 1338, 1456, 1541, 2115, 3018, 3127; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.40-1.56 (m, 2H), 1.60-1.85 (m, 2H), 1.94 (br s, 1H), 3.33 (t, *J*=6.7

Hz, 2H), 3.38-3.43 (m, 1H), 3.58-3.73 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 24.99, 30.16, 51.24, 66.15, 71.50; **Analysis: $C_5H_{11}N_3O_2$** requires C, 41.37; H, 7.64; N, 28.95%; found C, 41.19; H, 7.71; N, 28.91%.

(2*S*)-1-((*tert*-Butyl)dimethylsilyloxy)-5-azido-pentan-2-ol (35)

To a stirred solution of diol **34** (2.18 g, 15 mmol) and imidazole (1.23 g, 18 mmol) in CH_2Cl_2 (50 mL) was added TBDMSCl (2.26 g, 15 mmol) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C, solvent distilled off under reduced pressure and crude product purified by column chromatography over silica gel using EtOAc/Pet. ether as eluent (5:95) to give silylether **35** in 95% yield.

Yield: 3.7 g (95%); gum; **$[\alpha]^{25}_D$:** +49.04 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 0.03 (s, 6H), 0.87 (s, 9H), 1.40-1.51 (m, 4H), 3.40 (dd, *J*=10.9, 7.8 Hz, 1H), 3.59 (t, *J*=6.2 Hz, 2H), 3.65-3.68 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: -5.84, 18.10, 23.89, 25.74, 31.16, 52.11, 69.54, 72.52; **Analysis: $C_{11}H_{25}N_3O_2Si$** requires C, 50.93; H, 9.71; N, 16.20; Si, 10.83%; found C, 50.81; H, 9.79; N, 16.24; Si, 10.88%.

(2*R*)-2-((*tert*-Butyl)dimethylsilyloxymethyl)-pyrrolidine (36)

To a stirred solution of silylether **35** (2.33 g, 9 mmol) and Et_3N (1.38 mL, 9.9 mmol) in CH_2Cl_2 (60 mL) at 0 °C was added methanesulfonyl chloride (700 µL, 9 mmol) drop-wise using a syringe. After stirring at 0 °C for 0.5 h, the mixture was poured into ice-water (60 mL), washed with aqueous H_2SO_4 (20%), saturated aqueous $NaHCO_3$, and brine, dried over anhyd. Na_2SO_4. Solvent was distilled off under reduced pressure to give the crude mesylate, which was added to a stirred suspension of 10 % Pd/C (20 mg) and Et_3N (1.39 mL, 9.9 mmol) in MeOH (10 mL) under hydrogen atmosphere (H_2, 1 atm., balloon pressure) at 25 °C. After 2 h, the mixture was filtered through a pad of celite and the celite was rinsed with MeOH (3 x 30 mL). The combined organic layer was concentrated under reduced pressure and the crude product was

purified by column chromatography using $CHCl_3$/MeOH (92:8) as eluent to give pure pyrrolidine **36**.

Yield: 1.54 g (80% for 2 steps); gum; **$[\alpha]^{25}_D$:** +48.49 (*c* 0.6, MeOH); **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 0.0 (s, 6H), 0.84 (s, 9H), 1.33-1.45 (m, 1H), 1.60-1.77 (m, 3H), 2.35 (br s, 1H), 2.66-3.12 (m, 3H), 3.46 (dd, *J*=10.0, 5.8 Hz, 1H), 3.54 (dd, *J*=10.0, 4.9 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: -5.71, 18.12, 22.11, 25.80, 28.33, 46.23, 60.91, 68.54; **Analysis: $C_{11}H_{25}NOSi$** requires C, 61.33; H, 11.70; N, 6.50; Si, 13.04%; found C, 61.39; H, 11.59; N, 6.57; Si, 13.11%.

(2*R*)-*N*-Benzyloxycarbonyl-2-((*tert*-Butyl)dimethylsilyloxymethyl)-pyrrolidine (37)

To a stirred solution of pyrrolidine **36** (645 mg, 3 mmol) in dioxane (30 mL) and water (3 mL), was added $NaHCO_3$ (756 mg, 9 mmol). The reaction mixture was cooled to 0 °C and a solution of CbzCl (512 mg, 3 mmol) in dioxane (3mL) was added to it. After 12 h, the reaction mixture was quenched by the addition of water (20 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried over anhyd. Na_2SO_4, solvent distilled off under reduced pressure and the crude product purified by column chromatography over silica gel using EtOAc/Pet. ether (15:85) as eluent to give pure carbamate **37** in 99% yield.

Yield: 1.04 g (99%); gum; **$[\alpha]^{25}_D$:** +42.54 (*c* 0.9, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 721, 1031, 1223, 1362, 1456, 1701, 2977, 3012, 3212; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 0.0 (s, 3H), 0.07 (d, *J*=3.8 Hz, 3H), 0.90 (d, *J*=4.9 Hz, 9H), 1.86-2.07 (m, 4H), 3.41-3.53 (m, 3H), 3.71-3.75 (m ,1H), 3.91 (br s, 1H), 5.16 (s, 2H), 7.39 (s, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: -5.52, 18.14, 22.82, 23.82, 25.81, 27.45, 28.20, 46.84, 47.14, 58.35, 58.93, 63.03, 63.72, 66.42, 66.72, 127.65, 128.05, 128.38, 136.78, 137.02, 154.84;

Analysis: $\mathbf{C_{19}H_{31}NO_3Si}$ requires C, 65.29; H, 8.94; N, 4.01; Si, 8.03%; found C, 65.39; H, 8.82; N, 4.09; Si, 8.07%.

(*R*)-Benzyl 2-(hydroxymethyl)pyrrolidine-1-carboxylate (38)

To a stirred solution of carbamate **37** (1.04 g, 3 mmol) in THF was added a solution of tetrabutylammonium fluoride (TBAF) (0.97 mL, 1M in THF, 3 mmol) at 0 °C and stirred for 1 h. The reaction mixture was quenched by addition of water and the organic phase was separated. The aqueous layer was extracted with EtOAc (3 x 20 mL) and the combined organic layers were dried over anhyd. Na_2SO_4, the solvent distilled off under reduced pressure and the crude product purified by column chromatography over silica gel using EtOAc/Pet. ether as eluent (20:80) to give prolinol **38** as colorless gum in 90% yield.

Yield: 635 mg (90%); gum; $\mathbf{[\alpha]^{25}_D}$: -39.9 (*c* 1.0, CH_2Cl_2) {lit.[26] $[\alpha]_D$: -40 (*c* 1, EtOH)}; **IR** ($CHCl_3$, cm^{-1}): 696, 731, 771, 1047, 1109, 1217, 1362, 1420, 1541, 1686, 2881, 2977, 3012, 3258; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.64-2.05 (m, 4H), 3.32-3.55 (m, 2H), 3.62 (d, *J*=5.4 Hz, 2H), 3.92-4.00 (m, 1H), 5.12 (s, 2H), 7.33 (s, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 23.76, 28.24, 40.07, 60.30, 66.09, 67.0, 127.7, 127.87, 128.32, 136.31, 156.73; **Analysis:** $\mathbf{C_{13}H_{17}NO_3}$ requires C, 66.36; H, 7.28; N, 5.95%; found C, 66.44; H, 7.17; N, 6.11%.

(*R*)-Benzyl 2-(cyanomethyl)pyrrolidine-1-carboxylate (39)

To a stirred solution of prolinol **38** (470 mg, 2 mmol) and Et_3N (460 μL, 3.3 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added methanesulfonyl chloride (232 μL, 3 mmol) drop-wise *via* syringe. After stirring at 0 °C for 0.5 h, the reaction mixture was washed with aqueous H_2SO_4 (20%), saturated aqueous $NaHCO_3$, and brine, dried over anhyd. Na_2SO_4. Solvent was distilled off under reduced pressure to give the crude mesylate, which was then dissolved in 10 mL DMF and sodium cyanide (147 mg, 3 mmol) was

added to it. The reaction mixture was then heated at 50 °C for 12 h followed by quenching it by the addition of water. The aqueous layer was extracted with Et_2O (3 x 30 mL) and the combined organic layers were dried over anhyd. Na_2SO_4, solvent distilled off under reduced pressure and the crude product purified by column chromatography over silica gel using EtOAc/Pet. ether (15:85) as eluent to yield pure nitrile **39** in 82% yield.

Yield: 400 mg (82% for 2 steps); gum; **$[\alpha]^{25}_{D}$:** +104.61 (*c* 1.0, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 779, 1067, 1223, 1365, 1451, 1541, 1701, 2257, 2881, 2977, 3321; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.85-2.23 (m, 4H), 2.63 (dd, *J*=15.0, 4.9 Hz, 1H), 2.80 (dd, *J*=15.7, 6.1 Hz, 1H), 3.51 (t, *J*=6.6 Hz, 2H), 4.06 (septet, *J*=4.1 Hz, 1H), 5.12 (s, 2H), 7.33 (s, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 21.89, 22.65, 22.9, 23.47, 30.12, 30.98, 46.73, 47.08, 53.39, 54.0, 66.73, 67.05, 117.35, 117.62, 127.6, 127.84, 128.06, 128.12, 128.29, 128.41, 136.07, 136.29, 154.17, 154.66; **Analysis: $C_{14}H_{16}N_2O_2$** requires C, 68.83; H, 6.60; N, 11.47%; found C, 68.94; H, 6.54; N, 11.41%.

(*R*)-Benzyl 2-((*S*)-2-hydroxypropyl)pyrrolidine-1-carboxylate (40)

To a stirred solution of nitrile **39** (489 mg, 2 mmol) in CH_2Cl_2 (20 mL), a solution of DIBAL-H (350 µL, 2.5 mmol, 1 M in THF) was added drop-wise *via* syringe at -78 °C. After stirring for 1 h the reaction was quenched by the addition of saturated aqueous NH_4Cl solution followed by stirring for 0.5 h. After separation of layers, the aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic phase was dried over anhyd. Na_2SO_4 and solvent distilled off under reduced pressure to give the crude product which was taken in THF (20 mL). The solution was cooled to -78 °C followed by the addition of a solution of methylmagnesium bromide (338 µL, 3 mmol, 1 M in THF). After stirring for 0.5 h the reaction was quenched by the addition of saturated aqueous NH_4Cl solution. After separation of the organic phase, the

aqueous phase was extracted with EtOAc (3 x 30 mL). The combined organic phase was dried over anhyd. Na_2SO_4, solvent distilled off under reduced pressure and the crude product purified by column chromatography over silica gel using EtOAc/Pet. Ether (15:85) as eluent to give alcohol **40** in 85% yield.

Yield: 447 mg (85% for 2 steps); gum; **$[\alpha]^{25}_{D}$**: -12.7 (*c* 0.32, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 667, 771, 1037, 1114, 1223, 1343, 1451, 1541, 1696, 2884, 2923, 3012, 3281; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.18 (d, *J*=6.3 Hz, 3H), 1.40-1.65 (m, 3H), 1.85-2.00 (m, 3H), 3.39-3.48 (m, 2H), 3.70-3.80 (m, 1H), 4.20-4.38 (m, 1H), 5.15 (s, 2H), 7.36 (s, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 22.65, 23.66, 31.22, 45.61, 46.36, 54.67, 63.62, 67.19, 127.90, 128.06, 128.51, 136.62, 156.80; **Analysis: $C_{15}H_{21}NO_3$** requires C, 68.42; H, 8.04; N, 5.32%; found C, 68.55; H, 8.11; N, 5.23%.

(*R*)-Benzyl 2-((*R*)-2-((*tert*-butyl)diphenylsilyloxy)propyl)pyrrolidine-1-carboxylate (40a)

To a stirred solution of alcohol **40** (158 mg, 0.6 mmol) and imidazole (54 mg, 0.8 mmol) in CH_2Cl_2 (2 mL) was added at TBDPSCl (219 mg, 0.75 mmol) 0 °C. The reaction mixture was stirred for 1 h at 0 °C, solvent distilled off under reduced pressure and crude product purified by column chromatography over silica gel using EtOAc/Pet. ether as eluent (15:85) to give silylether **40a** in 85% yield.

Yield: 256 mg (85%); **$[\alpha]^{25}_{D}$**: -62.4 (*c* 1.8, $CHCl_3$); **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.04 (s, 9H), 1.18 (d, *J*=5.2 Hz, 3H), 1.36-1.46 (m, 1H), 1.59-1.67 (m, 3H), 1.91-2.06 (m, 2H), 3.20-3.33 (m, 2H), 3.53-3.78 (m, 2H), 5.10 (s, 2H), 7.33 (s, 5H), 7.39 (s, 5H), 7.69 (br s, 5H); **Analysis: $C_{31}H_{39}NO_3Si$** requires C, 74.21; H, 7.83; N, 2.79; Si, 5.60%; found C, 74.07; H, 7.92; N, 2.71; Si, 5.74%.

(*R*)-1-((*R*)-1-methylpyrrolidin-2-yl)propan-2-ol: (+)-Hygroline (5)

To a stirred suspension of $LiAlH_4$ (76 mg, 2 mmol) in THF (5 mL) was added drop-wise a solution of alcohol **40** (132 mg, 0.5 mmol) in THF (2 mL) at 0 °C. The reaction mixture was refluxed for 4 h and then cooled to 0 °C and the excess $LiAlH_4$ was quenched by the addition of EtOAc. The reaction mixture was treated with 20% NaOH (0.5 mL), the white precipitate formed was filtered off and the residue was washed with EtOAc (3 x 10 mL). The combine EtOAc layers were dried over anhyd. Na_2SO_4, solvent distilled off under reduced pressure and the crude product purified by column chromatography over silica gel using EtOAc/MeOH (90:10) as eluent to yield (+)-hygroline (**5**) in 50% yield.

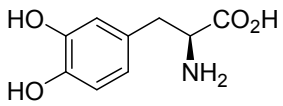
Yield: 36 mg (50%); gum; **$[\alpha]^{25}_{D}$**: +46.64 (*c* 0.8, EtOH); {lit.[15] $[\alpha]^{24}_{D}$: +50.7 (*c* 1, EtOH)}; **IR** ($CHCl_3$, cm^{-1}): 1264, 1434, 1458, 2794, 2846, 2878, 2928, 2970, 3322; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.13 (d, *J*=6.3 Hz, 3H), 1.37-1.44 (m, 1H), 1.63-1.96 (5H, m), 2.11-2.18 (1H, m), 2.34 (s, 3H), 2.58 (1H, m), 3.01-3.07 (1H, m), 4.11-4.18 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 24.06, 24.38, 29.0, 37.78, 41.18, 57.45, 65.28, 65.71; **Analysis: $C_8H_{17}NO$** requires C, 67.09; H, 11.96; N, 9.78%; found C, 67.22; H, 11.91; N, 9.74%.

SECTION II

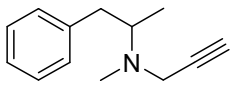
Asymmetric Synthesis of (*R*)-Selegiline using Proline-catalyzed Asymmetric α-Aminooxylation and α-Amination Reactions

1.2.1 Introduction

In recent years, the treatment of Parkinson's disease has undergone an immense amount of research, resulting in the development of new medications. Indeed, levodopa (**41**) remains the most effective therapeutic agent for the treatment of Parkinson's disease (PD). Initially, levodopa (**41**) provides a stable therapeutic response but during long-term treatment its beneficial effect declines and a gradually increasing number of patients experience fluctuations in motor response. Therefore, in the management of PD it is important to minimize the risk for the development of motor fluctuations. Deprenyl (selegiline) (**42**), a selective inhibitor of MAO (monoamineoxidase)-B, is effective in treating Parkinson's disease in combination with L-dopa and possibly Alzheimer's disease (AD).[27] Selegiline hydrochloride (**49**) is a laevorotatory acetylenic derivative of phenethylamine. It is commonly referred to in the clinical and pharmacological literature as L-deprenyl (**Fig. 13**).



41 Levodopa



42 (±)-Selegiline

Fig. 13

Alzheimer's disease (AD)[28]

Alzheimer's disease (AD) is named after Dr. Alois Alzheimer, a German medical doctor. Dementia is a brain disorder that seriously affects a person's ability to carry out daily activities. Alzheimer's disease (AD) is the most common form of dementia among older people. It involves the parts of the brain that control thought, memory,

and language. The disease usually begins after age 60, and risk goes up with age. There is a loss of nerve cells in areas of the brain that are vital to memory and other mental abilities.

Symptoms of Alzheimer's disease

Alzheimer's disease (AD) begins slowly. At first, the only symptom may be mild forgetfulness. However, as the disease goes on, symptoms are more easily noticed and become serious enough and they begin to have problems in speaking, understanding, reading, or writing.

What Causes AD?

While the cause of Alzheimer's remains largely unknown it has been definitely linked to oxidative damage to brain cells. There is overwhelming clinical evidence that antioxidants, those free radical fighters, are effective in preventing and beating back the symptoms of both dementia and Alzheimer's. Apart from ageing, family history genetics play an important role in many AD cases. However, several risk factor genes may interact with each other and with non-genetic factors to cause the disease. The only risk factor gene identified so far for late-onset AD is a gene that makes one form of a protein called apolipoprotein E (ApoE). Everyone has ApoE, which helps carry cholesterol in the blood.

Therapy for Alzheimer's disease (AD)

Currently, the only therapy for AD is based on a reduction of the cognitive defects by enhancing cholinergic transmission through inhibition of acetyl cholinesterase (AchE). These anti-AchE agents include tacrine (**43**), galanthamine (**44**), donepezil (**45**) and rivastigmine (**46**), which have been shown to induce a modest improvement in memory and cognitive function.[29] On the other hand, selegiline (**42**), a selective MAO-B inhibitor, has been reported to retard the further deterioration of cognitive

functions to more advanced milestones in AD.[30] The propargylamine pharmacophore of resagiline (**47**), selegiline (**42**), and related compounds also appears to have neuroprotective activity independent of MAO inhibition.[31] (*R*)-selegiline (**48**) was found to be more active than racemic selegiline (**42**) (**Fig. 14**).

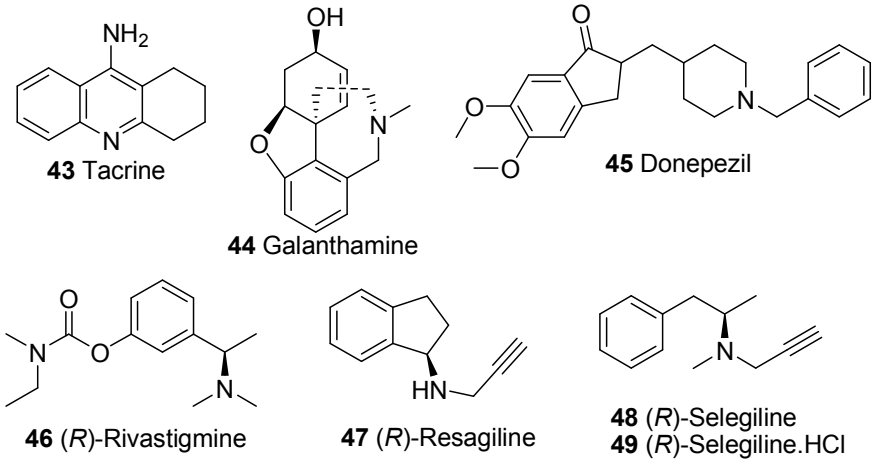


Fig. 14

Selegiline **48** and alpha-tocopherol (Vitamin-E) may slow important functional signs and symptoms of Alzheimer's disease. Taking selegiline **48**, vitamin E or a combination of the two drugs delayed by about 7 months the time it took for patients to reach one of four milestones: death, institutionalization (moving to a nursing home), loss of the ability to perform activities of daily living, or progression to severe dementia.

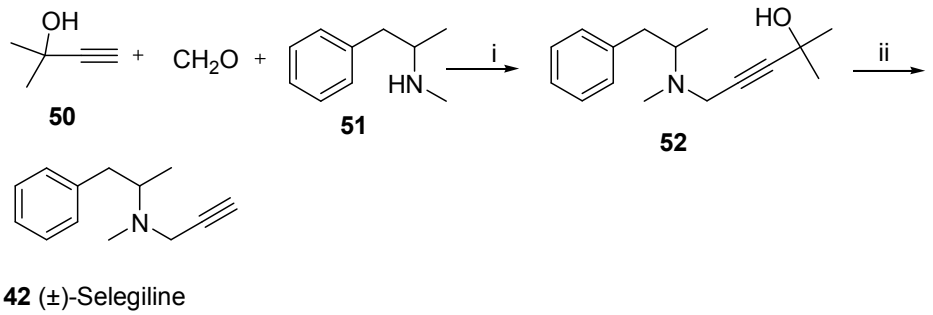
1.2.2 Review of Literature

Literature search reveals that there are some reports available for the synthesis of selegiline, which are described below.

Flower's approach (1977)[32]

Flower *et al.* have reported the synthesis of racemic selegiline (**42**) involving the Mannich reaction as a key step. Thus, reaction of 2-methyl-butyn-ol (**50**) and formaldehyde with deoxyephedrine (**51**) gave compound **52**, which on subsequent

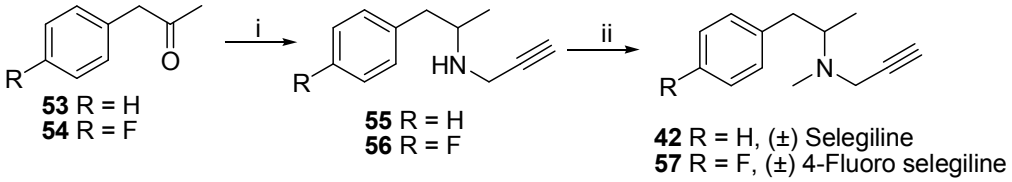
base-catalyzed elimination of acetone gave racemic selegiline (**42**) in 33% yield (**Scheme 8**).



Scheme 8: (i) CuCl, 110 °C, 4 h, 60%; (ii) KOH, 150 °C, 33%.

Gyogy's approach (1988)[33]

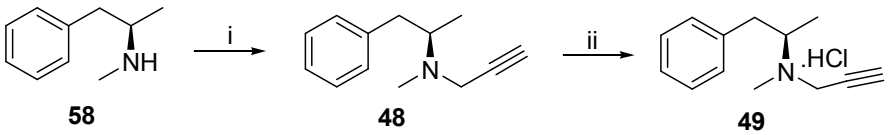
Gyogy *et al.* have reported the preparation of racemic selegiline (**42**) and 4-fluoroselegiline (**53**). Phenylacetone (**53**) and propargylamine on treatment with $HgCl_2$-activated aluminum at 60 °C gave amine (**55**), which on methylation yielded racemic selegiline (**42**). Similarly, (4-fluorophenyl)acetone (**54**) gave 4-fluoroselegiline (**57**) (**Scheme 9**).



Scheme 9: (i) propargylamine, EtOH, 60 °C, $HgCl_2$-Al; (ii) MeI, K_2CO_3, acetone.

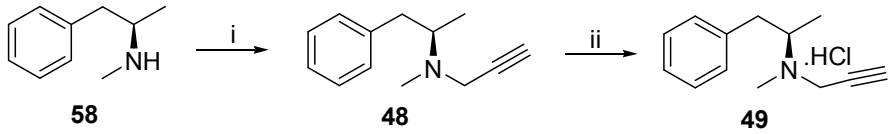
Hajicek's approach (1988)[34]

The title compound (**49**) was prepared by propargylation of deoxyephedrine (**58**) with propargyl bromide, K_2CO_3 in an inert solvent. Subsequent treatment with HCl afforded (*R*)-selegiline hydrochloride (**49**) (**Scheme 10**).



Scheme 10: (i) propargyl bromide, K_2CO_3 , 5 °C; (ii) HCl (gas)

Same group prepared (*R*)-selegiline hydrochloride (**49**) by reaction of (*R*)-deoxyephedrine (**58**) with $HC{\equiv}CCH_2OP^+Ph_3Cl^-$, followed by treatment with HCl (**Scheme 11**).

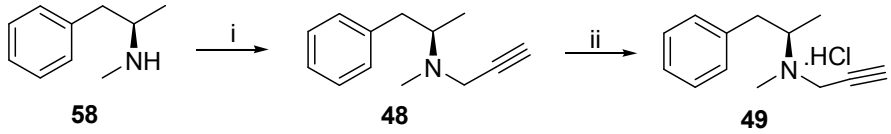


58 **48** **49**

Scheme 11: (i) $HC{\equiv}CCH_2OP^+Ph_3Cl^-$, Et_3N, CH_3CN 25 °C, 10 h; (ii) HCl (gas), *i*PrOH, 36%.

Ott-Dombrowski's approach (1996)[35]

This process for the synthesis of (*R*)-selegiline hydrochloride (**49**) involves *N*-alkylation of deoxyephedrine (**58**) with propargyl bromide in two-phase system comprising of water and organic hydrocarbon without a catalyst followed by conversion to the (*R*)-selegiline hydrochloride (**49**) using HCl (**Scheme 12**).

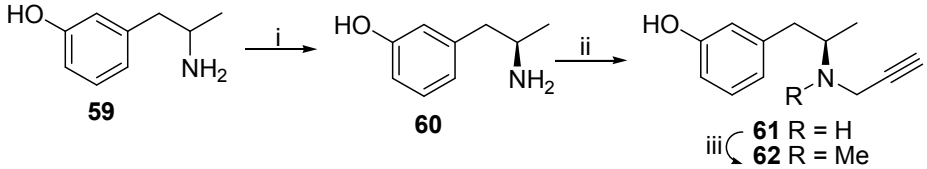


58 **48** **49**

Scheme 12: (i) propargyl bromide, H_2O and aromatic hydrocarbon; (ii) HCl (gas).

Sterling's approach (2002)[36]

Sterling *et al.* have reported the synthesis of (*R*)-3-hydroxy selegiline (**62**), involving classical resolution of amine **59** with D-tartaric acid to give optically pure amine **60**. Subsequent propargylation and reaction with ethyl formate gave formate derivative, which on reduction yielded (*R*)-3-hydroxy selegiline (**62**) (**Scheme 13**).

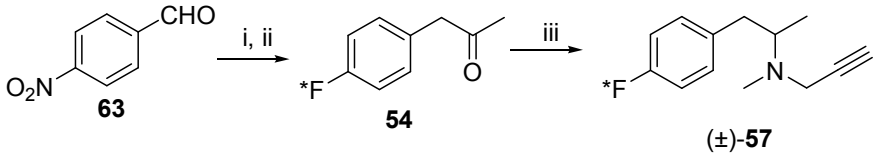


59 **60**

Scheme 13: (i) D-tartaric acid, MeOH, reflux; then 25% NH_4OH, 25 °C; (ii) propargyl bromide, K_2CO_3, 25 °C; (iii) HCO_2Et, reflux; then $LiAlH_4$, THF, 5 °C- 25 °C.

Plenevaux's approach (2002)[37]

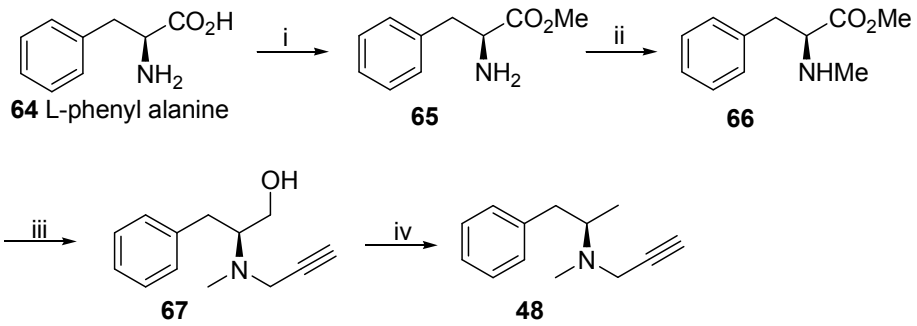
Racemic 4-[^{18}F]fluoroselegiline (**57**) was prepared *via* the three step procedure: (i) substitution by [^{18}F]fluoride on 4-nitrobenzaldehyde (**63**) (ii) reaction with (1-chloro-1-(trimethylsilyl)ethyl)lithium and hydrolysis to give 4-[^{18}F]flurophenylacetone (**54**), (iii) reductive alkylation of ketone **54** with *N*-methylpropnylamine (**Scheme 14**).



Scheme 14: (i) KF, 65%; (ii) 1-chloro-1-(trimethylsilyl)ethyl lithium, hydrolysis, 50%; (iii) *N*-methylpropynylamine, $NaBH_3CN$, 35%.

www.selegiline.com[38]

In this method, L-phenyl alanine (**64**) was used as the starting material for the preparation of (*R*)-selegiline (**48**). Methyl ester of phenyl alanine (**65**) on condensation with formic acid gave *N*-formyl derivative, which on subsequent reduction gave *N*-methyl derivative **66**. Propargylation and reduction of ester **66** with $LiAlH_4$ yielded alcohol **67**, which on subsequent reaction with thionyl chloride followed by reduction, gave (*R*)-selegiline (**48**) (**Scheme 15**).

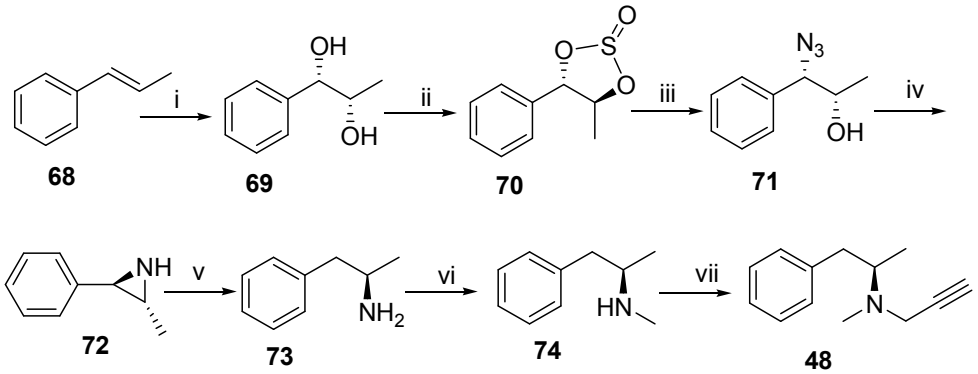


Scheme 15: (i) MeOH, 95%; (ii) HCO_2H then $NaBH_4$, 85%; (iii) propargyl bromide, then $LiAlH_4$; (iv) $SOCl_2$, reduction.

Sudalai's approach (2004)[39]

In this approach β-methyl styrene **68** was subjected to Shaprless AD reaction to give chiral diol **69** which on treatment with $SOCl_2$ gave the corresponding cyclic sulfite **70**.

Treatment of cyclic sulfite **70** with sodium azide gave the corresponding azido alcohol **71** which on treatment with triphenylphosphine gave chiral aziridine **72**. Aziridine **72** underwent stereospecific and regioselective ring opening at the benzylic position using Pd-catalyzed reductive ring opening with ammonium formate under transfer hydrogenation conditions to produce amine **73** which was converted to (*R*)-selegiline (**48**) using known sequence of reactions (**Scheme 16**).



Scheme 16: (i) OsO_4, $(DHQ)_2$–PHAL, $K_3Fe(CN)_6$, K_2CO_3, t-BuOH–H_2O, 0 °C, 82%; (ii) $SOCl_2$, Et_3N, CH_2Cl_2, 0 °C, 85%; (iii) NaN_3, acetone–H_2O, 80 °C, 82%; (iv) PPh_3, CH_3CN, 90%; (v) Pd/C (10%), HCO_2NH_4, MeOH, reflux, 88%; (vi) (a) $ClCO_2CH_3$, CH_2Cl_2, aq K_2CO_3, 45min, 90% (b) $LiAlH_4$, dry THF, 65 °C, 65%; (vii) propargyl bromide, K_2CO_3, CH_3CN, 25 °C, 72%.

1.2.3 Present Work

1.2.3.1 Objective

The high biological activity of selegiline is associated with (*R*)-enantiomer of selegiline (**48**). All the methods for the synthesis of (*R*)-selegiline (**48**) make use of either (*R*)-deoxyephedrine (**58**), or L-phenyl alanine (**64**) as the starting material, or by classical resolution of racemic amine **58** using D-tartaric acid. Recently, we have reported the synthesis of (*R*)-selegiline (**48**) using OsO_4-catalyzed asymmetric dihydroxylationas the key step.[39] However, these methods suffer from several disadvantages: (i) most of the information towards its synthesis is available in the form of patents; (ii) classical resolution of racemic selegiline leads to loss of half the material; (iii) toxic OsO_4 catalyst is used in one of the synthesis. The objective of the

present investigation is to prepare (*R*)-enantiomer of selegiline (**48**) using an organic catalyst such as proline-catalyzed α-aminooxylation and α-amination of readily available 3-phenylpropanaldehyde (**74**).

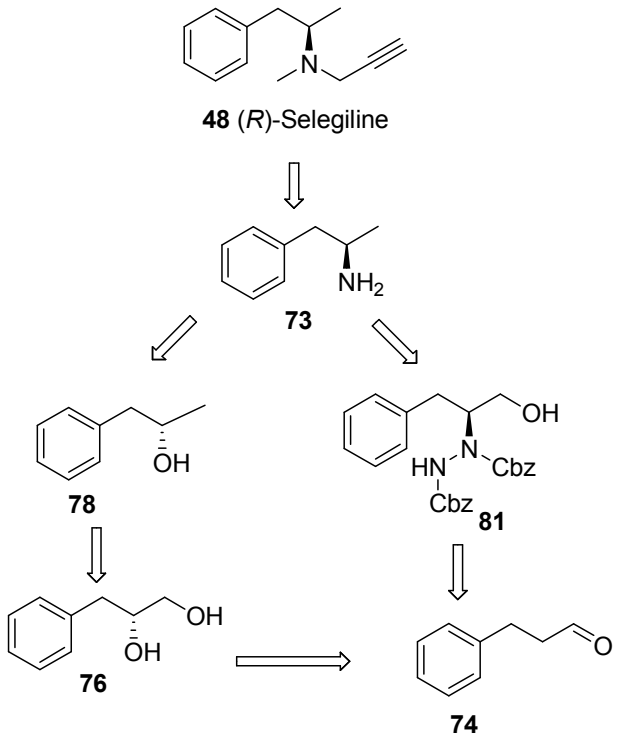
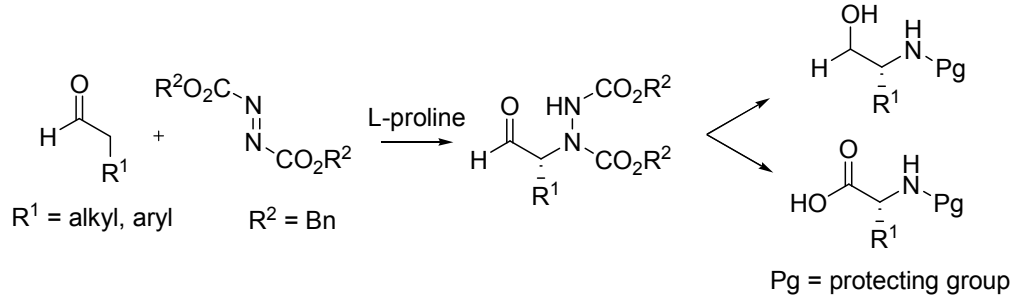


Fig. 15: Restrosynthesis of (*R*)-selegiline (**48**)

The Retrosynthesis of (*R*)-Selegiline (**48**) is shown in **Fig. 15**. The key chiral intermediate amine **73** can be synthesized either from the alcohol **78** or aminoalcohol **81**. The alcohol **78** can be readily obtained from diol **76**, which in turn can be obtained by L-proline-catalyzed α-aminooxylation[24] of 3-phenylpropanaldehyde (**74**). Alternately, the amnioalcohol **81** can be obtained by the D-proline-catalyzed α-amination[25] of 3-phenylpropanaldehyde (**74**). Since this section deals with proline catalyzed *α-aminooxylation* and *α-amination* of carbonyl compounds, thereby introducing stereogenicity into the prochiral molecule, a brief account of *α-amination* of carbonyl compounds is described (a brief account of *α-aminooxylation* is given in Section I of this chapter).

1.2.3.2 Proline-catalyzed α-Amination

One of the ultimate goals and challenges in organic chemistry is to develop stereoselective transformations for the creation of functionalized optically active molecules with structural diversity from simple and easily available starting materials. Several procedures to generate optically active molecules are known and among these asymmetric catalysis plays an important role. The motivation to investigate enantioselective α-amination of carbonyl compounds is provided by valuable synthetic targets such as α-amino acids and α-amino alcohols. The importance of optically active α-amino acids, α-amino aldehydes, and α-amino alcohols, formed by asymmetric catalysis, has stimulated an enormous development in synthetic strategies, and two different catalytic, enantioselective approaches are attractive: the C-C and the C-N bond-forming reactions. The catalytic enantioselective C-C bond-forming reactions include the addition to imines, such as the Strecker and Mannich reactions.[40] The catalytic, enantioselective, direct C-N bond-forming reaction using aldehydes and a nitrogen source, such as azodicarboxylates, would constitute one of the simplest procedures for the construction of a stereogenic carbon center attached to a nitrogen atom. These reactions give an easy and simple access to many classes of optically active molecules with high structural diversity. The molecules include α-amino aldehydes, α-amino alcohols, and α-amino acids, all key chiral elements in many natural products as well as in medicinal chemistry (**Scheme 17**).



Scheme 17: L-Proline-catalyzed α-amination of aldehydes

The mechanism of the α-amination reaction is given in **Figure 16**. The highly reactive enamine intermediates formed between aldehydes and proline might serve as nucleophiles and add stereoselectively to the diazo functional group. The observed stereochemistry can be explained with a proline-enamine-involving transition state (**A**). The proposed model is based on Houk's calculated transition state of the Hajos-Parrish-Eder-Sauer-Wiechert reaction (**B**)[41] and is also consistent with previously proposed transition states for intermolecular aldol and Mannich reactions.[42] Since proline is commercially available in both enantiopure forms, a one-pot sequence-catalytic α-aminoxylation and α-amination of aldehydes followed by *in situ* reduction with $NaBH_4$ affords *R*- or *S*- configured 1,2-diol and 1,2-aminoalcohol with excellent enantioselectivities and in good yields.

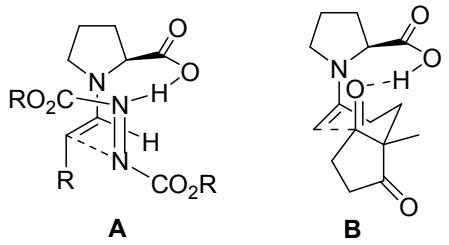


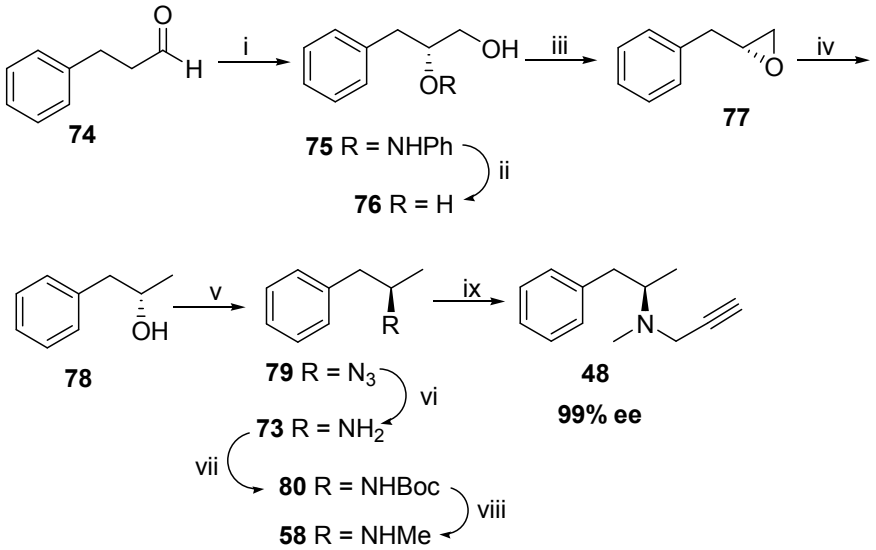
Fig. 16

1.2.4 Results and Discussion

Route 1: α-Aminooxylation approach

A short and effective procedure for the synthesis of (*R*)-selegiline (**48**) in a high enantiomeric purity from readily available starting materials using proline-catalyzed α-aminooxylation of cheaply available 3-phenylpropanaldehyde (**74**) is shown in **Scheme 18**. Firstly, α-aminooxylation[24e] of 3-phenylpropanaldehyde (**74**) was carried out using nitrosobenzene as the oxygen source and (*S*)-proline (10 mol %) at 25 °C to furnish aminooxy aldehyde *in situ*, which on reduction with $NaBH_4$ afforded the α-aminooxy alcohol **75** in 86% yields; $[\alpha]^{25}_D$: +42.08 (*c* 1.0, $CHCl_3$) { lit.[24e] $[\alpha]^{25}_D$:

+42.1 (*c* 0.9, $CHCl_3$)}. The ^1H NMR spectrum of the α-aminooxy alcohol **75** showed peaks at δ 2.84 (dd), 3.02 (dd) and δ 3.71 (dd), 3.86 (dd) corresponding to the benzylic protons and methylene group protons in the diol moiety (*i.e.* -CH(ONHPh)-C**H₂**OH) respectively. Its ^{13}C NMR spectrum showed typical peaks at δ 36.6, 64.4 and 84.9 corresponding to the benzylic carbon, methylene group and the homobenzylic carbon respectively.



Scheme 18: (i) (a) PhNO, L-proline (10 mol %), DMSO, 25 °C, 20 min. then MeOH, $NaBH_4$, 86%; (ii) H_2 (1atm.), 10% Pd/C, MeOH, 12 h, 88%; (iii) (a) *p*-TsCl, Et_3N, CH_2Cl_2, 0 °C, 1 h, (b) NaH, DMF, 0 °C, 0.5 h, 81% for 2 steps; (iv) $LiAlH_4$, THF, reflux, 2 h, 92%; (v) (a) MsCl, Et_3N, CH_2Cl_2, 0 °C, 0.5 h, (b) NaN_3, DMF, 80 °C, 12 h, 76% for 2 steps; (vi) H_2 (1atm.), 10% Pd/C, MeOH, 2 h, 98%; (vii) $(Boc)_2O$, Et_3N, 0 °C, 1 h, 95%; (viii) $LiAlH_4$, THF, reflux, 4 h, 90%; (ix) propargyl bromide, anhyd. K_2CO_3, CH_3CN, 12 h, 72%, 99% ee.

The aminooxy bond (*i.e.* O-N) in the aminooxy alcohol **75** was then reductively cleaved by hydrogenolysis (H_2 (1 atm., balloon pressure), 10% Pd/C, MeOH, 12 h) to give the corresponding diol **76** in 88% yield; $[\alpha]^{25}_D$: +35.1 (*c* 1, EtOH) {lit.[43] $[\alpha]^{18}_D$: +35.4 (*c* 1, EtOH)}. The ^1H NMR spectrum of the diol **76** showed peaks at δ 2.72 (d), 3.44 (dd) and 3.62 (dd) corresponding to the benzylic and the methylene protons in the diol moiety (*i.e.* -CH(OH)-C**H₂**OH) and a peak at δ 3.87 (m) corresponding to the homobenzylic proton. Its ^{13}C NMR spectrum showed peaks

at δ 39.7 and 73.1 due to the benzylic and homobenzylic carbons respectively and a peak at δ 65.7 corresponding to the carbon in primary alcohol moiety (-CH(OH)-**C**H_2OH) (**Fig. 17**).

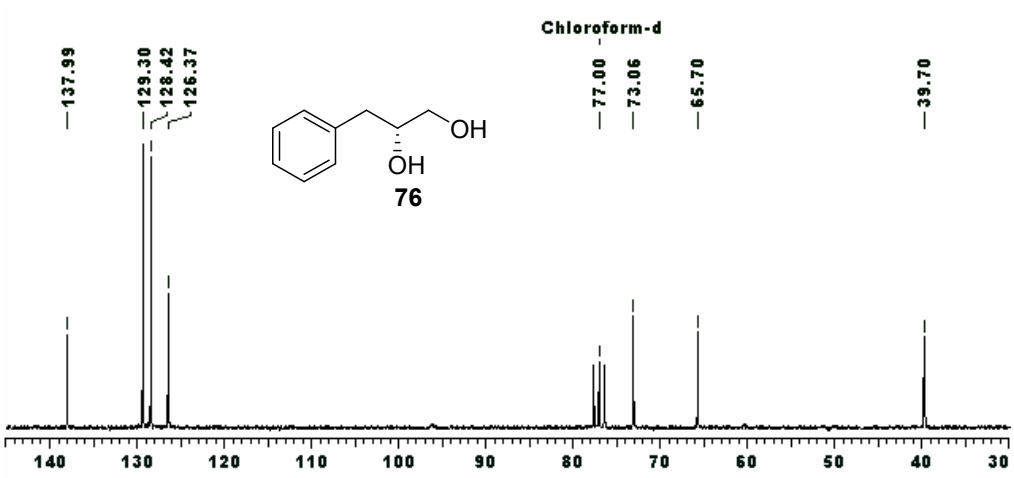


Fig. 17: ^{13}C NMR Spectrum of diol 76

The diol **76** was then protected as its primary tosylate (*p*-TsCl, Et_3N, CH_2Cl_2, 0 °C, 1 h) which on treatment with NaH gave the corresponding epoxide **77** in 81% yield; $[\alpha]^{25}_D$: +17.6 (*c* 1.9, EtOH) {lit.[44] $[\alpha]^{25}_D$: +17.5 (*c* 1.94, EtOH)}.

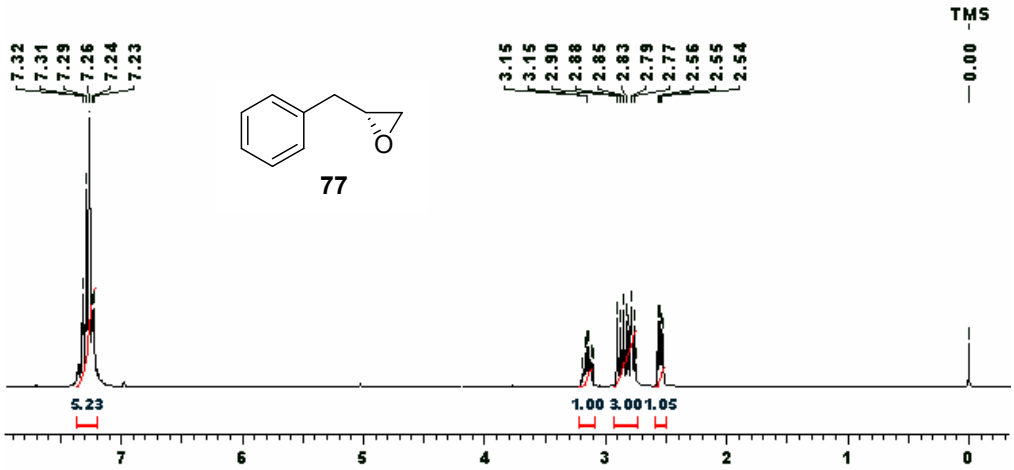


Fig. 18: ^{1}H NMR Spectrum of epoxide 77

The ^{1}H NMR spectrum of the epoxide showed a peak at δ 2.55 (dd) due to one of the diastereotopic protons of the methylene group of epoxide moiety and a multiplet at δ

2.75-2.90 corresponding to the other diastereotopic and benzylic protons (**Fig. 18**). Its ^{13}C NMR spectrum showed peaks at δ 38.7, 52.3 and 46.6 corresponding to the benzylic, homobenzylic carbons and the methylene group present in the epoxide moiety respectively (**Fig. 19**).

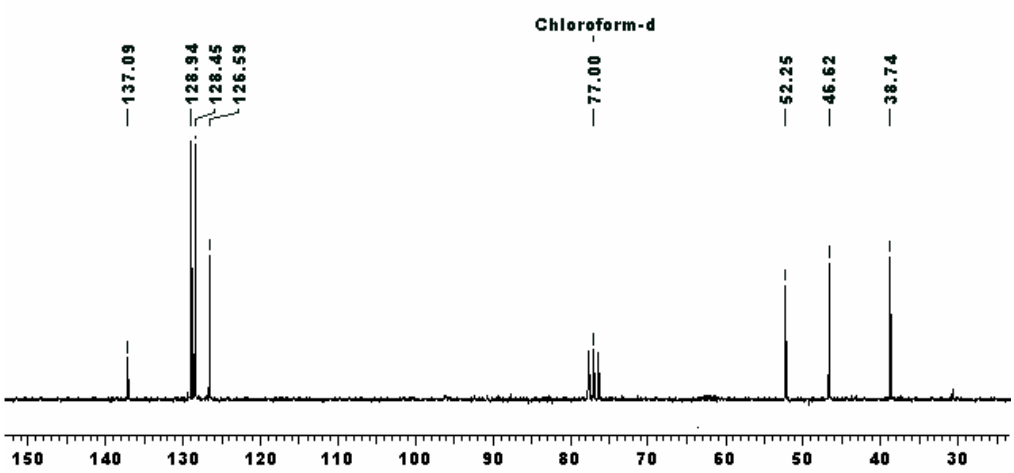


Fig. 19: ^{13}C NMR Spectrum of epoxide 77

The epoxide **77** was then subjected to regioselective reductive ring opening with $LiAlH_4$ at the terminal position to give the corresponding secondary alcohol **78** in excellent yield; $[\alpha]^{25}_D$: +50.8 (*c* 1.1, $CHCl_3$). The ^1H NMR spectrum of the alcohol **78** showed a doublet at δ 1.2 confirming the presence of the methyl group (**Fig. 20**).

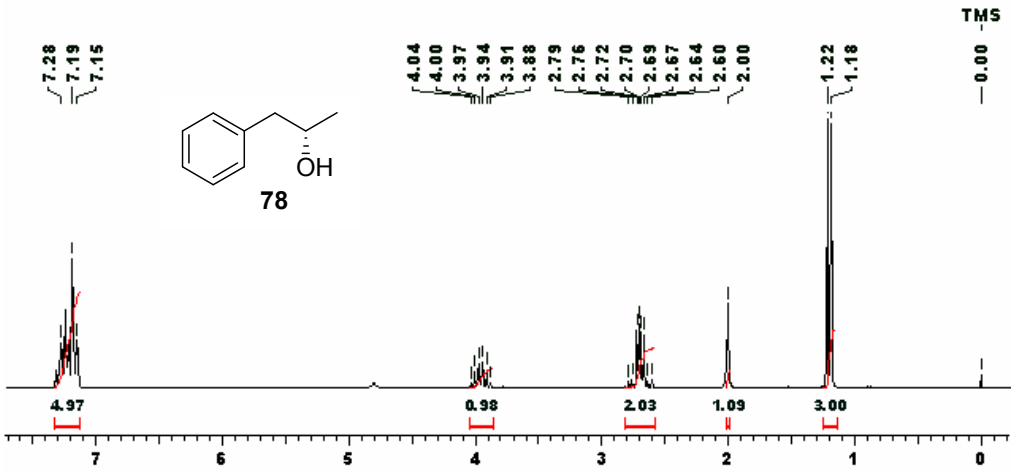


Fig. 20: ^1H NMR Spectrum of alcohol 78

Its ^{13}C NMR spectrum showed characteristic peaks at δ 22.39, 45.48 and 68.45 corresponding to the methyl, benzylic and homobenzylic carbons respectively (**Fig. 21**). The optical purity of alcohol **78** (99% ee) was determined from its ^{1}H NMR analysis of its Mosher ester (see experimental section for details).

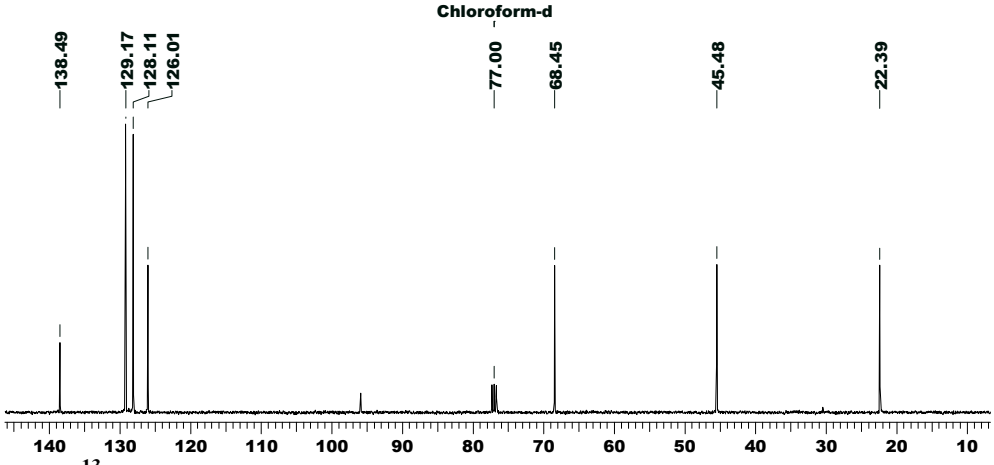


Fig. 21: ^{13}C NMR Spectrum of alcohol 78

Alcohol **78** was protected as its mesylate with methanesulfonyl chloride using Et_3N as the base and the mesylate was then subsequently treated with NaN_3 to give the corresponding azide **79**; $[\alpha]^{25}_{D}$: -49.5 (*c* 1.24, $CHCl_3$).

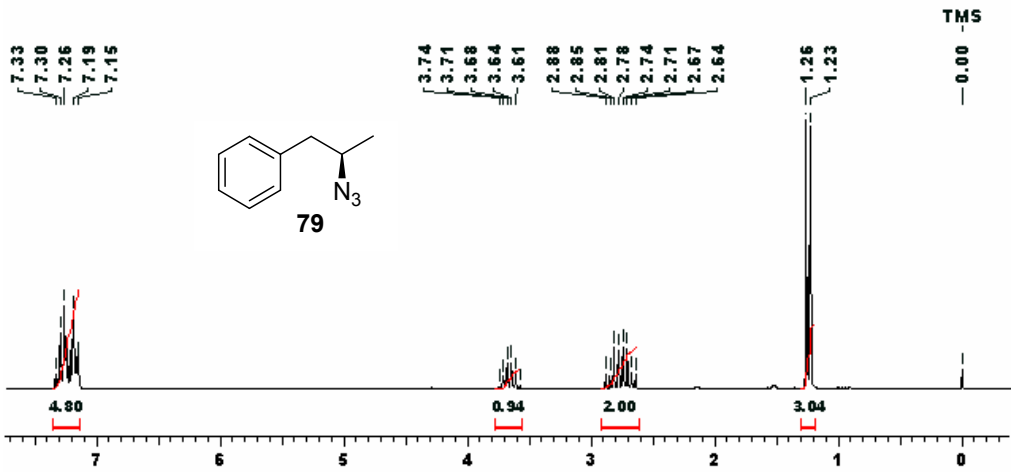


Fig. 22: ^{1}H NMR Spectrum of azide79

The ^{1}H NMR spectrum of the azide **79** showed signals at δ 1.25 (d), 2.64-2.88 (dd) and 3.64 (m) corresponding to the methyl group, benzylic and homobenzylic protons

respectively (**Fig. 22**). Its IR spectrum exhibited a characteristic strong band at 2100 cm^{-1} indicating the presence of azide group.

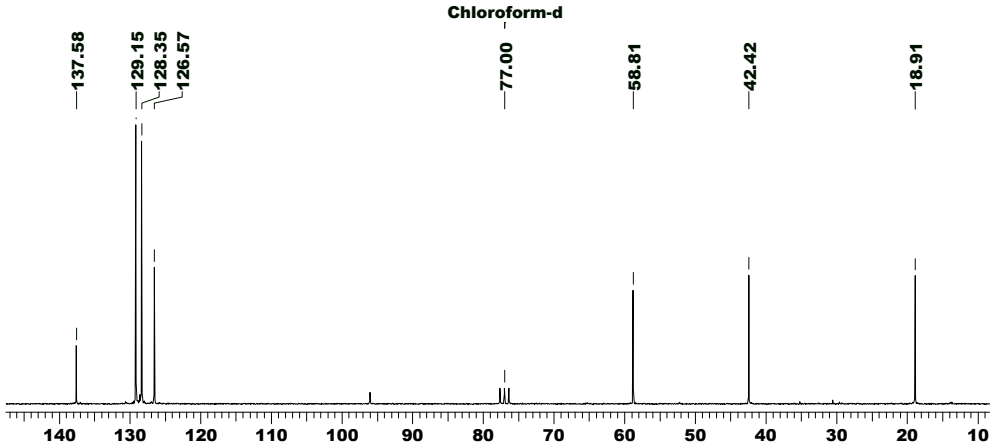


Fig. 23: ^{13}C NMR Spectrum of azide79

Azide **79** was then readily reduced to the corresponding amine **73** in 89% yield under hydrogenation conditions (H_2 (1atm.), 10% Pd/C, MeOH, 2 h); $[\alpha]^{25}_D$: -30.3 (*c* 2.0, MeOH); {lit.[45] $[\alpha]_D$: -30.2 (*c* 2.55, MeOH)}. The ^{1}H NMR spectrum of the amine **73** showed signals at δ 1.23 (d) and 1.77 (br s) corresponding to the methyl and the amine group protons respectively (**Fig. 24**). Its ^{13}C NMR spectrum showed peaks at δ 18.3, 41.7 and 50.4 corresponding to the methyl group, benzylic and homobenzylic carbons respectively.

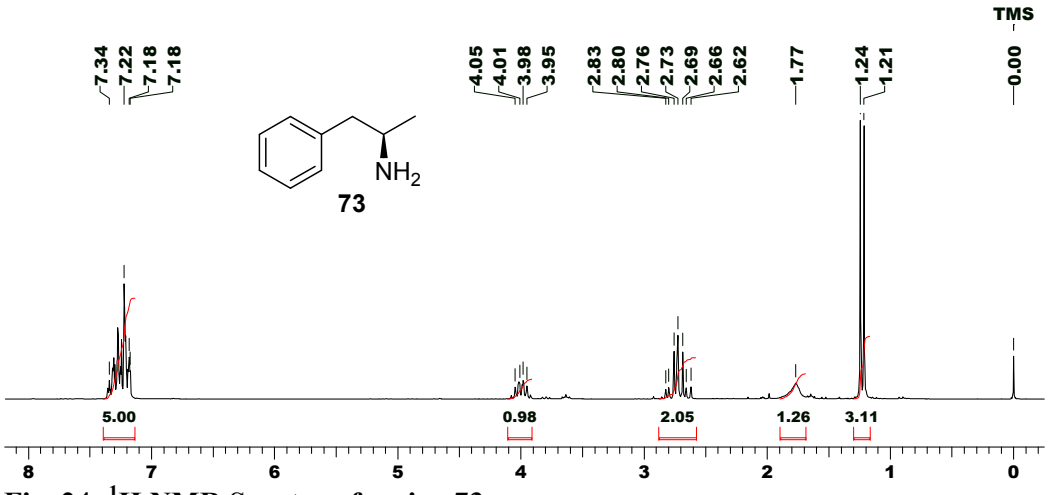


Fig. 24: ^{1}H NMR Spectra of amine 73

The protection of amine **73** with $(Boc)_2O$ gave the *N*-Boc protected (*R*)-2-amino-1-phenylpropane (**80**); $[\alpha]^{25}_D$**:** +7.62 (*c* 0.8, $CHCl_3$). The ^1H NMR spectrum of the protected amine **80** showed signals at δ 1.42 (s) and 4.37 (br s) corresponding to the *tert*-butyl and the NH protons respectively. Its ^{13}C NMR spectrum showed peaks at δ 28.4, 78.9 and 155.0 corresponding to the *tert*-butyl methyl groups, tertiary carbon in *tert*-butyl group and the carbonyl carbon in the carbamate respectively (**Fig. 25**). Its IR spectrum of **80** displayed a characteristic strong band at 1703 cm^{-1} indicative of the presence of carbonyl group.

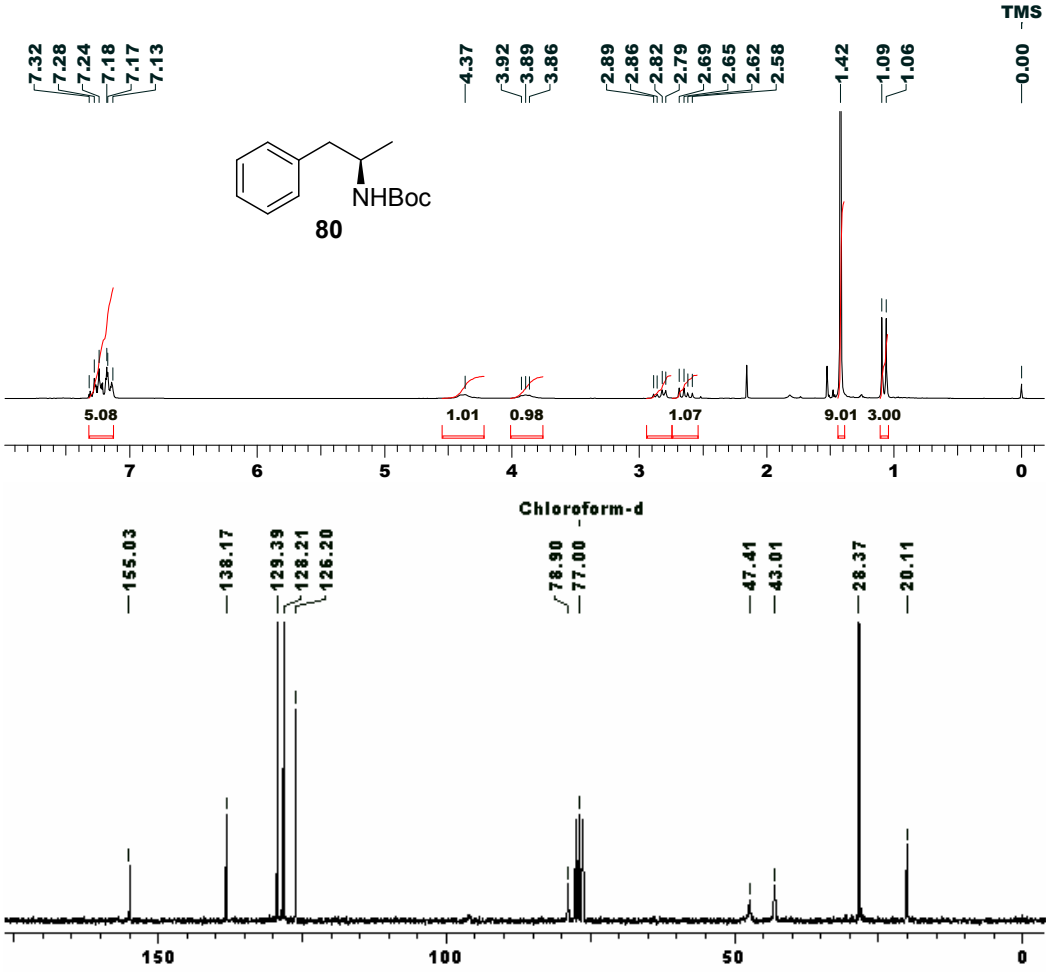


Fig. 25: ^1H and ^{13}C NMR Spectra of protected amine 80

Reduction of the carbamate group in the protected amine **80** was achieved using $LiAlH_4$ to give *N*-methylamine **57** in 92% yield; $[\alpha]^{25}_D$: -10.87 (*c* 0.8, EtOH); {lit.[45]

$[\alpha]^{21}_{D}$: -10.9 (*c* 4.2, EtOH)}. The ^{1}H NMR spectrum of *N*-methylamine **58** showed signals at δ 1.07 (d) and 2.38 (s) corresponding to the methyl group and the *N*-methyl protons respectively. Its ^{13}C NMR spectrum showed peaks at δ 43.0, 56.1 and 33.4 corresponding to the benzylic, homobenzylic and *N*-methyl carbons respectively (**Fig. 26**).

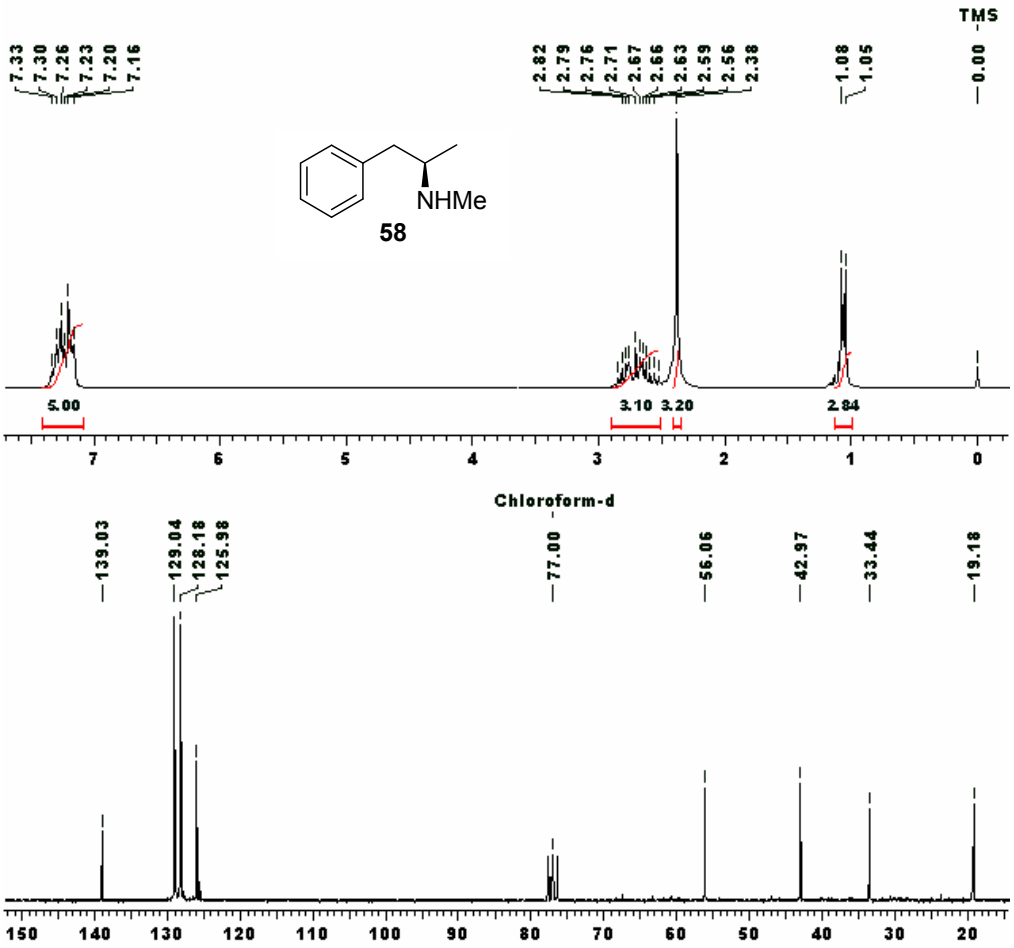


Fig. 26: ^{1}H and ^{13}C NMR Spectra of protected methyl amine 58

Finally, *N*-propargylation of *N*-methylamine **58** with propargyl bromide in presence of anhyd. K_2CO_3 at 25 °C furnished (*R*)-selegiline **48** in 72% yield; $[\alpha]^{25}_{D}$: -10.7 (*c* 6.5, EtOH) { lit.[46] $[\alpha]^{20}_{D}$: -10.8 (*c* 6.4, EtOH)}. The ^{1}H NMR spectrum of (*R*)-selegiline **48** showed signals at δ 2.38 (s), 3.55 (d) and 2.30 (t) corresponding to the *N*-methyl, N-CH_2 group and the acetylenic proton respectively (**Fig. 27**). Its ^{13}C NMR

showed typical peaks at δ 82.3, 43.0 and 56.1 corresponding to the quaternary alkyne carbon, benzylic and homobenzylic carbons respectively. The N-CH_3 carbon showed peak at δ 33.4. The spectral data obtained for (*R*)-selegiline (**48**) were in full agreement with the values reported in the literature.[39]

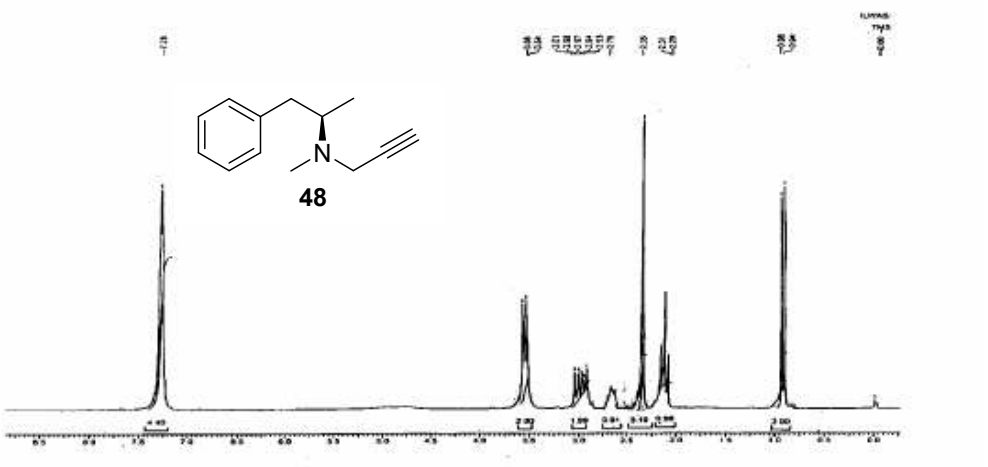
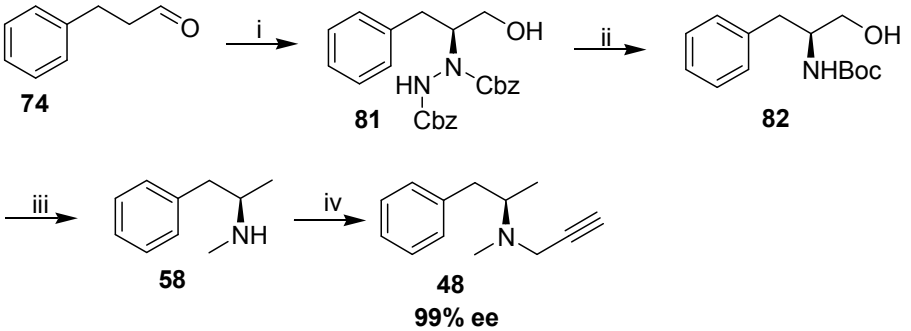


Fig. 27: ^{1}H NMR Spectrum of (*R*)-selegiline 48

Route 2: α-Amination approach

The synthesis of (*R*)-selegiline **48** using α-amination (List's protocol) [25a] not only reduces the total number of steps but also rules out the inversion of chiral center encountered in the α-aminooxylation approach (**Scheme 19**).



Scheme 19: (i) Dibenzyl azodicarboxylate , D-Proline (10 mol%), 0-20 °C, 3 h then $NaBH_4$, EtOH, 95%; (ii) (a) H_2 (60 psi), Raney Ni, MeOH, AcOH, 16 h, (b) $(Boc)_2O$, Et_3N, 0 °C, 1 h, 66% for 2 steps; (iii) (a) *p*-TsCl, Et_3N, CH_2Cl_2, 0 °C, 1 h, (b) $LiAlH_4$, THF, reflux, 4 h, 81% for 2 steps; (iv) propargylbromide, K_2CO_3, CH_3CN, 12 h, 72%.

Thus, 3-phenylpropanaldehyde (**74**) was α-aminated with dibenzyl azodicarboxylate as the amine source in the presence of D-proline (10 mol%) to give α-aminoaldehyde *in situ*, which on reduction with $NaBH_4$ afforded the protected amino alcohol **81** in 95% yield; $[\alpha]^{25}_D$: +29.86 (*c* 0.4, $CHCl_3$). The ^1H NMR spectrum of the protected amino alcohol **81** showed three multiplets at δ 3.57, 2.65 and 3.90-4.30 corresponding to the methylene protons in the aminoalcohol moiety, benzylic and the homobenzylic protons respectively. The N-H proton and the benzylic protons in the carbamate moiety showed two multiplets at δ 4.50-5.00 and 5.00-5.40. Its ^{13}C NMR spectrum showed peaks δ 33.80 and 68.28 correspond to the benzylic and the methelene carbons (**C**H_2OH) respectively (**Fig. 28**).

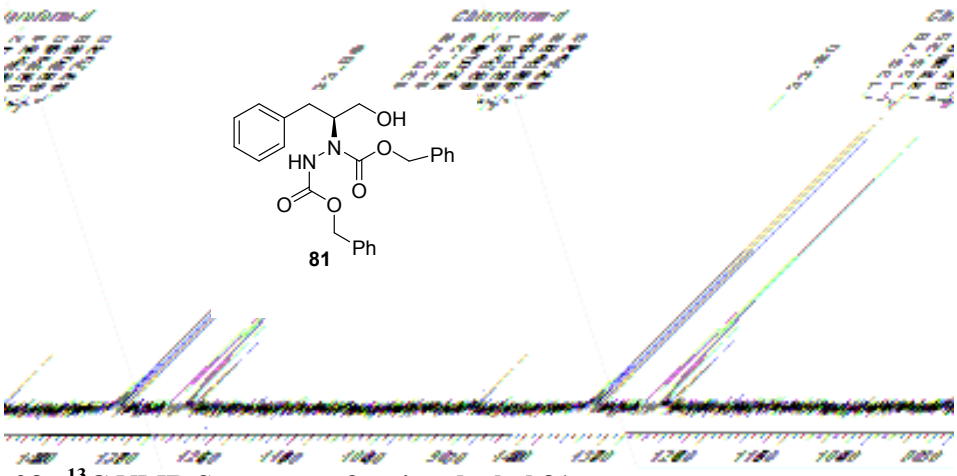


Fig. 28: ^{13}C NMR Spectrum of aminoalcohol 81

The aminoalcohol **81** underwent hydrogenolysis (H_2, 60 psi) with Raney Ni as catalyst to give amino alcohol *in situ*, which was subsequently protected as its carbamate **82** using $(Boc)_2O$; $[\alpha]^{25}_D$: -26.6 (*c* 1.0, MeOH), {lit.[45] $[\alpha]^{20}_D$: -27 (*c* 1.0, MeOH)}. The ^1H NMR spectrum of the carbamate **82** showed signals at δ 1.40 (s), 2.84 (d) and 4.90 (br s) corresponding to the *tert*-butyl, benzylic and N-H protons respectively. Its ^{13}C NMR spectrum showed peaks at δ 37.3, 53.5, 79.4 and 156.0 corresponding to the benzylic carbon, homobenzylic carbon, quaternary carbon in the

tert-butyl moiety and the carbonyl carbon present in the carbamate respectively (**Fig. 29**).

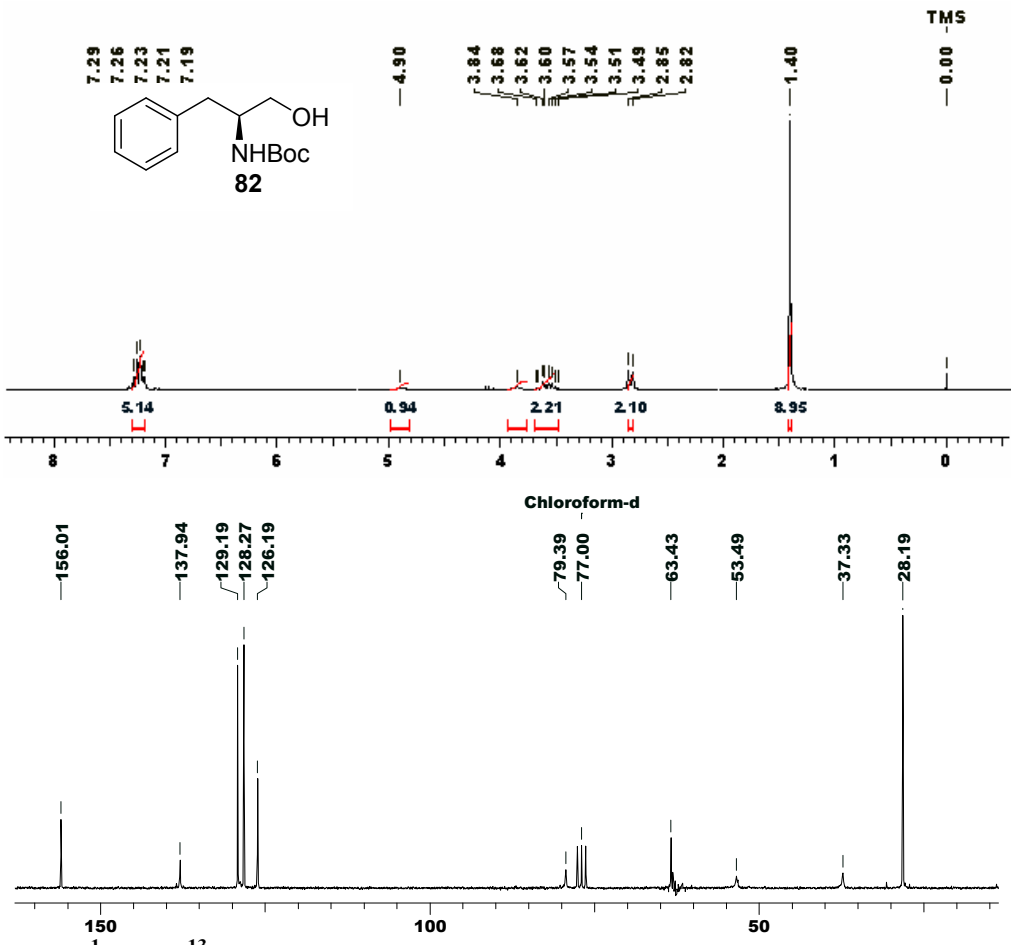


Fig. 29: ^{1}H and ^{13}C NMR Spectra of protected carbamate 82

The primary alcohol in carbamate **82** was then tosylted (*p*-TsCl, Et_3N, CH_2Cl_2, 0 °C, 1 h) to give the primary tosylate, which on reduction with excess $LiAlH_4$ gave the *N*-methylamine **58** (*vide infra* of the same section for other spectral details). The secondary amine **58** was propargylated using propargyl bromide under standard conditions to give (*R*)-selegiline (**48**) in 72% yield; $[\alpha]^{25}_{D}$: -10.3 (*c* 6.0, EtOH) {lit.[46] $[\alpha]^{20}_{D}$: -10.8 (*c* 6.4, EtOH)}.

1.2.5 Conclusion

In conclusion, we have successfully applied proline-catalyzed α-aminooxylation and α-amination strategies for the enantioselective synthesis of (*R*)-selegiline (**48**), which was obtained in high ee. The reactions are rapid, and require a relatively low amount of an inexpensive and nontoxic proline catalyst that is available in both enantiomeric forms. The high yields and less number of steps render our approach a good alternative to the known methods.

1.2.6 Experimental Section

(2*R*)-3-Phenyl-2-(*N*-phenylaminooxy)propan-1-ol (75)

To a stirred solution of 3-phenylpropanaldehyde (**74**) (3.35 g, 25 mmol) and nitrosobenzene (2.25 g, 21 mmol) in DMSO (30 mL) was added L-proline (483 mg, 4.2 mmol, 20 mol %) in one portion at 25 °C. After 2 h, the temperature was lowered to 0 °C, followed by dilution with anhydrous MeOH (20 mL) and careful addition of excess $NaBH_4$ (1.44 g, 38 mmol). The reaction was quenched after 10 min. by pouring of the reaction mixture into a vigorously stirred biphasic solution of Et_2O and aqueous HCl (1M). The organic layer was separated, and the aqueous phase was extracted with EtOAc (3 x 100 mL). The combined organic phases were dried over anhyd. Na_2SO_4, concentrated, and purified by column chromatography over silica gel using EtOAc/Pet. ether (40:60) as eluent to give pure aminooxy alcohol **75**.

Yield: 4.4 g (86%); gum; **$[\alpha]^{25}_D$:** + 42.08 (*c* 1.0, $CHCl_3$); {lit.[24e] **$[\alpha]^{25}_D$:** + 42.1 (*c* 0.9, $CHCl_3$)}; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 2.84 (dd, *J*=13.6, 6.6 Hz, 1 H), 3.02 (dd, *J*=13.6, 6.3 Hz, 1H), 3.71 (dd, *J*=12.3, 6.3 Hz, 1 H), 3.86 (dd, *J*=12.1, 3.0 Hz, 1H), 4.09 (m, 1 H), 6.82 (d, *J*=8.4 Hz, 2H), 6.92 (t, *J*=7.0 Hz, 1 H), 7.13-7.31 (m, 7H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 36.6, 64.4, 84.9, 114.5, 122.3, 126.5, 128.3, 128.7, 129.3,

137.6, 148.0; **Analysis: $C_{15}H_{17}NO_2$** requires C, 74.05; H, 7.04; N, 5.76%; found C, 74.19; H, 6.95; N, 5.70%.

(*R*)-3-Phenylpropane-1,2-diol (76)

The aminooxy alcohol **75** (5 mmol, 1.22 g) was dissolved in MeOH (15 mL) and to the solution was added 10% Pd/C (20 mg). The reaction mixture was stirred in hydrogen atmosphere (1atm., balloon pressure) for 12 h. After completion of reaction (monitored by TLC) the reaction mixture was filtered through celite pad, the contents concentrated and the crude product was then purified by column chromatography over silica gel using EtOAc/Pet. ether (30:70) as eluent to give pure diol **76**.

Yield: 0.67 g (88%); **mp:** 46-48 °C, {lit.[43] mp: 46-47 °C}; **$[\alpha]^{25}_D$:** +35.1 (*c* 1, EtOH); {lit.[43] **$[\alpha]^{18}_D$:** +35.4 (*c* 1, EtOH)}; **IR** ($CHCl_3$, cm^{-1}): 557, 657, 700, 750, 771, 858, 1031, 1089, 1176, 1218, 1456, 1602, 2860, 3026, 3392; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 2.35 (br s, 1H), 2.72 (d, *J*=6.3 Hz, 2H), 3.44 (dd, *J*=11.2 Hz, 7.2 Hz, 1H), 3.62 (dd, *J*=11.0 Hz, 1.8 Hz, 1H), 3.85-3.89 (m, 1H), 7.17-7.33 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 39.7, 65.7, 73.1, 126.4, 128.4, 129.3, 138.0; **Analysis: $C_9H_{12}O_2$** requires C, 71.03; H, 7.95%; found C, 71.15; H, 7.84%.

(*R*)-(2,3-Epoxypropyl)benzene (77)

To a stirred solution of diol **76** (457 mg, 3 mmol) and Et_3N (460 μL, 3.3 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added *p*-toluenesulfonyl chloride (572 mg, 3 mmol). After stirring at 0 °C for 1 h, the reaction mixture was poured into ice water (30 mL), washed with aqueous H_2SO_4 (20 %), saturated aqueous $NaHCO_3$, and brine, dried over anhyd. Na_2SO_4 and the solvent was distilled off under reduced pressure to give the crude product which was then dissolved in DMF (10 mL) followed by the addition of sodium hydride (60% oil dispersion, 120 mg, 3 mmol) at 0 °C. After 0.5 h, the reaction mixture was quenched with addition of water and the aqueous layer was

extracted with Et_2O (3 x 30 mL). The combined organic layers were dried over anhyd. Na_2SO_4 and solvent was distilled off under reduced pressure to give the crude epoxide **77** which was purified by column chromatography over silica gel using EtOAc/Pet. ether (5:95) as eluent to give pure epoxide **77**.

Yield: 0.33 g (81% for 2 steps); colorless liquid; **$[\alpha]^{25}_D$:** + 17.6 (*c* 1.9, EtOH); {lit.[44] **$[\alpha]^{25}_D$:** + 17.5 (*c* 1.94, EtOH)}; **IR** ($CHCl_3$, cm^{-1}): 698, 736, 847, 968, 1030, 1132, 1259, 1456, 1506, 1652, 2854, 2920; **^{1}H NMR** (200 MHz, $CDCl_3$) δ:2.55 (dd, *J*=5.1 Hz, 2.65 Hz, 1H), 2.75-2.90 (m, 3H), 3.11-3.20 (m, 1H), 7.24-7.32 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 38.7, 46.6, 52.3, 126.6, 128.5, 128.9, 137.1; **Analysis:** **$C_9H_{10}O$** requires C, 80.56; H, 7.51%; found C, 80.67; H, 7.55%

(*S*)-1-Phenylpropan-2-ol (78)

To a stirred suspension of $LiAlH_4$ (137 mg, 3.6 mmol) in THF (10 mL) was added drop-wise a solution of epoxide **77** (402 mg, 3 mmol) in THF (5 mL) at 0 °C. The reaction mixture was refluxed for 2 h and then cooled to 0 °C and the excess $LiAlH_4$ was quenched by addition of EtOAc. The reaction mixture was treated with 20% NaOH (2 mL), the white precipitate formed was filtered off and the residue was washed with EtOAc (3 x 30 mL). The combined EtOAc layers were dried over anhyd. Na_2SO_4, solvent distilled off under reduced pressure and the crude product purified by column chromatography over silica gel using EtOAc/Pet. ether (10:90) as eluent to yield the corresponding alcohol **78** in 92% yield.

Yield: 0.38 g (92%); colorless liquid; **$[\alpha]^{25}_D$:** +50.8 (*c* 1.1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 742, 771, 941, 1032, 1080, 1121, 1219, 1339, 1458, 1541, 1652, 2930, 2968, 3031, 3296; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.2 (d, *J*=6.2 Hz, 3 H), 2.0 (br s, 1H), 2.7 (m, 2 H), 3.88-4.04 (m, 1H), 7.15-7.28 (m, 5 H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 22.4, 45.5,

68.5, 126.0, 128.1, 129.2, 138.5; **Analysis: $C_9H_{12}O$** requires C, 79.37; H, 8.88%; found C, 79.24; H, 8.97%.

Mosher ester of alcohol 78:

To a solution of *N*,*N*'-dicyclohexylcarbodiimide (DCC) (44 mg, 0.21 mmol), and 4-dimethylaminopyridine (2 mg, 10 mol%) in CH_2Cl_2 (2 mL) at 0 ºC under argon atmosphere, was added drop-wise a solution of alcohol **77** (25 mg, 0.18 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was stirred for 10 min. and (*R*)-α-methoxy-α-trifluoromethylphenyl acetic acid (46 mg, 0.196 mmol) in CH_2Cl_2 (2 mL) was added drop-wise, stirred at 0 ºC for 1 h and then at 25 °C for 12 h. The reaction mixture was diluted with CH_2Cl_2 (50 mL), washed with saturated aqueous $NaHCO_3$ solution (50 mL), dried over anhyd. Na_2SO_4, concentrated under reduced pressure to give Mosher ester of the alcohol **78**.

Yield: 55 mg (87 %); gum; **$[\alpha]^{25}_D$:** +137.58 (*c* 0.5, $CHCl_3$)**; IR** ($CHCl_3$, cm^{-1}): 650, 735, 911, 957, 1015, 1122, 1217, 1242, 1348, 1495, 1519, 1606, 1753, 2850, 2927, 2952, 3158; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.36 (d, *J*=6.3 Hz, 3H), 2.79 (dd, *J*=13.9, 5.9 Hz, 1H), 2.95 (dd, *J*=13.9, 7.2 Hz, 1H), 3.46 (s, 3H), 5.39 (sextet, *J*=6.4 Hz, 1H), 7.06-7.43 (m, 10H).

1-((*R*)-2-Azidopropyl)benzene (79)

To a stirred solution of (*S*)-1-phenylpropan-2-ol (**78**) (408 mg, 3 mmol) and Et_3N (460 µL, 3.3 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added methanesulfonyl chloride (232 µL, 3 mmol) drop-wise using a syringe. After stirring at 0 °C for 0.5 h, the mixture was poured into ice-water (30 mL), washed with aqueous H_2SO_4 (20 %), saturated aqueous $NaHCO_3$, and brine, dried over anhyd. Na_2SO_4. Solvent was distilled off under reduced pressure to give the crude mesylate, which was then dissolved in DMF (10 mL) and sodium azide (195 mg, 3 mmol) was added to it. The reaction mixture

was then heated at 80 °C for 6 h followed by quenching it by the addition of water. The aqueous layer was extracted with Et_2O (3 x 30 mL) and the combined organic layers were dried over anhyd. Na_2SO_4, solvent distilled off under reduced pressure and the crude product purified by column chromatography over silica gel using EtOAc/Pet. ether (5:95) as eluent to yield pure azide **79**.

Yield: 0.37 g (76% for 2 steps); gum; **$[\alpha]^{25}_D$:** -49.5 (*c* 1.24, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 700, 744, 771, 873, 914, 1032, 1124, 1259, 1456, 1602, 2112, 2858, 2933, 3031; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.25 (d, *J* = 6.6 Hz, 3 H), 2.69 (dd, *J*=13.6, 6.7 Hz, 1H), 2.83 (dd, *J*=13.7, 7.0 Hz, 1 H), 3.66 (sextet, *J*=6.7 Hz, 1H), 7.14-7.33 (m, 5 H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 18.9, 42.4, 58.8, 126.6, 128.4, 129.2, 137.6; **Analysis: $C_9H_{11}N_3$** requires C, 67.06; H, 6.88; N, 26.07%; found 67.01; H, 6.84; N, 26.15%.

(*R*)-1-phenylpropan-2-amine (73)

1-((*R*)-2-azidopropyl)benzene **79** (483 mg, 3 mmol) was dissolved in MeOH (10 mL) and 10% Pd/C (20 mg) was added to it under hydrogen atmosphere (1 atm., balloon pressure). The mixture was stirred for 2 h and the reaction mixture was filtered through a pad of celite and solvent was distilled off under reduced pressure to give pure (*R*)-1-phenylpropan-2-amine (**73**).

Yield: 0.4 g (98%); gum; **$[\alpha]^{25}_D$:** -30.3 (*c* 2.0, MeOH); {lit.[45] **$[\alpha]_D$:** -30.2 (*c* 2.55, MeOH)}; **IR** ($CHCl_3$, cm-1): 700, 750, 810, 870, 1090, 1100, 1195, 1400, 1435, 1505, 1650, 2995, 3010, 3055, 3415; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.23 (d, *J*=6.1 Hz, 3H), 1.77 (br s, 2H), 2.68 (dd, *J*=13.6, 8.0 Hz, 1H), 2.78 (dd, *J*=13.5, 6.1 Hz, 1H), 3.95-4.05 (m, 1H), 7.18-7.34 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): 18.3, 41.7, 50.4, 128.4, 129.9, 130.5, 137.3; **Analysis: $C_9H_{13}N$** requires C, 79.95; H, 9.68; N, 10.36%; found C, 80.06; H, 9.62; N, 10.31%.

***tert*-Butyl (*R*)-1-phenylpropan-2-ylcarbamate (80)**

To a stirred solution of amine **73** (406 mg, 3 mmol) in CH_2Cl_2 (20 mL) at 0 °C, were added Et_3N (460 μL, 3.3 mmol) and $(Boc)_2O$ (654 mg, 3 mmol). After 1 h, the reaction mixture was quenched by the addition of water (20 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried over anhyd. Na_2SO_4, solvent distilled off under reduced pressure and the crude product purified by column chromatography over silica gel using EtOAc/Pet. ether (15:85) as eluent to give pure carbamate **80** in 95% yield.

Yield: 0.67 g (95%); gum; **$[\alpha]^{25}_D$:** +7.62 (*c* 0.8, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 700, 771, 876, 941, 1061, 1173, 1250, 1366, 1456, 1508, 1703, 2852, 2935, 2978, 3360; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.08 (d, *J*=6.7 Hz, 3 H), 1.42 (s, 9 H), 2.64 (dd, *J*=13.3, 7.3 Hz, 1H), 2.84 (dd, *J*=13.4, 5.6 Hz, 1H), 3.82-3.92 (m, 1H), 4.37 (br s, 1H), 7.14-7.32 (m, 5 H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 20.1, 28.4, 43.0, 47.41, 78.9, 126.2, 128.2, 129.4, 138.2, 155.0; **Analysis: $C_{14}H_{21}NO_2$** requires C, 71.46; H, 8.99; N, 5.95%; found C, 71.5; H, 8.97; N, 5.91%.

(*S*)-2-Amino-*N,N*-dibenzyloxycarbonyhydrazino-3-phenylpropan-1-ol (81)

To a stirred mixture containing dibenzyl azodicarboxylate (660 mg, 90%, 2 mmol) and (*S*)-proline (24 mg, 0.1 mmol, 10 mol%) in CH_3CN (20 mL) at 0 °C, 3-phenylpropanaldehyde (**74**) (402 mg, 3 mmol) was added and stirred for 2 h. The reaction mixture was warmed to 20 °C within 1 h during which it became colorless. It was then cooled to 0 °C, treated with ethanol (20 mL) and $NaBH_4$ (80 mg) and stirred for 5 min. at 0 °C. The reaction mixture was then quenched with aqueous NH_4Cl solution and extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over anhyd. Na_2SO_4, solvent distilled off under reduced pressure and the crude

product purified by column chromatography over silica gel using EtOAc/Pet. ether (30:70) as eluent to yield the amino alcohol **81** in 95% yield.

Yield: 1.24 g (95%); **mp:** 38-40 °C; **$[\alpha]^{25}_{D}$**: +29.86 (*c* 0.4, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 2.65 (m, 2H); 3.57 (m, 2H); 3.90-4.30 (m, 1H); 4.50-5.00 (m, 1H); 5.00-5.40 (m, 4H), 6.40 (s, 1H); 7.00-7.60 (m, 15H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 33.80, 67.81, 68.2, 68.15, 68.28, 127.25, 128.38, 128.46, 128.71, 129.12, 135.25, 135.78; **Analysis: $C_{25}H_{26}N_2O_5$** requires C, 69.11; H, 6.03; N, 6.45%; found C, 69.07; H, 6.06; N, 6.41 %.

***tert*-Butyl (*S*)-1-hydroxy-3-phenylpropan-2-ylcarbamate (82)**

Aminoalcohol **81** (270 mg, 0.62 mmol) was added to a stirred slurry of Raney Ni (300 mg, pre-washed with dry MeOH) in dry MeOH (10 mL) and AcOH (12 drops). The mixture was hydrogenated (H_2, 60 psi) in a Parr shaker for 16 h at 20 °C, filtered over celite, and solvent distilled off under reduced pressure to give the crude amino alcohol which was dissolved in CH_2Cl_2 (10 mL) followed by the addition of Et_3N (139 μL, 1mmol) and $(Boc)_2O$ (136 mg, 0.62 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and then quenched by the addition of aqueous $NaHCO_3$ (10%). The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic layers were dried over anhyd. Na_2SO_4, solvent distilled off under reduced pressure and the crude product purified by column chromatography over silica gel using EtOAc/Pet. ether (25:75) as eluent to give pure *N*-Boc protected amino alcohol **82**.

Yield: 0.1 g (66% for 2 steps); **mp:** 96-98 ^{0}C; **$[\alpha]^{25}_{D}$:** -26.6 (*c* 1.0, MeOH), {lit.[45] **$[\alpha]^{20}_{D}$:** -27 (*c* 1.0, MeOH) for 95% ee; recryst. (hexane/$CHCl_3$) 99% ee}; **IR** ($CHCl_3$, cm^{-1}): 775, 885, 1007, 1168, 1269, 1316, 1456, 1526, 1684, 2925, 2980, 3356; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.4 (s, 9H), 2.84 (d, *J*=7.1 Hz, 2H), 3.53 (dd, *J*=11.1,

5.32 Hz, 1H), 3.64 (dd, *J*=11.1, 3.9 Hz, 1H), 3.84 (br s, 1H), 4.9 (br s, 1H), 7.19-7.29 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 28.19, 37.33, 53.49, 63.43, 79.39, 126.19, 128.27, 129.19, 137.94, 156.01; **Analysis: $C_{14}H_{21}NO_3$** requires C, 66.91; H, 8.42; N, 5.57%; found C, 66.97; H, 8.37; N, 5.51%.

(*R*)-*N*-Methyl-1-phenylpropan-2-amine (58)

Route 1: To a stirred suspension of $LiAlH_4$ (76 mg, 2 mmol) in THF (5 mL) was added drop-wise a solution of *tert*-butyl (*R*)-1-phenylpropan-2-ylcarbamate (**80**) (235 mg, 1mmol) in THF (2 mL) at 0 °C. The reaction mixture was refluxed for 4 h and then cooled to 0 °C and the excess $LiAlH_4$ was quenched by the addition of EtOAc. The reaction mixture was treated with 20% NaOH (0.5 mL), the white precipitate formed was filtered off and the residue was washed with EtOAc (3 x 10 mL). The combine EtOAc layers were dried over anhyd. Na_2SO_4, solvent distilled off under reduced pressure and the crude product purified by column chromatography over silica gel using $CHCl_3$ as eluent to yield the corresponding *N*-methylamine **58** in 92% yield.

Yield: 137 mg (92%); gum; **$[\alpha]^{25}_D$:** -10.87 (*c* 1.0, EtOH); {lit.[45] **$[\alpha]^{21}_D$:** -10.9 (*c* 4.2, EtOH)}; **IR** ($CHCl_3$, cm^{-1}): 771, 878, 1036, 1130, 1219, 1344, 1458, 1541, 1651, 2829, 2928, 3252; **^{1}H-NMR** (200 MHz, $CDCl_3$) δ: 1.07 (d, *J*=6.1 Hz, 3H), 2.38 (s, 3H), 2.52-2.85 (m, 3H), 7.16-7.33 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 19.2, 33.4, 43.0, 56.1, 126.0, 128.2, 129.0, 139.0; **Mass** (m/z, % RI): 149 (M+, 4), 134 (10), 119 (5), 117 (5), 91 (45), 65 (16), 58 (100); **Analysis: $C_{10}H_{15}N$** requires C, 80.49; H, 10.12; N, 9.38%; found C, 80.41; H, 10.12; N, 9.45 %.

Route 2: To a stirred solution of *N*-Boc protected amino alcohol **82** (251 mg, 1 mmol) in CH_2Cl_2 (5 mL) at 0 °C were added Et_3N (153 µL, 1.1 mmol) and *p*-toluenesulfonyl chloride (210 mg, 1.1 mmol). The reaction mixture was stirred at 0 °C for 1 h and

then quenched with the addition of at aqueous $NaHCO_3$ (10%). The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic layers were dried over anhyd. Na_2SO_4, solvent distilled off under reduced pressure to give the crude tosylate. It was dissolved in THF (5 mL) and added drop-wise to a stirred suspension of $LiAlH_4$ (114 mg, 3 mmol) in THF (20 mL). The reaction mixture was refluxed for 4 h and then cooled to 0 °C and the excess $LiAlH_4$ was quenched by addition of EtOAc. The reaction mixture was treated with 20% NaOH (0.5 mL), the white precipitate formed was filtered off and the residue was washed with EtOAc (3 x 10 mL). The combine EtOAc layers were dried over anhyd. Na_2SO_4, solvent distilled off under reduced pressure and the crude product purified by column chromatography over silica gel using $CHCl_3$ as eluent to give the corresponding *N*-methylamine **58** (81% for two steps).

***N*-Methyl-*N*-((*R*)-1-phenylpropan-2-yl)prop-2-yn-1-amine: (*R*)-Selegiline (48)**

To a stirred solution of (*R*)-2-(methylamino)-1-phenylpropane (**58**), (200 mg, 1.34 mmol) in CH_3CN (10 mL) were added anhyd. K_2CO_3 (277 mg, 2.01 mmol) and propargyl bromide (478 mg, 360 µL, 4.02 mmol). The reaction mixture was then allowed to stir for 12 h at 25 °C. The solid residue was then filtered off and the solvent was distilled of under reduced pressure and purified by column chromatography over silica gel to give (*R*)-selegiline **48** in 72% yield.

Yield: 0.18 g (72%); gum; **$[\alpha]^{25}_D$:** -10.7 (*c* 6.5, EtOH); {lit.[46] **$[\alpha]^{25}_D$:** -10.8 (*c* 6.4, EtOH); **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.95 (d, *J*=6.0 Hz, 3H), 2.25 (t, *J*=2.0 Hz, 1H), 2.35 (s, 3H), 2.40-2.55 (m, 1H), 2.80-3.10 (m, 2H), 3.40 (d, *J*=2.0 Hz, 2H), 7.00-7.50 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): 21.1, 31.4, 46.8, 51.9, 60.8, 68.1, 82.2, 125.6, 128.3, 128.6, 140.2; **Analysis: $C_{13}H_{17}N$** requires C, 83.37; H, 9.14; N, 7.47%; found C, 83.34; H, 9.11; N, 7.53 %.

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The unique challenge which chemical synthesis provides for the creative imagination and the skilled hands ensures that it will endure as long as men write books, paint pictures and fashion things which are beautiful, or practical, or both.

- R. B. Woodward

Chapter II

Asymmetric Synthesis of (S,S)-Reboxetine and (S)-Toliprolol

Section I

Asymmetric Synthesis of (*S,S*)-Reboxetine

2.1.1 Depression

Depression is a common and disabling disorder. The World Health Organization has ranked depression fourth in a list of the most urgent health problems world wide.[1] Depression has major effects on economic productivity, individual well being and social functioning, around the globe. It is a huge burden on individuals, families, and society. The lifetime risk for major depression has been estimated to be 7%-12% for men and 20-25 % for women.[1-3] Medical treatment for depression favors prescription of antidepressant drugs that work by increasing neurotransmission for one or more of the monoamines-serotonin, norepinephrine, or dopamine. Before 1980, antidepressant treatment consisted primarily of the tricyclics antidepressants (TCADs), monoamine oxidase inhibitors (MAOI), and lithium. The antidepressant properties of these medications are attributed to modulation of noradrenergic and serotonergic function, but they also have many side effects due to binding to multiple unrelated receptors. The tricyclics antagonize muscarinic, H1 histaminic, and A1 adrenergic receptors causing constipation, urinary retention, dry mouth, sedation, and postural hypotension.[5] In addition to these, the monoamine oxidase inhibitors have the added risk of potentially severe hypertensive crisis due to pressor effects of dietary tyramine, which requires dietary restrictions. Both the tricyclics and the monoamine oxidase inhibitors can be lethal in overdose; the monoamine oxidase inhibitors interact dangerously with several over the counter and prescription drugs. In the late 1980's, an important class of antidepressant was introduced, the selective serotonin reuptake inhibitors (SSRIs), which includes fluvoxamine (**1**), sertraline (**2**), fluoxetine (**3**), paroxetine (**4**), and citalopram (**5**) (**Fig. 1**). This class has become a mainstay of

antidepressant treatment because of substantial advantages over the tricyclics and monoamine oxidase inhibitors in safety, tolerability and ease of dosing.

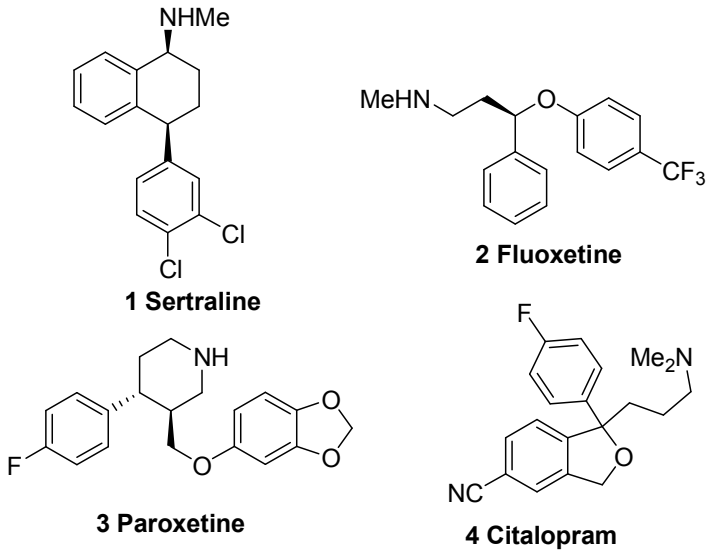


Fig. 1: Selective serotonin reuptake inhibitors (SSRIs)

The SSRI's also have limitations, especially response failure in many of those most severely affected. Many patients experience side effects like gastrointestinal complaints, nervousness and agitation, sexual dysfunction and weight gain with long term use.[5] All these lead to difficulty in long term treatment and non compliance. Hence, one of the most important goals in the pharmacological treatment of depression is to provide the patients with highly efficacious drugs that have few side effects, low or no toxicity and a high level of tolerability.

2.1.2 Reboxetine and pharmacology

Reboxetine (**7**) is a selective noradrenaline reuptake inhibitor (NaRI), the first drug of new antidepressant class introduced in 1997 (**Fig. 2**). It is α- aryloxybenzyl derivative of morpholine and its mesylate (*i.e.* methanesulfonate) salt is sold under trade names including Edronax®, Norebox®, Prolift®, Solvex® or Vestra®. Reboxetine (**7**) is a selective inhibitor of noradrenaline reuptake. It inhibits noradrenaline reuptake *in vitro* to a similar extent to the tricyclic antidepressant desmethylimipramine.

Reboxetine (**7**) does not affect dopamine or serotonin reuptake[5] and it has low *in vivo* and *in vitro* affinity for adrenergic, cholinergic, histaminergic, dopaminergic and serotonergic receptors.[6]

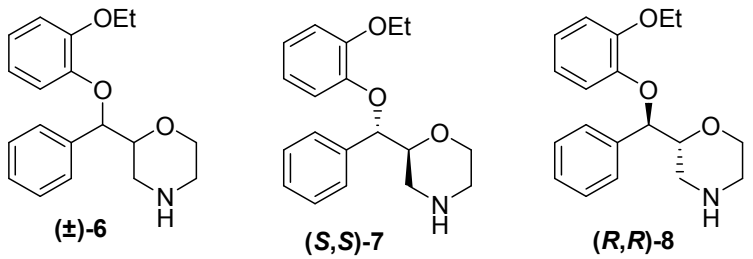


Fig. 2: Structures of reboxetine

Due to selectivity of reboxetine (**7**) for norepinephrine, it is generally well tolerated with a benign side effect profile.[2,5,7] Against comparator antidepressants, reboxetine is at least as effective in the treatment of patients with major depressive disorder in the adult and the elderly population and offers a significant advantage over imipramine in the treatment of melancholic patients. It has a significantly improved adverse event profile compared with TCADs. In severely depressed patients, reboxetine (**7**) was significantly more effective than fluoxetine. Reboxetine (**7**), the first selective NaRI, with its selective mechanism of action, offering even better efficacy in certain patient groups and acceptable tolerability profile is a valuable addition to the existing armamentarium of drugs used for the treatment of depression.

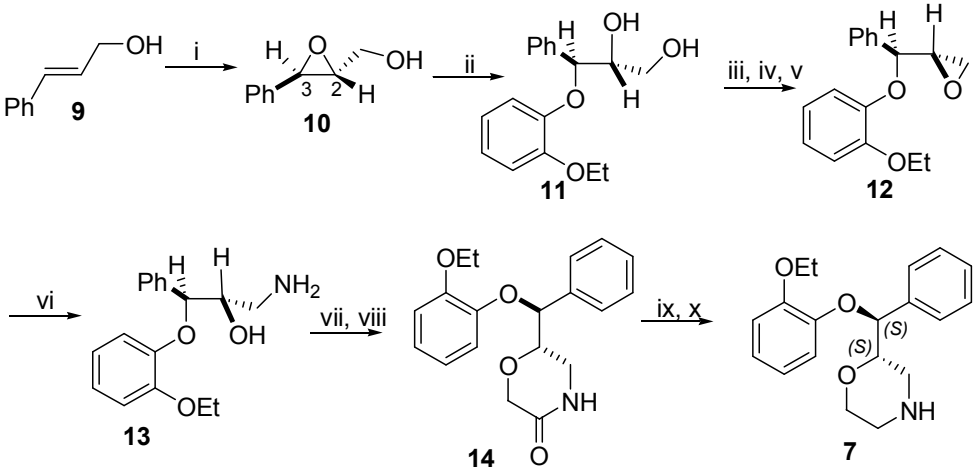
2.1.3 Review of Literature

Owing to its high biological importance, the synthesis of reboxetine in its optically pure form was reported by many groups world wide as described below.

Melloni's approach (1985)[8]

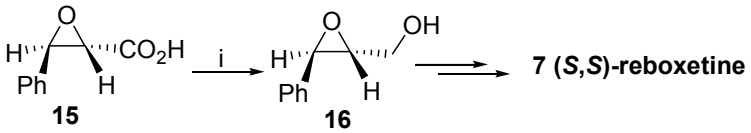
In this approach, cinnamyl alcohol (**9**) was subjected to diastreoselective epoxidation to give the (2*RS*,3*RS*) epoxide **10**. The epoxide **10** was then opened selectively at the benzylic position to give the diol **11** which was converted to the

epoxide **12**. The epoxide **12** was opened at primary position by NH_4OH to give the corresponding amino alcohol **13** (**Scheme 1**).



Scheme 1: (i) *m*-CPBA, CH_2Cl_2, 0 °C, 1 h, then 25 °C, 24 h, 94%; (ii) 2-ethoxy phenol, NaOH, H_2O, 70 °C, 2.5 h, 83%; (iii) 4-nitrobenzoyl chloride, pyridine, -10 °C, 2 h, 61%; (iv) CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0 °C, 0.5 h, 84%; (v) 2N NaOH, dioxane, 25 °C, 100%; (vi) 32% NH_4OH, MeOH, 6 h, 75%; (vii) $ClCH_2COCl$, Et_3N, CH_2Cl_2, -10 °C, 0.5 h, 98%; (viii) *t*-BuOK, *t*-BuOH, 25 °C, 2 h, 86%; (ix) Red-Al, toluene, 4 h, 72%; (x) L-(+)-mandelic acid, EtOH.

The amino alcohol **13** was treated first with chloroacetyl chloride and then with base to give the corresponding lactam **14**. Lactam **14** was reduced to the corresponding morpholine using Red-Al and the (*S*,*S*)-isomer was separated by resolution involving recrystallizing with L-(+)-mandelic acid in ethanol to give (*S*,*S*)-reboxetine (**7**). Melloni *et al*. also carried out the synthesis of (*S*,*S*)-reboxetine (**7**) using the chiral (2*R*,3*R*)-epoxide **16** obtained from chiral glycidic acid **15** (**Scheme 2**).

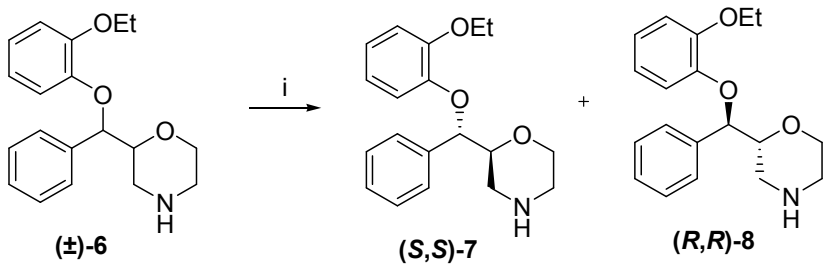


Scheme 2: (i) ethyl chlorocarbonate, Et_3N, CH_2Cl_2, 0 °C, 3 h, then $NaBH_4$, EtOH, 0 °C, 0.5 h, then 25 °C, 12 h, 31%.

Raggi's approach (2002)[9]

In this approach, Raggi *et al*. made use of capillary electrophoresis method to separate the enantiomers of racemic mixture of (*R*,*R*) and (*S*,*S*) reboxetine **7**. Sulfobutyl ether-

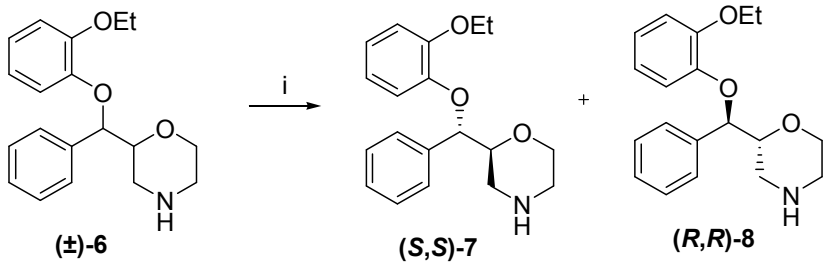
β-cyclodextrin was chosen as the chiral selector using an uncoated fused silica capillary (**Scheme 3**).



Scheme 3: (i) fused silica capillary (internal diameter 50 μm, total length 48.5 cm, effectivce length 40.0 cm), electrolyte pH 3.0, 100 mM phosphate buffer, 1.25 mM Sulfobutyl ether-β-cyclodextrin, 20 kV.

Öhman's approach (2002)[10]

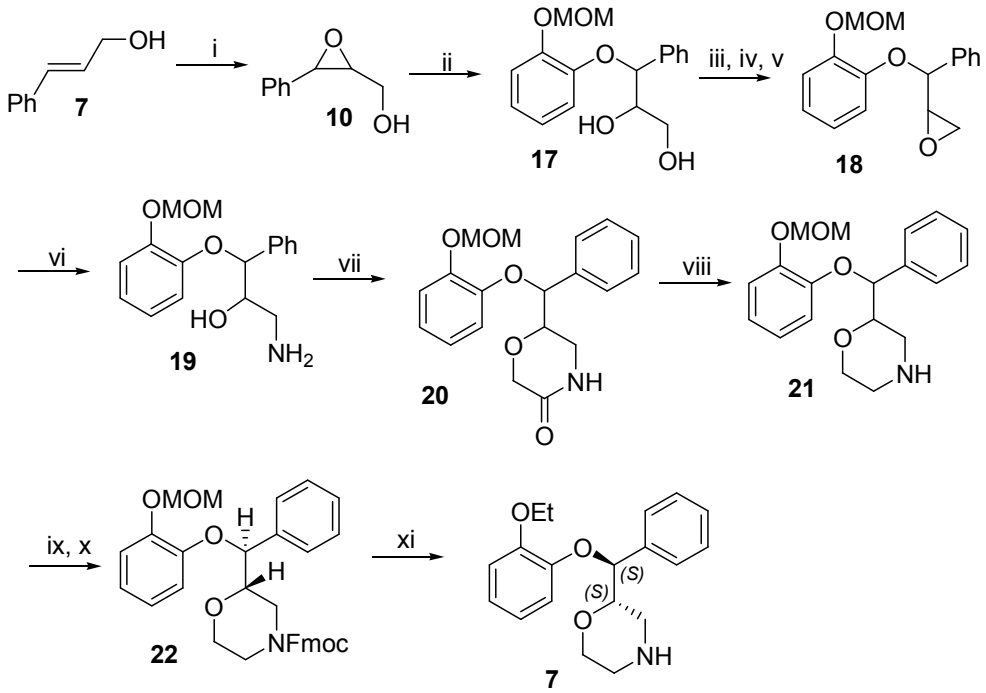
In this approach, the separation of the racemic mixture of reboxetine **7** was done using reversed-phase high-performance liquid chromatography using three different chiral columns, Chiral-AGP, ChiralGrom 2 and Chiral-CBH (**Scheme 4**).



Scheme 4: (i) chiral HPLC

Kumar's approach (2004)[11]

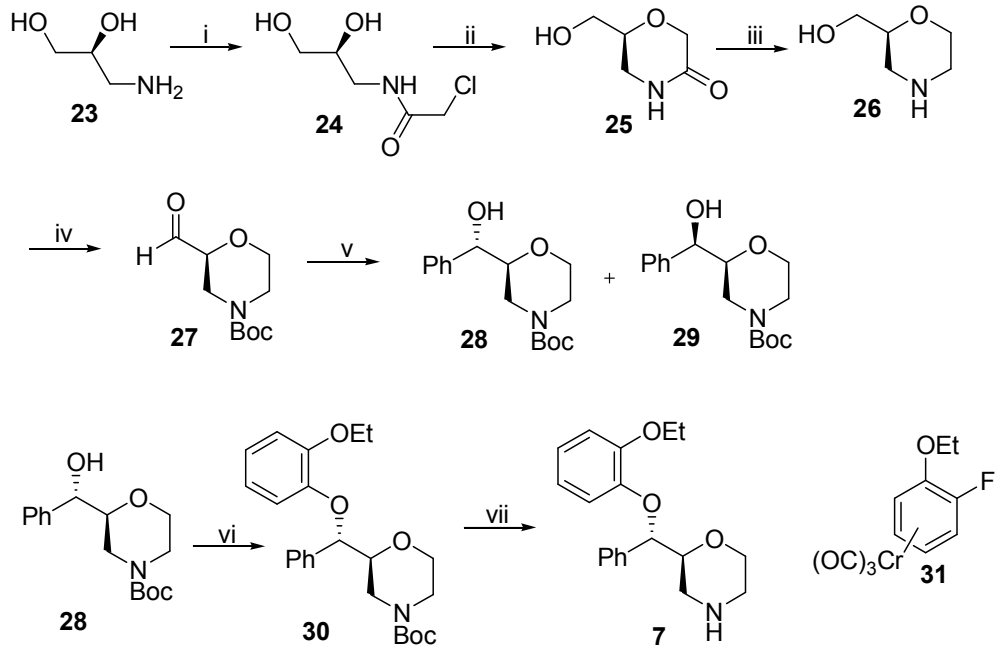
This approach is very much similar to the one repoted by Melloni *et al*. involving the epoxidation of cinnamyl alcohol (**9**) and opening the epoxide **10** at benzylic position with mono MOM-protected catechol. Lactam **20** was reduced to the corresponding secondary amine **21**, which was resolved with (+)-mandelic acid and protected to give the corresponding chiral morpholine **22**. Morpholine **22** was converted to (*S*,*S*)-reboxetine (**7**) using simple transformations (**Scheme 5**).



Scheme 5: (i) *m*-CPBA, CH_2Cl_2, 80%; (ii) 2-methoxymethoxyphenol, aq. NaOH, 64%; (iii) 4-nitrobenzoyl chloride, pyridine, 65%; (iv) CH_3SO_2Cl, Et_3N, CH_2Cl_2, 90%; (v) 2N NaOH, 25 °C, 4 h, 95%, (vi) 30% NH_4OH, MeOH, 88%; (vii) (a) $ClCH_2COCl$, Et_3N, CH_2Cl_2, (b) *t*-BuOK, *t*-BuOH, 64%; (viii) Red-Al, toluene, 88%; (ix) L-(+)-Mandelic acid, EtOH; (x) FMOC-Cl, Et_3N, Et_2O, 75%; (xi) (a) *p*TSA, MeOH, 94%, (b) TBAF.H_2O, THF, 87%, (c) $(Boc)_2O$, CH_2Cl_2, 87%, (d) *t*-BuOK, DMF, EtI, (e) TFA, 65%.

Tamagnan's approach (2005)[12]

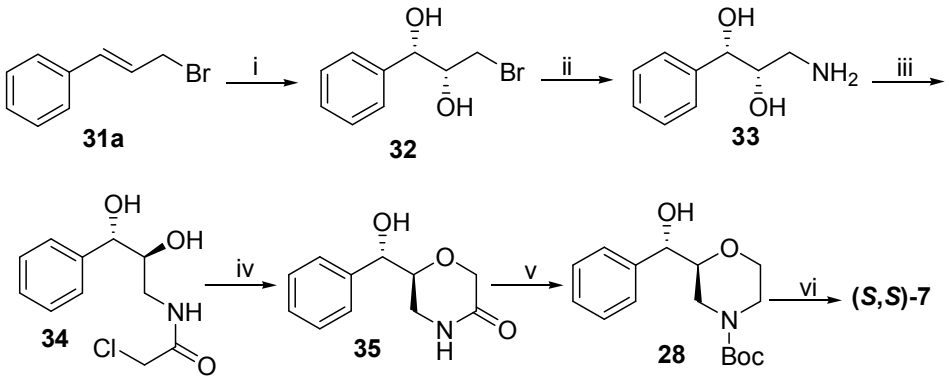
Tamagnan's aim was to build the chiral morpholine moiety first, before introducing the phenyl and aryloxy groups. Chiral aminoalcohol **23** was converted to morpholinone **25** using simple transformations. Aldehyde **27** was obtained from morpholinone **25** in 2 steps of (i) amine protection with $(Boc)_2O$ (ii) alcohol oxidation with trichloroisocyanuric acid (TCIA) and TEMPO in EtOAc. The aldehyde **27** was treated with excess Ph_2Zn to give the diastereomers (2*S*,3*S*)-**28** and (2*S*,3*R*)-**29** in 60 and 19% yields respectively. Sodium alkoxide of **28** was reacted with arylchromium **31** to provide two chromium complexes, which led to **30** in 95% yields after oxidative dechromination with iodine. Finally, treatment of carbamate **30** with excess CF_3CO_2H provided (*S*,*S*)-reboxetine (**7**) in 98% yield (**Scheme 6**).



Scheme 6: (i) $ClCH_2COCl$, Et_3N, CH_3CN, MeOH, -10 °C to 25 °C, 16 h, 94%; (ii) *t*-BuOK, *t*-AmOH, 25 °C, 3 h, 92%; (iii) Red-Al, THF, 0 °C to 25 °C, 16 h, 85%; (iv) (a) $(Boc)_2O$, NaOH, CH_2Cl_2/H_2O, 0 °C to 25 °C, 4 h, 83%, (b) TEMPO, TCIA, $NaHCO_3$, EtOAc, -5 °C, 2 h, 89%; (v) Ph_2Zn, THF, -10 °C to 25 °C, 18 h, **28** (60 %), **29** (19%); (vi) (a) **31**, NaH, DMF, 25 °C, 2h, (b) I_2 in THF, 0 ^{0}C to 25 °C, 1 h, 95%; (vii) TFA, CH_2Cl_2, 0 °C to 25 °C, 1.5 h, 98%.

Srinivasan's approach (2006)[13]

Srinivasan *et al*. have made use of Sharpless asymmetric dihydroxylation approach for the asymmetric synthesis of (*S*,*S*)-**7** (**Scheme 7**).



Scheme 7: (i) $(DHQ)_2$-PHAL, OsO_4, $K_3Fe(CN)_6$, K_2CO_3, $NaHCO_3$, $MeSO_2NH_2$, H_2O-*t*-BuOH (1:1), 0 °C, 24 h, 84%; (ii) (a) NaN_3, DMF, 68 °C, 16 h, 80%, (b) 10% Pd/C, H_2 (1 atm), 25 °C, 12 h, 90%; (iii) $ClCOCH_2Cl$, Et_3N, CH_2Cl_2 at –10 °C to 25 °C, 6 h, 70%; (iv) *t*-BuOK, *t*-BuOH, 25 °C, 4 h, 80%; (v) (a) Red-Al, THF, 0 °C, 83%, (b) $(Boc)_2O$, NaOH, CH_2Cl_2–H_20, 0 °C to 25 °C, 5 h, 83%; (vi) (a) **31**, NaH, DMF, 25 °C, 2h, (b) I_2 in THF, 0 °C to 25 °C, 1 h, 95%, (c) TFA, CH_2Cl_2, 0 °C to 25 °C, 1.5 h, 98%.

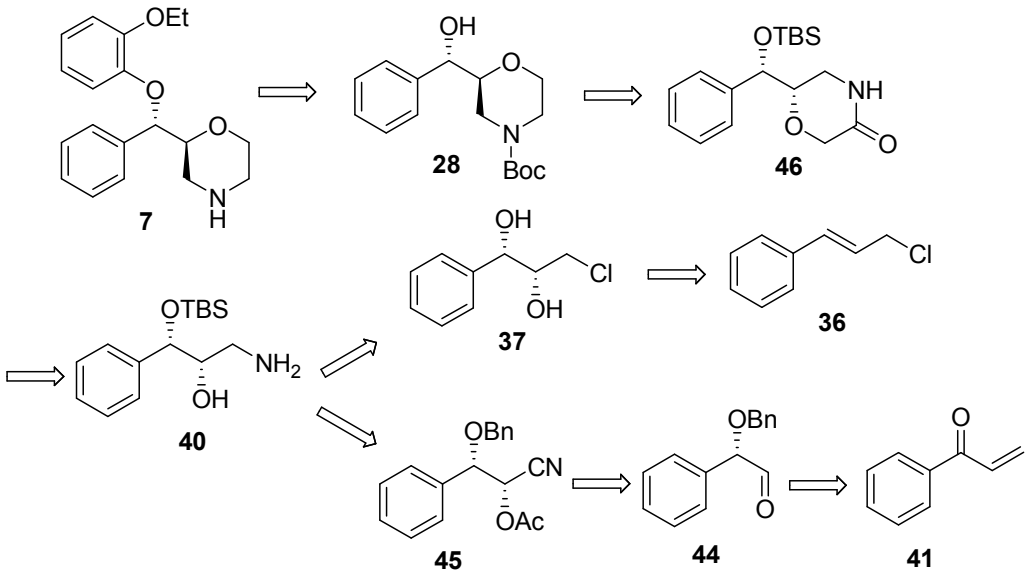
trans-Cinnamyl bromide (**31a**) on subjecting it to asymmetric dihydroxylation afforded diol (**32**). Nucleophilic displacement of the bromo group with sodium azide furnished the azido alcohol which was converted to amine **33** using 10% Pd/C and H_2. The free amine **33** was then treated with chloroacetyl chloride to furnish amide **34**, which was readily cyclized to compound **35**. This cyclic amide was reduced using Red-Al, to give the corresponding morpholine which was protected with $(Boc)_2O$ to afford **28**. The free hydroxyl group was coupled with chromium complex (**31**) and Boc protection was cleaved to give (*S,S*)-reboxetine (**7**).

2.1.4 Present Work

2.1.4.1 Objective

Among reboxetine enantiomers, (*S*,*S*)-reboxetine (**7**) exhibits the best affinity and selectivity for norepinephrine transporter. So far, the methods described in the literature for the synthesis of (*S*,*S*)-reboxetine (**7**) suffer from the following: they involve separation of reboxetine enantiomers by classical resolution, capillary electrophoresis, or chiral HPLC and are specific to the reboxetine structure. In this section, we describe in this section a new approach to the asymmetric synthesis of (*S*,*S*)-reboxetine (**7**) using asymmetric dihydroxylation and asymmetric reduction of ketones as the key reactions.

The retrosynthesis for (*S*,*S*)-reboxetine (**7**) is presented in **Scheme 8**. (*S*,*S*)-Reboxetine (**7**) can be obtained from morpholine **28** which can be realized through the lactam **46**. The lactam **46** can be obtained from the corresponding key intermediate, aminoalcohol **40** which in turn can be obtained from two routes: (i) from the corresponding diol **37** or (ii) reduction of nitrile **45**. The diol **37** can be obtained from cinnamyl chloride **36** by Sharpless asymmetric dihydroxylation and cyanide **45** could be obtained from the enone **41**.

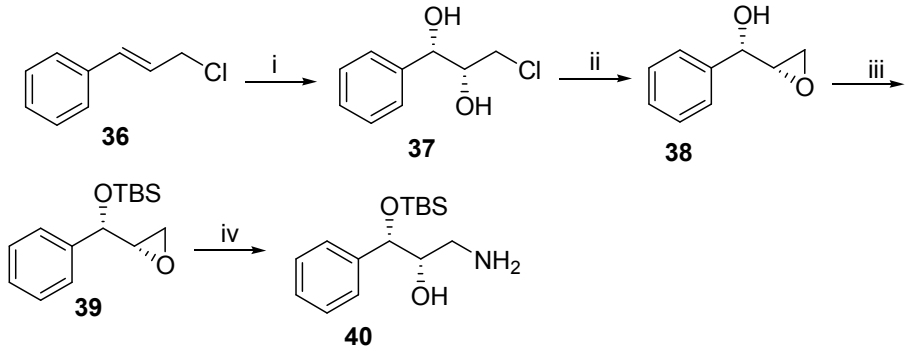


Scheme 8: Retrosynthetic analysis of (*S*,*S*)-reboxetine (**7**)

2.1.5 Results and Discussion

Route 1: Synthesis of aminoalcohol 40 *via* asymmetric dihydroxylation

The synthesis of the key intermediate, aminoalcohol **40** using asymmetric dihydroxylation of cheap and readily available cinnamyl chloride **36**, as the key step is shown in **Scheme 9**.



Scheme 9: (i) $(DHQ)_2$-PHAL, $K_2OsO_2(OH)_4$, $CH_3SO_2NH_2$, $K_3Fe(CN)_6$, K_2CO_3, $NaHCO_3$, *t*-BuOH:H_2O (1:1), 24 h, 0 °C, 80%; (ii) NaOH, THF, 0 °C, 0.5 h, 88%; (iii) TBDMSCl, imidazole, CH_2Cl_2, 0 °C, 1 h, 92%; (iv) 30% NH_4OH, MeOH, 25 °C, 12 h, 80%.

Cinnamyl chloride **36** was subjected to buffered AD conditions[14] using potassium osmate ($K_2OsO_2(OH)_4$) as the catalyst and $(DHQ)_2$-PHAL as the chiral ligand to give

the corresponding diol **37** in 80% yield; $[\alpha]^{25}_{D}$: + 2.96 (*c* 1.9, EtOH); {lit.[14] $[\alpha]_{D}$: - 3.0 (*c* 1.0, EtOH), for (1*R*,2*S*) isomer}. The ^{1}H NMR spectrum of the diol **37** showed signals at δ 3.31 (dd), 3.5 (dd), 3.79-3.87 (m) and 4.67 (d) corresponding to the methylene, homobenzylic and benzylic protons respectively. Its ^{13}C NMR spectrum displayed typical peaks at δ 45.96, 74.61 and 75.26 corresponding to the methylene, homobenzylic and benzylic carbons respectively (**Fig. 3**).

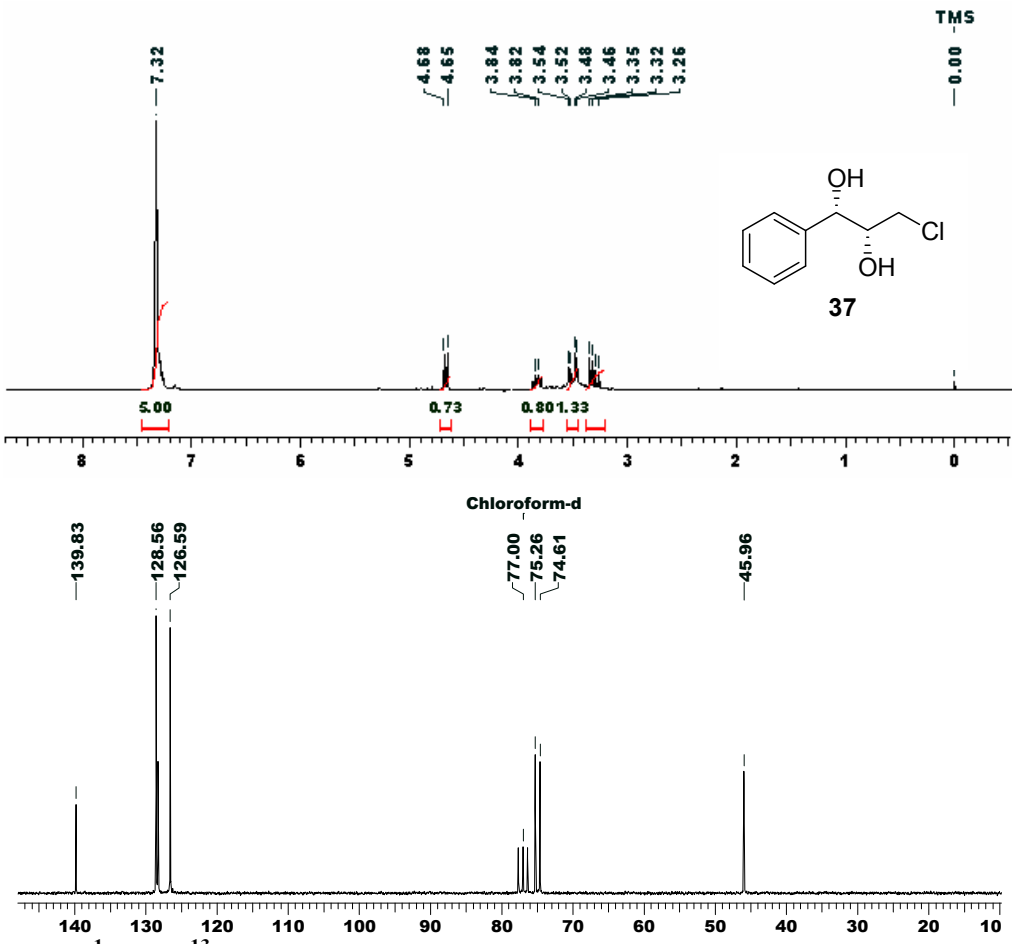


Fig. 3: ^{1}H and ^{13}C NMR spectra of diol 37

The chloro diol **37** was then treated with NaOH in THF at 0 °C to give the epoxy alcohol **38**. The optical purity of epoxy alcohol **38** (98% ee) was determined from its ^{1}H NMR analysis (**Fig. 5**) of its Mosher ester (see experimental section for details).

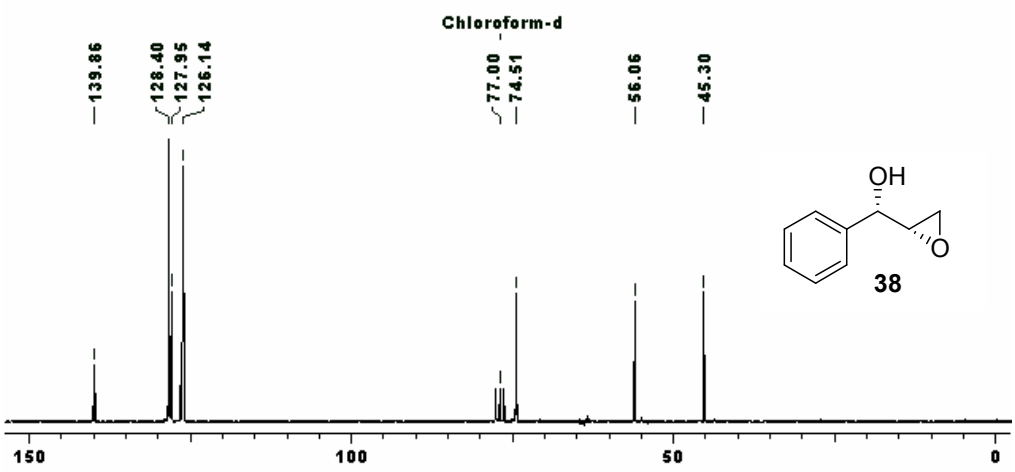


Fig. 4: ^{13}C NMR spectrum of the epoxy alcohol 38

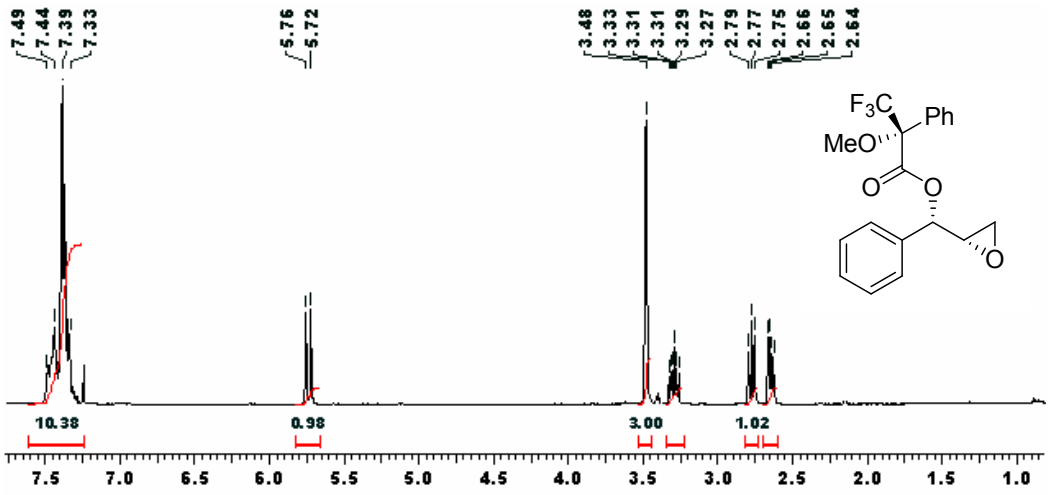


Fig. 5: ^{1}H NMR spectrum of the Mosher's ester of epoxy alcohol 38

The free hydroxyl in the epoxy alcohol **38** was then protected as its *tert*-butyldimethylsilyl ether **39** (TBDMSCl, imidazole, CH_2Cl_2, 0 °C, 1 h); $[\alpha]^{25}_D$: +23.85 (*c* 1.6, $CHCl_3$).

The ^{1}H NMR spectrum of the TBS-ether **39** showed signals at δ 0.0 (s), 0.12 (s) and 0.92 (s) corresponding to the two methyl and the *tert*-butyl groups in the *tert*-butyldimethylsilyl moiety. Its ^{13}C NMR spectrum displayed characteristic carbon signals at δ -4.98, -4.72 and 25.82 corresponding to the two methyl groups and the methyls in *tert*-butyl group attached to the silicon atom (**Fig. 6**).

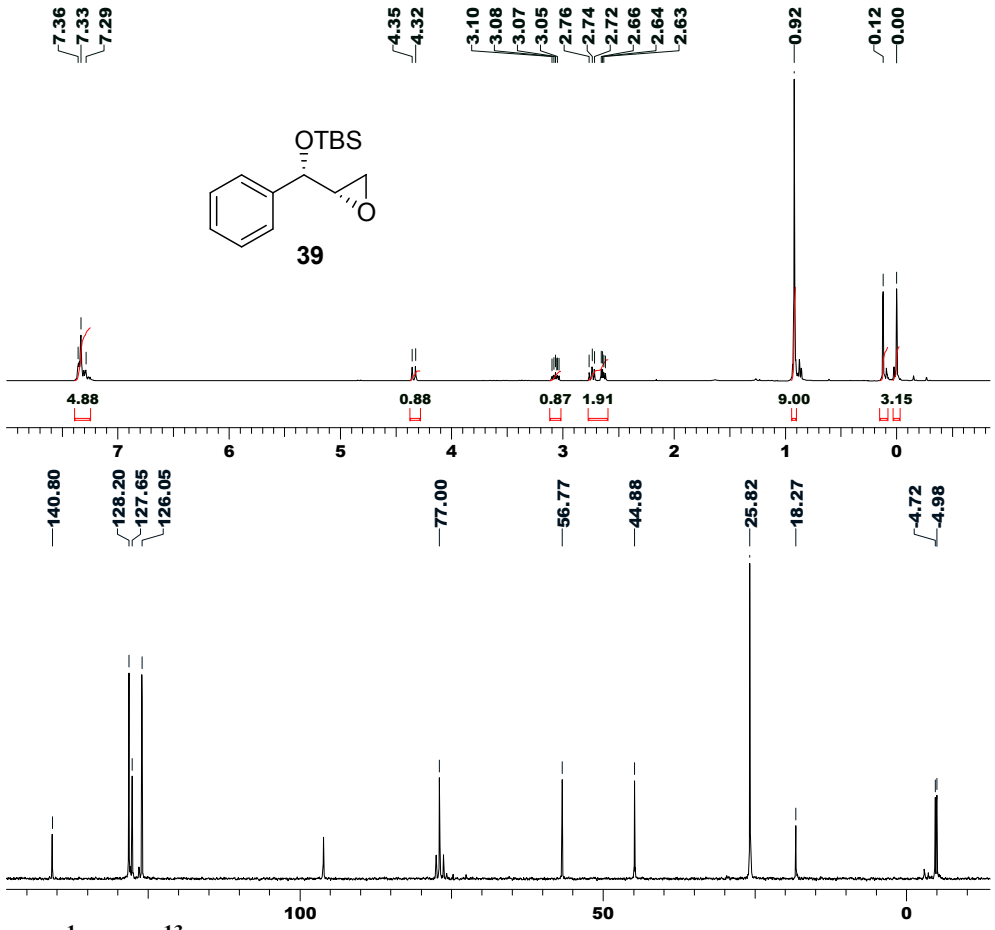


Fig. 6: ^{1}H and ^{13}C NMR spectra of TBS-ether 39

The protected epoxide **39** was then subjected to regioselective ring opening with aqueous 30% NH_4OH at the terminal position to give the corresponding aminoalcohol **40** in 80% yield; $[\alpha]^{25}_{D}$: +18.99 (*c* 1.0, $CHCl_3$).

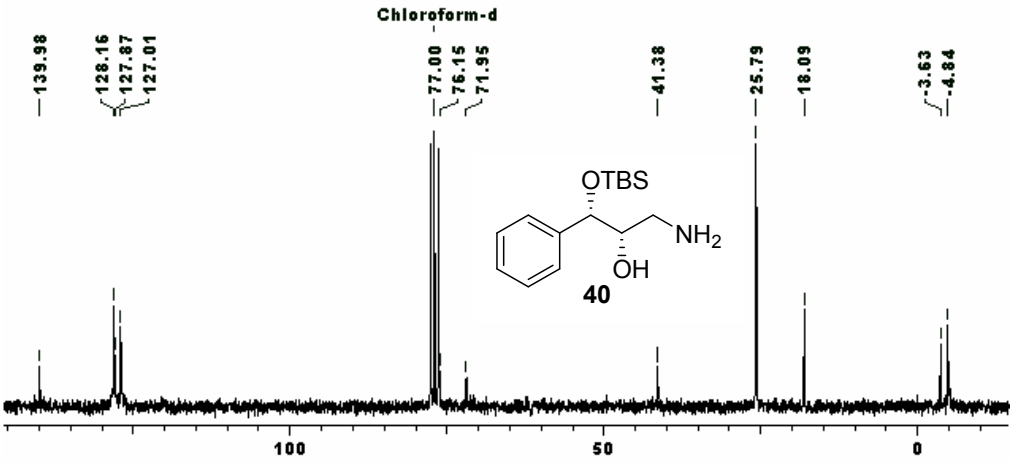
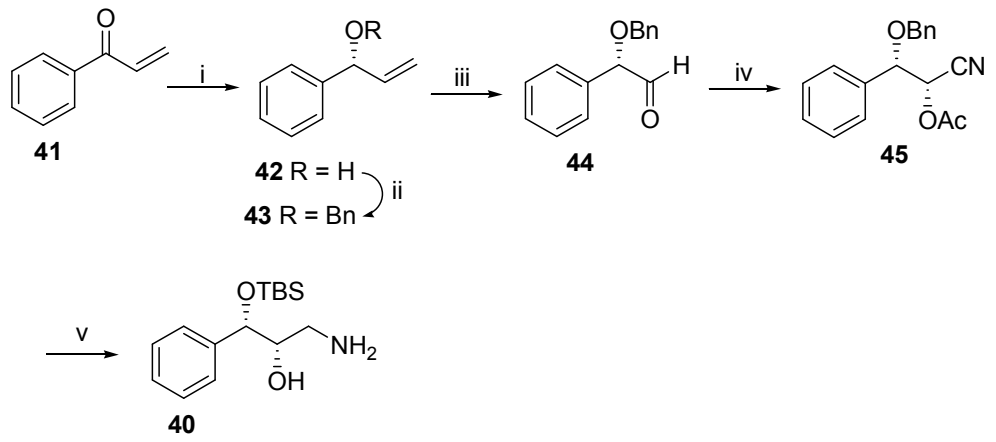


Fig. 7: ^{13}C NMR spectrum of amino alcohol 40

The ^{1}H NMR spectrum of the aminoalcohol **40** showed signals at δ 4.18-4.34 (m) and 4.67-4.80 (m) corresponding to the homobenzylic and benzylic protons respectively. Its ^{13}C NMR showed peaks at 71.95 and 76.15 corresponding to the homobenzylic and benzylic protons respectively. The other carbon signals at 41.38 and 25.79 are due to the methylene carbon ($-CH_2NH_2$) and the methyl groups in the *tert*-butyl moiety respectively (F**ig. 7**).

Route 2: Synthesis of aminoalcohol 40 *via* asymmetric reduction

The synthesis of aminoalcohol **40** using asymmetric reduction[15] is presented in **Scheme 10**.



Scheme 10: (i) (-)-Ipc_2BCl, THF, -25 °C, 10 h, then $NH(CH_2CH_2OH)_2$ 70%; (ii) NaH, BnBr, DMF, 0 °C, 1 h, 95%; (iii) OsO_4, $NaIO_4$, 2,6-lutidine, dioxane, H_2O, 2 h, 90% (iv) (a) TMSCN, $MgBr_2.OEt_2$, CH_2Cl_2, 0 °C, 1.5 h, (b) Ac_2O, pyridine, CH_2Cl_2, -78 to 0 °C, 80% for 2 steps; (v) (a) 10% Pd/C, H_2 (1 atm.), MeOH, 25 °C, 12 h, (b) TBDMSCl, imidazole, CH_2Cl_2, 0 °C, 1 h, (c) DIBAL-H, CH_2Cl_2, -78 °C, 72% for 3 steps.

Enone **41** was subjected to asymmetric reduction using H. C. Brown's reagent *i.e.* (-)-B-chloro-diisopinocamphenyl borane in THF at -25 °C to give the corresponding allylalcohol **42** in 70% yield; $[\alpha]^{25}_{D}$: +0.90 (*c* 3.2, $CHCl_3$); {lit.[16] $[\alpha]^{20}_{D}$: +1.0 (*c* 3.2, $CHCl_3$). The ^{1}H NMR spectrum of the alcohol **42** showed signals at δ 5.32 (dt) and 5.94-6.11 (m) corresponding to the benzylic and homobenzylic protons respectively. A peak at δ 75.3 in its ^{13}C NMR spectrum corresponding to the benzylic carbon confirms the formation of alcohol **42** (**Fig. 8**).

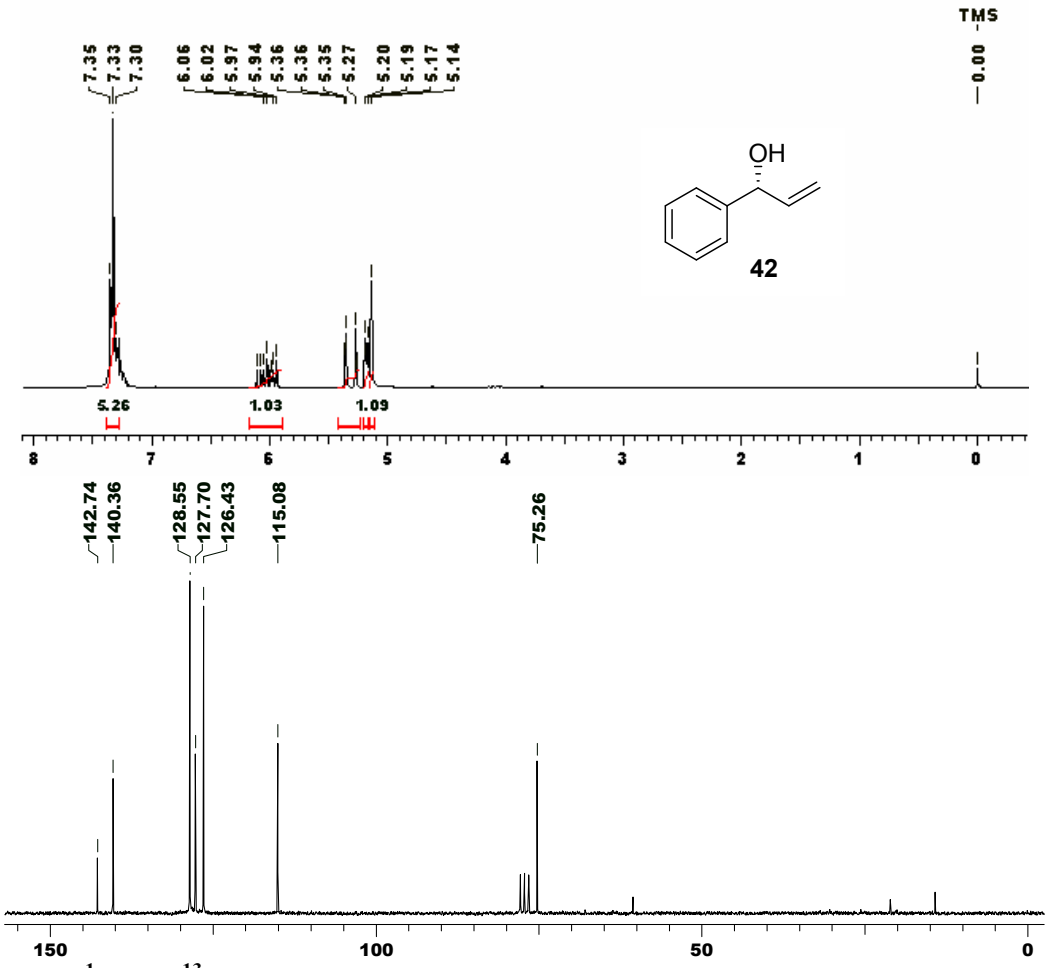


Fig 8: ^{1}H and ^{13}C NMR spectra of allylalcohol 42

The allylalcohol **42** was then protected as its benzyl ether using sodium hydride and benzyl bromide to give ether **43** in 95% yield. The ^{1}H NMR spectrum of the alcohol **42** showed signals at δ 4.84 (s) and 7.23-7.45 (m) corresponding to the benzylic and the aromatic protons in the benzyl group respectively.

The C=C bond in the benzyl ether **43** was then subjected to oxidative cleavage (OsO_4, $NaIO_4$, 2,6-lutidine, dioxane, H_2O, 25 °C) to give the corresponding aldehyde **44** *in situ*, which was subjected to the diastreoselective hydrocyanation (Ward's protocol)[17] using trimethylsilyl cyanide and $MgBr_2.OEt_2$ to give the corresponding cyanohydrin. Due to its instability, the cyanohydrin was protected as its acetate **45**; $[\alpha]^{25}_{D}$: +5.80 (*c* 0.6, $CHCl_3$). The diastereoselectivity (dr = 11:1) of cyanoacetate **45**

was determined by its ^{1}H NMR spectrum (**Fig. 9**). The ^{1}H NMR spectrum of the cyanoacetate **45** showed signals at δ 2.08 (s), 4.33 (d) and 5.58 (d) corresponding to the acetate, benzyl and homobenzylic protons respectively. Its ^{13}C NMR spectrum showed peaks at δ 114.67 and 168.41 corresponding to the nitrile and acetate carbons respectively (**Fig. 9**). Also its IR spectrum showed characteristic band at 2247 cm^{-1} corresponding to the CN stretching vibration.

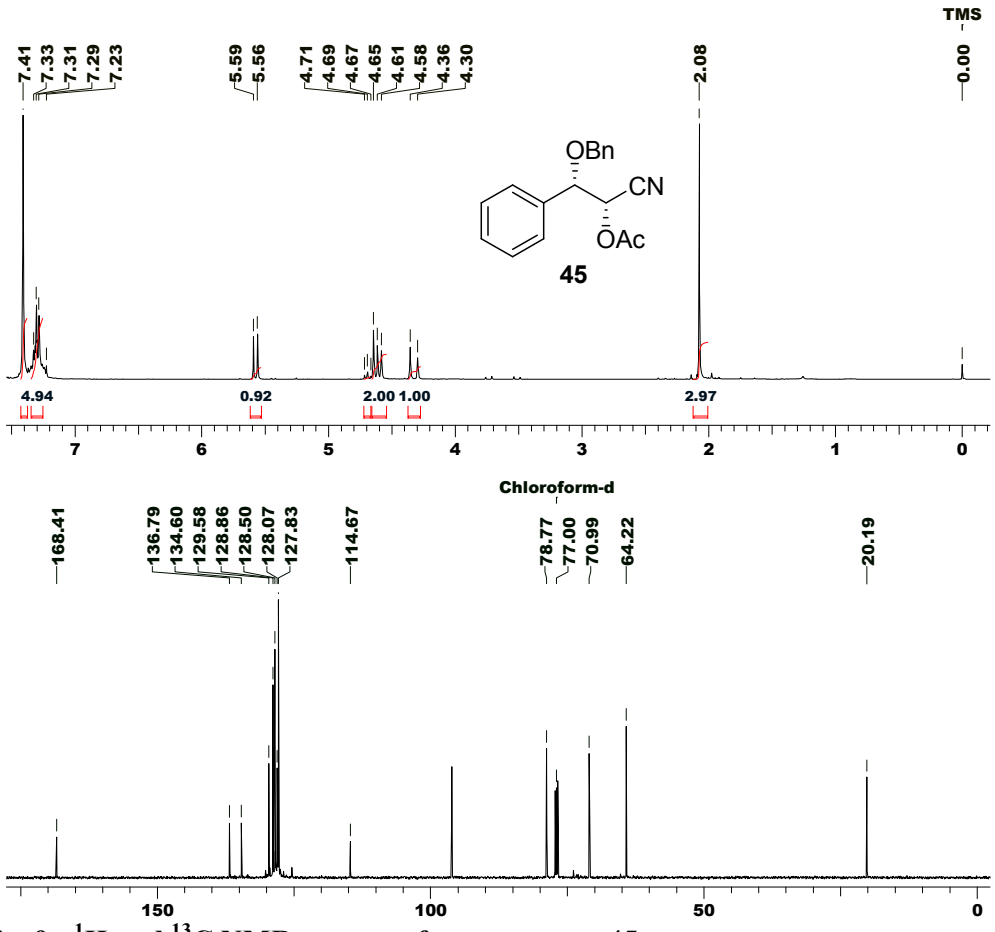


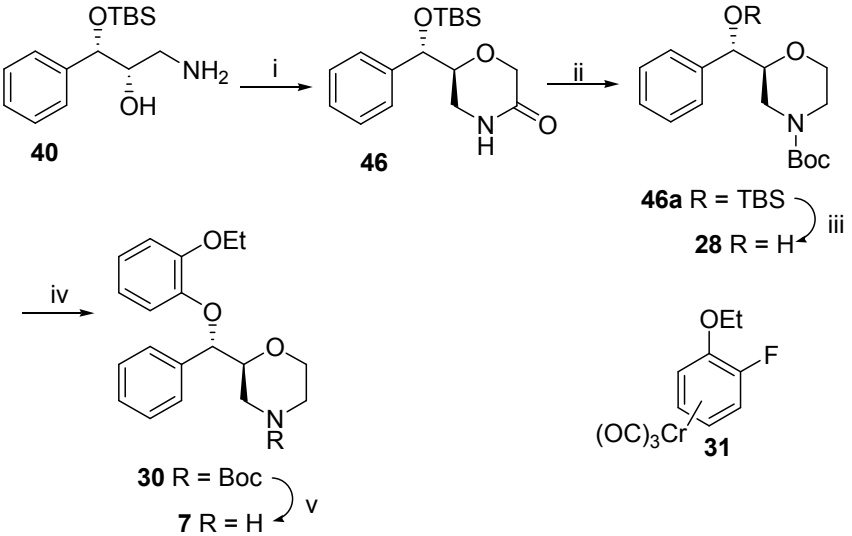
Fig. 9 : ^{1}H and ^{13}C NMR spectra of cyanoacetate 45

The cyanoacetate **45** was converted into the corresponding aminoalcohol **40** in 3 steps: (i) deprotection of the benzyl group and reduction of the cyanide in one step using 10% Pd/C, H_2 (1 atm., balloon pressure), (ii) protection of the alcohol as its *tert*-

butyldimethylsilyl ether using TBDMSCl and imidazole, (iii) reductive removal of acetate group with DIBAL-H; $[\alpha]^{25}_{D}$: +17.92 (*c* 1.0, $CHCl_3$).

Synthesis of (S,S)-reboxetine (7) starting from amino alcohol 40

The synthesis of (S,S)-reboxetine (**7**), starting from amino alcohol **40** is presented in **Scheme 11**.



Scheme 11: (i) (a) $ClCH_2CO_2Cl$, Et_3N, CH_2Cl_2, -10 °C, (b) KO^{t}Bu, *t*-BuOH, 3 h, 72% for 2 steps; (iii) (a) Red-Al, dry toluene, 25 °C, then 2N NaOH, (b) $(Boc)_2O$, Et_3N, CH_2Cl_2, 0 °C, 1 h, 75% for 2 steps; (iv) TBAF, THF, 0 °C, 1 h, 93%; (v) (a) arene-chromium complex **31**, NaH, DMF, 25 °C, 2h, (b) I_2 in THF, 0 °C to 25 °C, 1 h, 85%; (v) TFA, CH_2Cl_2, 0 °C, 1 h, 96%.

The amino alcohol **40** was first reacted with chloroacetyl choride using Et_3N as the base at -10 °C to give the corresponding amide *in situ*, which was readily converted to the corresponding lactam **46** using *t*-BuOK as the base; $[\alpha]^{25}_{D}$: -32.75 (*c* 1.0, $CHCl_3$). The ^{1}H NMR spectrum of the lactam **46** showed signals at δ 2.95 (td); 3.18 (t) (-CH**CH_2**NHC=O-), and 4.28 (dd) (-O**CH_2**C=ONH-) corresponding to the diastereotopic methylene protons present in the lactam moiety. The signals at δ 4.77 (d) and 3.77-3.87 (m) correspond to the benzylic and homobenzylic protons respectively. Its ^{13}C NMR spectrum showed characteristic carbon signals at δ 42.32 (-CH**CH_2**NHC=O-) and 67.33 (-O**CH_2**C=ONH-) corresponding to methylene carbons

present in the lactam moiety. The amide carbonyl in the lactam moiety showed a characteristic peak at δ 169.88 (**Fig. 10**). Its IR spectrum showed a characteristic strong band at 1684 cm^{-1} indicating the presence of amide carbonyl.

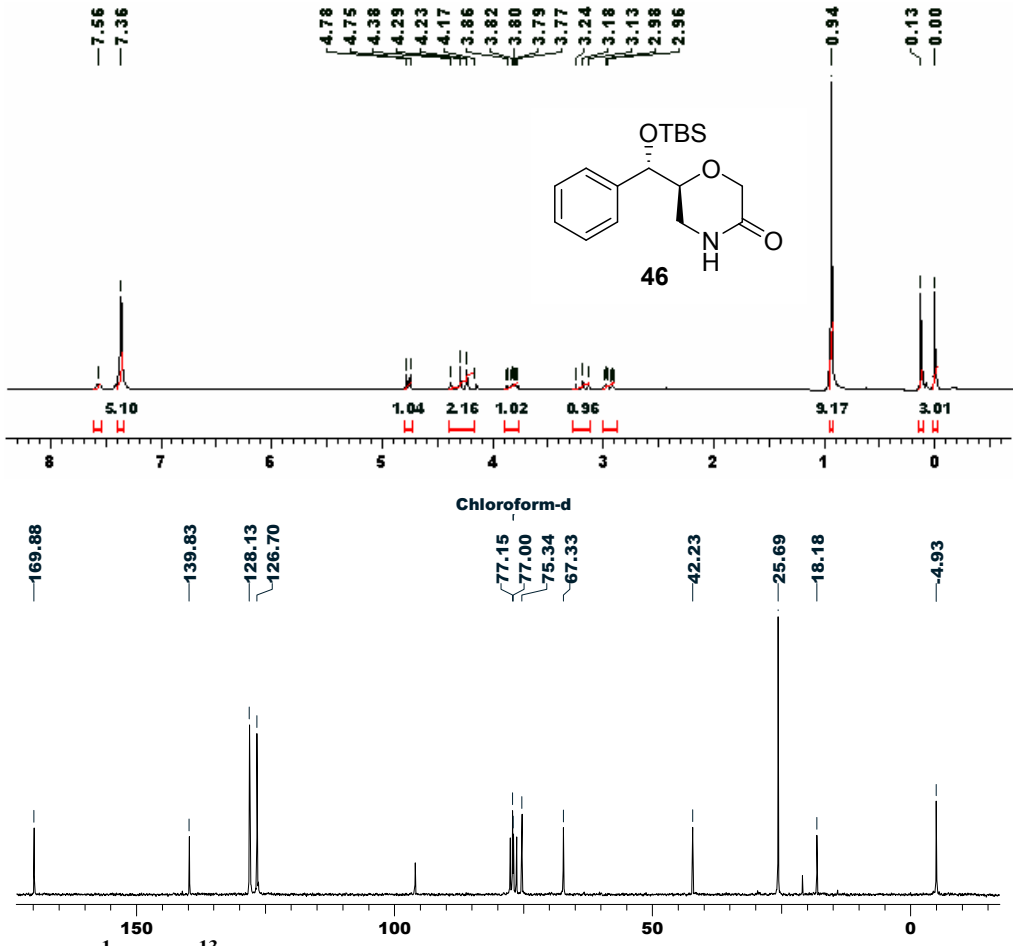


Fig. 10: ^{1}H and ^{13}C NMR spectra of lactam 46

The carbonyl group in lactam **46** was then reduced with Red-Al in toluene to give the corresponding amine *in situ*, which was subsequently protected as its carbamate using $(Boc)_2O$ to give the corresponding morpholine **46a** in 75% yield; $[\alpha]^{25}_{D}$: +52.39 (*c* 0.72, $CHCl_3$). The ^{1}H NMR spectrum of the morpholine **46a** showed signals at δ 3.48-3.68 (m) and 3.75-3.97 (m) corresponding to the methylene protons present in the morpholine moiety (6 H). The signals at δ 1.48 (s) and 4.75 (d) are due to the carbamate (*tert*-butyl) and the benzylic protons respectively. Its ^{13}C NMR

spectrum showed characteristic carbon signals at δ 43.45 (-OCH$_2$**C**H$_2$N(Boc)-), 44.47 (-CH**C**H$_2$N(Boc)-) and 66.50 (-O**C**H$_2$CH$_2$N(Boc)-), corresponding to the three methylene carbons present in the morpholine moiety (**Fig. 11**). Also Its IR spectrum showed a strong band at 1699 cm^{-1} corresponding to the carbonyl of the carbamate moiety.

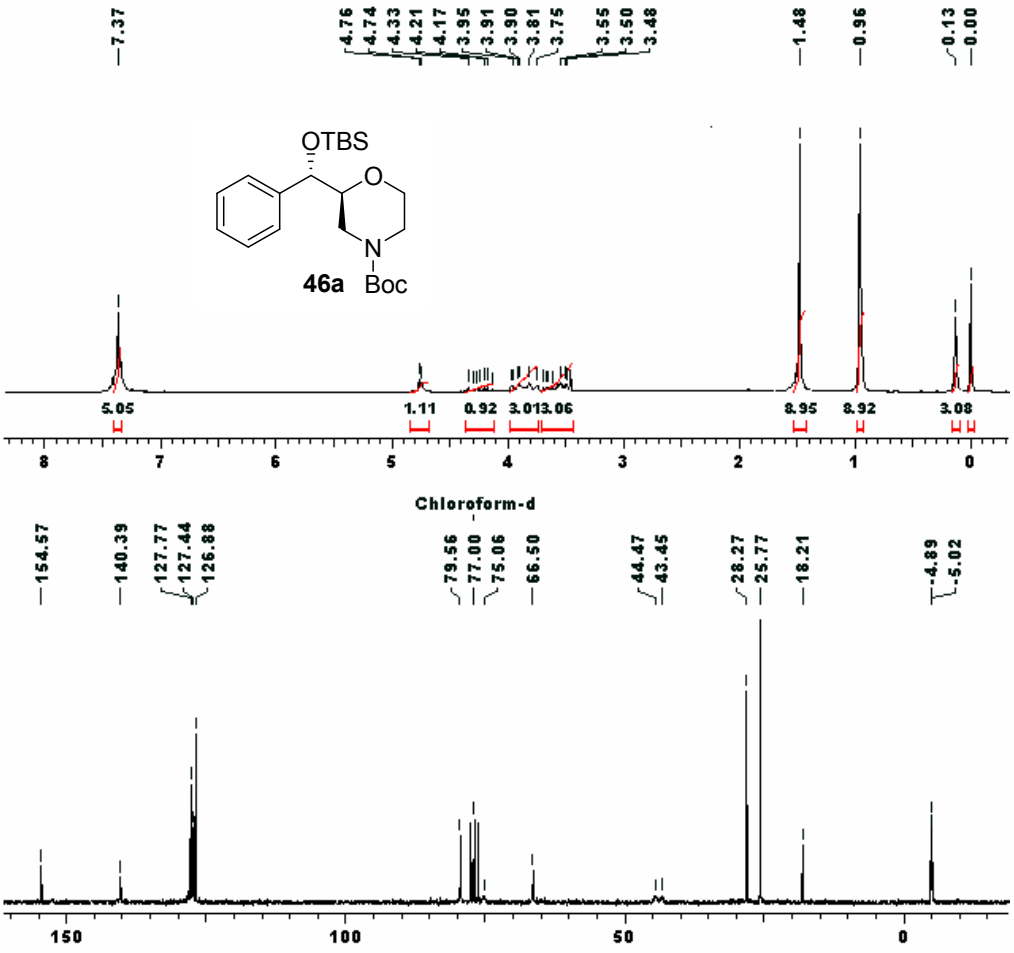


Fig. 11: ^{1}H and ^{13}C NMR spectra of morpholine 46a

The TBS group in the morpholine **46a** was deprotected using TBAF in THF to give the corresponding secondary alcohol **28** in 93% yield; $[\alpha]^{25}_{D}$: +33.24 (*c* 1.0, $CHCl_3$); {lit.[12] $[\alpha]^{20}_{D}$: +34.0 (*c* 1.24, $CHCl_3$)}. The ^{1}H NMR spectrum of the alcohol **28** showed signals at δ 1.4 (s) and 4.52 (d) corresponding to the *tert*-butyl and the

benzylic protons respectively. Its ^{13}C NMR spectrum showed peaks at δ 79.53 and 154.61 corresponding to the benzylic and the carbonyl carbons respectively (**Fig. 12**).

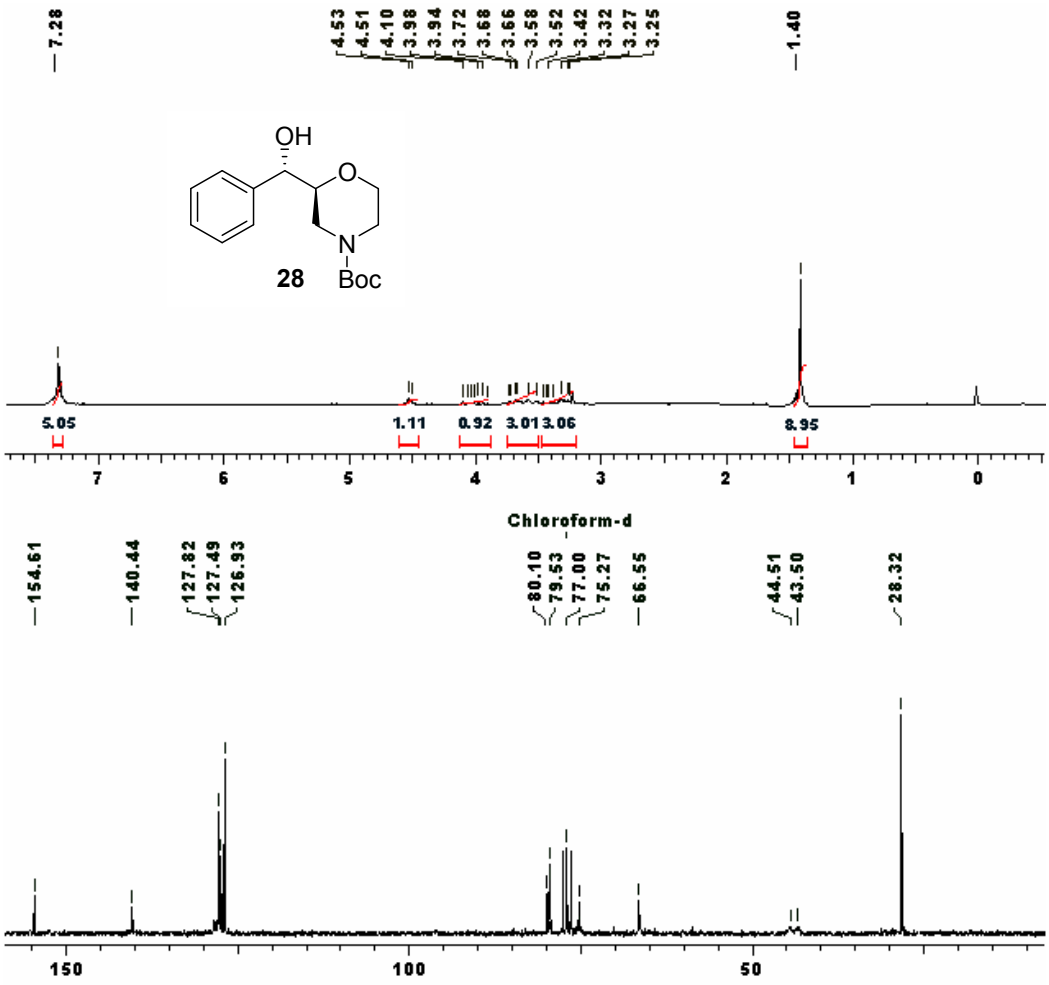


Fig. 12: ^{1}H NMR and ^{13}C NMR spectra of alcohol 28

The alcohol **28** was then converted to *N*-Boc protected reboxetine **30** in 85% yield by (i) nucleophilic displacement of the fluoride in arylchromium **31** by sodium alkoxide of alcohol **28** in DMF, (ii) oxidative dechromination with iodine; $[\alpha]^{25}_{D}$: +49.7 (*c* 1.0, $CHCl_3$); {lit.[12] $[\alpha]^{20}_{D}$: +51.0 (*c* 1.01, $CHCl_3$)}. The ^{1}H NMR spectrum of the *N*-Boc protected reboxetine **30** showed signals at δ 1.48 (s, 12H) and 5.17 (d) corresponding to the methyl protons present in the ethoxy and Boc groups (12H) and the benzylic proton respectively. Its ^{13}C NMR spectrum displayed characteristic broad peaks at

43.60 (br, N**C**H_2CH_2), 46.43 (br, NCH_2CH_2) and 82.1 (br, **C**HO) corresponding to the methylene and the methine carbons present in the morpholine moiety (**Fig. 13**).

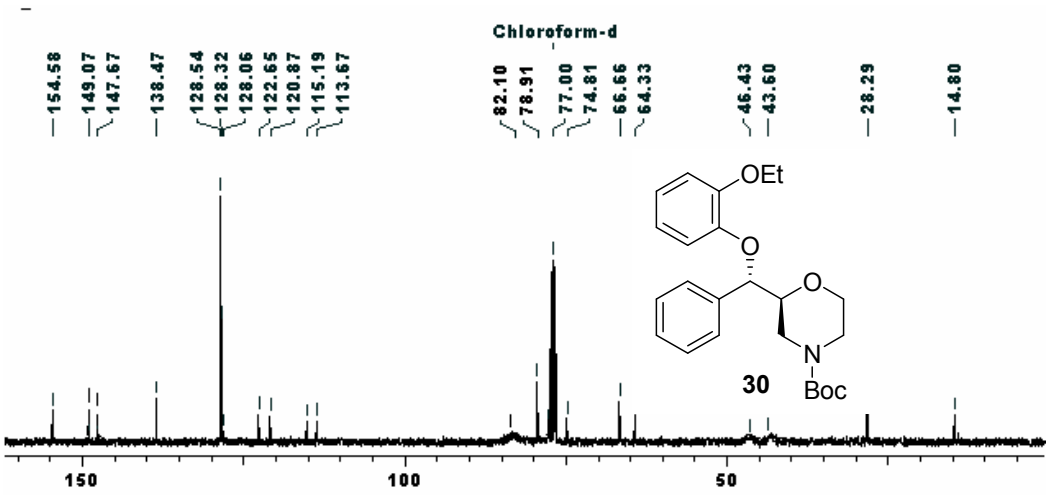


Fig. 13: ^{13}C NMR spectrum of *N*-Boc amide 30

Finally treatment of *N*-Boc reboxetine (**30**) with excess CF_3CO_2H in CH_2Cl_2 afforded (*S*,*S*)-reboxetine (**7**) in 98% yield; $[\alpha]^{25}_D$: +12.52 (*c* 1.1, MeOH); {lit.[12] $[\alpha]^{20}_D$: +13.0 (*c* 1.03, MeOH)}.

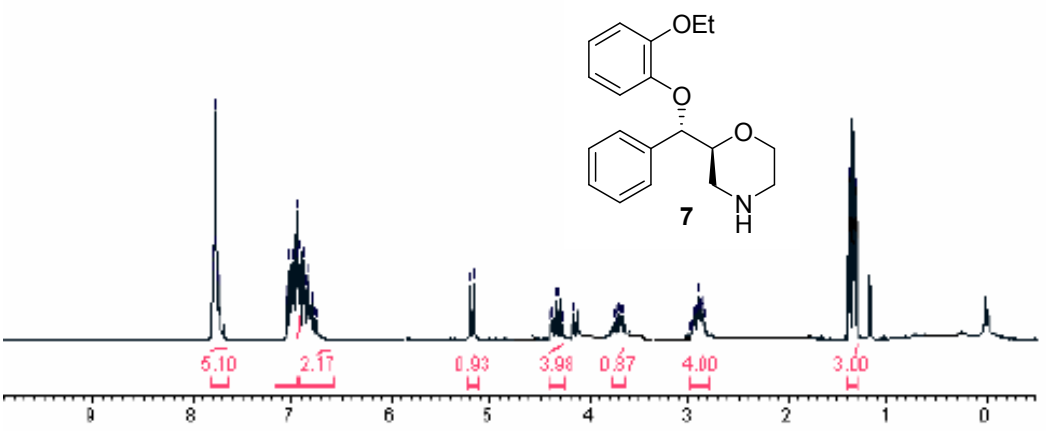


Fig. 14: ^{1}H NMR spectrum of (*S*,*S*)-reboxetine (7)

The ^{1}H NMR spectrum of (*S*,*S*)-reboxetine (**7**) showed signals at δ 1.44 (t) and 5.26 (d) corresponding to the methyl protons in the ethoxyl moiety and the benzylic proton respectively (**Fig. 14**). Its ^{13}C NMR displayed carbon signals at 15.3, 45.1

(NCH_2CH_2) and 46.8 (NCH_2CH_2) corresponding to the methyl group in the ethoxyl moiety and the methylene groups in the morpholine moiety. The spectral data obtained for (*S*,*S*)-reboxetine (**7**) were in full agreement with the values reported in the literature.[12]

2.1.6 Conclusion

In conclusion, we have achieved the asymmetric synthesis of (*S*,*S*)-reboxetine (**7**) using two routes namely, asymmetric dihydroxylation and asymmetric reduction constituting the key steps. The high yields and obtained in this method render our approach a good alternative to the known methods.

2.1.7 Experimental Section

(1*S*,2*R*)-3-Chloro-1-phenylpropane-1,2-diol (37)

To a well-stirred solution of $(DHQ)_2$-PHAL (80 mg, 1 mol%), $K_2OsO_2(OH)_4$ (18 mg, 0.5 mol%), $K_3Fe(CN)_6$ (9.88 g, 30 mmol), K_2CO_3 (4.15 g, 30 mmol), $NaHCO_3$ (2.52 g, 30 mmol) and $CH_3SO_2NH_2$ (950 mg, 10 mmol) in 1:1 *tert*-butanol-water (100 ml) at 0 °C, was added cinnamyl chloride **36** (1.52 g, 10 mmol). After completion of the reaction (24 h), 10 g of $Na_2S_2O_5$ was added to the reaction mixture and stirring was continued for 0.5 h. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with a 1N KOH, 5% aqueous HCl and brine, dried over anhyd. Na_2SO_4 and concentrated to give the crude diol which was purified by column chromatography over silica gel using EtOAc/Pet. ether as eluent (30:70) to give pure diol **37** in 80% yield.

Yield: 1.49 g (80%); gum; $[\alpha]^{25}_{D}$: + 2.96 (*c* 1.9, EtOH); {lit.[14] $[\alpha]_D$: -3.0 (*c* 1.0, EtOH), for (1*R*, 2*S*) isomer}; **IR** ($CHCl_3$, cm^{-1}): 702, 764, 860, 943, 1059, 1092, 1198, 1252, 1456, 1508, 1606, 2927, 2964, 3032, 3410; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 3.31 (dd, *J*=11.5, 5.6 Hz, 1H), 3.50 (dd, *J*=11.5, 3.9 Hz, 1H); 3.83 (m, 1H), 4.67 (d,

J=6.7 Hz, 1H); 7.32 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 45.96, 74.61, 75.26, 126.59, 128.29, 128.56, 139.83; **Analysis: $C_9H_{11}ClO_2$** requires C, 57.92; H, 5.94; Cl, 19.0%; found C, 57.85; H, 5.99; Cl, 19.09%.

(2*S*,3*S*)-3-Phenyl-3-(*tert*-butyldimethylsiloxy)-1,2-epoxypropane (39)

To a well-stirred solution of diol **37** (560 mg, 3 mmol) in THF (25 mL) was added powdered NaOH (180 mg, 4.5 mmol) at 0 °C. The reaction mixture was stirred for 0.5 h and then the solid was filtered off. The solvent was evaporated and the crude epoxide **38** was dissolved in CH_2Cl_2 (20 mL) and imidazole (245 mg, 3.6 mmol) was added to it at 0 °C followed by the addition of TBDMSCl (452 mg, 3mmol). The reaction mixture and stirred for 1 h at 0 °C, solvent distilled off under reduced pressure and crude product purified by column chromatography over silica gel using EtOAc/Pet. ether as eluent (5:95) to give the epoxide **39** in 81% yield.

Yield: 642 mg (81% for 2 steps); gum; **$[\alpha]^{25}_D$:** +23.85 (*c* 1.6, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 669, 700, 760, 837, 939, 1068, 1095, 1217, 1362, 1472, 1603, 2858, 2929, 2960, 3028; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 0.0 (s, 3H), 0.12 (s, 3H), 0.92 (s, 9H), 2.64 (dd, *J*=4.8, 2.3 Hz, 1H), 2.74 (t, *J*=4.8 Hz, 1H), 3.07 (m, 1H), 4.34 (d, *J*=6.3 Hz, 1H), 7.33 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: -4.98, -4.72, 18.27, 25.82, 44.88, 56.77, 126.05, 127.65, 128.20, 140.80; **Analysis: $C_{15}H_{24}O_2Si$** requires C, 68.13; H, 9.15; Si, 10.62%; found C, 68.21; H, 9.04; Si, 10.68%.

(2*R*)-(*S*)-((*S*)-oxiran-2-yl)(phenyl)methyl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate: Mosher ester of epoxyalcohol 38

To a solution of *N*,*N*'-dicyclohexylcarbodiimide (DCC) (44 mg, 0.21 mmol), and 4-dimethylaminopyridine (2 mg, 10 mol%) in CH_2Cl_2 (2 mL) at 0 ºC under argon atmosphere, was added drop-wise a solution of alcohol **38** (27 mg, 0.18 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was stirred for 10 min. and (*R*)-α-methoxy-α-

trifluoromethylphenyl acetic acid (46 mg, 0.196 mmol) in CH_2Cl_2 (2 mL) was added drop-wise, stirred at 0 °C for 1 h and then at 25 °C for 12 h. The reaction mixture was diluted with CH_2Cl_2 (50 mL), washed with saturated aqueous $NaHCO_3$ solution (50 mL), dried over anhyd. Na_2SO_4, concentrated under reduced pressure to give Mosher ester of the alcohol **38**.

Yield: 56 mg (85 %); gum; **$[\alpha]^{25}_D$:** +83.76 (*c* 0.3, $CHCl_3$)**;** **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 2.65 (dd, *J*=4.8, 2.5 Hz, 1H), 2.77 (dd, *J*=4.8, 4.2 Hz, 1H), 3.26-3.33 (m, 1H), 3.48 (s, 3H), 5.74 (d, *J*=6.6 Hz, 1H), 7.33-7.49 (m, 10H); **Analysis**: **$C_{19}H_{17}F_3O_4$** requires C, 62.29; H, 4.68; F, 15.56%; found C, 62.39; H, 4.54; F, 15.61%.

(*R*)-1-Phenylprop-2-en-1-ol (42)

To a stirred solution of enone **41** (1.32 g, 10 mmol) in THF (50 mL) was added a solution of (-)-B-chloro-diisopinocamphenyl borane (3.2 g, 10 mmol) in THF at -25 °C. After stirring for 10 h, the reaction mixture was warmed to 0 ^{0}C followed by the addition of diethanolamine (1.26 g, 12 mmol). After stirring for 2 h, the reaction was quenched by the addition of saturated aqueous NH_4Cl. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 40 mL). The combined organic layer was washed with water, brine, dried over anhyd. Na_2SO_4, solvent distilled off under reduced pressure to give the crude product which was purified by column chromatography over silica gel using EtOAc/Pet. ether as eluent (10:90) to give pure allylalcohol **42**.

Yield: 939 mg (70%); gum; **$[\alpha]^{25}_D$**: + 0.90 (*c* 3.2, $CHCl_3$); {lit.[16] $[\alpha]^{20}_D$: +1.0 (*c* 3.2, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 702, 735, 837, 910, 1097, 1256, 1389, 1472, 1605, 2856, 2929, 2955, 3371; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 5.14 (m, 1H), 5.17-5.20 (m, 1H), 5.31 (td, *J*=17.1, 1.9 Hz, 1H), 5.94-6.11 (m, 1H), 7.30-7.35 (m, 5H); **^{13}C NMR** (50

MHz, $CDCl_3$) δ: 76.15, 119.16, 125.4, 127.01, 128.16, 139.98; **Analysis: $C_9H_{10}O$** requires C, 80.56; H, 7.51%; found C, 80.67; H, 7.44%.

(*R*)-3-Benzyloxy-3-phenylprop-1-ene (43)

To a stirred solution of allylalcohol **42** (670 mg, 5mmol) in DMF was added sodium hydride (200 mg, 5 mmol) at 0 °C followed by the addition of benzyl bromide (595 μL, 5 mmol). After stirring for 1 h, the reaction mixture was quenched by the addition of water (30 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with water, brine, dried over anhyd. Na_2SO_4, solvent distilled off under reduced pressure to give the crude product which was purified by column chromatography over silica gel using EtOAc/Pet. ether as eluent (5:95) to give pure benzyl ether **43**.

Yield: 1.07 g (95%); gum; **IR** ($CHCl_3$, cm^{-1}): 702, 735, 837, 910, 1091, 1394, 1464, 1601, 2857, 2929, 2953; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 4.84 (s, 2H), 5.11 (m, 1H), 5.11-5.16 (m, 1H), 5.24 (m, 1H), 5.94-6.11 (m, 1H), 7.23-7.45 (m, 10H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 71.13, 81.15, 117.18, 120.43, 125.43, 127.81, 128.16, 129.45, 139.98; **Analysis: $C_{16}H_{16}O$** requires C, 85.68; H, 7.19%; found C, 85.80; H, 7.11%.

(2*S*,3*S*)-2-Acetoxy-3-benzyloxy-3-phenylpropionitrile (45)

To a stirred solution of benzyl ether **43** (673 mg, 3 mmol) in 3:1 dioxane-water mixture (20 mL) were added OsO_4 (150 μL, 1M in toluene, 0.06 mmol), $NaIO_4$ (2.56 g, 12 mmol) and 2,6-lutidine (642 mg, 6 mmol) at 25 °C. After stirring for 2 h, water (30 mL) and CH_3CN (60 mL) were added to the reaction mixture. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were washed with water, brine, dried over anhyd. Na_2SO_4, solvent distilled off under reduced pressure to give the crude aldehyde **44** (610 mg) which was dissolved in CH_2Cl_2 (10 mL). To this solution, at 0 °C, was added freshly

prepared magnesium bromide ethyl etherate $MgBr_2.OEt_2$ (3.87 g, 15 mmol) followed by the addition of timethylsilyl cyanide TMSCN (600 µL, 4.5 mmol). After stirring for 1.5 h, the reaction mixture was quenched by the sequential addition of trifluoroacetic acid (2.2 mL, 30 mmol) and water (30 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layer was washed with water, brine, dried over anhyd. Na_2SO_4, solvent distilled off under reduced pressure to give the crude cyanide which was dissolved in CH_2Cl_2 (20 mL) and subsequently cooled to -78 °C. Pyridine (237 mg, 3 mmol) was added to the reaction mixture followed by the addition of acetic anhydride (306 mg, 3 mmol). The reaction mixture was warmed to 0 °C and stirred for 0.5 h followed by quenching with 5% aqueous HCl (10 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with water, brine, dried over anhyd. Na_2SO_4, solvent distilled off under reduced pressure to give the crude product which was purified by column chromatography over silica gel using EtOAc/Pet. ether as eluent (5:95) to give pure cyanoacetate **45**.

Yield: 637 mg (80%); gum; $\mathbf{[\alpha]^{25}_D}$: +5.80 (*c* 0.6, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 702, 735, 837, 910, 1097, 1256, 1389, 1472, 1685, 2247, 2856, 2929, 2955; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 2.08 (s, 3H), 4.33 (d, *J*=12.0 Hz, 1H), 4.61 (t, *J*=6.1 Hz, 2H), 5.58 (d, *J*=6.6 Hz, 1H), 7.23-7.33 (m, 5H), 7.41 (s, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 20.19, 64.22, 70.99, 78.77, 114.67, 127.83, 128.07, 128.5, 128.86, 129.58, 134.6, 136.79, 168.41; **Analysis: $C_{18}H_{17}NO_3$** requires C, 73.20; H, 5.80; N, 4.74%; found C, 73.29; H, 5.68; N, 4.82%.

(2S,3S)-1-Amino-3-phenyl-3-(*tert*-butyldimethylsilyloxy)propane-2-ol (40)

Route 1: To a stirred solution of epoxide (793 mg, 3 mmol) in MeOH (10 mL) was added 30% NH_4OH (15 mL) and the mixture was stirred at 25 °C for 12 h. After completion of the reaction, the solvent was distilled off under reduced pressure and crude product was purified by column chromatography over silica gel using EtOAc/Pet. ether as eluent (70:30) to give the aminoalcohol **40** in 80% yield.

Yield: 676 mg (80%); gum; $[\alpha]^{25}_{D}$: +18.99 (*c* 1.0, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 702, 735, 837, 910, 1097, 1256, 1389, 1472, 1605, 1655, 2856, 2929, 3371, 3410; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 0.0 (s, 3H), 0.19 (s, 3H), 1.02 (s, 9H), 2.86-3.05 (m, 2H), 4.20-4.34 (m, 1H), 4.64-4.80 (m, 1H), 7.42 (s, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: -4.84, -3.63, 18.09, 25.79, 41.38, 71.95, 76.15, 127.01, 128.16, 139.98; **Analysis:** **$C_{15}H_{27}NO_2Si$** requires C, 64.01; H, 9.67; N, 4.98; Si, 9.98%; found C, 64.1; H, 9.61; N, 4.92; Si, 9.94%.

Route 2: cyanoacetate **45** (590 mg, 2 mmol) was dissolved in MeOH (10 mL) and 10% Pd/C (20 mg) was added to it under hydrogen atmosphere (1 atm., balloon pressure). The mixture was stirred for 12 h and the reaction mixture was filtered through a pad of celite and solvent was distilled off under reduced pressure to give the corresponding aminoalcohol which was dissolved in CH_2Cl_2 (10 mL) and imidazole (245 mg, 3.6 mmol) was added to it. The reaction mixture was cooled to 0 °C followed by the addition of TBDMSCl (452 mg, 3mmol). The reaction mixture and stirred for 1 h at 0 °C, the solid formed was filtered off, solvent distilled off under reduced pressure and crude product was dissolved in CH_2Cl_2 (10 mL) and cooled to -78 °C. A solution of DIBAL-H (350 μL, 2.5 mmol, 1 M in THF) was added to the reaction drop wise. After stirring for 1 h the reaction was quenched by the addition of saturated aqueous NH_4Cl solution followed by stirring for 0.5 h. After separation of

layers, the aqueous layer was extracted with MeOH/$CHCl_3$ (1:10, 3 x 30 mL). The combined organic phase was dried over anhyd. Na_2SO_4 and solvent distilled off under reduced pressure to give aminoalcohol 40 in 72% yield; **$[\alpha]^{25}_D$:** +17.92 (*c* 1.0, $CHCl_3$) (*vide infra* of the same section for spectral details).

(*S*)-6-{(*S*)-*tert*-Butyldimethylsilyloxy(phenyl)methyl}morpholin-3-one (46)

To a stirred solution of amine **40** (1.47g, 5.24 mmol) and Et_3N (1.60 mL, 11.5 mmol) in CH_2Cl_2 (40 mL), was added drop-wise at –10 °C, a solution of chloro acetylchloride (0.45 mL, 5.66 mmol) in CH_2Cl_2 (10 mL). After stirring for 0.5 h, the reaction mixture was diluted with CH_2Cl_2 (50 mL), washed with water followed by saturated brine. The combined organic phase was dried over anhyd. Na_2SO_4 and solvent distilled off under reduced pressure to give the crude product which was dissolved in *t*-BuOH (20 mL) and added to a stirred solution of KO^{t}Bu (1.18 g, 10.44 mmol) in *t*-BuOH (6 mL). The reaction mixture was stirred for 3 h at 25 °C and quenched by the addition of water. The organic phase was separated and the aqueous phase was extracted with EtOAc (3 x 30 mL). The combined organic phase was washed with water and brine, dried over anhyd. Na_2SO_4, the solvent distilled off under reduced pressure and crude product purified by column chromatography over silica gel using EtOAc/Pet. ether as eluent (25:75) to give the lactam **46** in 72% yield.

Yield: 1.21 g (72% for 2 steps); gum; **$[\alpha]^{25}_D$** : -32.75 (*c* 1.0, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 669, 700, 777, 860, 1029, 1105, 1251, 1362, 1462, 1541, 1684, 2856, 2885, 2927, 2954, 3219; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 0.0 (s, 3H), 0.13 (s, 3H), 0.94 (s, 9H), 2.95 (td, *J*=12.0 Hz, 3.67 Hz, 1H), 3.18 (t, *J*=10.87 Hz, 1H), 3.82 (m, 1H), 4.14-4.29 (m, 2H), 4.77 (d, *J*=6.10 Hz, 1H), 7.36 (m, 5H), 7.56 (br s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: -4.93, 18.18, 25.69, 42.23, 67.33, 75.33, 77.14, 126.70, 127.98, 128.13,

139.83, 169.88; **Analysis: $C_{17}H_{27}NO_3Si$** requires C, 63.51; H, 8.47; N, 4.36; Si, 8.74%; found C, 63.59; H, 8.4; N, 4.42; Si, 8.71%.

(*S*)-6-{(*S*)-*tert*-Butyldimethylsilyloxy(phenyl)methyl}*tert*-butyl morpholine-4-carboxylate (46a)

A solution of Red Al (3.5 mL, 10.48 mmol) in dry toluene (10 mL) was slowly added to a stirred solution of amide **46** (964 mg, 3 mmol) in dry toluene (40 mL) at 25 °C. The reaction mixture was stirred for 4 h and the excess Red Al was quenched by the addition of 2N NaOH (20 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layer was washed with water, brine, dried over anhyd. Na_2SO_4, solvent distilled off under reduced pressure and the crude product obtained was dissolved in CH_2Cl_2 (15 mL). The mixture was cooled to 0 °C and Et_3N (460 μL, 3 mmol) and $(Boc)_2O$ (654 mg, 3 mmol) were added to it. After 1 h the reaction mixture was quenched by the addition of aqueous $NaHCO_3$ (10%). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over anhyd. Na_2SO_4, solvent distilled off under reduced pressure and the crude product purified by column chromatography over silica gel using EtOAc/Pet. ether as eluent (15:85) to give morpholine **46a** in 75% yield.

Yield: 917 mg (75% for 2 steps); gum; **$[\alpha]^{25}_D$**: +52.39 (*c* 0.72, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 669, 700, 777, 862, 1072, 1122, 1173, 1254, 1366, 1456, 1608, 1703, 2856, 2927, 2943; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 0.0 (s, 3H), 0.13 (s, 3H), 0.96 (s, 9H), 1.48 (s, 9H), 3.48-3.70 (m, 3H), 3.75-3.97 (m, 3H), 4.14-4.33 (m, 1H), 4.75 (d, *J*=4.42 Hz, 1H), 7.37 (s, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: -5.02, -4.89, 18.21, 25.77, 28.27, 43.45, 44.47, 66.50, 75.30, 79.49, 79.56, 126.88, 127.44, 127.77, 140.39,

154.57; **Analysis: $C_{22}H_{37}NO_4Si$** requires C, 64.82; H, 9.15; N, 3.44; Si, 6.89%; found C, 64.89; H, 9.09; N, 3.49; Si, 6.82%.

(*S*)-*tert*-Butyl 2-{(*S*)-hydroxy(phenyl)methyl}morpholine-4-carboxylate (28)

To a stirred solution of morpholine **46a** (815 mg, 2 mmol) in THF was added a solution of tetrabutylammonium fluoride (0.97 mL, 1M in THF, 3 mmol) at 0 °C and stirred for 1 h. The reaction mixture was quenched by addition of water and the organic phase was separated. The aqueous layer was extracted with EtOAc (3 x 20 mL) and the combined organic layers were dried over anhyd. Na_2SO_4, the solvent distilled off under reduced pressure and the crude product purified by column chromatography over silica gel using EtOAc/Pet. ether as eluent (20:80) to give alcohol **28** as colorless solid in 93% yield.

Yield: 564 mg (93%); **mp:** 105-106 °C; **$[\alpha]^{25}_D$**: +33.24 (*c* 1.0, $CHCl_3$); {lit.[12] **$[\alpha]^{20}_D$**: +34.0 (*c* 1.24, $CHCl_3$)}; **IR** ($CHCl_3$, cm^{-1}): 669, 721, 862, 1068, 1114, 1181, 1241, 1323, 1456, 1610, 1701, 2861, 3214; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.40 (s, 9H), 3.46-3.25 (m, 3H), 3.52-3.74 (m, 3H), 3.91-4.10 (m, 1H), 4.52 (d, 1H, *J* = 4.3 Hz), 7.28 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 28.32, 43.50, 44.51, 66.55, 75.27, 79.53, 80.1, 126.93, 127.49, 127.82, 140.44, 154.61; **Analysis**: **$C_{16}H_{23}NO_4$** requires C, 65.51; H, 7.90; N, 4.77%; found C, 65.46; H, 7.97; N, 4.72%.

(*S*)-*tert*-Butyl 2-{(*S*)-(2-ethoxyphenoxy)(phenyl)methyl}morpholine-4-carboxylate (30)

To a stirred suspension of sodium hydride (60% oil dispersion, 60 mg, 1.5 mmol) in DMF (2 mL) was added dropwise alcohol **28** (293 mg, 1 mmol) in DMF (3 mL) at 25 °C under nitrogen atmosphere. After 1 h tricarbonylchromium complex **31** (416 mg, 1.5 mmol) in DMF (5 mL) was added to the mixture at 25 °C. The mixture was stirred for 2 h, then cooled to 0 °C and a solution of I_2 (1.52 g, 6 mmol) in THF (6 mL) was

added over 0.5 h. The reaction mixture was stirred for 0.5 h at 25 °C and quenched by the addition of aqueous solution of 10% $Na_2S_2O_3$ (40 mL). The organic phase was separated and the aqueous phase was extracted with EtOAc (3 x 30 mL) and the combined organic phase was washed twice with water, dried over anhyd. Na_2SO_4 and the solvent evaporated under reduced pressure. The crude product was purified by column chromatography over silica gel using EtOAc/Pet. ether (15:85) as eluent to provide *N*-Boc amide **30** as colorless oil in 85% yield.

Yield: 351 mg (85%); gum; **$[\alpha]^{25}_D$**: +49.7 (*c* 1.0, $CHCl_3$); {lit.[12] $[\alpha]^{20}_D$: +51.0 (*c* 1.01, $CHCl_3$)}; **IR** ($CHCl_3$, cm^{-1}): 761, 986, 1123, 1134, 1251, 1456, 1499, 1543, 1690, 2915, 2923; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.45 (s, 12H), 2.86-3.01 (m, 2H), 3.42-3.54 (m, 1H), 3.80-3.90 (m, 4H), 4.08-4.12 (m, 2H), 5.17 (d, 1H, *J*=3.5 Hz), 6.82-6.95 (m, 2H), 7.26-7.44 (m, 7H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 14.80, 28.29, 43.60, 46.43, 64.33, 66.66, 74.81, 78.91, 82.10, 113.67, 115.19, 120.87, 122.65, 128.06, 128.32, 128.54, 138.47, 147.67, 149.07, 154.58; **Analysis**: **$C_{24}H_{31}NO_5$** requires C, 69.71; H, 7.56; N, 3.39%; found C, 69.64; H, 7.61; N, 3.34%.

(*S*)-2-{(*S*)-(2-Ethoxyphenoxy)(phenyl)methyl}morpholine: (*S*,*S*)-reboxetine (7)

To a stirred solution of *N*-Boc amide **30** (267 mg, 0.646 mmol) in CH_2Cl_2 (5 mL), trifluoroacetic acid (0.74 mL, 9.69 mmol) was added dropwise at 0 °C. The reaction mixture was allowed to reach 25 °C and stirred for 1.5 h. The reaction mixture was cooled to 0 °C and quenched by the addition of 1M NaOH solution (15 mL). The organic phase was separated and the aqueous phase was extracted with EtOAc/MeOH (95:5, 3 x 30 mL). The combined organic phase was dried over anhyd. Na_2SO_4, solvent evaporated under reduced pressure and the crude product purified by column chromatography over silica gel using MeOH/$CHCl_3$ (10:90) as eluent to provide (S,S)-reboxetine **(7)** as colorless oil.

Yield: 198 mg (98%); gum; **$[\alpha]^{25}_{D}$**: +12.52 (*c* 1.1, MeOH); {lit.[12] $[\alpha]^{20}_{D}$: +13.0 (*c* 1.03, MeOH)}; **IR** ($CHCl_3$, cm^{-1}): 750, 997, 1119, 1154, 1251, 1453, 1499, 1593, 2915, 3031; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.44 (t, *J*=7.5 Hz, 3H), 2.98-2.80 (m, 4H), 3.77-3.68 (m, 1H), 4.13-3.97 (m, 4H), 5.26 (d, *J*=5.5 Hz, 1H), 6.71-6.79 (m, 2H), 6.84-6.97 (m, 2H), 7.27-7.43 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 15.3, 45.1, 46.8, 65.7, 67.0, 78.8, 83.4, 115.5, 118.9, 121.9, 123.5, 128.6, 129.3, 138.6, 148.7, 150.9; **Analysis**: **$C_{19}H_{23}NO_3$** requires C, 72.82; H, 7.40; N, 4.47%; found C, 72.69; H, 7.37; N, 4.44%.

Section II

Asymmetric Synthesis of (*S*)-Toliprolol

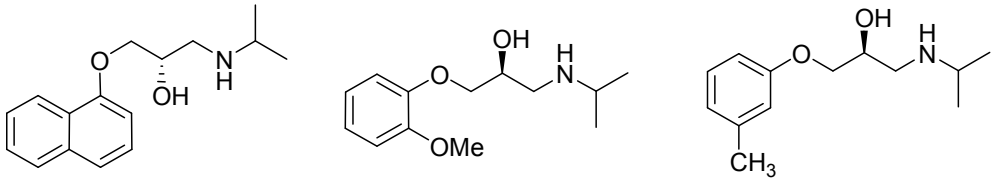
2.2.1 Introduction

The members of a pair of enantiomers often show different pharmacological and metabolic characteristics. The synthesis of homochiral drugs has become a key issue not only in academic research but also in the pharmaceutical industry.[18] Biological systems, in most cases, recognize the members of a pair of enantiomers as different substances, and the two enantiomers will exhibit different responses. Thus one enantiomer may act as a very effective therapeutic drug while the other is highly toxic.

2.2.2 β-Adrenergic Blockers

β-Adrenergic blocking agents (β-blockers) are important drugs used for the treatment of hypertension and angina pectoris.[19] Most of the β-blockers possess a general structure Ar-O-$CH_2CH(OH)CH_2NHCH(CH_3)_2$ (**Fig 15**) and have been used in the form of racemic mixtures.[20] Three fundamental goals of cardiovascular drugs are: the lowering of blood pressure (antihypertensive), return of the heart to rhythmic beating (antiarrhythmics) and the general improvement of the heart muscle tone (cardiotonics).[21] Biochemically, the mechanism of action involves the adrenergic system in which the hormonal system provides the communication link between the sympathetic nervous system and involuntary muscle.[22] Some of the representative β-blockers are shown in **Fig. 15**. There are four types of receptors for these molecules α_1, α_2, β_1 and β_2. Blocking of β-receptor system reduces the overall activity of the sympathetic nervous system. Agents, which are β-blockers, are thus used to increase life expectancy after the heart attack. Although (*S*)-isomers are known to be much

more effective (100-500 fold) than the (*R*)-isomer,[23] these antihypertensive drugs are presently sold as racemic mixtures. To avoid unnecessary stress or in some case toxicity to an organism caused by the (*R*)-isomers, the administration of optically pure (*S*)-isomer is desirable. (*S*)-propranolol (**47**), (*S*)-moprolol (**48**) and (*S*)-toliprolol (**49**) are amongst the most widely used β-blockers, which possesses antihypertensive, antianginal, and sympatholytic properties.



(S)-propranolol (47) **(S)-moprolol (48)** **(S)-toliprolol (49)**

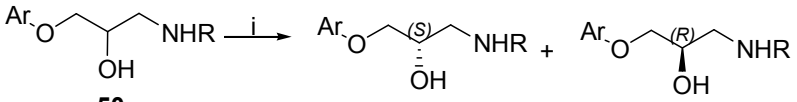
Fig. 15

2.2.3 Review of Literature

Literature search revealed that there few reports available for the synthesis of (*S*)-toliprolol (**49**), which are described below.

Howe's approach (1968)[24]

Howe *et al.* synthesized (*S*)-toliprolol (**49**) by resolution of its racemate. Thus 1-isopropylamino-3-(3-tolyloxy)-2-propanol (**50**) was resolved using (-)-O,O-di-*p*-toluoyltartaric acid (**Scheme 12**).



50

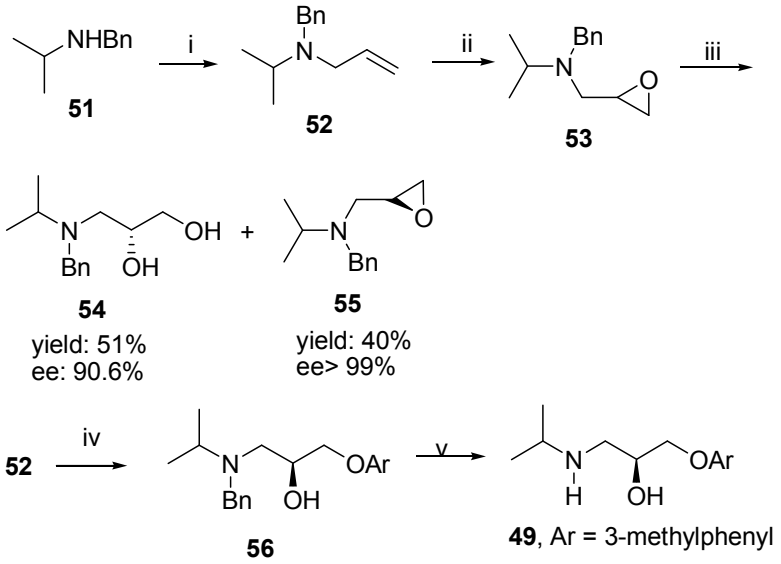
Ar = 3-methylphenyl
R = isopropyl

49 Ar = 3-methylphenyl

Scheme 12: (i) (-)-O,O-di-*p*-toluoyltartaric acid, MeOH, H_2O, fractional crystallization

Hou's approach (1999)[25]

The chiral building block (*S*)-*N*-benzyl-*N*-isopropyl-2,3-epoxypropylamine (**55**) was synthesized by means of chlorohydroxylation of allylamine **52**, followed by Jacobsen's hydrolytic kinetic resolution with water. A concise, divergent five step synthesis of (*S*)-toliprolol (**49**) in 28.4% overall yield and in >99% ee using (*S*)-*N*-benzyl-*N*-isopropyl-2,3-epoxypropylamine (**55**) as the key intermediate was developed (**Scheme 13**).

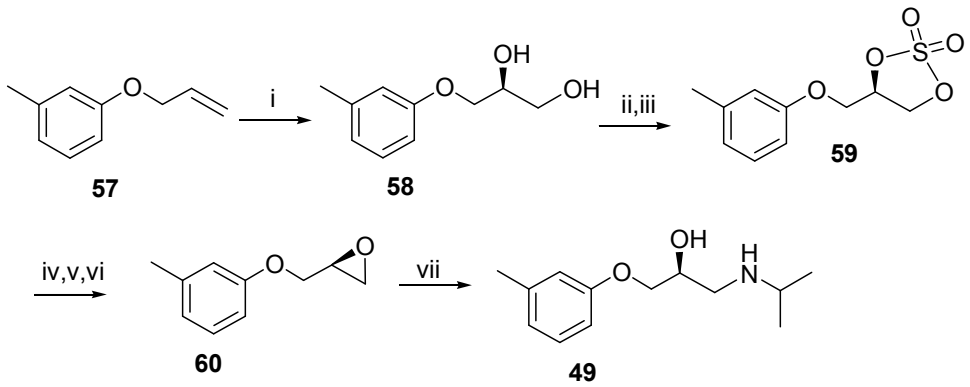


Scheme 13: (i) allylbromide, NaOH, DMF, 93%; (ii) a) Li_2PdCl_4 (10%), $CuCl_2$ (300%), DMF, -10 °C, H_2O; b) $Na_2S.9H_2O$; (iii) H_2O, (*S,S*)-(salen)-Co-(III)OAc; (iv) ArOH (Ar = 1-naphthyl, 2-methoxyphenyl, 3-methylphenyl), Et_3N, reflux; (v) H_2, 10% Pd/C, EtOH, 100%.

Sudalai's approach (2005)[26]

Sudalai *et al.* have developed the enantioselective synthesis of (*S*)-toliprolol (**49**) using asymmetric dihydroxylation of the allylether **57** as the key step (**Scheme 14**). Allylether **57** was subjected to Os-catalyzed Sharpless asymmetric dihydroxylation (AD) using $(DHQD)_2$-PHAL as chiral ligand to give the corresponding diol **58** which was converted to the corresponding cyclic sulfate **59** in two steps of (i) formation of cyclic sulfite with thionyl chloride and (ii) oxidation of cyclic sulfite to cyclic sulfate

59 with $RuCl_3$ and $NaIO_4$. The cyclic sulfate **59** was converted to the epoxide **60** which was opened with isopropyl amine to give toliprolol (**49**) in 78% ee.



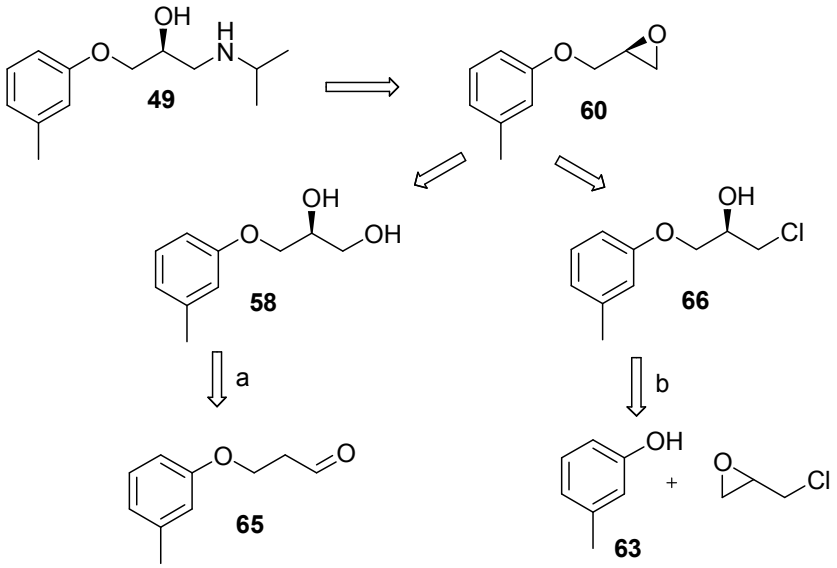
Scheme 14: (i) cat-OsO_4, $(DHQD)_2$-PHAL, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH:H_2O, 0 °C, 12 h, 94-98%, 80%ee; (ii) $SOCl_2$, Et_3N, CH_2Cl_2, 0 °C, 40 min., 96-99%; (iii) cat. $RuCl_3$ $3H_2O$, $NaIO_4$, CH_3CN:H_2O, 0 °C, 30 min., 94-98%; (iv) LiBr, THF 25 °C, 2-3 h; (v) 20% H_2SO_4, Et_2O, 25 °C, 10 h; (vi) K_2CO_3, MeOH, 0 °C, 2 h, 80-85% overall in three steps; (vii) *i*-Pr-NH_2, H_2O (cat.), reflux, 2 h, 99%.

2.2.4 Present Work

2.2.4.1 Objective

All the reported methods described above for the synthesis of β-blockers suffer from drawbacks such as use of expensive enzymes and resolving agents, low overall yields, low optical purity, *etc*. To develop a new route for the asymmetric synthesis of (*S*)-toliprolol **49** with good optical purity and yield, we have decided to make use of proline-catalyzed α-aminooxylation and Co-catalyzed kinetic resolution of terminal epoxides as the key reactions. The retrosynthesis of (*S*)-toliprolol **49** is shown in **Scheme 15**. As can be seen from **Scheme 15**, the target molecule, (*S*)-toliprolol **49**, can be obtained from the corresponding epoxide **60**. The epoxide **60** can be obtained from two intermediates (a) diol **58** and (b) chloroalcohol **66**. Proline-catalyzed α-aminooxylation of aldehyde **65** should lead to diol **58**. Further, the Co-catalyzed asymmetric kinetic resolution of (±)-epichlorohydrin with *m*-cresol (**63**) should give chloroalcohol **66**. Since this section deals with Co-catalyzed asymmetric kinetic

resolution of terminal epoxides and D-proline catalyzed *α-aminooxylation* of carbonyl compounds, for introducing stereogenicity into the prochiral molecule, a brief account of Co-catalyzed asymmetric kinetic resolution of terminal epoxides is described (a brief account of *α-aminooxylation* is given in Section I of Chapter I).

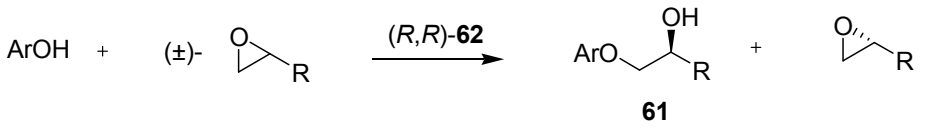


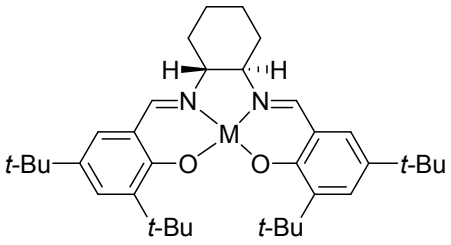
Scheme 15: Retrosynthesis of (*S*)-toliprolol **49**

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

Enantiopure α-aryloxy alcohols (**61**) are valuable targets for asymmetric synthesis as a result of their role as key synthetic intermediates in a variety of pharmaceutically important compounds.[27] In principle, access to these building blocks may be provided by several routes, including asymmetric reduction of aryloxy ketones[28] or the ring opening of enantiopure terminal epoxides with phenols. Of these, the latter is probably the most versatile and direct, but available methods for the addition of phenols to epoxides are extremely limited.

The ready accessibility of terminal epoxides in racemic form renders kinetic resolution of terminal epoxides with phenols a potentially attractive route to **61** (**Scheme 16**). The high selectivities obtained in the recently reported hydrolytic kinetic resolution of terminal epoxides with catalyst **62b**[29] suggested that (salen)Co(III) complexes might also serve as effective catalysts for the enantioselective addition of phenols to epoxides. This strategy has proven successful and the kinetic resolution of epoxides with phenols has been reported, with the isolation of 1-aryloxy 2-alcohols (**61**) in high ee's and yields.





(*R*,*R*)-**62a**: M = Co
(*R*,*R*)-**62b**: M = Co(OAc)(H_2O)
(*R*,*R*)-**62c**: M = Co[$OC(CF_3)_3$](H_2O)

Scheme 16: Kinetic resolution of terminal epoxides with phenols

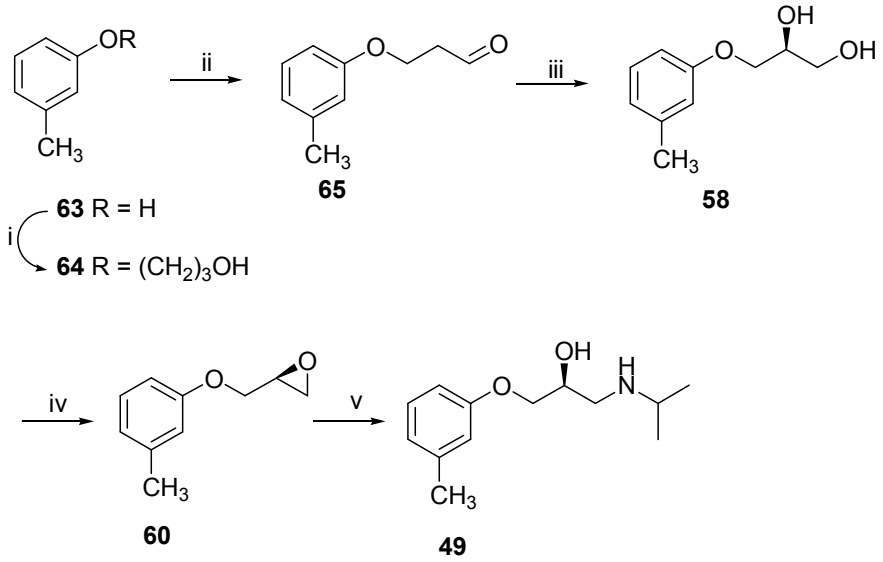
Reaction of 2.2 equiv of (±)-epoxide with phenol (ArOH) in the presence of (salen)Co(OAc) complex **62b** (0.044 equiv) in *tert*-butyl methyl ether (TBME) led to 61% conversion of phenol after 55 h at room temperature, with 1-aryloxy 2-alcohols (**27**) generated in 94% ee. Encouraged by the observation of high enantioselectivity in this reaction, a variety of reaction parameters with the goal of identifying a more reactive system has been evaluated. The identity of the counter ion for the (salen)cobalt complex proved to be important in this context, with the perfluoro *tert*-

butoxide complex displaying superior reactivity. Thus, the use of complex **62c** under conditions otherwise identical to those outlined above resulted in 80% conversion of phenol in 18 h and formation of 1-aryloxy 2-alcohols (**61**) as the major product in 96% ee. Small amounts of 1,2-diol were also generated, presumably as a result of epoxide hydrolysis with adventitious water,[29] but this pathway could be suppressed easily by the inclusion of 3 Å molecular sieves in the reaction mixture.

2.2.5 Results and Discussion

Route 1: α-Aminooxylation approach

A short and effective route for the synthesis of (*S*)-toliprolol (**49**) in high enantiomeric excess from readily available starting materials using D-proline-catalyzed α-aminooxylation of aldehyde **65** is shown in **Scheme 17**.



Scheme 17: (i) $Br(CH_2)_3OH$, K_2CO_3, acetone, 50 °C, 12 h, 92%; (ii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C, 0.5 h, 90%; (iii) (a) 20 mol% D-Proline, PhNO, CH_3CN, -20 °C, 24 h, then $NaBH_4$, EtOH, 0.5 h, (b) 10% Pd/C, H_2 (1 atm.), MeOH, 12 h 70% for 2 steps; (iv) (a) *p*-TsCl, pyridine, CH_2Cl_2, 0 °C, 1 h, (b) NaH, THF, 0 °C, 0.5 h, 84% for 2 steps; (v) *i*-$PrNH_2$, H_2O (cat.), reflux, 2 h, 99%.

Alcohol **64** was prepared in 92% yield from *m*-cresol **63** and 3-bromopropanol using K_2CO_3 as the base and acetone as the solvent. The ^1H NMR spectrum of the alcohol **64** showed signals at 3.48 (t) and 3.89 (t) corresponding to the methylene

protons (-O**CH$_2$**-). Its ^{13}C NMR spectrum displayed carbon signals at δ 31.74, 57.62 and 63.87 corresponding to the methylene carbons in the propyl chain.Oxidation of alcohol **64** to the corresponding aldehyde **65** was achieved using Swern oxidation in 90% yield. Diol **58** was prepared from the aldehyde **65** in two steps: (i) α-aminooxylation of the aldehyde **65** with nitrosobenzene as the oxygen source and D-proline (10 mol %) at -20 °C to furnish aminooxy aldehyde *in situ*, which on reduction with $NaBH_4$ afforded the corresponding α-aminooxy alcohol, (ii) reduction of the aminooxy bond (*i.e.* O-N) using 10% Pd/C and H_2 (1 atm.); $[\alpha]^{25}_D$: + 9.57 (*c* 1, EtOH); {lit.[26] + 9.5 (*c* 1, EtOH) 97% ee}. The optical purity (>99%) of the diol **58** was determined by its chiral HPLC analysis with CHIRACEL-ODH column using hexane and ethanol (95:5) as eluent. The chiral HPLC chromatogram of the diol **58** is given in **Fig. 16**.

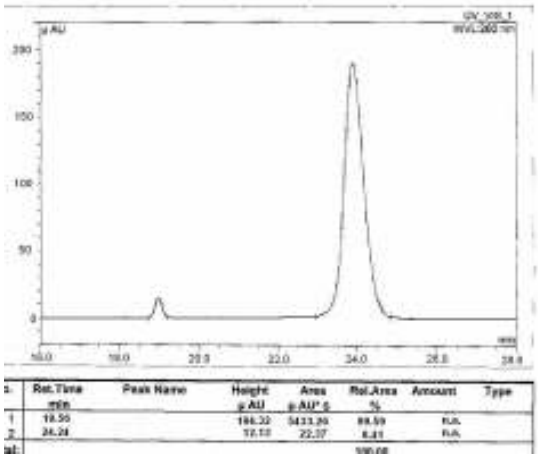


Fig. 16: Chiral HPLC chromatogram of diol 58

The ^{1}H NMR spectrum of the diol **58** showed signals at δ 2.24 (s), 3.65 (dd), 3.76 (dd) and 3.94-4.06 (m) corresponding to the aromatic methyl protons (Ar-CH_3), methylene (-CH(OH)**CH$_2$**OH) and the methine protons (-**CH**(OH)CH_2OH) in the diol moiety respectively. Its ^{13}C NMR spectrum showed peaks at δ 21.24, 63.42, 68.64 and 70.51

corresponding to the aromatic methyl, methylene and methine carbons in the diol moiety respectively (**Fig. 17**).

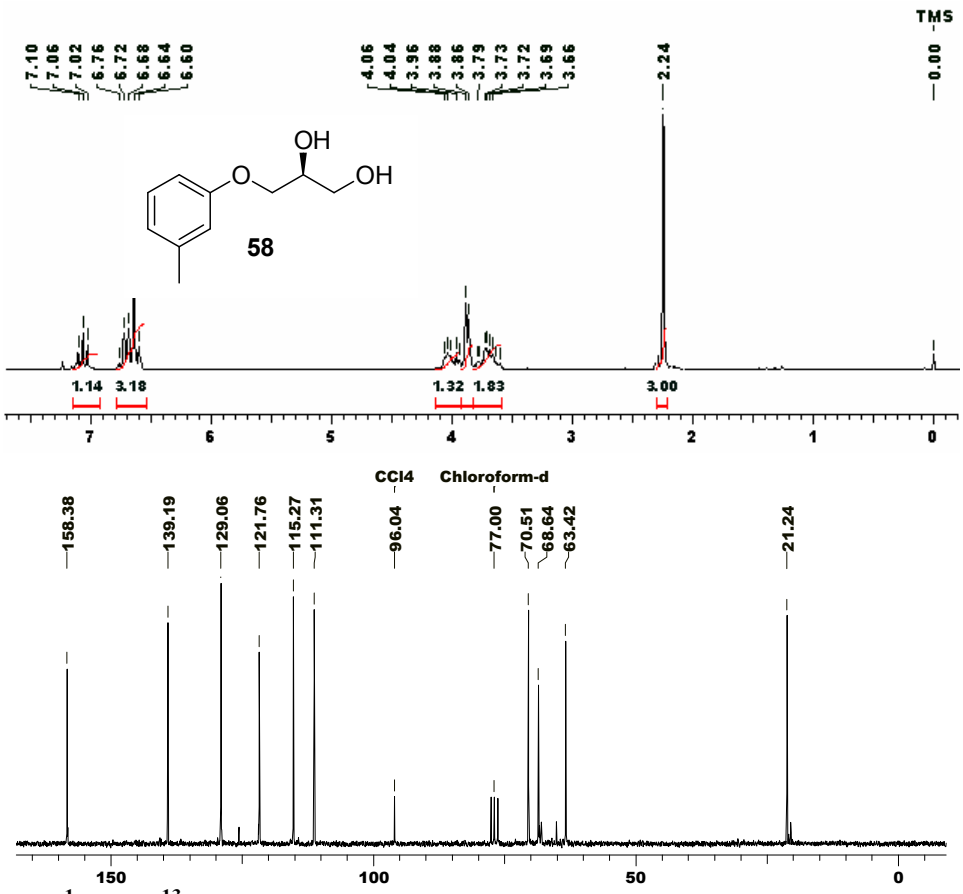


Fig. 17: ^{1}H and ^{13}C NMR spectra of diol 58

The diol **58** was then protected as its primary tosylate (*p*-TsCl, Et_3N, CH_2Cl_2, 0 °C, 1 h) which on treatment with sodium hydride gave the corresponding epoxide **60** in 85% yield; $[\alpha]^{25}_{D}$: + 16.6 (*c* 2.0, EtOH); {lit.[26] $[\alpha]^{25}_{D}$: + 13.43 (*c* 2.2, EtOH)}. The ^{1}H NMR spectrum of the epoxide **60** displayed upfield shift in the δ values for the methylene and methine protons (δ 2.70 (dd), 2.85 (dd) and 3.27-3.33 (m)) in the epoxide moiety in comparison to the diol **58**. The signals at δ 3.91 (dd) and 4.14 (dd) are due to the aryloxy methylene protons (ArO**C**$\mathbf{H_2}$-). Its ^{13}C NMR spectrum displayed carbon signals at δ 44.14 and 49.75 corresponding to the methylene and methine carbons in the epoxide moiety (**Fig. 18**).

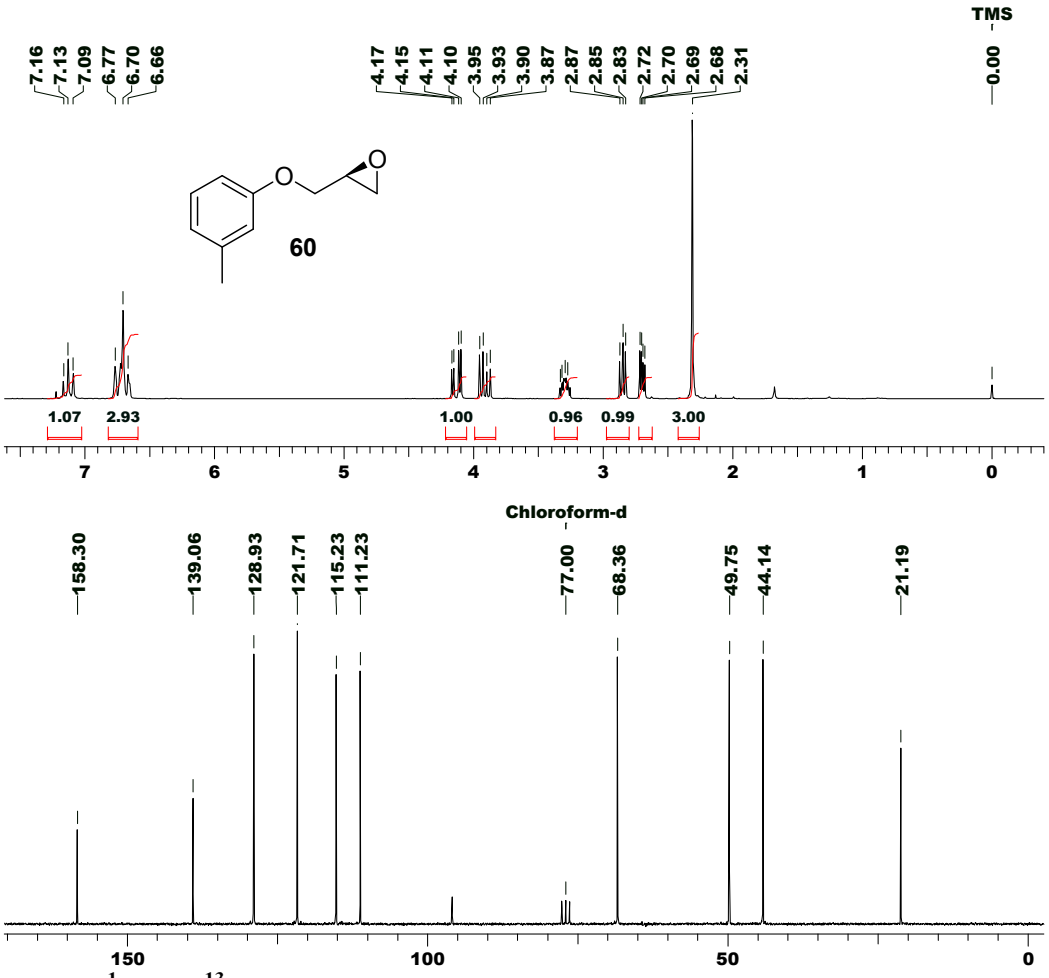


Fig. 18: ^{1}H and ^{13}C NMR spectra of epoxide 60

The final step involved the regiospecific ring opening of epoxide **60** with isopropylamine to furnish (*S*)-toliprolol (**49**) in excellent yield (99%); $[\alpha]^{25}_{D}$: -9.9 (*c* 1.0, EtOH); {lit.[25] $[\alpha]^{20}_{D}$: -9.9 (*c* 0.99, EtOH)}. The ^{1}H NMR spectrum of toliprolol (**49**) showed signals at δ 1.09 (d) and 2.32 (s) corresponding to the isopropyl and aromatic methyl protons respectively (**Fig. 19**). The methylene protons in the aminoalcohol moiety appeared as multiplets at δ 2.66-2.84. Also its ^{13}C NMR showed peaks at 21.65, 22.51 and 22.71 due to the isopropyl and aromatic methyl carbons respectively. The spectral data obtained for (*S*)-toliprolol (**49**) were in full agreement with the values reported in the literature.[25]

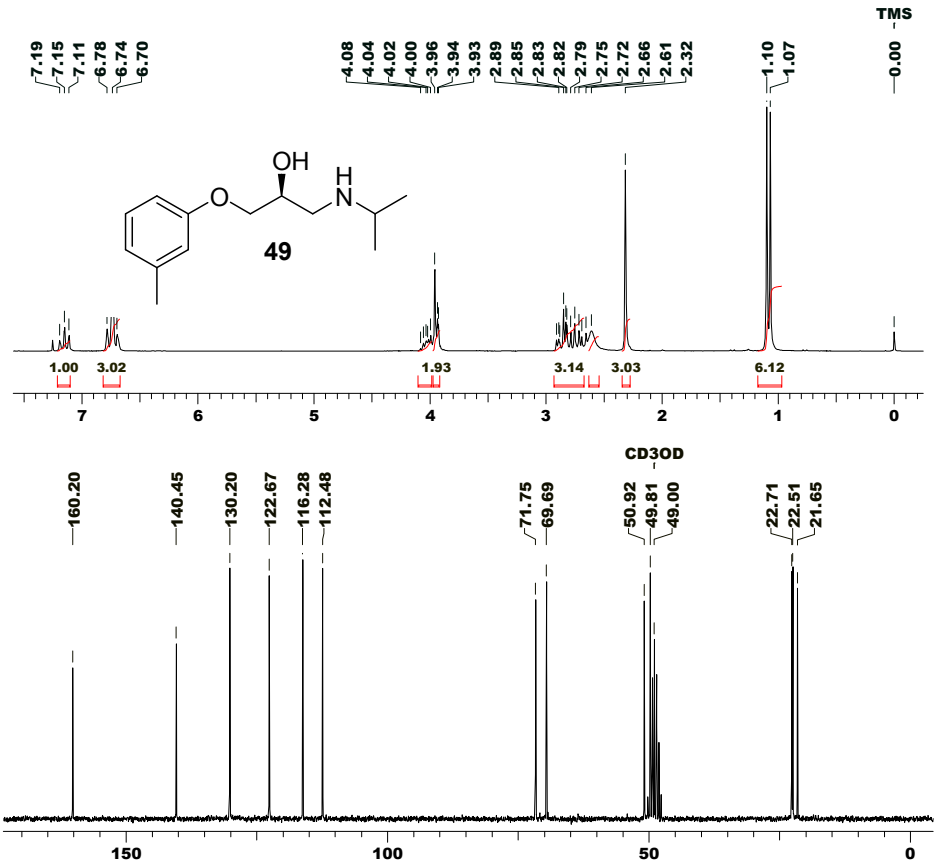
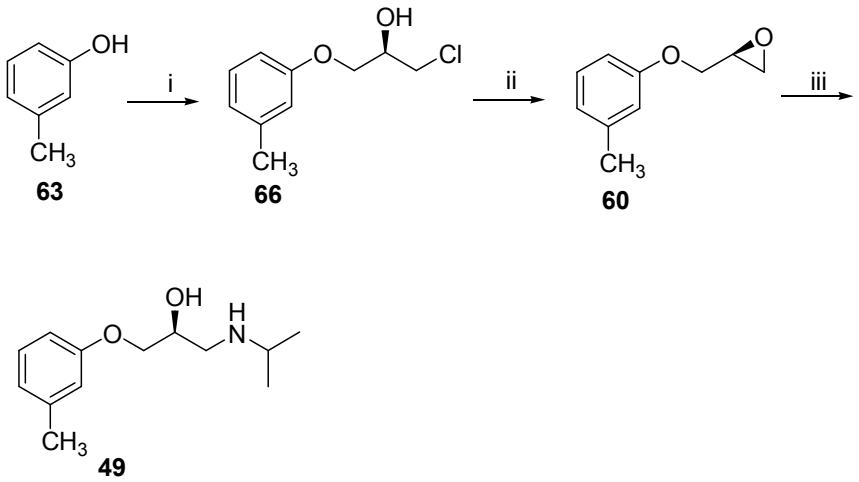


Fig. 19: ^{1}H and ^{13}C NMR spectra of (S)-toliprolol (49)

Route 2: Co-catalyzed asymmetric kinetic resolution approach

The synthesis of (*S*)-toliprolol (**49**) using Co-catalyzed asymmetric kinetic resolution of terminal epoxides is shown in **Scheme 18**.



Scheme 18: (i) (±)-Epichlorohydrin, (*R*,*R*)-Co-Salen, 12 h, 78%; (ii) KO*t*Bu, *t*-BuOH, 0 °C, 1 h, 91%; (iii) *i*-PrNH$_2$, H$_2$O (cat.), reflux, 2 h, 99%.

The cheaper and ready accessibility of (±)-epichlorohydrin renders kinetic resolution of its epoxide with phenolic substrates as a potentially attractive route for the preparation of chiral epoxide **60** using active Co(salen) complex as the chiral catalyst. Thus, the reaction of 2.5 equiv. of (±)-epichlorohydrin with *m*-cresol **63** in the presence of *(R,R)*-(salen)Co[$OC(CF_3)_3$] complex (0.044 equiv) in *tert*-butyl methyl ether at 25 °C led to isolation of chloro alcohol **66** in 86% yield based on *m*-cresol **63**; $[\alpha]^{25}_D$ = -1.3 (*c* 1, $CHCl_3$). The ^{1}H NMR spectrum of the chloroalcohol **66** showed signals at δ 2.80 (br s) (-O**H**), 3.67 (d) (-C**H**$_2$Cl) and 4.06 (d) (-C**H**$_2$O-Ar) corresponding to the hydroxyl and the methylene protons in the propyl moiety.

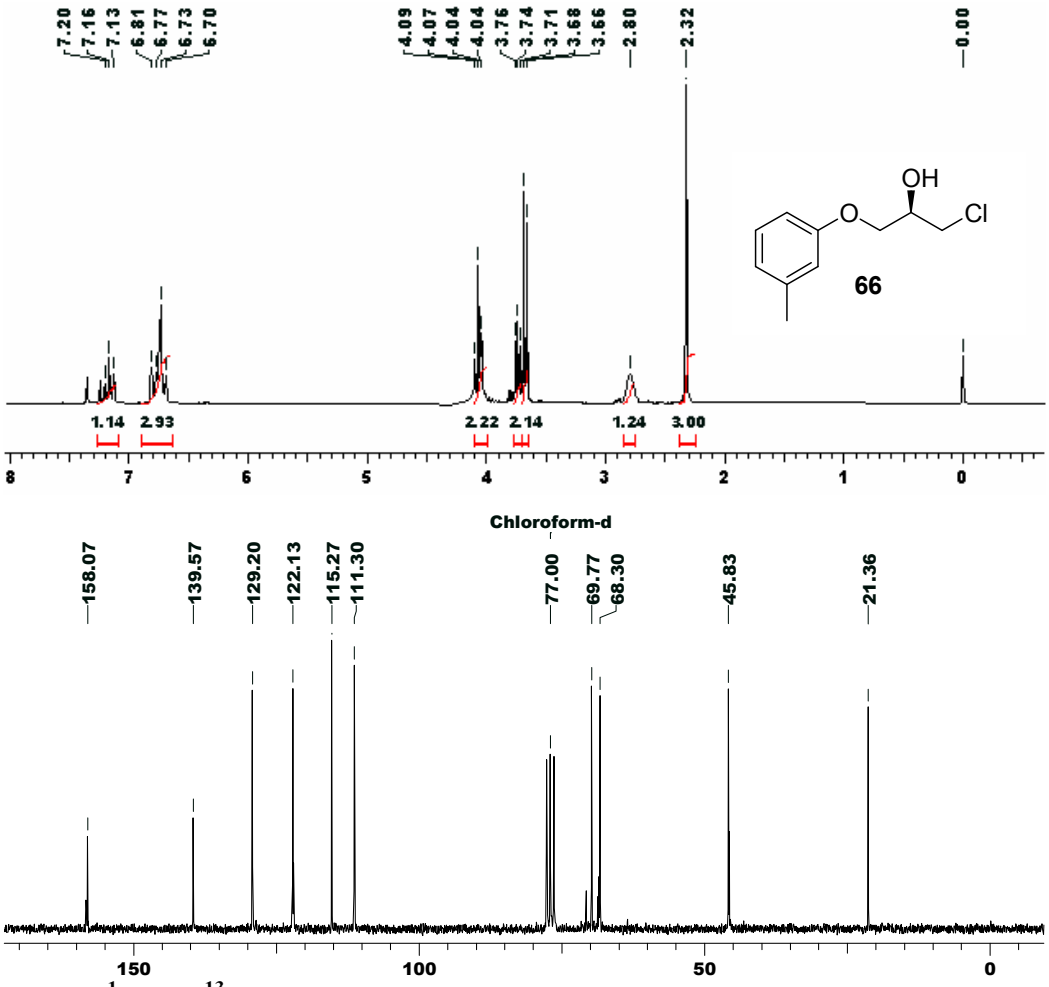


Fig. 20: ^{1}H and ^{13}C NMR spectra of chloro alcohol 66

Its ^{13}C NMR spectrum showed peaks at 45.83 (-C**H**$_2$Cl), 68.3 (-C**H**(OH)-) and 69.77 (-C**H**$_2$O-Ar) corresponding to the methylene and methine carbons in the propyl moiety. The chloroalcohol **66** was then converted to the corresponding epoxide **60** in 91% yield using KO^{t}Bu in *t*-BuOH at 0 °C; $[\alpha]^{25}_D$: + 16.4 (*c* 2.0, EtOH); {lit.[26] $[\alpha]^{25}_D$: + 13.43 (*c* 2.2, EtOH)}; (*vide infra* of the same section for spectral details). The regiospecific ring opening of epoxide **60** with isopropylamine furnished (*S*)-toliprolol (**49**) in excellent yield (99%); $[\alpha]^{25}_D$: -9.6 (*c* 1.0, EtOH); {lit.[25] $[\alpha]^{20}_D$: -9.9 (*c* 0.99, EtOH)} (*vide infra* of the same section for spectral details).

2.2.6 Conclusion

In conclusion, we have successfully applied proline-catalyzed α-aminooxylation and Co-catalyzed asymmetric kinetic resolution of terminal epoxides for the enantioselective synthesis of (*S*)-toliprolol (**49**). The reactions are rapid, and require a relatively low amount of an inexpensive and nontoxic proline catalyst and inexpensive Co-catalyst. The high yields and less number of steps render our approach a good alternative to the known methods.

2.2.7 Experimental Section

3-(3-Methylphenyl)propan-1-ol (64)

To a stirred solution of *m*-cresol **63** (1.08 g, 10 mmol) in acetone (50 mL) were added anhyd. K_2CO_3 (2.07 g, 15 mmol) and 1-bromopropanol (1.67 g, 12 mmol). After heating for 12 h at 50 °C, the reaction mixture was filtered through a sintered funnel and the solid residue was rinsed with acetone (3 x 20 mL). The combined organic layer was distilled off under reduced to give the crude alcohol which was purified by column chromatography over silica gel using EtOAc/Pet. ether (15:85) as eluent to give pure alcohol **64** in 92% yield.

Yield: 1.52 g (92%); gum; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.75-1.85 (m, 2H), 2.23 (s, 3H), 3.48 (t, *J*=7.1 Hz, 2H), 3.89 (t, *J*=7.4 Hz, 2H), 6.62-6.74 (m, 3H), 7.01-7.08 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 28.97, 31.74, 57.62, 63.87, 112.41, 13.21, 120.7, 128.54, 151.6; **Analysis**: **$C_{10}H_{14}O_2$** requires C, 72.26; H, 8.49%; found C, 72.39; H, 8.58%.

(*S*)-3-(3-Methylphenyl)propane-1,2-diol (58)

Swern oxidation: To a stirred solution of oxalyl chloride, $(COCl)_2$ (1.27 g, 10 mmol) in CH_2Cl_2 (30 mL) at -78 °C, was added a solution of DMSO (1.06 mL, 15 mmol). The reaction mixture was stirred for 20 min. followed by the addition of a solution of alcohol **64** (831 mg, 5 mmol) in CH_2Cl_2 (10 mL). After stirring for 0.5 h at -78 °C, the reaction was quenched by the addition of Et_3N (2.8 mL, 20 mmol) and water (40 mL). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were washed with water (3 x 30 mL), dried over anhyd. Na_2SO_4 and concentrated to give the corresponding aldehyde **65**.

α-Aminooxylation: Aldehyde **65** was dissolved in CH_3CN (40 mL) followed by the addition of nitrosobenzene (536 mg, 5 mmol) and L-proline (115 mg, 1 mmol, 20 mol %) at -20 °C. After 24 h, the reaction mixture was warmed to 0 °C, followed by dilution with anhydrous MeOH (20 mL) and careful addition of excess $NaBH_4$ (378 mg, 10 mmol). The reaction was quenched, after 10 min. by pouring into a vigorously stirred biphasic solution of Et_2O and aqueous HCl (1M). The organic layer was separated, and the aqueous phase was extracted with EtOAc (3 x 30 mL). The combined organic phase was dried over anhyd. Na_2SO_4 and concentrated to give the crude product, which was dissolved in MeOH (10 mL) followed by the addition of 10% Pd/C (10 mg). The reaction mixture was stirred in hydrogen atmosphere (1atm., balloon pressure) for 12 h. The reaction mixture was then filtered through celite pad,

the contents concentrated and the crude product purified by column chromatography over silica gel using EtOAc/Pet. ether (30:70) as eluent to give pure diol **58**.

Yield: 547 mg (60%); **mp**: 61-62 °C; **$[\alpha]^{25}_{D}$:** + 9.65 (*c* 1, EtOH); {lit.[26] + 9.5 (*c* 1, EtOH) 97% ee}; **HPLC**: >99% ee, Chiralcel OD-H, 5% EtOH/hexane, 1 mL/min. Retention time: (*R*): 19.56 min. (*S*): 24.24 min.; **IR** ($CHCl_3$, cm^{-1}): 690, 775, 933, 1055, 1159, 1259, 1290, 1453, 1490, 1585, 1602, 2877, 2927, 3390; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 2.24 (s, 3H), 3.65 (dd, *J*=11.6, 6.1 Hz, 1H), 3.76 (dd, *J*=11.5, 2.5 Hz, 1H), 3.87 (d, *J*=5.2 Hz, 2H), 3.94-4.06 (m, 1H), 6.60-6.76 (m, 3H), 7.06 (t, *J*=7.7 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 21.24, 63.42, 68.64, 70.51, 111.31, 115.27, 121.76, 129.06, 139.19, 158.38; **MS** m/z (% rel. intensity): 182 (M^+, 30), 133 (12), 121 (18), 109 (100), 92 (23), 77 (20); **Analysis: $C_{10}H_{14}O_3$** requires C, 65.91; H, 7.74%; found C, 65.91; H, 7.74%.

(*2S*)-3-(3-Methylphenyl)-1,2-epoxypropane (60)

To a stirred solution of diol **58** (547 mg, 3 mmol) and Et_3N (460 μL, 3.3 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added *p*-toluenesulfonyl chloride (572 mg, 3 mmol). After stirring at 0 °C for 1 h, the mixture was poured into ice water (30 mL), washed with aqueous H_2SO_4 (20 %), saturated aqueous $NaHCO_3$, and brine, dried over anhyd. Na_2SO_4 and the solvent was distilled off under reduced pressure to give the crude product, which was then dissolved in THF (10 mL) followed by the addition of sodium hydride (60% oil dispersion, 120 mg, 3 mmol) at 0 °C. After 0.5 h, the reaction mixture was quenched with addition of water and the aqueous layer was extracted with Et_2O (3 x 30 mL). The combined organic layers were dried over anhyd. Na_2SO_4, solvent concentrated *in vacuo* and the crude product purified by column chromatography over silica gel using EtOAc/Pet. ether (5:95) as eluent to give pure epoxide **60** in 84% yield.

Yield: 414 mg (84% for 2 steps); gum; **$[\alpha]^{25}_{D}$**: + 16.6 (*c* 2.0, EtOH); {lit.[26] $[\alpha]^{25}_{D}$: + 13.43 (*c* 2.2, EtOH)}; **IR** (Neat, cm^{-1}): 690, 775, 860, 900, 1041, 1053, 1161, 1261, 1290, 1454, 1488, 1585, 1602, 2871, 2923, 2999; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.33 (s, 3H), 2.73-2.76 (m, 1H), 2.87-2.92 (m, 1H), 3.32-3.36 (m, 1H), 3.91-3.99 (dd, *J*=12.10 Hz and 3.12 Hz, 1H), 4.15-4.23 (dd, *J*=12.10 Hz and 4.12 Hz, 1H), 6.71-6.80 (m, 3H), 7.13-7.25 (m, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 21.46, 44.69, 50.13, 68.66, 111.52, 115.56, 112.07, 129.23, 139.56, 158.53; **MS** m/z (% rel. intensity): 164 (M^+, 100), 134 (13), 119 (30), 108 (98), 91 (93), 77 (91), 65 (31), 57 (30); **Analysis**: **$C_{10}H_{12}O_2$** requires C, 73.15; H, 7.37%; found C, 73.21; H, 7.42%.

(*R*)-1-(3-Methylphenyl)-3-chloropropan-2-ol (66)

To a stirred mixture of *(R,R)*-(salen)Co[$OC(CF_3)_3$] complex (86 mg, 0.100 mmol), (±)-epichlorohydrin (0.462 g, 5.00 mmol), *tert*-butylmethylether (0.15 mL) and 3Å molecular sieves (100 mg) at 25 °C was added *m*-cresol (216 mg, 2.00 mmol). The reaction was stirred at 25 °C until GC analysis indicated complete conversion of *m*-cresol, at which time pyridinium *p*-toluenesulfonate (75 mg, 0.30 mmol) was added. The reaction mixture was filtered through a pad of silica and washed with 50% EtOAc/hexanes (15 mL). The filtrate was concentrated *in vacuo* to give the crude product, which was purified by chromatography using EtOAc/Pet. ether (20:80) as eluent to give chloroalcohol **66** in 78% yield.

Yield: 313 mg (78%); gum; **$[\alpha]^{25}_{D}$** : -1.3 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 690, 771, 1047, 1084, 1159, 1259, 1488, 1585, 1602, 2852, 2923, 2954, 3332; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.32 (s, 3H), 2.80 (br s, 1H), 3.67 (d, *J*=5.2 Hz, 2H), 3.74 (t, *J*=5.4 Hz, 1H), 4.04-4.09 (m, 2H), 6.70-6.81 (m, 3H), 7.13-7.24 (m, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): 21.36, 45.83, 68.30, 69.77, 111.30, 115.27, 122.13, 129.20, 139.57,

158.07; **Analysis**: $\mathbf{C_{10}H_{13}ClO_2}$ requires C, 59.86; H, 6.53; Cl, 17.67%; found C, 59.99; H, 6.47; Cl, 17.64%.

(*2S*)-3-(3-Methylphenyl)-1,2-epoxypropane (60)

To a stirred solution of chloroalcohol **66** (164 mg, 0.82 mmol) in dry THF (5 mL) at 0 °C was added potassium *t*-butoxide (184 mg, 1.64 mmol). The reaction mixture was stirred for 1 h, diluted with H_2O (10 mL) and extracted with Et_2O (3 × 10 mL). The collected organic layers were washed with brine and dried over anhyd. Na_2SO_4. The solvent was evaporated *in vacuo* to afford chiral epoxide **60** in 91% yield.

(*S*)-1-(3-Methylphenyl)-3-(isopropylamino)propan-2-ol: toliprolol (49)

Epoxide **60** (246 mg, 1.5 mmol) was dissolved in isopropylamine (10 mL) and the mixture was refluxed in presence of water (1 drop) for 1 h. Excess of isopropylamine was removed under reduced pressure and the resulting solid was recrystallized from *n*-hexane to afford pure (S)-toliprolol (**49**) in 99% yield.

Yield: 331 mg (99%); **mp**: 76-78 °C; {lit.[25] 76-77 °C}; $\mathbf{[\alpha]^{25}_D}$: -9.9 (*c* 1.0, EtOH); {lit.[25] $[\alpha]^{20}_D$: -9.9 (*c* 0.99, EtOH)}; **IR** ($CHCl_3$, cm^{-1}): 694, 775, 968, 1062, 1110, 1257, 1294, 1379, 1461, 1488, 1585, 1612, 2711, 2852, 2933, 3257, 3303; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.09 (d, *J*=6.3 Hz, 6H), 2.32 (s, 3H), 2.61 (br s, 1H), 2.66-2.83 (m, 2H), 2.85-2.91 (m, 1H), 3.93-3.96 (m, 2H), 4.0-4.08 (m, 1H), 6.74 (t, *J*=7.8 Hz, 3H), 7.11-7.19 (m, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 21.65, 22.51, 22.71, 49.81, 50.92, 69.69, 71.75, 112.48, 116.28, 122.67, 130.20, 140.45, 160.20; **Analysis**: $\mathbf{C_{13}H_{21}NO_2}$ requires C, 69.92; H, 9.48; N, 6.27%; found C, 69.81; H, 9.44; N, 6.36%.

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If a definitive history of twentieth century science is ever written, one of the highlights may well be a chapter on the chemical synthesis of complex molecules, especially total synthesis of naturally occurring substances

- Elias J. Corey

Chapter III

Asymmetric synthesis of Latifine and Cispentacin using Sharpless Asymmetric Dihydroxylation

Section I

Asymmetric Synthesis of (*S*)-Latifine

3.1.1 Introduction

Alkaloids are an important group of diversely distributed, chemically, biologically and commercially significant natural products. They are classified according to the amino acid, which provides both the nitrogen atom and the fundamental portion of the alkaloid skeleton. Anthranilic acid acts as a precursor to quinazoline, quinoline and acridine alkaloids, while histidine gives imidazole derivatives. However, many alkaloids are not derived from an amino acid core, but arise by amination of another type of substrate, which may a phenylalanine-derivative, a terpene or a steroid. Purine alkaloids are constructed by pathways that resemble those to purines in nucleic acids. Plants of the *Amaryllidaceae* family, a small group of monocotyledonous species, include about 860 to 1100 species in eighty five genera distributed largely over tropical and subtropical regions. The *Amaryllidaceae* family has produced a large number of structurally diverse alkaloids with a wide range of interesting physiological effects, including antitumor, antiviral, acetylcholinesterase inhibitory, immunostimulatory and antimalarial activities.

3.1.2 Pharmacology of C*rinum* species

The genus *Crinum latifolium* is the only pantropical genus of the *Amaryllidaceae*, with species occurring in Africa, America, Asia, and Australia. A comprehensive review focusing on ethnopharmacology, phytochemistry and biological activities of the genus *Crinum* has been published.[1] Four known alkaloids: crinine **1**, hamayne (bulbispermine) **2**, lycorine **3** and cherylline **4**, have been obtained from *Crinum lugardiae* and *Crinum macowanii*, respectively (**Fig. 1**).[2,3]

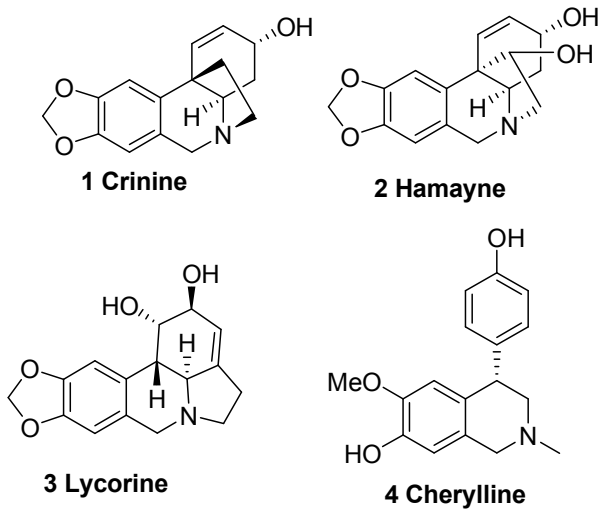


Fig. 1

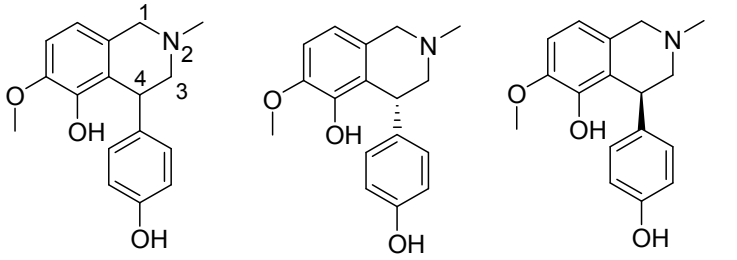
These isolated alkaloids were known to be produced exclusively by members of the *Amaryllidaceae* family and their presence in the *Crinum* species is in agreement with these findings. The medicinal uses of *Crinum* species both in traditional medical practices and as sources of pharmacologically active compounds have also been summarized.[4] In Vietnamese and Chinese traditional medicine, hot aqueous extract of *Crinum latifolium* (**Fig. 2**) is used because of its antitumor activity.

Fig. 2: *Crinum latifolium*

The genus *Crinum* is thought to possess antiviral and immunostimulative properties. A growing body of evidence suggests that moderate consumption of green and black tea derived from *Camellia sinensis* may protect, e.g., against several forms of cancer, cardiovascular diseases, and bacterial infections.

3.1.3 Tetrahydroisoquinolines and Latifine

Tetrahydroisoquinolines represent a class of biologically active phenyl ethylamines,[5] and these compounds are of great interest due to their biological and pharmacological properties.[6] They are also useful as key intermediates in the synthesis of isoquinoline alkaloids, such as cherylline **4** and latifine **5**.



5 (±)-Latifine **6 (*R*)-(+)-Latifine** **7 (*S*)-(-)-Latifine**

Fig. 3: Structures of latifine

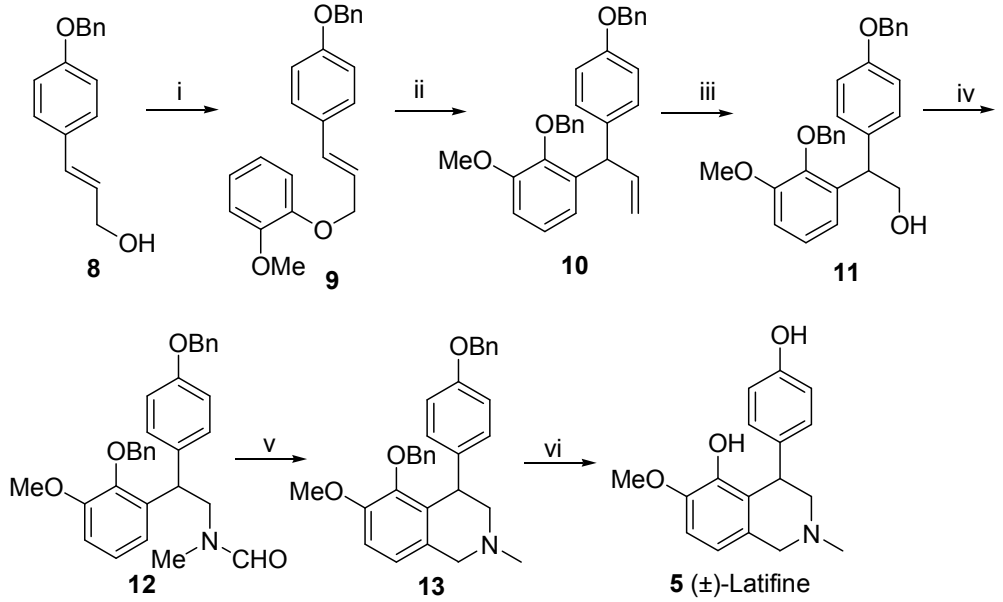
Isoquinoline fused-ring systems, such as pyrroloisoquinoline, show valuable pharmacological activity, *e.g.* antileukemic,[7] muscaricinic, agonostic[8] and antidepressant properties.[9] Their marked antidepressant, tranquilizing,[10] analgesic and sedative[11] activity renders 1(2*H*)-isoquinolinones an important class of compounds. These compounds have also been used as intermediates in the synthesis of a number of naturally occurring alkaloids.[12] Latifine **5** (**Fig. 3**),[13] an isoquinoline alkaloid, is a rare phenolic *Amaryllidaceae* alkaloid, which has been isolated from several *Crinum* species,[14,15] namely *Crinum latifolium*, a plant used as rubefaciant and tonic,[16] and *Crinum powelli*. Latifine has two novel features: (i) it has a 4-aryl group in an isoquinoline system and (ii) it is oxygenated at the less usual 5,6-positions.

3.1.4 Review of Literature

Literature study reveals that even though several reports are available for the synthesis of latifine in racemic from, asymmetric synthesis of latifine are rare generally involve resolution of racemic latifine (**5**) as described below.

Takano's approach (1985)[17]

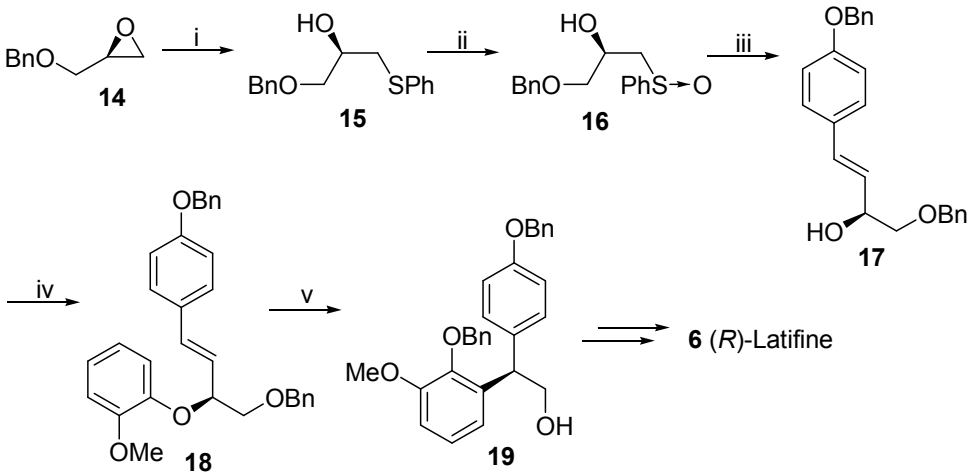
Racemic latifine (**5**) has been synthesized by employing the Claisen rearrangement of 4- benzyloxycinnamyl 2-methoxyphenyl ether (**9**) as a key step (**Scheme 1**). Claisen rearrangement of **9** gave the phenolic compound, which was alkylated with benzyl bromide to give the triether **10** in 83% yield. Ozonolysis of the double bond followed by reduction with $NaBH_4$ gave the primary alcohol **11**, which was converted to compound **12**. Compound **12** was then subjected to cyclization (Bischler-Napieralski conditions) and the subsequent removal of benzyl protection gave (±)-latifine **(5)**.



Scheme 1: (i) guaiacol, DEAD, PPh_3, THF, 34%; (ii) (a) *N,N*-diemthylaniline, reflux, 75%, (b) BnBr, K_2CO_3, DMF, 80 °C, 83%; (iii) O_3, -78 °C then $NaBH_4$, MeOH, 87%; (iv) (a) pthalimide, DEAD, PPh_3, THF, 83%, (b) H_2NNH_2, EtOH, reflux, 97%, (c) HCO_2COCH_3, pyirdine, CH_2Cl_2, 0 °C, 90%, (g) $LiAlH_4$, 89%, (e) HCO_2COCH_3, pyirdine, CH_2Cl_2, 0 °C, 85%; (v) $POCl_3$, C_6H_6, reflux, 45 min. then $NaBH_4$, MeOH, H_2O, 0 °C, 51%; (vi) H_2, 10% Pd/C, EtOH, 55 °C, 85%.

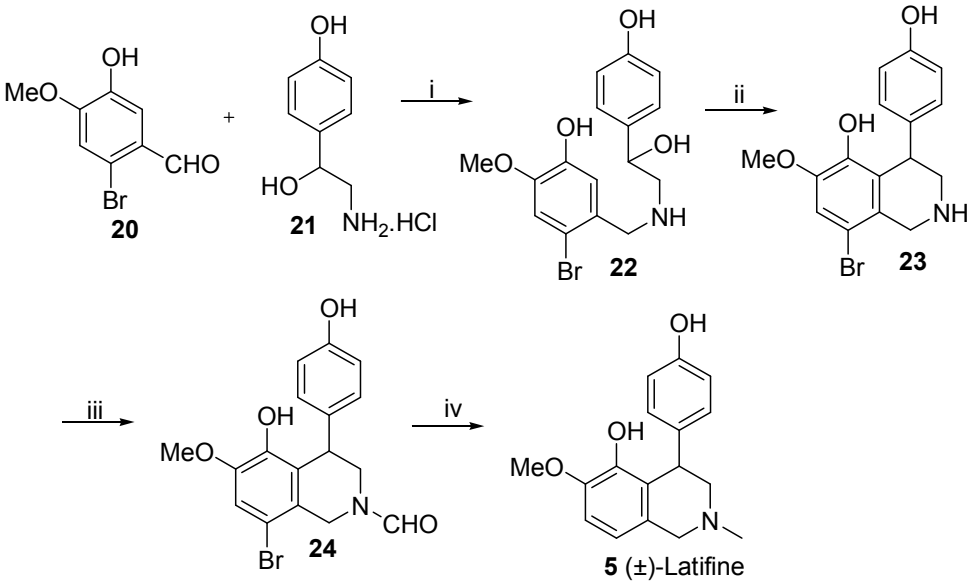
The same authors have also investigated the chiral synthesis of (*R*)-latifine (**6**) using the chiral allylalcohol **17**. Reaction of (*S*)-epoxide **14** with sodium benzenethiolate gave (*S*)-1-benzyloxy-3-phenylthiopropan-2-ol (**15**), which was converted into the corresponding sulfoxide **20**. Allylalcohol **17**, obtained from sulphoxide **16**, was subjected to Mitsunobu reaction with guaiacol and the subsequent Claisen

rearrangement afforded the phenol, which was then protected as its benzyl ether. Ozonolysis of the double bond followed by reduction with $NaBH_4$ gave the primary alcohol **19**. The rest of the synthetic sequences are similar to that of the racemic route to give (*R*)-Latifine (**6**) (**Scheme 2**).



Scheme 2: (i) PhSNa, THF, 0 °C, 89%; (ii) H_2O_2, aq. MeOH, 25 °C, 100%; (iii) $CaCO_3$, 4-benzyloxybenzyl chloride, toluene, reflux, 87%; (iv) guaiacol, DEAD, PPh_3, THF, 48%; (v) *N,N*-diemthylaniline, reflux, 76%; (vi) BnBr, K_2CO_3, DMF, 80 °C, 89%; (vii) O_3, -78 °C then $NaBH_4$, MeOH, 64%.

Kobayashi's approach (1986)[18]

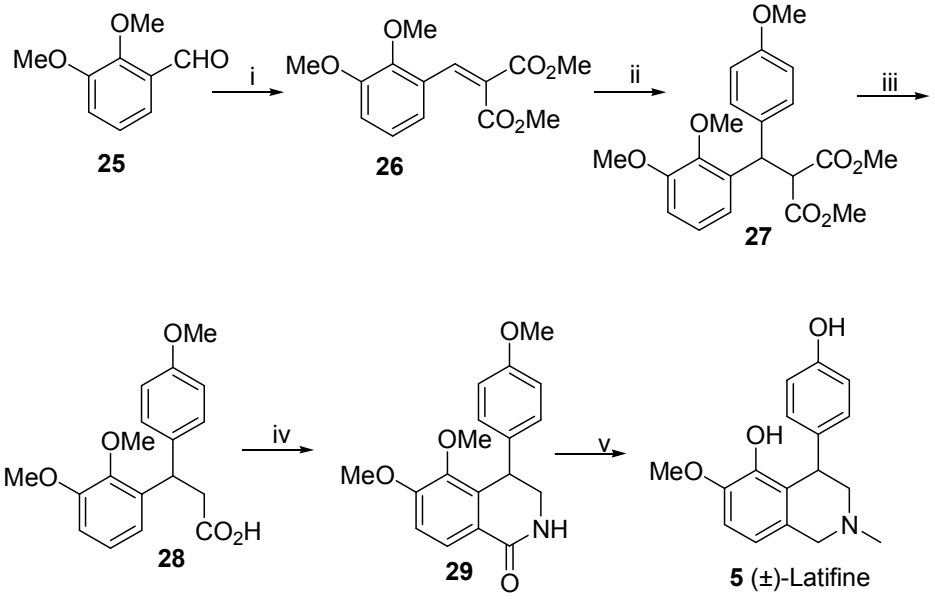


Scheme 3: (i) (a) $NaHCO_3$, MeOH, 50 °C, (b) $NaBH_4$, 25 °C, 41.7%; (ii) conc. HCl, EtOH, reflux, 63.8%; (iii) HCO_2Et-EtOH, K_2CO_3, 3 Å mol. Sieves, reflux; (iv) $LiAlH_4$, DME, reflux, 35.4%.

In this approach, cyclization of the bromo compound **22** (prepared from 6-bromoisovanillin (**20**) and (±)-octopamine hydrochloride (**21**)) under acidic conditions gave the isoquinoline **23**. *N*-Formylation of isoquinoline **23** with ethyl formate gave the amide **24**. Debromination of amide **24** with $LiAlH_4$, accompanied by reduction of the *N*-formyl group in **24** to methyl group gave (±)-latifine (**5**) (**Scheme 3**).

Irie's approach (1988)[19]

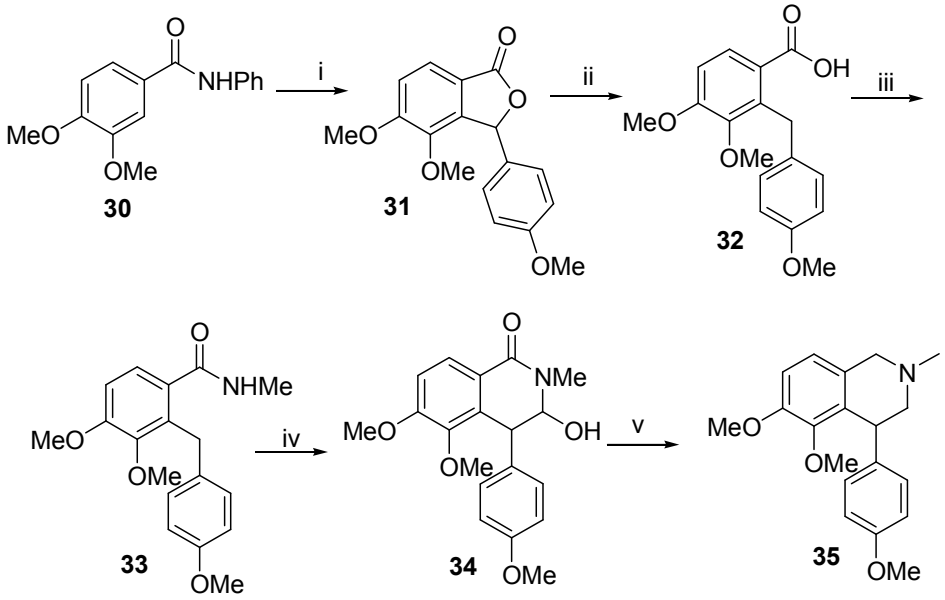
In this approach, 2,3-dimethoxybenzaldehyde (**25**) was treated with dimethylmalonate to give benzylidinemalonate (**26**) which underwent 1,4-additon with *p*-methoxyphenylmagnesium bromide in the presence of copper iodide to give diester **27**. Alkaline hydrolysis of **27** followed by decarboxylation gave the acid **28**. Acid **28** was converted to isoquinoline **29** using simple transformations. Methylation of isoquinoline **29** gave *N*-methyl lactam, which was subjected to selective demethylation followed by $LiAlH_4$ reduction to give (±)-latifine (**5**) (**Scheme 4**).



Scheme 4: (i) $CH_2(CO_2Me)_2$, $PhCO_2H$, piperidine, Dean-Stark, 85%; (ii) 4-OMePhMgBr, CuI, THF; (iii) (a) K_2CO_3, MeOH, H_2O, (b) 160-200 °C; (iv) (a) $(COCl)_2$, benzene, (b) NaN_3, H_2O, acetone, (c) $POCl_3$, benzene, 90 °C, (d) $BF_3.OEt_2$, CH_2Cl_2; (v) (a) NaH, MeI, (b) Me_2S, CH_3SO_3H, 65 °C, (c) $LiAlH_4$.

Narasimhan's approach (1988)[20]

In this approach, *N*-phenyl-3,4-dimethoxybenzamide (**30**) was lithiated with n-BuLi, specifically at the 2-position followed by the addition of 4-methoxybenzaldehyde to give 3-arylphthalide **31** in 70% yield. Phthalide **31** on treatment with Et_3SiH-CF_3CO_2H gave 3,4-dimethoxy-2-(4'-methoxybenzyl)-benzoic acid (**32**) which was converted into the *N*-methylamide **33** and lithiated with n-BuLi. Further, treatment of lithiated salt of amide **33** with dimethylformamide gave lactam **34**, which was reduced with $LiAlH_4$ in THF to give (±)-latifine dimethyl ether **35** (**Scheme 5**).

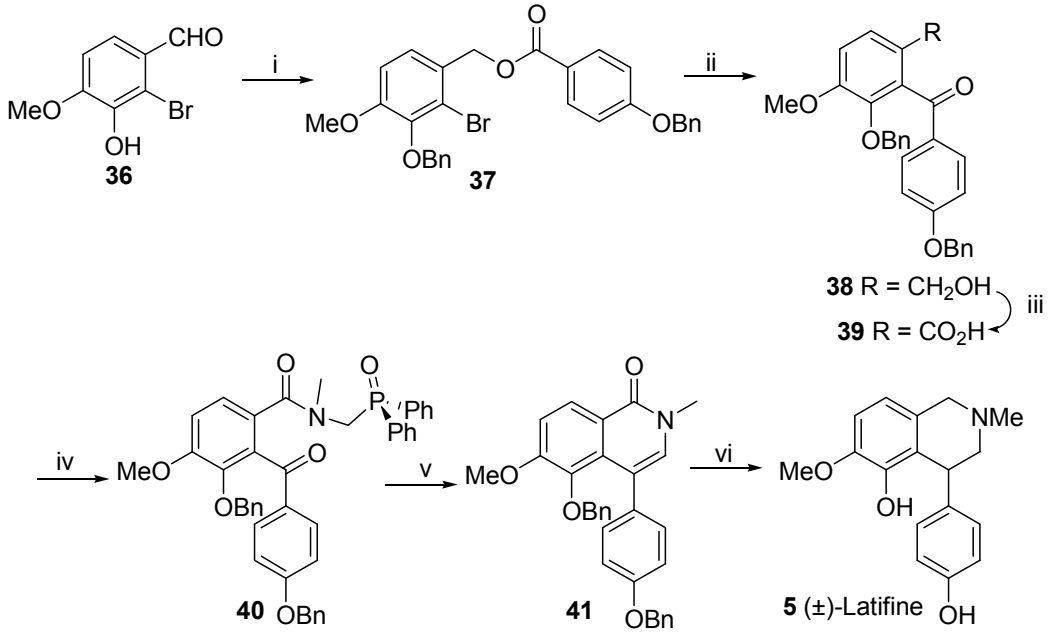


Scheme 5: (i) n-BuLi, TMEDA, 4-$MeOC_6H_4CHO$, THF, 70%; (ii) Et_3SiH, CF_3CO_3H, 88%; (iii) $SOCl_2$, then $MeNH_2$, 76%; iv, BuLi, DMF, 72%; (v) $LiAlH_4$, 66%.

Couture's approach (1999)[21]

In this approach, phenol **36** was converted to ester **37** in 3 steps: (i) benzyl protection, (ii) reduction of the aldehyde and (iii) Mitsonobu reaction with 4-benzyloxybenzoic acid. Ester **37** was lithiated with *n*-BuLi at -90 °C followed by warming the reaction mixture to -50 °C and protic work up gave alcohol **38**, which was oxidized to the corresponding carboxylic acid **39**. Reaction of acid **39** with *N*-

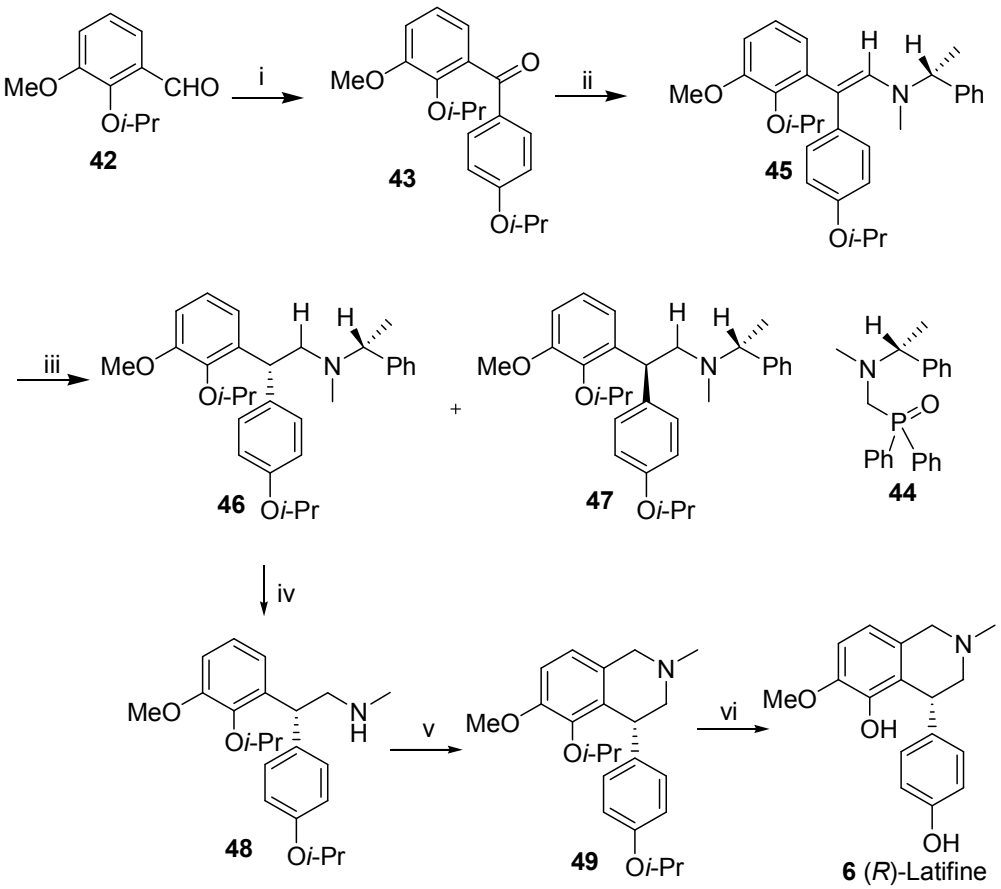
diphenylphosphinoylmethyl-*N*-methylamine gave amide **40**, which on treatment with KHMDS gave the cyclized product **41**. Reduction of lactam **41** with $LiAlH_4$ and HCO_2NH_4 gave (±)-latifine (**5**) (**Scheme 6**).



Scheme 6: (i) (a) BnBr, K_2CO_3, DMF, reflux, (b) $NaBH_4$, EtOH, 25 °C, (c) 4-$BnOC_6H_4CO_2H$, DEAD, Ph_3P, THF, 0 °C to 25 °C, 80%; (ii) (a) n-BuLi, THF, -90 °C to -50 °C, (b) $NaHCO_3$, H_2O, (c) NMO, tetrapropylammonium perruthenate, CH_3CN, 25 °C, 86%; (iii) $NaClO_2$, $NaHPO_4$, 2-methylbut-2-ene, THF, *t*-BuOH, H_2O, 25 °C, 89%; (iv) DCC, DMAP, $CH_3NHCH_2P(O)Ph_2$, CH_2Cl_2, 25 °C, 82%; (v) KHMDS, THF, -78 °C to 25 °C, 82%; (vi) (a) $LiAlH_4$, THF, reflux; (b) HCO_2NH_4, Pd/C, MeOH, reflux, 65%.

Couture *et al*.[22] have also carried out the asymmetric synthesis of (*R*)-latifine **6**. Reaction of protected isovanillin **42** with the aryllithium species obtainable from the corresponding (4-isopropyloxyl)bromobenzene and the subsequent oxidation with pyridinium dichromate (PDC) generated benzophenone **43**. Deprotonation of phosphonate **44** using *n*-BuLi in THF followed by its reaction with the benzophenone **43** resulted in the formation of prochiral enamine **45**, which on reduction with $NaBH(OAc)_3$ in MeOH/HCl gave amine **46** as the major diastereomer (85% de). Amine **46** was subjected to hydrogenolysis and the cyclomethylenation by the Pictet–

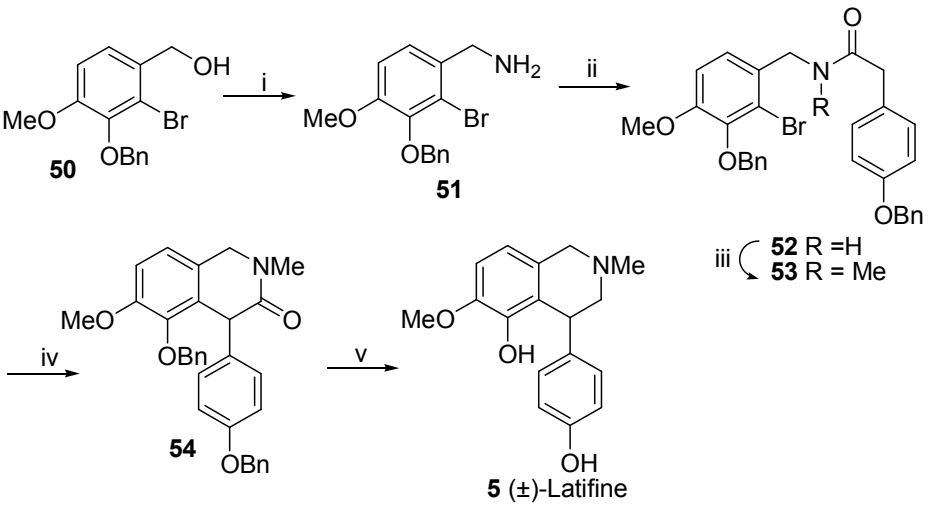
Spengler heterocyclization gave isoquinoline **49**, which on treatment with BCl_3 gave (*R*)-Latifine **6** in 90% yield (**Scheme 7**).



Scheme 7: (i) (a) 4-[$(CH_3)_2CHO$]-C_6H_4Li, THF, -100 °C, 85%, (b) PDC, CH_2Cl_2, 90%; (ii) 44, n-BuLi, THF, -15 °C, 95%; (iii) $NaBH(OAC)_3$, MeOH/HCl, -78 °C, 60%; (iv) H_2, $Pd(OH)_2$, MeOH, 97%; (v) $(CH_2O)_n$, aq. HCl, EtOH, reflux, 80%; (vi) BCl_3, CH_2Cl_2, -10 to 0 °C, 90%.

Honda's approach (2001)[23]

In this approach, alcohol **50** was converted into amine **51** in four steps, by adopting Cossy's procedure with slight modifications.[24] Reaction of amine **51** with *p*-benzyloxyphenylacetyl chloride gave amide **52**, which was further alkylated with methyl iodide to provide the desired amide **53**. The Pd-catalyzed intramolecular coupling reaction of **53** in the presence of $Pd(dba)_2$ proceeded smoothly to give six-membered lactam **54** in 81% yield. Reduction of amide to amine and deprotection of benzyl groups afforded (±)-latifine (**5**) (**Scheme 8**).



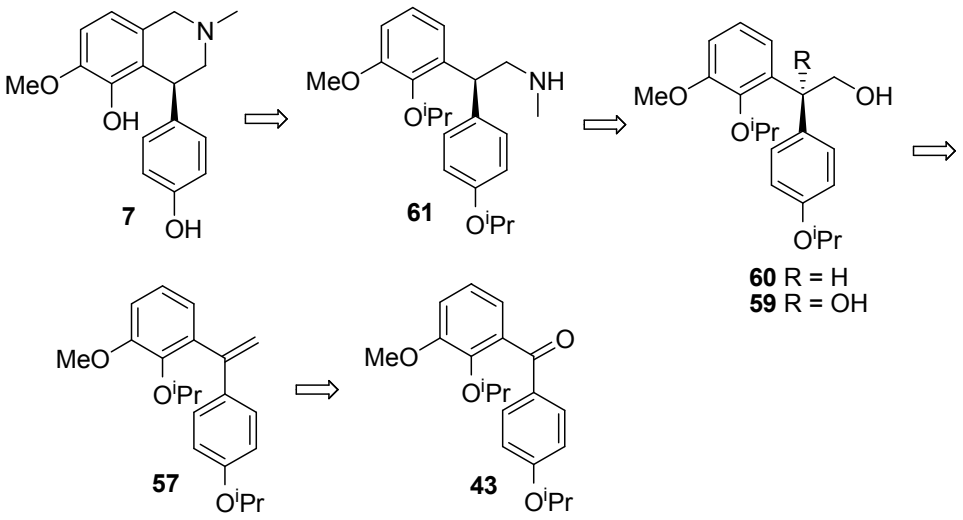
Scheme 8: (i) (a) $SOCl_2$, C_6H_6, reflux, 100%, (b) NaN_3, DMF; (c) Ph_3P, THF; (d) H_2O, reflux, 90%; (ii) *p*-benzyloxyphenylacetyl chloride, $NaHCO_3$, Et_2O, 87%; (iii) NaH, DMF, MeI, 77%; (iv) *t*-BuOK, $Pd(dba)_2$, dppe, dioxane, 100 °C, 54%; (v) (a) BMS, THF, 65 °C, 61%, (b) H_2, Pd/C, EtOH, 65 °C, 85%.

3.1.5 Present work

3.1.5.1 Objective

Despite the fact that synthetic studies on aryl 1,2,3,4-tetrahydroisoquinolines such as latifine (**5**) have attracted much attention, methods for the elaboration of this structurally challenging alkaloid genuinely lack flexibility and universality. So the objective of the current investigation is to synthesize (*S*)-latifne (**7**) using Sharpless asymmetric dihydroxylation as the key step.

The retrosynthetic analysis of (*S*)-latifine (**7**) is given in **Scheme 9**. The isoquinoline ring can be constructed from the corresponding *N*-methylamine **61**, which can be manipulated from the corresponding key intermediate alcohol **60**. Alcohol **60** can be obtained either by asymmetric hydroboration[25] of olefin **57** or from diol **59**, which in turn can be obtained by Sharpless asymmetric dihydroxylation of olefin **57**. Olefin **57** can be prepared from one carbon Wittig olefination of the corresponding aromatic ketone **43**.

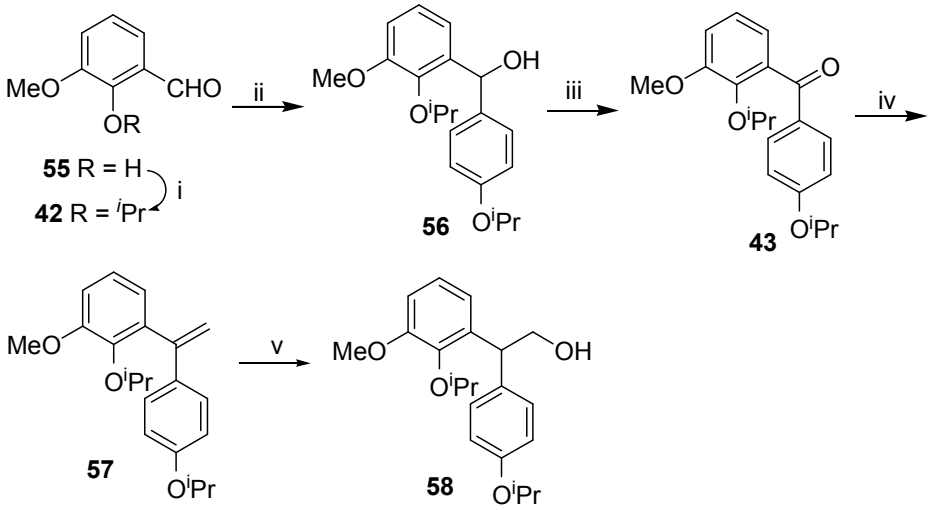


Scheme 9: Retrosynthesis of (S)-latifine (7)

3.1.6 Results and Discussion

Route 1: Asymmetric hydroboration approach

The synthesis of (*S*)-latifine (**7**) using asymmetric hydroboration of the olefin **57** is depicted in **Scheme 10**.



Scheme 10: (i) $(CH_3)_2CHBr$, K_2CO_3, DMF, 140 °C, 10 h, 68%; (ii) 4-[$(CH_3)_2CHO$]-C_6H_4MgBr, THF, -78 °C, 1 h, 86%; (iii) PDC, CH_2Cl_2, 10 h, 90%; (iv) CH_3PPh_3I, n-BuLi, THF, -40 °C, 1 h, 78%; (v) $BH_3.Me_2S$, THF, -20 °C, 12 h, 89%; (vi) (-)-Ipc_2BH, THF, -20 °C. 72 h.

Reaction of 4-isoproyloxyphenylmagnesium bromide with 2-isopropoxy-3-methoxybenzaldehyde (**42**), readily prepared from *o*-vanillin **55**, gave the

corresponding alcohol **56** in high yield. The ^{1}H NMR spectrum of the alcohol **56** showed typical signals at δ 1.17 (d), 1.21(d) and 1.30 (d) corresponding to the methyl groups present in the isopropyl moieties. The other signals at 3.80 (s) and 6.05 (s) correspond to the methoxy and the benzylic protons respectively. Its ^{13}C NMR spectrum showed peaks at δ 21.79, 22.06 and 22.35 corresponding to the methyl groups present in the isopropyl moieties; other peaks at δ 55.25 and 70.50 are due to the methoxy and the benzylic carbons respectively (**Fig. 4**).

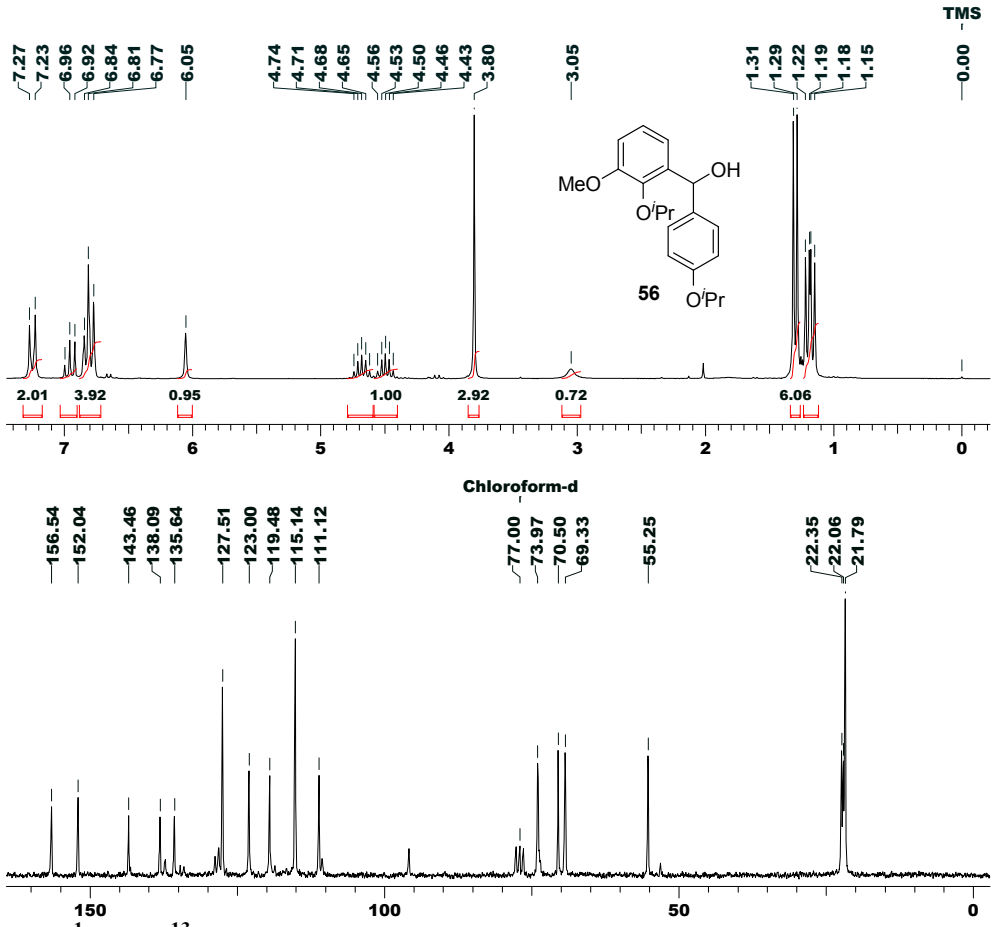


Fig. 4: ^{1}H and ^{13}C NMR spectra of biarylmethanol 56

The secondary alcohol **56** was then oxidized to the corresponding benzophenone **43** using standard oxidation conditions (PDC, CH_2Cl_2, 25 °C). The disappearance of the signal for the benzylic proton in ^{1}H NMR spectrum confirms the

formation of benzophenone **43**. The appearance of carbon signal at δ 194.56 (C=O) in the ^{13}C NMR spectrum of benzophenone **43** also confirmed the oxidation at benzylic position. Also its IR spectrum showed a strong band at 1750 cm^{-1} confirming the presence of the carbonyl moiety (**Fig. 5**).

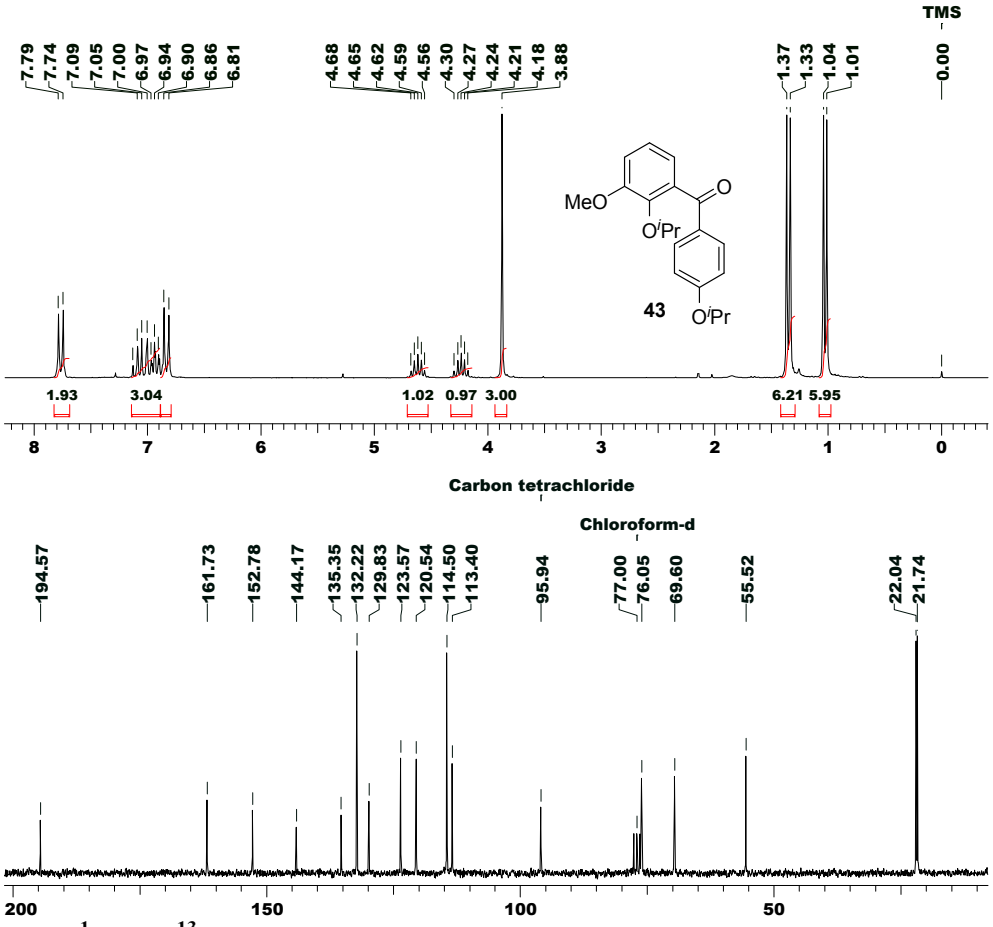


Fig. 5: ^{1}H and ^{13}C NMR spectra of benzophenone 43

The benzophenone **43** was then subjected to one-carbon Wittig olefination reaction (n-BuLi, $Ph_3P^+CH_3I^-$, THF, -40 °C) to obtain olefin **57** in 78% yield. The ^{1}H NMR spectrum of the olefin **57** showed characteristic signals at δ 5.25 (d) and 5.58 (d) corresponding to olefinic protons. The disappearance of the peak at δ 194.56 and the appearance of peak at δ 113.87 in its ^{13}C NMR spectrum confirmed the presence of olefin moiety (**Fig. 6**).

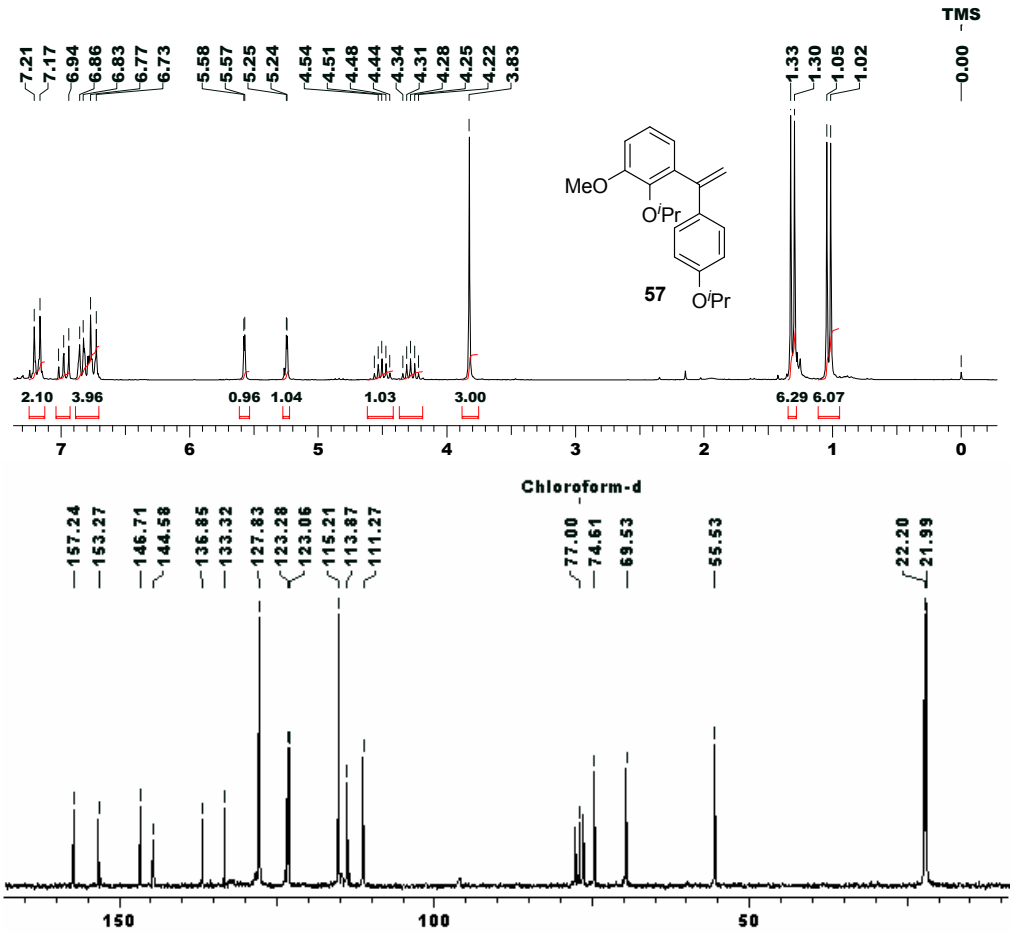


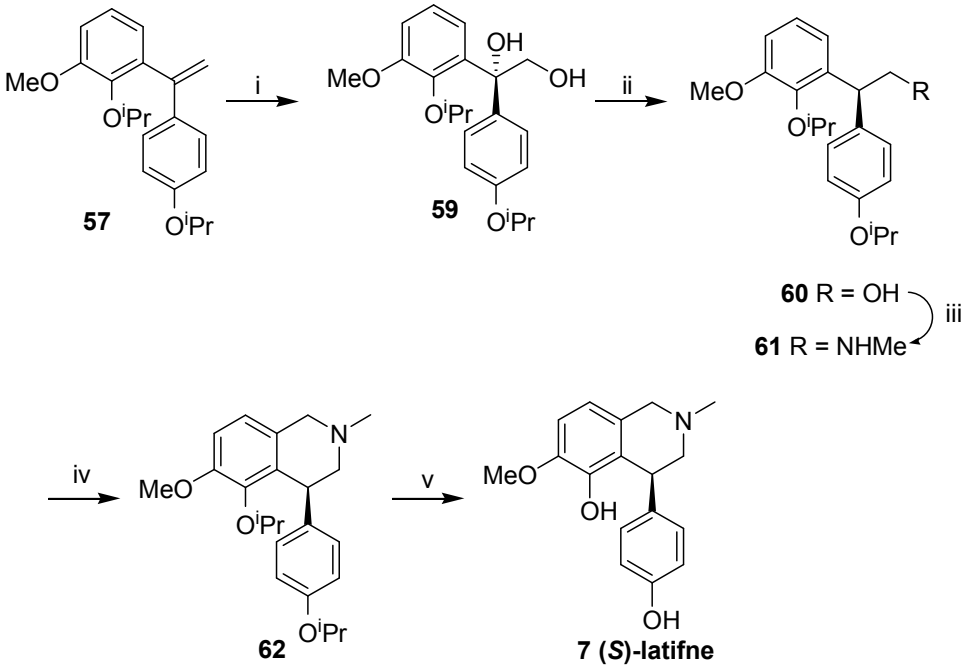
Fig. 6: ^{1}H and ^{13}C NMR spectra of olefin 57

When olefin **57** was subjected to asymmetric hydroboration[25] using (-)-diisopinocamphenylborane (Ipc_2BH) no product was isolated after 72 h. We may attribute this behavior to the fact that both the olefin **57** and the borane complex are hindered systems. However, it may be noted that, when the olefin **57** was subjected to hydroboration using borane-methylslufide complex under racemic conditions (in the absence of chiral auxiliary), the reaction proceeded smoothly to give the corresponding racemic alcohol **58** in 89% yield.

Route 2: Asymmetric dihydroxylation approach

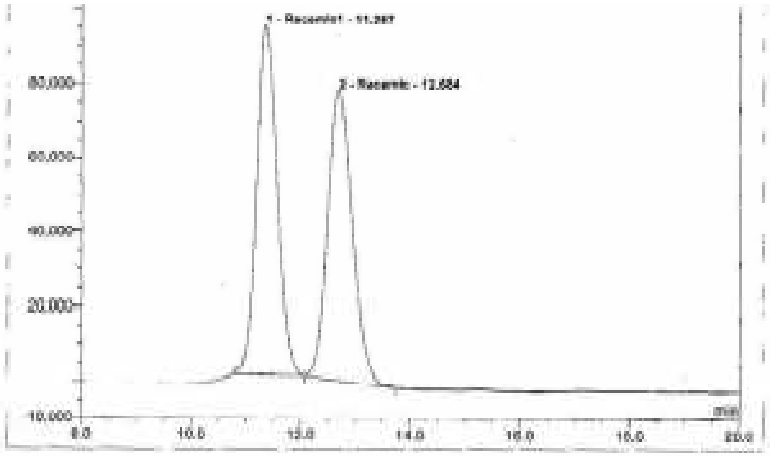
Since attempts to make the chiral alcohol **60** *via* asymmetric hydroboration failed, we turned our attention towards Sharpless asymmetric dihydroxylation[26] of the

olefin **57** as the key reaction for the synthesis of (*S*)-latifine (**7**) (**Scheme 11**). Literature study[27] revealed that for SAD of 1,1'-diaryl alkenes, anthraquinone (AQN)- and diphenylpyrimidine (PRY)-based ligands gave better enantioselectivity compared to phthalazine (PHAL) ligands. Thus, olefin **57** was subjected to the Sharpless asymmetric dihydroxylation (SAD) using potassium osmate [$K_2OsO_2(OH)_4$] as the catalyst and $(DHQD)_2$-AQN as the chiral ligand to give the corresponding diol **59** in 88% yield; $[\alpha]^{25}_D$: -77.09 (c 0.6, $CHCl_3$).



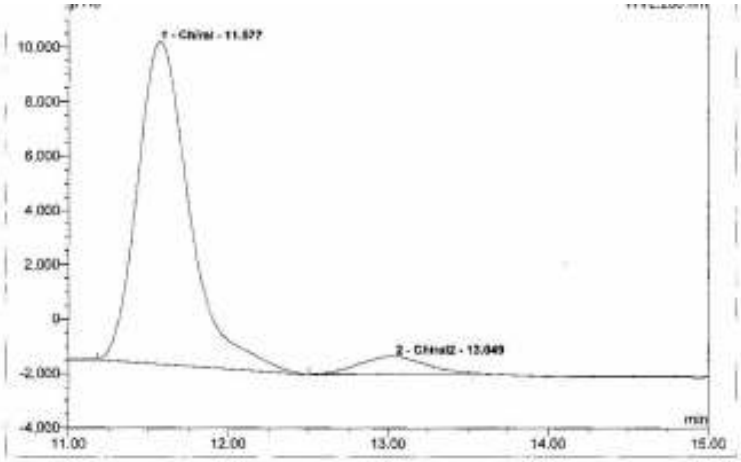
Scheme 11: (i) $(DHQD)_2$-AQN, $K_2OsO_2(OH)_4$, $K_3Fe(CN)_6$, $MeSO_2NH_2$, K_2CO_3, *t*-BuOH:H_2O (1:1), 72 h, 22 °C, 88%; (ii) Raney-Ni, EtOH, reflux, 1 h, 80%; (iii) (a) MsCl, Et_3N, cat. DMAP, CH_2Cl_2, 0 °C, 1 h; (b) $MeNH_2$ in MeOH, 70 °C, 4 h, 70% for 2 steps; (iv) (a) acetic formic anhydride, pyridine, 0 °C, 45 min., (b) $POCl_3$, C_6H_6, reflux, 45 min. then $NaBH_4$, MeOH, H_2O, 0 °C, 0.5 h, 46% for 2 steps; (v) BCl_3, CH_2Cl_2, -10-0 °C, 2 h, 90%, 89.2% ee.

The enantioselectivity of diol **59** (91.08% ee) was determined by chiral HPLC analysis using CHIRACEL-ODH column using hexane and isopropanol (95:5) as eluent. The chiral HPLC chromatogram of the diol **59** is given in **Fig. 7**.



No.	Ret.Time min	Peak Name	Height µ AU	Area µ AU*min	Rel.Area %	Amount	Type
1	11.38	Racemic	93480.072	##########	50.05	n.a.	BMB
2	12.05	Racemic	77704.792	##########	49.95	n.a.	BMB
Total:			##########	##########	100.00	0.000	

Racemic



No.	Ret.Time min	Peak Name	Height µ AU	Area µ AU*min	Rel.Area %	Amount	Type
1	11.58	Chiral	11852.384	4451.683	95.54	n.a.	BMB
2	13.05	Chiral	640.631	293.876	4.46	n.a.	BMB
Total:			12493.015	4745.559	100.00	0.000	

Chiral

Fig. 7: HPLC analysis of diol 59

The ^{1}H NMR spectrum of diol **59** showed typical signals at δ 1.96 (s), 2.08 (s) and 3.72 (s) corresponding to the hydroxyl and the methoxyl protons. The diastereotopic homobenzylic protons showed signals at δ 3.65 (d) and 3.95-4.05 (m) respectively. Its ^{13}C NMR spectrum showed peaks at δ 79.39 and 69.71 corresponding to the benzylic and homobenzylic carbons (**Fig. 8**).

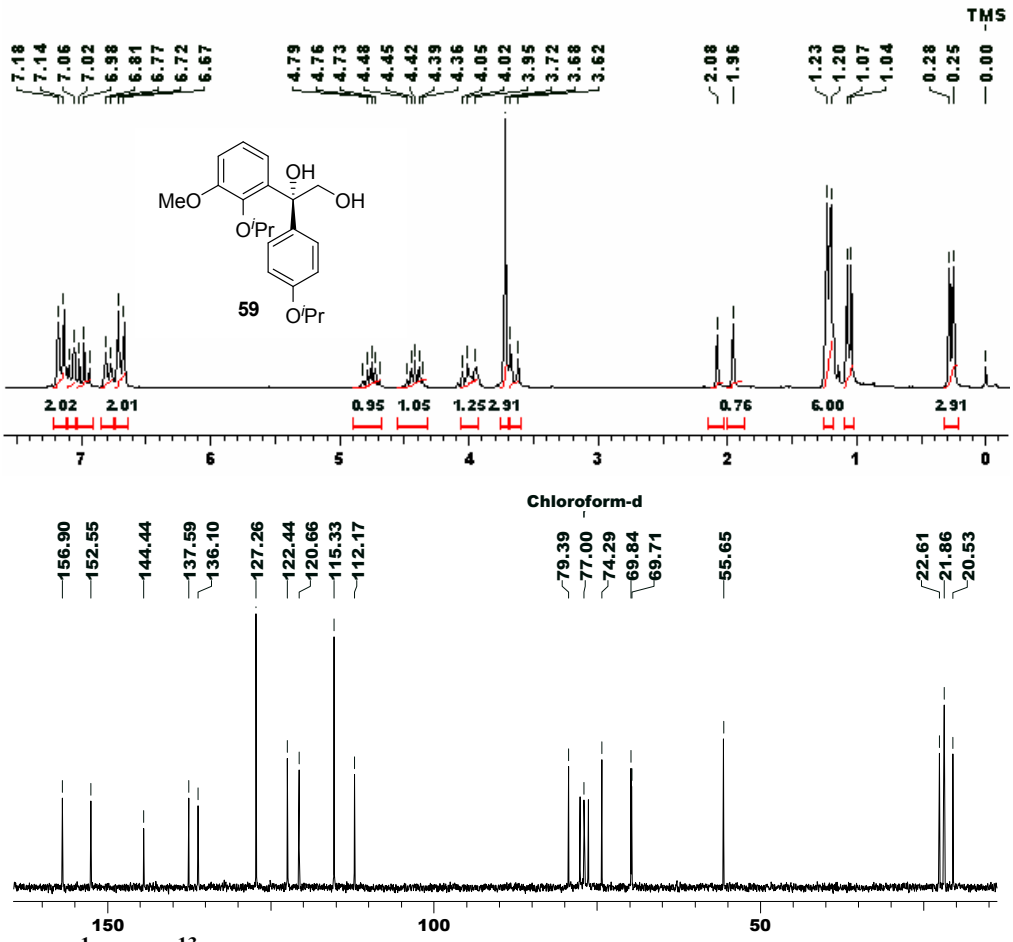


Fig. 8: ^{1}H and ^{13}C NMR spectra of diol 59

The diol **59** was then subjected to deoxygenation at benzylic position using Raney Ni in ethanol to give the corresponding alcohol **60** in 80% yield; $[\alpha]^{25}_{D}$: +66.21 (*c* 2.0, $CHCl_3$).

The ^{1}H NMR spectrum of the alcohol **60** showed signals at δ 1.76 (br s), 4.06 (d) and 4.40-4.74 (m) corresponding to the hydroxyl, homobenzylic and benzylic protons respectively. Its ^{13}C NMR spectrum showed typical carbon signals at δ 45.43 and 66.06 corresponding to the benzylic and homobenzylic carbons respectively. Its 13C NMR-DEPT spectrum showed a peak at δ 66.06 due to the homobenzylic methylene group (**Fig. 9**).

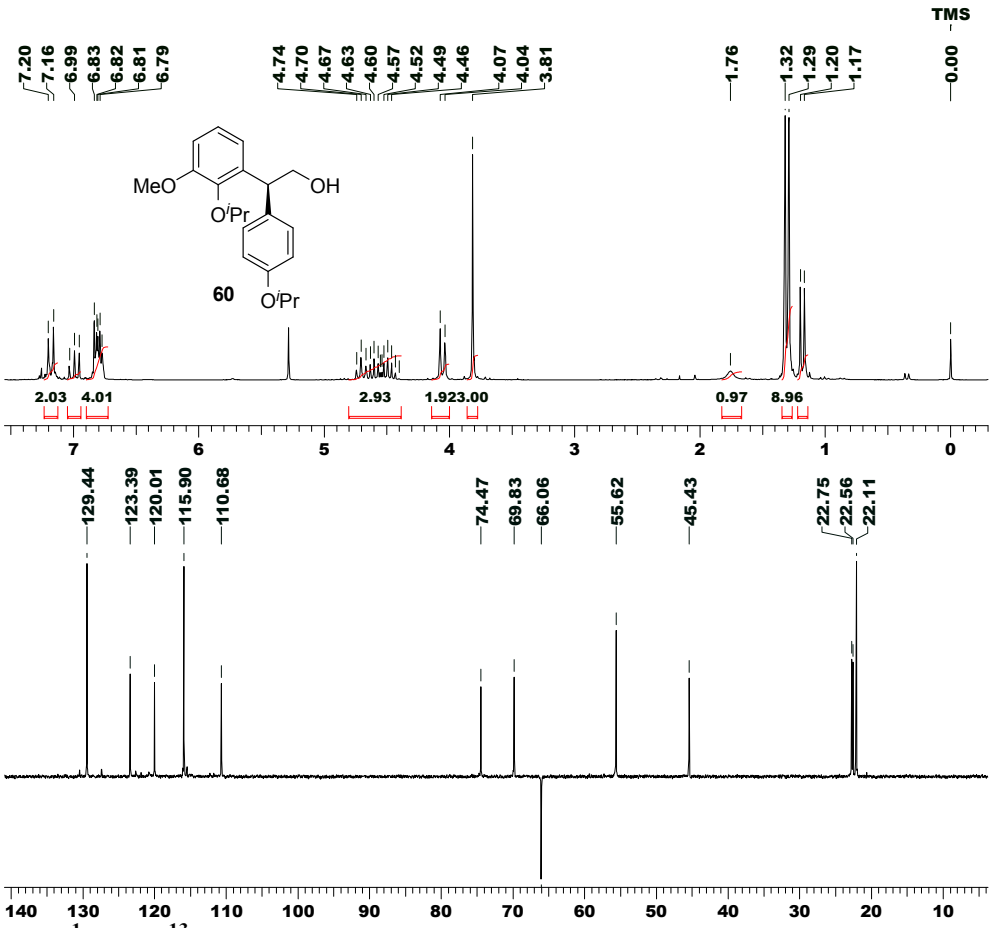


Fig. 9: ^{1}H and ^{13}C NMR-DEPT spectra of alcohol 60

The alcohol **60** was protected as its mesylate (MsCl, Et_3N, cat. DMAP, CH_2Cl_2, 0 °C), which was then subjected to nucleophilic displacement with methylamine to give the corresponding *N*-methylamine **61** in 70% yield; $[\alpha]^{25}_{D}$: +50.23 (*c* 1.2, $CHCl_3$); {lit.[22] $[\alpha]_D^{20}$: +55.4 (*c* 1.01, $CHCl_3$)}. The ^{1}H NMR spectrum of *N*-methylamine **61** showed signals at δ 1.67 (br s) and 2.43 (s) corresponding to proton on the secondary amine (NHMe) and the *N*-methyl groups respectively. Its ^{13}C NMR spectrum showed peaks at δ 36.16, 42.13, 55.43 and 56.57 due to the *N*-methyl, benzylic, methoxy and homobenzylic carbons respectively. Its ^{13}C NMR-DEPT spectrum also displayed a typical carbon signal at δ 56.57 confirming the presence of the homobenzylic methylene group attached to the NHMe moiety (**Fig. 10**).

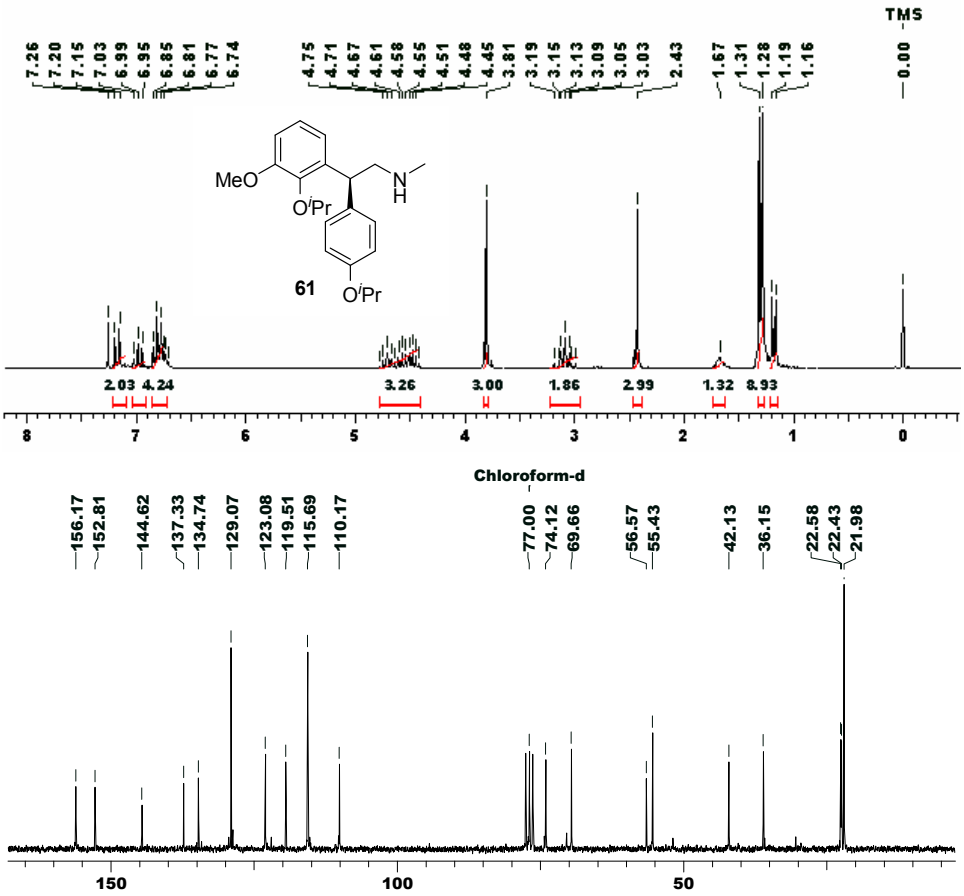


Fig. 10: ^{1}H and ^{13}C NMR spectra of *N*-methyl amine 61

The methylamine **61** was first *N*-formylated with acetic formic anhydride and the formyl derivative was subjected to Bischler-Napieralski cyclization[25] ($POCl_3$, C_6H_6, reflux, 45 min., then $NaBH_4$, MeOH, H_2O) to give the isoquinoline **62** $[\alpha]_D^{25}$: -2.89 (*c* 1.0, $CHCl_3$); {lit.[22] $[\alpha]_D^{20}$: -3.4 (c 0.76, $CHCl_3$)}. The ^{1}H NMR spectrum of the isoquinoline **62** showed characteristic signals at δ 2.32 (s), 2.58-2.71 (m) and δ 3.36 (d), 3.57 (d) corresponding to the *N*-methyl, homobenzylic methylene (**C-3**) and the cyclized carbon protons (**C-1**) respectively. Its ^{13}C NMR spectrum showed peaks at δ 45.99, 57.89 and 61.55 corresponding to the benzylic (**C-4**), homobenzylic (**C-3**) and the cyclized carbons (**C-1**) respectively. Its ^{13}C NMR-DEPT spectrum also displayed typical carbon signals at δ 57.90 and 61.56 confirming the presence of two methylene carbons, (**C-3**) and (**C-1**) respectively (**Fig. 11**).

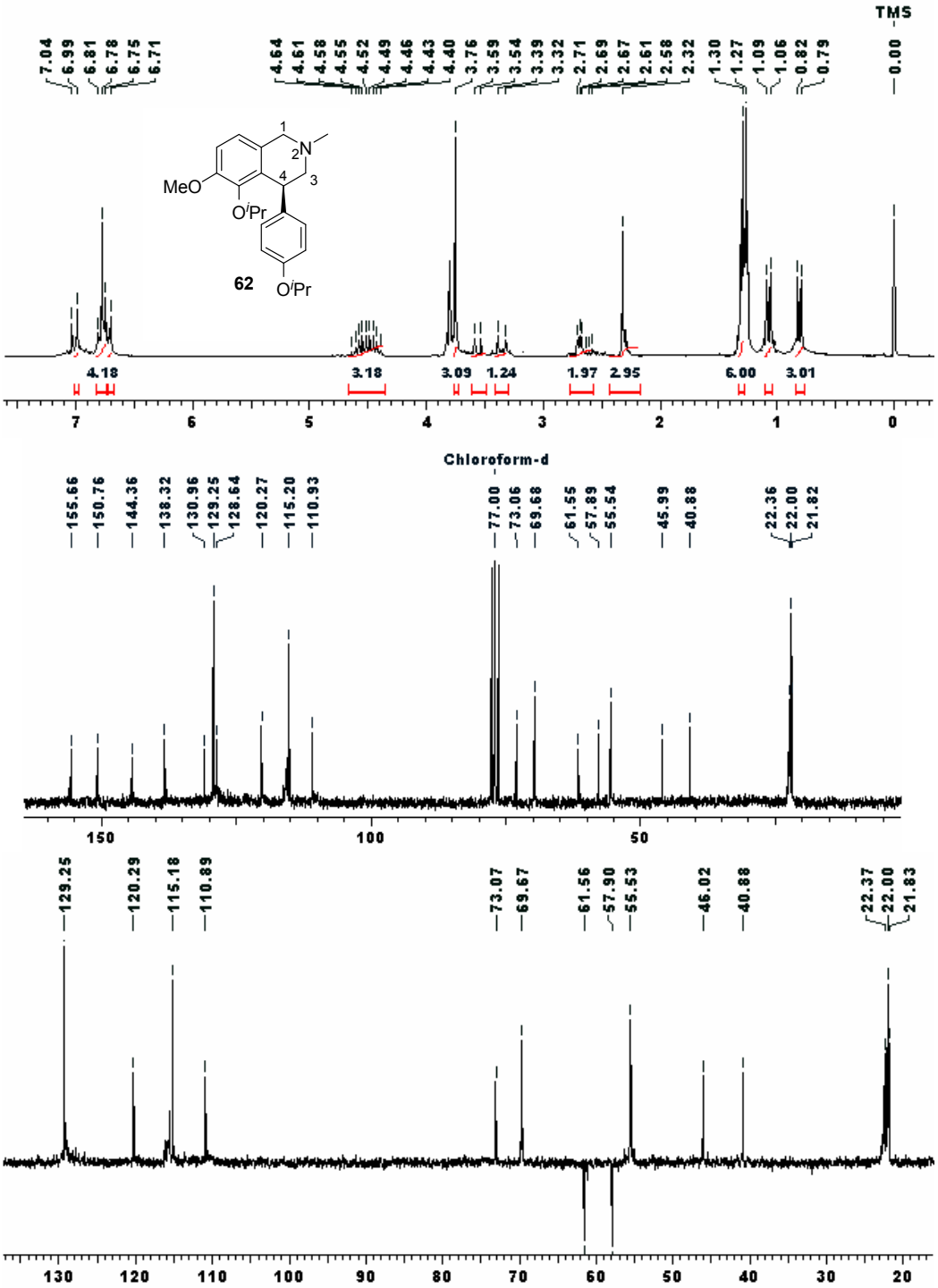


Fig. 11: ^{1}H, ^{13}C NMR and ^{13}C NMR-DEPT spectra of isoquinoline 62

The final step involved the dealkylation of the O-isopropyl groups. Thus, treatment of isoquinoline **62** with BCl_3 in CH_2Cl_2 at -10 °C gave (*S*)-latifine (**7**) in 90% yield, $[\alpha]_D^{25}$: -24.9 (c 0.4, MeOH); {lit.[13] $[\alpha]_D$: -27.9 (c 0.32, MeOH)}. The ^{1}H

NMR spectrum of (*S*)-latifine (**7**) showed signals at δ 2.37 (s), 2.63-2.75 (m) and 4.28 (t) corresponding to the *N*-methyl, homobenzylic and benzylic protons respectively (**Fig. 12**). Its ^{13}C NMR spectrum showed characteristic peaks at δ 46.0 and 57.9 corresponding to the benzylic and homobenzylic carbons. The spectral data obtained for (*S*)-latifine (**7**) were in full agreement with the values reported in the literature.[13]

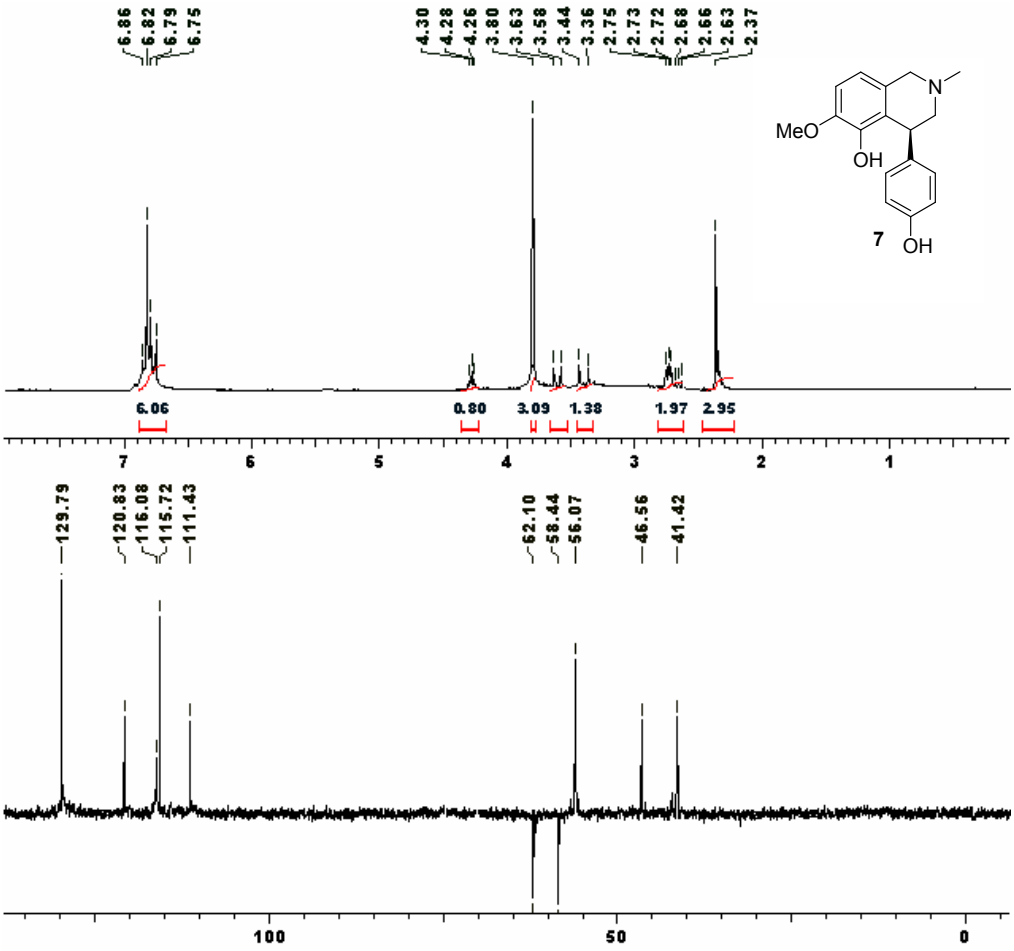


Fig. 12: ^{1}H and ^{13}C NMR-Dept spectra of (*S*)-latifine (7)

In addition, the synthesis of (±)-latifine has also been achieved following the same route as described in Scheme **11** starting from alcohol **58**.

3.1.7 Conclusion

In conclusion we have developed for the first time, a highly practical and enantioselective synthesis of (*S*)-latifine (**7**) using Sharpless asymmetric

dihydroxylation as the key step. The operationally simple and high yielding steps are the advantages in this method.

3.1.8 Experimental Section

2-Isopropoxy-3-methoxybenzaldehyde (42)

To a stirred solution of *o*-vanillin **55** (10 g, 65 mmol) and isopropyl bromide (8.85 g, 72 mmol) in DMF (100 mL) was added anhyd. K_2CO_3 (10.9 g, 79 mmol) and the mixture was refluxed for 12 h. After cooling, DMF was removed under reduced pressure and the residue was dissolved in Et_2O (200 mL) and washed with water (50 mL) and aqueous KOH (1N, 3 × 50 mL). The organic layer was dried over anhyd. Na_2SO_4 and evaporation of solvent left an oily residue which was purified by column chromatography over silica gel using EtOAc/Pet. ether (5:95) as eluent to give protected *ortho*-vanillin **42** as a colorless liquid.

Yield: 8.68 g (68%); gum; **^{1}H-NMR** (200 MHz, $CDCl_3$) δ: 1.22 (d, *J*=6.2 Hz, 6H), 3.77 (s, 3H), 4.54 (septet, *J*=6.2 Hz, 1H), 6.96–7.05 (m, 2H), 7.31 (dd, *J*=7.3 Hz, 2.1 Hz, 1H). **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 22.2, 55.9, 76.1, 117.8, 118.7, 123.6, 130.7, 150.5, 153.2, 190.7; **Analysis**: **$C_{11}H_{14}O_3$** requires C, 68.02; H, 7.27%; found C, 68.12; H, 7.14%.

2-Isopropoxy-3-methoxyphenyl-4-isopropoxyphenylmethanol (56)

To a stirred suspension of magnesium turnings (9.3 mmol, 223 mg) and few crystals of iodine in THF (100 mL), a solution of 4-isopropoxybromobenzene (2 g in 20 mL THF, 9.3 mmol) was added drop-wise at 25 °C. It was heated to reflux for 15 min. and the reaction mixture was cooled to -78 °C. To this a solution of 2-isopropoxy-3-methoxybenzaldehyde (**42**) (1.62 g in THF 2 mL, 8.37 mmol) was added drop-wise *via* syringe. After being stirred at -78 °C for 10 min, and for 1 h at 25 °C, saturated aqueous NH_4Cl (40 mL) was added and the organic layer separated. The aqueous

layer was extracted with Et_2O (3 × 40 mL) and the combined organic layers were dried over anhyd. Na_2SO_4, solvent distilled off under reduced pressure and the crude product purified by column chromatography over silica gel using EtOAc/Pet. ether (15:85) as eluent to yield **56** as a pale yellow solid.

Yield: 2.4 g (86%); **mp**: 63 °C; **IR** ($CHCl_3$, cm^{-1}): 674, 734, 887, 974, 1107, 1216, 1398, 1408, 1541, 1610, 2933, 2978, 3109; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.17 (d, *J*=6.2 Hz, 3H), 1.21 (d, *J*=6.2 Hz, 3H), 1.30 (d, *J*=5.9 Hz, 6H), 3.05 (br s, 1H, OH), 3.80 (s, 3H), 4.50 (septet, *J*=6.1 Hz, 1H), 4.68 (septet, *J*=6.2 Hz, 1H), 6.05 (br s, 1H), 6.77-6.84 (m, 4H), 6.96 (t, *J*=7.8 Hz, 1H), 7.25 (d, *J*=8.7 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 21.79, 22.06, 22.35, 55.25, 69.33, 70.50, 73.97, 111.12, 115.14, 119.48, 123.0, 127.51, 135.64, 138.09, 143.46, 152.04, 156.54; **Analysis: $C_{20}H_{26}O_4$** requires C, 72.70; H, 7.93%; Found C, 72.81; H, 8.04 %.

2-Isopropoxy-3-methoxyphenyl-4-isopropoxyphenylmethanone (43):

To a stirred solution of alcohol **56** (2 g, 6.1 mmol) in CH_2Cl_2 (100 mL) was added pyridinium dichromate (PDC, 4.6 g, 12.2 mmol) portion-wise. The reaction mixture was stirred at 25 °C for 10 h. After dilution with Et_2O (100 mL), filtration through a plug of celite and evaporation of solvent gave the crude product which was purified by column chromatography over silica gel using EtOAc/Pet. ether (15:85) as eluent to afford **43** as a colorless low melting solid.

Yield: 1.79 g (90%); **mp**: 34 °C; **IR** ($CHCl_3$, cm^{-1}): 691, 738, 845, 974, 1109, 1210, 1398, 1410, 1554, 1610, 1750, 2933, 2981; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.03 (d, *J*=6.19 Hz, 6H), 1.35 (d, *J*=6.1 Hz, 6H), 3.88 (s, 3H), 4.24 (septet, *J*=6.1 Hz, 1H), 4.62 (septet, *J*=6.1 Hz, 1H), 6.84 (d, *J*=8.8 Hz, 2H), 6.92 (dd, *J*=7.3 Hz, 1.8 Hz, 1H), 6.99 (dd, *J*=8.1 Hz, 1.8 Hz, 1H), 7.09 (t, *J*=7.8 Hz, 1H), 7.77 (d, *J*=8.7 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 21.74, 22.03, 55.52, 69.60, 76.05, 113.39, 114.49, 120.54,

123.56, 129.82, 132.21, 135.34, 144.16, 152.77, 161.73, 194.56; **Analysis: $C_{20}H_{24}O_4$** requires C, 73.15; H, 7.37%; Found C, 73.39; H, 7.55%.

2-Isopropoxy-1-(1-(4-isopropoxyphenyl)vinyl)-3-methoxybenzene (57):

n-BuLi (12.48 mL, 1.6 M in THF, 20 mmol) was added drop-wise, to a stirred solution of methyltriphenylphosphonium iodide (9.68 g, 24 mmol) in THF (100 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 0.5 h and further cooled to -40 °C. To this, a solution of benzophenone **43** (6.56 g, 20 mmol) in THF (20 mL) was added drop-wise *via* syringe. The mixture was stirred for further 0.5 h, quenched by the addition of saturated aqueous NH_4Cl, the organic layer separated and the aqueous layer was extracted with CH_2C1_2 (5 x 50 mL). The combined organic layer was washed with water (50 mL), dried over anhyd. Na_2SO_4, solvent distilled off and the crude product purified by column chromatography over silica gel using EtOAc/Pet. ether (6:94) as eluent to afford olefin **57** as the oily product.

Yield: 5.08 g (78%); gum; **IR** ($CHCl_3$, cm^{-1}): 669, 771, 837, 939, 1056, 1109, 1245, 1373, 1465, 1508, 1604, 2852, 2933, 2975; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.04 (d, *J*=6.1 Hz, 6H), 1.32 (d, *J*=6.1 Hz, 6H), 3.83 (s, 3H), 4.28 (septet, *J*=6.1 Hz, 1H), 4.61 (septet, *J*=6.1 Hz, 1H), 5.25 (d, *J*=1.4 Hz, 1H), 5.58 (d, *J*=1.5 Hz, 1H), 6.75 (d, *J*=8.8 Hz, 2H), 6.78-6.87 (m, 2H), 6.98 (t, *J*=7.5 Hz, 1H), 7.19 (d, *J*=8.7 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 21.99, 22.20, 55.53, 69.53, 74.61, 111.27, 113.87, 115.21, 123.06, 123.28, 127.83, 133.32, 136.85, 144.58, 146.71, 153.27, 157.24; **Analysis: $C_{21}H_{26}O_3$** requires C, 77.27; H, 8.03%; Found C, 77.15; H, 8.14%.

(*S*)-1-(2-Isopropoxy-3-methoxyphenyl)-1-(4-isopropoxyphenyl)ethane-1,2-diol (59):

To a stirred mixture of anhyd. K_2CO_3 (60 mmol, 8.4 g), $K_3[Fe(CN)_6]$ (60 mmol, 19.8 g), $(DHQD)_2$-AQN (1 mol %, 0.1 mmol, 86 mg) and methane sulfonamide (10 mmol,

0.95 g) in water (60 mL) and *tert*-butanol (50 mL) mixture, was added $K_2OsO_2(OH)_4$ (0.2 mol %, 0.02 mmol, 7.5mg) at 0 °C. After stirring for 5 min., olefin **57** (10 mmol, 3.26 g) in *tert*-butanol (10 mL) was added. The reaction mixture was then stirred for 24 h at 22 °C, quenched by addition of sodium sulfite (10 g) and then stirred for further 0.5 h. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic layers were dried over anhyd. Na_2SO_4, solvent distilled off under reduced pressure and the crude product purified by column chromatography over silica gel using EtOAc/Pet. ether (35:65) as eluent to give pure diol **59** in 88% yield.

Yield: 3.17 g (88%); gum; **$[\alpha]^{25}_{D}$:** -77.09 (*c* 0.6, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 669, 758, 860, 947, 1043, 1215, 1375, 1458, 1508, 1608, 2864, 2933, 2978, 3019; **HPLC**: 91.08% ee, CHIRACEL-ODH, 5% isopropanol/hexane, 1 mL/min. Retention time: (*R*): 11.58 min. (*S*): 13.05 min.; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 0.27 (d, *J*=6.2 Hz, 3H), 1.06 (d, *J*=6.2 Hz, 3H), 1.30 (d, *J*=5.9 Hz, 6H), 1.96 (br s, 1H, OH), 2.08 (br s, 1H, OH), 3.64 (d, *J*=11.6 Hz, 1H), 3.72 (s, 3H), 3.95-4.05 (m, 1H), 4.42 (septet, *J*=6.1 Hz, 1H), 4.76 (septet, *J*=6.2 Hz, 1H), 6.70 (d, *J*=8.7 Hz, 2H), 6.80 (dd, *J*=7.8 Hz, 1.3 Hz, 1H), 6.98 (t, *J*=8.0 Hz, 1H), 7.08 (m, 1H), 7.16 (d, *J*=8.7 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 20.53, 21.86, 22.61, 55.65, 69.71, 69.84, 74.29, 79.39, 112.17, 115.33, 120.66, 122.44, 127.26, 136.10, 137.59, 144.44, 152.55, 156.90; **Analysis:** **$C_{21}H_{28}O_5$** requires C, 69.98; H, 7.83%; Found C, 70.09; H, 7.79%.

(*S*)-2-(2-Isopropoxy-3-methoxyphenyl)-2-(4-isopropoxyphenyl)ethanol (60):

To a stirred solution of diol **59** (5 mmol, 1.8 g) in ethanol (20 mL), was added Raney nickel (10g) and heated to reflux. After 1 h, this suspension was filtered through a pad of celite, and the celite was rinsed with ethanol (2 x 25 mL). The combined solvent was distilled off under reduced pressure and crude product was purified by column

chromatography over silica gel using EtOAc/Pet. ether (20:80) as eluent to give pure alcohol **60**.

Yield: 1.38 g (80%); gum; **$[\alpha]^{25}_{D}$:** +66.21 (*c* 2.0, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 669, 756, 860, 931, 1107, 1215, 1387, 1458, 1508, 1654, 2933, 2978, 3079; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.19 (d, *J*=6.2 Hz, 3H), 1.31 (d, *J*=6.1 Hz, 9H), 1.76 (br s, 1H), 3.81(s, 3H), 4.06 (d, *J*=7.2 Hz, 2H), 4.40-4.74 (m, 3H), 6.77-6.83 (m, 4H), 6.99 (t, *J*=8.0 Hz, 1H), 7.18 (d, *J*=8.7 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 22.11, 22.56, 22.75, 45.43, 55.62, 66.06, 69.83, 74.47, 110.68, 115.90, 120.01, 123.39, 129.44, 133.14.10, 135.91, 145.51, 150.55, 155.90; **Analysis: $C_{21}H_{28}O_4$** requires C, 73.23; H, 8.19%; Found C, 73.12; H, 8.23%.

(*S*)-2-(2-Isopropoxy-3-methoxyphenyl)-2-(4-isopropoxyphenyl)-*N*-methylethanamine (61):

To a stirred solution of alcohol **60** (689 mg, 3 mmol) and Et_3N (460 µL, 3.3 mmol) in CH_2Cl_2 (30 mL) at 0 °C was added methanesulfonyl chloride (232 µL, 3 mmol) drop-wise *via* syringe. After stirring at 0 °C for 0.5 h, the reaction mixture was poured into ice-water (30 mL), the organic layer separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layer was washed with aqueous HCl (5%), saturated aqueous $NaHCO_3$, brine and dried over anhyd. Na_2SO_4. Solvent was distilled off under reduced pressure to give the crude mesylate *in situ*, which was then dissolved in 20 mL of 70% methyl amine in MeOH and heated at 70 °C for 4 h. The reaction mixture was then concentrated and the crude product was purified by column chromatography over silica gel using $CHCl_3$/MeOH (94:6) as eluent to give *N*-methylamine **61** in 70% yield.

Yield: 0.75 g (70%); **mp:** 123-125 °C; {lit.[22] **mp:** 121-123 °C}; **$[\alpha]^{25}_{D}$:** + 50.23 (*c* 1.2, CHC_3), {lit.[22] **$[\alpha]_D^{20}$:** +55.4 (c 1.01, $CHCl_3$)}; **IR** ($CHCl_3$, cm^{-1}): 669, 771, 878,

1036, 1130, 1219, 1344, 1458, 1541, 1610, 2830, 2921, 3258; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.18 (d, *J*=6.2 Hz, 3H), 1.30 (d, *J*=6.1 Hz, 9H), 1.67 (br s, 1H), 2.43 (s, 3H), 2.99-3.19 (m, 2H), 3.81 (s, 3H), 4.42-4.78 (m, 3H), 6.71-6.85 (m, 4H), 6.99 (t, *J*=7.8 Hz, 1H), 7.18 (d, *J*=8.6 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 21.98, 22.42, 22.58, 36.15, 42.13, 55.43, 56.57, 69.66, 74.12, 110.17, 115.69, 119.51, 123.08, 129.07, 134.74, 137.33, 144.62, 152.81, 156.17; **Analysis: $C_{22}H_{31}NO_3$** requires C, 73.91; H, 8.74, N, 3.92%; Found C, 74.08, H, 8.64; N, 3.81%.

(*S*)-1,2,3,4-Tetrahydro-5-isopropoxy-4-(4-isopropoxyphenyl)-6-methoxy-2-methylisoquinoline (62):

To a stirred solution of *N*-methylamine **61** (190 mg, 0.531 mmol) in pyridine (5 mL) at 0 °C was added acetic formic anhydride (0.1 mL, 2.12 mmol). After 45 min., the solvent was distilled off under reduced pressure and the residue was extracted with Et_2O (20 mL). The extract was washed successively with aqueous 10% HCl (2 x 10 mL), saturated aqueous $NaHCO_3$, brine, dried over anhyd. Na_2SO_4. Solvent was distilled off under reduced pressure to give the crude *N*-formamide which was subsequently added to a stirred solution of phosphorusoxy chloride (0.04 mL, 0.34 mmol) in benzene (1.5 mL) and refluxed for 45 min. After evaporation of solvent, residue was dissolved in 10% aqueous methanol (2 mL) and treated with $NaBH_4$ (25 mg, 0.67 mmol) at 0 °C and stirred for 1 h. Excess solvent was then distilled off under reduced pressure and extracted with Et_2O (10 mL). The combined organic phase was washed with water and brine, dried over anhyd. Na_2SO_4, and evaporated to leave crude product, which was purified by column chromatography over silica gel $CHCl_3$/MeOH (93:7) as eluent to give the isoquinoline **62** in 46% yield.

Yield: 90 mg (46% for 2 steps); gum; **$[\alpha]^{25}_{D}$:** -2.89 (*c* 1.0, $CHCl_3$); {lit.[22] **$[\alpha]^{20}_{D}$:** -3.4 (*c* 0.76, $CHCl_3$)}; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 0.81 (d, *J*=6.2 Hz, 3H), 1.09 (d, *J*=6.1 Hz, 3H), 1.29 (d, *J*=6.1 Hz, 6H), 2.32 (s, 3H), 2.58–2.71 (m, 2H), 3.36 (d, *J*=14.5 Hz, 1H), 3.57 (d, *J*=10.6 Hz, 1H), 3.76 (s, 3H), 4.40-4.64 (m, 3H), 6.74 (d, *J*=8.6 Hz, 1H), 6.76 (m, 4H), 7.05 (d, *J*=8.6 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 21.82, 22.0, 22.36, 40.88, 45.99, 55.54, 57.89, 61.55, 69.68, 73.06, 110.93, 115.20, 120.27, 128.64, 129.25, 130.96, 138.32, 144.36, 150.76, 155.66; **Analysis:** **$C_{23}H_{31}NO_3$** requires C, 74.76; H, 8.46; N, 3.79%; Found C, 74.84; H, 8.59; N, 3.67%.

(S)-1,2,3,4-Tetrahydro-4-(4-hydroxyphenyl)-6-methoxy-2-methylisoquinolin-5-ol : (*S*)-Latifine (7)

To a stirred solution of isoquinoline **62** (57 mg, 0.16 mmol) in CH_2Cl_2 (3 ml) was added at −10 °C, a solution of boron trichloride (1 M in CH_2Cl_2, 3 equiv., 0.47 mL). The reaction mixture was stirred at 0 °C for 2 h. The reaction mixture was quenched by the addition of water (10 mL) and the organic layer was separated. The aqueous layer was extracted with EtOAc (3 x 20 mL) and the combined organic layers were dried over anhyd. Na_2SO_4, solvent evaporated under reduced pressure and the solid obtained was recrystallized from MeOH to afford (*S*)-latifine (**7**) as a colorless solid in 90% yield.

Yield: 41 mg (90%); **mp**: 217-219 °C; {lit.[13] **mp**: 215-217 °C}; **$[\alpha]^{25}_{D}$:** -24.9 (*c* 0.4, MeOH); {lit.[13] **$[\alpha]_D$:** -27.9 (*c* 0.32, MeOH)}; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 2.37 (s, 3H), 2.63-2.75 (m, 2H), 3.40 (d, *J*=14.0 Hz, 1H), 3.61 (d, *J*=12.6 Hz, 1H), 3.80 (s, 3H), 4.28 (t , *J*=4.7 Hz, lH), 6.75-6.86 (m, 6H); **^{13}C NMR** (50 MHz, CD_3OD):δ 41.42, 46.56, 56.07, 58.44, 62.10, 111.43, 115.72, 116.08, 120.83, 129.79 , 130.45, 138.17, 144.85, 147.6, 156.1; **m/z** (%): 285 (M+) (SO), 242 (92), 241 (61), 225 (71), 211 (83),

210 (l00), 191 (74), 181 (71); **Analysis: $C_{17}H_{19}NO_3$** requires C, 71.56; H, 6.71; N, 4.91%; found C, 71.64; H, 6.67; N, 4.87%.

SECTION II

Asymmetric synthesis of (*1R,2S*)-Cispentacin

3.2.1 Introduction

Invasive fungal infections, particularly in immunosuppressed patients, have continued to increase in incidence during the past 20 years and are now significant causes of morbidity and mortality. This is particularly true in patients with haematological malignancies undergoing induction or consolidation chemotherapy (especially during the nadir of their granulocytopenia), in immunosuppressed organ transplant recipients, and in patients with acquired immunodeficiency secondary to infection by human immunodeficiency viruses.

These infections also occur in some iatrogenic or nosocomial clinical settings. Autopsy data indicate that more than half of the patients who die with malignancies are infected with *Candida* species, approximately one-third with *Aspergillus* species, and increasing numbers with *Cryptococcus* species or other fungi such as *Fusarium* species.[28-32] Major factors which predispose patients to invasive fungal disease include: prolonged neutropenia (chemotherapy induced); defective T-lymphocyte function (associated with organ transplantation and HIV infection); impaired macrophage function, particularly of pulmonary macrophages (associated with high doses and prolonged administration of corticosteroids); and barrier defects (associated with invasive medical procedures, vascular catheters, parenteral nutrition and haemodialysis and peritoneal dialysis) in compromised patients. Although invasive fungal diseases are now more frequent than during the first half of the century, they are still difficult to diagnose clinically.

During the latter half of the century, particularly during the past two decades, a number of different classes of anti-fungal agents have been discovered.

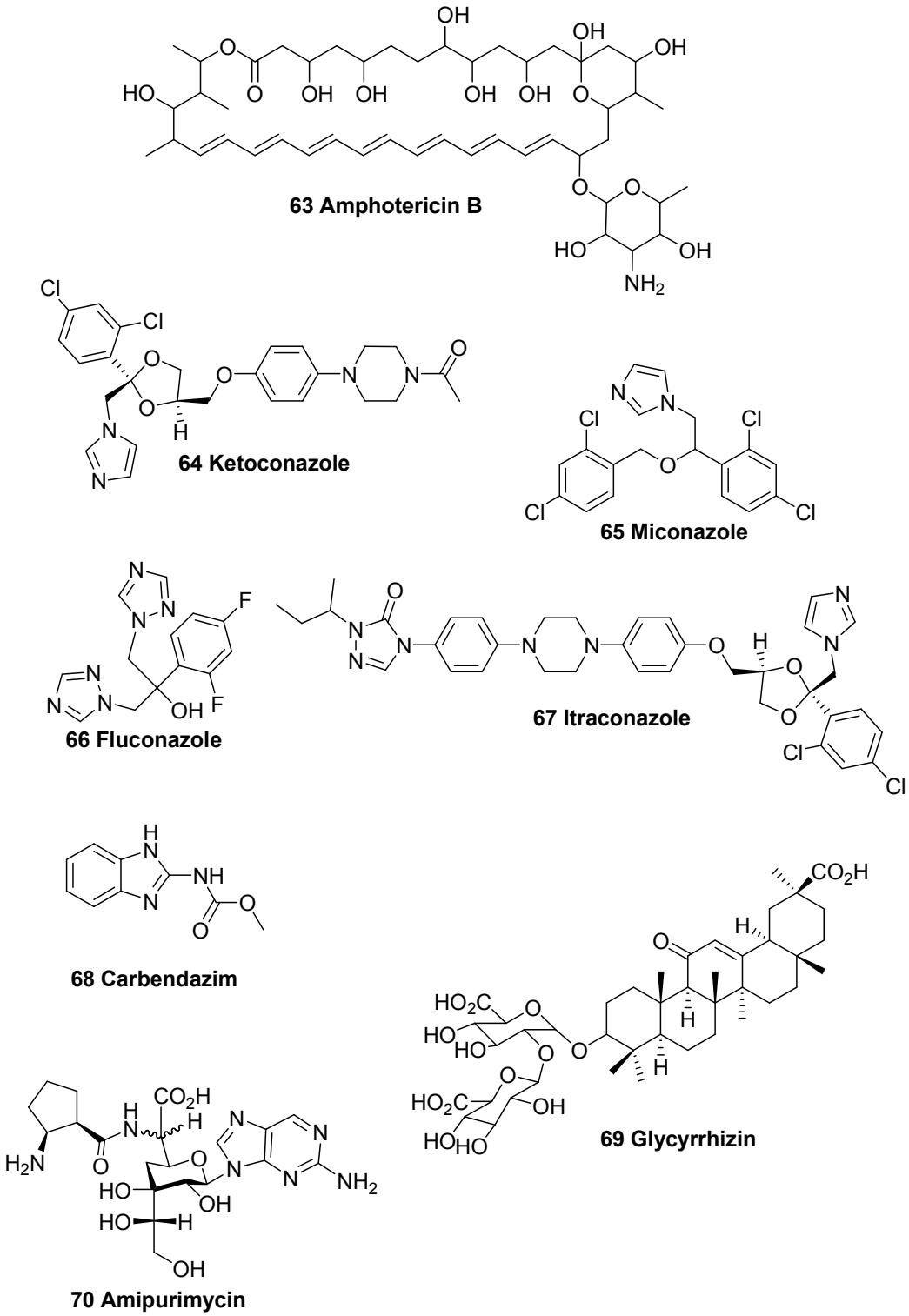


Fig. 13: Antifungal agents currently available

Although, since the discovery of amphotericin B (**63**), there has been much progress in this field, there is still a critical need for new antifungal agents to treat life-

threatening invasive mycoses. The antifungal agents currently available for the treatment of systemic fungal infections are: amphotericin B (**63**) and lipid formulations of amphotericin B; 5-fluorocytosine; and the azoles, ketoconazole (**64**), miconazole (**65**), fluconazole (**66**) and itraconazole (**67**) (**Fig. 13**). Currently, the optimal properties sought in a new antifungal drug candidate include: inhibition of fungal cell wall biosynthesis; potency comparable with that of amphotericin B (**63**); safety comparable with that of fluconazole (**66**); and fungicidal activity both *in vitro* and *in vivo*. The search for new antifungal agents has been expanded as progress in molecular biology has led to a better understanding of important and essential pathways in fungal cell growth and multiplication. A number of new compounds, some with unidentified mechanisms of action, are under study. One group includes dication-substituted carbazoles, furans and benzimidazoles, which are aromatic dicationic compounds with antimicrobial activity. Some are quite active *in vitro* against *Candida* species (including azole-resistant strains), *Cryptococcus neoformans, Aspergillus fumigatus* and *Fusarium* species. Carbendazim (**68**), a benzimidazole derivative, was used as an agricultural fungicide but recently was shown to cure experimental histoplasmosis. Glycyrrhizin (**69**, an extract from liquorice roots, has been shown to have antifungal activity against C*andida albicans* in thermally injured mice. Amipurimycin (**70**), with cispentacin moiety in its structure, was isolated from *Streptomyces novoguineensis* and was found strongly to be active both *in vitro* and *in vivo* against *Pyricularia oryzae*, the organism responsible for rice blast disease. It is also active *in vitro* against *Alternaria kikuchiana* and *Helminthosporium sigmoideum var. irregulare*. Amipurimycin (**70**) contains a nucleic base attached to the anomeric carbon of a branched-chain deoxy sugar.

3.2.1.1 Cispentacin and structural analogues

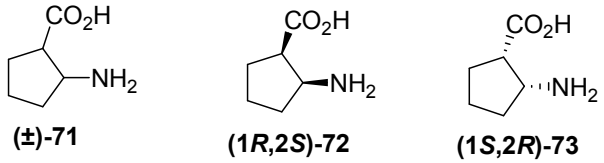


Fig. 15: Structures of cispentacins

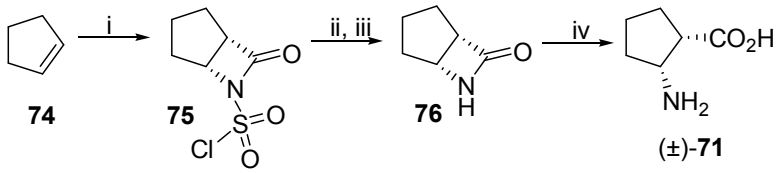
Cispentacin **72** (**Fig. 14**) is the (1*R*, 2*S*) enantiomer of 2-aminocyclopentanecarboxylic acid. It is a new antifungal antibiotic isolated independently by two groups from *Bacillus cereus*[33] and *Streptomyces setonii*[34] and shown to exhibit potent antifungal activity *in vivo* against *Candida albicans*. The racemic compound was also claimed to exhibit activity against pathogens of agrochemical interest. Interesting levels of antifungal activity were observed against Phycomycete pathogens both in the glasshouse and in the field.

3.2.2 Review of Literature

Due to its biological activity, various methods for the asymmetric synthesis of cispentacin have been reported as shown in the following sections:

Nativ's approach (1972)[35]

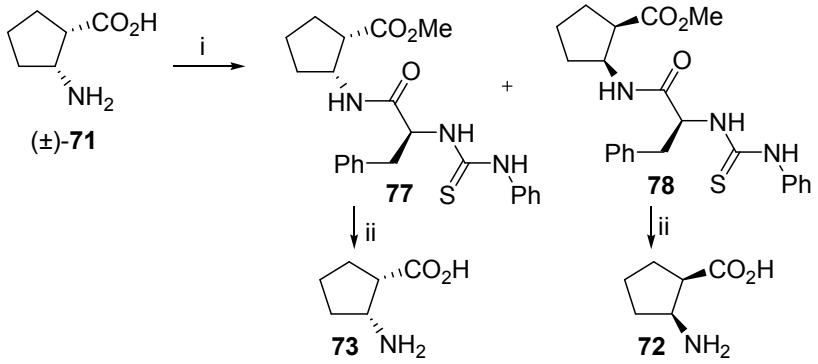
In this approach, racemic cispentacin (**71**) was synthesized *via* [2+2] cycloaddition of chlorosulfonyl isocyanate with cyclopentene **74** followed by hydrolysis of the intermediate β-lactam **76** (**Scheme 12**).



Scheme 12: (i) $ClSO_2NCO$, -78 °C to 8 h 0 °C then 25 °C overnight; (ii) KI; $NaHSO_4$; (iii) NaOH, pH 7; (iv) conc. HCl, 0 °C, 3 h.

Kawabata's approach (1990)[36]

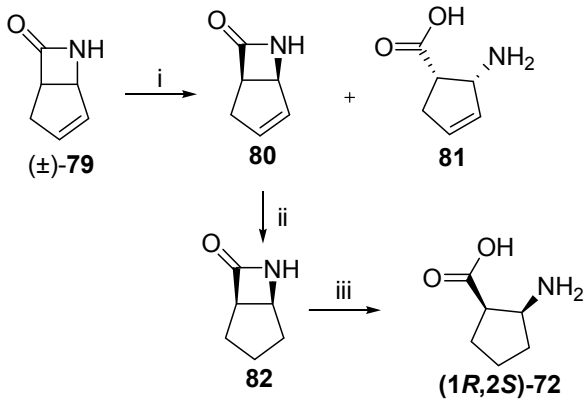
Enantiomerically pure cispentacin (**72**) and its antipode **73** were obtained for the first time by Kawabata *et al.* through separation of diastereomeric dipeptides followed by Edman degradation (**Scheme 13**). The absolute configurations of *cis*-(1*R*,2*S*) cispentacin (**72**) and its (1*S*,2*R*)-antipode **733** were determined through X-ray crystallographic analysis of diastereomers **77** and **78**.



Scheme 13: (i) (a) $SOCl_2$, MeOH, (b) *N*-Boc-L-phenylalanine, EDCI, HOBT, CH_2Cl_2, (c) fractional crystallization, (d) 4*N*-HCl, EtOAc, (e) phenyl isothiocyanate, EtOH, reflux; (ii) (a) 4*N*-HCl, CH_2Cl_2, (b) pH 6.7, water, anion exchange resin.

Evans' approach (1991)[37]

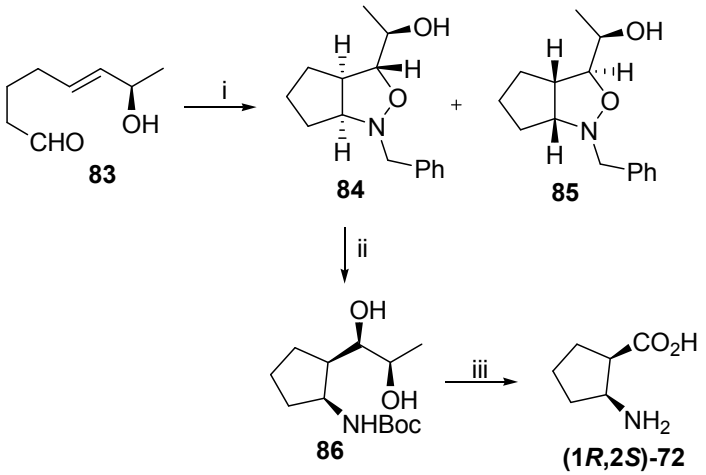
In this approach, kinetic resolution of the lactam (±)-**79** was achieved in a highly selective manner using a whole cell preparation ENZA-1 *(Rhodococcusequi* NCIB 40213). The lactam (+)-**80** was hydrogenated to give saturated analogue (-)-**82** which was, in turn, hydrolyzed to give (1*R*,2*S*)-cispentacin (**72**) in 95% yield (**Scheme 14**).



Scheme 14: (i) ENZA-1, pH 7, 20 °C [(+)-**80**, 53%, 75% ee]; (ii) H_2, Pd/C, EtOAc, 95%; (iii) HCl, H_2O, 95%.

Konosu's approach (1993)[38]

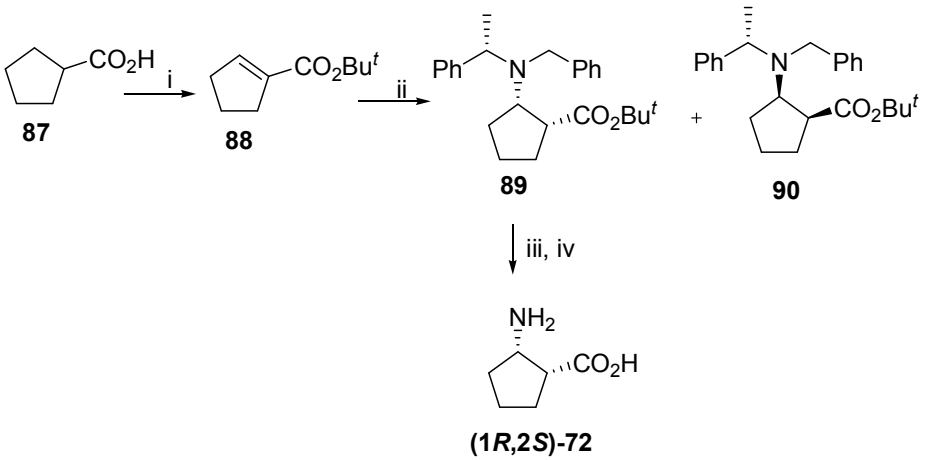
Konosu *et al.* have described a simple, but long enantioselective protocol starting from (*R*)-aldehyde **83**. It was transformed with *N*-benzylhydroxylamine to the nitrone, which underwent intramolecular cycloaddition to yield isoxazolidine with high diastereoselectivity (**84:85**=15:1). The cycloadduct **84** was readily separated and transformed into natural cispentacin (**72**) in four steps: ring opening, protection, oxidation, and removal of the protecting group (**Scheme 15**).



Scheme 15: (i) (a) $PhCH_2NHOH$, 25 °C, (b) C_6H_6, reflux, 95%; (ii) (a) Pd/C, H_2, (b) $(Bu^tO)_2CO$, 93%; (iii) (a) $NaIO_4$, $KMnO_4$, (b) HCl, dioxane, (c) salting.

Davies' approach (1993)[39]

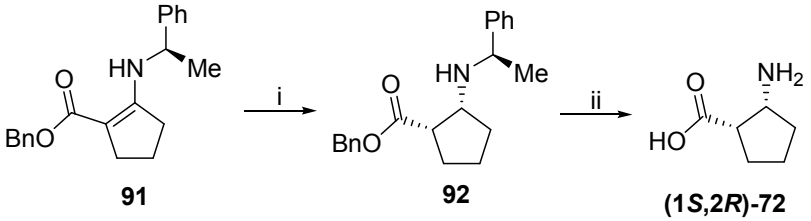
The asymmetric synthesis of cispentacin (**72**) was accomplished by Davies *et al*. *via* diastereoselective Michael addition. Esterification of cyclopentanecarboxylic acid **87** followed by iodination and elimination of hydrogen iodide from the resultant α-iodo ester afforded the *α*,β-unsaturated ester **88** in 36% overall yield. The homochiral lithium (S)-(α-methylbenzyl)benzylamide was added to *tert*-butyl 1-cyclopentene-1-carboxylate (**88**) to afford the protected β-amino acid **89** in 65% yield and >98% diastereomeric excess. Cispentacin (**72**) was obtained in 72% yield through three steps of debenzylation, ester hydrolysis and ion exchange chromatography (**Scheme 16**).



Scheme 16: (i) (a) 2-methylpropene, H_2SO_4, CH_2Cl_2, -78 °C to 25 °C, 20 h, (b) LDA, THF, -78 °C, 1 h, then I_2, (c) DBU, THF, 0 °C, 1 h, then 25 °C, 48 h, 36%; (ii) (a) (S)-(α-methylbenzyl)benzylamide in toluene then THF, -95 °C to -78 °C, 2 h, (b) 2,6-di-tert-butylphenol, 65%; (iii) H_2, Pd/C; (iv) TFA then Dowex 50x8-200, 95%.

Palmieri's approach (1994)[40]

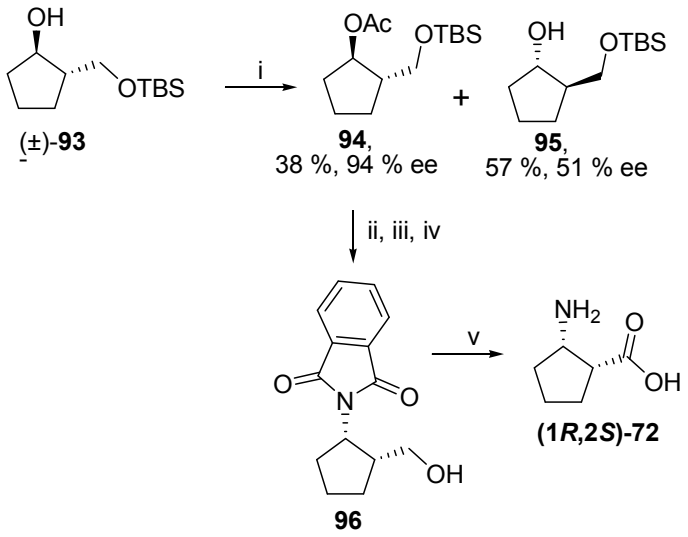
In this approach, reduction of the homochiral β-enamino ester **91** with sodium triacetoxyborohydride resulted in the formation of β-amino ester **92** in 71% yield and 67% d.e. The subsequent reduction of the benzyl moieties gave (1*S*,2*R*)-cispentacin (**72**) (**Scheme 17**).



Scheme 17: (i) $NaHB(OAc)_3$, CH_3CN, AcOH, 0 °C, 3 h; (ii) $Pd(OH)_2$, H_2.

Theil's Approach (1996)[41]

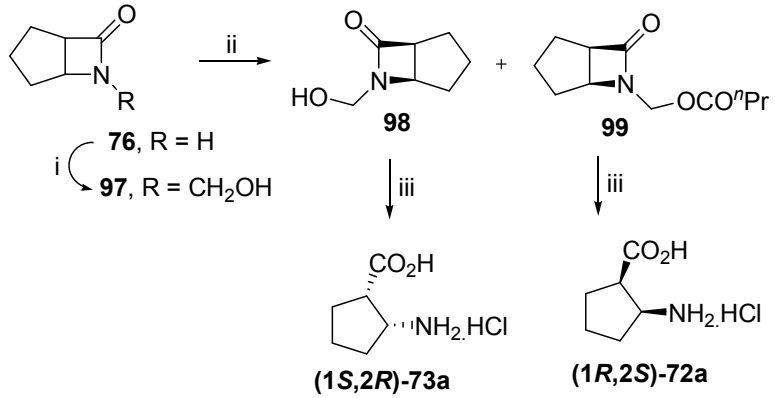
Lipase-catalysed kinetic resolution of the silyloxy alcohol (±)-**93** by trans-esterification with vinyl acetate in the presence of lipase from *Pseudomonas cepacia* leads to the synthesis of the β-amino acid, cispentacin (1*R*,2*S*)-**72** using simple functional group inter conversions (**Scheme 18**).



Scheme 18: (i) vinyl acetate, Lipase PS, 40 % conversion, (ii) Wofatit SBW (OH^-), MeOH, (iii) Phthalimide, PPh_3, DEAD, THF, 25 °C, 12 h, 70%; (iv) AcOH, THF, H_2O, 25 °C, 12 h, 95%; (v) (a) Jones' reagent, 25 °C, 0.5 h, 80%; (b) aq. $MeNH_2$, EtOH, H_2O, 25 °C, 1.5 h, 91%.

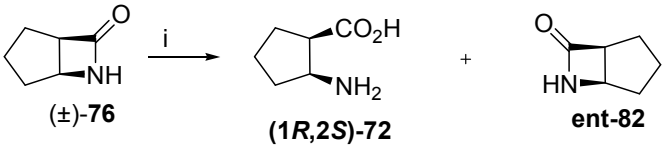
Fülöp's approach (1996)[42]

In this approach, a highly enantioselective enzymatic acylation was observed for *N*-hydroxymethylated *β*-lactam **97**, which was prepared from the corresponding racemic β-lactam **76** (**Scheme 19**). Lipase AK-catalyzed butyrylation with vinyl butyrate in acetone gave the readily separable azetidinones **98** and **99** with 98% yield and 90% *ee*, respectively. Hydrolysis of β-lactams **98** and **99** resulted in both enantiomers of cispentacin as its hydrochlorides, **72a** and **73a**.



Scheme 19: (i) $(HCHO)_n$, K_2CO_3, H_2O, sonication in THF; (ii) Lipase AK, vinyl butyrate, acetone; (iii) 18% HCl.

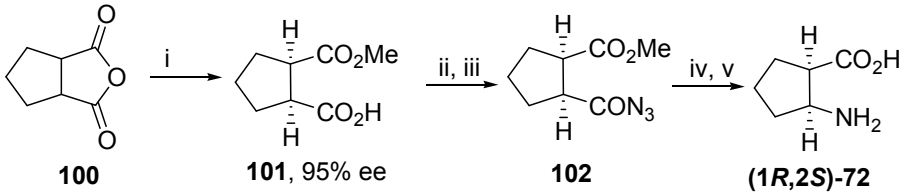
Fülöp *et al*.[43] also have developed lipase-catalyzed enantioselective ring opening of unactivated alicyclic β-lactams (±)-**76** to give enantiopure β-amino acids (**72**) and β-lactams (**82**) (**Scheme 20**).



Scheme 20: (i) Lipase B, diisiopropyl ether, H_20, 60 °C.

Bolm's approach (2001)[44]

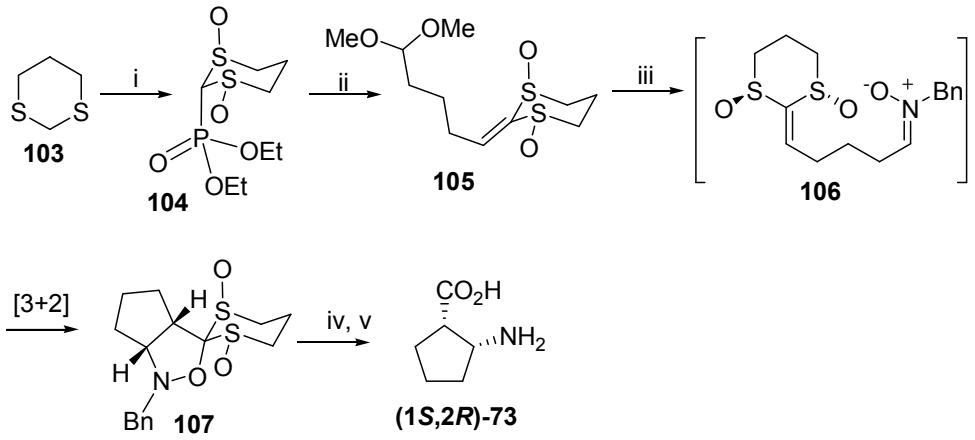
In this approach, the highly enantioselective methanolysis of cyclic *meso*-anhydride **100** mediated by cinchona alkaloid (quinine) led to the formation of dicarboxylic acid monomethyl ester **101** with 99% ee. Curtius degradation of the corresponding acyl azide **102** followed by acid hydrolysis led to the formation of cispentacin (**72**) (**Scheme 21**).



Scheme 21: (i) quinine, MeOH; (ii) Et_3N, $ClCO_2Et$, THF, -20 °C; (iii) NaN_3, H_2O, -10 °C to 25 °C, 2h; (iv) benzene, reflux, 2h; (v) HCl.

Aggarwal's approach (2002)[45]

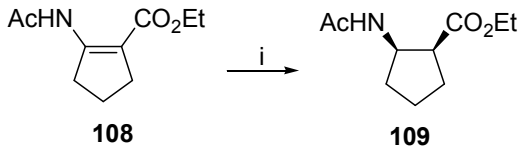
Aggarwal *et al.* have developed a highly diastereoselective intramolecular cycloaddition of nitrone onto a chiral ketene equivalent (**106**), obtained by Horner-Wadsworth-Emmons olefination of either enantiomer of bis-sulfinyl phosphonate **104** (**Scheme 22**). The [3+2] cycloaddition of the *in situ* generated intermediate **106** gave 5,5-disubstituted isoxazolidine **107** in good yield as a single diastereomer. Catalytic hydrogenolysis of isoxazolidine **107** furnished either enantiomers of optically pure cispentacin (**72**).



Scheme 22: (i) (a) NCS, benzene, 25 °C, 24 h, (b) $P(OEt)_3$, 60 °C, 4 h, 78%; (c) $PhC(CH_3)_2OOH$, $Ti(OiPr)_4$, (-)- Diethyl tartarate, CH_2Cl_2, 43%, >98% ee; (ii) 5,5-dimethoxypentanal, LiOH, H_2O, THF, 80 °C, 4 h, 80%; (iii) $PdCl_2(CH_3CN)_2$, acetone, 60 °C, 1 h then $BnNH_2OH.Cl$, $NaHCO_3$, 60 °C, 4 h, 70%; (iv) Pd/C, AcOH, H_2 (100 Psi), 48 h, 65%; (v) $Pd(OH)_2/C$, NEt_3, EtOH, 40 °C, H_2 (1 atm.), 4 h, 85%.

Zhang's approach (2003)[46]

Zhang *et al.* have developed a catalytic asymmetric synthesis of chiral cyclic β-amino acid derivatives **109** with 99% ee *via* asymmetric hydrogenation of tetrasubstituted olefins of cyclic β-(acylamino)acrylates **108** using Ru-catalyst with chiral biaryl ligands such as C3-TunaPhos (**Scheme 23**).



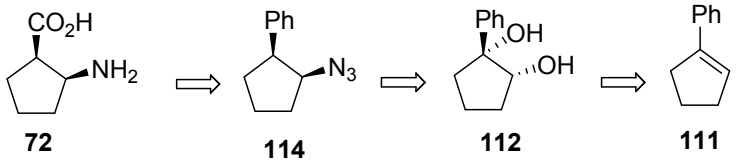
Scheme 23: (i) Ru(COD)(methallyl)$_2$, (*S*)-C3-TunaPhos, HBF_4, H_2 (50 atm), MeOH, 25 °C.

3.2.3 Present Work

3.2.3.1 Objective

The literature methods reveal that even though many routes are reported for the synthesis of cispentacin, most of them make use of either enzymes, expensive catalysts or chiral pool approaches for the introduction of chirality. This chapter describes the enantioselective synthesis of (1*R*,2*S*)-cispentacin (**72**) using Sharpless

Asymmetric Dihydroxylation (AD) as the key step. The retrosynthesis of cispentacin (**72**) is shown in **Scheme 24**. The amine unit can be realized by the reduction of an azide group using standard hydrogenation conditions. The carboxylic acid moiety can be obtained through the oxidative cleavage of phenyl ring in **114** using $RuCl_3$-$NaIO_4$ mediated oxidative cleavage. The azide group in turn can be obtained from an alcohol moiety with SN_2 inversion. Deoxygenation at benzylic position using Raney Ni can lead to diol **112**. The diol **112** can be obtained through Sharpless Asymmetric Dihydroxylation of the corresponding olefin **111**.

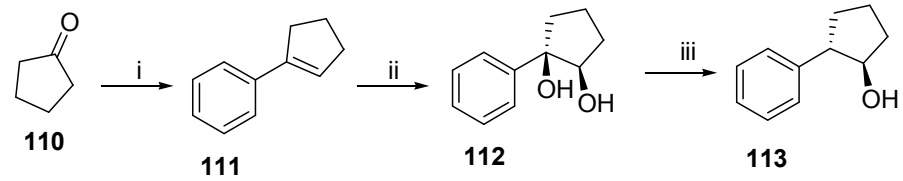


72 **114** **112** **111**

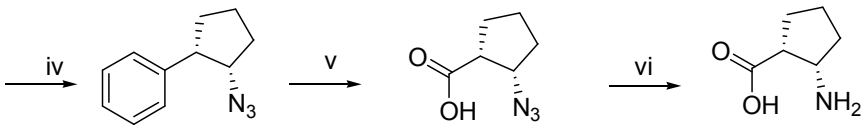
Scheme 24: Retrosynthetic analysis of Cispentacin

3.2.4 Results and Discussion

The present synthetic strategy for the preparation of (1*R*,2*S*)-cispentacin (**72**) is depicted in **Scheme 25**.



110 **111** **112** **113**



114 **115** **(1*R*,2*S*)-72**

Scheme 25: (i) (a) PhMgBr, Et_2O, 0 °C, 1 h, 90%; (b) *p*-TSA, C_6H_6, reflux (Dean-Stark), 10 h, 92%; (ii) $(DHQD)_2$-PHAL, $K_2OsO_2(OH)_4$, $MeSO_2NH_2$, $K_3[Fe(CN)_6]$, K_2CO_3, *t*-BuOH-H_2O, 0 °C, 12 h, 76%; (iii) Raney-Ni, EtOH, reflux, 2 h, 80%; (iv) (a) MsCl, Et_3N, CH_2Cl_2, 0 °C, 1 h, 94 %; (b) NaN_3, DMF, 80 °C, 6 h, 80% for 2 steps; (v) 20 mol% $RuCl_3$, $NaIO_4$, EtOAc, CH_3CN, H_2O, 18 h, 60 %; (vi) 5% Pd/C, H_2 (1 atm.), MeOH, 1 h, 92%.

Grignard reaction of cyclohexanone **110** with phenyl magnesium bromide (prepared from bromobenzene and magnesium turnings in diethyl ether at 0 °C) gave the corresponding tertiary alcohol *in situ* in 90% yield which was then dehydrated using catalytic amount of *p*-toluenesulfonic acid in benzene under reflux conditions to give the corresponding olefin **111** in 92 % yield. The ^{1}H NMR spectrum of **111** showed a multiplet at δ 6.13-6.17 indicating the presence of the olefinic proton (C=C-**H**). The ^{13}C NMR spectrum of **111** showed a peak at δ 125.11 confirming the presence of olefinic carbon and signals at δ 20.7, 31.6 and 38.2 corresponding to the aliphatic carbons.

The key precursor (1*R*,2*R*)-1-phenylcyclopentane-1,2-diol (**112**) was then obtained in 76% yield and 97% ee by Sharpless Asymmetric dihydroxylation of 1-cyclopentenylbenzene (**111**) using $(DHQD)_2$-PHAL as the chiral ligand and potassium osmate as the catalyst;[26] **$[\alpha]^{25}_{D}$:** -28.53 (*c* 1.08, $CHCl_3$).

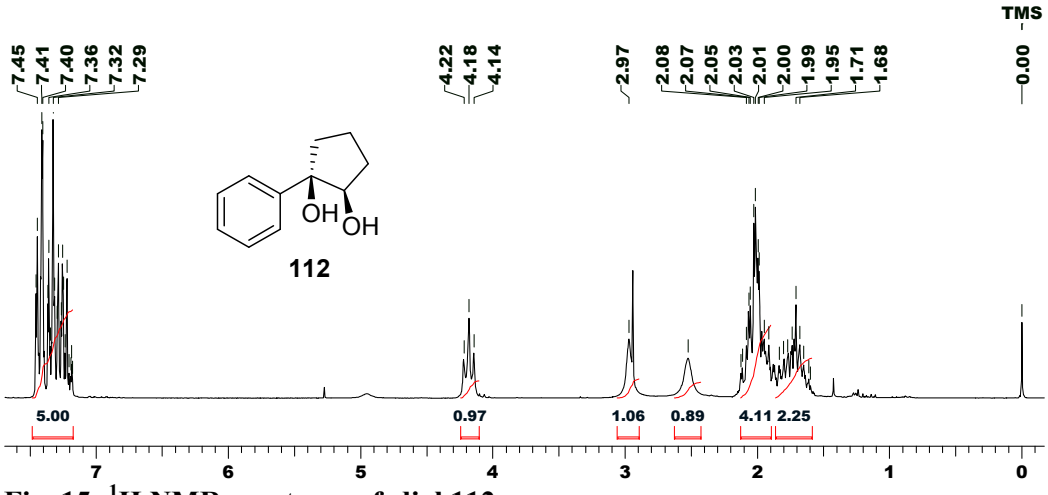


Fig. 15: ^{1}H NMR spectrum of diol 112

The ^{1}H NMR spectrum of the diol **112** showed two broad singlets at δ 2.52 and δ 2.97 due to the presence of two hydroxyl groups and a characteristic triplet at δ 4.18 due to the CHOH moiety (**Fig. 15**). Its ^{13}C NMR spectrum showed characteristic carbon signals at δ 79.6 and 81.2 due to the presence of two carbons attached to

hydroxyl groups (**Fig. 16**). The ^{13}C NMR DEPT spectrum of the diol **112** showed peaks at δ 19.5, 30.9, and 38.6 due to the three methelene groups.

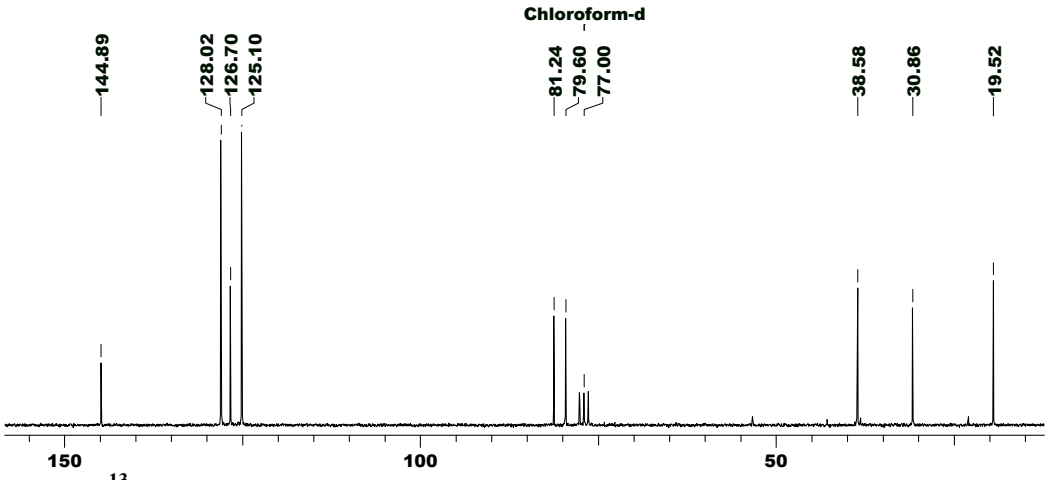


Fig. 16: ^{13}C NMR spectrum of diol 112

The next step required the deoxygenation of the benzylic hydroxyl group, which was carried out in presence of Raney Ni and ethanol. Thus, when the diol **112** was refluxed with Raney nickel in ethanol, (1*R*,2*S*)-2-phenylcyclopentane-1-ol (**113**) was obtained in 80% yield; **$[\alpha]^{25}_{D}$:** -31.53 (*c* 1.2, $CHCl_3$).

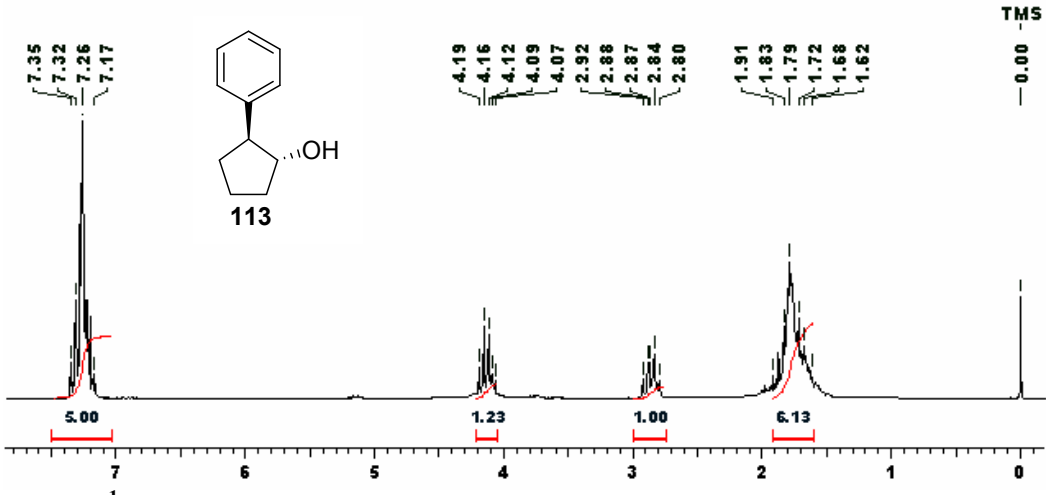


Fig. 17: ^{1}H NMR spectrum of alcohol 113

Its ^{1}H NMR spectrum showed of alcohol **113** characteristic multiplet at δ 4.09-4.19 due to the C**H**OH moiety (**Fig. 17**). Its ^{13}C NMR spectrum showed a characteristic

signal at δ 80.1 confirming the presence of a carbon attached to the hydroxyl group (**Fig. 18**). The optical purity of the alcohol **113** was determined from its ^{1}H NMR analysis of its Mosher ester, which showed the enantiomeric excess to be 95% (see experimental section).

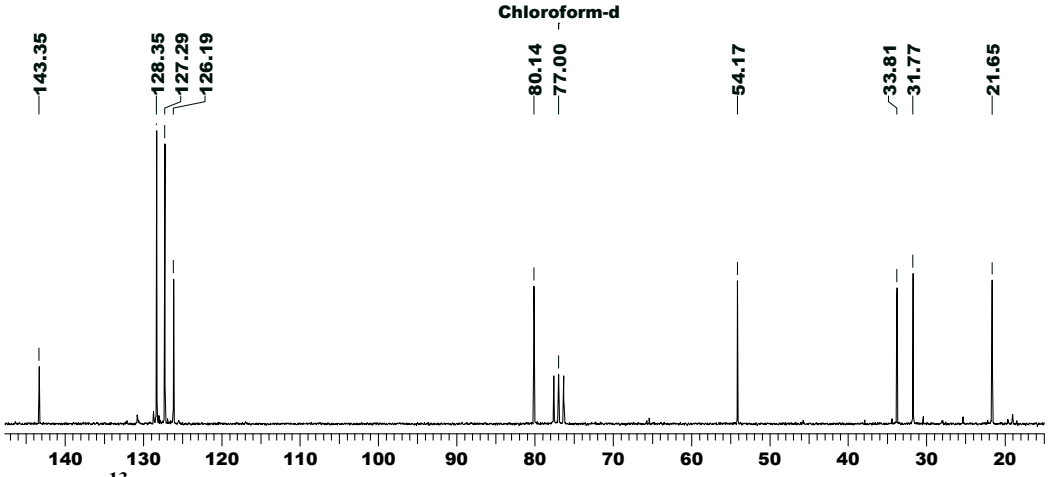


Fig. 18: ^{13}C NMR spectrum of alcohol 113

Alcohol **113** was then mesylated using methanesulfonyl chloride in the presence of Et_3N as base in CH_2Cl_2 to give the corresponding mesylate *in situ* in 94% yield, which was then treated with sodium azide in DMF at 80 °C to yield the corresponding azide, 1-(1*S*,2*S*)-2-azidocyclopentylbenzene (**114**) in 80% yield; **$[\alpha]^{25}_{D}$:** + 45.64 (*c* 2.0, $CHCl_3$). Its IR spectrum showed a band at 2100 cm^{-1} indicative of the presence of azide group. The ^{1}H NMR spectrum of azide **114** showed a multiplet at δ 4.08-4.13 indicating the presence of CHN_3 moiety and a multiplet at δ 3.14 corresponding to the benzylic proton. Its ^{13}C NMR spectrum showed peaks at δ 50.4 and 67.3 confirming the presence of the benzylic carbon and carbon attached to the azide group respectively (**Fig. 19**). The next step involved the oxidative cleavage of the phenyl ring in **114** to the corresponding carboxylic acid using $RuCl_3$ and $NaIO_4$ system.

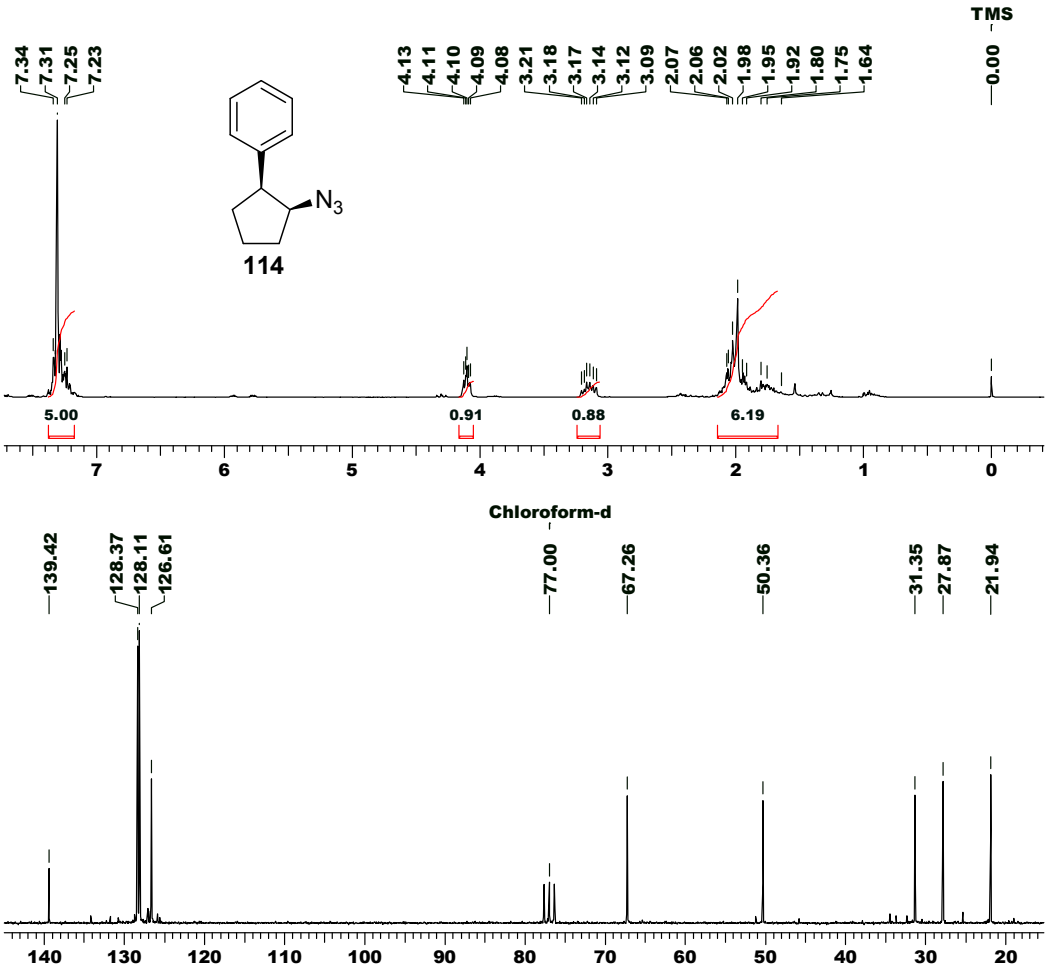


Fig. 19: ^{1}H NMR and ^{13}C NMR spectra of compound 114

Thus, treatment of **114** with catalytic amount of $RuCl_3$ along with $NaIO_4$ gave (1*R*,2*S*)-2-azidocyclopentane-1-carboxylic acid **115** in 63% yield; **$[\alpha]^{25}_{D}$:** +28.8 (*c* 0.6, $CHCl_3$). The ^{1}H NMR spectrum of acid **115** showed a broad singlet at δ 8.91 corresponding to the proton of the carboxylic acid moiety and two multiplets at δ 2.87-2.98 and 4.24-4.30 indicating the presence of methine protons, C**H**N_3 and C**H**CO_2H respectively. The ^{13}C NMR spectrum of the compound **115** displayed peaks at δ 64.6 and 49.4 due to the carbons attached to azide and acid moieties respectively and a peak at δ 177.6 corresponding to the carbonyl carbon in the acid moiety (**Fig. 20**). Also the IR spectrum of **115** showed bands at 1715 and 2112 cm^{-1} corresponding to the presence of acid carbonyl and azide group frequencies respectively.

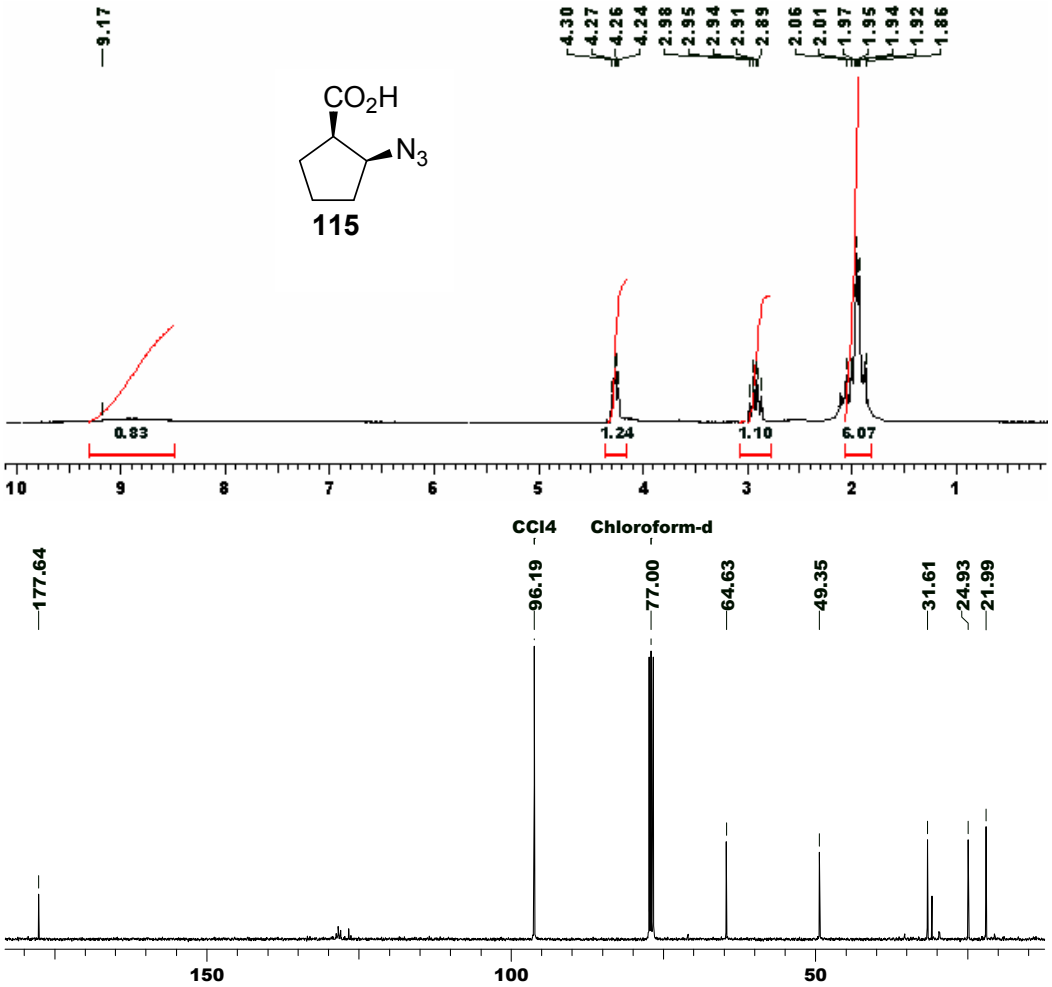


Fig. 20: ^{1}H NMR and ^{13}C NMR spectra of compound 115

Finally, (1*R*,2*S*)-2-azidocyclopentane-1-carboxylic acid (**115**) was subjected to hydrogenation conditions using 5% Pd/C and H_2 (1 atm., balloon pressure) to give the target molecule, cispentacin **72** [(1*R*,2*S*)-2-aminopentanecarboxylic acid] in 92% yields; **$[\alpha]^{25}_{D}$:** -10 (*c* 1.1, H_2O); {lit.[33] **$[\alpha]_{D}$:** -10.7 (*c* 1.0, H_2O)}. The ^{1}H NMR spectrum of cispentacin **72** showed multiplets at δ 1.82 and 2.10 corresponding to the aliphatic protons and multiplets at δ 2.85-2.96 and 3.71-3.79 for CH protons attached to the amine and acid groups respectively. The ^{13}C NMR spectrum of the compound **72** exhibited peaks at δ 50.5 and 56.1 due to the carbons attached to the amine and acid moieties respectively. The carbonyl carbon in the acid moiety showed a peak at δ

183.6 (**Fig. 21**). The analytical and spectroscopic data of the compound **72** were in complete agreement with the reported values.[41]

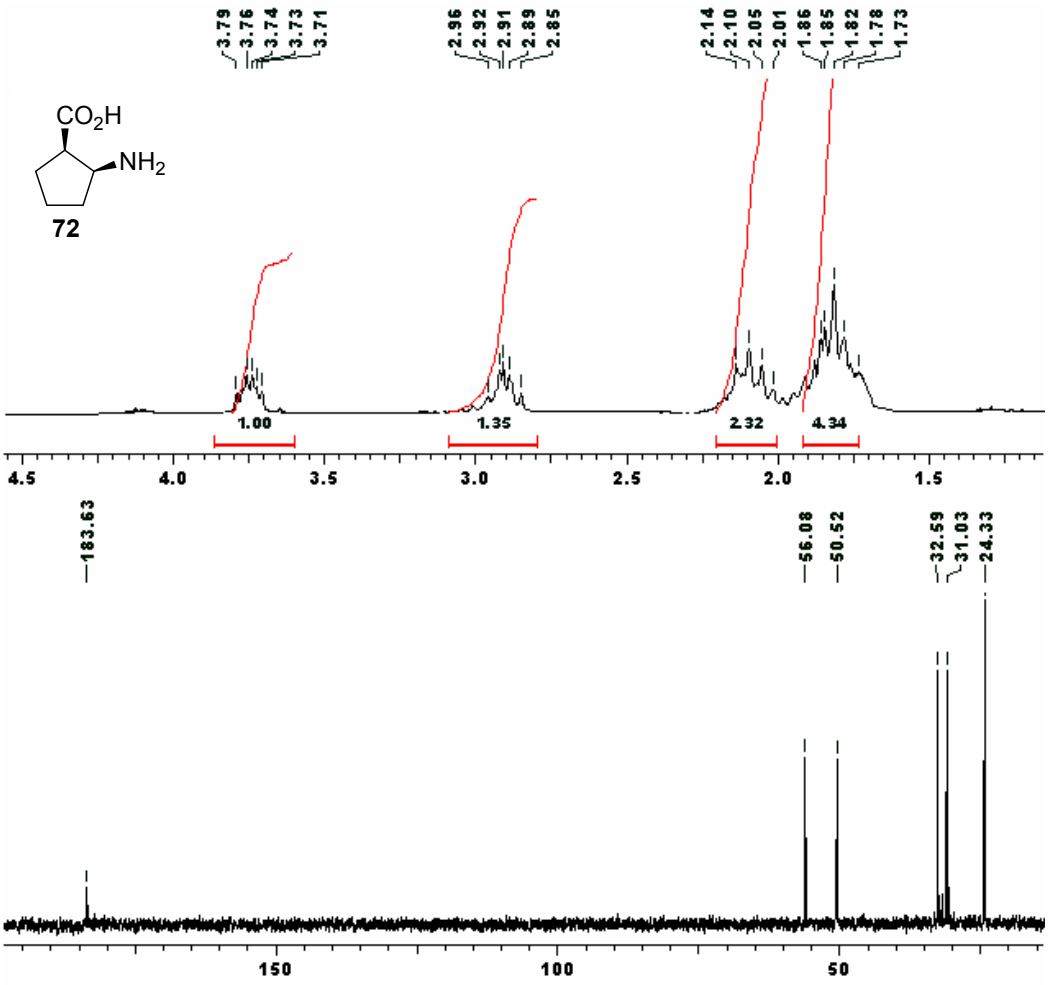


Fig. 21: ^{1}H NMR and ^{13}C NMR spectra of (1R,2S)-cispentacin (72)

3.2.5 Conclusion

In conclusion, we have achieved the synthesis of cispentacin, (1*R*, 2*S*)-**77** using Sharpless Asymmetric Dihydroxylation as the key step. The high yields and less number of steps render our approach a good alternative to the known methods.

3.2.6 Experimental Section

1-Cyclopentenylbenzene (111)

To a solution of Et_2O (100 mL) containing magnesium turnings (1.2 g, 50 mmol) and few crystals of iodine, a solution of bromobenzene (7.85 g in 25 mL Et_2O, 50 mmol)

was added drop-wise. After stirring for 15 min. at reflux temperature, the reaction mixture was cooled to 0 °C and cyclopentanone **110** (4.2 g in 25 mL Et_2O, 50 mmol) was added drop-wise. After stirring at 0 °C for 10 min. and for 1 h at 25 °C, the reaction was quenched by addition of saturated solution of NH_4Cl (40 mL) and the organic layer was separated. The aqueous layer was extracted with Et_2O (3 × 100 mL) and the combined organic layers were dried over anhyd. Na_2SO_4, evaporated to give an oily product (7.3 g, 90%) which was taken in a round bottom flask fitted with a Dean-Stark apparatus. Benzene (100 mL) was added to the flask along with catalytic amount of *p*-toulene sulfonic acid (100 mg). The mixture was refluxed for 12 h and washed with saturated $NaHCO_3$ solution, water and brine and dried over anhyd. Na_2SO_4. The solvent was distilled off under reduced pressure and the crude compound was then purified by column chromatography over silica gel using EtOAc/Pet. ether (5:95) as eluent to give 1-cyclopentylbenzene (**111**) in 92% yield.

Yield: 5.97 g (83% for 2 steps); gum; **IR** ($CHCl_3$, cm^{-1}): 667, 700, 770, 1070, 1217, 1371, 1406, 1448, 1495, 1582, 1599, 2339, 2359, 2401, 2968, 3018, 3464; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 2.01 (quintet, *J*=7.3 Hz, 2H), 2.48-2.56 (m, 2H), 2.65-2.74 (m, 2H), 6.13-6.17 (m, 1H), 7.13-7.42 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 20.7, 31.6, 38.2, 125.1, 126.7, 128.0, 128.4, 132.9, 138.2; **Analysis: $C_{11}H_{12}$** requires C 91.61, H 8.39%; found C 91.66, H 8.32%.

(1*R*,2*R*)-1-Phenyl cyclopentane-1, 2-diol (112):

To a mixture of potassium carbonate (8.3 g, 60 mmol), potassium ferricyanate (19.8 g, 60 mmol), $(DHQD)_2PHAL$ (156 mg, 0.2 mmol) and methane sulfonamide (1.902 g, 20 mmol) in water (120 mL) and *t*-BuOH (100 mL) mixture, $K_2OsO_2(OH)_4$ (15mg, 0.04 mmol) was added at 0 °C and stirred for 5 min. Then, 1-cyclopentylbenzene (**111**) (2.88 g, 20 mmol) was added in *t*-BuOH to the reaction mixture at 0 °C and

stirred for 24 h at the same temperature. The reaction was quenched by the addition of sodium sulfite (20 g) and the aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic layers were dried over anhyd. Na_2SO_4 and distilled off under reduced pressure and the crude compound was then purified by column chromatography over silica gel using EtOAc/Pet. ether (30:70) as eluent to give pure diol **112** (76% yield).

Yield: 2.7 g (76 %); gum; **$[\alpha]^{25}_D$:** -28.53 (*c* 1.08, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 667, 702, 856, 935, 1014, 1053, 1088, 1157, 1335, 1447, 1493, 1601, 2349, 2361, 2401, 2970, 3016, 3416; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.61-2.13 (m, 6H), 2.52 (br s, 1H), 2.97 (br s, 1H), 4.18 (t, *J*=7.5 Hz, 1H), 7.19-7.45 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 19.5, 30.9, 38.6, 79.6, 81.2, 125.1, 126.7, 128.0, 144.9; **Analysis: $C_{11}H_{14}O_2$** requires C, 74.13; H, 7.92%; found C, 74.09; H, 7.96%.

(1*R*,2*S*)-2-Phenylcyclopentane-1-ol (113):

(1*R*,2*R*)-1-Phenyl cyclopentane-1, 2-diol (**112**) (2 g, 11.22 mmol) and Raney nickel (20 g) were dissolved in ethanol (20 mL) and this suspension was heated to reflux. After 2 h, the reaction mixture was cooled and filtered through a pad of celite, and the celite was rinsed with ethanol (2 x 25 mL). The combined organic solvent was concentrated and the crude product was purified by column chromatography over silica gel using EtOAc/Pet. ether (15:85) as eluent to give pure alcohol **113**.

Yield: 1.45 g (80 %); gum; **$[\alpha]^{25}_D$:** -31.53 (*c* 1.2, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 667, 700, 756, 1045, 1074, 1217, 1292, 1381, 1452, 1493, 1601, 2341, 2359, 2401, 2874, 2961, 3026, 3402, 3562; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.62-1.91 (m, 6H), 2.80-2.92 (m, 1H), 4.09-1.19 (m, 1H), 7.17-7.35 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 21.7, 31.8, 33.8, 54.2, 80.1, 126.2, 127.3, 128.4, 143.4; **Analysis: $C_{11}H_{14}O$** requires C, 81.44; H, 8.70%; found C, 81.40; H, 8.66%.

(2R)-(1R,2S)-2-phenylcyclopentyl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (Mosher's ester of alcohol 113):

To a solution of *N*,*N*'-dicyclohexylcarbodiimide (DCC) (44 mg, 0.21 mmol), and 4-dimethylaminopyridine (2 mg, 10 mol%) in CH_2Cl_2 (2 mL) at 0 ºC under argon atmosphere, was added drop-wise a solution of alcohol **113** (29 mg, 0.18 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was stirred for 10 min, and (*R*)-α-methoxy-α-trifluoromethylphenyl acetic acid (46 mg, 0.196 mmol) in CH_2Cl_2 (2 mL) was added drop-wise, stirred at 0 ºC for 1 h and then at 25 ºC for 12 h. The reaction mixture was diluted with CH_2Cl_2 (50 mL), washed with saturated $NaHCO_3$ solution (50 mL), dried over anhyd. Na_2SO_4, concentrated under reduced pressure to give Mosher ester of the alcohol **113**.

Yield: 51 mg (75 %); gum; **$[\alpha]^{25}_D$:** +4.1 (*c* 1.0, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 3158, 2952, 2927, 2850, 2250, 1753, 1606, 1519, 1495, 1348, 1268, 1242, 1217, 1153, 1122, 1015, 957, 911, 735, 650; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.66-1.94 (m, 4H), 2.11-2.34 (m, 2H), 3.17-3.29 (m, 1H), 3.42 (s, 3H), 5.29-5.39 (m, 1H), 7.22-7.36 (m, 10H).

1-((1*S*,2*S*)-2-Azidocyclopentyl) benzene (114):

To a solution of (1*R*,2*S*)-2-phenylcyclopentane-1-ol (**113**) (486 mg, 3 mmol) and Et_3N (460 µL, 3.3 mmol) in CH_2Cl_2 (30 mL) at –10 ºC was added methanesulfonyl chloride (232 µL, 3 mmol) drop wise using a syringe. After stirring at -10 ºC for 0.5 h, the mixture was poured into ice water (30 mL), washed with 20 % H_2SO_4, saturated aqueous $NaHCO_3$, and brine, dried over anhyd. Na_2SO_4. The crude product (0.68 g, 94%) was then dissolved in DMF (10 mL) and sodium azide (195 mg, 3 mmol) was added to it. The reaction mixture was then heated at 80 ºC for 6 h and then quenched by addition of water. The aqueous layer was extracted with Et_2O (3 x 50 mL). The

combined organic layers were then washed with water (2 x 50 mL), dried over anhyd. Na_2SO_4, distilled off under reduced pressure and the crude product was then purified by column chromatography over silica gel using EtOAc/Pet. ether (5:95) as eluent to give azide **114** in 80 % yield.

Yield: 0.42 g (75% for 2 steps); gum; **$[\alpha]^{25}_D$:** + 45.64 (*c* 2.0, CHC_3); **IR** ($CHCl_3$, cm^{-1}): 667, 700, 758, 930, 966, 1032, 1068, 1217, 1263, 1329, 1450, 1497, 1603, 1686, 1720, 2106, 2341, 2361, 2401, 2878, 2966, 3018; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.64-2.07 (m, 6H), 3.09-3.21 (m, 1H), 4.08-4.13 (m, 1H), 7.23-7.34 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 21.9, 27.9, 31.4, 50.36, 67.3, 126.6, 128.1, 128.4, 139.4; **Analysis: $C_{11}H_{13}N$** requires C, 70.56; H, 7; N, 22.44%; found C, 70.51; H, 7.2; N, 22.48%.

(1*R*,2*S*)-2-Azidocyclopentane-1-carboxylic acid (115):

To a mixture of sodium metaperiodate (3.6 g, 17 mmol) and ruthenium chloride hydrate (60 mg, 0.3 mmol) in water (23 mL) and acetonitrile (11 mL) mixture, was added a solution of 1-((1*S*,2*S*)-2-azidocyclopentyl)benzene (**114**) (187 mg, 1 mmol) in EtOAc (11 mL) drop-wise and stirred for 18 h at 25 °C. The white precipitate formed was filtered through celite and the filtrate was extracted with EtOAc, washed with brine and evaporated under reduced pressure. The crude product was purified by column chromatography over silica gel using EtOAc/Pet. ether (60:40) as eluent to give (1*R*,2*S*)-2-azidocyclopentane-1-carboxylic acid (**115**) (60 % yield).

Yield: 93 mg (60 %); gum; **$[\alpha]^{25}_D$:** +28.8 (*c* 0.6, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 652, 743, 795, 912, 1097, 1253, 1715, 2112, 2253, 2329, 2356, 2891, 2913, 2960; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.83-2.06 (m, 6H), 2.87-2.98 (m, 1H), 4.24-4.30 (m, 1H), 8.91 (br s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 22.0, 24.9, 31.6, 49.4, 64.6, 177.6;

Analysis: $C_6H_9N_3O_2$ C, 46.45; H, 5.85; N, 27.08%; found C, 46.40; H, 5.89; N, 27.02%.

(1*R*,2*S*)-2-Aminocyclopentane-1-carboxylic acid (72):

(1*R*,2*S*)-2-Azidocyclopentane-1-carboxylic acid (**115**) (78 mg, 0.5 mmol) was dissolved in MeOH (2 mL) and 5% Pd/C (5 mg) was added to it under hydrogen atmosphere (1 atm., balloon pressure). The mixture was stirred for 1 h and the reaction mixture was filtered through a pad of celite and the celite was washed with MeOH. The combined solvents were distilled off under reduced pressure to give pure (1*R*,2*S*)-2-aminocyclopentane-1-carboxylic acid (**72**) in 92 % yield.

Yield: 59 mg (92 %); **mp:** >200 °C, (lit.[33] mp: >200 °C); **$[\alpha]^{25}_D$:** -10 (*c* 1.1, H_2O), lit.[33] **$[\alpha]_D$:** -10.7 (*c* 1.0, H_2O); **IR** ($CHCl_3$, cm^{-1}): 1073, 1122, 1311, 1337, 1386, 1410, 1505, 1580, 1623; **^{1}H NMR** (200 MHz, D_2O) δ: 1.68-1.91 (m, 4H), 2.01-2.14 (m, 2H), 2.85-2.96 (m, 1H), 3.71-3.79 (m, 1H); **^{13}C NMR** (50 MHz, D_2O) δ: 24.3, 31.0, 32.6, 50.5, 56.1, 183.6; **Analysis:** $C_6H_{11}NO_2$ C, 55.80; H, 8.58; N, 10.84%; found C, 55.88; H, 8.52; N, 10.80%.

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It is in the course of attack of the most difficult problems, without consideration of eventual applications, that new fundamental knowledge is most certainly garnered.

- Robert Robinson

Chapter IV

Synthetic Methodologies Involving Formation of C-N, C-O and C-Br Bonds

SECTION I

V_2O_5-Catalyzed 1,2-Aminobromination of Olefins

4.1.1 Introduction

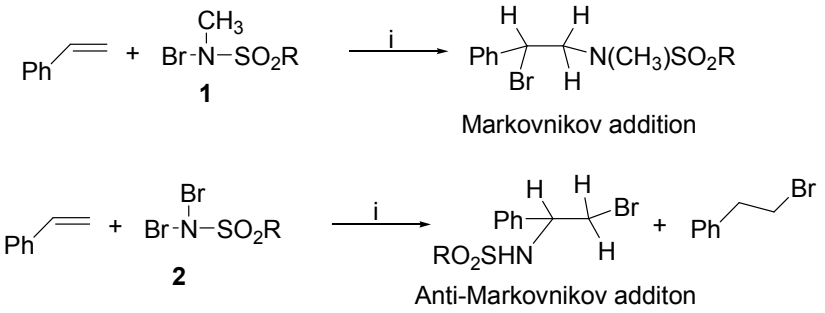
The fuctionalization of olefins by addition of two different functional groups in a single step provides access to wide range of functional group manipulation in organic synthesis. Variety of reactions such as aminohydroxylation, halohydration, haloazidation, azidohydroxylation and haloamination are some of the examples of this kind of synthetic transformation. 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]

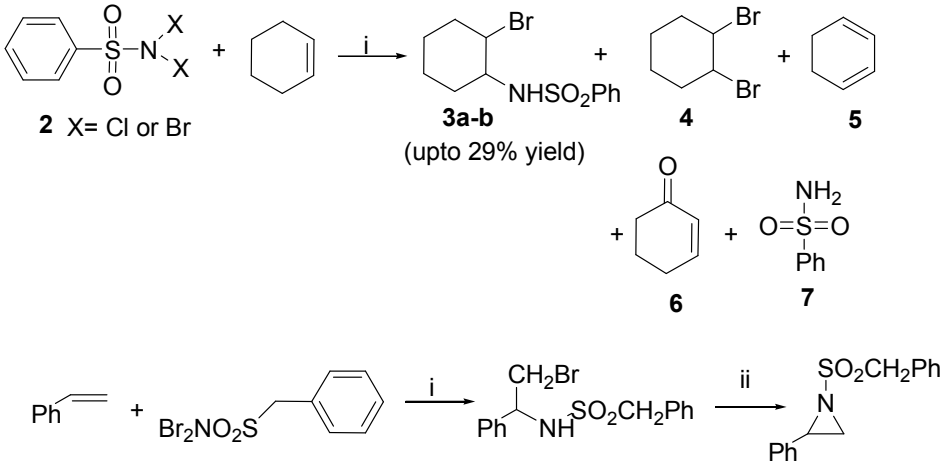
Kharasch *et al*. have studied the addition of *N*-bromo-*N*-methyl sulfonamides **1** and *N,N*-dibromosulfonamides **2** to styrene to give the corresponding bromoamine (**Scheme 1**).



Scheme 1: (i) 25 °C, stirring.

Terauchi's approach (1967)[3]

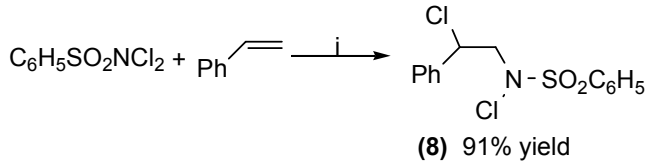
Terauchi *et al*. have studied the reaction between *N,N*-dihalosulfonamide with cyclohexene and styrene; cyclohexene gave many addition products such as *cis* and *trans*-2-halo-1-benzenesulfonamidocyclohexanes **3a** and **b**, *trans*-1,2-dihalocyclohexane (**4**), 1,3-cyclohexadiene (**5**), 1-cyclohexene-3-one (**6**) and benzene sulfonamide (**7**) (**Scheme 2**).



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

Danither's approach (1968)[4]

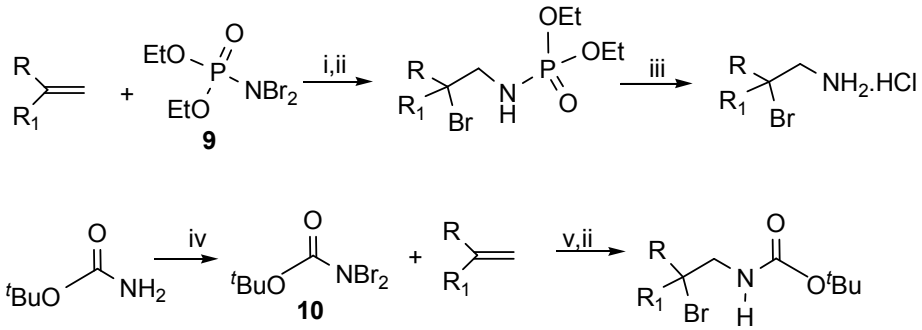
In this approach, the addition of *N,N*-dichlorosulfonamides to olefins and conjugated dienes has been examined. The reaction of these reagents with propylene and styrene gave high yields of *N*-chloro-*N*-(*β*-chloroalkyl)sulfonamides **8** which have predominantly anti-Markovnikov orientation (**Scheme 3**).



Scheme 3: (i) CH_2Cl_2, 0 - 25 °C

Zwierzak's approach (1981)[5]

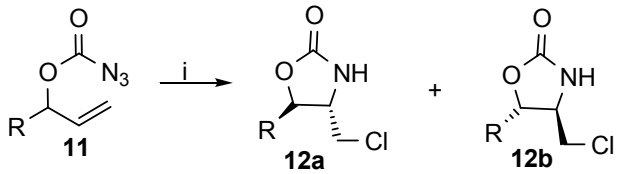
Diethyl *N,N*-dibromophosphoramidate (DBPA, **9**) and *t*-butyl *N,N*-dibromocarbamate (**10**), prepared from *t*-butyl carbamate, was added to phenyl ethylenes and terminal olefins to give *N*-bromo adducts, which were reduced *in situ* ($NaHSO_3$) to give diethyl-*N*-(*β*-bromoalkyl)phosphoramidates and β-bromo-*N*-Boc-amines respectively (**Scheme 4**). The addition followed *anti*-Markovnikov fashion.



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; (v) CH_2Cl_2, reflux.

Bach's approach (2000)[6]

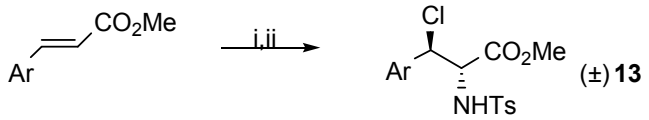
2-Alkenyloxycarbonyl azides **11** underwent an efficient intermolecular aminochlorination with TMSCl catalyzed by $FeCl_2$ to furnish the corresponding 4-(chloromethyl)-oxazolidinones **12 a-b** in 60-84% yield (**Scheme 5**).



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

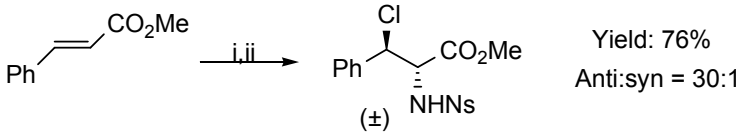
Li's approach (2001)[7]

Recently, Cu or Zn-catalyzed aminochlorination of cinnamic esters has been developed producing vicinal haloamine derivatives **13** 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**).



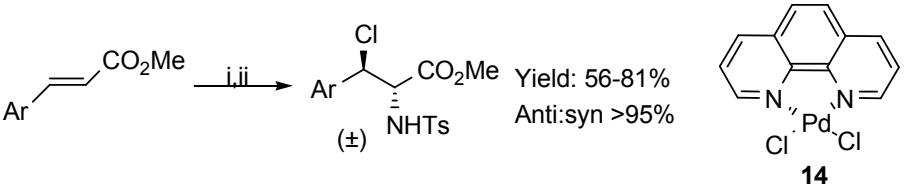
Scheme 6: (i) $TsNCl_2$, 4 Å MS, CuOTf or $ZnCl_2$ (8 mol%), CH_3CN, 25 °C; (ii) Na_2SO_3.

Same authors have developed new regio- and stereoselective aminohalogenation of cinnamic esters using the combination of 2-$NsNCl_2$/2-NsNHNa (Ns= nitrobenzenesulfonyl) as the nitrogen and chlorine sources respectively and CuOTf as catalyst (**Scheme 7**).[7b]



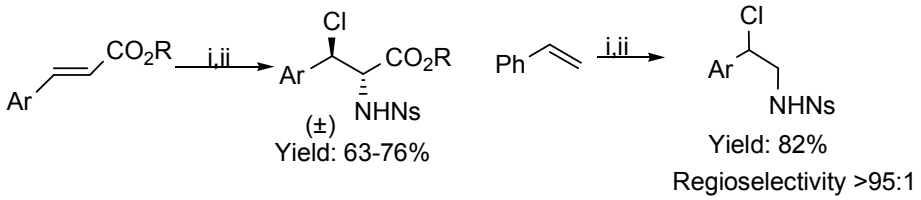
Scheme 7: (i) 2-$NsNCl_2$/2-NsNHNa, CuOTf (10 mol%), CH_3CN, 25 °C; (ii) aq. Na_2SO_3.

Li *et al*.[7c] used Pd-complex **14** for aminohalogenation of cinnamic esters has been developed using *p*-$TsNCl_2$ as the nitrogen and chlorine sources (**Scheme 8**).



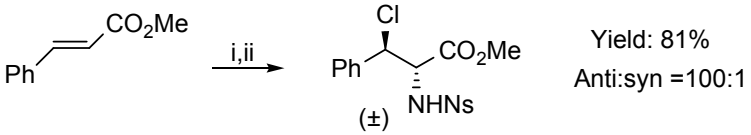
Scheme 8: (i) $TsNCl_2$, Pd-catalyst **14** (8 mol%), CH_3CN; (ii) aq. Na_2SO_3.

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



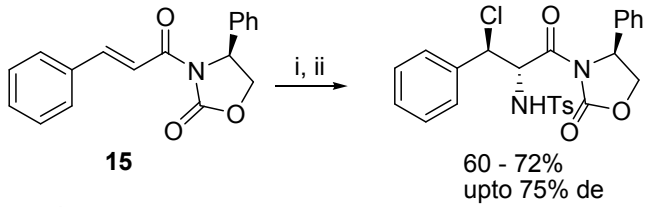
Scheme 9: (i) *o*-NsNClNa, CuOTf (10 mol%), CH_3CN; (ii) aq. Na_2SO_3.

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



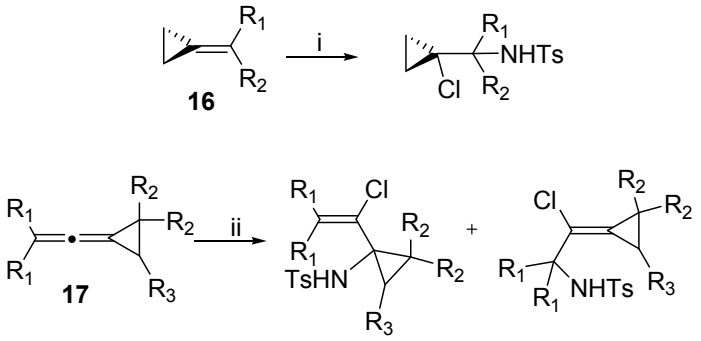
Scheme 10: (i) $TsNCl_2$, CuOTf (6 mol%), [Bmim][BF_4], CH_3CN, 25 °C; (ii) aq. Na_2SO_3.

Li *et al*.[7f] have also developed the asymmetric aminohalogentation of chiral α,β-unsaturated *N*-acyl 4-alkyloxazolidinones **15** using $TsNCl_2$ and CuOTf as the catalyst in ionic liquid [bmim][BF_4] to give the corresponding chiral aminohalogens in up to 72% yield and 75% diastereomeric ratio (**Scheme 11**).



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

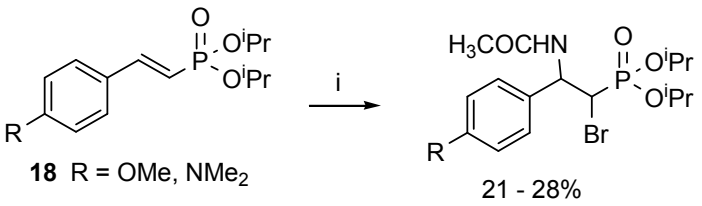
The same group has developed the aminochlorination of arylmethylene cyclopropanes and arylvinylidine cycclopropanes using $FeCl_3$ as the catalyst and $TsNCl_2$ as the nitrogen and chlorine sources (**Scheme 12**).[7g]



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]

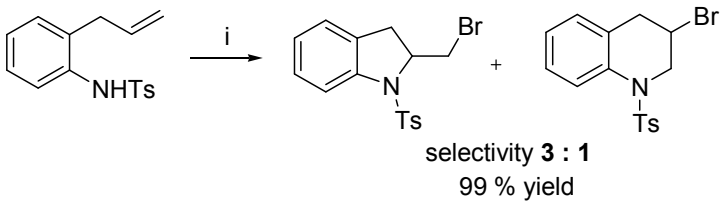
Yoon *et al.* have developed *syn*-β-amino-α-bromination of unsaturated phosphonates **18** under typical Sharpless asymmetric aminohydroxylation conditions using Os-catalyst, $(DHQD)_2$-PHAL as the ligand and excess *N*-bromoacetamide (**Scheme 13**).



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

Chemler's approach (2004)[9]

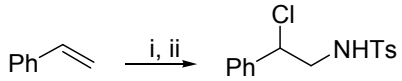
The intramolecular aminobromination and aminochlorination of olefins catalyzed by palladium (II) salts using copper (II) halides as the halogen source as well as catalyst oxidant is reported (**Scheme 14**).



Scheme 14: (i) $Pd(OCOCF_3)_2$ (10 mol%), $CuBr_2$, K_2CO_3, THF, 0 - 25 °C

Minakata's approach (2006)[10]

A new synthetic procedure for the aminochlorination of olefins for the synthesis of vicinal chloroamine derivatives using a combination of Chloramine-T and carbon dioxide (10 atm.) is described (**Scheme 15**).



Scheme 15: (i) TsN(Cl)Na, CO (10 atm.), PhH, 25 °C; (ii) Na_2SO_3 (aq.)

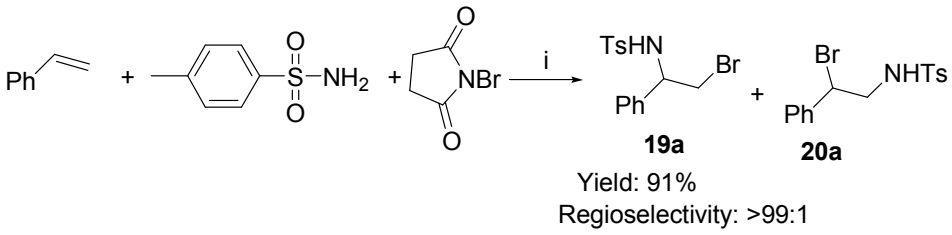
4.1.3 Present Work

4.1.3.1 Objective

Although there are many 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 mild and efficient method for the aminobromination of olefins using transition metal catalyst and *N*-bromosuccinnimide (NBS) and *p*-toluenesulfanamide ($TsNH_2$) as the bromo and amine sources respectively.

4.1.4 Results and Discussion

When styrene was treated with $TsNH_2$ and NBS (in equimolar quantities) in presence of catalytic amount of Vanadium (V) oxide (V_2O_5) in CH_2Cl_2, the corresponding bromoaminated product was obtained in very high yield with high regioselectivity (>99%) (**Scheme 16**).



Scheme 16: (i) CH_2Cl_2, V_2O_5 (10 mol%), 25 °C, 2 h.

We turned our attention to systematically explore the utility of this catalytic system for the bromoamination of olefins using $TsNH_2$ and NBS as nitrogen and bromine sources respectively. Accordingly, different metal salts were screened as catalysts for this reaction (**Table 1**).

Table 1: Bromoamination of styrene using $TsNH_2$ and NBS: Effect of catalysts[a]

Sr. No.	Catalyst	Time (h)	Product	Yield[b] (%)
1.	V_2O_5	2	**19a**	91
2.	$CuCl_2.2H_2O$	2.5	**19a**	85
3.	CuCN	4	**19a**	71
4.	$Cu(OAc)_2$	5	**19a**	65
5.	$NiCl_2.6H_2O$	8	**19a**	58
6.	$Ni(OAc)_2$	6	**19a**	64
7.	$Co(OAc)_2$	6	**19a**	65
8.	$FeCl_3$	12	**19a**	30
9.	$MnSO_4$	2	**19a**	90
10	WO_3	12	**19a:20a (1:1)**[c]	30%

(a) Reaction conditions: styrene (2 mmol), $TsNH_2$ (2 mmol), NBS (2.2 mmol), catalyst (10 mol%), CH_2Cl_2 (5 mL), 25 °C; (b) yields refer to isolated product after column chromatography; (c) determined by ^{1}H-NMR spectroscopy

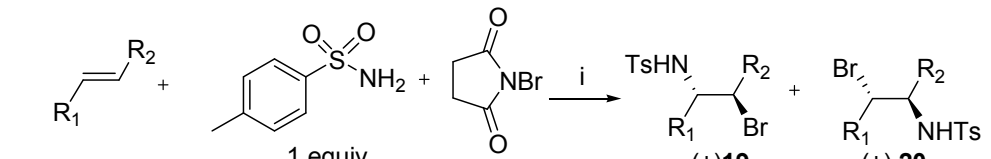
Among various metal salts screened, V_2O_5 was found to give better results. In order to screen the best solvent system, bromoamination of styrene was performed in a variety of solvents using V_2O_5 as the catalyst. The results of such solvent study are summarized in **Table 2**. Among all solvents used, dichloromethane and benzene gave the best results.

Table 2: Bromoamination of styrene: Effect of solvents[a]

No.	Catalyst	Solvent	Time (h)	Product	Yield[b] (%)
1.	V_2O_5	$CHCl_3$	3	**19a**	85
2.	V_2O_5	CH_3CN	6	**19a : 20a (1:1)**[c]	30
3.	V_2O_5	C_6H_6	3	**19a**	88
4.	V_2O_5	CH_2Cl_2	2	**19a**	91
5.	V_2O_5	CCl_4	4	**19a**	65
6.	V_2O_5	Acetone	8	**19a**	46
7.	V_2O_5	Toluene	2	**19a**	84
8.	V_2O_5	MeOH	6	**--**	0[d]

(a) Reaction conditions: styrene (2 mmol), $TsNH_2$ (2 mmol), NBS (2.2 mmol), catalyst (10 mol%), solvent (5 mL), 25 °C; (b) yields refer to isolated product after column chromatography; (c) determined by ^{1}H-NMR spectroscopy; d) starting material recovered back.

A variety of olefins were then subjected to bromoamination using CH_2Cl_2 as solvent (**Scheme 17**), the results of which are summarized in **Table 3**.

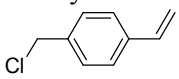
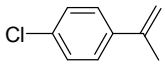
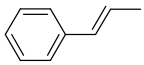
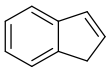
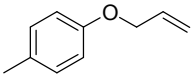


R_1 = H, Ph, 4-Cl-C_6H_4, 4-$ClCH_2$-C_6H_4, *etc*.
R_2 = H, CH_3, CH_2OH

Scheme 17: (i) V_2O_5 (5 mol%), CH_2Cl_2, 25 °C.

It can be seen from **Table 3** that a variety of olefins underwent bromoamination smoothly with $TsNH_2$ and NBS to give the corresponding bromoaminated product in excellent yields. Aromatic olefins gave better yields compared to aliphatic olefins.

Table 3: Bromoamination of olefins using V_2O_5 as the catalyst: Substrate scope[a]

No.	Olefin	Catalyst	Tine (h)	Product	*anti:syn*[c]	Yield[b] (%)
1.	Styrene	V_2O_5	2	**19a**	-	91
2.		V_2O_5	2.5	**19b**	-	92
3.		V_2O_5	2	**19c**	-	93
4.		V_2O_5	3	**19d**	>99:1	98
5.		V_2O_5	2	**19e**	>99:1	85
6.		V_2O_5	3	**19f**	>99:1	71
7.		V_2O_5	3	**19g**	>99:1	85
8.		V_2O_5	6	**19h**	-	70
9.	Styrene	V_2O_5	3	**19i**[d]	-	95[d]
10.		V_2O_5	24	**19j**	-	60

(a) Reaction conditions: olefin (2 mmol), $TsNH_2$ (2 mmol), NBS (2.2 mmol), catalyst (5 mol%), CH_2Cl_2 (5 mL), 25 °C; (b) yields refer to isolated product after column chromatography; (c) determined based on ^1H and ^{13}C NMR; (d) methane sulfonamide was used as nitrogen source.

The structures of both regioisomers were confirmed by ^1H-NMR, ^{13}C NMR and mass spectroscopy. For example, compound **19a** showed a doublet at δ 3.59 for

homobenzylic protons and a quartet at δ 4.51 for benzylic proton. Further a doublet at δ 5.33 is due to N-H proton, which is exchangeable with D_2O. Its ^{13}C NMR spectrum showed typical peaks at δ 36.39 and 58.11 for the homobenzylic and benzylic carbons respectively (**Fig. 1**).

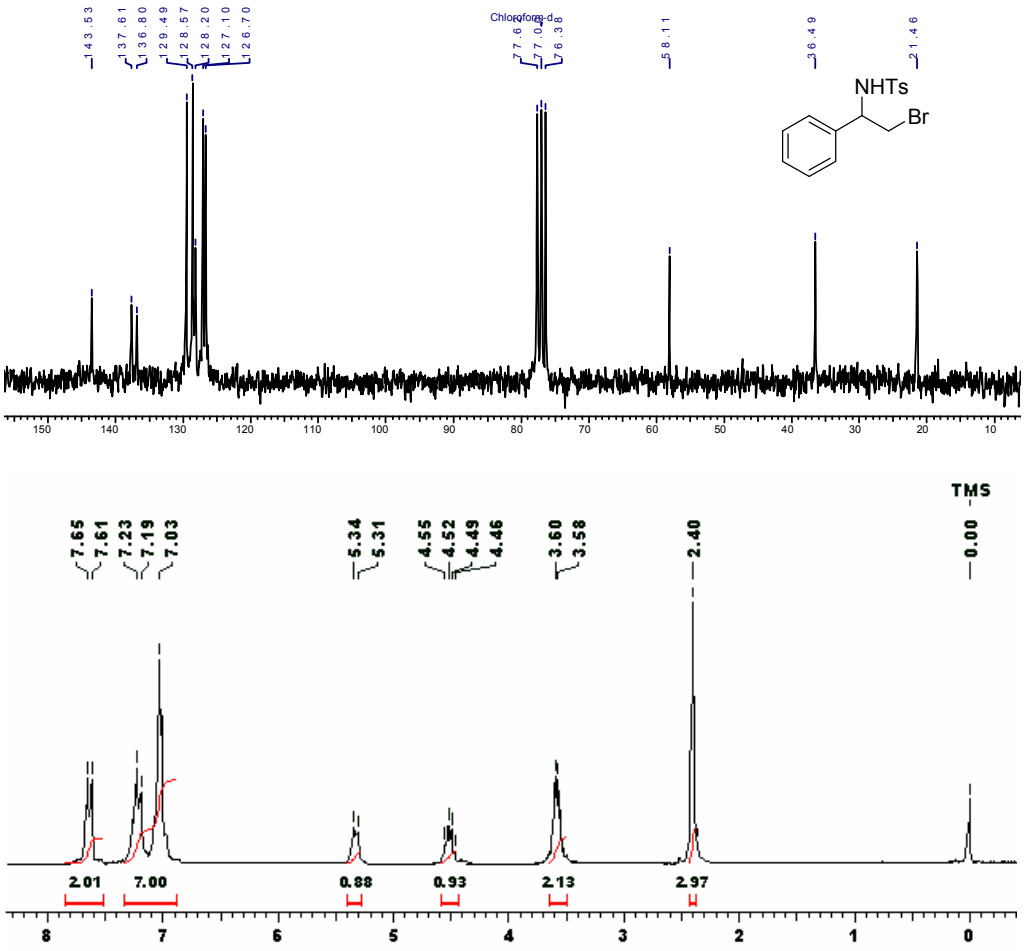


Fig. 1: ^{1}H and ^{13}C NMR spectra of bromoamine 19a

The ^{1}H-NMR spectrum of compound **20a**, regioisomer of **19a**, showed multiplets at δ 3.50-3.58 and δ 4.85-4.99 due to homobenzylic and benzylic protons respectively. On exchange with D_2O, multiplets at δ 4.85-4.99 and 3.50-3.58 simplified to a triplet and a doublet of doublet respectively, which confirms the presence of amino functionality on homobenzylic carbon. Its ^{13}C NMR spectrum showed signals at δ 49.84 and 52.45 due to homobenzylic and benzylic carbons respectively (**Fig. 2**).

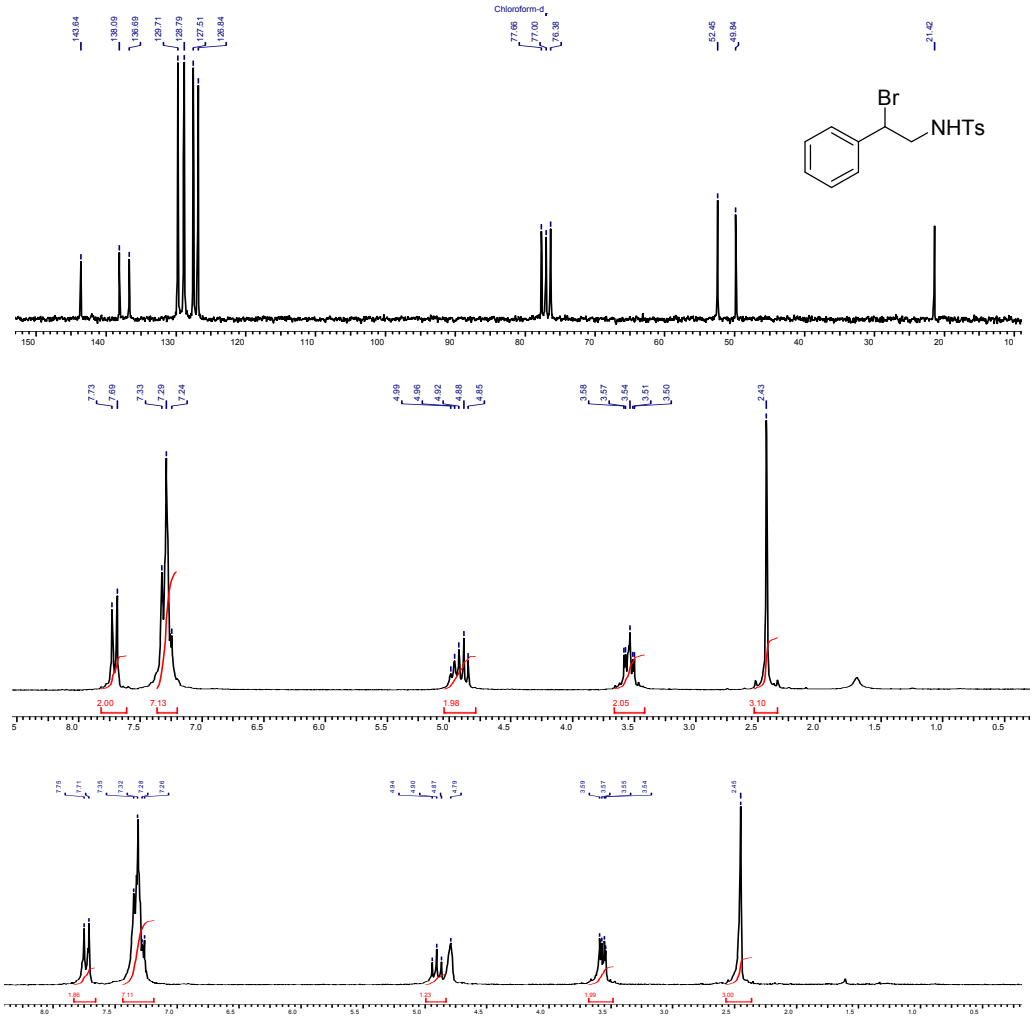
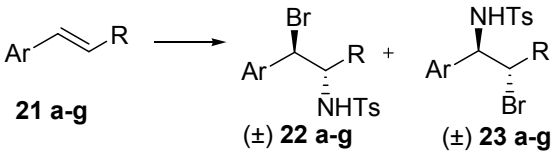


Fig. 2: ^{1}H ,^{13}C NMR and D_2O-exch. spectra of bromoamine 20a

Various α,β-unsaturated carbonyl compounds were also subjected to bromoamination (**Table 4**) using this catalytic system to give the corresponding bromoaminated products in good to excellent yields. However, it may be noted that reversal of regiochemistry was observed in the case of 4-OMe-phenyl case (**Scheme 18**).



Scheme 18: (i) V_2O_5 catalyst (10 mol%), $TsNH_2$ (1.0 equiv.), NBS (1.1 equiv.), CH_2Cl_2, 25 °C.

Table 4: Bromoamination of α,β-unsaturated carbonyl compounds.[a]

No.	Ar	R	Catalyst	Time (h)	Product	*anti:syn*[b]	Yield[c] (%)
1.	Ph	CO_2Me	V_2O_5	24	**22a**	>99:1	80
2.	4-Cl-C_6H_4	CO_2Et	V_2O_5	26	**22b**	>99:1	68
3.	Ph	COPh	V_2O_5	10	**22c**	>99:1	87
4.	4-Cl-C_6H_4	$COCH_3$	V_2O_5	28	**22d**	>99:1	61
5.	4-Cl-C_6H_4	COPh	V_2O_5	26	**22e**	>99:1	70
6.	4-OMe-C_6H_4	CO_2Et	V_2O_5	20	**23f**	>99:1	82
7.	4-OMe-C_6H_4	COPh	V_2O_5	15	**23g**	>99:1	84

(a)) Reaction conditions: olefin (2.0 mmol), $TsNH_2$ (2 mmol), NBS (2.2 mmol), catalyst (5 mol%), CH_2Cl_2 (5 ml), 25 °C; (b) determined based on ^1H and ^{13}C NMR; (c) yields refer to isolated product after column chromatography.

As can be seen from **Table 4**, a variety of α,β-unsaturated carbonyl compounds reacted smoothly to afford the corresponding bromoaminated products in good regio- and diastereoselectivity.

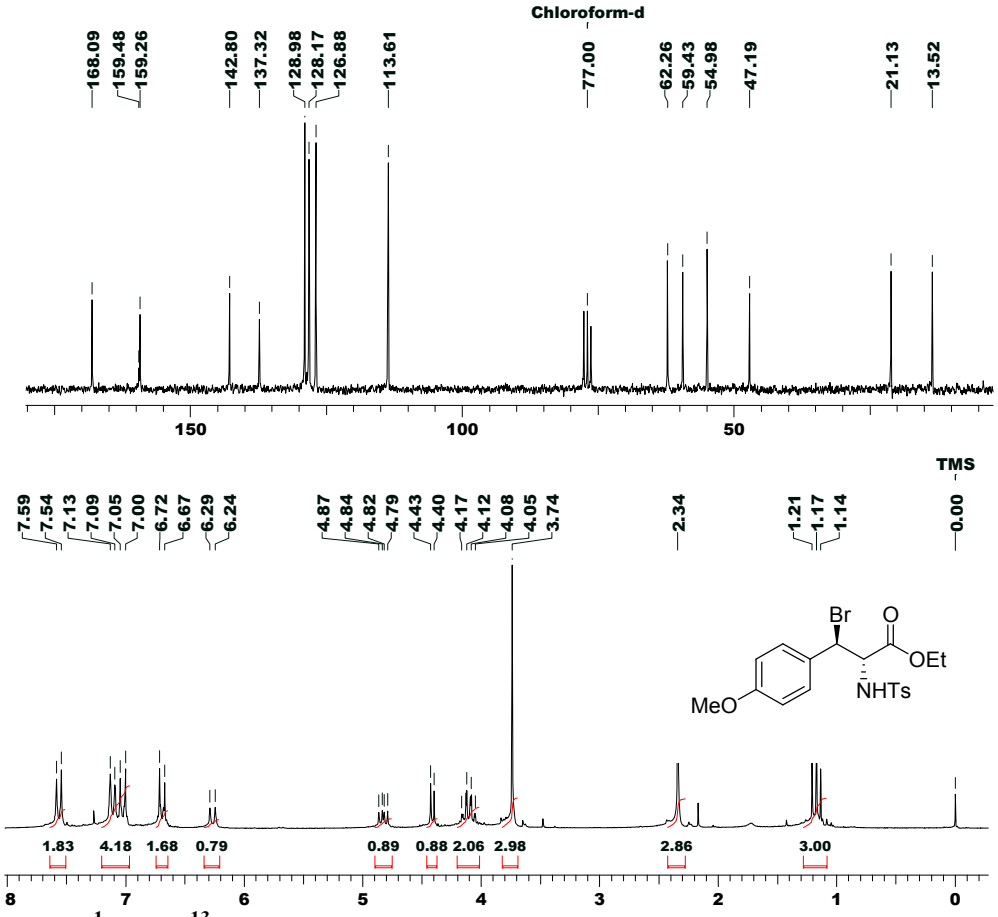


Fig. 3: ^1H and ^{13}C NMR spectra of bromoamine 23 f

The amine functionality is generally introduced at the α-position to carbonyl group except in case of **23 f** and **g** (entries 6 and 7). This may be due to the influence of electron donating nature of OMe group. The regiochemistry was confirmed by mass spectrum which showed a typical peak for CH(NHTs)COR fragment. The stereochemistry was confirmed by converting the bromoaminated compound **22a** into the corresponding known *trans*-aziridine.

The ^{1}H-NMR spectrum of **23 f** shows a doublet of doublet at δ 4.79-4.87 for C_3 proton due to coupling with C_2-H and N-H; which simplifies to a doublet after D_2O exchange, a doublet at δ 4.42 due to C_2 proton and a doublet at δ 6.27 due to N-H proton exchangeable with D_2O. Its ^{13}C-NMR showed typical peaks at δ 59.43 and 54.98 for C_2 and C_3 carbons (**Fig. 3**).

Other nitrogen sources like cyclohexyl amine, aniline and acetamide were also tried but in all these cases the reaction failed to give bromoaminated product and only the corresponding dibromides were isolated in low yields.

4.1.4.1 Mechanism

The mechanistic aspect of this reaction is not yet clear. Preliminary studies show that first $TsNH_2$ reacts with NBS to form TsNHBr (species **A**), which acts as an active species in presence of metal catalyst. The formation of TsNHBr was confirmed by isolating it and characterizing by the mass spectrometry when stoichiometric amount of $TsNH_2$ and NBS was allowed to react. The plausible mechanism for this reaction is shown in **Fig. 4**. The coordination of metal with nitrogen of species **A** weakens the N-Br bond so as to form $TsNH^{\delta-}$ $Br^{\delta+}$ species for subsequent electrophilic addition onto olefin (**B**). The electrophilic addition onto olefin results in formation of the species **C**. The metal associated $TsNH^{-}$ species as the nucleophile attacks the bromonium anion **C**; resulting in bromoaminated product and the metal

catalyst is regenerated to continue the catalytic cycle. In case of α,β-unsaturated system (R= Ar and R'= CO_2R), C_2 carbon undergoes the nucleophilic attack by $TsNH^-$ species to give the corresponding bromoaminated product. In case of *p*-OMe group, the benzylic carbocation is better stabilized with strong electron donating nature of OMe functionality so that the $TsNH^-$ attacks at C_3 position giving the other regioisomer exclusively.

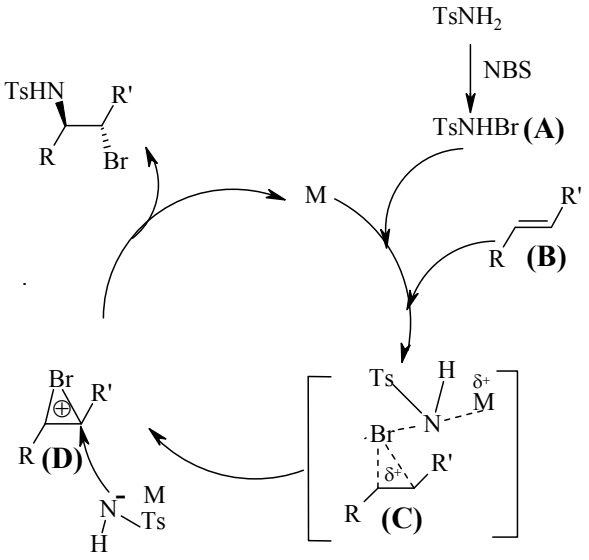


Fig. 4: Plausible mechanism for bromoamination of olefins

4.1.5 Conclusion

In conclusion, we have developed a novel method for the bromoamination of olefins catalyzed by V_2O_5 using $TsNH_2$ as nitrogen source and NBS as bromine source. The corresponding bromoaminated products were formed in excellent yields (upto 98%) with high regio- and stereoselectivity (>99%).

4.1.6 Experimental Section

General experimental procedure for bromoamination of olefins:

A mixture of olefin (2 mmol), V_2O_5 catalyst (10 mol%), $TsNH_2$ (0.342 g, 2 mmol) and NBS (0.427 g, 2.4 mmol) in CH_2Cl_2 (5 mL) was stirred at 25 °C. The

reaction was monitored by TLC. After completion the reaction, it was diluted with EtOAc (15 mL) and washed with water and brine. The organic layer was dried over anhyd. Na_2SO_4 and solvent was distilled off under reduced pressure to give crude product, which was purified by column chromatography on silica gel using pet. ether and EtOAc as eluent to afford pure product.

1-Phenyl-1-(p-toluenesulfonamido)-2-bromoethane (19a)

Yield: 91%; **mp**: 168-169 °C; **IR** ($CHCl_3$, cm^{-1}): 661, 705, 811, 935, 1093, 1165, 1325, 1334, 1461, 1596, 2854, 2923, 3257; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.39 (s, 3H), 3.58 (d, *J*=6.21 Hz, 2H), 4.57 (q, *J*=6.21 Hz, 1H), 5.38 (d, *J*=6.21 Hz, exchangeable with D_2O, 1H), 7.11-7.26 (m, 7H), 7.63 (d, *J*=9.11 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.46, 36.49, 58.11, 126.70, 127.10, 128.20, 128.57, 129.49, 136.80, 137.61, 143.53; **MS** m/z (% rel. intensity): 354 (M^+, 1), 260 (60), 155 (60), 118 (30), 104 (60), 91 (100), 77 (40), 65 (50); **Analysis**: **$C_{15}H_{16}BrNO_2S$** requires C, 50.86; H, 4.55; Br, 22.56; N, 3.95; S, 9.05%; found C, 50.83; H,4.50; Br, 22.58; N, 3.81; S, 9.12%.

1-(4-Chloromethylphenyl)-1-(*p*-toluenesulfonamido)-2-bromoethane (19b):

Yield: 92%; **mp**: 128-130 °C; **IR** ($CHCl_3$, cm^{-1}): 669, 761, 1159, 1215, 1377, 1463, 2921, 2952, 3236; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.38 (s, 3H), 3.55 (d, *J*=6.21 Hz, 2H), 4.51-4.64 (m, 3H), 5.54 (d, *J*=7.18 Hz, exchangeable with D_2O, 1H), 7.08-7.25 (m, 6H), 7.60 (d, *J*=8.24 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.42, 36.24, 45.50, 57.81, 127.14, 128.72, 129.49, 136.80, 137.47, 137.91, 143.57; **Analysis**: **$C_{16}H_{17}BrClNO_2S$** requires C, 47.72; H, 4.25; Halogen, 28.64; N, 3.48; S, 7.96%; found C, 47.62; H, 4.10; Halogen, 28.53; N, 3.41; S, 7.89%.

2-(4-Chlorophenyl)-2-(*p*-toluenesulfonamido)-3-bromopropane (19c):

Yield: 93%; **mp**: 144-146 °C; **IR** ($CHCl_3$, cm^{-1}): 565, 765, 825, 1091, 1151, 1319, 1458, 1596, 2854, 2923, 2954, 3253; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.72 (s, 3H), 2.42 (s, 3H), 3.64 (d, *J*=11.21 Hz, 1H), 3.83 (d, *J*=11.21 Hz, 1H), 5.55 (s, exchangeable with D_2O, 1H), 7.71-7.75 (m, 6H), 7.55 (d, *J*=8.24 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.39, 25.24, 42.89, 60.13, 126.88, 127.69, 128.24, 129.31, 133.68, 138.94, 139.12, 143.24; **MS** m/z (rel. intensity): 403 (M^+, 1), 388 (2), 308 (90), 231 (10), 166 (25), 155 (96), 138 (40), 125 (30), 91 (100), 65 (25); **Analysis**: **$C_{16}H_{17}BrClNO_2S$** requires C, 47.72; H, 4.25; Halogen, 28.64; N, 3.48; S, 7.96%; found C, 47.74; H, 4.18; Halogen, 28.51; N, 3.44; S, 7.83%.

(±)-*trans*-1-Phenyl-1-(*p*-toluenesulfonamido)-2-bromopropane (19d):

Yield: 98%; **mp**: 134-135 °C; **IR** ($CHCl_3$, cm^{-1}): 669, 759, 1161, 1215, 1377, 1460, 1598, 2854, 2925, 2954, 3269; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.56 (d, *J*=6.21 Hz, 3H), 2.41 (s, 3H), 4.35-4.55 (m, 2H), 5.07 (d, *J*=8.23 Hz exchangeable with D_2O, 1H), 7.05-7.35 (m, 7H), 7.52 (d, *J*=8.21 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.28, 22.05, 53.29, 62.63, 126.95, 127.62, 127.87, 128.13, 128.35, 129.16, 129.64, 136.33, 136.99, 143.09; **MS** m/z (rel. intensity): 368 (M^+, 1), 260 (20), 212 (10), 155 (45), 107 (48), 91 (100), 71 (40), 57 (50); **Analysis**: **$C_{16}H_{18}BrNO_2S$** requires C, 52.18; H, 4.93; Br, 21.70; N, 3.80; S, 8.71%; found C, 52.22; H, 4.90; Br, 21.55; N, 3.71; S, 8.68%.

(±)-*trans*-2-Bromo-1-(p-toluenesulfonamido)-indane (19e):

Yield: 85%; **mp**: 169-170 °C; **IR** ($CHCl_3$, cm^{-1}): 588, 665, 736, 923, 1081, 1153, 1331, 1377, 1463, 1595, 2872, 2923, 3245; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.46 (s, 3H), 3.11-3.24 (dd, *J*=16.14 Hz, 6.21 Hz, 1H), 3.51-3.63 (dd, *J* = 16.14 Hz, 6.21 Hz, 1H), 4.30 (q, *J*=6.14 Hz, 1H), 4.86-4.93 (dd, *J*=8.18 Hz, 6.14 Hz, 1H), 5.08 (d, *J*=8.18

Hz exchangeable with D_2O, 1H), 7.06-7.36 (m, 6H), 7.83 (d, *J*=8.42 Hz, 2H) ; **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.30, 40.91, 51.64, 66.74, 124.26, 124.67, 126.87, 127.24, 128.55, 129.38, 138.29, 139.79, 142.91; **MS** m/z (rel. intensity): 366 (M^+, 1), 286 (15), 221 925), 155 (23), 130 (100), 115 (60), 103 (50), 91 (96), 77 (30), 65 (40); **Analysis**: **$C_{16}H_{16}BrNO_2S$** requires C, 52.47; H, 4.40; Br, 21.82; N, 3.82; S, 8.76%; found C, 52.42; H, 4.28; Br, 21.83; N, 3.81; S, 8.72%.

(±)-*trans*-1-(*p*-Toluenesulfonamido)-2-bromocyclohexane (19f):

Yield: 71%; **mp**: 116-117 °C; **IR** ($CHCl_3$, cm^{-1}): 665, 813, 1093, 1159, 1326, 1448, 1598, 2862, 2929, 3276; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.21-1.39 (m, 3H), 1.64-1.80 (m, 3H), 2.12-2.40 (m, 2H), 2.43 (s, 3H), 3.20-3.30 (m, 1H), 3.81-3.95 (m, 1H), 5.40 (d, *J*=6.35 Hz, exchangeable with D_2O, 1H), 7.31 (d, *J*=9.13 Hz, 2H), 7.80 (d, *J*=9.13 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.28, 23.08, 24.77, 32.30, 35.32, 54.72, 58.18, 127.03, 129.34, 137.32, 143.23; **MS** m/z (rel. intensity): 333 (M^{+1}, 25), 210 (60), 172 (28), 155 (80), 91 (100), 81 (92), 65 (30); **Analysis**: **$C_{13}H_{18}BrNO_2S$** requires C, 46.99; H, 5.46; Br, 24.05; N, 4.22; S, 9.65%; found C, 46.92; H, 5.40; Br, 23.98; N, 4.21; S, 9.58%.

(±)-*trans*-1-(*p*-Toluenesulfonamido)-2-bromocyclooctane (19g):

Yield: 85%; **mp**: 98-99 °C; **IR** ($CHCl_3$, cm^{-1}): 669, 757, 1091, 1159, 1215, 1328, 1444, 1598, 2860, 2929, 3020, 3280; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.25-2.25 (m, 12 H), 2.43 (s, 3H), 3.42-3.52 (m, 1H), 4.02-4.10 (m, 1H), 4.97 (d, *J*=6.21 Hz, exchangeable with D_2O, 1H), 7.31 (d, *J*=8.44 Hz, 2H), 7.78 (d, *J*=8.44 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.31, 24.77, 25.21, 25.47, 31.64, 32.01, 59.32, 60.79, 127.28, 129.27, 136.77, 143.20; **MS** m/z (rel. intensity): 359 (M^{-1}, 1), 333 (10), 280 (25), 210 (40), 172 (20), 155 (65), 133 (20), 91 (100), 65 (20); **Analysis**:

$C_{15}H_{22}BrNO_2S$ requires C, 50.00; H, 6.15; Br, 22.18; N, 3.89; S, 8.90%; found C, 49.92; H, 6.10; Br, 22.04; N, 3.81; S, 8.88%.

3-(p-Toluenesulfonamido)-2-bromo-1-propanol (19h):

Yield: 70%; **gum**; **IR** ($CHCl_3$, cm^{-1}): 667, 813, 1093, 1159, 1290, 1326, 1429, 1596, 2923, 3278, 3480; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.43 (s, 3H), 3.33-3.39 (m, 2H), 3.87 (d, *J*=6.36 Hz, 2H), 4.06-4.11 (m, 1H), 5.50 (t, *J*=6.14 Hz, exchangeable with D_2O, 1H), 7.32 (d, *J*=8.43 Hz, 2H), 7.74 (d, *J*=8.43 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.35, 45.54, 52.54, 63.40, 126.77, 129.75, 136.29, 143.72; **MS** m/z (rel. intensity): 309 (M^{+1}, 1), 184 (20), 171 (40), 155 (50), 135 (20), 121 (20), 107 (80), 91 (100), 77 (15), 65 (20); **Analysis**: **$C_{10}H_{14}BrNO_3S$** requires C, 38.97; H, 4.58; Br, 25.93; N, 4.55; S, 10.40%; found C, 38.92; H, 4.50; Br, 25.88; N, 4.41; S, 10.32%.

1-Phenyl-1-methanesulfonamido-2-bromoethane (19i):

Yield: 94%; **mp**: 106-108 °C; **IR** ($CHCl_3$, cm^{-1}): 669, 757, 977, 1149, 1215, 1326, 1423, 1496, 3020, 3280; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.78 (s, 3H), 3.55-3.79 (m, 2H), 4.76-4.86 (m, 1H), 5.52 (d, *J*=8.41 Hz, exchangeable with D_2O, 1H), 7.35-7.45 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 36.58, 41.77, 58.47, 126.64, 128.59, 128.91, 138.33; **MS** m/z (rel. intensity): 277 (M^{-1}, 1), 184 (100), 118 (23), 106 (98), 91 (30), 78 (38), 65 (10); **Analysis**: **$C_9H_{12}BrNO_2S$** requires C, 38.86; H, 4.35; Br, 28.73; N, 5.04; S, 11.53%; found C, 38.82; H, 4.30; Br, 28.75; N, 4.91; S, 11.48%.

1-(3-Methylphenoxy)-2-bromo-3-(p-tolouenesulfonamido)propane (19k):

Yield: 76%; **gum**; **IR** ($CHCl_3$, cm^{-1}): 667, 754, 881, 842, 1024, 1091, 1161, 1240, 1290, 1330, 1477, 1573, 1596, 2871, 2923, 3024, 3282; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.35 (s, 3H), 2.40 (s, 3H), 3.35-3.80 (m, 2H), 4.15-4.21 (m, 3H), 5.17 (t, *J*=6.43 Hz, exchangeable with D_2O, 1H), 6.54 (d, *J*=8.42 Hz, 2H), 6.73 (s, 1H), 7.23-7.39 (m, 3H), 7.73 (d, *J*=8.42 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.36, 22.89, 46.14,

48.25, 68.91, 113.47, 117.13, 126.78, 129.65, 132.67, 136.36, 143.59, 156.72; **MS** m/z (rel. intensity): 324 (8), 219 (20), 199 (10), 188 (90), 171 (20), 155 (20), 107 (100), 91 (52), 77 (40); **Analysis**: **$C_{17}H_{20}BrNO_3S$** requires C, 51.26; H, 5.06; Br, 20.06; N, 3.52; S, 8.05%; found C, 51.32; H, 4.98; Br, 19.91; N, 3.51; S, 7.88%.

1-Phenyl-1-bromo-2-(p-toluenesulfonamido)ethane (20a):

Yield: 97%; **mp**: 113-114 °C; **IR** ($CHCl_3$, cm^{-1}): 662, 710, 1086, 1153, 1340, 1461, 1590, 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*=7.12 Hz on D_2O exchange, 2H), 7.24-7.33 (m, 7H), 7.71 (d, *J*=8.41 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.42, 49.84, 52.45, 126.84, 127.51, 128.79, 129.71, 136.69, 138.09, 143.64; **MS** m/z (rel. intensity): 354 (M^+, 1), 184 (30), 155 (35), 118 (20), 105 (20), 91 (100), 77 (20), 65 (25); **Analysis**: **$C_{15}H_{16}BrNO_2S$** requires C, 50.86; H, 4.55; Br, 22.56; N, 3.95; S, 9.05%; found C, 50.83; H,4.50; Br, 22.58; N, 3.81; S, 9.12%.

(±)-*trans*-Methyl 3-bromo-2-(p-toluenesulfonamido)-3-phenylpropionate (22a):

Yield: 80%; **mp**: 136-137 °C; **IR** ($CHCl_3$, cm^{-1}): 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*=8.42 Hz, exchangeable with D_2O, 1H), 7.22-7.29 (m, 7H), 7.63 (d, *J*=9.12 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.35, 51.20, 52.48, 61.60, 126.92, 127.10, 128.09, 128.50, 128.87, 129.38, 136.22, 143.61, 169.34; **MS** m/z (% rel. intensity): 411 (M^+, 1), 353 (1), 242 (36), 155 (55), 117 (36), 91 (100), 77 (25), 65 (30); **Analysis**: **$C_{17}H_{18}BrNO_4S$** requires C, 49.52; H, 4.40; Br, 19.38; N, 3.40; S, 7.78%; found C, 49.42; H, 4.33; Br, 19.24; N, 3.41; S, 7.72%.

(±)-*trans*-Ethyl 3-bromo-3-(4-chlorophenyl)-2-(*p*-toluenesulfonamido)propionate (22b):

Yield: 68%; **mp**: 119-121 °C; **IR** ($CHCl_3$, cm^{-1}): 676, 813, 1027, 1091, 1163, 1265, 1336, 1461, 1595, 1716, 2854, 2923, 3236; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.15 (t, *J*=6.42 Hz, 3H), 2.43 (s, 3H), 4.02 (q, *J*=6.42 Hz, 2H), 4.37-4.46 (dd, *J*=10.08 Hz and 8.14 Hz, 1H), 5.04 (d, *J*=8.14 Hz, 1H), 5.30 (d, *J*=10.08 Hz, exchangeable with D_2O, 1H), 7.19-7.32 (m, 6H), 7.60 (d, *J*=8.46 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.74, 21.42, 50.09, 61.60, 62.11, 127.10, 128.61, 129.42, 129.64, 134.71, 135.22, 136.62, 143.53, 169.12; **MS** m/z (% rel. intensity): 461 (M^+, 1), 388 (10), 307 (10), 256 (80), 155 (92), 117 (33), 91 (100), 65 (35); **Analysis**: **$C_{18}H_{19}BrClNO_4S$** requires C, 46.92; H, 4.16; Halogen, 25.03; N, 3.04; S, 6.96%; found C, 46.82; H, 4.10; Halogen, 25.23; N, 3.01; S, 6.85%.

(±)-*trans*-3-Phenyl-3-bromo-2-(*p*-toluenesulfonamido)propiophenone (22c):

Yield: 87%; **mp**: 142-144 °C; **IR** ($CHCl_3$, cm^{-1}): 662, 756, 921, 1091, 1161, 1217, 1338, 1450, 1596, 1687, 2925, 3022, 3274; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.25 (s, 3H), 5.12 (d, *J* = 8.14 Hz, 1H), 5.47-5.55 (dd, *J*=10.14 Hz and 8.14 Hz, 1H), 5.67 (d, *J*=10.14 Hz, exchangeable with D_2O, 1H), 6.98 (d, *J*=9.14 Hz, 2H), 7.25-7.59 (m, 10H), 7.78 (d, *J*=8.42 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.16, 51.45, 60.31, 125.26, 126.84, 127.21, 128.42, 128.76, 129.23, 133.97, 135.08, 136.55, 143.27, 196.54; **MS** m/z (% rel. intensity): 457 (M^+, 0.5), 377 (1), 354 (10), 288 (15), 273 (20), 155 (33), 117 (67), 105 (100), 91 (53), 77 (40), 65 (13); **Analysis**: **$C_{22}H_{20}BrNO_3S$** requires C, 57.65; H, 4.40; Br, 17.43; N, 3.06; S, 7.00%; found C, 57.52; H, 4.33; Br, 17.49; N, 2.91; S, 6.88%.

(±)-*trans*-4-(4-Chlorophenyl)-4-bromo-3-(*p*-toluenesulfonamido)2-butanone 22d):

Yield: 61%; **gum**; **IR** ($CHCl_3$, cm^{-1}): 667, 757, 1091, 1159, 1215, 1336, 1492, 1596, 1724, 3020, 3278; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.33 (s, 3H), 2.43 (s, 3H), 4.40-4.49 (m, 1H), 4.88 (d, *J*=8.21 Hz, 1H), 5.89 (d, *J*=10.13 Hz, exchangeable with D_2O, 1H), 7.04-7.17 (m, 6H), 7.41 (d, *J*=8.38 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.50, 30.43, 49.10, 64.76, 126.88, 128.64, 129.56, 134.78, 135.22, 136.40, 143.90, 205.21; **MS** m/z (% rel. intensity): 429 (M^+, 0.1), 388 (0.5), 246 (10), 226 (3), 196 (10), 155 (50), 125 (73), 91 (100), 65 (30); **Analysis**: **$C_{17}H_{17}BrClNO_3S$** requires C, 47.48; H, 3.98; Halogen, 26.78; N, 3.25; S, 7.44%; found C, 47.42; H, 3.90; Halogen, 26.65; N, 3.21; S, 7.41%.

(±)-*trans*-3-(4-Chlorophenyl)-3-bromo-2-(*p*-toluenesulfonamido)-propiophenone (22e):

Yield: 70%; **mp**: 168-170 °C; **IR** ($CHCl_3$, cm^{-1}): 667, 757, 1091, 1159, 1215, 1336, 1492, 1596, 1691, 3020, 3278; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.31 (s, 3H), 5.00 (d, *J*=6.21 Hz, 1H), 5.43-5.52 (m, 1H), 5.66 (d, *J*=10.11 Hz, exchangeable with D_2O, 1H), 6.98-7.26 (m, 6H), 7.39-7.50 (m, 5H), 7.87 (d, *J*=8.48 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.28, 49.98, 59.65, 126.66, 128.57, 128.98, 129.20, 129.89, 133.97, 134.71, 135.48, 135.63, 137.17, 143.13, 197.05; **MS** m/z (% rel. intensity): 493 (M^+, 3), 412 (6), 388 (32), 307 (50), 288 (73), 155 (33), 117 (45), 105 (100), 91 (73), 77 (73), 65 (23); **Analysis**: **$C_{22}H_{19}BrClNO_3S$** requires C, 53.62; H, 3.89; Halogen, 23.4; N, 2.84; S, 6.51%; found C, 53.42; H, 3.79; Halogen, 23.28; N, 2.81; S, 6.45%.

(±)-*trans*-Ethyl 3-(4-methoxyphenyl)-3-(p-tolylsulfonamido)-2-bromopropionate (23f):

Yeild: 82%; **mp**: 117-119 °C; **IR** ($CHCl_3$, cm^{-1}): 676, 813, 1027, 1091, 1163, 1265, 1336, 1461, 1595, 1708, 2854, 2923, 3246; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.17 (t,

J=6.31 Hz, 3H), 2.34 (s, 3H), 3.74 (s, 3H), 4.11 (q, *J*=6.31 Hz, 2H), 4.42 (d, *J*=6.25 Hz, 1H), 4.79-4.87 (dd, *J*=10.21 Hz, 6.25 Hz, 1H), 6.26 (d, *J*=10.21 Hz, exchangeable with D_2O, 1H), 6.67-6.72 (d, *J*=9.41 Hz, 2H), 7.00-7.13 (m, 4H), 7.57 (d, *J*=9.41 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.52, 21.13, 47.19, 54.98, 59.43, 62.26, 113.61, 126.88, 128.17, 128.98, 137.32, 142.80, 159.26, 168.09; **MS** m/z (% rel. intensity): 455 (M^+, 1), 410 (1), 370 (2), 290 (60), 155 (40), 134 (27), 91 (100), 65 (30); **Analysis**: **$C_{19}H_{22}BrNO_5S$** requires C, 50.00; H, 4.86; Br, 17.52; N, 3.07; S, 7.03%; found C, 49.82; H, 4.80; Br, 17.44; N, 3.11; S, 6.92%.

(±)-*trans*-3-(4-Methoxyphenyl)-3-(*p*-toluenesulfonamido)-2-bromopropiophenone (23g):

Yield: 84%; **mp**: 132-134 °C; **IR** ($CHCl_3$, cm^{-1}): 662, 756, 921, 1091, 1161, 1217, 1338, 1450, 1596, 1681, 2925, 3022, 3274; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.34 (s, 3H), 3.68 (s, 3H), 4.98-5.06 (dd, *J*=10.22 Hz and 6.21 Hz, 1H), 3.37 (d, *J*=6.21 Hz, 1H), 6.61 (d, *J*=8.41 Hz, 2H), 6.70 (d, *J*=10.22 Hz, exchangeable with D_2O, 1H), 7.06 (m, 3H), 7.36-7.56 (m, 6H), 7.78 (d, *J*=8.39 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.24, 46.64, 54.91, 59.72, 113.72, 126.99, 128.61, 128.94, 133.83, 134.38, 137.87, 142.50, 159.15, 193.30; **MS** m/z (% rel. intensity): 487 (M^+, 2), 407 (10), 290 (15), 252 (6), 208 (2), 155 (15), 105 (100), 91 (43), 77 (50), 65 (20); **Analysis**: **$C_{23}H_{22}BrNO_4S$** requires C, 56.56; H, 4.54; Br, 16.36; N, 2.37; S, 6.57%; found C, 56.42; H, 4.38; Br, 26.32; N, 2.41; S, 6.55%.

SECTION II

NBS-Catalyzed Hydroamination and Hydroalkoxylation of Activated Styrenes

4.2.1 Introduction

The most generally and extensively used chemical transformation of carbon–carbon multiple bonds is the addition of E-Nu (E=H, Br_2, Si, Hg, Sn, etc.; Nu=halogen, CN, CHO, OH, CO, COOR, NR_2, etc.) across the multiple bond. Such addition reactions are perfectly suited to fulfill today's need for green chemistry[11] because the atom economy[12] or atom efficiency[13] could be 100%. Due to the availability and price of starting materials, a significant number of industrially important processes involve such reactions. The refinement of ubiquitous olefins exemplified by C-C bond forming reactions, for example, hydroformylation, hydrocarboxylation, hydrocyanation, are prime examples for this type of reaction.

New techniques for the generation of C-N bonds are of tremendous current interest, especially reactions involving direct amination of common feedstock such as olefins and alkynes. A reaction used commercially for the generation of some amines (e.g. *tert*-butylamine) is the hydroamination of an olefin. The reaction merges perfect atom economy with thermodynamic feasibility. However, the kinetic barrier to the reaction is quite large and catalysis is a necessity. Hydroamination of unactivated olefins would provide a valuable tool for both the commodity and fine chemical industries. The catalytic addition of an organic amine R_2N-H bond to alkenes or alkynes (hydroamination) to give nitrogen containing molecules is of great interest for academic and industrial research. Since today most amines are made in multistep syntheses, hydroamination would offer the most attractive alternative synthetic route.

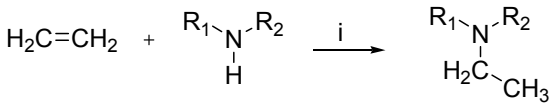
The regioselective inter- and intramolecular addition of oxygen nucleophiles to olefins has remained a longstanding challenge in organic synthesis.[14] A mild, direct coupling of an alkene with an oxygen nucleophile would be of significant value in the synthesis of natural and unnatural oxygen-containing molecules.

4.2.2 Review of Literature

Even though many reports are available for the catalytic hydroamination and hydroalkoxylation of the olefins, most of the methods suffer from the fact that many of these catalysts are difficult to synthesize, expensive, sensitive to air and moisture or highly toxic. Further, hydroamination of alkenes with sulfonamides and carbamates has been carried out generally under intramolecular fashion only.

Coulson's approach (1971)[15]

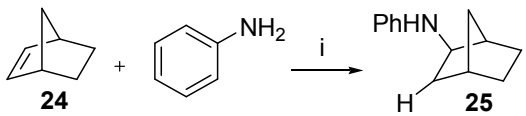
Coulson *et al.* have carried out the hydroamination of ethylene using secondary aliphatic amine and various metal complexes ($RhCl_3.3H_2O$, $RhI_3.3H_2O$, $Rh(NO_3)_3$, $IrCl_3.3H_2O$) as the catalyst (**Scheme 19**).



Scheme 19: (i) $RhCl_3.3H_2O$ (1 mol%), THF, 180 °C, 65%.

Casalnuovo's approach (1988)[16]

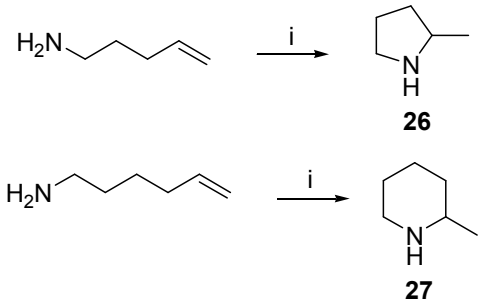
Casalnuovo *et al* have demonstrated the hydroamination of an olefin by a transition-metal-catalyzed N-H activation mechanism in a stepwise manner with an Ir(I) catalyst and aniline and norbornene (**24**) as the substrates (**Scheme 20**).



Scheme 20: (i) $Ir(PEt_3)_3Cl$, THF.

Marks' approach (1989)[17]

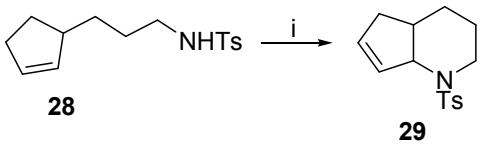
The regiospecific organolanthanide-catalyzed hydroamination/cyclization of *N*-unprotected aminoolefins resulting in the formation of substituted pyrrolidines **26** and piperidines **27** is reported (**Scheme 21**).



Scheme 21: (i) $(Cp'_2LaH_2)_2$, toluene.

Larrock's approach (1996)[18]

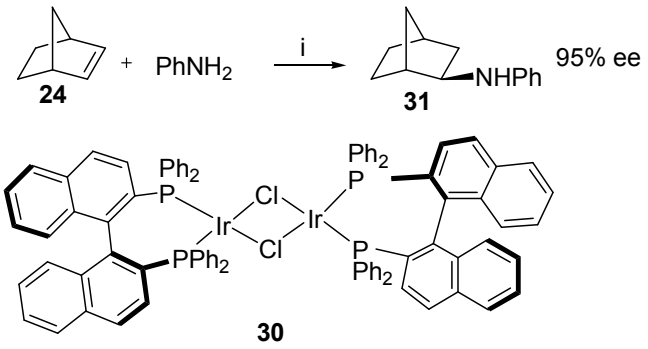
Larrock *et al.* reported the intramolecular hydroamination of olefinic tosylamides (**28**) using $Pd(OAc)_2$ as the catalyst to give the corresponding cyclized products (**29**) (**Scheme 22**).



Scheme 22: (i) 5 mol% $Pd(OAc)_2$, NaOAc, DMSO, 1 atm. O_2, 86%.

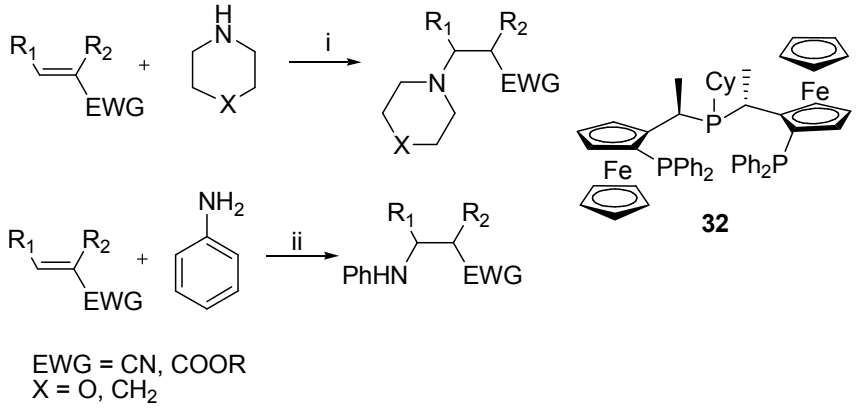
Togni's approach (1997)[19a]

Tolgni *et al*. have reported the intermolecular enantioselective olefin hydroamination catalyzed by an Ir-diphosphine system **30** for which a remarkable fluoride ion effect on both activity and selectivity was found. Selectivities of up to 95% ee and substrate to iridium ratio of 100 were obtained for the model reaction of norbornene (**24**) and aniline (**Scheme 23**).



Scheme 23: (i) 2 mol% Iridium catalyst **30**, P2-Fluoride (0.5 M in C_6H_6), 75 °C, 22%.

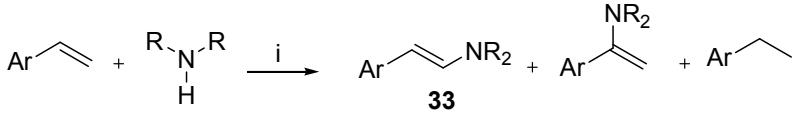
The same authors have developed the hydroamination of activated olefins using both anilines and aliphatic amines and Nickel complexes containing chiral tridentate ferrocenyl complexes **32** with enantioselectivities upto 69% (**Scheme 24**).[19b]



Scheme 24: 5 mol% $Ni(ClO_4)_2$, 32, THF, 35-99% .

Beller's approach (1997)[20]

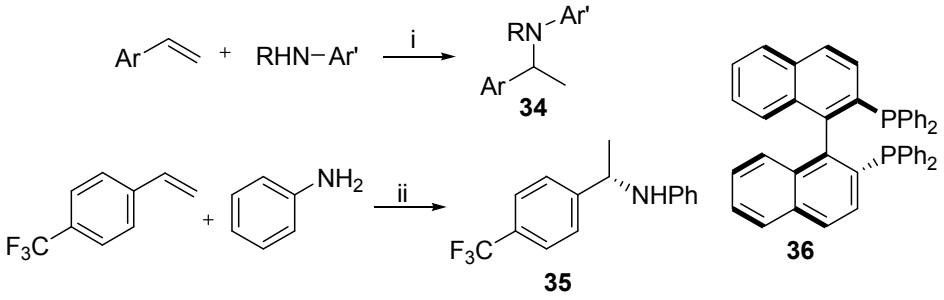
Beller *et al*. have examined the reaction of styrene with amines. In the reaction of styrene with a secondary amine, rhodium complexes with the general formula $[RhL_4]X$ (L = olefin, phosphane, X = BF;) surprisingly catalyze the selective formation of the enamines **33**, that is of the *anti*-Markovnikov products (**Scheme 25**).



Scheme 25: (i) $[Rh(cod)_2]BF_4$, PPh_3, THF, 25 °C, 14-99%.

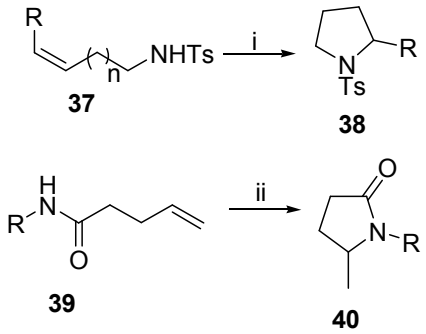
Hartwig's approach (2000)[21a]

Hartwig *et al*. reported the palladium-catalyzed hydroamination of vinylarenes using aromatic amines to give *sec*-phenethylamines **34** in the presence of acid cocatalyst. They have also demonstrated the asymmetric version using (*R*)-BINAP (**36**) as the ligand to give the hydroaminated product **35** in 81% ee (**Scheme 26**).



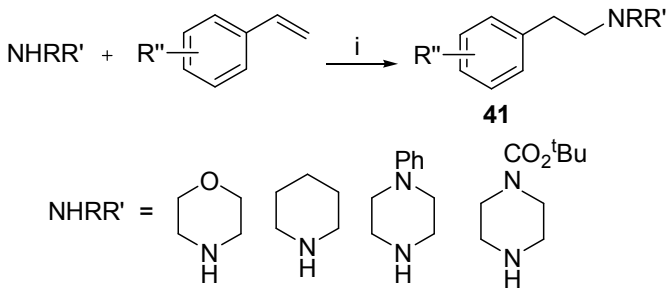
Scheme 26: (i) 2% $Pd(TFA)_2$, 3% Diphenylphosphinoferrocene (DPPF), 20% CF_3SO_3H, 100 °C; (ii) 10% [(R)-BINAP]$Pd(OTf)_2$, 25 °C, 55-99%.

The same group has developed[21b] triflic or sulfuric acid catalyzed cyclization of aminoalkenes bearing an electron-withdrawing group on the nitrogen atom in toluene. *N*-Phenylanilides **39** also underwent cyclization to form γ-lactams **40** (**Scheme 27**).



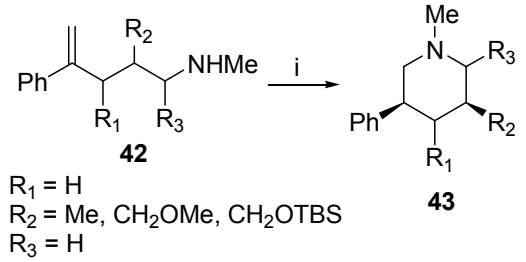
Scheme 27: (i) 20 mol% CF_3SO_3H or H_2SO_4, toluene, 100 °C, 51-99%; (ii) 1 eq. CF_3SO_3H, toluene. 100 °C, 99%.

Hartwig *et al*.[21c] have also reported that ruthenium complexes catalyzed the *anti*-Markovnikov hydroamination of vinylarenes with exquisite chemo- and regioselectivity. Reactions of cyclic or acyclic, functionalized or unfunctionalized secondary amines with vinylarenes form terminal amines **41** (**Scheme 28**).



Scheme 28: (i) 5 mol% Ru(COD)(2-methallyl)$_2$, 7 mol% 1,5-bis-diphenylphosphinopentane (DPPPent), 10 mol% CF_3SO_3H, dioxane, 100 °C, 40-91%.

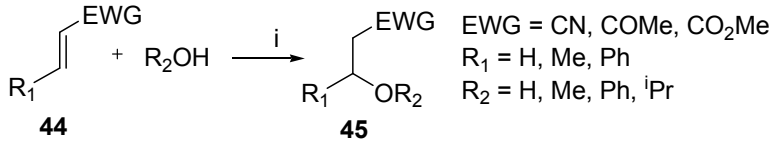
The same group has also developed[21d] rhodium-catalyzed intramolecular hydroamination of aminoalkenes 42 bearing substituents α, β, and γ to the nitrogen on the alkyl chain to form substituted piperidines 43. These reactions occurred with high diastereoselectivity for formation of the *cis* product **(Scheme 29)**.



Scheme 29: (i) 5 mol% [Rh(COD)(DPPB)]BF_4, THF (1M), 70 °C.

Toste's approach (2003)[22]

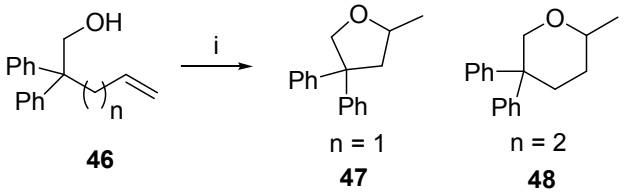
Hydroalkoxylation of various α,β-unsaturated systems **44** using trimethyl phosphine as the catalyst and several alcohols and phenols as the alkoxy source is described. Enones, crotonates and α,β-unsaturated nitriles underwent hydroalkoxylation to obtain the products **45** in excellent yields (**Scheme 30**).



Scheme 30: (i) 5 % PMe_3, 59-85%.

Widenhoefer's approach (2004)[23]

Widenhoefer *et al*. have developed Platinum-catalyzed intramolecular hydroalkoxylation of γ and δ hydroxyl olefins **46** to give the corresponding substituted tetrahydrofurans **47** and tetrahydropyrans **48** respectively in excellent yields (**Scheme 31**).

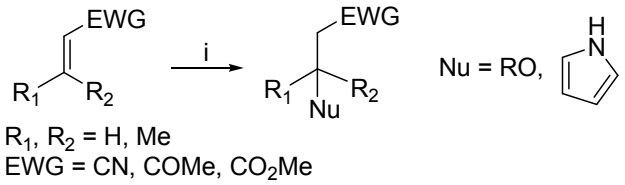


46 **47** **48**

Scheme 31: 1 mol% $[PtCl_2(H_2C{=}CH_2)]_2$, 2 mol% $P(4\text{-}C_6H_4CF_3)_3$, $Cl_2CHCHCl_2$, 70 °C, 47-98%.

Connon's approach (2005)[24]

Substoichiometric loadings of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) catalyze the efficient 1,4-addition of alcohols (hydroalkoxylation) and non-nucleophilic amines such as pyrrole to α,β-unsaturated compounds (**Scheme 32**).



R_1, R_2 = H, Me
EWG = CN, COMe, CO_2Me

Scheme 32: (i) 5 % DBU, NuH (3.6 M), 49-95%.

4.2.3 Present Work

4.2.3.1 Objective

Although there are many methods available in the literature for hydroamination of olefins, they suffer from certain drawbacks like low yields, multi-step reaction sequences, cumbersome experimental procedures many of the catalysts employed are difficult to synthesize, expensive, sensitive to air and moisture or highly

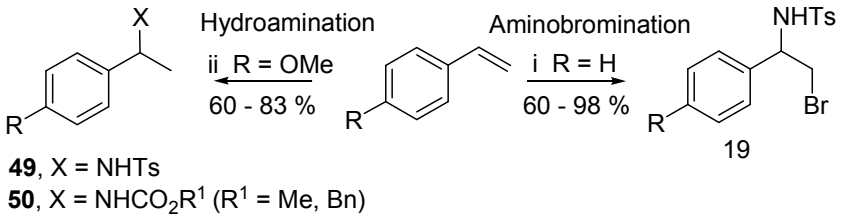
toxic. Hence, there arises a necessity to develop an efficient metal-free process for the hydroamination and hydroalkoxylation of olefins.

While screening various olefinic substrates for the aminobromination process reported in the previous section, we found that 4-methoxystyrene took a different course and furnished the unexpected hydroaminated product 49 in a Markovnikov fashion instead of the bromoaminated product 19, the results of which are described in this section.

4.2.4 Results and Discussion

4.2.4.1 Hydroamination

In continuation of this work, we present herein *N*-bromosuccinimide (NBS) catalyzed intermolecular hydroamination of activated styrenes using sulfonamides and carbamates as mild nucleophiles to produce hydroaminated products 49 and 50 respectively **(Scheme 33)**.



Scheme 33:

When 4-methoxystyrene was treated with either $TsNH_2$ or benzyl carbamate (1.0 equiv.) in the presence of catalytic amount of NBS (20 mol%) at 25 °C in CH_2Cl_2, the corresponding hydroaminated product **49** or **50**, was obtained in good yields with excellent regioselectivity (Markovnikov fashion). We then turned our attention to systematically explore the utility of this catalytic system for the hydroamination of activated styrenes using $TsNH_2$ as the nitrogen source. Accordingly, different bromine-based catalyst systems were screened as catalysts for this reaction (**Table 5**). Thus, various halogen-based catalyst systems like *N*-

bromoacetamide, pyridinium bromide perbromide, *N*-chlorosuccinimide, *etc* have been screened for the hydroamination of 4-methoxystyrene. Although pyridinium bromide perbromide and *N*-bromoacetamide have displayed comparable activity, activity of NBS is found to be superior, as it provides excellent yields of the hydroaminated product. Lowering the NBS concentration below 20 mol% led to a sharp decline in the yield (entry 1).

Table 5: Effect of catalyst on hydroamination of 4-methoxystyrene with $TsNH_2$.

entry	catalyst (mol%)	solvent	yield of **49**(%)[a]
1	*N*-bromosuccinimide (10)	CH_2Cl_2	60
2	*N*-bromosuccinimide (20)	CH_2Cl_2	82
3	*N*-bromosuccinimide (20)	CH_3CN	68
4	*N*-bromosuccinimide (20)	THF	18
5	*N*-bromoacetamide (20)	CH_2Cl_2	65
6	*N*-chlorosuccinimide (20)	CH_2Cl_2	25
7	pyridinium bromide perbromide (20)	CH_2Cl_2	70
8	zinc bromide (20)	CH_2Cl_2	0

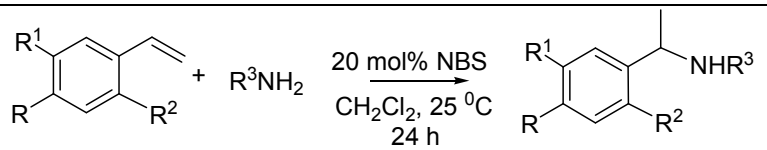
[a] Isolated yield after column chromatographic purification.

The NBS-catalyzed hydroamination reactions were generally conducted at ambient temperatures in methylene chloride as other solvents such as acetonitrile and THF were found to be less effective. Increase of temperatures (50 °C), for enhancing the rate, had deleterious effect on the yield and selectivity of the process. Other catalysts like $ZnBr_2$, I_2, etc. have failed to give the hydroaminated products. In absence of NBS, no product formation was observed even after 78 h of stirring.

We have applied the optimized procedure of NBS-catalyzed hydroamination to a variety of electron-rich styrenes to determine the scope of the hydroamination process and the results are presented in **Table 6**. As can be seen, both sulfonamides and carbamates were successfully employed as the amine sources to produce the corresponding amino derivatives in high yields. Activated styrenes with variety of substitutions like Me, Cl, OBn, O^{i}Pr, SMe, etc. on the aromatic ring were subjected to

the NBS-catalyzed hydroamination to obtain the corresponding hydroaminated product in excellent yields.

Table 6: NBS-catalyzed hydroamination of activated styrenes using sulfonamides and carbamates[a]



49 R^3 = Ts
50 R^3 = Cbz, CO_2Me

entry	R	R^1	R^2	R^3NH_2	Product	yield (%)[b]
1	OMe	H	H	$TsNH_2$	**49a**	82
2	OMe	H	H	$CbzNH_2$	**50b**	80
3	OMe	H	H	$MeOCONH_2$	**50c**	74
4	OEt	H	H	$TsNH_2$	**49d**	75
5	OEt	H	H	$CbzNH_2$	**50e**	60
6	OBn	H	H	$TsNH_2$	**49f**	78
7	SMe	H	H	$TsNH_2$	**49g**	83
8	SMe	H	H	$MeOCONH_2$	**50h**	80
9[c]	OMe	H	Me	$TsNH_2$	**49j**	60
10	OMe	Cl	H	$TsNH_2$	**49k**	78
11	OMe	Cl	H	$MeOCONH_2$	**50l**	80
12	O^iPr	H	H	$TsNH_2$	**49m**	66
13	OCp[d]	H	H	$TsNH_2$	**49n**	62

[a] all reactions were done at 25 ^oC for 24 h unless otherwise mentioned. [b] Isolated yield after column chromatographic purification. [c] Reaction was performed for 48 h. [d] Cp = cyclopentyl

However, the reaction of 2-methyl-4-methoxystyrene with $TsNH_2$ proceeded slowly (48 h) yielding 60% of the hydroaminated product (entry 9). Surprisingly, the methodology fails in case of aliphatic olefinic and electron deficient styrenic substrates as well as amines as nucleophiles. Also various amine sources like $TsNH_2$, $CbzNH_2$, $MeOCONH_2$ have been subjected successfully to the hydroamination. The structures of the hydroaminated products were confirmed by ^1H NMR and ^{13}C NMR spectroscopy.

Example 1: For instance, the ^1H NMR spectrum of **49a** showed a doublet at δ 1.38 for the homo benzylic methyl group and two singlets at δ 2.38 and 3.74 for the methyl

groups present in the tosyl and methoxy moieties respectively. Further, a doublet at δ 5.29 and a quintet at δ 4.40 are due to N-H proton and benzylic proton respectively. Its ^{13}C NMR spectrum showed typical peaks at δ 52.89 and 54.95 for the benzylic and methoxy carbons respectively (**Fig. 5**).

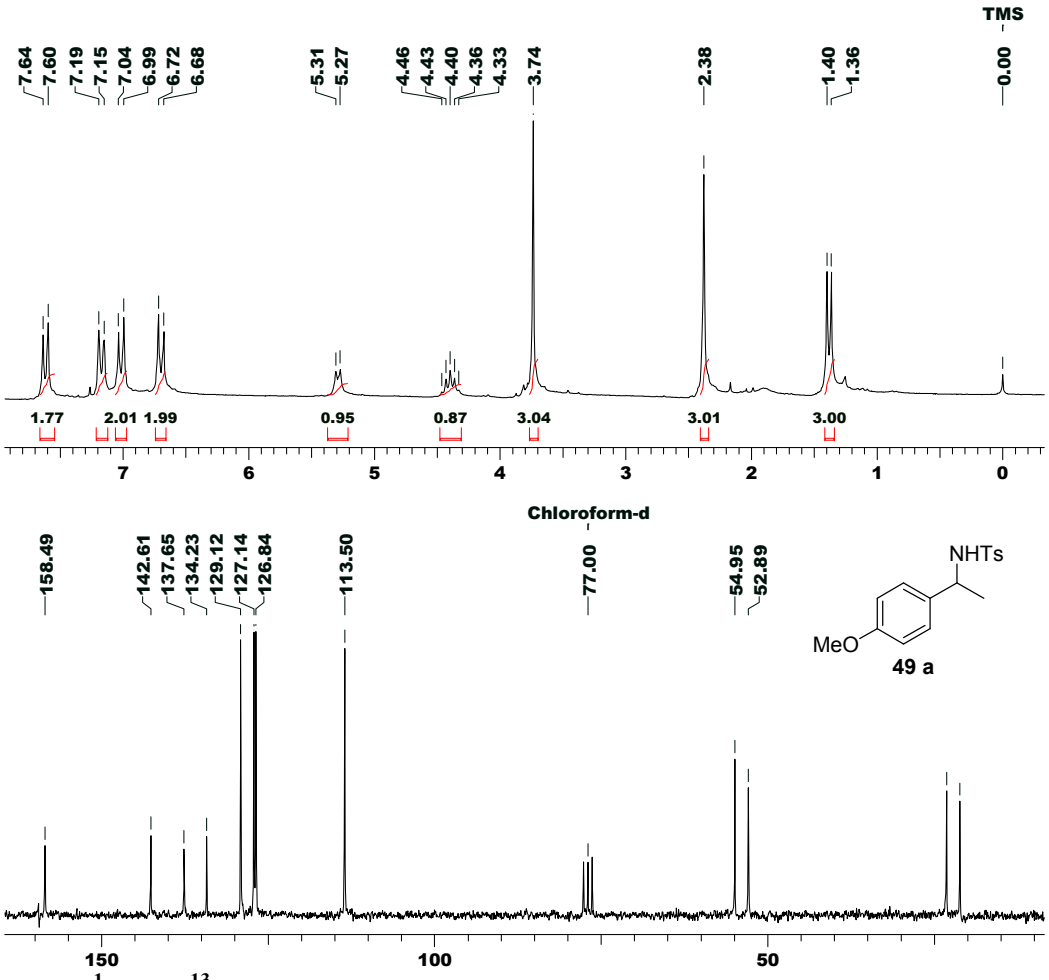


Fig. 5: ^{1}H and ^{13}C NMR spectra of 49a

Example 2: The ^{1}H NMR spectrum of **50b** showed a doublet at δ 1.45 and a singlet at δ 5.08 for the homo benzylic methyl and methylene of the Cbz moiety respectively. The methoxy and the N-H protons have shown two singlets at δ 3.77 and 5.06 respectively. Its ^{13}C NMR spectrum showed characteristic peaks at δ 49.76, 54.72 and

158.31 corresponding to the benzylic, methoxy and the Cbz-carbonyl carbons respectively (**Fig. 6**).

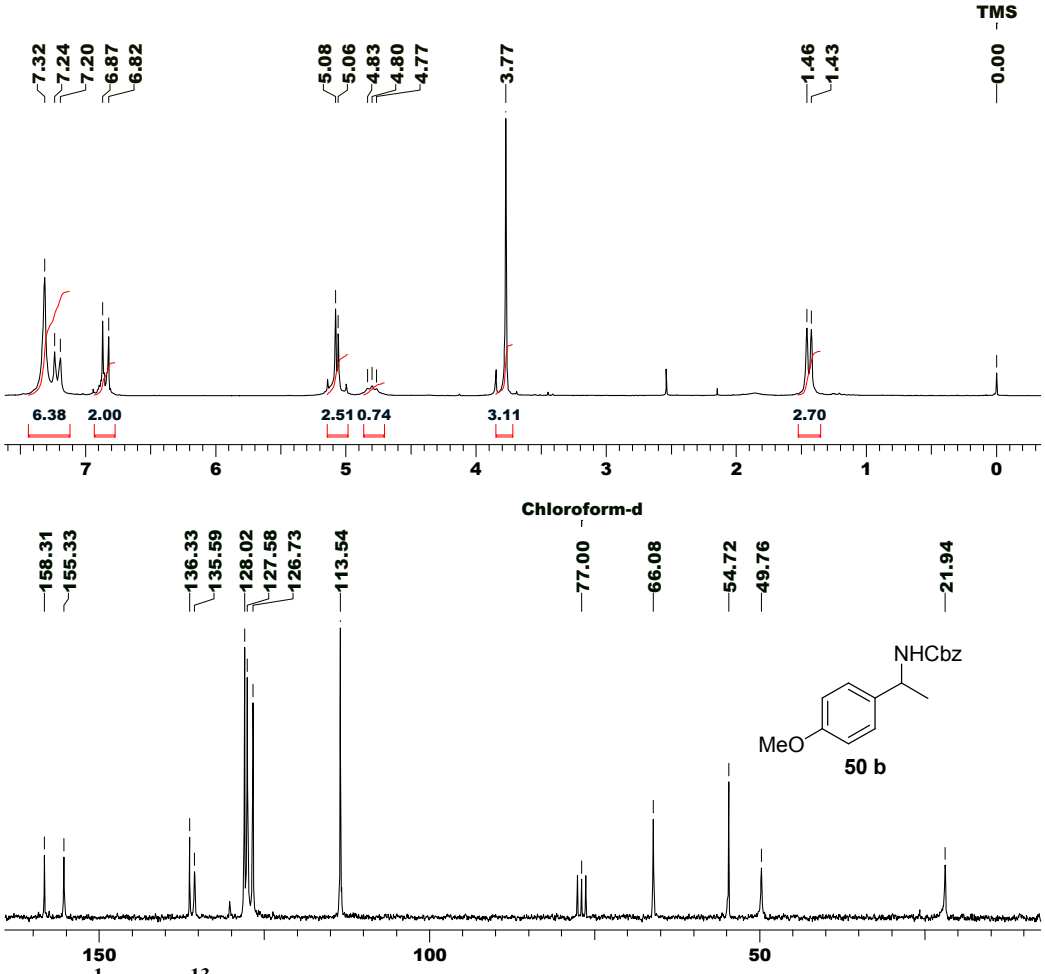


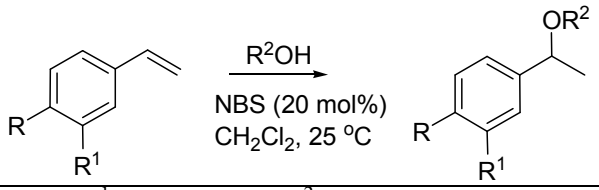
Fig. 6: ^{1}H and ^{13}C NMR spectra of 50b

4.2.4.2 Hydroalkoxylation

We further extended the scope of this methodology by subjecting a variety of alcohols as nucleophiles for the hydroalkoxylation of electron-rich styrenes (**Table 7**). Activated styrenes with variety of substitutions like SMe, Cl, etc. on the aromatic ring were subjected to the NBS-catalyzed hydroalkoxylation to obtain the corresponding hydroalkoxylated product in excellent yields. Various alcohols like benzylalcohol, methanol, allylalcohol, propargylalcohol etc. have been subjected to the

hydroalkoxylation and all of them underwent hydroalkoxylation to give the respective products in excellent yields.

Table 7: NBS-catalyzed hydroalkoxylation of activated styrenes using alcohols as nucleophiles



entry	R	R^1	R^2	Product	yield (%)[a]
1	OMe	H	benzyl	**51a**	85
2	OMe	H	methyl	**51b**	80
3	SMe	H	benzyl	**51c**	88
4	SMe	H	methyl	**51d**	85
5	OMe	Cl	benzyl	**51e**	81
6	OMe	H	allyl	**51f**	83
7	OMe	H	propargyl	**51g**	80

[a]Isolated yield after column chromatographic purification.

The ^{1}H NMR spectrum of **51b** showed singlet at δ 3.15 and doublet at 1.39 corresponding to the methoxy and the homobenzylic methyl groups respectively. The singlet at δ 3.78 and the quartet at δ 4.19 correspond to the methoxy group on the aromatic ring and the benzylic protons respectively (**Fig. 7**).

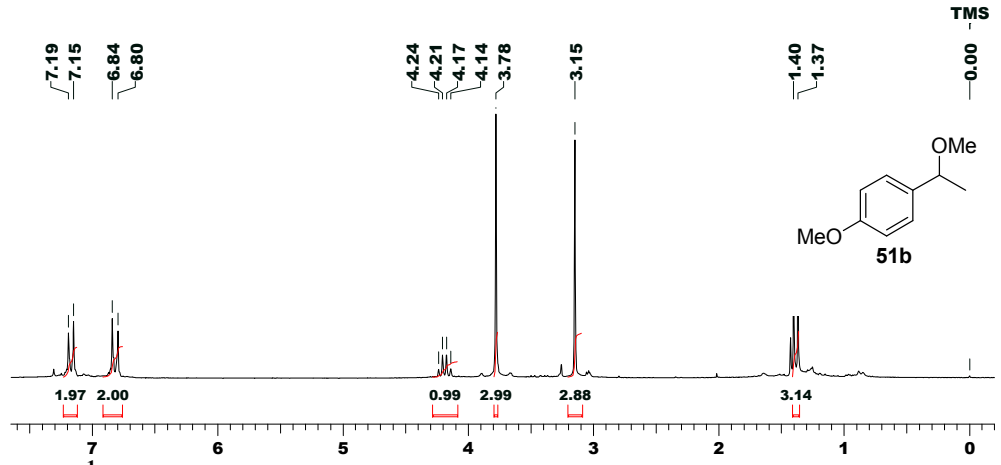


Fig. 7: ^{1}H NMR spectrum of 51b

Its ^{13}C NMR spectrum showed typical peaks at δ 54.50 and 55.59 for the benzylic and methoxy carbons respectively (**Fig. 8**).

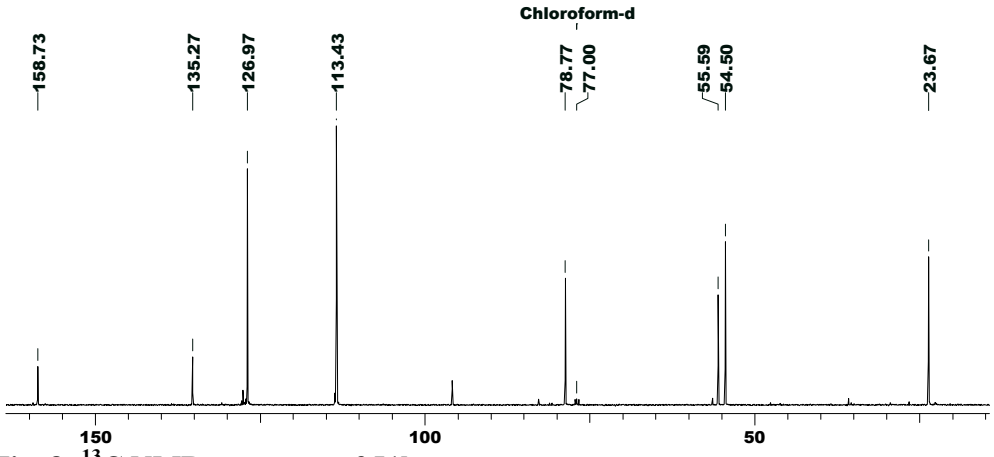


Fig. 8: ^{13}C NMR spectrum of 51b

4.2.4.3 Mechanism

The proposed mechanistic pathway for the NBS-catalyzed hydroamination process is shown in **Fig. 9**, based on the following observations.

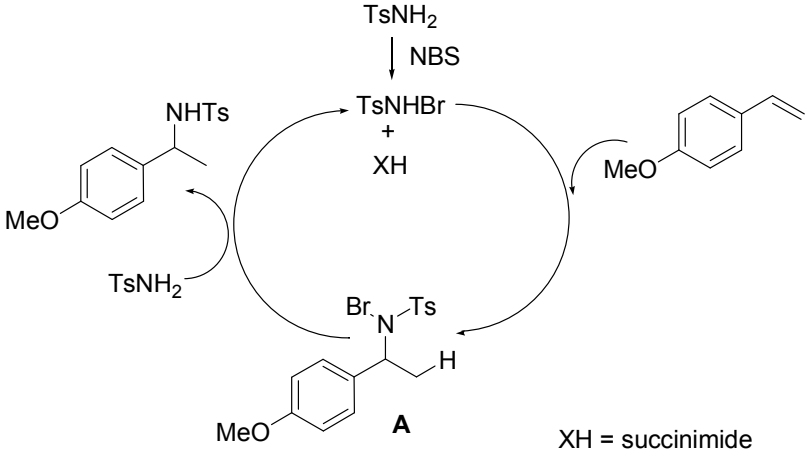


Fig. 9: Mechanism for the hydroamination of activated styrenes

When $TsNH_2$ was reacted with NBS (in equimolar proportions), the species TsNHBr was formed and characterized by (i) isolation, (ii) ^{1}H and ^{13}C NMR and (iii) MS. Subsequently, the interaction between TsNHBr and 4-methoxystyrene leads to the

protonation of styrenic double bond in Markovnikov fashion [as evidenced by the *in situ* UV studies, which showed λ_{max} at 590 nm typical of benzylic carbocation species[25] and by *in situ* ^{1}H NMR studies, which showed a doublet at δ 1.39 (*J*=6.6 Hz) for the methyl group]. Finally, the regeneration of the species TsNHBr takes place by the reaction of intermediate **A** with $TsNH_2$ thereby giving the hydroaminated product. Further, involvement of radical species in the reaction was ruled out as the reaction proceeded smoothly in presence of TEMPO free radical.

4.2.5 Conclusion

In conclusion, we have developed a new, practical and "metal-free" procedure for the hydroamination and hydroalkoxylation of activated styrenes catalyzed by NBS at ambient conditions using sulfonamides, carbamates and alcohols as nucleophiles. The corresponding products were formed in excellent yields with high regio-stereoselectivity (>99%).

4.2.6 Experimental Section

General experimental procedure for the Hydroamination of activated styrenes:

A mixture of olefin (2 mmol), *N*-bromosuccinimide (20 mol%), $TsNH_2$ (342 mg, 2 mmol) was taken in CH_2Cl_2 (4 mL) and stirred at 25 °C. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was concentrated under reduced pressure to give crude product, which was purified by column chromatography over silica gel (60-120 mesh) using pet. ether and EtOAc as eluent to afford pure product.

1-(4-Methoxyphenyl)-1-(*p*-toluenesulfonamido)ethane (49a):

Yield: 82%; **mp:** 87-88 °C; **IR** ($CHCl_3$, cm^{-1}): 669, 760, 1038, 1090, 1159, 1217, 1338, 1508, 1608, 2935, 2976, 3018; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.38 (d, *J*=6.8 Hz, 3H), 2.38 (s, 3H), 3.73 (s, 3H), 4.40 (quintet, *J*=6.8 Hz, 1H), 5.29 (d, *J*=6.8 Hz,

1H), 6.70 (d, *J*=8.8 Hz, 2H), 7.02 (d, *J*=8.8 Hz, 2H), 7.17 (d, *J*=8.3 Hz, 2H), 7.62 (d, *J*=8.3 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 23.2, 23.2, 52.9, 54.9, 113.5, 126.8, 127.1, 129.1, 134.2, 137.7, 142.6, 158.5; **Analysis: $C_{16}H_{19}NO_3$ S** requires C, 62.93; H, 6.27; N, 4.59; S, 10.5%; found C, 62.88; H, 6.21; N, 4.54; S, 10.44%.

1-(4-Methoxyphenyl)-1-(benzyloxycarbonylamino)ethane (50b):

Yield: 80%; **mp:** 78-79 °C; **IR** ($CHCl_3$, cm^{-1}): 667, 769, 831, 910, 1057, 1245, 1338, 1456, 1514, 1612, 1705, 2637, 2935, 3010, 3340, 3441; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.45 (d, *J*=6.8 Hz, 3H), 3.77 (s, 3H), 4.8 (t, *J*=6.8 Hz, 1H), 5.07 (d, *J*=4.4 Hz, 2H), 6.85 (d, *J*=8.8 Hz, 2H), 7.22 (d, *J*=8.3 Hz, 2H), 7.32 (s, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 21.9, 49.8, 54.7, 66.1, 113.5, 126.7, 127.6, 128.0, 135.6, 136.3, 155.3, 158.3; **Analysis: $C_{17}H_{19}NO_3$** requires C, 71.56; H, 6.71; N, 4.91%; found C, 71.51; H, 6.63; N, 4.85%.

1-(4-Methoxyphenyl)-1-(methoxycarbonylamino)ethane (50c):

Yield: 74%; **mp:** 42-43 °C; **IR** ($CHCl_3$, cm^{-1}): 669, 771, 1030, 1115, 1219, 1338, 1414, 1456, 1636, 1701, 2835, 2916, 2943, 3298; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.45 (d, *J*=6.7 Hz, 3H), 3.77 (s, 3H), 3.63 (s, 3H), 4.73-4.79 (m, 1H), 4.98 (d, *J*=6.3 Hz, 1H), 6.83 (d, *J*=8.6 Hz, 2H), 7.20 (d, *J*=8.2 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 22.3, 49.9, 51.7, 54.9, 113.8, 127.1, 135.8, 156.1, 158.7; **Analysis: $C_{11}H_{15}NO_3$** requires C, 63.14; H, 7.17; N, 6.69%; found C, 63.07; H, 7.09; N, 6.60%.

1-(4-Ethoxyphenyl)-1-(*p*-toluenesulfonamido)ethane (49d):

Yield: 75%; gum; **IR** ($CHCl_3$, cm^{-1}): 669, 760, 866, 924, 1049, 1163, 1217, 1508, 1608, 2930, 2980, 3022, 3068; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.34-1.44 (m, 8H), 2.38 (s, 3H), 3.88-4.06 (m, 3H), 4.30-4.43 (m, 1H), 5.49 (d, *J*=6.8 Hz, 1H), 6.64 (d, *J*=8.3 Hz, 2H), 6.97 (d, *J*=8.8 Hz, 2H), 7.15 (d, *J*=8.3 Hz, 2H), 7.60 (d, *J*=8.3 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 14.6, 23.1, 23.2, 52.9, 63.1, 114.1, 126.8, 127.1,

129.1, 134.1, 137.7, 142.6, 157.8; **Analysis: $C_{17}H_{21}NO_3S$** requires C, 63.92; H, 6.63; N, 4.39; S, 10.04%; found C, 63.81; H, 6.58; N, 4.32; S, 9.98%.

1-(4-Ethoxyphenyl)-1-(benzyloxycarbonylamino)ethane (50e):

Yield: 60%; **mp:** 77-79 °C; **IR** ($CHCl_3$, cm^{-1}): 669, 758, 835, 923, 1051, 1217, 1338, 1456, 1510, 1610, 1716, 2930, 2980, 3016, 3329, 3442; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.43 (m, 6H), 4.01 (quartet, *J*=7.1 Hz, 2H), 4.76-4.83 (m, 1H), 4.98 (d, *J*=9.0 Hz, 1H), 5.07 (d, *J*=3.1 Hz, 2H), 6.8 (d, *J*=8.61 Hz, 2H), 7.20 (d, *J*=8.6 Hz, 2H), 7.31 (s, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 14.8, 22.2, 49.9, 63.1, 66.4, 114.4, 127.0, 127.8, 127.9, 128.3, 135.4, 136.5, 155.3, 158.0; **Analysis: $C_{18}H_{21}NO_3$** requires C, 72.22; H, 7.07; N, 4.68%; found C, 72.18; H, 7.01; N, 4.53%.

1-(4-Benzyloxyphenyl)-1-(*p*-toluenesulfonamido)ethane (49f):

Yield: 78%; **mp:** 108-109 °C; **IR** ($CHCl_3$, cm^{-1}): 669, 771, 862, 960, 1024, 1090, 1159, 1217, 1319, 1456, 1508, 1608, 2870, 2934, 3020, 3265; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.40 (d, *J*=6.7 Hz, 3H), 2.40 (s, 3H), 3.73 (s, 3H), 4.40 (quintet, *J*=7.0 Hz, 1H), 4.99 (s, 2H), 5.24 (d, *J*=7.0 Hz, 1H), 6.76 (d, *J*=8.6 Hz, 2H), 7.01 (d, *J*=8.6 Hz, 2H), 7.17 (d, *J*=8.2 Hz, 2H), 7.33-7.40 (m, 5H), 7.62 (d, *J*=8.2 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 21.4, 23.41, 53.0, 69.8, 127.3, 127.8, 128.5 129.2, 134.6, 136.9, 138.1 142.5, 157.9; **Analysis: $C_{22}H_{23}NO_3$ S** requires C, 69.27; H, 6.08; N, 3.67; S, 8.41%; found C, 69.18; H, 6.01; N, 3.59; S, 8.38%.

1-(4-Methylthiophenyl)-1-(*p*-toluenesulfonamido)ethane (59g):

Yield: 83%; **mp:** 114-115 °C; **IR** ($CHCl_3$, cm^{-1}): 661, 772, 856, 960, 1024, 1142, 1217, 1332, 1456, 1508, 1610, 2920, 2954, 3020, 3315; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.37 (d, *J*=7.0 Hz, 3H), 2.38 (s, 3H), 2.40 (s, 3H), 4.37 (quintet, *J*=7.0 Hz, 1H), 5.58 (d, *J*=7.0 Hz, 1H), 6.99 (s, 4H), 7.13 (d, *J*=7.8 Hz, 2H), 7.57 (d, *J*=8.2 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 15.8, 21.4, 23.4 53.2 126.7 127.1 129.2, 137.4 137.9,

139.0, 142.6 **Analysis: $C_{16}H_{19}NO_2S_2$** requires C, 59.78; H, 5.96; N, 4.36; S, 19.95%; found C, 59.70; H, 5.89; N, 4.33; S, 19.88%.

1-(4-Methylthiophenyl)-1-(methoxycarbonylamino)ethane (50h):

Yield: 80%; **mp:** 53-54 °C; **IR** ($CHCl_3$, cm^{-1}): 669, 770, 862, 931, 1018, 1124, 1217, 1339, 1456, 1541, 1616, 1701, 2927, 3020, 3335; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.37 (d, *J*=6.4 Hz, 3H), 2.39 (s, 3H), 3.57 (s, 3H), 4.71 (br s, 1H), 4.86 (br s, 1H), 7.13 (s, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 15.9, 22.2, 29.5, 50.1, 126.4, 127.0, 137.2, 140.7, 155.9; **Analysis: $C_{11}H_{15}NO_2S$** requires C, 58.64; H, 6.71; N, 6.22; S, 14.23%; found C, 58.57; H, 6.67; N, 6.16; S, 14.1%.

1-(2-Methyl-4-methoxyphenyl)-1-(*p*-toluenesulfonamido)ethane (49j):

Yield: 60%; **mp:** 92-93 °C; **IR** ($CHCl_3$, cm^{-1}): **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.35 (d, *J*=6.7 Hz, 3H), 2.37 (s, 3H), 2.15 (s, 3H), 3.71 (s, 3H), 4.63 (quintet, *J*=7.0 Hz, 1H), 5.12 (br s, 1H), 6.50 (s, 2H), 7.01 (d, *J*=9.0 Hz, 1H), 7.13 (d, *J*=8.2 Hz, 2H), 7.57 (d, *J*=8.6 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 19.2, 21.4, 23.1, 49.2, 54.9, 111.5, 115.6, 126.8, 127.0, 129.2, 132.7, 135.7, 138.1, 142.5, 158.3; **Analysis: $C_{17}H_{21}NO_3S$** requires C, 63.92; H, 6.63; N, 4.39; S, 10.04%; found C, 63.90; H, 6.59; N, 4.41; S, 9.97%.

1-(3-Chloro-4-methoxyphenyl)-1-(*p*-toluenesulfonamido)ethane (49k):

Yield: 78%; gum; **IR** ($CHCl_3$, cm^{-1}): 669, 770, 883, 930, 1024, 1065, 1159, 1215, 1338, 1456, 1506, 1602, 2840, 2930, 2972, 3020, 3265, 3371; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.36 (d, *J*=6.7 Hz, 3H), 2.39 (s, 3H), 3.81 (s, 3H), 4.35 (quintet, *J*=7.0 Hz, 1H), 5.72 (d, *J*=7.4 Hz, 1H), 6.68 (d, *J*=8.2 Hz, 1H), 6.95 (s, 2H), 7.14 (d, *J*=8.2 Hz, 2H), 7.57 (d, *J*=8.2 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 21.4, 23.2, 52.7, 55.9, 111.7, 122.2, 125.5, 127.0, 128.2, 129.2, 135.3, 137.7, 142.8, 154.0; **Analysis:**

$C_{16}H_{18}ClNO_3S$ requires C, 56.55; H, 5.34; N, 4.12; S, 9.44; Cl, 10.43%; found C, 56.43; H, 5.30; N, 4.09; S, 9.47; Cl, 10.36%.

1-(3-Chloro-4-methoxyphenyl)-1-(methoxycarbonylamino)ethane (50l):

Yield: 80%; gum; **IR** ($CHCl_3$, cm^{-1}): 624, 779, 814, 883, 941, 1022, 1067, 1249, 1344, 1454, 1504, 1607, 1701, 2841, 2953, 3065, 3327; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.52 (d, *J*=7.0 Hz, 3H), 3.73 (s, 3H), 4.81-4.87 (m, 1H), 3.94 (s, 3H), 5.70 (d, *J*=5.8 Hz, 1H), 6.93 (d, *J*=8.2 Hz, 1H), 7.24 (d, *J*=8.6 Hz, 1H), 7.42 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 21.1, 49.6, 51.2, 55.9, 112.7, 122.2, 127.0, 128.2, 137.7, 152.2, 155.9; **Analysis: $C_{11}H_{14}ClNO_3$** requires C, 54.22; H, 5.79; N, 5.75; Cl, 14.55%; found C, 54.14; H, 5.84; N, 5.69; Cl, 14.51%.

1-(4-Isopropyloxyphenyl)-1-(*p*-toluenesulfonamido)ethane (49m):

Yield: 66%; gum; **IR** ($CHCl_3$, cm^{-1}): 667, 771, 862, 960, 1090, 1159, 1215, 1338, 1456, 1512, 1610, 2870, 2944, 3022, 3265, 3354; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.31-1.41 (9H, m), 2.39 (3H, s), 4.40-4.50 (2H, m), 5.79 (1H, d, *J*=7.3 Hz), 6.66 (2H, d, *J*=8.1 Hz), 7.01 (2H, d, *J*=8.8 Hz), 7.16 (2H, d, *J*=8.1 Hz), 7.64 (2H, d, *J*=8.1 Hz); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 21.3, 22.0, 23.4, 53.1, 69.6, 115.6, 127.1, 127.3, 129.2, 134.6, 138.3, 142.4, 157.1; **Analysis: $C_{19}H_{23}NO_3S$** requires C, 66.06; H, 6.71; N, 4.05; S, 9.28%; found C, 65.94; H, 6.77; N, 4.02; S, 9.21%.

1-(4-Cyclopentyloxyphenyl)-1-(*p*-toluenesulfonamido)ethane (49n):

Yield: 62%; gum; **IR** ($CHCl_3$, cm^{-1}): 669, 771, 813, 987, 1095, 1163, 1215, 1338, 1456, 1508, 1608, 2871, 2966, 3018, 3265, 3365; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.38 (d, *J*=6.7 Hz, 3H), 1.61-1.81 (m, 8H), 2.38 (s, 3H), 4.43-4.29 (m, 1H), 4.64 (br s, 1H), 5.35 (m, 1H), 6.59 (d, *J*=8.6 Hz, 2H), 6.94 (d, *J*=8.6 Hz, 2H), 7.13 (d, *J*=8.2 Hz, 2H), 7.62 (d, *J*=8.2 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 21.3, 24.7, 35.1, 53.1, 71.2, 115.6, 127.0, 128.2, 129.4, 134.7, 138.3, 144.4, 155.2; **Analysis: $C_{20}H_{25}NO_3S$**

requires C, 66.82; H, 7.01; N, 3.90; S, 8.92%; found C, 66.70; H, 7.08; N, 3.81; S, 8.90%.

General experimental procedure for the Hydroalkoxylation of activated styrenes:

A mixture of olefin (2 mmol), *N*-bromosuccinimide (20 mol%), alcohol (4 mmol) was taken in CH_2Cl_2 (4 mL) and stirred at 25 °C. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was concentrated under reduced pressure to give crude product, which was purified by column chromatography packed with silica gel (60-120 mesh) using Pet. ether and EtOAc as eluent to afford pure product (**51a-g**).

1-(4-Methoxyphenyl)-1-(benzyloxy)ethane (51a):

Yield: 85%; gum; **IR** ($CHCl_3$, cm^{-1}): 555, 609, 698, 736, 833, 1036, 1094, 1173, 1248, 1456, 1512, 1610, 2864, 2931, 2972, 3030; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.44 (d, *J*=6.3 Hz, 3H), 4.53-4.18 (m, 3H), 3.73 (s, 3H), 6.82-6.88 (m, 2H), 7.21-7.29 (m, 7H); **^{13}C NMR** (50 MHz, $CDCl_3$): 24.4, 55.3, 70.2, 80.6, 114.1, 127.6, 127.7, 127.9, 128.5, 135.9, 159.3; **Analysis: $C_{16}H_{18}O_2$** requires C, 79.31; H, 7.49%; found C, 79.2; H, 7.44%.

1-(4-Methoxyphenyl)-1-(methoxy)ethane (51b):

Yield: 80%; gum; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.39 (d, *J*=6.8 Hz, 3H), 3.15 (s, 3H), 3.78 (s, 3H), 4.19 (quartet, *J*=6.4 Hz, 1H), 6.82 (d, *J*=8.8 Hz, 2H), 7.17 (d, *J*=8.8 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 23.7, 54.5, 55.6, 78.8, 113.4, 126.9, 135.3, 158.7; **Analysis: $C_{10}H_{14}O_2$** requires C, 72.26; H, 8.49%; found C, 72.20; H, 8.39%.

1-(4-Methylthiophenyl)-1-(benzyloxy)ethane (51c):

Yield: 88%; gum; **IR** ($CHCl_3$, cm^{-1}): 544, 676, 745, 874, 1051, 1173, 1217, 1456, 1533, 1610, 2864, 2944, 2982, 3011; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.45 (d, *J*=6.3

Hz, 3H), 2.47 (s, 3H), 4.45-4.22 (m, 3H), 7.14-7.28 (m, 9H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 15.9, 24.0, 70.1, 76.7, 126.8, 126.9, 127.3, 127.5, 128.2, 137.5, 138.6, 140.7; **Analysis: $C_{16}H_{18}OS$** requires C, 74.38; H, 7.02; S, 12.41%; found C, 74.41; H, 7.01; S, 12.30%.

1-(4-Methylthiophenyl)-1-(methoxy)ethane (51d):

Yield: 85%; gum; **IR** ($CHCl_3$, cm^{-1}): **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.39 (d, *J*=6.1 Hz, 3H), 2.45 (s, 3H), 3.17 (s, 3H), 4.20 (quartet, *J*=6.1 Hz, 1H), 7.18 (s, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 15.1, 21.3, 56.5, 79.8, 126.9, 127.8, 133.1, 136.4; **Analysis: $C_{10}H_{14}OS$** requires C, 65.89; H, 7.74; S, 17.52%; found C, 65.80; H, 7.81; S, 17.52%.

1-(3-Chloro-4-methoxyphenyl)-1-(benzyloxy)ethane (51e):

Yield: 81%; gum; **IR** ($CHCl_3$, cm^{-1}): 578, 619, 687, 887, 1036, 1087, 1144, 1245, 1461, 1521, 1610, 2764, 2883, 2947, 3004; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.44 (d, *J*=6.3 Hz, 3H), 3.89 (s, 3H), 4.45-4.21 (m, 3H), 6.88 (d, *J*=8.2 Hz, 1H), 7.34-7.14 (m, 8H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 24.1, 56.2, 70.3, 76.3, 112.1, 122.5, 125.8, 127.6, 127.8, 128.3, 128.5, 136.9, 138.5, 154.8; **Analysis: $C_{16}H_{17}ClO_2$** requires C, 69.44; H, 6.19; Cl, 12.81%; found C, 69.32; H, 6.10; Cl, 12.93%.

1-(4-Methoxyphenyl)-1-(allyloxy)ethane (51f):

Yield: 83%; gum; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.42 (d, *J*=6.3 Hz, 3H), 3.79 (s, 3H), 4.16-3.89 (m, 2H), 4.38 (quartet, *J*=6.3 Hz, 1H), 5.26-5.09 (m, 2H), 5.94-5.77 (m, 1H), 6.83 (d, *J*=8.6 Hz, 2H), 7.20 (d, *J*=8.6 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 24.0, 54.9, 68.9, 76.6, 113.8, 116.0, 127.2, 127.9, 135.23, 158.9; **Analysis: $C_{10}H_{14}O_2$** requires C, 74.97; H, 8.39%; found C, 74.83; H, 8.31%.

1-(4-Methoxyphenyl)-1-(propargyloxy)ethane (51g):

Yield: 80%; gum; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.45 (d, *J*=6.7 Hz, 3H), 2.34 (m, 1H), 3.79 (s, 3H), 3.86-3.82 (m, 1H), 4.07-3.98 (m, 1H), 4.59 (quartet, *J*=6.7 Hz, 1H), 6.84 (d, *J*=8.6 Hz, 2H), 7.22 (d, *J*=8.6 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 23.7, 55.2, 55.2, 74.2, 76.1, 80.2, 113.9, 127.8, 128.4, 159.3; **Analysis: $C_{10}H_{14}O_2$** requires C, 75.76; H, 7.42%; found C, 75.62; H, 7.31%.

SECTION III

$BF_3.OEt_2$ Catalyzed aza-Michael Addition of Sulfonamides and Carbamates as the Nucleophiles onto α,β-unsaturated Enones

4.3.1 Introduction

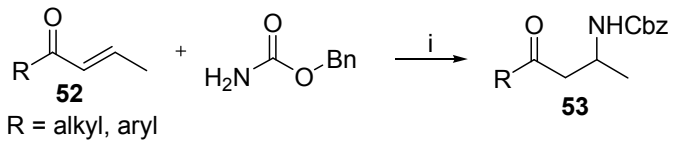
The development of novel synthetic methods leading to β-amino carbonyl compounds has attracted much attention in organic synthesis. These compounds are attractive targets for chemical synthesis because of their prevalence and wide utility. One of the earliest applications was in the synthesis of important γ-amino alcohols, versatile synthetic intermediates for a large number of natural products, antibiotics, chiral auxiliaries and β-lactams.[26] Further, the β-amino carbonyl moiety is common in a large variety of biologically active compounds[27] and finds use as an important intermediate for fine chemicals and pharmaceuticals[28] which can be synthesized using the Michael reaction. The Michael reaction, which was discovered many years ago, is one of the most important reactions in organic chemistry which involves the conjugate addition reaction of nucleophiles on to unsaturated carbonyl compounds.

4.3.2 Review of Literature

There are a large number of reports available in literature on Aza-Michael reaction. Some of the recent developments on this reaction are discussed below.

Kobayashi's approach (2002)[29]

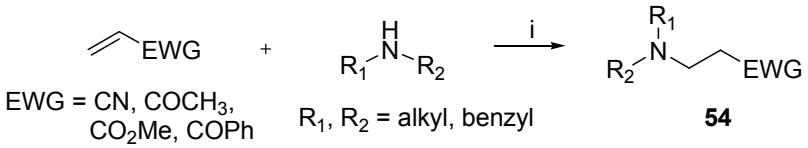
Several transition metal salts were found to catalyze aza-Michael reactions of enones with carbamates efficiently. Various metal salts such as $ReCl_5$, $RuCl_3.nH_2O$, $PtCl_4.5H_2O$ etc. exhibited higher catalytic activity. Aliphatic as well as aromatic enones **52** underwent aza-Michael reaction to the corresponding β-amino ketones **53** in excellent yields (**Scheme 34**).



Scheme 34: (i) 0.1 equiv. metal salt, CH_2Cl_2, 25 °C, 42-100%.

Yadav's approach (2003)[30]

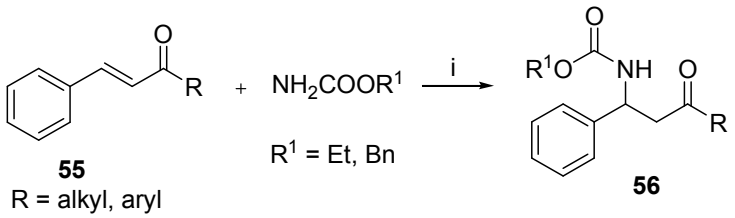
Electron-deficient olefins undergo smoothly aza-Michael reactions with a wide range of amines in ionic liquid (1-butyl-3-methylimidazolium hexafluorophosphate {[Bmim]PF_6}) to produce the corresponding β-amino compounds **54** in excellent yields with high 1,4-selectivity (**Scheme 35**).



Scheme 35: (i) [Bmim]PF_6, 25 °C, 72-95%.

Xia's approach (2003)[31]

Xia *et al.* have made use of $Me_3SiCl/FeCl_3.6H_2O$ as the catalyst system for the aza-Michael addition of various carbamates onto enones as well as chalcones **55** to give the corresponding β-amino ketones **56** in moderate yields (**Scheme 36**).

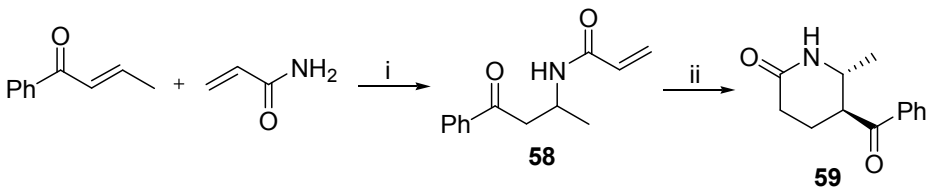


Scheme 36: (i) $FeCl_3.6H_2O$, Me_3SiCl, CH_2Cl_2, 25 °C, 45-52%.

Takasu's approach (2004)[32]

Takasu *et al.* have developed $Pd(PhCN)_2Cl_2$ promoted conjugate addition reaction of amides with enones to afford β-amidoketones under solvent-free conditions. Various amides like acetamide, acyl amide, benzyl amide were subjected

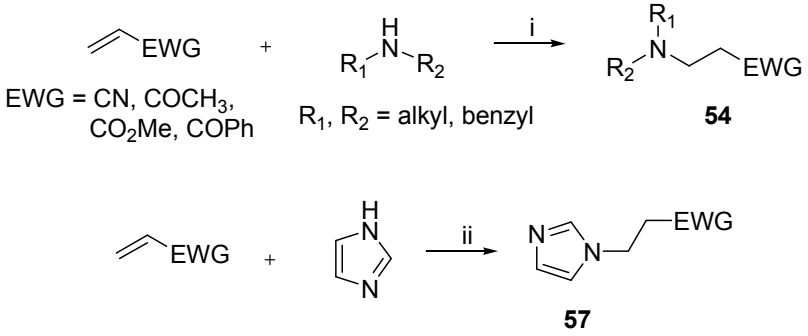
to the aza-Michael reaction. The amidoketones **58** were also transformed into the corresponding substituted piperidines **59** (**Scheme 38**).



Scheme 38: (i) $Pd(PhCN)_2Cl_2$, 60 °C, 60%; (ii) ^{t}BuOK, ^{t}BuOH, 95%.

Reddy's approach (2006)[33]

Cellulose-supported copper (0) efficiently catalyzes the aza-Michael reaction of *N*-nucleophiles, such as morpholine, piperidine and imidazole with α,β-unsaturated compounds to produce the corresponding β-amino compounds and *N*-substituted imidazoles **57** in excellent yields (**Scheme 37**).

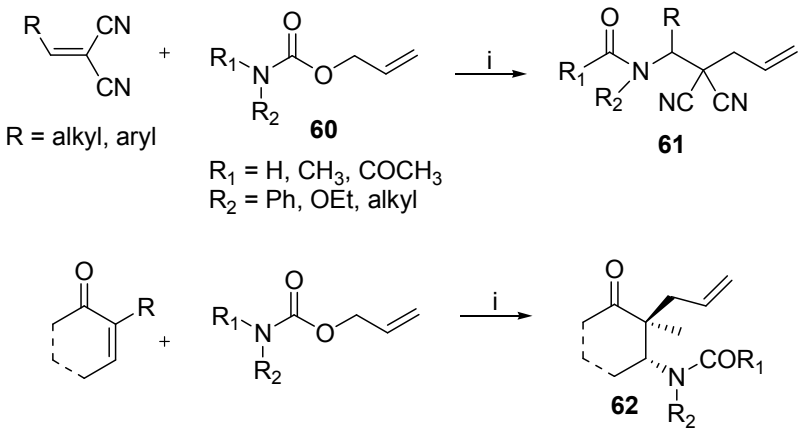


Scheme 37: (i) Cellulose-Cu (0), MeOH, 25 °C, 90-98%; (ii) CELL-Cu (0), toluene, reflux, 56-98%

Yamamoto's approach (2006)[34]

Yamamoto *et al.* have developed the reaction of allyl carbamates **60** with activated olefins in the presence of $Pd(PPh_3)_4$ catalyst in THF at 25 °C to give the corresponding β,α-bisadducts **61**, β-amino-α-allylated products **62**, in high yields. Not only highly activated olefins containing two cyano groups but also 2-cyano enones underwent facile aza-Michael addition-allylation with various allylic carbamates **60**

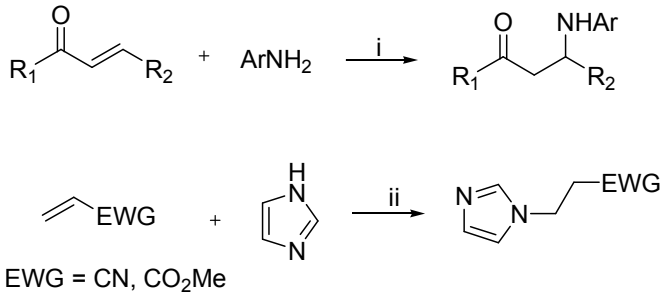
iving the corresponding products in high yields and with high diastereoselectivities (**Scheme 39**).



Scheme 39: (i) $Pd(PPh_3)_4$, THF, 25 °C, 52-96%.

Xu's approach (2006)[35]

Xu *et al.* have made use of a basic ionic liquid, 1-butyl-3-methylimidazolium hydroxide [Bmim]OH as the catalyst for the aza-Michael addition of aromatic amines and imidazole to cyclic or acyclic enones under neat conditions. The catalyst can be recycled for subsequent reactions without any appreciable loss of efficiency (**Scheme 40**).

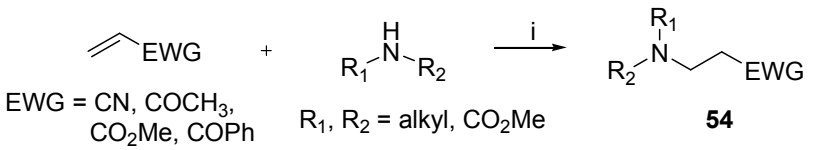


Scheme 40: (i) [Bmim]OH, 25 °C, 20-98%.

Samant's approach (2006)[36]

Polyvinyl pyridine (PVP), prepared by radical polymerization of 4-vinyl pyridine, was used as a heterogeneous basic catalyst for the aza-Michael reaction of secondary

amines and carbamates with α,β-unsaturated esters, cyanides and ketones to obtain the corresponding adducts in excellent yields (**Scheme 41**).



Scheme 41: (i) PVP, 25 ^{0}C, 75-90%.

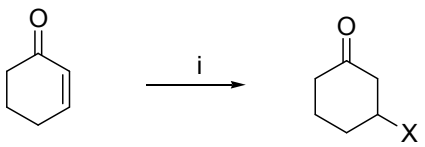
4.3.3 Present Work

4.3.3.1 Objective

Although there are many methods available in the literature for aza-Michael reactions of enones, they suffer from certain drawbacks like low yields, cumbersome experimental procedures and many of these procedures often requiring an excess of reagents, long reaction times, using expensive heavy metal salts and ionic liquids. Hence, there arises a necessity to develop an efficient metal-free process for the aza-Michael reactions of enones.

4.3.4 Results and Discussion

In our search for a much cheaper and effective method, we carried out the aza-Michael reaction of enones by replacing expensive transition metal catalysts with cheaper Lewis acid catalyst such as $BF_3.OEt_2$. When cyclohexenone was subjected to aza-Michael reaction using $BF_3.OEt_2$ as the catalyst and *p*-toluenesulfonamide ($TsNH_2$) and benzyl carbamate ($CbzNH_2$) as the nitrogen nucleophiles at 25 °C, the corresponding 1,4-addition products were obtained in good yields (**Scheme 42**).



63a, X = NHTs, 83%

64a, X = NHCbz, 72%

Scheme 42: (i) $BF_3.OEt_2$ (20 mol%), enone (2 mmol), *p*-toluene sulfonamide or benzyl carbamate (2 mmol), CH_2Cl_2, 25 °C.

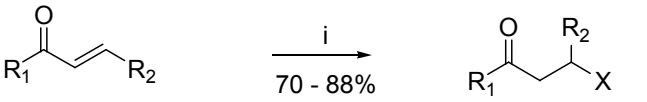
We then turned our attention to systematically explore the utility of this catalytic system for the aza-Michael reaction of various enones. In order to screen the best solvent system, aza-Michael reaction of cyclohexenone was performed in a variety of solvents using $BF_3.OEt_2$ as the catalyst and *p*-toluenesulfonamide as the nucleophile. The results of solvent study are summarized in **Table 8**. Among all solvents used, dichloromethane gave the best results.

Table 8: aza-Michael reaction of cyclohexenone: Effect of solvents[a]

No.	Catalyst	Solvent	Time (h)	Product	Yield[b] (%) of 63a
1.	$BF_3.OEt_2$	$CHCl_3$	3	**63a**	74
2.	$BF_3.OEt_2$	CH_3CN	6	**63a**	30
3.	$BF_3.OEt_2$	C_6H_6	3	**63a**	71
4.	$BF_3.OEt_2$	CH_2Cl_2	2	**63a**	83
5.	$BF_3.OEt_2$	CCl_4	4	**63a**	54
6.	$BF_3.OEt_2$	Acetone	8	**63a**	26
7.	$BF_3.OEt_2$	Toluene	2	**63a**	44
8.	$BF_3.OEt_2$	MeOH	6	**63a**	0

(a) Reaction conditions: $BF_3.OEt_2$ (20 mol%), enone (2 mmol), $TsNH_2$ or $CbzNH_2$ (2 mmol), CH_2Cl_2, 25 °C; (b) isolated yield after chromatographic separation

A variety of enones were then subjected to aza-Michael reaction using $BF_3.OEt_2$ as the catalyst and CH_2Cl_2 as solvent (**Scheme 43**), the results of which are summarized in **Table 9**.



R_1 = Me, cyclopentyl, Ph, 4-OMe-Ph, 6-Me-naphthyl, 2,4-OEt-Ph, etc

R_2 = H, Me

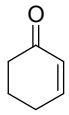
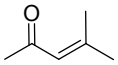
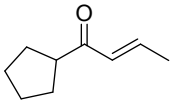
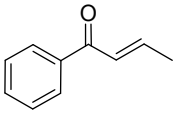
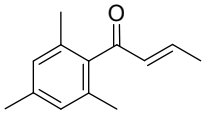
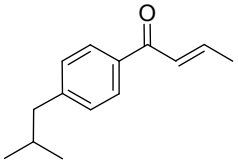
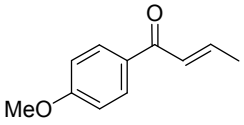
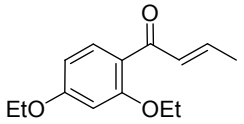
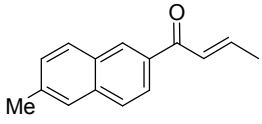
63, X = NHTs

64, X = NHCbz

Scheme 43: (i) $BF_3.OEt_2$ (20 mol%), enone (2 mmol), *p*-toluene sulfonamide or benzyl carbamate (2 mmol), CH_2Cl_2, 25 ^oC.

Table 9 presents the results of aza-Michael reaction of enones with varied functional groups on the aromatic ring which using CH_2Cl_2 as the solvent and *p*-toluenesulfonamide and benzyl carbamate as the nitrogen nucleophiles.

Table 9: aza-Michael reaction of enones with *p*-toluenesulfonamide and benzyl carbamate as the nucleophiles.

No.	Enone	X = NHTs (63)			X = NHCbz (64)		
		Time (h)	Yield (%)[b]	Product	Time (h)	Yield (%)[b]	Product
1		2	83	**63a**	2	72	**64a**
2		3	69	**63b**	2.5	78	**64b**
3		2	78	**63c**	3	70	**64c**
4		8	80	**63d**	2.5	75	**64d**
5		10	85	**63e**	8	75	**64e**
6		10	87	**63f**	6	76	**64f**
7		8	85	**63g**	7.5	73	**64g**
8		10	88	**63h**	8	72	**64h**
9		8	82	**63i**	8	70	**64i**
10		10	88	**63j**	7.5	73	**64j**

(a) Reaction conditions: $BF_3.OEt_2$ (20 mol%), enone (2 mmol), $TsNH_2$ or $CbzNH_2$ (2 mmol), CH_2Cl_2, 25 °C; (b) isolated yield after chromatographic separation.

Various aliphatic enones along with enones having alkoxy and alkyl substitutions on the aromatic ring underwent aza-Michael reaction to give the corresponding products in good yields.

Example 1: The ^{1}H NMR spectrum of compound **63e** showed characteristic signals at δ 2.98 (dd) and 3.13 (dd) corresponding to the diastereotopic homobenzylic protons and the terminal methyl group appeared as doublet at δ 1.13. Its ^{13}C NMR spectrum showed characteristic carbon signals at δ 44.46 and 46.73 corresponding to the homobenzylic carbon and the carbon attached to the NHTs moiety. The carbonyl carbon displayed a peak at δ 198.39 (**Fig. 10**).

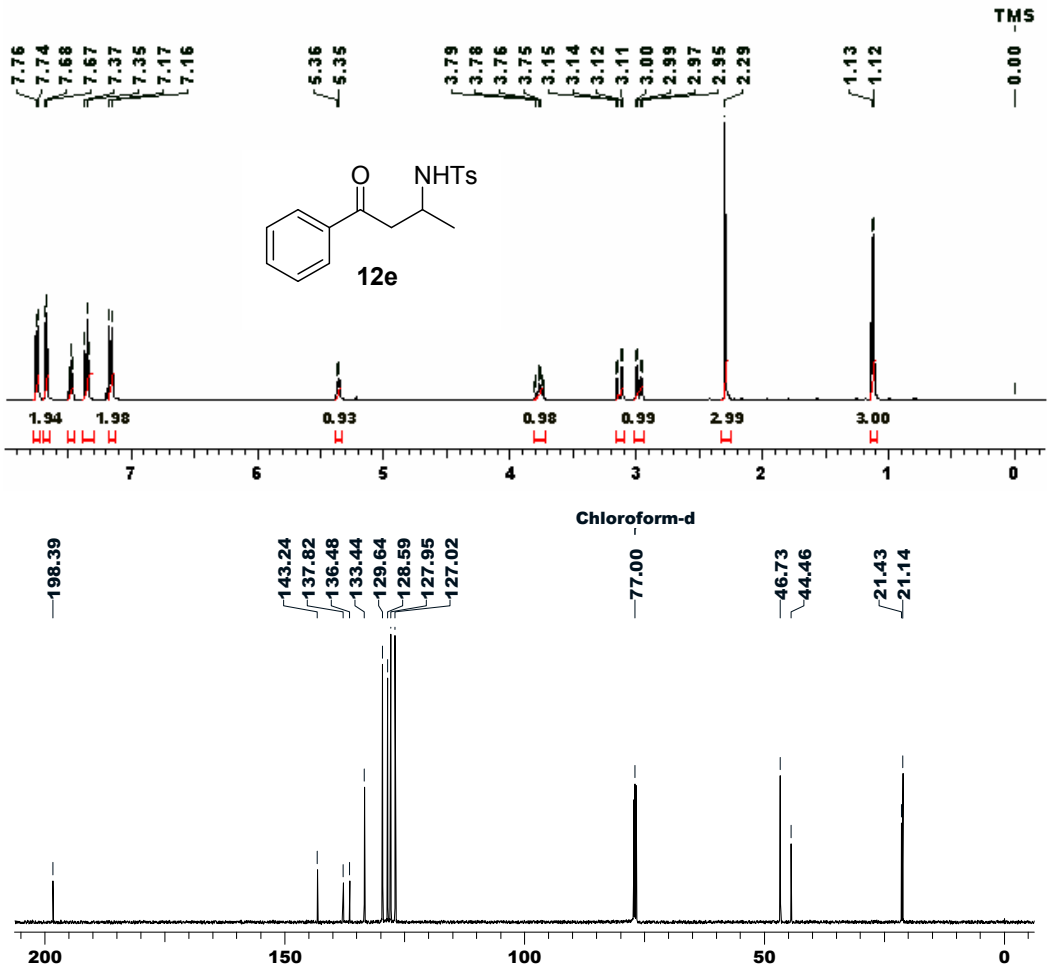


Fig. 10: ^{1}H and ^{13}C NMR spectra of compound 63e

Example 2: The ^{1}H NMR spectrum of compound **64e** showed characteristic signals at δ 3.06 (dd) and 3.38 (dd) corresponding to the diastereotopic homobenzylic protons and the terminal methyl group appeared as doublet at δ 1.31. The other signals at δ

5.08 (s) and 5.32 (br s) are due to methylene protons in the Cbz moiety and the NH protons respectively. Its ^{13}C NMR spectrum showed characteristic carbon signals at δ 43.84 and 44.29 corresponding to the homobenzylic carbon and the carbon attached to the NHTs moiety. The carbonyl carbon displayed a characteristic peak at δ 198.19 (**Fig. 11**). Its IR spectrum displayed characteristic strong band at 1717cm^{-1} corresponding to the carbonyl carbon (**Fig. 12**).

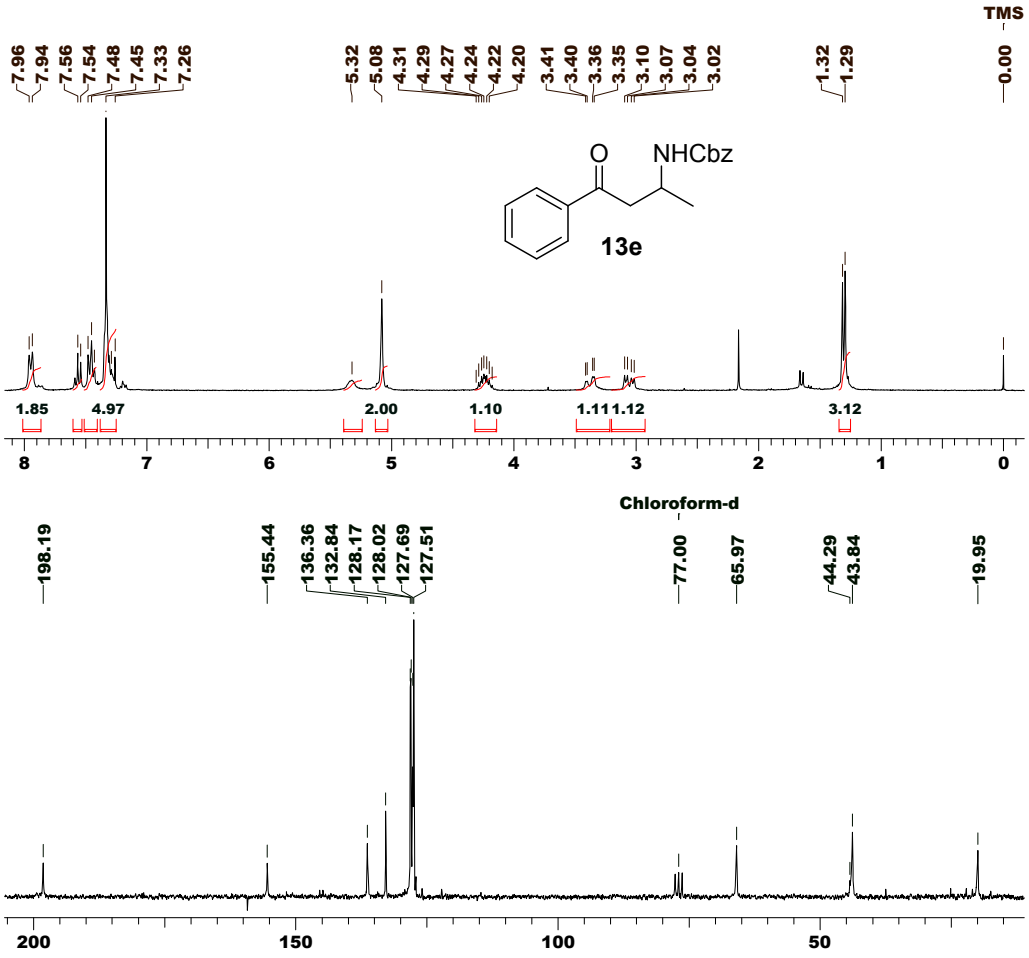


Fig. 11: ^{1}H and ^{13}C NMR spectra of compound 64e

Example 3: The ^{1}H NMR spectrum of compound **63d** showed characteristic signals at δ 2.53-2.59 (m) and 2.65 (dd) corresponding to the diastereotopic methylene

protons [C(O)**CH$_2$**CHNHTs] and the terminal methyl group appeared as doublet at δ 1.09 (**Fig. 13**).

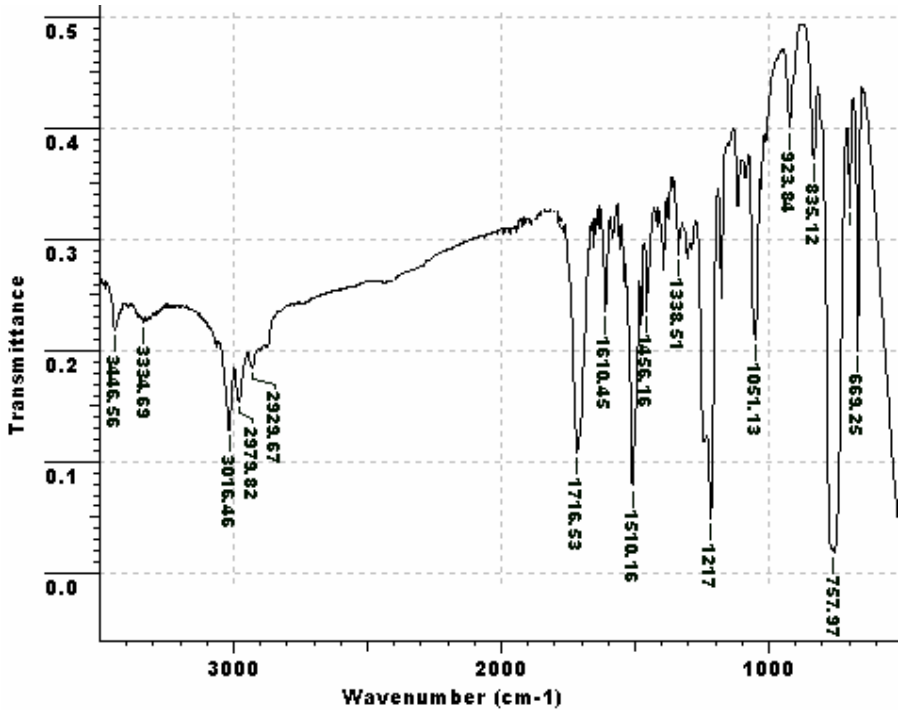


Fig. 12: IR spectrum of compound 64e

Its ^{13}C NMR spectrum showed characteristic carbon signals at δ 47.19 and 51.79 corresponding to the carbon attached to the carbonyl [C(O)**CH$_2$**CHNHTs] and the carbon attached to the NHTs moiety. The carbonyl carbon displayed a characteristic peak at δ 211.87 (**Fig. 14**).

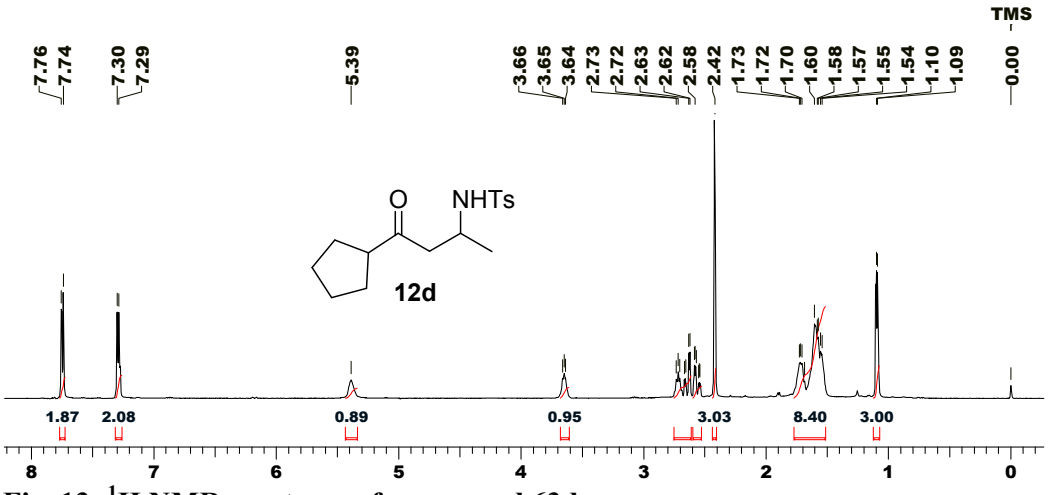


Fig. 13: ^{1}H NMR spectrum of compound 63d

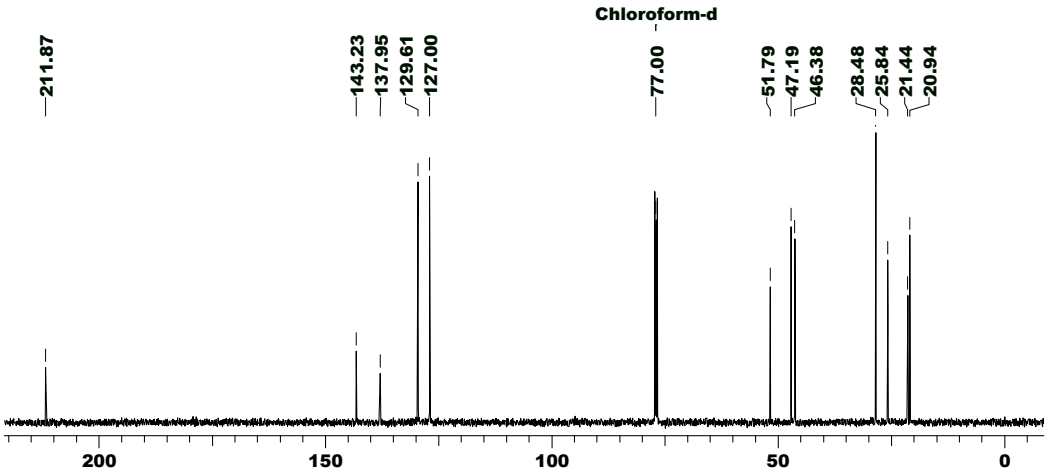


Fig. 14: ^{13}C NMR spectrum of compound 63d

4.3.4.1 Mechanism

The probable mechanistic pathway for the $BF_3.OEt_2$-catalyzed aza-Michael reaction of enones is shown in **Fig. 15**. Simultaneous co-ordination of $BF_3.OEt_2$ with ketone and amine functions results in the 1,4-addition of the amine onto the enone, resulting in the formation of product, with the regeneration of acid catalyst.

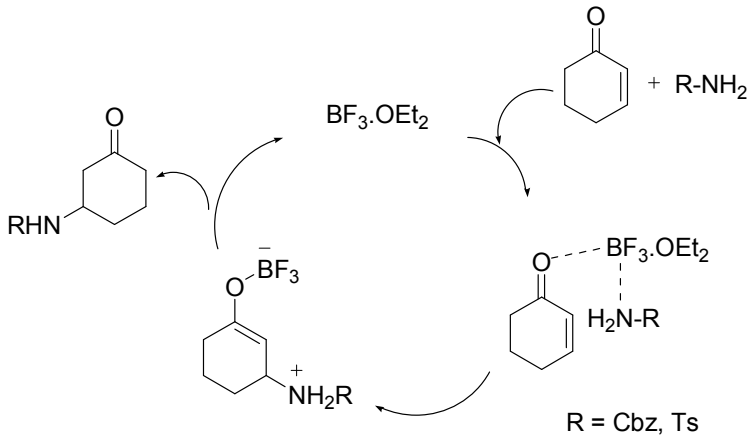


Fig. 15: Proposed mechanism for the aza-Michael reaction of enones

4.3.5 Conclusion

In conclusion, we have developed a new, practical and "metal-free" procedure for the aza-Michael reaction of enones catalyzed by $BF_3.OEt_2$ at ambient conditions using

sulfonamides and carbamates as nucleophiles. The corresponding products were formed in excellent yields. Mild nucleophiles such as sulfonamides and carbamates were used to enhance the synthetic utility of the current methodology.

4.3.6 Experimental Section

General experimental procedure for the aza-Michael reaction of enones:

A mixture of enone (2 mmol), $BF_3.OEt_2$ (20 mol%) and $TsNH_2$ (2 mmol) or $CbzNH_2$ (2 mmol) was taken in CH_2Cl_2 (20 mL) and stirred at 25 °C. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was concentrated under reduced pressure to give crude product, which was purified by column chromatography over silica gel (60-120 mesh) using Pet. ether and EtOAc as eluent to afford pure product.

3-(*p*-Toluenesulfonamido)cyclohexanone (63a)

Yield: 70%; **mp**: 120-122 °C; **IR** ($CHCl_3$, cm^{-1}): 669, 771, 851, 1086, 1123, 1323, 1456, 1701, 2875, 2965, 3362; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.80-1.90 (m, 4H), 2.11-2.21 (m, 4H), 2.23 (s, 3H), 3.51 (br s, 1H), 5.61 (d, *J*=6.3 Hz, 1H), 7.32 (d, *J*=8.3 Hz, 2H), 7.74 (d, *J*=8.3 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 21.16, 21.31, 31.31, 40.17, 48.07, 52.15, 126.62, 129.53, 137.58, 143.27, 208.45; **Analysis: $C_{13}H_{17}NO_3S$** requires C, 58.40; H, 6.41; N, 5.24; S, 11.99%; found C, 58.42; H, 6.45; N, 5.23; S, 11.97%.

4-(*p*-Toluenesulfonamido)butan-2-one (63b)

Yield: 69%; gum; **IR** ($CHCl_3$, cm^{-1}): 762, 854, 1045, 1106, 1339, 1456, 1701, 2881, 2954, 3362; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 2.05 (s, 3H), 2.36 (s, 3H), 2.60-2.77 (m, 2H), 3.05-3.29 (m, 2H), 5.28 (br s, 1H), 7.25 (d, *J*=8.3 Hz, 2H), 7.67 (d, *J*=8.3 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 21.05, 29.58, 37.60, 42.48, 126.62, 129.42,

136.58, 143.02, 207.49; **Analysis: $C_{11}H_{15}NO_3S$** requires C, 54.75; H, 6.27; N, 5.80; S, 13.29%; found C, 54.79; H, 6.25; N, 5.81; S, 13.25%.

4-Methyl-4-(*p*-toluenesulfonamido)pentan-2-one (63c)

Yield: 78%; gum; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.23 (s, 6H), 2.07 (s, 3H), 2.43 (s, 3H), 2.64 (s, 2H), 5.85 (br s, 1H), 7.27 (d, *J*=7.8 Hz, 2H), 7.75 (d, *J*=8.3 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 21.44, 27.77, 31.30, 53.31, 54.75, 127.09, 129.44, 140.36, 142.78, 207.99; **Analysis: $C_{13}H_{19}NO_3S$** requires C, 57.97; H, 7.11; N, 5.20; S, 11.90%; found C, 57.93; H, 7.12; N, 5.19; S, 11.91%.

1-Cyclopentyl-3-(*p*-toluenesulfonamido)butan-1-one (63d)

Yield: 80%; gum; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.09 (d, *J*=6.8 Hz, 3H), 1.54-1.73 (m, 8H), 2.42 (s, 3H), 2.53-2.59 (m, 1H), 2.65 (dd, *J*=17.9, 4.4 Hz, 1H), 2.70-2.73 (m, 1H), 3.64-3.66 (m, 1H), 5.39 (br s, 1H), 7.30 (d, *J*=7.6 Hz, 2H), 7.75 (d, *J*=8.0 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 20.94, 21.44, 25.84, 28.48, 46.38, 47.19, 51.79, 127.0, 129.61, 137.95, 143.23, 211.87; **Analysis: $C_{16}H_{23}NO_3S$** requires C, 62.11; H, 7.49; N, 4.53; S, 10.36%; found C, 62.15; H, 7.46; N, 4.51; S, 10.37 %.

1-Phenyl-3-(*p*-toluenesulfonamido)butan-1-one (63e)

Yield: 85%; **mp**: 98-99 °C; **IR** ($CHCl_3$, cm^{-1}): 669, 710, 1086, 1158, 1323, 1456, 1598, 1701, 2883, 2985, 3352; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.13 (3H, d, *J*=6.8 Hz), 2.29 (3H, s), 2.98 (1H, dd, *J*=17.1, 6.4 Hz), 3.13 (1H, dd, *J*=17.1, 4.4 Hz), 3.73-3.80 (m, 1H), 5.36 (d, *J*=8.0 Hz, 1H), 7.17 (d, *J*=8.4 Hz, 2H), 7.36 (t, *J*=7.6 Hz, 2H), 7.49 (t, *J*=7.6 Hz, 1H), 7.68 (d, *J*=7.9 Hz, 2H), 7.75 (d, *J*=7.12 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 21.14, 21.43, 44.46, 46.73, 127.02, 127.95, 128.59, 129.64, 133.44, 136.48, 137.82, 143.24, 198.39; **Analysis: $C_{17}H_{19}NO_3S$** requires C, 64.33; H, 6.03; N, 4.41; S, 10.10%; found C, 64.37; H, 6.01; N, 4.44; S, 10.08%.

1-Mesityl-3-(*p*-toluenesulfonamido)butan-1-one (63f)

Yield: 87%; **mp**: 126-127 °C; **IR** ($CHCl_3$, cm^{-1}): 669, 771, 862, 960, 1024, 1159, 1217, 1319, 1456, 1508, 1708, 2870, 2934, 3020, 3265; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.24 (d, *J*=6.8 Hz, 3H), 2.09 (s, 6H), 2.26 (s, 3H), 2.42 (s, 3H), 2.82 (dd, *J*=19.1, 6.4 Hz, 1H), 2.90 (dd, *J*=19.1, 4.0 Hz, 1H), 3.76-3.84 (m, 1H), 5.40 (d, *J*=8.4 Hz, 1H), 6.80 (s, 2H), 7.30 (d, *J*=8.0 Hz, 2H), 7.79 (d, *J*=8.0 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 18.71, 20.86, 20.92, 21.34, 46.02, 50.53, 126.94, 128.44, 129.61, 132.25, 138.02, 138.54, 143.18, 209.04; **Analysis: $C_{20}H_{25}NO_3S$** requires C, 66.82; H, 7.01; N, 3.90; S, 8.92%; found C, 66.80; H, 7.03; N, 3.92; S, 8.91%.

1-(4-Isobutylphenyl)-3-(*p*-toluenesulfonamido)butan-1-one (63g)

Yield: 85%; **mp**: 98-100 °C; **IR** ($CHCl_3$, cm^{-1}): 687, 764, 1091, 1174, 1223, 1336, 1456, 1596, 1724, 2880, 3020, 3321; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 0.90 (d, *J*=6.4 Hz, 6H), 1.20 (d, *J*=6.8 Hz, 3H), 1.89 (septet, *J*=6.8 Hz, 1H), 2.47 (s, 3H), 2.52 (d, *J*=7.2 Hz, 2H), 3.03 (dd, *J*=17.1, 6.4 Hz, 1H), 3.18 (dd, *J*=17.1, 4.4 Hz, 1H), 3.84 (quintet, *J*=6.4 Hz, 1H), 5.50 (br s, 1H), 7.20 (d, *J*=8.4 Hz, 2H), 7.24 (d, *J*=7.9 Hz, 2H), 7.76 (t, *J*=8.3 Hz, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 21.06, 22.08, 29.79, 44.5, 45.13, 46.69, 126.88, 127.86, 129.09, 129.43, 134.27, 137.92, 142.94, 147.73, 197.85; **Analysis: $C_{21}H_{27}NO_3S$** requires C, 67.53; H, 7.29; N, 3.75; S, 8.58%; found C, 67.56; H, 7.30; N, 3.73; S, 8.55%.

1-(4-Methoxyphenyl)-3-(*p*-toluenesulfonamido)butan-1-one (63h)

Yield: 88%; **mp**: 102-104 °C; **IR** ($CHCl_3$, cm^{-1}): 671, 762, 928, 1101, 1217, 1338, 1450, 1601, 1708, 2925, 3022, 3314; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.12 (d, *J*=6.8 Hz, 3H), 2.29 (s, 3H), 2.91 (dd, *J*=17.1, 6.4 Hz, 1H), 3.06 (dd, *J*=17.1, 4.4 Hz, 1H), 3.73 (m, 1H), 3.78 (s, 3H), 5.37 (d, *J*=8.0 Hz, 1H), 6.82 (d, *J*=8.7 Hz, 2H), 7.16 (d, *J*=8.3 Hz, 2H), 7.67 (d, *J*=7.9 Hz, 2H), 7.73 (d, *J*=9.1 Hz, 2H); **^{13}C NMR** (50 MHz,

$CDCl_3$) δ: 21.15, 21.35, 44.09, 46.89, 55.39, 66.59, 113.68, 126.99, 128.04, 128.28, 128.50, 129.55, 130.28, 132.94, 143.07, 163.71, 196.82; **Analysis: $C_{18}H_{21}NO_4S$** requires C, 62.23; H, 6.09; N, 4.03; S, 9.23%; found C, 62.26; H, 6.11; N, 4.01; S, 9.20%.

1-(2,4-Diethoxyphenyl)-3-(*p*-toluenesulfonamido)butan-1-one (63i)

Yield: 82%; **IR** ($CHCl_3$, cm^{-1}): 669, 756, 921, 1097, 1217, 1338, 1456, 1610, 1714, 2872, 3031, 3301; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.13 (d, *J*=6.8 Hz, 3H), 1.46 (q, *J*=7.2 Hz, 6H), 2.27 (s, 3H), 2.96 (dd, *J*=17.1, 6.0 Hz, 1H), 3.0 (dd, *J*=17.1, 5.6 Hz, 1H), 3.68 (quintet, *J*=6.8 Hz, 1H), 3.94-4.01 (m, 4H), 5.41 (d, *J*=7.6 Hz, 1H), 6.28 (s, 1H), 6.39 (dd, *J*=8.8, 2.4 Hz, 1H), 7.11 (d, *J*=8.0 Hz, 2H), 7.60 (d, *J*=8.7 Hz, 1H), 7.63 (d, *J*=8.4 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 14.53, 21.29, 21.49, 47.02, 49.16, 63.74, 64.04, 99.04, 105.76, 126.28, 126.94, 129.34, 129.47, 132.60, 137.92, 142.77, 160.23, 164.15, 197.93; **Analysis: $C_{21}H_{27}NO_5S$** requires C, 62.20; H, 6.71; N, 3.45; S, 7.91%; found C, 62.17; H, 6.69; N, 3.47; S, 7.94%.

1-(2-Methylnaphthalen-6-yl)-3-(*p*-toluenesulfonamido)butan-1-one (63j)

Yield: 88%; **mp**: 120-121 °C; **IR** ($CHCl_3$, cm^{-1}): 660, 754, 904, 1091, 1159, 1217, 1343, 1454, 1596, 1730, 2854, 2883, 3280; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.37 (d, *J*=6.6 Hz, 3H), 2.36 (s, 3H), 2.47 (s, 3H), 3.03 (dd, *J*=19.1, 5.9 Hz, 1H), 3.11 (dd, *J*=19.1, 4.4 Hz, 1H), 3.88-4.01 (m, 1H), 5.52 (d, *J*=8.1 Hz, 1H), 7.52 (d, *J*=8.1 Hz, 1H), 7.28-7.50 (m, 6H), 7.80 (d, *J*=8.1 Hz, 1H), 7.86 (d, *J*=8.1 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 18.98, 21.06, 21.36, 46.02, 51.21, 123.3, 125.4, 126.93, 128.18, 128.39, 128.79, 128.94, 129.65, 130.1, 131.51, 137.28, 143.23, 208.66; **Analysis: $C_{22}H_{23}NO_3S$** requires C, 69.26; H, 6.08; N, 3.67; S, 8.41%; found C, 69.30; H, 6.09; N, 3.64; S, 8.38%.

Benzyl 3-oxocyclohexylcarbamate (64a)

Yield: 72%; **mp**: 70-71 °C; **IR** ($CHCl_3$, cm^{-1}): 761, 814, 961, 1057, 1223, 1502, 1698, 2858, 2934, 3336; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.64-1.68 (m, 2H), 1.93-2.08 (m, 3H), 2.23-2.36 (m, 3H), 2.67 (dd, *J*=13.9, 4.4 Hz, 1H), 3.96 (br s, 1H), 4.94 (br s, 1H), 5.06 (s, 2H), 7.29-7.35 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 21.53, 30.69, 40.35, 47.52, 49.87, 66.34, 127.73, 128.2, 136.14, 155.26, 208.74; **Analysis:** **$C_{14}H_{17}NO_3$** requires C, 68.00; H, 6.93; N, 5.66%; found C, 68.09; H, 6.85; N, 5.71%.

Benzyl 3-oxobutylcarbamate (64b)

Yield: 78%; gum; **IR** ($CHCl_3$, cm^{-1}): 771, 812, 954, 1062, 1240, 1339, 1456, 1514, 1703, 2838, 2914, 3316; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 2.14 (s, 3H), 2.68 (t, *J* =5.9 Hz, 2H), 3.41 (quintet, *J* =5.9 Hz, 2H), 5.07 (s, 2H), 5.38 (br s, 1H), 7.34 (s, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 29.33, 35.10, 42.56, 65.79, 127.36, 127.84, 136.07, 155.92, 207.45; **Analysis: $C_{12}H_{15}NO_3$** requires C, 65.14; H, 6.83; N, 6.33%; found C, 65.19; H, 6.88; N, 6.25%.

Benzyl 2-methyl-4-oxopentan-2-ylcarbamate (64c)

Yield: 70%; gum; **IR** ($CHCl_3$, cm^{-1}): 766, 820, 969, 1063, 1229, 1341, 1502, 1699, 2841, 2928, 3356; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.37 (s, 6H), 2.08 (s, 3H), 2.86 (s, 2H), 5.02 (s, 2H), 5.22 (br s, 1H), 7.31 (s, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 26.97, 31.16, 50.75, 50.98, 65.42, 127.47, 127.98, 136.40, 154.45, 207.01; **Analysis:** **$C_{14}H_{19}NO_3$** requires C, 67.45; H, 7.68; N, 5.62%; found C, 67.37; H, 7.62; N, 5.68%.

Benzyl 4-cyclopentyl-4-oxobutan-2-ylcarbamate (64d)

Yield: 75%; **mp:** 79-80 °C; **IR** ($CHCl_3$, cm^{-1}): 714, 804, 970, 1130, 1240, 1361, 1410, 1508, 1710, 2881, 2923, 3324; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.22 (d, *J* =6.8 Hz, 3H), 1.58-1.85 (m, 9H), 2.61 (dd, *J* =17.1, 5.9 Hz, 1H), 2.78 (dd, *J* =17.1, 5.9 Hz, 1H), 3.94-4.18 (m, 1H), 5.08 (s, 2H), 5.35 (br s, 1H), 7.35 (s, 5H); **^{13}C NMR** (50

MHz, $CDCl_3$) δ: 20.06, 25.5, 28.22, 43.4, 46.9, 51.31, 65.94, 127.54, 128.02, 136.36, 155.26, 211.31; **Analysis: $C_{17}H_{23}NO_3$** requires C, 70.56; H, 8.01; N, 4.84%; found C, 70.51; H, 8.08; N, 4.89%.

Benzyl 4-oxo-4-phenylbutan-2-ylcarbamate (64e)

Yield: 75%; **mp:** 97-99 °C; **IR** ($CHCl_3$, cm^{-1}): 669, 696, 757, 835, 923, 1051, 1217, 1338, 1456, 1510, 1717, 2979, 3010, 3334, 3447; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.31 (d, *J*=6.6 Hz, 3H), 3.06 (dd, *J*=16.9, 6.6 Hz, 1H), 3.38 (dd, *J*=16.9, 3.7 Hz, 1H), 4.18-4.31 (m, 1H), 5.08 (s, 2H), 5.32 (br s, 1H), 7.26-7.56 (m, 8H), 7.95 (d, *J* =7.3 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 19.95, 43.84, 44.29, 65.97, 127.51, 127.69, 128.02, 132.84, 136.36, 155.44, 198.19; **Analysis: $C_{18}H_{19}NO_3$** requires C, 72.71; H, 6.44; N, 4.71%; found C, 72.78; H, 6.49; N, 4.64%.

Benzyl 4-mesityl-4-oxobutan-2-ylcarbamate (64f)

Yield: 76%; **mp**: 79-81 °C; **IR** ($CHCl_3$, cm^{-1}): 669, 758, 835, 923, 1051, 1217, 1338, 1456, 1510, 1716, 2930, 2980, 3329, 3442; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.37 (d, *J*=6.4 Hz, 3H), 2.16 (s, 6H), 2.27 (s, 3H), 2.87 (dd, *J*=18.6 Hz, 5.9 Hz, 1H), 3.04 (dd, *J*=18.6 Hz, 2.9 Hz, 1H), 4.13-4.19 (m, 1H), 5.09 (s, 2H), 5.45 (d, *J*=7.3 Hz, 1H), 6.82 (s, 2H), 7.35 (s, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 18.41, 19.99, 20.50, 43.15, 49.58, 65.90, 127.54, 127.98, 128.09, 131.95, 136.33, 137.91, 138.68, 155.22, 208.59; **Analysis: $C_{21}H_{25}NO_3$** requires C, 74.31; H, 7.42; N, 4.13%; found C, 74.24; H, 7.48; N, 4.17%.

Benzyl 4-(4-isobutylphenyl)-4-oxobutan-2-ylcarbamate (64g)

Yield: 73%; **IR** ($CHCl_3$, cm^{-1}): 662, 762, 1078, 1147, 1329, 1456, 1702, 2886, 2975, 3367; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 0.91 (d, *J*=6.8 Hz, 6H), 1.29 (d, *J*=6.8 Hz, 3H), 1.89 (m, 1H), 2.52 (d, *J*=7.3 Hz, 2H), 3.01 (dd, *J*=16.1, 6.3 Hz, 1H), 3.35 (dd, *J*=16.1, 3.9 Hz, 1H), 4.12-4.32 (m, 1H), 5.07 (s, 2H), 5.44 (d, *J*=7.3 Hz, 1H), 7.18-

7.39 (m, 7H), 7.86 (d, *J*=7.8 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 20.21, 22.23, 29.91, 43.92, 44.18, 45.2, 66.23, 127.84, 128.02, 128.28, 129.16, 134.56, 136.51, 147.46, 155.44, 197.90; **Analysis: $C_{22}H_{27}NO_3$** requires C, 74.76; H, 7.70; N, 3.96%; found C, 74.83; H, 7.77; N, 3.94%.

Benzyl 4-(4-methoxyphenyl)-4-oxobutan-2-ylcarbamate (64h)

Yield: 72%; **mp**: 95-96 °C; **IR** ($CHCl_3$, cm^{-1}): 667, 769, 831, 910, 1057, 1245, 1338, 1456, 1514, 1612, 1705, 2637, 2935, 3340, 3441; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.29 (d, *J*=6.8 Hz, 3H), 2.99 (dd, *J*=16.1, 6.4 Hz, 1H), 3.34 (dd, *J*=16.1, 3.9 Hz, 1H), 3.87 (s, 3H), 4.17-4.33 (m, 1H), 5.09 (s, 2H), 5.43 (br s, 1H), 6.93 (d, *J*=8.8 Hz, 2H), 7.35 (s, 5H), 7.95 (d, *J*=8.8 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 20.32, 43.88, 44.40, 55.28, 66.30, 113.65, 127.84, 128.31, 130.30, 136.55, 155.55, 163.53, 196.98; **Analysis: $C_{19}H_{21}NO_4$** requires C, 69.71; H, 6.47; N, 4.28%; found C, 69.65; H, 6.41; N, 4.37%.

Benzyl 4-(2,4-diethoxyphenyl)-4-oxobutan-2-ylcarbamate (64i)

Yield: 70%; **mp**: 96-98 °C; **IR** ($CHCl_3$, cm^{-1}): 669, 770, 883, 930, 1024, 1215, 1338, 1456, 1506, 1702, 2840, 2972, 3265, 3371; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.19 (d, *J*=6.4 Hz, 3H); 1.33 (t, *J*=7.2 Hz, 3H), 1.38 (t, *J* =7.2 Hz, 3H), 3.05 (dd, *J*=16.7, 4.8 Hz, 1H), 3.15 (dd, *J*=16.7, 5.2 Hz, 1H), 3.95-4.02 (m, 4H), 4.10-4.16 (m, 1H), 4.98 (s, 2H), 5.42 (br s, 1H), 6.32 (s, 1H), 6.40 (d, *J*=8.8 Hz, 1H), 7.18-7.27 (m, 5H), 7.69 (d, *J*=8.8 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: ; **Analysis: $C_{22}H_{27}NO_5$** requires C, 68.55; H, 7.06; N, 3.63%; found C, 68.47; H, 7.09; N, 3.68%.

Benzyl 4-(2-methylnaphthalen-6-yl)-4-oxobutan-2-ylcarbamate (64j)

Yield: 73%; **mp**: 110-112 °C; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 1.45 (d, *J*=6.8 Hz, 3H), 2.37 (s, 3H), 3.04 (dd, *J* =18.6, 5.9 Hz, 1H), 3.2 (dd, *J*=18.6, 4.4 Hz, 1H), 4.22-4.34 (m, 1H), 5.11 (s, 2H), 5.45 (d, *J* =7.3 Hz, 1H), 7.29-7.46 (m, 9H), 7.74-7.84 (m, 2H);

^{13}C NMR (50 MHz, $CDCl_3$) δ: 18.62, 20.11, 43.09, 50.21, 65.92, 123.13, 124.99, 126.47, 127.52, 127.81, 127.99, 128.08, 128.44, 128.54, 129.73, 131.18, 136.24, 137.4, 155.22, 208.29; **Analysis: $C_{23}H_{23}NO_3$** requires C, 76.43; H, 6.41; N, 3.88%; found C, 76.48; H, 6.31; N, 3.81%.

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LIST OF PUBLICATIONS

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