ASYMMETRIC SYNTHESIS OF BIOACTIVE MOLECULES AND FORMATION OF *C-C, C-N, C-Br, S-O* BONDS BY TRANSITION METAL CATALYSIS

A THESIS

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CERTIFICATE

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

(Dr. A. Sudalai)

Research Supervisor

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Vinay Thakur

ABBREVATIONS

AD	Asymmetric Dihydroxylation
AH	Asymmetric Hydrogenation
AIBN	2,2'-Azobisisobutyronitrile
Ac	Acetyl
Ar	Aryl
bp	Boiling Point
Bn	Benzyl
BOC	N-*tert*-Butoxycarbonyl
DHQ	Dihydoquinine
DHQD	Dihydroquinidine
DMF	Dimethyl formamide
DMSO	Dimethyl sulphoxide
ee	Enantiomeric excess
Et	Ethyl
EtOAc	Ethyl acetate
EtOH	Ethyl alcohol
g	Grams
h	Hours
HPLC	High pressure liquid chromatography
IR	Infra red
M^+	Molecular ion
Me	Methyl
min	Minutes
ml	Milliliter
mp	Melting point
MS	Mass spectrum
NMR	Nuclear Magnetic Resonance
NBS	N-Bromosuccinimide
Pet. ether	Petroleum ether
Ph	Phenyl
PTSA	*p*-Toluene sulfonic acid
RT	Room Temperature
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TBHP	*Tert*. Butyl hydrogen peroxide

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 glass plates coated with silica gel (5-25 μ) containing UV active G-254 additive.
6. IR spectra were recorded on a Perkin-Elmer model 683 B or 1605 FT-IR and absorptions were expressed in cm^{-1}.
7. ^{1}H and ^{13}C-NMR spectra were recorded on 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, bs = broad singlet, and dd = doublet of doublet.
8. Mass spectra (MS) were recorded on an automated finnigan MAT 1020C mass spectrometer using ionization energy of 70eV.
9. Optical rotations were carried out on JASCO-181 digital polarimeter at 25°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, $(DHQ)_2$-PHAL, $(DHQD)_2$-PYR, $(DHQ)_2$-PYR were purchased from Aldrich

ABSTRACT

The thesis entitled "**Asymmetric Synthesis of Bioactive Molecules and Formation of *C-C, C-N, C-Br, S-O* Bonds by Transition Metal Catalysis"** 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 (R)-baclofen [*g*-amino-*b*-(4-chlorophenyl)butyric acid, (**9**)], a novel $GABA_B$ receptor agonist. The stereogenic center in the molecule is introduced both by the OsO_4-catalyzed asymmetric dihydroxylation (AD) of the corresponding olefinic ester **1** and by the asymmetric reduction of *b*-keto ester **11** using (S)-BINAP-Ru (II) complex. **Chapter 2** deals with the asymmetric synthesis of three *b*-adrenergic blockers (S)-propranolol (**12a**), (S)-moprolol (**12b**), (S)-toliprolol (**12c**) by OsO_4-catalyzed AD reaction *via* its cyclic sulfate. **Chapter 3** presents the asymmetric synthesis of *a*-aryl propionic acids such as (S)-phenylpropionic acid (**22a**), (S)-ibuprofen (**22b**) and (S)-naproxen (**22c**) *via* kinetic resolution of secondary alcohols using palladium catalyst. This chapter also presents the synthesis of some novel sulfur and nitrogen palladacycles and their application in arylation reactions. **Chapter 4** deals with the use of transition metals for some important organic transformations such as asymmetric sulfoxidation, kinetic resolution of racemic sulfoxides and bromoamination of olefins. It also presents NBS-catalyzed aziridination of olefins.

CHAPTER 1

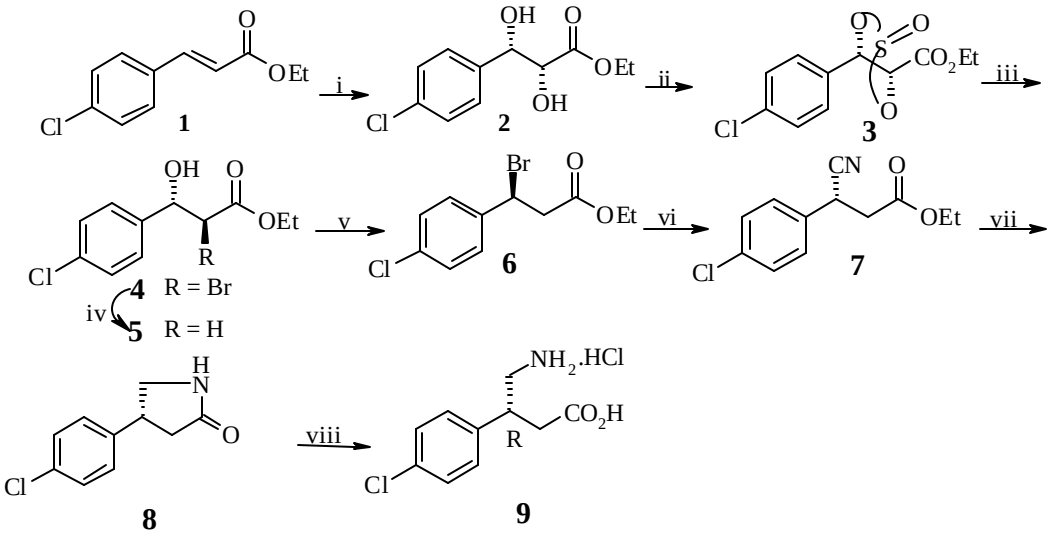
Enantioselective Synthesis of (R)-Baclofen, a Novel $GABA_B$ Receptor Agonist *via* Asymmetric Dihydroxylation and Asymmetric Hydrogenation

g-Aminobutyric acids (GABA) are important neurotransmitters used in the treatment of epilepsy. Their deficiency is associated with diseases that exhibit neuromuscular dysfunctions such as epilepsy, Huntington and Parkinson's diseases.[1] (R)-Baclofen (**9**) is one such neurotransmitter, the enantioselective synthesis of which is presented in this chapter.

(a) Asymmetric Dihydroxylation (AD) Approach: OsO_4-catalyzed asymmetric dihydroxylation (AD) of olefins is one of the most important and practical reactions to yield *vicinal* 1,2 *cis*-diols with high degree of optical purity and excellent yields.[2] The reaction is insensitive to oxygen, easy to perform and carried out in water-^{t}BuOH mixture

at room temperature. Cinchona alkaloids such as dihydroquinine, dihydroquinidine and their derivatives are used as chiral ligands in AD reactions to induce chirality in the resulting diols.

This chapter presents the enantioselective synthesis of (R)-baclofen (**9**) using asymmetric dihydroxylation (AD) (**Scheme 1**) and asymmetric hydrogenation (**Scheme 2**) as key reactions to introduce stereogenic center in the molecule.

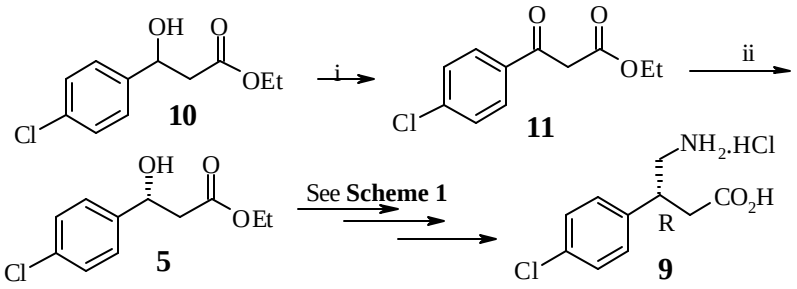


Scheme 1: (i) cat. OsO_4, $(DHQ)_2$-PHAL, $K_3Fe(CN)_6$, $MeSO_2NH_2$, K_2CO_3, *t*-BuOH:H_2O (1:1), 0^0-25^0C, 24 h, 94% yield, 95% ee; (ii) $SOCl_2$, Et_3N, CH_2Cl_2, 0^0C, 30 min. 86%; (iii) a) cat. $RuCl_3.3H_2O$, $NaIO_4$, CH_3CN: H_2O, 0^0C, 10 min. b) anhydrous LiBr, THF, 25^0C, 45 min. c) 20% H_2SO_4, Et_2O, 25^0C, 4 h, over all 65%; (iv) Bu_3SnH, AIBN, benzene, 80^0C, 75%; (v) PBr_3, pyridine, Et_2O -20^0 to 0^0C, 79%; (vi) NaCN, DMF, 70^0C, 18 h, 88%; (vii) $NiCl_2.6H_2O$, $NaBH_4$, MeOH, 25^0C, 1 h, 75%; (viii) 6N HCl, reflux, 16 h, 78%, $[\alpha]_D = -1.70$ (c 0.6, H_2O), 85% ee.

Reformatsky reaction of 4-chlorobenzaldehyde with ethyl bromoacetate followed by dehydration gave the corresponding *a,b*-unsaturated ester **1** in an overall yield of 85%. AD reaction of **1** using cat. OsO_4 and $(DHQ)_2$-PHAL [hydroquinine 1,4-phthalazinediyl diether] as chiral ligand gave chiral diol **2** in 94% yield and 95 % ee. Diol **2** was converted to cyclic sulfite **3** followed by its conversion to bromoalcohol **4** in a three-step procedure with 65% overall yield. The bromoalcohol **4** was subjected to selective *C-Br* reduction with Bu_3SnH without affecting aryl *C-Cl* function to afford *b*-hydroxy alcohol **5** in 75% yield. The bromoester **6**, obtained by the bromination of **5** with PBr_3, was subjected to displacement with NaCN in DMF to afford the nitrile **7** in 88% yield. Chemoselective reduction of *b*-cyanoester **7** was carried out by using either $NaBH_4$, $NiCl_2.6H_2O$ or PtO_2

and H_2 (40 *psi*) to give the lactam **8** which was hydrolyzed with 6N HCl to afford (R)-baclofen (**9**) in 78% yield and 85% ee.

b) Asymmetric Hydrogenation (AH) Approach: Asymmetric reduction of *b*-ketoesters using BINAP [2,2'-bis(diphenylphosphino)-1,1'-binaphthyl]-Ru (II) complexes[3] is a well-known method for the preparation of optically active *b*-hydroxy esters because of high yields, clean reaction procedures and excellent optical purity. High efficiency of chiral multiplication (a substrate to catalyst mol ratio > 1000) makes this method much more impressive and practical. Since the optical purity of (R)-baclofen (**9**) obtained by AD route was only moderate (85% ee), it was of interest to provide an alternative synthesis by AH route.



Scheme 2: (i) PCC, CH_2Cl_2, 25^0C, 3 h or $H_2Cr_2O_7$, Et_2O, 0^0-25^0C, 4 h, 75%; (ii) Ru(II)-(S)-BINAP, MeOH, H_2 (400 *psi*), 95% yield, 96% ee.

Scheme 2 describes the enantioselective synthesis of (R)-baclofen (**9**) *via* the asymmetric reduction of *b*-ketoester **11**, using (S)-BINAP-Ru (II) complex as catalyst. *b*-Ketoester **11** was synthesized in two steps starting from 4-chlorobenzaldehyde. Asymmetric hydrogenation of *b*-ketoester **11** was carried out using Noyori's catalyst [(S)-BINAP-Ru-(II)] under H_2 (400 *psi*) pressure to afford *b*-hydroxy ester **5** in 95% yield and 96% ee. The transformation of *b*-hydroxy ester **5** into (R)-baclofen (**9**) {$[\alpha]_D$= – 1.81 (c 0.6, H_2O), 91% ee} was achieved by essentially following the sequence of reactions as shown in **Scheme 1**.

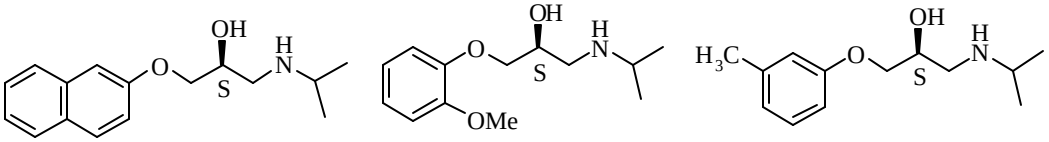
CHAPTER 2

Asymmetric Synthesis of (S)-Propranolol, (S)-Moprolol and (S)-Toliprolol *via* OsO_4- Catalyzed Asymmetric Dihydroxylation

b-Adrenergic blocking agents (*b*-blockers) are important drugs widely used for the treatment of hypertension and angina pectoris.[4] Blocking of *b*-receptor system reduces the overall activity of the sympathetic nervous system. *b*-Blockers are thus used to increase

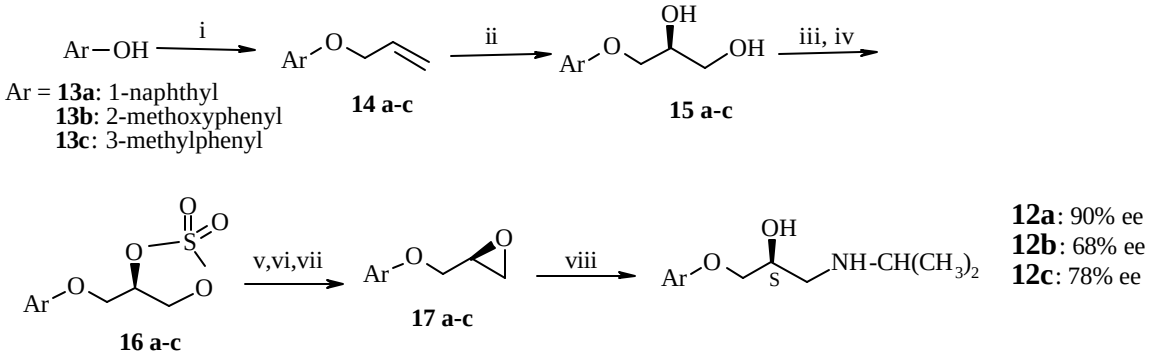
life expectancy after the occurrence of the heart attack. Although (S)-isomers are known to be much more effective (50-500 fold) than the (R)-isomers,[5] these antihypertensive drugs are sold as racemic mixtures. To avoid unnecessary stress or in some cases toxicity to an organism caused by the (R)-isomers, the administration of optically pure (S)-isomers is desirable.

This chapter describes the asymmetric synthesis of three *b*-adrenergic blockers, (S)-propranolol (**12a**), (S)-moprolol (**12b**) and (S)-toliprolol (**12c**).



Propranolol (12a) **Moprolol (12b)** **Toliprolol (12c)**

O-Allylation of phenols **13a-c** gave O-allyl ethers **14a-c**, which were subjected to AD in presence of $(DHQD)_2$-PHAL [hydroquinidine 1,4-phthalazinediyl diether] as chiral ligand to yield chiral diols **15a-c**. The diols **15a-c** were converted to cyclic sulfates **16a-c** in a two step sequence. As nucleophilic opening of cyclic sulfates with amines have resulted in lower yields, the cyclic sulfates **16a-c** were further transformed to the corresponding epoxides **17a-c** in three steps. The regiospecific opening of epoxides **17a-c** by isopropyl amine gave the corresponding drugs **12a-c** in high yields and moderate optical purity (**Scheme 3**).



Scheme 3: (i) K_2CO_3, CH_2=$CHCH_2Br$, acetone, reflux, 12 h; 97-99%; (ii) cat-OsO_4, $(DHQD)_2$-PHAL, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH:H_2O, 0°C, 12 h, 94-98%; 73-90% ee; (iii) $SOCl_2$, Et_3N, CH_2Cl_2, 0°C, 40 min.; 96-99%; (iv) cat. $RuCl_3.3H_2O$, $NaIO_4$, CH_3CN:H_2O, 0°C, 30 min., 94-98%; (v) LiBr, THF 25°C, 2-3 h; (vi) 20% H_2SO_4, Et_2O, 25°C, 10 h; (vii) K_2CO_3, MeOH, 0°C, 2 h, 80-85% overall in three steps; (viii) ^{i}Pr-NH_2, H_2O (cat.), reflux, 2 h, 99%.

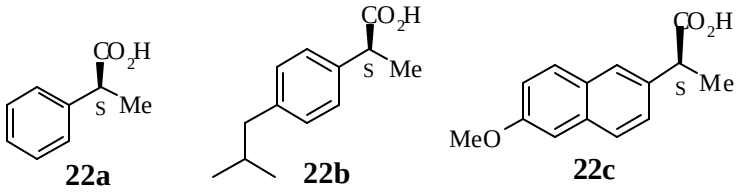
CHAPTER 3

Applications of Pd (II) Complexes in Synthesis of (S)-α-Aryl Propionic Acids and *C-C* Bond Formation

SECTION I: Asymmetric Synthesis of (S)-α-Aryl propionic Acids via Pd-Catalyzed Kinetic Resolution of Secondary Alcohols

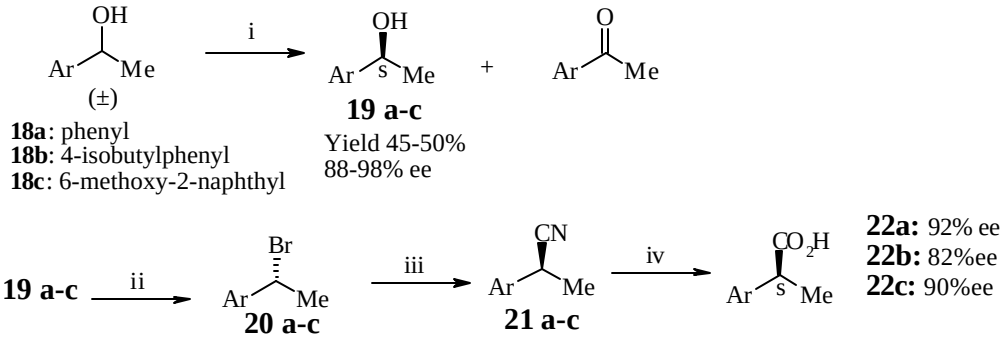
Enantioselective synthesis has produced a strong impact on pharmaceutical and agricultural industry, where efficiency of a chiral biological agent often depends upon the enantiomer administered. For example, (S)-naproxen [(S)-2-(6-methoxy-2-naphthyl) propionic acid] (**22c**), one of the most potent non-steroidal anti-inflammatory drugs, is about 28 times more active than its (R)-isomer.

Recently, Pd-catalyzed oxidative kinetic resolution of secondary alcohols has been reported using molecular oxygen as the terminal oxidant in conjunction with the naturally occurring diamine ligands such as (–)-sparteine.[6]



22a **22b** **22c**

This section describes the enantioselective synthesis of three aryl propionic acids (**22a-c**) using Pd-catalyzed oxidative kinetic resolution as the key reaction (**Scheme 4**).

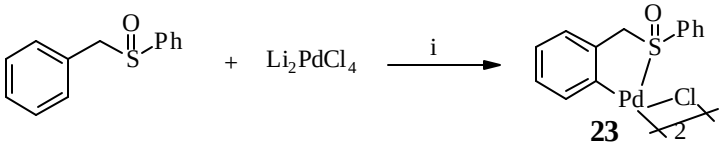


Scheme 4: (i) Pd $(OAc)_2$ (5 mol %), (–) sparteine, O_2, toluene, MS 3Å, 80^0C, 45-50%; (ii) PBr_3, Et_2O, -20^0 to 0^0C, 70-88%; (iii) NaCN, DMF, 80^0C, 80-92%; (iv) 4N HCl, reflux, 78-83%.

Secondary aryl alcohols **18a-c** were subjected to palladium catalyzed kinetic resolution using (−)-sparteine as chiral auxiliary to give enantiomerically pure alcohols **19a-c** along with the corresponding ketones. Subsequently, chiral alcohols **19a-c** were converted to the corresponding bromides **20a-c** with complete inversion of configuration using PBr_3.[7] The nucleophilic displacement of bromides **20a-c** with NaCN gave the corresponding cyano compounds **21a-c** with desired stereochemistry. Finally, acid hydrolysis of cyano compounds **21a-c** afforded the corresponding (S)-aryl propionic acids **22a-c** in excellent optical purity (82-92% ee).

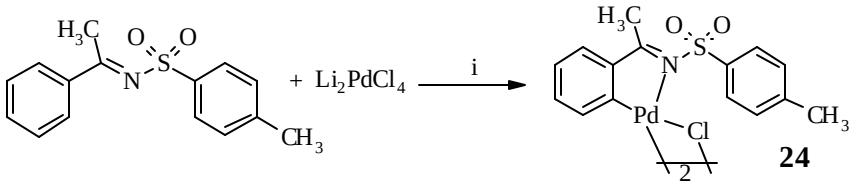
SECTION II: Synthesis of Novel Sulfur and Nitrogen Palladacycles and Their Applications in Arylation Reactions

Palladacycles are among the most active catalyst precursors reported to date for Heck reaction.[8] These highly active and thermally stable catalysts allow Heck reactions to be performed with activated as well as non-activated aryl halides using very low catalyst concentration. This section describes the synthesis of novel air, water and thermally stable sulfur **23** and nitrogen **24** palladacycles respectively (**Scheme 5** and **6**).



23 mp 143-145^{0}C

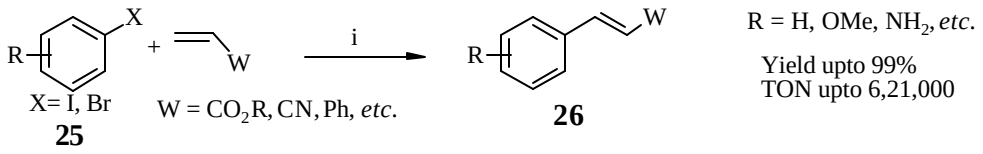
Scheme 5: (i) MeOH, 25^{0}C, 72 h, 72%.



24 mp 135-141^{0}C

Scheme 6: (i) MeOH, NaOAc, 25^{0}C, 72 h, 66%.

Both palladacycles **23** and **24** showed a remarkable activity towards Heck reaction of aryl halides **25** with various olefins to give corresponding *b*-substituted olefins **26** in excellent yields (upto 99%) and high turn over number (TON upto 6,21,000) (**Scheme 7**).



Scheme 7: (i) cat **24** or **25,** base, NMP, 150 ^{0}C.

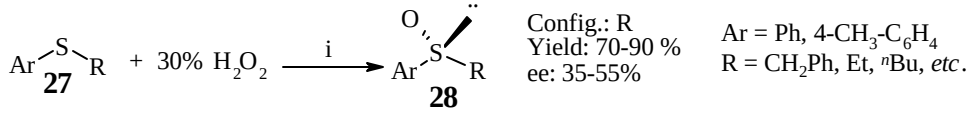
CHAPTER 4

Transition Metal Catalyzed *S-O, C-N, C-Br* Bond Formation and NBS-Catalyzed Aziridination of Olefins

SECTION I: This section is divided into two sub-sections as given bellow.

A) Tungsten Catalyzed Asymmetric Sulfoxidation of Aryl Alkyl Sulfides using Chiral Cinchona Alkaloids

Chiral sulfoxides have been extensively used as building blocks and source for chiral auxiliaries in various asymmetric synthesis of biologically active compounds.[9] Asymmetric sulfoxidation is the most effective route to make enantiomerically pure sulfoxides There are various methods known in the literature for asymmetric oxidation of sulfides using transition metal catalysts.[10] This section describes tungsten-catalyzed asymmetric oxidation of aryl alkyl sulfides **27** using cinchona alkaloids as chiral ligands and 30% aqueous H_2O_2 as oxidant to give optically active sulfoxides **28** in moderate to good enantiomeric excess (upto 55%) and excellent yields (upto 90%) (**Scheme 8**). Among the various ligands screened such as (–)-quinine, (–)-sparteine, DHQ-CLB, $(DHQD)_2$-PYR, $(DHQD)_2$-PHAL, (–)-menthol, *etc*. (–)-quinine and $(DHQD)_2$-PYR gave the best enantiomeric excess.

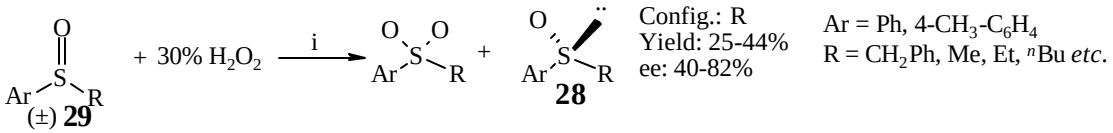


Scheme 8: (i) WO_3 (5 mol %), (–)-quinine or $(DHQD)_2$-PYR (10 mol %), THF, 0 ^{0}C, 18-48 h.

B) Tungsten Catalyzed Kinetic Resolution of Sulfoxides

Kinetic resolution of sulfoxides is one of the most important transformations in organic synthesis. There are only few examples of procedures based on the kinetic resolution of racemic sulfoxides known in the literature which involve the employment of titanium (IV)-binaphthol complex[11] and manganese(III)-salen complex as catalysts.[12]

This section deals with the kinetic resolution of racemic sulfoxides **29** using WO_3 as catalyst and chiral cinchona alkaloids such as (–)-quinine and $(DHQD)_2$-PYR as ligands in conjunction with 30% aqueous H_2O_2 as oxidant (**Scheme 9**).

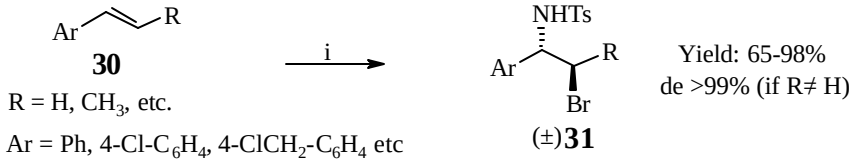


Scheme 9: (i) WO_3 (5mol%), $(DHQD)_2$-PYR (10 mol%), 30% H_2O_2, THF, 25^{0}C, 20-24 h.

SECTION II: Cu and Mn-Catalyzed Bromoamination of Olefins

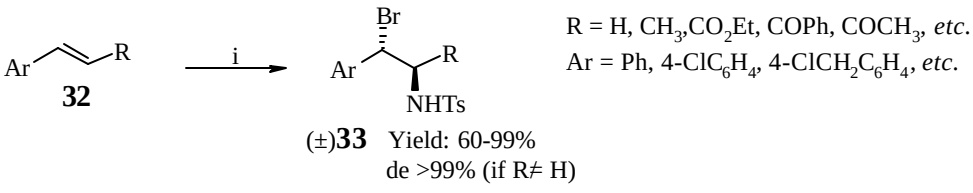
The functionalization of olefins by addition of the two different functional groups in a single step is an important transformation (for e.g. aminohydroxylation, halohydration, haloazidation, haloamination, *etc*.). Among all these, haloamination is one of the most useful reactions[13] as the halogens can be replaced by a variety of nucleophiles such as N_3, CN, OAc, OMe, NHR, SR, *etc*. thereby providing a new class of functionalized reactive intermediates in organic synthesis.

This section describes regiospecific and stereoselective bromoamination of olefins **30** catalyzed by Cu (I and II) and Mn (II) salts using NBS (N-bromosuccinimide) as the bromine source and *p*-toluene sulfonamide as the nitrogen source (**Scheme 10**).



Scheme 10: (i) CuI or $MnSO_4$ (10 mol%), $TsNH_2$ (1.1 equiv.), NBS (1.2 equiv), CH_2Cl_2, 25^{0}C, 2-24 h.

However, when the catalytic system was changed from Mn (II) salts to Mn (III) salts or Mn(III)-salen there was remarkable reversal in the regioselectivity of the resulting product giving other regioisomer **33** exclusively (**Scheme 11**).



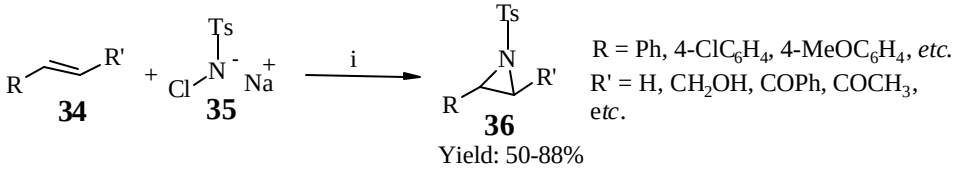
Scheme 11: (i) Mn(III)-salen or CuI/$MnSO_4$ (10 mol%), NBS (1.2 equiv.), $TsNH_2$ (1.1 equiv.), CH_2Cl_2, 25^0C, 2-24 h.

Bromoamination of various *a,b*-unsaturated (**32**, R= CO_2Et, COPh, *etc.*) compounds were also carried out using Cu or Mn-catalysts in good to excellent yields (60-88%) in highly regiospecific and stereoselective manner (**Scheme 11**).

SECTION III: NBS-Catalyzed Aziridination of Olefins Using Chloramine-T as Nitrogen Source

Because of their highly regio- and stereoselective ring opening reactions, aziridines are valued as building blocks for the synthesis of wide range of nitrogen-containing compounds.[14] Several groups have developed transition metal-catalyzed aziridinations based on PhI=NTs as the nitrogen source.[15]

This section deals with the use of NBS or N-bromoacetamide as catalysts for aziridination of olefins **34** including *a,b*-unsaturated compounds, using Chloramine-T (**35**) as the nitrogen source to yield *trans*-aziridines **36** in 50-88% yields (**Scheme 12**).



Scheme 12: (i) NBS or N-bromoacetamide (20 mol%), CH_3CN, 25^0C.

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CHAPTER 1

Enantioselective Synthesis of (R)-(–)-Baclofen, a Novel $GABA_B$ Receptor Agonist, *via* Asymmetric Dihydroxylation and Asymmetric Hydrogenation

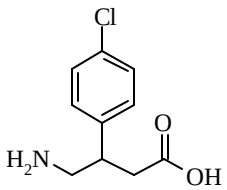
Enantioselective Synthesis of (R)-(-)-Baclofen, a Novel $GABA_B$ Receptor Agonist, *via* Asymmetric Dihydroxylation and Asymmetric Hydrogenation

1.0.1 Introduction

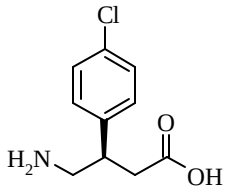
Baclofen [*g*-amino-*b*-(*p*-chlorophenyl)butyric acid, **1**] is a derivative of *g*-aminobutyric acid (GABA). It plays an important role as an inhibitory neurotransmitter in central nervous system (CNS) of mammalians.[1] A simple amino acid has two major receptor subtypes, $GABA_A$ and $GABA_B$. These receptors play a distinct role in central and peripheral nervous system through ion-channel regulation.[2] The overall physiological effect is transmission inhibition, pre and post-synaptically mediated by $GABA_A$ sites and pre-synaptically by $GABA_B$ sites. However, baclofen is the only potent and selective $GABA_B$ agonist known so far against bicuculline receptor.[3] In contrast to that of simple GABA, baclofen is the most lipophilic and can penetrate to blood/brain barrier. Consequently, baclofen helps to reduce the excitatory effect of active compounds such as benzodiazepine, barbiturate, *etc*.[4]

The deficiency of GABA is associated with diseases that exhibit neuromuscular dysfuntions such as epilepsy, Huntigton, Parkinsons' diseases *etc*.[5] Baclofen is one of the most promising drugs in treatment of the paroxysmal pain of trigeminal neuralgia[6] as well as spasticity of spinal without influencing the sedation.[7]

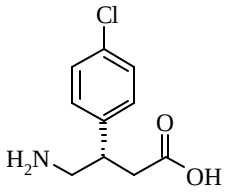
1.0.2 The Pharmacology of Baclofen



(±)-Baclofen **(1)**



(R)-(-)-Baclofen **(1a)**



(S)-(+)-Baclofen **(1b)**

Bowery *et al.*[1,2] has demonstrated that baclofen helps to decrease the neurotransmitter release in mammalian central nervous system by action at the GABA-receptor. This effect is associated with the stereospecificity of (R)-(–)-baclofen (**1a**) isomer being 100-fold more active in producing neural depression than (S)-(+)-baclofen (**1b**) isomer.

The $GABA_B$ receptors of peripheral and central nervous systems are associated with many biological processes including analgesia, muscle relaxation, hypertension, increased gastric mutility and inhibition of the liberation of corticotropin releasing hormone. There are only few agonist and antagonists available concerning these factors. Baclofen is one of them and used in treatment of spasticity, a serious disease characterized by increase muscle tone, usually perceived muscle tightness or achiness in the limbs.[8] These symptoms are normally associated with multiple sclerosis. Although baclofen is commercially available in its racemic form, only the (R)-enantiomer (**1a**) shows entire medicinal activity.[1,9]

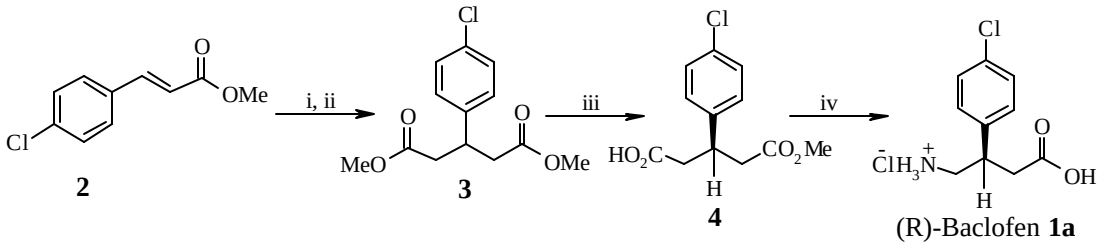
1.0.3 Review of Literature

Literature search revealed that there are several reports available on the synthesis of (R)-(–)-baclofen (**1a**). They are concerned mostly with resolution, chemo-enzymatic or enantioselective synthesis, which are described below.

Chenevert's approach (1991)

Chenevert *et al.*[10] have achieved the synthesis of both (R)- and (S)-baclofen by enantioselective hydrolysis of intermediate **3** using *Chymotrypsin* enzyme (**Scheme 1**). Michael addition of dimethyl malonate with **2** followed by demethoxycarbonylation afforded the key intermediate **3**. It was then subjected to enantioselective hydrolysis with *Chymotrypsin* enzyme to afford chiral monoester **4** in 98% ee and 85% yield. The chiral

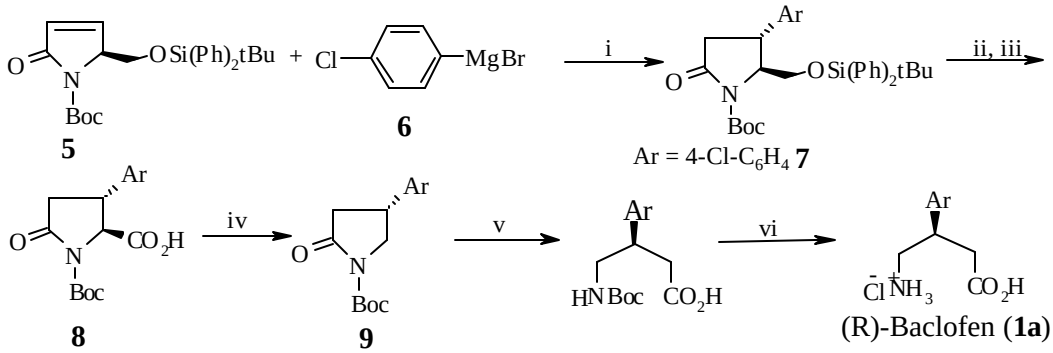
monoester **4** upon Curtius rearrangement followed by acid hydrolysis gave (R)-(–)-baclofen (**1a**).



Scheme 1: (i) Dimethyl malonate, CH_3ONa, THF, reflux; (ii) NaCl, H_2O, DMSO, 160°C; (iii) *a-Chymotrypsin*, phosphate buffer, pH 7.7, 25°C; (iv) a: Ethyl chloroformate, Et_3N, acetone, 0°C; b: NaN_3, H_2O, acetone; c: toluene, reflux; d: HCl, H_2O.

Hubmann's approach (1992)[11]

Hubmann's strategy to synthesize (R)-baclofen (**1a**) involved stereoselective Michael addition of (S)-pyroglutamic acid derivative **5** with Grignard reagent **6** (**Scheme 2**).

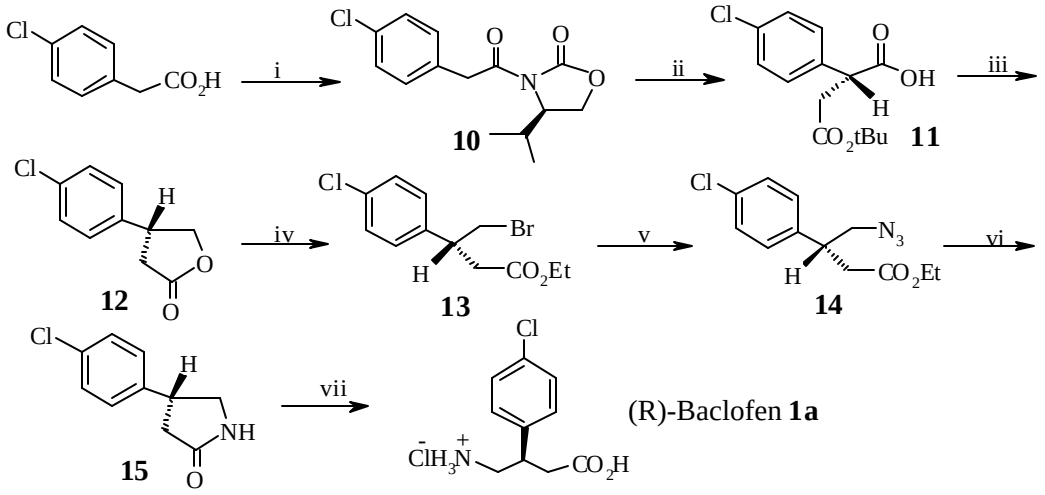


Scheme 2: (i) $CuBr.SMe_2$, Et_2O, -35°C, 20 min; -78°C, TMS-Cl, NH_4Cl; (ii) Et_3NHF, THF, RT, 4-5 days; (iii) $RuCl_3$, $NaIO_4$, CH_3CN:CCl_4 (2:1), H_2O; (iv) N-methylmorpholine, isobutyl chloroformate, –15°C, N-hydroxy-2-thiopyridone, Et_3N, THF, 2 h; (v) aq. 1M LiOH, 1.5 h, (vi) 6M HCl, reflux, 3 h.

Schoenfelder's approach (1993)[12]

This strategy makes use of enantioselective alkylation of chiral 2-(4-chlorophenyl) acetyl oxozolidone (**10**). The oxozolidone **10** was prepared from 2-(4-chlorophenyl)acetic acid. It was then converted to chiral *t*-butyl-2-(4-chlorophenyl)succinate **11** in two steps. Chemoselective reduction of the acid functionality of **11** followed by dehydration gave *g*-butyrolactone **12**. The lactone **12** was then converted to azidoester **14**, which on reduction

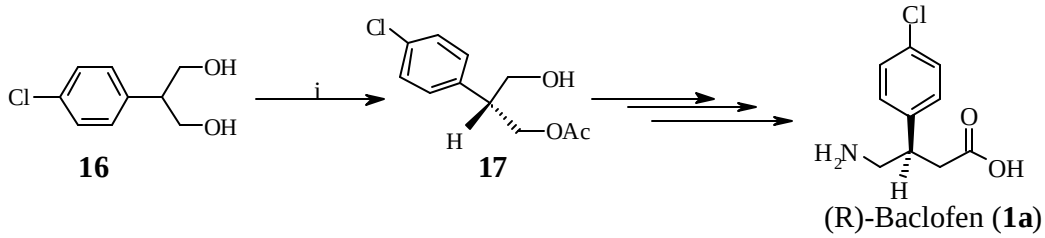
followed by cyclization gave lactam **15**. Lactam **15** was then hydrolyzed with HCl to afford (R)-baclofen (**1a**) hydrochloride salt (**Scheme 3**).



Scheme 3: (i) a) $ClCO^tBu$, Et_3N; b) Li-oxazolidine, THF, -78°C; (ii) a) NaHMDS, $BrCH_2CO_2{}^tBu$, -78°C; b) H_2O_2-LiOH; (iii) a) BH_3.DMS; b) *p*-TSA, toluene, reflux; (iv) EtOH, HBr; (v) NaN_3, DMSO; (vi) a) PPh_3, H_2O; b) DMAP, toluene, reflux; (vii) 6N HCl, reflux.

Desjardins's approach (1994)[13]

In this approach *lipase* was used to carry out the enantioselective acetylation of 2-(4-chlorophenyl)-1,3-propane diol (**16**) to give optically active mono acetate **17** as a key step. The mono acetate **17** was further converted to (R)-baclofen (**Scheme 4**).

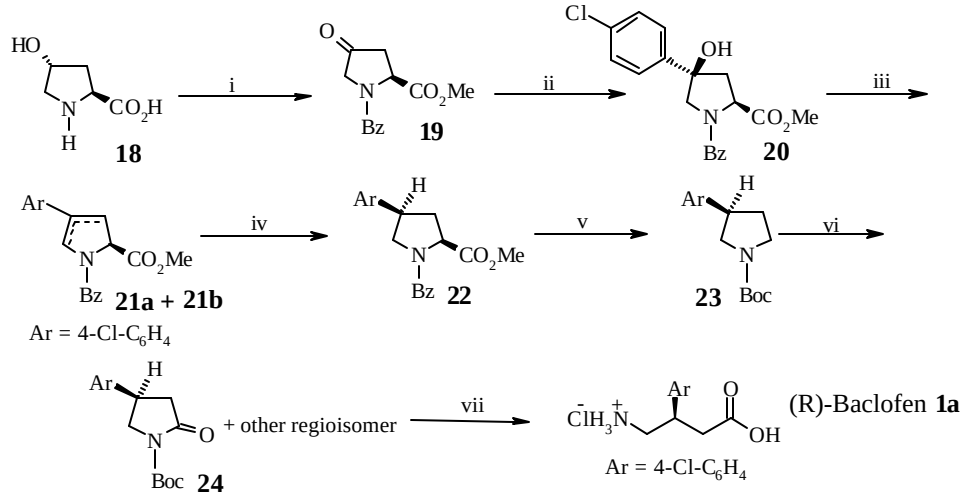


Scheme 4 : (i) *lipase*, Ac_2O.

Yashifuji's approach (1995)[14]

This approach consists of chiral *trans*-4-hydroxy-L-proline (**18**) as a chiral precursor for the synthesis of both (R)- and (S)- baclofen (**Scheme 5**). The strategy is based on the following two key steps (i) a stereoselective hydrogenation of dehydroproline

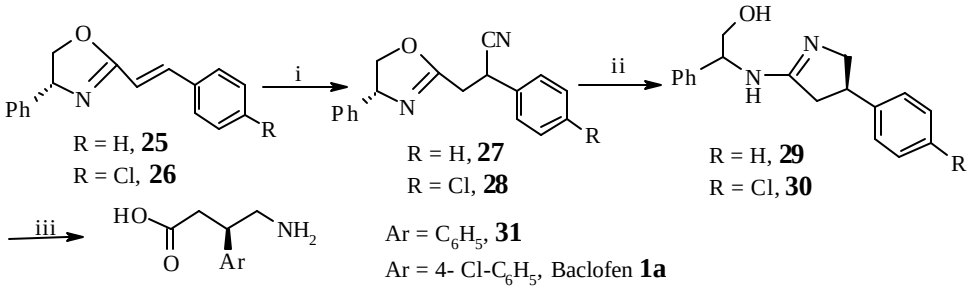
derivative **21a** and **21b**, controlled by C_2-carboxyl functionality (ii) an effective Ru-catalyzed oxidation of pyrrole **23** to pyrrolidone **24**.



Scheme 5: (i) a) MeOH; b) benzoyl chloride, Et_3N; $COCl_2$, DMSO, Et_3N, -78°C, 92%; (ii) 4Cl-Ph-Br, Mg, $CeCl_3$, Et_2O, RT, 78%; (iii) $SOCl_2$, pyridine, RT, 79%; (iv) Pt, H_2 (1 atm), RT, 6N HCl AcOH, 110°C; (v) a) cyclohexanol, 2-cyclohexen-1-one, 155°C; b) *tert.* Butoxylchloride; (vi) RuO_2, aq. $NaIO_4$, AcOEt : H_2O, RT, 3 h; (vii) 6N HCl, reflux, 18 h.

Langlois's approach (1997)[15]

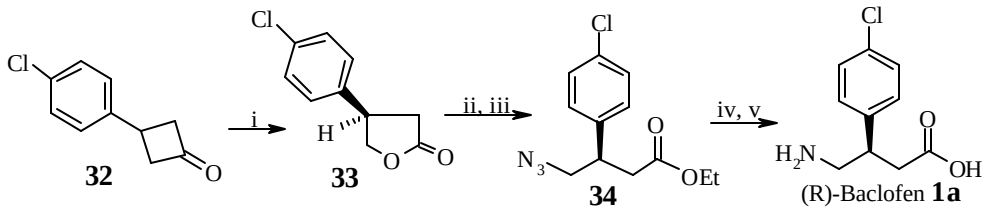
Using this method both (R)-4-amino-3-phenylbutyric acid (**31**) and (R)-baclofen (**1a**) have been synthesized in 50% ee. The chiral precursors, *a*,*b*-unsaturated oxazoline **25** and **26**, were derived from the reaction of (R)-phenylglycinol with the corresponding cinnamic acids and these were subjected to hydrocyanation reaction to afford cyanooxazolines **27** and **28**. Subsequently, these were reduced to imides **29** and **30** respectively. Finally, imides **29** and **30** were hydrolyzed to give (R)- (**31**) and (R)-baclofen (**1a**) respectively (**Scheme 6**).



Scheme 6: (i) $AlEt_2CN$, DCM, -30°C, RT, 48 h, 30-40%, 50% de; (ii) $NaBH_4$, $NiCl_2$, THF:H_2O (2:1); (iii) 2N NaOH:EtOH, 100°C, 14 h, 97%.

Mazzini's approach (1997)

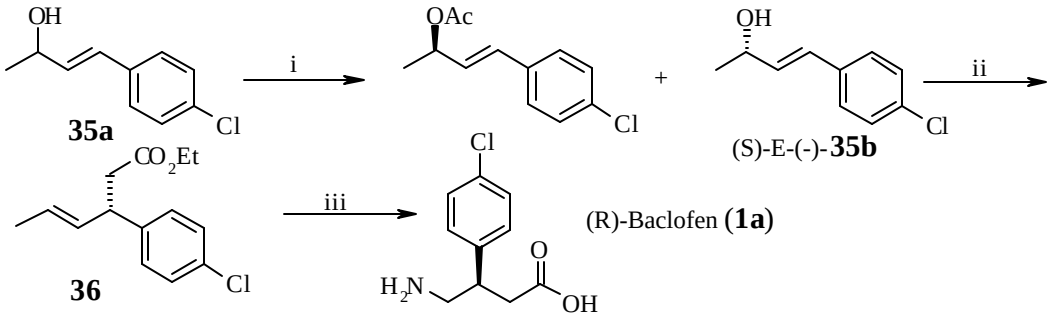
Mazzini *et al.*[16] have synthesized (R)-baclofen *via* chemoenzymatic Baeyer-Villiger oxidation as a key step (**Scheme 7**). 3-(4-Chlorophenyl)cyclobutanone (**32**) was subjected to enantioselective Baeyer-Villiger oxidation in presence of *Cunninghamell echinulata* (NRLL 3655) enzyme to obtain (3R)-chlorophenyl-*g*-butyrolactone **33** in 30% yield and >99% ee which was further converted to azidoester **34**. Subsequently, hydrolysis with NaOH and Pd-catalyzed hydrogenation afforded (R)-baclofen (**1a**).



Scheme 7: (i) culture *C. echinulata*; (ii) Me_3SiI, EtOH, DCM, 0°C to RT, 95%; (iii) NaN_3, DMF, 75°C, 95%;(iv) 2M NaOH, conc. HCl, RT, 95%; (v) Pd-C, H_2, Et_2O/EtOH, RT.

Brenna's approach (1997)[17]

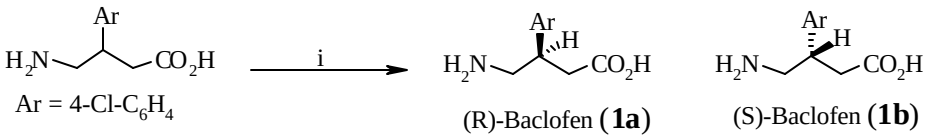
This approach involves enzymatic resolution of substituted allyl alcohol **35a** in presence of *Porcine pancreas lipase* (PPL, Sigma type II) to yield optically active allylic alcohol **35b** in >99% ee as key step (**Scheme 8**). Subsequently, it was transformed to ester **36** *via* Claisen orthoester rearrangement, which on ozonolysis followed by reductive amination afforded (R)-baclofen (**1a**).



Scheme 8: (i) *PPL*, *t*-butylmethyl ether, vinyl acetate; (ii) $CH_3C(OEt)_3$ propanoic acid, 120-130°C; (iii) O_3, CH_2Cl_2:MeOH (1:1), NH_4OAc, $NaBH_3CN$, -78°C, 12 h, 2N NaOH, HCl, RT, 2 h.

Levadoux's approach (1998)

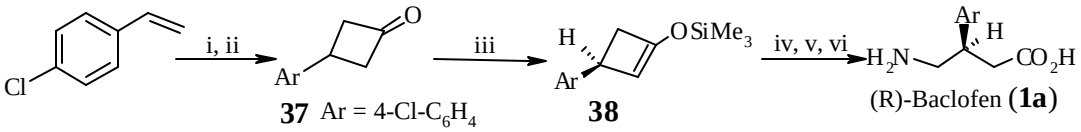
Levadoux *et al.*[18] have developed a process for obtaining optically active baclofen and its analogues by *Streptomyces microrganism*-mediated resolution (**Scheme 9**).



Scheme 9: (i) *Streptomyces microorganism.*

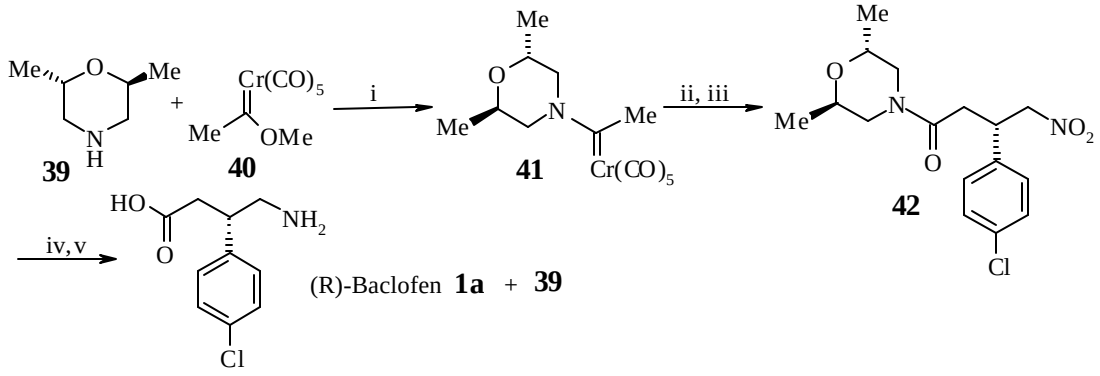
Resende's approach (1999)[19]

Resende's approach involves enantioselective deprotonation of **37** with lithium (S, S')-*a*,*a*'-dimethylbenzylamide followed by silylation afforded the chiral silylenol ether **38** in 70% yield and 98% ee. Finally, it was transformed to (R)-baclofen (**1a**) in three steps (**Scheme 10**).



Scheme 10: (i) Zn-Cu, $POCl_3$, CCl_3COCl, Et_2O, RT, 12 h, 91%; (ii) Zn/AcOH, RT, 14 h, 93%; (iii) Lithium (S,S')-*a*,*a*'-dimethylbenzylamide, THF, TMSCl, -100°C, 15 min 70%; (iv) O_3, DCM, -78°C, 40 min; (v) Me_2S, –78°C to RT, 12 h; (vi) $NaBH_3CN$, NH_4OAc, 12 h, 6N HCl (one pot sequence)

Licandro's approach (2000)

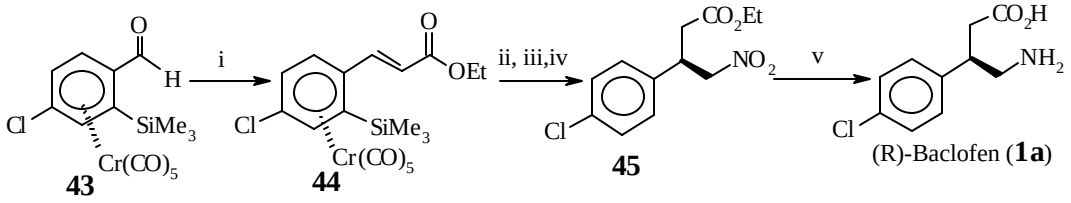


Scheme 11: (i) aminolysis (ii) *n*-BuLi, THF, -97°C, *p*-Cl-PhCH=CHNO$_2$; (iii) CAN, acetone, RT, 4 h; (iv) Raney -Ni, dry-MeOH, 5 atm, 1 h; (v) 6M HCl, reflux, 8 h.

Licandro *et al.*[20] have achieved the synthesis of (R)-baclofen (**1a**) using diastereoselective Michael addition of enantiopure Cr-carbene complex **41** to *p*-chloronitrostyrene to give **42** (**Scheme 11**). The optically active chromium-carbene complex **41** was obtained by condensation of (S, S)-2,6-diemethylmorpholine (**39**) with pentacarbonyl(methoxymethylcarbene)chromium (**40**). The nitro group in **42** was then reduced with Raney-Ni and finally hydrolyzed with 6M HCl to afford (R)-baclofen (**1a**).

Baldoli's approach (2000)[21]

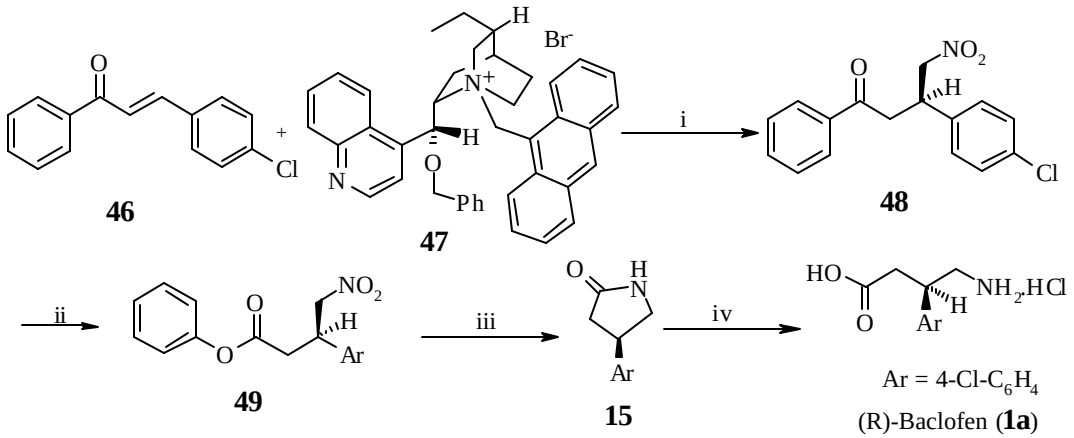
This approach involves stereoselective Michael addition of nitromethane to chiral chromium (0) complex **44** as a key step. The chiral aldehyde **43** was obtained by resolution of its diastereoisomeric-semioxamazone derivative. Aldehyde **43** was subjected to Wittig-Horner reaction to obtain ester **44** (**Scheme 12**). The Michael addition of nitromethane onto ester **44** followed by desilylation and de-complexation yielded nitroester **45**. Finally, hydrogenation of nitroester **45** followed by hydrolysis afforded (R)-baclofen (**1a**).



Scheme 12: (i) $(EtO)_2OPCH_2CO_2Et$, $(Me_3Si)_2NLi$, THF, RT; (ii) CH_3NO_2, K_2CO_3, TEBA, RT; (iii) Bu_4NF, CH_2Cl_2, RT; (iv) hν, air, CH_2Cl_2; (v) a. PtO_2, H_2, MeOH, RT; b. 6N HCl reflux.

Corey's approach (2000)[22]

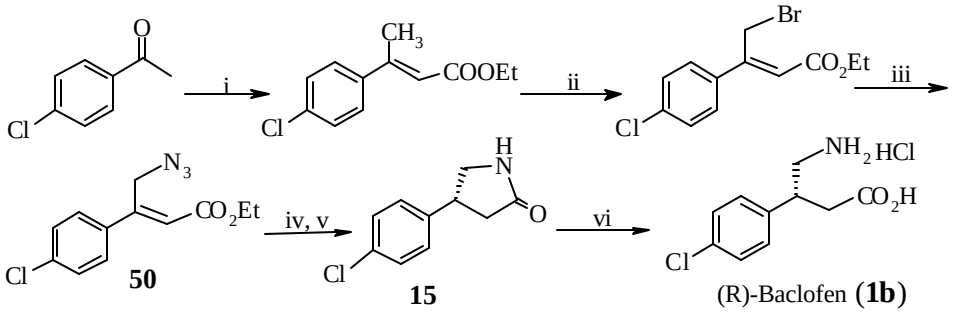
In this approach chiral quaternary ammonium salt **47** was used as a chiral catalyst for the enantioselective Michael addition of nitromethane to *a*,*b*-enone **46** to afford nitroketone **48**. Nitroketone **48** was converted to nitroester **49** followed by reduction of nitro group in **49** to give lactam **15**, which was hydrolyzed to afford (R)-baclofen (**1a**) as a hydrochloride salt (**Scheme 13**).



Scheme 13: (i) CH_3NO_2, CsF, toluene, –40°C, 36 h; (ii) *m*-CPBA, EDC, reflux, 36 h; (iii) $NaBH_4$, $NiCl_2$, MeOH, 23°C, 10 min; (iv) 5N HCl, reflux, 4 h.

Sudalai's Approach (2002)[23]

Our group have developed a simple method for the enantioselective synthesis of (R)-baclofen (**1b**) using asymmetric reduction of azido ester **50** using Ru (II)- (S)-BINAP complex to give lactam **15** which on hydrolysis gave (R)-baclofen (**Scheme 14**).



Scheme 14: i) Br-CH_2CO_2Et, Zn, benzene, reflux, *p*-TSA, toluene, 120°C, 78%; ii) NBS, AIBN, CCl_4, reflux, 10 h, 92%; ii) NaN_3, EtOH:H_2O (80:20), 80°C, 8 h, 78%; iv) Ru (II)-(S) BINAP, H_2 (200 *psi*), MeOH, 50°C, 20 h, 68%; v) $CoCl_2$, $NaBH_4$, H_2O, 25°C, 30 min, 80%; vi) 20% HCl, 100°C, 3 h, 76%.

1.0.4 Present Work

1.0.4.1 Objective

Although racemic baclofen (**1**) is commercially available in bulk quantities, its entire biological activity is associated only with the (R)-enantiomer **1a**. Various methods such as resolution, chemo-enzymatic or enantioselective synthesis have been developed to synthesize (R)-baclofen (**1a**) (*vide supra*). However, these methods suffer from disadvantages such as low overall yields, the need for separation of diastereoisomers and the use of expensive reagents. In this context, a more practical approach for the synthesis of (R)-baclofen (**1a**) is highly desirable.

Retrosynthetic analysis (**Fig. 1**) of (R)-baclofen (**1a**) reveals that either *b*-hydroxy ester **52** or nitroketone **48** could be visualized as a key intermediate. In order to prepare optically pure *b*-hydroxy ester **52**, Pd-catalyzed oxidative kinetic resolution of the corresponding racemic β-hydroxyester **55** was attempted (Route 1). However, the desired chiral alcohol **52** was obtained in low optical purity (7% ee). Further, L-proline catalyzed Michael addition of nitromethane onto 4-chlorochalcone **46** was also attempted to get the chiral nitroketone **48** (Corey's intermediate) but with poor enantioselectivity (15% ee) (Route 2).

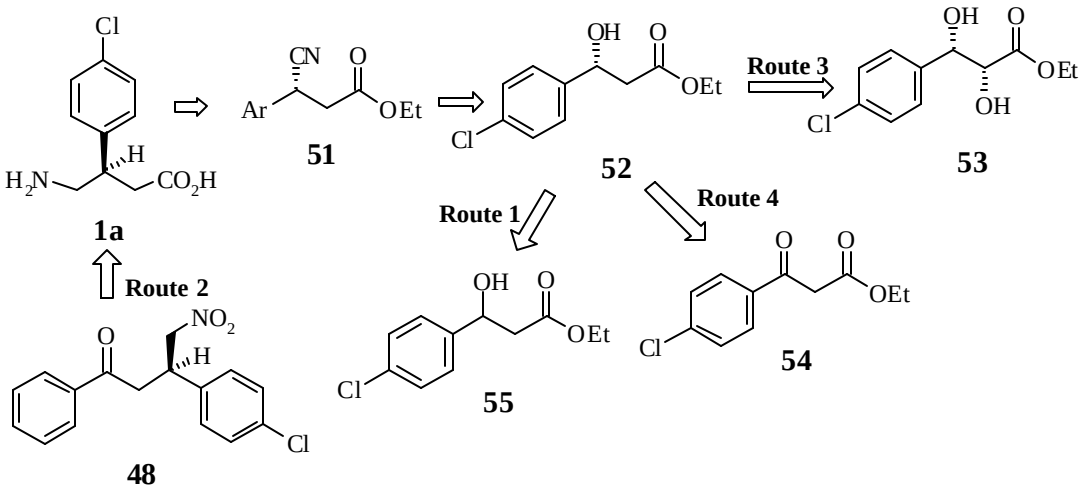


Fig. 1: Retrosynthetic analysis of (R)-baclofen (1a)

The key intermediate **52**, was successfully synthesized by the methods of asymmetric dihydroxylation (AD) *via* chiral diol **53** (Route 3) and by asymmetric hydrogenation (AH) of *b*-ketoester **54** (Route 4). This chapter describes the asymmetric synthesis of (R)-baclofen (**1a**) from **52** by employing both the AD and AH methods (**Schemes 18** and **19**).

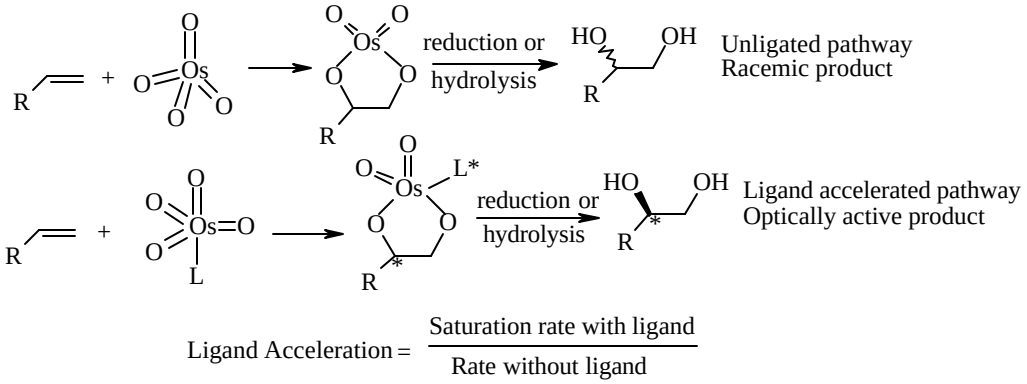
Since this chapter deals with two important asymmetric reactions (AD and AH), which introduce stereogenicity into the prochiral molecule, a brief account of each is presented in the following sections.

1.0.4.2 Asymmetric Dihydroxylation (AD)

In recent years much attention has been focused on the catalytic asymmetric synthesis. There are several methods to obtain enantiomerically pure compounds that include classical optical resolution, chromatographic separation of enantiomer, enzymatic resolution and asymmetric synthesis.[24] It often has significant economic advantages over stoichiometric asymmetric synthesis for industrial-scale production of enantiomerically pure compounds. All these asymmetric reactions crucially depend on ligand acceleration effect (LAE).[25] Among all these reactions, Sharpless's catalytic asymmetric dihydroxylation (AD) is one of the most important practical and widely used reaction in organic synthesis. It has become the most general method for the preparation of optically active *vicinal-cis*-diols from activated as well as inactivated olefins.[26]

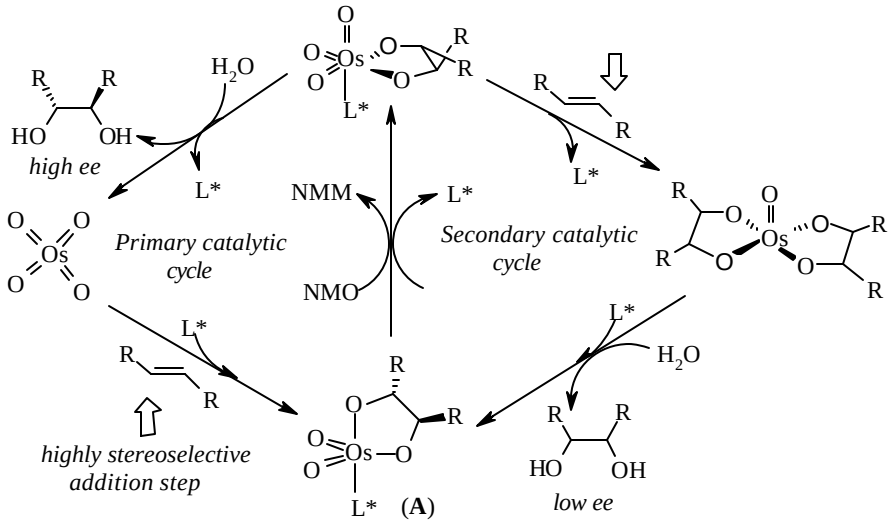
In 1936, Criegee *et al.*[27] have found that addition of pyridine or any other tertiary amine to osmylation of olefins, accelerates the rate of reaction considerably. A major breakthrough has occurred in field of asymmetric oxidation when Sharpless *et al.*[26b] demonstrated that asymmetric induction could be achieved when chiral amines were added to OsO_4-mediated asymmetric oxidation of olefins. Among the various ligands screened best results were obtained with ligands which were representatives of the cinchona

alkaloid family, dihydroquinidine (DHQD) and dihydroquinine (DHQ).[28] A number of recent methods employ chiral diamine ligands for the asymmetric osmylation of olefins. The simplified mechanism of achiral and chiral dihydroxylation is given in the **Scheme 15**.



Scheme 15: Mechanism of OsO_4-catalyzed dihydroxylation of olefin

In order to develop a catalytic method, several co-oxidants such as sodium or potassium chlorate,[29] hydrogen peroxide,[30] *tert*-butyl hydroperoxide[31] and N-methylmorpholine N-oxide (NMO)[32] were introduced. The idea to use these co-oxidants was to minimize the amount of toxic and costly osmium so as to make the process more economical.



Scheme 16: Catalytic cycle for AD using NMO as co-oxidant.

Sharpless *et al.*[33] have established that the most practical and suitable catalytic method is with NMO as co-oxidant but the ee's of the diol was less than those produced by the stoichiometric reactions (primary catalytic cycle, **Scheme 16**). The reason was thought to be the involvement of second catalytic cycle (secondary catalytic cycle, **Scheme 16**), which results in low or no ee at all. To improve the %ee of the chiral diol, the second catalytic cycle of AD should be avoided and this was achieved by employing the $K_3Fe(CN)_6$ as reoxidant and using biphasic conditions (**Fig. 2**).[24,34] These conditions helped in protecting the organic osmate-(VI) monoglycolate ester (species **A**, **Scheme 16**) from inopportune oxidation prior to hydrolysis and thereby releasing the diol and ligand to the organic phase and osmium-(VI) to the aqueous phase. Subsequently, osmium-(VI) gets reoxidized and recycled into the catalytic cycle. Further improvement in the AD was realized by the addition of methyl sulfonamide ($MeSO_2NH_2$) to the reaction mixture. It also helps to accelerate the hydrolysis of the species **A**, thus facilitating the dihydroxylation smoothly.[24].Addition of methyl sulfonamide also allowed carrying out the reactions of 1, 2-di, tri and tetra substituted olefins at 0^0C, which improved the selectivity as well as %ee.

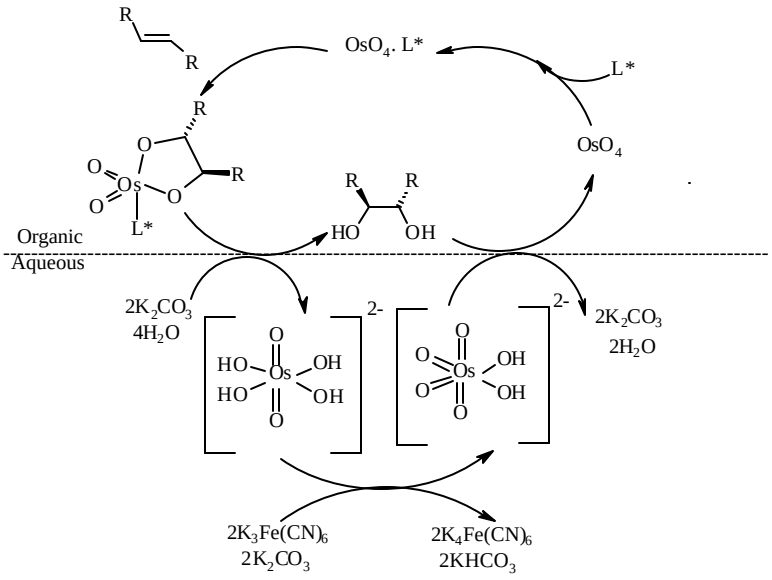
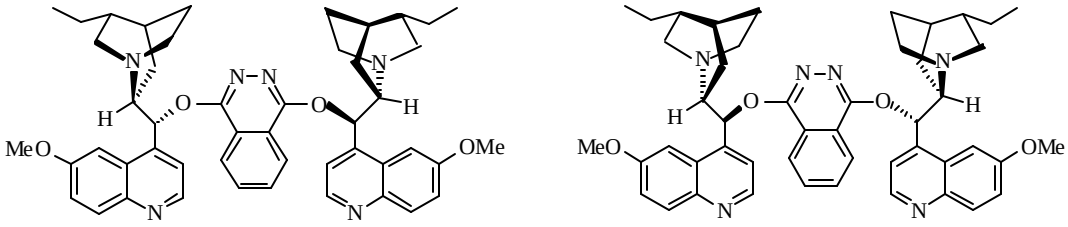


Fig. 2: Catalytic cycle for AD using $K_3Fe(CN)_6$ as co-oxidant.

In order to develop the asymmetric version of the Os-catalyzed AD reaction, Sharpless and coworkers have screened various chiral ligands and found out that the derivatives of cinchona alkaloids gave excellent results. Among all the 250 derivatives of cinchona alkaloid ligands screened, the bis-DHQ **56** or DHQD **57** ethers of phthalazine-1, 4-diol have proven to be the best for obtaining high enantioselectivities of the chiral diols.[35]



$(DHQ)_2$-PHAL (56) **$(DHQD)_2$-PHAL (57)**

Fig. 3: Ligands for asymmetric dihydroxylation reaction

The recent studies have demonstrated the importance of enzyme-like binding pocket of the dimeric cinchona alkaloid for high enantioselectivity of the chiral diols.[35,36] Sharpless *et al.*[26] have shown that the facial selectivity for both ligands **56** and **57** is different based on their ability to induce the ee into the diols. This observation has led to the development of mnemonic model (**Fig. 4**) in which olefin with the constraints will be attacked either from the top (i. e. β) face the presence of dihydroquinidine (DHQD) derivatives or from the bottom (i.e. α) face in the presence of dihydroquinine (DHQ) derived ligand.

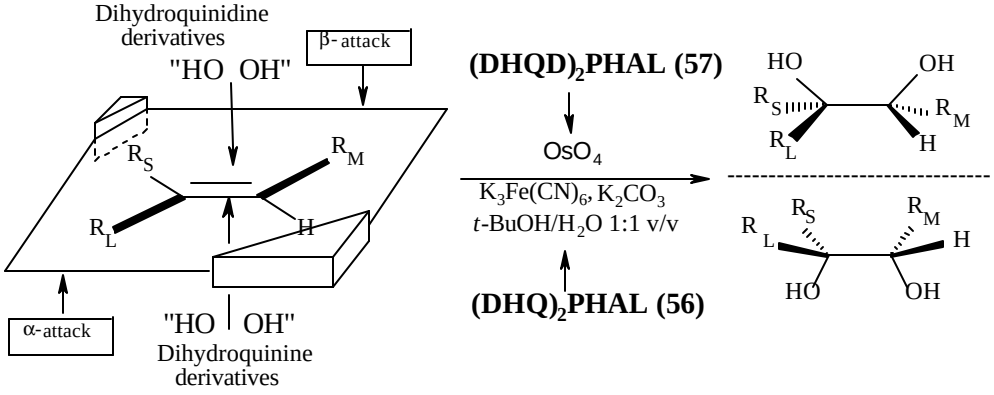
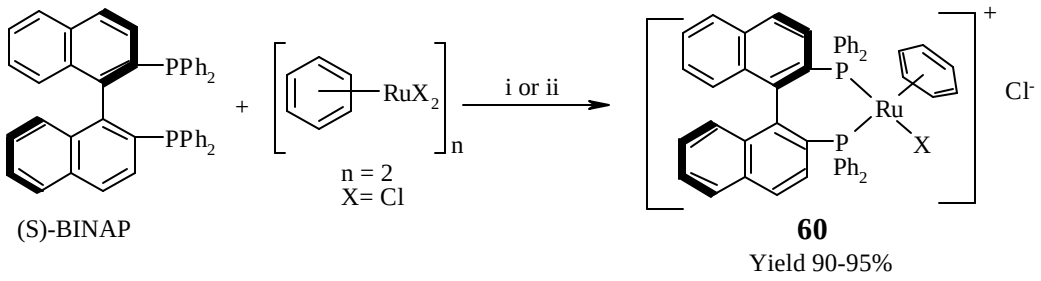


Fig. 4: Enantioselectivity mnemonic scheme

1.0.4.3 Asymmetric Hydrogenation (AH)

Optically active secondary alcohols with neighboring functional groups are extremely useful starting materials for the synthesis of various biologically active compounds. As a consequence the asymmetric hydrogenation of functionalized ketones catalyzed by chiral transition metal complexes has attracted much interest. Diphosphine complexes of Rh and Ru have been used as catalysts for this reaction.[37] Asymmetric hydrogenation of prochiral *b*-ketoesters catalyzed by BINAP [2,2'-bis(diphenylphosphino)-1,1'-binaphthyl]-Ru (II) complexes (**60**) gives the corresponding alcohols with enantiomeric excess exceeding 98%. The Ru-chiral complex is very easy to prepare as shown below (**Scheme 17**).[38]



Scheme 17: Preparation of Ru(II)-BINAP complex (i) DMF, 100^{0}C, 10 min. or (ii) EtOH:benzene (8:1), 50-55^{0}C, 1 h.

Catalytic cycle of asymmetric hydrogenation of *b*-ketoester with $RuCl_2[P(C_6H_5)_3]_3$is described below in **Fig. 5**. The hydrogenation seems to occur by the monohydride mechanism. The catalyst precursor has a polymeric structure but perhaps dissociated to the monomer by alcoholic solvents. Upon exposure to hydrogen, $RuCl_2$ loses chloride to form RuHCl species **A**, which in turn, reversibly forms the ketoester complex **B**. The hydride transfer in **B**, from the Ru center to the coordinated ketone to form **C**, would be the stereochemistry-determining step. The alcoholic solvent facilitates the liberation of the hydroxyester. The reaction of **D** with hydrogen competes the catalytic

cycle. Two diastereomers are possible for the (R)-BINAP-Ru complex **B** that has a *b*-ketoester as a bidentate *s*-donor ligand. Because of the stereochemical deposition of the hydrogen atoms, these diastereomers must be stereospecifically converted to the respective enantiomeric hydroxyester products. The characteristic chiral feature of the BINAP ligand provides clear bias for hydride delivery to occur *via* four-membered transition state. The (R)-alcohol-generating transition state is more stable than the diastereomeric (S)-alcohol-forming structure, which suffers substantial phenyl-alkyl nonbonded repulsion, which results in high enantioselectivities. Clean reaction procedures and excellent optical purity of resulting products coupled with high efficiency of chiral multiplication (a substrate to catalyst mol ratio > 1000) makes this method much more impressive and practical.

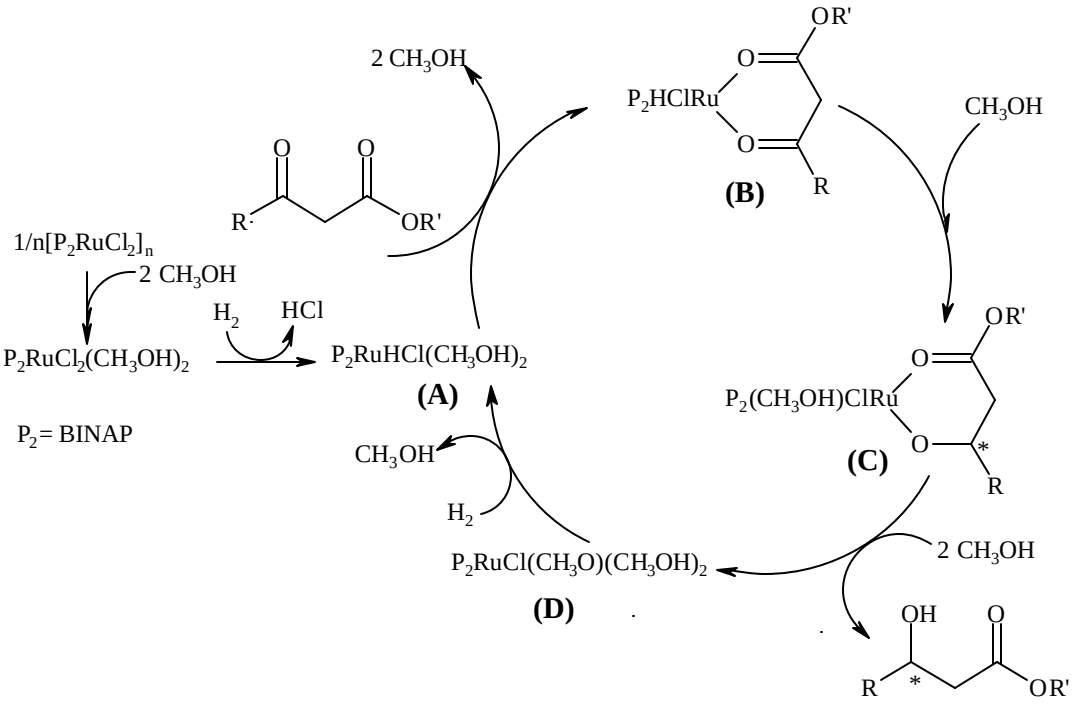
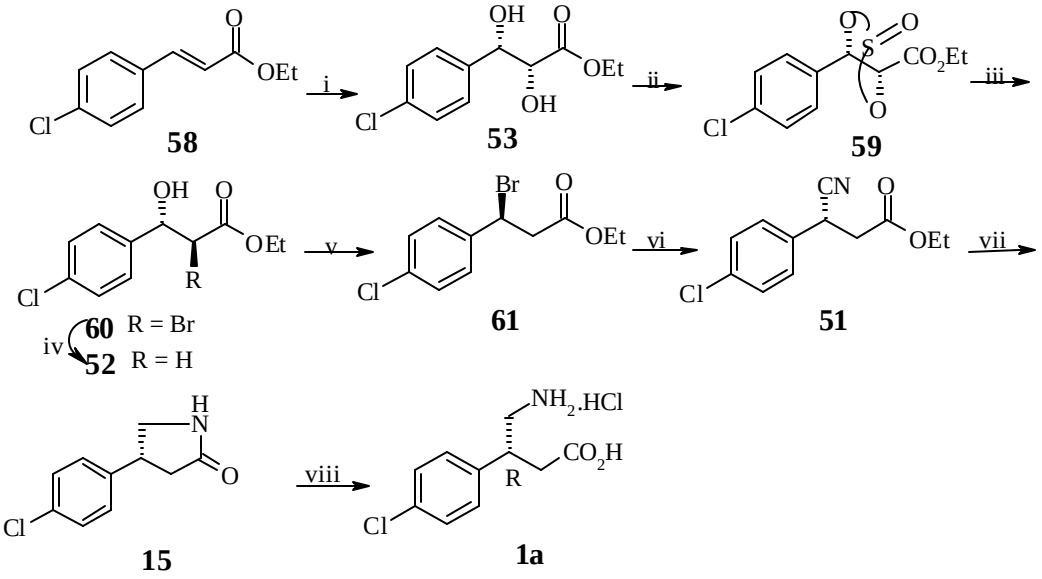


Fig. 5: Catalytic cycle for asymmetric hydrogenation

1.0.5 Results and Discussion

The synthetic strategy for (R)-baclofen (**1a**) is shown in **Scheme 18** wherein Os-catalyzed asymmetric dihydroxylation (AD) constitutes a key step in introducing chirality into the molecule (**Scheme 18**).



Scheme 18: (i) cat. OsO_4, $(DHQ)_2$-PHAL, $K_3Fe(CN)_6$, $MeSO_2NH_2$, K_2CO_3, $^tBuOH:H_2O$ (1:1), 0^0-25^0C, 24 h, 94% yield, 95% ee; (ii) $SOCl_2$, Et_3N, CH_2Cl_2, 0^0C, 30 min. 86%; (iii) a) cat. $RuCl_3.3H_2O$, $NaIO_4$, CH_3CN: H_2O, 0^0C, 10 min. b) anhydrous LiBr, THF, 25^0C, 45 min. c) 20% H_2SO_4, Et_2O, 25^0C, 4 h, over all 65%; (iv) Bu_3SnH, AIBN, benzene, 80^0C, 75%; (v) PBr_3, pyridine, Et_2O -20^0 to 0^0C, 79%; (vi) NaCN, DMF, 70^0C, 18 h, 88%; (vii) $NiCl_2.6H_2O$, $NaBH_4$, MeOH, 25^0C, 1 h, 75%; (viii) 6N HCl, reflux, 16 h, 78%, $[\alpha]_D$ = – 1.70 (c 0.6, H_2O), 85% ee.

The *trans*-olefinic ester **58** was prepared in 85% yield by the Reformatsky reaction of 4-chlorobenzaldehyde with ethyl bromoacetate followed by *p*-TSA catalyzed dehydration of the corresponding *b*-hydroxy alcohol. The *trans* geometry of the double bond of olefin **58** was confirmed by the ^{1}H-NMR spectrum, which showed doublets at δ 6.40 and 7.63 respectively with the coupling constant J = 16.12 Hz. The olefinic ester **58** was then subjected to AD reaction using catalytic amount of $(DHQ)_2$-PHAL [hydroquinine 1,4-phthalazinediyl diether, **56**] as chiral ligand to give the chiral diol **53** in 94% yield and 95% ee [determined by using $Eu(hfc)_3$ as a shift reagent[40]]. The formation of diol **53** was

confirmed by the disappearance of doublets at δ 6.40 and 7.63 and the appearance of proton signals in the region 4.0 –5.0 δ for methine protons in its ^{1}H-NMR spectrum. Further, its ^{13}C-NMR spectrum showed signals at δ 73.91 and 74.61 due to the two carbons bearing the OH functions. The carbon signal at δ 172.53 confirmed the presence of the ester functionality in the molecule (**Fig. 6**).

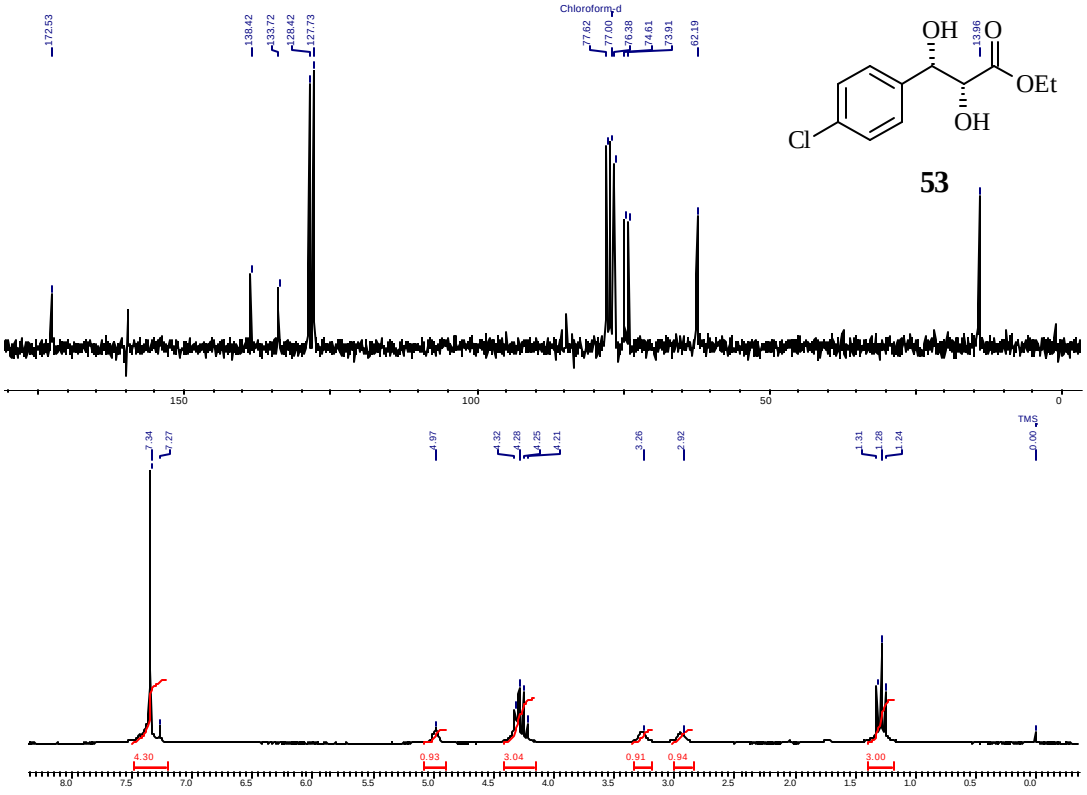


Fig. 6: ^{1}H and ^{13}C NMR spectra of diol 53

The diol **53** was then treated with $SOCl_2$ in presence of Et_3N in CH_2Cl_2 at 0^0C for 30 min. to yield the cyclic sulfite **59** in 86% yield. The ^{1}H-NMR spectrum of cyclic sulfite **59** showed the presence of the diastereomeric mixtures as evidenced by a set of four doublets in the region δ 4.74-6.13. Its ^{13}C-NMR spectrum also showed signals at δ 81.30, 82.44, 83.21, 86.81, 165.77 and 166.62 indicating the presence of diastereomeric mixtures (**Fig. 7**).

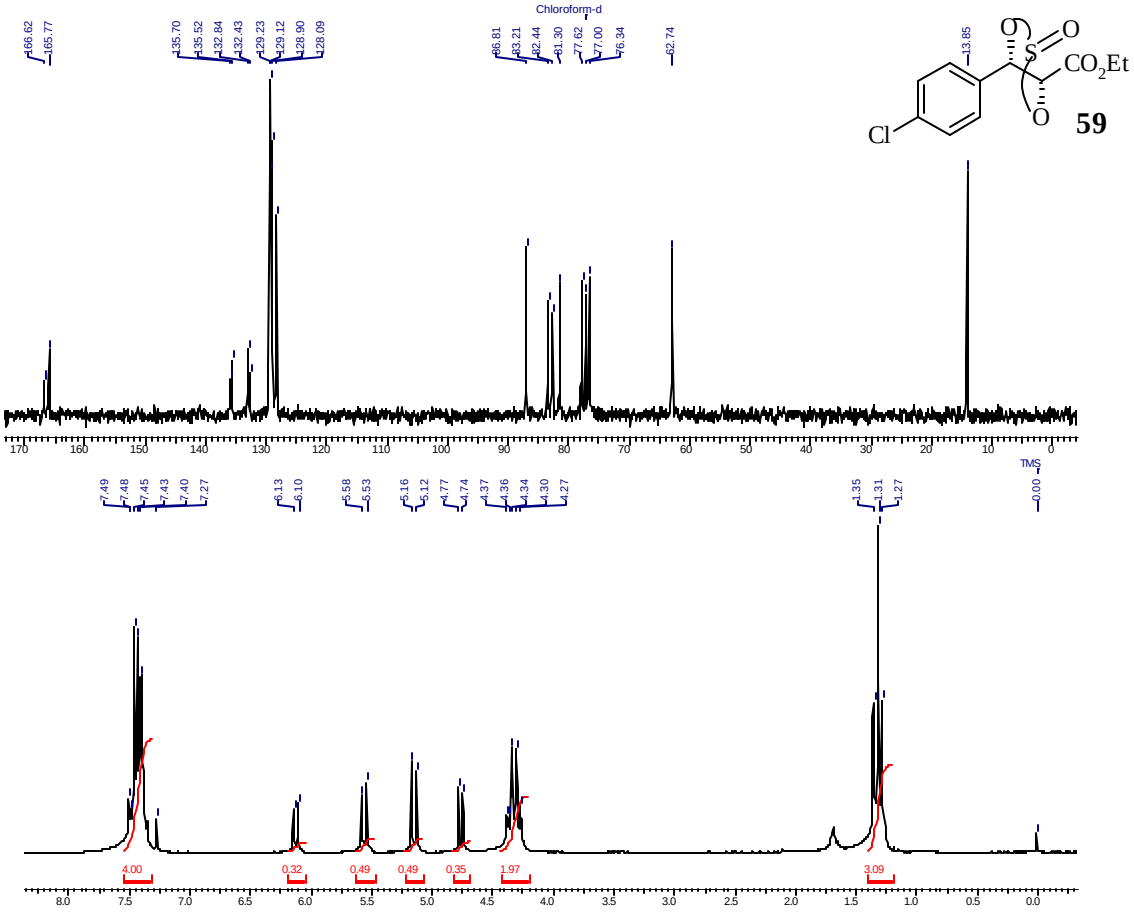


Fig. 7: ^{1}H and ^{13}C NMR spectra of cyclic sulfite 59

The cyclic sulfite **59** was then subjected to oxidation with catalytic amount of $RuCl_3.3H_2O$ in presence of $NaIO_4$ as oxidant in CH_3CN: H_2O at 0^0C, but all attempts to isolate the corresponding cyclic sulfate failed. To overcome this difficulty, the cyclic sulfate formed *in situ* was directly reacted with LiBr followed by acid hydrolysis gave the corresponding bromoalcohol **60** in 65% yield. The formation of bromoalcohol **60** was confirmed from its ^{1}H-NMR, which showed disappearance of the diastereotopic peaks of cyclic sulfite **59** and the appearance of doublets at δ 4.68 and 5.25 due to C_2 carbon bearing Br and C_3 carbon bearing OH functionalities respectively (**Fig. 8**). Its mass spectrum also showed the molecular ion peak at m/e 308 corresponding to bromoalcohol **60**.

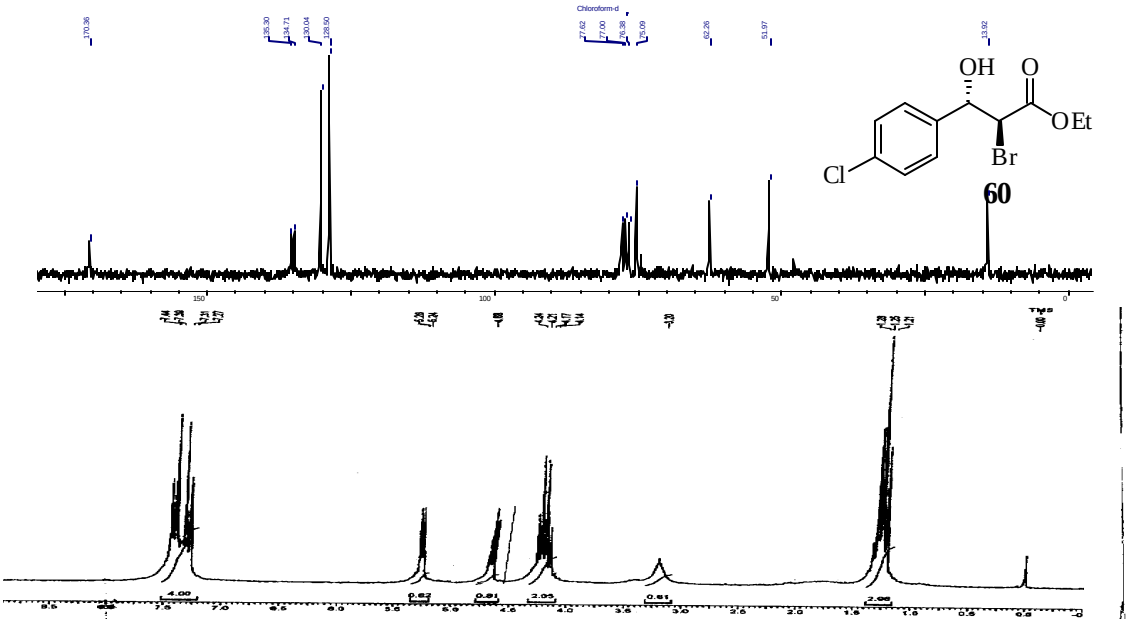


Fig. 8: ^{1}H and ^{13}C NMR spectra of bromo alcohol 60

The bromoalcohol **60** was then reduced with Bu_3SnH in presence of catalytic amount of AIBN in benzene at 80^0C to afford corresponding *b*-hydroxy ester **52** in 75% yield and 90% ee [determined by using shift reagent $Eu(hfc)_3$]. The ^{1}H-NMR spectrum of **52** showed multiplets at δ 2.67-2.71 and 5.06-5.13 indicating the presence of *b*-hydroxy ester (**Fig. 9**). Its mass spectrum confirms the molecular ion peak at m/e 228.

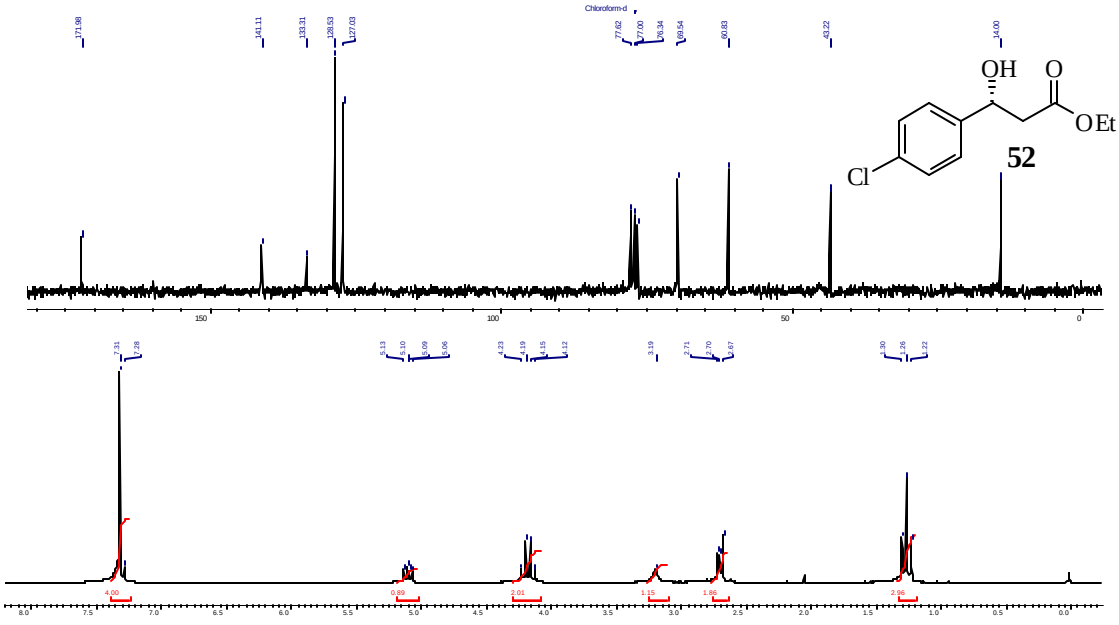


Fig. 9: ^{1}H and ^{13}C NMR spectra of hydroxy ester 52

Alcohol **52** was then brominated using PBr_3 and pyridine in Et_2O at -10^0 to give the corresponding *b*-bromoester **61** in 79% yield with complete inversion of configuration.[39] Its ^{1}H-NMR showed downfield shift for C_2 and C_3 protons but ^{13}C-NMR spectrum showed upfield shift for C_3 carbon signal (at δ 46.42). The mass spectrum also showed its molecular ion at m/e 292 confirming its formation (**Fig 10**).

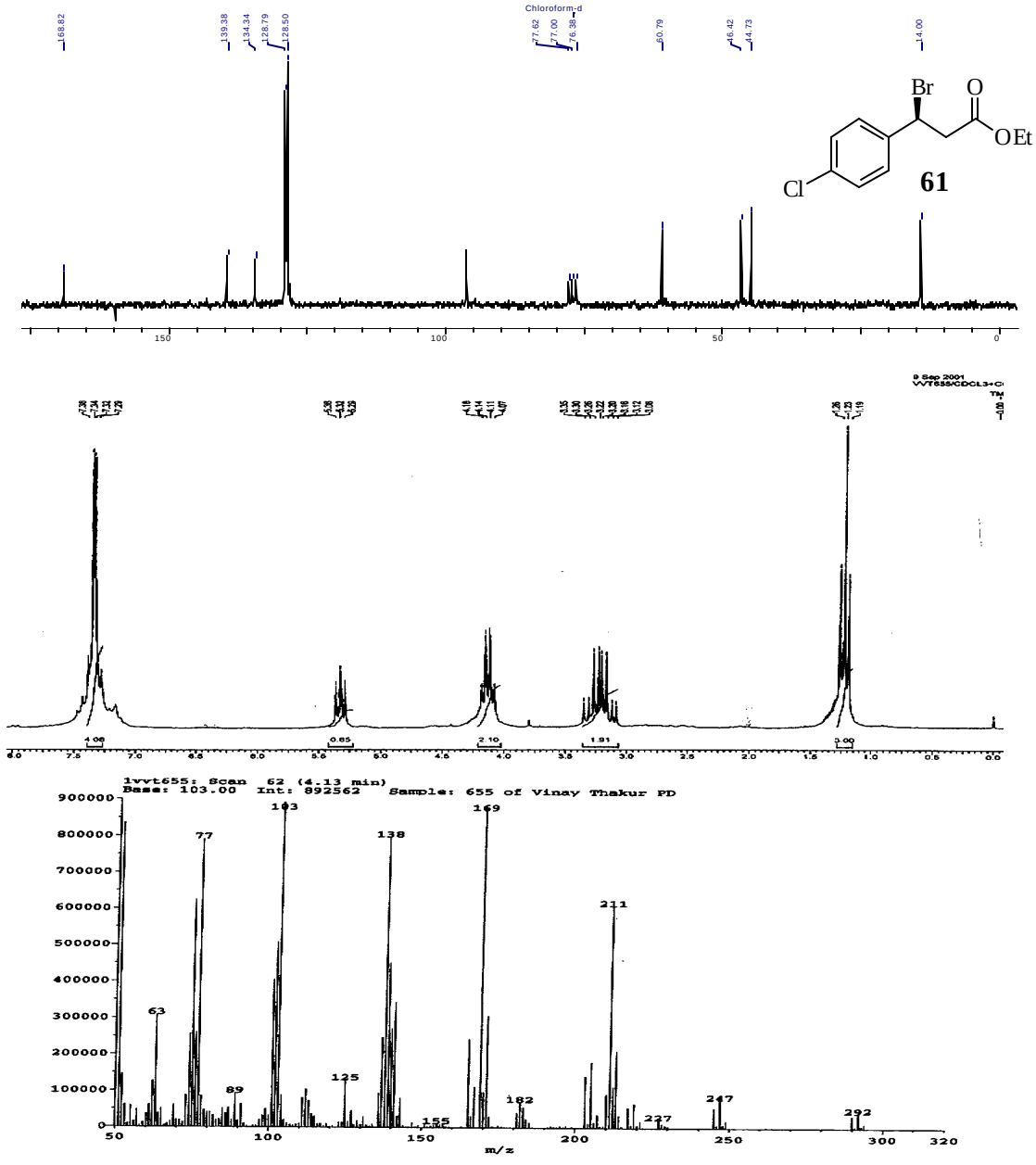


Fig. 10: ^{1}H, ^{13}C NMR and Mass spectra of bromo ester 61

The *b*-bromo ester **61** underwent S_N2 nucleophilic displacement using NaCN in DMF at 70^0C to afford the *b*-cyanoester **51** in 88% yield. Its ^{1}H and ^{13}C-NMR spectra showed upfield shifts for protons and C_2, C_3 carbon signals (**Fig. 11**). Its mass spectrum showed the molecular ion peak at m/e 237 confirming the formation of **51**. The functional group interconversions have thus generated required stereogenic center at the benzylic position.

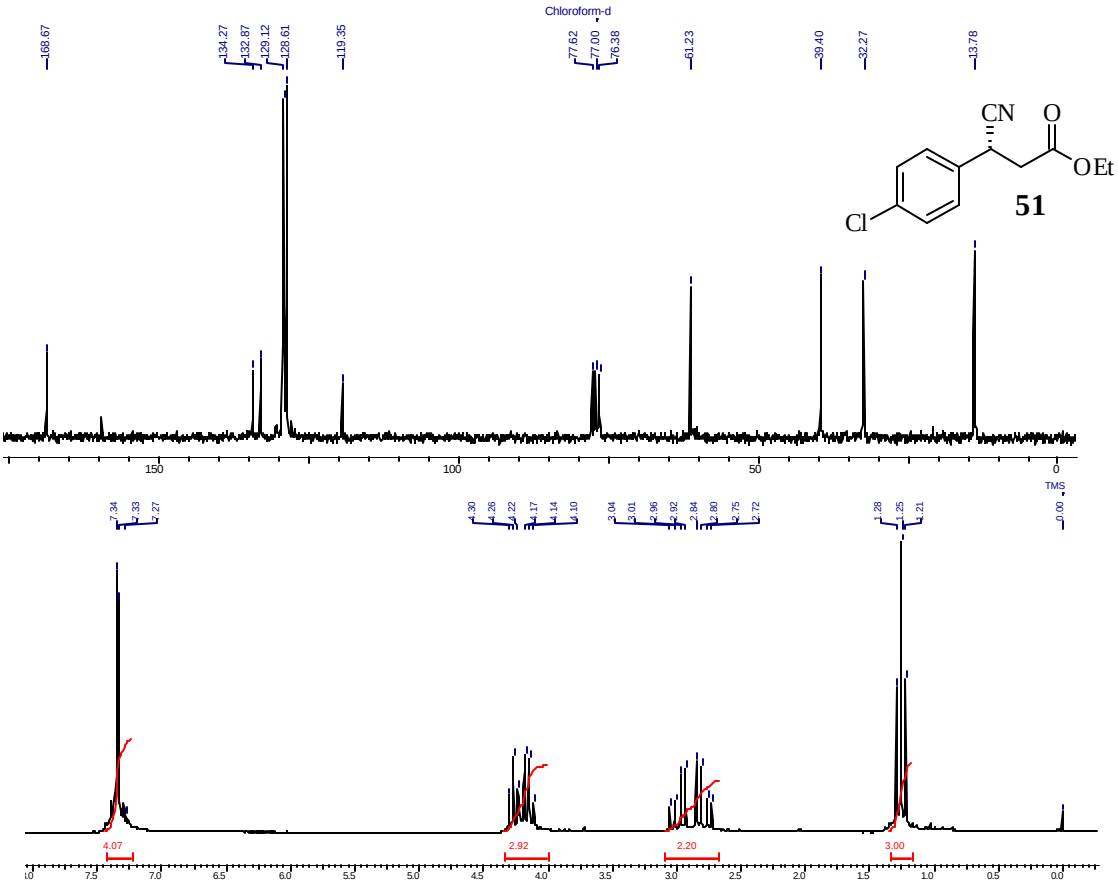


Fig. 11: ^{1}H and ^{13}C NMR spectra of cyano ester 51

Cyano ester **51** was chemoselectively reduced either with $NaBH_4$ and $NiCl_2$ or with catalytic amount of PtO_2 in presence of H_2 (40 psi) to afford lactam **15** in 75% yield. Its ^{1}H-NMR spectrum showed presence of typical ABX pattern in the region of δ 2.39-3.84 indicating diastereotopic natures of *a*-CH_2 and *g*-CH_2 protons of **15** (**Fig. 12**). Its ^{13}C-NMR

spectrum showed peaks at δ 38.22, 39.51, 49.43 and 178.01. The ee of lactam **15** was found to be 87% based on comparison of its data on optical rotation {$[\alpha]^{25}_{D}$: – 35.8 (c 1.0, EtOH), Lit.[12,21] $[\alpha]^{25}_{D}$: – 39.0 (c 1.0, EtOH)}.

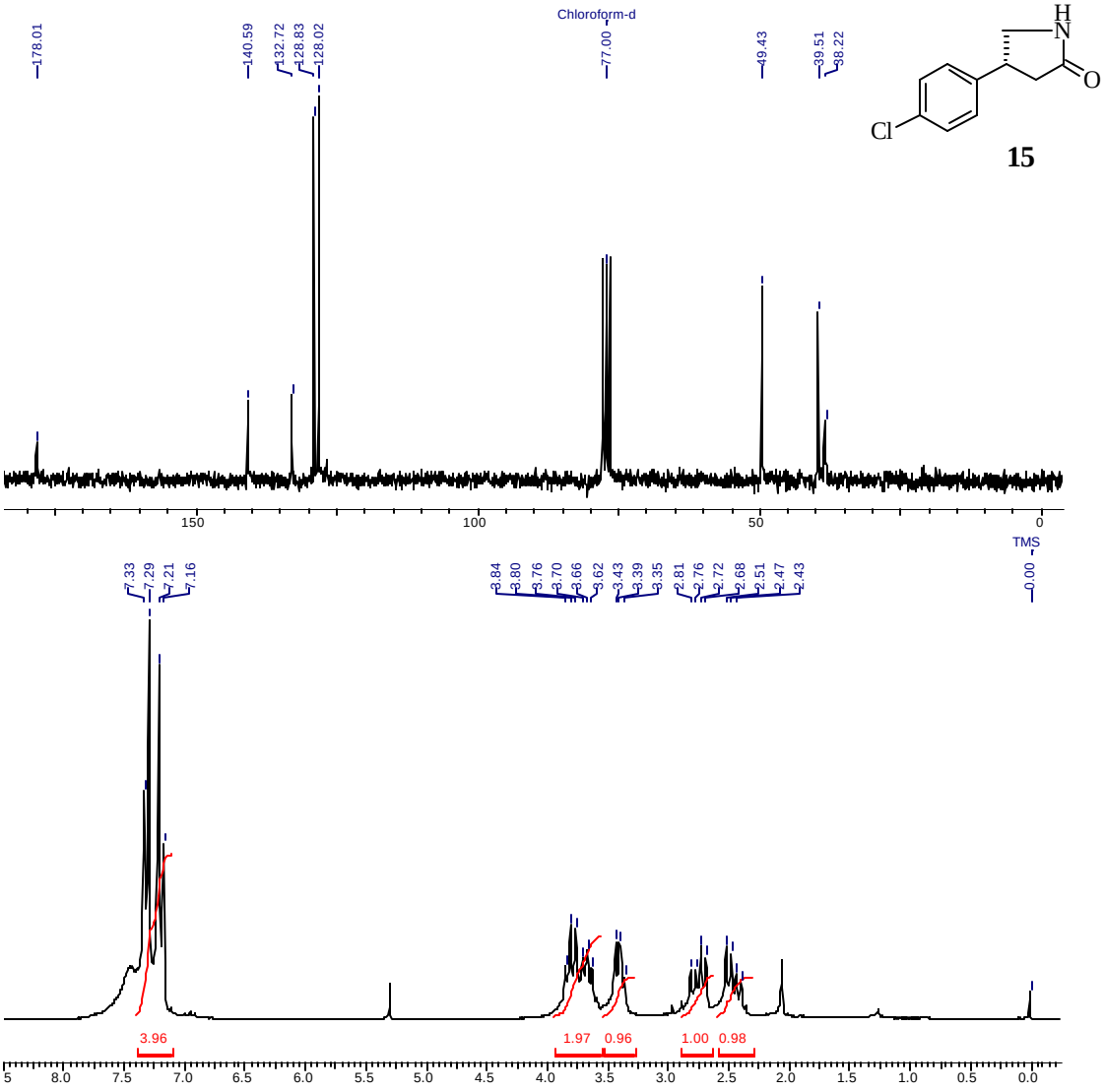
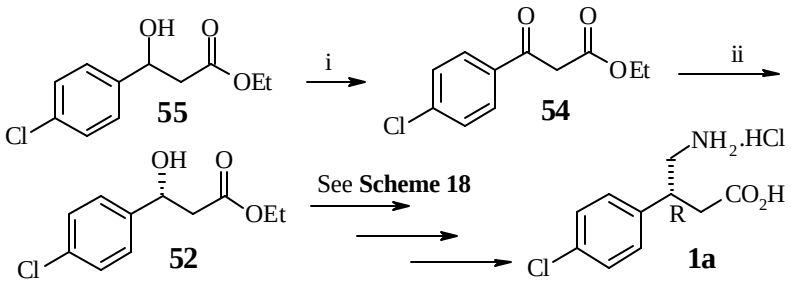


Fig. 12: ^{1}H and ^{13}C NMR spectra of lactam 15

Lactam **15** was finally hydrolyzed with 6N HCl to give (R)-baclofen (**1a**) as its hydrochloride salt in 78% yield and 85% ee, $[\alpha]_D$ = – 1.70 (c 0.6, H_2O).

Since the optical purity of (R)-baclofen (**1a**) obtained by AD route was only moderate (85% ee), it was of interest to provide its alternative synthesis by employing

asymmetric hydrogenation (AH) route. The AH strategy for the synthesis of (R)-baclofen (**1a**) is depicted in **Scheme 19**.



Scheme 19: (i) PCC, CH_2Cl_2, 25^0C, 3 h or $H_2Cr_2O_7$, Et_2O, 0^0-25^0C, 4 h, 75% (ii) Ru(II)-(S)-BINAP, MeOH, H_2 (400 psi), 95% yield, 96% ee.

b-Hydroxyester **52**, the key intermediate was synthesized by the enantioselective reduction of *b*-ketoester **54**, which was in turn prepared from 4-chlorobenzaldehyde in two steps with an overall yield of 72%. Its ^{1}H-NMR spectrum showed presence of keto and enol form of the compound **54**. Singlets at δ 3.92 and 5.60 are assigned to CH_2 of keto form and CH of enol forms respectively. The asymmetric reduction of keto function was performed using (S)-BINAP-Ru (II) complex and H_2 at a pressure of 400 *psi* to afford the corresponding (R)-*b*-hydroxy ester **52** in 95 % yield and 96% ee [determined by using $Eu(hfc)_3$ as shift reagent[40] where benzylic proton shows clear shift] (**Fig. 13**).

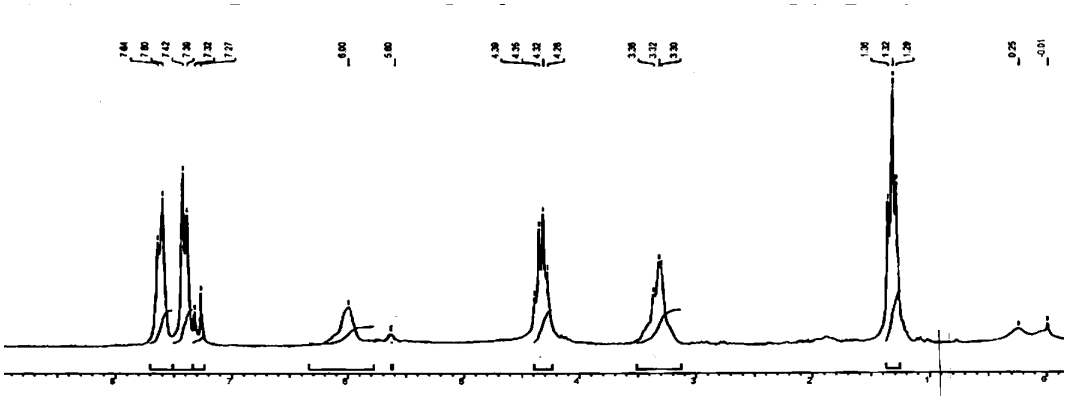


Fig. 13

The *b*-hydroxy ester **52** was then transformed to (R)-baclofen (**1a**) {$[\alpha]_D$= – 1.81, (c 0.6 H_2O), 91% ee} following exactly the same reaction sequences as shown in **Scheme**

18. The IR, ^{1}H-NMR and ^{13}C-NMR spectral data of **1a** matched very well with that of the published values (**Fig 14**).[19]

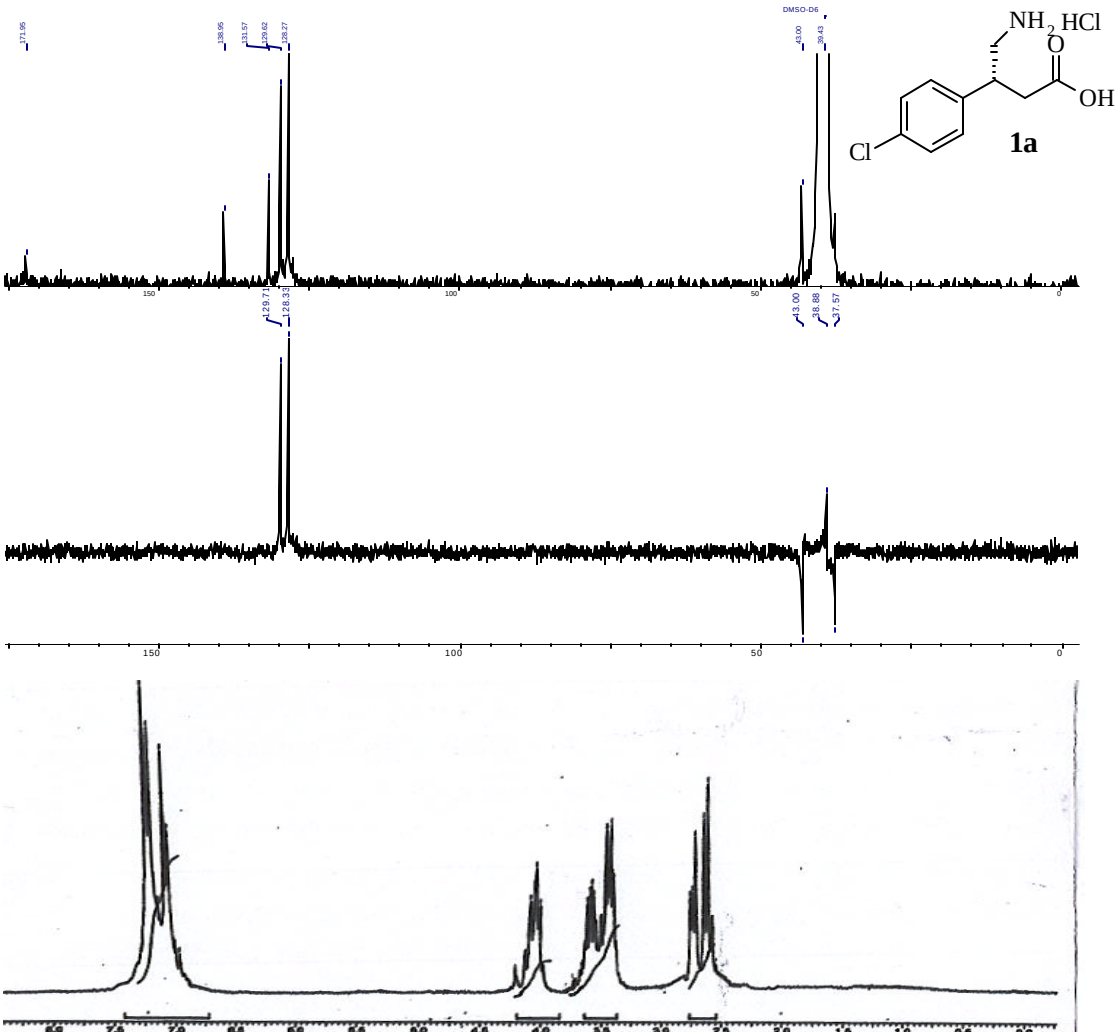


Fig. 14: ^{13}C, DEPT and ^{1}H NMR spectra of (R)-baclofen (1a)

1.0.6 Conclusion

We have achieved the enantioselective synthesis of (R)-(-)-baclofen (**1a**) in nine steps with 14% overall yield and 85% ee *via* the Os-catalyzed asymmetric dihydroxylation (AD) as a key step and with 26% overall yield and 91% ee in seven steps using Ru- (S)-BINAP catalyzed asymmetric hydrogenation (AH) as a key step.

1.0.7 Experimental Section

Preparation of ethyl 2-(4-chlorophenyl)-2-propeonate (58):

A 100 ml two-necked RB flask was charged with activated zinc (2.32 g, 35.7 mmol), and kept under N_2 atmosphere. Dry benzene (30 ml) was introduced and the reaction mixture was heated to 80^oC (oil bath temp.). A solution of ethyl bromoacetate (5.88 g, 35.7 mmol) and *p*-chlorobenzaldehyde (4.56 g, 32.46 mmol) in dry benzene (20 ml) was added dropwise to the reaction mixture. After completion of the addition, the resulting reaction mixture was refluxed for 6 h, cooled to RT and quenched by adding ice cold 4N H_2SO_4 (30 ml). The crude hydroxyester was extracted with diethyl ether evaporated under reduced pressure and then was subjected to dehydration with *p*-toluenesulphonic acid (0.7 g, 3.68 mmol) in toluene at reflux. Water generated during the dehydration was azeotropically separated and then toluene was distilled off. The crude olefinic ester **58** was purified by column chromatography packed with silica gel, eluting with pet. ether to give 5.81 g of **58**.

Yield: 85% overall in two steps; **gum**; **IR** (Neat, cm^{-1}): 685, 712, 998, 1064, 1172, 1202, 1312, 1450, 1578, 1640, 1720, 2874, 2933, 2960; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.33 (t, *J* = 7.14 Hz, 3H), 4.26 (q, *J* = 7.14 Hz, 2H), 6.40 (d, *J* = 16.12 Hz, 1H), 7.33 (d, *J* = 9.08 Hz, 2H), 7.45 (d, *J* = 9.08 Hz, 2H), 7.63 (d, *J* = 16.12 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 13.92, 60.13, 118.54, 128.83, 132.61, 135.63, 142.58, 166.10; **MS** m/z (% rel. intensity): 210 (M^+, 50), 182 (30), 165 (100), 155 (70), 139 (55), 101 (50), 75 (40); **Analysis**: $C_{11}H_{11}ClO_2$ requires C, 62.72; H, 5.25; Cl, 16.83; found C, 62.47; H, 5.12; Cl, 16.68%.

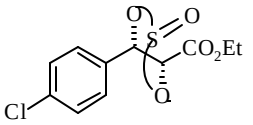
Preparation of ethyl (2R,3S)-2,3-dihydroxy-(4-chlorophenyl) propionate (53):

A double-walled 250 ml RB flask was charged with K_3FeCN_6 (9.4 g, 28.5 mmol), K_2CO_3 (3.93 g, 28.5 mmol), $(DHQ)_2$-PHAL (200 mg, 0.2 mmol), $MeSO_2NH_2$ (0.901 g, 9.5 mmol) and *t*-BuOH:H_2O (1:1, v/v, 90 ml) and stirred for five minutes at 25^0C. Then cooled to 0^0C and a solution of OsO_4 (200 µl, 0.1 mmol, 0.5M solution in toluene) was added followed by 4-chloroehtyl cinnamate **58** (2.0 g, 9.5 mmol). The reaction mixture was stirred for 24 h at 25^0C (monitored by TLC). The reaction was quenched with sodium sulfite (10g) and extracted with ethyl acetate (3 x 60 ml). The organic layer was washed with brine (50 ml), dried over anhydrous sodium sulfate and evaporated to dryness under

reduced pressure. The crude product was purified by column chromatography using EtOAc: pet. ether (1:1) as eluent to yield **53** as a white solid (2.18 g).

Yield: 94%; **mp**: 112-113^{0}C (recrystallized from EtOH); **[**a**]$^{25}_D$**: + 15.6 (c 0.4, EtOH), 95% ee; **IR** ($CHCl_3$, cm^{-1}): 715, 1018, 1121, 1220, 1288, 1455, 1560, 1608, 1715, 2978, 2980, 3445; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.28 (t, *J* = 7.18 Hz, 3H), 2.92 (bs, 1H), 3.26 (bs, 1H), 4.21-4.32 (m, 3H), 4.97 (bs, 1H), 7.34 (S, 4H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 13.96, 62.19, 73.91, 74.61, 127.73, 128.42, 133.72, 138.42, 172.53; **MS** m/z (% rel. intensity): 244 (M^+, 4), 227 (4), 153 (14), 141 (72), 104 (97), 76 (100), 58 (14); **Analysis**: $C_{11}H_{13}ClO_4$ requires C, 54.00; H, 5.36; Cl, 14.49; found C, 54.12; H, 5.32; Cl, 14.24%.

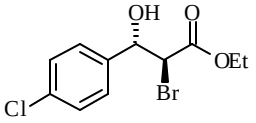
Preparation of ethyl (4S,5R)-4-carbethoxy-5-(4-chlorophenyl)1,3,2-dioxathiolane-2-oxide (59): The diol **53** (1.9 g, 7.8 mmol) was dissolved in triethylamine (23 ml) and cooled to 0^{0}C in an icebath under argon atmosphere. Freshly distilled thionyl chloride (1.18 g, 0.72 ml, 9.88 mmol) was added drop-wise and the reaction mixture was stirred at 0^{0}C for 30 minutes (monitored by TLC). After completion, was added ice-cold water (20 ml) and extracted with ether (3 x 30 ml). The ethereal layer was washed with 10% HCl, saturated sodium bicarbonate solution and with brine successively. The ether extract was dried over anhydrous sodium sulfate and evaporated under reduced pressure. The crude product was purified by column chromatography using pet. ether : EtOAc (9:1) as eluent to furnish **59** as light yellow oil (1.94 g).



59

Yield: 86%; **yellow oil**; **[**a**]$^{25}_D$**: – 109.0 (c 0.44, EtOH); **IR** ($CHCl_3$, cm^{-1}): 738, 757, 827, 966, 1047, 1091, 1217, 1267, 1373, 1494, 1600, 1740, 2863; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.31 (t, *J* = 7.21 Hz, 3H), 4.27-4.32 (m, 2H), 4.75 (d, *J* = 6.14 Hz), 5.14 (d, *J* = 6.14 Hz), 5.56 (d, *J* = 6.14 Hz), 6.12 (d, *J* = 6.14 Hz) for 2H, 7.27-7.48 (m, 4H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 23.58, 62.74, 82.30, 82.44, 83.21, 86.81, 128.09, 128.90, 129.12, 132.43, 132.84, 135.52, 135.70, 165.77, 166.62; **MS** m/z (% rel. intensity): 290 (M^+, 1), 226 (27), 188 (13), 180 (25), 154 (25), 139 (93), 125 (86), 104 (64), 89 (54), 77 (100), 63 (25); **Analysis**: $C_{11}H_{11}ClO_5S$ requires C, 45.45; H, 3.81; Cl, 12.20; S, 11.03; found C, 45.43; H, 3.69; Cl, 12.31; S, 11.08%.

Preparation of ethyl (2S,3S)-2-bromo-3-hydroxy-3-(4-chlorophenyl) propionate (60): To a solution of cyclic sulfite **59** (1.45 g, 5 mmol) in CH_3CN: H_2O mixture (9:1, 10 ml) at 0^0C was added solid $NaIO_4$ (1.61 g, 7.5 mmol) and $RuCl_3$ (0.11 g, 0.5 mmol). The reaction mixture was stirred for 5 minutes at 0^0C and immediately filtered through pad of silica and celite directly into the solution of anhydrous LiBr (4.35 g, 50 mmol) in dry THF (30 ml). The resulting solution was stirred at 25^0C for 1 h and then concentrated under reduced pressure to dryness. To this was added 20% H_2SO_4 and diethyl ether (1:1, 40 ml) and stirred at 25^0C for 5 h. The organic layer was separated and the aqueous layer was extracted with diethyl ether (3 x 15 ml) the combined ether extracts were washed with saturated $NaHCO_3$ solution, brine and dried over anhydrous Na_2SO_4. The ether layer was evaporated under reduced pressure to give crude product which was further purified by column chromatography on silica gel to give pure bromoalcohol **60** (1.00 g) as a colorless viscous liquid.

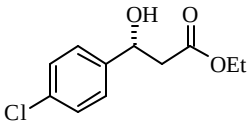


(2S,3S)-60

Yield: 65% overall; **viscous liquid**; **[**a **]$^{25}_D$**: – 120.43 (c 0.5, EtOH); **IR** ($CHCl_3$, cm^{-1}): 700, 1010, 1121, 1200, 1260, 1445, 1725, 2976, 2990, 3450; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.25 (t, *J* = 7.18 Hz, 3H), 3.20 (bs, 1H), 4.19 (q, *J* = 7.18 Hz, 2H), 4.68 (d, *J* = 4.12 Hz, 1H), 5.25 (d, *J* = 4.12 Hz, 1H), 7.29 (d, *J* = 8.24 Hz, 2H), 7.42 (d, *J* = 8.24 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 13.92, 51.57, 62.26, 75.09, 128.50, 130.04, 134.71, 135.30, 170.36; **MS** m/z (% rel. intensity): 308 (M^+, 7), 210 (20), 282 (10), 255 (15), 139 (20), 125 (100), 91 (60), 75 (40), 63 (23); **Analysis**: $C_{11}H_{12}BrClO_3$ requires C, 42.96; H, 3.93; Br, 25.98; Cl, 11.53; found C, 42.85; H, 3.82; Br, 25.84; Cl, 11.48%.

Preparation of ethyl (3R)-3-hydroxy-3-(4-chlorophenyl) propionate (52):

To a solution of bromoalcohol **60** (1.00 g, 3.3 mmol) in benzene (10 ml) in 50 ml RB flask, was added AIBN (2, 2'-azobisisobutyronitrile, 2 mg, 0.012 mmol) and Bu_3SnH (1.16 g, 4.0 mmol) and the reaction mixture was heated at 80^0C for 3 h (monitored by TLC). The reaction mixture was then cooled to room temperature and concentrated under reduced pressure to give crude product, which was further purified by column chromatography on silica gel using pet. ether: EtOAc (8:2) as eluent to give **52** (0.555 g).

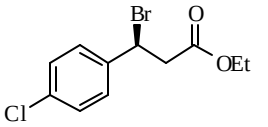


(R)-52

Yield: 75%; **gum**; **[**a **]$^{25}_{D}$**: + 38.7 (c 1.5, $CHCl_3$), 90% ee; **IR** (Neat, cm^{-1}): 831, 1014, 1091, 1193, 1284, 1375, 1400, 1490, 1595, 1718, 2981, 3461; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.26 (t, *J* = 7.11 Hz, 3H), 2.67-2.71 (m, 2H), 3.19 (bs, 1H), 4.17 (q, *J* = 7.11 Hz, 2H), 5.06-5.13 (m, 1H), 7.31 (s, 4H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 14.00, 43.22, 60.83, 69.54, 127.03, 128.53, 133.31, 141.11, 171.98; **MS** m/z (% rel. intensity): 228 (M^+, 3), 182 (6), 156 (53), 139 (100), 111 (54), 75 (73); **Analysis**: $C_{11}H_{13}ClO_3$ requires C, 57.78; H, 5.73; Cl, 15.50; found C, 57.47; H, 5.65; Cl, 15.58%.

Preparation of ethyl (3S)- 3-bromo -3-(4-chlorophenyl) propionate (61):

To a mixture containing *b*-hydroxy ester **52** (0.500 g, 2.2 mmol) in dry ether (15 ml), pyridine (0.40 ml, 4.84 mmol) was added under argon atmosphere. The reaction mixture was cooled to -20^0C. Then PBr_3 (0.650 g, 0.230 ml, 2.4 mmol) in ether (5 ml) was added drop wise at -20^0C. The reaction mixture was then stirred for 3 h at -20^0C and then for 48 h at 0^0C (monitored by TLC). The reaction was quenched by the addition of crushed ice the ether layer was washed with ice water, 85% phosphoric acid, cold saturated sodium bicarbonate, twice with cold water and brine, and dried over anhydrous Na_2SO_4. The crude product was finally purified by column chromatography on silica using pet. ether: EtOAc (9:1) as eluent to afford *b*-bromoester **61** (0.504 g).

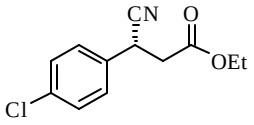


(S)-61

Yield: 79%; **gum**; **[**a **]$^{25}_{D}$**: – 96.3 (c 2.0, $CHCl_3$), from ADH; – 104.2 (c 2.0, $CHCl_3$), from AH; **IR** ($CHCl_3$, cm^{-1}): 617, 829, 1014, 1093, 1199, 1263, 1313, 1411, 1492, 1595, 1735, 2935, 2981; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.23 (t, *J* = 7 Hz, 3H), 3.08-3.35 (m, 2H), 4.12 (q, *J* = 7 Hz, 2H), 5.33 (t, *J* = 6 Hz, 1H), 7.29-7.38 (m, 4H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 14.00, 44.73, 46.42, 60.79, 128.50, 128.79, 134.34, 139.38, 168.82; **MS** m/z (% rel. intensity): 292 (M^+, 6), 247 (10), 211 (69), 169 (98), 138 (88), 103 (100), 77 (88), 63 (36); **Analysis**: $C_{11}H_{12}BrClO_2$ requires C, 45.31; H, 4.15; Br, 27.41; Cl, 12.61; found C, 45.53; H, 4.13; Br, 27.44; Cl, 12.55%.

Preparation of ethyl (3R)-3-cyano-3-(4-chlorophenyl) propionate (51):

In a 25 ml flask were added *b*-bromoester **61** (0.474 g, 1.6 mmol), NaCN (0.106 g, 4 mmol) and dry DMF (10 ml) under argon atmosphere. The reaction mixture was heated at 70^0C for 14 h (monitored by TLC). After completion of the reaction it was diluted with water (5 ml) and extracted with EtOAc (4 x 15 ml) combined organic extracts were washed with brine (10 ml), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude product. The crude product was further purified by column chromatography on silica gel using pet. ether: EtOAc (8:2) as eluent to afford cyanoester **51** (0.340 g).



(R)-51

Yield: 88%; **mp**: 62-63^{0}C; **[**a **]$^{25}_D$**: + 12.9 (c 1.5, $CHCl_3$), from ADH; + 14.1(c 1.5, $CHCl_3$), from AH; **IR** ($CHCl_3$, cm^{-1}): 831, 1016, 1093, 1190, 1251, 1375, 1492, 1737, 2294, 2917, 2983; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.24 (t, *J* = 8.04 Hz, 3H), 2.72-2.84 (dd, *J* = 16.08 Hz and 8.12 Hz, 1H), 2.92-3.04 (dd, *J* = 16.08 Hz and 8.12 Hz, 1H), 4.10-4.30 (m, 3H), 7.33 (s, 4H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 13.78, 32.27, 39.40, 61.23, 119.35, 128.61, 129.12, 132.87, 134.27, 168.67; **MS** m/z (% rel. intensity): 237 (M^+, 7), 163 (30), 150 (27), 137 (13), 101 (15), 88 (15), 75 (100), 63 (50); **Analysis**: $C_{12}H_{12}ClNO_2$ requires C, 60.64; H, 5.09; Cl, 14.92; N, 5.89; found C, 60.83; H, 5.12; Cl, 14.88; N, 5.98%.

Preparation of (3R)-3-(4-chloropheny)-2-pyrrolidone (15):

To a 25 ml RB flask containing a mixture of cyanoester **51** (0.300 g, 1.3 mmol) and $NiCl_2.6H_2O$ (0.619 g, 2.6 mmol) in MeOH (8.0 ml), at 25^{o}C was added in portions under stirring solid $NaBH_4$ (0.532 g, 14 mmol). Evolution of hydrogen was observed and the black precipitate appeared during the addition of $NaBH_4$. The resulting reaction mixture was stirred for 30 min. After the reaction was complete (monitored by TLC), the mixture was extracted with chloroform (10 x 3 ml). The chloroform layer was washed with brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue obtained was then purified by column chromatography using pet. ether and EtOAc as eluents to give pure 3-(4-chloropheny)-2-pyrrolidone **15**, 0.186 g as light yellow colored solid.

Yield: 75%; **mp**: 115-117^{o}C; **[**a **]$^{25}_D$**: – 33.9 (c 1.0, EtOH), from ADH, 87% ee**,** – 35.8 (c 1.0, EtOH), from AH, 92% ee {Lit.[12,21] **[**a **]$^{25}_D$ =** – 39 (c 1.0, EtOH)}; **IR** ($CHCl_3$, cm^{-1}):

3420, 3200, 2103, 1698, 1492, 1090, 1374, 1216, 758, 700, 668; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.39-2.51 (dd, *J* = 16.90 Hz and 8.41 Hz, 1H), 2.68-2.81 (dd, *J* = 16.90 Hz and 8.72 Hz, 1H); 3.35-3.43 (m, 1H), 3.62-3.84 (m, 2H), 7.18 (d, *J* = 9.12 Hz, 2H), 7.31 (d, *J* = 9.12 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 38.22, 39.51, 49.43, 128.02, 128.83, 132.72, 140.59, 178.01; **MS** m/z (% rel. intensity): 195 (M^+, 15), 140 (24), 138 (100), 75 (5); **Analysis**: $C_{10}H_{10}ClNO$, requires C, 61.39; H, 5.15; Cl, 18.12; N, 7.16; found: C, 61.29; H, 4.98; Cl, 18.18; N, 7.09%.

Preparation of (R)-(–)-Baclofen hydrochloride (1a):

Lactam **15** (0.170 g, 0.9 mmol) in 6N HCl (4 ml) was heated at 100°C for 16 h. The excess of water in the reaction mixture was removed under reduced pressure to obtain solid residue, which was triturated in isopropanol affording (R)-baclofen hydrochloride (**1a**) as a colorless solid (0.170 mg).

Yield: 78%; **mp**: 195-197°C; **[**a **]$^{25}_D$**: – 1.70 (c 0.6, H_2O) from ADH, 85 % ee, – 1.81 (c 0.6 H_2O) from AH, 91% ee {Lit.[19] **[**a **]$^{25}_D$** = – 2.00 (c 0.6, H_2O)}; **IR** ($CHCl_3$, cm^{-1}): 698, 704, 758, 1090, 1490, 1550, 1620, 2955, 2092, 3200; **^{1}H-NMR** (200 MHz, DMSO-d6 + $CDCl_3$): 2.51-2.71 (m, 2H), 3.42-3.65 (m, 2H), 4.15-4.21 (m, 1H), 7.01-7.21 (m, 4H); **^{13}C-NMR** (50 MHz, DMSO-d_6): δ 37.57, 38.88, 43.00, 128.27, 129.62, 131.57, 138.95, 171.95; **MS** m/z (% rel. intensity): 195 (10), 140 (61), 138 (100), 125 (6), 115 (10), 103 (45), 89 (9), 77 (29); **Analysis**: $C_{10}H_{13}Cl_2NO_2$ requires C, 48.02; H, 5.24; Cl, 28.35; N, 5.60; found C, 48.24; H, 5.15; Cl, 28.41; N, 5.49%.

Preparation of ethyl 4-chlorophenylbenzoyl acetate 54:

To a mixture of *b*-hydroxy ester **55** (4.56 g, 20 mmol) in diethyl ether (40 ml) was added drop wise through addition funnel freshly prepared chromic acid solution (15 ml) under ice-cold condition with vigorous stirring. The reaction mixture was allowed to come to room temperature and stirring continued for 3 h (monitored by TLC). The organic layer was separated and the aqueous layer was extracted with ether (2 x 15 ml). The combined ethereal extracts were washed with water (15 ml) followed by brine (15 ml) and concentrated under reduced pressure to give crude product, which was further purified by column chromatography on silica gel using pet. ether: EtOAc (9:1) as eluent to afford *b*-ketoester **54** (3.39 g).

Yield: 75%; **viscous oil**; **IR** ($CHCl_3$, cm^{-1}): 819, 840, 1012, 1091, 1201, 1265, 1325, 1423, 1490, 1589, 1623, 1689, 1739, 2927, 2981; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.21-1.36 (m,

3H), 3.96 (s, 2H), 4.19-4.30 (m, 2H), 5.62 (s, 1H), 7.34-7.45 (m, 2H), 7.69 (d, *J* = 8.21 Hz, 1H), 7.88 (d, *J* = 8.24 Hz, 1H), 12.60 (s, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): 13.48, 13.67, 45.17, 59.91, 60.83, 87.07, 126.81, 127.95, 128.20, 128.42, 128.68, 129.20, 129.38, 131.29, 133.90, 136.66, 139.45, 166.65, 169.41, 172.50, 190.77; **MS** m/z (% rel. intensity): 226 (M^+, 16), 180 (8), 139 (100), 111 (19), 75 (10); **Analysis**: $C_{11}H_{11}ClO_3$ requires C, 58.29; H, 4.89; Cl, 15.64; found C, 58.31; H, 4.80; Cl, 15.55%.

Preparation of (S)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl Ru(II) complex:[38a]

A dry, 25 ml two-necked, round bottomed flask was charged with [$RuCl_2$(benzene)$_2$] (38.3 mg, 0.0765 mmol) and (S)-BINAP (100 mg, 0.16 mmol). The flask was then evacuated, filled with argon and then N,N'-dimethylformamide (2.6 ml) was introduced through syringe. The suspension was stirred under argon atmosphere at 100^{o}C for 10 min the resulting clear reddish brown reaction mixture was cooled and concentrated at 60^{o}C (3 mm Hg) with vigorous stirring. Finally, it was dried at 3 mm Hg for 3 h to yield reddish brown solid of Ru (II) (S)-BINAP complex (135 mg) (**Scheme 17**). This solid was directly used as catalyst for the asymmetric hydrogenation.

Asymmetric reduction of 4-chlorophenylbenzoyl acetate 54:

A dry two-necked round-bottomed flask was charged with *b*-ketoester **54** (2.27 g, 10 mmol) and dry ethanol (60 ml). To this mixture was added (S)-BINAP-Ru (II) complex (40 mg, 0.05 mmol) under a stream of argon. The resulting yellowish orange solution was degassed with argon and then transferred by cannula to dry and clean autoclave. Hydrogen was introduced into the autoclave until the pressure gauge indicates 5 atm. The pressure was then carefully released to 1 atm. This procedure was repeated for 2 times, and finally hydrogen was pressurized to 400 psi. The reaction mixture was vigorously stirred at 30^{0}C for 100 h. The stirring was stopped and excess hydrogen was carefully bled off. The deep reddish orange reaction mixture was transferred to 100 ml round bottom flask and the autoclave was rinsed with dichloromethane (3 x 15 ml). The solvent was removed in *vacuo* and the residue was subjected to column chromatography (10% ethyl acetate in pet. ether as eluent) to get pure (R)-alcohol **52** (2.24 g).

Yield: 95%; **gum**; $[\alpha]^{25}_D$: + 41.3 (c 1.5, $CHCl_3$), 96% ee; **IR** (Neat, cm^{-1}): 831, 1014, 1091, 1193, 1284, 1375, 1400, 1490, 1595, 1718, 2981, 3461; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.25 (t, *J* = 7.10 Hz, 3H), 2.65-2.70 (m, 2H), 4.17 (q, *J* = 7.10 Hz, 2H), 5.07-

5.14 (m, 1H), 7.31 (s, 4H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 14.00, 43.22, 60.83, 69.54, 127.03, 128.53, 133.31, 141.11, 171.98; **MS** m/z (% rel. intensity): 228 (M^+, 3), 182 (6), 156 (53), 139 (100), 111 (54), 75 (73); **Analysis**: $C_{11}H_{13}ClO_3$ requires C, 57.78; H, 5.73; Cl, 15.50; found C, 57.77; H, 5.69; Cl, 15.68%.

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CHAPTER 2

Asymmetric Synthesis of (S)-Propranolol, (S)-Moprolol and (S)-Toliprolol *via* OsO_4-Catalyzed Asymmetric Dihydroxyaltion

Asymmetric Synthesis of (S)-Propranolol, (S)-Moprolol and (S)-Toliprolol *via* OsO_4-Catalyzed Asymmetric Dihydroxyaltion

2.0.1 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.[1] Biological systems, in most cases, recognize the members of a pair of enantiomers as different substances, and the two enantiomers will exhibit different responses. Thus one enantiomer may act as a very effective therapeutic drug whereas the other enantiomer is highly toxic. It has been shown for many pharmaceuticals that only one enantiomer contains all the desired activity, and the other is either totally inactive or highly toxic.

There are several methods to obtain enantiomerically pure materials, which include classical resolution *via* diastereomers, chromatographic separation of enantiomers, enzymatic resolution, chiral kinetic resolution and asymmetric synthesis. OsO_4-catalyzed asymmetric dihydroxylation (AD), developed by Sharpless *et al.*[2] (for introduction see **chapter 1**, section 1.0.4.2) is a simple, efficient and the most reliable method for asymmetric synthesis of chiral vicinal diols.

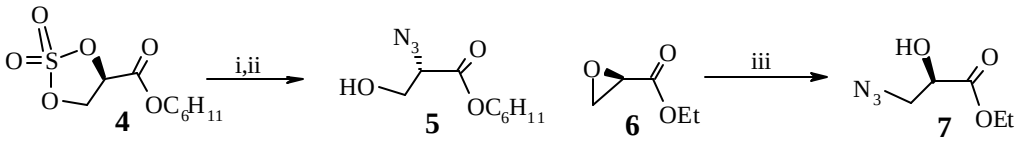
2.0.2 Chemistry of Cyclic Sulfites and Sulfates

The chemistry of cyclic sulfites and sulfates is very old.[3] These are esters of 1,2; 1,3 or 1,4 diols and possess properties similar to epoxides. Unlike epoxide, chemistry of cyclic sulfites and sulfates is less explored in organic synthesis due to lack of an efficient method for their preparation. The significant role of cyclic sulfates in organic synthesis is realized due to their unique properties such as (i) high reactivity towards nucleophiles which is comparable to epoxides (ii) attack of nucleophile is regiospecific and thereby

serving as a protecting group at a second position (iii) nucleophilic opening of five-membered cyclic sulfates generates two contiguous stereocenters.[4] The recent developments in Ru-catalyzed oxidation of the cyclic sulfites with sodium periodate extend the scope of cyclic sulfates in organic synthesis.[5] Cyclic sulfates are important intermediates in obtaining bioactive molecules containing hydroxyl functionality.[4] Chiral cyclic sulfates are easily prepared from the corresponding chiral glycols, which could be obtained from a variety of olefins by OsO_4-catalyzed asymmetric dihydroxylation.

2.0.3 Reactivity of Cyclic Sulfates

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

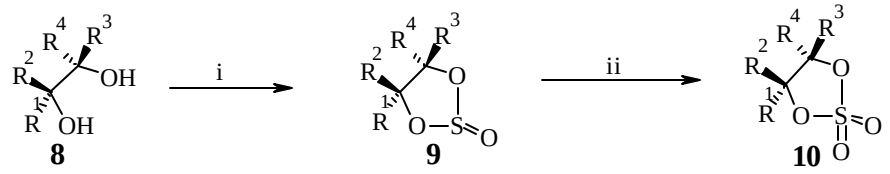


Scheme 1 : **Reactivity pattern of cyclic sulfate *vs* epoxide (i) NaN_3; (ii) H_2SO_4; (iii) NaN_3, H_2O.**

2.0.4 Preparation of Cyclic Sulfites and Sulfates

Cyclic sulfites 9 are conveniently prepared by condensation of 1, 2-, 1, 3- and 1, 4-diols 8 with thionyl chloride (Scheme 2).[5,8] In case of acid sensitive substrates, triethyl

amine or pyridine is required to scavenge the hydrogen chloride generated in the reaction. It is then transformed to cyclic sulfates 10 by Ru-catalyzed oxidation with $NaIO_4$.[4,5]



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

2.0.5 *b*-Adrenergic Blockers

b-Adrenergic blocking agents (*b*-blockers) are important drugs used for the treatment of hypertension and angina pectoris.[9] Most of the *b*-blockers possess a general structure Ar-O-CH_2CH(OH)CH_2NHCH$(CH_3)_2$ (**Fig 1**) and have been used in the form of racemic mixtures.[10]

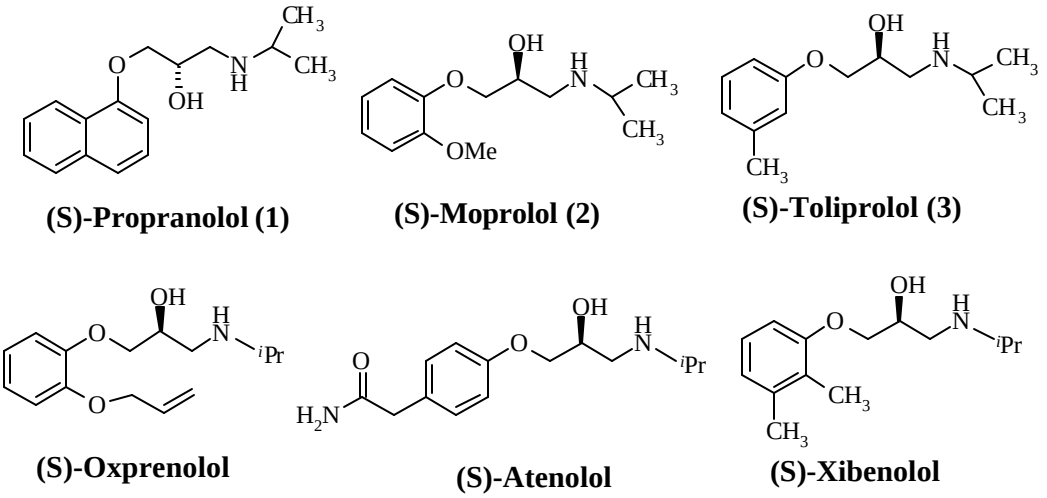


Fig.1

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).[11] 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.[12] Some of the representative *b*-blockers is shown in **Fig. 1**. There are four types of

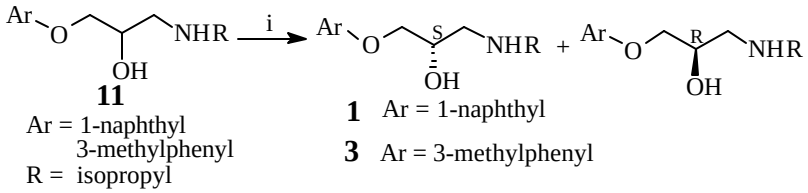
receptors for these molecules a_1, a_2, b_1 and b_2. Blocking of b-receptor system reduces the overall activity of the sympathetic nervous system. Agents, which are b-blockers, are thus used to increase life expectancy after the heart attack. Although (S)-isomers are known to be much more effective (100-500 fold) than the (R)-isomer,[13] 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 (**1**), (S)-moprolol (**2**) and (S)-toliprolol (**3**) are amongst the most widely used b-blockers, which possesses antihypertensive, antianginal, and sympatholytic properties.

2.0.6 Review of Literature

Literature search revealed that there are several reports available on the synthesis of b-blockers **1**-**3**, which are described below.

Howe's approach (1968)

Howe *et al.*[14] synthesized (S)-propranolol (**1**) and (S)-toliprolol (**3**) by resolution of their racemates. Thus 1-isopropylamino-3-(1-naphthoxy)-2-propanol (**11**, Ar = 1-naphthyl) and 1-isopropylamino-3-(3-tolyloxy)-2-propanol (**11**, Ar = 3-toluoyl) were resolved using (-)-O,O-di-*p*-toluoyltartaric acid (**Scheme 3**).



11
Ar = 1-naphthyl
3-methylphenyl
R = isopropyl

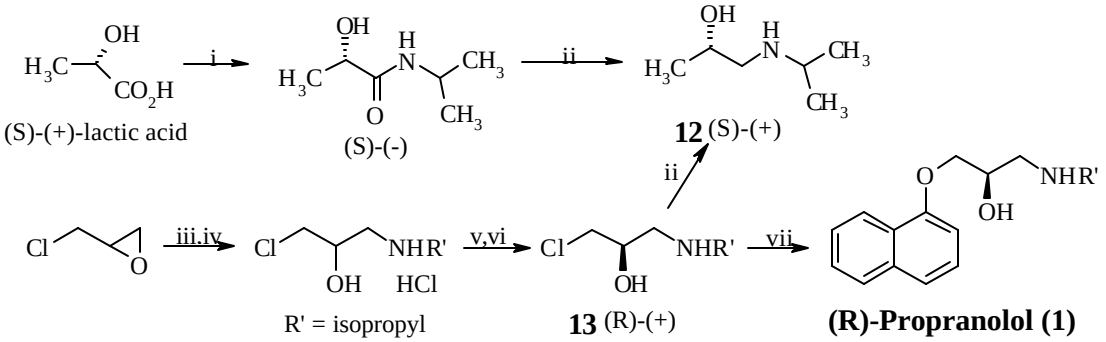
1 Ar = 1-naphthyl
3 Ar = 3-methylphenyl

Scheme 3: (i) (-)-O,O-di-*p*-toluoyltartaric acid, MeOH, H_2O, fractional crystallization.

Smith's approach (1971)

Smith *et al.*[15] reported the synthesis of (R)-(+)-propranolol (**1**) (**Scheme 4**) and confirmed its configuration by correlation with (S)-(+)-lactic acid. The compound **12** was

prepared from (S)-(+)-lactic acid in three steps. The key intermediate (R)-(+)-**13** was prepared starting from epichlorohydrine in four steps. After resolution the (±)-chloroaminoalcohol afforded the (R)-(+)-chloroamonoalcohol **13**. The intermediate **13** was treated with LAH to give **12** which was also prepared from (S)-(+)-lactic acid thereby confirming the configuration of the final product.



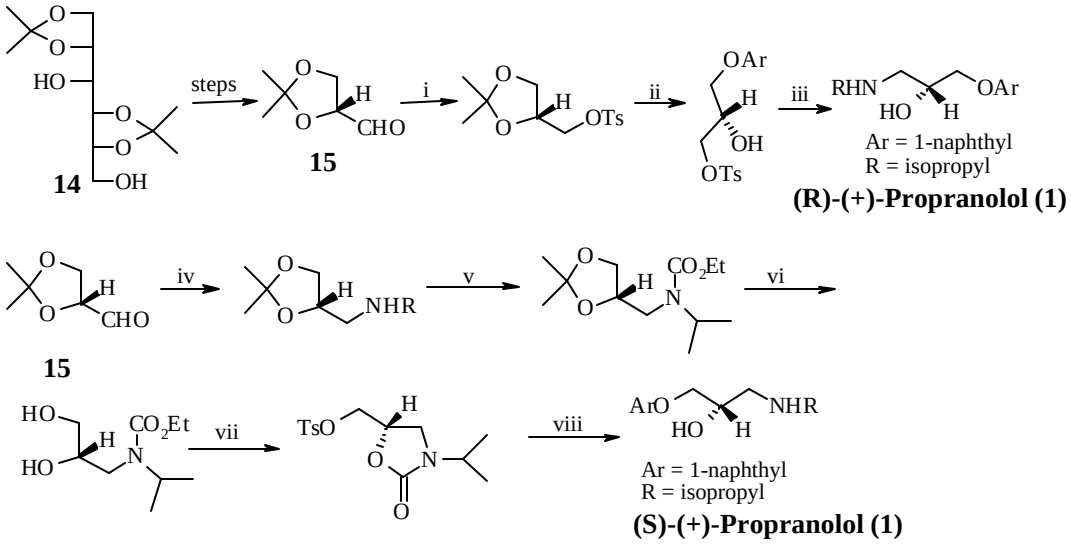
Scheme 4: (i) a. CH_2N_2, ether; b. isopropylamine, 50^0C, 18 h; (ii) $LiAlH_4$, ether; (iii) isopropylamine, MeOH; (iv) etheral HCl; (v) 2N NaOH; (vi) (-)-di-O,O-*p*-toluoyltartaric acid, Et_2O; (vii) a. *a*-naphthol, NaOH; b. etheral HCl.

Ferrari's approach (1980)

Ferrari *et al.*[16] developed a process for the separation of racemic moprolol into its two optical antipodes. In this process racemic moprolol was treated with equimolar quantity of L-(+)-glutamic acid in an alcohol/ water mixture and, after solvent evaporation the mixture of the two optically active salts were obtained. This mixture was then treated with an appropriate quantity of isopropanol/ methanol/ water in the ratio 80/15/5 to yield a crystalline solid which is optically pure L-(+)-glutamic (+)-moprolol salt. The mother liquors of crystallization brought to dryness and then treated with isopropanol/ methanol in a 95/5 ratio, after filtration of the insoluble part resulted in the solution which contained L-(+)-glutamic (–)-moprolol salt. After treatment of this salt with aqueous NaOH yielded the pure (–)-moprolol (**2**) in a crystalline form.

Tsuda's approach (1981)

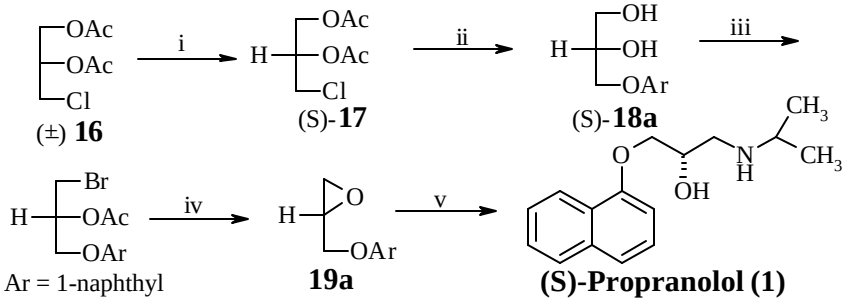
Tsuda *et al.*[17] have developed a synthetic route for the synthesis of both (R)- and (S)-isomers of propranolol (**1**) using D-mannitol derivative **14**. The aldehyde **15** was used to synthesize both (R)- and (S)-propranolol (**Scheme 5**).



Scheme 5: (i) a. $NaBH_4$, b. TsCl, pyridine; (ii) a. *a*-naphthol, NaH; b. TsCl, pyridine; (iii) isopropylamine; (iv) $NaBH_4$ in excess isopropylamine; (v) ethylchloroformate; (vi) hydrolysis; (vii) a. K_2CO_3, DMF; b. TsCl, pyridine; (viii) a. *a*-naphthol;, NaH; b. alkaline hydrolysis.

Kojima's approach (1982)[18]

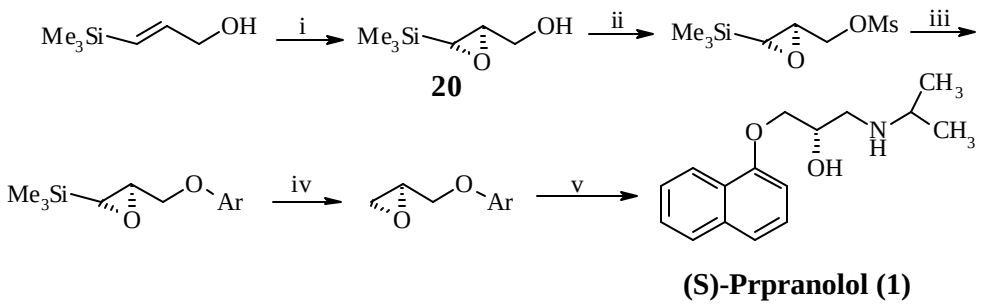
Kojima and coworkers have reported the asymmetric hydrolysis of (±)-1,2-diacetoxy-3-chloropropane (**16**) with a lipoprotein *lipase* (1/ 3000 to the substrate) to give (S)-**17** in 20% yield but in high ee (90%). Reaction of (S)-**17** with *a*-naphthol yielded the (S)-3-(1-naphthoxy)-1,2-propanediol (**18a**) that was converted to (S)-propranolol (**1**) *via* epoxide **19a** (**Scheme 6**).



Scheme 6: (i) lipoprotein *lipase Amano 40*, sodium phosphate buffer, 20%; (ii) 1-naphthol, $Ca(OH)_2$, Hyflo Super-Cel, water, 60^0C, 2 h; (iii) 30% HBr in AcOH; (iv) NaOMe, MeOH, 0^0C; (v) isopropylamine, EtOH, 77%.

Katsuki's approach (1984)[19]

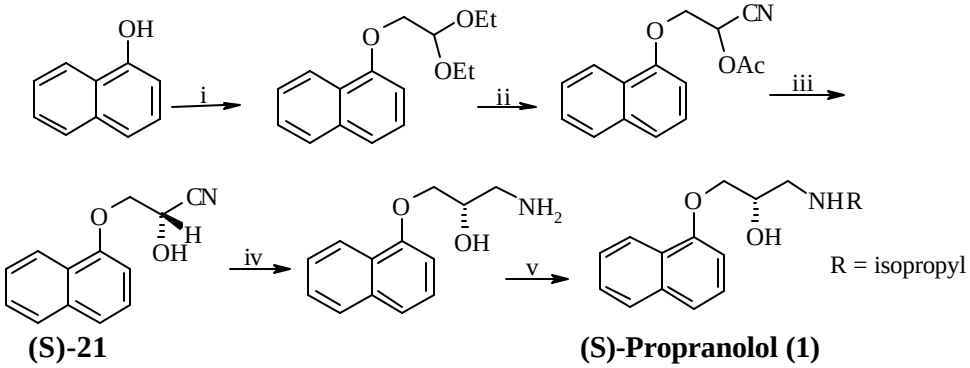
Katsuki has reported the synthesis of (S)-(–)-propranolol (**1**) by using titanium mediated asymmetric epoxidation *via* the key intermediate, epoxide **20** (**Scheme 7**).



Scheme 7: (i) $Ti(O^iPr)_4$, (–)-DIPT, TBHP, CH_2Cl_2; (ii) MsCl, Et_3N; (iii) 1-naphthol, NaH; (iv) $^tBu_4NF$; (v) isopropylamine.

Matsuo's approach (1985)[20]

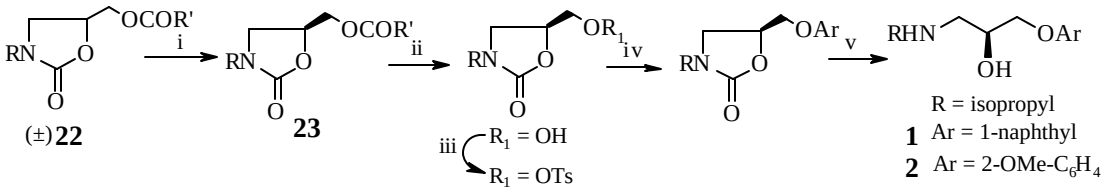
(S)-1-Acetoxy-2-naphthoxypropionitrile (**21**) was synthesized by the asymmetric hydrolysis of racemate with an enzyme. (S)-Propranolol (**1**) was synthesized from (S)-**21** by LAH reduction followed by reaction with isopropylamine in 87% ee (**Scheme 8**).



Scheme 8: (i) bromoacetal, K_2CO_3; (ii) a. HCl, AcOH; b. Ac_2O, NaCN, Bu_4NBr; (iii) *lipase*; (iv) LAH; (v) $NaBH_4$, acetone.

Kazunori's approach (1985)

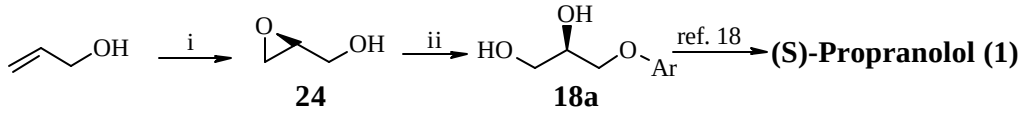
Kazunori *et al.*[21] have reported the synthesis of (S)-propranolol (**1**) and (S)-moprolol (**2**) *via* asymmetric hydrolysis of (±)-oxazolidinone **22**. Asymmetric hydrolysis of **22** with lipoprotein *lipase Amano 3* (L.P.L. Amano 3, origin: *Pseudomonas aeruginosa*) afforded (S)-**23** in high ee (99%). This intermediate compound was then converted to the corresponding *b*-blockers **1** or **2** (**Scheme 9**).



Scheme 9: (i) *lipase Amano 3*; (ii) chemical hydrolysis; (iii) TsCl, Et_3N, CH_2Cl_2; (iv) ArOH (Ar = 1-naphthyl or 2-OMe-C_6H_4), NaH; (v) NaOH, EtOH, H_2O.

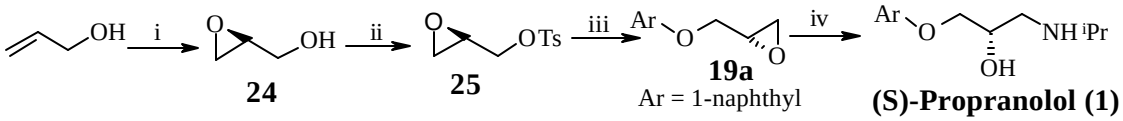
Sharpless's approach (1986)

Sharpless *et al.*[22] have described two different routes for the synthesis of (S)-propranolol (**1**); both the routes involved Ti-catalyzed asymmetric epoxidation of allyl alcohol as key step. In the first procedure after asymmetric epoxidation of allylic alcohol, the reaction mixture was treated with Na-1-naphthoxide to give diol **18a**. The diol **18a** was then converted to (S)-propranolol hydrochloride (48% overall yield from allyl alcohol) (**Scheme 10**).



Scheme 10: (i) $Ti(O^iPr)_4$, (+)-DIPT, cumene hydroperoxide; (ii) ArONa, $Ti(O^iPr)_4$ (1 equiv.), ^tBuOH.

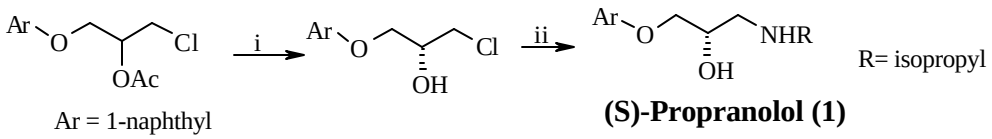
In the second procedure, the glycidol **24** obtained *via* asymmetric epoxidation was converted to glycidyl tosylate **25**, which on treatment with Na-1-naphthoxide in DMF afforded the epoxy ether **19a**. This epoxyether **19a** further on treatment with isopropylamine gave (S)-propranolol (**1**) in 70% yield from **25** (**Scheme 11**).



Scheme 11: (i) $Ti(O^iPr)_4$, (+)-DIPT, cumene hydroperoxide; (ii) TsCl, Et_3N; (iii) 1-naphthol, NaH, DMF; (iv) isopropylamine, H_2O.

Wang's approach (1986)[23]

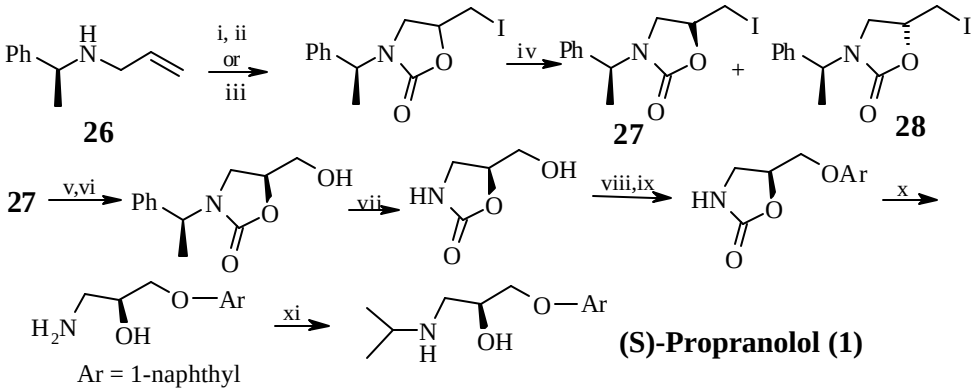
(S)-Propranolol (**1**) was synthesized by the enzyme-mediated asymmetric hydrolysis of (±)-2-acetoxy-1-chloro-3-(1-naphthoxy)-2-propanol (**Scheme 12**).



Scheme 12: (i) enzyme; (ii) isopropylamine.

Giuliana's approach (1987)[24]

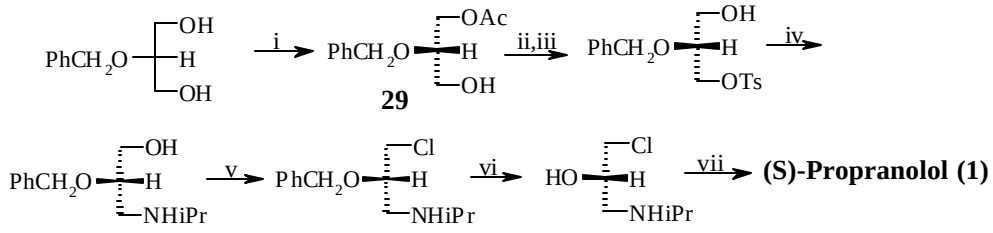
In this approach oxazolidinones **27** and **28** were prepared by cyclization of chiral amine **26** with iodine and Amberlyst A 26 in the CO_3^{--} form. Compounds **27** and **28** were then converted in 8 steps to (S)- and (R)-propranolol (**1**) respectively (**Scheme 13**).



Scheme 13: (i) $PhCH_2OCOCl$; (ii) I_2, $CHCl_3$; (iii) Amberlyst A 26 in the CO_3^{--} form, MeOH, I_2; (iv) silica gel chromatography; (v) Amberlyst A 26 in the AcO^- form, benzene, reflux; (vi) K_2CO_3, EtOH; (vii) Li, NH_3; (viii) MsCl, pyridine, CH_2Cl_2; (ix) Amberlyst A 26 in the *a*-naphtholate form, benzene; (x) LiOH, H_2O, MeOH, reflux; (xi) acetone, $NaBH_4$, EtOH.

Yoshiyasu's approach (1988)

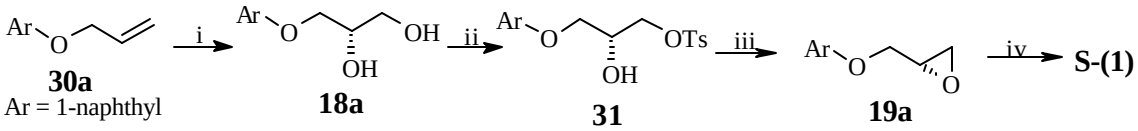
Yoshiyasu *et al.*[25] have developed efficient system for the asymmetric synthesis of chiral glycerol derivatives **29** by *lipase* catalyzed reaction in organic medium. This chiral derivative **29** was then converted into (S)-propranolol (**1**) in seven steps (**Scheme 14**).



Scheme 14: (i) *lipase*, CH_3-CO_2-CH=CH_2, 92% yield, 94% ee; (ii) TsCl, Et_3N; (iii) NaOH, EtOH, 0^0C; (iv) isopropylamine; (v) $SOCl_2$; (vi) H_2, Pd/ C, HCl, EtOH; (vii) 1-naphthol, MeONa, MeOH then HCl gas.

Rama Rao's approach (1990)[26]

Sharpless asymmetric dihydroxylation of the 1-naphthylallyl ether **30a** afforded diol **18a**. Diol **18a** was then converted to monotosylate **31**, which was further transformed to epoxide **19a**. The epoxide **19a** on treatment with isopropylamine gave (S)-propranolol (**1**) in 60% ee (**Scheme 15**).

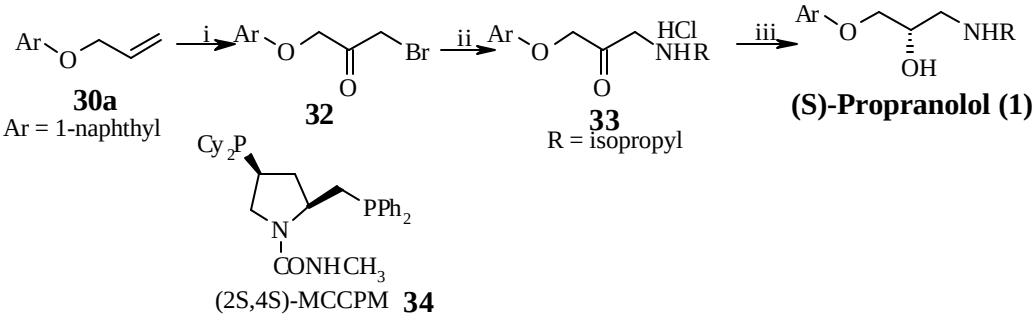


30a Ar = 1-naphthyl **18a** **31** **19a**

Scheme 15: (i) AD mix-*b*; (ii) TsCl, pyridine; (iii) K_2CO_3, MeOH; (iv) isopropylamine.

Achiwa's approach (1990)[27]

This approach makes use of highly efficient rhodium catalyzed asymmetric hydrogenation of oxoamine **33** to give (S)-propranolol (**1**) in 91% ee. The oxoamine **33** was prepared from allyl ether **30a** *via* its oxobromo compound **32** (**Scheme 16**). The complexes of pyrrolidine biphosphine ligands (CMPs) such as (2S,4S)-MCCPM **34** with Rh-(I) were found to be efficient catalysts for asymmetric hydrogenation of *a*-aminoketone derivatives.



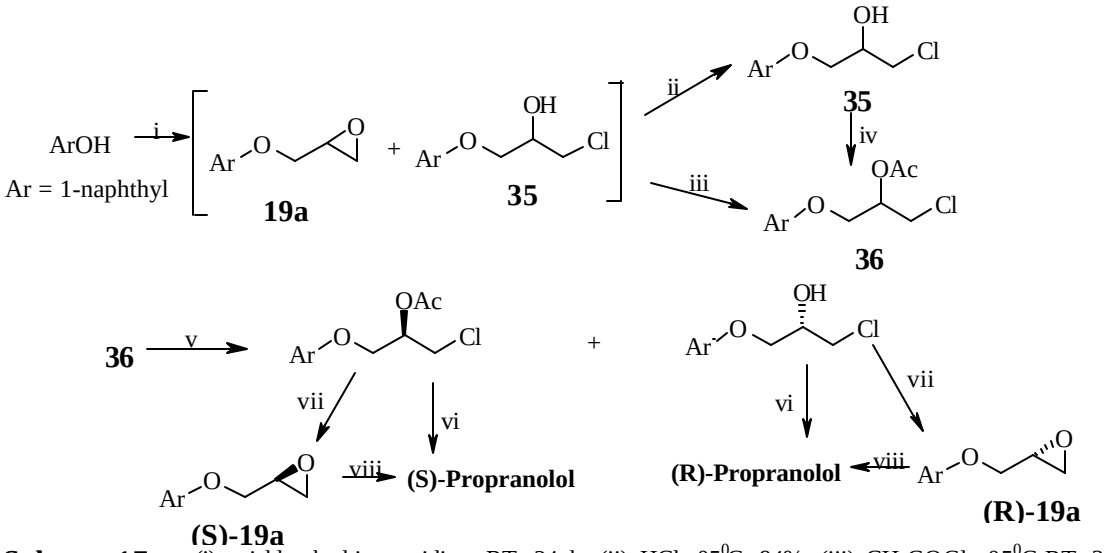
30a Ar = 1-naphthyl **32** **33** R = isopropyl **(S)-Propranolol (1)**

(2S,4S)-MCCPM **34**

Scheme 16: (i) sodium bromite, AcOH:H_2O; (ii) isopropylamine then HCl gas; (iii) H_2, $[Rh(COD)Cl]_2$, (2S,4S)-MCCPM, Et_3N, MeOH, 50^0C, 20 h.

Bevinakatti's approach (1991)

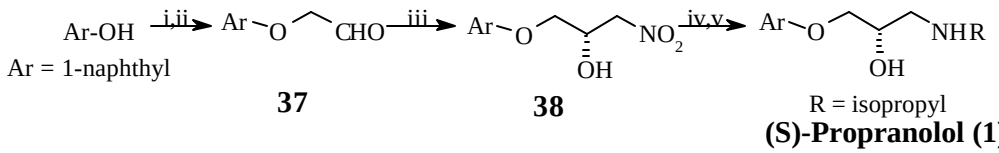
Bevinakatti *et al.*[28] have reported the synthesis of both the optical isomers of propranolol (**1**) with high optical purity (>95% ee) and moderate chemical yields (>30%). *Lipase* catalyzed kinetic resolution of **35** and **36** were used as key steps (**Scheme 17**).



Scheme 17: (i) epichlorohydrin, pyridine, RT, 24 h; (ii) HCl, 0–5^{0}C, 94%; (iii) CH_3COCl, 0–5^{0}C-RT, 3 h, 93%; (iv) Ac_2O, Et_3N, 80-90^{0}C, 1 h, 92%; (v) *lipase PS*, *n*-BuOH or H_2O, RT; (vi) isopropylamine, aqueous NaOH; (vii) aqueous NaOH, *i*-PrOH; (viii) isopropylamine.

Shibasaki's approach (1993)[29]

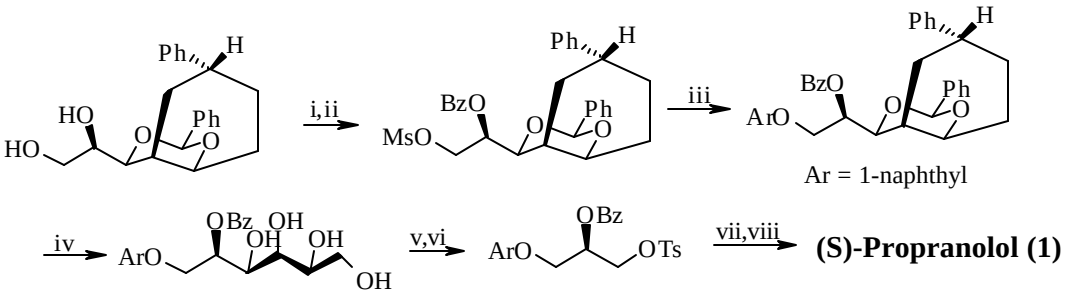
(S)-Propranolol (**1**) was synthesized in enantioselective manner by the lanthanum-(R)-(+)-binaphthol catalyzed asymmetric nitroaldol reaction. The aldehyde **37** reacted with nitromethane in presence of La-catalyst to give nitroalcohol **38**, which was then transformed to (S)-propranolol (**1**) (**Scheme 18**).



Scheme 18: (i) 3-chloro-2-hydroxy propanol, K_2CO_3, CH_3CN; (ii) $NaIO_4$, SiO_2, H_2O, CH_2Cl_2; (iii) La-(R)-BINOL complex (10 mol%), CH_3NO_2, THF, -50^{0}C, 60 h; (iv) 10% PtO_2, H_2, MeOH, RT, 2 h; (v) acetone, 50^{0}C, 16 h.

Ronald's approach (1993)[30]

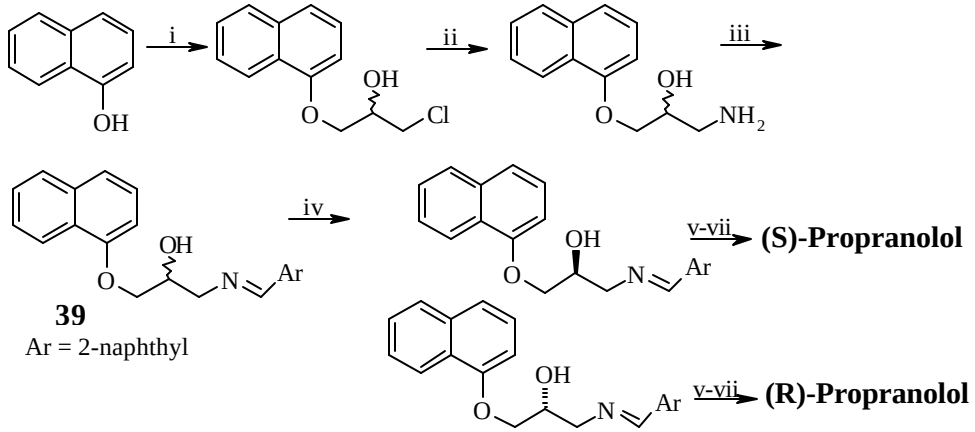
Synthesis of enantiomerically pure (S)-(–)-propranolol (**1**) was achieved in high optical yield starting from sorbitol, an inexpensive and easily available carbohydrate (**Scheme 19**).



Scheme 19: (i) MsCl (1.1 eq.), pyridine, -20^{0}C, 1 h; (ii) BzCl (1.2 eq.), RT, 3 h, 74% (2 steps); (iii) 1-naphthol, KO^{t}Bu, DMSO, RT, 17 h, 58%; (iv) $HOCH_2CH_2OH$, MeOH, HCl, reflux, 4 h, 84%; (v) $NaIO_4$ (4 eq.), dioxane, RT, 17 h; (vi) $NaBH_4$ (2 eq.), dioxane, RT, 1 h, 77% (2 steps); (vii) *p*-TsCl, pyridine, DMAP, RT, 7 days, 72%; (viii) MeOH, isopropylamine, reflux, 4 h, 78%.

Sinisterra's approach (1996)[31]

Synthesis of (R)- and (S)-propranolol (**1**) was achieved using a new chiral stationary phase for the separation of the derivative **39**, which was prepared from 1-naphthol. This simple methodology shows a significant improvement in the separation of the enantiomers of propranolol derivative over the previous methods (**Scheme 20**).

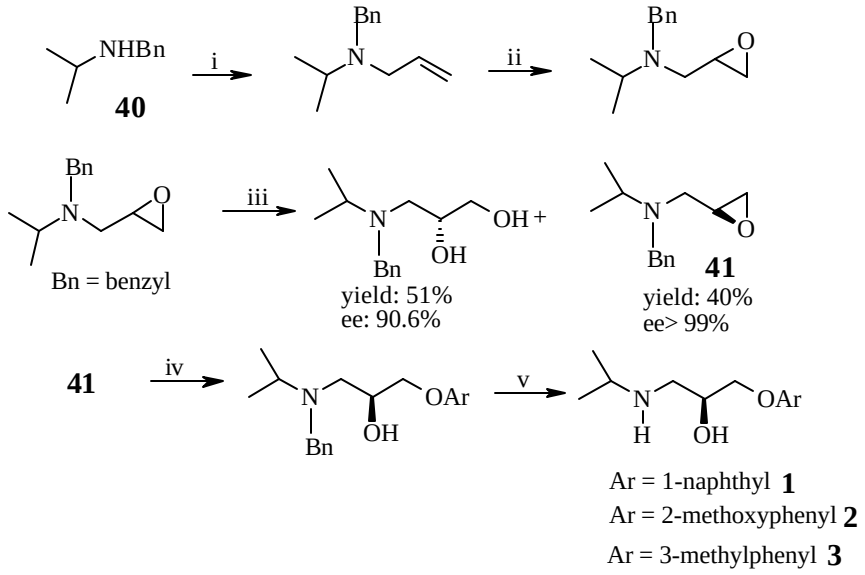


Scheme 20: (i) epichlorohydrin, pyridine, then HCl, 0-5^{0}C; (ii) NH_3, NH_4OAc; (iii) naphthalene-2-carbaldehyde, molecular sieves; (iv) aspartic acid based chiral stationary phase; (v) $PhCH_2Br$; (vi) *i*-PrCl, NaOMe; (vii) H_2, Pd/C.

Hou's approach (1999)[32]

The chiral building block (S)-N-benzyl-N-isopropyl-2,3-epoxypropylamine (**41**) was synthesized by means of chlorohydroxylation of allylamine, followed by Jacobsen's hydrolytic kinetic resolution with water. A concise, divergent five step synthesis of three

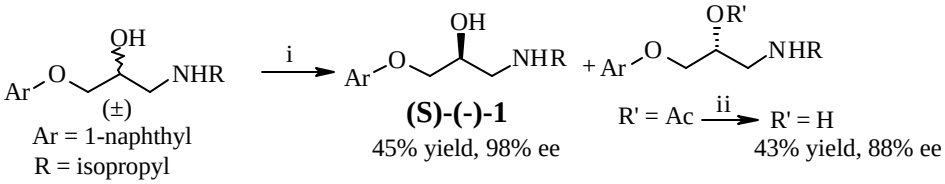
b-blockers in high enantiomeric excess using (S)-N-benzyl-N-isopropyl-2,3-epoxypropylamine (**41**) as the key intermediate is developed. *b*-Blockers (S)-propranolol (**1**), (S)-moprolol (**2**) and (S)-toliprolol (**3**) were prepared in 26.6%, 28.4% and 28.4% overall yields and in >99% ee respectively from benzylisopropylamine **40** in five steps. It is noteworthy that water was the reagent used in the second and third steps. It involved short synthetic sequences; produced uniformly good overall yields, high ee (**Scheme 21**).



Scheme 21: (i) allylbromide, NaOH, DMF, 93%; (ii) a) Li_2PdCl_4 (10%), $CuCl_2$ (300%), DMF, -10^0C, 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%.

Salunkhe's approach (1999)

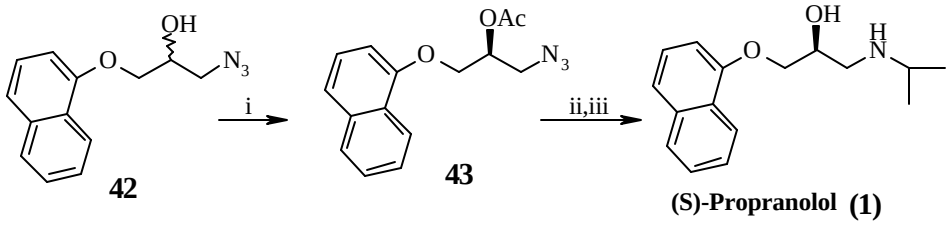
Salunkhe *et al.*[33] have reported *lipase* catalyzed enantioselective esterification of racemic propranolol to give (S)-propranolol (**1**) and the corresponding acetate, which was hydrolyzed, to give (R)-propranolol (**Scheme 22**).



Scheme 22: (i) *lipase PS-D*, vinylacetate; (ii) K_2CO_3, MeOH.

Backvall's approach (2001)

Backvall *et al.*[34] have developed efficient method for enzymatic resolution of *b*-azidoalcohols in combination with ruthenium-catalyzed alcohol isomerization, which led to successful dynamic kinetic resolution. The synthetic utility of this procedure has been illustreted by the practical synthesis of (S)-propranolol (**1**) by kinetic resolution of azidoalcohol **42** to give azidoacetate **43**, which was converted to (S)-**1** (**Scheme 23**).



42 **43** **(S)-Propranolol (1)**

Scheme 23: (i) *novozyme 435 (N-435),* Ru-catalyst (4 mol%), *p*-Cl-C_6H_4-OAc (3 equiv.); (ii) LiOH, MeOH, 2 h, RT; (iii) PtO_2, acetone, H_2 (1 atm.), 4 h, RT, 98%.

2.0.7 Present Work

2.0.7.1 Objective

Although racemic *b*-blockers have been administered over the last two decades, there is now a great demand for enantiomerically pure isomers, which show higher affinity to *b*-receptors. All the reported methods described above for the synthesis of this class of compounds suffer from drawbacks such as use of expensive enzymes and resolving agents, low overall yields, low optical purity, *etc*. To develop a new general route for the asymmetric synthesis of *b*-adrenergic blockers with good optical purity and yield, we have decided to make use of Sharpless Asymmetric Dihydroxylation (AD) [see **Chapter 1** for its introduction] of aryl allyl ethers and chemistry of chiral cyclic sulfates.

Retrosynthetic analysis of these homochiral *b*-adrenergic blocking agents (**A**) is shown in **Fig. 2**. Evidently, there are three possible disconnections of bonds shown at a, b and c positions. However most of the synthetic routes are based on the disconnection of bonds at either a or b.

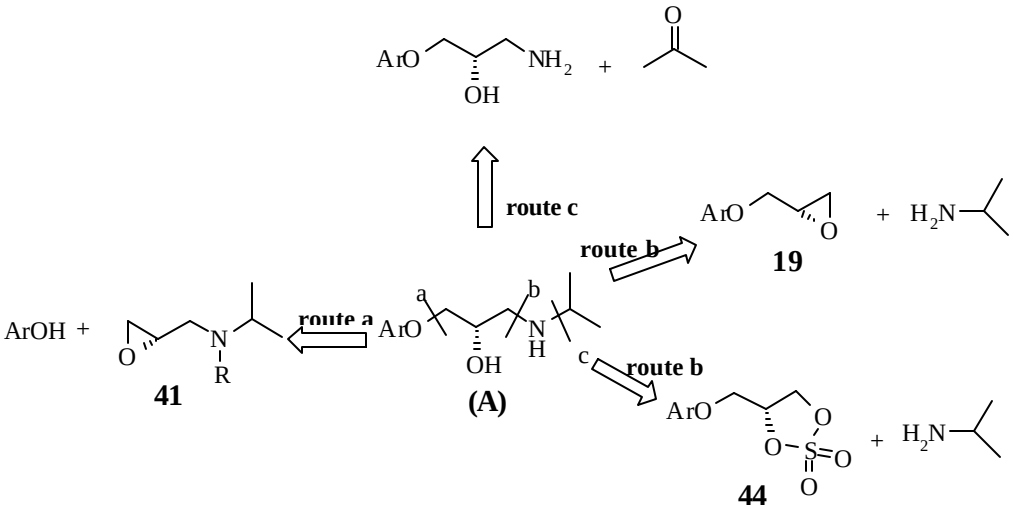
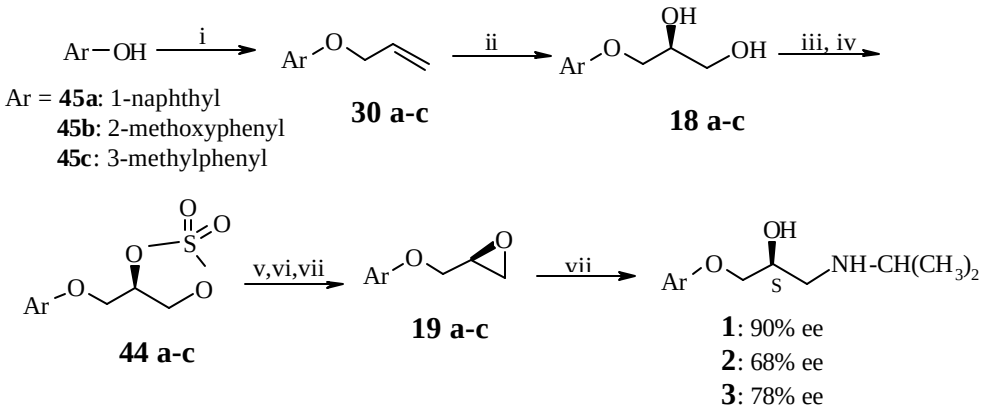


Fig.2: Retrosynthetic analysis of *b*-blockers (A)

2.0.8 Results and Discussion

Our approach for the synthesis of *b*-blockers **1-3** is based on the disconnection route b, which results in two chiral synthons (cyclic sulfate **44** and epoxide **19**), both of which are accessible using AD method. The general synthetic scheme employed for the synthesis of (S)-propranolol (**1**), (S)-moprolol (**2**) and (S)-toliprolol (**3**) is presented in **Scheme 24**.



Scheme 24: (i) K_2CO_3, CH_2=$CHCH_2Br$, acetone, reflux, 12 h, 97-99%; (ii) cat-OsO_4, $(DHQD)_2$-PHAL, $K_3Fe(CN)_6$, K_2CO_3, ^{t}-BuOH:H_2O, 0°C, 12 h., 94-98%, 73-90%ee; (iii) $SOCl_2$, Et_3N, CH_2Cl_2, 0°C, 40 min. 96-99%; (iv) cat. $RuCl_3$ $3H_2O$, $NaIO_4$, CH_3CN:H_2O, 0°C, 30 min. 94-98%; (v) LiBr, THF 25°C, 2-3 h; (vi) 20% H_2SO_4, Et_2O, 25°C, 10 h; (vii) K_2CO_3, MeOH, 0°C, 2 h, 80-85% overall in three steps; (viii) *i*-Pr-NH_2, H_2O (cat.), reflux, 2 h, 99%.

Allylation of phenols **45 a-c** [**45a**= *a*-naphthol, **45b**= *o*-methoxyphenol (guaiacol), **45c**= 3-methylphenol (*m*-cresol)] with allylbromide gave allyl ethers **30 a-c** in >97% yield. ^{1}H-NMR showed pattern typical for the allylic functionality in the region of δ 4.00-6.00. ^{13}C-NMR also showed the signals for the carbons of the allylic functionality in the region of δ 68-118.

These allylic ethers **30 a-c** were then subjected for the Os-catalyzed Sharpless asymmetric dihydroxylation (AD) using $(DHQD)_2$-PHAL [hydroquinidine 1,4-phthalazinediyl diether] as chiral ligand in the presence of $K_3Fe(CN)_6/K_2CO_3$ as co-oxidant to give optically active diols **18 a-c**. The IR spectrum of these diols showed a

broad band in the region of 3400-3500 cm^{-1} indicating the presence of hydroxyl functionality in the molecules. The ^{1}H-NMR spectrum showed disappearance of signals for allylic protons in the region of δ 4.0-6.0. Multiplets in the region of δ 3.65-3.80 and δ 4.00-4.15 for 5 protons and broad singlet at δ 3.25 confirmed the formation of the diols (see **Fig. 3 for 18c**)

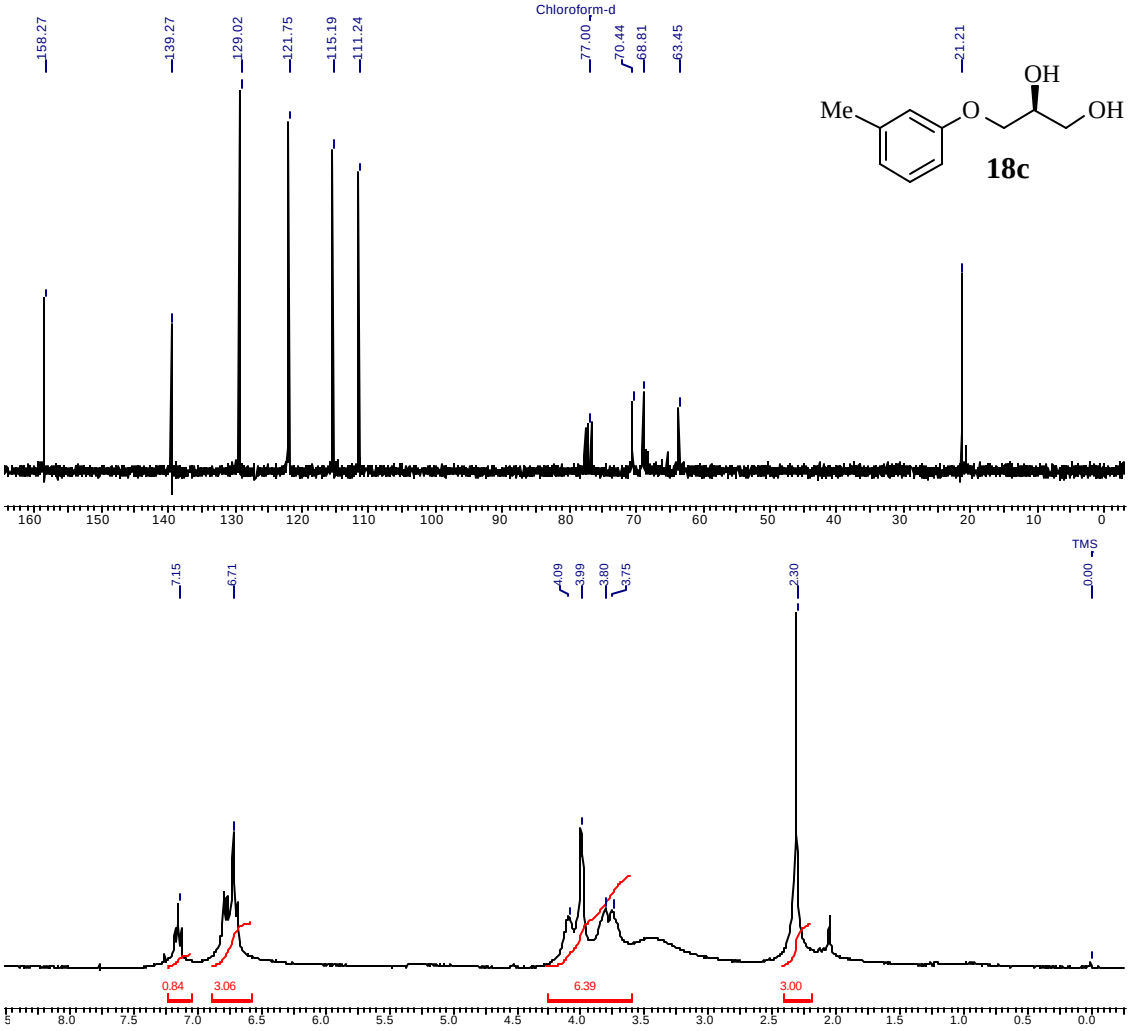


Fig. 3: ^{1}H and ^{13}C NMR spectra of the diol 18c

The ^{13}C-NMR showed signals at δ 21.21 for aromatic CH_3 group and at δ 63.45, 68.81 and 70.44 for the three aliphatic carbons bearing oxo-functionality. The diols **18a-c**

were obtained in 91%, 73% and 80% ee respectively (measured by both chiral HPLC using Chiralcel OD-H column and optical rotation).

The diols **18 a-c** were treated with freshly distilled $SOCl_2$, Et_3N in CH_2Cl_2 at 0^0C to afford cyclic sulfites in 96-99% yield. The formation of cyclic sulfite was clearly evident from the appearance of multiplets in its ^{1}H-NMR in the region δ 4.00-5.50 due to the presence of diastereomeric mixtures. The cyclic sulfites of the corresponding diols were then converted into cyclic sulfates **44 a-c** in 94-98% yield using Ru-catalyzed oxidation. The ^{1}H-NMR spectrum of cyclic sulfate **44c** showed the disappearance of multiplets at δ 4.25-4.32, 4.72-4.86 and at 5.22-5.26 due to diastereomeric mixtures. The ^{13}C-NMR spectrum also showed simplified pattern because of the absence of diastereomeric mixtures (**Fig 4**). Its mass spectrum showed molecular ion (M^+) peak at m/z 244, which confirms the formation of cyclic sulfate moiety.

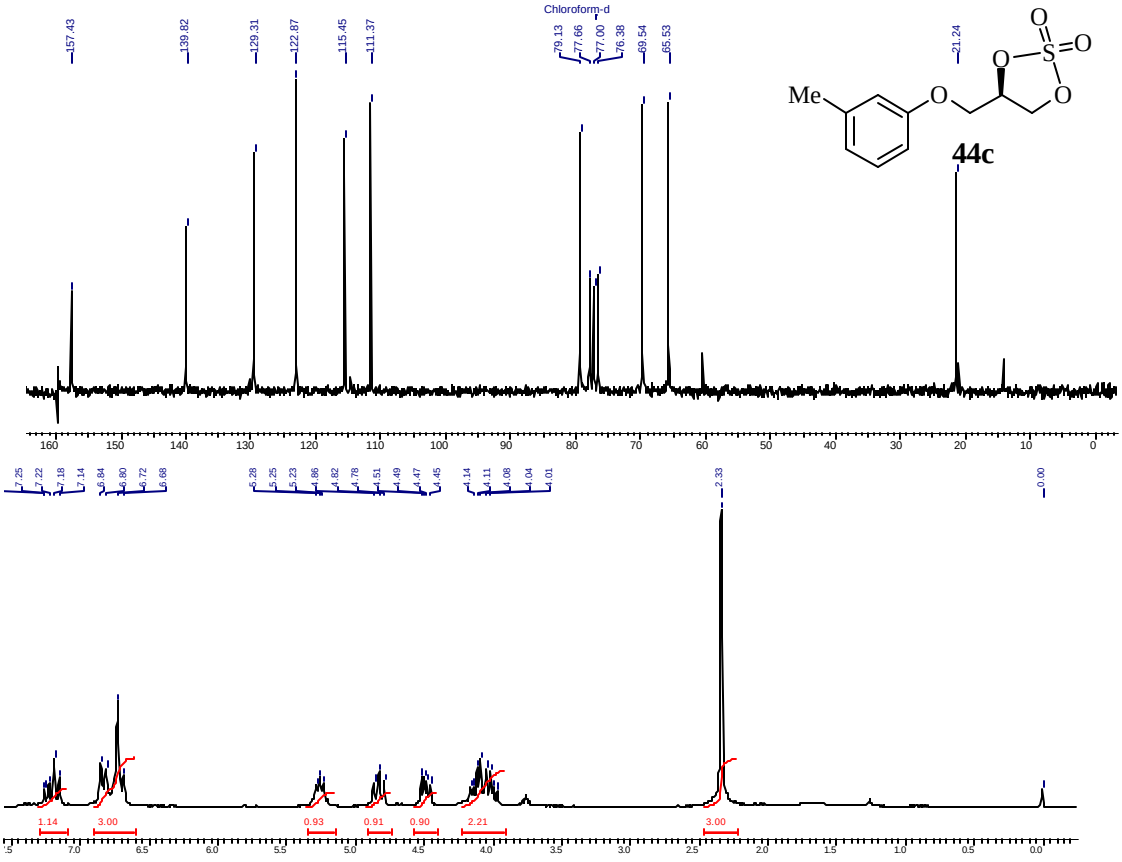


Fig. 4: ^{1}H and ^{13}C NMR spectra of cyclic sulfate 44c

Finally, the cyclic sulfates **44 a-c** were subjected to nucleophilic displacement with isopropylamine followed by hydrolysis of the resulting salts afforded the corresponding *b*-blockers **1**, **2** and **3** respectively. However, the opening and hydrolysis of the cyclic sulfates **44 a-c** resulted in very low yields of the final *b*-blockers (yields were <30%). Various reaction conditions such as 20% H_2SO_4 in ether, 50% H_2SO_4 in ether, 20% HCl, concentrated HCl, 20% aqueous NaOH and 50% aq. NaOH were tried but all of them failed to improve the yields of the final products.

Hence, we decided to convert these cyclic sulfates **44 a-c** into the corresponding epoxides **19 a-c** using a three-step procedure in high overall yields (80-85% in three steps).

Thus, cyclic sulfates **44 a-c** were first treated with anhydrous LiBr, then with 20% aqueous H_2SO_4 in ether to give bromoalcohol. It was then treated with K_2CO_3 in MeOH at 0^0C to afford the corresponding epoxides **19 a-c**.

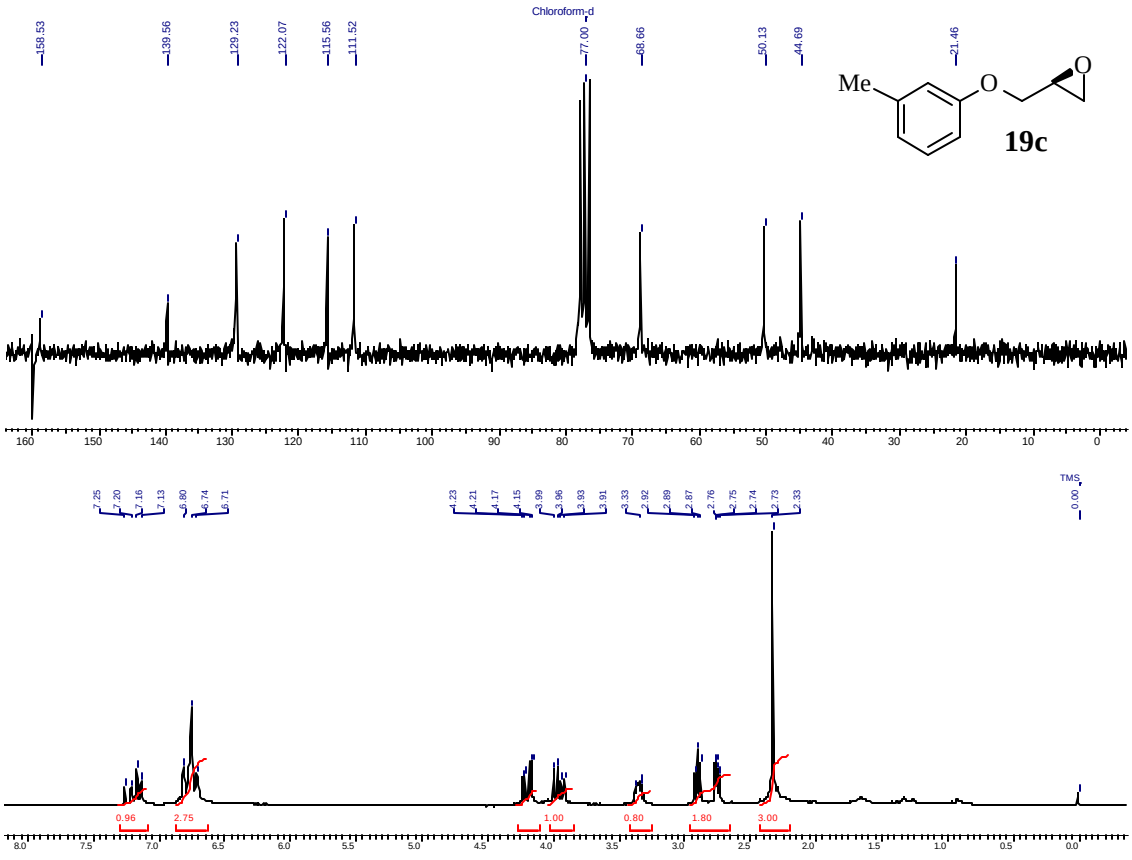


Fig. 5: ^{1}H, ^{13}C NMR and mass spectra of epoxide 19c

The ^{1}H-NMR of **19c** showed signals at δ 2.73-2.76, δ 2.87-2.92, δ 3.32-3.36, δ 3.91-3.99 (dd, *J* = 4.11 and 12.14 Hz) for 1H and δ 4.15-4.23 (dd, *J* = 4.11 and 12.14 Hz) for 1H, which indicate the presence of the epoxide functionality. The ^{13}C-NMR spectrum also showed the upfield shift in case of the carbons belonging to O-side chain (**Fig. 5**). The mass spectrum showed very strong M^{+} peak at m/z 164 confirming the formation of epoxide **19c**.

The epoxides **19 a-c** were then subjected to regiospecific nucleophilic attack with isopropyl amine to furnish the corresponding *b*-blockers **1**, **2** and **3** in excellent yields (99%). The ^{1}H-NMR spectrum of **1** showed a doublet at δ 1.08-1.11 for two methyls of isopropyl group and multiplets in the region δ 2.76-3.01 and δ 4.08-4.19 confirming the formation of (S)-propranolol (**1**) (**Fig 7**). Similarly ^{1}H-NMR spectrum of **2** is shown in **Fig. 6**.

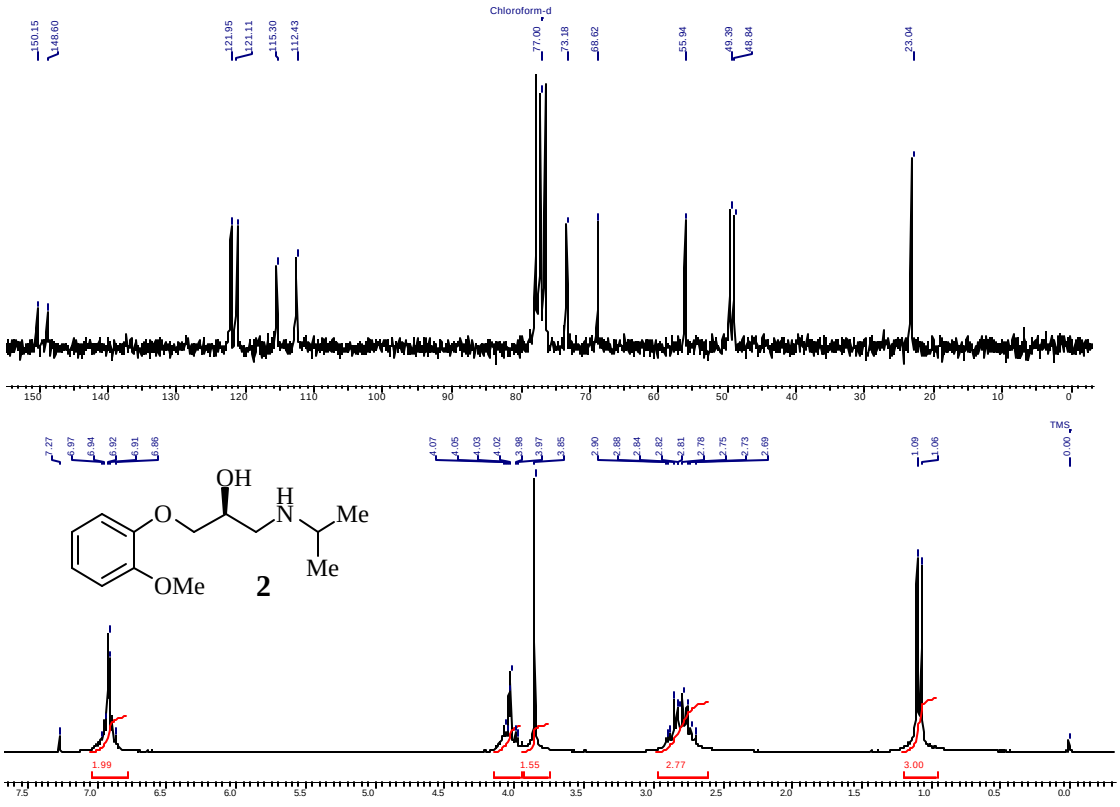


Fig. 6: ^{1}H and ^{13}C NMR spectra of (S)-moprolol

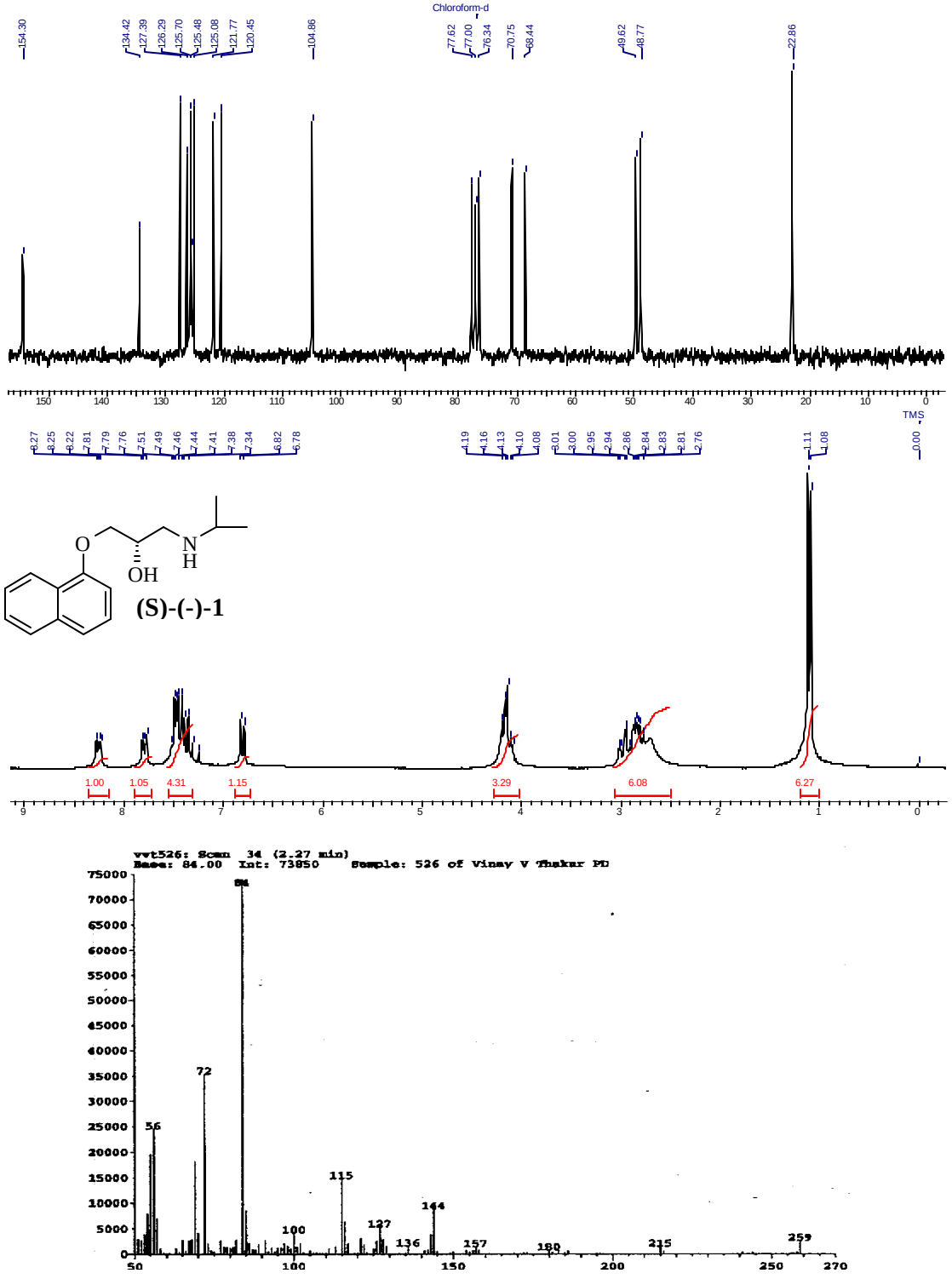


Fig. 7: ^{1}H ^{13}C NMR and Mass spectra of compound (S)-propranolol

2.0.9 Conclusion

In conclusion, we have developed a simple and efficient method for the asymmetric synthesis of three *b*-blockers namely (S)-propranolol (**1**) [66.6% overall yield, 90% ee], (S)-moprolol (**2**) [74% overall yield, 68% ee] and (S)-toliprolol (**3**) [77.3% overall yield, 78% ee] in eight steps starting from the corresponding phenols **45 a-c**. We have also demonstrated a simple and efficient method for the conversion of cyclic sulfates **44 a-c** to the corresponding epoxides **19 a-c** in high yields (80-85% overall yield in three steps) using a three-step procedure.

2.0.10 Experimental Section

Preparation of allyl phenyl ethers 30 a-c:

A mixture of one of the phenols **45 a-c** (10 mmol), allylbromide (1.45 g, 12 mmol) and anhydrous K_2CO_3 (2.07 g 15 mmol) in dry acetone (20 ml) was refluxed under N_2 for 20 h (reactions monitored by TLC). The reaction mixture then cooled to room temperature, filtered through sintered funnel to remove solid residue and the filtrate was evaporated to dryness. The residue was purified by column chromatography using pet. ether: EtOAc (9:1) as eluent to get pure allyl phenyl ethers **30 a-c** in 97-99% yield.

Allyl 1-naphthyl ether (30a): **Yield**: 97%; **gum**; **IR** (Neat, cm^{-1}): 744, 927, 999, 1012, 1028, 1125, 1200, 1260, 1458, 1520, 2829, 2930; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 4.68 (d, *J* = 4.23 Hz, 2H), 5.29-5.54 (m, 2H), 6.08-6.24 (m, 1H), 6.78 (d, *J* = 8.14 Hz, 1H), 7.34-7.49 (m, 4H), 7.76-7.81 (m, 1H), 8.29-8.34 (m, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 68.69, 104.94, 117.07, 120.26, 122.03, 125.08, 125.70, 126.29, 127.36, 133.24, 134.49, 154.23; **Analysis**: $C_{13}H_{12}O$ requires C, 84.75; H, 6.57; found C, 84.69; H, 6.51%.

Allyl 2-methoxyphenyl ether (30b): **Yield**: 99%; **gum**; IR (Neat, cm^{-1}): 742, 927, 997, 1026, 1124, 1224, 1251, 1454, 1504, 1593, 2835, 2935; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.85 (s, 3H), 4.57-4.67 (m, 2H), 5.24-5.45 (m, 2H), 6.00-6.24 (m, 1H), 6.87-6.90 (m, 4H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 55.58, 69.55, 111.58, 113.41, 117.53, 120.49, 121.01, 133.22, 147.81, 149.27; **MS** m/z (% rel. intensity): 164 (M^+, 80), 149 (10), 123 (94), 109 (25), 95 (100), 80 (30), 77 (95), 65 (25); **Analysis**: $C_{10}H_{12}O_2$ requires C, 73.15; H, 7.37; found C, 73.28; H, 7.34%.

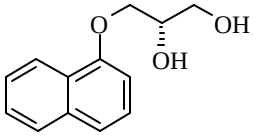
Allyl 3-methylphenyl ether (30c): **Yield**: 97%; **gum**; **IR** (Neat, cm^{-1}): 670, 738, 780, 927, 1020, 1127, 1224, 1260, 1458, 1490, 1510, 1594, 2859, 2945; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.36 (s, 3H), 4.49-4.55 (m, 2H), 5.25-5.48 (m, 2H), 5.97-6.21 (m, 1H), 6.75-6.79 (m, 3H), 7.16 (s, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 21.39, 68.52, 111.49, 115.49, 117.26, 121.56, 129.07, 133.40, 139.29, 158.55; **MS** m/z (% rel. intensity): 148 (M^+, 50), 133 (60), 119 (65), 105 (70), 91 (100), 77 (50); **Analysis**: $C_{10}H_{12}O$ requires C, 81.04; H, 8.16; found C, 81.12; H, 8.21%.

Preparation of 1-(aryloxy)-2,3-dihydroxypropane 18 a-c:

A 100 ml RB flask was charged with $K_3Fe(CN)_6$ (5.92 g, 18.0 mmol), K_2CO_3 (2.48 g, 18.0 mmol), $(DHQD)_2$-PHAL (0.192 g, 0.24 mmol) and *t*-BuOH : H_2O (1:1, 60 ml) and the resulting mixture was stirred for 10 minutes at 25^0C. It was then cooled to 0^0C and a

solution of OsO_4 (256 μl, 0.124 mmol, 0.5 M solution in toluene) was added. The resulting reaction mixture was stirred at 0^0C for 5 minutes and then one of the olefins **30 a-c** (6 mmol) was added. The reaction mixture was stirred at 0^0C for 20-22 h (monitored by TLC). It was quenched with sodium sulfite (4.0 g) and extracted with ethyl acetate (4 x 25 ml). Combined organic extracts were washed with brine (20 ml), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by column chromatography using 50% EtOAc in pet. ether as eluent to yield pure diols **18 a-c** as white solids in 94-98% yield.

(2S)-1-(1-Naphthoxy)-2,3-propanediol (18a)



Yield: 96%; **mp**: 113-114^{0}C; **[**a**]$^{25}_D$**: + 6.10 (c 1.1, MeOH), , [lit.[26] +4.01 (c 1.1, MeOH), 60% ee]; **HPLC**: 91% ee, Chiralcel OD-H, 5% EtOH/hexane, 1 ml/min. Retention time: (R): 13.23 min. (S): 16.55 min.; **IR** ($CHCl_3$, cm^{-1}): 740, 780, 845, 993, 1020, 1130, 1257, 1379, 1390, 1458, 1515, 1598, 2845, 2910, 3280; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.55 (bs, 1H), 3.80-3.95 (m, 3H), 4.10-4.25 (m, 3H), 6.83 (d, *J* = 6.10 Hz, 1H), 7.32-7.49 (m, 4H), 7.77-7.81 (m, 1H), 8.24-8.29 (m, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 63.75, 69.13, 70.44, 104.86, 120.34, 121.77, 124.98, 125.43, 125.65, 126.20, 127.27, 134.32, 154.21; **MS** m/z (% rel. intensity): 218 (M^+, 70), 144 (100), 127 (10), 115 (43), 89 (7), 77 (5); **Analysis**: $C_{13}H_{14}O_3$ requires C, 71.54; H, 6.47; found C, 71.52; H, 6.49%.

(2S)-1-(2-Methoxyphenyl)-2,3-propanediol (18b): **Yield**: 94%; **mp**: 101-102^{0}C; **[**a**]$^{25}_D$**: + 6.70 (c 1.1, MeOH), 73% ee [lit.[35] + 5.8 (c 1.1, MeOH), 63% ee]; **HPLC**: 73% ee, Chiralcel OD-H, 5% EtOH/hexane, 1 ml/min. Retention time: (R): 11.18 min. (S): 15.21 min.; **IR** ($CHCl_3$, cm^{-1}): 744, 837, 993, 1022, 1128, 1257, 1377, 1456, 1510, 1593, 2854, 2953, 3234; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.75-3.84 (m, 2H), 3.86 (s, 3H), 4.04-4.17 (m, 3H), 6.90-6.97 (m, 4 H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 55.98, 63.22, 69.83, 70.68, 111.55, 113.65, 120.63, 121.18, 147.76, 148.97, 159.45; **MS** m/z (% rel. intensity): 198 (M^+, 28), 149 (10), 124 (100), 109 (80), 77 (13); **Analysis**: $C_{10}H_{14}O_4$ requires C, 60.60; H, 7.12; found C, 60.56; H, 7.14%.

(2S)-1-(3-Methylphenyl)-2,3-propanediol (18c): **Yield**: 98%; **mp**: 61-62^{0}C; **[**a**]$^{25}_D$**: + 7.86 (c 1, EtOH) 80% ee [lit.[36] + 9.5 (c 1, EtOH) 97% ee]; **HPLC**: 80% ee, Chiralcel OD-H, 5% EtOH/hexane, 1 ml/min. Retention time: (R): 19.18 min. (S): 24.15 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 2.30 (s, 3H), 3.65-3.80 (m, 2H), 4.00-4.25 (m, 3H), 6.66-6.85 (m, 3H), 7.20-7.30 (m, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 21.21, 63.45, 68.81, 70.44, 111.24, 115.19, 121.75, 129.02, 139.27, 158.27; **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, 65.92; H, 7.74; found C, 65.86; H, 7.79%.

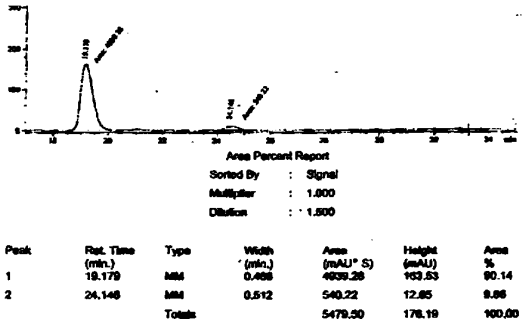
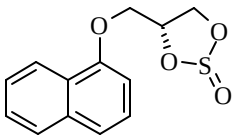


Fig. 10: HPLC chromatogram of diol 18c

Preparation of cyclic sulfates 44 a-c:

[A] To a solution of one of the diols **18 a-c** (4 mmol) and triethylamine (2.21 ml, 16 mmol) in CH_2Cl_2 (10 ml) at 0^0C was added freshly distilled thionyl chloride (0.44 ml, 6 mmol) drop-wise under nitrogen atmosphere. The reaction mixture was stirred at 0^0C for 30-45 minutes (monitored by TLC). The reaction mixture was quenched by the addition of cold water (10 ml). The organic layer was separated and the aqueous layer extracted with EtOAc (3 x 15 ml). The combined organic extracts were washed with water, brine and dried over anhydrous Na_2SO_4. Evaporation of solvent under reduced pressure yielded pale yellow colored liquid, which was purified by the column chromatography using 10% EtOAc in pet. ether as a eluent to afford the corresponding cyclic sulfite **58 a-c** as viscous yellow liquid in 96-99% yield.

(4S)-4-(1-Naphthoxymethyl)-1,3,2-dioxathiolane-2-oxide (58a)



Yield: 96%; **gum**; **[a]$^{25}_D$**: + 80.51 (c 1.2, EtOH); **IR** ($CHCl_3$, cm^{-1}): 750, 972, 1125, 1208, 1277, 1319, 1402, 1470, 1584, 2800, 2920; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 4.22-5.39 (m, 5H), 6.73-6.81 (m, 1H), 7.31-7.52 (m, 4H), 7.78-7.82 (m, 1H), 8.15-8.27 (m, 1H); **^{13}C-**

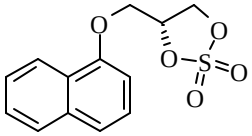
NMR (50 MHz, $CDCl_3$): δ 66.83, 67.52, 68.47, 69.06, 78.03, 80.01, 104.79, 104.94, 121.29, 121.66, 125.23, 125.52, 126.62, 127.47, 134.42, 153.46; **MS** m/z (% rel. intensity): 264 (M^+, 55), 157 (48), 143 (100), 121 (30), 115 (21), 89 (10); **Analysis**: $C_{13}H_{12}SO_4$ requires C, 59.08; H, 4.58; S, 12.13; found C, 59.12; H, 4.67; S, 12.21%.

(4S)-4-[(2-Methoxyphenyl)methyl]-1,3,2-dioxathiolane-2-oxide (58b): **Yield**: 99%; **gum**; **[**a **]$^{25}_D$**: + 51.50 (c 2.2, EtOH); **IR** ($CHCl_3$, cm^{-1}): 578, 667, 757, 1027, 1126, 1217, 1255, 1456, 1506, 1593, 3016, 3056; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.86 (s, 3H), 4.01-5.28 (m, 5H), 6.90-7.04 (m, 4H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 55.72, 68.47, 68.69, 70.35, 77.85, 79.94, 112.47, 116.15, 120.85, 123.06, 147.47, 150.15; **MS** m/z (% rel. intensity): 244 (M^+, 70), 137 (25), 123 (80), 109 (52), 95 (62), 77 (100), 65 (15); **Analysis**: $C_{10}H_{12}SO_5$ requires C, 49.17; H, 4.95; S, 13.13; found C, 49.21; H, 4.91; S, 13.21%

(4S)-4-[(3-methylphenyl)methyl]-1,3,2-dioxathiolane-2-oxide (58c): **Yield**: 99%; **gum**; **[**a **]$^{25}_D$**: + 60.26 (c 1.2, EtOH); **IR** ($CHCl_3$, cm^{-1}): 688, 738, 773, 854, 962, 1053, 1161, 1211, 1261, 1290, 1454, 1490, 1585, 1602, 2923, 2952, 3035; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.33 (s, 3H), 3.99-5.28 (m, 5H), 6.68-6.84 (m, 3H), 7.14-7.26 (dd, *J* = 8.20 Hz and 2.11 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 21.28, 66.16, 68.03, 68.62, 69.65, 77.77, 79.87, 111.26, 115.30, 122.47, 129.23, 139.60, 157.76; **MS** m/z (% rel. intensity): 228 (M^+, 70), 147 (10), 135 (23), 121 (95), 108 (40), 91 (100), 77 (30); **Analysis**: $C_{10}H_{12}SO_4$ requires C, 52.62; H, 5.30; S, 14.05; found C, 52.57; H, 5.27; S, 14.16%.

[B] To a solution of one of the cyclic sulfites **58 a-c** (3 mmol) in CH_3CN: H_2O mixture (9: 1, 8 ml) at 0^0C was added solid $NaIO_4$ (0.963 g, 4.5 mmol) and $RuCl_3.3H_2O$ (0.012 g, 0.06 mmol). The reaction mixture was stirred for 30-40 minutes at 0^0C (monitored by TLC). After the reaction was completed, it was filtered through a pad of celite. Solvent evaporated under reduced pressure to give the crude product, which was purified by column chromatography using pet. ether: EtOAc (8:2) as eluent to afford cyclic sulfates **44 a-c** in 94-98% yield.

(4S)-4-[(1-Naphthoxymethyl]-1,3,2-dioxathiolane-2,2-dioxide (44a)



Yield: 94%; **gum**; **[**a **]$^{25}_D$**: + 17.4 (c 0.5, EtOH); **IR** ($CHCl_3$, cm^{-1}): 651, 753, 984, 1024, 1130, 1190, 2113, 1255, 1398, 1460, 1510, 1600, 2854, 2940; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 4.25-4.29 (m, 2H), 4.60-4.67 (m, 1H), 4.88-4.96 (m, 1H), 5.36-5.41 (m, 1H),

6.79 (d, *J* = 8.14 Hz, 1H), 7.26-7.53 (m, 4H), 7.70-7.84 (m, 1H), 8.16-8.21 (m, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 66.52, 68.36, 77.99, 104.75, 121.15, 121.48, 125.08, 125.45, 126.51, 127.36, 134.31, 153.38; **MS** m/z (% rel. intensity): 280 (M^+, 100), 157 (55), 144 (56), 137 (25), 123 (28), 118 (10), 91 (8); **Analysis**: $C_{13}H_{12}SO_5$ requires C, 55.71; H, 4.32; S, 11.44; found C, 55.56; H, 4.29; S, 11.42%.

(4S)-4-[(2-Methoxyphenyl)methyl]-1,3,2-dioxathiolane-2,2-dioxide (44b): **Yield**: 97%; **gum**; **[**a **]$^{25}_D$**: + 20.12 (c 1, EtOH); **IR** ($CHCl_3$, cm^{-1}): 651, 754, 819, 981, 1026, 1126, 1178, 1213, 1255, 1392, 1456, 1506, 1595, 2839, 2935, 3018; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.85 (s, 3H), 4.31 (t, *J* = 6.23 Hz, 2H), 4.81-4.85 (dd, *J* = 6.23 Hz and 2.12 Hz, 2H), 5.22-5.28 (m, 1H), 6.94-7.10 (m, 4H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 55.68, 68.03, 69.76, 79.28, 112.43, 116.92, 120.93, 123.65, 146.91, 150.22; **MS** m/z (% rel. intensity): 260 (M^+, 100), 216 (5), 137 (45), 123 (65), 109 (58), 95 (46), 77 (50); **Analysis**: $C_{10}H_{12}SO_6$ requires C, 46.15; H, 4.65; S, 12.32; found C, 46.21; H, 4.63; S, 12.26%.

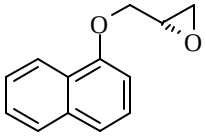
(4S)-4-[(3-methylphenyl)methyl]-1,3,2-dioxathiolane-2,2-dioxide (44c): **Yield**: 98%; **gum**; **[**a **]$^{25}_D$**: + 21.39 (c 1, EtOH); **IR** ($CHCl_3$, cm^{-1}): 652, 750, 819, 944, 1097, 1208, 1291, 1347, 1444, 1584, 2431, 2926, 3020; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.33 (s, 3H), 4.01-4.14 (m, 2H), 4.45-4.51 (m, 1H), 4.78-4.86 (m, 1H), 5.23-5.28 (m, 1H), 6.68-6.84 (m, 3H), 7.14-7.26 (m, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 21.24, 65.53, 69.54, 79.13, 111.37, 115.45, 122.87, 129.31, 139.82, 157.43; **MS** m/z (% rel. intensity): 244 (M^+, 23), 228 (16), 147 (10), 121 (96), 108 (92), 91 (100), 77 (15); **Analysis**: $C_{10}H_{12}SO_5$ requires C, 49.17; H, 4.95; S, 13.13; found C, 49.21; H, 4.86; S, 13.06%.

Preparation of epoxides 19 a-c:

[A] To a solution of one of the cyclic sulfates **44 a-c** (2.5 mmol) in dry THF (15 ml) was added anhydrous LiBr (1.04 g, 12 mmol) and the resulting reaction mixture was stirred for 40-50 minutes (monitored by TLC for the disappearance of cyclic sulfate) at 25^{0}C. After completion of the reaction the solvent was removed under reduced pressure. In the resulting residue diethyl ether (25 ml) and 20% H_2SO_4 (25 ml) were added and stirred at 25^{0}C for 4-5 h (monitored by TLC). After completion of the reaction the two layers were separated, the aqueous layer extracted with diethyl ether (3 x 15 ml), combined organic extracts were washed with saturated $NaHCO_3$, water and brine, dried over anhydrous sodium sulfate and evaporated under reduced pressure to give the corresponding bromoalcohols.

[B] The crude bromoalcohol (2 mmol) was dissolved in MeOH (20 ml) and treated with anhydrous K_2CO_3 (1.10 g, 8 mmol) at 0^0C. The resulting reaction mixture was stirred at 0^0C for 2 h (monitored by TLC). After completion the reaction was quenched by the addition of saturated NH_4Cl solution (10 ml) and extracted with CH_2Cl_2 (4 x 15 ml), washed with water and brine, dried over anhydrous Na_2SO_4, evaporated under reduced pressure to give crude product. It was then purified by column chromatography using pet. ether: EtOAc (8:2) as eluents to give pure epoxides **19 a-c** as oil in 91-93% yield.

(2S)-3-(1-Naphthyloxy)-1,2-epoxypropane (19a)



Yield: 80% overall in two steps; **gum**; **[**a **]$^{25}_{D}$**: + 10.91 (c 1.3, EtOH); **IR** (Neat, cm^{-1}): 748, 790, 916, 1021, 1123, 1190, 1240, 1260, 1454, 1510, 1590, 2890, 2990; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.75-2.79 (m, 1H), 2.86-2.95 (m, 1H), 3.39-3.44 (m, 1H), 3.89-4.08 (dd, *J* = 12.12 Hz and 6.24 Hz, 1H), 4.28-4.35 (dd, *J* = 12.12 Hz and 2.12 Hz, 1H), 6.73 (d, *J* = 8.14 Hz, 1H), 7.28-7.48 (m, 4H), 7.74-7.79 (m, 1H), 8.26-8.31 (m, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 44.51, 50.09, 68.84, 104.94, 120.74, 121.92, 125.23, 125.63, 126.40, 127.36, 134.45, 154.15; **MS** m/z (% rel. intensity): 200 (M^+, 100), 157 (28), 144 (65), 127 (18), 115 (53), 89 (10); **Analysis**: $C_{13}H_{12}O_2$ requires C, 77.98; H, 6.04; found C, 77.96; H, 6.04%.

(2S)-3-(2-methoxyphenyl)-1,2-epoxypropane (19b): **Yield**: 85% overall in two steps; **gum**; **[**a **]$^{25}_{D}$**: + 9.83 (c 1.2, EtOH); **IR** (Neat, cm^{-1}): 746, 779, 916, 1027, 1124, 1180, 1224, 1255, 1454, 1504, 1593, 2837, 2929, 3001; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.72-2.76 (dd, *J* = 6.11 Hz and 4.09 Hz, 1H), 2.89 (t, *J* = 4.09 Hz, 1H), 3.35-3.44 (m, 1H), 3.87 (s, 3H), 3.99-4.07 (dd, *J* = 12.12 Hz and 6.11 Hz, 1H), 4.20-4.28 (dd, *J* = 12.12 Hz and 4.09 Hz, 1H), 6.90-6.93 (m, 4H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 44.76, 50.13, 55.97, 70.39, 112.54, 115.54, 120.96, 122.10, 148.31, 150.04; **MS** m/z (% rel. intensity): 180 (M^+, 98), 150 (13), 137 (20), 124 (100), 109 (80), 95 (37), 81 (30), 77 (43), 65 (21); **Analysis**: $C_{10}H_{12}O_3$ requires C, 66.65; H, 6.71; found C, 66.67; H, 6.81%.

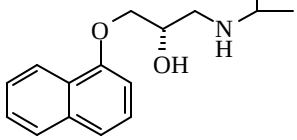
(2S)-3-(3-Methylphenyl)-1,2-epoxypropane (19c): **Yield**: 84% overall in two steps; **gum**; **[**a **]$^{25}_{D}$**: + 13.43 (c 2.2, EtOH); **IR** (Neat, cm^{-1}): 690, 775, 860, 900, 1041, 1053, 1161, 1261, 1290, 1454, 1488, 1585, 1602, 2871, 2923, 2999; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.33 (s, 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%.

Preparation of (S)-propranolol (1), (S)-moprolol (2) and (S)-toliprolol (3) *via* opening of epoxides 19 a-c:

One of the epoxides **19 a-b** (1.5 mmol) was dissolved in isopropylamine (10 ml) and 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 **1** and **2**.

(S)-(-)-Propranolol (1)



Yield: 99%; **mp**: 73-74^{0}C, (lit.[32] 72-73^{0}C); **[a]$^{25}_D$**: – 9.00 (c 0.5, EtOH), 90% ee [lit.[52] – 9.9 (c 0.5, EtOH)]; **IR** ($CHCl_3$, cm^{-1}): 570, 667, 750, 1029, 1120, 1175, 1210, 1240, 1450, 1500, 1594, 2930, 2960, 3300, 3432; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.09 (d, *J* = 6.10 Hz, 6H), 2.76-3.01 (m, 5H), 4.08-4.19 (m, 3H), 6.79 (d, *J* = 8.14 Hz, 1H), 7.34-7.51 (m, 4H), 7.76-7.81 (m, 1H), 8.22-8.27 (m, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 22.86, 48.77, 49.62, 68.44, 70.75, 104.86, 120.45, 121.77, 125.08, 125.48, 125.70, 126.29, 127.39, 134.42, 154.30; **MS** m/z (% rel. intensity): 259 (M^+, 3), 144 (13), 115 (20), 84 (100), 72 (50), 69 (23), 56 (33); **Analysis**: $C_{16}H_{21}NO_2$ requires C, 74.10; H, 8.16; N, 5.40; found C, 74.25; H, 8.16; N, 5.30%.

(S)-(–)-Moprolol (2): **Yield**: 98%; **mp**: 84-85^{0}C, (lit.[32]: 82-83^{0}C); **[a]$^{25}_D$**: – 3.90 (c 4.5, EtOH), 68% ee [lit.[32] – 5.6 (c 4.5, EtOH)]; **IR** ($CHCl_3$, cm^{-1}): 667, 757, 1029, 1124, 1178, 1217, 1253, 1454, 1506, 1593, 2933, 2966, 3313, 3400; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.07 (d, *J* = 6.09 Hz, 6H), 2.69-2.90 (m, 5H), 3.85 (s, 3H), 3.97-4.07 (m, 3H), 6.86-6.97 (m, 4H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 23.04, 48.84, 49.39, 55.94, 68.62, 73.18, 112.43, 115.30, 121.11, 121.95, 148.60, 150.15; **MS** m/z (% rel. intensity): 239 (M^+, 5), 224 (10), 195 (52), 124 (7), 109 (6), 77 (12), 72 (100), 56 (12); **Analysis**: $C_{13}H_{21}NO_3$ requires C, 65.25; H, 8.84; N, 5.85; found C, 65.11; H, 8.64; N, 5.75%.

In case of **19c**, the resulting gum after evaporation of isopropylamine was dissolved in ether and dry HCl gas was passed through it for 15 minutes, the solvent was removed under reduced pressure and resulting solid recrystallized from MeOH + EtOAc to afford (S)-toliprolol (**3**) as its hydrochloride salt.

(S)-(–)-Toliprolol hydrochloride (3): **Yield**: 99%; **mp**: 117-118, (lit.[14]: 119^{0}C); **[**a **]$^{25}_D$**: – 21.54 (c 1.01, EtOH) 78% ee [lit.[14] – 27.4 (c 1.01, 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 1.48 (s, 6H), 2.30 (s, 3H), 3.19-3.48 (m, 3H), 3.94-4.15 (m, 2H), 4.55-4.63 (m, 1H), 6.71-6.79 (m, 3H), 7.10-7.18 (m, 1H), 8.50 (bs, 1H), 8.57 (bs, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 18.67, 18.85, 21.20, 47.85, 51.20, 65.53, 69.32, 111.22, 115.19, 121.88, 129.01, 139.30, 158.05; **MS** m/z (% rel. intensity): 259 (M^+, 2), 236 (30), 223 (9), 208 (13), 179 (19), 108 (7), 91 (10), 72 (100); **Analysis**: $C_{13}H_{22}ClNO_2$ requires C, 60.11; H, 8.54; Cl, 13.65; N, 5.39; found C, 60.20; H, 8.55; Cl, 13.75; N, 5.41%.

2.0.11 References

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CHAPTER 3

Applications of Pd (II) Complexes in Synthesis of (S)-α-Aryl Propionic Acids and *C-C* Bond Formation

SECTION-I

Asymmetric Synthesis of (S)-*a*-Arylpropionic Acids *via* Pd-Catalyzed Kinetic Resolution of Secondary Alcohols

3.0.1 Introduction

a-Arylpropionic acids (**A**) have emerged as an important class of non-steroidal anti-inflammatory agents during the past three decades.[1] The therapeutic efficiency of this class of drugs is well demonstrated by the introduction and extensive use of more than a dozen compounds such as naproxen (**1**), ibuprofen (**2**), ketoprofen (**4**), and flurbiprofen (**5**) as drugs (**Fig. 1**). All compounds of this class have a similar mode of action *i. e*. they stop the arachidonic acid cascade to prostaglandins and thromboxane A_2 by cyclooxygenase inhibition, which are responsible for the inflammation mechanism.

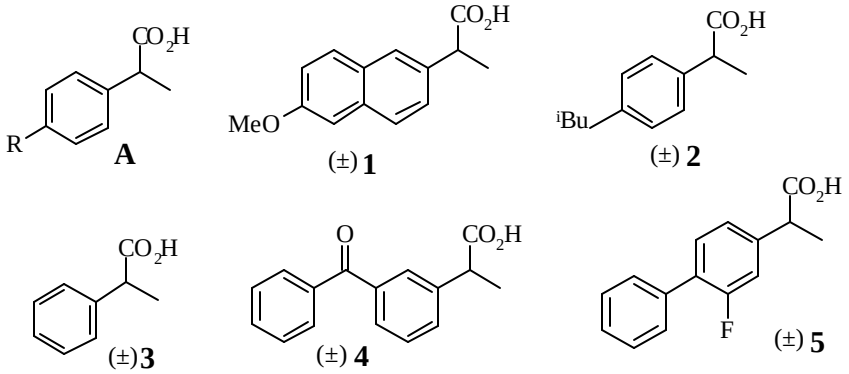


Fig. 1

However, in recent years use of enantiomerically pure drugs in chemotherapy has became mandatory not only to realize enhanced specificity of drug action but also to avoid the possible toxicity and undesired load on the metabolism by the other enantiomer. This is also true in case of *a*-arylpropionic acids. It is known that in case of **1** and **2**, the (S)-isomer is more active than the (R)-isomer.[2] For example, (S)-naproxen [(S)-2-(6-methoxy-2-naphthyl)-propionic acid, **1**] is about 28 times more active than its (R)-isomer.[2] This awareness led to great synthetic efforts to obtain optically pure compounds of this class.

3.0.1.1 Kinetic Resolution, an overview

Kinetic resolution (KR) may be defined as a process in which one of the enantiomer constituents of a racemic mixture is more readily transformed into a product than is the other (enantioselective reaction).

$$\mathbf{R} \xrightarrow{K_R} \mathbf{P}$$

$$\mathbf{S} \xrightarrow{K_S} \mathbf{Q}$$

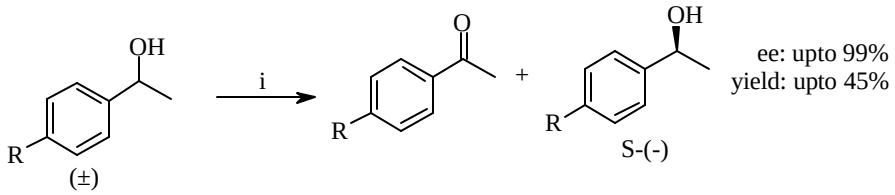
Kinetic resolution occurs if $k_R \neq k_S$ and the reaction is stopped at some stage between 0% to 100% conversion. An ideal situation is that in which only one enantiomer reacts, for e.g. **R** ($k_R >> k_S$) so that at 50% conversion, a mixture of 50% (S)-enantiomer and 50% product **P** is obtained. The difference in specific rate constants originates because a chiral catalyst or a chiral reagent mediates the transformation. The products **P** and **Q** can be achiral (identical or not) or chiral (with or without the incorporation of moiety derived from the chiral reagent). The nature of products is irrelevant to the kinetic resolution process itself, where one looks mainly for the enantiomeric excess of recovered starting material. KR essentially requires the partial transformation of a racemic mixture in contrast to the classical methods of resolution, which usually involve complete transformation of a racemic mixture into a mixture of diastereomers.

For the production of enantiomerically pure substances, KR is generally regarded as a poor cousin to asymmetric synthesis. Kinetic resolution (KR) suffers from the disadvantage that at least half of the starting material is lost. There is one striking advantage KR holds over asymmetric synthesis. The enantiomeric excess (ee) realized in asymmetric synthesis simply a consequence of the energy difference ($\Delta G^{\#}$) between two diastereomeric transition states; the only way to improve the %ee is to increase that energy difference. KR too depends on there being an energy difference between diastereomeric

transition states, but the manner in which that energy difference is expressed is unique to kinetic resolutions. The energy difference, manifested as a relative rate difference, represents a constant and unrelenting differential pressure upon the two enantiomers. This process should continue until the last molecule of more reactive enantiomer is swept away and one is left with a substance possessed of absolute enantiomeric purity. This concept of being able to achieve absolute enantiomeric purity in kinetic resolutions by removal of the last molecule of the fast reacting enantiomer has attracted chemists to use it as a tool for the preparation of optically active compounds. The realization that kinetic resolutions can lead to extremely high, if not absolute, optical purities is clearly evident from large number of publications occurring in this field.[3]

3.0.1.2 Oxidative Kinetic Resolution of alcohols

Although excellent catalytic enantioselective methods exist for a variety of oxidation processes such as epoxidation,[4] dihydroxylation,[5] and aziridination,[6] there are relatively few catalytic enantioselective examples of ubiquitous alcohol oxidation.[7] A recent advance in this regard is the catalytic oxidative kinetic resolution of secondary alcohols using molecular oxygen as the terminal stoichiometric reoxidant.[8] The use of molecular oxygen in combination with a catalytic metal complex has exceptional advantages for applications in organic synthesis.[9] This is partly due to the favorable economics associated with molecular oxygen and the formation of environmentally benign byproducts in the oxidation manifold (water and H_2O_2). Recently Pd-catalyzed kinetic resolution of secondary alcohols that uses molecular oxygen as the terminal oxidant and naturally occurring diamine (–)-sparteine as a chiral ligand has been reported (**Scheme 1**).[10]



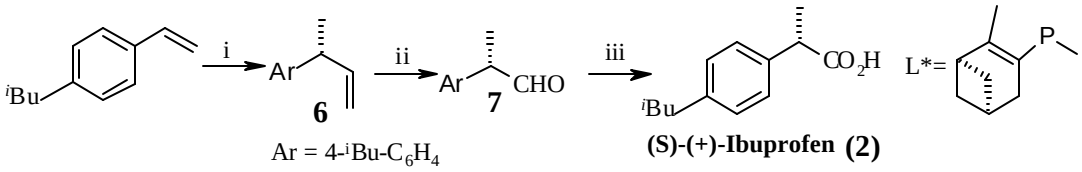
Scheme 1: (i) $Pd(OAc)_2$, (–)-sparteine, MS 3Å, O_2 (1 atm.), toluene, 80^0C.

3.0.2 Review of Literature

Literature search revealed that there are various methods known for the synthesis of *a*-arylpropionic acids. Most of these methods make use of enzymatic resolution or asymmetric catalysis to create the chiral center.

Wilke's approach (1984)[11]

Hydrovinylation reactions discovered by Wilke *et al.*[11a] in the late sixties has been a useful reaction for the homologation of olefins. The same authors have demonstrated the synthetic utility of this reaction in obtaining optically pure (S)-(+)-**2** (**Scheme 2**).[11b] The primary product **6** obtained by the addition of ethylene to *p*-isobutylstyrene on ozonolysis furnished the chiral aldehyde **7** with high enantiomeric purity. The aldehyde **7** was then transformed to (S)-(+)-ibuprofen (**2**).



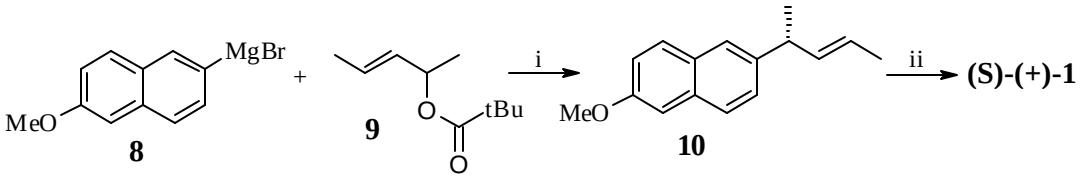
Ar = 4-^{i}Bu-C_6H_4

Scheme 2: (i) η^3-C_3H_5-Ni L*.$Et_3Al_2Cl_4$, -70^0C, CH_2Cl_2; (ii) O_3; (iii) $KMnO_4$.

Hiyama's approach (1985)

Hiyama *et al.*[12] carried out the reaction of 3-penten-2-yl-pivalate (**9**) with different aryl magnesium bromides in the presence of $NiCl_2$-(S,S)-chiraphos catalyst and obtained high optical yields in C-C bond formation. Thus, the reaction of 6-methoxy-2-naphthyl magnesium bromide (**8**) with 3-pentene-2-yl-pivalate (**9**) using $NiCl_2$[(2S,3S)-bis-(diphenylphosphino) butane] as a catalyst [abbreviated as $NiCl_2$-(S,S)-chiraphos] afforded

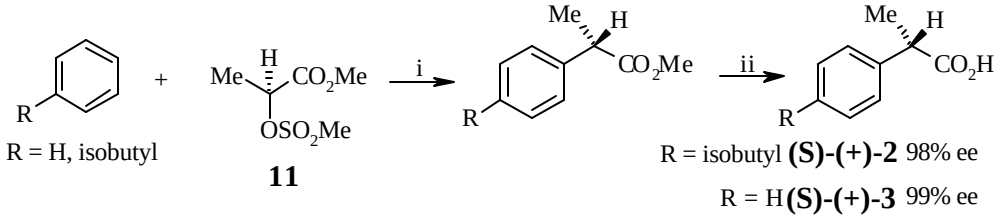
olefin **10** which on oxidative cleavage of the double bond lead to (S)-(+)-naproxen (**1**) in 62% yield and 64% ee (**Scheme 3**).



Scheme 3: (i) $NiCl_2$(S,S)-chiraphos, THF, RT; (ii) $NaIO_4$, $KMnO_4$.

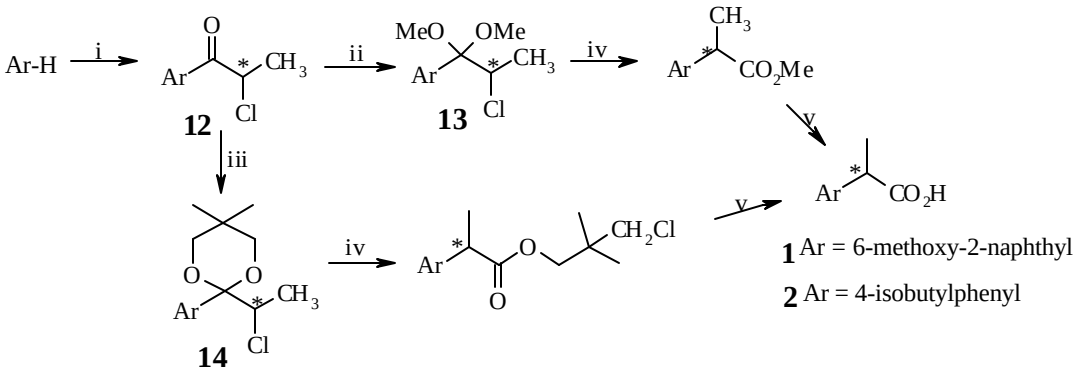
Piccolo's approach (1985)

Piccolo *et al.*[13] have provided first example of Friedel-Crafts alkylation with an acyclic chiral alkylating reagent **11** leading to high orders of enantioselectivity. Lactic acid derivative *viz*. (S)-2-(mesyloxy)propanoate (**11**) was used as alkylating reagent for the alkylation of isobutylbenzene to obtain (S)-(+)-**2** in excellent 98% optical yield but moderate chemical yield (40-80%) (**Scheme 4**).



Scheme 4: (i) $AlCl_3$, RT; (ii) hydrolysis.

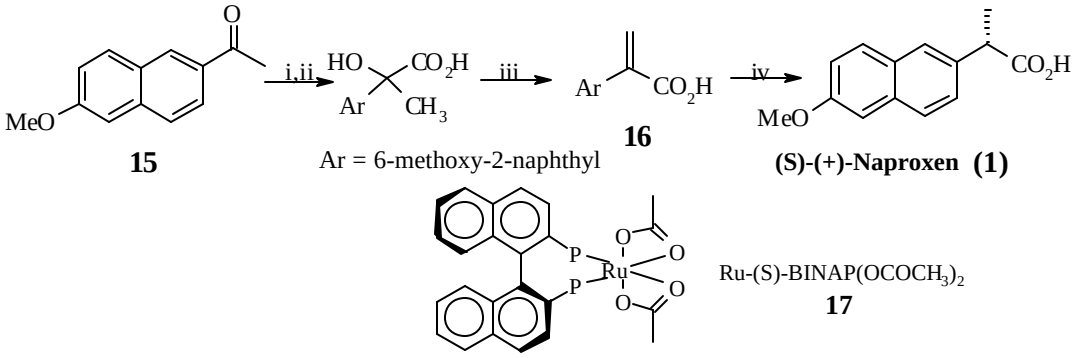
(S)-2-(4'-isobutylphenyl)propionic acid [(S)-ibuprofen (**2**)] and (S)-2-(6'-methoxy-2'-naphthyl)propionic acid [(S)-naproxen (**1**)] were synthesized in 82% and 96% optical purity respectively.[14] Optically pure (S)-2-chloropropionyl chloride on Friedel-Crafts reaction with the Ar-H (Ar = 4-isobutylbenzene or 6-methoxy-2-naphthyl) gave the corresponding 1-chloroethyl ketone **12**, which was then converted to acetals **13** or **14**. $ZnCl_2$-catalyzed stereospecific rearrangement of optically active acetals **13** and **14** to corresponding esters was used as the key step for the synthesis of **1** or **2** in good optical purity (**Scheme 5**).



Scheme 5: (i) (S)-2-chloropropionyl chloride, $AlCl_3$; (ii) trimethylorthoformate, MeOH; (iii) 2,2-dimethyl-1,3-propanediol, azeotropic distillation; (iv) $ZnCl_2$; (v) 30-37% aqueous HCl, acetone.

Noyori's approach (1987)[15]

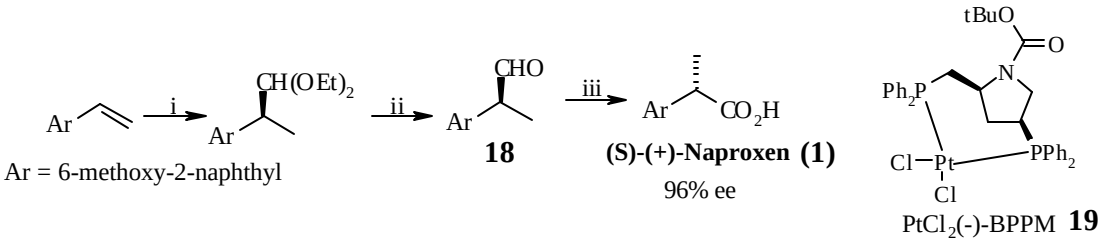
The Monsanto process is one of the industrial processes for the synthesis of *a*-arylpropionic acids using electrochemistry. One of the biggest advantages of this process is that the key "process reagent" the electron, is environmental friendly and is quite economical. The *a*, *b*-unsaturated acid **16** was prepared from ketone **15** in three steps and was reduced using a chiral catalyst. The recent Monsanto naproxen process (**Scheme 6**) involves two key steps; electrocarboxylation and asymmetric hydrogenation using Ru-catalyst **17** to afford (S)-naproxen (**1**) in 98.5% ee. Even at lower pressure (upto 500 psi) the reaction gives good ee.



Scheme 6: (i) CO_2, electrolysis at anode, Pb cathode; (ii) H_3O^+; (iii) dehydration; (iv) H_2 (135 atm.), Ru(II)-BINAP (**17**), MeOH, 98.5% ee.

Stille's approach (1987)[16]

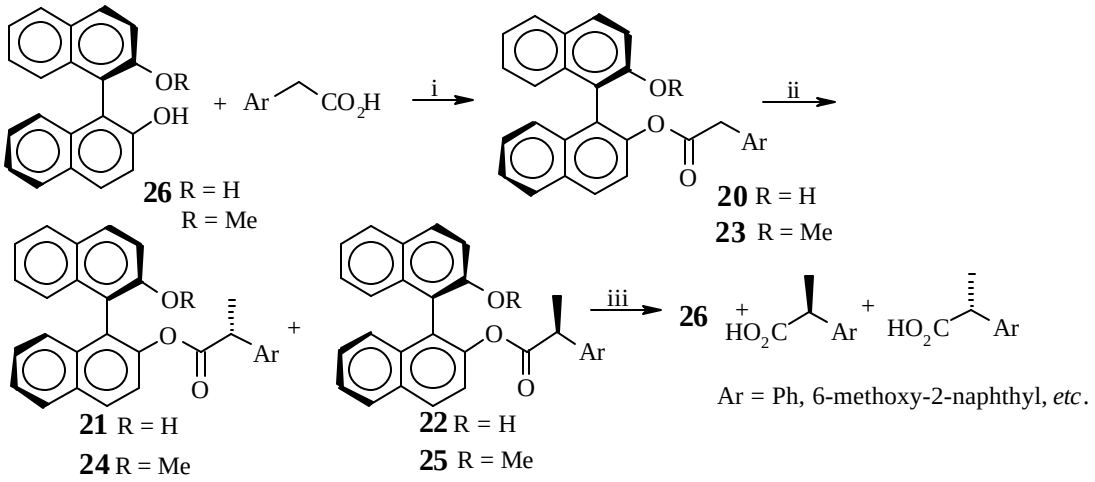
Stille and coworkers have carried out hydroformylation using chiral catalyst $PtCl_2$[(-)-BPPM], (2S, 4S)-N-(t-butoxycarbonyl)-4-(diphenylphosphino)-2-(diphenylphosphino)-methyl pyrrolidine i.e. BPPM (**19**) in the presence of $SnCl_2$ to get the chiral aldehyde **18**. The aldehyde **15** after oxidation afforded the desired acid (**Scheme 7**).



Scheme 7: (i) H_2, CO (2700 psi), **19**, $SnCl_2$, 60^0C, 9 h, 90% conversion; (ii) pyridinium *p*-toluene sulfonate; (iii) $KMnO_4$.

Fuji's approach (1989)

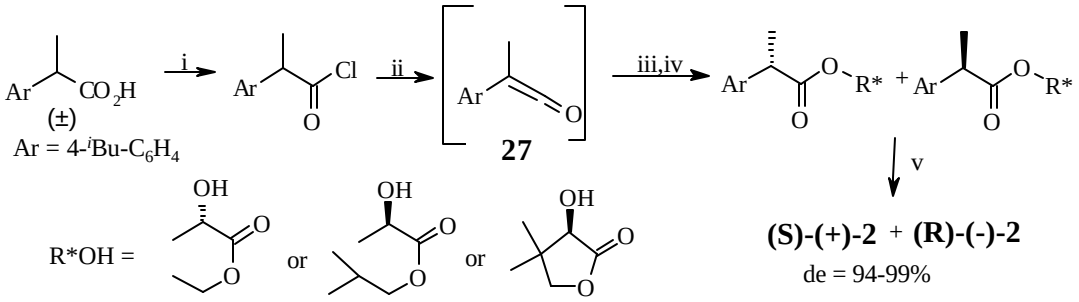
Synthesis of optically active *a*-arylpropionic acids *via* diastereoselective alkylation of binaphthyl esters of arylacetic acids have been reported by Fuji *et al.*[17] Significant diastereoselectivity (92-96%) in the alkylation of the ester **20** containing the free hydroxy group leading to **21** and **22** while the corresponding methyl ether **23** furnished 1:1 mixture of diastereomers **24** and **25** (**Scheme 8**).



Scheme 8: (i) H^+; (ii) LDA, THF, HMPA, MeI, -78^0C, 4 h; (iii) H^+, H_2O, recrystallization.

Larsen's approach (1989)[18]

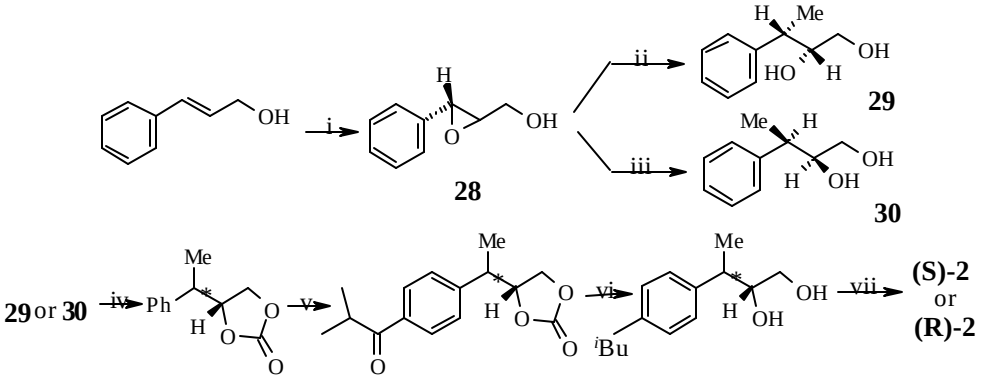
Tertiary amine mediated addition of the chiral alcohols such as (S)-ethyl lactate, (R)-iso-butyl lactate or (R)-pentolactone to ketenes **27** prepared from corresponding 2-arylpropionic acids provided the respective esters in 94-98% diastereomeric excess (de). The (S) and (R)-hydroxy esters afforded the S and R stereochemistry at the benzylic carbon respectively. Synthesis of (S)-ibuprofen (**2**) using this method is shown in **Scheme 9**. The naproxen ester [Ar= (6-methoxy-2-naphthyl)] was obtained with a de of 80%.



Scheme 9: (i) $SOCl_2$ (110 mol%), DMF (5 mol%), heptane or toluene, 50-55^{0}C; (ii) Me_3N or Me_2NEt (300 mol%), 25^{0}C; (iii) R*OH (120 mol%), toluene, -78^{0}C; (iv) 3-(dimethylamino) propylamine (5-10 mol%), 25^{0}C or AcOH-H_2O, 70^{0}C; (v) AcOH-2N HCl, 85^{0}C or LiOH, heptane-CH_3CN-H_2O, 5^{0}C.

Tokano's approach (1989)[19]

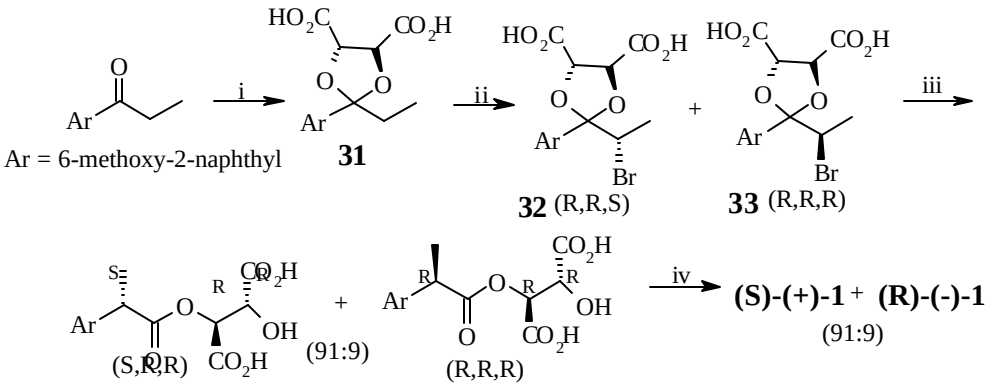
The enantiodivergent synthesis of both enantiomers of ibuprofen (**2**), from a common starting material, (2S, 3S)-3-phenylglycerol (**28**) is reported using Sharpless asymmetric epoxidation as the key step (**Scheme 10**).



Scheme 10: (i) $Ti(O^iPr)_4$, (+)-DET, TBHP, CH_2Cl_2; (ii) Me_3Al, CH_2Cl_2, -70^{0}C; (iii) $Me_2CuCNLi_2$, Et_2O, -50^{0}C; (iv) $(EtO)_2CO$, K_2CO_3, 80^{0}C; (v) $Me_2CHCOCl$, $AlCl_3$; (vi) NH_2-$NH_2.H_2O$, KOH, $O(CH_2CH_2OH)_2$, 180^{0}C; (vii) $RuCl_3.H_2O$, $NaIO_4$, $MeCN/CCl_4/H_2O$ (2:2:3)

Giordano's approach (1989)[20]

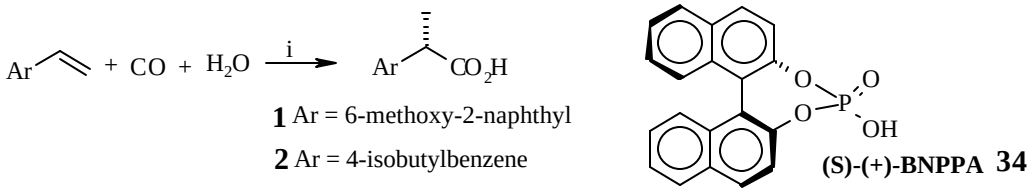
A synthesis of (S)-naproxen (**1**), with tartaric acid as chiral auxiliary is reported. Enantiomerically pure naproxen (**1**) was obtained by using the differential rate of rearrangement *vs* an intermolecular carboxylate alkylation (**Scheme 11**). This procedure has been applied by the Zambon Company of Italy to prepare (S)-(+)-naproxen (**1**) commercially.



Scheme 11: (i) $MeSO_3H$, (2R, 3R)-diethyl tartarate, triethyl orthoformate, 100^0C; (ii) Br_2, $PhNO_2$, toluene, -10^0C; (iii) $AgBF_4$, EDC, 15^0C; (iv) CH_3CO_2H, conc. HCl, water, 85^0C.

Alper's approach (1990)[21]

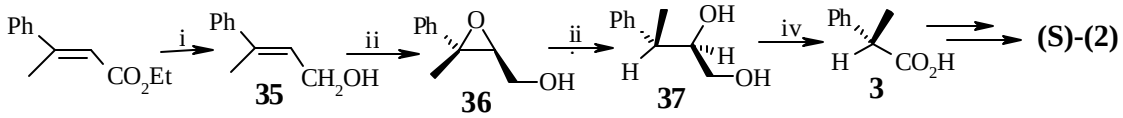
(S)-Naproxen (**1**) and (S)-ibuprofen (**2**) was synthesized in 89-64% yields and 91-83% optical purity by the $PdCl_2$-catalyzed carbonylation of olefins in the presence of (S)-BNPPA [(S)-(+)-2,2'-(1,1'-binaphthyl)phosphoric acid, **34**]. The hydrocarbonylation reaction is completely regiospecific and proceeds at room temperature and 1 atm. pressure (**Scheme 12**).



Scheme 12: (i) O_2 (1 atm), THF, (S)-(+)-BNPPA (**34**), $PdCl_2$, $CuCl_2$, RT.

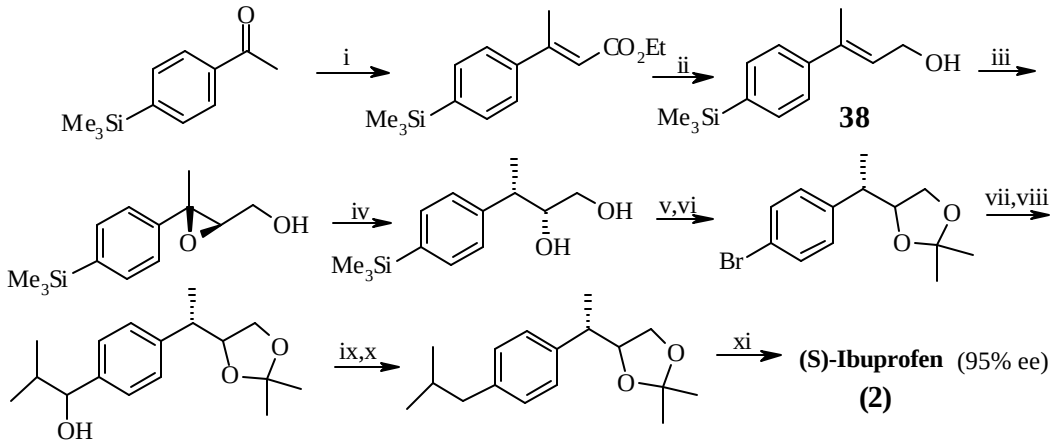
Hamon's approach (1990)

Hamon *et al.*[22] subjected the enantiomerically pure epoxide **36**, obtained by Sharpless epoxidation from the olefin **35**, to hydrogenolysis. The resulting diol **37** on oxidative cleavage afforded (S)-2-phenylpropionic acid (**3**) as an intermediate for (S)-ibuprofen (**2**) (**Scheme 13**).



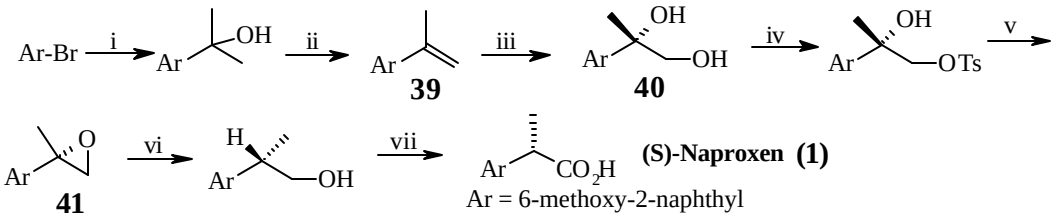
Scheme 13: (i) LAH; (ii) $Ti(O^iPr)_4$, (+)-DET, TBHP, 85% ee; (iii) 10% Pd/C, EtOH, NaOH, -45^0C; (iv) $RuCl_3.3H_2O$, $NaIO_4$.

Hamon *et al.*[23] have synthesized (S)-ibuprofen (**2**) in 95% ee. Control of the stereochemistry was achieved by a combination of Sharpless epoxidation of olefin **38** followed by catalytic hydrogenolysis of benzylic epoxide oxygen bond (**Scheme 14**).



Scheme 14: (i) triethylphosphono acetate, LiOEt; (ii) LAH; (iii) $Ti(O^iPr)_4$, (+)-DET, TBHP, 98% ee; (iv) 10% Pd/C, -60^0C; (v) LiBr, NCS; (vi) acetone, H^+; (vii) ^tBuLi; (viii) isobutylalcohol; (ix) H^+; (x) hydrogenolysis, 10% Pd/C; (xi) $RuCl_3.3H_2O$, $NaIO_4$.

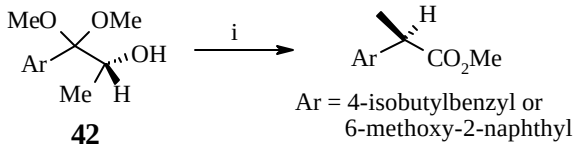
(S)-Naproxen (**1**) was synthesized in high optical purity using Sharpless asymmetric dihydroxylation (AD) as a key step.[24] AD of the corresponding methyl styrene **39** gave diol **40**, which was then converted to epoxide **41** and then to **1** in 96% ee (**Scheme 15**).



Scheme 15: (i) Mg, acetone; (ii) $MeSO_2Cl$, Et_3N; (iii) AD-mix-α; (iv) TsCl, pyridine; (v) NaH; (vi) 10% Pd/C, EtOH, trace ^-OH, -40^0C; (vii) Jones oxidation.

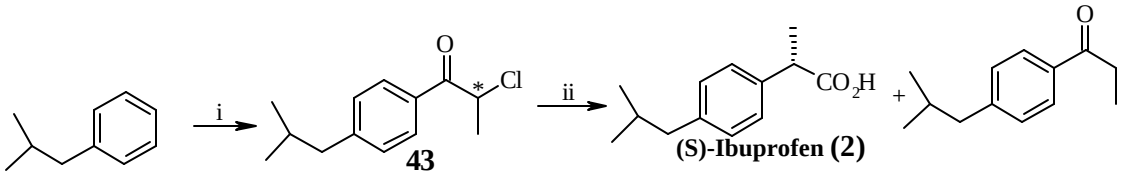
Sonawane's approach (1991)[25]

Treatment of 2-hydroxy acetals **42** with PPh_3 and CCl_4 resulted in a stereospecific 1,2-aryl migration leading to asymmetric synthesis of ibuprofen and naproxen esters (**Scheme 16**).



Scheme 16: (i) PPh_3, CCl_4, pyridine, CH_2Cl_2, RT.

Sonawane *et al.* reported single-step efficient photochemical approach for the synthesis of (S)-ibuprofen (**2**) from the corresponding *a*-chloropropiophenone **43** (**Scheme 17**).

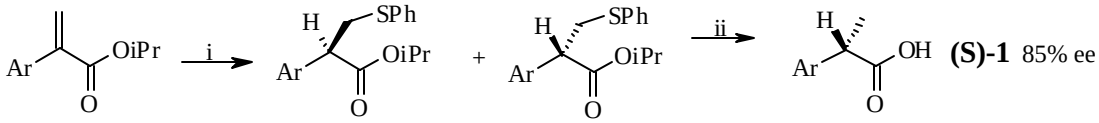


Scheme 17: (i) (S)-(+)-$CH_3CH(Cl)COCl$, $AlCl_3$; (ii) hν, aqueous acetone, propylene oxide.

Kumar's approach (1991)[26]

A novel synthesis of chiral 2-phenylpropionic acids or esters *via* catalytic enantioselective protonation in the Michael addition of PhSH has been described. (S)-Naproxen (**1**) has been prepared starting from naphthyl acrylate **44**, by Michael addition

with PhSH in presence of (–)-quinine as catalyst, followed by Raney nickel desulfurization and hydrolysis of the Michael adduct (**Scheme 18**).

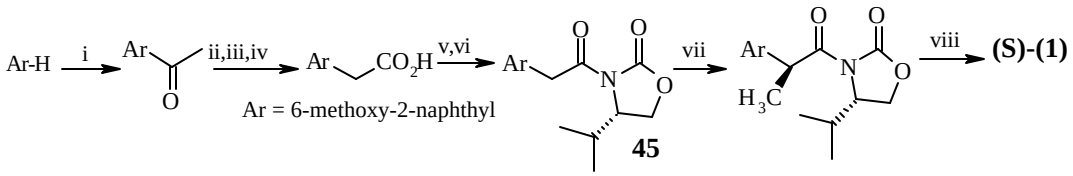


44 Ar = 6-methoxy-2-naphthyl

Scheme 18: (i) PhSH, (–)-quinine (20 mol%), toluene; (ii) Raney nickel, AcOH-HCl, crystallization.

Gonzalez's approach (1991)

Gonzalez *et al.*[27] have reported the preparation of (S)-naproxen (**1**) and (S)-ibuprofen (**2**) based on asymmetric alkylation of oxazolidinones **45** (**Scheme 19**).



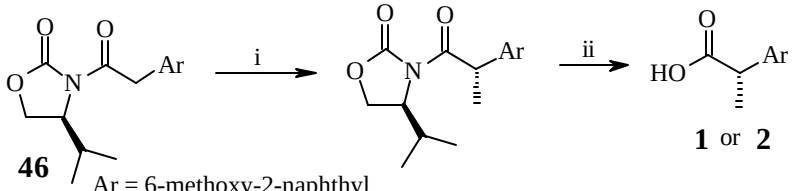
Ar = 6-methoxy-2-naphthyl

45

Scheme 19: (i) CH_3COCl, $AlCl_3$, nitrobenzene, 25^0C; (ii) S, morpholine, reflux; (iii) AcOH-HCl (1:1), reflux; (iv) Me_2SO_4, NaOH; (v) $SOCl_2$; (vi) sodium oxazolidinone; (vii) LDA, THF, MeI, -78^0C; (viii) H_3O^+.

Fadel's approach (1992)[28]

The chiral imides (3-arylacetyl-4-isopropyl/benzyl-2-oxazolidinones (**46**), were alkylated *via* the imide enolates with methyl iodide, subsequent removal of the chiral auxiliary provided (S)-2-arylpropionic acids **1** and **2** in good yield and with high stereoselectivity (**Scheme 20**).

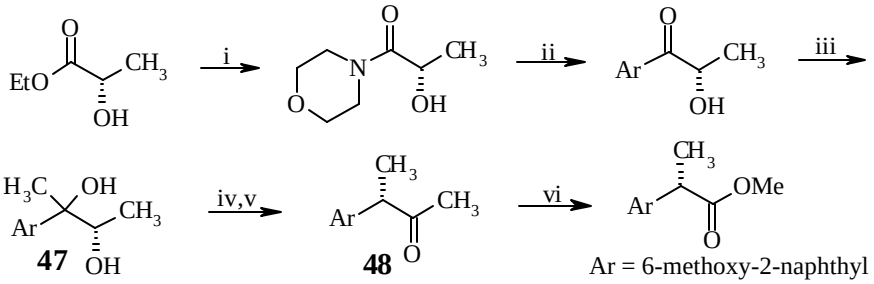


46 Ar = 6-methoxy-2-naphthyl
4-isobutylbenzene

Scheme 20: (i) NaHMDS, MeI, $CHCl_3$, –78 to -30^0C; (ii) LiOOH, dioxane or LiOH, $THF-H_2O$.

Brown's approach (1992)[29]

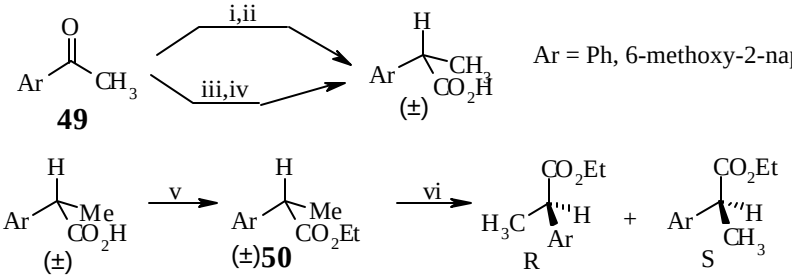
Methyl ester of (S)-naproxen was synthesized by the asymmetric pinacol-type rearrangement. The pinacol-type reaction of *sec-tert*-vicinal diol **47** provided aryl ketone **48**, which was oxidized with NaOCl in presence of MeOH to give methyl ester of **1** in 97.3% ee (**Scheme 21**). This is the first report of the use of a haloform reaction in the synthesis of optically active *a* -arylpropionic acids.



Scheme 21: (i) morpholine, reflux; (ii) a. ArLi, THF, -78^{0}C to RT; b. H_3O^+; (iii) 2.2 equiv. MeMgCl, THF, –10 to 0^{0}C; iv) MsCl, Et_3N, CH_2Cl_2, 0^{0}C; (v) Et_3Al, CH_2Cl_2, –78^{0}C; (vi) NaOCl, MeOH, 0-5^{0}C.

Sinisterra's approach (1993)[30]

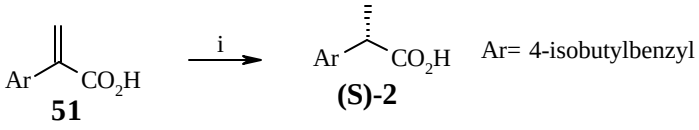
One pot synthesis of (±)-2-arylpropionic acids was carried out by addition of dichlorocarbene to the C=O bond of aryl methyl ketone **49** and hydrogenolysis of the addition product. The racemic mixture was resolved by enantiospecific hydrolysis of the racemic ethyl esters **50** using native lipase from *Candida rugosa* (**Scheme 22**)..



Scheme 22: (i) $CHCl_3$, NaOH, H_2O; (ii) H_2, Pd/C or $NaCNBH_3/ZnI_2$; (iii) $CHCl_3$, ^{t}BuOK, (iv) H_2, Pd/C or HCO_2H, Pd/C; (v) EtOH; (vi) lipase *C. rugosa*, H_2O.

Fronczek's approach (1993)[31]

Various chiral ruthenium complexes such as [(S)-BINAP-Ru(acac)$_2$] and [(DIOP)Ru(acac)$_2$] were prepared from appropriate phosphine and Ru(acac)$_3$. Hydrogenation of **51** at about 1000 psig, afforded (S)-ibuprofen (**2**) in good ee (upto 90%) (**Scheme 23**).



51 **(S)-2**

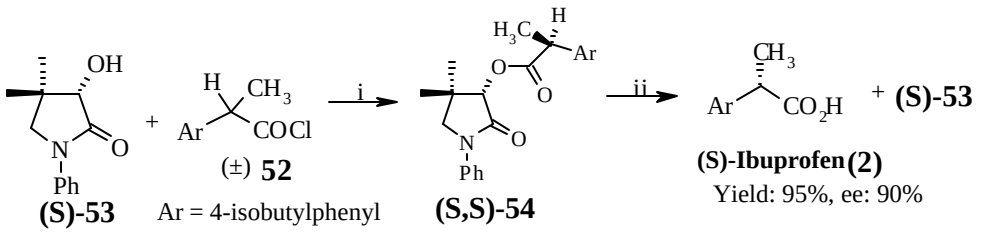
Scheme 23: (i) Ru-catalyst, H_2 (1000 psig), M eOH.

Wan's approach (1994)[32]

A supported aqueous phase asymmetric hydrogenation catalyst, SAP-Ru-BINAP-4SO_3Na was synthesized and used for the hydrogenation of 2-(6'-methoxy-2'-naphthyl)acrylic acid (**16**) to give (S)-naproxen (**1**) in ~70% ee (**Scheme 6**).

Camps's approach (1995)

Camps *et al.*[33] have reported the reaction of (±)-*a*-methylareneacetyl chlorides **52** with (R)- or (S)-3-hydroxy-4,4-dimethyl-1-phenyl-2-pyrrolidinone **53** in the presence of triethylamine to give (R,R) or (S,S)-2-oxo-3-pyrrolidinyl-*a*-methylareneacetates **54** respectively with high diastreoselectivity. Controlled acidic hydrolysis afforded the corresponding (R)- or (S)-*a*-arylpropionic acids with high enantioselectivity, the chiral auxiliary being recovered efficiently (**Scheme 24**).

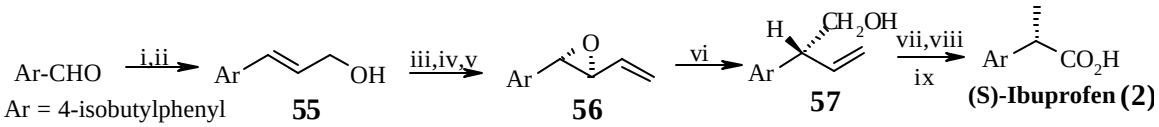


(S)-53 Ar = 4-isobutylphenyl (±) **52** **(S,S)-54**

Scheme 24: (i) Et_3N, CH_2Cl_2, 0^0C; (ii) 2N HCl-AcOH, 120^0C.

Jung's approach (1997)[34]

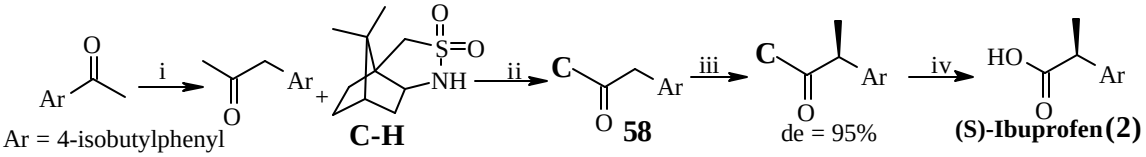
Wittig reaction of 4-isobutylbenzaldehyde (prepared from isobutylbenzene in three steps) has afforded cinnamyl alcohol **55**; Sharpless epoxidation, followed by Swern oxidation and methylation gave the key substrate **56**. Rearrangement using triethylsilane afforded the desired alcohol **57** in 67% yield and 84% ee. A vinyl group migrates faster to a benzylic cation than an Ar group migrates to an allyl cation. Tosylation, reduction with super-hydride®, and oxidative cleavage of the alkene with $RuCl_3$ and periodate gave (S)-ibuprofen (**2**) (**Scheme 25**).



Scheme 25: (i) $Ph_3P{=}CHCO_2Me$; (ii) DIBAL; (iii) TBHP, (+)-DIPT, $Ti(O^iPr)_4$, 65% yield, 84% ee; (iv) Swern oxidation; (v) Wittig; (vi) Et_3SiH, $BF_3{:}Et_2O$, 67% yield, 84% ee; (vii) TsCl, pyridine; (viii) $LiEt_3BH$; (ix) $RuCl_3.3H_2O$, $NaIO_4$, $CH_3CN/CCl_4/H_2O$, 57% yield.

Oppolzer's approach (1997)[35]

A very short, four step synthesis of (S)-ibuprofen (**2**) was achieved in 57% overall yield and 95% ee, using a highly diastereoselective alkylation of the chiral enolate derived from N-(4-isobytylphenyl)acetyl bornanesultam **58** as the key step (**Scheme 26**).

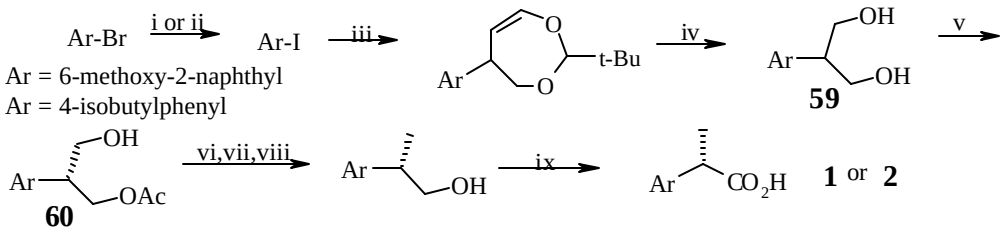


Scheme 26: (i) I_2, $AgNO_3$, MeOH/ trimethylorthoformate, 98%; (ii) Me_3Al, CH_2Cl_2, reflux, 79%; (iii) a. *n*-BuLi, THF; b. MeI, N,N'-dimethylpropyleneurea (DMPU); (iv) LiOH, H_2O_2, THF/H_2O, 89%.

Bando's approach (1997)[36]

(S)-Naproxen (**1**) and (S)-ibuprofen (**2**) were synthesized by employing the lipase-mediated asymmetric acetyaltion of prochiral 1-aryl-1,3-propanediol **59**, which was

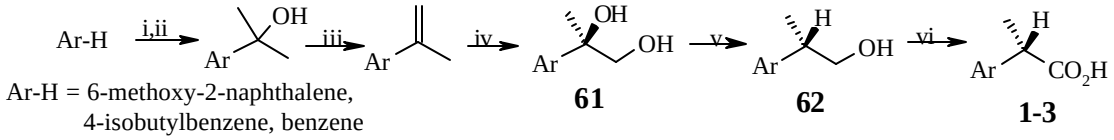
derived using Heck reaction as the key step (**Scheme 27**). Monoacetate **60** was then converted to the corresponding 2-arylpropionic acids (**1** or **2**) by tosylation, reduction and oxidative cleavage.



Scheme 27: (i) KI, CuI, HMPA, 150-160^{0}C, 82%; (ii) IPy_2BF_4, CF_3SO_3H, CH_2Cl_2, RT, 100%; (iii) 2-^{t}butyl-4,7-dihydro-1,3-dioxepin, $Pd(OAc)_2$, PPh_3, $^iPr_2NEt$, DMF, 80^{0}C; (iv) O_3, CH_2Cl_2 then $NaBH_4$, MeOH, –78-0^{0}C-RT; (v) *PPL*, vinylacetate, Et_2O, RT; (vi) TsCl, Et_3N, 4-DMAP, CH_2Cl_2, 0^{0}C; (vii) $NaBH_4$, DMSO, 60^{0}C; (viii) LAH, THF, 0^{0}C; (ix) Jones' oxidation, 0^{0}C.

Sudalai's approach (1998)[37]

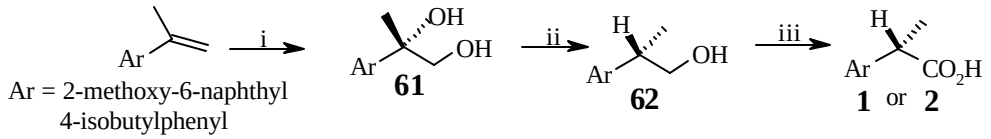
Asymmetric synthesis of *a*-arylpropionic acids, naproxen (**1**), and ibuprofen (**2**) was achieved by employing Sharpless asymmetric dihydroxylation followed by the stereoselective hydrogenolysis of the chiral diols coupled with Jones oxidation as the key steps (**Scheme 28**).



Scheme 28: (i) $AlCl_3$, CH_2Cl_2, AcCl (80-95%); (ii) MeMgI, ether, 0^{0}C, (90-95%); (iii) $POCl_3$, pyridine (90%); (iv) AD mix-β, 28 h; (v) 10% Pd-C, HCO_2NH_4, ethanol, reflux, 6 h; (vi) Jones' reagent, 8 h.

Ishibashi's approach (1999)

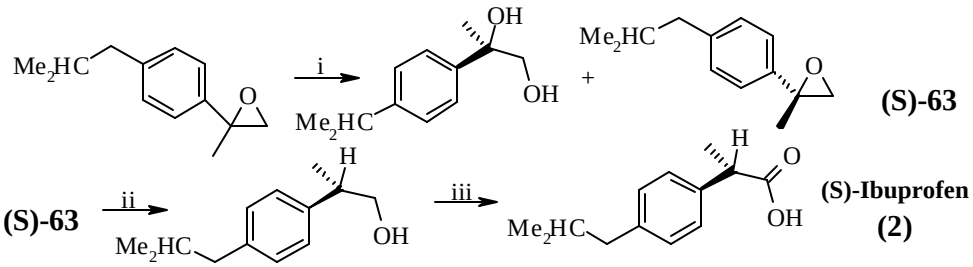
Ishibashi *et al.*[38] synthesized **1** and **2** by hydrogenolysis of (S)-aryl-1,2-propanediol **61** prepared by AD of the corresponding α-methyl styrene with AD-mix-*a* over Pearlman's catalyst to give (S)-2-aryl-1-propanol **62**. The chiral alcohol **62** was further converted to **1** or **2** by oxidative cleavage (**Scheme 29**).



Scheme 29: (i) AD-mix-*a*; (ii) H_2, $Pd(OH)_2/C$; (iii) Jones' oxidation (CrO_3, H_2SO_4).

Cleij's approach (1999)

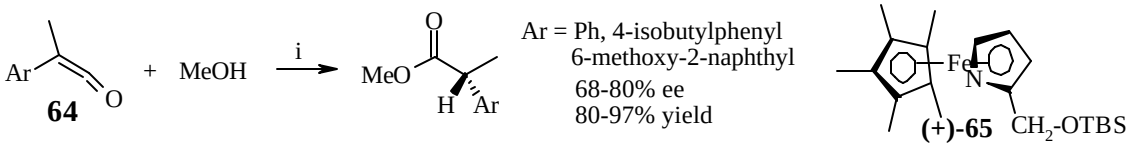
Cleij *et al.*[39] investigated biohydrolysis of various *a*-methylstyrene oxide derivatives **63** differently substituted at the aromatic ring using epoxide hydrolases from different origins. Using a combined chemoenzymic stategy they developed a four-step synthesis of (S)-ibuprofen (**2**) in optically pure form with a 47% overall yield (**Scheme 30**).



Scheme 30: (i) *Aspergillus niger* enzyme extract; (ii) Pd, H_2; (iii) $KMnO_4$, H_2SO_4.

Hodous's approach (1999)[40]

Arylpropionic acid esters were obtained in high yield and ee by reaction of arylketenes **64** with MeOH in presence of chiral azaferrocene catalyst **65** (**Scheme 31**).

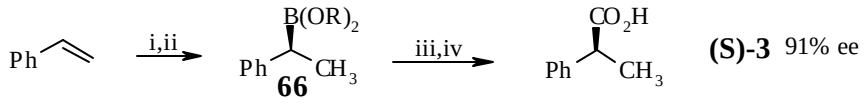


Scheme 31: (i) 10% (+)-**65**, toluene, –78^{0}C, 2,6-di-t-butylpyridinium triflate (12%).

Crudden's approach (1999)

Crudden *et al.*[41] reported a new catalytic asymmetric one step one-carbon homologation strategy. Reaction of styrene using catalytic amounts of $[Rh(COD)_2]^+$ BF_4^-

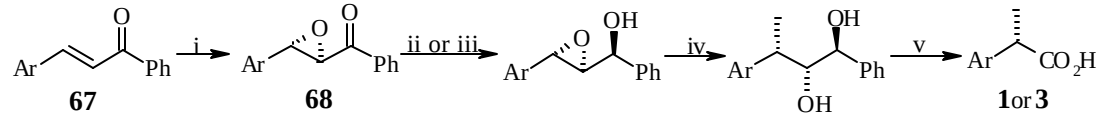
and (S)-BINAP generated the boronate ester **66** asymmetrically which was then homologated with $LiCHCl_2$ followed by oxidation to afford the (S)-phenylpropionic acid (**3**) in 91% ee (**Scheme 32**).



Scheme 32: (i) catechol borane, $[Rh(COD)_2]^+ BF_4^-$, (S)-BINAP (2%); (ii) pinacol; (iii) $LiHCl_2$, $ZnCl_2$; (iv) $NaClO_2$ oxidation.

Carde's approach (2000)[42]

Poly-(D)-leucine-catalyzed epoxidation of chalcones **67** furnished (+)-epoxides **68**, treatment of these epoxides with $AlMe_3$ followed by oxidative cleavage furnished (S)-2-arylpropionic acids (**1** or **3**) (**Scheme 33**).

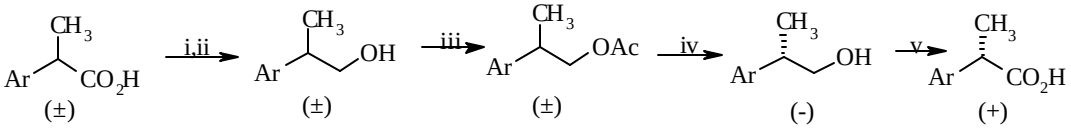


Ar = Ph, 6-methoxy-2-naphthyl

Scheme 33: (i) Poly-(L)-leucine adsorbrd on solica, urea-H_2O_2, DBU, THF, upto 95% ee; (ii) $Zn(BH)_4$, Et_2O, 0^0C; (iii) MeMgI, THF, Et_2O, -78^0C, 2.5 h, 85%; (iv) Me_3Al (3 equiv.), hexane, 0^0C; (v) $NaIO_4/SiO_2$, CH_2Cl_2 then Jones oxidation.

Bhattacharya's approach (2000)[43]

The racemic anti-inflammatory drugs naproxen (**1**) and ibuprofen (**2**) were resolved to give corresponding (S)-isomers by reduction to their alcohols, acetylation of the alcohols, *porcine pancreatic lipase* (PPL) catalyzed deacetylation and then oxidation of the chiral alcohols (**Scheme 34**).

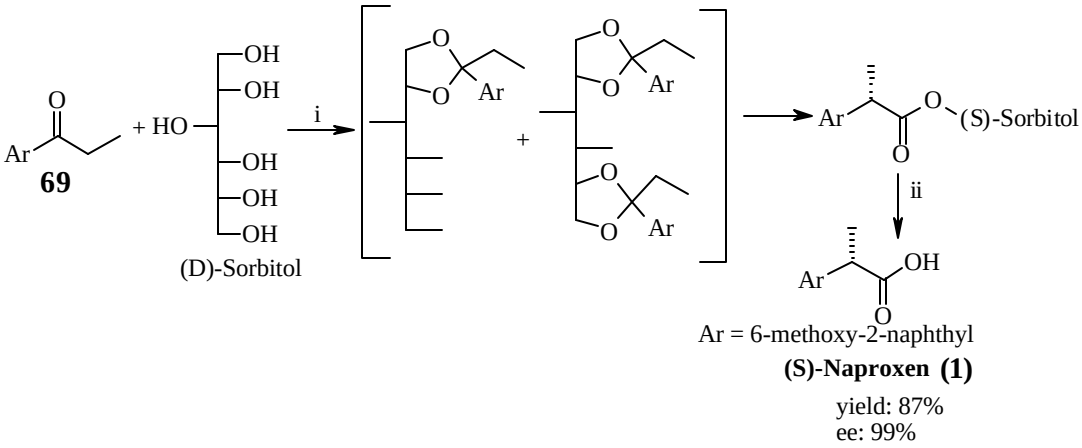


Ar = 6-methoxy-2-naphthyl
4-isobutylphenyl

Scheme 34: (i) MeOH, H^+; (ii) $NaBH_4$; (iii) Ac_2O, Et_3N, DMAP; (iv) *PPL*, phosphate buffer, pH 8.0, acetone; (v) PDC, DMF.

Wang's approach (2001)[44]

(S)-2-(6-Methoxy-2-naphthyl)propionic acid [(S)-naproxen, **1**] has been prepared by the reaction of 1-(6-methoxy-2-naphthyl)propan-1-one (**69**) and D-sorbitol under $ZnCl_2$ catalysis, followed by hydrolysis (**Scheme 35**).



Scheme 35: (i) $ZnCl_2$, trimethoxy orthoformate, DMF, 130-140^{0}C; (ii) periodate oxidation.

3.0.3 Present Work

3.0.3.1 Objective

Although there are various methods known in the literature for the synthesis of *a*-arylpropionic acids, many of them make use of chiral starting materials, large number of steps, use of costly enzymes in case of kinetic resolution (KR)and often resulting in low overall yields However, there is no report on the application of metal catalyzed KR for the synthesis of *a*-arylpropionic acids. Hence, we decided to explore the usefulness of Pd-catalyzed KR of secondary alcohols for the enantioselective synthesis of *a*-arylpropionic acids.

Retrosynthetic analysis of *a*-arylpropionic acids is shown in **Fig. 2**. There are four possible ways (*a, b, c* and *d*) to disconnect *a*-arylpropionic acid **A**.

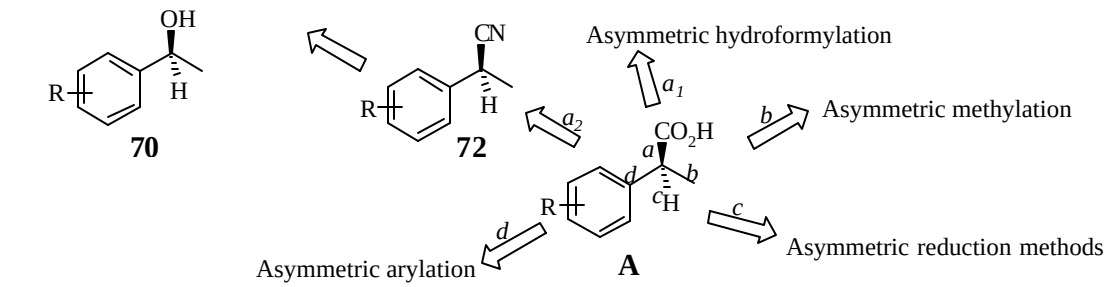
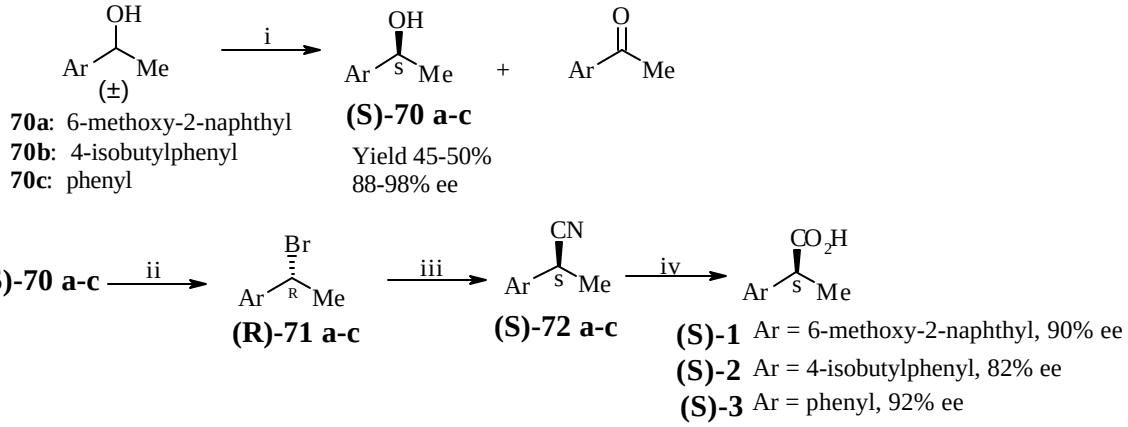


Fig. 2: Retrosynthetic analysis of arylpropionic acid (A)

While route a_1 involves asymmetric hydroformylation of olefins, route *b* asymmetric methylation, route *c* asymmetric reduction of corresponding aryl acrylic acid, route *d* constitutes asymmetric arylation reaction. Disconnection approach a_2 leads to precursor, chiral arylcyanide **72**, which could be readily converted to *a*-arylpropionic acids by simple hydrolysis. The chiral cyanide **72** could in turn be obtained from olefinic hydrocyanation or from chiral alcohol **70**, readily prepared by Pd-catalyzed KR of secondary alcohols.

3.0.4 Results and Discussion

We present here a novel approach for the synthesis of three members of *a*-arylpropionic acids: (S)-naproxen (**1**), (S)-ibuprofen (**2**) and (S)-phenylpropionic acid (**3**) by following the disconnection route a_2. Palladium-catalyzed kinetic resolution (KR) of secondary alcohols constitutes the key step here. Detailed synthetic sequence is presented in **Scheme 36**.



Scheme 36: (i) $Pd(OAc)_2$ (5 mol %), (–) sparteine (20 mol %), O_2 (1 atm.), toluene, MS 3 Å, 80^0C, 45-50%; (ii) PBr_3, Et_2O, pyridine, -15^0 to 0^0C, 70-88%; (iii) NaCN, DMF, 80^0C, 80-92%; (iv) 4N HCl, reflux, 78-83%.

(±)-Secondary alcohols **70 a-c**, readily prepared by Friedel-Crafts acylation, followed by $NaBH_4$ reduction of the corresponding aromatic ketones, was used as the starting materials. Palladium-catalyzed KR of these (±)-alcohols **70 a-c** using (–)-sparteine as a chiral ligand in toluene at 80^0C afforded the corresponding (S)-(–)-alcohols **71 a-c** in excellent optical purity (upto 98% ee) confirmed by both HPLC analysis using chiralcel OD column and the optical rotation. Typically, the ^{1}H-NMR spectrum of **70 c** showed a doublet at δ 1.42 for CH_3 group and a quartet at δ 4.79 for the benzylic C-H proton. Its ^{13}C- NMR spectrum showed the required signals at δ 24.99 and 69.83 for the homobenzylic and benzylic carbons respectively (**Fig. 3**).

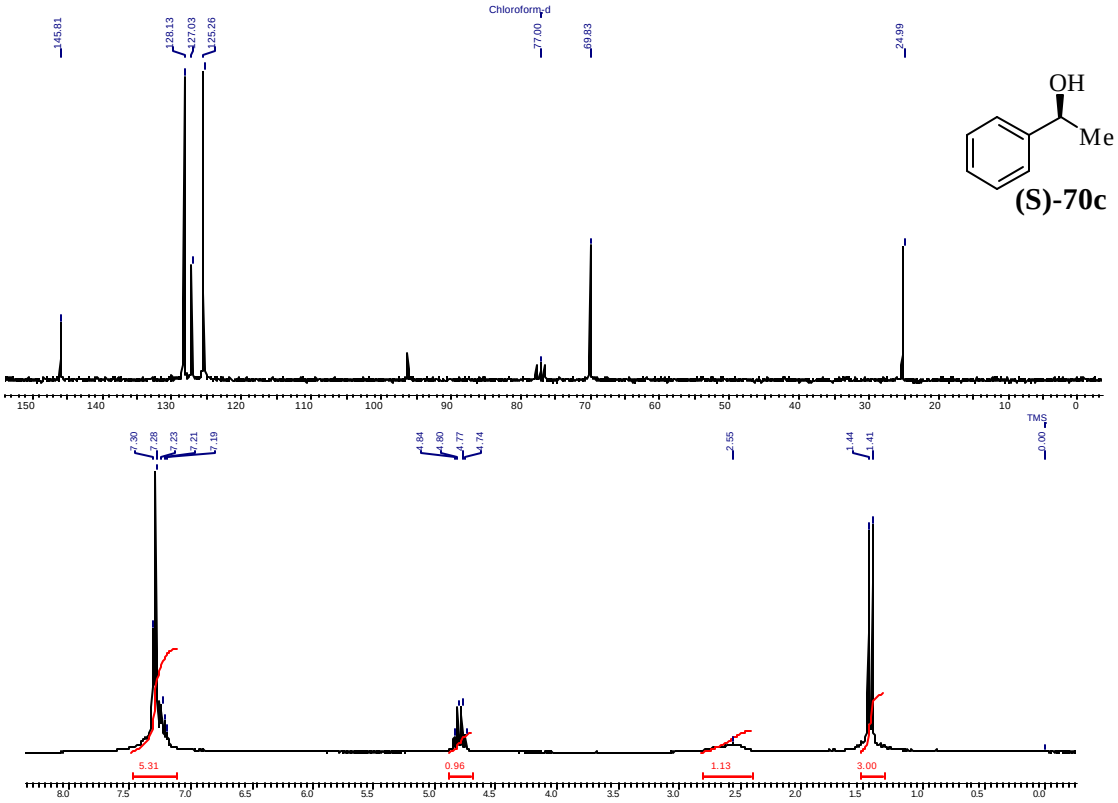


Fig. 3: ^{1}H and ^{13}C NMR spectra of chiral alcohol (S)-70c

Chiral (S)-(–)-alcohols **(S)-70 a-c** were then treated with PBr_3 in presence of pyridine as a scavenger to quench the HBr generated, to afford the bromo compounds **(R)-71 a-c** with complete inversion of configuration.[45] This was possible as the reaction was done at a lower temperature -15^0-0^0C and for a longer time (for 50-82 h at 0^0C) in order to achieve complete cleavage of the intermediate phosphite esters and to achieve high enantiomeric excess of the bromo compounds **(R)-71 a-c**. The ^{1}H-NMR spectrum of **(R)-71c** showed a doublet at δ 1.98 and a quartet at δ 5.11, little downfield shift than the corresponding alcohol. The ^{13}C-NMR spectrum also shows little downfield shift in case of homobenzylic CH_3 group at δ 27.01, but the benzylic carbon shows an upfield shift at δ 49.03 (**Fig 4**).

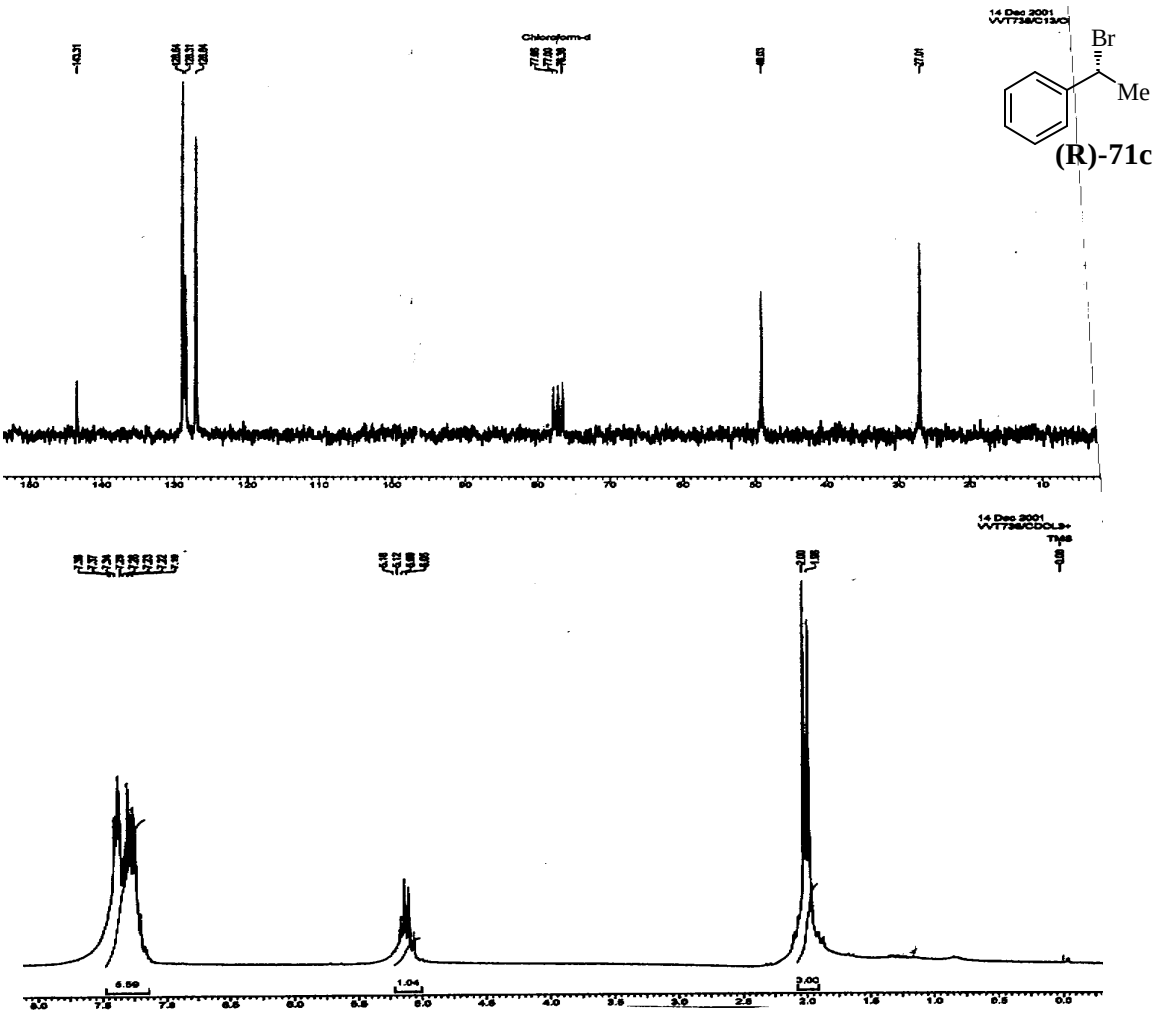


Fig. 4: ^{1}H and ^{13}C NMR spectra of chiral bromide (R)-71c

Bromo compounds **(R)-71 a-c** were then treated with NaCN in DMF as solvent to yield the corresponding (S)-cyano compounds **(S)-72 a-c**, again with complete inversion of configuration at benzylic carbon atom. The ^{1}H-NMR spectrum of **(S)-72 c** showed a doublet at δ 1.59 and a quartet at δ 3.87, upfield shift compared to **(R)-71 c**. Its ^{13}C-NMR spectrum also showed a drastic upfield shift as compared to **(R)-71 c**, for its homobenzylic and benzylic carbons occurring at δ 21.24 and 31.02 respectively (**Fig. 5**).

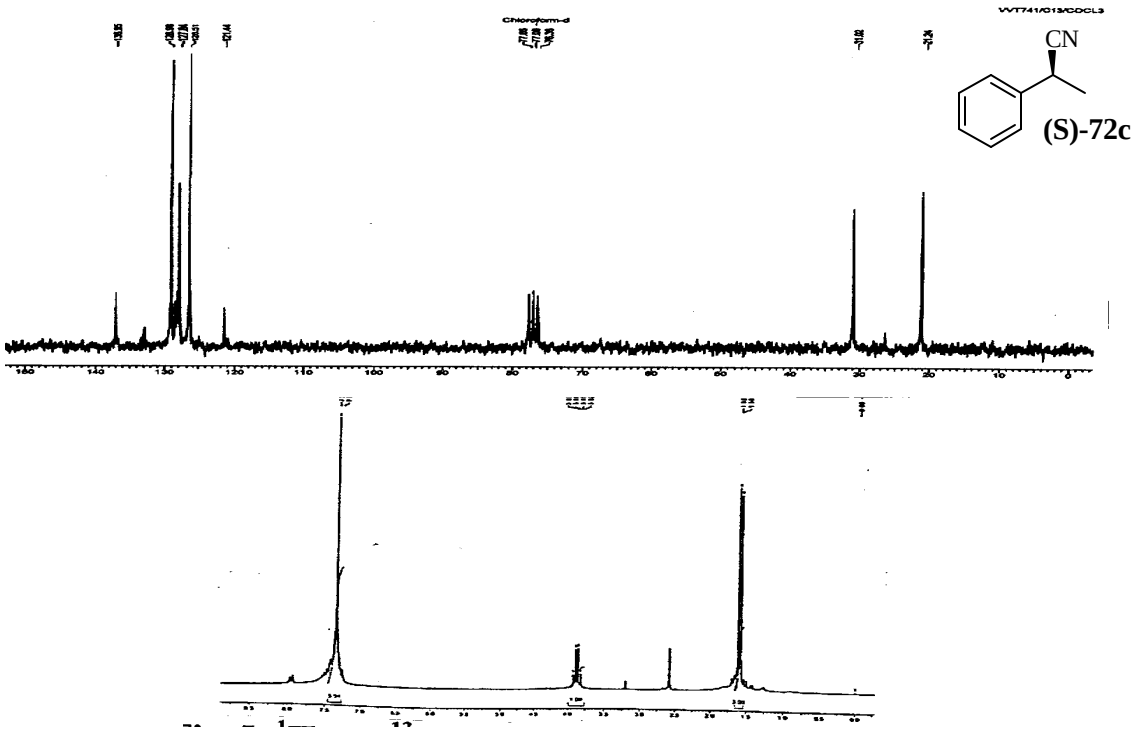


Fig. 5: ^{1}H and ^{13}C NMR spectra of chiral nitrile (S)-72c

The cyano compounds **(S)-72 a-c** were finally hydrolyzed using 4N HCl to afford the corresponding (S)-*a*-arylpropionic acids (**1**, **2** and **3**) in good yields and excellent optical purity (ee upto 92%). Their ^{1}H NMR and ^{13}C-NMR spectra match very well with those reported in the literature [for **(S)-1** see **Fig. 6**, **Fig. 7** and for **(S)-3 Fig. 8**].

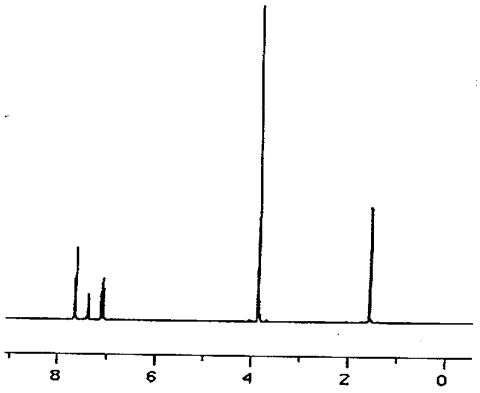


Fig. 6: ^{1}H-NMR spectrum of (S)-naproxen (1)

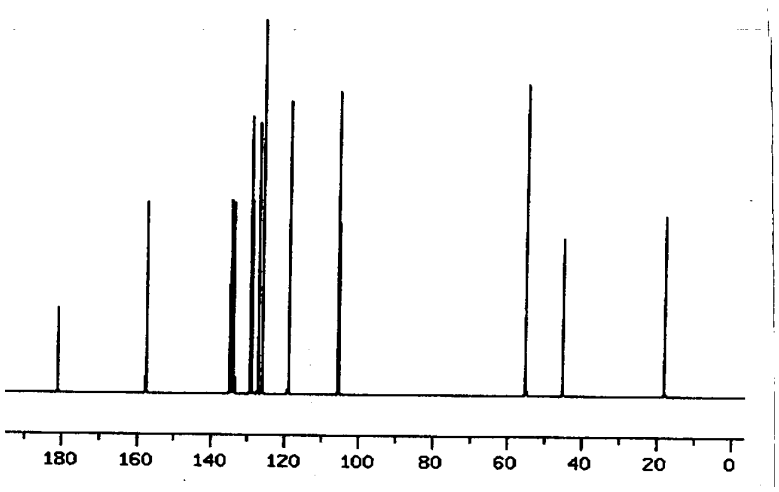


Fig. 7: ^{13}C NMR spectra of compound (S)-naproxen (1)

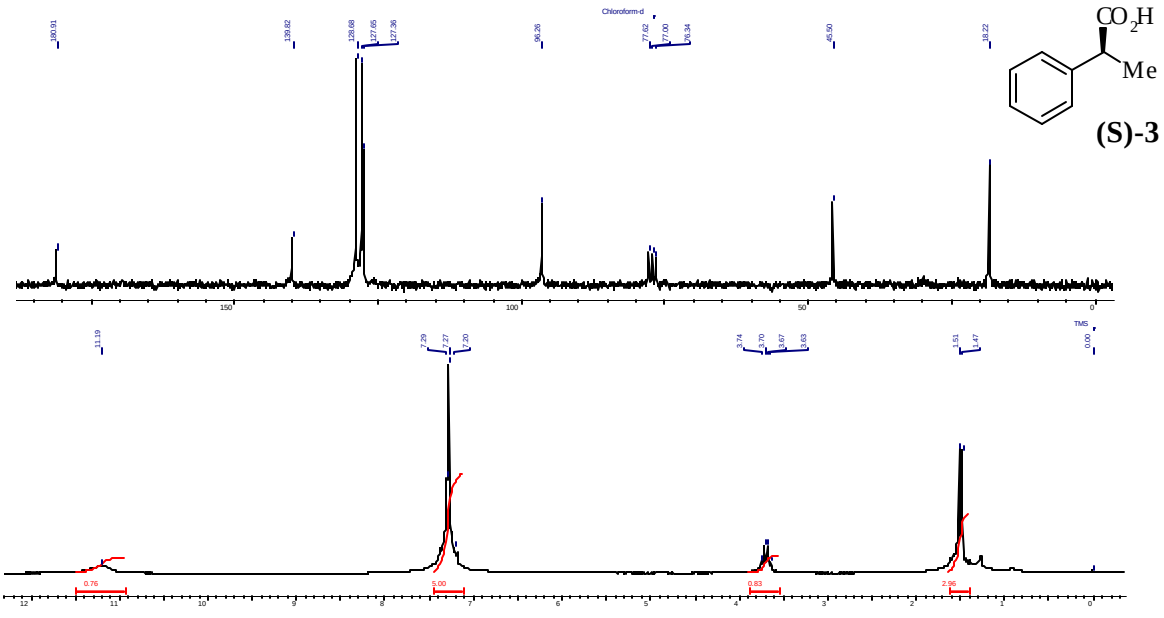


Fig. 8: ^{1}H and ^{13}C-NMR spectra of (S)-phenylpropionic acid (3)

3.0.5 Conclusion

We have successfully demonstrated the use of a new methodology involving Pd-catalyzed kinetic resolution of secondary alcohols, for the synthesis of *a*-arylpropionic acids such as (S)-naproxen (27% overall yield, 90% ee), (S)-ibuprofen (22% overall yield,

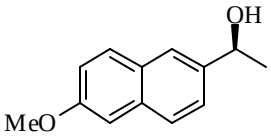
82% ee) and (S)-phenylpropionic acid (29% overall yield, 92% ee) in four steps starting from the corresponding (±)-secondary alcohols.

3.0.6 Experimental Section

Preparation of (S)-70 a-c via Pd-catalyzed kinetic resolution of (±)-70 a-c:

Two-necked RB flask was charged with $Pd(OAc)_2$ (0.055 g, 0.25 mmol), (–)-sparteine (0.234 g, 1.00 mmol) and toluene (12 ml) and flushed with oxygen (five times) and was covered with O_2 (1 atm) balloon. The contents of the flask were heated in an oil bath under O_2 atmosphere at 80^0C for 30-40 minutes. Then solution of secondary alcohols **(±)-70 a-c** (5 mmol) in toluene (12 ml) was added slowly at 80^0C. The reaction mixture was heated at 80^0C for 72-80 h. Then it was allowed to cool to room temperature and filtered through the pad of silica gel and celite. The filtrate was concentrated under reduced pressure and purified by column chromatography using 10% EtOAc in pet. ether as eluent to afford enantiomerically pure alcohols **(S)-(-)-70 a-c** in 45 to 50% yields and the corresponding ketones. The ee was determined by HPLC as well as by optical rotation.

(S)-(-)-1-(6-Methoxy-1-naphthyl)ethanol (70a)



Yield: 47%; **mp**: 62-63^{0}C; **[a]$^{25}_D$**: – 39.8 (c 2, EtOH); **HPLC**: 95% ee, Chiralcel OJ, λ = 254 nm, 4% 2-propanol/hexane, 1 ml/min., Retention time: (S) 31.32 min. (R) 38.69 min.; **IR** ($CHCl_3$, cm^{-1}): 761, 907, 1088, 1200, 1461, 1593, 2953, 3029, 3465; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.62 (d, *J* = 6.20 Hz, 3H), 3.83 (s, 3H), 5.67 (q, *J* = 6.20 Hz, 1H), 7.14 (d, *J* = 10.12 Hz, 1H), 7.25-7.44 (m, 2H), 7.64-7.75 (m, 2H), 8.09 (d, *J* = 10.12 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 23.62, 56.08, 65.61, 113.17, 122.84, 123.35, 125.41, 126.33, 128.39, 129.20, 131.11, 153.97, 159.41; **MS** m/z (% rel. intensity): 202 (M^+, 20), 187 (70), 163 (13), 157 (23), 144 (55), 127 (39), 115 (100), 89 (29), 77 (30), 62 (39); **Analysis**: $C_{13}H_{14}O_2$ requires C, 77.20; H, 6.98; found C, 77.14; H, 7.10%.

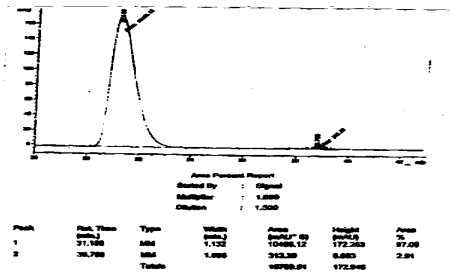


Fig. 9: HPLC chromatogram for alcohol (S)-70a

2-Acetyl-6-methoxynaphthalene: **Yield**: 51%; **mp**: 68-69^{0}C; **IR** (Neat, cm^{-1}): 688, 994, 761, 1360, 1456, 1583, 1599, 1690, 2857, 2951, 3087; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.60 (s, 3H), 3,88 (s, 3H), 7.16 (d, *J* = 9.21 Hz, 1H), 7.23-7.45 (m, 2H), 7.70-7.79 (m, 3H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 32.30, 55.94, 112.43, 123.46, 123.72, 124.82, 127.25, 127.87, 128.57, 130.12, 131.11, 153.68, 203.63; **Analysis**: $C_{13}H_{12}O_2$ requires C, 77.98; H, 6.04; found C, 77.72; H, 6.09%.

(S)-(–)-1-(4-Isobutylohenyl)ethanol (70b): **Yield**: 50%; **viscous liquid**; **[**a**]$^{25}_D$**: – 38.9 (c 0.9, $CHCl_3$); **HPLC**: 88% ee, Chiralcel OD-H, λ = 254 nm, 3% EtOH/hexane, 1.0 ml/min. Retention time: (R) 14.60 min, (S) 16.52 min.; **IR** ($CHCl_3$, cm^{-1}): 669, 920, 1080, 1204, 1461, 1493, 1540, 2903, 3029, 3382; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.89 (d, *J* = 6.31 Hz, 6H), 1.44 (d, *J* = 6.20 Hz, 3H), 1.78-1.91 (m, 1H), 2.45 (d, *J* = 6.14 Hz, 2H), 4.80 (q, *J* = 6.20 Hz, 1H), 7.08 (d, *J* = 8.41 Hz, 2H), 7.22 (d, *J* = 8.41 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 22.49, 25.10, 30.28, 45.20, 70.20, 125.23, 129.16, 140.74, 143.27; **MS** m/z (% rel. intensity): 178 (M^+, 20), 162 (100), 134 (33), 122 (30), 120 (37), 117 (40), 114 (27), 90 (53); **Analysis**: $C_{12}H_{18}O$ requires C, 80.85; H, 10.18; found C, 80.63; H, 10.21%.

4-Acetyl-isobutylbenzene: **Yield**: 45%; **gum**; **IR** ($CHCl_3$, cm^{-1}): 698, 991, 761, 966, 1360, 1450, 1583, 1599, 1686, 2857, 3087; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.90 (d, *J* = 8.21 Hz, 6H), 1.85-1.92 (m, 1H), 2.52 (d, *J* = 8.11 Hz, 2H), 2.58 (s, 3H), 7.22 (d, *J* = 8.44 Hz, 2H), 7.87 (d, *J* = 8.44 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 22.08, 26.24, 29.88, 45.17, 128.09, 129.09, 134.78, 147.32, 197.49; **Analysis**: $C_{13}H_{14}O_3$ requires C, 71.54; H, 6.47; found C, 71.52; H, 6.49%.

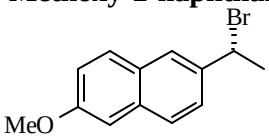
(S)-(–)-1-Phenylethanol (70c): **Yield**: 45%; **bp**: 88-89^{0}C/10mm; **[**a**]$^{25}_D$**: – 46.2 (c 5, MeOH); **HPLC**: 98% ee, λ = 254 nm, Chiralcel OD-H, 3% EtOH/hexane, 1.0 ml/min. Retention time: (R) 10.69 min. (S) 13.37 min.; **IR** (Neat, cm^{-1}): 669, 761, 907, 1078, 1204, 1461, 1493, 2973, 3029, 3365; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.42 (d, *J* = 6.31 Hz, 3H), 2.55 (bs, 1H), 4.79 (q, *J* = 6.31 Hz, 1H), 7.21-7.30 (m, 5H); **^{13}C-NMR** (50 MHz,

$CDCl_3$): δ 24.99, 69.83, 125.26, 127.03, 128.13, 145.81; **MS** m/z (% rel. intensity): 122 (M^+, 35), 107 (100), 79 (76), 77 (38), 51 (16), 43 (17); **Analysis**: $C_8H_{10}O$ requires C, 78.65; H, 8.25; found C, 78.62; H, 8.38%.

Preparation of aryl bromides (R)-(+)-71 a-c:

The two-necked RB flask was charged with any one of the alcohols **(S)-(–)-70 a-c** (3 mmol) and dry pyridine (0.73 ml, 9 mmol). Dry ether (3 ml) was added to it through syringe under nitrogen atmosphere. The solution was cooled to –15 to -20^0C followed by the slow addition of a solution of PBr_3 (0.95 g, 0.33 ml, 3.5 mmol) in 5 ml dry ether. It was stirred at -20^0C for 2 h then at 0^0C for 72-80 h (monitored by TLC). The excess PBr_3 was destroyed by the addition of ice water to the reaction mixture; it was then extracted with ether (3 x15 ml) washed with ice water, 85% orthophosphoric acid, cold saturated $NaHCO_3$ solution again with ice water and brine. The organic layer was dried over anhydrous sodium sulfate, concentrated under reduced pressure to get the crude products as gum. The crude products were then purified by column chromatography by using 5% EtOAc in pet. ether as eluent to afford the corresponding optically pure bromides **(R)-(+)-**

(R)-(+)-1-(6-Methoxy-2-naphthalene)bromoethane (71a)



71 a-c as viscous liquids. The products were stored at 0^0C in refrigerator and used immediately for the next reaction.

Yield: 78%; **gum**; **[a]$^{25}_D$**: + 148.4 (c 1.5, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 768, 1036, 1055, 1181, 1313, 1377, 1445, 1466, 1494, 1520, 2922, 2975, 3032; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.02 (d, *J* = 7.12 Hz, 3H), 3.86 (s, 3H), 6.01 (q, *J* = 7.14 Hz, 1H), 7.08-7.42 (m, 3H), 7.62-7.69 (m, 2H), 8.10 (d, *J* = 8.42 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 25.12, 46.75, 55.81, 113.21, 122.86, 123.40, 125.44, 126.32, 128.37, 128.91, 129.34, 132.14, 154.51, 159.62; **MS** m/z (% rel. intensity): 185 (100), 170 (25), 154 (12), 115 (8), 89 (10), 70 (20), 62 (15); **Analysis**: $C_{13}H_{13}BrO$ requires C, 58.89; H, 4.94; Br, 30.14; found C, 58.82; H, 4.99; Br, 30.18%.

(R)-(+)-1-(4-isobutylphenyl)-bromoethane (71b): **Yield**: 70%; **gum**; **[a]$^{25}_D$**: + 124.3 (c 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 563, 695, 766, 1026, 1045, 1191, 1326, 1383, 1441, 1490, 1494, 2943, 2975, 3050; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.92 (d, *J* = 6.11 Hz, 6H), 1.53 (d, *J* = 8.11 Hz, 3H), 1.77-1.89 (m, 1H), 2.47 (d, *J* = 7.12 Hz, 2H), 3.93 (q, *J* = 8.11 Hz,

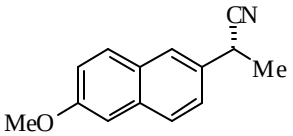
1H), 7.13 (d, J = 8.44 Hz, 2H), 7.24 (d, J = 8.44 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 21.94, 22.52, 30.66, 39.20, 45.28, 125.31, 130.11, 140.09, 142.87; **MS** m/z (% rel. intensity): 161 (100), 146 (8), 118 (10), 117 (5), 77 (2); **Analysis**: $C_{12}H_{17}Br$ requires C, 59.76; H, 7.11; Br, 33.13; found C, 59.52; H, 7.19; Br, 33.21%.

(R)-(+)-1-Phenylbromoethane (71c): **Yield**: 88%; **gum**; **[**a**]$^{25}_D$**: + 161.3 (neat){lit.[45] **[**a**]$^{25}_D$**: + 160.8 (neat) 94% ee} ; **IR** (Neat, cm^{-1}): 563, 592, 695, 763, 1026, 1045, 1181, 1313, 1377, 1441, 1466, 1494, 2922, 2975, 3032; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.98 (d, J = 8.18 Hz, 3H), 5.11 (q, J = 8.18 Hz, 1H), 7.19-7.38 (m, 5H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 27.01, 49.03, 126.84, 128.31, 128.61, 143.31; **MS** m/z (% rel. intensity): 185 (M^+, 1), 105 (100), 91 (15), 77 (20); **Analysis**: C_8H_9Br requires C, 51.92; H, 4.90; Br, 43.18; found C, 51.86; H, 4.78; Br, 43.36%.

Preparation of aryl cyanides (S)(-)-72 a-c:

A 25 ml RB flask was charged with any one of the aryl bromides **71 a-c** (2 mmol) and NaCN (0.196 gm, 4 mmol) and dry DMF (4 ml) was added through syringe under nitrogen atmosphere. The resulting reaction mixture was heated at 80^{0}C for 10-12 h (monitored by TLC). The reaction mixture was cooled to room temperature, diluted with ethyl acetate washed with water and brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography using 15% EtOAc in pet. ether as eluent to afford **(S)-(-)-72 a-c**.

(S)-(-)-2-(6-Methoxy-2-naphthalene)propionitrile (72a)



Yield: 89%; **mp**: 68-69^{0}C; **[**a**]$^{25}_D$**: – 26.5 (c 1.0, $CHCl_3$), 90% ee, {lit.[45b] **[**a**]$^{25}_D$**: – 29.4 (c 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 699, 744, 760, 1267, 1463, 1510, 1600, 2238, 2876, 2939, 2988, 3042; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.71 (d, J = 7.88 Hz, 3H), 3.88 (s, 3H), 4.00 (q, J = 7.89 Hz, 1H), 7.01-7.90 (m, 6H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 21.44, 32.21, 57.12, 114.08, 121.64, 122.88, 123.35, 125.44, 126.45, 128.41, 128.92, 129.20, 131.26, 153.14, 158.21; **MS** m/z (% rel. intensity): 211 (M^+, 42), 196 (100), 181 (44), 165 (15), 115 (8), 89 (20), 77 (12); **Analysis**: $C_{14}H_{13}NO$ requires C, 79.60; H, 6.20; N, 6.63; found C, 79.52; H, 6.29; N, 6.62%.

(S)-(–)-2-(4-isobutylphenyl)propionitrile (72b): **Yield**: 80%; **gum**; **[**a**]$^{25}_D$**: – 19.34 (c 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 733, 760, 1277, 1463, 1498, 1580, 1610, 2248, 2880, 2939,

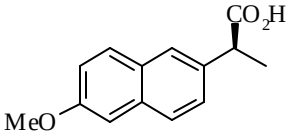
2958, 3033; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.91 (d, *J* = 6.21 Hz, 6H), 1.60 (d, *J* = 7.12 Hz, 3H), 1.79-1.92 (m, 1H), 2.47 (d, *J* = 7.05 Hz, 2H), 3.84 (q, *J* = 7.12 Hz, 1H), 7.17 (d, *J* = 8.45 Hz, 2H), 7.27 (d, *J* = 8.45 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 22.63, 28.15, 30.68, 44.86, 55.86, 121.66, 125.44, 130.11, 140.21, 143.12; **MS** m/z (% rel. intensity): 187 (M^+, 17), 172 (100), 171 (10), 144 (22), 117 (20), 90 (13); **Analysis**: $C_{13}H_{17}N$ requires C, 83.37; H, 9.15; N, 7.48; found C, 83.32; H, 9.10; N, 7.41%.

(S)-(–)-2-phenylpropionitrile (72c): **Yield**: 92%; **gum**; **[**a**]$^{25}_D$**: – 21.92 (c 1.2, $CHCl_3$); **IR** (Neat, cm^{-1}): 699, 733, 760, 1267, 1463, 1494, 1600, 2243, 2876, 2939, 2988, 3032; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.59 (d, *J* = 8.21 Hz, 3H), 3.87 (q, *J* = 8.21 Hz, 1H), 7.34 (s, 5H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 21.24, 31.02, 121.44, 126.51, 127.84, 128.98, 136.95; **MS** m/z (% rel. intensity): 131 (M^+, 34), 116 (100), 104 (7), 89 (10), 77 (9), 51 (10); **Analysis**: C_9H_9N requires C, 82.41; H, 6.92; N, 10.68; found C, 82.48; H, 6.89; N, 10.66 %.

Preparation of (S)(+)-*α*-aryl propionic acids (1, 2 and 3) by hydrolysis of aryl cyanides (S)-(-)-72 a-c:

Aryl cyanides **(S)-72 a-c** (1mmol) were dissolved in CH_2Cl_2 (3 ml) and 3 ml of 8N HCl was added to it. The resulting reaction mixture was refluxed in an oil bath for 10-12 h (monitored by TLC). Excess solvent was removed under reduced pressure by distillation. The resulting gum was purified by column chromatography (in case of **3**) using 50% EtOAc in pet. ether as eluent or recrystallized from EtOAc and hexane (in case of **1** and **2**) to afford the corresponding *α*-arylpropionic acids (**1**, **2** or **3**) in pure form.

(S)-(+)-2-(6-methoxy-2-naphthyl)-propionic acid (naproxen) (1)



Yield: 83%; **mp**: 155-157^{0}C; **[**a**]$^{25}_D$**: + 59.56 (c 1, $CHCl_3$) 90% ee {lit. **[**a**]$^{25}_D$**: + 66 (c 1, $CHCl_3$)}; **IR** (Nujol, cm^{-1}): 896, 926, 1029, 1159, 1176, 1260, 1378, 1606, 1630, 1664, 1728, 2866, 2925, 2954; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.56 (d, *J* = 7.13 Hz, 3H), 3.85-3.88 (m, 4H), 7.08-7.41 (m, 3H), 7.66 (d, *J* = 2.14 Hz, 1H), 7.69 (d, *J* = 8.21 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 18.10, 45.29, 55.26, 105.55, 119.02, 126.14, 126.18, 127.22, 128.86, 129.29, 133.79, 134.83, 157.66, 181.05; **MS** m/z (% rel. intensity): 230 (M^+, 53),

185 (100), 170 (10), 154 (7), 141 (11), 115 (9), 77 (2), 63 (2); **Analysis**: $C_{14}H_{14}O_3$ requires C, 72.40; H, 6.08; found C, 72.52; H, 6.19%.

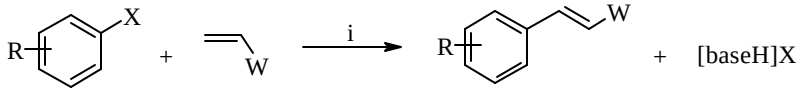
(S)-2-(4'-Isobutylphenyl)propionic acid [(S)-ibuprofen (2)]:**Yield**: 78%; **mp**: 50-52^{0}C; **[**a**]$^{25}_D$**: + 49.14 (c 2, EtOH) 82% ee {lit. **[**a**]$^{25}_D$**: + 59 (c 2, EtOH)}; **IR** ($CHCl_3$, cm^{-1}): 729, 947, 1137, 1413, 1459, 1601, 1707, 2946, 2982, 3088; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.89 (d, *J* = 7.13 Hz, 6H), 1.49 (d, *J* = 7.21 Hz, 3H), 1.80-1.84 (m, 1H), 2.44 (d, *J* = 7.13 Hz, 2H), 3.70 (q, *J* = 7.21 Hz, 1H), 7.09 (d, *J* = 8.14 Hz, 2H), 7.21 (d, *J* = 8.14 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 18.11, 22.40, 30.15, 45.06, 127.31, 129.40, 137.02, 140.84, 181.11; **MS** m/z (% rel. intensity): 206 (M^+, 50), 163 (94), 161 (100), 119 (42), 107 (30), 91 (49); **Analysis**: $C_{13}H_{18}O_2$ requires C, 75.69; H, 8.80; found C, 75.52; H, 8.79%.

(S)-(+)-2-Phenyl propanoic acid (3): **Yield**: 80%; **gum**; **[**a**]$^{25}_D$**: + 73.28 (c 1.6, $CHCl_3$) 92% ee {lit. **[**a**]$^{25}_D$**: + 73 (c 1.6, $CHCl_3$, 97% ee)}; **IR** (Neat, cm^{-1}): 698, 729, 937, 1130, 1413, 1454, 1600, 1706, 2935, 2981, 3087; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.49 (d, *J* = 8.12 Hz, 3H), 3.69 (q, *J* = 8.12 Hz, 1H), 7.20-7.29 (m, 5H), 11.19 (bs, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 18.22, 45.50, 127.65, 128.68, 139.82, 180.9; **MS** m/z (% rel. intensity): 150 (M^+, 13), 105 (100), 91 (13), 77 (50), 63 (13); **Analysis**: $C_9H_{10}O_2$ requires C, 71.98; H, 6.71; found C, 71.82; H, 6.66%.

Synthesis of Novel Sulfur and Nitrogen Palladacycles and Their Applications in Arylation Reactions

3.1.1 Introduction

The palladium-catalyzed arylation of olefins with aryl halides generally referred to as the Heck reaction (**Scheme 34**) has received increasing attention in the last two decades.[46] This is primarily due to the enormous synthetic potential of this versatile method for generating new C-C bonds. This reaction represents a powerful and popular method for the formation of C-C bonds; in particular the Heck reaction is an important method for the preparation of aryl-functionalized alkenes in synthetic organic chemistry as applicable to pharmaceutical industry.[47] Thus, organopalladium compounds play an important role in homogeneous catalysis due to their versatility and nontoxicity.



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

Scheme 34: Heck coupling reaction, (i) Pd-catalyst, base, solvent.

Traditionally, variety of palladium sources such as $Pd(OAc)_2$, $PdCl_2$, $PdCl_2(PPh_3)_2$, $Pd(dba)_2$, $Pd_2(dba)_3$, *etc*. were used as catalysts with or without phosphine (for e.g. PPh_3) ligands. However, these catalytic systems suffer from some severe limitations, such as non-applicability of this reaction on industrial scale. Typically a relatively large amount of catalyst (1-5 mol%) is needed for reasonable conversions and the catalyst recycling is often hampered by early precipitation of palladium black.[48] Due to the fast catalyst deactivation the turn over number (TON= mole of product/mole of Pd) and turn over frequency (TOF= mole of product/mole of Pd h^{-1}) was very less for all these conventional catalysts. During the past few years very active systems have been developed in order to improve the stability of palladium-based catalysts and to increase their efficiency. Carbometalated Pd^{II} complexes, especially palladacycles have emerged as very promising

catalysts for C-C bond forming reaction. Although these reactions can be mediated by a variety of Pd^0 and Pd^{II} compounds, phosphorous or nitrogen containing palladacycles are among the most active catalyst precursors reported to date.[49]

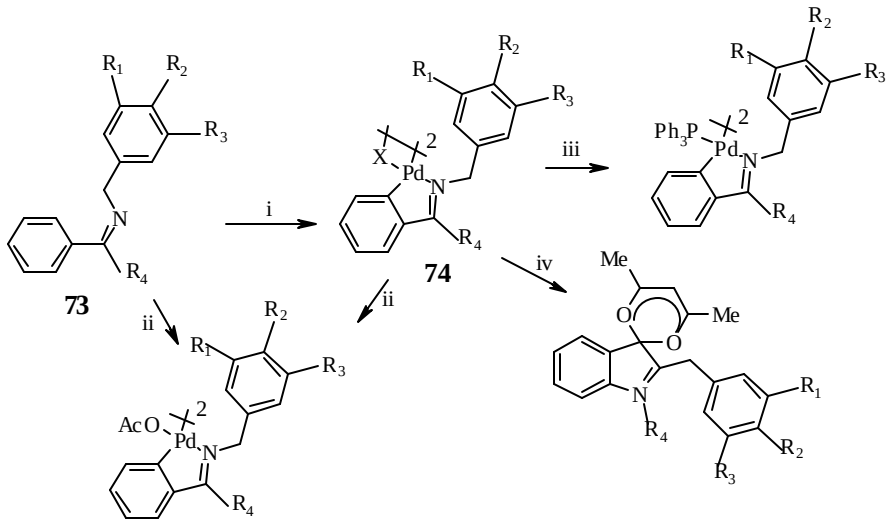
The discovery of these catalyst precursors allowed the Heck reactions to be performed with activated and nonactivated aryl halides using very low catalyst concentrations (down to ppm in case of aryl iodides).[50] Two of the most intriguing aspects of the use of palladacycles in the Heck reaction are the probable involvement of Pd^{IV} species and that the Pd^{II} catalyst precursors are recovered unchanged after catalysis.

3.1.2 Review of Literature

Literature search revealed that there are several reports on use of palladacycles (mostly phosphorous or nitrogen) for C-C bond formation reactions like Heck reaction, biaryl formation, Suzuki coupling, *etc*. Palladacycles offer a much wider variety of catalytic applications and several new and efficient complexes based on different ligand backbone have since been developed.

Clark *et al.*

Clark *et al.*[51] studied the cyclopalladation of benzylidenebenzylamines **73** with one equivalent Li_2PdCl_4 to give dimer **74**.

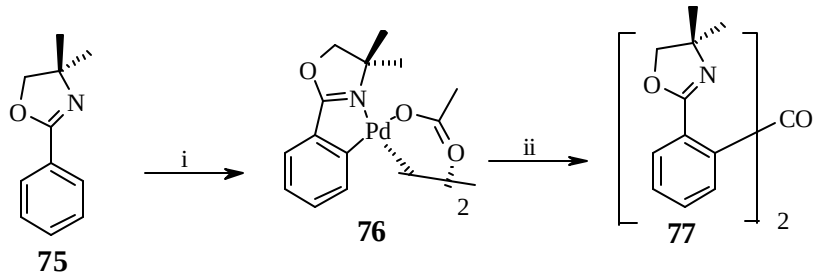


Scheme 35: (i) Li_2PdCl_4; (ii) $Pd(OAc)_2$; (iii) PPh_3; (iv) NaOAc, acac (acetylacetone).

The cyclopalladated product **74** was reacted with acetylacetone (acac), PPh_3 or NaOAc to give various products, which were characterized by ^1H and ^{13}C-NMR spectroscopy (**Scheme 35**).

Balavoine *et al.*[52]

Aryloxazolines **75**, with various substituents on the aromatic ring, have given dimeric cyclopalladated complexes **76** by reaction with $Pd(OAc)_2$.The reaction of these complexes with carbon monoxide to afford diaryl ketones **77** in aprotic solvents has been studied (**Scheme 36**).

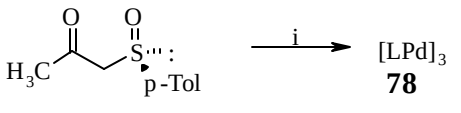


75 **76** **77**

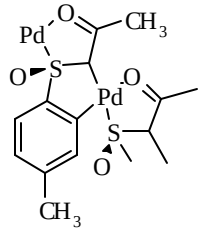
Scheme 36: (i) $Pd(OAc)_2$, benzene; (ii) CO (1 atm,) CH_2Cl_2/acetone.

Gonzalez *et al.*[53]

The reaction of $Pd(OAc)_2$ with (R)-3-*p*-tolylsulfinyl-2-propanone gave trimeric palladacycle **78** containing a stereogenic carbon directly joined to the Pd atom (**Scheme 37**).



78

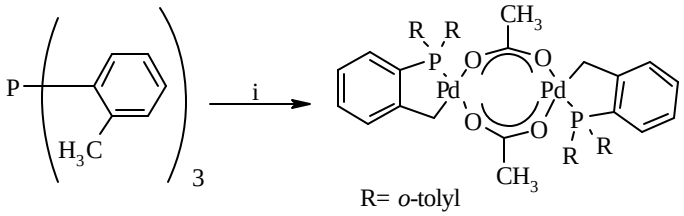


a section of the structure of the catalyst **78**

Scheme 37: (i) $Pd(OAc)_2$, AcOH, 70^0C, 48-72 h.

Herrmann *et al.*

Palladacycle **79** was synthesized and used as efficient catalyst for the Heck reaction of aryl bromides as well as aryl chlorides (**Scheme 38**).[54] Turn over number (TON, mmol of product/ mmol of Pd) upto 2,00,000 was achieved in case of Heck reaction of aryl bromides (**Scheme 34**).

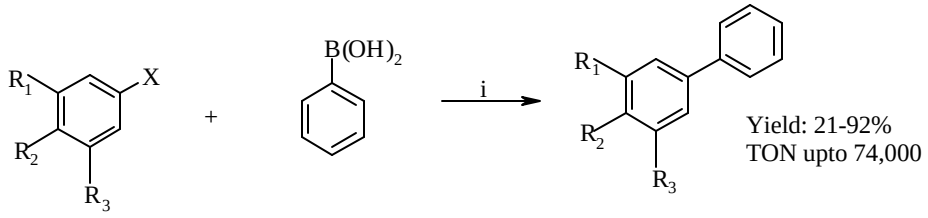


R= *o*-tolyl

79

Scheme 38: (i) $Pd(OAc)_2$, toluene, 50^0C.

Herrmann *et al.*[55] have reported the use of the same catalyst **79** for the Suzuki coupling to synthesize unsymmetrical biphenyl derivatives (**Scheme 39**). Yield in the range of 21-92% and TON upto 74,000 were achieved with this catalyst.

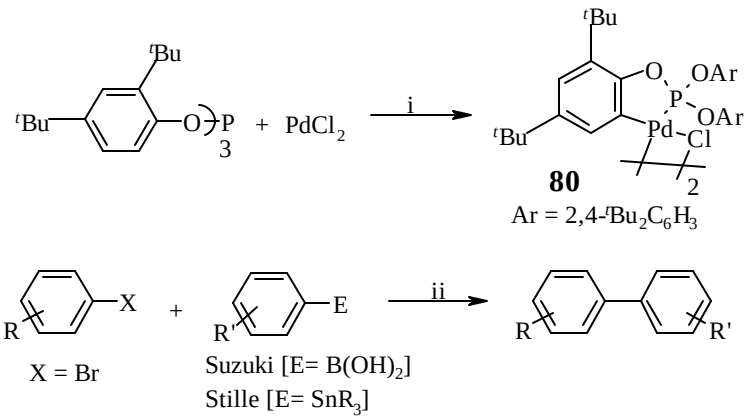


X= Br, Cl

Scheme 39: (i) palladacycle **79**, xylol, K_2CO_3, 130^0C.

Bedford *et al.*[56]

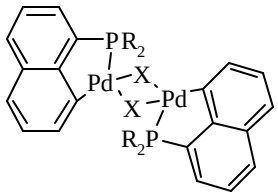
The reaction of tris(2,4-di-*tert*-butylphenyl)phosphite with $PdCl_2$ afforded the orthometallated dimer **80** (**Scheme 40**). For coupling of aryl halides with phenyl boronic acid (Suzuki coupling), TON upto 10,00,000 and TOF (turn over frequency) upto 9,00,000 were obtained. In case of Stille reaction, TON upto 8,30,000 were achieved.



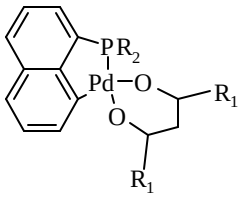
Scheme 40: (i) solvent, 96%; (ii) catalyst **80**, base (K_2CO_3) DMA or toluene.

Shaw *et al.*

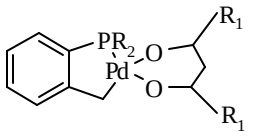
Shaw *et al.*[59] have synthesized palladacycles **81**, **82** and **83** (**Scheme 41**) and used them for Heck reaction. The catalysts **81a**, **82a** and **82b** were found to be excellent catalysts for the Heck reaction (**Scheme 34**). TON upto 11,20,000 was achieved with the catalyst **82b**.



81a R_2= naphthyl, X= OAc
81b R_2= naphthyl, X= Br
81c R_2= naphthyl, X= Br



82a R_2= naphthyl, R_1= Me
82b R_2= naphthyl, $R_{1=}$ CF_3

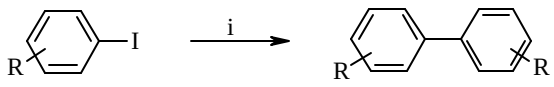


83a R_2= *o*-tolyl, R_1= Me
83b R_2= *o*-tplyl, R_1= CF_3

Scheme 41: Phosphorous palladacycles for Heck reaction.

Luo *et al.*

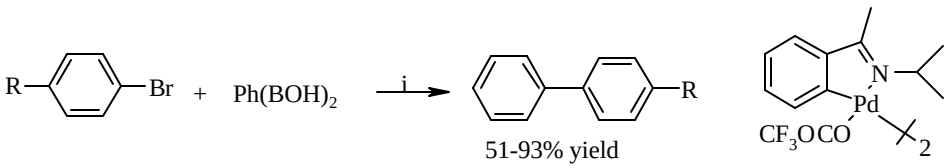
Luo *et al.*[58] demonstrated the use of palladacycle **79** (**Scheme 38**) as efficient catalyst for the symmetric biaryl formation from aryl iodides. Aryl chlorides and aryl bromides failed to give any reaction even at elevated temperatures (**Scheme 42**).



Scheme 42: (i) cat. **79** (0.5 mol%), DMF, base, 110^0C, 12 h.

Milstein *et al.*

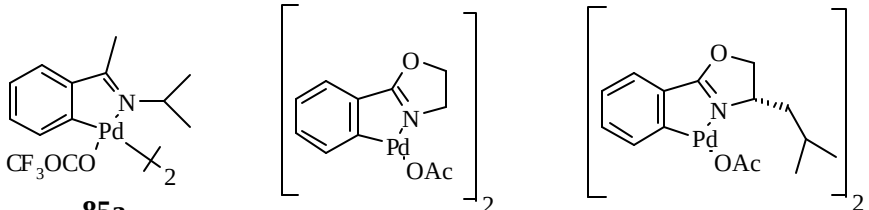
The cyclopalladated, phosphine free imine complex **84** proved to be an excellent catalyst for the Suzuki cross coupling,[59] leading to the TON upto 590 x 10^3 with aryl bromides. The catalyst is air and thermally stable (**Scheme 43**).



84

Scheme 43: (i) cat. **84**, *o*-xylene, base, 130^{0}C.

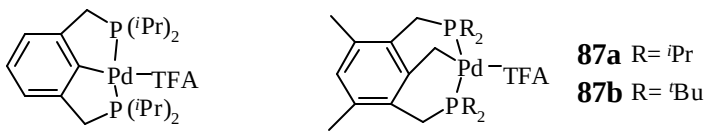
The new cyclopalladated, phosphine free imine complexes **85 a-c** (**Scheme 44**) have shown to be exceptional catalysts for the Heck arylation of olefins (**Scheme 34**).[60] The maximum TON observed was 14,29,000 with PhI and methyl acrylate with catalyst **85a**.



85a **85b** **85c**

Scheme 44: Phosphine free nitrogen palladacycles.

Milstein *et al.*[61] have reported the synthesis of palladacycles **86** and **87** from $Pd(TFA)_2$ (TFA= $OCOCF_3$) and the corresponding diphosphine in THF at 80^{0}C and their application in Heck reaction (**Scheme 34**). Very high TON (maximum TON observed was 5,28,700 with **87a**) and 77-100% yield was observed with all three catalysts, while the complex **87a** showed higher turn over rates (**Scheme 45**).

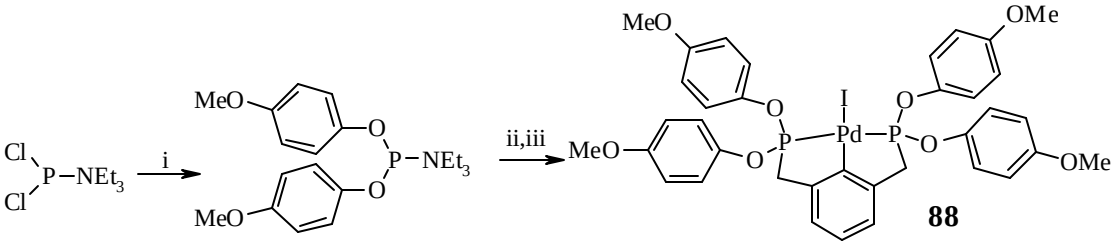


86

Scheme 45: Diphosphine palladacycles for Heck reaction.

Shibasaki *et al.*

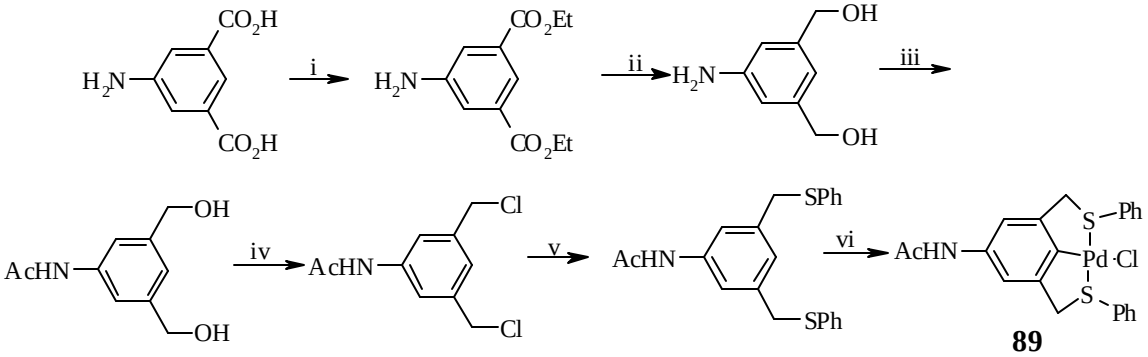
Shibasaki *et al.*[62] synthesized a new palladacycle **88** (**Scheme 46**) and this showed high catalytic activity with TON upto 89,00,000 and TOF upto 4,00,000 in the coupling of aryl halides with olefins (**Scheme 34**).



Scheme 46: (i) *p*-OMe-C_6H_4-OH (2 mol equiv.), Et_3N, THF, –78^{0}C-RT, 12 h; (ii) 2,5-dihydroxyiodobenzene (3 equiv.), tetrazole (6 equiv.), THF, –78^{0}C-RT, 2 days; (iii) $Pd_2(dba)_3.CHCl_3$ (0.5 mol equiv.), toluene, 23^{0}C, 12 h, 26%.

Osburn *et al.*[63]

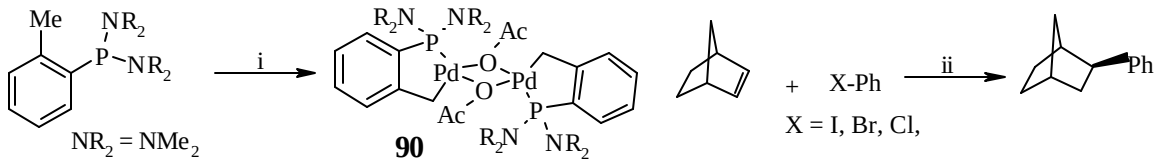
Sulfur palladacycle **89** was synthesized (**Scheme 47**) and used as an efficient catalyst for the Heck reaction of aryl iodides with olefins to yield *b*-substituted olefins (**Scheme 34**) in 91-96% yields.



Scheme 47: (i) H_2SO_4, EtOH, reflux, 16 h, 85%; (ii) LAH, reflux, 8 h, 91%; (iii) Ac_2O, Et_3N, THF, RT, 3 h, 85%; (iv) $SOCl_2$, pyridine, CH_2Cl_2, RT, 12 h, 89%; (v) PhSH, K_2CO_3, DMF, 70^{0}C, 16 h, 89%; (vi) $Pd(PhCN)_2Cl_2$, MeCN, reflux, 14 h, 85%.

Brunel *et al.*

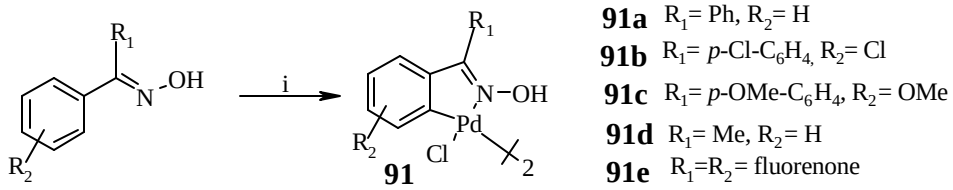
Brunel *et al.*[64] synthesized palladacycle **90**, and used it as a catalyst for the hydroarylation of norbornene (**Scheme 48**). Very high TON upto 196 x 10^6 was observed in presence of hydrogen donor NEt_3/HCO_2H.



Scheme 48: (i) $Pd(OAc)_2$, toluene, 110^0C, 2 h; (ii) cat. **90**, solvent, NEt_3/HCO_2H, Δ, 16 h.

Alonso *et al.*[65]

Oxime palladacycles **91 a-e** were prepared from very cheap starting materials (**Scheme 49**) and were used as versatile and very efficient catalysts for different C-C bond forming reactions (**fig. 10**).



Scheme 49: (i) Li_2PdCl_4, NaOAc, MeOH, RT, 72 h.

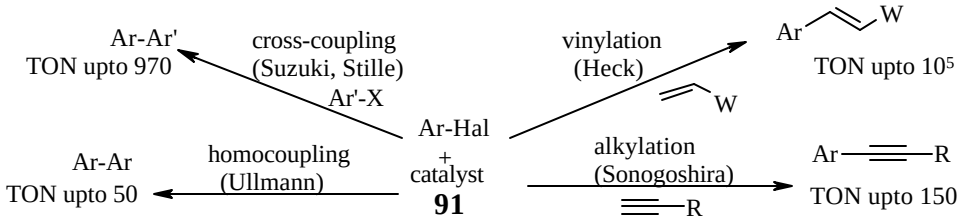
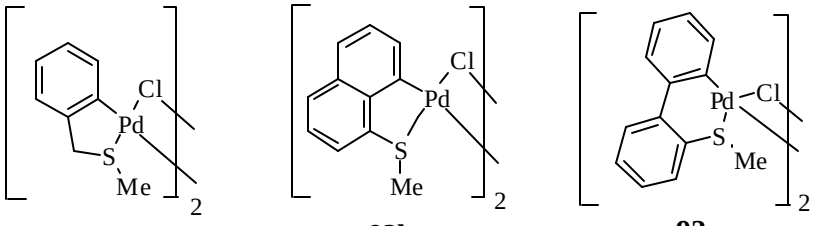


Fig. 10: Use of palladacycles **91 a-e** for C-C bond forming reactions.

Dupont *et al.*

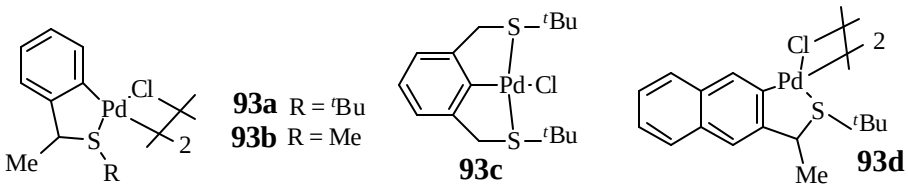
The cyclopalladation reactions of several sulfur-containing ligands have been investigated by Dupont *et al.*[66] The thioethers were metallated by $Pd(OAc)_2$ in acetic acid at either aryl or alkyl carbon atoms to afford, after reaction with lithium chloride in acetone, the dimeric chloride bridged cyclopalladated complexes **92 a-c** in 22-81%yields (**Scheme 50**).



92a **92b** **92c**

Scheme 50: Palladacycles prepared by cyclopalladation of thioethers.

The air, water and highly thermally stable sulfur-containing palladacycles **93 a-d** (**Scheme 51**), mainly derived from the orthopalladation of benzylic thioethers, are used as catalyst precursors for the Heck reaction.[67] The reaction can be performed with aryl iodides, bromides and chlorides with acrylic esters and styrene, leading to TON upto 18,50,000.

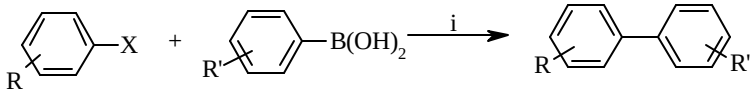


93a R = ^{t}Bu
93b R = Me

93c **93d**

Scheme 51: Sulfur-containing palladacycles used as catalyst precursors for the Heck reaction (**Scheme 34**)

Sulfur-palladacycle **93a** was shown to be efficient catalysts for the Suzuki cross-coupling reaction of aryl bromides and chlorides with phenyl boronic acid (**Scheme 52**).[68]



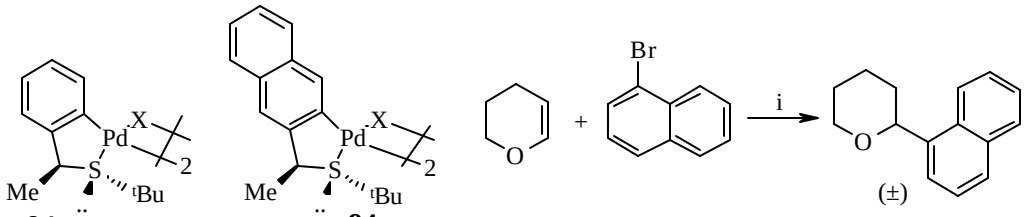
X= Br, Cl Yield= 54-100%

Scheme 52: (i) cat. **93a** (0.1 to 0.5%), K_3PO_4, DMF, Bu_4NBr (20%), 25^{0}C.

Sulfur palladacycles **93a** and **93c** (**Scheme 51**) were proved to be an efficient catalyst under relatively mild conditions (100-130^{0}C) for the homocoupling of aryl iodides (50-100% yields) and aryl bromides (12-70% yields).[69]

The reaction of (R)-(1-alkylsulfanylethyl)benzenes with palladium acetate in acetic acid at 90^{0}C afforded the corresponding orthopalladated compounds **94 a-d**. The

palladacycle **94b** is an excellent catalyst precursor, for the arylation of 3,4-dihydro-2-H-pyran under mild conditions. However asymmetric induction was not observed (**Scheme 53**).[70]

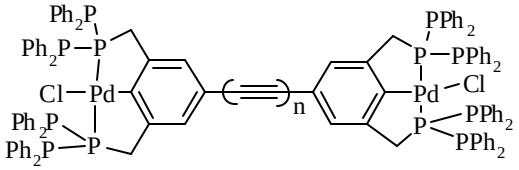


94a X = OAc
94b X = Cl
94c X = OAc
94d X = Cl

Scheme 53: (i) **94b**, Et_3N, DMA, 90^{0}C.

Beletskaya *et al.*

Beletskaya *et al.*[71] demonstrated that cationic derivatives of binuclear conjugated palladacycles **95** (**Scheme 54**) could act as highly active catalyst precursors for the Heck reaction of iodobenzene with styrene or methyl acrylate (**Scheme 34**).

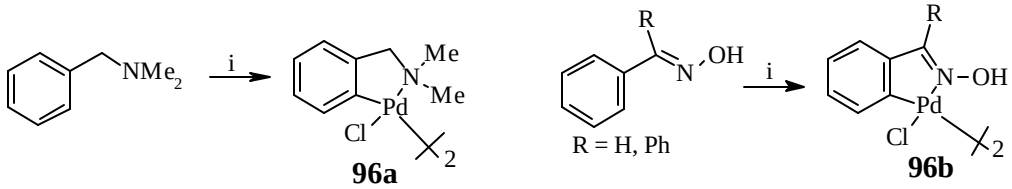


95
n = 1,2

Scheme 54: Binuclear conjugated palladacycles.

Iyer *et al.*[72]

Amine and oxime based palladacycles **96a** and **96b** were found to be excellent catalysts for the Heck reaction. High TON upto 1,45,454 were obtained. (**Scheme 55**)

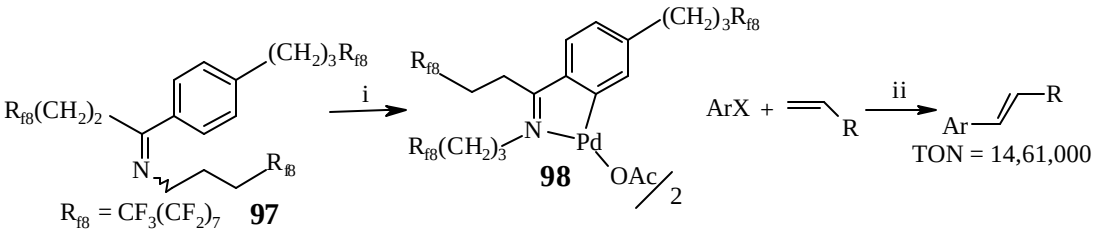


96a **96b**

Scheme 55: (i) Li_2PdCl_4, MeOH, RT.

Gladysz*et al.*[73]

The fluorous Schiff base **97** was prepared and cyclopalladated to afford highly effective catalyst precursor **98** for Heck reaction (**Scheme 56**).



Scheme 56: (i) $Pd(OAc)_2$, AcOH, 95^0C; (ii) cat. **98**, NEt_3, DMF, 140^0C.

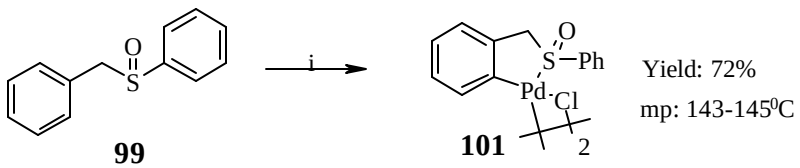
3.1.3 Present Work

3.1.3.1 Objective

The Heck reaction is widely used in academic research institutions for C-C bond formations, but industrial applications are rare. To make the process more economical it is necessary to reduce the amount of catalyst required for impressive conversions. Another challenge of equal importance is the desire to simplify the catalyst by working under phosphine-free conditions.[74] Palladacycles are popular and thoroughly investigated class of organopalladium compounds. The sulfur and nitrogen containing palladacycles are emerged as alternative catalyst precursors for the phosphine palladacycles due to their high stability towards moisture, air and high temperature. There are some reports in the literature, which make use of benzyl sulfides and benzyl amines as ligands for making these palladacycles. However, sulfoxides and sulfimines are not used as ligands for the synthesis of palladacycles. This prompted us to make use of sulfoxide **99** and sulfimine **100** as ligands to make palladacycles **100** and **102** and to explore their utility as catalysts for the Heck reaction and other C-C bond forming reactions such as biaryl synthesis Sonogoshira coupling, *etc*.

3.1.4 Results and Discussion

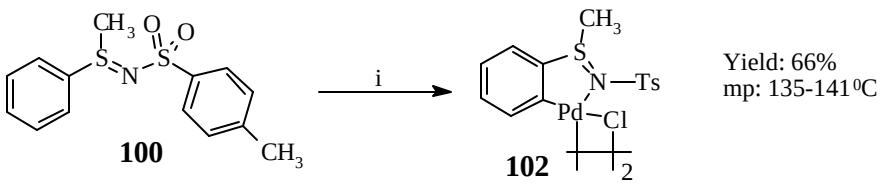
Palladacycles **101** and **102** were readily prepared from sulfoxide **99** and sulfimine **100** respectively using Li_2PdCl_4 as palladium source in good yields (**Schemes 57** and **58**).



99 **101**

Yield: 72%
mp: 143-145^{0}C

Scheme 57: (i) Li_2PdCl_4, MeOH, 25^{0}C, 72 h.



100 **102**

Yield: 66%
mp: 135-141 ^{0}C

Scheme 58: (i) Li_2PdCl_4, NaOAc, 25^0C, 72 h.

Both the palladacycles were characterized by IR, ^{1}H-NMR, ^{13}C-NMR and C, H, Cl, N, S analysis. For example, compound **101** shows two doublets at δ 4.07 and δ 4.25 corresponding to two benzylic protons. Its ^{13}C-NMR spectrum shows signals at δ 61.75 and δ 127.00-144.00 for benzylic and aromatic carbons respectively (**Fig. 11**).

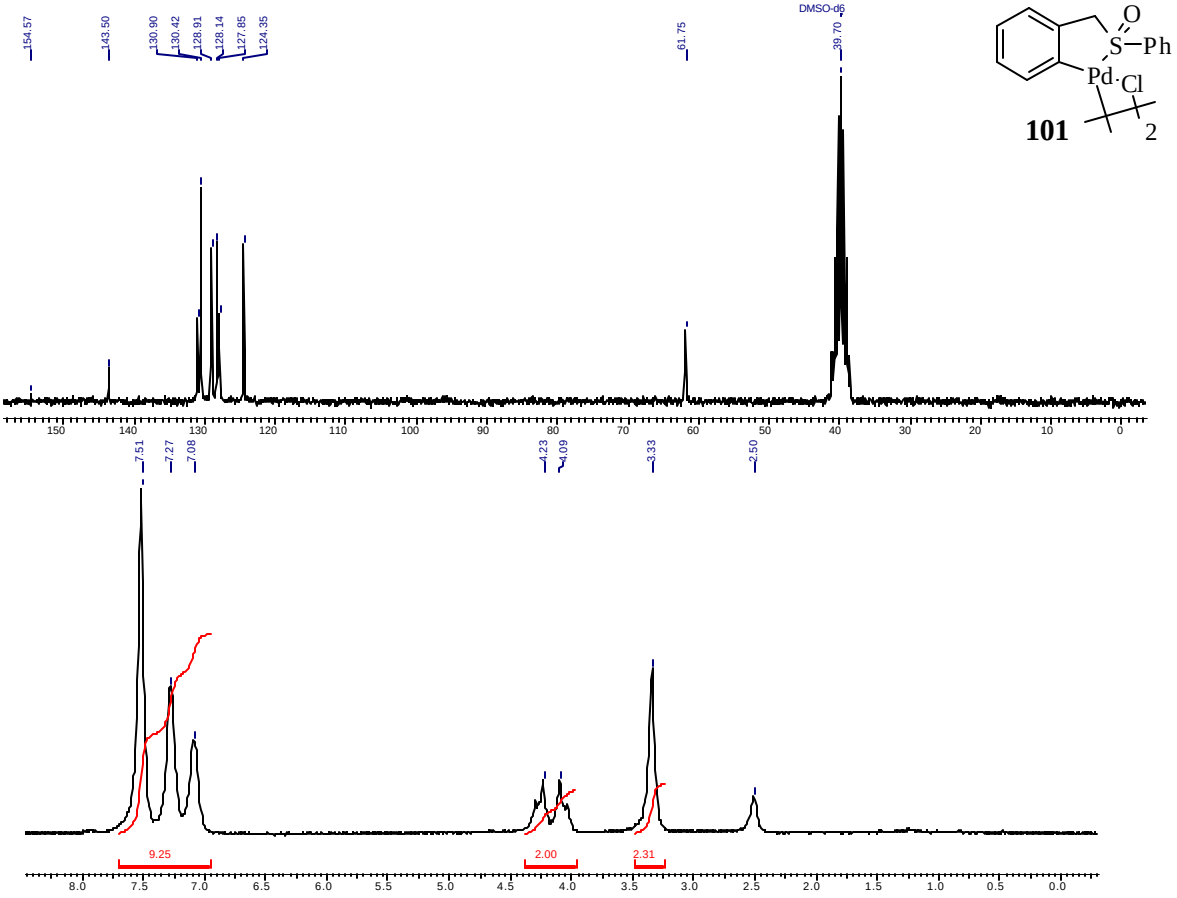


Fig. 11: ^{1}H and ^{13}C NMR spectra of palladacycle 101

^{1}H-NMR Spectrum of compound **102** showed singlets at δ 2.32 and δ 2.95 for aromatic methyl and the CH_3 group attached to nitrogen respectively. Its ^{13}C-NMR

spectrum showed signals at δ 20.88 and 37.42 for CH_3 groups, where as aromatic carbons showed signals in the range δ 125.00 to 142.00 (**Fig. 12**).

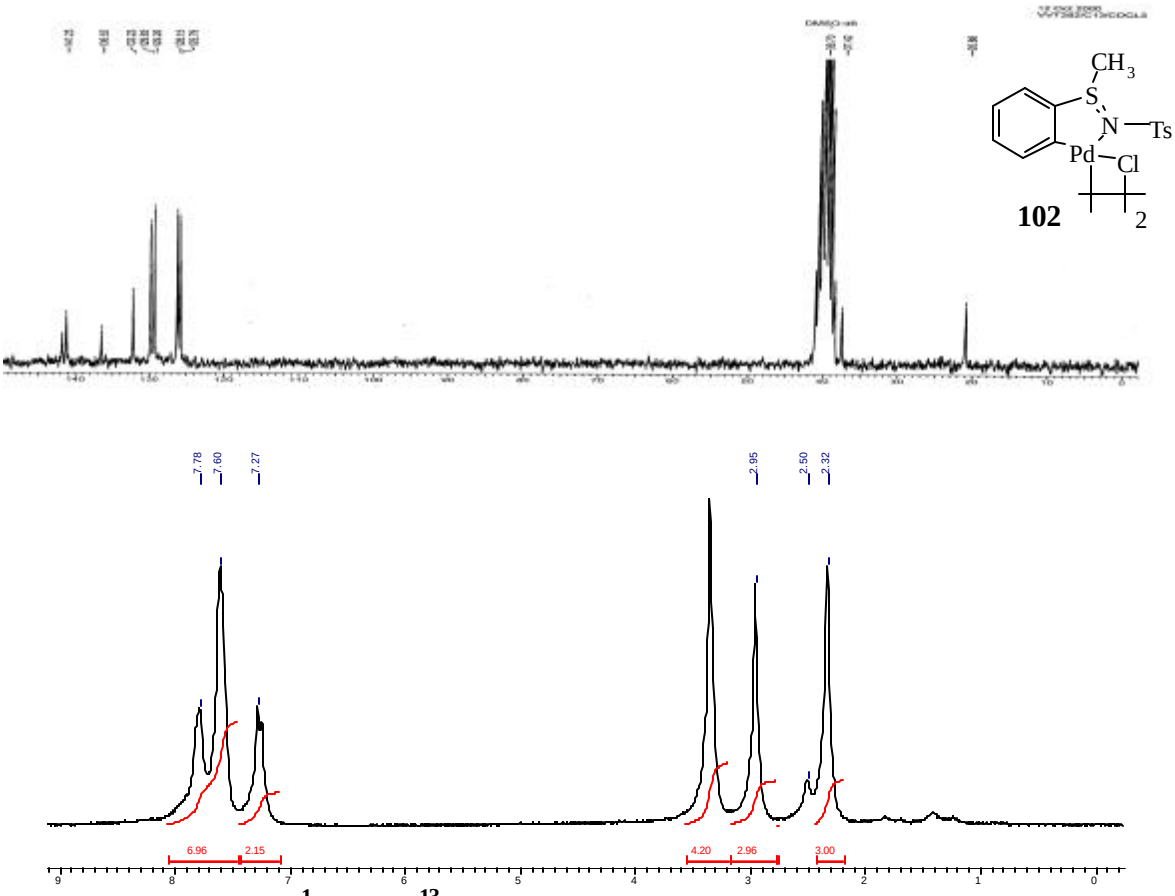
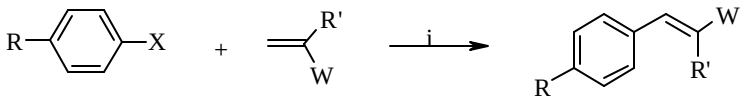


Fig. 12: ^{1}H and ^{13}C NMR spectra of palladacycle 102

We then turned our attention to systematically evaluate the effectiveness of these palladacycles (**101** and **102**) for C-C bond forming reactions.

Both the palladacycles were employed as catalysts for the Heck reaction of aryl halides (X= I, Br) with a variety of olefins (**Scheme 59**).



R = OMe, H, NO_2, Cl, NH_2, *etc*.

X = I, Br, Cl

W = CO_2R, CN, Ph, *etc*.

R' = H or Me

103

60-99% yield

Scheme 59: (i) catalyst **101** or **102**, base (K_2CO_3 or Et_3N), NMP or DMF, 140-150^{0}C.

As can be seen from **Table 1**, a wide range of *p*-substituted halides (entries 1, 15 to 26) were allowed to react with a variety of olefins such as styrene, butylacrylate, acrylonitrile (entry 12), methyl methacrylate (entry 14), methyl acrylate, and ethyl acrylate. The reaction gave yields in the range of 60-99%. NMP, DMF and DMSO can be employed as solvents for the reaction. While DMSO gave very less yield (<10%), DMF and NMP have proved to be solvents of choice for the reaction. Poor yield (37%) was observed when triethylamine was used as base in DMF whereas triethylamine was proved to be a suitable base in case of NMP as a solvent. Other bases such as K_2CO_3 (20% yield) and NaOAc (16% yield) were less effective. NaOAc was better base in DMF (entry 8) than triethylamine (entry 7). Maximum TON was observed in case of reaction of *p*-iodoanisole with *n*-butylacrylate using catalyst **102**. The catalyst **102** has shown better catalytic activity than catalyst **101** (for comparison see entries 2 and 3 or 23 and 24). Catalyst **102** was able to activate bromobenzene also but the yield and TON were poor (entry 26) whereas there was no reaction when chloroarenes such as chlorobenzene, *p*-nitrochlorobenzene were used as substrate. The reaction was also performed at lower temperature (90^0C, entry 25) using acetonitrile as a solvent but it gave very less yield as well as low TON. Reactions were also performed without inert atmosphere (entries 10 and 11) also resulted in sufficiently high TON.

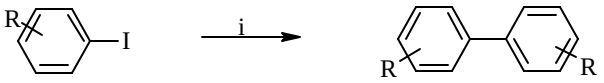
Table 1: Heck reaction (**Scheme 59**) catalyzed by catalysts **101** and **102**[a]

Sr. No	R	W	R'	Catalyst	Catalyst (mmol)	Base	Temp (^{o}C)	Time (h)	Yield[b] (%)	TON[c]
1.	NH_2	Ph	H	**102**	$5x10^{-6}$	NEt_3	140	14	99	3,97,200
2.	H	Ph	H	**101**	$5x10^{-6}$	NEt_3	140	10	82	3,26,400

3.	H	Ph	H	**102**	$5x10^{-6}$	NEt_3	150	10	94	3,92,800
4.	H	Ph	H	**102**	$5x10^{-06}$	K_2CO_3	150	11	20	80,000
5.	H	Ph	H	**102**	$5x10^{-6}$	NaOAc	150	11	38	1,53,600
6.	H	Ph	H	**101**	$5x10^{-6}$	NaOAc	150	23	16	62,400
7.	H	Ph	H	**101**	$5x10^{-6}$	NEt_3	150	24	37	1,49,600[d]
8.	H	Ph	H	**101**	$5x10^{-6}$	NaOAc	150	24	64	2,57,600[d]
9.	H	Ph	H	**102**	$5x10^{-6}$	NEt_3	150	23	70	2,78,400[d]
10.	H	Ph	H	**101**	$5x10^{-6}$	NaOAc	150	24	60	2,41,600[e]
11.	H	Ph	H	**102**	$5x10^{-6}$	NaOAc	150	24	84	3,37,600[e]
12.	H	CN	H	**102**	10^{-5}	NEt_3	150	12	68	1,36,000
13.	H	$CO_2{}^nBu$	H	**102**	$5x10^{-6}$	NEt_3	150	4	97	3,96,000
14.	H	CO_2Me	Me	**102**	$5x10^{-6}$	NEt_3	150	8	67	2,69,000
15.	OMe	$CO_2{}^nBu$	H	**102**	$2x10^{-6}$	NEt_3	150	24	62	6,21,000
16.	OH	$CO_2{}^nBu$	H	**102**	$5x10^{-6}$	NEt_3	150	18	65	2,60,000
17.	OMe	CO_2Et	H	**102**	$5x10^{-6}$	NEt_3	150	10	94	3,76,000
18.	OMe	CO_2Et	H	**101**	$5x10^{-6}$	NEt_3	150	10	78	3,12,000
19.	NO_2	CO_2Me	H	**102**	$5x10^{-6}$	NEt_3	150	8	87	3,48,000
20.	Cl	CO_2Me	H	**102**	$5x10^{-6}$	NEt_3	150	18	86	4,44,000
21.	NO_2	CO_2Et	H	**102**	$5x10^{-6}$	NEt_3	150	12	99	5,94,000[f]
22.	Cl	CO_2Et	H	**102**	$5x10^{-6}$	NEt_3	150	16	88	5,28,900[f]
23.	NO_2	Ph	H	**102**	$5x10^{-6}$	NEt_3	150	25	97	3,88,000
24	NO_2	Ph	H	**101**	$5x10^{-6}$	NEt_3	150	25	86	3,44,000
25.	NO_2	CO_2Et	H	**101**	$5x10^{-6}$	NEt_3	90	52	25	1,00,000[g]
26	H	CO_2Me	H	**102**	$5x10^{-6}$	NEt_3	150	38	21	76,000[h]

(a) reaction conditions: aryl halide (2 mmol), olefin (5 mmol), base (4 mmol), solvent (2 ml); (b) isolated yields; (c) TON= mmol of product/mmol of Pd; (d) in DMF; (e) in DMF without inert atmosphere; (f) reaction was carried out on 3 mmol of aryl halide; (g) in CH_3CN; (h) bromobenzene was used.

The catalyst **102** has also been found to be an effective catalyst for other C-C bond forming reactions such as biaryl formation from aryl halides in presence of hydroquinone (**Scheme 60**).[75] The symmetrical biaryl formation was carried out at relatively milder temperature to produce the corresponding biaryls in moderate yields (**Table 2**).



R = H, OMe, NO_2 **104** Yield: 35-48%

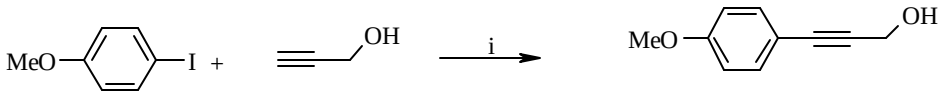
Scheme 60: (i) catalytic **102**, hydroquinone (50 mol%), K_2CO_3, NMP, 125^0C.

Table2: Biaryl formation from aryl halides catalyzed by **102**.[a]

Sr. No.	R	Catalyst (mmol)	Temp. (^{0}C)	Time (h)	Yield[b]	TON[c]
1.	H	0.005	125	24	41	164
2.	4-CN	0.005	125	24	35	140
3.	2-NO_2	0.005	125	22	48	192
4.	4-Cl	0.005	125	24	44	176

(a) reaction conditions: aryl halide (2 mmol), hydroquinone (1 mmol), K_2CO_3 (2 mmol), **102** (0.005 mmol), NMP (2 ml), 125^0C; (b) yields are isolated yields after chromatography; (c) TON= mmol of product/ mmol of Pd.

The Sonogoshira coupling[76] between aryl halide and acetylene derivative (propargyl alcohol) was also attempted using the catalyst **102** (**Scheme 61**). The Sonogoshira coupling was performed at 25^0C using diethylamine both solvent as well as base. However, the reaction took longer time (40 h) giving only 35% yield (TON= 14).



105

Scheme 61: (i) catalyst **102** (0.05 mmol), CuI (10 mol%), Et_2NH, 25^0C.

As can be seen, both the palladacycles **101** and **102** showed remarkably high activity in catalyzing the Heck reaction. The catalysts **101** and **102** are stable at reaction temperature, as the formation of palladium black is not observed even after 24 h, demonstrating their thermal stability. These catalysts were not affected by air or moisture and can be stored at room temperature for a long time.

Mechanism

The mechanism of these reactions involves the mediation of Pd^{II} and Pd^{IV} species. The mechanism for the Heck reaction is shown in **Fig. 13**. In the first step of catalytic cycle (step **I**) haloarene oxidatively add to palladacycle to generate Pd^{IV} species. This then undergoes *syn*-addition on alkene (step **II**). The internal rotation (step **III**) followed by *b*-hydride elimination (step **IV**) results in formation of *trans*-1,2-disubstituted olefin. The catalyst is regenerated after the reductive elimination of HX in presence of base.

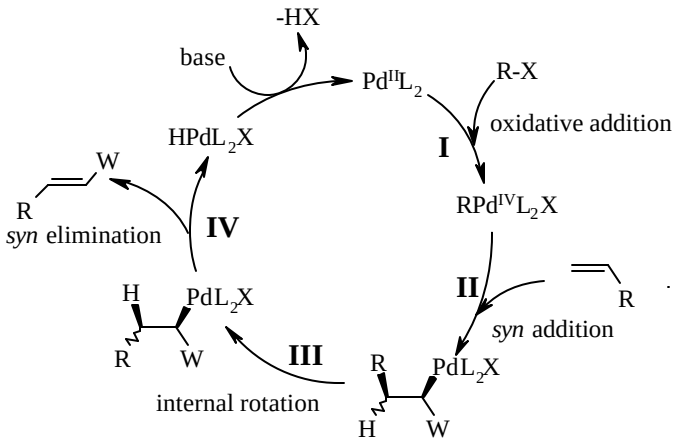


Fig. 13: **Catalytic cycle for the Heck reaction**

A plausible mechanism for hydroquinone-mediated palladium catalyzed biaryl formation is shown in **Fig. 14**. The first step involves the oxidative addition of aryl halide to Pd^{II} species to form Pd^{IV} species **A**. Under basic conditions, hydroquinone displaces the iodide group to form the species **B**. This Pd^{IV} species **B** then undergoes the elimination of benzoquinone to form anionic aryl palladium species **C**. The reaction of **C** with ArI followed by the loss of I^- would produce diaryl palladium species **D**, from which reductive elimination of Pd^{I} would regenerate the catalyst and the corresponding biaryl product.

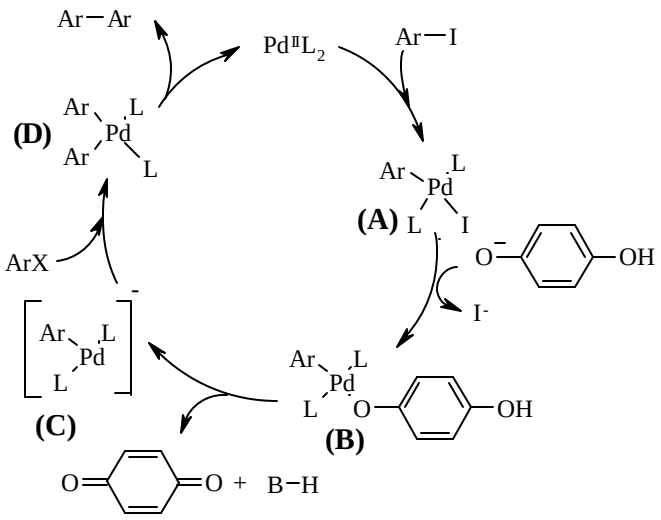


Fig. 14: **Plausible catalytic cycle for Pd-catalyzed biaryl formation**

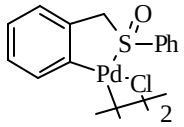
3.1.5 Conclusion

We have synthesized novel, air, and moisture and thermally stable sulfur and nitrogen palladacycles (**101** and **102**) from easily available precursors and employed them as effective catalysts for the Heck reaction as well as other C-C bond forming reactions such as biaryl formation from aryl iodides and Sonogoshira coupling. It is remarkable that the palladacycle **102** gave excellent yields (upto 99%) as well as high TON (upto 6,21,000).

3.1.6 Experimental Section

Preparation of Palladacycle 101:

Two-necked 25-ml RB flask was charged with $PdCl_2$ (0.177 g, 1 mmol), LiCl (0.100 g, 2.4 mmol) and MeOH (2 ml); the resulting reaction mixture was stirred under argon atmosphere at 25^0C for 2.5 h. Then to the same reaction mixture was added a solution of phenyl benzyl sulfoxide (**99**, 0.216 g, 1 mmol) in MeOH (2 ml). The stirring was continued at 25^0C for 72 h (monitored by TLC). Then distilled water (8 ml) was added to the reaction mixture, which resulted in precipitation of yellow colored solid. The solid was filtered on a sintered funnel, washed with distilled water and dried under reduced pressure (5 mm) for 3 h to afford complex **101** (0.258 g, 72% yield) as a yellow colored solid.

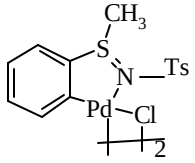


101

Yield: 72%; **mp**: 143-146^{0}C; **IR** (KBr, cm^{-1}): 495, 694, 744, 765, 1037, 1085, 1442, 1456, 1494, 2910, 2960, 3060; **^{1}H-NMR** (200 MHz, DMSO-d_6): δ 4.06 (d, *J* = 12.15 Hz, 1H), 4.25 (d, *J* = 12.15 Hz, 1H), 7.08-7.51 (m, 9H); **^{13}C-NMR** (50 MHz, DMSO-d_6): δ 61.75, 124.35, 127.85, 128.14, 128.90, 130.42, 130.90, 143.50; **Analysis**: $C_{13}H_{11}ClSOPd$ requires C, 43.72; H, 3.10; Cl, 9.27; S, 8.98; found C, 43.42; H, 3.13; Cl, 9.58; S, 8.89%.

Preparation of Palladacycle 102:

Two-necked 25-ml RB flask was charged with $PdCl_2$ (0.177 g, 1 mmol), LiCl (0.100 g, 2.4 mmol) and MeOH (2 ml); the resulting reaction mixture was stirred under argon atmosphere at 25^0C for 2.5 h. Then to the same reaction mixture was added NaOAc (0.123 g, 1.5 mmol), and a solution of sulfimine **100** (0.293 g, 1 mmol) in MeOH (2 ml). The resulting reaction mixture was stirred at 25^0C for 72 h. Then, distilled water (6 ml) was added to it and resulting solid was filtered on sintered funnel, washed with water and dried under reduced pressure (5 mm) for 3 h to afford palladacycle **102** as brown colored solid (0.286 g, 66%).



102

Yield: 66%; **mp**: 135-141^{0}C (decomp.); **IR** (KBr, cm^{-1}): 547, 576, 688, 746, 825, 933, 1087, 1141, 1280, 1296, 1446, 1539, 1595, 2866, 2922, 3024; **^{1}H-NMR** (200 MHz, DMSO-d_6): δ 2.32 (s, 3H), 2.95 (s, 3H), 7.23 (d, *J* = 8.14 Hz, 2H), 7.60-7.78 (m, 6H); **^{13}C-**

NMR (50 MHz, DMSO-d_6): δ 20.88, 37.42, 125.79, 126.15, 129.28, 129.83, 132.22, 136.22, 141.23, 141.30; **Analysis**: $C_{14}H_{14}ClNS_2O_2Pd$ requires C, 38.72; H, 3.25; Cl, 8.16; N, 3.23; S, 14.77; found C, 38.68; H, 3.50; Cl, 8.24; N, 3.34; S, 14.77%.

General experimental procedure for the Heck reaction:

A 25 ml two-necked RB flask with double walled water condenser was charged with aryl halide (2.0 mmol), triethylamine (0.303 g, 3.0 mmol), olefin (2.0 mmol) and NMP (N-methylpyrrolidone) (2 ml). To this 5 μL (5x 10^{-6} mmol) 0.001 M solution of catalyst (**101** or **102**) in NMP was added *via* micro syringe under argon atmosphere. The reaction mixture was heated in an oil bath at specified temperature and time (**Table 1**) (the progress of the reaction was monitored by TLC or GC). The reaction mixture was then allowed to cool to room temperature. It was quenched with 10% HCl (5 ml) and extracted with ethyl acetate (3 x 10 ml). The combined organic extracts were washed with water, brine and dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford crude product. It was then purified by column chromatography on silica gel using pet. ether and ethyl acetate as eluents to afford the products in pure form.

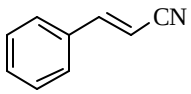
***(E)*-1-(4-Aminophenyl)-2-phenylethylene: Yield**: 99%; **mp**: 148-150^{0}C; **IR** (Nujol, cm^{-1}): 692, 756, 821, 970, 1178, 1286, 1377, 1465, 1515, 1589, 1616, 2854, 2923, 3361, 3448; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 6.67 (d, *J* = 9.13 Hz, 2H), 6.98 (d, *J* = 9.13 Hz, 2H), 7.25-7.49 (m, 5H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 115.15, 125.08, 126.07, 126.84, 127.73, 127.95, 128.57, 137.94, 146.14; **MS** m/z (% rel. intensity): 195 (100, M^+), 177 (13), 165 (13), 97 (16), 89 (12), 77 (10); **Analysis**: $C_{14}H_{13}N$ requires C, 86.12; H, 6.71; N, 7.17; found C, 86.22; H, 6.78; N, 7.21%.

***(E)*-1-(4-Nitrophenyl)-2-phenylethylene: Yield**: 97%; **mp**: 155-157^{0}C; **IR** (Nujol, cm^{-1}): 788, 1378, 1449, 1463, 1510, 1596, 1632, 2854, 2925, 2966; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 7.12 (d, *J* = 16.12 Hz, 1H), 7.24 (d, *J* = 16.12 Hz, 1H), 7.31-7.58 (m, 7H), 8.00 (d, *J* = 8.60 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 123.84, 126.12, 126.67, 126.82, 128.58, 128.65, 133.17, 136.06, 143.71, 146.62; **MS** m/z (% rel. intensity): 225 (100, M^+), 179 (77), 165 (8), 152 (14), 89 (10), 77 (6); **Analysis**: $C_{14}H_{11}NO_2$ requires C, 74.65; H, 4.92; N, 6.22; found C, 74.62; H, 4.88; N, 6.24%.

***trans*-Stilbene: Yield**: 99%; **mp**: 123-124^{0}C; **IR** (Nujol, cm^{-1}): 766, 962, 1378, 1452, 1464, 1496, 1598, 2866, 2869, 2926, 2966; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 7.07 (s, 2H), 7.22-7.36 (m, 6H), 7.48 (d, *J* = 8.03 Hz, 4H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 126.53,

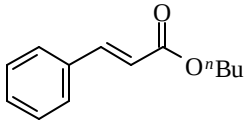
127.61, 128.67, 137.36; **MS** m/z (% rel. intensity): 180 (M^+, 100), 165 (31), 152 (6), 89 (14), 76 (10); **Analysis**: $C_{14}H_{12}$ requires C, 93.29; H, 6.71; found C, 93.24; H, 6.67%.

***(E)*-2-Phenyl acrylonitrile**



Yield: 68%; **gum**; **IR** (Neat, cm^{-1}): 690, 749, 967, 1206, 1449, 1578, 1622, 2218, 3020, 3062; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 5.86 (d, *J* = 17.11 Hz, 1H), 7.32-7.40 (m, 6H); **^{13}C-NMR** (50 MHz, $CDCl_3$): 94.86, 95.86, 117.58, 127.06, 128.79, 130.81, 133.31, 149.96; **MS** m/z (% rel. intensity): 129 (100, M^+), 102 (47), 76 (23), 63 (20); **Analysis**: C_9H_7N requires C, 83.69; H, 5.46; N, 10.85; found C, 83.69; H, 5.26; N, 10.78%.

***(E)*-*n*-Butyl 3-phenyl-2-propeonate**



Yield: 97%; **gum**; **IR** (Neat, cm^{-1}): 572, 684, 711, 979, 1026, 1172, 1201, 1255, 1280, 1311, 1326, 1384, 1450, 1496, 1577, 1639, 1712, 2873, 2933, 2960; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.90 (t, *J* = 7.12 Hz, 3H), 1.27-1.42 (m, 2H), 1.54-1.68 (m, 2H), 4.12 (t, *J* = 7.12 Hz, 2H), 6.33 (d, *J* = 16.14 Hz, 1H), 7.25-7.45 (m, 5H), 7.57 (d, *J* = 16.14 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 13.37, 18.85, 30.50, 63.77, 118.10, 127.65, 128.40, 129.71, 134.27, 144.07, 166.17; **MS** m/z (% rel. intensity): 204 (12, M^+), 148 (57), 131 (93), 103 (80), 77 (100); **Analysis**: $C_{13}H_{16}O_2$ requires C, 76.44; H, 7.90; found C, 76.41; H, 7.86%.

***(E)*-*n*-Butyl 3-(4-methoxyphenyl)-2-propeonate**: **Yield**: 94%; **gum**; **IR** (Neat, cm^{-1}): 580, 720, 780, 979, 1186, 1210, 1276, 1329, 1455, 1498, 1579, 1646, 1709, 2890, 2943; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.97 (t, *J* = 7.20 Hz, 3H), 1.38-1.49 (m, 2H), 1.64-1.71 (m, 2H), 3.81 (s, 3H), 4.17 (t, *J* = 7.14 Hz, 2H), 6.26 (d, *J* = 16.11 Hz, 1H), 6.86 (d, *J* = 8.18 Hz, 2H), 7.44 (d, *J* = 8.18 Hz, 2H), 7.60 (d, *J* = 16.11 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 13.59, 19.11, 30.83, 54.98, 63.80, 114.20, 115.89, 127.28, 129.45, 143.90, 161.29, 166.69; **MS** m/z (% rel. intensity): 234 (52, M^+), 178 (100), 161 (81), 133 (71), 121 (39), 105 (23), 90 (65), 77 (64), 63 (45); **Analysis**: $C_{14}H_{18}O_3$ requires C, 71.77; H, 7.74; found C, 71.73; H, 7.78%.

***(E)*-*n*-Butyl 3-(4-hydroxyphenyl)-2-propeonate**: **Yield**: 65%; **gum**; **IR** ($CHCl_3$, cm^{-1}): 578, 690, 780, 1030, 1173, 1210, 1278, 1320, 1498, 1580, 1620, 1723, 2873, 2933, 3260; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.95 (t, *J* = 7.13 Hz, 3H), 1.37-1.48 (m, 2H), 1.62-1.72

(m, 2H), 4.21 (t, *J* = 7.11 Hz, 2H), 6.30 (d, *J* = 16.16 Hz, 1H), 6.86 (d, *J* = 8.14 Hz, 2H), 7.41 (d, *J* = 8.14 Hz, 2H), 7.63 (d, *J* = 16.16 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 13.63, 19.11, 30.69, 64.65, 115.08, 115.34, 155.96, 126.77, 129.56, 130.00, 145.00, 158.35, 168.38; **MS** m/z (% rel. intensity): 220 (M^+, 17), 164 (87), 147 (100), 119 (63), 107 (18), 91 (73), 65 (50); **Analysis**: $C_{13}H_{16}O_3$ requires C, 70.89; H, 7.52; found C, 70.78; H, 7.33%.

***(E)*-Methyl 3-phenyl-2-propeonate (Methyl *trans*-cinnamate)**: **Yield**: 67%; **mp**: 36-38^{0}C; **IR** (Nujol, cm^{-1}): 689, 716, 776, 986, 1014, 1030, 1169, 1183, 1202, 1514, 1531, 1722, 2863, 2946, 3029; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.81 (s, 3H), 6.45 (d, *J* = 16.08 Hz, 1H), 7.29-7.64 (m, 5H), 7.73 (d, *J* = 16.08 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 51.54, 117.92, 128.08, 128.89, 130.26, 134.49, 144.79, 167.25; **MS** m/z (% rel. intensity): 162 (M^+, 100), 131 (52), 103 (28), 77 (17); **Analysis**: $C_{10}H_{10}O_2$ requires C, 74.06; H, 6.21; found C, 74.12; H, 6.18%.

***(E)*-Methyl 3-(4-nitrophenyl)-2-propeonate**: **Yield**: 87%; **mp**: 160-161^{0}C; **IR** (Nujol, cm^{-1}): 875, 1010, 1178, 1232, 1356, 1532, 1620, 1656, 1726, 2868, 2980, 3056; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.84 (s, 3H), 6.57 (d, *J* = 16.11 Hz, 1H), 7.68 (d, *J* = 8.13 Hz, 2H), 7.73 (d, *J* = 16.11 Hz, 1H), 8.25 (*J* = 8.13 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 51.60, 121.62, 123.76, 128.42, 140.22, 141.80, 149.10, 166.58; **MS** m/z (% rel. intensity): 207 (7, M^+), 176 (60), 152 (12), 118 (8), 106 (12), 90 (100), 77 (26), 65 (12); **Analysis**: $C_{10}H_9NO_4$ requires C, 57.97; H, 4.38; N, 6.76; found C, 57.89; H, 4.41; N, 6.77%.

***(E)*-Methyl 3-(4-chlorophenyl)-2-propeonate**: **Yield**: 86%; **gum**; **IR** ($CHCl_3$, cm^{-1}): 575, 695, 1032, 1068, 1192, 1212, 1318, 1455, 1568, 1630, 1722, 2874, 2960; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.81 (s, 3H), 6.40 (d, *J* = 16.11 Hz, 1H), 7.35 (d, *J* = 9.21 Hz, 2H), 7.45 (d, *J* = 9.21 Hz, 2H), 7.64 (d, *J* = 16.11 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 51.31, 118.06, 128.31, 128.76, 130.59, 132.54, 135.74, 142.91, 166.62; **MS** m/z (% rel. intensity): 196 (M^+, 6), 192 (68), 161 (100), 133 (42), 118 (23), 89 (35); **Analysis**: $C_{10}H_9ClO_2$ requires C, 61.09; H, 4.61; Cl, 18.03; found C, 61.12; H, 4.55; Cl, 18.14%.

***(E)*-Methyl 2-methyl-3-phenyl-2-propeonate**: **Yield**: 67%; **gum**; **IR** (Neat, $CHCl_3$): 689, 716, 776, 986, 1014, 1030, 1169, 1183, 1202, 1514, 1531, 1722, 2863, 2946, 3029; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.11 (s, 3H), 3.79 (s, 3H), 7.33-7.37 (m, 5H), 7.67 (s, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 13.92, 51.64, 128.28, 129.49, 136.00, 138.75, 168.53; **MS** m/z (% rel. intensity): 176 (M^+, 60), 161 (5), 145 (28), 115 (100), 91 (41), 77 (14); **Analysis**: $C_{11}H_{12}O_2$ requires C, 74.98; H, 6.86; found C, 74.87; H, 6.88%.

***(E)*-Ethyl 3-(4-methoxyphenyl)-2-propeonate**: **Yield**: 94%; **gum**; **IR** (Neat, $CHCl_3$): 820, 844, 970, 1020, 1177, 1298, 1340, 1435, 1510, 1580, 1620, 1722, 2998, 3018; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.33 (t, *J* = 6.24 Hz, 3H), 3.82 (s, 3H), 4.24 (q, *J* = 6.24 Hz, 2H), 6.30 (d, *J* = 16.12 Hz, 1H), 6.89 (d, *J* = 8.18 Hz, 2H), 7.46 (d, *J* = 8.18 Hz, 2H), 7.64 (d, *J* = 16.12 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 13.96, 54.84, 59.83, 113.94, 115.41, 126.81, 129.31, 143.83, 161.03, 166.80; **MS** m/z (% rel. intensity): 206 (100, M^+), 178 (19), 161 (99), 134 (57), 118 (20), 89 (44), 77 (38), 63 (51); **Analysis**: $C_{12}H_{14}O_3$ requires C, 69.88; H, 6.85; found C, 69.79; H, 6.82%.

***(E)*-Ethyl 3-(4-nitrophenyl)-2-propeonate**: **Yield**: 99%; **mp**: 139-140^{0}C; **IR** (Nujol, cm^{-1}): 873, 1000, 1166, 1211, 1356, 1525, 1644, 1720, 2855, 2956, 3075; **^{1}H-NMR** (200 MHz, $CDCl_3$): 1.26 (t, *J* = 6.28 Hz, 3H), 4.21 (q, *J* = 6.28 Hz, 2H), 6.84 (d, *J* = 16.19 Hz, 1H), 7.72 (d, *J* = 16.19 Hz, 1H), 8.00 (d, *J* = 9.12 Hz, 2H), 8.22 (d, *J* = 9.12 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): 13.96, 60.25, 122.30, 123.72, 129.23, 140.31, 141.56, 147.90, 165.48; **MS** m/z (% rel. intensity): 221 (M^+, 31), 193 (32), 177 (12), 176 (100), 160 (16), 129 (19), 102 (33), 76 (10); **Analysis**: $C_{11}H_{11}NO_4$ requires C, 59.73; H, 5.01; N, 6.33; found C, 59.68; H, 5.21; N, 6.25%.

***(E)*-Ethyl 3-(4-chlorophenyl)-2-propeonate**: **Yield**: 88%; **gum**; **IR** (Neat, cm^{-1}): 572, 685, 712, 998, 1064, 1172, 1202, 1312, 1450, 1578, 1640, 1720, 2874, 2933, 2960; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.33 (t, *J* = 7.14 Hz, 3H), 4.27 (q, *J* = 7.14 Hz, 2H), 6.40 (d, *J* = 16.15 Hz, 1H), 7.34 (d, *J* = 9.11 Hz, 2H), 7.45 (d, *J* = 9.11 Hz, 2H), 7.63 (d, *J* = 16.15 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 13.92, 60.13, 118.54, 128.83, 132.61, 135.63, 142.58, 166.10; **MS** m/z (% rel. intensity): 210 (M^+, 50), 182 (30), 165 (100), 155 (70), 139 (55), 101 (50), 75 (40); **Analysis**: $C_{11}H_{11}ClO_2$ requires C, 62.72; H, 5.25; Cl, 16.83; found C, 62.47; H, 5.12; Cl, 16.68%.

General experimental procedure for biaryl formation:

A 25 ml two-necked RB flask charged with aryl iodide (2.0 mmol), hydroquinone (0.110 g, 1.0 mmol), K_2CO_3 (0.280 g, 2 mmol) and catalyst **102** (0.002 g, 0.005 mmol), NMP (2 ml) was added to it. The reaction mixture was heated under inert atmosphere at 125^{0}C for a specified time (**Table 2**). The reaction mixture was allowed to cool to room temperature. 10% HCl solution (4 ml) was added to it and extracted with ethyl acetate (3x15 ml). The combined organic extracts were washed with water, brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was

purified by column chromatography on silica gel using pet. ether: ethyl acetate (9:1) as eluent to give pure products.

Biphenyl: **Yield**: 41%; **mp**: 71-72^{0}C; **IR** (Nujol, cm^{-1}): 698, 734, 1008, 1074, 1261, 1377, 1431, 1463, 1481, 1568, 2854, 2923, 2954; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 7.37-7.47 (m, 10H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 126.78, 126.85, 128.35, 140.83; **MS** m/z (% rel. intensity): 154 (M^+, 100), 126 (9), 115 (10), 102 (7), 76 (38), 63 (7); **Analysis**: $C_{12}H_{10}$ requires C, 93.46; H, 6.54; found C, 93.43; H, 6.52%.

2,2'-Dinitrobiphenyl: **Yield**: 48%; **mp**: 122-123^{0}C; **IR** (Nujol, cm^{-1}): 681, 747, 767, 786, 861, 1266, 1300, 1364, 1377, 1468, 1521, 2726, 2924, 2954; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 7.31 (d, *J* = 8.35 Hz, 2H), 7.59-7.88 (m, 4H), 8.20-8.25 (m, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 124.74, 129.12, 130.96, 133.38, 134.17, 147.28; **MS** m/z (% rel. intensity): 198 (M^+, 100), 168 (34), 141 (11), 139 (33), 115 (27), 63 (10); **Analysis**: $C_{12}H_8N_2O_4$ requires C, 59.02; H, 3.30; N, 11.47; found C, 58.88; H, 3.27; N, 11.39%.

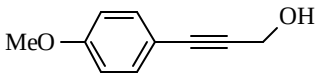
4,4'Biphenyldicarbonitrile: **Yield**: 35%; **mp**: 231-232^{0}C; **IR** (Nujol, cm^{-1}): 816, 1377, 1404, 1492, 1604, 2287, 2855, 2924; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 7.70-7.82 (m, 8H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 112.48, 118.41, 127.98, 132.90, 143.55; **MS** m/z (% rel. intensity): 204 (M^+, 100), 177 (8), 151 (2), 102 (4), 88 (4), 75 (5); **Analysis**: $C_{14}H_8N_2$ requires C, 82.34; H, 3.95; N, 13.71; found C, 82.33; H, 3.98; N, 13.69%.

4,4'-Dichlorobiphenyl: **Yield**: 44%; **mp**: 148-149^{0}C; **IR** (Nujol, cm^{-1}): 572, 685, 712, 998, 1064, 1172, 1202, 1312, 1450, 2854, 2923, 2954; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 7.34-7.38 (m, 4H), 7.40-7.45 (m, 4H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 127.89, 128.74, 133.55, 138.21; **Analysis**: $C_{12}H_8Cl_2$ requires C, 64.60; H, 3.61; Cl, 31.78; found C, 64.63; H, 3.57; Cl, 31.68%.

Sonogoshira coupling of *p*-iodoanisole with propargyl alcohol:

A two-necked 25 ml RB flask was charged with *p*-iodoanisole (0.468 g, 2 mmol), propargyl alcohol (0.168 g, 3 mmol), CuI (0.040 g, 0.2 mmol), catalyst **102** (0.22 g, 0.05 mmol) and diethylamine (8.0 ml). The resulting mixture was stirred at 25^0C for 40 h. Then the reaction was diluted with ethyl acetate (20 ml), washed with 10% HCl (10 ml), water, brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give black colored thick oil. This crude product was purified on column chromatography using 20% ethyl acetate in pet. ether as eluent to afford pure **105** (0.113 g, 35%) as pale yellow colored solid.

3-(4-Methoxyphenyl)-propargyl alcohol (105)



Yield: 35%; **mp**: 74-75^{0}C; **IR** ($CHCl_3$, cm^{-1}): 669, 757, 833, 1033, 1172, 1215, 1249, 1292, 1463, 1510, 1606, 2856, 2927, 3018, 3421; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.78 (s, 3H), 4.44 (s, 2H), 6.79 (d, *J* = 8.21 Hz, 2H), 7.33 (d, *J* = 8.21 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 51.05, 54.87, 85.27, 86.12, 113.76, 114.79, 132.98, 159.45; **MS** m/z (% rel. intensity): 162 (M^+, 100), 145 (33), 131 (40), 108 (30), 102 (33), 91 (57), 77 (30), 63 (43); **Analysis**: $C_{10}H_{10}O_2$ requires C, 74.06; H, 6.21; found C, 74.12; H, 6.23%.

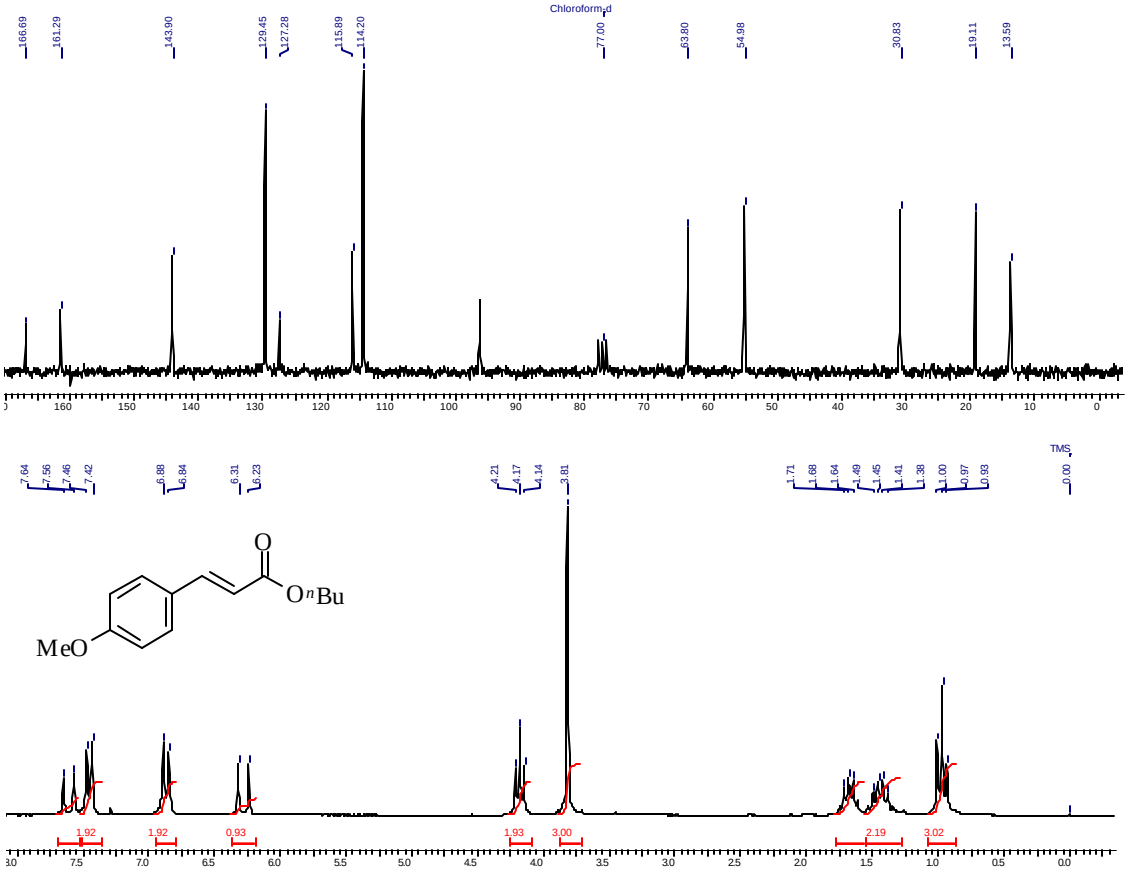
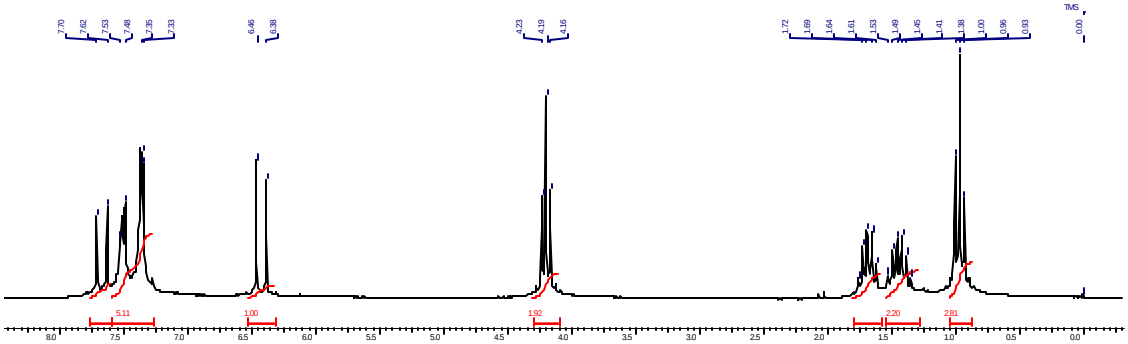


Fig. 15: ^{1}H and ^{13}C-NMR spectrum of (E)-^{n}butyl 3-(4-methoxyphenyl)-2-propeonate



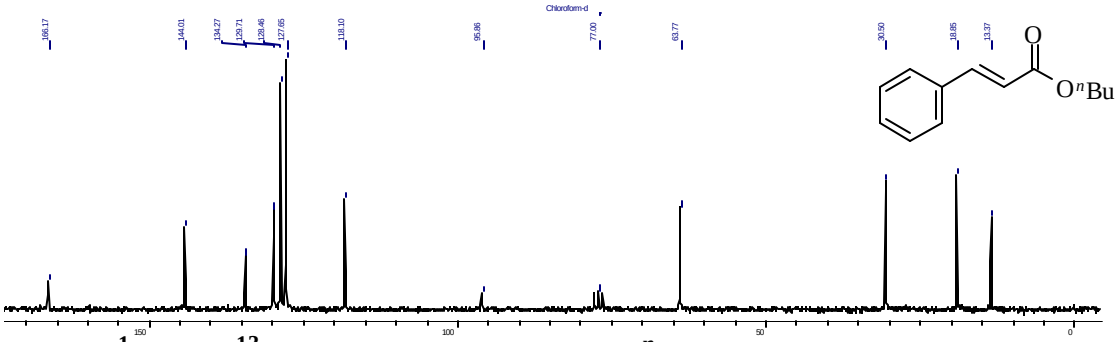


Fig. 16: ^{1}H and ^{13}C-NMR spectrum of (E)-^{n}butyl 3-phenyl-2-propeonate

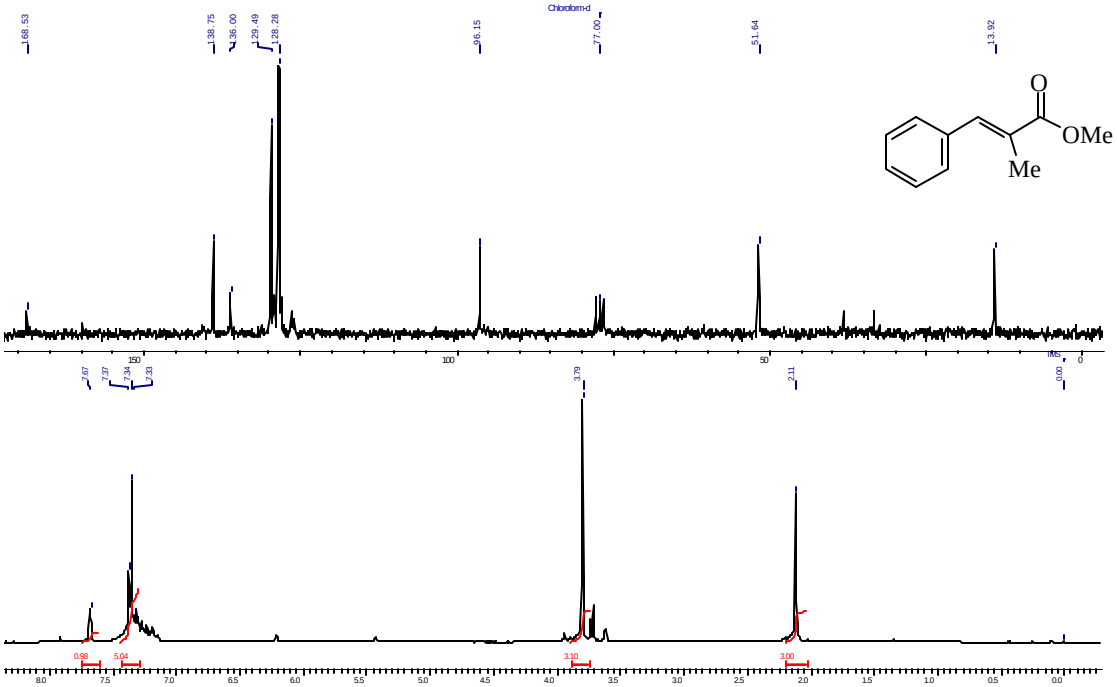


Fig. 17: ^{1}H and ^{13}C-NMR spectra of *(E)*-methyl 2-methyl-3-phenyl-2-propeonate

3.1.7 References

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CHAPTER 4

Transition Metal Catalyzed *S-O*, *C-N*, *C-Br* Bond Formation and NBS-Catalyzed Aziridination of Olefins

SECTION-I

Tungsten Catalyzed Asymmetric Sulfoxidation and Kinetic Resolution of Aryl Alkyl Sulfides using Chiral Cinchona Alkaloids

4.0.1 Introduction

The oxidation of thioethers to give either sulfoxide or sulfone is one of the important synthetic reactions in organic chemistry. Gentle oxidation to sulfoxide alone requires highly selective conditions, which are generally difficult to achieve, whereas complete oxidation to sulfone is much easier to achieve. Asymmetric oxidation of thioethers to chiral sulfoxides has gained considerable importance in past few years. Chiral sulfoxides are important class of compounds that are finding increasing uses as chiral auxiliaries in asymmetric synthesis.[1] Current interest in chiral sulfoxides is also due to the existence of products with biological properties that contains sulfinyl group for e.g. anti-ulcer drugs such as lansoprazole, omeprazole, leminoprazole, rabeprazole, NMDA $NR_{1A/2B}$ antagonist PD-196860, *etc*. (**Fig. 1**).

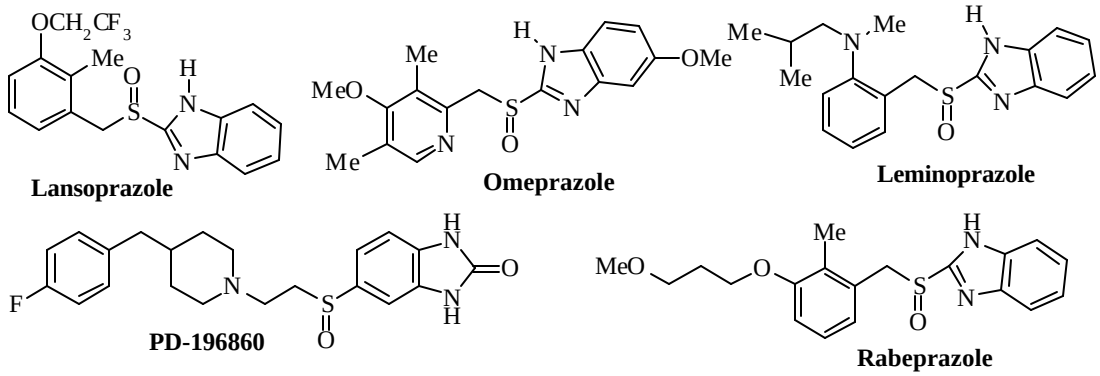


Fig. 1: **Some of anti-ulcer drugs with sulfinyl group.**

Chiral sulfoxides are also important chiral synthons for the asymmetric C-C bond formation,[1,2] These compounds are of interest in the pharmaceutical industry also.[3]

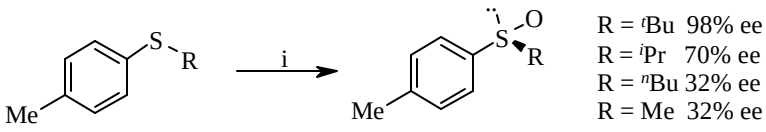
4.0.2 Review of Literature

Asymmetric oxidation of prochiral sulfides is in principle a straightforward route to chiral sulfoxides. Unfortunately, for a long time the enantioselectivity of such reactions remained very low. Renewed interest came in the early 80's with progress obtained in

various approaches. Among these methods, oxidation by hydroperoxides in the presence of chiral complexes, the use of chiral oxaziridines, electrochemical oxidation with chiral electrodes and enzymatic or microbial reactions seems to be the most attractive for the synthesis. There are very few examples of procedures based on kinetic resolution of racemic sulfoxides known in the literature, which involve employment of chiral Ti or Mn-complexes as catalysts.

Ross *et al.*

Ross *et al.*[4] have reported microbial oxidation of sulfides (**Scheme 1**). Enantioselectivities were very high but the yields were low (upto 30%).



R = ^{t}Bu 98% ee
R = ^{i}Pr 70% ee
R = ^{n}Bu 32% ee
R = Me 32% ee

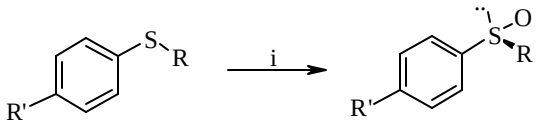
Scheme 1: (i) *Aspergillus niger*.

Czarnik A. W.[5]

A "template directed" asymmetric sulfoxidation has been attempted in the presence of excess of *b*-cyclodextrin. Oxidation reactions were performed by using *m*-CPBA in water. The best result (33% ee) was attained for *m-t*-butyphenylethyl sulfoxide.

Ohta *et al.*[6]

Corynebacterium equi IFO 3730 gave high ee's in the oxidation of aryl alkyl sulfides with no formation of sulfones (**Scheme 2**).



R' = H, R = ^{n}Bu 29% yield, 100% ee
R' = H, R = Me 100% yield, 70% ee
R' = R = Me 33% yield, 82% ee

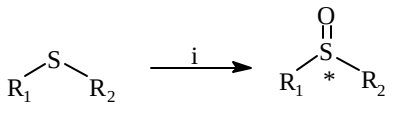
Scheme 2: (i) *Corynebacterium equi* IFO 3730.

Drabowicz *et al.*

Drabowicz *et al.*[7] observed modest asymmetric induction (27% ee) in oxidation of Ph-S-^{n}Bu with H_2O_2 in the presence of *b*-cyclodextrin.

Furia *et al.*

Furia *et al.*[8] reported asymmetric sulfoxidation of thioethers using stoichiometric amount of Sharpless' asymmetric epoxidation reagent (**Scheme 3**).



R_1 = *p*-tolyl, R_2 = Me	88.3% ee
R_1 = phenyl, R_2 = ^{t}Bu	34.5% ee
R_1 = 4-Cl-C_6H_4, R_2 = CH_2CH_2OH	14% ee
R_1 = Ph-CH_2, R_2 = Me	46% ee

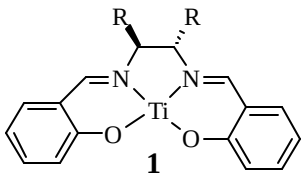
Scheme 3: (i) Ti($O^{i}Pr$)$_4$, (+)-diethyl tartarate, TBHP (1:2:1:4), CH_2Cl_2 or toluene, -20^{0}C.

Komori *et al.* [9]

The authors prepared various types of polyamino acid coated electrodes. The electrodes were platinum or graphite plates and in some cases polypyrrole films were coated or covalently bound to the base electrode surface. Oxidations were carried out by means of a controlled potential method in acetonitrile containing $^{n}Bu_4NBF_4$ and water. The best results were obtained for sulfides bearing bulky alkyl groups (e.g. Ph-S-^{t}Bu gave 93% ee).

Pasini *et al.*

Pasini *et al.*[10] have developed chiral oxotitanium(IV)-Schiff base complexes **1** (**Scheme 4**), (catalyst:substrate ratio = 1:1000 to 1:1500) for the oxidation of Ph-S-Me with 35% H_2O_2 but ee was low (<20%) and some sulfone is also formed.



1

R = Me or Ph

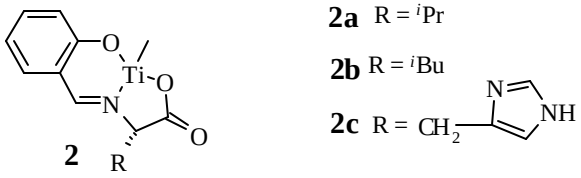
Scheme 4: Chiral Ti-Schiff base complex for asymmetric sulfoxidation.

Yamagishi *et al.* [11]

Clay-chiral chelate adducts were also used as templates in the presence of an oxidant such as $NaIO_4$, *m*-CPBA or $K_2S_2O_8$ in water. Δ-$Ni(phen)_3^{+}$-montmorillonite clay showed an appreciable enantioselectivity. Cyclohexyl-S-Ph at room temperature gave the corresponding sulfoxide in 78% ee (90% yield) using $NaIO_4$ and 62% ee (90% yield) using *m*-CPBA. Unfortunately, the sulfide must be preadsorbed on montmorillonite clay, with the latter in large excess.

Colonna *et al.*

Colonna *et al.*[12a] have investigated a wide range of sulfides to study periodate oxidation catalyzed by bovin serum albumin (BSA). The reactions were performed by stirring a heterogeneous mixture of sulfides, $NaIO_4$ and BSA (0.05 mol%). The ee obtained was in the range of 33-40%. Same authors observed a low level of enantioselectivities with chiral titanium complexes of N-salicylidene-L-amino acids **2** (**Scheme 5**).[12b] These catalysts (0.1 mol equiv.) gave ee below 25% in oxidation of various sulfides with TBHP in benzene at room temperature.



2 **2a** R = ^{i}Pr **2b** R = ^{i}Bu **2c** R = CH_2 N NH

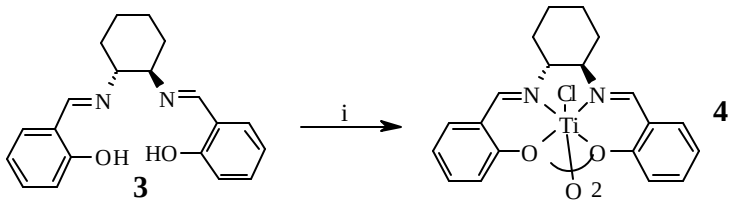
Scheme 5: Chiral Ti-aminoacid complex for asymmetric sulfoxidation.

Dioxiranes were generated *in situ* from ketones and caroate ($KHSO_5$) in presence of *BSA* and sulfides at pH 7.5-8.0. Reactions were performed at 4^0C. Yields were satisfactory and enantioselectivities were upto 89% ee.[12c]

Fujita *et al.*

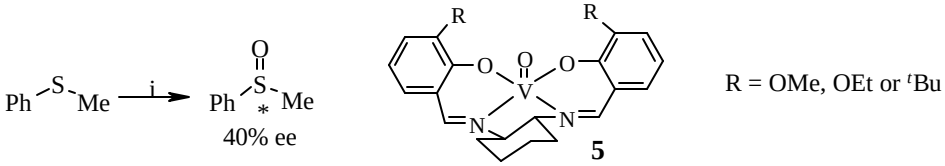
Fujita *et al.*[13a] prepared the catalyst by the reaction of a Schiff base of (R,R)-cyclohexanediamine **3** with $TiCl_4$ in pyridine (**Scheme 6**). The isolated complex **4** was used as a catalyst (4 mol% equiv.) for the asymmetric oxidation of methyl phenyl sulfide

by trityl hydroperoxide in methanol at 0^0C. The (R)-sulfoxide with 53% ee was isolated in good yield.



Scheme 6: (i) $TiCl_4$, pyridine.

Asymmetric oxidation of sulfides with cumene hydroperoxide using the Schiff base-oxovanadium(IV) complex **5** (**Scheme 7**) was also reported by Fujita and coworkers.[13b]



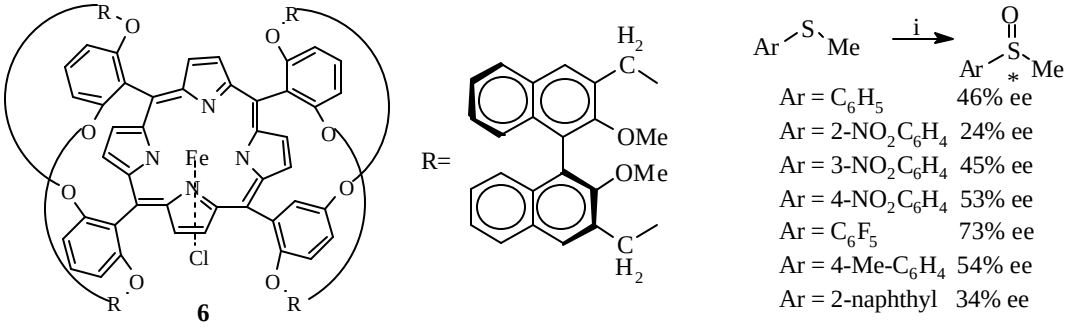
Scheme 7: (i) Catalyst **5** (0.1 mol equiv.), CH_2Cl_2, RT.

Sugimoto *et al.*

Sugimoto *et al.*[14] found that BSA, a carrier protein in biological systems, is a host for aromatic sulfides. Based on this observation, the oxidation of sulfides with $NaIO_4$ was attempted in aqueous solution (pH 9.2) in the presence of BSA (0.06 to 0.5 mol equiv. with respect to sulfide). The enantioselectivities were in range of 7-81% ee.

Naruta *et al.*

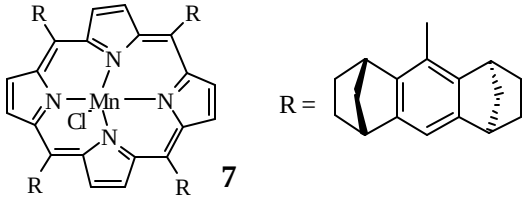
Naruta *et al.*[15] prepared chiral "twin coronet" iron porphyrin **6** (**Scheme 8**). This C_2 symmetric complex efficiently catalyzed the oxidation of sulfides with PhIO. Addition of 1-methylimidazole, which acts as an axial ligand of iron, is necessary to get good ee.



Scheme 8: (i) catalyst **6**, PhIO (iodosylbenzene), CH_2Cl_2, 1-methylimidazole.

Halterman *et al.*

Halterman *et al.*[16] provided a new example of the asymmetric oxidation of sulfides by iodosylbenzene, catalyzed by a D_4 symmetric manganese-porphyrin complex **7** (**Scheme 9**).



Scheme 9: Mn-tetraphenylporphyrin complex.

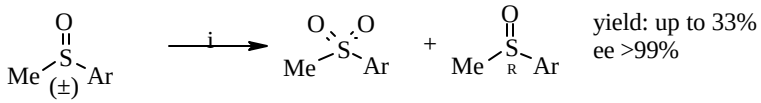
Jacobsen *et al.*

Jacobsen *et al.*[17] used chiral Mn(III)-(salen) complexes as catalyst for asymmetric oxidation of aryl alkyl sulfides with unbuffered 30% H_2O_2 in acetonitrile. The catalytic activity is excellent (2-3 mol%), but the maximum enantioselectivity achieved was 68% ee.

Umeura *et al.*

Umeura *et al.*[18] found that kinetic resolution of racemic sulfoxides can be catalyzed by a chiral Ti(IV)-binaphthol complex to give the optically pure sulfoxides in moderate chemical yields under very mild conditions (**Scheme 10**). The catalytic system used was

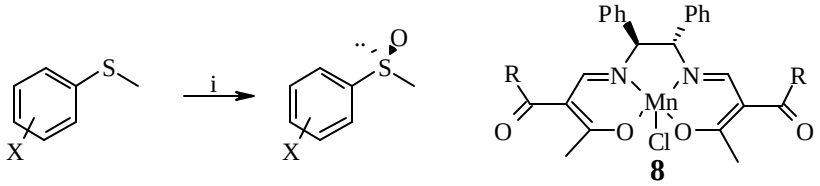
(R)-(+)-binaphthol/Ti(OiPr)$_4$/H_2O = 0.10/0.050/1.0 mol equiv. relative to racemic sulfoxide.



Scheme 10: (i) Ti(O^{i}Pr)$_4$, (R)-binaphthol, H_2O, 70% aqueous TBHP (0.05/0.1/1.0/1.0), CCl_4, 25^{0}C.

Imagakawa *et al.*[19]

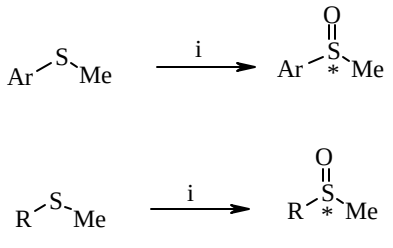
Enantioselective aerobic oxidation of sulfides as well as kinetic resolution of sulfoxides into optically active sulfoxides was achieved by using pivalaldehyde in the presence of a catalytic amount of optically active β-oxo Mn-(III) complexes **8** (**Scheme 11**).



Scheme 11: (i) cat. **8**, O_2(1 atm.), pivalaldehyde, toluene, RT.

Kagan *et al.*[20]

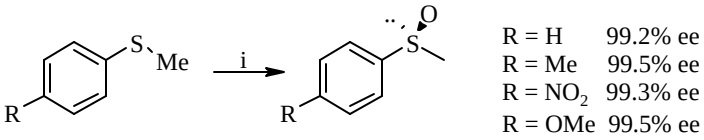
The Sharpless reagent for asymmetric epoxidation was modified by the addition of 1 mol equivalent of H_2O to give a new homogeneous reagent [Ti(O^{i}Pr)$_4$/diethyl tartarate/H_2O/TBHP = 1:2:1:1). This reagent was used for oxidation of alkyl aryl sulfoxides (ee ranged between 70-90% for R isomer) and dialkyl sulfoxides (ee 50-71%) (**Scheme 12**).



Ar = *p*- tolyl	91% ee
Ar = phenyl	89% ee
Ar = *p*-Br-C_6H_4	80% ee
Ar = *p*-(CO_2Me)Ph	91% ee
R = $CH_3(CH_2)_7$	71% ee
R = $C_6H_5(CH_2)_3$	50% ee
R = cyclohexyl	54% ee
R = ^{t}Bu	53% ee

Scheme 12: (i) Ti(O^{i}Pr)$_4$, (R,R)-diethyl tartarate, H_2O, TBHP (1:2:1:1.1), CH_2Cl_2, -20^{0}C.

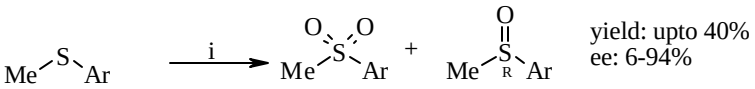
Kagan *et al.*[20b] reported the optimization of the water-modified Sharpless titanium complex ($Ti(O^iPr)_4$/(R,R)-DET/H_2O = 1:2:1) which gave rise to very high enantioselectivities (ee over 99%) (**Scheme 13**).



Scheme 13: (i) 1 equiv. of $Ti(O^iPr)_4$/(R,R)-DET/H_2O = 1:2:1, cumyl hydroperoxide, CH_2Cl_2, -20^{0}C.

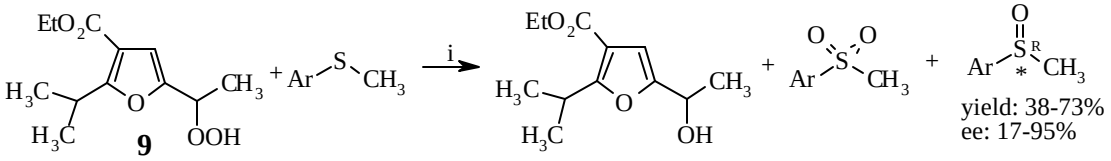
Scettri *et al.*[21]

Kinetic resolution of racemic sulfoxides was achieved by enantioselective oxidation to sulfones under Sharpless-type conditions (**Scheme 14**).



Scheme 14: (i) $Ti(O^iPr)_4$ (0.5 equiv.), L-DET (2 equiv.), cumene hydroperoxide (CHP, 0.65 equiv.), CH_2Cl_2, -23^{0}C.

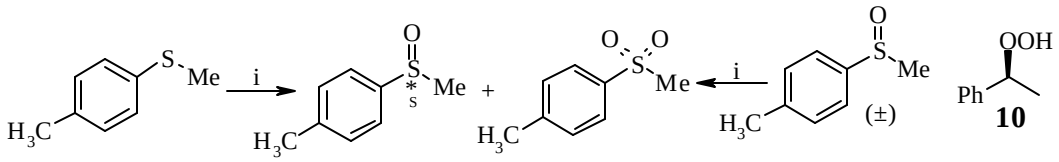
Scettri *et al.*[51] reported the use of furulhydroperoxides **9** as oxidant for the Ti-catalyzed kinetic resolution of racemic sulfoxides (**Scheme 15**).



Scheme 15: (i) $Ti(O^iPr)_4$ (0.5 equiv.), L-DET (4 equiv.), CH_2Cl_2, -23^{0}C or 0^{0}C.

Adam *et al.*[22]

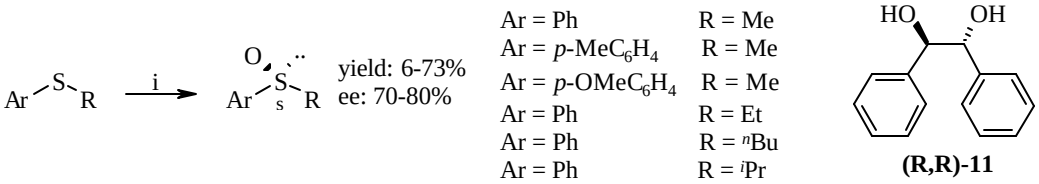
Adam and coworkers have examined the Ti-catalyzed asymmetric oxidation of alkyl aryl sulfides (ee 99%) by enantiomerically pure hydroperoxide **10** (**Scheme 16**). In case of kinetic resolution of (±)-methyl *p*-tolyl sulfoxide ee upto 44% was achieved.



Scheme 16: (i) $Ti(O^iPr)_4$ (5 mol%), **10** (1.5 equiv), CCl_4, -20^{0}C.

Rosini *et al.*[23]

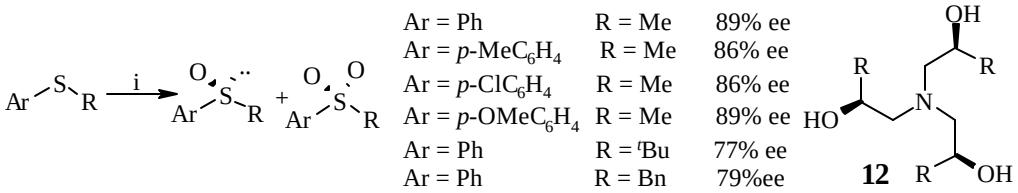
Asymmetric oxidation of prochiral sulfides to optically active sulfoxides mediated by a chiral Ti-complex with diol **11** and TBHP as oxidant was developed (**Scheme 17**).



Scheme 17: (i) $Ti(O^iPr)_4$ (cat.), (R,R)-**11**, H_2O, *t*-BuOOH, CCl_4, 0^{0}C.

Bonchio *et al.*[24]

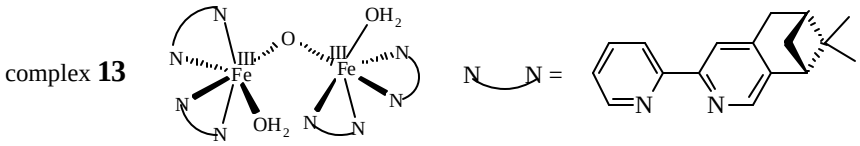
Partially hydrolyzed zirconium catalyst bearing the polydentate ligand **12** (**Scheme 18**) was used as a catalyst for asymmetric sulfoxidation with high ee (80-90%).



Scheme 18: (i) $[(ZrL^*_2(^nBuO)(OH).nH_2O]_m$, cumene hydroperoxide, $ClCH_2CH_2Cl$, 0^{0}C. (L*= **12**)

Fontecave *et al.*[25]

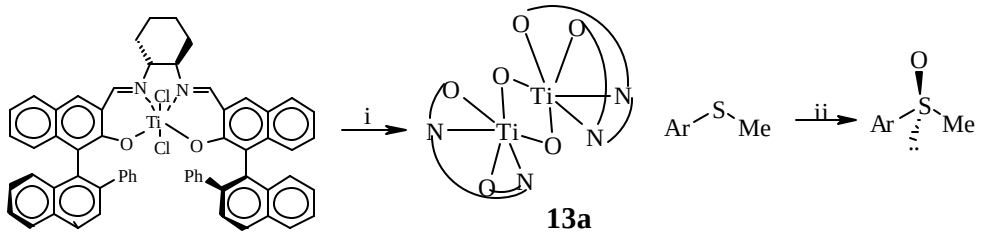
Complex **13** efficiently catalyzes the oxidation of aryl sulfides to the corresponding sulfoxides by H_2O_2, with yields ranging from 45-90% and ee upto 40% (**Scheme 19**).



Scheme 19: Fe-Chiral bipyridine derivative complex.

Katsuki *et al.*[26]

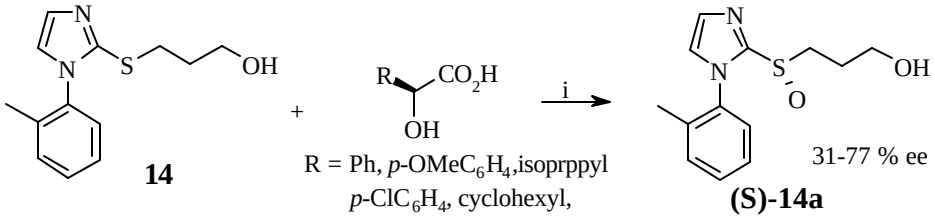
(R,R)-Di-μ-oxo Ti(salen) **13a** was found to serve as an efficient catalyst for asymmetric oxidation of various sulfides with urea-H_2O_2 (**Scheme 20**). High enantioselectivities (ee upto 94%) were achieved using this catalyst.



Scheme 20: (i) H_2O, Et_3N, CH_2Cl_2; (ii) **13a** (2 mol%), urea-H_2O_2 (UHP), MeOH, 0^0C, 24 h.

Matsugi *et al.*[27]

An effective catalytic asymmetric oxidation of prochiral sulfide **14** to (S)-**14a** was achieved by the use of chiral Ti-mandelic acid complex (**Scheme 21**).



Scheme 21: $Ti(O^iPr)_4$, cumene hrdroperoxide (CHP), MS 4Å, CH_2Cl_2, 25^0c, 7 h.

4.0.3 Present Work

4.0.3.1 Objective

Although there are many methods known in the literature for asymmetric oxidation of sulfides to chiral sulfoxides,[1] they involve use of costly enzymes, cumbersome

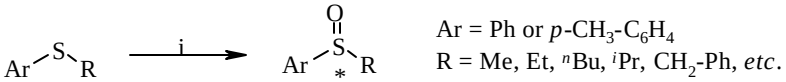
experimental procedures and use of ligands, which are either costly or very difficult to prepare. There are very few reports available on metal catalyzed kinetic resolution (KR) of racemic sulfoxides. In order to overcome these difficulties a new method for asymmetric sulfoxidation as well as for KR of racemic sulfoxides involving commercially available cheap reagent is highly desirable.

Tungsten is known for catalyzing or assisting a variety of oxidation reactions like hydroxylation of dienes,[28] epoxidation of allylic alcohol[29a] and *a*, *b*-unsaturated acids[29c] as well as oxidation of sulfides to sulfoxides or sulfones.[30] Even though it has excellent ability to catalyze oxidation reactions, its use in asymmetric oxidation has not been reported. We have decided to explore the use of tungsten salts [such as sodium tungstate (Na_2WO_4) and tungsten trioxide (WO_3)] in combination with chiral ligands and various oxidants for effecting asymmetric oxidation of aryl alkyl sulfides as well as KR of racemic sulfoxides.

4.0.4 Results and Discussion

a) WO_3-catalyzed asymmetric sulfoxidation of aryl alkyl sulfides

Phenyl benzyl sulfide was selected as a model substrate for studying the asymmetric sulfoxidation reaction (**Scheme 22**). Various catalytic systems were screened for the enantioselective oxidation of thioethers, the results of which are summarized in **Table 1**. Among all the systems studied, a combination of tungsten trioxide (WO_3) and chiral cinchona alkaloids (entries 4, 6, 7 and 16) was found to be the best catalytic system (70% yield, 53% ee), which was taken for further studies.



Scheme 22: (i) catalyst (10-20 mol%), oxidant (1.5 equiv.), solvent.

Table 1: Asymmetric oxidation of Bn-S-Ph[a] using 30% H_2O_2: effect of catalysts[b]

Sr. No	Catalyst	Chiral auxiliary	Solvent	Temp (^{0}C)	Time (h)	Yield[c] (%)	ee[d] (%) (ac)[e]
1.	Na_2WO_4	Quinine sulfate	MeOH	25	0.5	47[f]	2 (R)
2.	-	(R)-Camphor	CH_3CN	25	38	2	-
3.	-	(R)-Camphor	CH_3CN[g]	25	24	3	-
4.	WO_3	(-)-Quinine	CH_3CN	25	15	28	29 (R)
5.	**WO_3**	(-)-Sparteine	CH_3CN	25	40	9[h]	2 (S)
6.	**WO_3**	DHQD[i]	CH_3CN	0	46	79	27 (S)
7.	WO_3[j]	(-)-Quinine,	CH_3CN	0	48	83	25 (R)
8.	-	(-)-Quinine	THF	25	28	62[k]	13 (R)
9.	WO_3[l]	(-)-Quinine	THF	0	45	39	15 (R)
10.	$Ti(O^iPr)_4$	(+)-Menthol	CH_2Cl_2	-20	2	89	3 (R)
11.	-	L-Tartaric acid	H_2O	25	48	37	0
12.	$Pd(OAc)_2$	(-)-Sparteine[m]	Toluene	60	48	0	-
13.	-	(-)-Quinine	-	0-25	30	83	3 (R)
14.	-	(-)-Sparteine	-	0-25	48	0	-
15.	WO_3	PTC[n]	CH_2Cl_2-H_2O	25	8	86	13 (R)
16.	WO_3	$(DHQD)_2$-PYR[o]	THF	25	5	70	53 (R)
17.	WO_3[p]	Hydroquinidine	H_2O	25	26	58	0
18.		PTC[n]	CH_2Cl_2-H_2O	25	47	34	6
19.	WO_3	(-)-Quinine[q]	CH_3CN	25	24	0	-

a) Bn= benzyl; b) reaction conditions: catalyst (10 mol%), chiral auxiliary (20 mol%), aq. 30% H_2O_2 (1.5 equiv.), solvent; c) yield refer to isolated yields after column chromatography; d) based on $[\alpha]_D$ values; e) absolute configuration (ac) determined by comparison of $[\alpha]_D$ with literature values; f) 44% sulfone; g) MeOH (20 vol%) used as co solvent; h) 30% sulfone; i) dihydroquinidine; j) $NaHCO_3$ (2 equiv.) used as additive; k) 16% sulfone; l) $CuCl_2$ (10 mol%) used as cocatalyst; m) O_2 (1 atm.) used as oxidant; n) N-benzyl cinchoninium chloride; o) hydroquinidine 2,5-diphenyl-4,6-pyrimidinediyl diether; p) sodium dodecyl sulfate (SDS, 10 mol %); q) isovaleraldehyde and O_2 were used as oxidant.

The catalytic system consisting of WO_3 and chiral cinchona alkaloids was tested with variety of solvents like CH_3CN, MeOH, acetone, THF, *etc*. The results of sulfoxidation are summarized in **Table 2**. The reaction was carried out at 25^{0}C as well as 0^{0}C to study the effect of temperature on various catalytic systems. THF was proved to be the best solvent among all solvents used, whereas water and acetic acid system have proved to be detrimental for oxidation.

Table 2: WO_3-catalyzed oxidation of sulfides (Ar-S-R) using 30% aqueous H_2O_2[a]

Sr. No.	Sulfide	Ligand	Solvent	Temp. (^{0}C)	Time (h)	Yield[b] (%)	% ee[c]
1.	Ph-S-Me	(-)-Quinine	CH_3CN	25	5	88	14
2.	Ph-S-Me	(-)-Quinine	CH_3CN	0	28	85	25
3.	Ph-S-Me	(-)-Quinine	MeOH	25	2	86	3
4.	Ph-S-Me	(-)-Quinine	MeOH	0	16	89	4
5.	Bn-S-Ph	(-)-Quinine	Acetone	25	10	79	17
6.	Bn-S-Ph	(-)-Quinine	Acetone	0	30	75	23
7.	Bn-S-Ph	(-)-Quinine	THF	25	4	58[d]	34
8.	Bn-S-Ph	(-)-Quinine	THF	0	27	88	41
9.	Bn-S-Ph	(-)-Quinine	AcOH	25	0.5	96	-
10.	Bn-S-Ph	(-)-QS[e]	H_2O	25	24	65	-
11.	Bn-S-Ph	(-)-Quinine	CH_2Cl_2	25	20	68	9
12.	Bn-S-Ph	(-)-Quinine	CH_2Cl_2	0	42	62	13
13.	Bn-S-Ph	(-)-Quinine	-	0-25	20	84	5
14.	Bn-S-Ph	(-)-Sparteine	-	0-25	48	-	-

a) reaction conditions: WO_3 (5 mol%), ligand (10 mol%), aq. 30% H_2O_2 (1.5 equiv.); b) yields are isolated yields after column chromatography; c) (R)-isomer, determined by comparison of $[\alpha]_D$ values reported in literature; d) 24% sulfone formed; e) quinine sulfate.

Various oxidants such as aq. 30% H_2O_2, aq. 70% TBHP, H_2O_2-urea complex, Oxone®, *etc*. were also screened for this catalytic system, the results of which are summarized in **Table 3**. Among all oxidants employed for this reaction, 30% H_2O_2 as well as H_2O_2-urea complex was found to work well with the present catalytic system. 1.5 Equivalent of aq. 30% H_2O_2 was necessary to give excellent yields of sulfoxides, but if it was increased to 2 or 3 equivalent, formation of considerable amounts of sulfones was observed. However, it may be noted that the catalytic system failed to induce optical induction with oxidants like *m*-CPBA, $NaIO_4$, aq. 70% TBHP, Oxone®, *etc*.

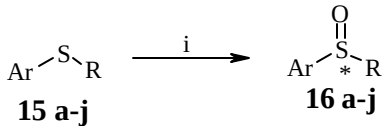
Table 3: WO_3-catalyzed oxidation of Bn-S-Ph[a]: effect of oxidants

Sr. No.	Ligand	Oxidant	Solvent	Temp. (^{0}C)	Time (h)	Yield[b] (%)	% ee[c]

1.	(-)-Quinine	70% TBHP	CH_3CN	25	48	2	0
2.	(-)-Quinine	O_2 (1 atm.)	THF	25	30	0	-
3.	(-)-Quinine	H_2O_2-urea	THF	25	32	25	33
4.	(-)-Quinine	30% H_2O_2	THF	25	4	58	34
5.	(-)-Quinine	70% TBHP	THF	25	24	16	0
6.	(-)-Quinine	*m*-CPBA	CH_2Cl_2	25	36	35	0
7.	Hydroquinidine	70% TBHP	CH_2Cl_2	25	48	30	0
8.	Hydroquinidine	$NaIO_4$	THF	25	2.5	35	0
9.	Hydroquinidine	Oxone®	Acetone	25	0.1	67	0

a) reaction conditions: catalyst (5 mol%), ligand (10 mol %), oxidant (1.5 equiv.); b) yields are isolated yields after column chromatography; c) (R)-isomer, determined by comparison of $[\alpha]_D$ values reported in literature.

After all these initial studies, WO_3 (5 mol %), chiral cinchona alkaloid (10 mol %) and aq. 30% H_2O_2 (1.5 equiv.) in THF as solvent has emerged as the best catalytic system for the asymmetric oxidation of aryl alkyl sulfides. Various aryl alkyl sulfides **15 a-j** (**Scheme 23**) were subjected to oxidation with this catalytic system to get optically active sulfoxides **16 a-j** (**Table 4**).



15 a-j **16 a-j**

Ar= Ph or *p*-CH_3-C_6H_4
R= Me, Et, *n*-Bu, *i*-Pr, CH_2-Ph etc.

Scheme 23: (i) WO_3 (5 mol %), $(DHQD)_2$-PYR (10 mol %), aq. 30 % H_2O_2 (1.5 equiv.), THF .

Table 4: WO_3-catalyzed asymmetric oxidation of aryl alkyl sulfides[a]

Sr. No	Ar	R	Temp (^{0}C)	Time (h)	Yield (%)[b]	$[\alpha]_D^{25}$	% ee[c]	abc[d]
1.	Ph	CH_3	0	49	88	+ 60.01 (c 1.7, acetone)	41	R
2.	Ph	Et	0	44	82	+ 95.70 (c 0.03 acetone)	51	R
3.	Ph	*i*-Pr	0	44	83	+ 76.52 (c 1.6, acetone)	45	R

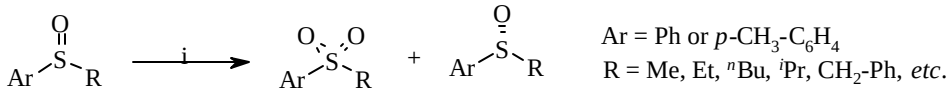
4.	Ph	*n*-Bu	0	40	90	+ 62.63 (c 2.0, EtOH)	35	R
5.	Ph	C_6H_{11}	0	36	78	+ 90.53 (c 2.0, CH_3CN)	46	R
6.	Ph	Bn[e]	0	24	88	+129.71 (c 1.5, acetone)	51	R
7.	Ph	CH_3	0	46	83	– 49.75 (c 2.2, EtOH)	39[f]	S
8.	Ph	Bz	25	10	61[g]	+109.28 (c 1.5, acetone)	43	R
9.	Ph	*n*-Bu	25	24	35[h]	+ 82.31 (c 2.0, EtOH)	46	R
10.	Ph	**Me**	0	40	77	+ 65.78 (c 1.7, acetone)	45[i]	R
11.	4-CH_3-C_6H_4	CH_3	0	44	81	+ 63.90 (c 2, acetone)	44	R
12.	4-CH_3-C_6H_4	Et	0	46	86	+ 81.04 (c 1.3, acetone)	43	R
13.	4-CH_3-C_6H_4	*i*-Pr	0	42	83	+ 72.28 (c 2.6, acetone)	41	R
14.	4-CH_3-C_6H_4	Bn	0	34	85	+ 137.50 (c 1, acetone)	55	R
15.	4-CH_3-C_6H_4	CH_3	0	32	87	– 30.16 (c 3, EtOH)	52[f]	S

a) reaction conditions: WO_3 (5 mol %), $(DHQD)_2$-PYR (10 mol %), aq. 30 % H_2O_2 (1.5 equiv.), THF; b) yields refer to isolated yield after column chromatography; c) ee based on comparison of $[\alpha]_D$ values reported in literature[20,31]; d) absolute configuration; e) Bn = CH_2-Ph; f) $(DHQ)_2$-PYR (hydroquinine 2,5-diphenyl-4,6-pyrimididinediyl diether) (10 mol %) used as ligand; g) 30% corresponding sulfone is also formed; h) 60% corresponding sulfone is formed; i) 50 mol% ligand used.

It is evident from **Table 4** that a variety of aryl alkyl sulfides **15 a-j** underwent oxidation under the reaction conditions to yield the corresponding optically active sulfoxides **16 a-j** in 70-90% yields and 35-55% enantiomeric excess. Sulfides possessing bulky R groups such as benzyl showed better enantioselectivity than other alkyl groups. Reactions performed at room temperature (25^0C) resulted in less enantioselectivity as compared to reactions at 0^0C. Increasing amount of ligand (upto 50 mol%) does not have any significant effect on the enantiomeric excess of the product. Both antipodes (R) and (S) of sulfoxides can be prepared by changing the chiral ligand (entries 7 and 15). Continuing the reaction at 25^0C for longer time results in formation of considerable amount of the corresponding sulfone with improvement in enantioselectivity of sulfoxide (entry 9), which indicates that kinetic resolution of sulfoxide formed *in situ* is probably taking place resulting in the enrichment of its enantiomer. This gave us the idea that this catalytic system could also be used for the kinetic resolution of racemic sulfoxides as discussed in the following section.

b) WO_3-catalyzed kinetic resolution of (±)-sulfoxides

Various racemic sulfoxides **(±)-16 a-j** were subjected to the tungsten-catalyzed kinetic resolution using $(DHQD)_2$-PYR as ligand (**Scheme 24**).



(±)-16 a-j **17 a-j** **(+)-16 a-j**

Scheme 24: (i) WO_3 (5 mol %), $(DHQD)_2$-PYR (10 mol %), aq. 30 % H_2O_2 (1.5 equiv.), THF , 25^0C.

Kinetic resolution was performed at 25^0C to afford optically active sulfoxides **(+)-16 a-j** in 25-44% yields and 40-82% ee along with the corresponding sulfones **17 a-j**. The results are summarized in **Table 5**. Pd-catalyzed system, reported for the kinetic resolution of secondary alcohols,[32a] was used for the kinetic resolution of sulfoxides but failed to give any kinetically resolved product. Sulfoxides bearing bulky R substituents like benzyl gave higher enantioselectivity as compared to other sulfoxides.

Table 5: WO_3-catalyzed kinetic resolution of aryl alkyl sulfoxides.[a]

Sr. No.	Ar	R	Time (h)	Yield[b,c] (%)	$[\alpha]_D^{25}$	% ee[d]
1.	Ph	CH_3	12	40 (55)	+ 86.22 (c 1.7, acetone)	59
2.	Ph	Et	10	39 (52)	+ 123.78 (c 0.03, acetone)	66
3.	Ph	*i*-Pr	12	32 (60)	+ 101.96 (c 1.6, acetone)	60
4.	Ph	*n*-Bu	10	44 (48)	+ 44.74 (c 2.0, EtOH)	25
5.	Ph	C_6H_{11}	13	35 (62)	+ 139.69 (c 2.0, CH_3CN)	71
6.	Ph	Bn	20	31 (57)	+ 201.00 (c 1.5, acetone)	79
7.	4-CH_3-C_6H_4	CH_3	16	29 (66)	+ 97.21 (c 2.0, acetone)	67
8.	4-CH_3-C_6H_4	Et	14	33 (67)	+ 109.31 (c 1.3, acetone)	58
9.	4-CH_3-C_6H_4	*i*-Pr	12	28 (66)	+ 109.25 (c 2.6, acetone)	62
10.	4-CH_3-C_6H_4	Bn	18	25 (72)	+ 205.11 (c 1.0, acetone)	82

a) reaction conditions: WO_3 (5 mol %), $(DHQD)_2$-PYR (10 mol %), aq. 30 % H_2O_2 (1.5 equiv.), THF , 25^0C; b) yield refers to isolated yields after column chromatography; c) yield in parenthesis refers to corresponding sulfone; d) (R)-isomer, ee based on comparison of $[\alpha]_D$ values reported in literature as well as by chiral HPLC analysis using Chiralcel OD-H column (see experimental section).

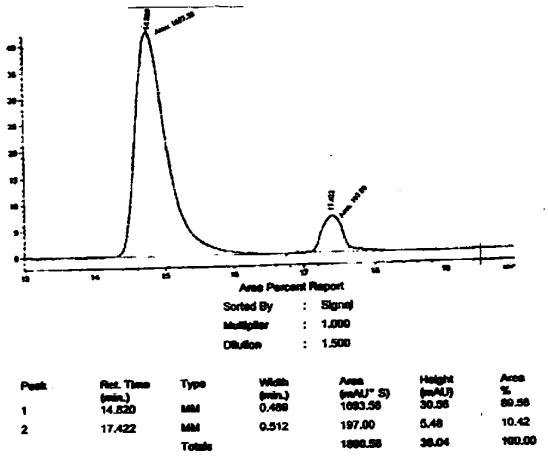
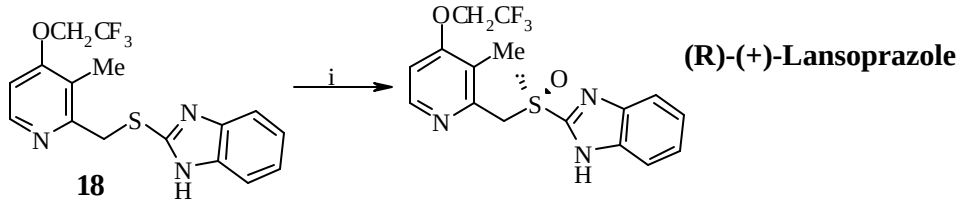


Fig. 2: HPLC chromatogram for (R)-phenyl benzyl sulfide

c) Asymmetric synthesis of anti-ulcer drug lansoprazole

The asymmetric sulfoxidation methodology was applied for the enantioselective synthesis of both the isomers of anti-ulcer drug, lansoprazole, from sulfide **18** (prepared by following the reported procedure[32b]) (**Scheme 25**).



18

Scheme 25: (i) WO_3 (5 mol %), $(DHQD)_2$-PYR (10 mol %), 30 % H_2O_2 (1.5 equiv.), THF

d) Mechanism

The following pieces of information throw light on the mechanism of the reaction. The asymmetric sulfoxidation proceeded well in presence of chiral PTC (N-benzyl cinchoninium chloride, **Table 1** entry 15 and 18). Further, the catalyst (WO_3) remained undissolved in the reaction mixture throughout the reaction so that it might be possible that the ligand is acting as an excellent phase-transfer catalyst for transferring the peroxo species **A** formed by the reaction of WO_3 with H_2O_2 (**Fig. 3**). The coordination of ligand with tungsten could also be seen as other possibility but the insolubility of tungsten in the

reaction mixture rules out this possibility. The quinine-catalyzed reaction gave 62% yield and 13%ee (**Table 1** entry 8), which indicates that the presence of tungsten is necessary to improve the %ee. Although mechanism is not quite clear at this stage, it can be said that ligand acts as a PTC for the transfer of tungsten peroxo species, which results in optical induction in the resulting sulfoxide.

The plausible mechanism for the WO_3-catalyzed sulfoxidation is shown in **Fig. 3**. The peroxo species **A** formed by the reaction of WO_3 with H_2O_2 is believed to coordinate with ligand (L*) to form species **B** *in situ*. Aryl alkyl sulfide also coordinates with one of the oxygen to form the species **C** where oxygen transfer takes place in a chiral environment of ligand (L*) to form chiral sulfoxide and the catalyst is regenerated to continue the catalytic cycle

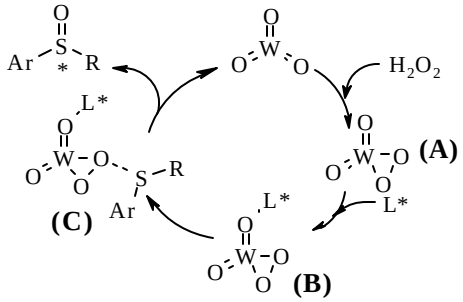


Fig. 3: Plausible mechanism for WO_3 catalyzed asymmetric sulfoxidation

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4.0.5 Conclusion

In conclusion, we have successfully demonstrated for the first time, the use of tungsten trioxide as a catalyst for the asymmetric oxidation of aryl alkyl sulfoxides in presence of chiral cinchona alkaloids such as (-)-quinine, $(DHQD)_2$-PYR, $(DHQ)_2$-PYR and dihydroquinidine to give optically active sulfoxides in 70-90% yield and 35-55% ee. The catalytic system is also very effective for the kinetic resolution of racemic aryl alkyl sulfoxides to give chiral sulfoxides in 24-44% yield and 40-81% ee.

4.0.6 Experimental Section

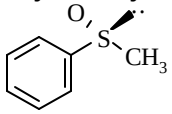
General procedure for asymmetric sulfoxidation of aryl alkyl sulfides:

To a cooled (0^0C) mixture of WO_3 (0.012 g, 0.05 mmol), $(DHQD)_2$-PYR (0.088 g, 0.1 mmol) and sulfide **15 a-j** (1mmol) in THF (2 ml), 30% aq. H_2O_2 (0.17 ml, 1.5 mmol) was added and the reaction mixture was stirred at 0^0C. After stirring for the specified time (Table 4), the reaction mixture was diluted with EtOAc (10 ml) and washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography by using pet. ether and EtOAc as eluents to afford the corresponding pure sulfoxides **(+)-16 a-j**.

General procedure for kinetic resolution of racemic sulfoxides:

A 25 ml RB flask was charged with WO_3 (0.012 g, 0.05 mmol), $(DHQD)_2$-PYR (0.088 g, 0.1 mmol) and racemic sulfoxide **(±)-16 a-j** (1 mmol) in THF (2 ml). To this reaction mixture was added 30% H_2O_2 (0.17 ml, 1.5 mmol) at 25^0C. The reaction mixture was further stirred at 25^0C for the specified time (Table 5). Then the reaction mixture was diluted with EtOAc (10 ml) and washed with water and brine. Organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude reaction mixture was purified on column chromatography using pet. ether and EtOAc as eluents to afford optically active sulfoxides **(+)-16 a-j** and the corresponding sulfones **17 a-j**.

(R)-(+)-Phenyl methyl sulfoxide (16a)



Yield: 40%; **gum**; **[a]$^{25}_D$**: + 86.22 (c 1.7, acetone); **HPLC**: 59% ee, Chiralcel OD-H, λ = 254 nm, hexane:2-propanol (9:1), 0.5 ml/min. Retention time: (R) = 21.72 min, (S) = 26.31 min.; **IR** (Neat, cm^{-1}): 692, 750, 958, 1037, 1089, 1253, 1296, 1415, 1444, 1477, 2914, 2999, 3050; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.75 (s, 3H), 7.51-7.54 (m, 3H), 7.64-7.69 (m, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 42.96, 123.06, 128.83, 130.59, 144.56; **MS** m/z (% rel. intensity): 140 (M^+, 90), 125 (100), 109 (10), 97 (65), 94 (20), 77 (52); **Analysis**: C_7H_8SO requires C, 59.97; H, 5.75; S, 22.87; found C, 59.88; H, 5.72; S, 22.81%.

(R)-(+)-Phenyl ethyl sulfoxide (16b): **Yield**: 39%; **gum**; **[a]$^{25}_D$**: + 123.78 (c 0.03, acetone), 66% ee; **IR** (Neat, cm^{-1}): 692, 748, 997, 1020, 1045, 1085, 1145, 1255, 1307, 1401, 1444, 1477, 1583, 2875, 2975, 3056; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.20 (t, *J* = 7.18 Hz, 3H), 2.79-2.97 (m, 2H), 7.50-7.63 (m, 5H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 5.40,

49.47, 123.76, 128.68, 130.59, 142.63; **MS** m/z (% rel. intensity): 154 (M^+, 48), 126 (98), 109 (15), 97 (45), 91 (20), 78 (100), 69 (10); **Analysis**: $C_8H_{10}SO$ requires C, 62.30; H, 6.54; S, 20.79; found C, 62.28; H, 6.48; S, 20.81%.

(R)-(+)-Phenyl isopropyl sulfoxide (16c): **Yield**: 32%; **gum**; **[**a**]$^{25}_D$**: + 101. 96 (c 1.6, acetone), 60% ee; **IR** (Neat, cm^{-1}): 536, 692, 752, 1022, 1087, 1365, 1382, 1442, 1477, 1630, 2827, 2931, 2970, 3056; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.13 (d, *J* = 7.06 Hz, 3H), 1.22 (d, *J* = 7.07 Hz, 3H), 2.78-2.91 (m, 1H), 7.49-7.52 (m, 3H), 7.57-7.60 (m, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 13.35, 15.50, 54.10, 124.60, 128.53, 130.63, 141.25; **MS** (m/z, RI): 168 (M^+, 8), 126 (80), 110 (10), 97 (12), 78 (100), 65 (10); **Analysis**: $C_9H_{12}SO$ requires C, 65.25; H, 7.19; S, 19.06; found C, 65.12; H, 7.23; S, 19.03%.

(R)-(+)-Phenyl ^{n}butyl sulfoxide (16d): **Yield**: 44%; **gum**; **[**a**]$^{25}_D$**: + 44.74 (c 2.0, EtOH), 25% ee; **IR** (Neat, cm^{-1}): 536, 692, 750, 1037, 1087, 1145, 1305, 1444, 1465, 1583, 2871, 2933, 2958; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.92 (t, *J* = 7.15 Hz, 3H), 1.35-1.51 (m, 2H), 1.61-1.78 (m, 2H), 2.81 (t, *J* = 8.18 Hz, 2H), 7.50-7.51 (m, 3H), 7.53-7.63 (m, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 13.23, 21.42, 23.66, 56.45, 123.61, 128.79, 130.52, 143.42; **Analysis**: $C_{10}H_{14}SO$ requires C, 65.89; H, 7.74; S, 17.59; found C, 65.82; H, 7.63; S, 17.53%.

(R)-(+)-Phenyl cyclohexyl sulfoxide (16e): **Yield**: 35%; **gum**; **[**a**]$^{25}_D$**: + 139.69 (c 2.0, CH_3CN), 71% ee; **IR** (Neat, cm^{-1}): 689, 997, 1022, 1050, 1080, 1142, 1255, 1401, 1444, 1477, 1583, 2975, 3056; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.25-2.10 (m, 10H), 2.52-2.63 (m, 1H), 7.50-7.58 (m, 5H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 23.74, 25.06, 25.32, 26.02, 62.85, 124.79, 128.69, 130.70, 141.47; **MS** m/z (% rel. intensity): 208 (M^+, 2), 126 (100), 110 (10), 78 (7); **Analysis**: $C_{12}H_{16}SO$ requires C, 69.19; H, 7.74; S, 15.39; found C, 69.08; H, 7.72; S, 15.23%.

(R)-(+)-Phenyl benzyl sulfoxide (16f): **Yield**: 31%; **mp**: 124-125^{0}C; **[**a**]$^{25}_D$**: + 201.00 (c 1.5, acetone); **HPLC**: 79% ee, Chiralcel OD-H, λ = 254 nm, hexane:2-propanol (9:1), 0.5 ml/min. Retention time: (R) = 14.82 min, (S) = 17.42 min; **IR** (Neat, cm^{-1}): 694, 746, 765, 914, 1035, 1085, 1149, 1215, 1377, 1442, 1454, 1463, 1494, 2854, 2921, 2958; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.99 (d, *J* = 14.13 Hz, 1H), 4.11 (d, *J* = 14.13 Hz, 1H), 6.98-7.00 (m, 2H), 7.27-7.45 (m, 8H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 63.44, 124.31, 128.09, 128.28, 128.72, 129.05, 130.23, 131.00, 142.69; **MS** m/z (% rel. intensity): 216 (M^+, 5), 200 (2),

125 (5), 97 (6), 91 (100), 65 (10); **Analysis**: $C_{13}H_{12}SO$ requires C, 72.19; H, 5.59; S, 14.82; found C, 72.12; H, 5.53; S, 14.83%.

(R)-(+)-*p*-Tolyl methyl sulfoxide (16g): **Yield**: 29%; **gum**; **[a]$^{25}_{D}$**: + 97.21 (c 2.0, acetone); **HPLC**: 67% ee, Chiralcel OD-H, λ = 254 nm, hexane:2-propanol (9:1), 0.5 ml/min. Retention time: (R) = 18.51 min, (S) = 20.42 min.; **IR** (Neat, cm^{-1}): 692, 750, 958, 1037, 1089, 1253, 1296, 1415, 1444, 1477, 2914, 2999, 3050; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.29 (s, 3H), 2.60 (s, 3H), 7.21 (d, *J* = 8.46 Hz, 2H), 7.44 (d, *J* = 8.46 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 20.98, 43.47, 123.24, 129.67, 141.18, 141.80; **Analysis**: $C_8H_{10}SO$ requires C, 62.30; H, 6.54; S, 20.79; found C, 62.22; H, 6.53; S, 20.63%.

(R)-(+)- *p*-Tolyl ethyl sulfoxide (16h): **Yield**: 33%; **gum**; **[a]$^{25}_{D}$**: + 109.31 (c 1.3, acetone); **HPLC**: 58% ee, Chiralcel OD-H, λ = 254 nm, hexane:2-propanol (9:1), 0.5 ml/min. Retention time: (R) = 14.91 min, (S) = 17.83 min.; **IR** (Neat, cm^{-1}): 540, 692, 752, 1021, 1097, 1365, 1386, 1442, 1477, 1630, 2827, 2970, 3056; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.17 (t, *J* = 8.00 Hz, 3H), 2.40 (s, 3H), 2.69-2.94 (m, 2H), 7.31 (d, *J* = 8.18 Hz, 2H), 7.50 (d, *J* = 8.18 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 5.47, 20.91, 49.76, 123.72, 129.38, 139.60, 140.85; **MS** m/z (% rel. intensity): 168 (M^+, 18), 152 (7), 139 (50), 92 (100), 91 (79), 77 (39), 65 (61); **Analysis**: $C_9H_{12}SO$ requires C, 64.25; H, 7.19; S, 19.06; found C, 64.22; H, 7.13; S, 19.13%.

(R)-(+)- *p*-Tolyl isopropyl sulfoxide (16i): **Yield**: 28%; **gum**; **[a]$^{25}_{D}$**: + 109.25 (c 2.6, Retention time: (R) = 15.40 min, (S) = 16.82 min.; **IR** (Neat, cm^{-1}): 698, 756, 1012, 1088, 1368, 1388, 1444, 1479, 1632, 2828, 2931, 2978, 3056; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.12 (d, *J* = 6.14 Hz, 3H), 1.19 (d, *J* = 6.14 Hz, 3H), 2.39 (s, 3H), 2.75-2.88 (m, 1H), 7.30 (d, *J* = 8.24 Hz, 2H), 7.50 (d, *J* = 8.24 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 13.41, 15.21, 20.83, 53.88, 124.45, 129.05, 137.01, 140.81; **MS** m/z (% rel. intensity): 182 (M^+, 3), 140 (50), 124 (6), 92 (100), 91 (68), 77 (13), 65 (26); **Analysis**: $C_{10}H_{14}SO$ requires C, 65.89; H, 7.74; S, 17.59; found C, 65.82; H, 7.63; S, 17.53%.

(R)-(+)- *p*-Tolyl benzyl sulfoxide (16j): **Yield**: 25%; **mp**: 140-141^{0}C; **[a]$^{25}_{D}$**: + 205.11 (c 1, acetone), 82% ee; **IR** ($CHCl_3$, cm^{-1}): 698, 748, 765, 914, 1035, 1095, 1159, 1215, 1378, 1444, 1454, 1468, 1494, 2854, 2924, 2958; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.34 (s, 3H), 3.94 (d, *J* = 14.12 Hz, 1H), 4.04 (d, *J* = 14.12 Hz, 1H), 6.95-6.99 (m, 2H), 7.16-7.28 (m, 7H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 21.05, 63.22, 124.09, 127.80, 128.06, 129.20, 130.00, 139.27, 141.18; **MS** m/z (% rel. intensity): 230 (M^+, 3), 91 (100), 77 (5), 65 (30);

Analysis: $C_{14}H_{14}SO$ requires C, 73.01; H, 6.13; S, 13.92; found C, 73.12; H, 6.13; S, 13.83%.

Spectral data for some selected sulfones

Phenyl methyl sulfone (17a): **Yield**: 55%; **mp**: 88-89^{0}C; **IR** ($CHCl_3$, cm^{-1}): 501, 540, 692, 748, 956, 997, 1049, 1089, 1151, 1305, 1415, 1444, 1477, 1593, 2914, 2997, 3056; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.07 (s, 3H), 7.58-7.68 (m, 3H), 7.95 (d, *J* = 8.28 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 44.14, 126.39, 129.12, 133.46, 140.30; **MS** m/z (% rel. intensity): 156 (M^+, 78), 141 (70), 125 (8), 94 (64), 77 (100); **Analysis**: $C_7H_8SO_2$ requires C, 53.83; H, 5.16; S, 20.53; found C, 53.82; H, 5.13; S, 20.43%.

Phenyl ethyl sulfone (17b): **Yield**: 52%; **mp**: 42-43^{0}C; **IR** ($CHCl_3$, cm^{-1}): 544, 697, 758, 966, 997, 1049, 1091, 1152, 1305, 1416, 1448, 1477, 1593, 2925, 2997, 3066; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.13 (t, 3H), 3.02 (q, *J* = 6.24 Hz, 2H), 7.42-7.55 (m, 3H), 7.79 (d, *J* = 8.44 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 6.98, 50.17, 127.23, 128.94, 133.31, 138.42; **MS** m/z (rel. intensity): 170 (M^+, 75), 141 (60), 125 (20), 94 (75), 77 (100); **Analysis**: $C_8H_{10}SO_2$ requires C, 56.45; H, 5.92; S, 18.84; found C, 56.32; H, 5.93; S, 18.63%.

Phenyl isopropyl sulfone (17c): **Yield**: 60%; **mp**: 46-47^{0}C; **IR** (Neat, cm^{-1}): 729, 763, 1053, 1087, 1143, 1263, 1303, 1446, 1467, 1585, 2939, 2981, 3066; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.30 (d, *J* = 7.21 Hz, 6H), 3.14-3.28 (m, 1H), 7.57-7.66 (m, 3H), 7.89 (d, *J* = 8.24 Hz, 2H); **Analysis**: $C_9H_{12}SO_2$ requires C, 58.67; H, 6.56; S, 17.40; found C, 58.62; H, 6.43; S, 17.33%.

Phenyl "butyl sulfone (17d): **Yield**: 48%; **gum**; **IR** ($CHCl_3$, cm^{-1}): 588, 671, 729, 768, 1053, 1088, 1143, 1273, 1304, 1446, 1467, 1585, 2939, 3068; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.90 (t, *J* = 6.21 Hz, 3H), 1.33-1.44 (m, 2H), 1.63-1.78 (m, 2H), 3.10 (t, *J* = 6.14 Hz, 2H), 7.58-7.64 (m, 3H), 7.92 (d, *J* = 8.11 Hz, 2H); **Analysis**: $C_{10}H_{14}SO_2$ requires C, 60.57; H, 7.12; S, 16.17; found C, 60.52; H, 7.23; S, 16.13%.

Phenyl benzyl sulfone (17f): **Yield**: 67%; **mp**: 150-151^{0}C; **IR** ($CHCl_3$, cm^{-1}): 668, 758, 785, 914, 1035, 1095, 1154, 1215, 1379, 1434, 1454, 1468, 1510, 2854, 2934; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 4.31 (s, 2H), 7.08 (d, *J* = 8.24 Hz, 2H), 7.25-7.64 (m, 8H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 62.70, 127.98, 128.46, 128.46, 128.76, 130.70, 133.61, 137.12; **MS** m/z (% rel. intensity): 232 (M^+, 10), 167 (8), 132 (15), 91 (100), 77 (10), 65 (98); **Analysis**: $C_{13}H_{12}SO_2$ requires C, 67.22; H, 5.21; S, 13.80; found C, 67.12; H, 5.23; S, 13.73%.

***p*-Tolyl ethyl sulfone (17h)**: **Yield**: 57%; **gum**; **IR** ($CHCl_3$, cm^{-1}): 544, 687, 759, 968, 997, 1051, 1091, 1152, 1305, 1406, 1438, 1478, 1593, 2905, 2957, 3066; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.28 (t, *J* = 7.18 Hz, 3H), 3.13 (q, *J* = 7.18 Hz, 2H), 7.28-7.68 (m, 3H), 7.92 (d, *J* = 8.23 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 6.90, 50.02, 127.62, 128.83, 133.28, 138.05; **Analysis**: $C_9H_{12}SO_2$ requires C, 58.67; H, 6.56; S, 17.40; found C, 58.62; H, 6.43; S, 17.43%.

***p*-Tolyl benzyl sulfone (17j)**: **Yield**: 72%; **mp**: 151-152^{0}C;**IR** ($CHCl_3$, cm^{-1}): 748, 775, 914, 1035, 1095, 1149, 1215, 1378, 1404, 1424, 1458, 1494, 2854, 2914, 2958, 3015; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.42 (s, 3H), 4.29 (s, 2H), 7.07-7.32 (m, 7H), 7.50 (d, *J* = 8.18 Hz, 2H); **Analysis**: $C_{14}H_{14}SO_2$ requires C, 68.26; H, 5.73; S, 13.02; found C, 68.12; H, 5.73; S, 13.13%.

Asymmetric synthesis of (R)-(+)-lansoprazole from sulfide 18: A 25 ml RB flask was charged with WO_3 (0.012 g, 0.05 mmol), $(DHQD)_2$-PYR (0.088 g, 0.1 mmol) and sulfide **18**[32b] (0.353 g, 1mmol) in THF (2 ml) and the mixture was cooled to 0^{0}C. To this was added aq. 30% H_2O_2 (0.17 ml, 1.5 mmol) and the reaction mixture was stirred at 0^{0}C (monitored by TLC). After completion the reaction mixture was diluted with EtOAc (10 ml) and washed with water and brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography by using pet. ether: EtOAc (6:4) as eluent to afford 0.312 g (84%) (R)-lansoprazole.

(R)-(+)-Lansoprazole: **Yield**: 84%; **mp**: 162-165^{0}C (dec.); **[a]$^D_{25}$**: + 150.60 (c 0.5, acetone); **HPLC**: 82% ee, Chiralcel OD-H, λ = 254 nm, hexane:2-propanol (9:1), 0.5 ml/min. Retention time: (R) = 18.4 min, (S) = 21.3 min. **IR** (Nujol, cm^{-1}): 576, 746, 858, 973, 1037, 1110, 1163, 1263, 1267, 1379, 1444, 1579, 1658, 2852, 2950, 3053, 3200; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.18 (s, 3H), 4.35 (q, *J* = 8.14 Hz, 2H), 4.81 (d, *J* = 6.30 Hz, 2H), 6.64 (d, *J* = 6.30 Hz, 1H), 7.27-7.66 (m, 5H), 8.32 (d, *J* = 6.31 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 11.08, 30.19, 61.11, 66.25 (q, *J* = 0.40 Hz), 107.27, 116.61, 124.66, 148.88, 150.54, 153.52, 163.07; **MS** m/z (rel. intensity): 369 (M^+, 26), 353 (20), 308 (4), 320 (60), 252 (16), 238 (83), 204 (40), 165 (56), 150 (32), 137 (51), 122 (72), 106 (82), 90 (73), 77 (50), 65 (76), 52 (100); **Analysis**: $C_{16}H_{14}F_3N_3SO_2$ requires C, 52.03; H, 3.82; N, 11.38; S, 8.68 found C, 52.02; H, 3.72; N, 11.31; S, 8.73%.

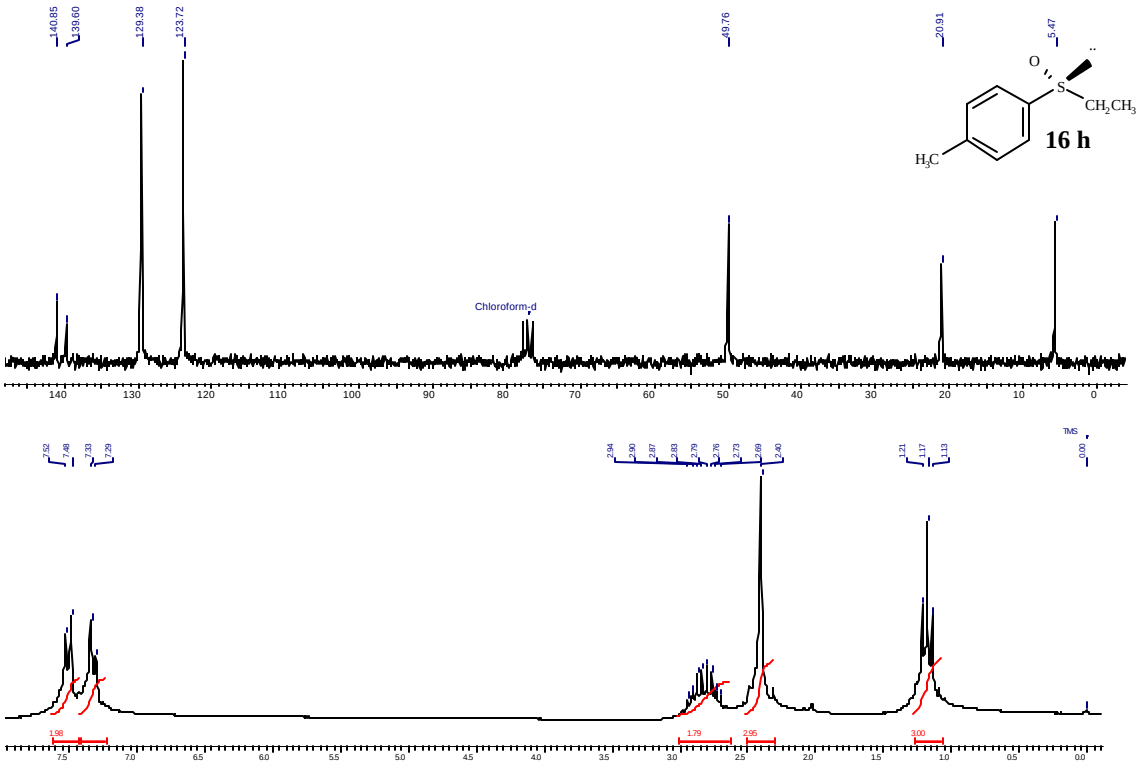


Fig. 4: ^{1}H and ^{13}C-NMR spectra of 16h

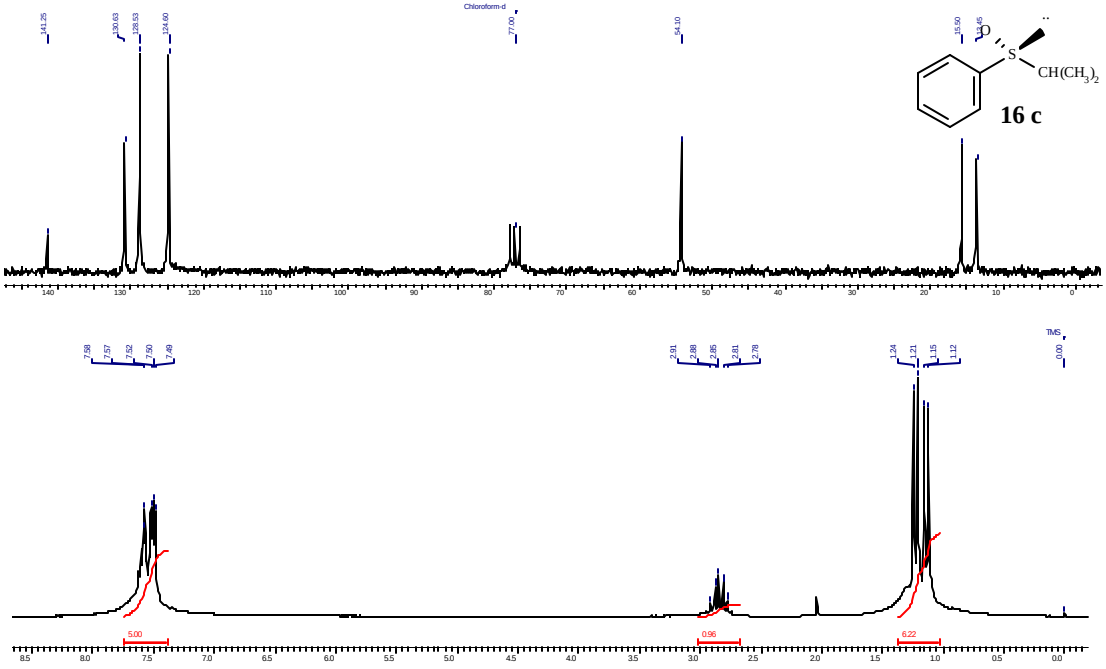


Fig. 5: ^{1}H and ^{13}C-NMR spectra of 16c

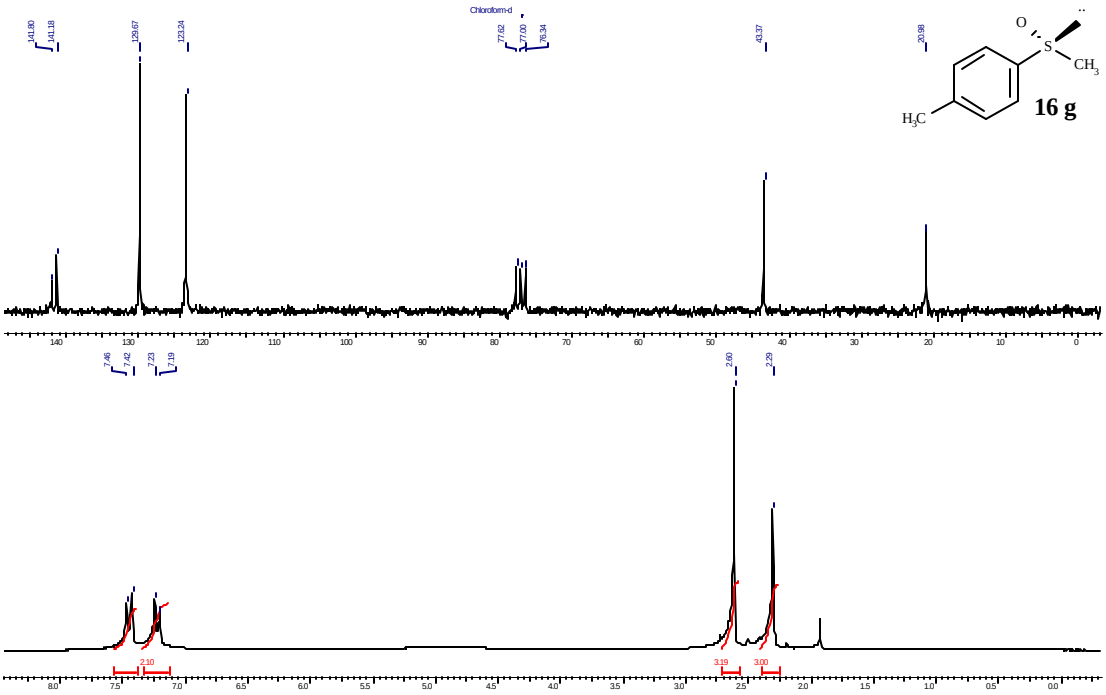


Fig. 6: ^{1}H and ^{13}C-NMR spectra of 16g

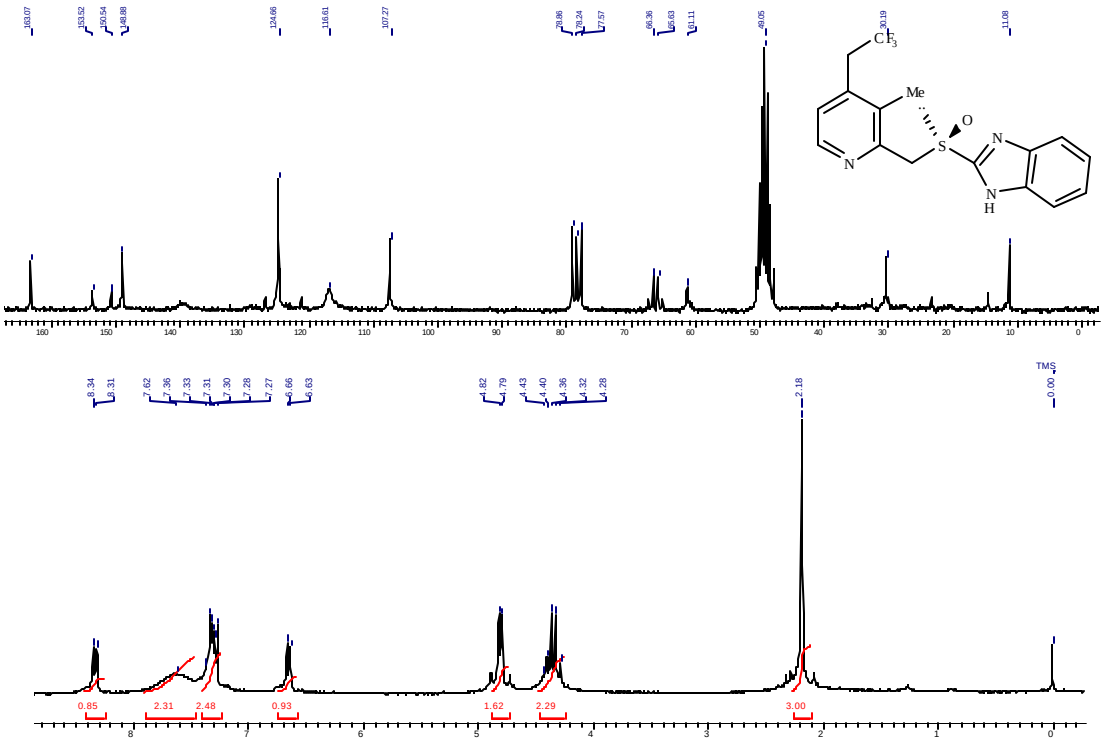


Fig. 7: ^{1}H and ^{13}C-NMR spectra of (R)-lansoprzaole

Cu and Mn-Catalyzed Bromoamination of Olefins

4.1.1 Introduction

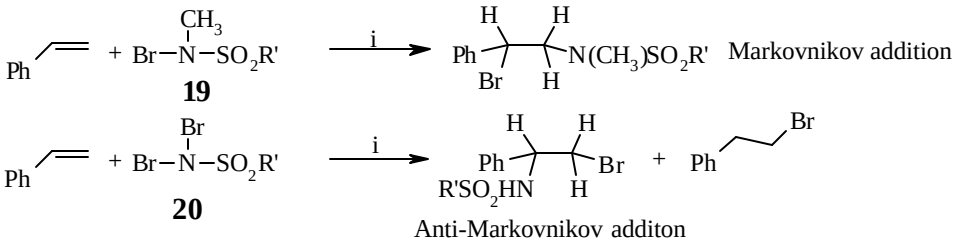
The fuctionalization of olefins by addition of two different functional groups in a single step provides access to wide range of functional group manipulation in organic synthesis. Variety of reactions such as aminohydroxylation, halohydration, haloazidation, azidohydroxylation and haloamination are 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.[33]

4.1.2 Review of Literature

Literature search revealed that even though the initial work has been started in the late forties, 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 *et al.*

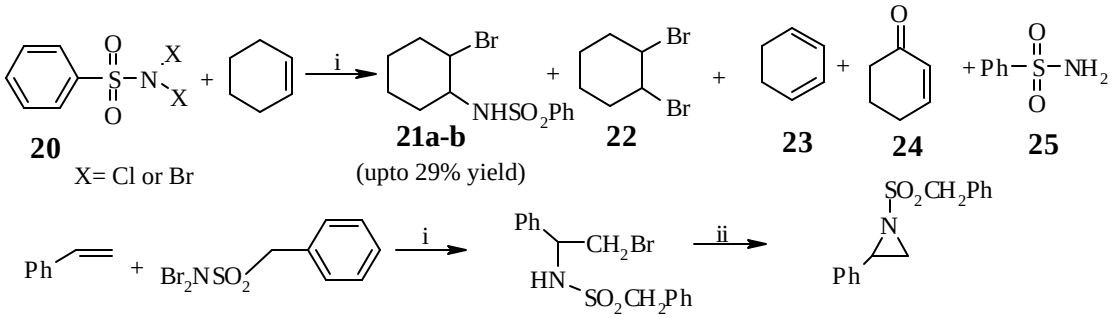
Kharasch *et al.*[34] have studied the addition of N-bromo-N-methyl sulfonamides **19** and N, N-dibromosulfonamides **20** to styrene to give the corresponding bromoamine (**Scheme 26**).



Scheme 26: (i) RT, stirring.

Terauchi *et al.*[35]

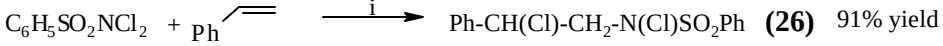
Reaction between N, N-dihalosulfonamide with cyclohexene and styrene was studied, cyclohexene gave many addition products such as *cis* and *trans*-2-halo-1-benzenesulfonamidocyclohexanes **21 a** and **b**, *trans*-1,2-dihalocyclohexane (**22**), 1,3-cyclohexadiene (**23**), 1-cyclohexene-3-one (**24**) and benzene sulfonamide (**25**) (**Scheme 27**).



Scheme 27: (i) reflux 10 min. then 50^{0}C for 30 min; (ii) 5% NaOH.

Danither *et al.*[36]

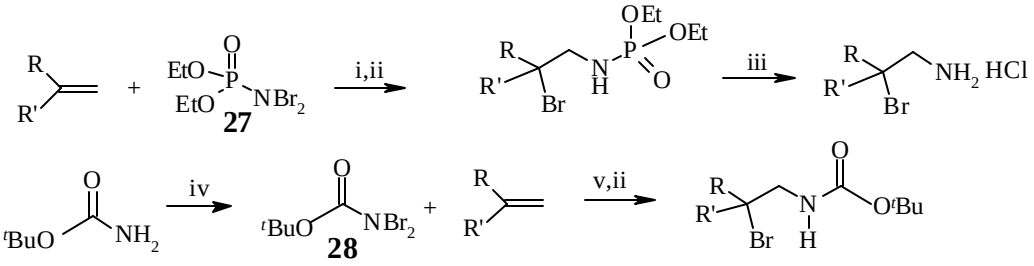
The addition of N,N-dichlorosulfonamides to olefins and conjugated dienes has been examined. The reaction of these reagents with propylene and styrene gave high yields of N-chloro-N-(*b*-chloroalkyl)sulfonamides **26** which have predominantly anti-Markovnikov orientation (**Scheme 28**).



Scheme 28: (i) CH_2Cl_2, 0^0-RT

Zwierzak *et al.*[37]

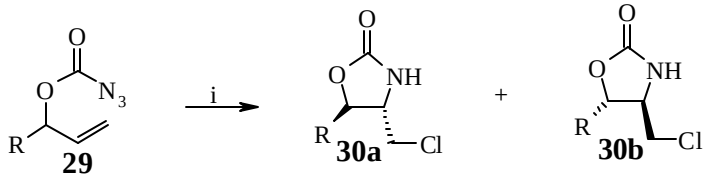
Diethyl N,N-dibromophosphoramidate (DBPA, **27**) and *t*-butyl N,N-dibromocarbamate (**28**), prepared from *t*-butyl carbamate, was added to phenyl ethylenes and terminal olefins to give N-bromo adducts, which were reduced *in-situ* ($NaHSO_3$) to give diethyl-N-(*b*-bromoalkyl)phosphoramidates and *b*-bromo-N-Boc-amines respectively (**Scheme 29**). The addition followed anti-Markovnikov fashion.



Scheme 29: (i) CH_2Cl_2, reflux; (ii) 12% aq. Na_2SO_3, 5-10^{0}C; (iii) HCl, benzene; (iv) Br_2 (2 equiv.), K_2CO_3, H_2O, RT; (v) CH_2Cl_2, reflux.

Bach *et al.* [38]

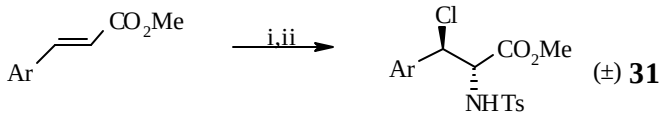
2-Alkenyloxycarbonyl azides **29** underwent an efficient intermolecular aminochlorination with TMSCl catalyzed by $FeCl_2$ to furnish the corresponding 4-(chloromethyl)-oxazolidinones **30 a-b** in 60-84% yield (**Scheme 30**).



Scheme 30: (i) $FeCl_2$, TMSCl, EtOH, 0^{0}C to RT.

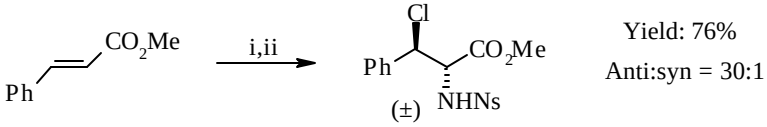
Li *et al.*[39]

Recently, Cu or Zn-catalyzed aminochlorination of cinnamic esters had been developed producing vicinal haloamine derivatives **31** in 52-85% yields and >95% regio- and stereoselectivities.[39a] N,N-dichloro-*p*-toluenesulfonamide was used as chlorine as well as nitrogen source (**Scheme 31**).



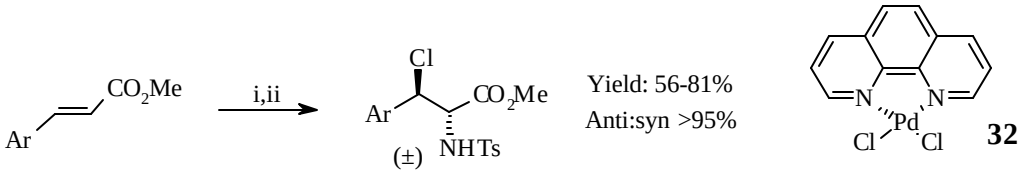
Scheme 31: (i) $TsNCl_2$, 4 Å MS, CuOTf or $ZnCl_2$ (8 mol%), CH_3CN, RT; (ii) Na_2SO_3.

Same authors 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 32**).[39b]



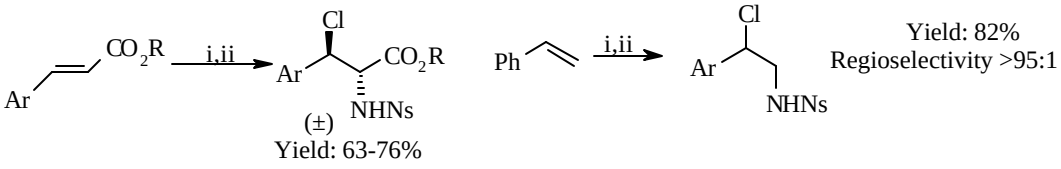
Scheme 32: (i) 2-$NsNCl_2$/2-NsNHNa (2/1), CuOTf (10 mol%), CH_3CN, RT; (ii) aq. Na_2SO_3.

Li *et al.*[39c] used Pd-complex **32** catalyzed aminohalogenation of cinnamic esters has been developed using *p*-$TsNCl_2$ as the nitrogen and chlorine sources (**Schene 33**).



Scheme 33: (i) $TsNCl_2$, Pd-catalyst **32** (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 instead of aziridines (**Scheme 34**).[39d]



Scheme 34: (i) *o*-NsNClNa, CuOTf (10 mol%), CH_3CN; (ii) aq. Na_2SO_3.

4.1.3 Present Work

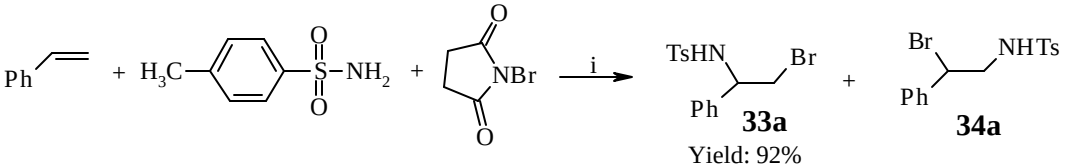
4.1.3.1 Objective

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.

Initially, we were interested in developing a simple and efficient procedure for transition metal catalyzed aziridination of olefins using *p*-toluene sulfonamide as nitrogen source in presence of N-bromosuccinimide (NBS). It is believed that bromosulfonamide formed *in situ*, by the reaction of NBS and *p*-toluene sulfonamide is expected to form nitrene in presence of copper salts, which then reacts with olefins to form aziridines. However, such a reaction took altogether a different course in furnishing bromoaminated products in high yields, the results of which are discussed in this section.

4.1.4 Results and Discussion

When styrene was treated with $TsNH_2$ and NBS (all in equimolar quantities) in presence of catalytic amount of CuI in dichloromethane, the corresponding bromoaminated product was obtained in very high yield with high regioselectivity (>99%) (**Scheme 35**). Change of either solvent or catalyst has not affected the product selectivity (**Table 6**).



Yield: 92%
Regioselectivity: >99:1

Scheme 35: (i) CH_2Cl_2, CuI (10 mol%), 25^0C, 2 h.

We then 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 6**).

Table 6: Bromoamination of styrene using $TsNH_2$ and NBS: Effect of catalysts[a]

Sr. No.	Catalyst	Time (h)	Product	Yield[b] (%)
1.	CuI	2	**33a**	92
2.	$CuCl_2.2H_2O$	2.5	**33a**	85
3.	CuCN	4	**33a**	71
4.	$Cu(OAc)_2$	5	**33a**	65
5.	$NiCl_2.6H_2O$	8	**33a**	58
6.	$Ni(OAc)_2$	6	**33a**	64
7.	$Co(OAc)_2$	6	**33a**	65
8.	$FeCl_3$	12	**33a**	30
9.	$MnSO_4$	2	**33a**	89
10.	Mn(III)-salen[c]	1	**34a**	97

a) reaction conditions: styrene (2.0 mmol), $TsNH_2$ (2 mmol), NBS (2.2 mmol), catalyst (10 mol%), CH_2Cl_2 (5 ml), 25^0C; b) yields refer to isolated product after column chromatography; c) N, N'-bis(3,5-di-*tert*-butylsalicylidene)-1, 2-cyclohexanediaminomanganese(III) chloride.

Among various metal salts screened, Cu and Mn metal salts (particularly CuI and $MnSO_4$) were found to give better results. However, in the case of Mn(III)-salen complex, there was a reversal in the regioselectivity of the product to give **34a** exclusively.

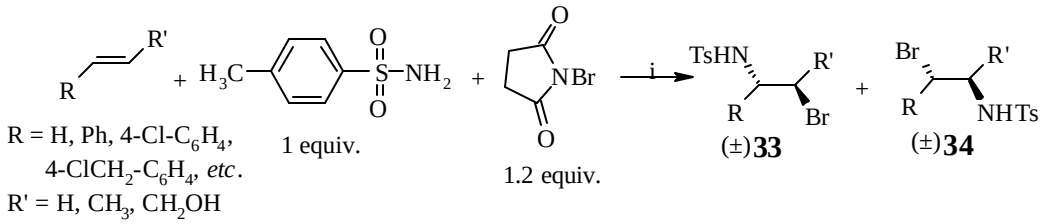
In order to screen the best solvent system, bromoamination of styrene was performed in a variety of solvents using salts of copper or manganese as catalysts. The results of such solvent study are summarized in **Table 7**. Among all solvents used, dichloromethane (CH_2Cl_2) and benzene gave the best results.

Table 7: Bromoamination of styrene: Effect of solvents[a]

Sr. No.	Catalyst	Solvent	Time (h)	Product	Yield[b] (%)
1.	CuI	$CHCl_3$	3	**33a**	88
2.	CuI	CH_3CN	6	**33a**, **34a** (1:1)[c]	15
3.	CuI	C_6H_6	3	**33a**	91
4.	CuI	CH_2Cl_2	2	**33a**	92
5.	CuI	CCl_4	4	**33a**	75
6.	CuI	Acetone	8	**33a**	45
7.	$MnSO_4$	C_6H_6	3	**33a**	86
8.	$MnSO_4$	CH_2Cl_2	3	**33a**	90
9.	Mn(III)-salen[d]	C_6H_6	1	**34a**	94
10.	Mn(III)-salen	CH_2Cl_2	1	**34a**	97
11.	Mn(III)-salen	Toluene	2	**34a**	92
12.	Mn(III)-salen	MeOH	6	--	0[e]

a) reaction conditions: styrene (2.0 mmol), $TsNH_2$ (2 mmol), NBS (2.2 mmol), catalyst (10 mol%), solvent (5 ml), 25^0C; b) yields refer to isolated product after column chromatography; c) determined by ^{1}H-NMR spectroscopy; d) N, N'-bis(3,5-di-*tert*-butylsalicylidene)-1, 2-cyclohexanediaminomanganese(III) chloride; e) starting material recovered back.

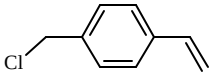
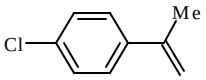
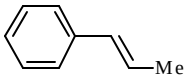
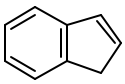
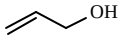
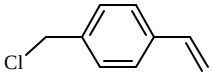
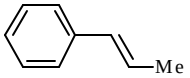
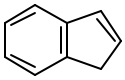
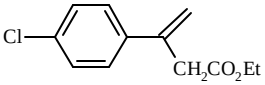
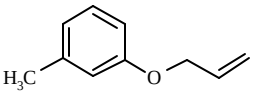
A variety of olefins were then subjected to bromoamination using CH_2Cl_2 as solvent (**Scheme 36**), the results of which are summarized in **Table 8**.



Scheme 36: (i) Cu or Mn catalyst (5 mol%), CH_2Cl_2, 25^0C.

As can be seen from **Table 8** 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 8: Bromoamination of olefins using Cu or Mn catalysts: Substrate scope[a]

Sr. No.	Olefin	Catalyst	Tine (h)	Product	*anti:syn*[c]	Yield[b] (%)	Mp (^{0}C)
1.	Styrene	CuI	2	**33a**	-	92	168-169
2.		CuI	2.5	**33b**	-	90	128-130
3.		CuI	2	**33c**	-	93	144-146
4.		CuI	3	**33d**	>99:1	92	134-135
5.		CuI	2	**33e**	>99:1	89	169-170
6.		CuI	3	**33f**	>99:1	78	116-117
7.		CuI	3	**33g**	>99:1	80	98-99
8.		CuI	6	**33h**	-	75	gum
9.	Styrene	CuI	3	**33i**[d]	-	94[d]	106-108
10.	Styrene	$MnSO_4$	3	**33a**	-	90	168-169
11.	Styrene	Mn(III)-salen	1	**34a**	-	97	113-114
12.		Mn(III)-salen	1.5	**34b**	-	95	111-112
13.		Mn(III)-salen	2	**34d**	>99:1	97	gum
14.		Mn(III)-salen	2	**34e**	>99:1	90	136-137
15.		CuI	3	**34j**	-	94	gum
16.		CuI	24	**33k**	-	76	gum

(a) reaction conditions: olefin (2.0 mmol), $TsNH_2$ (2 mmol), NBS (2.4 mmol), catalyst (10 mol%), CH_2Cl_2 (5 ml), 25^{0}C; (b) yields refer to isolated product after column chromatography; c) determined based on ^{1}H and ^{13}C-NMR; (d) methane sulfonamide ($MeSO_2NH_2$) was used as nitrogen source.

The structures of both regioisomers were confirmed by mp, ^{1}H-NMR, ^{13}C-NMR and mass spectroscopy. For example, compound **33a** showed a doublet at δ 3.58 for homobenzylic protons and a quartet at δ 4.57 for benzylic proton. Further a doublet at δ 5.38 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. 8**).

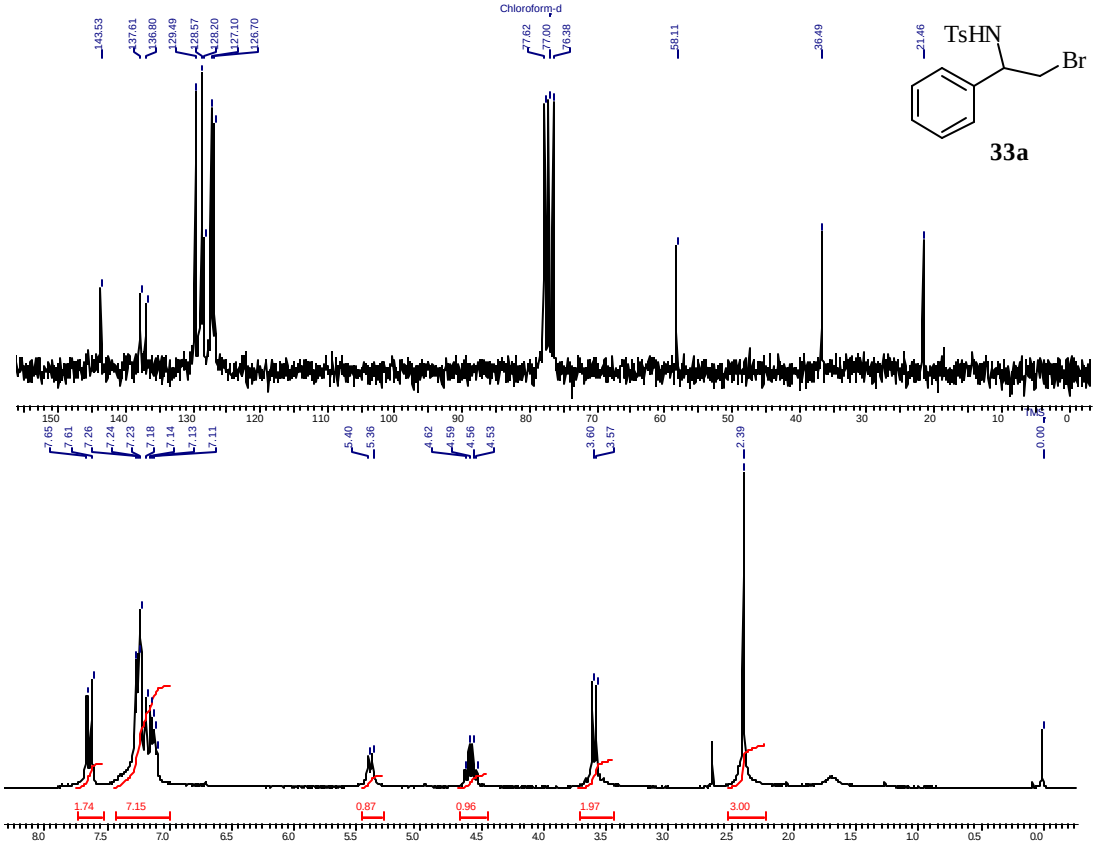


Fig. 8: ^{1}H and ^{13}C NMR spectra of bromoamine 33a

The ^{1}H-NMR spectrum of compound **34a**, the regioisomer of **33a**, shows multiplets at δ 3.50-3.58 and δ 4.85-4.99 corresponding to homobenzylic and benzylic protons respectively. On exchange with D_2O, multiplet at δ 4.85-4.99 and 3.50-3.58 simplifies to a triplet and doublet of doublet respectively which shows that the amino functionality is

present on homobenzylic carbon. Its ^{13}C-NMR spectrum shows signals at δ 49.84 and 52.45 due to homobenzylic and benzylic carbons respectively. Its mass spectrum showed a fragmented ion peak at m/e 184, due to TsNH-CH_2 (**Fig. 9**).

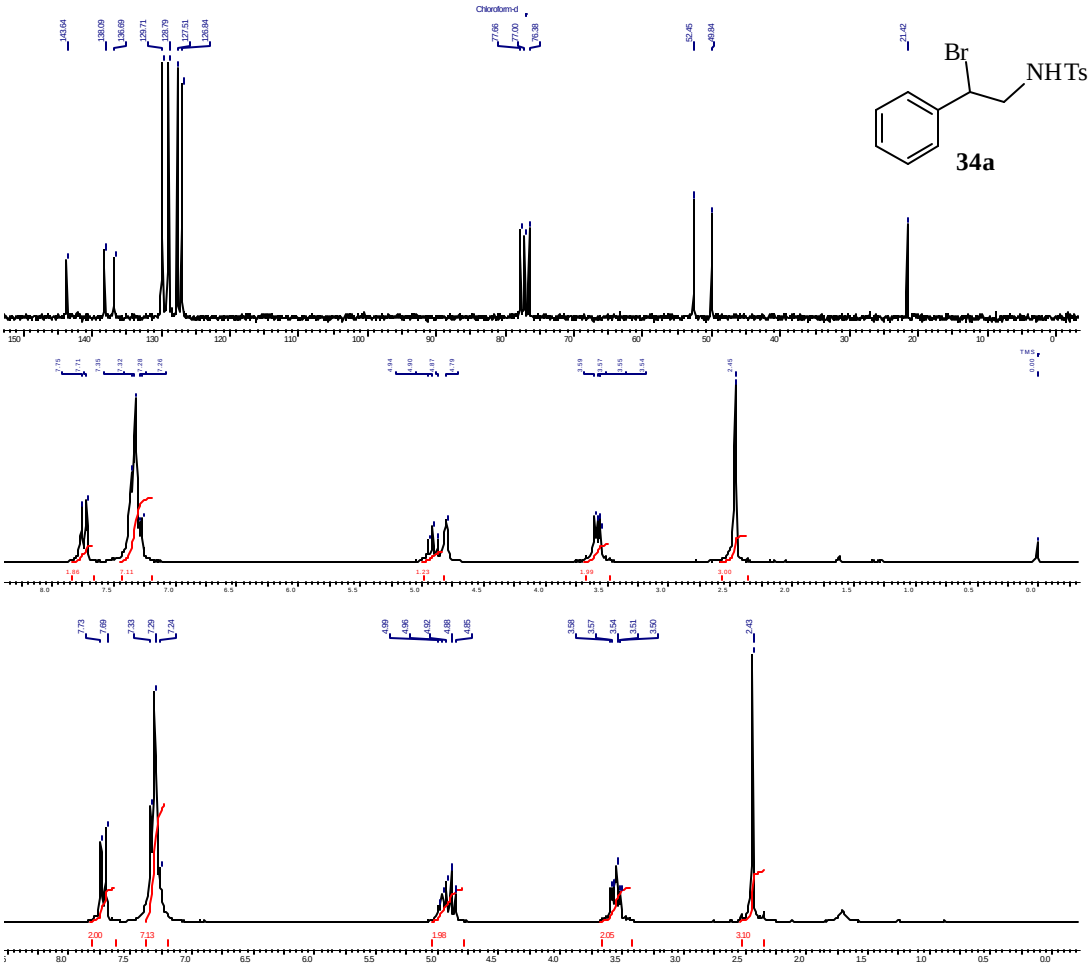
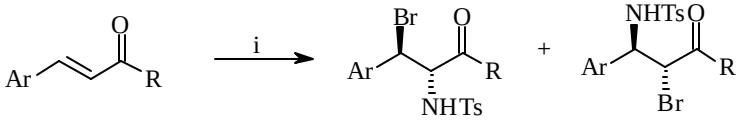


Fig. 9: ^{1}H ,^{13}C NMR and D_2O-exch. spectra of bromoamine 34a

Various *a* , *b*-unsaturated carbonyl compounds were also subjected to bromoamination (**Table 9**) using this catalytic system to give the corresponding bromoaminated products in good to excellent yields. However it may be noted that both Cu and Mn catalysts gave the same regioisomer and no reversal of regiochemistry was observed except in the case of 4-OMe-phenyl case (**Scheme 37**).



35a-g (±) **36a-g** (±)**37a-g**

Scheme 37: (i) Cu or Mn-catalyst (10 mol%), $TsNH_2$ (1.0 equiv.), NBS (1.2 equiv.), CH_2Cl_2, 25^0C.

Table 9: Bromoamination of α, β-unsaturated carbonyl compounds.[a]

Sr. No	Ar	R	Catalyst	Time (h)	Product	*anti:syn*[b]	Yield[c] (%)
1.	Ph	CO_2Me	CuI	28	36a	>99:1	75
2.	Ph	CO_2Me	Mn(III)-salen[d]	24	36a	>99:1	80
3.	Ph	CO_2Me	$MnSO_4$	24	36a	>99:1	82
4.	4-Cl-C_6H_4	CO_2Et	$MnSO_4$	26	36b	>99:1	78
5.	Ph	COPh	$MnSO_4$	10	36c	>99:1	88
6.	4-Cl-C_6H_4	$COCH_3$	$MnSO_4$	28	36d	>99:1	60
7.	4-Cl-C_6H_4	COPh	$MnSO_4$	26	36e	>99:1	72
8.	4-OMe-C_6H_4	CO_2Et	$MnSO_4$	20	37f	>99:1	80
9.	4-OMe-C_6H_4	COPh	$MnSO_4$	15	37g	>99:1	88
10.	4-Cl-C_6H_4	CO_2Et	CuI	40	36b	>99:1	63

(a)) reaction conditions: olefin (2.0 mmol), $TsNH_2$ (2 mmol), NBS (2.4 mmol), catalyst (10 mol%), CH_2CL_2 (5 ml), 25^0C; (b) determined based on ^1H and ^{13}C-NMR; c) yields refer to isolated product after column chromatography; d) N, N'-bis(3,5-di-*tert*-butylsalicylidene)-1, 2-cyclohexanediaminomanganese(III) chloride.

As can be seen from **Table 9**, a variety of *a*, *b*-unsaturated carbonyl compounds reacted smoothly to afford the corresponding bromoaminated products in good regio- and diastereoselectivity. $MnSO_4$ proved to be better catalyst than those of either CuI or Mn(III)-salen. The amine functionality is generally introduced at the *a* position to carbonyl group except in case of **37 f** and **g** (entries 8 and 9). 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 **36a** into the corresponding known *trans*-aziridine.

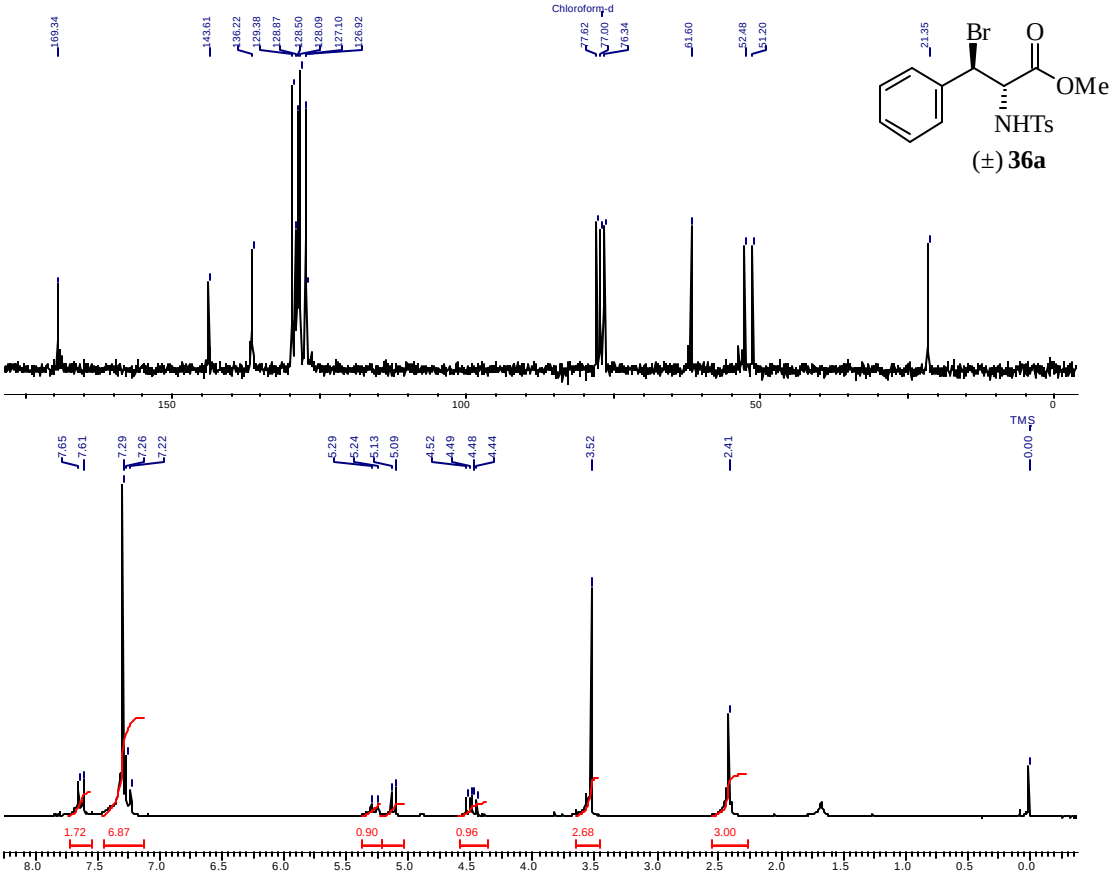


Fig. 10: ^{1}H and ^{13}C NMR spectra of bromoamine 36a

The ^{1}H-NMR spectrum of **36a** shows a multiplet at δ 4.44-4.52 for C_2 proton due to coupling with C_3-H and N-H; which simplifies to a doublet after D_2O exchange. A doublet at δ 5.11 is due to C_3 proton; a doublet at δ 5.27 is due to N-H proton exchangeable with D_2O. Its ^{13}C-NMR showed typical peaks at δ 51.20 and 52.48 for C_2 and C_3 carbons (**Fig. 10**).

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. Asymmetric version of this reaction was also attempted by using the chiral Mn(III)-salen complex [(R,R)-(-)-N,N'-bis(3,5-di-tert-butylsalicylidine)-1,2-cyclohexanediaminomanganese(III) chloride, Jacobsen's catalyst]. The reaction proceeded well to give the products in excellent yield but very low specific rotation {$[\alpha]_D$= – 0.4-1.5}values were observed.

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 stochiometric amount of $TsNH_2$ and NBS was allowed to react. The plausible mechanism for this reaction is shown in **Fig. 11**. 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. The regiochemistry of the products can be explained based on the stearic factors. In case of CuI or $MnSO_4$ the $TsNH^-$ attacks the benzylic position, which is more electrophilic for styrene type substrates. However, when Mn-(III)-salen is used as catalyst, the less hindered homobenzylic site is preferred for attack rather than benzylic position due to bulky nature of ligand. In case of *a*, *b*-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.

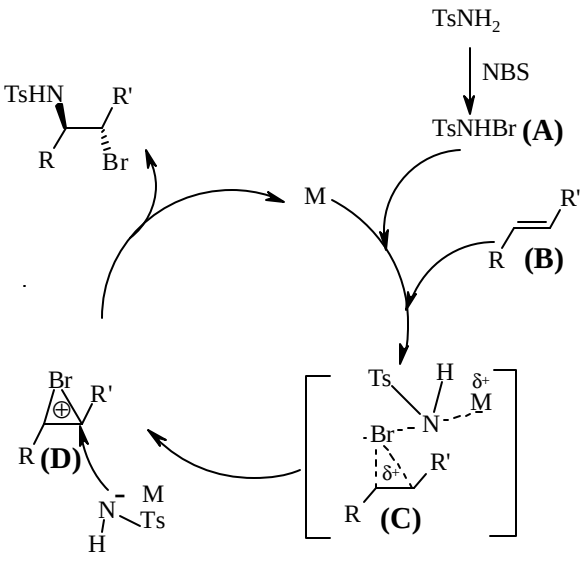


Fig. 11: Plausible mechanism for bromoamination of olefins

4.1.5 Conclusion

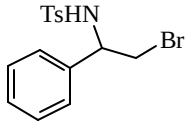
In conclusion, we have developed a novel method for the bromoamination of olefins catalyzed by Cu and Mn using $TsNH_2$ as nitrogen source and NBS as bromine source. The corresponding bromoaminated products were formed in excellent yields (upto 97%) with high regio- and stereoselectivity (>99%).

4.1.6 Experimental Section

General experimental procedure for bromoamination of olefins:

A mixture of olefin (2 mmol), Cu or Mn 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 25^0C. 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 anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude product, which was purified on column chromatography on silica gel using pet. ether and EtOAc as eluents to afford pure product.

1-Phenyl-1-(*p*-toluenesulfonamido)-2-bromoethane (33a)



Yield: 92%; **mp**: 168-169^{0}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* = 621 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%.

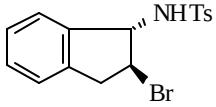
1-(4-Chloromethylphenyl)-1-(*p*-toluenesulfonamido)-2-bromoethane (33b): **Yield**: 90%; **mp**: 128-130^{0}C; **IR** ($CHCl_3$, cm^{-1}): 669, 761, 1159, 1215, 1377, 1463, 2921, 2952, 3236; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.38 (s, 3H), 3.55 (d, *J* = 6.21 Hz, 2H), 4.51-4.64 (m, 3H), 5.54 (d, *J* = 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; **MS** m/z (rel. intensity): 403 (M^+, 1), 354 (8), 308 (40), 155 (20), 132 920), 118 (100), 105 (25), 91 (98), 77 (10), 65 (10); **Analysis**: $C_{16}H_{17}BrClNO_2S$ requires C, 47.72; H, 4.25; Br, 19.84; Cl, 8.80; N, 3.48; S, 7.96; found C, 47.62; H, 4.10; Br, 19.86; Cl, 8.66; N, 3.41; S, 7.89%.

2-(4-Chlorophenyl)-2-(*p*-toluenesulfonamido)-3-bromopropane (33c): **Yield**: 93%; **mp**: 144-146^{0}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; Br, 19.84; Cl, 8.80; N, 3.48; S, 7.96; found C, 47.74; H, 4.18; Br, 19.76; Cl, 8.86; N, 3.44; S, 7.83%.

(±)-*trans*-1-Phenyl-1-(*p*-toluenesulfonamido)-2-bromopropane (33d): **Yield**: 92%; **mp**: 134-135^{0}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 (33e)



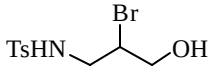
Yield: 89%; **mp**: 169-170^{0}C; **IR** ($CHCl_3$, cm^{-1}): 588, 665, 736, 923, 1081, 1153, 1331, 1377, 1463, 1595, 2872, 2923, 3245; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.46 (s, 3H), 3.11-3.24 (dd, *J* = 16.14 Hz and 6.21 Hz, 1H), 3.51-3.63 (dd, *J* = 16.14 Hz and 6.21 Hz, 1H), 4.30 (q, *J* = 6.14 Hz, 1H), 4.86-4.93 (dd, *J* = 8.18 Hz and 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 (33f): **Yield**: 78%; **mp**: 116-117^{0}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 (33g): **Yield**: 80%; **mp**: 98-99^{0}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%.

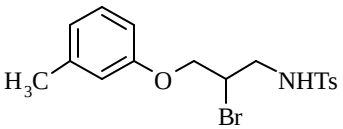
3-(*p*-Toluenesulfonamido)-2-bromo-1-propanol (33h)



Yield: 75%; **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 (33i): **Yield**: 94%; **mp**: 106-108^{0}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,

1-(3-Methylphenoxy)-2-bromo-3-(*p*-tolouenesulfonamido)propane (33k)



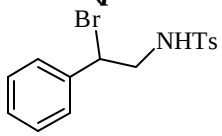
exchangeable with D_2O, 1H), 7.35-7.45 (m, 5H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 36.58, 41.77, 58.47, 126.64, 128.59, 128.91, 138.33; **MS** m/z (rel. intensity): 277 (M^{-1}, 1), 184 (100), 118 (23), 106 (98), 91 (30), 78 (38), 65 (10); **Analysis**: $C_9H_{12}BrNO_2S$ requires C,

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%.

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%.

Yield: 97%; **mp**: 113-114^{0}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,

1-Phenyl-1-bromo-2-(*p*-toluenesulfonamido)ethane (34a)



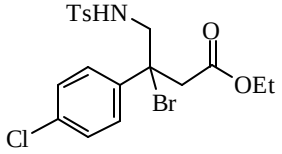
2H), 4.85-4.99 (m, simplifies to triplet with *J* = 7.12 Hz on D_2O exchange, 2H), 7.24-7.33 (m, 7H), 7.71 (d, *J* = 8.41 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 21.42, 49.84, 52.45, 126.84, 127.51, 128.79, 129.71, 136.69, 138.09, 143.64; **MS** m/z (rel. intensity): 354 (M^+, 1), 184 (30), 155 (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%.

1-(4-Chloromethylphenyl)-1-bromo-2-(*p*-toluenesulfonamido)ethane (34b): **Yield**: 95%; **mp**: 111-112^{0}C; **IR** ($CHCl_3$, cm^{-1}): 549, 669, 757, 1093, 1161, 1215, 1334, 1419, 1456, 1598, 2854, 2925, 3018, 3284; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.43 (s, 3H), 3.51-3.62 (m, 2H), 4.55 (s, 2H), 4.83 (t, *J* = 7.23 Hz, exchangeable with D_2O, 1H), 4.92 (t, *J* = 7.23 Hz, 1H), 7.25-7.40 (m, 6H), 7.72 (d, *J* = 8.43 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 21.42, 45.35, 49.76, 51.75, 126.88, 127.98, 128.98, 129.78, 136.69, 138.17, 138.81, 143.72; **MS** m/z (rel. intensity): 403 (M^+, 1), 219 (10), 184 (100), 155 (80), 139 (15), 130 (30), 117 (30), 103 (25), 91 (85); **Analysis**: $C_{16}H_{17}BrClNO_2S$ requires C, 47.72; H, 4.25; Br, 19.84; Cl, 8.80; N, 3.48; S, 7.96; found C, 47.62; H, 4.10; Br, 19.86; Cl, 8.66; N, 3.41; S, 7.89%.

(±)-*trans*-1-Phenyl-1-bromo-2-(*p*-toluenesulfonamido)propane (34d): **Yield**: 97%; **gum**; **IR** ($CHCl_3$, cm^{-1}): 584, 667, 700, 757, 813, 896, 987, 1093, 1161, 1211, 1332, 1380, 1450, 1494, 1598, 2927, 2981, 3029, 3276; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.11 (d, *J* = 7.32 Hz, 3H), 2.44 (s, 3H), 3.56-3.64 (m, 1H), 5.00-5.10 (m, simplifies to d, *J* = 4.21 Hz on D_2O exchange, 2H), 7.29-7.33 (m, 7H), 7.77 (d, *J* = 8.41 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 17.01, 21.28, 55.06, 61.34, 126.81, 128.06, 128.28, 129.56, 137.76, 143.27; **MS** m/z (rel. intensity): 368 (M^+, 1), 212 (10), 198 (65), 171 (15), 155 (60), 120 (20), 91 (100); **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, 52.15; H, 4.86; Br, 21.65; N, 3.78; S, 8.61%.

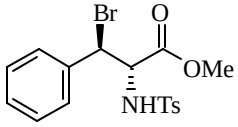
(±)-*trans*-1-Bromo-2-(*p*-toluenesulfonamido)indane (34e): **Yield**: 90%; **mp**: 136-137^{0}C; **IR** ($CHCl_3$, cm^{-1}): 667, 752, 767, 1093, 1161, 1215, 1340, 1429, 1598, 3020, 3274; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.47 (s, 3H), 2.74-2.87 (dd, *J* = 16.10 Hz and 10.21 Hz, 1H), 2.93-23.04 (dd, *J* = 6.13 Hz and 16.10 Hz, 1H), 3.90-3.99 (m, 1H), 5.13 (d, *J* = 5.55 Hz, 1H), 5.35 (d, *J* = 10.20 Hz, exchangeable with D_2O, 1H), 7.19-7.37 (m, 6H), 7.83 (d, *J* = 8.36 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 21.50, 36.49, 56.31, 59.54, 125.04, 127.10, 127.60, 129.75, 137.43, 139.49, 140.52, 143.75; **MS** m/z (rel. intensity): 365 (M^{-1}, 1), 286 (30), 196 (15), 155 (20), 130 (100), 115 (25), 103 (40), 91 (38); **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, 52.38; H, 4.48; Br, 21.79; N, 3.81; S, 8.74%.

Ethyl 3-(4-chlorophenyl)-3-bromo-4-(*p*-toluenesulfonamido)butanoate (34j)



Yield: 94%; **gum**; **IR** ($CHCl_3$, cm^{-1}): 551, 667, 732, 813, 1012, 1093, 1163, 1184, 1334, 1494, 1596, 1731, 2925, 2981, 3274; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.15 (t, *J* = 7.21 Hz, 3H), 2.42 (s, 3H), 3.83-3.88 (m, 2H), 4.04 (q, *J* = 7.21 Hz, 2H), 5.44 (t, *J* = 10.11 Hz, exchangeable with D_2O, 1H), 7.21-7.44 (m, 6H), 7.70 (d, *J* = 8.45 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 13.67, 21.20, 44.84, 52.67, 60.68, 64.54, 126.70, 128.17, 129.49, 133.90, 136.36, 138.97, 143.35, 168.38; **MS** m/z (% rel. intensity): 474 (M^{-1}, 2), 283 (15), 246 (20), 194 (70), 171 (80), 165 (100), 155 (70), 136 (40), 107 (20), 91 (95); **Analysis**: $C_{19}H_{22}BrClNO_4S$ requires C, 47.96; H, 4.66; Br, 16.79; Cl, 7.45; N, 2.94; S, 6.74; found C, 47.92; H, 4.50; Br, 16.65; Cl, 7.32; N, 2.91; S, 6.72%.

(±)-*trans*-Methyl 3-bromo-2-(*p*-toluenesulfonamido)-3-phenylpropionate (36a)



Yield: 75%; **mp**: 136-137^{0}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%.

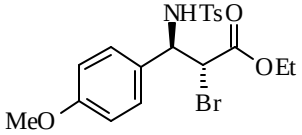
(±)-*trans*-Ethyl 3-bromo-3-(4-chlorophenyl)-2-(*p*-toluenesulfonamido)propionate (36b): **Yield**: 78%; **mp**: 119-121^{0}C; **IR** ($CHCl_3$, cm^{-1}): 676, 813, 1027, 1091, 1163, 1265, 1336, 1461, 1595, 1716, 2854, 2923, 3236; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.15 (t, *J* = 6.42 Hz, 3H), 2.43 (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; Br, 17.34; Cl, 7.69; N, 3.04; S, 6.96; found C, 46.82; H, 4.10; Br, 17.28; Cl, 7.66; N, 3.01; S, 6.85%.

(±)-*trans*-3-Phenyl-3-bromo-2-(*p*-toluenesulfonamido)propiophenone (36c): **Yield**: 88%; **mp**: 142-144^{0}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 (36d): **Yield**: 60%; **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; Br, 18.55; Cl, 8.23; N, 3.25; S, 7.44; found C, 47.42; H, 3.90; Br, 18.45; Cl, 8.21; N, 3.21; S, 7.41%.

(±)-*trans*-3-(4-Chlorophenyl)-3-bromo-2-(*p*-toluenesulfonamido)-propiophenone (36e): **Yield**: 72%; **mp**: 168-170^{0}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; Br, 16.21; Cl, 7.19; N, 2.84; S, 6.51; found C, 53.42; H, 3.79; Br, 16.12; Cl, 7.12; N, 2.81; S, 6.45%.

(±)-*trans*-Ethyl 3-(4-methoxyphenyl)-3-(*p*-tolylsulfonamido)-2-bromopropionate (37f)



Yeild: 80%; **mp**: 117-119^{0}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 and 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 (37g): Yield: 88%; **mp**: 132-134^{0}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-III

NBS-Catalyzed Aziridination of Olefins Using Chloramine-T as Nitrogen Source

4.2.1 Introduction

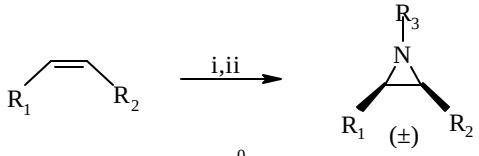
Aziridines and azirines can be regarded as representatives of the first and most simple of all heterocyclic systems, which are characterized by the presence of two carbon atoms and one nitrogen atom in a three-membered ring. Interest in these nitrogen containing small rings is due to the general influence of ring strain upon chemical reactivity. The stabilities and overall profiles of chemical reactivity of these heterocycles are attributable not only to the combined effects of bond shortening and angle compression but also to the presence of the electron rich nitrogen atom.[40] The chemistry of aziridines has been a very active area of research. Synthetic approaches to the aziridine ring, modifications of functionalized aziridines and the reactions of aziridines have received particular attention. The aziridine ring is a versatile building block for organic synthesis, not only because the ring opening of aziridines provides a convenient entry to the stereoselective preparation of functionalized amino compounds but also because the exocyclic N-substituent controls the properties and reactivity of the three membered ring. Many biologically active compounds such as amino acids, *b*-lactam antibiotics and alkaloids have been derived from aziridines.[41]

4.2.2 Review of Literature

Literature search revealed that there are various catalytic as well as non-catalytic approaches available for the synthesis of aziridines. Important catalytic methods for the synthesis of aziridines are discussed below.

Baeckvall *et al.* [42]

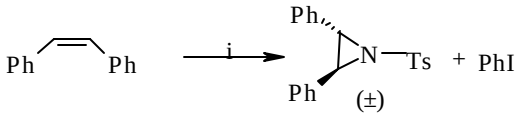
Aminopalladation of alkenes followed by oxidation by bromine gave N-substituted aziridines (**Scheme 38**).



Scheme 38: (i) $PdCl_2(PhCN)_2$, R_3NH_2, -50^0C; (ii) Br_2.

Mahy *et al.*[43]

N-Substituted aziridines are formed by $Fe^{(III)}$- or $Mn^{(III)}$-porphyrin catalyzed reactions of PhI=NR compounds (R= tosyl or $COCF_3$) with alkenes (**Scheme 39**).

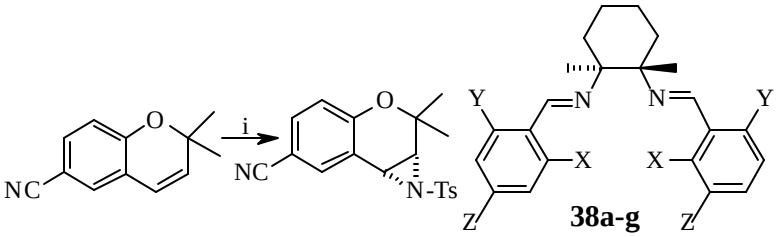


Catalyst: $Fe^{(III)}$(TPP) = 21-63% yield
$Mn^{(III)}$(TPP) = 20-80% yield

Scheme 39: (i) catalyst, PhI=NTs, CH_2Cl_2.

Jacobsen *et al.*[44]

A new class of chiral bisbenzylidenediaminocyclohexane ligands **38 a-g** has been developed which, in association with CuOTf catalyze aziridination of alkenes by PhI=NTs. Moderate to excellent enantioselectivities were attained in the aziridination of a range of different substrates (**Scheme 40**).

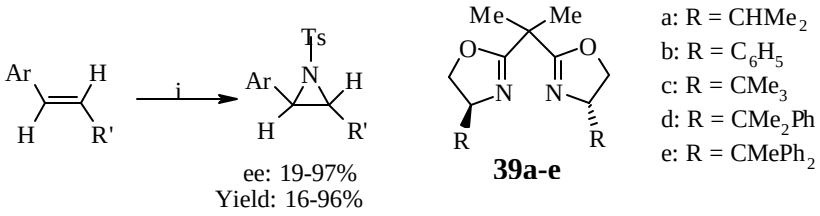


a: X=Y=Z= H, 50%ee
b: X= F, Y=Z= H, 64%ee
c: X= Cl, Y=Z= H, 72% ee
d: X= Br, Y=Z= H, 81% ee
e: X=Y= H, Z= Br, 42% ee
f: X=Y= Cl, Z= H, >98% ee
g: X=Y=Z= CH_3, 92% ee

Scheme 40: (i) CuOTf (10 mol%), **38g** (11 mol%), PhI=NTs, CH_2Cl_2, -78^0C.

Evans *et al.* [45]

Copper (I) and (II) salts such as CuOTf, $Cu(OTf)_2$, *etc*. were found to be superior catalysts compared to other metal complexes such as Mn-(TPP)Cl, Fe-(TPP)Cl, $Rh_2(OAc)_4$ and $Co(acac)_2$ for the aziridination of olefins employing PhI=NTs as a nitrene source. Asymmetric version of this reaction was also developed using bis(oxazolines) **39 a-e** with CuOTf ; ee up to 97% was achieved (**Scheme 41**).

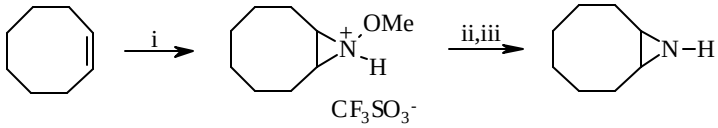


ee: 19-97%
Yield: 16-96%

Scheme 41: (i) PhI=NTs, CuOTf (10 mol%), **39a-e**.

Vedejs *et al.*[46]

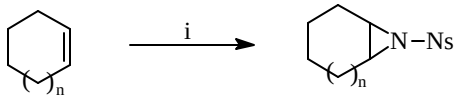
Electron rich alkenes are converted into N-methoxyaziridines by treatment with $HN(OMe)_2$ and trimethylsilyl triflate. Reduction with Li/ammonia afforded the aziridines (**Scheme 42**).



Scheme 42: (i) $HN(OMe)_2$, TMSOTf; (ii) NaOH; (iii) Li/NH_3.

Muller *et al.* [47]

The $Rh_2(OAc)_4$ catalyzed decomposition of PhI=NNs (Ns: *p*-nitrobenzenesulfonyl) in the presence of olefins afforded aziridines in 18-85% yield. With chiral catalysts asymmetric induction up to 73% ee was obtained (**Scheme 43**).



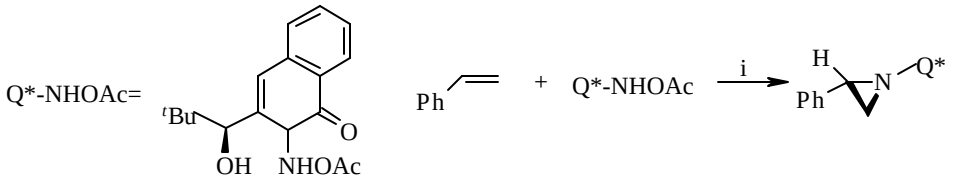
Scheme 43: (i) $Rh_2(OAc)_4$, PhI=NNs, CH_2Cl_2.

Perez *et al.*[48]

The copper (I) complex Tp'Cu(C_2H_4) [Tp'= hydrotris(3,5-dimethyl-1-pyrazolyl)borate] catalyzes nitrene transfer from PhI=NTs to olefins to produce aziridines in 40-90% yields.

Atkinson *et al.*[49]

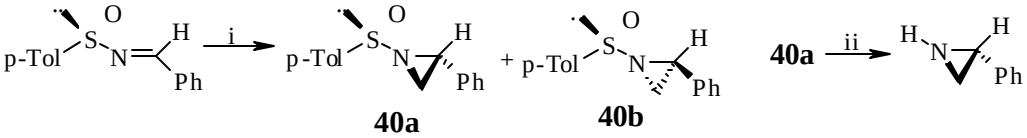
3-Acetoxyaminoquinazoline in the presence of Ti(O^tBu)$_4$, aziridinates olefins such as styrene, butadiene and indene in a stereoselective manner (**Scheme 44**).



Scheme 44: (i) Ti(O^tBu)$_4$, CH_2Cl_2.

Ruano *et al.*[50]

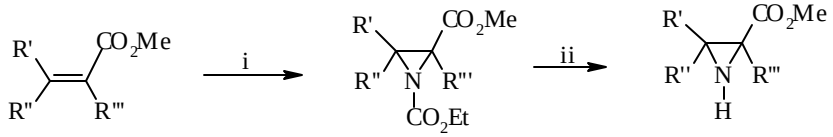
The reaction of optically pure N-sulfinyl phenylamine with dimethyloxosulfonium methylide afforded a mixture of N-sulfinylaziridines **40a-b**, epimers at C_2, which are easily separated. The sulfinyl group can be eliminated under mild conditions to give optically pure phenylaziridines (**Scheme 45**).



Scheme 45: (i) Me_2SOI, base, THF; (ii) MeLi, THF, -78^{0}C.

Pellacani *et al.*[51]

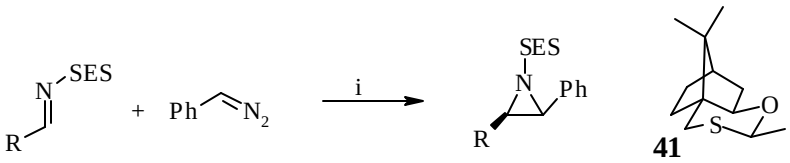
a,*b*-Unsaturated esters were aziridinated (**Scheme 46**) using CaO and ethyl N-[(4-nitrobenzenesulfonyl)oxy]carbamate ($NsONHCO_2Et$) in good yields (57-72%).



Scheme 46: (i) $NsONHCO_2Et$, CaO, CH_2Cl_2; (ii) MeONa, MeOH.

Aggarwal *et al.*[52]

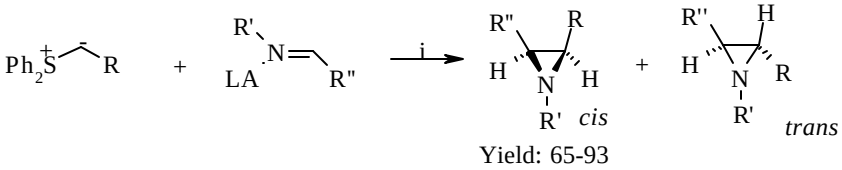
A new method for the preparation of aziridines from SES {N-[*b*-(trimethylsilyl)ethanesulfonyl]} protected imines and diazo compounds using Rh-catalyst in presence of sulfide as co-catalyst was developed. The use of chiral sulfide **41** derived from (+)-camphor sulfonyl chloride gave the required aziridine (55% yield, 97% ee) (**Scheme 47**).



Scheme 47: (i) $Rh_2(OAc)_4$ or $Cu(acac)_2$ (1 mol%), **41** (20 mol%).

Wang *et al.*[53]

Aziridines were prepared in high yields and stereoselectivity by aziridination of N-aryl or N-alkyl imines with S-ylides in the presence of Lewis acids (**Scheme 48**).

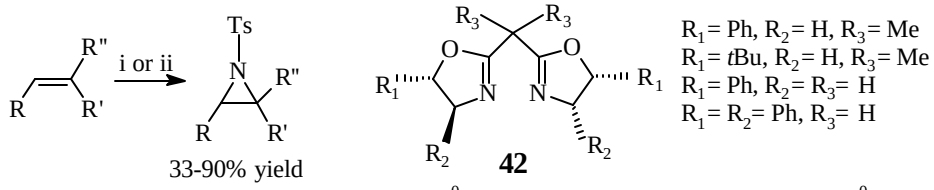


Yield: 65-93

Scheme 48: (i) -78^0C-RT, Me_3SiCl or $BF_3.OEt_2$, THF.

Langham *et al.*[54]

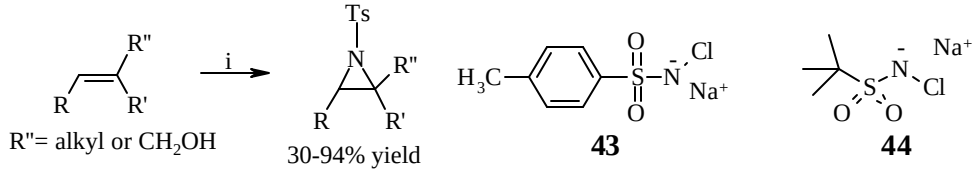
Copper-exchanged zeolite Y was used as a highly active catalyst for the aziridination of olefins. Modification of the catalyst with chiral bis(oxazolines) **42** induced enantioselectivity upto 61% ee (**Scheme 49**).



Scheme 49: (i) CuHY, PhI=NTs, CH_3CN, 25^{0}C or (ii) CuHY, **42**, PhI=NTs, CH_3CN, 25^{0}C.

Sharpless *et al.*[55]

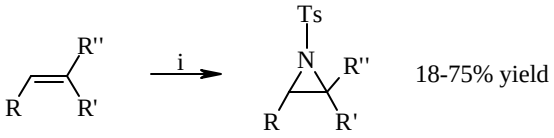
Aziridination of olefins and allylic alcohols by Chloramine-T (**43**) or N-chloramine salt of *tert*-butylsulfonamide **44** was carried out using PTAB (phenyltrimethylammonium tribromide, $PhNMe_3^+Br_3^-$) as catalyst (**Scheme 50**).



Scheme 50: (i) PTAB (10 mol%), anhydrous **43** or **44**, CH_3CN, RT.

Minakata *et al.*[56]

Various Cu(I) and Cu(II) salts were used as catalysts for aziridination of olefins with Chloramine-T as the nitrogen source (**Scheme 51**).[56a] Catalytic amount of iodine was also used for the same reaction. Use of neutral buffer (phosphate buffer, pH 6.86) improved the yield of the aziridines.[56b]

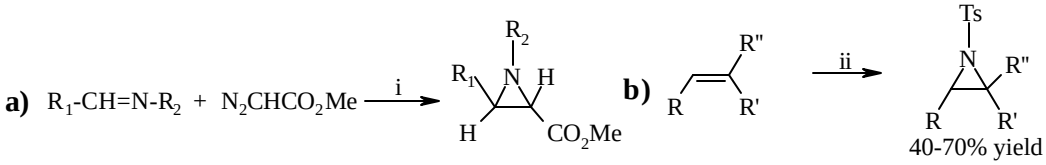


Scheme 51: (i) CuCl (5 mol%) or catalytic I_2, Chloramine-T, MS 5 Å, CH_3CN, 25^{0}C.

Sudalai *et al.*[57]

A heterogeneous catalytic method for the preparation of *trans*-aziridines from imines and methyl diazoacetate was developed using Rh^{III} and Mn^{III}-exchanged montmoritinolite K 10 clays as catalysts (**Scheme 52a**). Same group reported pyridinium

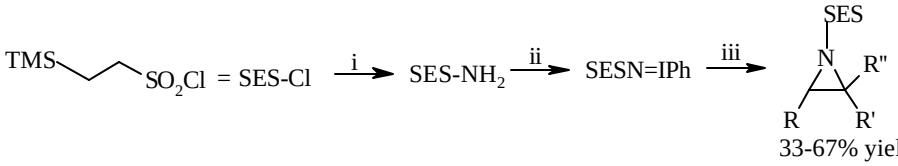
hydrobromide perbromide as a catalyst for the aziridination of electron deficient as well as electron rich olefins using Chloramine-T as a nitrogen source (**Scheme 52b**).



Scheme 52: **52a**: (i) Rh-clay (10% m/m), benzene, reflux. **52b**: (ii) $Py.HBr_3$ (10 mol%), Chloramine-T, CH_3CN, 25^0C.

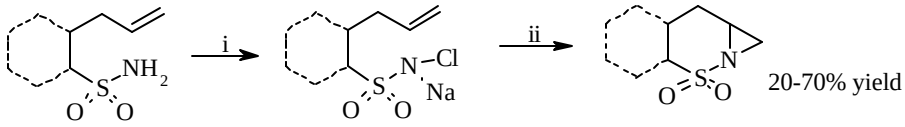
Dauban *et al.*[58]

PhI=N-SES (SES= $Me_3SiCH_2CH_2SO_2$) reacted with olefins in presence of catalytic amount of CuOTf to give the corresponding N-SES aziridines in synthetically useful yields (**Scheme 53**).



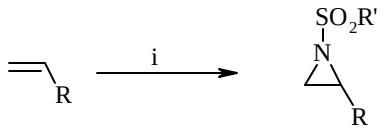
Scheme 53: (i) NH_3, CH_2Cl_2; (ii) $PhI(OAc)_2$, KOH, MeOH, 95-100%; (iii) olefin, CuOTf, MS 4Å, CH_3CN.

N-Chloramine salts of *w*-unsaturated sulfonamides were allowed to react in intramolecular fashion in the presence of PTAB to yield bicyclic aziridines (**Scheme 54**).



Scheme 54: (i) *t*-BuOCl, NaOH, H_2O, RT, 1 h; (ii) PTAB, CH_3CN, RT, 24 h.

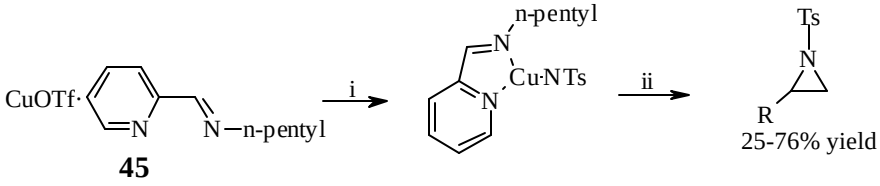
Dauban *et al.* have also developed a direct copper-catalyzed nitrogen transfer mediated by the powerful oxygen atom donor iodosylbenzene (PhI=O) to afford aziridines (**Scheme 55**). Use of chiral oxazoline ligands afforded corresponding chiral aziridines in 59-86% ee.



Scheme 55: (i) PhI=O, R'SO_2NH_2, $Cu(CH_3CN)_4PF_6$ (10 mol%), CH_3CN, MS 3Å.

Taylor *et al.*[59]

Cu-catalyst **45** was used for aziridination of olefins using Chloramine-T. $3H_2O$ as a nitrogen source (**Scheme 56**).

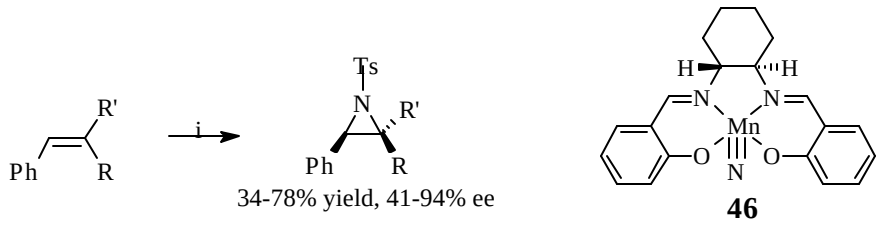


45

Scheme 56: (i) Chloramine-T, $3H_2O$ (**43**); (ii) olefin, CH_3CN, 3 days.

Komatsu *et al.*[60]

The chiral nitridomanganese complex **46** was used to carry out aziridination of styrenes to afford N-tosylaziridines in good to excellent ee. Additive like Ts_2O (*p*-toluenesulfonic anhydride) was found to be effective for the activation of the complex **46**. Both the yield and ee were improved by the addition of pyridine N-oxide (**Scheme 57**).

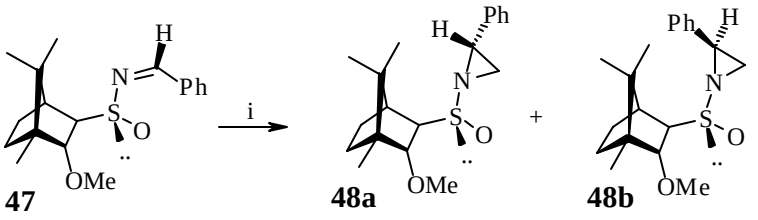


46

Scheme 57: (i) **46**, pyridine, Ts_2O, pyridine N-oxide, CH_2Cl_2, 0^0C, 3 h.

Zhu *et al.*[61]

Addition of dimethyloxosulfonium methylide, Me_2SOI, to chiral non-racemic pure (+)-camphor derived sulfinimine **47**, afforded sulfinyl aziridines **48 a-b**, which are readily separable. The sulfinyl auxiliary can be removed without ring opening by the treatment with MeLi (**Scheme 58**).

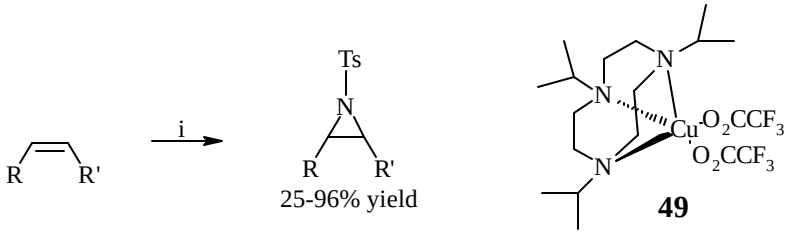


47 **48a** **48b**

Scheme 58: (i) base, Me_2SOI, THF.

Halfen *et al.*[62]

Copper complex **49** was used as a catalyst for aziridination of olefins using PhI=NTs as nitrogen source (**Scheme 59**).

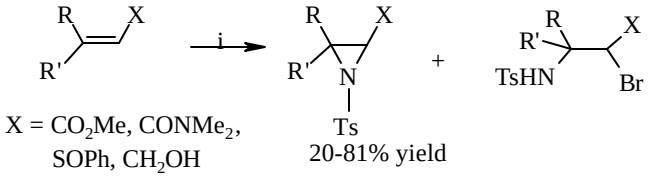


49

Scheme 59: (i) **49**, PhI=NTs, CH_3CN.

Antunes *et al.*[63]

Pd-Catalyzed one pot procedure for preparation of N-tosyl aziridines was developed using Bromamine-T as nitrogen source (**Scheme 60**).



Scheme 60: (i) $PdCl_2$ (20 mol%), Bromamine-T (1.2 equiv.), CH_3CN, RT.

Bedekar *et al.*[64]

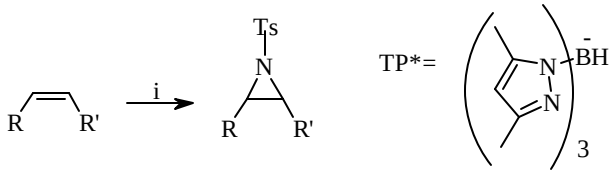
Variety of transition metal salts such as $CuCl_2$, $NiCl_2$, $CoCl_2$, $FeCl_3$, $MnCl_2$, $MgCl_2$, $SrCl_2$, $CuBr_2$, *etc*. were used as catalysts for aziridination of olefins using Bromamine-T as nitrogen source.

Nguyen *et al.*[65]

Methyltrioxorhenium (MTO) was found to catalyze the transfer of nitrene unit of PhI=NTs to a number of olefins providing aziridines in moderate to good yields (28-70%).

Handy *et al.*[66]

Copper-poly(pyrazolyl)borate complex generated in situ from copper chloride and a sodium poly(pyrazolyl)borate salt was found to be effective catalyst for the aziridination of variety of olefins (**Scheme 61**).



Scheme 61: (i) TP*Na (10 mol%), CuCl (10 mol%), PhI=NTs, CH_3CN, RT.

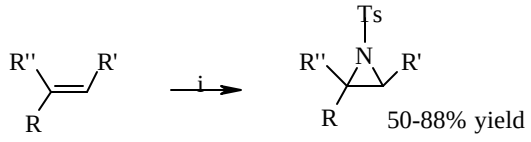
4.2.3 Present Work

4.2.3.1 Objective

Although there are many methods available in the literature for aziridination of olefins many of them suffer from certain drawbacks such as use of metal salts, PhI=NTs as nitrogen source, limited substrate scope, *etc*. Our objective is to use nonmetallic sources such as N-bromosuccinimide (NBS) and N-bromoacetamide as catalysts for aziridination of variety of olefins including *a*, *b*-unsaturated carbonyl compounds.

4.2.4 Results and Discussion

When styrene was reacted with Chloramine-T (**43**) in the presence of catalytic amount of NBS, the corresponding aziridinated product was obtained in 65% yield. Among various solvents such as THF, CH_2Cl_2, $CHCl_3$, acetone, CH_3CN and dioxane, only CH_3CN gave the aziridinated product in reasonably good yield.



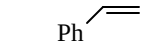
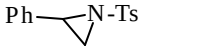
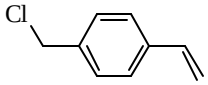
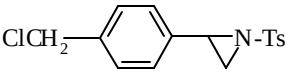
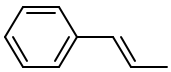
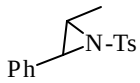
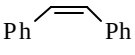
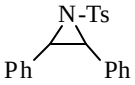
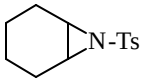
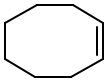
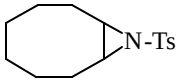
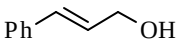
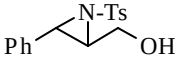
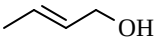
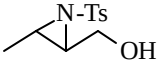
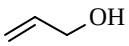
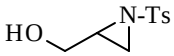
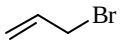
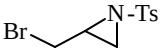
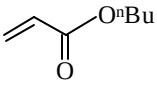
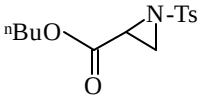
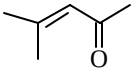
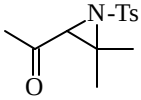
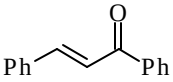
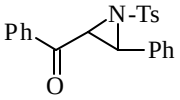
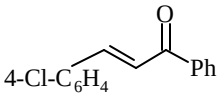
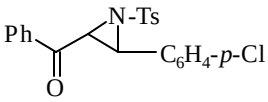
50 a-n **51 a-n**

R = Ph, Me, 4-Cl-C_6H_4, *etc*.
R' = H, CH_2OH, Me, *etc*.
R'' = H, Me

Scheme 62: (i) NBS or N-bromoacetamide (20 mol%), Chloramine-T (**43**), CH_3CN, 25^0C.

Variety of olefins **50 a-n** were successfully aziridinated to afford the corresponding aziridines **51 a-n** in moderate to good yields (**Scheme 62**). The results of aziridinations are summarized in **Table 10**.

Table 10: NBS-catalyzed aziridination of olefins (**Scheme 62**)[a].

Sr. No.	Olefin	Tine (h)	Product	Yield[b] (%)	Mp (^{0}C)
1.		8		65 (55[c])	88-89
2.		6		67	100-102
3.		6		68[d]	73-75
4.		12		75	155-157
5.		10		82	55-56
6.		11		79	123-124
7.		14		73[d]	Gum
8.		5		88	Gum
9.		8		68	Gum
10.		3		87	76-77
11.		24		51	Gum
12.		8		70	Gum
13.		28		53[d]	143-145
14.		30		50[d]	150-152

a) reaction conditions: NBS or N-bromoacetamide (20 mol%), Chloramine-T (**43**, 1 mmol), olefin (1 or 3 equiv.), CH_3CN, 25^{0}C; b) yields refer to isolated product after column chromatography; c) yield in parenthesis refer to chloramine-T.3H_2O; d) *trans* isomer formed exclusively (confirmed by *J* values in ^{1}H-NMR spectrum).

As can be seen from **Table 10**, aziridines were formed in good to excellent yields (50-88%) using Chloramine-T as nitrogen source. Chloramine-T.3H_2O also afforded the

N-(*p*-tolylsulfonyl-2-phenylaziridine from styrene in reasonable yield (55%). Variety of aromatic and non-aromatic olefins afforded the corresponding aziridines in good yields. Allylic alcohols and allyl bromide also reacted very well under these reaction conditions to afford the corresponding aziridines in excellent yields (entries 7-10). *a*, *b*-Unsaturated carbonyl compounds are of great interest for the aziridination reactions because they can act as synthons for synthesis of biologically active compounds. It may be noted that previously reported catalytic systems such as PTAB[55] and I_2[56b] were not effective against these systems. It is remarkable that NBS catalyzes the aziridination of *a*, *b*-unsaturated ester as well as ketones efficiently to afford the corresponding aziridines in 50-70% yields. However, cinnamates such as methyl cinnamate and *a*, *b*-unsaturated amides such as acrylamide failed to give aziridines under these conditions. Further 1-2 disubstituted olefins also underwent the reaction successfully. The stereochemistry of 1-2 disubstituted aziridines was found to be *trans*, confirmed by its ^{1}H-NMR spectrum (J = 4.5 Hz).

Mechanism

Although the mechanistic aspect of aziridination is not yet clear, we believe that NBS acts as the source for the generation of Br^+ species. The proposed catalytic pathway is shown in **Fig. 12**. Initially, NBS reacts with Chloramine-T to give the species **A**, which then reacts with the corresponding olefin to afford the bromonium ion **B**. The bromonium ion **B** then undergoes regiospecific opening by TsNCl$^-$ species to give *b*-bromo-N-chloro-N-toluenesulfonamide (**C**). Cyclization of **C** leads to the formation of aziridine. The reaction between Chloramine-T and Br-Cl regenerates species **A**, thus completing the catalytic cycle. It has been observed that there was very slow reaction of olefin with stoichiometric amount of NBS in the absence of Chloramine-T to yield the corresponding dibromo compounds, indicating that NBS is not directly reacting with olefin. It is quite possible that species **A** is formed first which subsequently reacts with olefin. Also we

found that N-chlorosuccinimide failed to catalyze the aziridination reaction under similar reaction conditions which indicates that species **A** is probably the key intermediate.

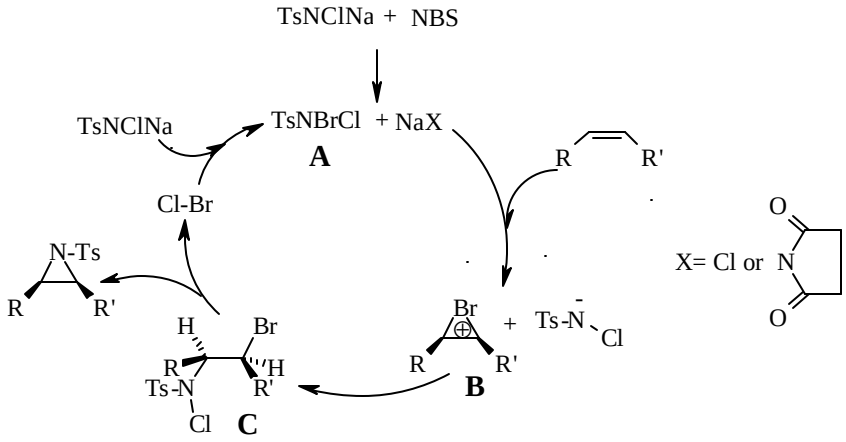


Fig. 12: Catalytic cycle for NBS-catalyzed aziridination of olefins

4.2.5 Conclusion

In conclusion, we have successfully demonstrated the use of easily available, simple, safe and cheap NBS and N-bromoacetamide as catalysts for aziridination of olefins to afford the corresponding aziridines in good to excellent yields. Under these reaction conditions *a*, *b*-unsaturated compounds also reacted efficiently to give the corresponding aziridines in 50-70% yield.

4.2.6 Experimental Section

General procedure for aziridination of olefins:

A 25 ml RB flask was charged with olefin **50 a-n** [3 mmol (1 mmol in case of *a, b*-unsaturated systems)], anhydrous Chloramine-T (0.228 g, 1 mmol) NBS or N-bromoacetamide (20 mol%) and acetonitrile (5 ml). The resulting reaction mixture was stirred at 25^0C (monitored by TLC). After completion, the reaction mixture was diluted with EtOAc (15 ml) and washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure to afford crude product, which was purified by column chromatography on silica gel using pet. ether and EtOAc as eluent to afford pure aziridines **51 a-n**.

N-(*p*-Tolylsulfonyl)-2-phenylaziridine (51a): **Yield**: 65%; **mp**: 88-89^{0}C (recrystallized from hexane-EtOAc); **IR** ($CHCl_3$, cm^{-1}): 665, 696, 715, 769, 783, 916, 1161, 1217, 1327, 3017; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.35 (d, *J* = 4.01 Hz, 1H), 2.46 (s, 3H), 2.97 (d, *J* = 7.11 Hz, 1H), 3.73-3.78 (dd, *J* = 7.11 Hz and 4.01 Hz, 1H), 7.18-7.34 (m, 7H), 7.86 (d, *J* = 8.41 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 21.53, 35.76, 40.76, 126.44, 126.91, 128.13, 128.42, 129.56, 135.08, 135.37, 144.16; **MS** m/z (% rel. intensity): 273 (M^+, 8), 171 (18), 155 (10), 118 (75), 91 (100), 65 (20); **Analysis**: $C_{15}H_{15}NO_2S$ requires C, 65.91; H, 5.53; N, 5.12; S, 11.73; found C, 65.82; H, 5.50; N, 5.21; S, 11.72%.

N-(*p*-Tolylsulfonyl)-2-(4-chloromethylphenyl)aziridine (51b): **Yield**: 67%; **mp**: 100-102^{0}C ; **IR** ($CHCl_3$, cm^{-1}): 574, 667, 754, 813, 912, 1093, 1161, 1215, 1325, 1450, 1515, 1595, 2925, 2964, 3020; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.31 (d, *J* = 4.11 Hz, 1H), 2.42 (s, 3H), 2.94 (d, *J* = 7.10 Hz, 1H), 3.69-3.75 (dd, *J* = 7.10 Hz and 4.11 Hz, 1H), 4.49 (s, 2H), 7.16-7.35 (m, 6H), 7.83 (d, *J* = 8.38 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 21.53, 35.83, 40.43, 45.50, 126.84, 127.87, 128.72, 129.67, 135.08, 135.37, 137.50, 144.45; **MS** m/z (% rel. intensity): 286 (2), 166 (100), 155 (4), 139 (74), 130 (34), 104 (29), 91 (39), 77 (26), 65 (25); **Analysis**: $C_{16}H_{16}ClNO_2S$ requires C, 59.72; H, 5.01; Cl, 11.02; N, 4.35; S, 9.96; found C, 59.62; H, 5.10; Cl, 10.88; N, 4.41; S, 9.92%.

***trans*-N-(*p*-Tolylsulfonyl)-2-methyl-3-phenylaziridine (51c)**: **Yield**: 68%: **mp**: 73-75^{0}C; **IR** ($CHCl_3$, cm^{-1}): 536, 590, 686, 750, 815, 891, 974, 1037, 1089, 1157, 1321, 1413, 1456, 1496, 1596, 2933, 3031; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.85 (d, *J* = 6.12 Hz, 3H), 2.40 (s, 3H), 2.90-2.95 (m, 1H), 3.81 (d, *J* = 4.38 Hz, 1H), 7.20-7.27 (m, 7H), 7.84 (d, *J* = 8.31 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 13.96, 21.35, 48.95, 126.18, 127.03, 128.35, 129.38,

135.41, 137.83, 143.45; **MS** m/z (% rel. intensity): 132 (100), 117 (10), 105 (70), 98 (15), 91 (40), 77 (20), 65 (18); **Analysis**: $C_{16}H_{17}NO_2S$ requires C, 67.06; H, 5.91; N, 4.88; S, 11.18; found C, 67.12; H, 5.90; N, 4.71; S, 11.12%.

***cis*-N-(*p*-Tolylsulfonyl)-2,3-diphenylaziridine (51d)**: **Yield**: 75%; **mp**: 155-157^{0}C (recrystallized from pet.ether); **IR** ($CHCl_3$, cm^{-1}): 532, 588, 657, 696, 756, 900, 1085, 1153, 1217, 1340, 1454, 1496, 1596, 3031, 3060; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.44 (s, 3H), 4.22 (s, 2H), 7.02-7.10 (m, 10H), 7.35 (d, *J* = 8.31 Hz, 2H), 7.96 (d, *J* = 8.31 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 21.53, 47.37, 127.65, 127.87, 129.75, 131.95, 134.78, 144.67; **MS** m/z (% rel. intensity): 349 (M^+, 2), 260 (13), 194 (100), 165 (13), 91 (12); **Analysis**: $C_{21}H_{19}NO_2S$ requires C, 72.18; H, 5.48; N, 4.01; S, 9.17; found C, 72.22; H, 5.44; N, 4.11; S, 9.12%.

N-(*p*-Tolylsulfonyl)-7-azabicyclo[4,1,0]heptane (51e): **Yield**: 82%; **mp**: 55-56^{0}C; **IR** ($CHCl_3$, cm^{-1}): 921, 965, 1091, 1156, 1305, 1311, 1395, 1444, 1600, 2860, 2954, 3050; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.21-1.44 (m, 5H), 1.76-1.81 (m, 3H), 2.44 (s, 3H), 2.97 (s, 2H), 7.33 (d, *J* = 8.41 Hz, 2H), 7.82 (d, *J* = 8.41 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 19.29, 21.35, 22.67, 39.62, 127.47, 129.42, 136.11, 143.79; **MS** m/z (% rel. intensity): 252 (M^+, 3), 210 (5), 155 (13), 96 (100), 92 (27), 69 (33); **Analysis**: $C_{13}H_{17}NO_2S$ requires C, 62.12; H, 6.82; N, 5.57; S, 12.76; found C, 62.22; H, 6.70; N, 5.41; S, 12.62%.

N-(*p*-Tolylsulfonyl)-9-azabicyclo[6,1,0]nonane (51f): **Yield**: 79%; **mp**: 123-124^{0}C (recrystallized from hexane); **IR** ($CHCl_3$, cm^{-1}): 610, 922, 970, 1091, 1160, 1306, 1314, 1391, 1442, 1498, 1600, 2926, 2982, 3028; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.38-1.57 (m, 10 H), 2.02 (d, *J* = 14.12 Hz, 2H), 2.44 (s, 3H), 2.76-2.81 (m, 2H), 7.33 (d, *J* = 8.48 Hz, 2H), 7.82 (d, *J* = 8.48 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 21.42, 25.10, 26.02, 26.24, 43.73, 127.39, 129.45, 135.78, 143.90; **MS** m/z (% rel. intensity): 279 (M^+, 2), 210 (10), 155 (5), 125 910), 124 9100), 98 (15), 91 (23), 90 (15); **Analysis**: $C_{15}H_{21}NO_2S$ requires C, 64.48; H, 7.58; N, 5.01; S, 11.48; found C, 64.32; H, 7.48; N, 5.11; S, 11.42%.

***trans*-N-(*p*-Tolylsulfonyl)-3-phenyl-2-aziridinemethanol (51g)**: **Yield**: 73%; **gum**; **IR** ($CHCl_3$, cm^{-1}): 549, 655, 702, 756, 813, 1001, 1159, 1232, 1326, 1452, 1598, 2883, 2925, 3028, 3506; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.41 (s, 3H), 3.19-3.23 (m, 1H), 4.04 (d, *J* = 4.12 Hz, 1H), 4.18-4.37 (m, 2H), 7.15-7.31 (m, 7H), 7.84 (d, *J* = 8.46 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 21.35, 46.34, 54.10, 60.31, 126.31, 126.81, 126.99, 128.20, 129.49, 134.34, 136.92, 144.19; **MS** m/z (% rel. intensity): 288 (3), 246 (17), 193 (15), 133 (20),

106 (20), 82 (100), 59 (40); **Analysis**: $C_{16}H_{17}NO_3S$ requires C, 63.35; H, 5.65; N, 4.62; S, 10.57; found C, 63.32; H, 5.50; N, 4.41; S, 10.42%.

***trans*-N-(*p*-Tolylsulfonyl)-3-methyl-2-aziridinemethanol (51h)**: **Yield**: 88%; **gum**; **IR** ($CHCl_3$, cm^{-1}): 549, 655, 702, 756, 813, 1001, 1159, 1232, 1326, 1452, 1598, 2883, 2925, 3028, 3506; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.44 (d, *J* = 6.18 Hz, 3H), 2.44 (s, 3H), 2.97 (d, *J* = 8.12 Hz, 2H), 3.72-3.82 (m, 1H), 3.97-4.03 (m, 1H), 7.34 (d, *J* = 8.48 Hz, 2H), 7.84 (d, *J* = 8.48 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 14.59, 21.35, 42.52, 50.53, 60.64, 126.95, 129.49, 137.28, 144.05; **MS** m/z (% rel. intensity): 241 (M+, 61), 218 (6), 193 (13), 178 (25), 139 (55), 82 (100); **Analysis**: $C_{11}H_{15}NO_3S$ requires C, 54.75; H, 6.27; N, 5.81; S, 13.29; found C, 54.62; H, 6.10; N, 5.91; S, 13.12%.

N-(*p*-Tolylsulfonyl)-2-aziridinemethanol (51i): **Yield**: 68%; **gum**; **IR** ($CHCl_3$, cm^{-1}): 545, 655, 702, 756, 813, 1101, 1155, 1232, 1322, 1452, 1598, 2883, 2925, 3028, 3520; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.44 (s, 3H), 3.35-3.55 (m, 2H), 3.85-4.09 (m, 2H), 5.36-5.50 (m, 1H), 7.32 (d, *J* = 8.48 Hz, 2H), 7.75 (d, *J* = 8.48 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 21.46, 30.91, 40.35, 60.72, 127.87, 129.67, 134.31, 144.74; **MS** m/z (% rel. intensity): 227 (M^+, 2), 184 (3), 155 (10), 91 (52), 72 (100), 65 (31); **Analysis**: $C_{10}H_{13}NO_3S$ requires C, 52.85; H, 5.77; N, 6.16; S, 14.11; found C, 52.82; H, 5.70; N, 6.21; S, 14.12%.

N-(*p*-Tolylsulfonyl)-2-aziridinebromomethane (51j): **Yield**: 87%; **mp**: 76-77^{0}C; **IR** ($CHCl_3$, cm^{-1}): 1093, 1119, 1160, 1292, 1328, 1403, 1597, 2929, 2957, 2985, 3030, 3132; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.44 (s, 3H), 3.26-3.44 (m, 1H), 3.52-3.70 (m, 1H), 4.12-4.30 (m, 2H), 5.07-5.20 (m, 1H), 7.32 (d, *J* = 8.48 Hz, 2H), 7.76 (d, *J* = 8.48 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 21.28, 33.15, 45.43, 49.84, 126.88, 129.49, 236.36, 143.64; **MS** m/z (% rel. intensity): 290 (M^+, 2), 184 (57), 155 (52), 91 (100), 65 (33); **Analysis**: $C_{10}H_{12}BrNO_2S$ requires C, 41.39; H, 4.17; Br, 27.54; N, 4.83; S, 11.05; found C, 41.32; H, 4.10; Br, 27.55; N, 4.61; S, 11.12%.

N-(*p*-Tolylsulfonyl)-2-(carbo^{n}butoxy)aziridine (51k): **Yield**: 51%; **gum**; **IR** ($CHCl_3$, cm^{-1}): 642, 692, 710, 733, 781, 816, 909, 1096, 1167, 1189, 1211, 1229, 1292, 1309, 1333, 1396, 1442, 1756, 2950; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.90 (t, *J* = 6.13 Hz, 3H), 1.26-1.38 (m, 2H), 1.56-1.65 (m, 2H), 2.41 (s, 3H), 2.57 (d, *J* = 4.11 Hz, 1H), 2.77 (d, *J* = 7.81 Hz, 1H), 3.29-3.34 (dd, *J* = 7.81 and 4.11 Hz, 1H), 4.14 (q, *J* = 6.13 Hz, 2H), 7.36 (d, *J* = 8.44 Hz, 2H), 7.85 (d, *J* = 8.44 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 12.41, 18.74, 21.46, 30.17, 31.71, 35.90, 65.68, 128.02, 129.71, 134.01, 145.04, 166.65; **MS** m/z (% rel.

intensity): 297 (M^+, 7), 242 (4), 224 (4), 155 (21), 92 (52), 86 (100), 65 (21), 57 (41); **Analysis**: $C_{14}H_{19}NO_4S$ requires C, 56.55; H, 6.44; N, 4.71; S, 10.78; found C, 56.32; H, 6.48; N, 4.71; S, 10.72%.

N-(*p*-Tolylsulfonyl)-2-acetyl-3,3'-dimethylaziridine (51l): **Yield**: 70%; **gum**; **IR** ($CHCl_3$, cm^{-1}): 551, 671, 707, 815, 881, 1091, 1159, 1326, 1380, 1598, 1722, 2929, 2977; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.30 (s, 3H), 1.82 (s, 3H), 1.97 (s, 3H), 2.44 (s, 3H), 3.48 (s, 1H), 7.34 (d, *J* = 8.44 Hz, 2H), 7.86 (d, *J* = 8.44 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 20.66, 21.25, 21.51, 28.38, 52.93, 54.85, 127.07, 129.39, 137.00, 144.09, 201.66; **MS** m/z (% rel. intensity): 267 (M^+, 2), 224 (7), 155 (14), 112 (100), 91 (23), 70 (22); **Analysis**: $C_{13}H_{17}NO_3S$ requires C, 58.41; H, 6.41; N, 5.24; S, 11.99; found C, 58.32; H, 6.40; N, 5.21; S, 11.82%.

***trans*-N-(*p*-Tolylsulfonyl)-2-benzoyl-3-phenylaziridine (51m)**: **Yield**: 53%; **mp**: 143-145^{0}C (recrystallized from $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): ; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.39 (s, 3H), 4.29 (d, *J* = 4.12 Hz, 1H), 4.52 (d, *J* = 4.12 Hz, 1H), 7.22 (d, *J* = 8.54 Hz, 2H), 7.34 (s, 5H), 7.44-7.62 (m, 3H), 7.71 (d, *J* = 8.34 Hz, 2H), 8.06 (d, *J* = 8.54 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 21.28, 47.08, 50.02, 127.25, 127.39, 128.39, 128.64, 129.27, 132.69, 133.83, 135.67, 136.33, 144.16, 190.07; **MS** m/z (% rel. intensity): 377 (M^+, 7), 278 (9), 222 (86), 167 (27), 105 (100), 91 (46), 77 (68), 65 (23); **Analysis**: $C_{22}H_{19}NO_3S$ requires C, 70.00; H, 5.07; N, 3.71; S, 8.50; found C, 70.12; H, 5.10; N, 3.81; S, 8.42%.

***trans*-N-(*p*-Tolylsulfonyl)-2-benzoyl-3-(4-chlorophenyl)aziridine (51n)**: **Yield**: 50%; **mp**: 150-152^{0}C (recrystallized from pet. ether-EtOAc); **IR** ($CHCl_3$, cm^{-1}): ; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.38 (s, 3H), 4.25 (d, *J* = 4.11 Hz, 1H), 4.48 (d, *J* = 4.11 Hz, 1H), 7.20-7.28 (m, 6H), 7.42-7.61 (m, 3H), 7.69 (d, *J* = 8.44 Hz, 2H), 8.03 (d, *J* = 8.42 Hz, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 21.50, 46.49, 50.17, 127.62, 128.87, 129.49, 131.51, 134.08, 135.00, 136.02, 137.21, 144.49, 189.99; **MS** m/z (% rel. intensity): 411 (M^+, 6), 307 (3), 278 (6), 255 (100), 227 (12), 201 (19), 165 (39), 139 (13), 105 (45), 90 (26), 77 (50); **Analysis**: $C_{22}H_{18}ClNO_3S$ requires C, 64.15; H, 4.40; Cl, 8.61; N, 3.40; S, 7.79; found C, 64.32; H, 4.32; Cl, 8.55; N, 3.41; S, 7.71%.

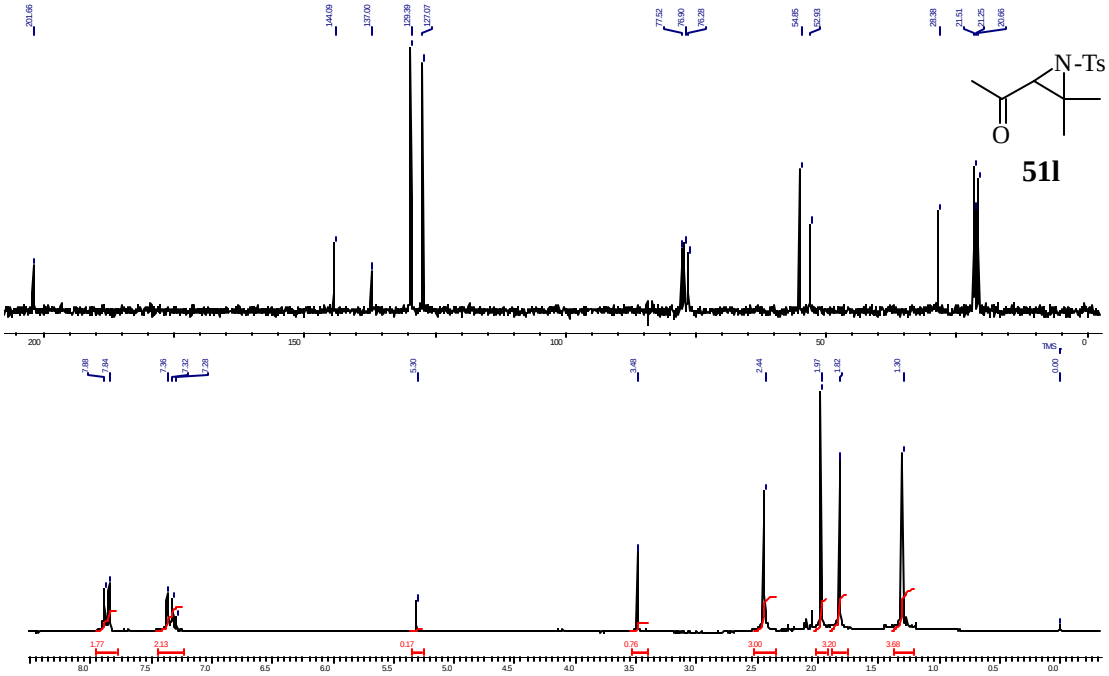


Fig. 13: ^{1}H and ^{13}C-NMR spectra of 51l

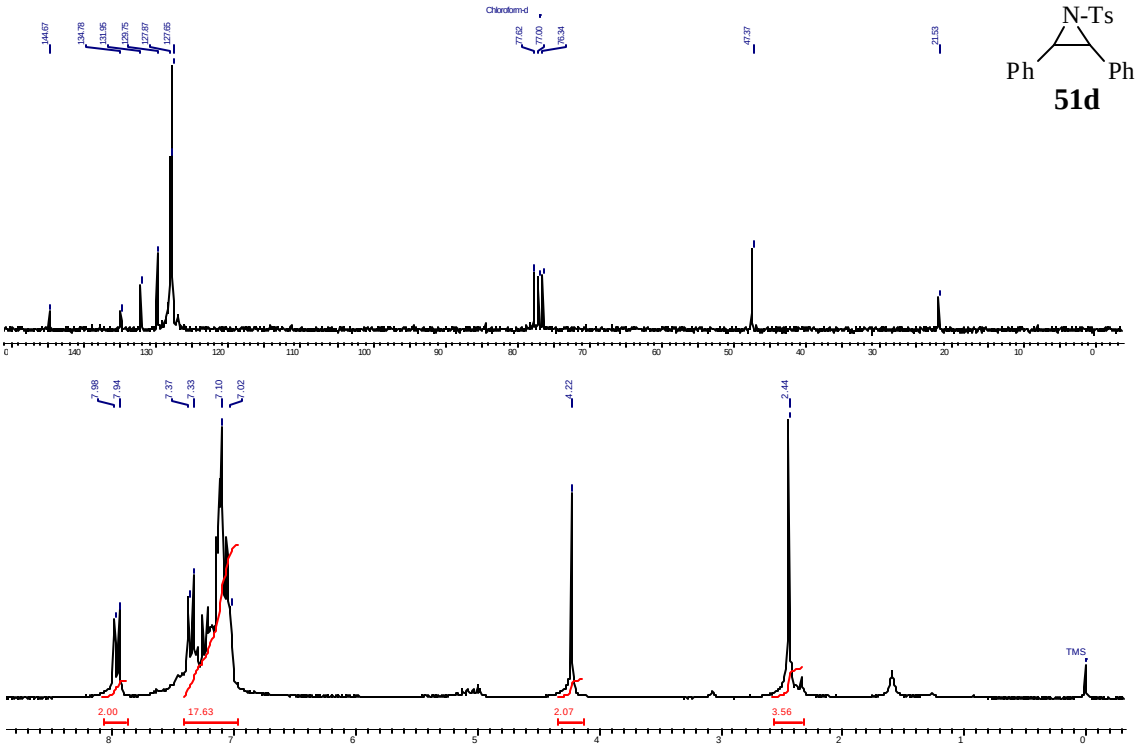


Fig. 14: ^{1}H and ^{13}C-NMR spectra of 51d

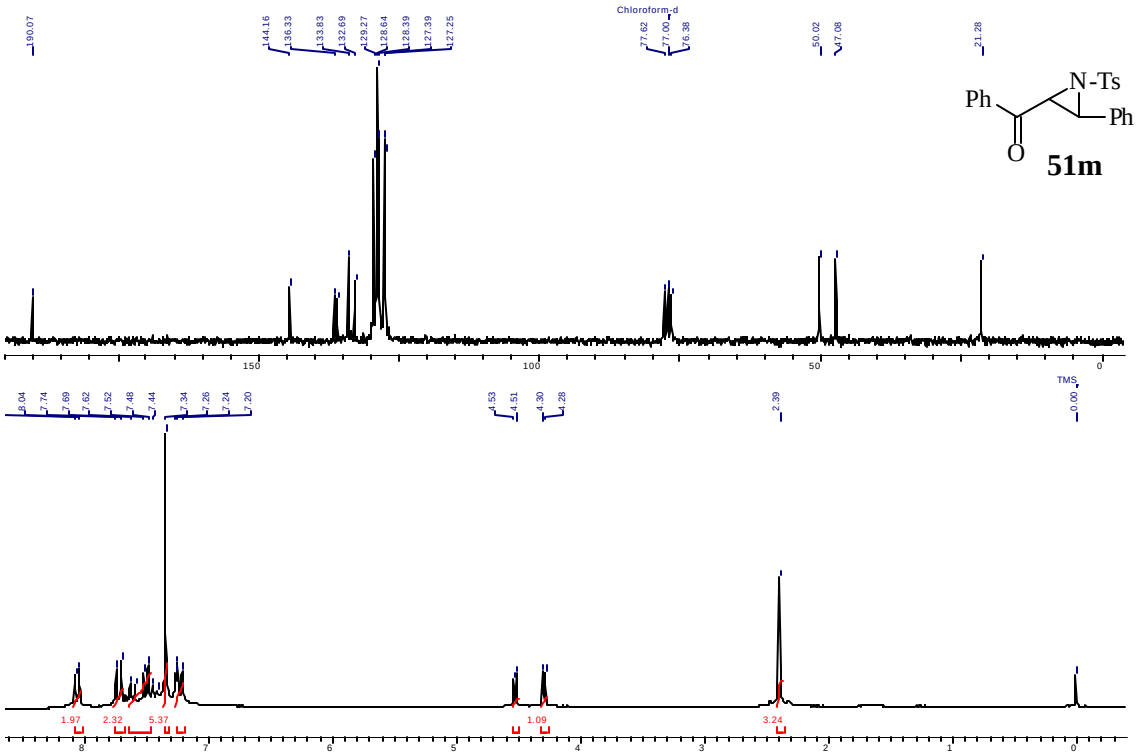


Fig. 15: ^{1}H and ^{13}C-NMR spectra of 51m

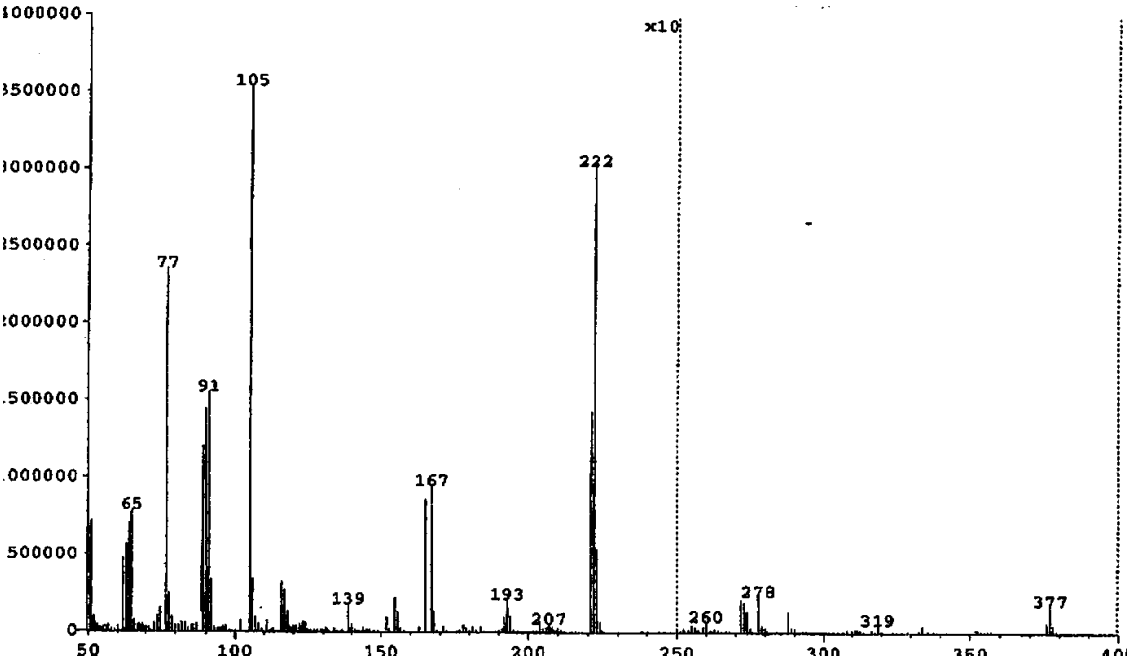


Fig. 16: Mass spectrum of 51m

4.2.7 References

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