Asymmetric Synthesis of Bioactive Molecules and Methodologies Involving Oxidative Functionalization of Alkanes, Alkenes and Hydrosilylation of Ketones

A THESIS

SUBMITTED FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

(IN CHEMISTRY)

To

UNIVERSITY OF PUNE

By

Pandurang Vilasrao Chouthaiwale

UNDER THE GUIDANCE OF

Dr. A. Sudalai

Chemical Engineering and Process Development Division

National Chemical Laboratory

Pune- 411008, INDIA

March 2011

DEDICATED TO

MY BELOVED FAMILY

MEMBERS

AND

FRIENDS

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

CERTIFICATE

Certified that the work incorporated in the thesis entitled "**Asymmetric Synthesis of Bioactive Molecules and Methodologies Involving Oxidative Functionalization of Alkanes, Alkenes and Hydrosilylation of Ketones**" 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.

March 2011 **(Dr. A. Sudalai)**

Pune Research Supervisor

NATIONAL CHEMICAL LABORATORY

DECLARATION

I here by declare that the thesis entitled **"Asymmetric Synthesis of Bioactive Molecules and Methodologies Involving Oxidative Functionalization of Alkanes, Alkenes and Hydrosilylation of Ketones"** submitted for the degree of Doctor of Philosophy in Chemistry to the University of Pune, has not been submitted by me to any other university or institution. This work was carried out at the National Chemical Laboratory, Pune, India.

March 2011
Pune

Pandurang Vilasrao Chouthaiwale
CE & PD Division
National Chemical Laboratory
Pune – 411 008

CONTENTS

		Page No.
Acknowledgements		i
Abbreviations		iii
General Remarks		v
Abstract		vi
Chapter I	**Cobalt-catalyzed Hydrolytic Kinetic Resolution of Azido Epoxides: A Short Enantioselective Synthesis of (+)-*Epi*-cytoxazone, (-)-Cytoxazone and (+)-2-Oxazolidone**	
Section I	**Cobalt-catalyzed hydrolytic kinetic resolution of azido epoxides**	
1.1.1	Introduction	1
1.1.2	Hydrolytic kinetic resolution (HKR)	1
1.1.3	Review of Literature	4
1.1.4	Present Work	8
1.1.4.1	Objective	8
1.1.5	Results and Discussion	8
1.1.5.1	Synthesis of racemic azido epoxide	9
1.1.5.2	HKR of racemic azido epoxide	13
1.1.6	Conclusion	18
1.1.7	Experimental Section	18
Section II	**Enantioselective synthesis of (+)-*epi*-Cytoxazone and (-)-Cytoxazone *via* hydrolytic kinetic resolution of azido epoxides**	
1.2.1	Introduction	25
1.2.2	Pharmacology of cytoxazone	25
1.2.3	Review of Literature	26
1.2.4	Present Work	36
1.2.4.1	Objective	36
1.2.5	Results and Discussion	36
1.2.6	Conclusion	45
1.2.7	Experimental Section	45

Section III	**Formal synthesis of *N*-thiolated 2-oxazolidone**	
1.3.1	Introduction	49
1.3.2	Pharmacology of *N*-thiolated 2-oxazolidinone	49
1.3.3	Review of Literature	50
1.3.4	Present Work	51
1.3.4.1	Objective	51
1.3.5	Results and Discussion	51
1.3.6	Conclusion	56
1.3.7	Experimental Section	56
1.3.8	References	58
Chapter II	**Enantioselective Synthesis of (+)-L-733,060 *via* Hydrolytic Kinetic Resolution of Azido epoxide and Synthesis of (S)-Dapoxetine *via* Sharpless Asymmetric Epoxidation**	
Section I	**A short enantioselective synthesis of (+)-L-733,060 *via* hydrolytic kinetic resolution of azido epoxide**	
2.1.1	Introduction	61
2.1.2	Review of Literature	62
2.1.3	Present Work	70
2.1.3.1	Objective	70
2.1.4	Results and Discussion	71
2.1.5	Conclusion	78
2.1.6	Experimental Section	79
Section II	**Enantioselective synthesis of (*S*)-dapoxetine *via* Sharpless asymmetric epoxidation**	
2.2.1	Introduction	87
2.2.2	Dapoxetine and Pharmacology	87
2.2.3	Review of Literature	88
2.2.4.	Present Work	93
2.2.4.1	Objective	93
2.2.4.2	Sharpless asymmetric epoxidation	94
2.2.5	Results and Discussion	96
2.2.6	Conclusion	102
2.2.7	Experimental Section	102

2.2.8	References	107
Chapter III	**$NaIO_4$-mediated Azidoiodination of Olefins, 1,2-Diazidation of Olefins and α,α-Diazidation of Aryl Ketones and C-H Functionalization of Hydrocarbons**	
Section I	**$NaIO_4$–KI-NaN_3–mediated regioselective azidoiodination of alkenes**	
3.1.1	Introduction	110
3.1.2	Review of Literature	110
3.1.3	Present Work	114
3.1.3.1	Objective	114
3.1.4	Results and Discussion	114
3.1.5	Mechanism	118
3.1.6	Conclusion	118
3.1.7	Experimental Section	119
Section II	**$NaIO_4$–NaN_3–mediated diazidation of olefins and α,α-diazidation of aryl ketones**	
3.2.1	Introduction	123
3.2.2	Review of Literature	123
3.2.3	Present Work	126
3.2.3.1	Objective	126
3.2.4	Results and Discussion	126
3.2.4.1	1,2-Diazidation of alkenes	126
3.2.4.2	α,α-Diazidation of aryl ketones	129
3.2.5	Conclusion	132
3.2.6	Experimental Section	132
Section III	**$NaIO_4$–KI-NaN_3–mediated C-H functionalization of hydrocarbons**	
3.3.1	Introduction	137
3.3.2	Review of Literature	137
3.3.3	Present Work	142
3.3.3.1	Objective	142
3.3.4	Results and Discussion	142
3.3.4.1	Direct iodination of alkanes	142

3.3.4.2	Direct azidation at benzylic position	147
3.3.5	Mechanism	150
3.3.6	Conclusion	151
3.3.7	Experimental Section	152
3.3.8	References	158
Chapter IV	**Palladium-catalyzed Hydrosilylation of Aryl Ketones and Enantioselective Rearrangement of 2-Alkyl Pyridine *N*-oxides and Synthesis of 4-Substituted Chromanes *via* Gold-catalyzed Intramolecular Friedel-Crafts Reaction**	
Section I	**Palladium catalyzed hydrosilylation of aryl ketones with triethylsilane**	
4.1.1	Introduction	161
4.1.2	Review of Literature	161
4.1.3	Present Work	167
4.1.3.1	Objective	167
4.1.4	Results and Discussion	168
4.1.5	Mechanism	174
4.1.6	Conclusion	175
4.1.7	Experimental Section	175
Section II	**Enantioselective rearrangement of 2-alkyl pyridine *N*-oxides**	
4.2.1	Introduction	181
4.2.2	Review of Literature	181
4.2.3	Present Work	187
4.2.3.1	Objective	187
4.2.4	Results and Discussions	187
4.2.5	Mechanism	191
4.2.6	Conclusion	192
4.2.7	Experimental Section	192
Section III	**Synthesis of 4-substituted chromanes *via* gold-catalyzed intramolecular Friedel-Crafts reaction of 3-aryloxy benzyl alcohols**	
4.3.1	Introduction	195
4.3.2	Review of Literature	195

4.3.3	Present Work	199
4.3.3.1	Objective	199
4.3.4	Results and Discussions	199
4.3.5	Mechanism	203
4.3.6	Conclusion	204
4.3.7	Experimental Section	204
4.3.8	References	210
	List of Publications	213

ACKNOWLEDGEMENT

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

I thank Dr. B. D. Kulkarni sir, Deputy Director and Head, CE-PD division, for his help and support. My special thanks go to Dr. S. Gurunath for his constant encouragement and moral support. I also want to thank Dr. Bhaval, Dr. V.G. Kulkarni Dr. G. Pandey, Dr. S. P. Chavan, Dr. Thulasiram, Dr. Kalkote, Dr. Mulla, and Dr. Ramana for their help and encouragement. I am immensely thankful to my seniors Drs. Milind, Gajanan, Vinay, Iliyas, Abhimanyu, Shriram, Sivakumar, Srinu, Ramesh, Arun and Victor, for useful training in the initial phase of my career which made me what I am today.

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

I wish to thank my friendly and cooperative lab mates Drs. Emmanuvel, Tanveer, and Shyla, Santhosh, Pratibha, Varun, Dayanand, Chaithanya, Senthil, Dattatraya, Venkat, Brij, Souman, Sunita, Ravindra, Anil, Komal, Deepak, Ravi, Asif, Ramchandra, Sawant, Balaji, Prakash, Vijay, Hari, Kuppu, Amol, Satish, Santosh, Shobhana, Vandana, Geetanjali, Shaheen, Deepali, Nagesh, Nana, Rana, Baba, sandeep, Arvind and pramod for providing a cheerful atmosphere in the lab. I am also thankful to project students Rohini and Nilesh for helping me in this work.

My special thanks go to friends-cum-family Vinod (Dada), Awadut (Maharaj), Amol, Laxman, Namdev, Kulbhushan, Nagendra, Ram, Shital, Archana, Sharda, Prerna,

Pallavi, Sonali, Kalpana, Sphurti, Priya and Chotu gang Adi, Shravu, Shreya, Sharayu, Shivam, Sarthak, Arnav, Astha, Kshitija, Keya for making Home away from Home.

I am deeply indebted to my friends Deepak, Anand, Sharad, Kishan (Anna), Kiran, Bapu, Lalita, Sofia, Nitin, manmat, Nilkanth, Deepak, Sudhir, Shafi, Tatya, Satendra, Sambhaji, Dushant, Ramdas, Bhargav, Raghupati, Vasu, Aaba, Ganesh, Sulemaan, Amit, Jayprakash, wasif, Panjab, Mahesh, Bhuvan, Sunil, Umesh, Prasad, Mahesh, Majid, Kishor, Dharmedra, Pinak, Sangram, Tukaram, Sachin, Ravi, Mangesh, Pushpesh, Abhishek, Divya, Sijo, Aarif, Pranjal, Srinivas, Panchami, Kishor, Baag, Bhalchandra, Bhaskar, Prassana, Ravindra, Rajedra, Debashis, Swarup, Bharat, Om, Harish, vivek, Indu, Sitaram, Sabita, Srinivas, Venkatesh, Palimkar, Suresh, Chopade, Vijay, Shailesh, Pankaj, Sangmesh, Mahendra, Abhijeet .

I acknowledge all my college teachers Drs. Despande, Sharma, Kuberkar, Gurav, Vibhute, Kulkarni, Dawne, Shaikh, Wartale and friends Drs. Bhosale, Badne and Madje, Bharat, Prasad, Bhagwat. I am greatly indebted to my school teacher Dr. Bhramane sir for igniting the spark of science in me.

Without understanding what I am doing, my beloved parents have supported me through out my career with lots of patience. I am indeed very grateful to them whose constant love, care, support and encouragement have been the main force and motivation so far and will continue so in the days to come. The best wishes of my Late.brother Dnyanoba, sisters and nephews have made me what I am and I owe much to them. I also thank my uncle, brothers Tukaram, and Pundalik for their support, also, my in-laws for their best wishes. Special thanks to my Grandmother and Mamas for their blessings.

I wish to thank Shital, my wife, for her love, affection and support extended to me during this work

Finally, I wish to thank great scientific community whose achievements are constant source of inspiration for me.

Pandurang V. Chouthaiwale

ABBREVATIONS

Ac	Acetyl
Ar	Aryl
Bn	Benzyl
Boc	*N-tert*-Butoxycarbonyl
$(Boc)_2O$	Ditert-butyl dicarbonate
n-Bu	*n*-Butyl
n-BuLi	*n*-Butyl Lithium
CAN	Cerric ammonium nitrate
Cbz	Benzyloxy carbonyl
CH_2Cl_2	Methylene chloride
$CHCl_3$	Chloroform
CH_3CN	Acetonitrile
$CuSO_4$	Copper(II) sulfate
DBU	1,8-Diazabicyclo[5.4.0]undecene-7
DIBAL-H	Diisobutyl alulinum hydride
DET	Diethyl Tartarate
DMF	Dimethyl formamide
DMSO	Dimethyl sulphoxide
DMAP	*N,N*-dimethyl-4-aminopyridine
ee	Enantiomeric excess
Et	Ethyl
Et_3N	Triethylamine
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
EtOH	Ethyl alcohol
g	Grams
h	Hours
HCl	Hydrochloric acid
HPLC	High pressure liquid chromatography
H_2SO_4	Sulfuric acid
IR	Infra red
IBX	2-Iodoxybenzoic acid
KHMDS	potassium hexamethyl disilazide
K_2CO_3	Potassium carbonate
KOH	Potassium hydroxide
$LiAlH_4$	Lithium aluminum hydride
LDA	Lithium diisopropyl amide
LiHMDS	Lithium hexamethyl disilazide
M+	Molecular ion
Me	Methyl
MeOH	Methyl alcohol

MOM	Methoxymethyl
min	Minutes
mL	Milliliter
mp	Melting point
MS	Mass spectrum
Ms	Mesyl
$NaBH_4$	Sodium borohydride
$NaHCO_3$	Sodium bicarbonate
NaOH	Sodium hydroxide
Na_2SO_4	Sodium sulfate
NH_4Cl	Ammonium chloride
NH_4OH	Ammonium hydroxide
NBS	*N*-Bromosuccinimide
NMR	Nuclear Magnetic Resonance
NMO	*N*-Methyl morpholine *N*-oxide
Pd/C	Palladium on activated charcoal
Pet. ether	Petroleum ether
Ph	Phenyl
p-TSA	*p*-Toluene sulfonic acid
PhNO	Nitrosobenzene
Py	Pyridine
Red-Al	Bis(2-methoxyethoxy)aluminum hydride
TBS	*tert*-Butyldimethylsilyl
TBHP	*tert*-Butyl hydroperoxide
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TBAF	Tetrabutylammonium fluoride
TBDMSCl	*tert*-Butyldimethylsilyl chloride
TBDPSCl	*tert*-Butyldiphenylsilyl chloride
TFA	Trifluoroacetic acid
TMSCN	Trimethylsilyl cyanide
Ts	Tosyl

GENERAL REMARKS

1. All solvents were distilled and dried before use.
2. Petroleum ether refers to the fraction collected in the boiling range 60-80 °C.
3. Organic layers after every extraction were dried over anhydrous sodium sulfate.
4. Column Chromatography was performed over silica gel (60-120 mesh).
5. TLC analyses were performed over aluminum plates coated with silica gel (5-25 m) containing UV active G-254 additive.
6. IR spectra were recorded on a Perkin-Elmer model 683 B or 1605 FT-IR and absorptions were expressed in cm^{-1}.
7. ^{1}H and ^{13}C NMR spectra were recorded on Brucker FT AC-200 and MSL-300 MHz instruments using TMS as an internal standard. The following abbreviations were used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, brs = broad singlet, dd = doublet of doublet, dt = doublet of triplet and ddd = doublet of doublet of doublet.
8. Mass spectra (MS) were recorded on an automated finnigan MAT 1020C mass spectrometer using ionization energy of 70eV.
9. Optical rotations were carried out on JASCO-181 digital polarimeter at 25 °C using sodium D light.
10. 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 Chiral Cobalt (Salen) complexes were purchased from Aldrich

ABSTRACT

The thesis entitled "**Asymmetric Synthesis of Bioactive Molecules and Methodologies Involving Oxidative Functionalization of Alkanes, Alkenes and Hydrosilylation of Ketones**" is divided into four chapters.

The title of the thesis clearly reflects the objective, which is to synthesize enantiomerically pure bioactive molecules and to develop useful synthetic methodologies. **Chapter 1** describes the cobalt-catalyzed hydrolytic kinetic resolution of azido epoxides and their application in the asymmetric synthesis of (+)-*epi*-cytoxazone, (−)-cytoxazone and (+)-2-oxazolidone. **Chapter 2** deals with the synthesis of two bioactive molecules namely (+)-L-733,060 *via* hydrolytic kinetic resolution of azido epoxide and (*S*)-dapoxetine *via* asymmetric epoxidation of cinnamyl alcohol. **Chapter 3** presents $NaIO_4$-mediated synthetic transformations involving regioselective azido iodination and diazidation of olefins, α,α-diazidation of aryl ketones and C-H functionalization of hydrocarbons. **Chapter 4** describes synthetic transformations involving palladium-catalyzed hydrosilylation of aryl ketones, enantioselective rearrangement of 2-alkyl pyridine N-oxides (Boekelheide reaction) and synthesis of 4-substituted chromanes *via* gold-catalyzed intramolecular Friedel-Crafts reaction.

CHAPTER I

Cobalt-catalyzed Hydrolytic Kinetic Resolution of Azido Epoxides: A Short Enantioselective Synthesis of (+)-*Epi*-cytoxazone, (-)-Cytoxazone and (+)-2-Oxazolidone

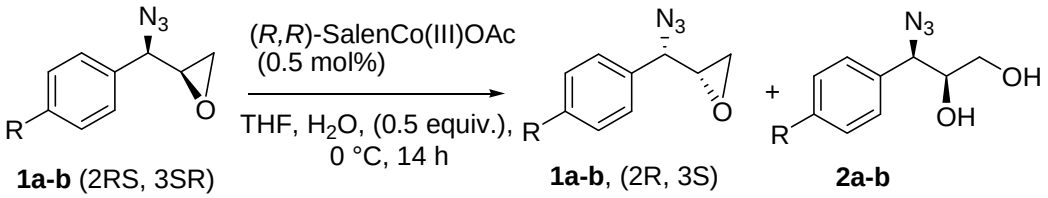
Hydrolytic kinetic resolution (HKR) developed by Jacobsen *et al.* has emerged as a powerful tool to obtain terminal epoxides as well as their corresponding diols in enantiomerically pure form.[1] These compounds are important intermediates for the synthesis of various bioactive molecules.[2] The enantiomerically pure *syn*- or *anti*-azido epoxides and the corresponding diols are also valuable 'building blocks' for the asymmetric synthesis of bioactive molecules and as chiral auxiliaries and ligands.[3] This chapter deals with the development of a novel method in which HKR of azido epoxides catalyzed by chiral (salen)Co(III)-OAc complex was employed, for the first time to produce chiral azido epoxides and azido diols, followed by its application in the

asymmetric synthesis of (+)-*epi*-cytoxazone, (–)-cytoxazone and (+)-2-oxazolidone. It is divided into three sections.

Section 1: Cobalt-catalyzed hydrolytic kinetic resolution of azido epoxides

The hydrolytic kinetic resolution of racemic *syn*- or *anti*-azido epoxide derivatives was carried out. In this strategy, the relative stereochemistry between the azide and the epoxide functions is established prior to the HKR step and thus a single asymmetric reaction is employed to form compounds with two asymmetric centers.[4] The racemic *syn*- and *anti*- azido epoxides, the substrates for HKR, were efficiently prepared in highly diastereoselective manner[5] from the corresponding (E)- and (Z)- allylic alcohols respectively, involving essentially a two-step reaction sequence of NBS-bromination in the presence of azide, as the case may be, followed by treatment with base to form the corresponding racemic epoxides. In this section, we have described a flexible, novel method that employs HKR of racemic azido epoxides to generate two stereocentres of high optical purities in a single step. When HKR of racemic *syn*-azido epoxide (±)-**1a-b** was performed with (*R,R*)-Salen Co(III)(OAc) complex (0.5 mol%) and H_2O (0.5 equiv.), the corresponding chiral epoxides **1a-b** and diols **2a-b** were isolated in high yields and optical purity (**Table 1**).

Table 1: Co-catalyzed HKR of *syn*-azido epoxides



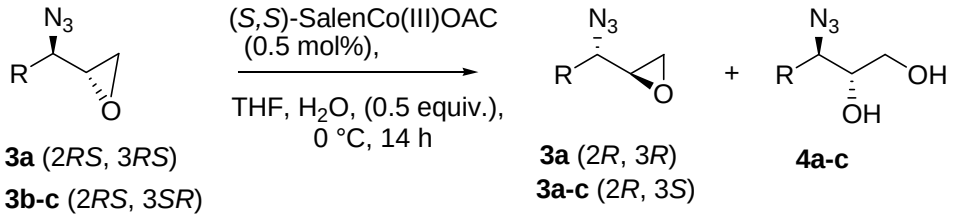
1a-b (2RS, 3SR) **1a-b**, (2R, 3S) **2a-b**

		Azido epoxides (1)		**Azido diols (2)**	
Sr.No	**R**	**Yield (%)[a]**	**ee (%)**	**Yield (%)[a]**	**ee (%)**
a	H	48	96	47	98[b]
b	OMe	48	98	48	97[b]

[a] Isolated yield after column chromatographic purification. [b]ee determined by chiral HPLC Chiralpak OD-H

Similarly, *anti* azido epoxides (±)-**3a-c**, when subjected to (*S,S*)-SalenCo(III)OAc-catalyzed HKR, produced chiral *anti*-azido epoxides (+)-**3a-c** and the corresponding *anti* diols **4a-c** with high enantio purity (**Table 2)**.

Table 2: Co-catalyzed HKR of *anti*-azido epoxides



3a (2*RS*, 3*RS*)
3b-c (2*RS*, 3*SR*)

3a (2*R*, 3*R*)
3a-c (2*R*, 3*S*)

4a-c

		Azido epoxides			Azido diols	
R		**Yield (%)[a]**	**ee (%)**	**4a-c**	**Yield (%)[a]**	**ee (%)**
CH_2OTBS	**3a**	48	96	**4a**	46	98[b]
Ph	**3b**	48	97	**4b**	47	98[c]
p-OMe- C_6H_4	**3c**	47	96	**4c**	47	97

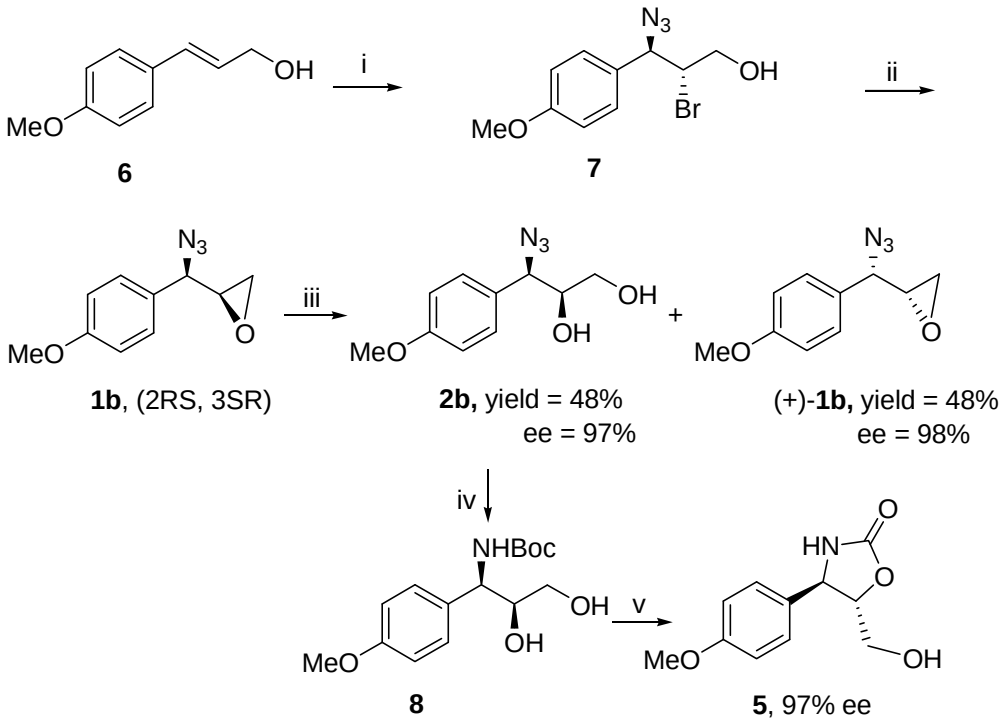
[a] Isolated yield after column chromatographic purification. [b] ee determined by Mosher's ester analysis. [c]ee determined by chiral HPLC analysis (see the ESI).

Section 2: Enantioselective synthesis of (+)-*epi*-Cytoxazone and (-)- Cytoxazone *via* hydrolytic kinetic resolution of azido epoxides

(−)-Cytoxazone and (+)-*epi*-cytoxazone, both containing a novel 4,5-disubstituted-2-oxazolidinone moiety were isolated from *Streptomyces* sp.[6] and found to exhibit cytokine-modulating activity by inhibiting the signaling pathway of Th2 cells. Inhibitors of Th2-dependant cytokine production would be a potent chemotherapeutic agent in the field of immunotherapy. In this section, we describe a concise enantioselective synthesis of (+)-*epi*-cytoxazone **5** and (−)-cytoxazone **9** using HKR of azido epoxides.

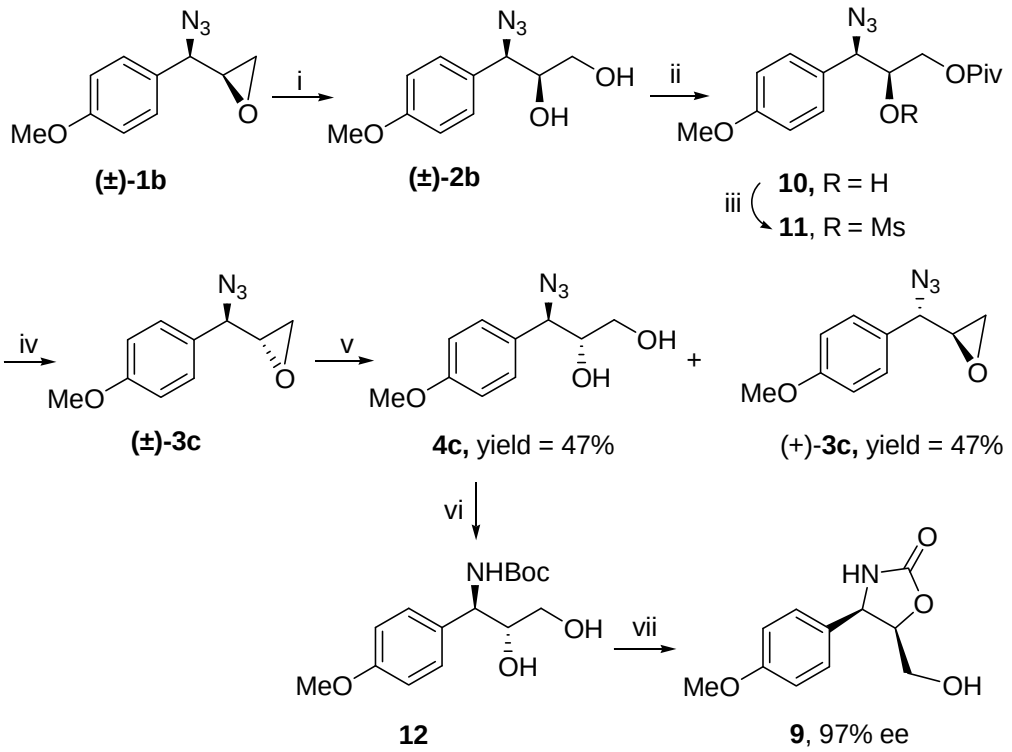
Our synthesis of (+)-*epi*-cytoxazone **5** started with the azido bromination of 4-methoxy-cinnamyl alcohol **6** using NBS and NaN_3 to give azido bromoalcohol **7** in 76% yield. Azido bromoalcohol **7** on treatment with LiOH, in THF: water (4:1) at 0 °C afforded racemic azido epoxide (±)-**1b** in 70% yield**,** which was then subjected to HKR using (*R,R)*-Co(salen)OAc to furnish the chiral azido diol **2b** in 48% chemical yield and 97% ee along with the corresponding azido epoxide (+)-**1b** in 48% yield and 98% ee. Both chiral azido diol **2b** and azido epoxide (+)-**1b** could be readily separated by column

chromatographic purification. Azido diol **2b** was then subjected to azide reduction and Boc protection [10% Pd/C, polymethylhydrosiloxane (PMHS), $(Boc)_2O$, EtOH] to give *N*-Boc amino diol **8** in 95 % yield. Finally, the regioselective intramolecular cyclization of **8** using NaH in THF gave (+)-*epi*-cytoxazone **5** in 96 % yield and 97% ee (**Scheme 1**).



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

For (-)-cytoxazone **9**, the racemic azido epoxide (±)-**1b** was subjected to epoxide opening with 0.5M aq. NaOH, *tert*-BuOH to furnish racemic azido diol **2b**. The selective protection of primary alcohol as pivolyl ester and the secondary alcohol as mesylate in **10** was carried out to give **11** in 95% yield. The subsequent hydrolysis of **11** with K_2CO_3, in methanol gave the racemic azido epoxide **(±)-3c** in 81% yield. Recemic azido epoxide **(±)-3c** was then subjected to HKR using (*S,S)*-Co(salen)OAc to furnish the required chiral azido diol **4c** in 47% chemical yield and 97% ee along with azido epoxide (+)-**3c** in 47% yield and 96% ee. Azido diol **4c** was transformed to (-)-cytoxazone **9** using standard sequence of reactions *via* azide reduction, amine protection followed by base-mediated cyclization (**Scheme 2**).

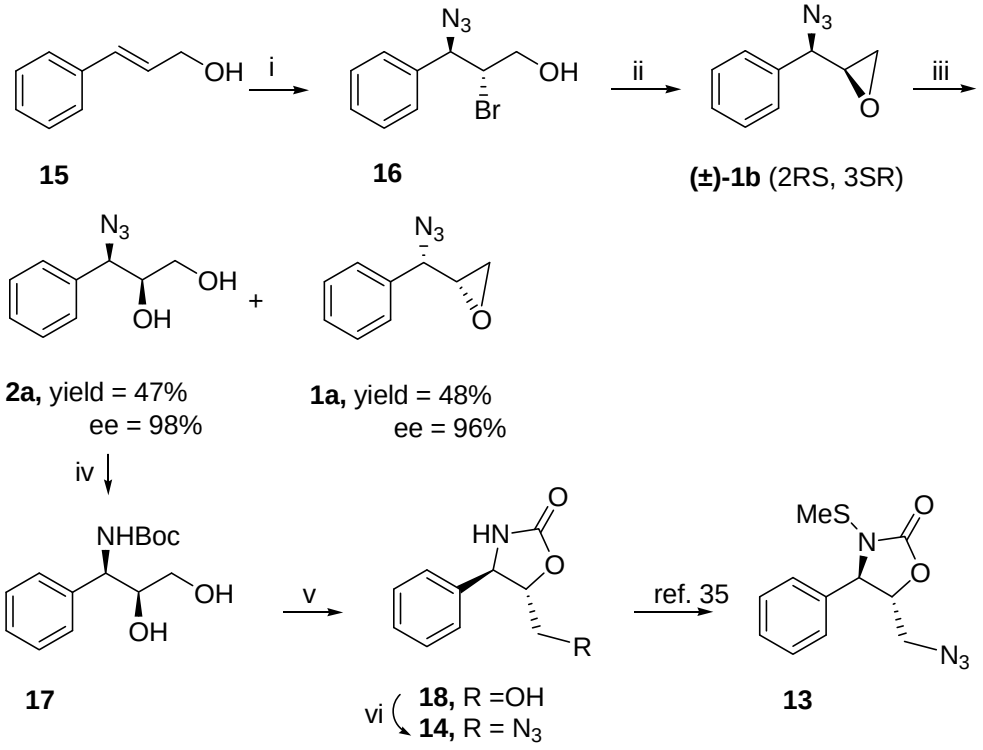


Scheme 2: (i) 0.5N aq. NaOH, *tert*-BuOH, 12 h, 70 °C, 90%; (ii) PivCl, Pyridine/CH_2Cl_2 (1: 1), 0 °C, 5 h, 96%; (iii) MsCl, Et_3N, DMAP, CH_2Cl_2, 25 °C, 10 h, 90%; (iv) K_2CO_3, MeOH, 25 °C, 6 h, 81% over two step; (v) (*S,S*)-Co(salen)OAc (0.5 mol%), THF, H_2O (0.5 equiv.), 0 ºC, 14 h; (vi) poly(methylhydrosiloxane) (PMHS), 10% Pd/C, $(Boc)_2O$, EtOH, 25 °C, 4 h, 90%; (vii) NaH, dry THF, 25 °C, 3 h.

Section 3: Formal synthesis of *N*-thiolated 2-oxazolidone

Recent studies have shown that N-thiolated 2-oxazolidinone **13** possesses antibacterial activity against methicillin-resistant *Staphylococcus aureus* and *Bacillus anthracis*.[7] This section deals with the synthesis of (+)-2-oxazolidone **14**, precursor to **13**, Our synthesis starts with commercially available cinnamyl alcohol **15**, which was transformed into the *syn*-azido epoxiode (±)-**1a** in two steps: (i) azidobromination of cinnamyl alcohol and (ii) formation of epoxide from **16** to give racemic *syn*-azido epoxiode (±)-**1a** in 70% yield. The *syn*-azido epoxiode (±)-**1a** was then subjected to HKR using (*R,R)*-Co(salen)OAc to give the chiral *syn*-azido diol **2a** in 47% yield with 98% ee along with chiral *syn*-azido epoxide **1a** in 48% yield with 96% ee. Azido diol **2a** was subjected to azide reduction as well as Boc protection [10% Pd/C, polymethylhydrosiloxane (PMHS), $(Boc)_2O$, EtOH] to give *N*-Boc amino diol **17** in 95 % yield. The regioselective intramolecular cyclization of *N*-Boc amino diol **17** using NaH in THF gave (+)-2-oxazolidone **18** in 96% yield.

Finally, mesylation of primary alcohol in oxazolidone **18** gave the mesylate **19**, which on subsequent treatment with NaN_3 in DMF at 60 °C afforded (+)-2-oxazolidone **14** in 80% yield. The conversion of (+)-2-oxazolidone **14** to *N*-thiolated 2-oxazolidinone **14** has been reported in the literature[7] (**Scheme 3**).



Scheme 3: (i) NBS, NaN_3, CH_3CN: H_2O (4:1),0 °C, 70%; (ii) *tert*-BuOK, THF, 0 °C, 3 h; (iii) (*R,R)*-Co(salen)OAc (0.5 mol%), H_2O (0.5 equiv), 0 ºC, 14 h; (iv) poly(methylhydrosiloxane), 10% Pd/C, $(Boc)_2O$, EtOH, 25 ºC, 4 h, 96%; (v) NaH, dry THF, 25 °C, 3 h, 96%; (vi) (a) MsCl, Et_3N, CH_2Cl_2, 0 °C, 1 h then; (b) NaN_3, DMF, 60 °C, 12 h, 80%.

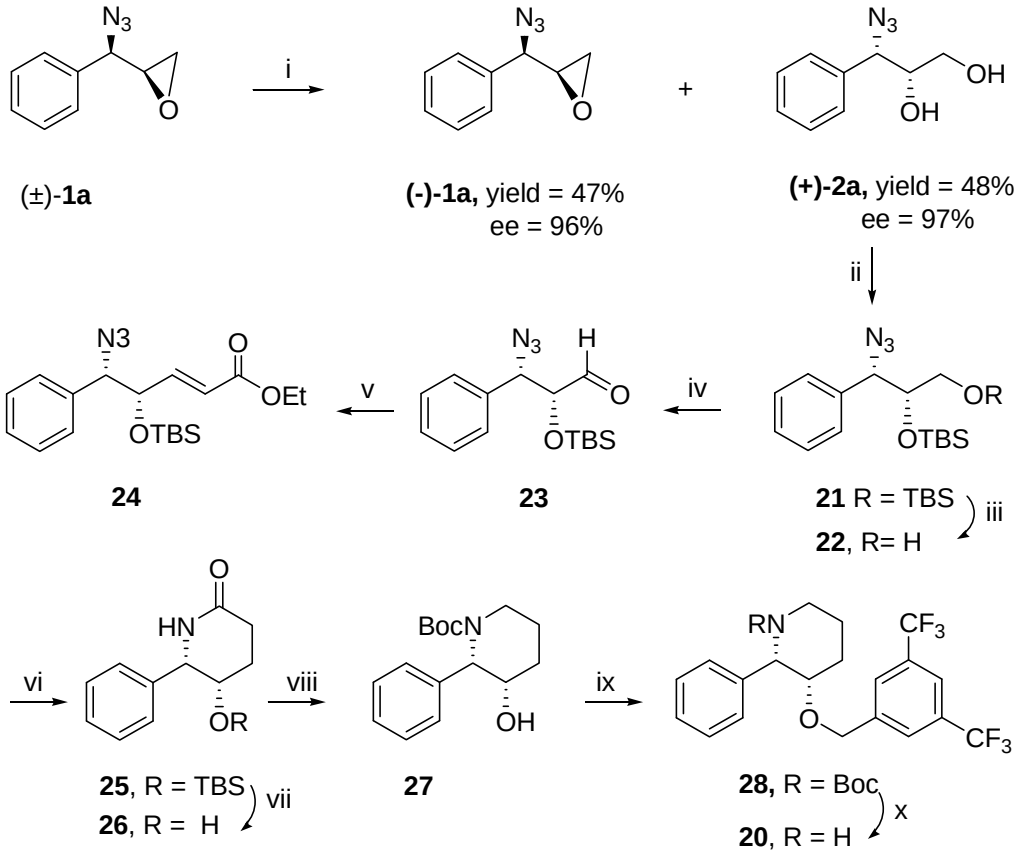
CHAPTER II

Enantioselective Synthesis of (+)-L-733,060 *via* Hydrolytic Kinetic Resolution of Azido epoxide and Synthesis of (S)-Dapoxetine *via* Sharpless Asymmetric Epoxidation

Chapter II is divided into two sections. **Section 1** presents the enantioselective synthesis of (+)-L-733,060 *via* HKR of azido epoxide while **Section 2** describes the asymmetric synthesis of (*S*)-dapoxetine *via* Sharpless asymmetric epoxidation.

Section 1: A short enantioselective synthesis of (+)-L-733,060 *via* hydrolytic kinetic resolution of azido epoxide

(+)-L-733,060 (**20)** possessing 2-alkyl-3-hydroxypiperidine structural unit has proven to be selective and potent non-peptide neurokinin substance P receptor antagonist.[8] Recent studies have shown that (+)-L-733,060 (**20)** can act both as an antitumor agent and as a promising new target for the treatment of retinoblastoma. This section describes a practical, enantioselective synthesis of (+)-L-733,060 (**20)** by employing hydrolytic kinetic resolution of azido epoxide as a key reaction (**Scheme 4**).



Scheme 4: (i) (*S,S)*-salen-Co(III)OAc (0.5 mol%), H_2O (0.5 equiv), 0 ºC, 14 h; (ii) TBSCl, imid, CH_2Cl_2, 25 °C, 98%; (iii) CSA, MeOH:CH_2Cl_2 (1:1), 0 °C 6 h, 95%; (iv) Dess-Martin periodinane, CH_2Cl_2, 25 °C, 98%;v) PPh_3=$CHCO_2Et$, THF, 25 °C, 14 h, 94%; (vi) 10% Pd/C, H_2, MeOH, 25 °C, than reflux in EtOH, 85%; (vii) TBAF, THF, 25 °C, 96% ; (viii) a) $Me_2S.BH_3$, THF, reflux, 10 h; b) $(Boc)_2O$, Et_3N, cat. DMAP, CH_2Cl_2, 0 – 25°C, 73% over two steps; (ix) 3, 5-bis (trifluoromethyl)benzyl bromide, NaH, DMF: THF (3:1), 0 °C, 6 h; (x) TFA, CH_2Cl_2, 18 h, 82% over two steps.

Our approach to the synthesis of L-733,060 (**20)** commenced with *syn* azido epoxide (±)-**1a,** which was subjected to HKR using (*S,S)*-Co(salen)OAc to furnish the required chiral

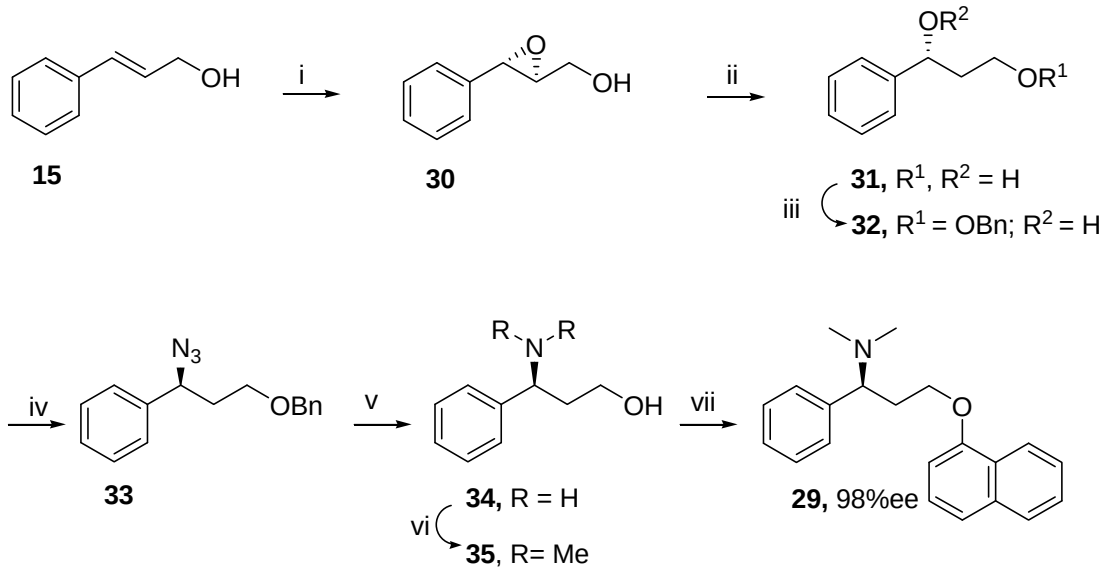
azido diol, (+)-**2a** in 48% chemical yield and 97% ee. It was then converted into *bis*-TBS ether (TBS chloride and imid.) to get **21** in 98% yield. The selective deprotection of TBS group in **22** was achieved using camphor sulfonic acid (CSA) in MeOH to produce azido alcohol **23** in 95% yield. Azido alcohol **22** on oxidation with Dess-Martin periodinane condition followed by Wittig olefination gave (*E*)-α,β-unsaturated azido ester **23** in 94% yield. Reduction of azide group along with C=C double bond was achieved under hydrogenation condition (H_2 and 10% Pd/C). Subsequently on reflux with EtOH, it gave TBS protected lactam **24** in 85% yield. Deprotection of TBS group in **24** was achieved using TBAF in THF to produce hydroxy lactam **25** in 96% yield. Reduction of lactam **25** with $BH_3.SMe_2$ in THF followed by the protection of the secondary amine with $(Boc)_2O$ gave the *syn* amino alcohol **26** in 73% yield over two steps. *O*-Alkylation of **26** with 3,5-bis(trifluoromethyl)benzyl bromide in the presence of NaH furnished **27**, which underwent deprotection under acidic conditions affording L-733,060 (**20)** in 82% yield and 97% ee.

Section 2: Enantioselective synthesis of (*S*)-dapoxetine *via* Sharpless asymmetric epoxidation

Depression, a common psychiatric disorder, is one of the most frequent illnesses in the World affecting people of all genders, ages and backgrounds. Dapoxetine **29** is structurally related to fluoxetine with anti-depressant activity.[9] Also, (*S*)-dapoxetine **29** is currently being tested as a treatment for premature ejaculation in men. Phase 3 clinical trials in patients with premature ejaculation have shown (*S*)-dapoxetine to be effective in improving the time of ejaculation, without any adverse effects.[10]

The synthesis of (*S*)-dapoxetine **29** starts with commercially available cinnamyl alcohol **15** which was subjected to the Sharpless asymmetric epoxidation[11] using Ti(O*iPr*)$_4$ and (+)-DET as ligand to give the epoxy alcohol **30** in 83% yield and 98% ee. Regioselective reductive ring opening of chiral epoxide **30** using Red-Al® gave 1,3-diol **31** in 88% yield, which on selective mono benzyl protection using benzyl bromide furnished OBn protected alcohol **32** in 80% yield. Mesylation of free alcohol **32** followed by subsequent displacement of the mesyl group with NaN_3 afforded azido benzyl ether **33** in 99% yield. The reduction of azide group coupled with the benzyl deprotection [10% Pd/C, H_2, (40 psi)] gave amino alcohol **34**, which was then condensed with formaldehyde and formic

acid as hydrogen source to give **35** in 80% yield. Finally, coupling of alcohol **36** with 1-naphthol was achieved *via* Mitsunobu reaction that afforded (*S*)-dapoxetine **29** in 71% yield and 98% ee **(Scheme 5**).



Scheme 5: (i) (+)-Diethyl tartarate, $Ti(O^iPr)_4$, anhyd. TBHP, CH_2Cl_2, -33 °C, 83%; (ii) Red Al®, DME, 0 -25 °C; (iii) NaH, benzyl bromide, DMF, -70 °C, 80%. (iv) a) MsCl, Et_3N, CH_2Cl_2, 0 °C, 1h ; (b) NaN_3, DMF, 60 °C, 5 h, 98%; (v) 10% Pd/C, H_2, MeOH, AcOH, 25 °C ; (vi) HCHO, HCO_2H, reflux, 8 h, 80%; (vii) PPh_3, DEAD, 1-naphthol, THF, 25 °C, 71%.

CHAPTER III

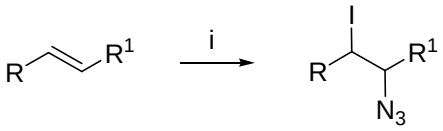
$NaIO_4$-mediated Azidoiodination of Olefins, 1,2-Diazidation of Olefins and α,α-Diazidation of Aryl Ketones and C-H Functionalization of Hydrocarbons

Chapter III is divided into three sections. **Section 1** deals with $NaIO_4$-mediated synthetic transformation involving regioselective azido iodination of olefins; **Section 2** describes 1,2-diazidation of olefins as well as α,α-diazidation of aryl ketones and **Section 3** deals with C-H functionalization of hydrocarbons.

Section I: $NaIO_4$–KI-NaN_3–mediated regioselective azidoiodination of alkenes

Azido iodination of alkenes constitutes an important method for introducing nitrogen functionality into a carbon skeleton leading to vinyl azides, amines and heterocycles, particularly aziridines.[12] The conventional method for synthesis of azido iodides involves the use of iodine azide reagent, which is prepared *in situ* from sodium azide and iodine chloride in polar solvent. During the course of our study on $NaIO_4$-mediated oxidative

halogenations,[13] We noticed that $NaIO_4$-KI-NaN_3 combination was found to be excellent for regiospecific azidoiodination of styrene in acetic acid as solvent. This prompted us to explore the effectiveness of the $NaIO_4$-KI-NaN_3 combination in the azidoiodination of alkenes. Several alkenes **36a-l** (aliphatic, styrenic, allylic and disubstituted) underwent azidoiodinations to give the corresponding β-iodoazides **37a-l** in excellent yields. It is interesting to note that the regiochemistry of the addition, for all the cases examined, proceeded in an *anti*-Markovnikov fashion, indicating a possible radical pathway. Internal olefins such as β-methylstyrene, cyclohexene and cinnamyl alcohol have proceeded to give products in excellent yields with diastereoselectivities reaching up to 1:4 as confirmed by their ^{1}H-NMR spectra. Terminal functionalized olefin such as allyl acetate also underwent regiospecific azidoiodination in 92% yield. However, no reactions took place in the case of conjugated alkenes with electron-withdrawing groups, which may be a limitation of this method (**Scheme 6)**.



36a-l
R = H, alkyl, aryl
R^1 = H, alkyl, CH_2OH
CH_2OAc

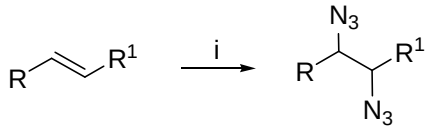
37a-l
yield = 70-96%
12 examples

Scheme 6: alkenes (1 equiv.), KI (1 equiv.), $NaIO_4$ (1 equiv.), NaN_3 (3 equiv.), glacial AcOH, 25 °C.

Section 2: $NaIO_4$–NaN_3–mediated diazidation of olefins and α,α-diazidation of aryl ketones

(a) 1,2-Diazidation of alkenes:

Vicinal diazides are important precursors for the synthesis of 1,2-diamines, which have become important synthetic targets, in variety of natural products, various biologically active molecules, and are also used as ligands or catalysts in organo- and transition – metal catalyzed reaction.[14] During the course of this study of $NaIO_4$-mediated oxidative functionalization of alkenes, we observed that treatment of alkenes **38a-h** with stochiometric amount $NaIO_4$ and sodium azide in AcOH : DMSO (1: 4) as a solvent at 75 °C, gave 1,2-diazides **39a-h** in good yields (**Scheme 7)**.



38a-h **39a-h**

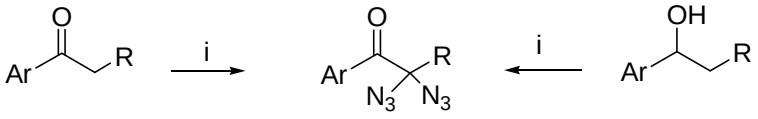
R = H, alkyl, aryl yield = 63-80%

R^1= H, alkyl 9 examples

Scheme 6: i) alkenes (1 equiv.), $NaIO_4$ (1 equiv.), NaN_3 (3 equiv.), DMSO: AcOH (4:1), 75 °C, 2 h .

(b) α,α-Diazidation of aryl ketones:

Under the similar reaction condition, we have observed that aryl ketones **40** with α-methylene group (-CO-CH_2-) underwent oxidative diazidation with $NaIO_4$ and sodium azide in AcOH: DMSO (1:4) as a solvent at 75 °C, to give α,α-diazido aryl ketones **41** in 91-95% yields. Surprisingly, when benzylic alcohols **42** were subjected to α,α-diazidation condition. The corresponding α,α-diazido aryl ketones were obtained in good yields probably *via* oxidation followed by diazidation (**Scheme 8**).



40 **41** **42**

R = alkyl yield= 75-96%

6 examples

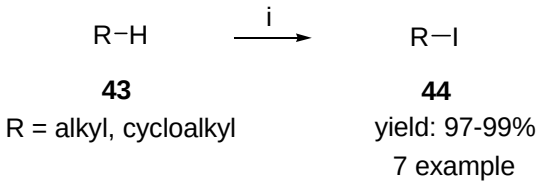
Scheme 8: (i) ketones (5 mmol), $NaIO_4$ (5 mmol), NaN_3 (15 mmol), DMSO: AcOH (4:1), 75 ^oC, 2 h.

Section 3: $NaIO_4$–KI-NaN_3–mediated C-H functionalization of hydrocarbons

(a) Direct iodination of alkanes:

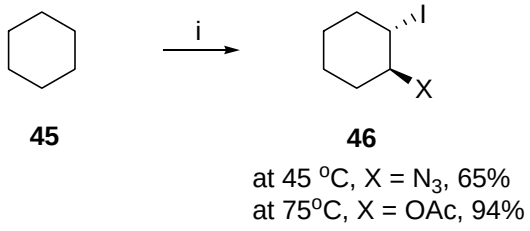
Direct and selective replacement of C-H bonds in hydrocarbons with C-C, C-O, C-N and C-X groups is an important and long-standing goal in chemistry.[15] In particular, a new, effective method for 1,2-functionalization of unactivated C-H bonds in a single step represents a major challenge for chemists. During the course of our study on $NaIO_4$-mediated regiospecific aziodo iodination, we noticed that IN_3 generated *in situ*, undergoes addition onto olefins in an *anti* Markovnikov fashion, suggesting probably a radical

pathway. This prompted us to explore the effectiveness of the $NaIO_4$-KI-NaN_3 combination in radical induced C-H activation of alkane. We thus observed that alkanes **43,** when treated with $NaIO_4$-KI-NaN_3 in acetic acid at 25 °C, produced iodoalkanes **44** in excellent yields **(Scheme 9**).



Scheme 9: (i) alkane (5mL), $NaIO_4$ (5 mmol), KI (5 mmol), NaN_3 (15 mmol), AcOH (15 mL), 25 °C; yield (%) was calculated based on KI.

With a simple variation in temperature, we have observed that cycloalkane **45** was smoothly converted to either 1-acetoxy- or 1-azido-2-iodocycloalkane **46** (**Scheme 10**).

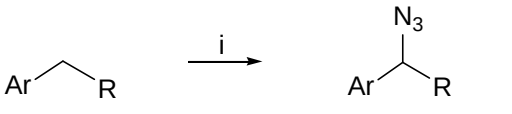


Scheme 10: (i) cycloalkane (5 mL), $NaIO_4$ (5 mmol), KI (5 mmol), NaN_3 (5-15 mmol), glacial AcOH (15 mL), 45-75 °C.

(b) Direct azidation at benzylic position:

The direct azidation of alkyl arene C-H bond is one of the challenging areas in organic synthesis.[16] During the course of substrate study with $NaIO_4$-KI-NaN_3 system (1:1:3 molar ratio), we found that alkyl arenes **47** are functionalized smoothly at the benzylic position to give benzyl azides **48** along with benzyl acetates **49** (10%). Further, on increasing the concentration of azide (6 equiv), exclusive formation of monobenzyl azides **48** were realized in excellent yields (**Scheme 11**). However, in similar reaction condition no reactions took place in the case of secondary alkyl arene such as ethyl benzene and indane. However, when ethyl benzene and indane were subjected to oxidative functionalization in the absence of KI, with $NaIO_4$ (1 equiv) in the presence

NaN_3 (3 equiv) in AcOH: DMSO (1: 4) as a solvent at 75 °C, the corresponding secondary benzyl azides were produced in 20% and 50% yields respectively.



47 **48**

R = H, alkyl yield = 20-95%

Scheme 11: (i) arene (5 mL), $NaIO_4$ (5 mmol), KI (5 mmol), NaN_3 (30 mmol), AcOH (20 mL), 25 °C.

CHAPTER IV

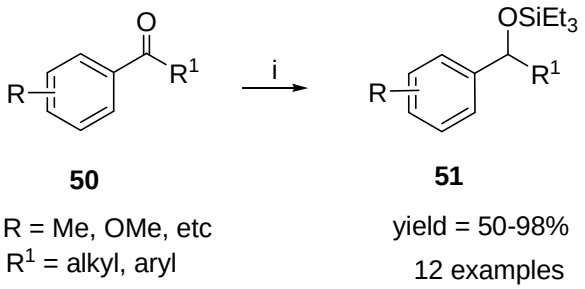
Palladium-catalyzed Hydrosilylation of Aryl Ketones and Enantioselective Rearrangement of 2-Alkyl Pyridine *N*-oxides and Synthesis of 4-Substituted Chromanes *via* Gold-catalyzed Intramolecular Friedel-Crafts Reaction

Chapter **IV** is divided into three sections. **Section 1** deals with Pd-catalyzed hydrosilylation of aryl ketones using triethylsilane while **Section 2** describes an enantioselective rearrangement of 2-alkyl pyridine N-oxides. **Section 3** deals with the synthesis of 4-substituted chromanes *via* $AuCl_3$-catalyzed intramolecular Friedel-Crafts reaction.

Section: 1 Palladium catalyzed hydrosilylation of aryl ketones with triethylsilane

In recent years hydrosilylation of various organic carbonyl compounds has made considerable progress and became a major tool of synthetic organic chemistry and organosilicon chemistry as well as providing efficient and versatile access to new organo silicon compounds.[17] There are many methods available in the literature for hydrosilylation of carbonyl compounds using a variety of metal catalysts and hydrosilanes. Moreover, metals such as palladium have not been studied extensively for the hydrosilylation of ketones.[18] In this section, we describe an efficient and selective method for the hydrosilylation of various aryl ketones catalyzed by palladium using triethylsilane as hydride source. We found that palladium catalysts were more effective for hydrosilylation of ketones **50** in DMF at room temperature using triethylsilane as a hydride source to produce silyl ethers **51** in 88-98% yield **(Scheme 12**). All the palladium catalysts gave excellent yield of hydrosilylated products **51**. The maximum yield of

silylether obtained was with $Pd(OAc)_2$ (98%) whereas $Pd(dba)_2$ (60%) gave the lowest yield.

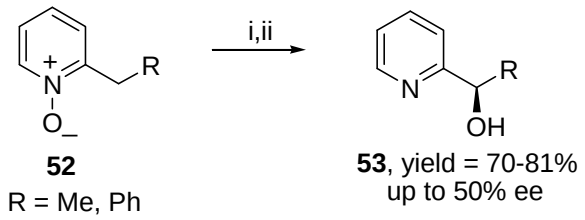


Scheme 12: aryl ketones (1 mmol), 10% $Pd(OAc)_2$ (0.5 mol%), Et_3SiH (1.2 mmol), DMF (2 ml), 25 ^oC, 1 h.

A noteworthy feature of this protocol is that when the reaction was carried out in DMF-water (4:1) solvent system, the corresponding alcohols were produced in high yields. Thus, both hydrosilylation and deprotection of the silyl ether were achieved in a single step by using a simple modification of solvent systems.

Section: 2 Enantioselective rearrangement of 2-alkyl pyridine *N*-oxides

Optically active pyridyl alcohols are useful key compounds, not only as pharmaceutical intermediates, but also as useful chiral ligands and auxiliaries in asymmetric synthesis.[19] Although there have been many reports on the synthesis of this important class of compounds by means of asymmetric alkylation to pyridyl aldehydes, stoichiometric or catalytic asymmetric reduction of acetyl pyridines and enzymatic resolution of racemic pyridyl alcohols. As an alternative to these methods, We have developed an enantioselective rearrangement of 2-alkyl pyridine *N*-oxide **52** (Boekelheide reaction)[20] using acid chlorides and chiral bases that afforded 2-alkyl pyridyl ester, which on subsequent hydrolysis produced chiral 2-alkyl pyridyl alcohols **53**, in 70-80% yields and up to 50% ee (**Scheme 13**).

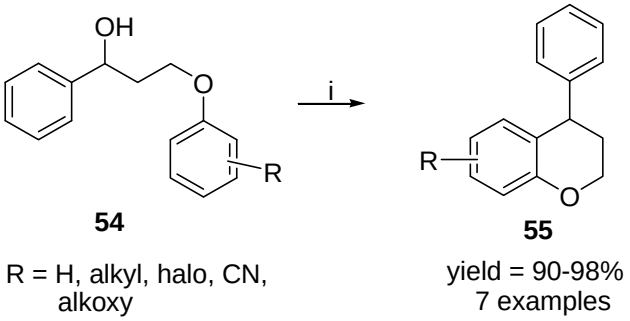


Scheme 13: (i) $C_6H_{11}COCl$ (1.2 mmol), (-)-sparteine (1 mmol),

Lewis acid (20 mol%), CH_2Cl_2 (4 mL) -78 °C; (ii) LiOH (2.0 mmol) THF: water (4 :1), 25 °C, 4 h.

Section: 3 Synthesis of 4-substituted chromanes *via* gold-catalyzed intramolecular Friedel-Crafts reaction of 3-aryloxy benzyl alcohols

The chromane and benzopyran structures are abundant in natural products that possess a broad array of biological activities such as antimicrobial, antiviral, mutagenicity, antiproliferative, sex pheromone, antitumor, and central nervous system activity.[21] Organic transformations catalyzed by gold have been a focus of attention recently.[22] In contrast, gold-catalyzed arene functionalization has been less developed. Such processes could provide efficient ways to construct C-C bonds from simple arene substrates. Alkylation of aromatic groups is typically achieved with Friedel-Crafts reactions.[23] During the course of our study, we observed that 3-aryloxy benzyl alcohols **54** when subjected to intramolecular Friedel-Crafts reaction using gold(III) chloride as a catalyst, gave 4-aryl substituted chromanes **55** in 90-98% yields (**Scheme 14).** Substrate such as 3-phenoxy benzyl alcohols as well as 3-naphthoxy benzyl alcohols gave good yields. In the case of both electron-donating as well as electron-withdrawing substituted 3-aryloxy benzyl alcohols gave the corresponding chromanes in excellent yield.



Scheme 14: (i) 3-aryloxy benzyl alcohols (1 mmol), $AuCl_3$ (1 mol%), CH_2Cl_2 (5 mL) 25 °C, 5 h.

References:

1 Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936.

2 (a) Yu, Q.; Wu, Y.; Xia, L. J.; Tang, M. H.; Wu, Y. L. *J. Chem. Soc. Chem. Commun*., **1999**, 129; (b) Kumar, P.; Naidu, S. V.; and Gupta, P. *Tetrahedron,* **2007**, *63*, 2745.

3 (a) Grajewska, A.; Rozwadowska, M. D.; *Tetrahedron: Asymmetry*, **2007**, *18*, 803; (b) Gravier-

Pelletier, C.; Milla, M.; Merrer, Y. L.; Depezay, J-C. *Eur. J. Org. Chem.* **2001**, 3089.

4 Kim, Y.-J.; Tae, J. *Synlett* **2006**, 61.

5 Van Ende, D.; Krief, A. *Angew. Chem., Int. Ed.* **1974**, *13*, 279.

6 (a) Kakeya, H.; Morishita, M.; Kobinata, K.; Osono, M.; Ishizuka, M.; Osada, H. *J. Antibiot.* **1998**, *51*, 1126; (b) Kakeya, H.; Morishita, M.; Koshino, H.; Morita, T.; Kobayashi, K.; Osada, H. *J. Org. Chem.* **1999**, *64*, 1052.

7 Mishra, R. K.; Revell, K. D.; Coates, C. M.; Turos, E.; Dickeyb, S.; Limb, D. V. *Bioorganic & Medicinal Chemistry Letters*, **2006**, *16*, 2081–2083.

8 (a) Baker, R.; Harrison, T.; Hollingworth, G. J.; Swain, C. J.; Williams, B. J. EP 0528 495A1, 1993; (b) Harrison, T.; Williams, B. J.; Swain, C. J.; Ball, R. G. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2545.

9 Anon, N. Z. *Drugs in R & D* **2005,** *6*, 307.

10 Pryor, J. *The Lancet* **2006,** *368*, 929.

11 (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc*. **1980**, *102*, 5974; (b) Martin, V. S.; Woodward, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc*. **1981**, *103*, 6237.

12 (a) Hassner, A.; Fowler, F. W. *J. Org. Chem.* **1968**, *33*, 2686; (b) Wasserman, H. H.; Brunner, R. K.; Buynak, J. D.; Carter, C. G.; Oku, T.; Robinson, R. P. *J. Am. Chem. Soc*. **1985**, *107*, 519; (c) Ranganathan, S.; Ranganathan, D.; Mehrotra, A. K. *Tetrahedron Lett*. **1973**, *14*, 2265. (d) Moorthy, S. N.; Devaprabhakara, D. *Tetrahedron Lett*. **1975**, *16*, 257.

13 (a) Dewkar, G. K.; Narina S. V.; Sudalai, A. *Org. Lett.* **2003**, *5*, 4501; (b) Emmanuvel, L.; Shaikh T. M. A.; Sudalai, A. *Org. Lett.* **2005**, *7*, 5071; (c) Emmanuvel, L.; Shukla, R. K.; Sudalai, A.; Suryavanshi, G.; Sivaram, S. *Tetrahedron Lett*. **2006**, *47*, 4793.

14 (a) Kemp J. E. G. in *Comprehensive Organic Synthesis*, Vol. *7* (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, 469; (b) Lucet, D.; Gall, T. L.; Mioskowski, C. *Angew. Chem. Int.Ed.* **1998**, *37*, 2580; (c) Saibabu Kotti, S. R. S.; Timmons, C.; Li, G. *Chem. Biol. Drug Des.* **2006**, *67*, 101; (d) De Figueiredo, R. M. *Angew. Chem. Int.Ed.* **2009**, *48*, 1190.

15 (a) Goldberg, K. I.; Goldman, A. S. Eds. *Activation and Functionalization of C-H Bonds*; ACS Symposium Series 885; American Chemical Society. Washington, DC, 2004. (b) Curci, R.; D'Accolti L.; Fusco, C. *Acc. Chem. Res.* **2006**, *39*, 1; (c) Godula K.; Sames, D. *Science* **2006**, *312*, 67; (d) Labinger J. A.; Bercaw, J. E. *Nature* **2002**, *417*, 507.

16 Eric, F. V.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 297.

17 (a) Ojima, I. *"The Chemistry of Organic Silicon Compounds"*, Vol. *2*, Patai, **S.;** Rappoport, Z. Wiley/Interscience, New York, **1989;** (b) **I.** Ojima, Z. Li and **J.** Zhu, *"Recent Advances in the Hydrosilylation Reaction: Chemisty of Organic Silicon Compounds"*, Vol. *2***,** Rappoport, **Z.;** Apeloig, **Y.;** John Wiley & Sons, Ltd, New York, **1998.**

18 (a) Diez-Gondlez, S.; Nolan, S. P. *Organic Preparations and Procedures Int*. **2007**, *39*, 523; (b)

Marciniec, B. in Hydrosilylation: A Comprehensive Review on Recent Advances (Eds.: B. Marciniec), Springer, Netherlands, **2009**, chap. 9.

19 (a) Wishka, D. G.; Graber, D. R.; Seest, E. P.; Dolak, L. A.; Han, F.; Watt, W.; Morris, J. *J. Org. Chem*. **1998**, *63*, 7851. (b) Uenishi, J.; Takagi, T.; Ueno, T.; Hiraoka, T.; Yonemitsu, O.; Tsukube, H. *Synlett* **1999**, 41; (c) Collomb, P.; Zelewsky, A. V. *Tetrahedron*: *Asymmetry* **1998**, *9*, 3911; (d) Uenishi, J.; Ueno, T.; Hata, S.; Nishikawa, K.; Tanaka, T.; Watanabe, S.; Yonemitsu, O.; Oae, S. *Heterocycles* **1999**, 50, 341.

20 Boekelheide, V.; Linn, W.; J. *J. Am. Chem. Soc.* **1954** , *76* , 1286.

21 (a) Ellis, G. P.; Lockhart, I. M. *The Chemistry of Heterocyclic Compounds, Chromenes, Chromanones, and Chromones*; Ellis,G. P., Ed.;Wiley-VCH: New York, **2007**; Vol. *31*, pp 1. (b) Horton, D. A.; Bourne, G. T.; Smythe,M. L. *Chem. Rev*. **2003**, *103*, 893; (c) Kumar, S.; Malachowski, W. P.; DuHadaway, J. B.; LaLonde, J. M.; Carroll, P. J.; Jaller, D.; Metz, R.; Prendergast, G. C.; Muller, A. J. *J. Med. Chem*. **2008**, *51*, 1706.

22 (a) Hashmi, A. S. K. *Gold Bull*. **2004**, *37*, 51; (b) Arcadi, A.; Di Giuseppe, S. *Curr. Org. Chem*. **2004**, *8*, 795; (b) Hashmi, A. S. K. *Chem. Rev*. **2007**, *107*, 3180.

23 (a) Olah, G. A. *Friedel-Crafts and Related Reactions*; Wiley: New York, **1973**; (b) Bandini, M.; Melloni, A.; Umani-Ronchi, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 550.

CHAPTER I

Cobalt-catalyzed Hydrolytic Kinetic Resolution of Azido Epoxides: A Short Enantioselective Synthesis of (+)-*Epi*-cytoxazone, (-)-Cytoxazone and (+)-2-Oxazolidone

Section I:

Cobalt-catalyzed hydrolytic kinetic resolution of azido epoxides

1.1.1 Introduction

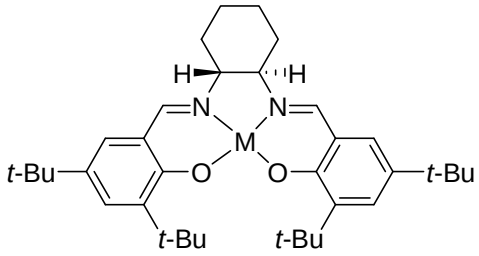
The enantiomerically pure *syn*- or *anti*-azido epoxides and the corresponding diols are valuable 'building blocks' for asymmetric synthesis of bioactive pharmaceuticals and as chiral auxiliaries and ligands.[1] In principle, access to these building blocks may be provided by several routes including Sharpless' methods of epoxidation and dihydroxylation, and other tedious methods. However, they generally lead to multi-step reaction sequences including protection/deprotection of various functional groups, thereby limiting the overall yield and the enantioselectivity of the process particularly unsuitable for atom economic synthesis. Jacobsen's Hydrolytic Kinetic Resolution (HKR) that uses readily accessible Co-based chiral salen complexes as catalyst and water as the only reagent to afford chiral epoxides and diols of high ee in excellent yields, has been comprehensively studied in recent years to reveal its mechanistic and synthetic aspects.[2] In the present section, we have described a flexible, novel method that employs HKR of racemic azido epoxides to generate two stereocentres of high optical purities in a single step.

1.1.2 Hydrolytic kinetic resolution (HKR)

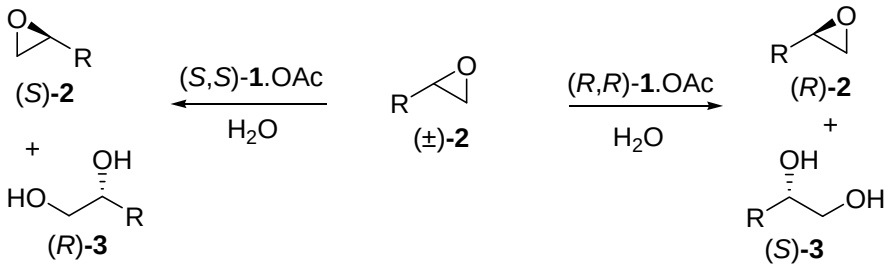
The importance of epoxides in organic synthesis arises partly from the occurrence of the strained three-membered ring unit in a number of interesting natural products[3] but more so because the ring opening of epoxides allows straightforward elaboration to useful new functionality, often with generation of new carbon-carbon bonds. Indeed, reactions of epoxides with nucleophiles, Lewis acids, radicals, reducing agents, oxidizing agents, acids, and bases have all been well documented and utilized in synthesis.[4] Thus epoxides

are versatile building blocks for organic synthesis. However, terminal epoxides are arguably the most important subclass of these compounds, and no general and practical method exists for their production in enantiomerically pure form. Terminal epoxides are available very inexpensively as racemic mixtures, and kinetic resolution is an attractive strategy for the production of optically active epoxides, given an economical and operationally simple method. Readily accessible synthetic catalysts (chiral cobalt-salen complexes)[5] have been used for the efficient asymmetric hydrolysis of terminal epoxides. This process uses water as the only reagent, no added solvent, and low loadings of a recyclable catalyst (0.5 mol%), and it affords highly valuable terminal epoxides and 1,2-diols in high yields with high enantiomeric enrichment. One of the most attractive features of kinetic resolution processes in general is the fact that the enantiomeric composition of unreacted substrate can be controlled by adjusting the degree of conversion, and virtually enantiopure material can be obtained at appropriately high conversions. This is an important consideration in the present case, since low-molecular weight terminal epoxides are typically liquids at room temperature and are not readily derivatized as salts, and therefore it is not a straightforward matter to upgrade their enantiomeric composition by crystallization. However, in the absence of straightforward substrate racemization protocols, kinetic resolutions have the significant disadvantage of a 50% maximum yield of substrate recovery. With a specific interest in devising a practical method for obtaining highly enantioenriched terminal epoxides, the following criteria must be met in order for a kinetic resolution approach to be viable.[6] (1) The racemic epoxides must be inexpensive or easily accessible from inexpensive commercial starting materials. (2) The catalyst for the resolution must be readily available in both

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



1, M = Co



Scheme 1: Hydrolytic kinetic resolution (HKR) of racemic epoxide

The (salen)Co complex **1** catalyzed the efficient hydrolytic kinetic resolution (HKR) of a variety of terminal epoxides (**Scheme 1**).[7] This new method appeared to hold considerable promise with regard to meeting all of the criteria outlined above. First, racemic 1,2-epoxides are generally available directly from commercial suppliers at low cost or are obtainable in one step from inexpensive olefins or aldehydes. In fact, certain racemic epoxides, such as propylene oxide, epichlorohydrin, styrene oxide, and butadiene

monoepoxide, are commodity chemicals and are no more expensive than common organic solvents. Second, the ligands for catalyst **1** had previously been commercialized and manufactured on a ton scale in the context of (salen)Mn epoxidation catalysts.[8]

The cobalt analogues (*R*,*R*)-**1** and (*S*,*S*)-**1** proved equally accessible, and these are also now available in bulk. Third, water is perhaps the ideal reagent for effecting the resolution reaction: it is inexpensive and safe, and the rate of the ring-opening reaction can be controlled simply by modulating the rate of addition of water to the epoxide-catalyst mixture. Fourth, for those examples that were described in the preliminary report, highly enantioenriched epoxides were recovered from the HKR. Finally, the HKR provided useful enantioenriched 1,2-diols, including many that are otherwise not readily accessible using existing asymmetric dihydroxylation methods.[9] Two useful methods for the generation of complex **1.**OAc have been developed. Method A involves isolation of **1.**OAc as a crude solid prior to the HKR. The Co(II) complex **1** is dissolved in toluene to generate ~ 1 M solution, and acetic acid (2 equiv.) is added. The resulting solution is stirred open to air at room temperature for 30 min, during which time the color of the mixture changes from orange to dark brown. All volatile materials are removed *in vacuo*, affording **1.**OAc as a brown solid residue that can be used without further purification. Method B involves in situ generation of **1.**OAc under HKR conditions by suspension of the Co(II) complex **1** in epoxide or epoxide/solvent and addition of HOAc under an aerobic atmosphere.**1.1.3.**

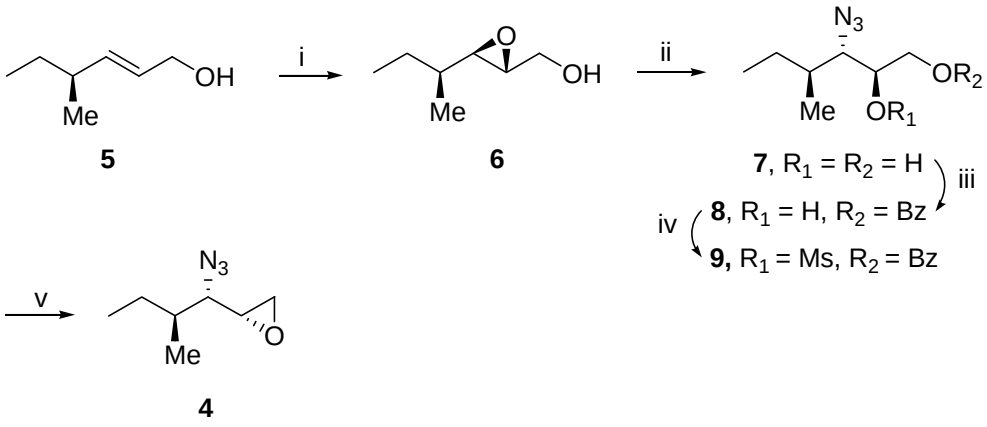
Review of Literature

Various syntheses of enantiomerically pure *syn*- or *anti*-azido epoxides and the corres-

ponding diols have been documented in the literature by several routes including Sharpless' methods of epoxidation and dihydroxylation, and other tedious methods. Some of the interesting and important synthetic routes are described below.

Kihlberg's approach (2003)[10]

Kihlberg et al. have reported synthesis of chiral azido epoxide **4** which was obtained with Katsuki-Sharpless asymmetric epoxidation of allylic alcohol **5** to furnish epoxy alcohol **6** in 82%, yield with 88% de. Regioselective opening of the epoxide in **6** by $Ti(OiPr)_2(N_3)_2$ then yielded azido diol **7**. Benzoylation of the primary hydroxyl group of **7** directly followed by mesylation of the secondary hydroxyl group gave **9**. Finally, treatment of **9** with sodium ethoxide resulted in removal of the benzoyl group and intramolecular ring closure to give azido epoxide **4** in 41% overall yield from **5** with 90% de (**Scheme 2**).

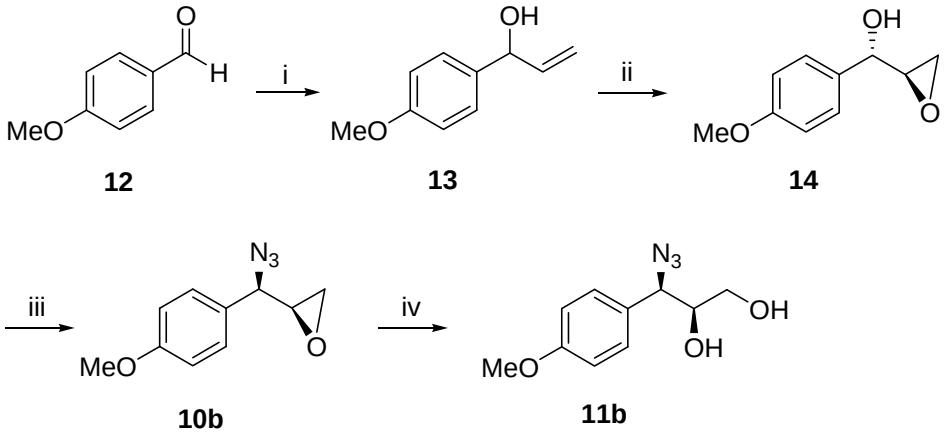


Scheme 2: (i) D-(-)-diisopropyl tartrate, $Ti(OiPr)_4$, *t*BuOOH in toluene, CH_2Cl_2, -20 – 25 °C, 82%; (ii) $Ti(OiPr)_2(N_3)_2$, benzene, reflux, 92%; (iii) collidine, BzCl, -10 °C; (iv) MsCl, CH_2Cl_2, 0 – 25 °C, 66%; (v) NaOEt in EtOH, THF, room temp, 83%.

Reddy's approach (2005)[11]

Reddy et al. have reported synthesis of chiral azido epoxide **10** and azido diol **11** starting from anisaldehyde **12**, which was treated with vinyl magnesium bromide to give allyl alcohol **13**. The enantioselective epoxidation of the racemic allyl alcohol **13** gave, in the

presence of L-diisopropyl tartarate, the epoxy alcohol **14** in 46% yield. The epoxy alcohol **14** was then subjected to a Mitsunobu reaction, in which hydrazoic acid served as an azide nucleophile and gave the epoxy azide **10b** in 91% yield. Next, opening of the epoxide ring by treatment with aqueous sodium hydroxide in *tert*-butanol furnished the azido diol **11b** (**Scheme 3**).

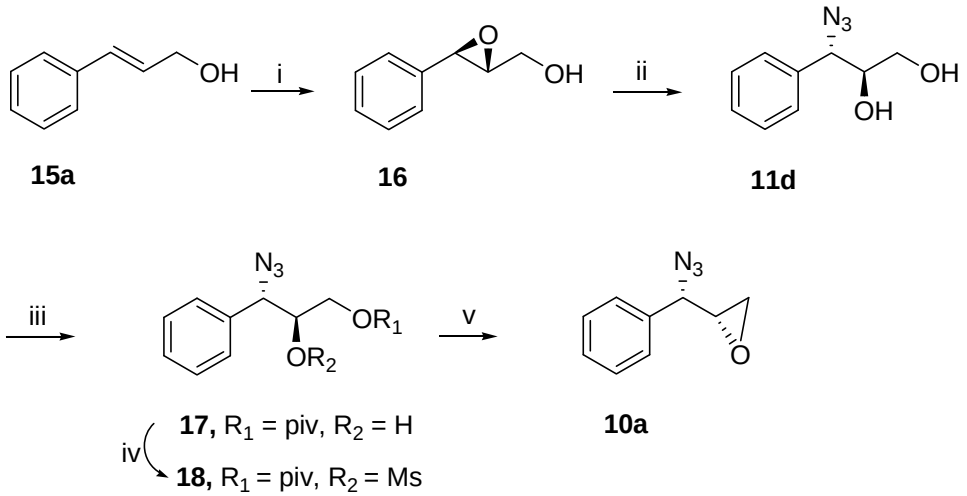


Scheme 3: (i) 1M vinyl magnesium bromide in THF, dry ether, 0 °C, 4 h, 96%; (ii) diisopropyl L-tartarate, $Ti(iPrO)_4$, tert-butyl hydroperoxide, CH_2Cl_2, -20 °C, 14 h, 46%; (iii) PPh_3, diisopropyl azadicarboxylate, HN_3, benzene, 0 °C, 1 h, 91%; (iv) 0.5M aq. NaOH, *t*-BuOH, 75 °C, 5 h, 92%.

Kumar's approach (2007)[12]

Kumar et al. have described the synthesis of chiral *syn* azido epoxide **10a** and *anti* azido diol **11d,** which were with Sharpless asymmetric epoxidation of commercially available cinnamyl alcohol **15a** to furnish epoxide **16** in 89% yield with >99% ee. The regioselective epoxide opening of **16** with NaN_3 gave a single regioisomer **11d** in excellent yield. In order to establish the desired *syn* configuration, authors have planned a three-step sequence: (i) chemoselective pivalation **17** of diol **11d**; (ii) mesylation of secondary hydroxyl **17** using MsCl; (iii) final treatment of crude mesylate **18** with K_2CO_3

in methanol to furnish the appropriately oriented *syn* azido epoxide **10a** in 80% overall yield (**Scheme 4**).

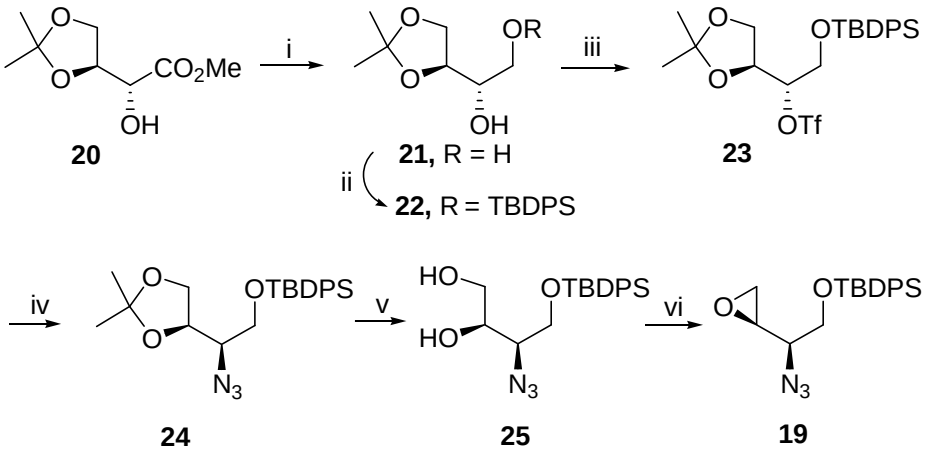


Scheme 4: (1) (*S*,*S*)-(-)-DET, Ti(O-*i*Pr)$_4$, TBHP, MS 4A˚, CH_2Cl_2, -20 °C, 3 h, 89%; (ii) NaN_3, NH_4Cl, MeOH/ H_2O (8: 1), 65 °C, 5 h, 98%; (iii) PivCl, Py/CH_2Cl_2 (1: 1), 0– 25 °C, 5 h; (iv) MsCl, Et_3N, DMAP, CH_2Cl_2, 0- 25°C, 1 h; (v) K_2CO_3, MeOH, 25 °C, overnight, 80% (overall 3 steps).

Gravier-Pelletier's approach (2009)[13]

Gravier-Pelletier et al. have described synthesis of chiral *anti* azido epoxide **19** and *anti* azido diol **25** starting from ethyl 3,4-*O*-methylethylidene-L-threonate **20**, which is readily available from L-ascorbic acid. The carboxylic acid moiety of **20** was reduced to a primary alcohol **21** for stability reasons, which was then protected as its *tert*-butyldiphenylsilyl derivative **22**. The azido group was introduced with inversion of the configuration by two-step, one-pot protocol involving initial activation of the secondary alcohol function as a triflate **23** followed by nucleophilic substitution with tetramethylguanidinium azide, which furnished the azido compound **24** in 81% yield. Acetal hydrolysis of **24** [trifluoroacetic acid: H_2O: THF (3:3:1)] to give the corresponding diol **25**. Epoxidation was then efficiently achieved under Sharpless conditions gave the

anti azido epoxide **19** in 87% yield (**Scheme 5**).



Scheme 5: (i) $LiAlH_4$, THF, 95%; (ii) TBDPSCl, imid, DMF, 97%; (iii) Tf_2O, 2,6-lutidine, CH_2Cl_2, -78 °C; (iv) TMGA, -78 °C to 20 °C, 81%; (v) TFA, H_2O, THF, 0 °C, 65%; (vi) a) $MeC(OMe)_3$, PPTS (cat.), CH_2Cl_2; (b) AcBr, CH_2Cl_2; (c) K_2CO_3, MeOH, 87%.

1.1.4 Present Work

1.1.4.1 Objective

As can be seen from the above discussion, the literature methods for the synthesis of enantiomerically pure *syn*- or *anti*-azido epoxides and the corresponding diols employ either chiral starting materials, or involve multi-step reaction sequences including protection/deprotection of various functional groups, thereby limiting the overall yield and the enantioselectivity of the process. This is particularly unsuitable for atom economic synthesis. Despite achievements, HKR has only been applied to the resolution of simple terminal epoxides with one stereocentre.[14] To the best our knowledge, study related to HKR of functionalized epoxides with two stereocentres is rare.[15]

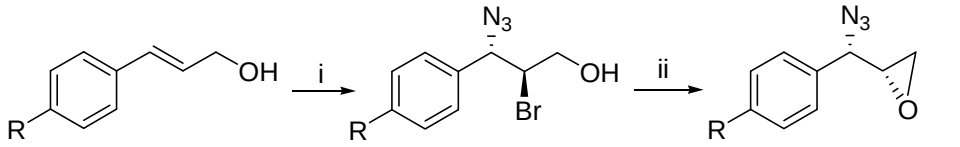
1.1.5 Results and Discussion

In the present work, we have thus extended the scope of the applicable substrates for

HKR to cover multi-functionalized molecules with two stereocentres. The aim of such an investigation is to access enantiomerically enriched azido epoxides and diols by a direct and simple method from the respective racemic materials; thus complementing the other tedious routes. Due to its importance as 'building-blocks' for the synthesis of highly functionalized molecules, racemic azido epoxides are chosen for the study and subjected to HKR with chiral Co-catalysts. In this section, we have described a flexible, novel method that employs HKR of racemic azido epoxides to generate azido diols and azido epoxides with two stereocentres of high optical purities in a single step.

1.1.5.1 Synthesis of racemic azido epoxidews

The racemic *syn*-azido epoxides **10a-b** the substrates for HKR, were efficiently prepared in two step sequence, in a highly diastereoselective manner[16] from the corresponding (E)-allylic alcohols (**15a-b**). Thus, cinnamyl alcohols **15a-b**, which were subjected to azidobromination in presence of NBS and NaN_3 to give *anti*-azido bromides, (±)-**26a-b** in 70-75% yields (**Schemes 6**).



15a, R = H
15b, R = OMe

26a-b, (2*RS*, 3*RS*)

10a-b, (2*RS*, 3*SR*)
70-75%

Scheme 6: (i) NBS, NaN_3, CH_3CN: water (4: 1), 0- 25 °C, 3 h, 70-75%; (ii) LiOH, THF: water (4: 1), 0- 25 °C, 3 h 70-76%.

The formation of azido bromides, (±)-**26a-b** was confirmed by ^1H and ^{13}C-NMR spectroscopy. The ^1H NMR spectrum of (±)-**26b** showed typical signals at δ 4.20-4.24 (m, 1H) and 4.85 (d, 1H) for bromo methine (-CH-Br) and azido methine (Ar-CH-N_3)

protons respectively. Its ^{13}C-NMR showed a typical signal at δ 66.5 due to benzylic carbon attached to azide group (**Fig. 1).**

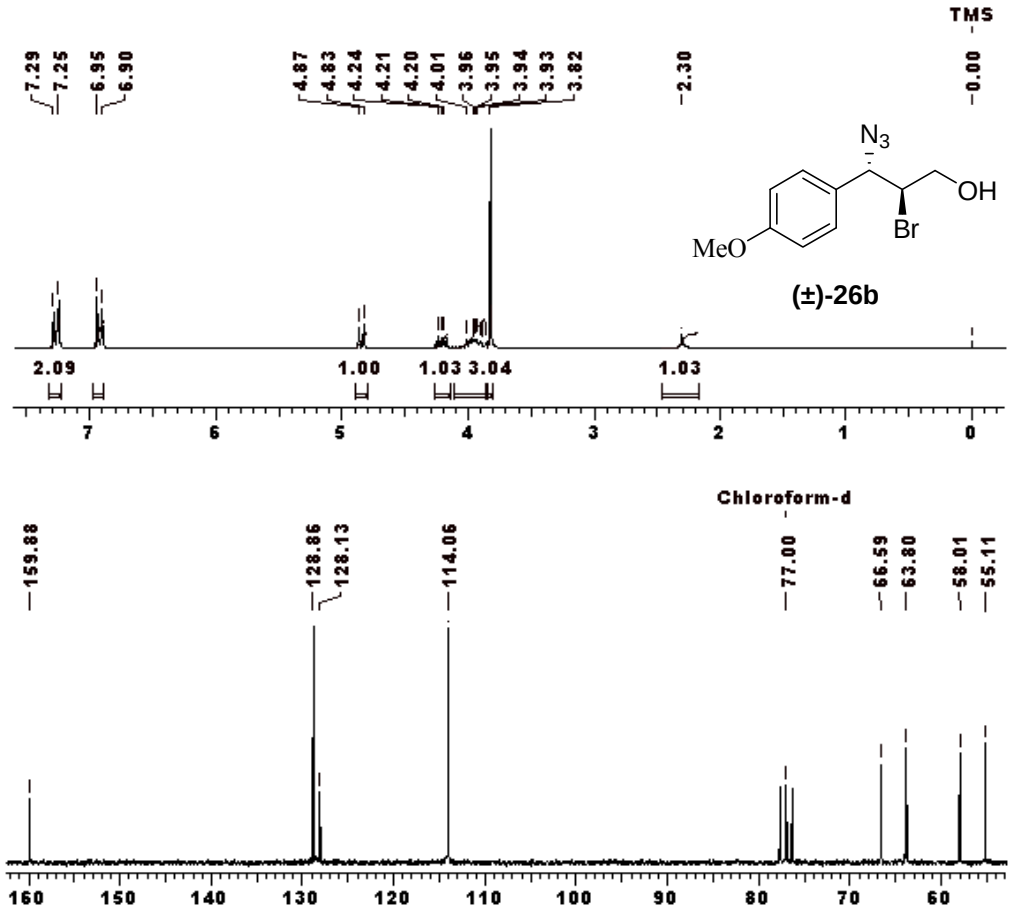


Fig. 1: ^{1}H and ^{13}C NMR spectra of **(±)-26b**

Azido bromides, (±)-**26a-b** were then subjected to epoxidation [LiOH, THF: water (4: 1)] to give *syn*-azido epoxides, (±)-**10a-b** in 75-76% yield.

The formation of *syn*-azido epoxides, (±)-**10a-b** was confirmed by ^{1}H and ^{13}C-NMR spectroscopy. The ^{1}H NMR spectrum of *syn*-azido epoxide, (±)-**10a** showed typical signals at δ 2.74-2.83 (m, 2H) and δ 3.25-3.28 (m, 1H) for methylene and methine protons respectively. Its ^{13}C-NMR showed characteristic signals at δ 44.6 and 54.6 due to carbons of the epoxide ring (**Fig. 2).**

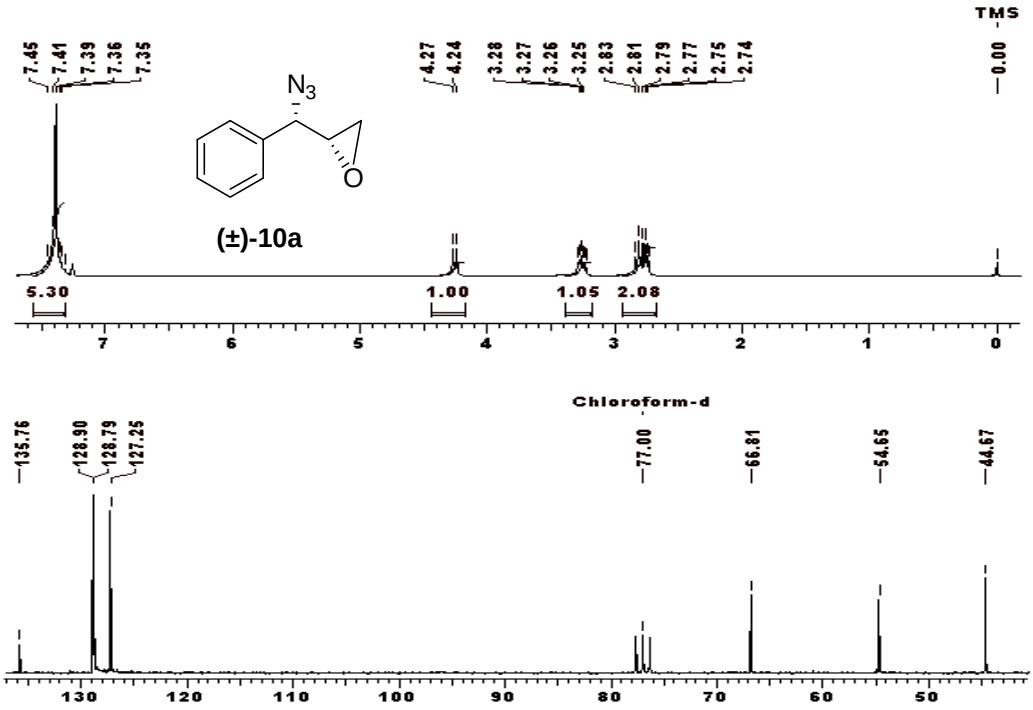
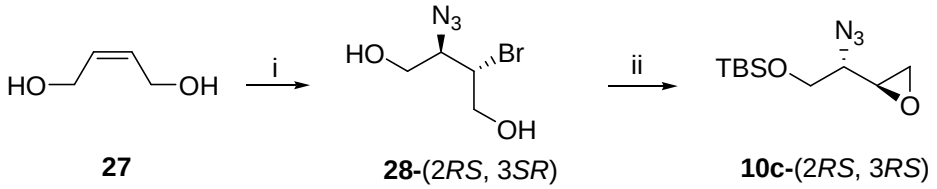


Fig. 2: ^{1}H and ^{13}C NMR spectra of **(±)-10a**

Similarly, *anti*-azido epoxide, (±)-**10c** was readily prepared from *cis*- 1,4-butenediol **27** in two step. Thus compound **27** was subjected to azidobromination in presence of NBS and NaN_3 to give azido bromide, (±)-**28** in 75% yield (**Scheme 7**).



27 **28-**(2*RS*, 3*SR*) **10c-**(2*RS*, 3*RS*)

Scheme 7: (i) NBS, NaN_3, CH_3CN: water (4: 1), 0- 25 °C, 3 h, 75%; (ii) NaOH powder, THF, 2 h; (iii) TBSCl, imid., CH_2Cl_2, 25 °C, 2.5 h, 76%.

The formation of azido bromide, (±)-**28** was confirmed by ^{1}H and ^{13}C-NMR spectroscopy. The ^{1}H NMR spectrum of (±)-**28** showed a typical signal at δ 4.12-4.16 (m, 1H) for methine (-CH-N_3) proton. Its ^{13}C-NMR showed a typical carbon signal at δ 53.62 due to carbon attached to bromo group (**Fig. 3).**

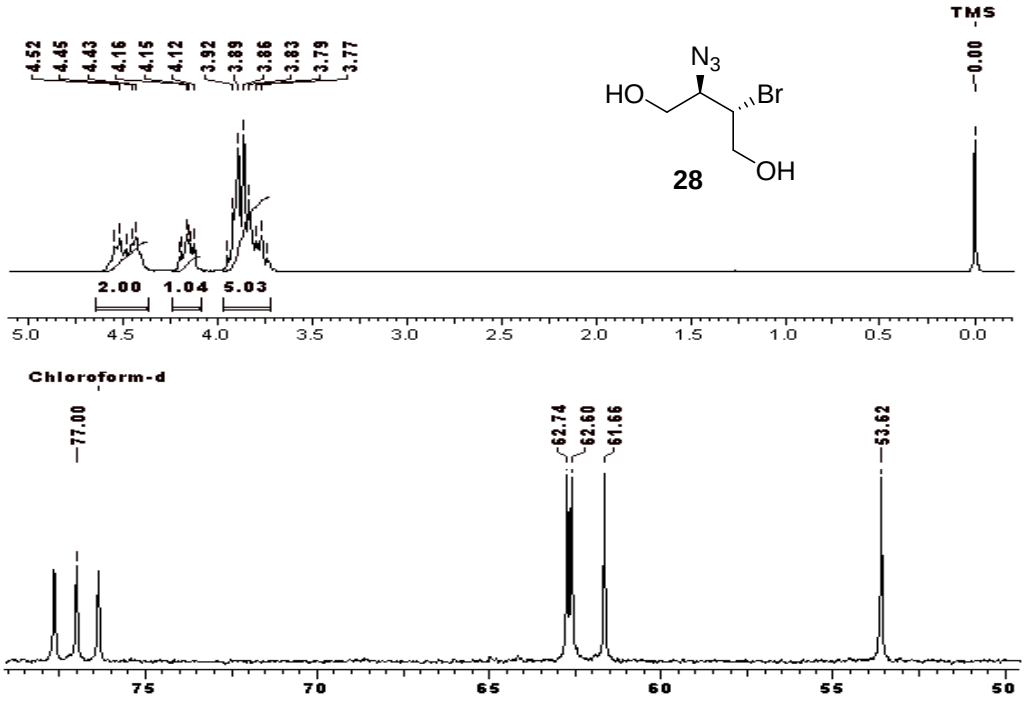


Fig. 3: ^{1}H and ^{13}C NMR spectra of **(±)-28**

The azido bromide (±)-**28** was then subjected to epoxidation (NaOH, THF), followed by protection of primary alcohol with TBS-ether to give TBS protected *anti*-azido epoxide, (±)-**10c** in 76% yield. The ^{1}H NMR spectrum of (±)-**10c** showed signals at δ 2.71-2.80 (m, 2H) and δ 3.23-3.26 (m, 1H) for methylene and methine protons respectively. Its ^{13}C-NMR showed typical signals at δ 45.2 and 50.2 due to carbons of the epoxide ring (**Fig. 4).** The synthesis of *anti*-azido epoxide, (±)-**10d** was achieved following a reported procedure from racemic epoxy alcohol.[12] **16,** which was subjected to selective opening with NaN_3 followed by its mesylation and treatment with base. For the preparation of *anti*-azido epoxide, (±)-**10e**, see Section II. Thus in this strategy, the relative stereochemistry between the azido and epoxide groups is established prior to the HKR step itself and in this way a simple asymmetric reaction can be carried out to form the key enantiomerically pure azido epoxides with two stereocentres.

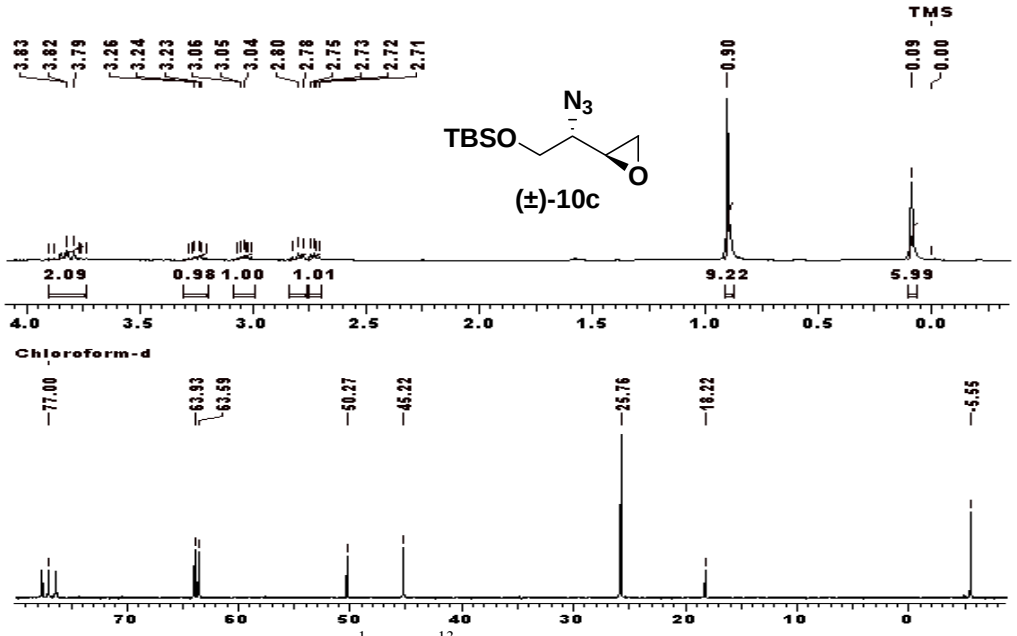
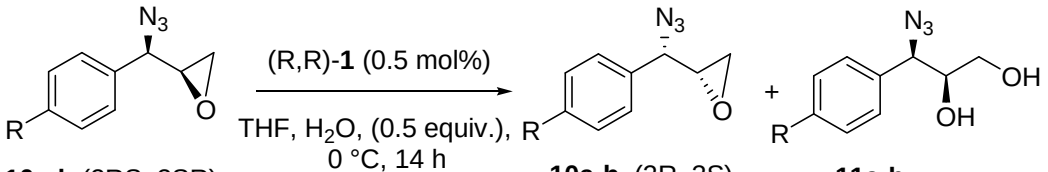


Fig. 4: ^{1}H and ^{13}C NMR spectra of **(±)-10c**

1.1.5.2 HKR of racemic azido epoxides

The HKR of racemic *syn*-azido epoxides, (±)-**10a-b** was performed with (*R,R*)-salen Co(OAc) complex (**1**) (0.5 mol%) and H_2O (0.5 equiv.) and the corresponding chiral epoxides **10a-b** and diols **11a-b** were isolated in high yields and optical purity (**Table 1**).

Table 1: Co-catalyzed HKR of *syn*-azido epoxides



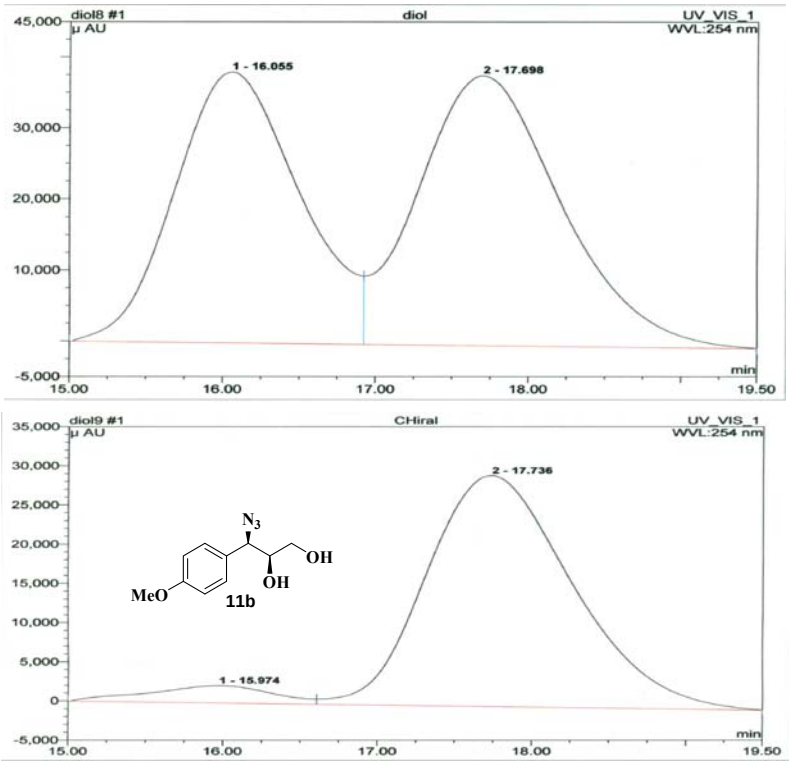
10a-b (2RS, 3SR) **10a-b**, (2R, 3S) **11a-b**

		Azido epoxides (10)		Azido diols (11)	
Sr.No	**R**	**Yield (%)[a]**	**ee (%)**	**Yield (%)[a]**	**ee (%)**
a	H	48	96	47	98[b]
b	OMe	48	98	48	97[b]

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

Both the racemic azido epoxides (±)-**10a-b** were subjected to hydrolytic kinetic resolution using catalytic amount (0.5 mol%) of (*R,R*)-salen Co(OAc) complex (**1**) to

give chiral *syn*-azido diols **11a** (48%) and **11b** (47%), with 98 % ee and 97% ee respectively along with chiral *syn*-azido epoxides in **10a** (48%) and **10b** (48%), with 96% ee and 98% ee respectively. The enantiomeric excess of *syn*-azido diol in **11** was determined by chiral HPLC analysis: Chiralpak OD-H (**Fig.5**).



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

Fig. 5: HPLC chromatogram of **11b**

The formation of *syn*-azido diols **11a-b** was confirmed by ^{1}H and ^{13}C-NMR spectroscopy. For example, the ^{1}H NMR spectrum of **11b** exhibited signals at δ 3.35 (dd, 1H) and 3.55 (dd, 1H) due to methylene (-CH_2-OH) protons. Its ^{13}C NMR spectrum showed characteristic signals at δ 62.7 and 75.0 due to the methine and methylene carbons attached to hydroxyl groups respectively (**Fig. 6)**. The configuration of both

chiral azido epoxides and diols was further ascertained by comparing their optical rotations with those reported in the literature.[10-13]

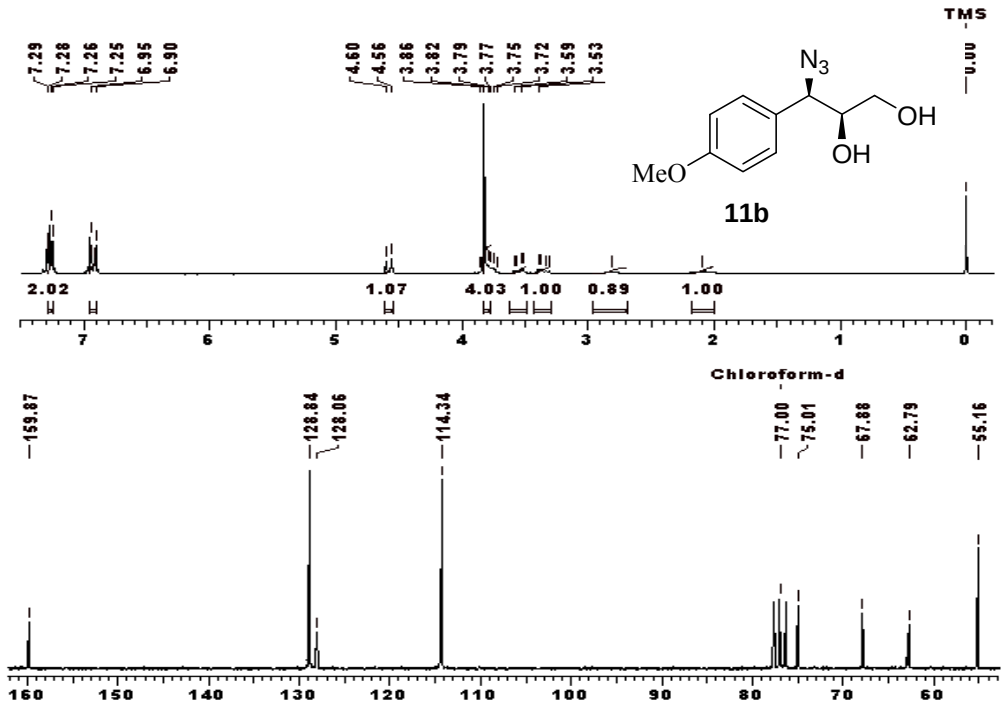
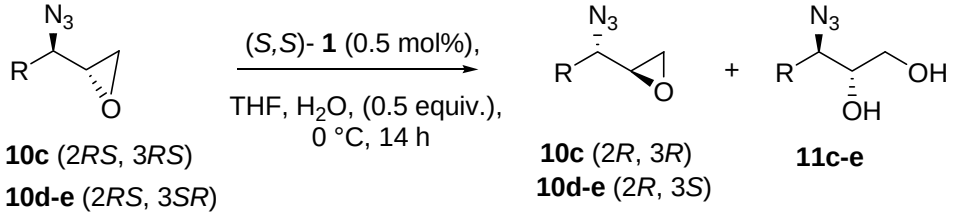


Fig. 6: ^{1}H and ^{13}C NMR spectra of **11b**

Similarly, *anti*-azido epoxides (±)-**10c-e**, when subjected to (*S*,*S*)-Co(salen)OAc-catalyzed HKR, produced chiral *anti*-azido epoxides (+)-**10c-e** and *anti* diols **11c-e** with high enantio purity (**Table 2)**.

Table 2: Co-catalyzed HKR of *anti*-azido epoxides



10c (2*RS*, 3*RS*)
10d-e (2*RS*, 3*SR*)

10c (2*R*, 3*R*)
10d-e (2*R*, 3*S*)

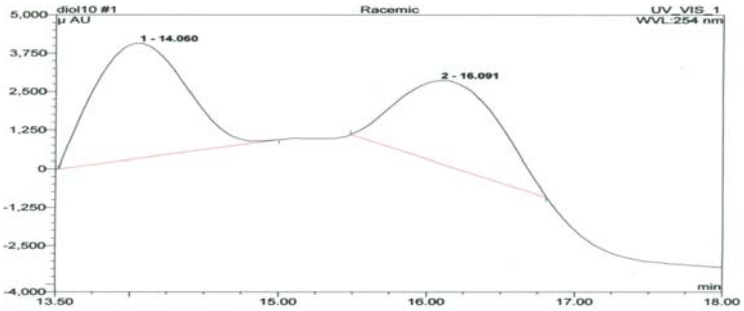
11c-e

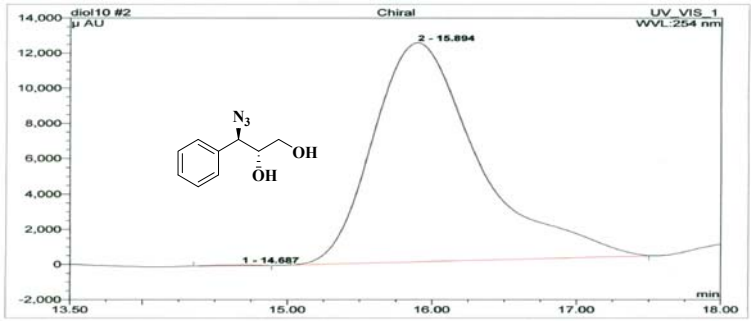
	Azido epoxides			Azido diols		
R	**10c-e**	**Yield (%)[a]**	**ee (%)**	**11c-e**	**Yield (%)[a]**	**ee (%)**
CH_2OTBS	**10c**	48	96	**11c**	46	98[b]

Ph	**10d**	48	97	**11d**	47	98[c]
p-OMe- C_6H_4	**10e**	47	96	**11e**	47	97

[a] Isolated yield after column chromatographic purification; [b] ee determined by Mosher's ester analysis; [c] ee determined by chiral HPLC analysis.

The enantiomeric excess of *anti*-azido diol in **11d** was determined by chiral HPLC analysis: Chiralpak OD-H (**Fig 7)**.





No	Ret. Time	Height	Area	Rel. Area
	min	μ AU	μ AU* min	%
1	14.68	91.878	251.906	0.86
2	15.89	10591.692	29039.522	99.14

Fig. 7: HPLC chromatogram of **11b**

The formation of *anti*-azido diols **11c-e** was confirmed by ^{1}H and ^{13}C-NMR spectroscopy. Example 1: The ^{1}H NMR spectrum of *anti*-azido diol **11c** showed a typical signal at δ 3.39-3.48 (m, 2H) for methylene (-CH_2-OH) protons. Its ^{13}C NMR spectrum showed a characteristic signal at δ 71.4 due to the methine carbons attached to hydroxyl group (**Fig. 8).**

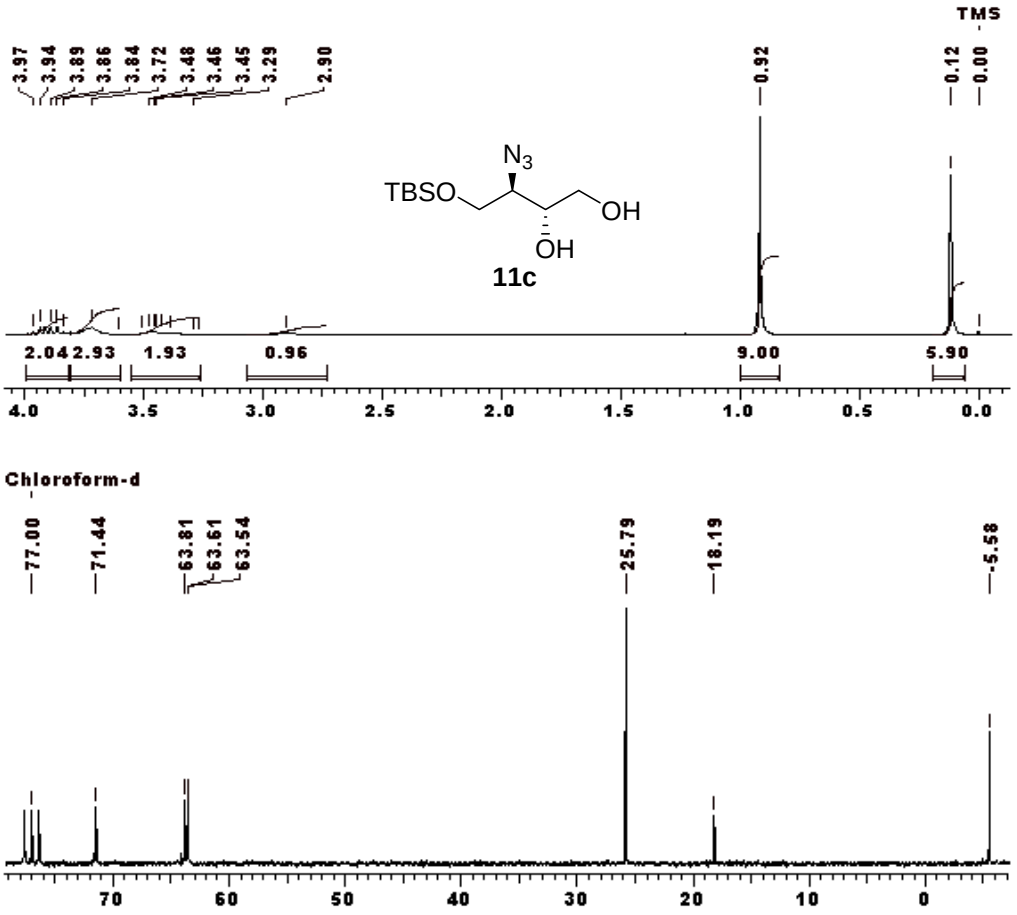


Fig. 8: ^{1}H and ^{13}C NMR spectra of **11c**

Example 2: The ^{1}H NMR spectrum of *anti*-azido diol **11d** showed signals at δ 3.56-3.71 (m, 2H) for methylene (-CH_2-OH) protons. Its ^{13}C NMR spectrum showed characteristic signals at δ 62.8 and 74.0 due to the methine and methylene carbons attached to hydroxyl groups respectively (**Fig. 9).**

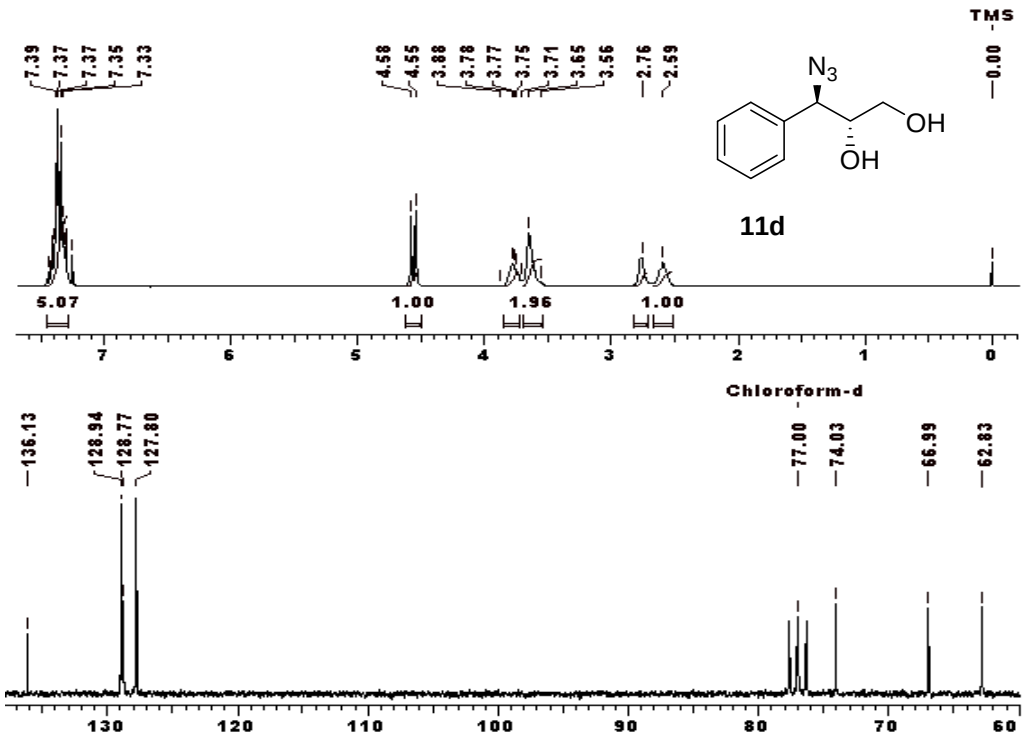


Fig. 9: ^{1}H and ^{13}C NMR spectra of **11d**

1.1.6 Conclusion

In conclusion, the (salen) Co(III)-catalyzed HKR of racemic azido epoxides provides a highy practical route to enantiopure *syn*- or *anti*-azido epoxides, as the case may be and the corresponding 1,2-diols in a single step. The reaction is convenient to carry out under mild conditions. We believe that this HKR strategy will find applications in the field of asymmetric synthesis of bioactive molecules owing to the flexible nature of synthesis of racemic azido epoxides and the ready availability of cobalt salen catalysts in both enantiomeric forms.

1.1.7 Experimental section

A general experimental procedure for the preparation of racemic azido bromides (26a-b, **28):**

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

3-Azido-2-bromo-3-phenylpropane-1-ol (26a):

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

3-Azido-2-bromo-3-(4-methoxyphenyl)propane-1-ol (26b):

Yield: 76%; yellow liquid; **IR** ($CHCl_3$, cm^{-1}): 740, 1106, 1263, 1473, 2106, 2931, 3393; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.30 (brs, 1H), 3.82 (s, 3H), 3.86-4.01 (m, 2H), 4.20-4.24 (m, 1H), 4.85 (d, *J* = 8.7, 1H), 6.92 (dd, *J* = 2.0, 8.7, 2H), 7.27 (dd, *J* = 2.0, 8.7, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 55.1, 58.0, 63.8, 66.5, 114.0, 128.1, 128.8, 159.8; **Anal.** Calcd for $C_{10}H_{12}BrN_3O_2$ requires C, 41.98; H, 4.23; N, 14.69; found: C, 41.90; H, 4.20; N, 14.69%.

2-Azido-3-bromobutane-1,4-diol (28):

Yield: 76%; colorless solid **m.p.**: 52 °C; **IR** ($CHCl_3$, cm^{-1}): 740, 1109, 1265, 2104, 3395; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.74-3.95 (m, 5H), 4.12-4.20 (m, 1H), 4.43-4.54 (m, 2H);

^{13}C NMR (50 MHz, $CDCl_3$): δ 54.3, 62.3, 63.3, 63.4; **Anal.** Calcd for $C_4H_8BrN_3O_3$ requires C, 22.87; H, 3.84; N, 20.01; found: C, 22.80; H, 3.82; N, 20.06%.

A general experimental procedure for the preparation of racemic *syn*-azido epoxides (10a-b):

Azido bromide (**26a-b)** (13 mmol) was taken in THF: H_2O (20: 5 mL) and LiOH powder (375 mg, 15.6 mmol) was added slowly with stirring at 0 °C for 2 h (monitored by TLC). The reaction mixture was diluted with EtOAc (25 mL) and water (30 mL). The organic layer was separated and the aq. layer was extracted with EtOAc (2 x 20 mL). The combined organic extracts were washed with brine and dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give crude products which were purified by column chromatography [silica gel (60-120 mesh) and petroleum ether: EtOAc (90:10) as an eluent] to give **10a-b** in 70-76% yields.

A general experimental procedure for the preparation of racemic *anti*-azido epoxide (10c):

Azido bromide **28** (10 mmol) was taken in THF (20 mL) and NaOH powder (0.4 g, 10 mmol) was added slowly with stirring at 0 °C for 2 h (monitored by TLC). The reaction mixture was diluted with EtOAc (25 mL) and water (30 mL). The organic layer was separated and the aq. layer was extracted with EtOAc (2 x 20 mL). The combined organic extracts were washed with brine and dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give crude product, which was dissolved in dry CH_2Cl_2 (20 mL) followed by the addition of imidazole (10 mmol) and *t*-butyl dimethyl silyl chloride (10 mmol). It was stirred for 0.5 h and quenched with aq. $NaHCO_3$ solution (20 mL). The aq. layer was extracted with CH_2Cl_2 (2 × 30 mL), dried over anhyd. Na_2SO_4 and concentrated

in vacuo to give the crude product, which was purified by column purified by column chromatography [silica gel (60-120 mesh) and petroleum ether:EtOAc (90:10) as an eluent] to give **10c** in 76% yield.

A general experimental procedure for the Hydrolytic Kinetic Resolution (HKR) of racemic azido epoxides:

To a solution of (*R,R*)-**1** or (S,S)-**1** (0.043 g, 0.07 mmol) in toluene (2.0 mL) was added acetic acid (0.04 g, 7.3 mmol). It was allowed to stir at 25 °C in open air for 30 min. over which time the color changed from orange-red to a dark brown and it was then concentrated in vaccuo to get the Co-salen complex as brown colored solid.

To a solution of Co-salen complex **-1** (0.004 g, 0.5 mol%) and azido epoxide (1.41 mmol) in THF (0.5 mL) at 0 °C was added H_2O (0.012 g, 0.5 mmol) dropwise over 5 min. The reaction was allowed to warm to 25 °C and stirred for 14 h. After completion of reaction (monitored by TLC), solvent was removed *in vaccuo*. The crude product was purified by column chromatography over silica gel to give chiral azido epoxides **10a-e,** (solvent system; pet ether: EtOAc = 90:10) and chiral azido diols **11a-e** (solvent system; pet ether: EtOAc = 70:30) in pure form.

(2*R*,3*S*)-2-(Azidophenylmethyl)-oxirane (10a):

Yield: 48%; yellow liquid; **$[\alpha]^{25}_{D}$**: +120 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 758, 860, 1125, 1250, 1460, 1493, 1602, 2105, 2932, 3025; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.73-2.84 (m, 2H), 3.23-3.29 (m, 1H), 4.25 (d, *J* = 6.1, 1H), 7.35-7.47 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 44.6, 54.6, 66.8, 127.2, 128.8, 128.9, 135.7; **Anal.** Calcd for $C_9H_9N_3O$ requires C, 61.70; H, 5.18; N, 23.99; found: C, 61.79; H, 5.14; N, 23.90%.

(2*R*,3*S*)-2-(Azido-4-methoxyphenylmethyl)oxirane (10b):

Yield: 48%; yellow gum; **[α]$^{25}_{D}$**: +82 (*c* 0.9, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 1039, 1250, 1516, 1609, 2106, 2932, 3025; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.72-2.73 (m, 1H), 2.78-2.80 (m, 1H), 3.21-3.24 (m, 1H), 3.82 (s, 1H), 4.21(d, *J* = 5.1 Hz, 1H), 6.91 (d, *J* = 8.6, Hz, 2H) 7.30 (d, *J* = 8.6 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 44.6, 54.6, 55.1, 66.1, 114.2, 127.7, 128.5, 159.8; **Anal.** Calcd for $C_{10}H_{11}N_3O_2$ requires C, 58.53; H, 5.40; N, 20.48; found C, 58.48; H, 5.45; N, 20.56%.

(2*S*,3*S*)-3-Azido-4-*tert*-butyldimethylsilyloxy-1,2-epoxybutane (10c):

Yield: 48%; yellow liquid; **[α]$^{25}_{D}$**: +26 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 740, 839, 1127, 1250, 1463, 1493, 1602, 2106, 2932, 3025; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.09 (s, 6H), 0.90 (s, 9H), 2.73 (dd, *J* = 5.0, 2.6 Hz, 1H), 2.80 (dd, *J* = 5.0, 3.6 Hz, 1H), 3.01-3.07 (m, 1H), 3.21-3.29 (m, 1H), 3.74-3.90 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.5, 18.2, 25.7, 45.2, 50.2, 63.5, 63.9; **Anal.** Calcd for $C_{10}H_{21}N_3O_2Si$ requires C, 49.35; H, 8.70; N, 17.27; found: C, 49.20; H, 8.75; N, 17.30%.

(2*S*,3*S*)-2-(Azido-phenylmethyl)oxirane (10d):

Yield: (48%); yellow liquid; **[α]$^{25}_{D}$**: +170 (*c* 1.5, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 758, 862, 1127, 1250, 1463, 1493, 1602, 2106, 2932, 3025; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.82-2.84 (m, 1H), 2.86-2.88 (m, 1H), 3.21-3.23 (m, 1H), 4.59 (d, *J* = 4.5, 1H), 7.34-7.40 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 44.5, 53.6, 64.9, 127.2, 128.6, 128.7, 135.7; **Anal.** Calcd for $C_9H_9N_3O$ requires C, 61.70; H, 5.18; N, 23.99; found: C, 61.79; H, 5.14; N, 23.90%.

(2*S*,3*S*)-2-(Azido-4-methoxyphenyl-methyl)oxirane (10e):

Yield: 47%; yellow gum; **[α]$^{25}_{D}$**: +90 (*c* 0.8, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 1039, 1250, 1516, 1609, 2106, 2932, 3025; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.83 (d, *J* = 5.0 Hz, 2H),

3.19-3.21 (m, 1H), 3.82 (s, 1H), 4.55 (d, *J* = 5.1 Hz, 1H), 6.91 (d, *J* = 8.6, Hz, 2H) 7.30 (d, *J* = 8.6 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 44.9, 53.2, 55.10, 64.7, 114.2, 127.7, 128.7, 159.8; **Anal.** Calcd for $C_{10}H_{11}N_3O_2$ requires C, 58.53; H, 5.40; N, 20.48; found: C, 58.48; H, 5.45; N, 20.56%.

(2*S*, 3*R*)-3-Azido-3-phenylpropane-1,2-diol (11a):

Yield: 47%; gum; **$[\alpha]^{25}_D$**: -188 (*c* 1, $CHCl_3$); 98% ee by chiral HPLC analysis (Chiralpak OD-H, *n*-hexane/*i*PrOH, 90:10, 0.5 mL/min) retention time 13.020 (0.90%) and 13.512 (99.20%); **IR** ($CHCl_3$, cm^{-1}): 859, 828, 1039, 1100, 1384, 1454, 1493, 1602, 2099, 2932, 3052, 3392 (broad); **^{1}H NMR** (200 MHz, $CDCl_3$): δ 3.30 (dd , *J* = 11.5, 6.0 Hz, 1H), 3.44 (d, *J* = 11.5 Hz, 1H), 3.80 (br s, 1H), 3.62-3.94 (m, 1H), 4.52 (d, *J* = 8.1 Hz, 1H), 7.28-7.35 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 62.8, 68.1, 75.0, 127.5, 128.7, 128.9, 136.2; **Anal.** Calcd for $C_9H_{11}N_3O_2$ requires C, 55.95; H, 5.74; N, 21.75; found: C, 56.10; H, 5.65; N, 21.60%.

(2*S*, 3*R*)-3-Azido-3-(4-methoxyphenyl)propane-1,2diol (11b):

Yield: 48%; yellow liquid; **$[\alpha]^{25}_D$**: -190 (*c* 1, $CHCl_3$); 98% ee by chiral HPLC analysis (Chiralpak OD-H, *n*-hexane/*i*PrOH, 90:10, 0.5 mL/min) retention time 15.97 (1.50%) and 17.73 (98.50%); **IR** ($CHCl_3$, cm^{-1}): 1035, 1195, 1513, 1616, 2100, 2920, 3050, 3368; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.09 (br s , 1H), 2.81 (br s , 1H), 3.35 (dd, *J* = 11.2, 4.8 Hz, 1H), 3.55 (dd, *J* = 11.6, 2.3 Hz, 1H), 3.75-3.86 (m, 1H), 3.82 (s, 3H), 4.58 (d, *J* = 8.4 Hz, 1H), 6.92 (dd, *J* = 8.7, 2.1 Hz, 2H) 7.27 (dd, *J* = 6.0, 2.1 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 55.1, 62.7, 67.8, 75.0, 114.3, 128.0, 128.8, 159.8; **Anal.** Calcd for $C_{10}H_{13}N_3O_3$ requires C, 55.95; H, 5.74; N, 21.75; found: C, 56.10; H, 5.65; N, 21.60%.

(2*R*,3*R*)-3-Azido-4-(*tert*-butyldimethylsilyloxy)butane-1,2-diol (11c):

Yield: 47%; yellow liquid; **[α]$^{25}_{D}$**: -29 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 740, 839, 1109, 1265, 1471, 2100, 2931, 3390; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.12 (s, 6H), 0.90 (s, 9H), 2.92 (br s, 1H), 3.39-3.48 (m, 2H), 3.61-3.81 (m, 3H), 3.81-3.97 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.5, 18.1, 25.7, 63.5, 63.6, 63.8, 71.4; **Anal.** Calcd for $C_{10}H_{23}N_3O_3Si$ requires C, 45.95; H, 8.87; N, 16.08; found: C, 45.90; H, 8.92; N, 16.13%.

(2*R*, 3*R*)-3-Azido-3-phenylpropane-1,2-diol (11d):

Yield: 46%; yellow gum; **[α]$^{25}_{D}$**: -180 (*c* 0.35, $CHCl_3$); 98% ee by chiral HPLC analysis (Chiralpak OD-H, *n*-hexane/*i*PrOH, 90:10, 0.5 mL/min) retention time 14.68 (0.80%) and 15.89 (99.14%); **IR** ($CHCl_3$, cm^{-1}): 859, 828, 875, 1039, 1101, 1386, 1456, 1493, 1602, 2099, 2934, 3032, 3392; **^{1}H NMR** (200 MHz, $CDCl_3$) : δ 2.59 (br s, 1H), 2.77 (br s, 1H), 3.58-3.71 (m, 2H), 3.72-3.86 (m, 1H), 4.57 (d, *J* = 7.0 Hz, 1H), 7.30-7.44 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 62.8, 66.9, 74.0, 127.8, 128.7, 128.9, 136.1; **Anal.** Calcd for $C_9H_{11}N_3O_2$ requires C, 55.95; H, 5.74; N, 21.75%; found: C, 56.08; H, 5.66; N, 21.61%.

(2*R*, 3*R*)-3-Azido-3-(4-methoxyphenyl)propane-1,2-diol (11e)

Yield: 47%; yellow liquid; **[α]$^{25}_{D}$**: -110 (*c* 0.35, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 1035, 1195, 1513, 1616, 2100, 2920, 3050, 3368 (broad); **^{1}H NMR** (200 MHz, $CDCl_3$): 3.08 (br s , 2H), 3.56-3.68 (m, 2H), 3.70-3.78 (m, 1H), 3.80 (s, 3H), 4.47 (d, *J* = 6.9 Hz, 1H), 6.90 (d, *J* = 8.1, Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 55.1, 62.9, 66.5, 73.9, 114.3, 127.9, 129.1, 159.8; **Anal.** Calcd for $C_{10}H_{13}N_3O_3$ requires C, 55.95; H, 5.74; N, 21.75; found: C, 56.10; H, 5.65; N, 21.60%.

Section II

Enantioselective synthesis of (+)-*epi*-Cytoxazone and (-)- Cytoxazone *via* hydrolytic kinetic resolution of azido epoxides

1.2.1 Introduction

In 1998, Osada and co-workers reported the isolation of (4*R*,5*R*)-5-(hydroxymethyl)-4-(4-methoxyphenyl)-1,3-oxazolidine-2-one [(-)-**29**, generic name cytoxazone],[17] which was shown to possess high cytokine modulator activity by acting on the Th2 cells.[18] Because of these biological properties, several total syntheses of (-)-**29** and its *trans*-diastereoisomer (+)-*epi*-cytoxazone (**30**) (**Fig. 10)** have been reported. [19]

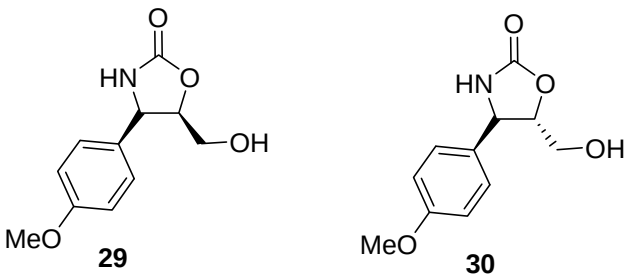


Fig. 10: Structures of (-)-cytoxazone (**29)** and (+)-*epi*-cytoxazone (**30)**

Prompted by the first positive biological results, many researchers have also reported the preparation of *cis*- and *trans*-isocytoxazones which are structural isomers of cytoxazone **29** and its *trans* epimer **30** (**Fig 10**).[20]

1.2.2 Pharmacology of cytoxazone

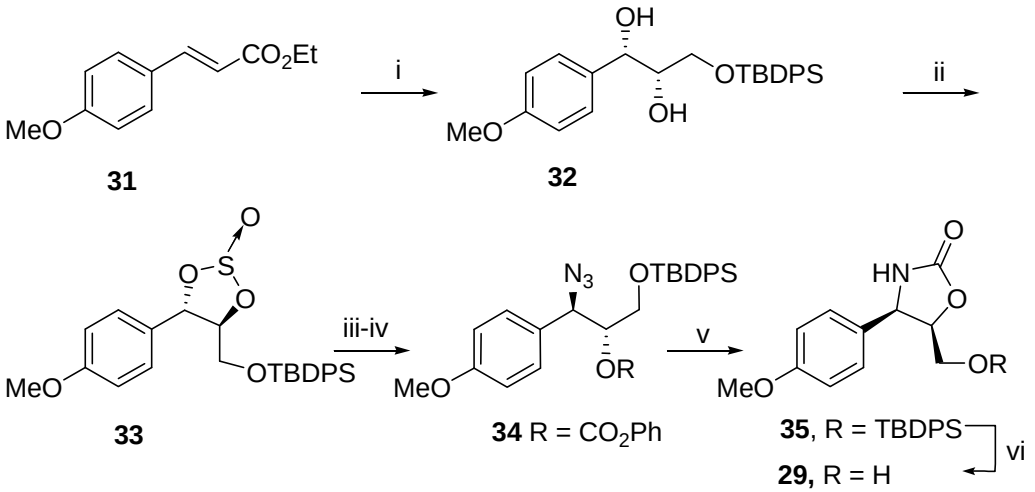
It is well established that the induction of humoral or cellular response is influenced by the development of distinct subsets of $CD4^+$ T cells.[21] The Th1 cell subset produces predominantly IL-2, GM-CSF, INF-γ, and TNF-β, (type 1 cytokines) and is involved in delayed-type hypersensitivity reactions, whereas the Th2 cell subset secretes IL-4, IL-5,

IL-6, IL-10, and IL-13 (type 2 cytokines), which are important factors for β cell growth and differentiation to Ig secretion. The imbalance of cytokine production by $CD4^+$ T cells leads to a wide variety of immunological disorders, i.e. allergy, progressive lymphoproliferation, and severe immunodeficiency.[22] Skin and lung biopsies from allergic patients indicate that the pivotal cells in the allergic site are the Th2 cells.[23] Treatments effectively suppressing the function or the differentiation of these allergen-specific Th2 cells will most likely provide efficient ways to intervene in Ig-mediated allergic diseases. In the course of screening for chemical immunomodulators that inhibit the type 2 cytokine productions in Th2 cells, it was found that cytoxazone containing a 2-oxazolidinone ring, which is rare in microbial metabolites, as a novel cytokine modulator produced by *Streptomyces* sp. Cytoxazones show a cytokine-modulating activity by inhibiting the signaling pathway of Th2 cells, but not Th1 cells.

1.2.3 Review of literature

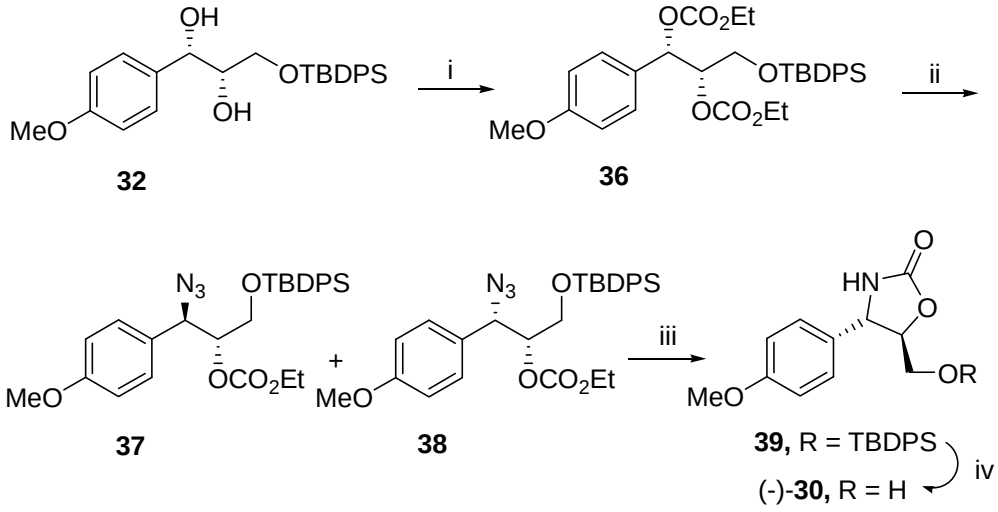
Nakata's approach (1999)[24]

Nakata *et al.* have achieved the synthesis of (-)-cytoxazone (**29)** using Sharpless asymmetric dihydroxylation of ester **31**. The cyclic sulfite **33** was obtained (in 99% yield and 97% ee) from ethyl *p*-methoxycinnamate **31** by a two-step process involving the Sharpless catalytic asymmetric dihydroxylation followed by treatment with $SOCl_2$. The cyclic sulfite **33** was then opened using LiN_3 and the alcohol obtained was protected as the corresponding carbonate **34**. Intramolecular cyclization of carbonate **34** with PPh_3 followed by the deprotection of TBDPS group gave (-)-cytoxazone (**29**) in 89% ee and 96% yield (**Scheme 8**).



Scheme 8: (i) (a) AD-mix-α, *tert*-BuOH: H_2O (1:1), 25 °C, 93 %, 99% ee; (b) $NaBH_4$, THF, 0 °C, 66%; (c) TBDPSCI, imid., DMF, 0 °C, 99%; (ii) $SOCl_2$, Et_3N, CH_2Cl_2, 0 °C, 99%; (iii) LiN_3, DMF, 70 °C, 74 %; iv) $ClCO_2Ph$, Py, CH_2Cl_2, 25 ºC, 96%; (v) PPh_3, THF/ H_2O, 50 °C, 90%; (vi) n-Bu_4NF, THF, 0 °C, 89% ee, 96%.

The same group has achieved the synthesis of (-)-*epi*-cytoxazone **30** from the common intermediate **32** by using an efficient one-step process of stereoselective azidation (**Scheme 9**).

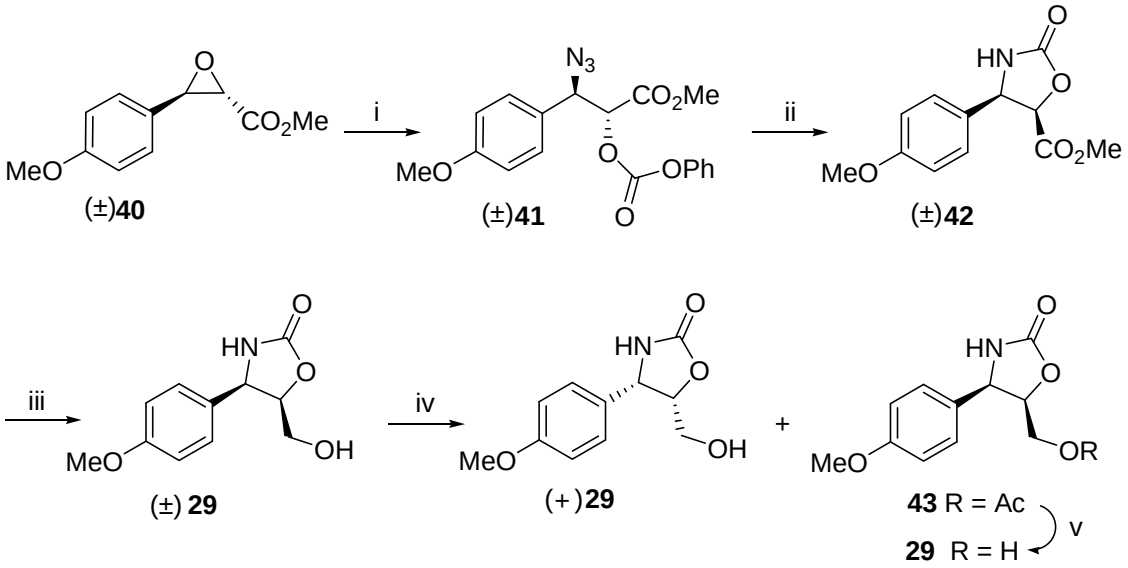


Scheme 9: (i) $ClCO_2Et$, Py, CH_2Cl_2, 0 °C, 92%; (ii) $TMSN_3$, TMSOTf, MeCN, -43 °C, 99%; (iii) PPh_3, THF/H_2O, 50 °C, 100%; (iv) n-Bu_4NF, THF, 0 °C, 99%.

Thus, (4*S*,5*S*)-di(ethylcarbonate) **36**, prepared from diol **32**, was treated with $TMSN_3$ (6 eq.) in the presence of TMSOTf to afford a 6:1 mixture of the desired α-azide **37** and its β-isomer **38**. The α-azide **37** was then treated with PPh_3 in THF/H_20 to give 2-oxazolidinone **39**, which was converted to *4-epi*-cytoxazone (**30**) in 99% yield using tetrabutylammonium fluoride.

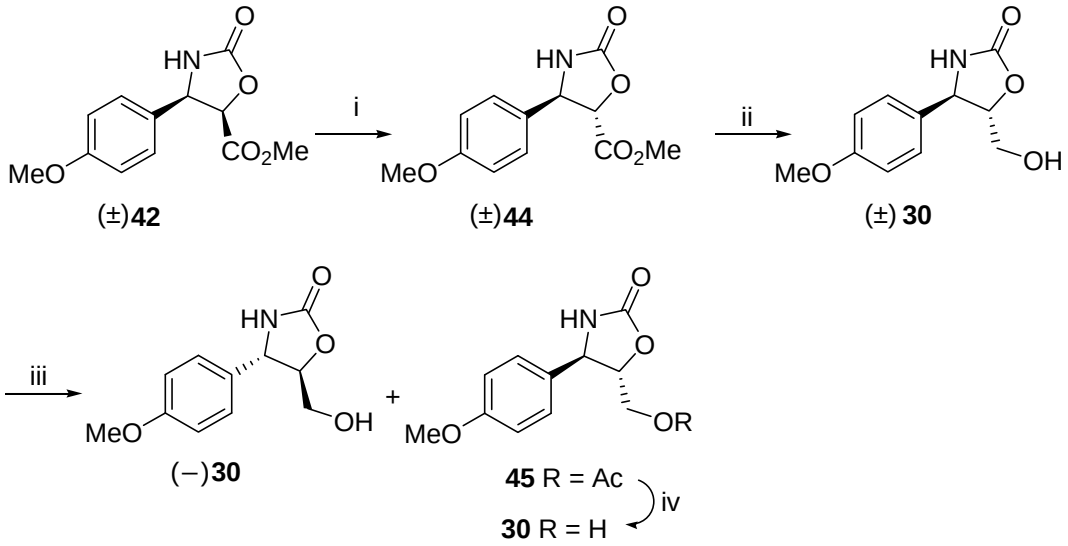
Sunjic's approach (2001)[25]

In this approach, synthesis of (-)-cytoxazone (±)-(**29**) was achieved starting from the glycidic ester (±)-**40** using enzymatic kinetic resolution. Nucleophilic ring opening of the epoxide (±)-**40** with NaN_3, followed by protection of the alcohol and intramolecular cyclization gave ester (±)-**42**. Reduction of the ester (±)-**42** and the subsequent kinetic resolution of racemic (±)-**29** using *Penicillium camemberti* lipase (PcamL) afforded (-)-cytoxazone (**29)** in 33% overall yield and 88.2% ee (**Scheme 10**).



Scheme 10: (i) aq. NaN_3, dioxane, 50 °C, 3 h, 56%; (ii) $ClCO_2Ph$, CH_2Cl_2, –5 °C, 1 h, 100%; (iii) (a) Ph_3P, aq THF, 50 °C, 1.5 h, 88%; (b) $NaBH_4$, $CaCl_2$, absolute EtOH, 25 ºC, 20 min, 79%; (iv) PcamL, vinyl acetate, 30 °C; (v) KOH, MeOH, 25 ºC, 1 h.

Also, (±)-*epi*-cytoxazone (±)-**30b** was synthesized from the common intermediate, oxazolidinone (±)-**42** (**Scheme 11**). Epimerization at C(5) in oxazolidinone (±)-**42** using potassium hydroxide followed by esterification with methyl iodide gave ester **44**. Reduction of ester **44** with calcium chloride/sodium borohydride and the subsequent kinetic resolution using CAL in SOL-Gel-AK afforded (+)-*epi*-cytoxazone **30** in 49% overall yield and 87.3% ee.

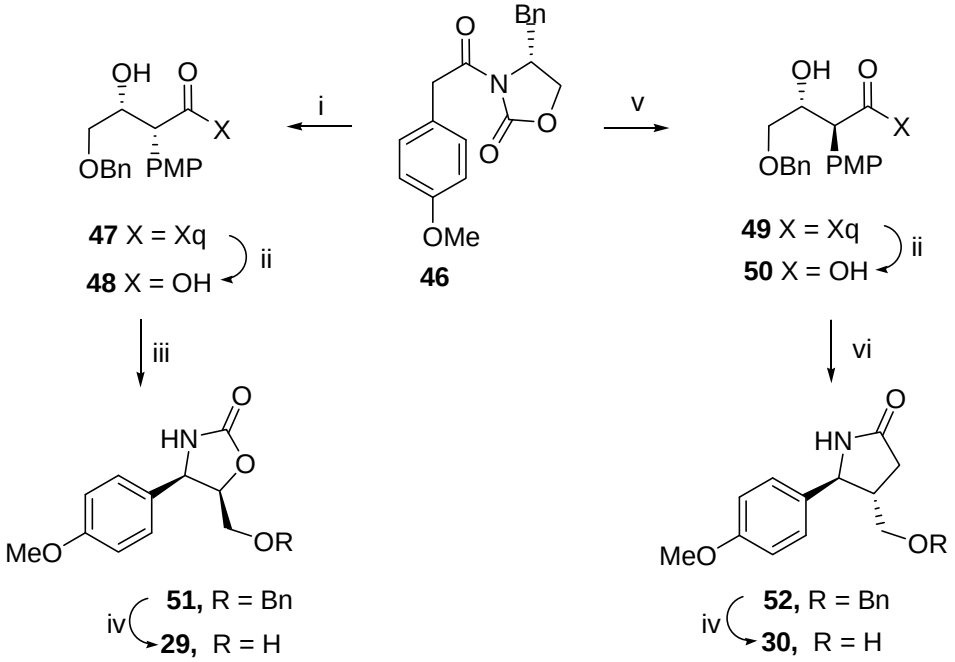


Scheme 11: (i) (a) KOH, EtOH, reflux, 1 h; (b) MeI, K_2CO_3, DMF, 25 ºC, 16 h, 46%; (ii) $NaBH_4$, $CaCl_2$, absolute EtOH, 25 ºC, 20 min., 82%; (iii) CAL in SOL-Gel-AK, vinyl acetate, 30 °C; (iv) KOH, MeOH, 25 ºC, 1 h.

Carter's approach (2003)[26]

Carter *et al*. have made use of the Evans'aldol approach as the key reaction for the synthesis of (-)-cytoxazone **29** as well as (+)-*epi*-cytoxazone **30**. The reaction of dibutylboron enolate of **46** with the benzyloxyacetaldehyde provided the aldol **47** in good *syn*-diastereoselectivity. Removal of the chiral auxiliary from **47** provided the acid **48**, which was transformed into the oxazolidinone **51** in a one-pot 3 step procedure: (i) acyl azide formation, (ii) Curtius rearrangement and (iii) isocyanate trapping. Ether **51** was

debenzylated using Pearlman's catalyst to provide (-)-cytoxazone **29**. The synthesis of (+)-*epi*-cytoxazone required the use of an *anti*-selective aldol product **49**, which was obtained by the addition of a pre-complexed solution of benzyloxyacetaldehyde and 0.5 equiv. of $SnCl_4$ to the dibutylboryl enolate of **46**. The same sequence of reactions was used to synthesize (+)-*epi*-cytoxazone (**30**) starting from aldol product **49** (**Scheme 12**).



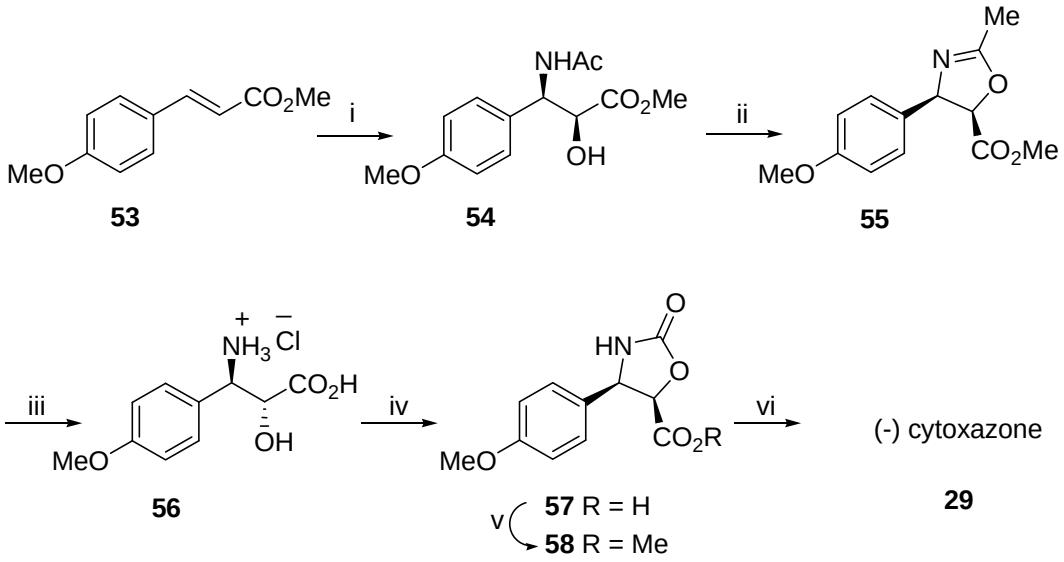
,.

Scheme 12: (i) Bu_2BOTf, *i*-Pr_2EtN, -78 ºC, 20 min.; $BnOCH_2CHO$, -78 ºC to 0 ºC, 1.5 h, 51%; (ii) 4:1 THF:H_2O, H_2O_2, LiOH, 0 ºC, 1 h; $NaHSO_3$, 99%; (iii) $(PhO)_2PON_3$, $PhCH_3$, 23 ºC, 40 min., 110 ºC, 3h, 77%; (iv) H_2 (1 atm), $Pd(OH)_2$, MeOH, 23 ^{0}C, 24 h, 84%; (v) Bu_2BOTf, *i*-Pr_2EtN, 0 ºC, 30 min., add $BnOCH_2CHO$ precomplexed w/0.5 equiv $SnCl_4$, -78 ºC, 3 h, 64%; (vi) $(PhO)_2PON_3$, CH_2Cl_2, 23 ºC, 40 min., 45 ºC, 12 h, 61%.

Saicic's approach (2004)[27]

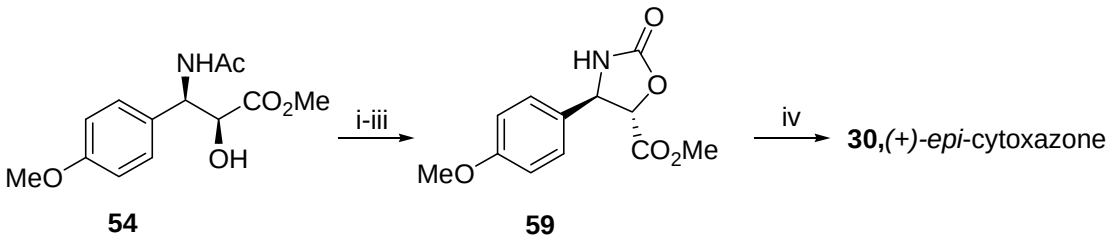
Saicic's approach was based on the Sharpless asymmetric aminohydroxylation reaction, starting from methyl *p*-methoxycinnamate, **53** in six steps and 31% overall yield (**Scheme 13**). The required *anti*-aminoalcohol **56** was synthesized using Sharpless asymmetric aminohydroxylation and subsequent inversion of configuration in

amidoalcohol **54** *via* an oxazoline **55**.



Scheme 13: (i) $K_2[OsO_2(OH)_4]$ (4 mol %), BrNHAc, $(DHQD)_2PHAL$ (1 mol%), LiOH, H_2O, t-BuOH, 4 ºC, 20 h, 72%; (ii) Tf_2O, DMAP, CH_2Cl_2, 80%; (iii) 12% HCl, 25 ºC, 1.5 h; (iv) $ClCO_2CCl_3$, NaOH, H_2O, 0 ºC; (v) CH_2N_2, THF, 72%; (vi) $NaBH_4$, THF, 0 ºC, 75%.

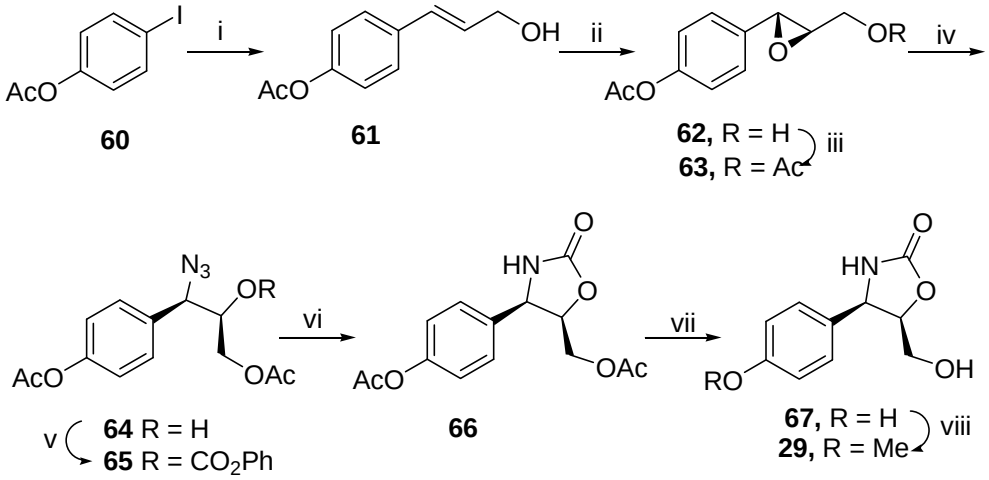
Subjecting amidoalcohol **54** to the sequence of reactions already described for cytoxazone (hydrolysis/cyclization/esterification), gave the methyl ester **59**, which on reduction with sodium borohydride gave (+)-*epi*-cytoxazone **30** (**Scheme 14**).



Scheme 14: (i) 10% HCl, reflux, 4 h; (ii) $ClCO_2CCl_3$, NaOH, H_2O, 0 ºC; (iii) CH_2N_2, THF, 63%; (iv) $NaBH_4$, THF, 0 ºC, 80%.

Sudalai's approach (2006),(2007)[28,29]

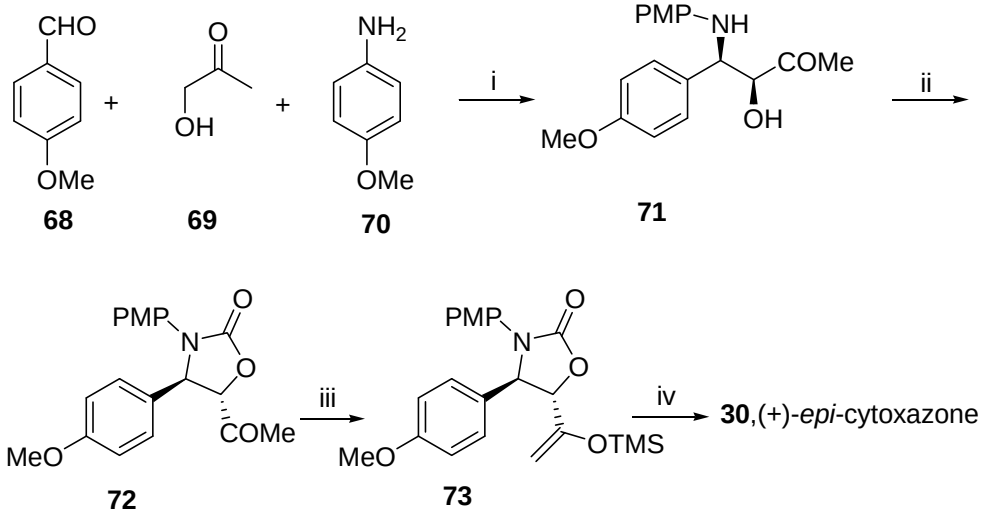
Sudalai *et al*. have developed a simple method for the enantioselective synthesis of (-)-cytoxazone **29** using Sharpless asymmetric epoxidation as the key step. Thus, asymmetric epoxidation of allylalcohol **61** gave chiral epoxide **62**, which was further acylated to give acetate **63**. The nucleophilic opening of the epoxide **63** at the benzylic position with NaN_3 gave azido alcohol **64** in 88% yield. The protection of the alcohol followed by reductive cyclization with PPh_3 and deprotection of acetate group gave oxazolidinone **67**, which was directly subjected to methylation with methyl iodide in the presence of NaH to afford (-)-cytoxazone (**29**) in 65% yield and 83% ee (**Scheme 15**).



Scheme 15: (i) allyl alcohol, AgOAc, $Pd(OAc)_2$, PPh_3, DMF, 70 ºC, 16 h, 81%. (ii) anhyd. 5.4 M TBHP in CH_2Cl_2, 4 Å molecular sieves, $Ti(OiPr)_4$, (+)-DIPT, CH_2Cl_2, -20 ºC, 20 h, 78%. (iii) AcCl, Et_3N, DMAP, CH_2Cl_2, 25 ºC, 87%. (iv) NaN_3, NH_4Cl, THF/H_2O (2:1), 50 ºC, 3 h, 79%. (v) PhOCOCl, pyridine, CH_2Cl_2, -5 to 25 ºC, 1 h, 93%. (vi) PPh_3, THF/H_2O (10:1), 50 ºC, 2 h, 87%. (vii) aq $NaHCO_3$, MeOH, reflux, 1 h. (viii) NaH, MeI, THF, 0–25 ºC, 3 h, 69%, 83% ee.

The same group has achieved the synthesis of (+)-*epi*-cytoxazone (**30**) using L-proline catalyzed asymmetric Mannich reaction. Thus, key intermediate *syn*-amino alcohol **71** was obtained from L-proline catalyzed asymmetric Mannich reaction of 4-methoxybenzaldehyde, **68** hydroxyacetone **69** and p-anisidine **70** in 76% yield with *syn*/*anti* ratio (2:1). Amino alcohol **71** was then protected with triphosgene to give

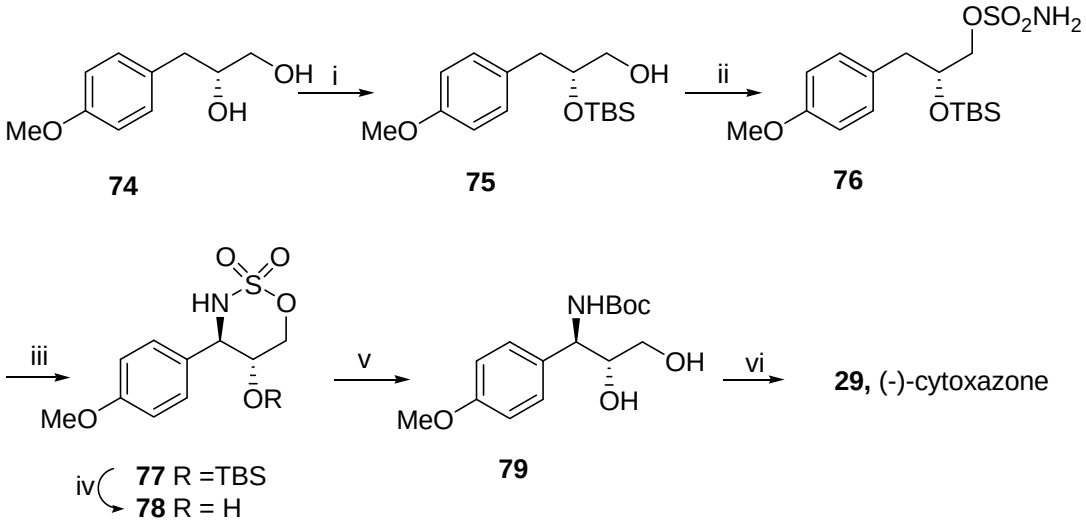
oxazolidinone **72** in 82% yield. *In situ* generated silyl enol ether **73** was subjected for ozonolysis without purification. Reductive work up of ozonide and PMP deprotection with CAN gave (+)-*epi*-cytoxazone (**30**) in 59% yield and 81% ee (**Scheme 16**).



Scheme 16: (i) *p*-anisidine, hydroxyacetone,. L-proline, DMSO, 25 ºC, 24 h, 76%. (ii) triphosgene, Et_3N, CH_2Cl_2, -10 to 25 ºC, 82%. (iii) Li-HMDS, TMSCl, THF, -78 ºC. (iv) (a) O_3, PPh_3, CH_2Cl_2, -78 ºC. (b) $NaBH_4$, MeOH, 25 ºC. (c) CAN, CH_3CN, 5 h, 59% (in three steps), 81% ee.

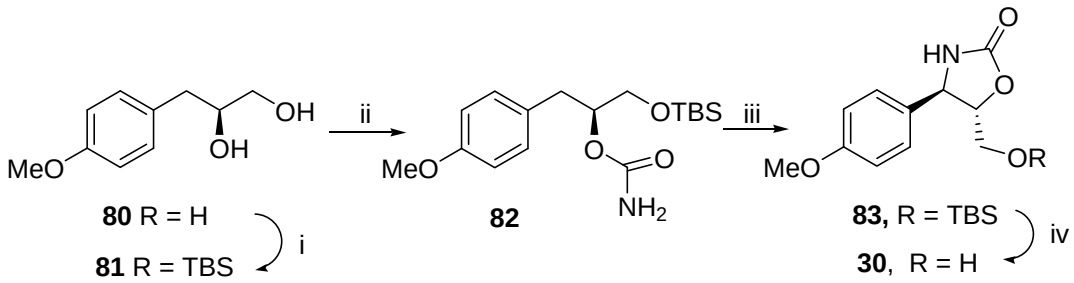
Sudalai *et al*. have also developed a simple method for the enantioselective synthesis of (-)-cytoxazone **29** and (+)-epi-cytoxazone **30** commencing from the diol **74** and **80** respectively which were obtained by two different routes: hydrolytic kinetic resolution and proline-catalyzed α-aminooxylation. Diol **74** was converted to *bis*-TBS-protected silyl ether followed by selective deprotection of the primary OH group with camphorsulfonic acid to afford **75** which was converted into sulfamate ester **76** in 76% yield using HCO_2H and chlorosulfonyl isocyanate. The γ-C-H insertion of **76** was carried out with a catalytic amount of $Rh_2(OAc)_4$ (2 mol%), $PhI(OAc)_2$ and MgO in CH_2Cl_2 to give sulfamate ester **77** with *anti* (10:1) diastereoselectivity. The TBS deprotection, carbamoylation and ring opening of *N*-Boc protected oxathiazinane furnished the *anti*-

amino alcohol **79** in 84% which was converted to (-)-cytoxazone (**29**) by intramolecular cyclization using NaH in THF (**Scheme 17**).



Scheme 17: (i) (a) TBSCl, imidazole, DMF, 25 °C, 4 h, 98%; (b) camphorsulfonic acid, MeOH, 95%; (ii) HCO_2H, chlorosulfonyl isocyanate, 0 °C, 76%; (iii) 2 mol% $Rh_2(OAc)_4$, $PhI(OAc)_2$, MgO, CH_2Cl_2, 40 °C, 2 h, 82%, *anti*:*syn* (10:1); (iv) (a) camphorsulfonic acid, MeOH, 25 °C, 1 h, 97%; (b) (a) $(Boc)_2O$, DMAP, Et_3N, CH_2Cl_2, 25 °C, 1 h; (c) CH_3CN:H_2O (4:3), 60 °C, 4 h, 84%; (v) NaH, THF, 0 °C, 1 h, 96%.

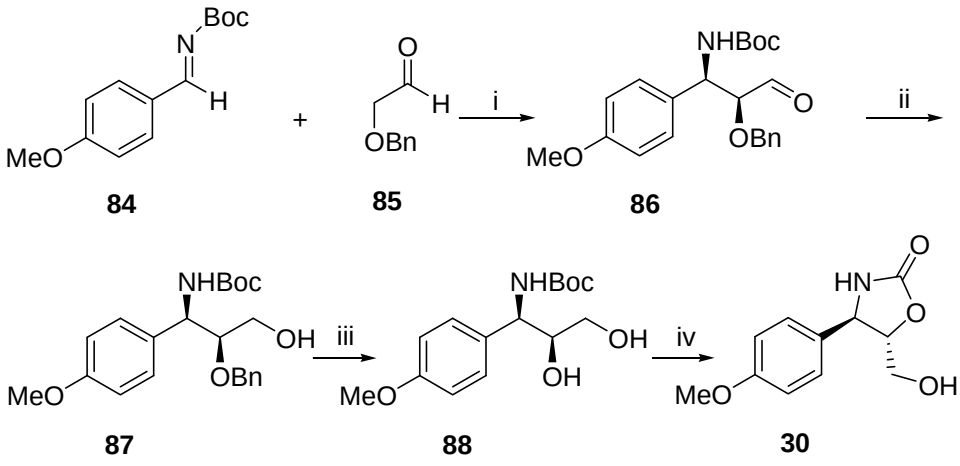
In the case of (+)-epi-cytoxazone **30**, protection of the primary alcohol of diol **80** with TBSCl gave the secondary alcohol **81**, which was converted into carbamate **82** in 92% yield using reported conditions (trichloroacetyl isocyanate, CH_2Cl_2, then K_2CO_3, MeOH, H_2O). Carbamate **82** underwent C–H insertion on treatment with 2 mol % $Rh_2(OAc)_4$, $PhI(OAc)_2$ and MgO in CH_2Cl_2 at 40 °C to afford the corresponding oxazolidinone **83** with syn diastereoselectivity (5.5:1) (determined from ^1H NMR analysis) in 87% combined yield. The syn-diastereomer, oxazolidinone **83**, was readily separated by column chromatography. Finally, deprotection of the TBS group using TBAF in THF furnished (+)-epi-cytoxazone **30** in 92% yield (**Scheme 18**).



Scheme 18: (i) TBSCl, imidazole, CH_2Cl_2, 25 °C, 98%; (ii) trichloroacetyl isocyanate, CH_2Cl_2, 0 °C-25 °C, 2 h then K_2CO_3, MeOH, H_2O, 0-25 °C, 12 h, 92%; (iii) 2 mol% $Rh_2(OAc)_4$, $PhI(OAc)_2$, MgO, CH_2Cl_2, 40 °C, 87%, *syn*: *anti* (5.5: 1); (iv) TBAF, THF, 92%.

Kim's approach (2008)[30]

Kim et al synthesis of (+)-epi-cytoxazone **30** the Mannich reaction between N-Boc-imine **84** and benzyloxyacetaldehyde **85** afforded the corresponding β-amino aldehyde 10 in high yield with excellent enantioselectivity. β-amino aldehyde **86** was reduced with sodium borohydride to afford β-amino alcohol **87**in 98 % yield. Deprotection of **87** by hydrogenolysis of the benzyl group afforded the desired diol **88** in 91% yield. Finally, treatment of compound **88** with sodium hydride in THF led to regioselective cyclization to give (+)-epi-cytoxazone **30** in 85% yield (**Scheme 19**).



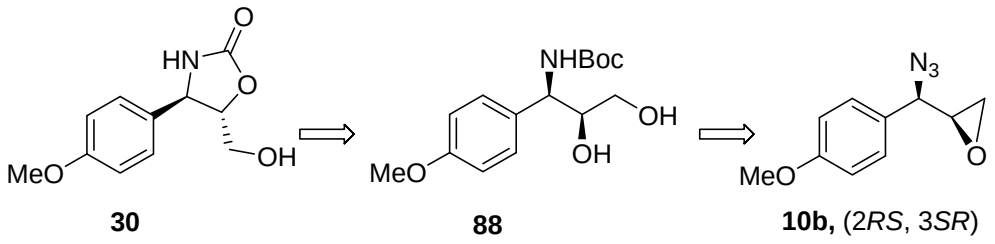
Scheme 19: (i) (2*S*,5*S*)-5-Benzyl-3-methyl-2-pyrrole-imidazolidine-4-one (20 mol%), $CHCl_3$, -30 °C, 78%; (ii) $NaBH_4$, MeOH, 0 °C-25 °C, 98%; (iii) 10% Pd/C, H_2, EtOH, 91%; (iv) NaH, THF, 85%.

1.2.4 Present Work:

1.2.4.1 Objective

Literature search revealed that several methods such as classical resolution, chemo-enzymatic or enantioselective synthesis have been reported for the synthesis of (-)-cytoxazone **29** and its epimer (+)-*epi*-cytoxazone **30**. However, these methods suffer from many disadvantages such as low overall yields, the need for separation of diastereomers and the use of expensive chiral reagents. The synthetic precursors of (-)-cytoxazone **29** and (+)-*epi*-cytoxazone **30** are 1,2-aminoalcohols, which have been the subject of thorough synthetic efforts in recent years.[1a] Most of the syntheses for cytoxazone have made use of indirect methods to establish the *anti*-amino alcohol functionality. In this context, a more practical method for the synthesis of (+)-*epi*-cytoxazone **30** and (-)-cytoxazone **29** is highly desirable. In this section, we describe a concise enantioselective synthesis of (+)-*epi*-cytoxazone **30** and (–)-cytoxazone **29** using HKR of racemic azido epoxides.

Retrosynthetic analysis (**Scheme. 20**) of (+)-*epi*-cytoxazone **30** reveals that *syn*-amino alcohol **88** could be visualized as the key intermediate.



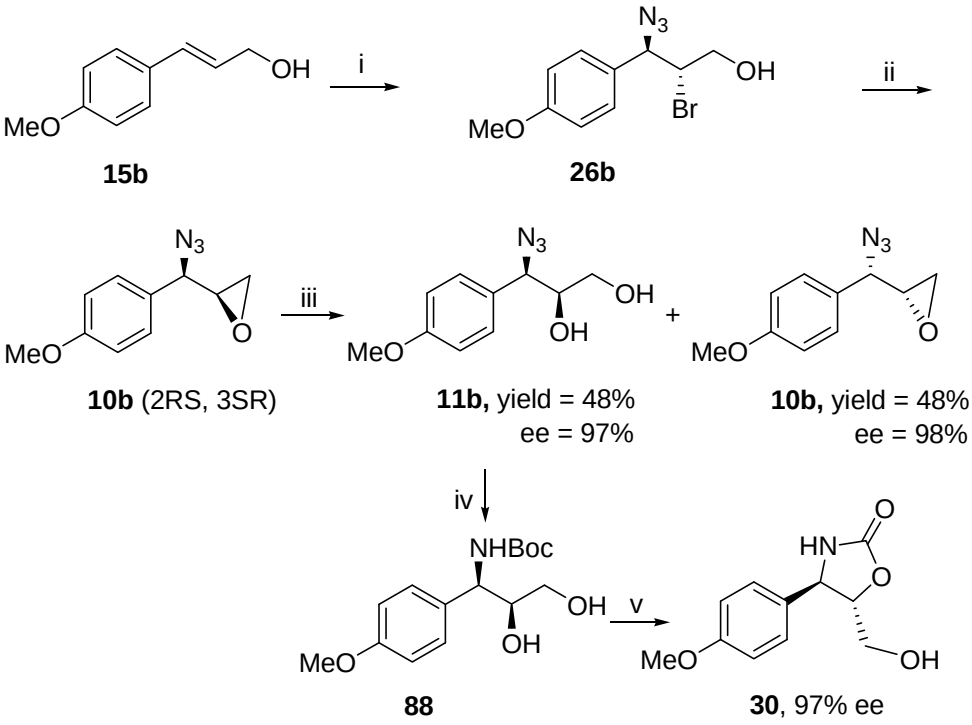
30 **88** **10b,** (2*RS*, 3*SR*)

Scheme 20: Retrosynthetic analysis of (+)-*epi*-cytoxazone **30**

The *anti*-isomer **88** could be prepared from *syn*-azido diol **11b** obtained by the cobalt-catalyzed hydrolytic kinetic resolution of racemic azido epoxide (±)**-10b** (see **Section I**).

1.2.5 Results and Discussion

Our synthesis of (+)-*epi*-cytoxazone **30** has started from 4-methoxycinnamyl alcohol 1**5b,** which was transformed into *syn*-azido epoxide (±)-**10b** in two steps: (i) azidobromination; (ii) formation of epoxide to give *syn*-azido epoxide (±)-**10b** in 75% yield. The *syn*-azido epoxide (±)-**10b** was then subjected to HKR using (*R,R)*-Co(salen)OAc (**1**) to give chiral *syn*-azido diol in **11b** 48% yield with 97% ee along with chiral *syn*-azido epoxide in **10b** 48% yield with 98% ee (**Scheme 21)**. The compound **10b** and **11b** were then readily separated by column chromatographic purification. The enantiomeric excess of *syn*-azido diol in **11b** was determined by chiral HPLC analysis; (Chirapalk OD-H, see **Section I).**



Scheme 21: (i) NBS, NaN_3, CH_3CN: H_2O (4:1), 0 °C, 75%; (ii) LiOH, THF: water (4: 1), 0- 25 °C, 3 h 76%; (iii) *(R,R)*-Co(salen)OAc (0.5 mol%), THF, H_2O (0.5 equiv), 0 ºC, 12 h; (iv) polymethylhydrosiloxane (PMHS), 10% Pd/C, $(Boc)_2O$, EtOH, 25 °C, 4 h, 95%; (v) NaH, dry THF, 25 °C, 3 h, 96%.

Azido diol **11b** was then subjected to one pot azide reduction and Boc protection [10% Pd/C, polymethylhydrosiloxane (PMHS) and $(Boc)_2O$ in EtOH] to give N-Boc amino diol **88** in 95 % yield, which was confirmed by ^1H and ^{13}C-NMR spectroscopy. The ^1H NMR spectrum of **88** showed a typical signal at δ 1.43 (s, 9H) for *tert*-butyl protons. Its ^{13}C NMR spectrum showed characteristic signal at δ 28.3 due to the methyl carbons of *tert*-butyl group (**Fig. 11).**

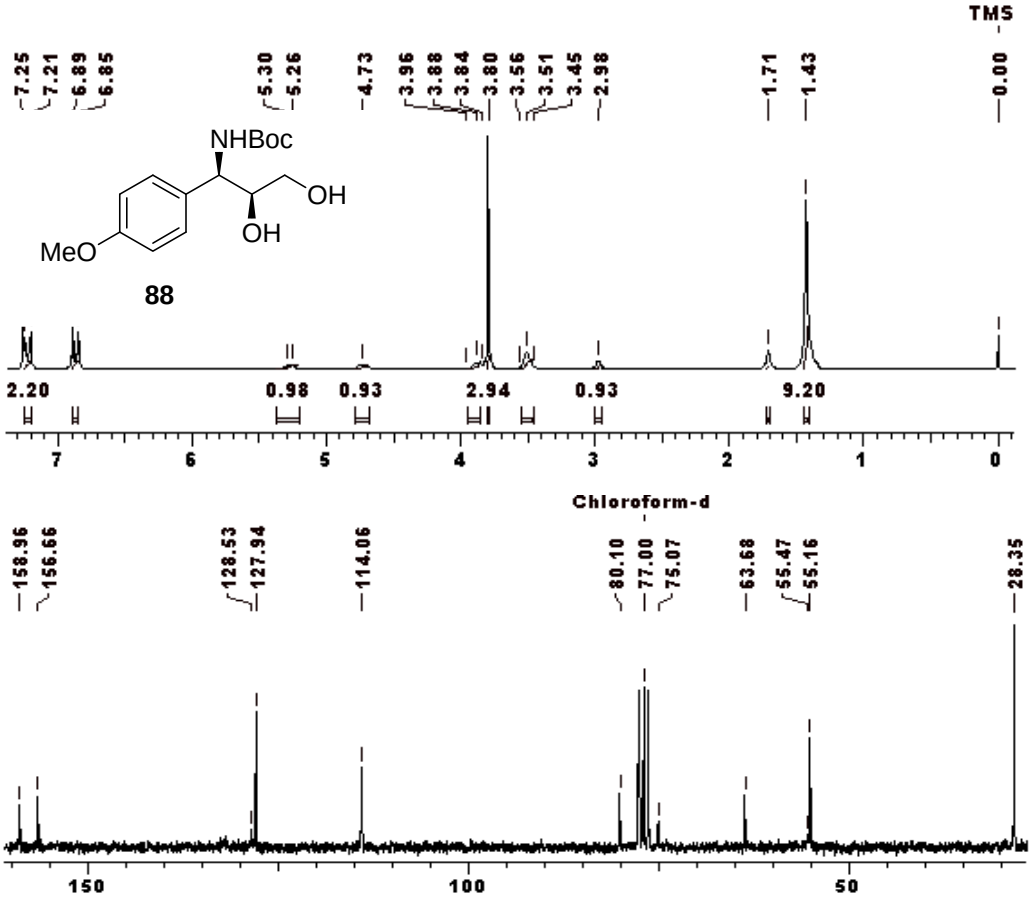


Fig. 11: ^1H and ^{13}C NMR spectra of **88**

Finally, the regioselective intramolecular cyclization of 8**8** using NaH in THF gave (+)-*epi*-cytoxazone **30** (mp 158-160 ºC; lit.[30] mp 159-160 ºC) in 96 % yield and 98% ee. The formation of (+)-*epi*-cytoxazone **30** was confirmed by ^1H and ^{13}C-NMR spectroscopy.

The ^{1}H NMR spectrum of (+)-*epi*-cytoxazone **30** showed a typical signal at δ 8.0 (br s, 1H) for N-H proton of oxazolidinone ring. Its ^{13}C NMR spectrum showed a characteristic signal at δ 159.2 due to the carbonyl carbons in oxazolidinone ring. The ^{1}H NMR and ^{13}C NMR spectral data of (+)-*epi*-cytoxazone **30** matched very well with that of the reported values (**Fig. 12).**[30]

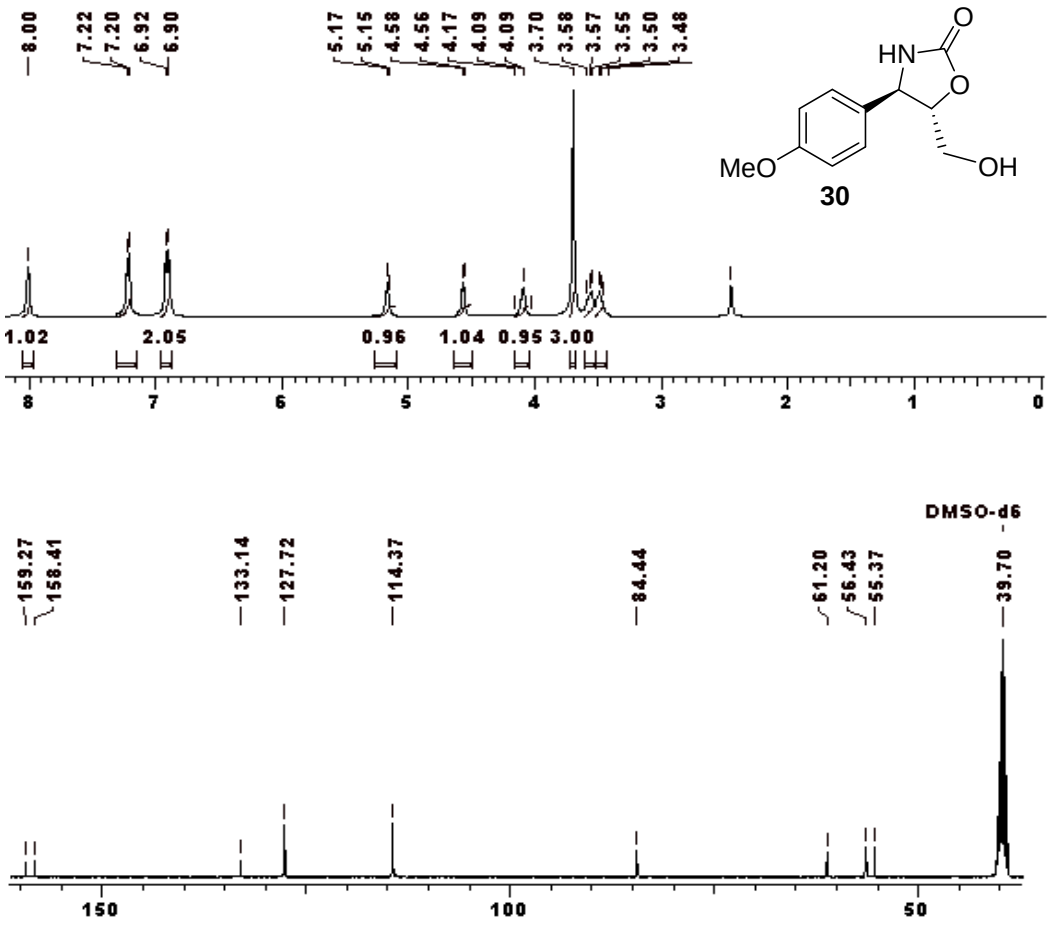
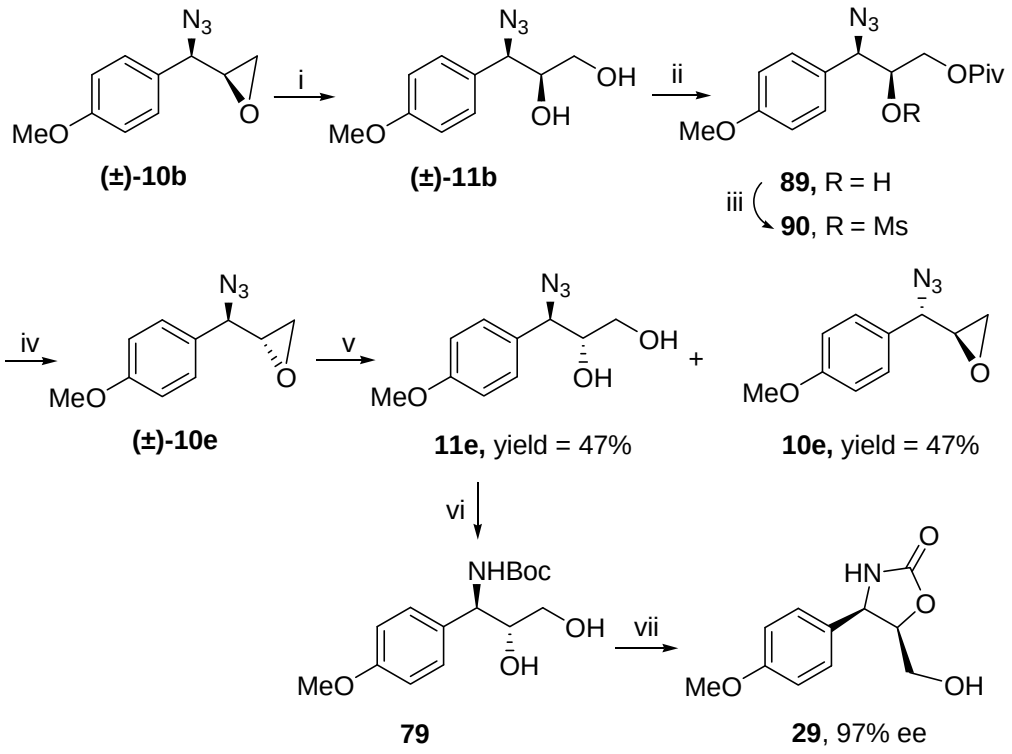


Fig. 12: ^{1}H and ^{13}C NMR spectra of (+)-*epi*-cytoxazone **30**

Synthesis of (-)-cytoxazone **29**, has started from racemic azido epoxide **(±)-10b,** which was subjected to epoxide opening with 0.5M aq. NaOH, in *tert*-BuOH to furnish racemic azido diol **11b.** The selective protection of primary alcohol as pivolyl ester gave azido

pivalate ester (±)**-89** in 96% yield (**Scheme 22)**.



Scheme 22: (i) 0.5N aq. NaOH, *tert*-BuOH, 12 h, 70 °C, 90%; (ii) PivCl, Pyridine/CH_2Cl_2 (1: 1), 0 °C, 5 h, 96%; (iii) MsCl, Et_3N, DMAP, CH_2Cl_2, 25 °C, 10 h, 90%; (iv) K_2CO_3, MeOH, 25 °C, 6 h, 81% over two step; (v) (*S,S)*-Co(salen)OAc (0.5 mol%), THF, H_2O (0.5 equiv), 0 ºC, 14 h; (vi) poly(methylhydrosiloxane) (PMHS), 10% Pd/C, $(Boc)_2O$, EtOH, 25 °C, 4 h, 90%; (vii) NaH, dry THF, 25 °C, 3 h, 89%.

The formation of pivalate (±)**-89** was confirmed by ^1H and ^{13}C-NMR spectroscopy. The ^1H NMR spectrum of pivalate (±)**-89** showed a typical signal at δ 1.15 (s, 9H) for *tert*-butyl protons. Its ^{13}C NMR spectrum showed a characteristic signal at δ 178.2 due to the ester carbonyl carbon (**Fig. 13).**

The secondary alcohol in pivalate (±)**-89** was mesylated (pyridine, MsCl) followed by hydrolysis (K_2CO_3, MeOH) gave the *anti*-azido epoxide (±)-**10e** in 81% yield. Its formation was confirmed by ^1H and ^{13}C-NMR spectroscopy.

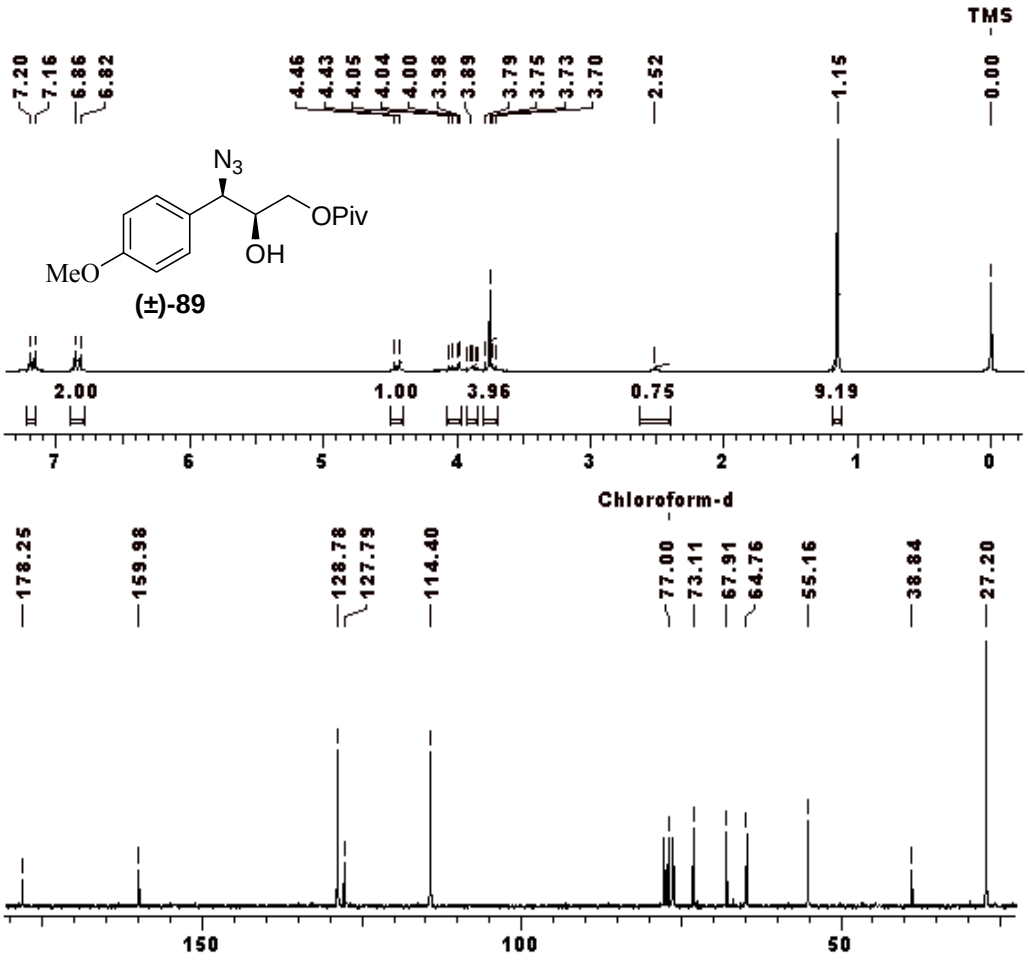


Fig. 13: ^{1}H and ^{13}C NMR spectra of **89**

The ^{1}H NMR spectrum of *anti*-azido epoxide (±)**-10e** showed signals at δ 3.17-3.22 (m, 1H) for methine proton. Its ^{13}C-NMR spectrum showed a typical signal at δ 44.7 due to methylene carbon of the epoxide ring (**Fig. 14).**

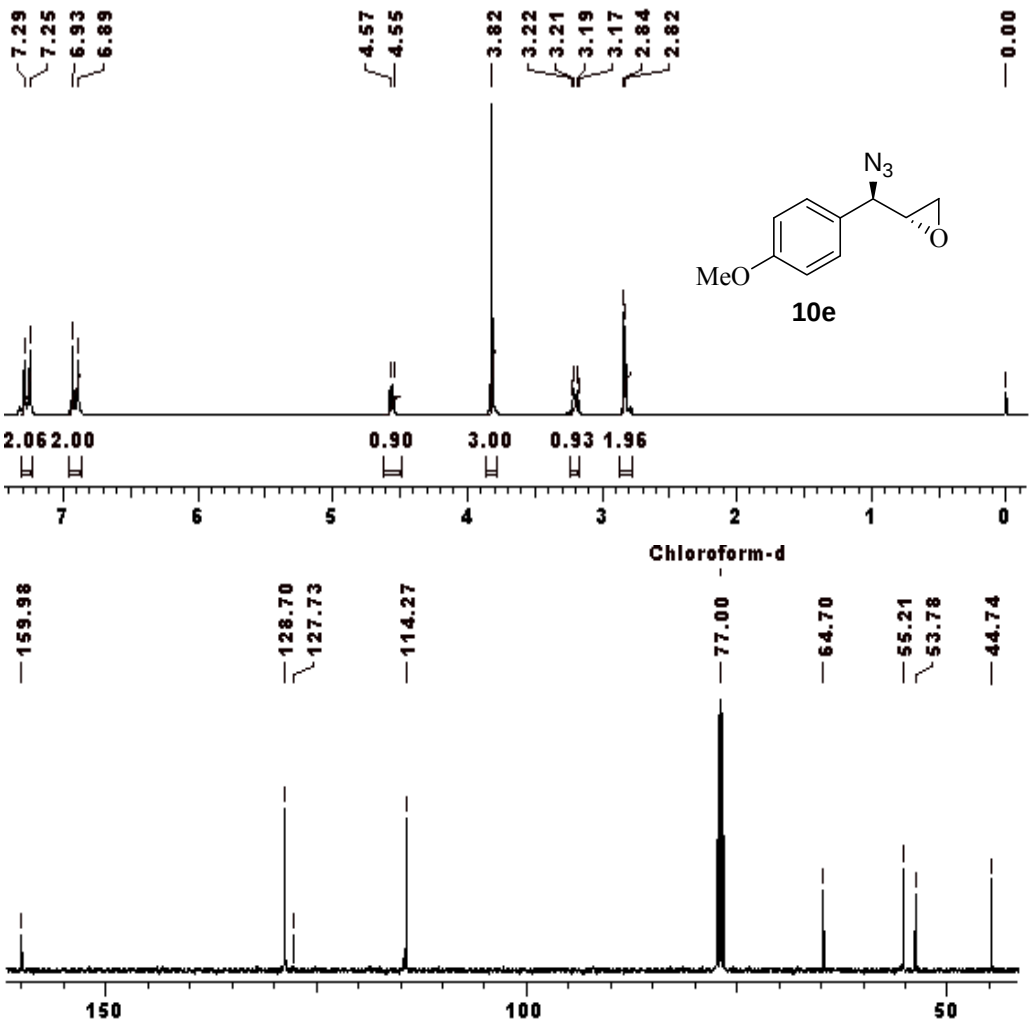


Fig. 14: ^{1}H and ^{13}C NMR spectra of **(±)-10e**

Racemic azido epoxide (±)**-10e** was then subjected to HKR using (*S,S)*-Co(salen)OAc to furnish the required chiral azido diol **11e** in 48% chemical yield and 97% ee along with azido epoxide (+)-**10e** in 48% yield and 98% ee (**Fig. 15)**.

Azido diol **11e**, obtained from **10e,** was then subjected to one pot azide reduction and Boc protection [10% Pd/C, polymethylhydrosiloxane (PMHS) and $(Boc)_2O$ in EtOH] to give N-Boc amino diol **79** in 95% yield, which was confirmed by ^{1}H and ^{13}C-NMR spectroscopy.

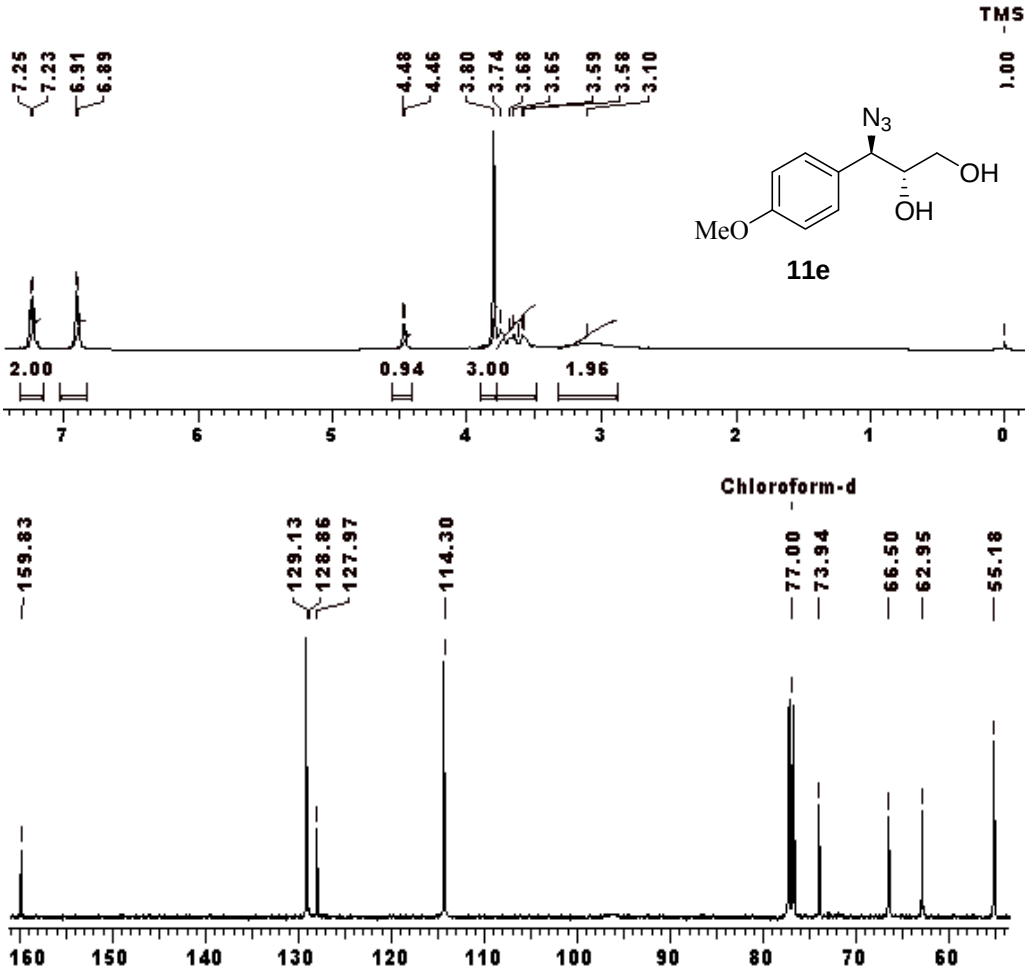


Fig. 15: ^{1}H and ^{13}C NMR spectra of **11e**

The ^{1}H NMR spectrum of N-Boc amino diol **79** showed a typical signal at δ 1.43 (s, 9H) for *tert*-butyl protons. Its ^{13}C NMR spectrum showed characteristic signal at δ 28.2 due to the methyl carbons of *tert*-butyl group (**Fig. 16).** Finally, the regioselective intramolecular cyclization of **79** using NaH in THF gave (-)-cytoxazone **29** in 90 % yield and 97% ee. It is a colorless solid; **mp**: 118-121 ºC (lit.[29] **mp**: 118-121 ºC); $[\alpha]^{25}_{D}$: -70 (*c* 0.5, MeOH) {lit.[29] $[\alpha]^{25}_{D}$: -71 (*c* 1, MeOH)};. Its ^{13}C NMR spectrum showed a characteristic signal at δ 160.0 due to presence of the oxazolidinone carbonyl carbon.

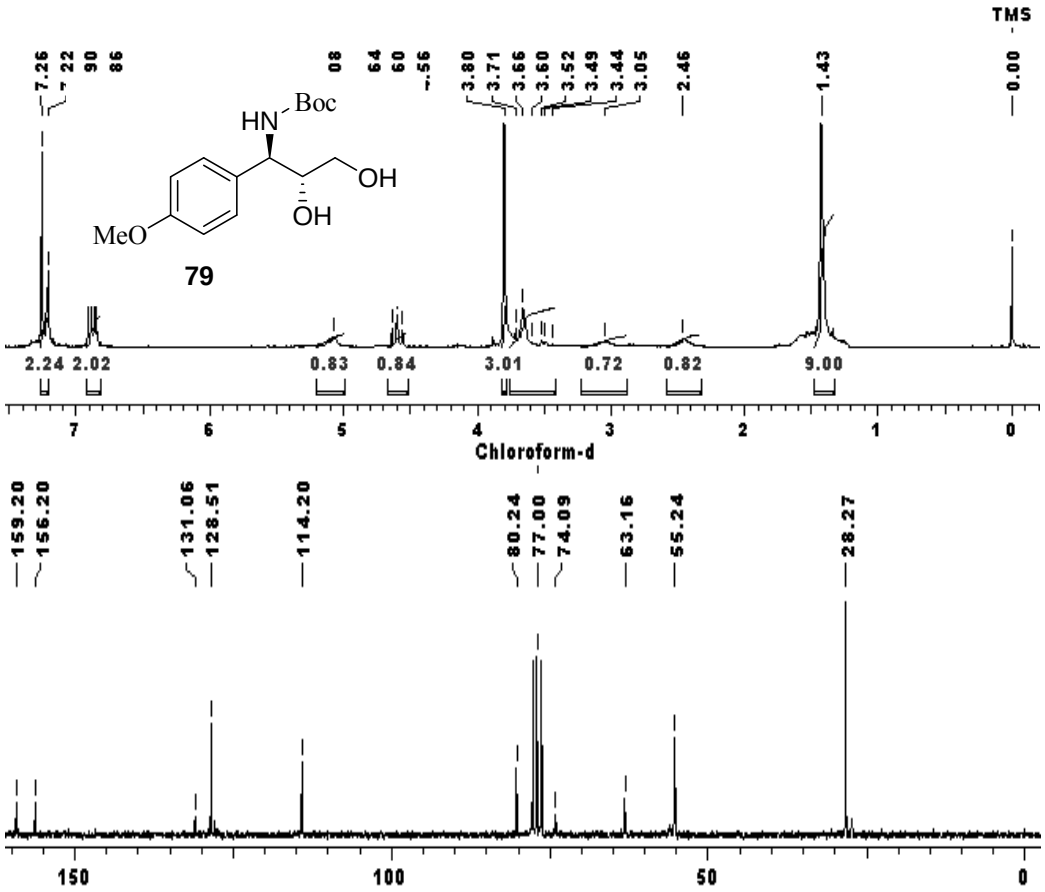


Fig. 16: ^{1}H and ^{13}C NMR spectra of **79**

The ^{1}H NMR and ^{13}C NMR spectral data of (-)-cytoxazone **29** matched very well with that of the reported values (**Fig. 17).**[28, 29]

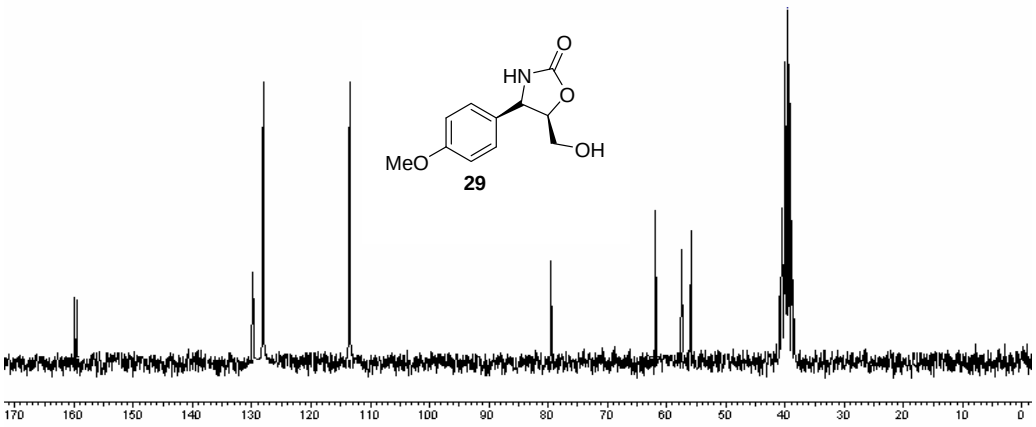


Fig. 17: ^{13}C NMR spectrum of (-)-cytoxazone **(29)**

1.2.6 Conclusion

The enantioselective syntheses of (+)-*epi*-cytoxazone **30** (43.7% overall yield with 97% ee) and (-)-cytoxazone **29** (37.6% over all yield with 97% ee) have been achieved, starting from the respective racemic azido epoxides **10b** and **10e**. The method involved a cobalt-catalyzed hydrolytic kinetic resolution of azido epoxides as the key reaction.

1.2.7 Experimental section

For the preparation of (**10b**, **11b**, **11e** and **26b**) see Section I of this chapter

(2*S*, 3*R*)-3-*tert*-Butoxycarbonylamino-3-(4-methoxyphenyl)propane-1,2-diol (88):

To a solution of azido diol **11b** (0.798 mg, 3.58mmol) in ethyl alcohol (25 mL) was added 10% Pd-C (0.15 mg), polymethylhydrosiloxane (0.64 mg, 10.76 mmol), and di-*tert*-butyl dicarbonate (0.86 g, 3.94 mmol). After stirring for 4 h, the reaction mixture was filtered, and the filtrate was evaporated in vacuo. The residue was purified by column chromatography to give NHBoc diol **88** in 95% yield (1.0 g).

Yield: 95%; colourless solid **mp**: 141-143 °C {lit.[30] **mp**: 141-142 °C}; $[\alpha]^{25}_{D}$: -37.3 (*c* 1.0, $CHCl_3$) {lit.[30] $[\alpha]^{25}_{D}$: -36.1 (c 1.0, $CHCl_3$)}; **IR** ($CHCl_3$, cm^{-1}): 1035, 832, 1070, 1250, 1512, 1688, 2934, 3384; **^{1}H NMR** ($CDCl_3$, 200MHz): δ 1.43 (s, 9H), 1.71 (br s, 1H), 2.98 (br s, 1H), 3.45-3.54 (m, 2H), 3.80 (s, 3H), 3.84.3.96 (m, 1H), 4.73 (br s, 1H), 5.28 (d, *J* = 8.1 Hz, 1H), 6.87 (d, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 8.4 Hz, 2H); **^{13}C NMR** ($CDCl_3$, 50MHz): δ 28.3, 55.1, 55.4, 63.6, 75.0, 80.1, 114.0, 127.9, 128.5, 156.6, 158.9; **Anal.** Calcd for $C_{15}H_{23}NO_5$ requires C, 60.59; H, 7.80; N, 4.71; found: C, 60.62; H, 7.83; N, 4.73%.

(4*S*,5*S*)-5-(Hydroxymethyl)-4-(4-methoxyphenyl)oxazolidin-2-one:(+)-*epi*-cytoxazone (30):

To a solution of NHBoc diol **88** (0.3g, 1.0 mmol) in dry THF (10 mL) was added sodium hydride (0.05 g, 60% w/w, 2.0 mmol) at room temperature, and the mixture was stirred under nitrogen atmosphere for 2.5 h. The reaction mixture was concentrated, ethyl acetate (10 mL) was added, and washed with saturated aq. NH_4Cl (5 mL) and brine solution (5 mL). The organic layer was separated, dried over Na_2SO_4, and concentrated. The crude product was purified by column chromatography to give **30** as a colorless solid (0.216 g, 96% yield).

Yield: 96%; colourless solid, **m.p.**:159-160 °C {lit.[30] **mp**: 161-162 °C}; **$[\alpha]^{25}_D$**: +32.60 (*c* 1, MeOH) {lit.[30] **$[\alpha]^{25}_D$**: +32.8 (c 0.6, MeOH)}; **IR** ($CHCl_3$, cm^{-1}): 772, 832, 1104, 1252, 1522, 1570, 1724, 3244; **^{1}H NMR** (200 MHz, DMSO-d_6): δ 3.43-3.50 (m, 1H), 3.56-3.59 (m, 1H), 3.70 (s, 3H), 4.03-4.17 (m, 1H), 4.58(d, *J* = 5.8 Hz, 1H), 5.17 (t, *J* = 5.56 Hz, 1H), 6.91 (d, *J* = 8.6 Hz, 2H), 7.22(d, *J* = 8.6 Hz, 2H); **^{13}C NMR** (50 MHz, $DMSOd_6$) δ: 55.37, 56.43, 61.20, 84.44, 114.37, 127.72, 133.14, 158.41, 159.27; **Anal.** Calcd for $C_{11}H_{13}NO_4$ requires C, 59.19; H, 5.87; N, 6.27%; found: C, 59.20; H, 5.80; N, 6.23%.

3-Azido-2-hydroxy-3-(4-methoxyphenyl)propylpivalate (±)-89:

Racemic *syn*-azido diol **(±)-11b** (0.802 g, 3.6 mmol) was dissolved in dry pyridine (5 mL) and dry CH_2Cl_2 (5 mL) at 0 °C under argon and pivaloyl chloride (0.44 mL, 3.6 mmol) was added dropwise over a period of 30 min. The mixture was stirred at room temperature for 5 h. Concentration followed by azeotropic removal of pyridine gave a crude compound **(±)-89**, which was purified by column chromatography using petroleum ether/ethyl acetate (9:1) which afforded **(±)-89** (1.06 g) as a colorless liquid.

Yield: 96%; colourless liquid; **IR** ($CHCl_3$, cm^{-1}): 669, 831, 1035, 1252, 1585, 1710, 2104, 3383; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.15 (s, 9H), 2.52 (br s, 1H), 3.70-3.79 (m, 1H),

3.75 (s, 3H), 3.84-3.92 (m, 1H), 4.02 (dd, *J* = 3.1, 8.1 Hz, 1H), 4.45 (d, *J* = 7.5 Hz, 1H), 6.84 (d, *J* = 8.7 Hz, 2H), 7.18 (d, *J* = 8.7 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 27.2, 38.8, 55.1, 64.7, 67.9, 73.1, 114.4, 127.7, 128.7, 159.9, 178.2; **Anal.** Calcd for $C_{15}H_{21}N_3O_4$ requires C, 58.62; H, 6.89; N, 13.67; found: C, 58.65; H, 6.93; N, 13.60%.

2-(Azido-4-methoxyphenyl-methyl)oxirane (±)-10e:

To a solution of pivalate ester **(±)-89** (1.105g, 3.6 mmol) in dry CH_2Cl_2 (10 mL) was added was methane sulfonyl chloride (0.28 mL, 3.6 mmol), Et_3N (0.6 mL, 4.3. mmol) and a catalytic amount of DMAP. The reaction mixture was stirred at room temperature for 1 h, and then quenched with water. The water layer was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated to give a crude product **90**, which was dissolved in MeOH (10 mL) and treated with K_2CO_3 (0.5 g, 3.6 mmol). This mixture was stirred overnight at room temperature and then filtered through Celite. Removal of the volatiles under reduced pressure, followed by column chromatography on silica gel (eluent: petroleum ether/EtOAc 19:1) produced racemic *anti*-azido epoxide **(±)-10e** in 90% yield.

***tert*-Butyl(1*R*,2*R*)-2,3-dihydroxy-1-(4-methoxyphenyl)propylcarbamate (79)**

To a solution of azido diol **11e** (0.798 mg, 3.58mmol) in ethyl alcohol (25 mL) was added 10% Pd-C (0.15 mg), polymethylhydrosiloxane (0.64 mg, 10.76 mmol), and di-*tert*-butyl dicarbonate (0.86 g, 3.94 mmol). After stirring for 4 h, the reaction mixture was filtered, and the filtrate was evaporated in vacuo. The residue was purified by column chromatography to give NHBoc diol **79** in 90% yield (0.95 g).

Yield: 90%; colourless solid, **m.p.**: 116 ºC; **$[\alpha]^{25}_D$**: -51.0 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}):669, 757, 831, 927, 1035, 1167, 1216, 1368, 1585, 1612, 1701, 2400, 2839, 2981,

3019, 3438, 3682; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.43 (s, 9H), 2.46 (br s, 1H), 3.05 (br s, 1H), 3.44-3.71 (m, 3H), 3.80 (s, 3H), 4.60 (t, *J* = 7.9 Hz, 1H), 5.08 (br s, 1H), 6.88 (d, *J* = 8.7 Hz, 2H), 7.24 (d, *J* = 8.2 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 28.2, 55.2, 63.1, 74.0, 80.2, 114.2, 128.5, 131.0, 156.2, 159.2; **Anal.** Calcd for $C_{15}H_{23}NO_5$ requires C, 60.59; H, 7.80; N, 4.71; found: C, 60.31; H, 8.09; N, 4.60%.

(4*R*,5*R*)-5-(Hydroxymethyl)-4-(4-methoxyphenyl)oxazolidin-2-one (29)

To a solution of the amino alcohol **79** (0.15 g, 0.5 mmol) in dry THF (5 mL) was added NaH [0.024 g, 1 mmol (60% w/w in wax)] at room temperature and the mixture was stirred under nitrogen atmosphere for 2 h. The reaction mixture was concentrated, extracted with CH_2Cl_2, washed with saturated NH_4Cl, brine and dried over anhyd. Na_2SO_4. The organic layer was concentrated under reduced pressure and the residue was purified by column chromatography using petroleum ether/ethyl acetate (3:7) to afford (-)-cytoxazone, **29** (0.10 g) as a colorless solid.

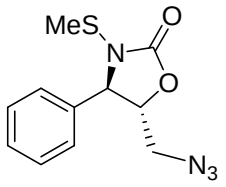
Yield: 89%; colorless solid, **m.p.**: 118-121 ºC (lit.[29] **mp**: 118-121 ºC); **$[\alpha]^{25}_D$**: -71 (*c* 0.5, MeOH) {lit.[29] **$[\alpha]^{25}_D$**: -71 (*c* 1, MeOH)}; **IR** ($CHCl_3$, cm^{-1}): 1050, 1181, 1250, 1400, 1514, 1739, 2975, 3325, 3745; **^{1}H NMR** (200 MHz, DMSO-d_6): δ 2.95-2.97 (m, 2H), 3.75 (s, 3H), 4.62–4.73 (m, 1H), 4.82 (t, *J* = 5.1 Hz, 1H), 4.90 (d, *J* = 4.3 Hz, 1H), 6.91 (d, *J* = 8.7 Hz, 2H), 7.15 (d, *J* = 8.46 Hz, 2H), 8.02 (br s, 1H); **^{13}C NMR** (50 MHz, DMSO-d_6): δ 55.1, 56.8, 61.9, 80.4, 113.7, 128.1, 129.4, 158.8, 160.0; **Anal.** Calcd for $C_{11}H_{13}NO_4$ requires C, 59.19; H, 5.87; N, 6.27; found: C, 58.88; H, 6.09; N, 6.14%.

Section III

Formal synthesis of *N*-thiolated 2-oxazolidinone

1.3.1 Introduction

The problem of bacterial drug resistance has reached a crisis level such that successful treatment of antibiotic resistant infections in hospitals and health care centers can no longer be taken for granted. Infections caused by methicillin-resistant *Staphylococcus* aureus (MRSA) are becoming particularly difficult to treat with conventional antibiotics such as penicillin, leading to a sharp rise in clinical complications and deaths. The need for new antibacterial agents and protocols for treating MRSA infections is becoming extremely serious. Oxazolidinones are already recognized for their favorable pharmacological properties and are the only new class of antibacterial drugs introduced into clinical use in the last three decades.[31] Recent studies have shown that *N*-thiolated 2-oxazolidinone **91** possesses antibacterial activity against methicillin-resistant *Staphylococcus* aureus and *Bacillus anthracis*.[32]



91

Fig 18: Structure of *N*-thiolated 2-oxazolidinone **91**

1.3.2 Pharmacology of *N*-thiolated 2-oxazolidinone

N-thiolated oxazolidinones, like their β-lactam counterparts,[33] react covalently with their biological target through transfer of the organothio side chain as shown in **Fig 19**. Further studies to assess the mode of action of this anti-MRSA, anti-Bacillus compounds, and to

identify their cellular target(s), are currently underway.

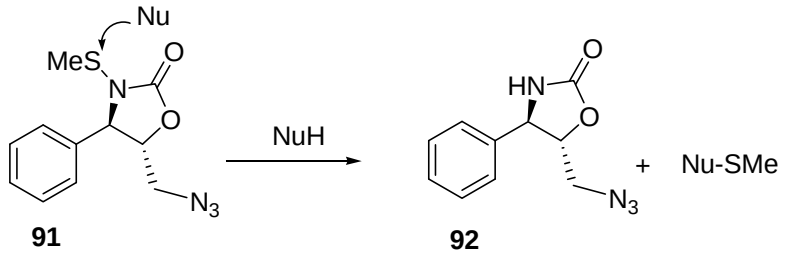


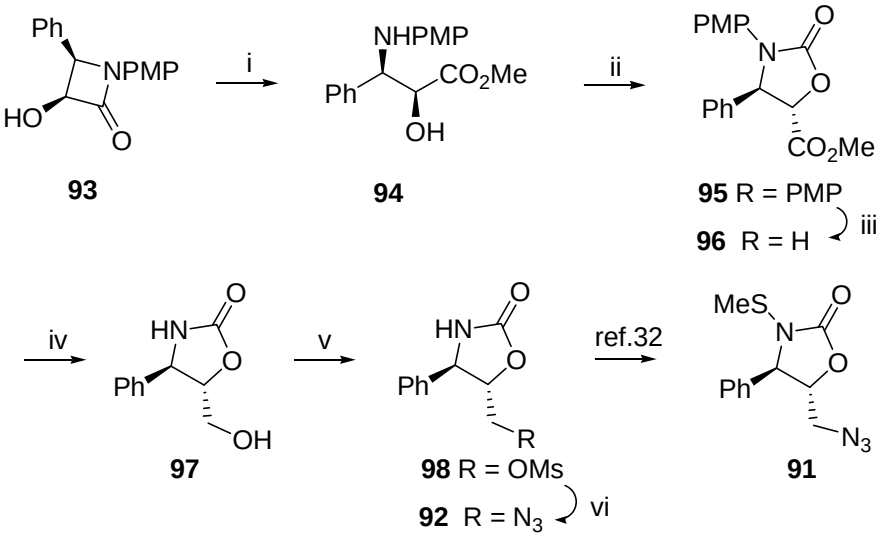
Fig 19: Pharmacology of *N*-thiolated 2-oxazolidinone

1.3.3 Review of literature

In section II, we have described several reports for the synthesis of oxazolidinones. Only one report for the racemic synthesis of anti-MRSA *N*-thiolated 2-oxazolidinone (**91**) and its precursor, 2-oxazolidinone **92** has been disclosed as can be seen below.

Turos's approach (2007)[34]

Turos *et al.* have reported the synthesis of (±)-*N*-thiolated 2-oxazolidinone (**91**), starting from lactam **93.** This was hydrolyzed with Me_3SiCl in refluxing methanol to afford the *syn*-aminol **94** in 95% yield. Treatment of **94** with triphosgene and Hunig's base in CH_2Cl_2 led to isolation of oxazolidinone **95** (80% yield). The *N*-methoxyphenyl moiety on the oxazolidinone ring was then cleaved (ceric ammonium nitrate, CH_3CN and water) to give the *N*-protio oxazolidinone **96** in 70% yield. The ester functionality of oxazolidinone **96** was selectively reduced ($NaBH_4$, aq. THF) to furnish the alcohol **97** in 92% yield. Exchange of the hydroxyl group for an azide proceeded through mesylate **98**, which gave azide **92** in 72% yield after treatment with sodium azide in DMF (**Scheme 23**).



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

1.3.4. Present Work

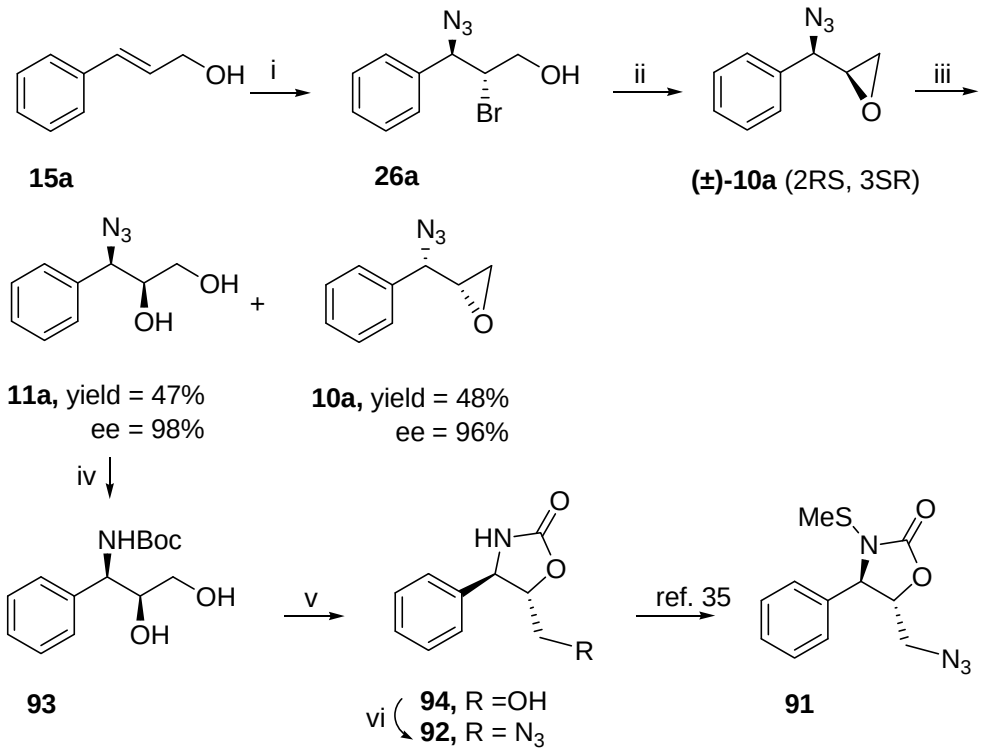
1.3.4.1. Objective

As can be seen from the above discussion, only one report is presently available for the synthesis of *anti*-MRSA *N*-thiolated 2-oxazolidinone **91** and its precursor, 2-oxazolidinone **92**. Hence, the enantioselective synthesis of *N*-thiolated 2-oxazolidinone **91** employing a simple catalytic enantioselective reaction is undertaken. This section describes a short synthesis of 2-oxazolidinone **92**, using hydrolytic kinetic resolution of racemic azido epoxide **10a** as the key step to induce chirality in the molecule.

1.3.5. Results and Discussion

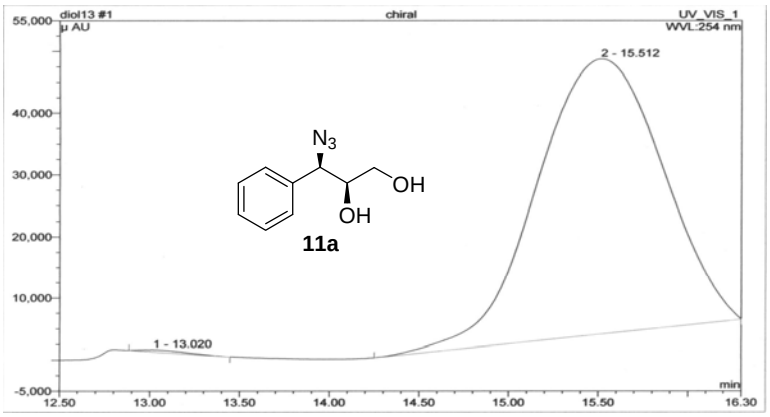
The present synthetic route employed for the synthesis of *N*-thiolated 2-oxazolidinone **91** is shown in **Scheme 24**. Our synthesis starts with commercially available cinnamyl alcohol **16a**, which was transformed into the *syn*-azido epoxiode (±)-**10a** in two steps: (i) azidobromination of cinnamyl alcohol; (ii) formation of epoxide from **26a** to give *syn*-

azido epoxide (±)-**10a** in 70% yield.



Scheme 24: (i) NBS, NaN_3, CH_3CN: H_2O (4:1),0 °C, 70%; (ii) *tert*-BuOK, THF, 0 °C, 3 h; (iii) (*R,R)*-Co(salen)OAc (0.5 mol%), H_2O (0.5 equiv), 0 ºC, 14 h; (iv) poly(methylhydrosiloxane), 10% Pd/C, $(Boc)_2O$, EtOH, 25 ºC, 4 h, 96%; (v) NaH, dry THF, 25 °C, 3 h, 96%; (vi) (a) MsCl, Et_3N, CH_2Cl_2, 0 °C, 1 h then; (b) NaN_3, DMF, 60 °C, 12 h, 80%.

The *syn*-azido epoxide (±)-**10a** was then subjected to HKR using (*R,R)*-Co(salen)OAc (**1**) to give the chiral *syn*-azido diol **11a** in 47% yield with 98% ee along with chiral *syn*-azido epoxide **10a** in 48% yield with 96% ee. The compound **11a** and **10a** were then readily separated by column chromatographic purification. The enantiomeric excess of *syn*-azido diol in **11a** was determined by chiral HPLC analysis; Chiralpak OD-H (**Fig.20**).



No	Ret. Time min	Height µ AU	Area µ AU* min	Rel. Area %
1	13.020	560.800	512.360	1.50
2	15.512	36825.916	33644.986	98.50

Fig. 20: HPLC chromatogram of azido diol **11a**

Azido diol **11a** was then subjected to one pot azide reduction and Boc protection [10%

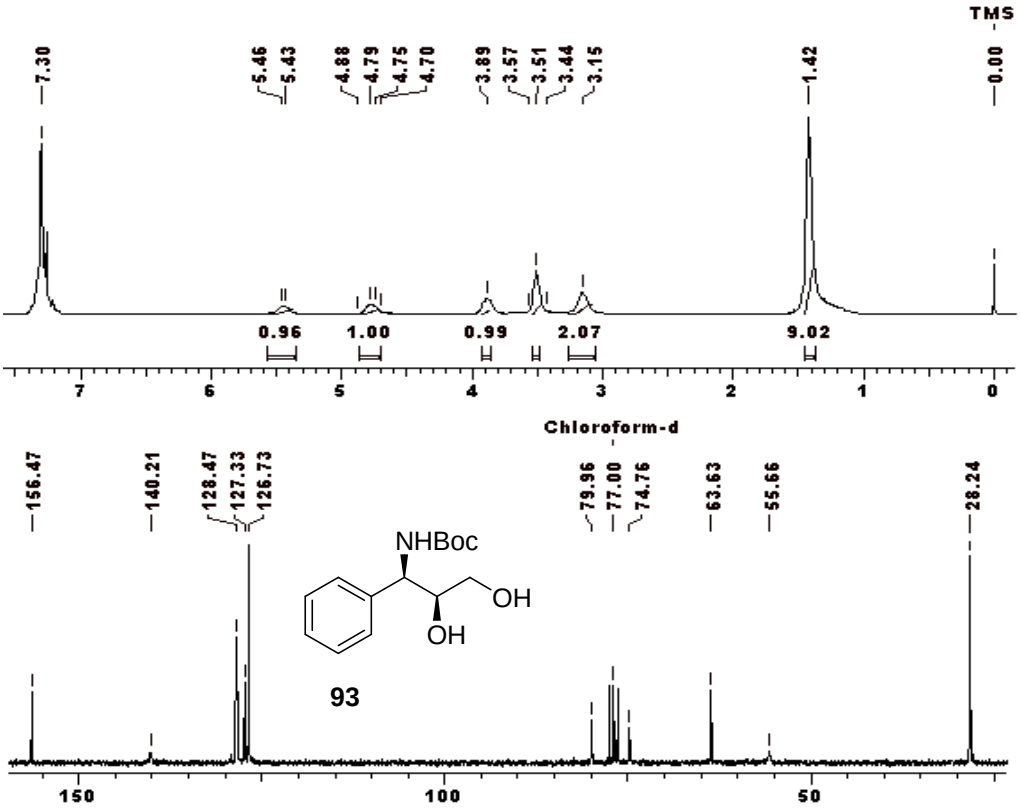


Fig. 21: ^{1}H and ^{13}C NMR spectra of **93**

Pd/C, polymethylhydrosiloxane (PMHS) and $(Boc)_2O$ in EtOH] to give N-Boc amino diol **93** in 96 % yield, which was confirmed by ^1H and ^{13}C-NMR spectroscopy. The ^1H NMR spectrum of **93** showed a typical signal at δ 1.42 (s, 9H) for *tert*-butyl protons. Its ^{13}C NMR spectrum showed a characteristic signal at δ 28.2 due to the methyl carbons of *tert*-butyl group (**Fig. 21).**

The regioselective intramolecular cyclization of **93** with NaH in THF gave oxazolidinone **94** (mp 106-107 ºC; lit.[34] mp 105-107 ºC) in 96 % yield. The formation of oxazolidinone **94** was confirmed by ^1H and ^{13}C-NMR spectroscopy. The ^1H NMR spectrum of (+)-2-oxazolidinone **94** showed a typical signal at δ 7.0 (br s, 1H) for N-H proton of oxazolidinone ring. Its ^{13}C NMR spectrum showed a characteristic signal at δ 157.1 due to the carbonyl carbon of oxazolidinone ring (**Fig. 22).**

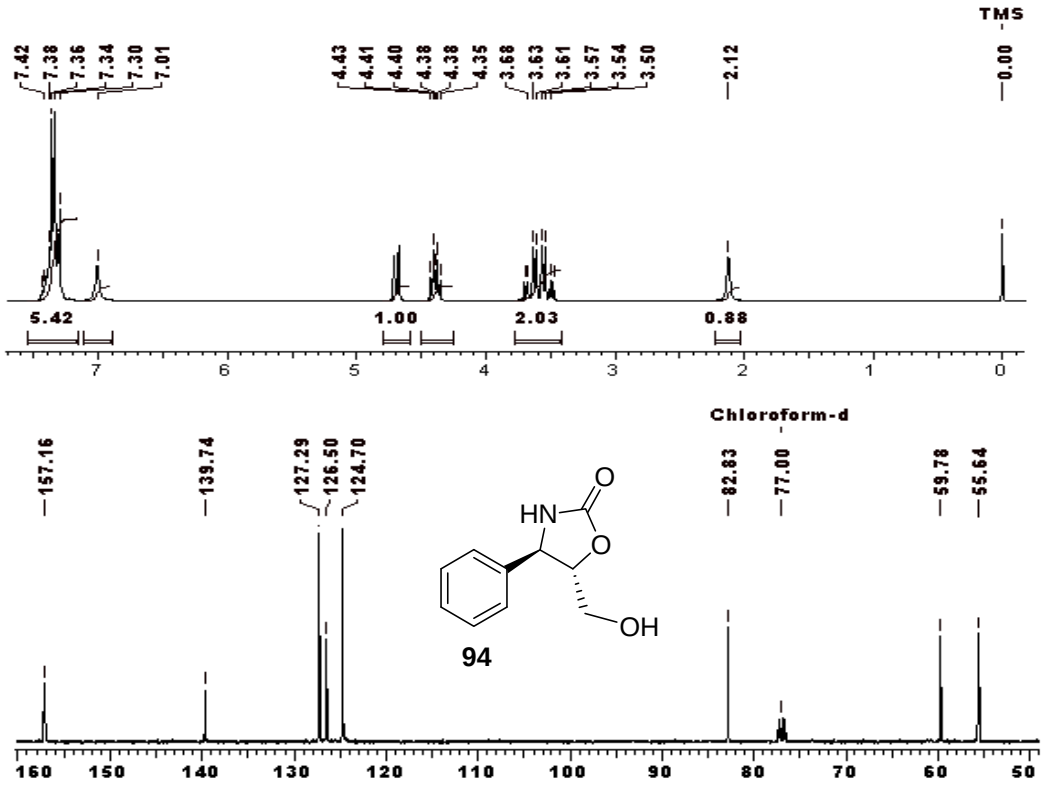


Fig. 22: ^1H and ^{13}C NMR spectra of **94**

Finally, mesylation of primary alcohol in oxazolidinone **94** gave the mesylate, which on subsequent treatment with NaN_3 in DMF at 60 °C afforded (+)-2-oxazolidinone **92** in 80% yield. The formation of (+)-2-oxazolidinone **92** was confirmed by ^{1}H and ^{13}C-NMR spectroscopy. The ^{1}H NMR spectrum of (+)-2-oxazolidinone **92** showed a typical signal at δ 3.62 (dddd, J = 4.3, 9.5 Hz (each), 2H), for methylene protons. Its ^{13}C NMR spectrum showed a characteristic signal at δ 51.9 due to the carbon attached to azide group (**Fig. 23).**

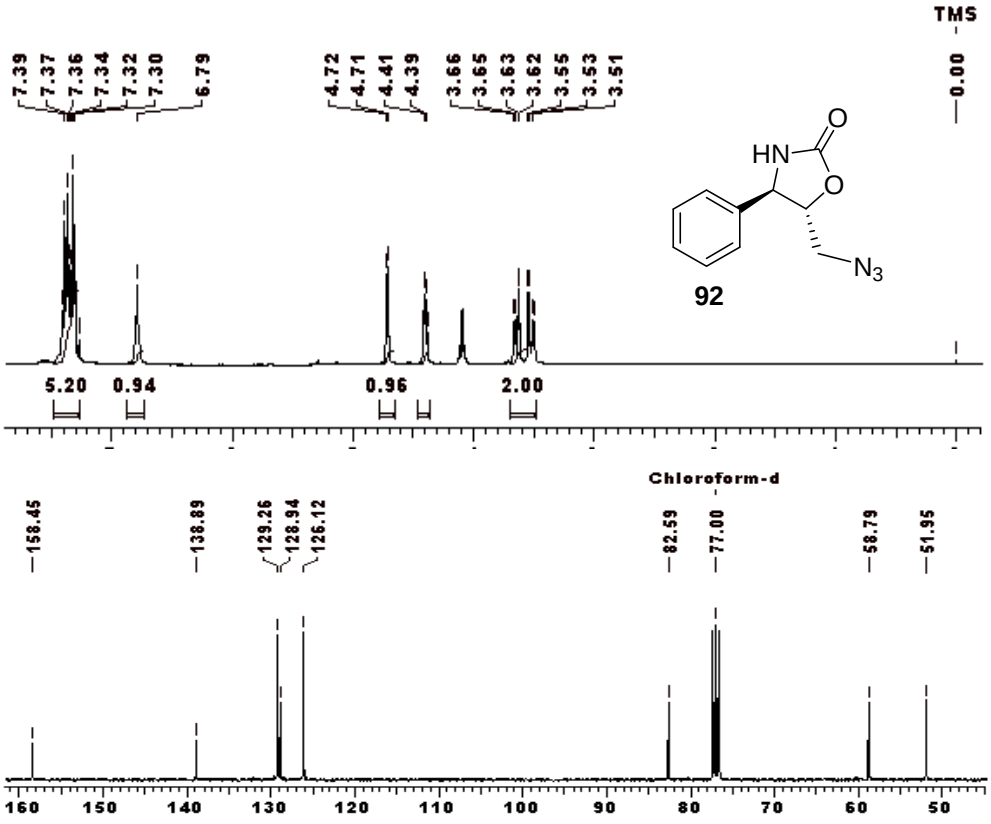


Fig. 23: ^{1}H and ^{13}C NMR spectra of **92**

The conversion of (+)-2-oxazolidone **92** to *N*-thiolated 2-oxazolidinone **91** has already been reported in the literature.[32]

1.3.6 Conclusion

The enantioselective syntheses of (+)-2-oxazolidinone **92 (**36% over all yield with 98% ee) have been achieved, starting from the racemic *syn*-azido epoxides **10a**. The method involved a cobalt-catalyzed hydrolytic kinetic resolution of azido epoxides as the key reaction.

1.3.7 Experimental section

***tert*-Butyl(1*R*,2*S*)-2,3-dihydroxy-1-phenylpropylcarbamate (93):**

To a stirred solution of azido diol **11a** (0.69 mg, 3.58mmol) in ethyl alcohol (25 mL) was added 10% Pd-C (0.15 mg), polymethylhydrosiloxane (0.64 mg, 10.76 mmol) and di-*tert*-butyl dicarbonate (0.86 g, 3.94 mmol). After stirring for 4 h, the reaction mixture was filtered, and the filtrate was evaporated *in vacuo*. The residue was purified by column chromatography to give NHBoc diol **93** in 96% yield (0.91 g).

Yield: 96%; colourless oil; $[\alpha]^{25}_{D}$: -28.0 (*c* 0.7, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 832, 1035, 1070, 1250, 1512, 1699, 2934, 3363; **^{1}H NMR** ($CDCl_3$, 200MHz): δ 1.42 (s, 9H), 3.15 (br s, 2H), 3.44-3.57 (m, 2H), 3.89 (br s, 1H), 4.70-4.88 (m, 1H), 5.45 (d, *J* = 5.0 Hz, 1H), 7.23-7.40 (m, 5H); **^{13}C NMR** ($CDCl_3$, 50 MHz): δ 28.2, 56.6, 63.6, 74.7, 79.9, 126.7, 127.3, 128.4, 140.2, 156.4; **Anal.** Calcd for $C_{14}H_{21}NO_4$ requires C, 62.90; H, 7.90; N, 5.24; found: C, 62.82; H, 7.88; N, 5.28%.

(4*S*,5*S*)-5-Hydroxymethyl-4-phenyloxazolidin-2-one (94):

To a stirred solution of NHBoc diol **93** (0.267g, 1.0 mmol) in dry THF (10 mL) was added sodium hydride (0.05 g, 60% w/w, 2.0 mmol) at room temperature and the mixture was stirred under nitrogen atmosphere for 2.5 h. The reaction mixture was concentrated, followed by the addition of ethyl acetate (10 mL), and washed with saturated aq. NH_4Cl

(5 mL) and brine solution (5 mL). The organic layer was separated, dried over anhyd. Na_2SO_4 and concentrated. The crude product was purified by column chromatography to give **94** as a colourless solid (0.185 g, 96% yield).

Yield: 96%; colourless solid **m.p.**:106-107 °C {lit.[34] **m.p.**: 105-107 °C}; **$[\alpha]^{25}_D$**: +24.6 (*c* 0.5, MeOH); **IR** ($CHCl_3$, cm^{-1}): 772, 832, 1104, 1252, 1522, 1570, 1724, 3244; **^{1}H NMR** (200 MHz, DMSO-D_6): δ 2.12 (br s, 1H), 3.60 (dddd, *J* = 3.1, 9.1 Hz, 2H), 4.35-4.43 (m, 1H), 4.70 (d, *J* = 6.3 Hz, 1H), 7.01 (br s, 1H), 7.30-7.40 (m, 5H); **^{13}C NMR** (50 MHz, $DMSOd_6$) δ: 55.6, 59.7, 82.8, 124.7, 126.5, 127.2, 139.7, 157.1; **Anal.** Calcd for $C_{10}H_{11}NO_3$ requires C, 62.17; H, 5.74; N, 7.25%; found: C, 62.20; H, 5.80; N, 7.23%.

(4*S*,5*S*)-5-Azidomethyl-4-phenyloxazolidin-2-one (92):

To a stirred solution of alcohol **94** (0.791 g, 4.1 mmol) in CH_2Cl_2 (5 mL) was added Et_3N (0.82 g, 8.2 mmol) at 0 ^oC. After 5 min of stirring, methane sulfonyl chloride (0.47 g, 4.1 mmol) was added drop-wise over a period of 5 min. The reaction mixture was then stirred for another 1 h at 0 ^oC and brought to room temperature. After the completion of the reaction, as monitored by TLC, it was extracted with CH_2Cl_2 (3x 20 ml) washed with water, brine and dried over anhyd. Na_2SO_4. The combined organic layer was concentrated under reduced pressure to get crude methane sulfonate ester **95** in almost quantitative yield. To a solution of the crude mesylate **95** in DMF (10 mL) was added sodium azide (0.53g, 8.2 mmol) and the reaction mixture was heated at 60 ^oC for 7 h. After the completion of the reaction, as monitored by TLC, it was extracted with CH_2Cl_2 (3x 20 mL) washed with water, brine and dried over anhyd. Na_2SO_4. The combined organic layer was concentrated under reduced pressure to give the crude 2-oxazolidinone

92, which was purified by column chromatography using pet. ether: ethyl acetate (9: 2) to produce **92** as colourless solid.

Yield: 80% (0.715 g); colourless solid **m.p.**: 82-85 °C {lit.[34] **mp**: 82-84 °C}; **[α]$^{25}_{D}$**: +30.0 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 772, 832, 1104, 1252, 1522, 1570, 1724, 2106, 3244; **^{1}H NMR** (200 MHz, $CDCl_3$): **δ** 3.62 (dddd, *J* = 4.3, 9.5 Hz, 2H), 4.30-4.43 (m, 1H), 4.71 (d, *J* = 6.3 Hz, 1H), 6.79 (br s, 1H), 7.30–7.41 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): **δ** 51.9, 58.7, 73.0, 82.5, 126.1, 129.9, 129.27, 138.8, 128.3, 158.4; **Anal.** Calcd for $C_{10}H_{10}N_4O_2$ requires C, 55.04; H, 4.62; N, 25.68; found: C, 55.01; H, 4.60; N, 25.65%.

1.3.8 References

1 (a) Grajewska, A.; Rozwadowska, M. D.; *Tetrahedron: Asymmetry*, **2007**, *18*, 803; (b) Gravier-Pelletier, C.; Milla, M.; Merrer, Y. L.; Depezay, J-C. *Eur. J. Org. Chem.* **2001**, 3089.

2 Tokunaga, M.; larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science,* **1997**, *277*, 936.

3 (a) Wilkinson, R. G.; Shepherd, R. G.; Thomas, J. P.; Baughn, C. *J. Am. Chem. Soc*. **1961**, *83*, 2212; (b) Shepherd, R. G.; Wilkinson, R. G. *J. Med. Chem*. **1962**, *5*, 823; (c) Wilkinson, R. G.; Cantrall, M. B.; Shepherd, R. G. *J. Med. Chem*. **1962**, *5*, 835.

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

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

6 Furrow, M. E.; Schaus, S. E.; Jacobsen, E. N. *J. Org. Chem*. **1998**, *63*, 6776.

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

8 a) Larrow, J. F.; Jacobsen, E. N.; Gao, Y.; Hong, Y.; Nie, X.; Zepp, C. M. *J. Org. Chem.* **1994**, *59*, 1939; (b) Larrow, J. F.; Jacobsen, E. N. *Org. Synth*. **1997**, *75*, 1.

9 For the most effective catalyst developed thus far for the asymmetric dihydroxylation of terminal olefins, see: (a) Becker, H.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 448. For a general review of the AD reaction, see: (b) Kolb, H. C.; Vannieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.

10 Yuan, Z. Q.; Blomberg, D.; Sethson, I.; Brickmann, K.; Ekholm, K.; Johansson, B.; Nilsson, A.; Kihlberg, J. *J. Med. Chem.* **2002,** *45,* 2512.

11 Smitha, G.; C. Reddy, S. *Synth. Commn.* **2006**, *36*,1795.

12 Cherian, S. K.; Kumar, P. *Tetrahedron: Asymmetry,* **2007**, *18*,982.

13 Monasson, O.; Ginisty, M.; Mravljak, J.; Bertho, G.; Gravier-Pelletier, C.; Merrer Y. L. *Tetrahedron: Asymmetry,* **2009**, *20*, 2320.

14 (a) Kumar, P.; Naidu, S. V.; Gupta, P. *Tetrahedron,* **2007**, *63*, 2745; (b) Kumar, P.; Gupta, P. *Synlett,* **2009**, *9*, 1367; (c) Yu, Q.; Wu, Y.; Xia, L. J.; Tang M. H.; Wu, Y. L. *J. Chem. Soc. Chem. Commun*., **1999**, 129.

15 Kim, Y. J.; Tae, J. *Synlett,* **2006**, 61.

16 Ende, D. V.; Krief, A. *Angew. Chem, Int. Ed. Engl.,* **1974**, *13,* 279.

17 Kakeya, H.; Morishita, M.; Kobinata, K.; Osono, M.; Ishizuka, M.; Osada, H. *J. Antibiot.* **1998**, *51*, 1126.

18 Kakeya, H.; Morishita, M.; Koshino, H.; Morita, T.; Kobayashi, K.; Osada, H. *J. Org. Chem.* **1999**, *64*, 1052.

19 Hamersak, Z.; Sepac, D.; Ziher, D.; Sunjic, V. *Synthesis* **2003**, 375.

20 List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336.

21 (a) Seder, R. A.; Paul, W. E. *Annu. Rev. Immunol.* **1994**, *12*, 635. (b) Finkelman, F. D.; Shea-Donohue, T.; Goldhill, J.; Sullivan, C. A.; Morris, S. C.; Madden, K. B.; Gause, W. C.; Urban, J. F. *Annu. Rev. Immunol.* **1997**, *15*, 505.

22 Stirling, R. G.; Chung, K. F. *Eur. Respir. J.* **2000**, *16*, 1158. (b) Renauld, J. C. *J. Clin. Pathol.* **2001**, *54*, 577.

23 (a) Gazzinelli, R. T.; Makino, M.; Chattopadhyay, S. K.; Snapper, C. M.; Sher, A.; Hugin, A. W.; Morise, H. C. III *J. Immunol.* **1992**, *148*, 182. (b) Romagnani, S. *Immunol. Today* **1990**, *11*, 316. (c) Secrist, H.; Chelen, C. J.; Wen, Y.; Marshell, J. D.; Umetsu, D. T. *J. Exp. Med.* **1993**, *178*, 2123.

24 Sakamoto, Y.; Shiraishi, A.; Seonhee, J.; Nakata, T. *Tetrahedron Lett.* **1999**, *40*, 4203.

25 Hamerak, Z.; Ljubovic, E.; Mercep, M.; Mesic, M.; Sunjic V. *Synthesis* **2001**, 1989.

26 Carter, P. H.; LaPorte, J. R.; Scherle, P. A.; Decicco, C. P. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1237.

27 Milicevic, S.; Matovic, R.; Saicic, R. N. *Tetrahedron Lett.* **2004**, *45*, 955.

28 Paraskar, A. S.; Sudalai, A. *Tetrahedron* **2006**, *62*, 5756.

29 Narina, S. V.; Siva Kumar, T.; George, S.; Sudalai, A. *Tetrahedron Lett.* **2007**, *48*, 65.

30 Sung-Gon Kim, S-G.; Park, T. H. *Tetrahedron: Asymmetry,* **2008**, *19,* 1626.

31 Brickner, S. J. *Curr. Pharm. Des.* **1996**, *2*, 175 ; (b) Phillips, O. A. *Curr. Opin. Invest. Drugs* **2003**, *4*, 117 ; (c) Brickner, S. J.; Hutchinson, D. K.; Barbachyn, M. R.; Manninen, P. R.; Ulanowicz, D. A.; Garmon, S. A.; Grega, K. C.; Hendges, S. K.; Toops, D. S.; Ford, C. W.; Zurenko, G. E. *J. Med. Chem.* **1996**, *39*, 673.

32 Mishra, R. K.; Revell, K. D.; Coates, C. M.; Turos, E.; Dickeyb, S.; Limb, D. V. *Bioorganic & Medicinal Chemistry Letters,* **2006**, *16*, 2081–2083.

33 Turos, E.; Coates, C.; Shim, J.-Y.; Wang, Y.; Leslie, J. M.; Long, T. E.; Reddy, G. S. K.; Ortiz, A.; Culbreath, M.; Dickey, S.; Lim, D. V.; Alonso, E.; Gonzalez, *J. Bioorg. Med. Chem.* **2005**, *13*, 6289.

34 Mishra, R. K.; Coates, C. M.; Revell, K. D.; Turos, E. *Org. Lett.*, **2007,** *9*, 4.

CHAPTER II

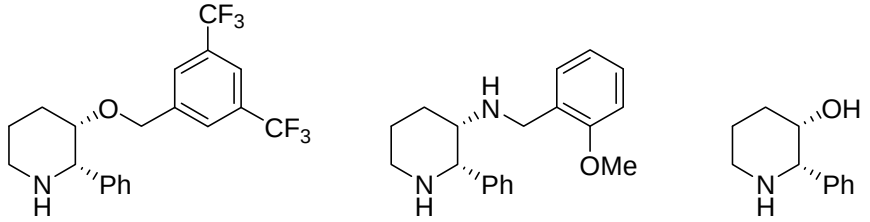
Enantioselective Synthesis of (+)-L-733,060 *via* Hydrolytic Kinetic Resolution of Azido epoxide and Synthesis of (S)-Dapoxetine *via* Sharpless Asymmetric Epoxidation

Section I

A short enantioselective synthesis of (+)-L-733,060 *via* hydrolytic kinetic resolution of azido epoxide

2.1.1. Introduction

Substance P (SP), a peptide neurotransmitter, is a member of the tochynin family of peptides, which include neurokinins A and B (NKA, NKB). These peptides bind to a series of three neurokinin receptors, NK1, NK2, and NK3, which have selective affinity for SP, NKA and NKB respectively.[1] For example SP has been shown to elicit a IL-I production in macrophages, sensitize neutrophils and enhance dopamine release in the *substantia nigra* region in cat brain. The neurokinin substance P has also been associated with a variety of biological effects including smooth muscle contraction, neurogenic inflammation and pain transmission. Recently, (+)-L-733,060 (**1**)[2] and (+)-CP-99,994 (**2**)[3] possessing 2-alkyl-3-hydroxypiperidine and 2-alkyl-3-aminopiperidine structural units respectively, have proven to be selective and potent non-peptide neurokinin substance P receptor antagonists (**Fig. 1**). Also, they have been implicated in a variety of disorders including migraine, rheumatoid arthritis and pain.[4] Recent studies shown that (+)-L-733,060 (**1**) can act both as an antitumor agent and as a promising new target for the treatment of retinoblastoma.[5]



(+)-L-733,060 (**1**) (+)-CP-99,994 (**2**) **3**

Fig. 1: Structures of 2-aryl-3-hydroxypiperidine and 2-aryl-3-aminopiperidine derivatives

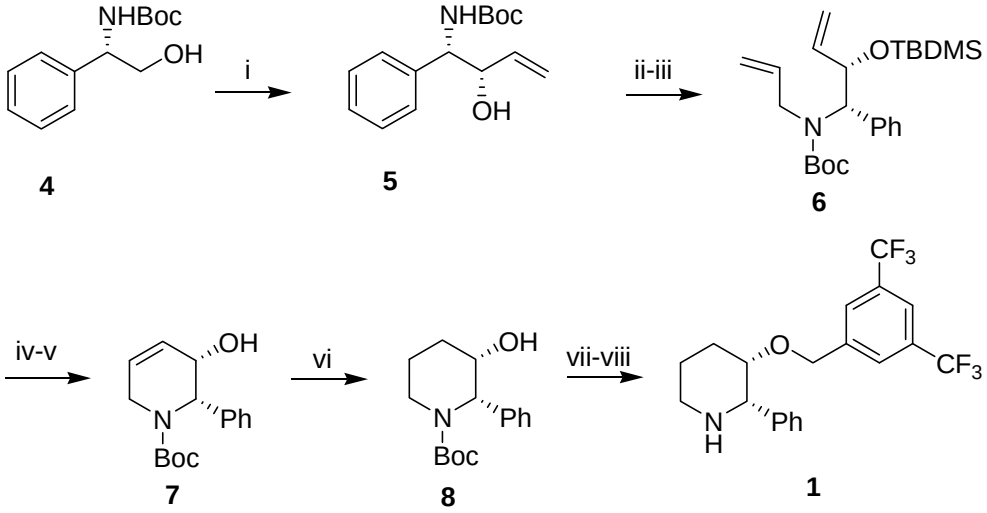
In view of these potential pharmacological applications, several reports on the synthesis of **1** and **2** both in racemic and optically active forms, have been published.[6]

2.1.2. Review of Literature

Various syntheses of non-peptidic neurokinin NK1 receptor antagonist namely (+)-L-733,060 (**1)** and (2*S*, 3*S*)-3-hydroxy-2-phenyl piperidine (**3**) have been documented in the literature.[2,6] Some of the interesting and important synthetic routes to (+)-L-733,060 (**1**) are described below.

Rao's approach (2003)[7]

Rao *et al.* have achieved the synthesis of (+)-L-733,060 (**1**) starting from *N*-Boc protected amino alcohol **4,** which was subjected to Swern oxidation conditions [$(COCl)_2$, DMSO, Et_3N] followed by addition of vinyl magnesium bromide to give allylic alcohol **5 (Scheme 1)**.

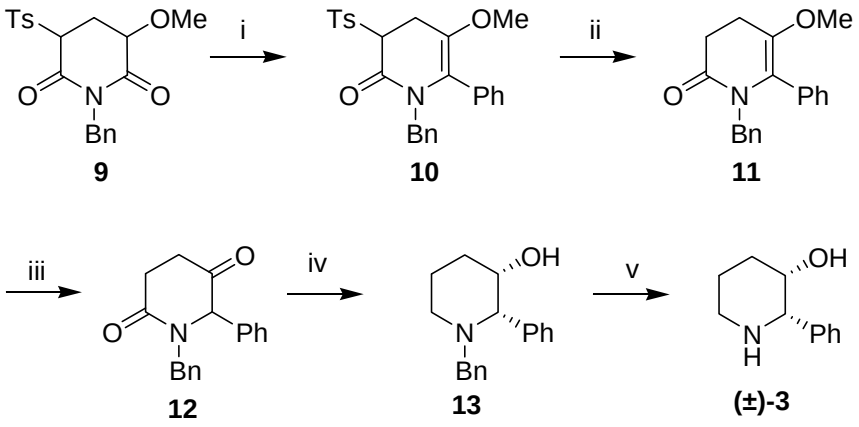


Scheme 1: (i) DMSO, $(COCl)_2$, *i*-Pr_2NEt, CH_2Cl_2; then CH_2=CHMgBr, THF, 2 h, 90%; (ii) TBDMS-Cl, imid., CH_2Cl_2, 24 h, 90%; (iii) allyl bromide, NaH, DMF, 0- 25 ºC, 24 h, 90%; (iv) TBAF-AcOH, THF, 0- 25 ºC, 24 h, 85%; (v) Grubbs' catalyst, CH_2Cl_2, 25 ºC, 6 h, 82%; (vi)10% Pd/C, H_2, EtOH, 4 h, 65%; (vii) 3,5-bis(trifluoromethyl)benzyl bromide, NaH, DMF, 80%; (viii) TFA, CH_2Cl_2, 79%.

Protection of allylic alcohol **5** as silyl ether followed by *N*-allylation of the amine resulted in diene **6**, which upon ring closing metathesis using Grubbs' catalyst gave the unsaturated piperidine moiety **7**. The catalytic hydrogenation of olefin **8** furnished the intermediate **8** in 65% yield. Etherification of alcohol group in **8** with 3,5-bis(trifluromethyl)benzyl bromide followed by deprotection of the Boc-group provided (+)-L-733,060 (**1**).

Chang's approach (2005)[8]

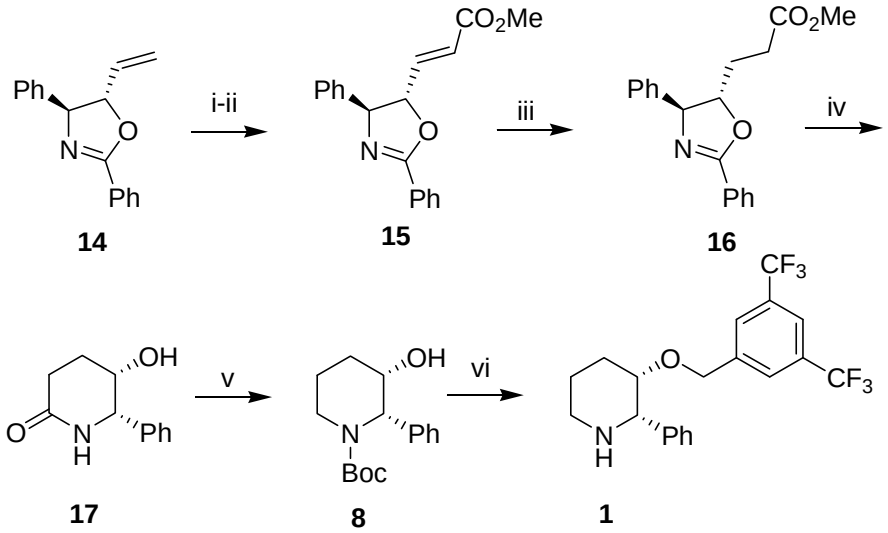
Chang *et al.* have employed a new method of addition of Grignard reagent onto glutarimide **9** for the synthesis of racemic 3-hydroxy-2-phenyl piperidine **3**. Accordingly, addition of phenyl magnesium bromide to glutarimide **9** followed by trapping the resulted –OH group with Ac_2O proceeded regioselectively to provide the enol ether **10** in 82% yield. Removal of the sulfonate ester group was achieved using Na/Hg to obtain enol ether **11**, which was hydrolysed by using BBr_3 that afforded ketolactam **12.** The reduction of ketolactam **12** with $LiAlH_4$ gave piperidine **13**. Benzyl group was deprotected to produced racemic 3-hydroxy-2-phenyl piperidine **3** (**Scheme 2**).



Scheme 2: (i) NaH, PhMgBr, THF, 25 ºC, 1 h, 82%; (ii) Na-Hg, MeOH, 25 ºC, 90%; (iii) BBr_3, CH_2Cl_2, -78 ºC, 90%; (iv) $LiAlH_4$, THF, reflux, 87%; (v) $Pd(OH)_2$, H_2, MeOH, 25 ºC, 90%.

Ham's approach (2005)[9]

This approach describes the synthesis of (+)-L-733,060 starting from chiral oxazoline **14** prepared from the corresponding amino alcohol. Ozonolysis of double bond in **14** followed by Horner-Wittig reaction of the resulting aldehyde furnished α, β-unsaturated ester **15** in 87% yield. 1,4-Reduction of **15** with copper bromide, Red-Al® and 2-butanol gave the saturated methyl ester **16** in 83% yield. Reduction of oxazoline was achieved using $Pd(OH)_2/H_2$ (70 psi) during which process intramolecular lactamization took place to give lactam **17**. Reduction of lactam **17** with $BH_3{\cdot}SMe_2$ and protection of amine gave the required intermediate **8**. Etherification of alcohol **8** with 3,5-bis(trifluromethyl)benzyl bromide followed by deprotection afforded (+)-L-733060 (**1**) (**Scheme 3**).

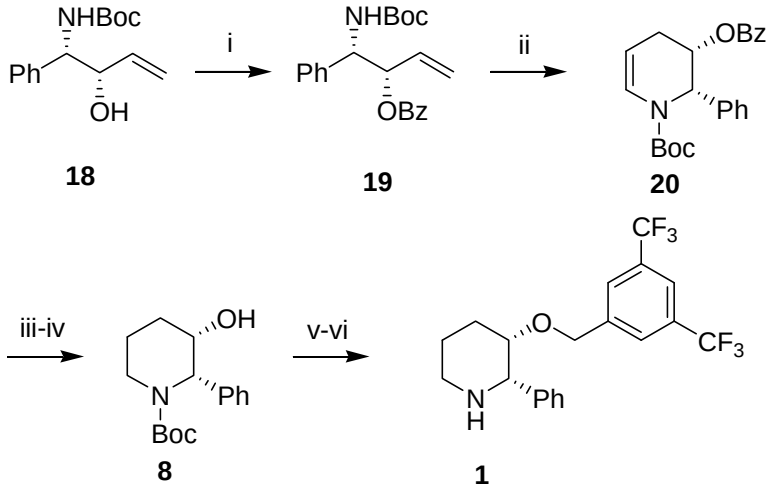


Scheme 3: (i) O_3, MeOH, -78 °C, then $(CH_3)_2S$; (ii) $(MeO)_2POCH_2CO_2Me$, LiCl. $^iPr_2NEt$, CH_3CN, 87%; (iii) CuBr, Red-Al®, 2-butanol, THF, 83%; (iv) 20% $Pd(OH)_2/C$, H_2, (70 psi), MeOH:AcOH (10:1), 76% ; (v) (a) $BH_3{\cdot}SMe_2$, MeOH, THF; (b) $(Boc)_2O$, CH_2Cl_2, 62%; (vi) (a) 3,5-bis(trifluoromethyl)benzyl bromide, NaH, DMF, 76%; (b) trifluoroacetic acid, 93%.

Oshitari's approach (2006)[10]

Oshitari *et al.* have achieved the synthesis of (+)-L-733,060 starting from optically active

amino alcohol **18**. Protection of amine functionality in **18** with $(Boc)_2O$ followed by esterification of the free alcohol group with benzoyl chloride gave the protected amino alcohol **19**. One carbon extension and ring closure to obtain enamine **20** was achieved in one-pot *via* $Rh(acac)(CO)_2$-catalyzed hydroformylation of olefin **19**. Hydrogenation of C=C bond in **20** followed by hydrolysis gave the intermediate **8** which was converted to (+)-L-733,060 (**1**) *via* standard reaction sequences (**Scheme 4**).

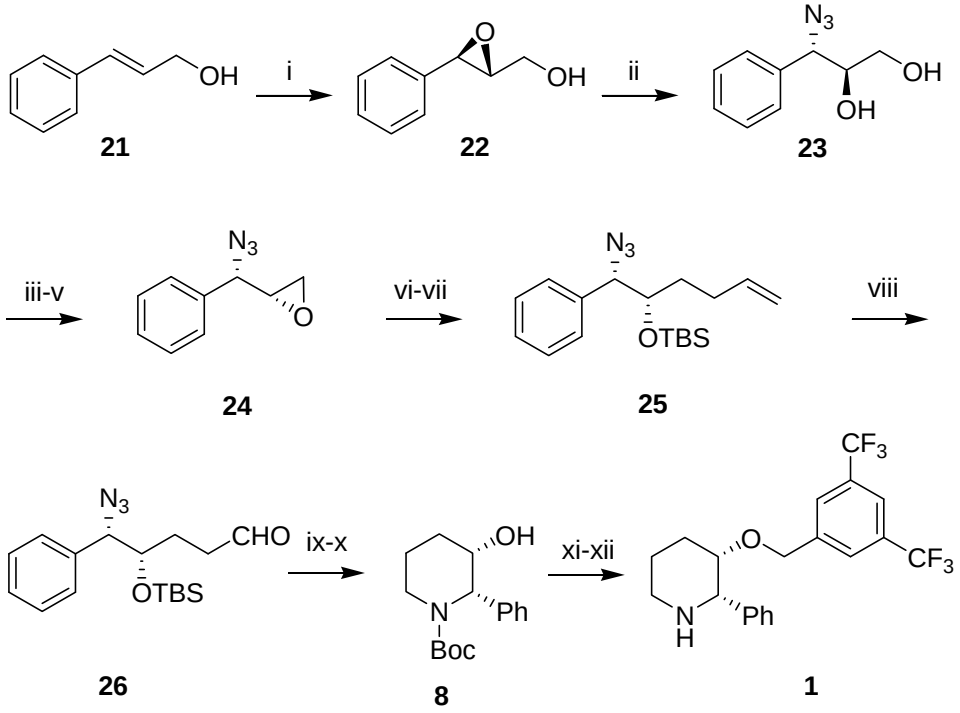


Scheme 4: (i) BzCl, pyridine, 25 °C, 10 h; (ii) $Rh(acac)(CO)_2$ (3 mol%), biphephos (6 mol%), CO/H_2 (5 atm), THF, 65 °C, 5 h; (iii) 10% Pd/C, H_2 (1 atm), EtOH, 25 °C, 20 h; (iv) 1M NaOH, MeOH: 1,4-dioxane (1:2), 25 °C, 1 h; (v) $3,5\text{-}(CF_3)_2C_6H_3CH_2Br$, NaH, THF: DMF (1: 3), 0 °C, 6 h; (vi) TFA, 25 °C, 1.5 h, $NaHCO_3$.

Kumar's approch (2007)[11]

Kumar *et al*. have achieved the synthesis of (+)-L-733,060 using Sharpless asymmetric epoxidation of cinnamyl alcohol **21** to get epoxy alcohol **22** in 99%ee. Regioselective opening of epoxide with NaN_3 resulted in *tran*-azido diol **23**, which was converted to the *cis* azido epoxide **24** *via* standard reaction sequences. Among the several reagents screened, allyltrimethyl silane opened azido epoxide **24** regioselctively to give the azido alcohol in moderate yield, which was protected as silyl ether **25**. One carbon degradation

of **25** was achieved *via* one-pot dihydroxylation followed by diol cleavage to get the crucial azido aldehyde **26**. Azido aldehyde **26** underwent aza-Wittig reaction in the presence of PPh_3 to provide six-membered imine, which upon reduction with $NaBH_4$ gave piperidine moiety **8**. Etherification of alcohol **8** with 3,5-bis(trifluromethyl)benzyl bromide followed by deprotection afforded (+)-L-733,060 (**1**) (**Scheme 5**).

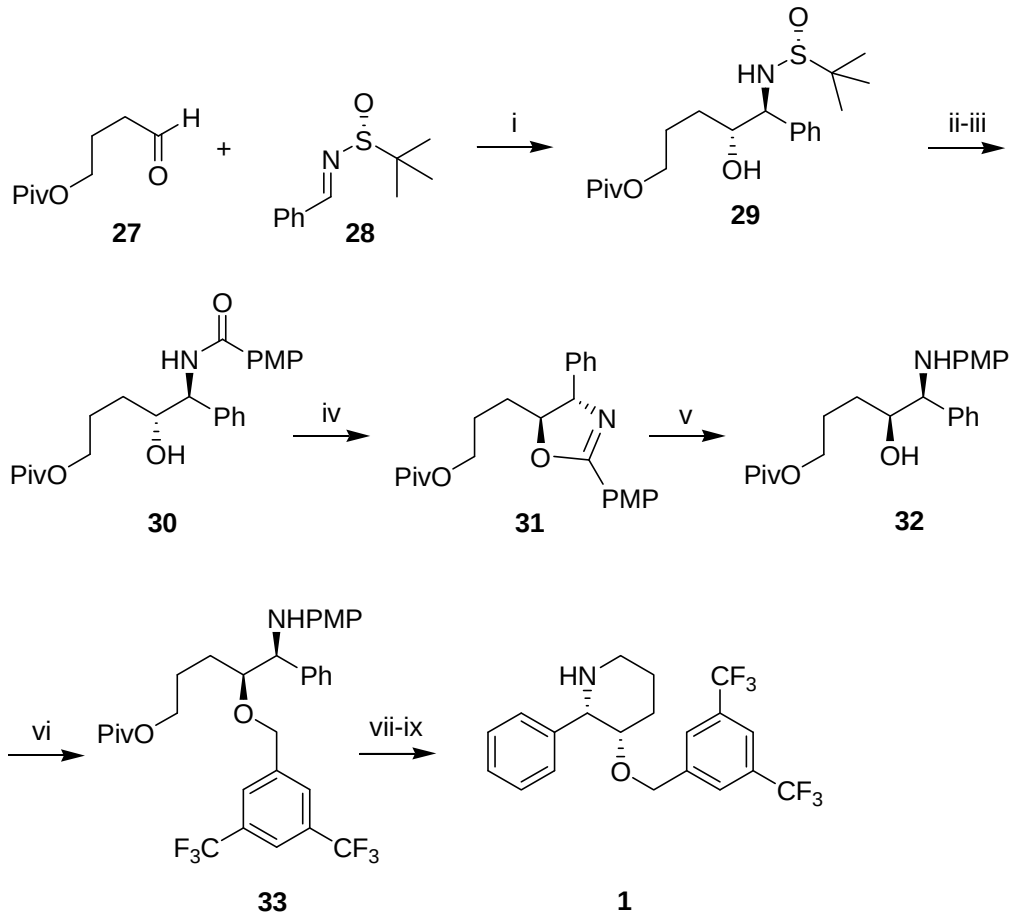


Scheme 5: (i) Ti(OPr-*i*)$_4$, (*S*,*S*)-(−)-DET, TBHP, MS 4 Å, CH_2Cl_2, −20 °C, 3 h, 89%; (ii) NaN_3, NH_4Cl, MeOH:H_2O (8:1), 65 °C, 5 h, 98%; (iii) PivCl, Pyridine, CH_2Cl_2 (1:1), 0 °C–25 °C, 5 h; (iv) MsCl, Et_3N, DMAP, CH_2Cl_2, 0 –25 °C, 1 h; (v) K_2CO_3, MeOH, 25 °C, 10 h, 80% (3 steps); (vi) allyltrimethylsilane, $TiCl_4$, CH_2Cl_2, -78 °C, 1 h, 65%; (vii) TBSOTf, 2,6-lutidine, 0 °C, 1 h, 95%; (viii) OsO_4, $NaIO_4$, 1,4-dioxane:H_2O (3:1), 0 °C, 3 h; (ix) PPh_3, THF, 25 °C, 16 h; (x) $NaBH_4$, MeOH, 0 °C, 30 min., 65%; (xi) $(Boc)_2O$, Et_3N, CH_2Cl_2, 2 h, 95%; (xii) TBAF, THF, 0 °C–25 °C, 10 h, 90%; (xiii) NaH, 3,5-bis(trifluoromethyl)benzyl bromide, DMF, 80 °C, 12 h, 78%; (xiv) TFA, MeOH, 25 °C, 12 h, 70%.

Wang's approach (2008)[12]

Wang *et al*. employed the reductive coupling of 4-pivaloxybutanal **27** with (*R*)-phenyl *N*-*tert*-butanesulfinyl imine **28** in the presence of SmI_2 to afford amino alcohol **29** with

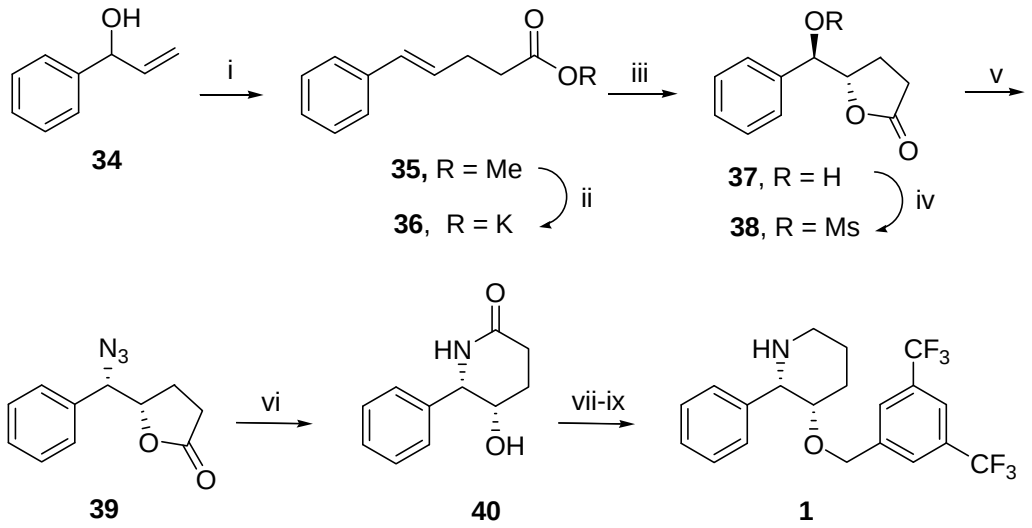
required stereochemistry. Removal of the chiral auxiliary followed by selective *N*-acylation with 4-methoxybenzoic anhydride afforded amide **30**. Mesylation of free alcohol group in **30** furnished oxazoline **31** in 85% yield, with complete inversion of configuration at C-2. Reductive ring-opening of oxazoline **31** ($NaBH_3CN$, HOAc, 40 °C) gave *syn*-1,2-amino alcohol **32** in excellent yield. Selective *O*-alkylation with 3,5-bis(trifluromethyl)benzyl bromide provided **33** in 82% yield. The intermediate **33** was converted to (+)-L-733,060 (**1**) by standard reaction sequences (**Scheme 6**).



Scheme 6: i) SmI_2, ^tBuOH, -78 ^oC, 78%; (ii) HCl, MeOH; (iii) $(PMPCO)_2O$, Et_3N, CH_2Cl_2, 88%; (iv) MsCl, Et_3N, CH_2Cl_2, 85%; (v) $NaCNBH_3$, AcOH, 90%; (vi) NaH, 3,5-bis(trifluoromethyl)benzyl bromide, TBAI, DMF, 82%; (vii) NaOMe, MeOH; (viii) MsCl, Et_3N, CH_2Cl_2, 78%; (ix) DDQ, CH_2Cl_2, 0 ^oC.

Sudalai's approach (2008)[13]

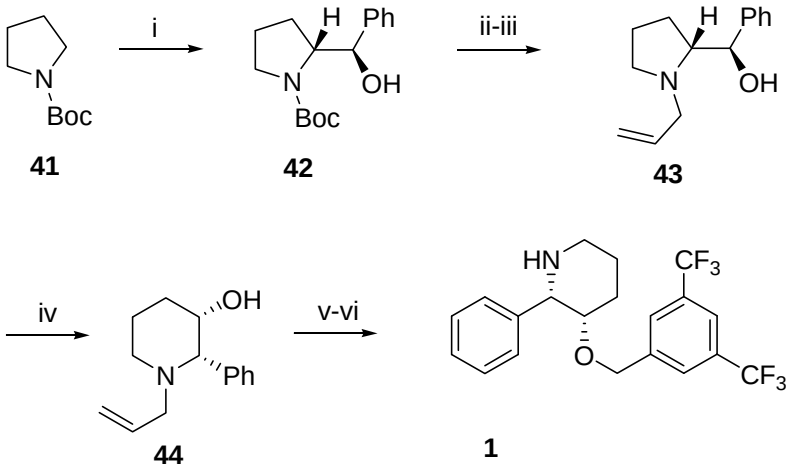
This approach describes the synthesis of (+)-L-733,060 starting from allylic alcohol **34,** which was subjected to Johnson–Claisen [3,3]- sigmatropic rearrangement to give homoallylic ester **35** in 82% yield. Alkaline hydrolysis of ester **35** using aq. KOH furnished potassium alkenoate **36**, which was subjected to Shi-epoxidation using D-fructose-derived ketone as the chiral catalyst (30 mol%) and Oxone as the stoichiometric oxidant to afford hydroxylactone **37** in 62% yield. Mesylation of hydroxylactone **37** gave the corresponding mesylate **38**, which was subjected to S_N2 displacement with NaN_3 to afford azidolactone **39**. Reduction of azide **39** under Staudinger conditions produced lactam **40** which was converted to (+)-L-733,060 (**1**) *via* standard reaction sequences (**Scheme 7**).



Scheme 7: i) $CH_3C(OMe)_3$, propanoic acid, 135 °C, 6 h, 82%; ii) aq. KOH, reflux; iii) pH 10-11, Oxone, chiral ketone, KOH, CH_3CN, -5 °C, 1 h then 15 °C, 5 h, 62%; iv) MsCl, Et_3N, CH_2Cl_2, 0 °C, 2 h, 96%; v) NaN_3, DMF, 60 °C, 12 h, 94%; vi) PPh_3, THF, 25 °C , 2 h then H_2O refluxed 3 h, 91% ; vii) a) $BH_3.SMe_2$, THF, reflux, 6 h; b) $(Boc)_2O$, Et_3N, DMAP (cat.), CH_2Cl_2, 0–25°C, 73% over two steps; viii) 3,5-bis(trifluoromethyl)benzyl bromide, NaH, DMF: THF (3:1), 0 °C, 6 h; ix) TFA, CH_2Cl_2, 18 h, 81% over two steps.

O'Brien's approach (2008)[14]

O'Brien *et al*. have reported synthesis of (+)-L-733,060 using catalytic asymmetric deprotonation of *N*-Boc pyrrolidine **41** as a key step. Accordingly *N*-Boc pyrrolidine **41** was subjected to asymmetric deprotonation by using s-BuLi, (-)-sparteine to give the organolithium reagent, which was subsequently trapped with benzaldehyde to afford alcohol **42** with dr = 3:1 (*syn*: *anti*). Deprotection of Boc group in alcohol **42** followed by its treatment with allyl bromide in presence of K_2CO_3 gave *N*-allylated alcohol **43** in 58% yield. The *N*-allylated alcohol **43** was subjected to ring-expasion with TFAA followed by hydrolysis to give piperidine derivative **44** in 83% yield. *O*-Benzylation of **44** was achieved by using NaH and the corresponding benzyl bromide. Finally, *N*-deallylation was achieved with Pd(0) and *N*,*N*′-dimethylbarbituric acid to give (+)-L-733,060 (**1**) (**Scheme 8**).



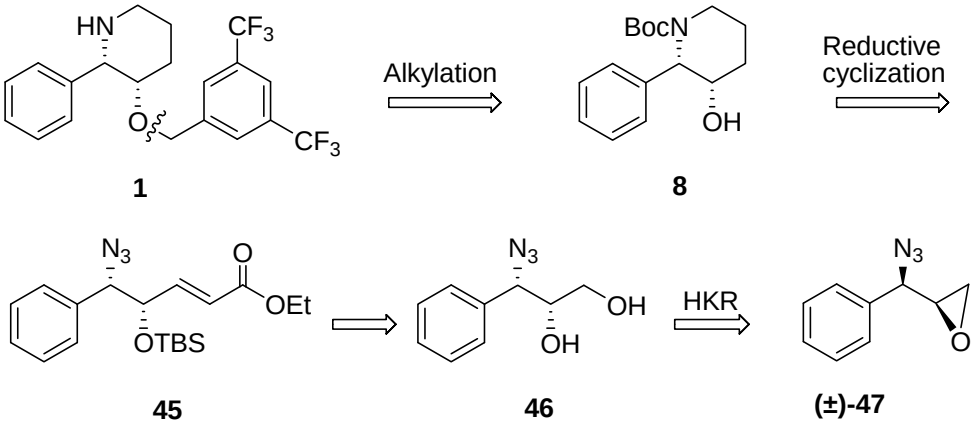
Scheme 8: i) a) BuLi, (-)-spareine, LiDMAE, Et_2O, -78 °C; b) PhCHO, 64% (3:1 dr). ii) TFA, CH_2Cl_2, 25 °C, 16; iii) K_2CO_3, AllylBr, MeCN, 25 °C, 6 h, 58%; iv) $(CF_3CO)_2O$, Et_3N, THF, reflux, 72 h, then aq NaOH, 83%; v) 3,5-bis(trifluoromethyl)benzyl bromide, NaH, THF, 0 °C, 30 min; vi) $Pd(PPh_3)_4$, *N*,*N*′-dimethylbarbituric acid CH_2Cl_2, 25 °C, 24 h.

2.1.3. Present Work

2.1.3.1. Objective

As can be seen from the above discussion, the literature methods for the synthesis of (+)-L-733,060 (**1**), either employ chiral starting material, expensive reagents, involve longer reaction sequences or lack of selectivity. Hence, the synthesis of (+)-L-733,060 using catalytic enantioselective reactions is desirable. This section describes a short synthesis of (+)-L-733,060 (**1**), using hydrolytic kinetic resolution[15] of azido epoxide **47** as the key step to induce chirality in the molecule.

The retrosynthetic analysis of (+)-L-733,060 (**1**) is shown in **Scheme 9**. It reveals that *syn* 1,2-amino alcohol **8** could be considered as a key intermediate. We have thus planned to employ intramolecular reductive cyclization of (*E*)-α,β-unsaturated azidoester **45** under hydrogenation conditions for the construction of the 6-membered heterocyclic nucleus **8**.



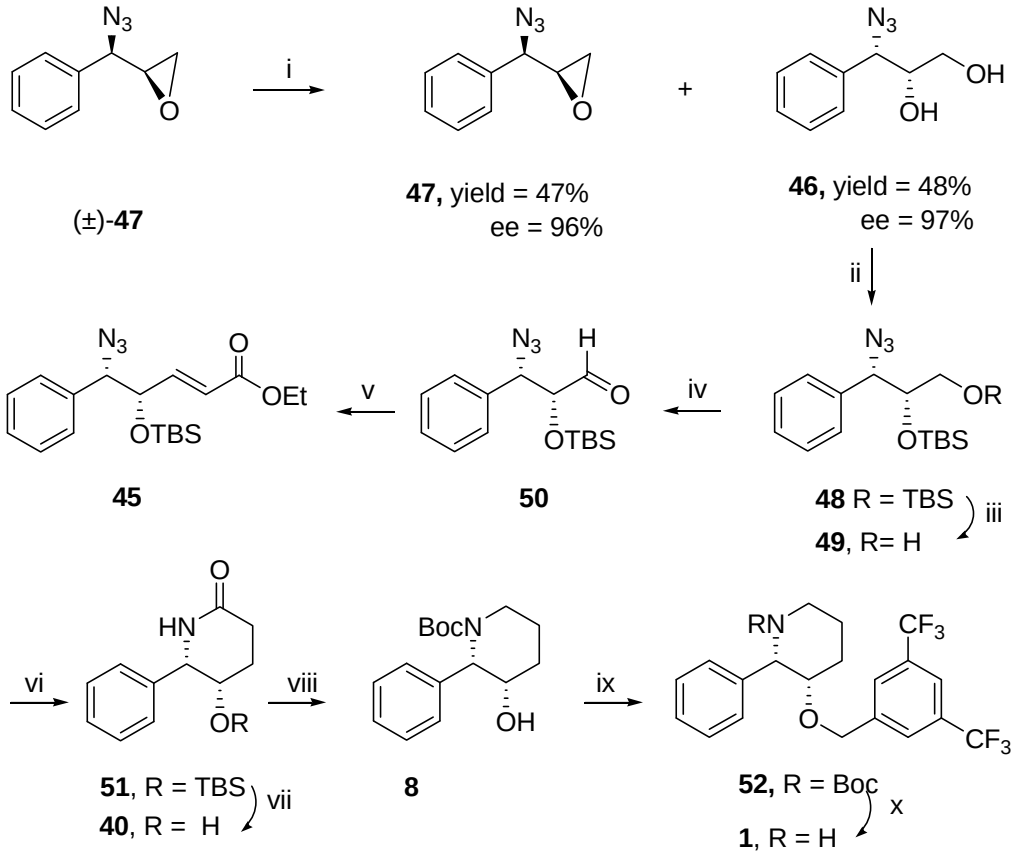
Scheme 9: Retrosynthesis of (+)-L-733, 060 (**1**)

The azidoester **45** can be readily made from the corresponding azido diol **46** by a two-step reaction sequence of Dess-Martin periodinane oxidation[16] of primary alcohol followed by Wittig olefination.[17] We envisaged further that introduction of chirality in **46**

with *syn* stereochemistry could be realized *via* hydrolytic kinetic resolution of racemic azido epoxide **47.**

2.1.4. Results and Discussion

The present synthetic route employed for the synthesis of L-773,060 **1** is shown in **Scheme 10**.



Scheme 10: (i) (*S,S)*-salen-Co(III)OAc (0.5 mol%), H_2O (0.5 equiv), 0 ºC, 14 h; (ii) TBSCl, imid., CH_2Cl_2, 25 °C, 98%; (iii) CSA, MeOH:CH_2Cl_2 (1:1), 0 °C 6 h, 95%; (iv) Dess-Martin periodinane, CH_2Cl_2, 25 °C, 98%;v) $Ph_3P{=}CHCO_2Et$, THF, 25 °C, 14 h, 94%; (vi) 10% Pd/C, H_2, MeOH, 25 °C, then reflux in EtOH, 85%; (vii) TBAF, THF, 25 °C, 96% ; (viii) a) $Me_2S.BH_3$, THF, reflux, 10 h; b) $(Boc)_2O$, Et_3N, cat. DMAP, CH_2Cl_2, 0 – 25°C, 73% over two steps; (ix) 3, 5-bis (trifluoromethyl)benzyl bromide, NaH, DMF: THF (3:1), 0 °C, 6 h; (x) TFA, CH_2Cl_2, 18 h, 82% over two steps.

Racemic azido epoxide (±)-**47** was subjected to hydrolytic kinetic resolution using catalytic amount (0.5 mol%) of (*S,S)*-salen-Co(III)OAc complex to give chiral azido diol

46 in 48% yield and 97% ee along with chiral azido epoxide (-)-**47** in 47% yield and 96% ee. The compounds **46** and **47** were then readily separated by column chromatographic purification. The enantiomeric excess of azido diol **46** was determined by chiral HPLC analysis; Chiralpak OD-H.

The formation of azido diol **46** was confirmed by its ^{1}H NMR spectrum wherein the appearence of a multiplet at δ 3.80 and a doublet of doublet at δ 3.30 and 4.25 are due to methine (C-H) and methylene (CH_2) protons respectively. Its ^{13}C NMR spectrum showed characteristic signals at δ 62.8 and 75.0 for the methine and methylene carbons attached to hydroxyl groups respectively (**Fig. 2**).

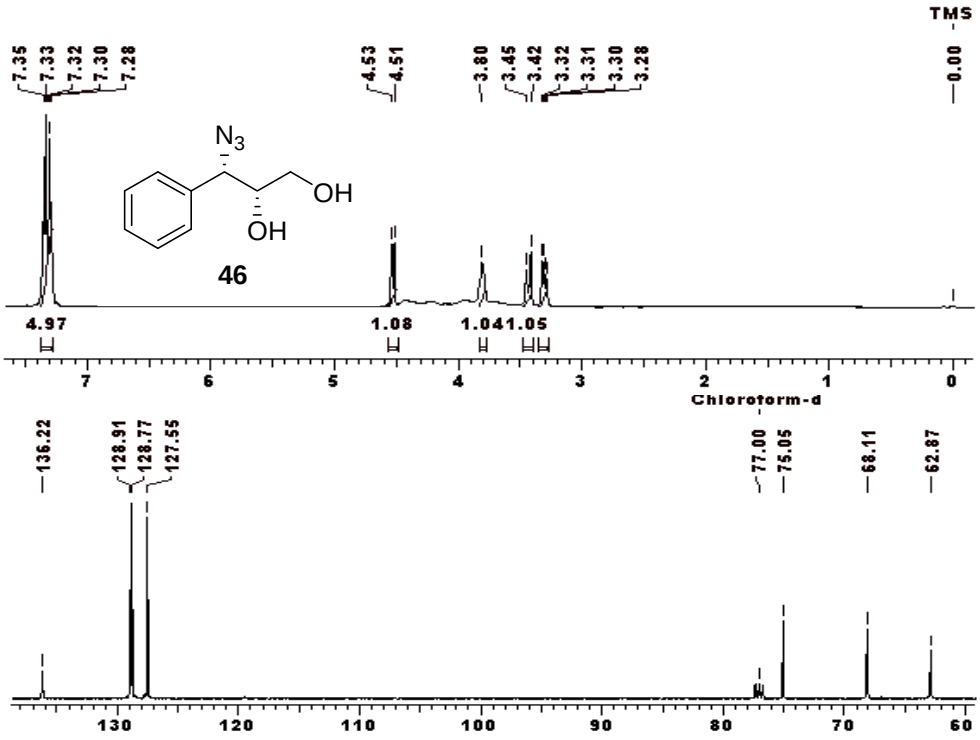


Fig. 2: ^{1}H and ^{13}C NMR spectra of azido diol **46**

The azidodiol **46** was then protected as its *bis*-TBS ether (TBS chloride and imid.) to give **48** in 98% yield. The formation of coupound **48** was confirmed by its ^{1}H NMR spectrum,

which showed the appearance of singlets at δ 0.84 and 0.90 due to *tert*-butyl protons. The other proton signals at δ -0.22, -0.08, 0.03 and 0.05 are assigned to methyl protons attached to silyl group (**Fig. 3**).

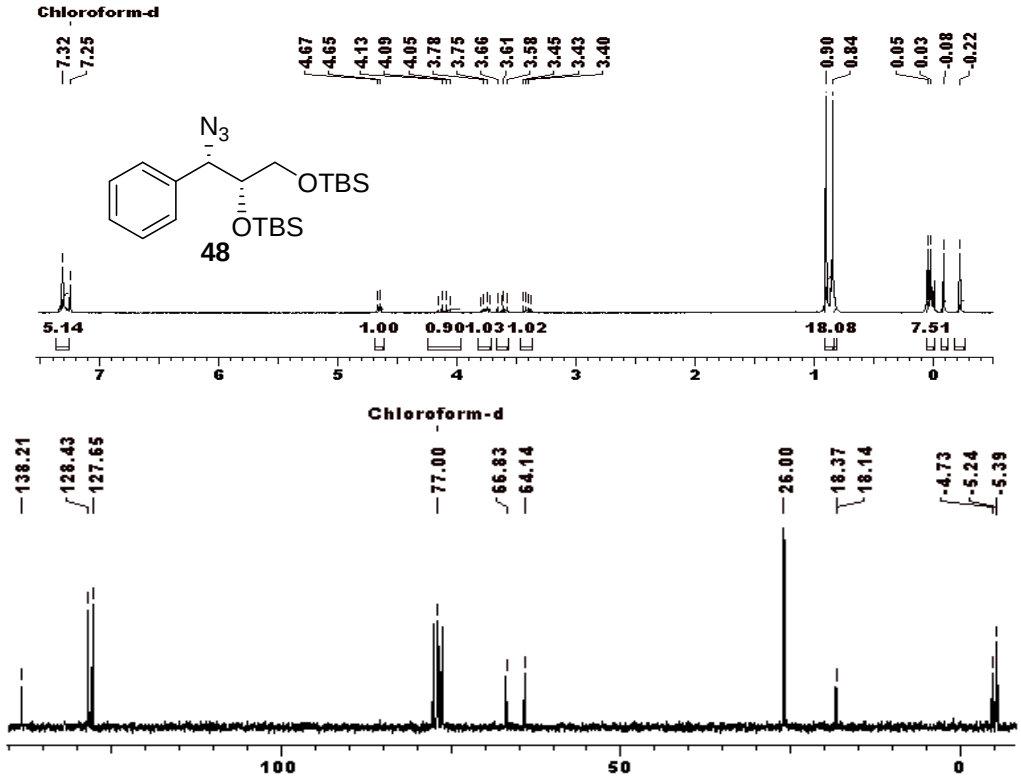


Fig. 3: ^{1}H and ^{13}C NMR spectra of bis-TBS ether **48**

The selective deprotection of the primary silyl ether in **48** was then achieved with camphorsulfonic acid (5 mol%) in MeOH[18] to produce alcohol **49** in 95% yield. The formation of alcohol **49** was confirmed by its ^{1}H NMR spectrum, which showed the appearance of only one singlet at δ 0.78 for *tert*-butyl protons. The alcohol group in **49** was then oxidized under Dess-Martin periodinane condition to produce azido aldehyde **50** in 98% yield. The ^{1}H NMR spectrum of aldehyde **50** displayed a typical doublet at δ

9.7 due to aldehydic proton. Its ^{13}C NMR spectrum showed a typical signal at δ 201.3 for the aldehydic carbonyl function (**Fig. 4**).

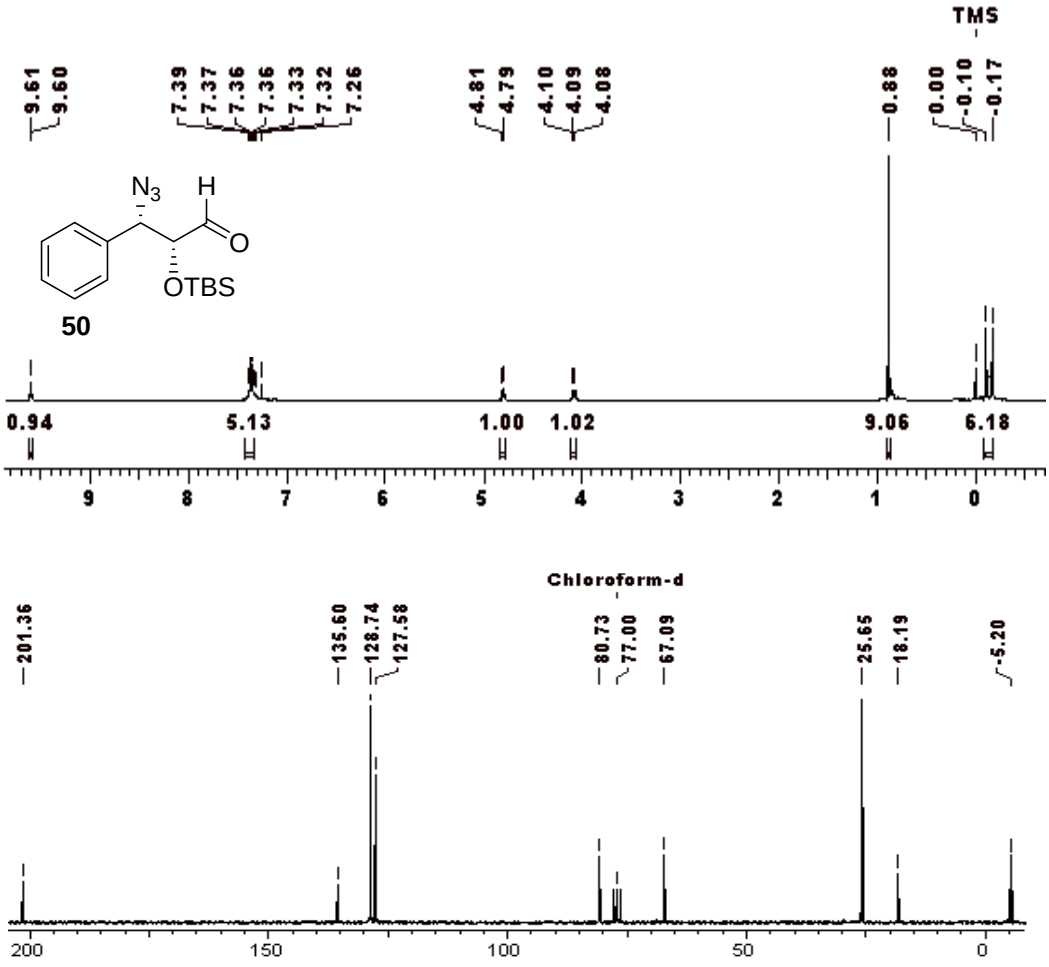


Fig. 4: ^{1}H and ^{13}C NMR spectra of azidoaldehyde **50**

Then the resulting aldehyde was subjected to Wittig olefination to give α,β-unsaturated azidoester **45** in 94% yield. The formation of α,β-unsaturated azidoester **45** was confirmed by its ^{1}H NMR spectrum, which showed the appearance of doublets of doublets at δ 5.88 (dd, J = 1.0, 15.6 Hz, 1H) and 6.63 (dd, J = 4.3, 15.6 Hz, 1H) due to olefinic protons. Its ^{13}C NMR spectrum showed typical signals at δ 122.62 and 146.15 due to the olefinic carbons (**Fig. 5**).

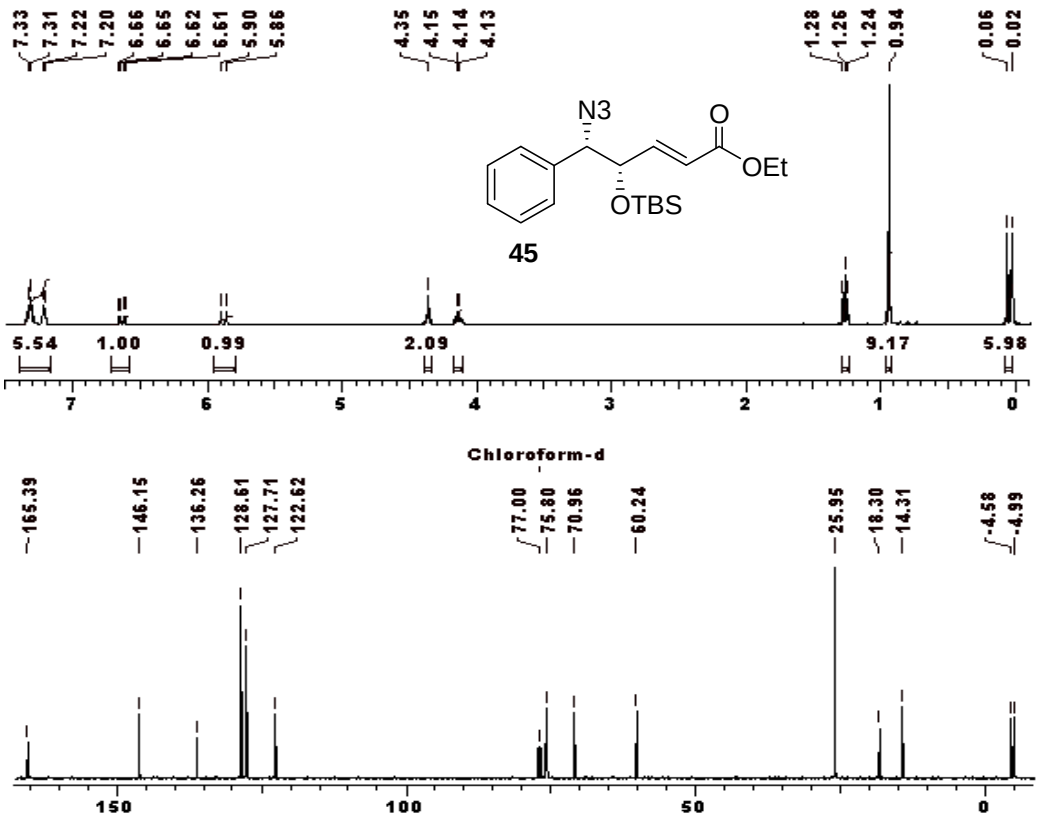


Fig. 5: ^{1}H and ^{13}C NMR spectra of α,β-unsaturated azidoester **45**

Reduction of azide group along with double bond (C=C) was achieved under hydrogenation condition (H_2 and 10% Pd/C). Subsequently, on refluxing with EtOH, TBS protected lactam **51** was obtained in 85% yield. The formation of lactam **51** was confirmed by its ^{1}H NMR spectrum, which showed the appearance of multiplets at 1.99-2.83 due to methylene protons and the absence of signals in the olefinic region. Its ^{13}C NMR spectrum showed a typical signal at δ 172.1 corresponding to amide carbonyl (-CO-NH) group (**Fig. 6**). The presence of amide group was further evidenced by the exhibition of two characteristic absorption bands at 1346 and 1664 cm^{-1} in its IR spectrum.

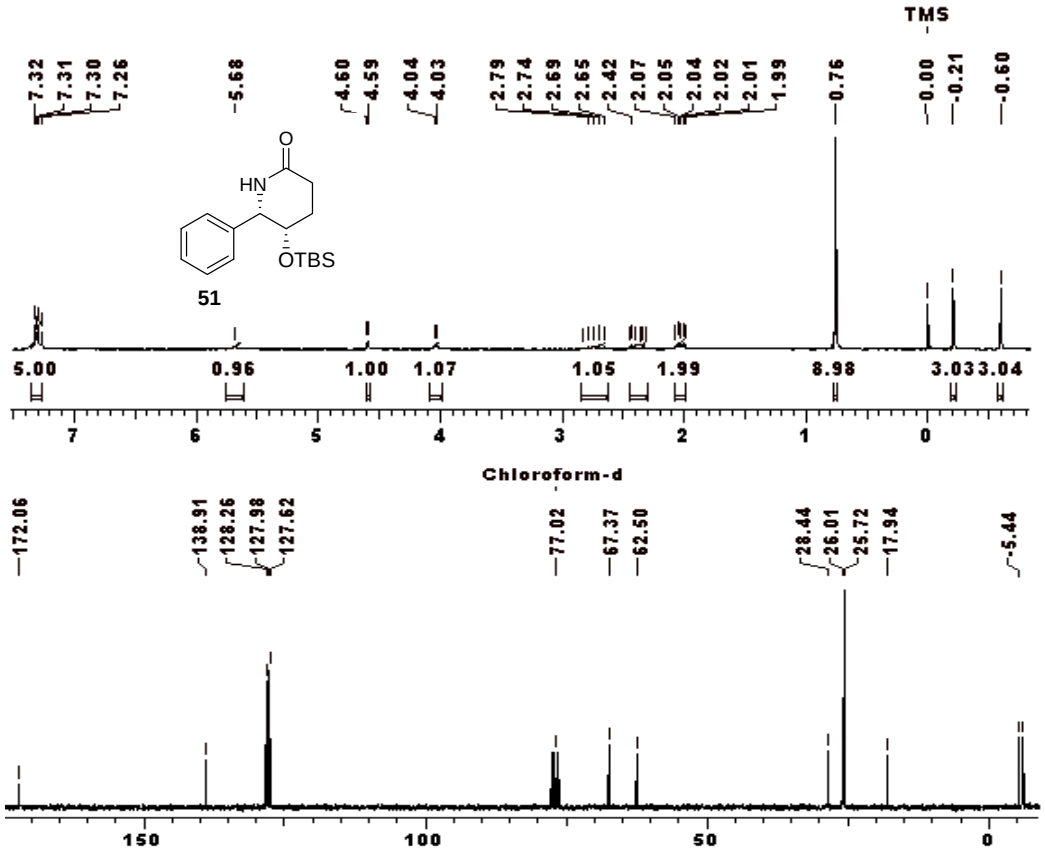


Fig. 6: ^{1}H and ^{13}C NMR spectra of lactam **51**

The TBS group in **51** was deprotected (TBAF in THF) to give hydroxylactam **40** in 96% yield. The formation of hydroxylactam **40** was confirmed from its ^{1}H NMR spectrum, which displayed signals at δ 4.48 and 3.85 corresponding to the methine protons (-C**H**-NHCO and -C**H**OH). Its ^{13}C NMR spectrum showed carbon signals at δ 73 and 67.1 corresponding to the methine carbons (-**C**H-NHCO and -**C**HOH). The other signal at δ 177.4 corresponds to amide carbonyl carbon (-**C**ONH-) and signals at δ 30.99 and 28.65 are due to methylene carbons (-**C**H_2- and –**C**H_2CO-) respectively.

Reduction of lactam **40** was achieved using $BH_3 \cdot SMe_2$ in THF to give the amino alcohol whose N-H bond protection with $(Boc)_2O$ gave the *syn*- amino alcohol **8** in 73% yield over two steps. The ^{1}H NMR spectrum of **8** indicated the presence of Boc methyl protons

at δ 1.43 as a singlet (**Fig. 7**). The proton signals at δ 5.30 and 4.44 correspond to the methine protons (CH-N and CH-O) of the substituted piperidine moiety of aminoalcohol **8**. Its ^{13}C NMR spectrum displayed signals at δ 156.72 and 80.12 indicating the presence of Boc carbonyl (-N**C**O-) and *tert*-butyl carbon (Me_3**C**-O) groups respectively.

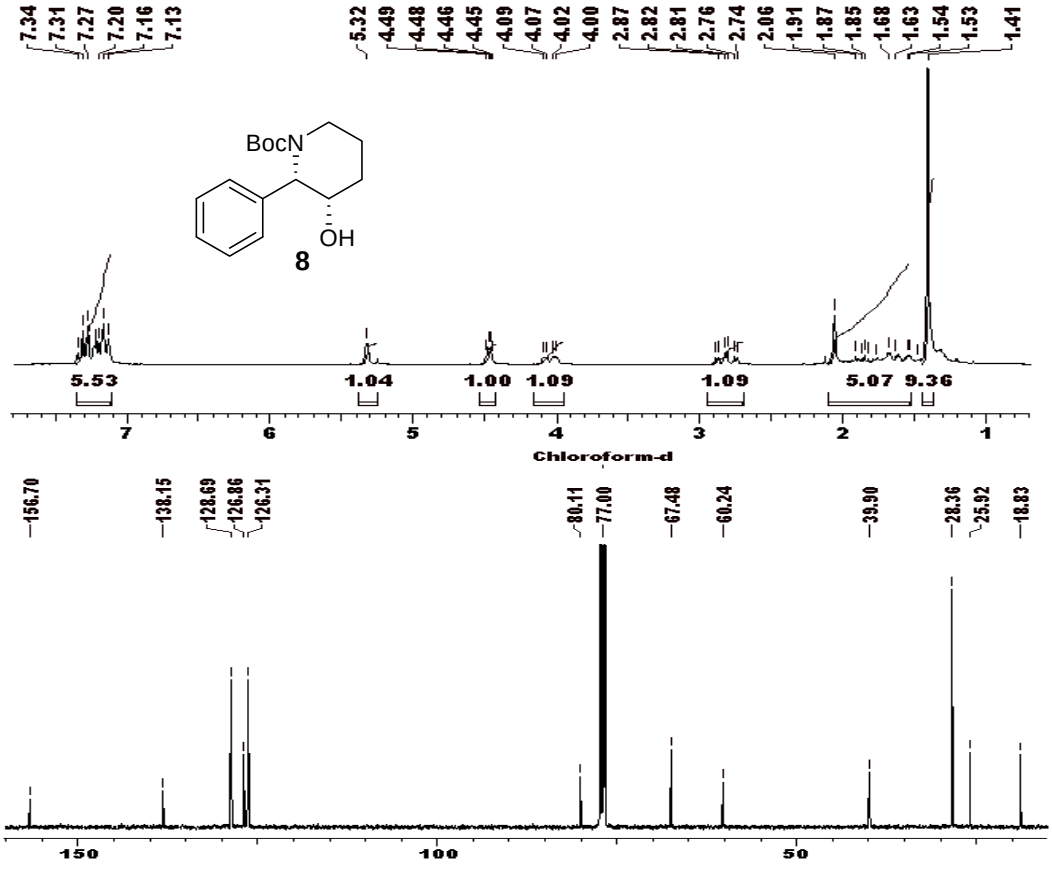


Fig. 7: ^{1}H and ^{13}C NMR spectra of *syn*- amino alcohol **8**

Having constructed the piperidine ring with the desired *syn*-stereochemistry, *O*-alkylation of **8** with 3,5-bis(trifluoromethyl)benzyl bromide in the presence of NaH was performed to give **52** {$[\alpha]^{25}_{D}$ +30.9 (*c* 0.8, $CHCl_3$); lit.[5h] $[\alpha]^{25}_{D}$ +30.38 (*c* 1.55, $CHCl_3$)}. Finally, deprotection of the Boc group under acidic conditions afforded (+)-L-733,060 (**1**) {$[\alpha]^{25}_{D}$ +35.2 (*c* 0.5, $CHCl_3$); [lit.[5h] $[\alpha]^{25}_{D}$ +34.29 (*c* 1.32, $CHCl_3$]}. The ^{1}H, ^{13}C NMR and other spectral data were in complete agreement with the reported values (**Fig. 8**).[7]

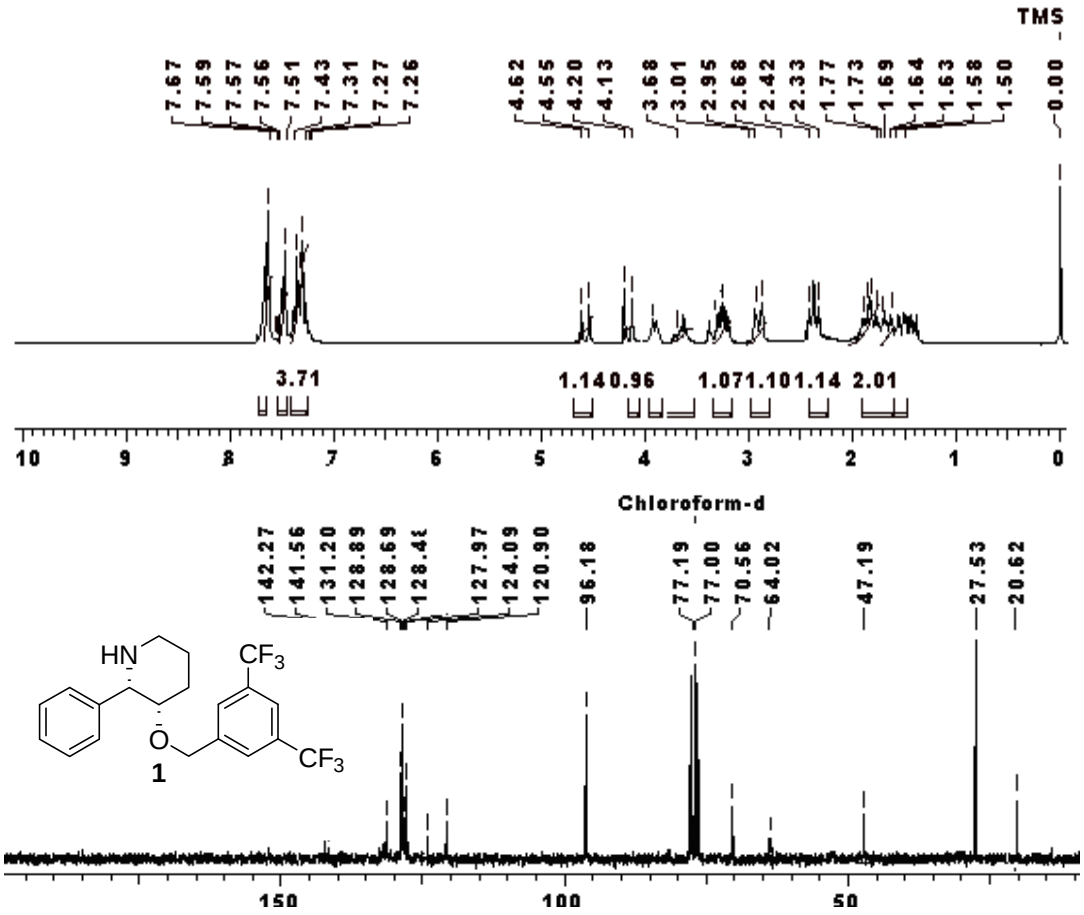


Fig. 8: ^{1}H and ^{13}C NMR spectra of (+)-L-733, 060 (**1**)

2.1.5. Conclusion

In summary, the enantioselective synthesis of (+)-L-733, 060 (**1**) has been achieved in 98% ee using hydrolytic kinetic resolution of azido epoxide **46** as the chiral inducing step. The intramolecular reductive cyclization of (*E*)-α,β-unsaturated azido ester **45** was the important step used for the construction of piperidine ring. The synthetic strategy described herein has significant potential for further extension to piperidine-based bioactive molecules as well as other NK1 receptor antagonists.

2.1.6. Experimental Section

(2*R*, 3*S*)-3-Azido-3-phenyl-propane-1,2diol (46)

To solution of (*S,S)*-salen-cobalt(III)OAc complex (see chapter I) (0.066 g, 1 mol%) and racemic azido epoxide **47** (1.75 g, 10 mmol) at 0 °C was added H_2O (86.4 g, 4.8 mmol) drop wise over 5 min then the resulting reaction mixture was stirred at 0 ºC for 14 h. The reaction mixture was filtered through a pad of silica gel and washed with 50% EtOAc/hexanes (40 mL) and the filtrate was concentrated *in vacuo* to give the crude products, which were purified by column chromatography packed with silica gel using petroleum ether/EtOAc (9:1) to give chiral azido epoxide **(-)-47** (0.83 g, 48%) and using petroleum ether/EtOAc (7:3) to give chiral azido diol **46** (0.90 g, 47%). The ee of the diol was determined to be 98% ee by chiral HPLC analysis.

Yield: **(**0.90 g) 47%; yellow colored liquid; $[\alpha]^{25}_{D}$: +188 (*c* 1, $CHCl_3$); 98% ee by chiral HPLC analysis (Chiralpak OD-H, *n*-hexane/*i*-PrOH, 90:10, 0.5 mL/min) retention time 14.848 (0.90%) and 16.876 (99.20%); **IR** ($CHCl_3$, cm^{-1}): 859, 828, 1039, 1100, 1384, 1454, 1493, 1602, 2099, 2932, 3052, 3392 (broad); **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 3.30 (dd, *J* = 11.5, 6.0 Hz, 1H), 3.44 (d, *J* = 11.5 Hz, 1H), 3.80 (br s, 1H), 3.62-3.94 (m, 1H), 4.52 (d, *J* = 8.1, 1H), 7.28-7.35 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 62.8, 68.1, 75.0, 127.5, 128.7, 128.9, 136.2; **Anal.** Calcd for $C_9H_{11}N_3O_2$ requires C, 55.95; H, 5.74; N, 21.75%; found: C, 56.10; H, 5.65; N, 21.60%.

(2*R*, 3*S*)-3-Azido-1,2-bis(*tert*-butyldimethylsilyloxy)-3-phenyl-propane-1,2-diol (48)

To a solution of azido diol **46** (0.77 g, 4.0 mmol) in CH_2Cl_2 (20 mL) at 25 ºC was added TBSCl (1.50 g, 10 mmol) and imidazole (0.680 g, 10 mmol). The resulting solution was stirred at 25 ºC for 24 h, then quenched with water and extracted with CH_2Cl_2. The

combined organic extracts were washed with brine, dried over anhyd. Na_2SO_4 and concentrated *in vacuo* to give the crude product, which was purified by column chromatography packed with silica gel using pet. Ether: EtOAc (9.5:0.5) to give pure bis-TBS ether **48** as colorless oil.

Yield: (1.65g) 98%; colourless oil; **[α]$^{25}_{D}$**: +56.20 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 668, 765, 835, 1111, 1250, 1464, 1513, 1585, 1612, 2103, 2931, 2955, 3017; **^{1}H NMR** (200 MHz, $CDCl_3$): δ -0.22 (s, 3H), -0.08 (s, 3H), 0.03 (s, 3H), 0.05 (s, 3H), 0.84 (s, 9H), 0.90 (s, 9H), 3.42 (dd, *J* = 10.0, 4.4 Hz, 1H), 3.62 (dd, *J* = 10.0, 6.4 Hz, 1H), 3.73 (m, 1H), 4.66 (d, *J* = 4.6 Hz, 1H), 7.27-7.35 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.4, -5.2, -4.7, 18.1, 18.3, 25.8, 26.0, 64.1, 66.8, 76.8, 127.5, 127.97, 128.4, 138.1; **Anal.** Calcd for $C_{21}H_{39}N_3O_3Si_2$ requires C, 59.81; H, 9.32; N, 9.96; found: C, 59.90; H, 9.20; N, 10.0 %.

(2*R*, 3*S*)-3-Azido-2-(*tert*-butyldimethylsilyloxy)-3-phenyl-1-propanol (49)

To a solution of *bis*-TBS ether **48** (1.263g, 3 mmol) in MeOH (10 mL) was added camphorsulfonic acid (0.070g, 10 mole%) at 0 °C and the mixture stirred for 5 h. After completion of the reaction (monitored by TLC), it was neutralized with $NaHCO_3$ and concentrated to give the crude product, which was purified by column chromatography packed with silica gel using pet. ether: EtOAc (9:1) as eluent to furnish TBS-protected azido alcohol **49** as colorless liquid.

Yield: (0.875 g) 95%; colourless liquid; **[α]$^{25}_{D}$**: +120.21 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 668, 765, 835, 1115, 1250, 1515, 1585, 1610, 2101, 2955, 3470; **^{1}H NMR** (200 MHz, $CDCl_3$): δ -0.04 (s, 3H), 0.01 (s, 3H), 0.78 (s, 9H), 1.75 (br s, 1H), 3.02 (m, 1H), 3.27 (m, 1H), 3.57 (m, 1H), 4.45 (d, *J* = 8.2 Hz, 1H), 7.12-7.21 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -4.7, -4.6, 18.2, 25.6, 63.2, 68.3, 76.6, 127.6, 128.4, 128.7, 137.2; **Anal.** Calcd

for $C_{15}H_{25}N_3O_2Si$ requires C, 58.60; H, 8.20; N, 13.67; found: C, 58.50; H, 8.35; N, 13.50%.

(2*R*, 3*S*)-3-Azido-2-(*tert*-butyldimethylsilyloxy)-3-phenyl-1-propanal (50)

To a stirred solution of TBS-protected azido alcohol **49** (0.614g, 2 mmol) in dry CH_2Cl_2 (10 mL) was added Dess-Martin periodinane (1.017g, 2.4 mmol) at room temperature. After the completion of the reaction, it was quenched with water. The precipitate formed was filtered through a sintered funnel and the filtrate was concentrated and subjected to column chromatographic purification using ethyl acetate and pet. ether (1:9) as eluent to give azido aldehyde **50** as yellow liquid.

Yield: **(**0.60 g) 98%; yellow coloured liquid; **$[\alpha]^{25}_{D}$**: +110.41 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 668, 765, 835, 1110, 1250, 1515, 1585, 1610, 1730, 2106, 2850, 2955; **^{1}H NMR** (200 MHz, $CDCl_3$): δ -0.17 (s, 3H), -0.10 (s, 3H), 0.86 (s, 9H), 4.07 (dd, *J* = 4.6, 1.4 Hz, 1H), 4.80 (d, *J* = 4.4 Hz, 1H), 7.32-7.39 (m, 5H), 9.60 (d, *J* = 1.5 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.4, -5.2, 18.2, 25.6, 67.1, 80.7, 127.6, 128.7, 135.6, 201.3; **Anal.** Calcd for $C_{15}H_{23}N_3O_2Si$ requires C, 58.98; H, 7.59; N, 13.76; found: C, 59.10; H, 7.50; N, 13.70 %.

(4*R*,5S)-5-Azido-4-(*tert*-butyldimethylsilyloxy)-5-phenylpent-2-enoicacidethylester (45):

To a solution of azido aldehyde **50** (1.0 g, 3.27 mmol) in dry THF (20 mL), was added ylide $Ph_3P{=}CHCO_2Me$ (1.30 g, 3.92 mmol) at 25 ^oC. The reaction mixture was stirred at 25 ^oC for 10 h, and then quenched with water (5 mL). The product was extracted with EtOAc (3 x 20 mL). The combined organic phase was dried over anhyd. Na_2SO_4 and concentrated under *vacuum*. The crude product was purified by column chromatography

on silica gel using ethyl acetate and pet. ether (1:9) as eluent to give (*E*)-α,β-unsaturated azidoester **45** as yellow liquid.

Yield: **(**1.152 g) 94%; yellow colored liquid; **[α]$^{25}_{D}$**: +66.11 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 668, 765, 835, 1110, 1250, 1515, 1585, 1610, 1740, 2106, 2955; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.02 (s, 3H), 0.06 (s, 3H), 0.94 (s, 9H), 1.26 (t, *J* = 7.0 Hz, 1H), 4.09-4.17 (m, 1H), 4.34-4.39 (m, 1H), 5.88 (dd, *J* = 15.9, 1.0 Hz, 1H), 6.63 (dd, *J* = 15.9, 4.2 Hz, 1H), 7.20 (dd, *J* = 7.8, 1.5 Hz, 2H), 7.29-7.25 (m, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.0, -4.5, 14.3, 18.30, 25.9, 60.2, 70.9, 75.8, 122.6, 127.7, 128.6, 136.2, 14.15, 165.39; **Anal.** Calcd for $C_{19}H_{29}N_3O_3Si$ requires C, 60.77; H, 7.78; N, 11.19; found: C, 60.40; H, 7.85; N, 11.25 %.

(4*R*, 5*S*)-5 -(*tert*-Butyldimethylsilyloxy)-6-phenylpipridine-2-one (51)

To a solution of (*E*)-α,β-unsaturated azidoester **45** (1.0 g, 2.66 mmol) in methanol (20 mL), was added 10% Pd/C (60 mg) and the mixture stirred under hydrogen (20 psi) atmosphere at 25 ^oC. The reaction mixture was stirred at 25 ^oC for 5 h, and the progress monitored by TLC. After completion of reaction, it was filtered through a Celite pad and washed with EtOAc (3 x 20 mL). The combined organic phase was concentrated under *vacuum*. The crude product thus obtained was refluxed in ethanol (20mL) for 4h. Ethanol was concentrated under *vacuum*. The crude product was purified by column chromatography on silica gel using ethyl acetate and pet. ether (4:6) as eluent to give TBS protected lactam **51** (0.431 g) as yellow gum.

Yield: (0.431 g) 85%; yellow colored gum; **[α]$_D$** +29.32 (*c* 0.5, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 700, 748, 1190, 1321, 1450, 1654, 2930, 3282; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ -0.60 (s, 3H), -0.21 (s, 3H), 0.76 (s, 9H), 1.99-2.07 (m, 1H), 2.40 (m, 2H), 2.65-2.83 (m, 1H),

4.02-4.05 (m, 1H), 4.60 (d, *J* = 2.7 Hz), 5.68 (brs, 1H), 7.29-7.36 (m, 5H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ -6.0, -5.4, 17.9, 25.7, 26.1, 28.4, 62.5, 67.3, 127.6, 127.9, 128.2, 138.9, 172.1; **Anal.** Calcd for $C_{17}H_{27}NO_2Si$ requires C, 66.84; H, 8.91; N, 4.59; found: C, 66.50; H, 9.02; N, 4.65%.

5-Hydroxy-6-phenylpiperidin-2-one (40)

To a stirred solution of TBS protected lactam **51** (0.610 g, 2 mmol) in THF was added a solution of tetrabutylammonium fluoride (TBAF) (0.528 g, 1M in THF, 2 mmol) at 0 °C and stirred for 6 h. The reaction mixture was quenched by the addition of water and the organic phase was separated. The aqueous layer was extracted with ethyl acetate (3x 50 mL) washed with water, brine and dried over anhydrous Na_2SO_4. The combined organic layer was concentrated under reduced pressure to give the crude lactam **40**, which was purified by column chromatography using petroleum ether: ethyl acetate (3: 7) to obtain lactam **40**.

Yield: (0.366 g) 96%; yellow colored gum; **$[\alpha]^{25}_D$** +32.48 (*c* 0.8, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 700, 748, 1196, 1321, 1452, 1654, 2930, 3282; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.97-2.04 (m, 1H), 2.11-2.17 (m, 1H), 2.35-2.41 (m, 1H), 2.68-2.75 (m, 1H), 4.06-4.07 (m, 1H), 4.66 (d, *J* = 3.0 Hz, 1H), 7.32-7.42 (m, 5H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 26.2, 26.6, 61.8, 66.2, 127.0, 127.6, 129.1, 137.8, 172.9; **Anal.** Calcd for $C_{11}H_{13}NO_2$ requires C, 69.09; H, 6.85; N, 7.32; found: C, 69.98; H, 6.02; N, 7.55%.

(2S, 3S)-1-(3-Hydroxy-2-phenyl piperidin-1-yl)-2,2-dimethyl propan-1-one (8)

To a solution of the lactam **40** (191 mg, 1 mmol) in dry THF (10 mL) at 25 ^oC was added $BH_3.SMe_2$ (152 mg, 2 mmol) drop-wise and the mixture was then refluxed for 6 h. After the completion of the reaction, the solvent was removed under reduced pressure and the

residue was extracted with ethyl acetate to give the corresponding amino alcohol. Without purification, amino alcohol was dissolved in CH_2Cl_2 (5 mL) and Et_3N (2 mmol) followed by catalytic amount of DMAP were added. After stirring for 5 min at 0 ^oC, $(Boc)_2O$ (1 mmol) was added drop-wise and the reaction mixture was allowed to stir for another three hours. After the completion of the reaction, it was extracted with ethyl acetate, washed with water, brine and dried over anhydrous Na_2SO_4 to get crude product. Chromatographic purification of the crude product using petroleum ether: ethyl acetate gave the pure **8** as viscous liquid.

Yield: (202 mg) 73% (over two steps); viscous liquid; **$[\alpha]^{25}_D$** +37.80 (*c* 1.0, $CHCl_3$) {lit.[7] $[\alpha]_D^{25}$ +38.3 (*c* 1.92, $CHCl_3$)}; **IR** ($CHCl_3$, cm^{-1}): 756, 851, 876, 984, 1137, 1168, 1326, 1365, 1417, 1495, 1602, 1675, 2955, 3015, 3447; **^{1}H- NMR** (200 MHz, $CDCl_3$): δ 1.41 (s, 9H), 1.55–2.01 (m, 5H), 2.74–2.89 (ddd, *J* = 3.2, 9.7, 12.9 Hz, 1H), 4.45–4.49 (m, 1H), 4.0–4.09 (m, 1H), 5.32 (m, 1H), 7.13–7.35 (m, 5H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 23.98, 25.92, 28.36, 39.90, 60.24, 67.48, 80.11, 126.86, 126.89, 138.15, 156.70; **Anal.** Calcd for $C_{16}H_{23}NO_3$ requires C, 69.29; H, 8.36; N, 5.05; found: C, 69.43; H, 8.13; N, 4.92%.

(2*S*,3*S*)-1-(*tert*-Butyoxycarbonyl)-2-phenyl-3-[(3,5-bis(trifluoromethyl)benzyloxy] piperidine (52)

To a stirred solution of **8** (99 mg. 0.36 mmol) in dry DMF (1 mL) at 0 ^oC was added sodium hydride (10 mg, 60% dispersion in mineral oil, and 0.43 mmol) in one portion. After 5 min of stirring at the same temperature, 3,5-bis(trifluoromethyl)benzyl bromide (110 mg, 0.36 mmol) in dry DMF (1 mL) was added *via* syringe. The reaction mixture was stirred for 12 h at 80 ^oC and it was then quenched with water (3 mL) and extracted

with Et_2O (5 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography on silica gel column using petroleum ether: ethyl acetate (7: 3) to provide **52** as colorless oil.

Yield: (0.14 g) 78%; colorless oil; **[α]**$_D^{25}$ +30.90 (*c* 1.0, $CHCl_3$) {lit.[7] $[\alpha]_D^{25}$ +30.4 (*c* 1.55, $CHCl_3$)}; **IR** (neat, cm^{-1}): 665, 875, 1172, 1253, 1345, 1381, 1644, 2945; **^{1}H-NMR** ($CDCl_3$, 200 MHz): δ 1.42 (s, 9H), 1.32-1.66 (m, 2H), 1.78-2.12 (m, 2H), 2.76 (ddd, *J* = 11.2, 9.8, 4.6 Hz, 1H), 3.79-3.98 (m, 2H), 4.66 (d, *J* = 11.4 Hz, 1H), 4.74 (d, *J* = 12.2 Hz, 1H), 5.67 (d, *J* = 4.6 Hz, 1H), 7.22-7.38 (m, 3H), 7.42-7.52 (m, 2H), 7.66 (s, 2H), 7.78 (s, 1H); **^{13}C-NMR** ($CDCl_3$, 50 MHz): δ 20.2, 25.3, 26.3, 27.2, 44.4, 63.2, 71.2, 77.0, 120.2, 123.1, 126.7, 127.3, 127.8, 132.4, 141.2, 142.4, 159.0; **Anal.** Calcd for $C_{25}H_{27}F_6NO_3$ requires C, 59.64; H, 5.41; N, 2.78; found: C, 59.61; H, 5.38; N, 2.76%.

Preparation of (+)-L-733,060 (1)

To an ice-cooled solution of **52** (100 mg, 0.2 mmol) in dry CH_2Cl_2 (4 mL) was added trifluoroacetic acid (228 mg, 2 mmol). The reaction mixture was stirred at room temperature for 12 h and then quenched with saturated $NaHCO_3$ and extracted with dichloromethane (3x5 mL). The combined organic layers were washed with brine and dried over anhyd. Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using CH_3OH: $CHCl_3$ (1: 9) as eluent to give pure **1** as colorless viscous liquid.

Yield: (79 mg) 89%; colorless viscous liquid; **[α]**$_D^{25}$ +35.2 (*c* 0.66, $CHCl_3$) {lit.[7] $[\alpha]_D^{25}$ +34.29 (*c* 1.32, $CHCl_3$)};)}; **IR** (neat, cm^{-1}): 663, 877, 1123, 1170, 1277, 1370, 2950; **^{1}H-NMR** ($CDCl_3$, 200 MHz) : δ 1.42-204 (m, 3H), 2.22 (br d, *J* = 13.0 Hz, 1H), 2.62 (s,

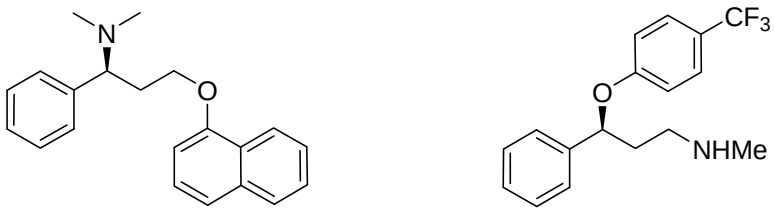
1H), 2.76-2.81 (m,1H), 3.23-3.38 (m, 1H), 3.66 (s, 1H), 3.84 (br s, 1H), 4.12 (d, J = 12.0 Hz, 1H), 4.54 (d, J = 12.2 Hz, 1H), 7.20-7.50 (m, 7H), 7.78 (s, 1H); **^{13}C-NMR** ($CDCl_3$, 50 MHz): 20.6, 27.5, 47.1, 64.0, 70.5, 77.2, 120.9, 124.1, 127.7, 128.5, 128.7, 131.2, 141.6, 142.3; **Anal.** Calcd for $C_{20}H_{19}F_6NO_3$ requires C, 59.55; H, 4.75; N, 3.47; found. C, 59.52; H, 4.81; N, 3.56%.

Section II

Enantioselective synthesis of (*S*)-dapoxetine *via* Sharpless asymmetric epoxidation

2.2.1. Introduction

Discovery of (*S*)-dapoxetine (**53**) is credited to David T. Wong[19] of *Eli Lilly and company*. (*S*)-Dapoxetine **53** is found to be a potent selective serotonin re-uptake inhibitor (SSRIs) but is slightly different from the SSRIs (such as (*S*)-Fluoxetine, (-)-Paroxetine and Sertraline) widely prescribed for depression and other psychiatric disorders as bulimia or anxiety. It is very much structurally related to Fluoxetine **54** (Prozac) with antidepressant activity (**Fig 9**).



53, (*S*)-Dapoxetine **54**, (*S*)-Fluoxetine

Fig. 9: Structures of (*S*)-dapoxetine and (*S*)-Fluoxetine

Dapoxetine is the D-enantiomer of LY 243917 and found to be 3.5 times more potent as a serotonin reuptake inhibitor than the L-enantiomer of LY 243917. It would make it join the ranks of sildenafil (Viagra®), tadalafil (Cialis®), vardenafil (Levittra®), the erectile dysfunction drugs and cabergoline (Dostinex ®) as a drug invented to improve male sexual health.[20]

2.2.2 Dapoxetine and Pharmacology

Delay in ejaculation is one of the side effects of serotonine-specific reuptake inhibitors (SSRIs) and TCAs that make them useful in the treatment of premature ejaculation (PE)

with physiological rather than physical etiologies.[21] Although it has been found in the literature that PE is more common among men with higher levels of education because of their interest in the sexual satisfaction of their partner.[22] SSRI antidepressants have been shown to delay ejaculation in men treated for different psychiatry disorders. These are considered to be the most effective treatment currently available for PE. The use of these drugs that require chronic therapy is limited by the neuropsychiatric side effects. New SSRI drugs specifically targeted to treat premature ejaculation (e.g. dapoxetine) can be taken on as needed basis and have recently shown positive results in large phase III studies. Nevertheless dapoxetine is not yet approved by any regulatory authority around the world. There is a speculation that some of the associated effects are caused by lowered libido and blood pressure as well as lowered anxiety levels. Other pharmaceutical products known to delay male orgasm are; opioids, cocaine, and diphenhydramine.[23]**2.2.3.**

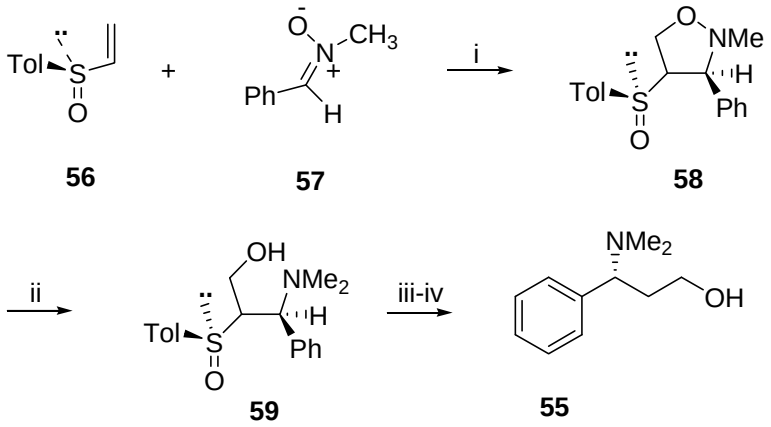
Review of Literature

Various asymmetric syntheses of (*S*)-dapoxetine (**53)** and (*R*) and (*S*)-3-amino-3-phenyl-1-propanol have been documented in the literature.[24] Some of the interesting and important synthetic routes to dapoxetine are described below.

Koizumi's approach (1982)[25]

Koizumi *et al.* have reported the synthesis of (*R*)-amino alcohol **55** (intermediate for (R)-dapoxetine) starting from optically active (*R*)-(+)-*p*-tolyl vinyl sulfoxide **56** which on 1,3-dipolar cycloaddition with nitrones **57** in refluxing benzene gave sulfinyl isoxazolidines **58** in 40% yield. The isoxazolidines **58** was then converted to (*R*)-amino alcohol **55** by using sequence of reactions such as *N*-methylation, reductive cleavage of N-O bond

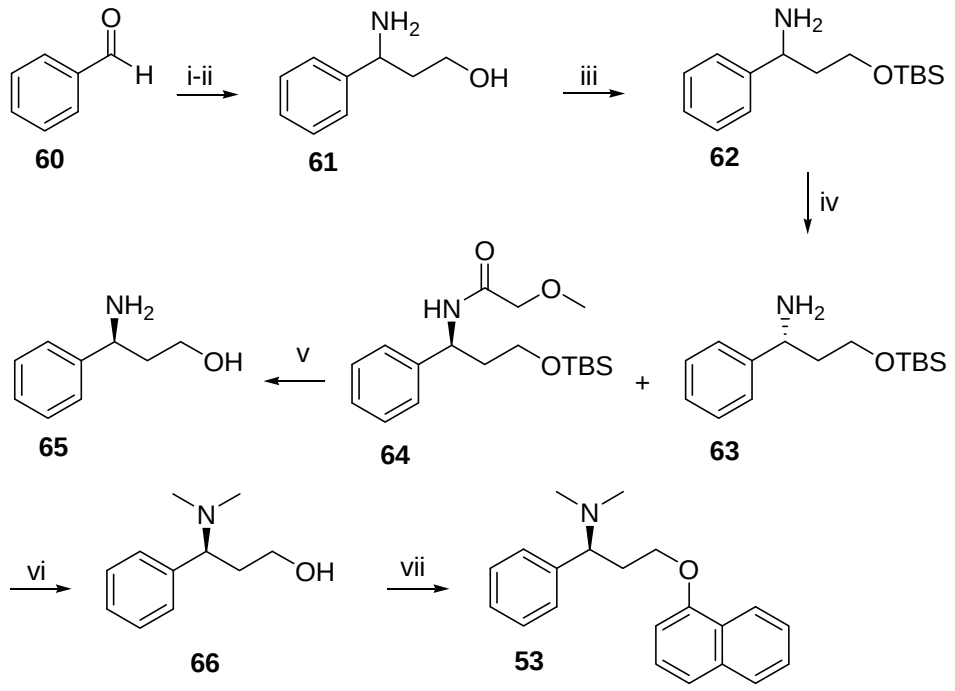
followed by desulfurization (**Scheme 11**).



Scheme 11: i) benzene, reflux, 20 h, 40%; ii) (a) MeI; (b) Zn-AcOH, rt; iii) $TiCl_4$-AcOH-AcONa, rt; iv) Raney Ni-EtOH, rt.

Gotor approach (2006)[26]

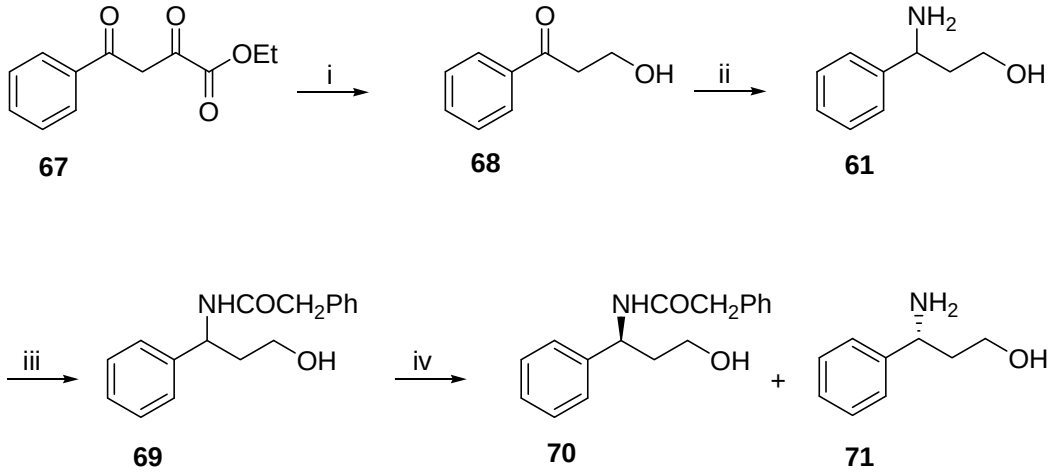
This approach describes the synthesis of (*S*)-dapoxetine starting from benzaldehyde **60** which on reaction with malonic acid, ammonium acetate in refluxing ethanol followed by the reduction with $LiAlH_4$ in THF at 65 °C to give amino alcohol **61** in 77% yield. The alcohol group was protected by *tert*-butyl dimethyl silyl chloride (TBDMSCl) using imidazole in CH_2Cl_2 which gave amine **62** in 95% yield. The amine **62** on enzymatic resolution using ethyl methoxyacetate as acyl donor, *antarctica lipase* type A as enzyme in TBME solvent after 47 h at 30 °C gave **64** in 93% ee along with the hydrolyzed intermediate **63**. The intermediate **64** on treatment with 6M HCl at 50 °C gave amino alcohol **65** in 84% yield. The primary amine function in **65** was converted into tertiary amine **66** in 83% yield using formaldehyde and formic acid as hydrogen source. This on reaction with 1-napthol, triphenyl phosphine, DEAD in THF gave (*S*)-dapoxetine **53** in good yield with 93% ee (**Scheme 12**).



Scheme 12: i) $CH_2(CO_2H)_2$, NH_4OAc, EtOH, 80 ºC,12 h, 68%; ii) $LiAlH_4$, THF, 65 ºC, 3 h, 77%; iii) TBDMSCl, imid., $CH_2Cl_2$25 ºC, 95%; iv) Acyl donor, enzyme, solvent, 30 ºC, 250 rpm; v) HCl 6M, 50 ºC, 84%; vi) $(CH_2O)n$, HCO_2H, 25 ºC, 83%; vii) PPh_3, DEAD, 1-napthol, THF, 25 ºC, 72%.

Fadnavis approach (2006)[27]

Fadnavis *et al.* have achieved the synthesis of (*R*) and (*S*)-3-amino-3-phenyl-1-propanol,

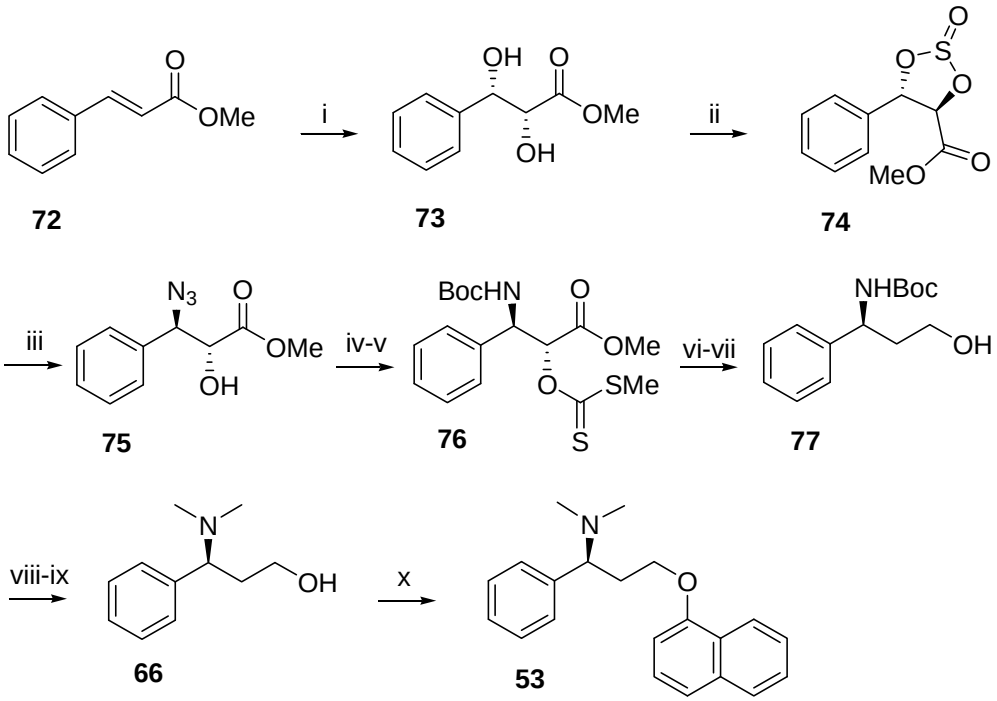


Scheme 13: i) Baker's yeast, diisopropyl ether, 48 h, 90%; ii) NH_4OAc, $NaBH_3CN$, EtOH, 25 ºC, 36 h, 65%. iii) $PhCH_2COCl$, NaOH, 25 ºC, 4 h, 80%. iv) *penicillin G acylase*, 4 h, water.

a prominent intermediate of (*S*)-dapoxetine, starting from ethyl 2,4-dioxo-4-phenylbutyrate **67** which was converted to 3-oxo-3-phenyl-1-propanol **68** in 90% yield by reaction with baker's yeast. Reductive amination with sodium cyanoborohydride in the presence of ammonium acetate gave the racemic 3-amino-3-phenyl-1-propanol **61** in 65% yield. The enzymatic resolution of the corresponding *N*-phenyl acetyl derivative **69** with *penicillin G acylase,* immobilized on an epoxy resin gave (*S*)-amide **70** and (*R*)-amino alcohol **71** in high enantiomeric purity (99% ee) (**Scheme 13**).

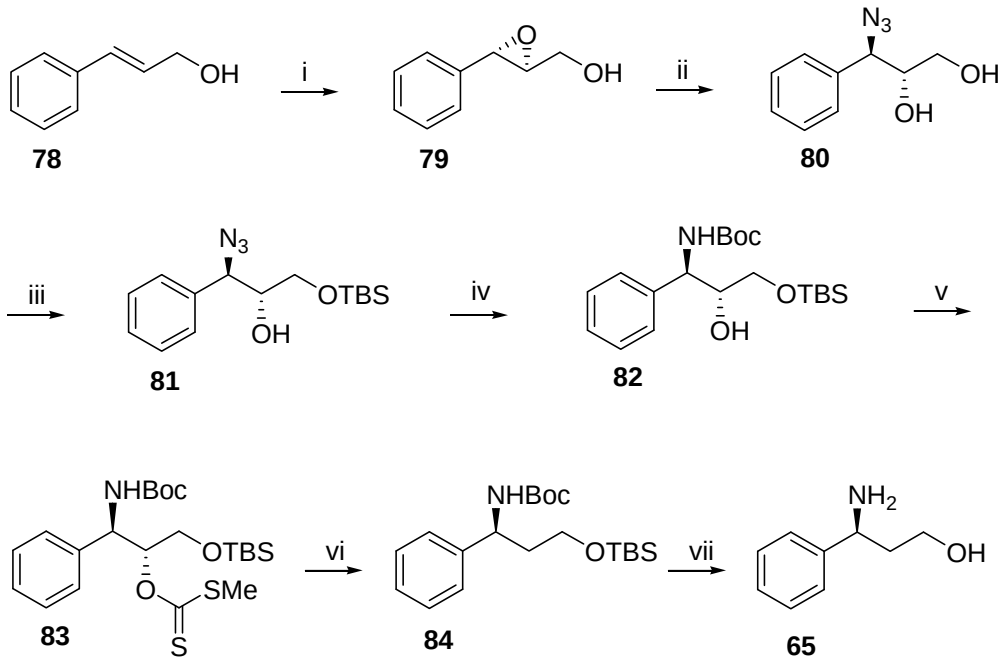
Srinivasan approach (2007, 2008)[28,29]

Srinivasan *et al*. have achived the synthesis of (*S*)-dapoxetine using Sharpless asymmetric dihydroxylation of *trans*-cinnamyl ester, **72** to get diol **73** in 80% yield with 99% ee (**Scheme 14**).



Scheme 14: (i) $(DHQ)_2PHAL$ (5 mol %), OsO_4, NMO, *tert*-BuOH, , 25 ºC, 16 h, 80%; (ii) CH_2Cl_2, Et_3N, $SOCl_2$, 0 °C to , 25 ºC, 1 h; (iii) NaN_3 (5 equiv), DMF, , 25 ºC, 48 h, 85%; (iv) H_2/Pd-C, EtOAc, , 25 ºC, 24 h, $(Boc)_2O$, Et_3N; (v) MeI, CS_2, MsCl, Et_3N, CH_2Cl_2, 0 °C to , 25 ºC, 12 h; (vi) n-Bu_3SnH, AIBN, toluene, reflux, 75% after two steps; (vii) $LiAlH_4$, THF, , 25 ºC, 12 h; (viii) TFA, CH_2Cl_2, 25 ºC; (ix) HCHO, HCO_2H; (x) Ph_3P, DEAD, 1-naphthol, THF, 25 ºC.

Srinivasan *et al*. have also achieved the synthesis of (*S*)-amino alcohol **65** using Sharpless asymmetric epoxidation of cinnamyl alcohol (**78**) to get epoxy alcohol **79** in 98%ee. Regioselective opening of epoxide with NaN_3 resulted in *trans* azido diol **80**, which was converted to (S)-amino alcohol **65** *via* deoxygenation of xanthate **83** followed by deprotection (**Scheme 15**).

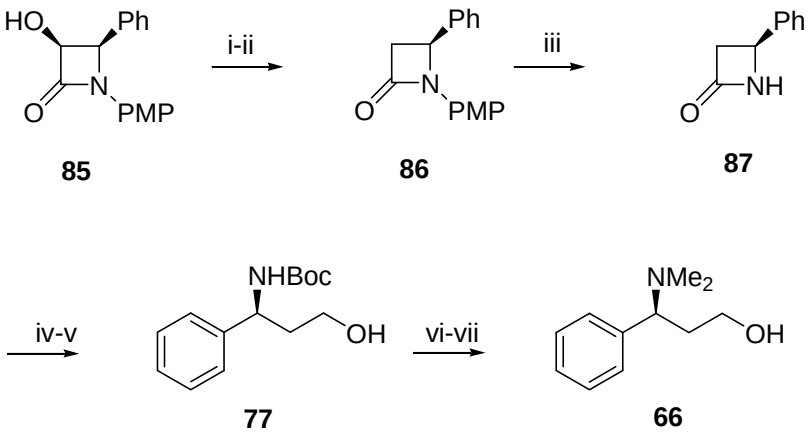


Scheme 15: (i) (*R*,*R*)-(+)-DET, Ti(O-*i*Pr)$_4$, TBHP, MS 4 Å, CH_2Cl_2, −20 °C, 3 h, 88%; (ii) NaN_3, MeOH:H_2O (8:1), 65 °C, 5 h, 97%; (iii) TBSCl, imid., 0– 25 °C, 5 h, 96%; (iv) 10% Pd/C, H_2, $(Boc)_2O$, EtOAc, 25 °C, 12 h, 88%; (v) CS_2, NaH, MeI, THF, 0– 25 °C, 84%; (vi) n-Bu_3SnH, AIBN, 0– 25 °C, 84%. (vii) TFA, CH_2Cl_2, 0 °C, 5 h, 81%.

Deshmukh approach (2009)[30]

Deshmukh *et al.* have achieved the synthesis of (S)-amino alcohol **66** from optically active hydroxyl β-lactam **85,** which was converted to its xanthate derivatives [NaH, CS_2 , and methyl iodide] followed by reduction with n-Bu_3SnH, and AIBN to furnish PMP protected β-lactam **86.** The oxidative removal of PMP using CAN to give β-lactam **87** in

60% yield. N-Boc protection of amine functionality in **87** with $(Boc)_2O$ followed by reduction with $LiAlH_4$ gave Boc protected amino alcohol **77**, which was converted to amine **66** *via* standard reaction sequences (**Scheme 16**).



85 **86** **87** **77** **66**

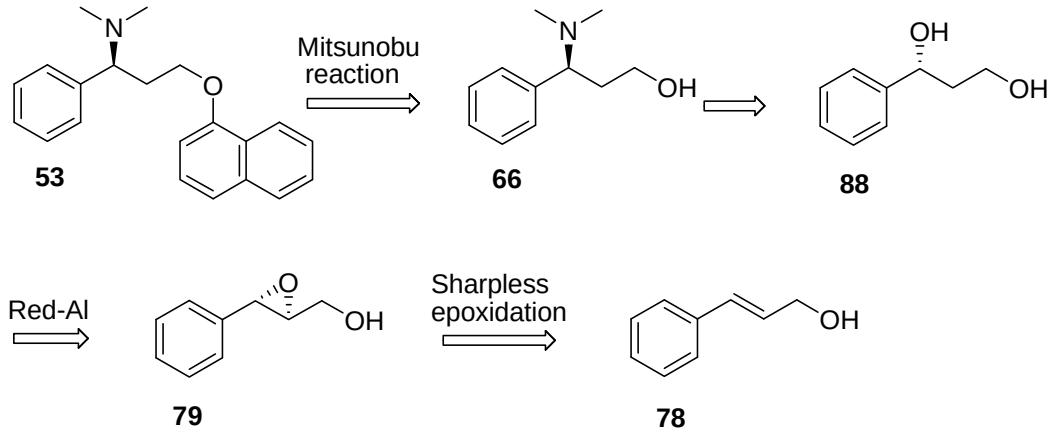
Scheme 16: (i) NaH, CS_2, CH_3I, THF, 0- 25 °C, 6 h, 75%; (ii) Bu_3SnH, AIBN, toluene, reflux, 3-4 h, 92%; (iii) CAN, CH_3CN/ H_2O, 0 °C, 1 h, 60%; (iv) $(Boc)_2O$, DMAP, CH_2Cl_2, 0- 25 ºC, 6 h, 70%; (v) $LiAlH_4$, THF, 0- 25 ºC, 4 h, 80%; (vi) TFA, CH_2Cl_2, 0- 25 ºC, 2 h, 89%; (vii) HCHO, $NaBH_3CN$, CH_3CO_2H, CH_3CN, 25 ºC, 2 h, 80%.

2.2.4. Present Work

2.2.4.1. Objective

As can be seen from the above discussion, literature methods for the synthesis of (*S*)-dapoxetine (**53**), employ chiral starting materials and expensive reagents, involve longer reaction sequences or require radical reaction conditions. This section describes a short synthesis of (*S*)-dapoxetine (**53**), using Sharpless asymmetric epoxidation[31] and regioselective reductive ring opening[32] of chiral epoxy alcohol **79** as key reactions. The retrosynthetic analysis for the synthesis of (*S*)-dapoxetine (**53**) is shown in (**Scheme 17)**. Retrosynthetic analysis of (*S*)-dapoxetine (**53**) shows that amino alcohol **66** emerges as the key intermediate, which could be obtained from 1,3-diol **88** by azide displacement

and reductive N-alkylation. The precursor **88** can be prepared from epoxy alcohol **79**, which in turn could be readily obtained from cinnamyl alcohol **78** by the Sharpless asymmetric epoxidation protocol.



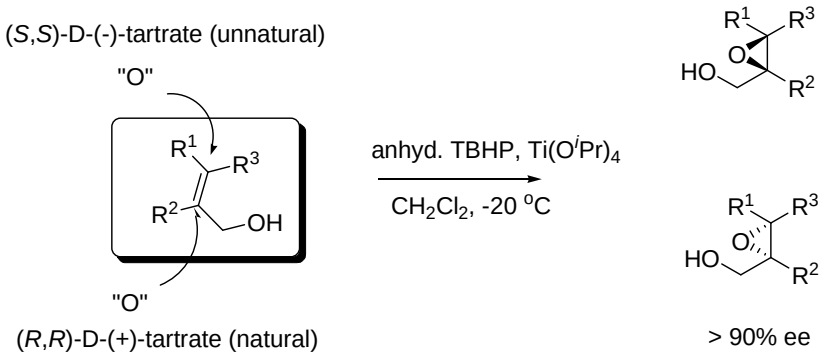
Scheme 17: The retrosynthesis of (*S*)-dapoxetine (**53**)

2.2.4.2 Sharpless asymmetric epoxidation

Asymmetric epoxidation of allylic alcohols is one of the leading areas of investigation in synthetic organic chemistry, mainly due to the fact that very high enantioselective induction for a wide range of substrates is possible using several classes of reagents. Today, the most successful asymmetric epoxidation reaction is the titanate-mediated epoxidation of allylic alcohols, or Sharpless epoxidation,[31] which enables the achievement of an enantiomeric excess of more than 90% in most cases. The Sharpless epoxidation is a popular laboratory and industrial process due to its both enantioselective and catalytic nature. The reaction mixture includes a titanium tetraalkoxide, a chiral tartrate diester, an allylic alcohol substrate, and an alkyl hydroperoxide as the oxidant. The consistency of the reaction is remarkable, excellent enantiofacial selectivity is realized for allylic alcohol substrates of widely varying structure. In addition to being

able to asymmetrically oxidize prochiral substrates to products of predictable absolute configuration, the reaction is extremely sensitive to preexisting chirality in selected positions of the allylic alcohols. For example, kinetic resolution of racemic secondary allylic alcohols is very efficient since it can be used for generating chiral allylic alcohols as well as *trans*-epoxyalcohols in high enantiomeric excess.

Selection of the proper chirality in the starting tartrate esters and proper geometry of the allylic alcohols allows one to establish both the chirality and relative configuration of the product (**Scheme 18**).



Scheme 18: The Sharpless epoxidation reaction

Since its discovery in 1980, the Sharpless expoxidation of allylic alcohols has become a benchmark classic method in asymmetric synthesis. One factor that simplifies the standard epoxidation reaction is that the active chiral catalyst is generated *in situ*, which means that the pre-preparation of the active catalyst is not required. It is believed that the species containing equal moles of Ti and tartrate is the most active catalyst. It promotes the reaction much faster than Ti(IV) tetraalkoxide alone and exhibits selective ligand-accelerated reaction.[33]

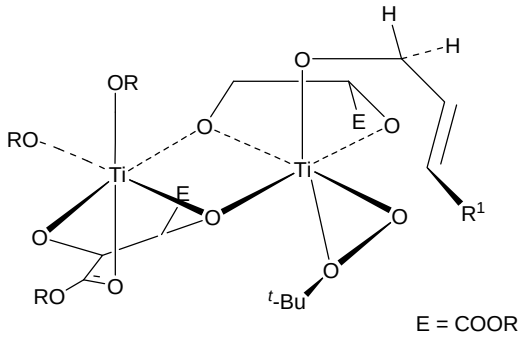
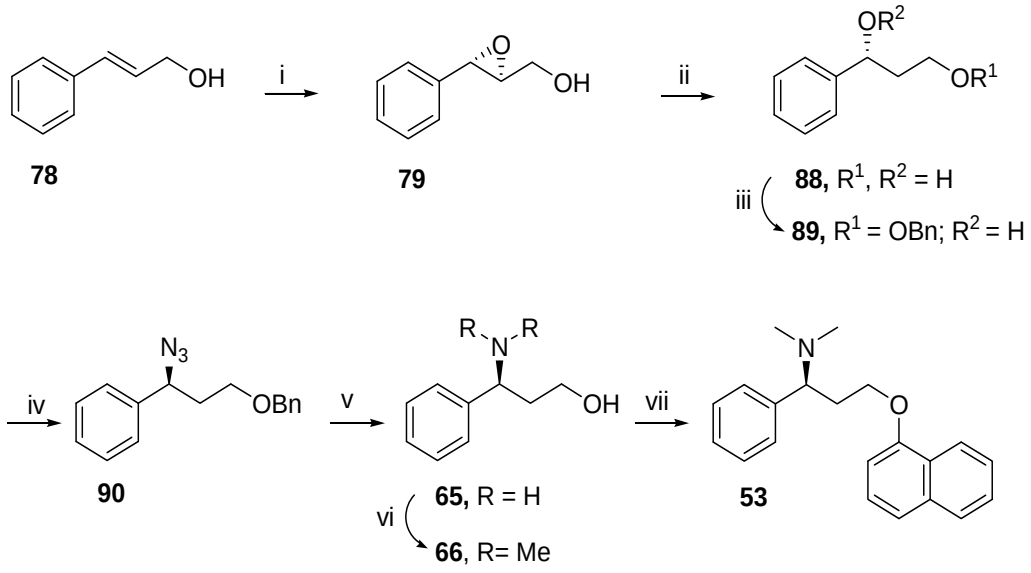


Fig. 10: Structure of dinuclear Ti-tartrate complex

Sharpless suggested that epoxidation was catalyzed by a single Ti center in a dimeric complex with a C_2 symmetric axis (**Fig. 10**).[34]

2.2.5. Results and Discussion

The present synthetic route employed for the synthesis of (*S*)-dapoxetine (**53**) is shown in **Scheme 19**.



Scheme 19 : (i) (+)-Diethyl tartarate, $Ti(O^iPr)_4$, anhyd. TBHP, CH_2Cl_2, -33 °C, 83%; (ii) Red Al®, DME, 0 -25 °C, 85%; (iii) NaH, benzyl bromide, DMF, -70 °C, 80%. (iv) a) MsCl, Et_3N, CH_2Cl_2, 0 °C, 1h ; (b) NaN_3, DMF, 60 °C, 5 h, 98%; (v) 10% Pd/C, H_2, MeOH, AcOH, 25 °C ; (vi) HCHO, HCO_2H, reflux, 8 h, 80%; (vii) PPh_3, DEAD, 1-naphthol, THF, 25 °C, 71%.

Cinnamyl alcohol **78** was subjected to Sharpless asymmetric epoxidation using (+)-diethyl tartarate, [(+)-DET] to furnish the corresponding chiral epoxide **79** as a yellow crystal {m.p. : 53.5–54 °C and $[\alpha]^{25}_{D}$ = -49.4 (*c* 1, $CHCl_3$)} in 83% yield with 98% ee. Its optical purity was determined from ^{1}H NMR analysis of the corresponding Mosher's ester **79b** (**Fig. 11**).

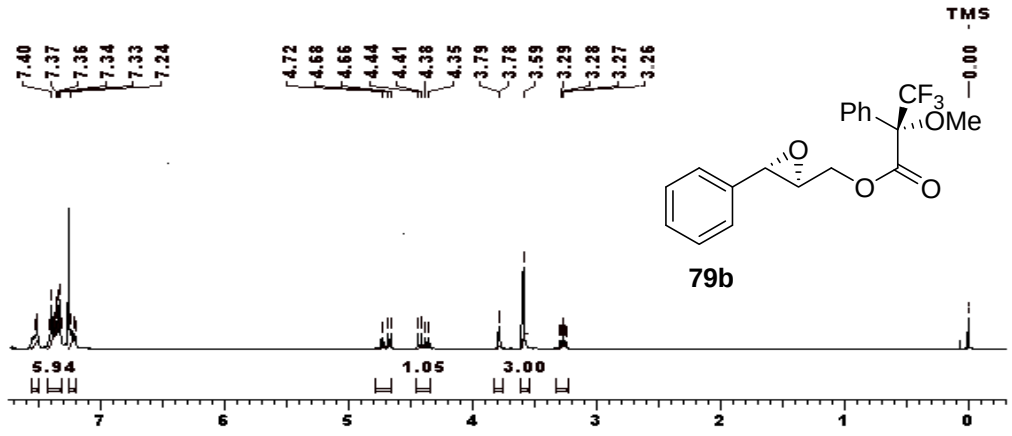


Fig. 12: ^{1}H NMR spectra of Mosher's ester **79b**

The ^{1}H NMR spectrum of **79b** showed. characteristic proton signals at δ 3.90 (d, *J* = 2.0 Hz, 1H) and 3.18-3.22 (m, 1H) for the epoxide protons. Its ^{13}C NMR spectrum displayed typical peaks at δ 55.5 and 62.4 corresponding to methine carbons of epoxide moiety.

Our next task was to make 1,3-diol **88** from epoxide **79**. In order to achieve this transformation with high regioselectivity and yield, a strategy involving Red-Al®, originally published by Sharpless *et al.* was undertaken.[32] Thus, epoxide **79** was treated with Red-Al® in DME at 0 -25 ^{o}C to give 1,3-diol **88** in 85% yield. Its ^{1}H NMR spectrum showed typical signals at δ 3.82 (t, 2H) and δ 4.92 (dd, 1H) due to methylene (-CH_2OH) and methine (-CHOH) protons respectively. Its ^{13}C NMR spectrum displayed a typical

carbon signals at δ 60.5 and 73.1 due to methylene and methine carbons attached to hydroxyl group (**Fig. 12**).

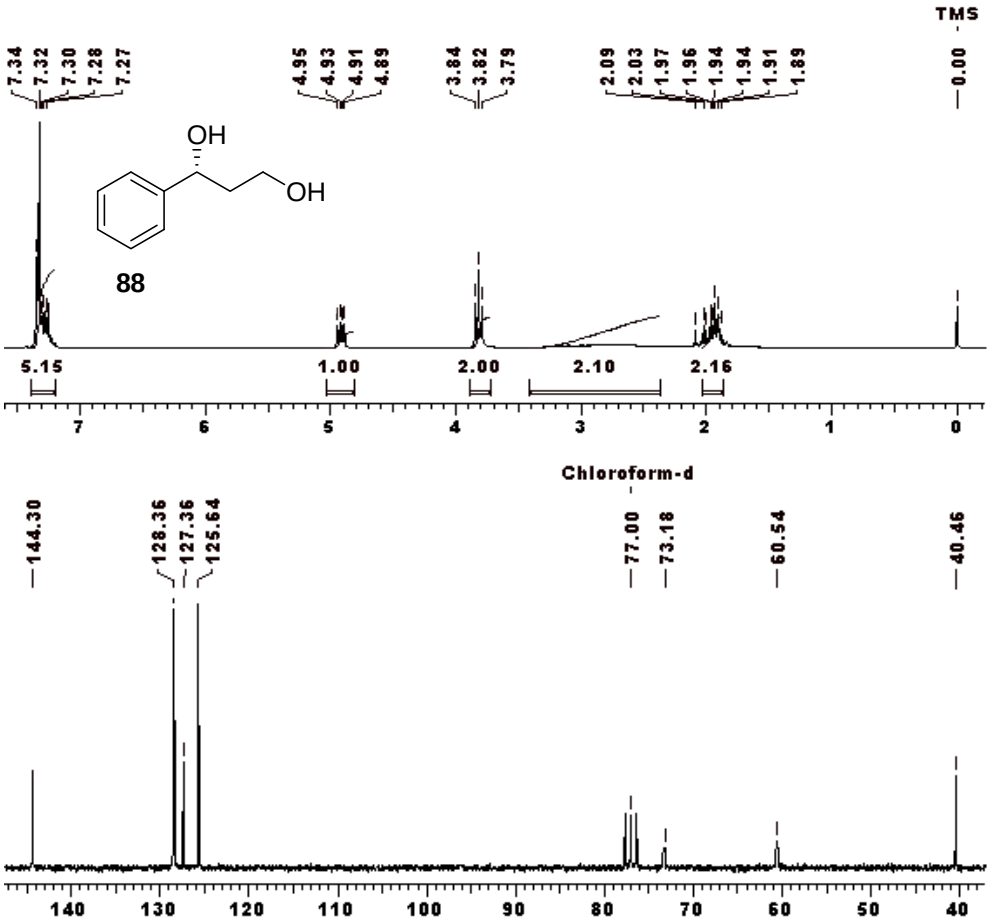


Fig. 12: ^{1}H and ^{13}C NMR spectra of diol **88**

1,3-Diol **88** was then selectively monobenzylated[35] (BnBr, NaH, DMF at -70 ^{o}C) to give the monobenzylated 1,3-diol **89**. Its ^{1}H NMR spectrum showed a typical singlet at δ 4.45 for the benzyloxy methylene proton ($PhCH_2O$-) while its ^{13}C NMR spectrum displayed characteristic signals at δ 68.44 and 73.28 for alkoxy and benzyloxy ($PhCH_2$-O-CH_2-) methylene carbons respectively (**Fig. 13**). The nucleophilic displacement of mesylate, obtained from alcohol **89**, with NaN_3 in DMF at 80 ^{o}C yielded the corresponding azide **90** in 98% yield.

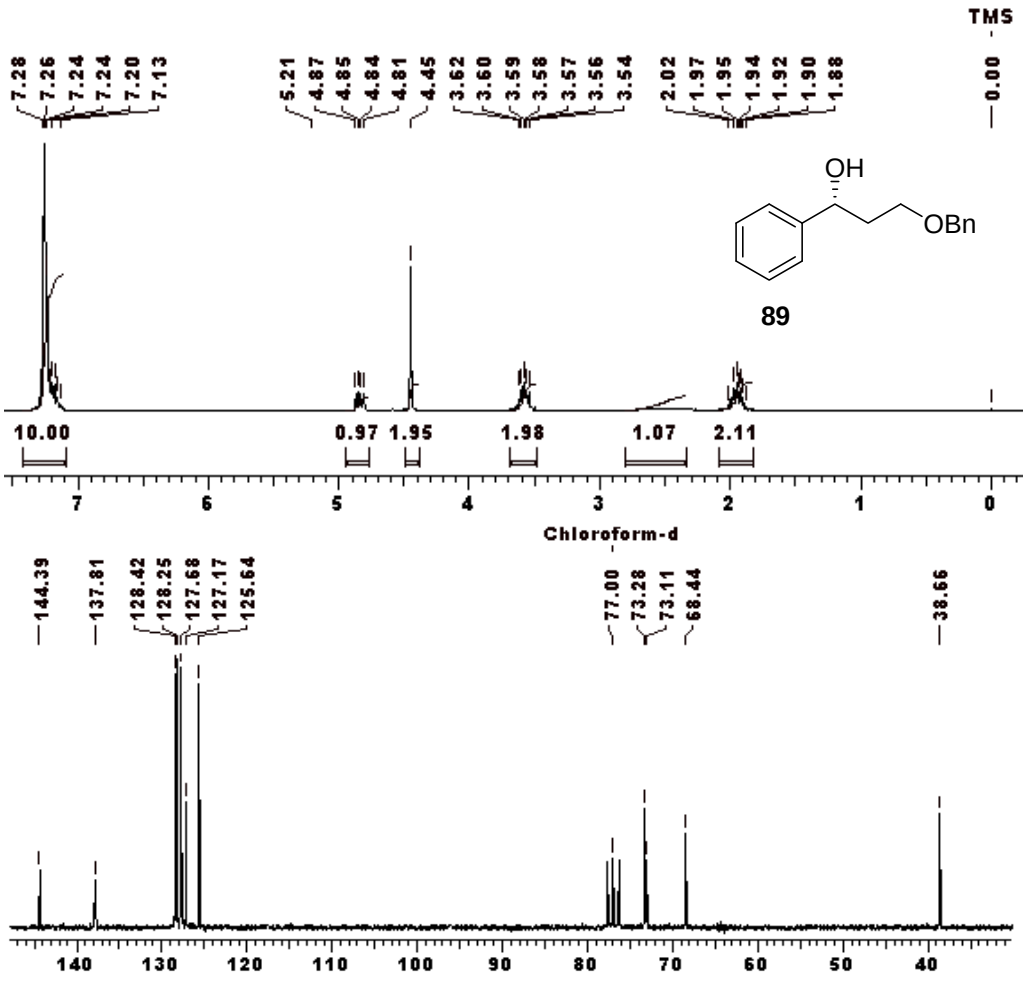


Fig. 13: ^{1}H and ^{13}C NMR spectra of monobenzylated 1,3-diol **89**

Its ^{1}H NMR spectrum showed a typical signal at δ 4.70 (dd, J = 6.6, 8.1 Hz) due to methine proton (Ph-CH-N_3) while its ^{13}C NMR spectrum displayed a characteristic signal at δ 63.10 for carbon attached to azido group (Ph-CH-N_3) (**Fig. 14**). The presence of azide group was further evidenced by the characteristic absorption band exhibited at 2106 cm^{-1} in its IR spectrum. Reduction of azide group with simultaneous deprotection of OBn was achieved by using H_2 (60 psi) and 10% Pd/C to give amino alcohol **65**. The presence of primary amine group was confirmed by the two characteristic absorption bands at 3387 and 3348 cm^{-1} in its IR spectrum. Subsequently the primary amine **65** was reductive

alkylated using Clarke-Eschweiler protocol (formaldehyde, excess of formic acid and reflux) to give **66** in 85% yield.[36]

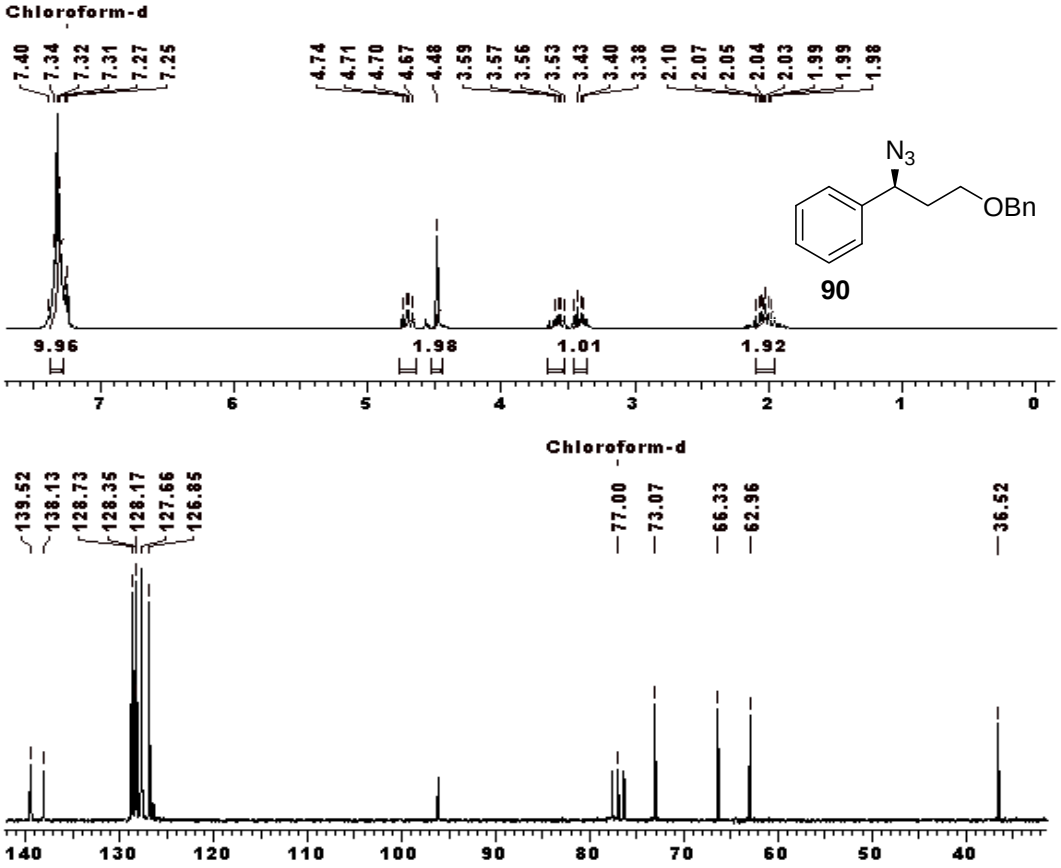


Fig. 14: ^{1}H and ^{13}C NMR spectra of azide **90**

The ^{1}H NMR spectrum of **66** showed a singlet of six protons at δ 2.21 corresponding to methyl groups. The ^{13}C NMR spectrum of **66** showed a signal at δ 32.0 for two methyl groups attached to nitrogen atom (**Fig. 15**). The final reaction in the sequence was the coupling between the hydroxyl group of **66** with α-naphthol. We ultimately opted for Mitsunobu reaction[37] of nucleophilic substitution conditions, with α-naphthol in the presence of DEAD, PPh_3 and THF as solvent that produced (+)-(*S*)-dapoxetine **53** in 72% yield, {$[\alpha]^{25}_{D}$ +64.6 (*c* 1.0, $CHCl_3$); [lit.[28] $[\alpha]^{25}_{D}$ +64.2 (*c* 0.3, $CHCl_3$]}.

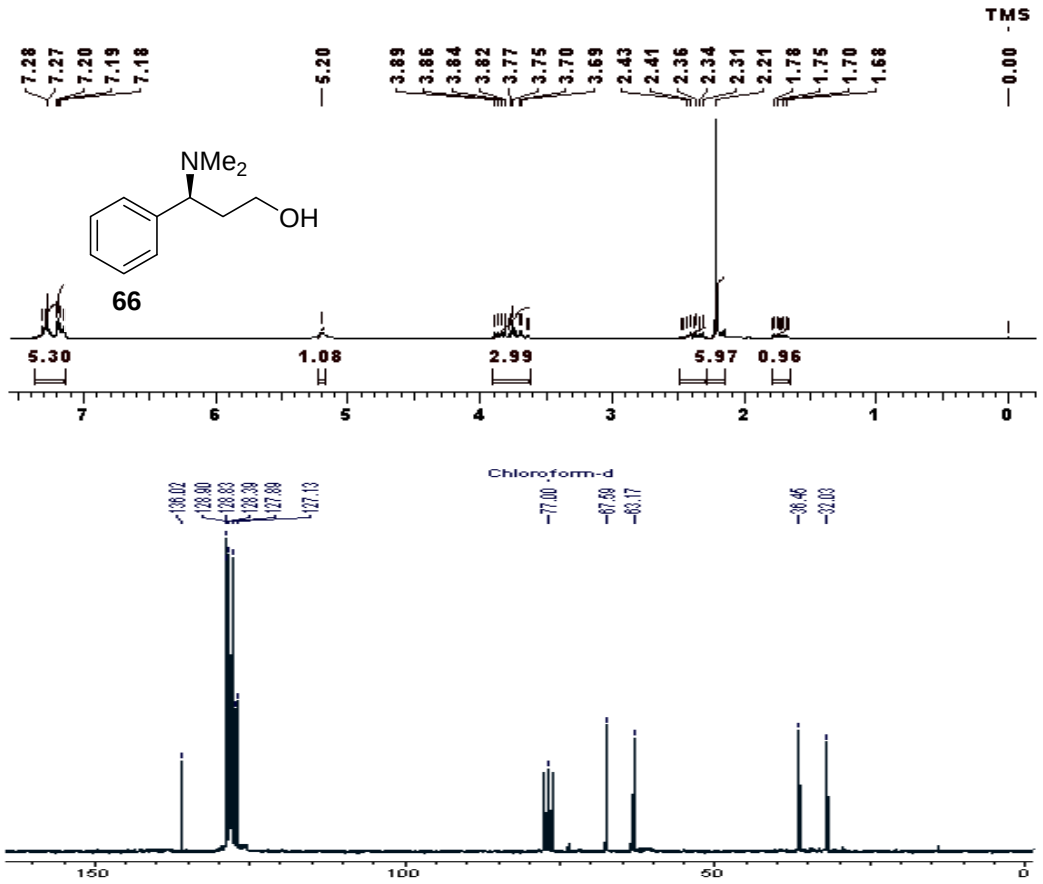


Fig. 15: ^{1}H and ^{13}C NMR spectra of

The ^{1}H, ^{13}C NMR and other spectral data of (+)-(*S*)-dapoxetine **53** were in complete agreement with the reported values (**Fig. 16**).[28]

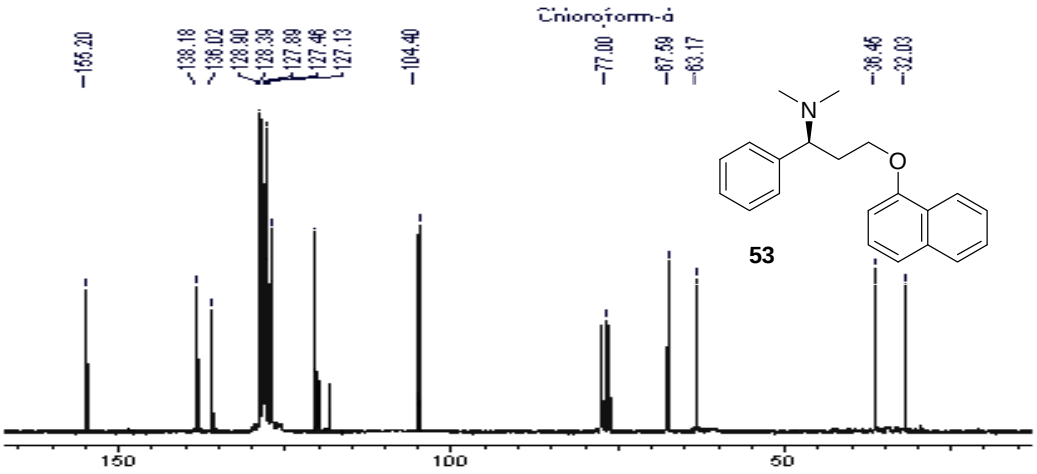


Fig. 16: ^{13}C NMR spectra of **53**

2.2.6 Conclusion

We have achieved, a short synthesis of (*S*)-dapoxetine with 98% ee, using Sharpless asymmetric epoxidation and regioselective reductive ring opening of chiral epoxy alcohol as a key reactions.

2.2.7. Experimental Section

(2*S*,3*S*)-(3-Phenyl-oxiranyl)methanol (79)

To a stirred solution of (*R*,*R*)-(+)-diethyl tartarate (0.80 g, 3.91 mmol) in CH_2C1_2 (45 mL) at -20 °C, (2.8 g) activated powdered 4A˚ molecular sieves, Ti(O-*i*Pr)$_4$ (0.78 mL, 0.74 g, 2.61 mmol) and 3 M solution of TBHP in toluene (34.78 mL, 104.34 mmol) were added sequentially. The mixture was allowed to stir at -20 °C for 1 h and then a solution of freshly distilled (E)-3-phenyl-2-propenol (7.0 g, 52.17 mmol) in 10 mL of CH_2C1_2 was added drop wise over 30 min. After 3 h at -20 °C, the reaction was quenched at -20 °C with 10% aqueous solution of NaOH saturated with NaCl (4.2 mL). After diethyl ether (60 mL) was added, the cold bath was allowed to warm to 10 °C, stirring was maintained at 10 °C while $MgSO_4$ (5 g) and Celite (500 mg) were added. After another 15 min of stirring, the mixture was allowed to settle and clear solution was filtered through a pad of celite and washed with diethyl ether. Azeotropic removal of TBHP with toluene at a reduced pressure and subjection to high vacuum gave **79** as yellow oil. Recrystallization from petroleum ether/diethyl ether gave yellow crystals of **79** (6.5 g, 83%, >98% ee determined by spectroscopic analysis of the ester derived from (+)-MTPA chloride).

Yield: 83% (5.6 g); yellow crystals mp = 53.5–54 °C; **$[\alpha]^{25}_D$**: -49.4 (*c* 1, $CHCl_3$) {lit.[32] $[\alpha]_D^{25}$ -49.6, (*c* 2.40, $CHCl_3$)}; **IR** ($CHCl_3$, cm^{-1}): 758, 840, 863, 881, 1027, 1068, 1108, 1256, 1392, 1462, 1606, 2871, 2927, 3017, 3428; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.77

(br s, 1H), 3.18–3.32 (m, 1H), 3.70–3.81 (m, 1H), 3.90 (d, *J* = 2.1 Hz, 1H), 3.97–4.12 (m, 1H), 7.23–7.34 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 55.4, 61.1, 62.4, 125.5, 127.8, 128.1, 136.4; **Anal.** Calcd for $C_9H_{10}O_2$ requires C, 71.98; H, 6.71; found: C, 71.92; H, 6.86%.

(*R*)-3-Phenyl-1,3-dihydroxypropane (88)

(2*S*,3*S*)-2,3-Epoxycinnamyallc alcohol **79** (1.5 g, 10.0 mmol) in dimethoxyethane (50 mL) was added a 3.4 M solution of sodium *bis*-(2-methoxyethoxy)aluminum hydride (Red-Al®) in toluene (3.1 mL, 10.5 mmol) dropwise under nitrogen at 0 °C. After stirring at room temperature for 3 h, the solution was diluted with ether and quenched with 5% HCl solution. After further stirring at room temperature for 30 min, the white precipitate formed was removed by filtration and boiled with ethyl acetate and filtered again. The combined organic extracts were dried with magnesium sulfate. The solution was concentration and the crude compound was purified by column chromatography using petroleum ether/EtOAc (6:3) to give (*R*)-3-phenyl-1,3-dihydroxypropane, (**88**)**.**

Yield: 98% (1.5 g); colourless viscous liquid; **$[\alpha]^{25}_D$**: +53.8 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 758, 840, 863, 881, 1027, 1068, 1108, 1256, 1392, 1462, 1606, 2871, 2927, 3017, 3428; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.89-2.09 (m , 2H), 2.85 (br s, 2H), 3.82 (t, *J* = 5.1, 10.9 Hz, 2H), 4.92 (dd, *J* = 4.4, 8.2 Hz, 1H), 7.24–7.34 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 40.4, 60.5, 73.1, 125.6, 127.3, 128.3, 144.3; **Anal.** Calcd for $C_9H_{12}O_2$ requires C, 71.03; H, 7.95; found: C, 71.48; H, 7.80%.

(*R*)-3-(Benzyloxy)-1-phenylpropan-1-ol (89)

To a solution of NaH (0.40 g, 10 mmol) in dry DMF (12 mL) at -70 °C was added 1,3-diol **88** (1.52 g, 10 mmol) in (2 mL) dry DMF over 10 min. The resulting mixture was

stirred for an additional 15 min and then benzyl bromide (1.2 mL, 10 mmol) was added drop wise. The reaction was stirred for 5 h at the same temperature. After completion, the reaction mixture was quenched with cold water (5 mL) and the aq. phase was extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with water followed by brine and dried over anhyd. Na_2SO_4. The solvent was removed under reduced pressure and the crude compound was purified by column chromatography using petroleum ether/EtOAc (6: 2) to afford mono protected alcohol **89** as a colorless liquid.

Yield: 80% (1.93 g); colourless liquid; $[\alpha]^{25}_{D}$: +29.4 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 750, 881, 1027, 1068, 1100, 1108, 1250, 1463, 1601, 2871, 2927, 3017, 3428; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.85-2.01 (m, 2H), 2.54 (br s, 1H), 3.54–3.62 (m, 2H), 4.45 (s, 2H), 4.83 (dd, *J* = 4.4, 7.5 Hz, 1H), 7.16–7.28 (m, 10H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 38.6, 68.4, 73.1, 73.2, 125.6, 127.1, 127.6, 127.7, 128.2, 128.4, 137.8, 144.3; **Anal.** Calcd for $C_{16}H_{18}O_2$ requires C, 79.31; H, 7.49; found: C, 79.20; H, 7.60%.

1-(*S*)-3-Azido-3-phenylpropoxymethyl)benzene (90)

To a solution of alcohol **89** (0.99 g, 4.1 mmol) in CH_2Cl_2 (5 mL) was added Et_3N (0.82 g, 8.2 mmol) at 0 ^oC. After 5 min of stirring, methane sulfonyl chloride (0.47 g, 4.1 mmol) was added drop-wise over a period of 5 min. The reaction mixture was then stirred for another 1 h at 0 ^oC and brought to room temperature. After the completion of the reaction, as monitored by TLC, it was extracted with CH_2Cl_2 (3x 20 ml) washed with water, brine and dried over anhydrous Na_2SO_4. The combined organic layer was concentrated under reduced pressure to get crude methane sulfonate ester in almost quantitative yield. To a solution of mesylate in DMF (10 mL) was added sodium azide (0.53g, 8.2 mmol) and the reaction mixture was heated at 60 ^oC for 7 h. After the

completion of the reaction, as monitored by TLC, it was extracted with CH_2Cl_2 (3x 20 mL) washed with water, brine and dried over anhydrous Na_2SO_4. The combined organic layer was concentrated under reduced pressure to give the crude azidobenzyloxyether **90**, which was purified by column chromatography using petroleum ether: ethyl acetate (9:1) to produce **90** as pale yellow oil.

Yield: 98% (1.07 g); pale yellow oil; $[\alpha]^{25}_{D}$: -65.6 (*c* 2, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 750, 1108, 1250, 1463, 1601, 2106, 2871, 2927, 3017; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.98-2.10 (m, 2H), 3.46-3.53 (m, 1H), 3.54-3.59 (m, 1H), 4.48 (s, 2H), 4.70 (dd, *J* = 6.6, 8.1 Hz, 1H), 7.27–7.40 (m, 10H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 36.5, 62.9, 66.3, 73.0, 126.8, 127.6, 127.7, 128.1, 128.3, 128.7, 138.1, 139.5; **Anal.** Calcd for $C_{16}H_{17}N_3O$ requires C, 71.89.31; H, 6.41; N, 15.72; found: C, 72.01; H, 6.50; N, 15.55%.

(*S*)-3-Amino-3-phenylpropan-1-ol (65)

To a solution of azidobenzyloxyether **90** (0.27 g, 1 mmol) in methanol (5 mL), was added 10% Pd/C (10 mg) and glacial acetic acid (0.5 mL) at 25 ^oC. The reaction mixture was stirred stirred under hydrogen (60 psi) for 20 h, and the progress of the reaction monitored by TLC. After completion of reaction, it was filtered through a celite pad and washed with EtOAc (3 x 20 mL). The combined organic phase was concentrated under *vacuum*. The crude product was obtained, purified by column chromatography on silica gel using ethyl acetate / MeOH (1:1) as eluents to give amino alcohol **65**.

Yield: 92% (0.14 g); white hygroscopic solid **m.p**.: 76-77 °C; $[\alpha]^{25}_{D}$ = -11.6 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 758, 840, 1050, 1460, 1575, 2940, 3280, 3386; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.77-2.32 (m, 2H), 3.63–3.69 (m, 3H), 3.86 (brs, 3H), 7.15–7.38 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 35.9, 55.1, 58.9, 126.2, 127.0, 128.6, 138.9;

Anal. Calcd for $C_9H_{13}NO$ requires C, 71.49; H, 8.67; N, 9.26; found: C, 71.40; H, 8.60; N, 9.30%.

(*S*)-3-(*N, N*-Dimethylamino)-3-phenylpropan-1-ol (66)

To a solution of (S)-3-amino-3-phenylpropan-1-ol **65** (0.05g, 0.19 mmol) in formic acid (39 μL), was added a 30% aqueous solution of formaldehyde (78 μL, 1.05 mmol) and the mixture refluxed over 8 h when the reaction is complete as monitored by TLC. After that the solution was acidified with conc. HCl to pH = 1 and basified with 4 N NaOH. The organic phases were combined, dried over $MgSO_4$ and the solvent evaporated under reduced pressure. The crude product was purified by flash column chromatography.

Yield: (28.9 mg) 85%; hygroscopic solid (turned in to semisolid immediately); $[\alpha]^{25}_D$: +39.8 (*c* 0.4, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 733, 847, 914, 1047, 1162, 1455, 2780, 2868, 2948, 3384; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.66-1.79 (m, 1H), 2.21 (s, 6H), 2.32-2.48 (m, 1H), 3.69-3.90 (m, 3H), 5.20 (br s, 1H), 7.15-7.32 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 32.1, 36.4, 63.1, 67.5, 127.1, 127.8, 128.3, 128.8, 128.9, 136.1; **Anal.** Calcd for $C_{11}H_{17}NO$ requires C, 73.70; H, 9.56; N, 7.81; found C, 73.65; H, 9.50; N, 7.90%.

(*S*)-*N, N*-Dimethyl-3-(naphthalen-1-yloxy)-1-phenylpropan-1-amine (53)

To a solution of **66** (40mg, 0.22 mmol) in dry THF (5 mL) under nitrogen atmosphere was added 1-naphthol (64 mg, 0.44 mmol). The mixture was cooled to 0 °C and PPh_3 (118 mg, 0.44 mmol) and DEAD (71 mg, 0.44 mmol) were successively added. The solution was allowed to warm till room temperature and stirred further for 15 h. After reaction was completed, the solution was evaporated and the crude product was purified by flash column chromatography using EtOAc/ MeOH (10:1) mixture which afforded (*S*)-dapoxetine as colorless oil in 74% yield.

Yield: 74% (49.6 mg); colorless oil; $[\alpha]^{25}_{D}$ = +64.8 (*c* 0.4, $CHCl_3$) {lit.[28] $[\alpha]_D^{25}$ +64.2 (*c* 0.3, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 733, 847, 914, 1047, 1167, 1265, 1345, 1727, 2950, 2960; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.22 (s, 6H), 2.34-2.45 (m, 1H), 2.59-2.71 (m, 1H), 3.55-3.63 (m, 1H), 3.93-4.12 (m, 2H), 7.19-7.52 (m, 9H), 7.70-7.74 (m, 1H), 7.95-8.21 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 32.0, 36.4, 63.1, 67.5, 104.5, 120.1, 127.1, 127.4, 127.8, 128.3, 128.9, 136.0, 138.1, 155.2; **Anal.** Calcd for $C_{21}H_{23}NO$ requires C, 82.58; H, 7.59; N, 4.59; found: C, 82.30; H, 7.65; N, 4.70%.

2.2.8 References

1 (a) von Euler, V. S.; Gaddum, J. H. *J. Physiol.* **1931**, *72*, 577; (b) Chang, M. M.; Leeman, S. E. *J. Biol. Chem.* **1970**, *245*, 4784; (c) Pernow, B. *Pharmacol. Rev*. **1983**, *35*, 85; (d) Naanishi, S. *Physiol. Rev*. **1987**, *67*, 1117; (e) Vaught, J. *Life Sci*. **1988**, *43*, 1419; (f) Lotz, M.; Vaughan, J. H.; Carson, D. A. *Science* **1988**, *241*, 1218;

2 (a) Baker, R.; Harrison, T.; Hollingworth, G. J.; Swain, C. J.; Williams, B. J. EP 0528 495A1, 1993; (b) Harrison, T.; Williams, B. J.; Swain, C. J.; Ball, R. G. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2545.

3 Desai, M. C.; Lefkowitz, S. L.; Thadeio, P. F.; Longo, K. P.; Snider, R. M. *J. Med. Chem.* **1992**, *35*, 4911.

4 (a) Perianan, A.; Snyderman, R.; Malfroy, B. *Biochem. Biophy. Res. Commun.* **1989**, *161*, 520; (b) Snijdelaar, D. G.; Dirksen, R.; Slappendd, R.; Crul, B. J. P. *Eur. J. Pain* **2000**, *4*, 121; (c) Datar, P.; Srivastava, S.; Coutinho, E.; Govil, G. *Curr. Top. Med. Chem.* **2004**, *4*, 75; (d) Lotz, M.; Vaughan, J. H.; Carson, D. A. *Science* **1987**, *235*, 893; (e) Moskowitz, M. A. *Trends Pharmacol. Sci*. **1992**, *13*, 307; (f) Takeuchi, Y.; Shands, E. F. B.; Beusen, D. D.; Marshall, G. R. *J. Med. Chem*. **1998**, *41*, 3609; (g) Swain, C. J. *Prog. Med. Chem*. **1998**, *35*, 57.

5 (a) Muñoz, M.; Rosso, M.; Pérez, A.; Coveñas, R.; Rosso, R.; Zamarriego, C.; Soult, J, A.; Montero, I. *Invest. Ophthalmol. Vis. Sci.* **2005**, *46*, 2567; (b) Miguel, M.; Marisa, R.; Rafael, C. *Lett. Drug Des. Discov.* **2006**, *3*, 323.

6 (a) Takahashi, K.; Nakano, H.; Fujita, R. *Tetrahedron Lett*. **2005**, *46*, 8927; (b) Lee, J.; Hoang, T.; Lewis, S.; Weissman, S. A.; Askin, D.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett*. **2001**, *42*, 6223; (c) Liu, R. H.; Fang, K.; Wang, B.; Xu, M. H.; Lin, G, Q. *J. Org. Chem.* **2008**, *73*, 3307; (d) Huang, P, Q.; Liu, L, X.; Wei, B, G.; Ruan, Y, P. *Org. Lett.* **2003**, *5*, 1927; (e) Davis, F. A.; Ramachandar, T.; *Tetrahedron Lett*. **2008**, *49*, 870.

7 Bhaskar G.; Rao, B. V.; *Tetradedron Lett.* **2003**, *44*, 915.

8 Tsai, M.-R., Chen, B.-F., Cheng, C.-C., Chang, N.-C. *J. Org. Chem*. **2005**, *70*, 1780.

9 Yoon, Y.-J.; Joo, J.-E.; Lee, K.-Y.; Kim, Y.-H.; Oh, C.-Y.; Ham, W.-H. *Tetrahedron Lett.* **2005**, *46*, 739

10 Oshitari, T.; Mandai, T. *Synlett* **2006**, 3395.

11 Cherian, S. K.; Kumar, P. *Tetrahedron: Asymmetry* **2007,** *18*, 982.

12 Liu, R.-H., Fang, K., Wang, B., Xu, M.-H., Lin, G.-Q. *J. Org. Chem*. **2008**, *73*, 3307

13 Emmanuvel, L.; Sudalai, A. *Tetrahedron Lett.* **2008**, *49*, 5736.

14 Bilke, J, L.; Moore, S, P.; O'Brien, P.; Gilday, J. *Org. Lett.* **2009**, *11*, 1935.

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

16 (a) Zhdankin, V. V.; Stang, P, J. *Chem. Rev.* **2002**, *102*, 2523. *(b*) Stang, P, J.; Zhdankin, V, V.; *Chem. Rev.* **1996**, *96*, 1123.

17 Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *99*, 863.

18 Pattenden, G.; Plowright, A. T.; Tornos, J. A.; Ye, T. *Tetrahedron Lett*. **1998**, *39*, 6099.

19 Anon, N. Z. *Drugs in R & D* **2005,** *6*, 307.

20 Pryor, J. *The Lancet* **2006,** *368*, 929.

21 Sadock, B. J.; Sadock, V. *Kaplan & Sadock's Comprehensive Textbook of Psychiatry*, Vol. 2, Philadelphia, Pa.: Lippincott Williams and Wilkins; **2000**, 1577.

22 Sadock, B. J.; Sadock, V. *Kaplan & Sadock's Synopsis of Psychiatry*, Philadelphia, Pa.: Lippincott Williams and Wilkins; **2003**, 710.

23 Waldinger, M. D.; Quinn, P.; Dilleen, M.; Mundayat, R.; Schweitzer, D. H.; Boolell, M. *J. Sex Med.* **2005**, *2*, 492.

24 Yang, J. W.; Chandler, C.; Stadler, M.; Kampen, D.; List, B. *Nature* **2008**, *452*, 453.

25 Koizumi, T.; Hirai, H.; Yoshii, E. *J. Org. Chem.* **1982,** *47*, 4005.

26 Torre, O.; Gotor-Fernandez, V.; Gotor, V. *Tetrahedron: Asymmetry* **2006,** *17*, 860.

27 Fadnavis, N. W.; Radhika, K. R.; Devi, A. V. *Tetrahedron: Asymmetry* **2006,** *17*, 240.

28 Siddiqui, S. A.; Srinivasan, K. V. *Tetrahedron: Asymmetry* **2007**, *18*, 2099.

29 Venkatesan, K.; Srinivasan, K. V. *ARKIVOC* **2008**, *xvi*, 302.

30 Chincholkar, P. M.; Kale, A. S.; Gumaste, V. K.; Deshmukh, A. R. A. S. *Tetrahedron* **2009**, *65*, 2605.

31 (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc*. **1980**, *102*, 5974; (b) Martin, V. S.; Woodward, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc*. **1981**, *103*, 6237.

32 Gao, Y.; Sharpless, K. B. *J. Org. Chem.* **1988,** *53*, 4081.

33 Woodward, S. S.; Finn, M. G.; Sharpless, K. B. *J. Am. Chem. Soc*. **1991**, *113*, 106.

34 (a) Finn, M. G.; Sharpless, K. B. *J. Am. Chem. Soc*. **1991**, *113*, 113; (b) Potvin, P. G.; Bianchet, S. J. *J. Org. Chem.* **1992**, *57*, 6629.

35 Fukuzawa, A., Sato, H., Masamune, T. *Tetrahedron Lett*. **1987**, *28*, 4303.

36 (a) Eschweiler, W. *Chem. Ber*. **1905**, *38*, 880. (b) Clarke, H. T. *J. Am. Chem. Soc*. **1933**, *55*, 4571.

37 Mistunobu, O. *Synthesis* **1981**, 1.

CHAPTER III

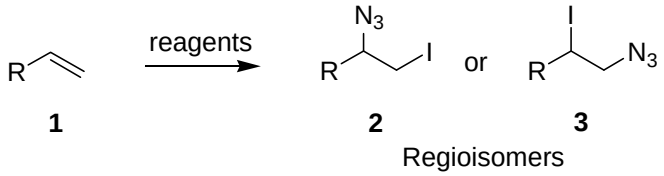
$NaIO_4$-mediated Azidoiodination of Olefins, 1,2-Diazidation of Olefins and α,α-Diazidation of Aryl Ketones and C-H Functionalization of Hydrocarbons

Section I

$NaIO_4$–KI-NaN_3–mediated regioselective azidoiodination of alkenes

3.1.1 Introduction

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



Scheme 1: azidoiodination of olefins

The resulting azidoiodides can be subjected to further synthetic manipulations to achieve a variety of compounds such as vinyl azide,[1] amines,[2] aziridines[3] and tetrazoles.[4] Since the pioneering work of Hassner *et al*.,[5] azidoiodination of alkenes involves the use of iodine azide reagent, which is generated insitu from sodium azide and iodine chloride in polar solvents. However, its explosive character is regarded to be a major disadvantage.

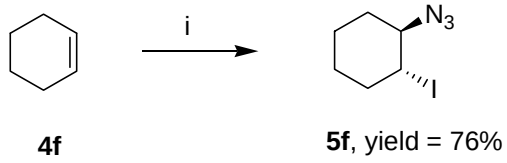
3.1.2 Review of literature

Literature survey revealed that there are various methods available for the azidoiodination of alkenes, using a variety of reagents such as I_2/NaN_3/Adogen,[6] $PhI(OAc)_2/Et_4NI/TMSN_3$, CAN/NaI/NaN_3, IPy_2BF_4/TMS-N_3 and Oxone/wet

$Al_2O_3/KI/NaN_3$ reagent combination. Some of the recent developments on this reaction are discussed in the following section.

Hassner's approach (1965)[7]

Hassner *et al*. have reported in *situ* preparation of I-N_3 from reaction of I-Cl with NaN_3 in polar solvent and addition of this on to alkenes **4** to give the corresponding azidoiodides **5** (**Scheme 2**).

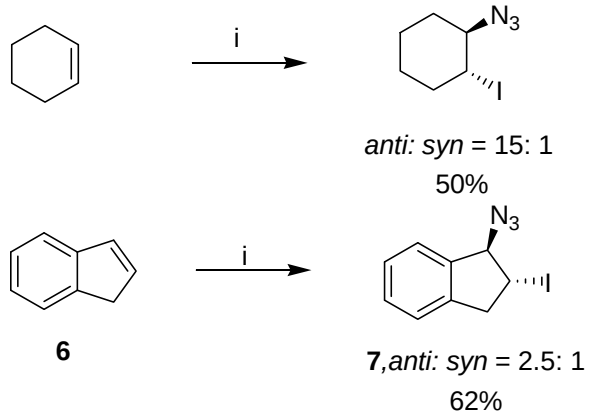


4f **5f**, yield = 76%

Scheme 2: (i) ICl, NaN_3 , CH_3CN, 25 °C.

Krisching's approach[8, 9]

Krisching *et al*. have developed a new reagent system consisting of reagents such as $PhI(OAc)_2$, tetraalkylammonium halide and $TMSN_3$. This reagent system is equivalent to I-N_3 system. The treatment of these reagents with indene **6** and cyclohexene **4f** gave the corresponding azidoiodides 62% and 50% yields respectively (**Scheme 3**).



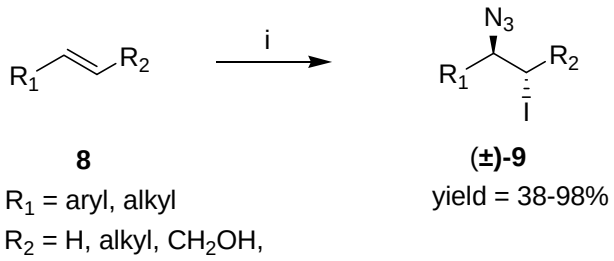
anti: syn = 15: 1
50%

6

7,*anti: syn* = 2.5: 1
62%

Scheme 3: (i) $PhI(OAc)_2$, $TMSN_3$, Et_4NI, CH_2Cl_2, 25 °C .

Same authors have also developed a new polymer-supported azide source, which was employed for the azidoiodination of alkenes to give the corresponding vicinal azidoiodides in 38-98% yield (**Scheme 4)**.



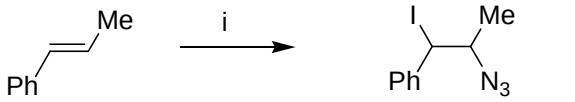
8
R_1 = aryl, alkyl
R_2 = H, alkyl, CH_2OH,

(±)-9
yield = 38-98%

Scheme 4: (i) polystyrene-NMe_3I, $PhI(OAc)_2$, $TMSN_3$, CH_2Cl_2, 25 °C .

Nair's approach[10]

In this approach, NaN_3/NaI/CAN (3equiv) reagent combination was used for the azidoiodination of alkenes. The addition followed *anti*-Markovnikov fashion (**Scheme 5**).



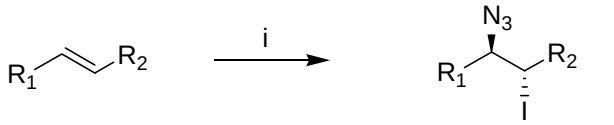
4c

5c, yield = 46%
anti:syn = 1:1

Scheme 5: (i) CAN (2.1 equiv.), NaN_3, NaI, MeOH, 0 °C.

Barluenga's approach (2000)[11]

Barluenga *et al*. used IPy_2BF_4 and Me_3SiN_3 reagent combination for the azidoiodination of alkenes **10** in the presence of $BF_3.OEt_2$ to furnish the corresponding azidoiodides **11** in 45-95% yield (**Scheme 6**).



10 **(±)-11**

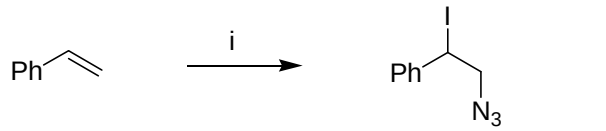
R_1 = aryl, alkyl, OMe yield = 45-95%

R_2 = H, alkyl, CH_2OMe

Scheme 6: (i) IPy_2BF_4, $TMSN_3$, $BF_3.OEt_2$, CH_2Cl_2, 0 °C, 3h.

Marcolullio's approach[12]

In this approach, NaN_3/KI/Oxone® supported on wet alumina was used for the azidoiodination of alkenes. Here again the addition followed an *anti*-Markovnikov fashion with moderate yields (**Scheme 7**).

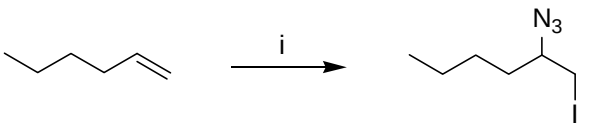


4a **5a,** yield = 92%
regioselectivity: >99

Scheme 7: (i) Oxone-wet (5 equiv.), Al_2O_3, KI (5 equiv.), NaN_3, $CHCl_3$, 25 °C.

Terent'ev's approach [13]

Terent'ev et al. have reported a new synthesis of vicinal azidoiodides in 62-77% yields by the reaction of sodium azide and iodine with unsaturated olefinic compounds in aqueous methanol solvent system (**Scheme 8**).



4h **5h**, yield = 74%

Scheme 8: (i) I_2, NaN_3 , $MeOH/H_2O$ 25 °C, 62-77%

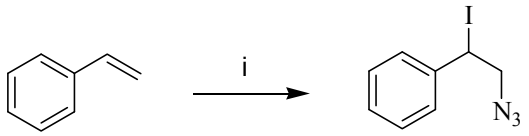
3.1.3. Present Work

3.1.3.1 Objective

From the above discussion, it is clear that most of the reported methods suffer from certain drawbacks such as use of expensive reagents and large excess of oxidants or halide sources. Hence, a practical method that involves less toxic yet readily available reagents is of paramount importance. This section describes one such process, in which an excellent regiospecific azidoiodination of alkenes takes place using $NaIO_4$ as the stoichiometric oxidizing agent and NaN_3 and KI as the azide and iodine sources respectively, in acetic acid as solvent.

3.1.4. Results and Discussion

In connection with our interest on $NaIO_4$-mediated oxidative functionalization of alkenes,[14] we thought of providing a cheaper method of azidoiodination of alkenes using $NaIO_4$-KI-NaN_3 combination. We noticed that $NaIO_4$-KI-NaN_3 combination was found to be an excellent system for the regiospecific azidoiodination of styrene in acetic acid as solvent. This prompted us to explore the effectiveness of the $NaIO_4$-KI-NaN_3 combination in the azidoiodination of alkenes. Thus, when styrene **4a** was treated initially with $NaIO_4$, KI and NaN_3 (all equimolar) in acetic acid at 25 °C, the corresponding 2-azido-1-iodo-ethylbenzene **5a** was obtained in 33% yield. However, this yield could be increased to 95% when stoichiometry of NaN_3 was altered to increase of 3 equiv. (**Scheme 9**). This prompted us to explore the effectiveness of the $NaIO_4$-KI-NaN_3 system in the 1, 2- azidoiodination of several alkenes. This new azidoiodination procedure was indeed found to be quite general for a variety of olefins and the results of this study are summarized in **Table 1**

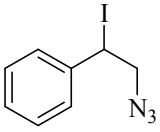
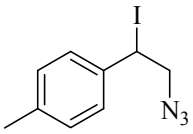
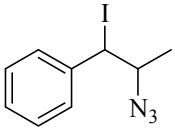


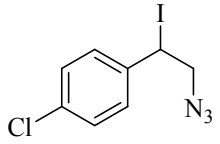
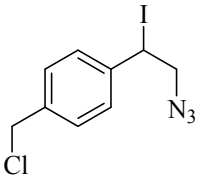
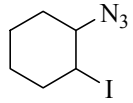
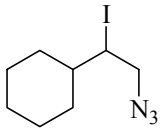
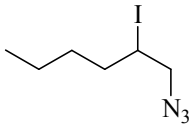
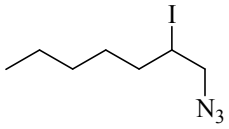
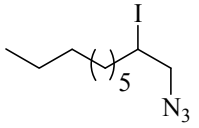
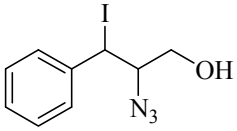
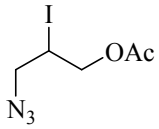
4a **5a,** 95%

Scheme 9: styrene (1 equiv.), KI (1 equiv.), $NaIO_4$ (1 equiv.), NaN_3 (3 equiv.), glacial AcOH, 25 °C, 2 h.

As can be seen from **Table 1**, a variety of alkenes **4a-l** (aliphatic, styrenic, allylic and disubstituted) underwent azidoiodinations to give the corresponding β-iodoazides **5a-l** in excellent yields. It is interesting to note that the regiochemistry of the addition, for all the cases examined, proceeded in an *anti*-Markovnikov fashion, indicating a possible radical pathway. Internal olefins such as β-methylstyrene, cyclohexene and cinnamyl alcohol have proceeded to give products in excellent yields with diastereoselectivities reaching up to 1: 4 (**5c**, **5f** and **5k**) as confirmed by their ^{1}H-NMR spectra. Terminal functionalized olefin such as allyl acetate also underwent regiospecific azidoiodination in 92% yield. However, no reaction took place in the case of conjugated alkenes with electron-withdrawing groups, which may be a limitation of this method.

Table 1: $NaIO_4$-mediated azidoiodination of alkenes.[a]

Entry	Alkenes (4a-l)	Products (5a-l)	Yield (%)[b]
a	Styrene		95
b	4-Methylstyrene		70
c	β-Methylstyrene		95[c]

d	4-Chlorostyrene		92
e	4-Chloromethylstyrene		85
f	Cyclohexene		93[d]
g	Vinylcyclohexane		88
h	1-Hexene		93
i	1-Heptene		94
j	1-Decene		90
k	*trans*-Cinnamyl alcohol		90[c]
l	Allyl acetate		92

[a] Reaction conditions: alkene (5 mmol), KI (5 mmol), $NaIO_4$ (5 mmol), NaN_3 (15 mmol), glacial AcOH (15 mL), 25 °C, 2 h; [b]isolated yield. [c]*syn*: *anti* = 1: 1; [d] *syn*: *anti* = 1: 4.

The formation of azidoiodides **5a-l** was confirmed by ^{1}H, ^{13}C-NMR and IR spectroscopy. For example, the ^{1}H-NMR spectrum of 2-azido-1-iodoethyl-4-chloromethylbenzene (**5e**) showed a doublet at δ 3.92 and a triplet at δ 5.12 due to -CHI and $-CH_2N_3$ protons respectively. Its ^{13}C-NMR spectrum showed typical signals at δ 26.8 and 58.5 for carbons

attached to iodo and azido groups respectively (**Fig. 1**).

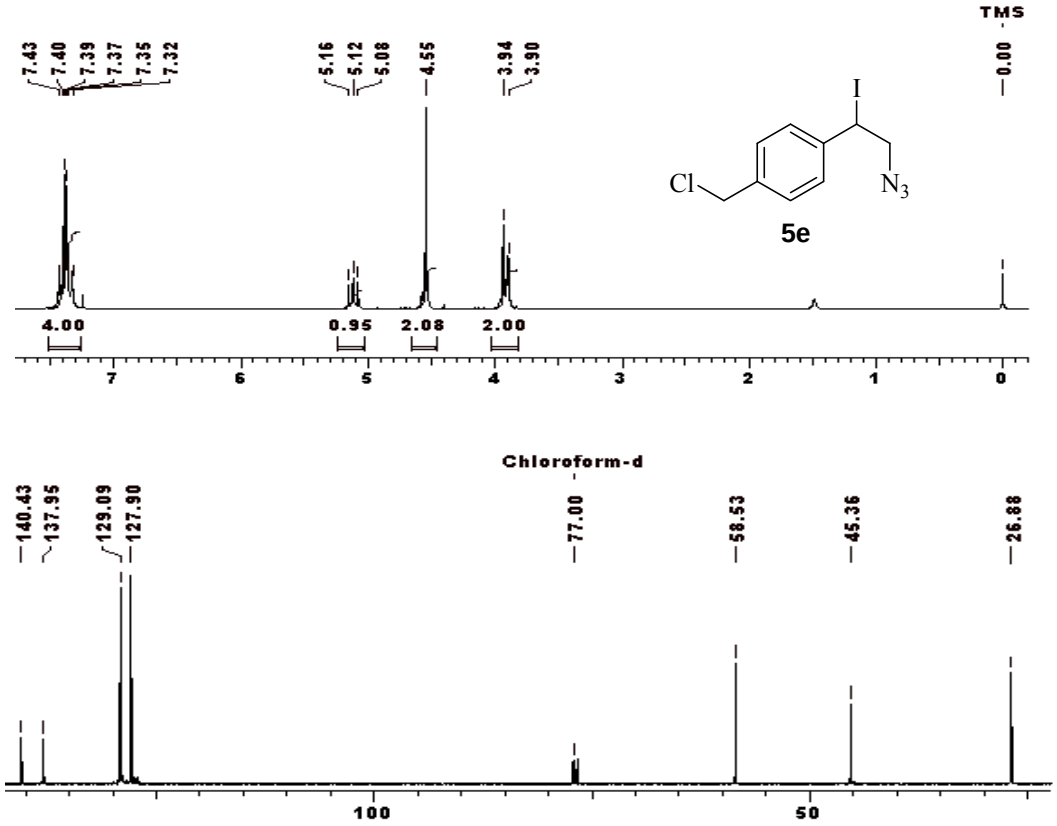


Fig. 1: ^{1}H and ^{13}C NMR spectra of **5e**

In the case of 1-azido-2-iodocyclohexane (**5f**), *anti: syn* ratio (4:1) was confirmed by ^{1}H-NMR spectrum (**Fig. 2**).

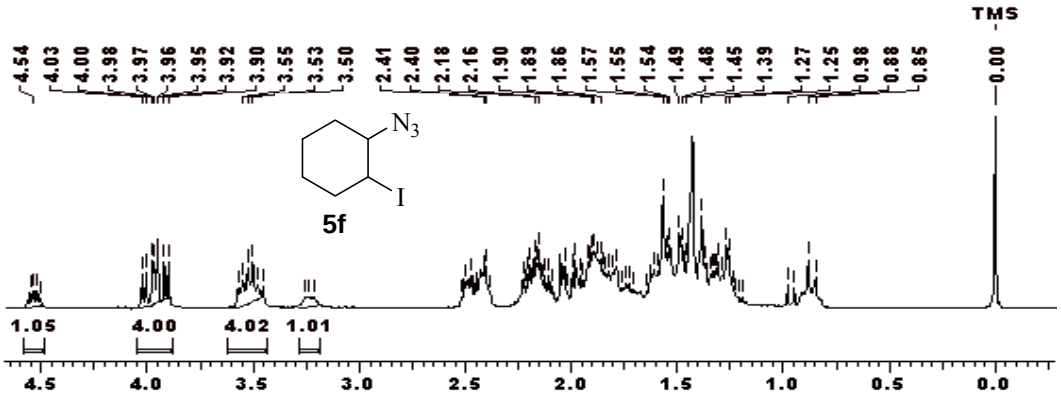
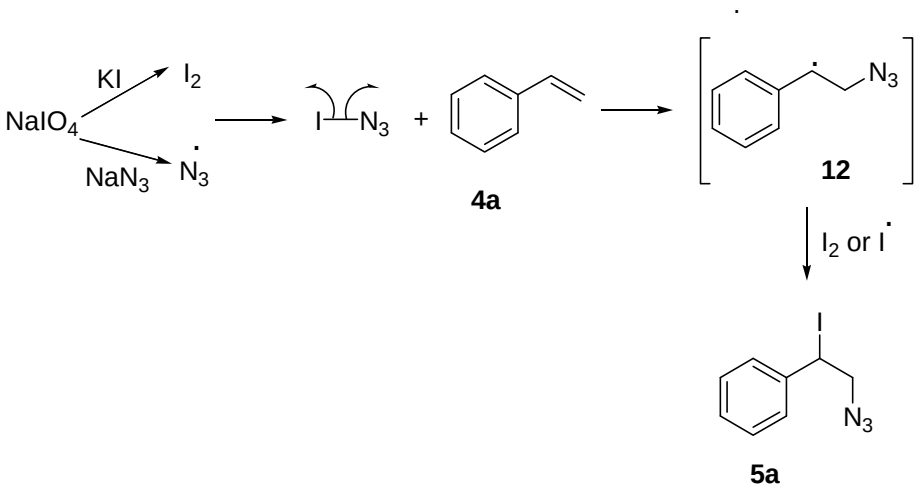


Fig. 2: ^{1}H NMR spectrum of **5f**

3.1.5. Mechanism

Mechanistically, we have proved that $NaIO_4$ oxidizes both KI and NaN_3 simultaneously to liberate I_2[15] and an azide radical[16] respectively; combination of which probably results in the formation of IN_3.[17] Homolysis of IN_3[18] provides an azide radical, which then adds onto alkenes to produce a more stable alkyl radical species **12**, thus controlling the regiochemistry of the process. The combination of alkyl radical either I_2 or iodine radical results in the formation of β-iodoazides **5a-l** (**Scheme 10**).



Scheme 10: Proposed mechanism for the azidoiodination of alkenes

3.1.6. Conclusion

In conclusion, we have developed a simple procedure with $NaIO_4$-KI-NaN_3 as a new combination for the 1, 2- azidoiodination of alkenes that provides a mild, efficient entry to vicinal azidoiodoalkanes in high yields under ambient conditions. The azidoiodination reaction proceeds to give β-iodoazides **5a-l** in a regiospecific manner.

3.1.7. Experimental section

General experimental procedure for azidoiodination of alkenes: To a suspension of NaN_3 (0.975 g, 15 mmol) and KI (0.830 g, 5 mmol) in acetic acid (20 ml) at 25 °C was added $NaIO_4$ (1.069 g, 5 mmol) and the reaction mixture was stirred for 5 min. when a dark brown color was observed. This was followed by the addition of alkenes **4a-l** (5 mmol) and the entire reaction mixture was stirred at the same temperature for 2h. After the reaction was complete as monitored by TLC, it was poured into water (100 mL) and extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were washed with a saturated solution of $NaHCO_3$ (50 mL), washed with aq. $Na_2S_2O_3$ (5%, 50 mL), dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give the crude product, which was then purified by column chromatography (packed with silica gel 60-120 mesh) using pet. ether as eluents to afford the pure product **5a-l**.

2-Azido-1-iodoethylbenzene (5a)

Yield: 95%; pale yellow oil; **IR** ($CHCl_3$, cm^{-1}): 693, 1257, 1446, 1605, 2100, 2921, 3027; **^{1}H NM**R (200 MHz, $CDCl_3$) δ 3.94 (d, *J* = 7.7 Hz, 2H), 5.14 (t, *J* = 7.7 Hz, 1H), 7.30-7.45 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 27.8, 58.5, 127.4, 128.7, 128.9, 140.1; **Anal.** Calcd for $C_8H_8IN_3$ requires C, 35.19; H, 2.95; N, 15.39; found: C, 35.10; H, 2.90; N, 15.44%.

2-Azido-1-iodoethyl-4-methylbenzene (5b)

Yield: 70%; pale yellow oil; **IR** ($CHCl_3$, cm^{-1}): 1257, 1446, 2101, 2920, 3027; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 2.30 (s, 3H), 3.87 (d, *J* = 7.7 Hz, 2H), 5.09 (t, *J* = 7.7 Hz, 1H), 7.10 (d, *J* = 7.8 Hz, 2H), 7.27 (d, *J* = 7.8 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.2, 28.1,

58.6, 127.3, 129.5, 137.2, 138.5; **Anal**. Calcd for $C_9H_{10}IN_3$ requires C, 37.65; H, 3.51; N, 14.64; found: C, 37.70; H, 3.48; N, 14.60%.

2-Azido-1-iodopropylbenzene (5c)

Yield: 95%; pale yellow oil; mixture of *anti:syn* (1:1); **IR** ($CHCl_3$, cm^{-1}): 1258, 1605, 1458, 2101, 2990; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 1.23 (d, *J* = 6.4 Hz, 3H), 1.52 (d, *J* = 6.4 Hz, 3H), 3.74-3.99 (m, 2H), 4.91(d, *J* = 7.0 Hz, 1H), 4.96 (d, *J* = 8.0 Hz, 1H), 7.26-7.40 (m, 10H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.2, 28.1, 58.6, 127.3, 129.5, 137.2, 138.5; **Anal**. Cald for $C_9H_{10}IN_3$ requires C, 37.65; H, 3.51; N, 14.64; found: C, 37.70; H, 3.48; N, 14.62%.

2-Azido-1-iodoethyl-4-chlorobenzene (5d)

Yield: 92%; pale yellow oil; **IR** ($CHCl_3$, cm^{-1}): 693, 1257, 1489, 1589, 2100; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 3.88-3.94 (m, 2H), 5.10 (dd, *J* = 8.2, 7.0 Hz, 1H), 7.30-7.40 (m, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 26.0, 58.5, 128.8, 129.1, 134.4, 138.7; **Anal.** Calcd for $C_8H_7ClIN_3$ requires C, 31.25; H, 2.29; N, 13.66; found: C, 31.30; H, 2.25; N, 13.68%.

2-Azido-1-iodoethyl-4-chloromethylbenzene (5e)

Yield: 85%; pale yellow oil; **IR** ($CHCl_3$, cm^{-1}): 1257, 1489, 2101, 2920, 3027; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 3.92 (d, *J* = 6.9 Hz, 2H), 4.55 (s, 2H), 5.12 (t, *J* = 7.2 Hz, 1H), 7.32 -7.43 (m, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 26.8, 45.3, 58.5, 127.9, 129.0, 137.9, 140.4; **Anal.** Calcd for $C_9H_9ClIN_3$ requires C, 33.62; H, 2.82; N, 13.07; found: C, 33.55; H, 2.85; N, 13.01%.

1-Azido-2-iodocyclohexane (5f)

Yield; 93%; pale yellow oil; mixture of *anti:syn* (4:1); **IR** ($CHCl_3$, cm^{-1}): 669, 769, 923, 1217, 1257, 1448, 2100, 2860, 2939; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 1.31-1.57 (m, 4H), 1.99-2.50 (m, 4H), 3.46-3.58 (m, 1H), 3.90-4.03 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 23.7, 26.9, 31.8, 33.2, 38.3, 67.1; **Anal**. Calcd for $C_6H_{10}IN_3$ requires C, 28.70; H, 4.01, N, 16.74; found: C, 28.64; H, 4.10, N, 16.78%.

2-Azido-1-iodoethylcyclohexane (5g)

Yield: 88%; pale yellow oil; **IR** ($CHCl_3$, cm^{-1}): 669, 769, 923, 1217, 1257, 1448, 2102, 2860, 2939; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 1.02-1.45 (m, 6H), 1.63-1.93 (m, 5H), 3.63-3.82 (m, 2H), 4.07-4.15 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 25.6, 25.8, 26.0, 30.5, 32.8, 41.0, 42.1, 56.5; **Anal**. Calcd for $C_6H_{14}IN_3$ requires C, 34.42; H, 5.06, N, 15.05; found: C, 34.50; H, 5.01, N, 14.98%.

1-Azido-2-iodohexane (5h)

Yield: 93%; pale yellow oil; **IR** ($CHCl_3$, cm^{-1}): 667, 769, 925, 1258, 1446, 2103, 2939; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 0.9 (t, J = 6.9 Hz, 3H), 1.27-1.52 (m, 4H), 1.73 1.84 (m, 2H), 3.60-3.83 (m, 2H), 4.04-4.17 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.8, 22.3, 28.4, 31.5, 37.1, 58.9; **Anal.** Calcd for: $C_6H_{12}IN_3$ requires C, 28.47; H, 4.78, N, 16.60; found: C, 28.50; H, 4.69, N, 16.65%.

1-Azido-2-iodoheptane (5i)

Yield: 94%; pale yellow oil; **IR** ($CHCl_3$, cm^{-1}): 669, 769, 923, 1257, 1448, 2102, 2939; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 0.9 (t, J = 6.6 Hz, 3H), 1.27-1.50 (m, 6H), 1.69 1.84 (m, 2H), 3.57-3.80 (m, 2H), 4.04-4.17 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.9, 22.3,

28.8, 30.7, 32.2, 37.0, 58.9; **Anal.** Calcd for: $C_7H_{14}IN_3$ requires C, 31.48; H, 5.28, N, 15.73; found: C, 31.40; H, 5.33, N, 15.65%.

1-Azido-2-iododacane (5j)

Yield: 90%; pale yellow oil; **IR** ($CHCl_3$, cm^{-1}): 668, 770, 923, 1257, 1448, 2103, 2939; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 0.9 (t, *J* = 6.1 Hz, 3H), 1.28-1.51 (m, 12H), 1.72 1.82 (m, 2H), 3.59-3.80 (m, 2H), 4.01-4.11 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 14.1, 22.6, 25.8, 28.7, 29.2, 29.3, 31.8, 32.0, 37.1, 59.0; **Anal.** Calcd for $C_{10}H_{20}IN_3$ requires C, 38.85; H, 6.52, N, 13.59; found: C, 38.75; H, 6.60, N, 13.65 %.

2-Azido-3-iodo-3-phenylpropan-1-ol (5k)

Yield: 90%; pale yellow oil; mixture of *anti:syn* (1:1); **IR** ($CHCl_3$, cm^{-1}): 757, 1153, 1217, 1258, 1458, 2096, 2927, 3004, 3330; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 2.36 (br s, 2H), 3.40-3.49 (m, 1H), 3.59-3.66 (m, 1H), 3.75-3.94 (m, 2H), 4.02-4.17 (m, 2H), 5.13 (d, *J* = 8.5 Hz, 1H), 5.16 (d, *J* = 9.2 Hz, 1H), 7.28-7.48 (m, 10H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 28.9, 32.1, 63.1, 64.8, 68.6, 70.0, 127.8, 128.2, 128.6, 128.9, 129.0, 140.1, 140.2; **Anal.** Calcd for $C_9H_{10}ION_3$ requires C, 35.66; H, 3.33; N, 13.86; found: C,35.70; H, 3.30; N, 13.85%.

3-Azido-2-iodopropylacetate (5l)

Yield: 92%; pale yellow oil; **IR** ($CHCl_3$, cm^{-1}): 669, 769, 923, 1257, 1448, 1735, 2101, 2940; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 2.10 (s, 3H), 3.74-3.82 (m, 2H), 4.15-4.37 (m, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 20.5, 23.8, 55.3, 65.9, 169.3; **Anal.** Calcd for $C_5H_8IN_3O_2$ requires C, 22.32; H, 3.0; N, 15.62; found: C, 22.38; H, 2.98; N, 15.73%.

Section II

$NaIO_4$–NaN_3–mediated diazidation of olefins and α,α-diazidation of aryl ketones

3.2.1 Introduction

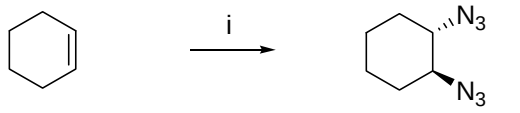
Vicinal diazides are important precursors for the synthesis of 1,2-diamines, which have become important synthetic targets in a variety of natural products, various biologically active molecules and are also used as ligands or catalysts in organo- and transition –metal catalyzed reactions.[19-23] Despite their extensive utility, the development of new method allowing efficient preparation of 1,2-diamine remains a stimulating challenge. The general methods of diamine synthesis usually involves vicinal diazides *via* diazidation, epoxides[24] or 1,2 diols[25] *via* dimesylation. In contrast, the direct oxidative diazidation of alkenes to diazides presents an attractive strategy.

3.2.2 Review of literature

Literature search revealed that there are only few reports available for direct diazidation of alkenes, which involve the use of stoichiometric amounts of $Mn(OAc)_2$, oxidants and azide sources, the details of which are presented below.

Fristad's approach (1985)[26]

Fristad *et al.* have reported the 1,2-diazidation of alkenes with stoichiometric amounts of $Mn(OAc)_2$ and NaN_3 to give the corresponding mixture of *syn*- and *anti*-diazides products **13** in 51-68% yield (**Scheme 11**).



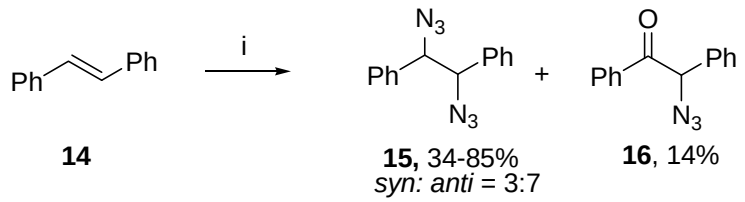
4 **13**

syn: anti = 1: 6

Scheme 11: (i) $Mn(OAc)_2$, NaN_3, 85-110 °C, 51-68%.

Moriarty's approach (1986)[27]

Moriarty *et al.* have reported 1,2-diazidation of a variety of alkenes **14** with PhIO-AcOH-NaN_3 reagent system to give vicinal diazides **15** in 34-85% yields, along with α-azidoketone **16** in 14% yields (**Scheme 12**).

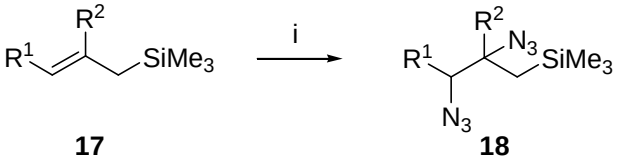


14 **15,** 34-85% *syn: anti* = 3:7 **16**, 14%

Scheme 12: (i) PhIO, NaN_3, AcOH, 50 °C, 34-85%.

Arimoto's approach (1989)[28]

In this approach, β-substituted allyltrimethylsilane were converted into the corresponding vic-diazides **18** with $(PhIO)_n$ (iodosylbenzene) and $TMSN_3$ in moderate yields (**Scheme 13**).



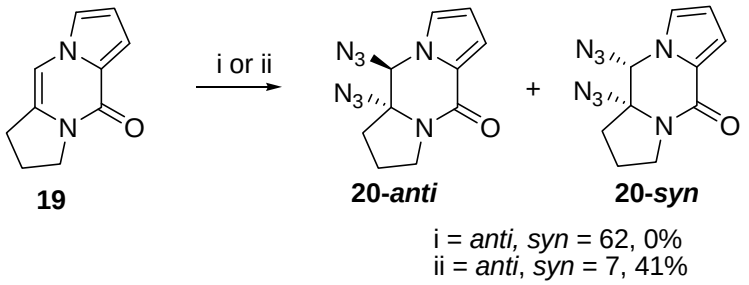
17 **18**

R^1 = H,
R^2 = n-$C_7H_{15}CH(OAc)(CH_2)_2$-,
$C_6H_5(CH_2)CH(OAc)CH_2$-

Scheme 13: (i) $(PhIO)_n$, $TMSN_3$, CH_2Cl_2, -78 -25 °C, 52-86%.

Austin's approach (2004)[29]

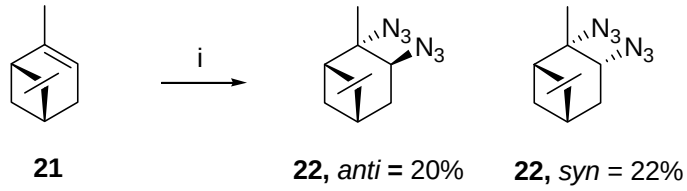
Austin *et al*. have studied the diazidation of pyrazinone **19** to give the corresponding *syn* and *anti* diazidopyrazinone, **20** which is intermediate of dibromophakellstatin (**Scheme 14**).



Scheme 14: (i) ICl, NaN_3, MeCN, -10 °C; (ii) $PhI(OAc)_2$, $TMSN_3$, -10 °C.

Ohba's approach (2005)[30]

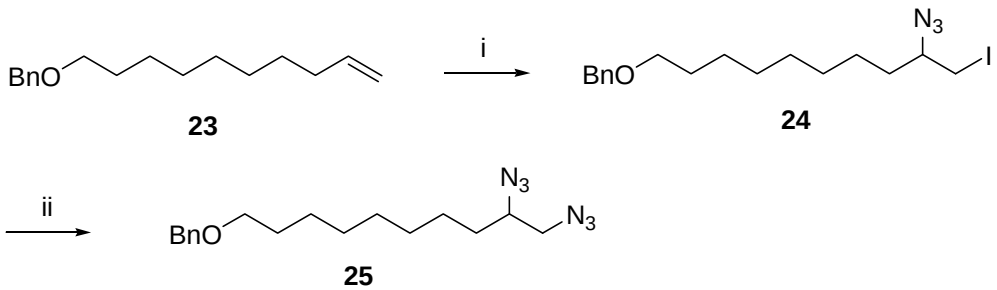
In this approach, the authors have described vic-diazidation of α-pinene **21** to give the corresponding mixtures of diazides **22** by using $Mn(OAc)_2$ and NaN_3 in acetic acid (**Scheme 15**).



Scheme 15: (i) $Mn(OAc)_2$, NaN_3, AcOH, 50 °C.

Pfaendler's approach (2004)[31]

Pfaendler *et al.* have reported a mild and two step procedures for the vic-diazidation of olefins. The sequence includes azidoiodination followed by substitution with azide ion (**Scheme 16**).

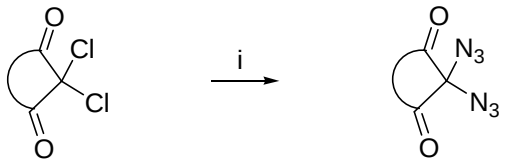


Scheme 16: (i) IN_3, NaN_3, 99%; ii) NaN_3, DMSO, 78%.

However the direct α,α-diazidation of ketones was not known in the literature.

Moore's approach (1976)[32]

Moore *et al.* have reported gem-diazidation of carbonyl derivatives from the corresponding gem-dihalo **26** derivatives by using sodium azide in water to give the corresponding gem-diazides **27** in high yields (**Scheme 17**).



26 **27**

Scheme 17: (i) NaN_3, H_2O, 140 °C, 90-98%.

3.2.3 Present Work

3.2.3.1 Objective

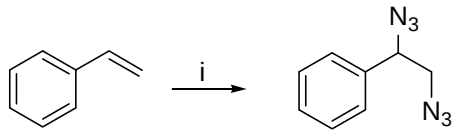
There are only five methods available in the literature for the direct diazidation of alkenes. However, some of them suffer from certain drawbacks like low yields, multi-step reaction sequences, expensive metal salts and oxidants. This section describes a new method of diazidation of alkenes and aryl ketones that provided the corresponding vicinal and geminal diazide derivatives using $NaIO_4$ as the oxidant and sodium azide as the azide source.

3.2.4 Results and Discussion

3.2.4.1: 1,2-Diazidation of alkenes

In our earlier section, we have described a method of $NaIO_4$-mediated azidoiodination of alkenes that afforded the corresponding azidoiodides. During the course of this study of $NaIO_4$-mediated oxidative functionalization of alkenes, we observed that the treatment of alkenes **4a-h** with stoichometric amount of $NaIO_4$ and sodium azide in AcOH : DMSO

(1: 4) as solvent at 75 °C, gave 1,2-diazides **28a-h** in good yields. In particular when styrene **4a** was subjected to oxidative functionalization with $NaIO_4$ (1 equiv) in the presence of NaN_3 (3 equiv.) in AcOH: DMSO (1: 4) as solvent at 75 °C, gave diazide **28a** in 75% yield (**Scheme 18**).

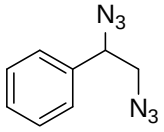
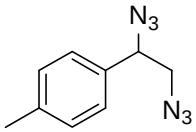
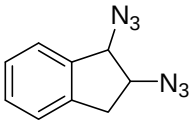


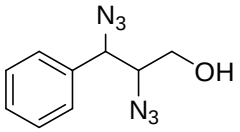
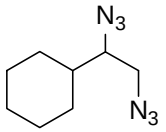
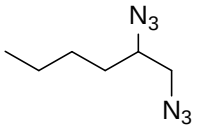
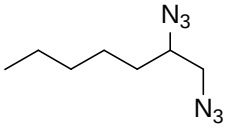
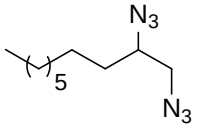
4a **28a,** 75% yield

Scheme 18: i) alkenes (1 equiv.), $NaIO_4$ (1 equiv.), NaN_3 (3 equiv.), DMSO:AcOH (4:1), 75 °C, 2h .

To study the generality of the reaction, a variety of alkenes were subjected to diazidation with $NaIO_4$-NaN_3 reagent combination and the results are presented in (**Table 2)**. Aromatic olefins as well as aliphatic olefins gave good yields of the corresponding 1,2-diazides. Internal olefins such as indene and cinnamyl alcohol have proceeded to give products in excellent yields with 1:1 diastereoselectivity (**28c** and **28d**) as confirmed by their ^{1}H-NMR spectra. However, no reaction took place in the case of α,β–unsaturated carbonyl compounds, which may be a limitation of this method.

Table 2: $NaIO_4$-mediated diazidation of alkenes[a]

No	Substrate (4)	Products (28)	Yield (%)[b]	*anti : syn*
a	Styrene		75	
b	4-Methylstyrene		74	
c	Indene		75	1:1

d	Cinnamyl alcohol		78	1:1
e	Vinylcyclohexane		80	
f	1-Hexene		70	
g	1-Heptene		68	
h	1-Decene		63	

Reaction conditions: [a] alkenes (5 mmol), NaIO4 (5 mmol), NaN_3 (15 mmol), 20ml DMSO: AcOH (4:1), 75 °C, 2 h; [b] yields refer to isolated yield after column chromatography.

The formation of diazides **28a-h** was confirmed by ^{1}H-NMR, ^{13}C-NMR and IR spectroscopy. The ^{1}H NMR spectrums of **28a** showed a doublet of doublet at δ 4.65 for benzylic proton and a typical signal at δ 3.37-3.55 (m, 2H) for homobenzylic protons. Its ^{13}C NMR spectrum showed a typical signal at δ 65.4 and 55.8 for the homobenzylic and benzylic carbons respectively (**Fig. 3**). Its IR spectrum showed a strong absorption at 2103 cm^{-1} confirming the formation of azide function. The diasteromeric ratios (*anti: syn*) for internal olefins were determined from ^{1}H-NMR spectroscopic studies.

The probable mechanism for the direct diazidation of alkenes to the corresponding diazides is proposed, that involves a radical pathway. Accordingly, the $NaIO_4$ is able to oxidize NaN_3 to give the corresponding azide radical,[14] which is then added onto alkene to give the secondary radical **12**.

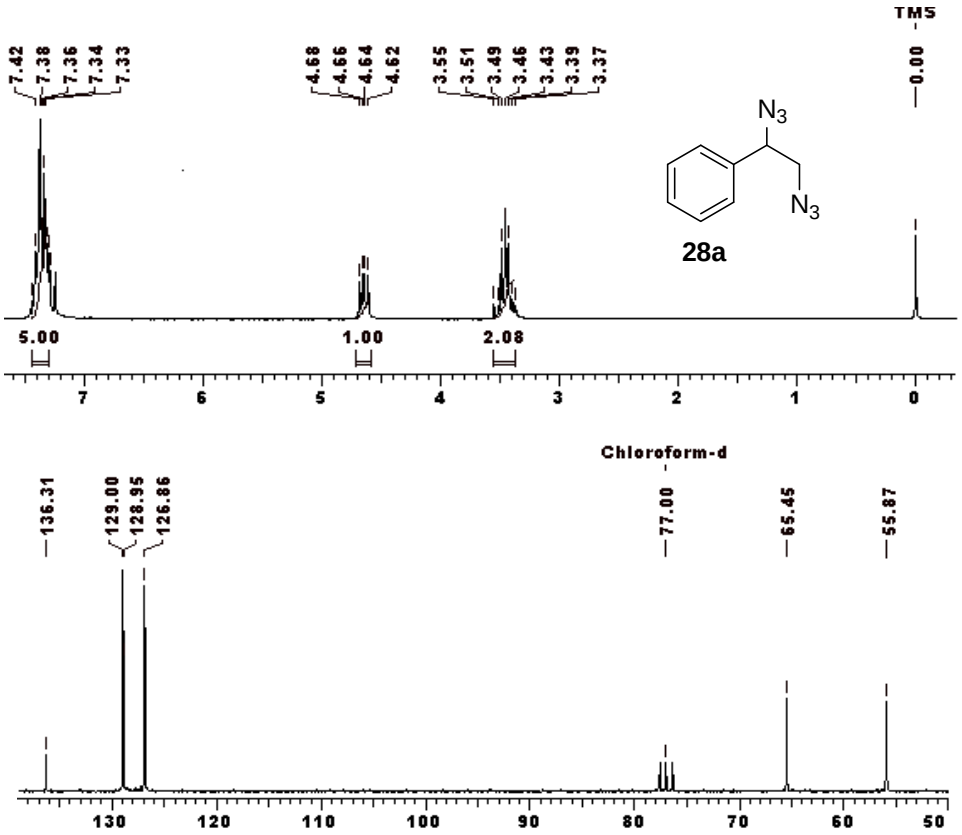
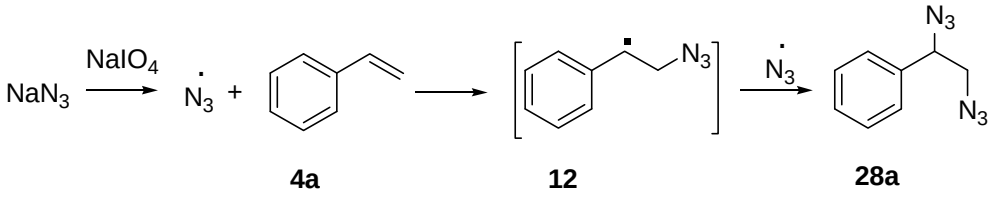


Fig. 3: ^{1}H and ^{13}C NMR spectra of styrene diazide **28a**

Subsequently, the secondary radical is further believed to be trapped with another azide radical to give diazides (**Scheme 19**).



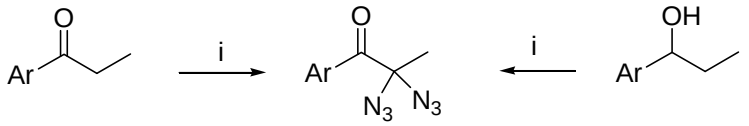
Scheme 19: Proposed mechanism for the 1,2-diazidation of alkenes

3.2.4.2: α,α-Diazidation of aryl ketones

We further extended the scope of this reagent system to aryl ketones **29** and alcohols **30** for the direct azidation and the results are presented in (**Table 3)**. As can be seen from **Table 3,** aryl ketones with α-methylene group (-CO-CH_2-) underwent selective oxidative

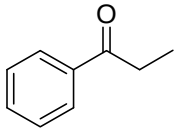
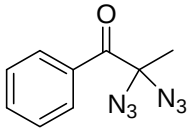
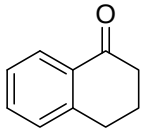
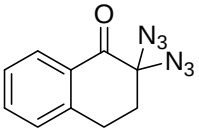
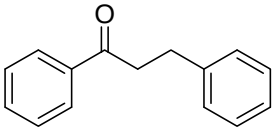
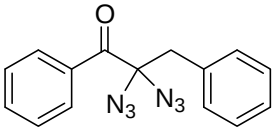
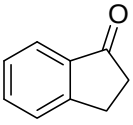
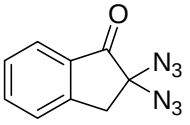
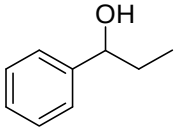
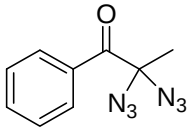
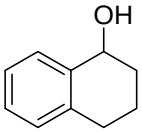
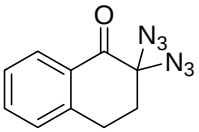
diazidation with $NaIO_4$ and sodium azide in AcOH:DMSO (1:4) as solvent at 75 °C, to give α,α-diazido aryl ketones **31** in 91-95% yields. Moreover, when benzylic alcohols were subjected to α,α-diazidation condition, the corresponding α,α-diazido aryl ketones were obtained in good yields, occurring probably *via* oxidation of alcohol followed by diazidation of ketones.

Table 3: $NaIO_4$-mediated α,α-diazidation of aryl ketones and benzylic alcohols[a]



29 **31** **30**

i) $NaIO_4$, NaN_3, DMSO:ACOH (4:1), 75 ^oC.

Sr.No	Substrate	Product (31)	Yield (%)[b]
a			96
b			93
c			94
d			95
e			75
f			70

Reaction conditions: [a] aryl ketone (5 mmol), $NaIO_4$ (5 mmol), NaN_3 (15 mmol), 20ml DMSO:AcOH (4:1), 75 °C, 2 h ; [b] yields refer to isolated yield after column chromatographic purification.

The structures of α,α-diazido aryl ketones **31** were established by ^{1}H-NMR, ^{13}C-NMR and IR spectroscopy. The ^{1}H NMR spectrum of **31a** showed a typical singlet at δ 1.86 for methyl proton. Its ^{13}C NMR spectrum showed characteristic signals at δ 83.10 and 191.72 due to the geminal diazido and carbonyl (-C=O) quaternary carbons respectively. Its IR spectrum showed a strong band at 2109 cm^{-1} due to the presence of azide functional group in the molecule (**Fig. 4).**

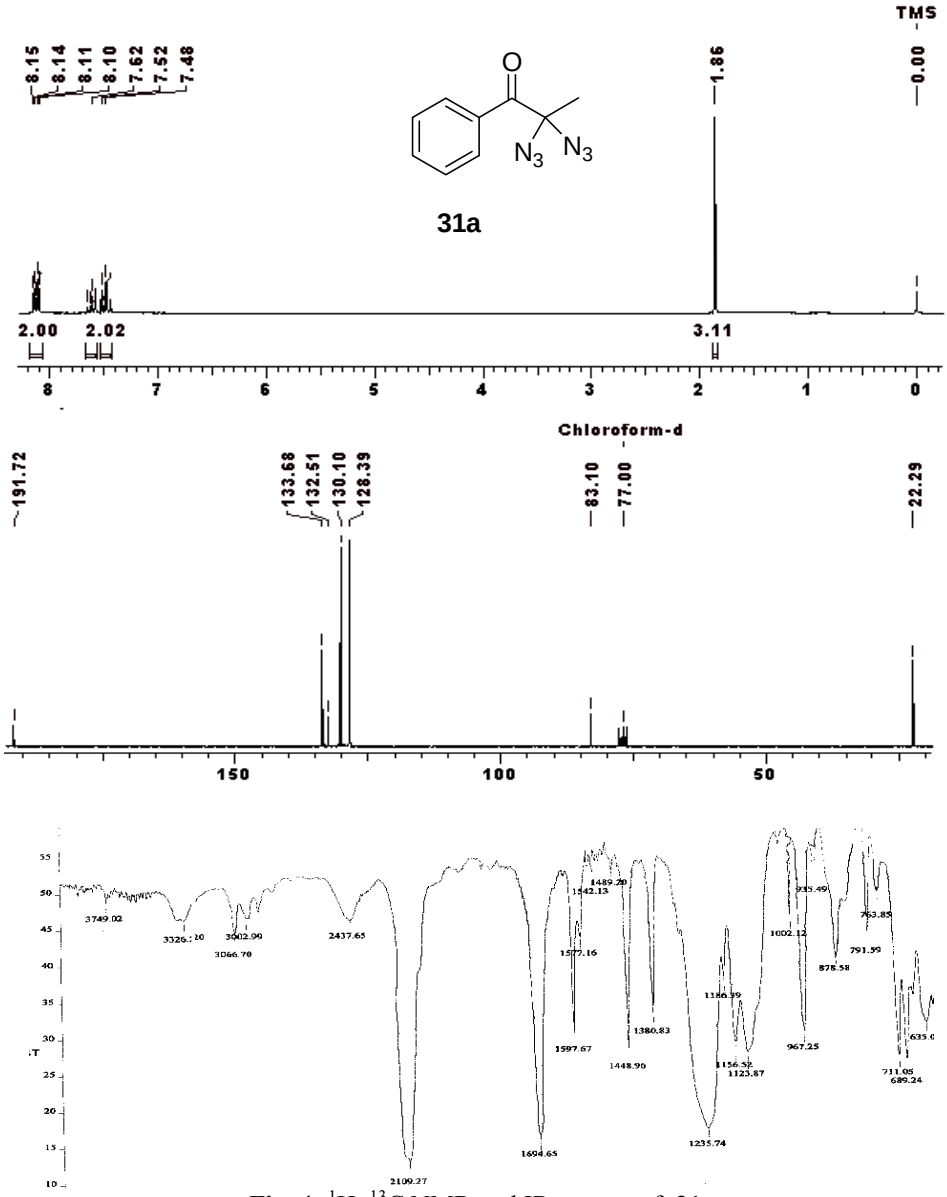


Fig. 4: ^{1}H, ^{13}C NMR and IR spectra of **31a**

3.2.5. Conclusion

In conclusion, we have developed a new reagent system consisting of $NaIO_4$-NaN_3 as a new efficient system suitable for direct diazidation of alkenes and aryl ketones into their corresponding vicinal and geminal diazides. The reaction is believed to proceed *via* radical pathway.

3.2.6. Experimental

General experimental procedure for 1,2-diazidation of alkenes: To a suspension of NaN_3 (0.975 g, 15 mmol) and $NaIO_4$ (1.069 g, 5 mmol) in 20 mL of DMSO: glacial AcOH (4: 1) was added alkenes **4** (5 mmol) and the reaction mixture was stirred at 75 °C for 2 h until the mixture became dark brown in color. Then the reaction mixture was poured into water (100 ml) and extracted with EtOAc (3 × 50 ml)). The combined organic layers were washed with a saturated solution of $NaHCO_3$ (50 ml) followed by aqueous $Na_2S_2O_3$ (5%, 50 ml), dried over anhyd. Na_2SO_4. Concentration of the organic layer gave diazides, which was subjected to column purification using hexane/ethyl acetate (19:1) as eluent to obtain pure 1,2-diazides **28a-h**.

1,2-Diazido-1-phenylethane (28a)

Yield: 75%; pale yellow liquid; **IR** (neat, cm^{-1}): 700, 759, 1257, 1454, 2100, 2926; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.37-3.55 (m, 2H), 4.65 (dd, *J*= 5.4, 7.8 Hz, 1H), 7.29-7.55 (m, 5H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 55.8, 65.4, 126.8, 128.9, 129.0, 136.3; **Anal.** Calcd for. $C_8H_8N_6$: C, 51.06; H, 4.28; N, 44.66; Found: C, 51.30; H, 4.08; N, 44.50%.

1,2-Diazido-1-(4-methylphenyl)ethane (28b)

Yield: 74%; pale yellow liquid; **IR** (neat, cm^{-1}): 701, 765, 1254, 1454, 2101, 2926; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.36 (s, 3H), 3.42-3.49 (m, 2H), 4.64 (dd, *J* = 5.9, 7.9 Hz, 1H), 7.22 (s,

4H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 21.1, 55.7, 65.2, 126.8, 129.6, 133.2, 138.8; **Anal.** Calcd for. $C_8H_8N_6$: C, 51.06; H, 4.28; N, 44.66; Found: C, 51.30; H, 4.08; N, 44.50%.

1,2-Diazidoindane(28c)

Yield: 70%; pale yellow liquid; mixture of *anti*:*syn* (1:1); **IR** (neat, cm^{-1}): 704, 738, 1265, 2104, 2926; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.94 (dd, *J* = 6.7, 16 Hz, 1H), 3.17 (d, *J* = 6.7 Hz, 2H), 3.35 (dd, *J* = 6.8, 16 Hz, 1H), 4.16 (dd, *J* = 6.7, 12 Hz, 1H), 4.29 (dd, *J* = 6.7, 12 Hz, 1H), 4.76 (d, *J* = 5.6 Hz, 1H), 4.82 (d, *J* = 5.7 Hz, 1H), 7.23-7.42 (m, 8H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 35.4, 35.9, 63.9, 66.8, 67.5, 124.41, 124.7, 125.0, 125.2, 127.5, 127.6, 129.3, 129.5, 137.4, 137.6, 138.9, 139.6; **Anal.** Calcd for. $C_{10}H_{10}N_6$: C, 56.07; H, 4.71; N, 39.23; Found: C, 55.60; H, 4.88; N, 39.50%.

1,2-Diazido-1-phenylpropanol (28d)

Yield: 78%; pale yellow liquid; mixture of *anti*:*syn* (1:1); **IR** (neat, cm^{-1}): 702, 763, 1049, 1261, 1454, 1492, 2104, 2935, 3034, 3416; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.91 (br s, 2H), 3.32-3.42 (m, 1H), 3.54-3.81 (m, 5H), 4.67 (d, *J* = 8.1 Hz, 2H) 7.32-7.48 (m, 10H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 61.9, 65.3, 66.5, 66.6, 67.5, 127.2, 127.6, 128.9, 12.0, 135.4, 135.6; **Anal.** Calcd for $C_8H_8N_6$: C, 51.06; H, 4.28; N, 44.66; Found: C, 51.30; H, 4.08; N, 44.50%.

1,2-Diazido-1-cyclohexylethane (28e)

Yield: 80%; pale yellow liquid; **IR** (neat, cm^{-1}): 1252, 2102, 2937; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.96-1.35 (m, 5H), 1.45-1.17 (m, 6H), 3.21-3.30 (m, 1H), 3.36-3.49 (m, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 25.7, 25.8, 28.5, 29.6, 40.0, 52.9, 67.5; **Anal** Calcd for. $C_8H_{14}N_6$: C, 49.47; H, 7.26; N, 43.27; Found: C, 49.25; H, 7.50; N, 43.20%.

1,2-Diazidohexane (28f)

Yield: 70%; pale yellow liquid; **IR** (neat, cm^{-1}): 1253, 2103, 2930; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.93 (t, *J* = 6.7, 3H), 1.25-1.41 (m, 4H), 1.51-1.58 (m, 2H), 3.25-3.53 (m, 3H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 13.7, 22.2, 27.8, 31.3, 54.7, 61.9; **Anal.** Calcd for. $C_6H_{12}N_6$: C, 42.84; H, 7.19; N, 49.96; Found: C, 42.50; H, 7.31; N, 49.90%.

1,2-Diazidoheptane (28g)

Yield: 68%; pale yellow liquid; **IR** (neat, cm^{-1}): 1253, 2104, 2945; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.91 (t, *J* = 6.5, 3H), 1.32-1.59 (m, 8H), 3.25-3.37 (m, 2H), 3.41-3.49 (m, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 13.7, 22.3, 25.4, 31.3, 31.6, 54.7, 61.9; **Anal.** Calcd for. $C_7H_{14}N_6$: C, 46.14; H, 7.74; N, 46.12; Found: C, 46.01; H, 7.80; N, 46.20%.

1,2-Diazidodecane (28h)

Yield: 63%; pale yellow liquid; **IR** (neat, cm^{-1}): 1254, 2103, 2940; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.89 (t, *J* = 6.6, 3H), 1.28-1.58 (m, 14H), 3.25-3.37 (m, 2H), 3.42-3.47 (m, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 13.9, 22.5, 25.7, 29.0, 29.2, 29.3, 31.6, 37.7, 54.7, 62.0; **Anal.** Calcd for. $C_{10}H_{20}N_6$: C, 53.55; H, 8.99; N, 37.47; Found: C, 53.65; H, 8.89; N, 37.40%.

General experimental procedure for diazidation of α,α-diazidation of aryl ketones and alcohols:

To a suspension of NaN_3 (0.975 g, 15 mmol) and $NaIO_4$ (1.069 g, 5 mmol) in 20 mL DMSO: glacial AcOH (4: 1) was added aryl ketones 2**9** /alcohols **30** (5 mmol) and the reaction mixture was stirred at 75 °C for 2 h until the mixture became dark brown in color. Then the reaction mixture was poured into water (100 ml) and extracted with EtOAc (3×50 ml). The combined organic layers were washed with a saturated solution of $NaHCO_3$ (50 ml) followed by aq. $Na_2S_2O_3$ (5%, 50 ml), dried over anhyd. Na_2SO_4. Concentration of the organic layer

gave crude gem-diazides, which were subjected to column chromatographic purification using hexane/ethyl acetate (19: 1) as eluent to obtain pure gem-diazides **31a-d**.

2,2-Diazido-1-phenyl-propane-1-one (31a)

Yield: 96%; pale yellow liquid; **IR** (Neat, cm^{-1}): 739, 1230, 1456, 1602, 1690, 2104, 2937; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.86 (s, 3H), 7.44-7.53 (m, 2H), 7.57-7.66 (m, 1H), 8.11 (t, *J* = 1.5 Hz, 1H), 8.14 (t, *J* = 1.3 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 20.0, 83.1, 128.3, 130.1, 132.5, 133.6, 191.7; **Anal.** Calcd for. $C_9H_6N_6O$: C, 50.00; H, 3.73; N, 38.87 Found: C, 50.62; H, 3.24; N, 38.72 %.

2,2-Diazido-3,4-dihydronapthalen-1-one (31b)

Yield: 91%; pale yellow liquid; **IR** (Neat, cm^{-1}): 738, 1228, 1456, 1602, 1693, 2104, 2937; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.33 (t, *J* = 6.4 Hz, 1H), 3.06 (t, *J* = 6.0 Hz, 1H), 7.28 (d, *J* = 7.5 Hz, 1H), 7.39 (t, *J* = 7.3 Hz, 1H), 7.57 (ddd, *J* = 1.5, 7.4, 15 Hz, 1H), 8.12 (d, *J* = 7.8 Hz, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 25,3, 32.9, 80.2, 127.3, 128.6, 129.17, 128.9, 134.8, 143.0, 187.5; **Anal**. Calcd for. $C_{10}H_8N_6O$: C, 52.63; H, 3.53; N, 36.83 Found: C, 52.32; H, 3.60; N, 36.93 %.

2,2-Diazido-1,3-diphylpropane-1-one (31c)

Yield: 94%; pale yellow liquid; **IR** (Neat, cm^{-1}): 738, 1230, 1456, 1602, 1695, 2103, 2937; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.39 (s, 2H), 7.15-7.30 (m, 5H), 7.41-7.49 (m,2H), 7.55-7.63 (m, 1H), 7.98-8.03 (m, 2H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 43.0, 32.9, 85.5, 127.9, 128.5, 128.8, 130.1, 130.6, 132.2, 133.5, 133.6, 192.7; **Anal**. Calcd for. $C_{15}H_{12}N_6O$: C, 61.64; H, 4.14; N, 28.75 Found: C, 61.60; H, 4.10; N, 28.83 %.

2,2-Diazido-3,4-dihydronapthalen-1-one (31d)

Yield: 95%; pale yellow liquid; **IR** (Neat, cm^{-1}): 738, 1228, 1456, 1602, 1698, 2105, 2937; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.29 (s, 2H), 7.46 (dd, *J* = 6.0, 7.5 Hz, 2H), 7.71 (t, *J* = 7.6 Hz, 1H), 7.86 (d, *J* = 7.5, 1H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 39,5, 80.1, 125.9, 126.4, 128.7, 132.1, 136.9, 149.1, 194.6; **Anal**. Calcd for. $C_9H_6N_6O$: C, 50.47; H, 2.82; N, 39.24 Found: C, 50.55; H, 2.78; N, 39.30 %.

Section III

$NaIO_4$-KI-NaN_3 as a new reagent system for C-H functionalization in hydrocarbons

3.3.1 Introduction

Direct and selective replacement of C-H bonds in hydrocarbons with C-C, C-O, C-N and C-X groups is an important and long-standing goal in chemistry.[33] Generally, for monofunctionalization of unactivated C-H bonds, such catalytic systems as organometallic compounds,[34a] metallo-porphyrin complexes,[34b] superacids,[34c] Gif and Gif-Orsay systems,[34d] $MeReO_3/H_2O_2$,[34e] OsO_4,[34f] polyoxometallates,[34g] and other systems[33] have been reported. In particular, a new, effective method for 1,2-functionalization of unactivated C-H bonds in a single step which represents a major challenge for chemist. In addition, free-radical iodinations of hydrocarbons with iodine, despite its endothermic nature, have emerged as useful route for the activation of C-H bonds in hydrocarbons. During the course of our study on $NaIO_4$-mediated oxidative halogenations,[14-15] (see the Section I for details) we noticed that regiospecific addition of I-N_3, generated *in situ*, onto styrenes took place in an *anti*-Markovnikov fashion, suggesting a probable radical pathway.[35] This prompted us to explore the effectiveness of the $NaIO_4$-KI-NaN_3 combination in the C-H activation of alkanes.

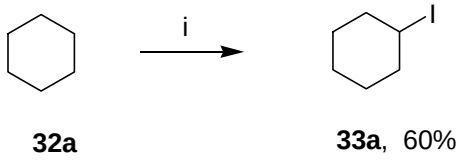
3.3.2 Review of literature

Literature search reveals that while there are several reports available for the iodination of hydrocarbons, very few methods are reported for the direct 1,2-difunctinalization and benzylic azidation of hydrocarbons. Some of these methods are briefly discussed below.

(a) Direct C-H activation

Gidley's approach (1968)[36]

Gidley *et al*. have reported a photochemical free radical method for C-H activation of primary, secondary and benzylic C-H bonds of hydrocarbons to the corresponding iodides **33** in 20-60% yields (**Scheme 20**).

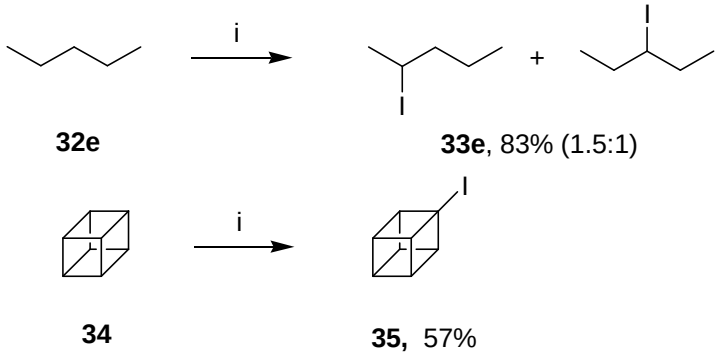


32a **33a**, 60%

Scheme 20: (i) *t*-BuCOI, Feron 113 (1.2 M), hydrocarbon (4.2 M), *hv*, NaN_3 , 40 °C.

Schreiner's approach (1999, 2000)[37, 38]

Schreiner *et al*. have used CHI_3 and NaOH reagent combination for iodination of alkanes to give the corresponding alkyl iodides **35,** in 27-92% yield (**Scheme 21**). The procedure is simple yet efficient and even normally completely unreactive straight chain alkanes can be iodinated readily.



32e **33e**, 83% (1.5:1)

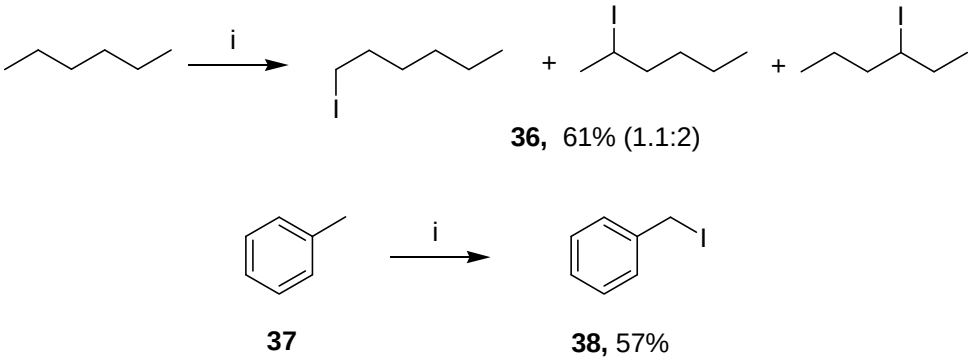
34 **35,** 57%

Scheme 21: (i) CHI_3, NaOH, hydrocarbon , CH_2Cl_2 25 °C.

Writh's approach (2003)[39]

Writh *et al*. have reported iodination of hydrocarbons by using *in situ* generated *tert*-butyl hypoiodite from iodine and sodium *tert*-butoxide to give the iodides in 62-77% yields

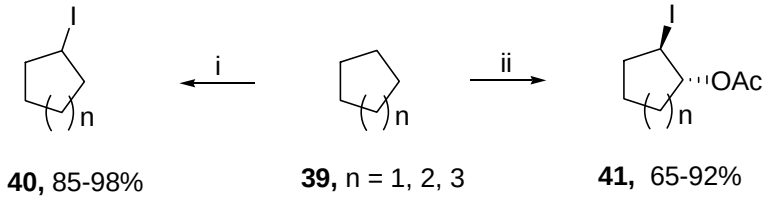
(**Scheme 22**). However this iodination procedure gave less yield and poor selectivity for straight chain alkanes.



Scheme 22: (i) I_2, hydrocarbons (excess), *t*-BuONa, 25 °C , 15 h.

Barluenga's approach (2002, 2005)[40, 17]

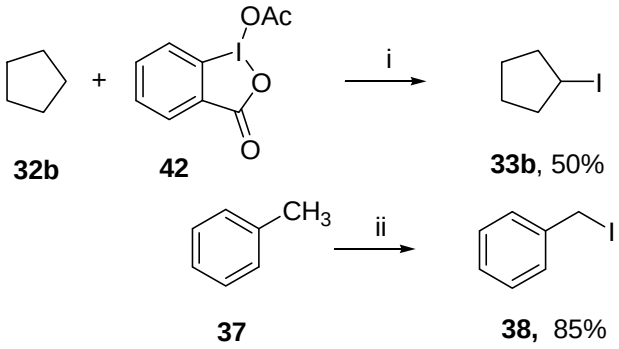
Barluenga *et al.* have reported the photochemical iodination of alkanes and thermally vic-acetoxyiodination of cycloalkanes **39** by using $PhI(OAc)_2$ and molecular I_2 to gave corresponding iodoalkanes **40** and acetoxyiodo compounds **41** in 85-98% and 65-92% yields respectively. The reported examples leading to the synthesis of 1,2-difunctional derivatives constitute the first diastereoselective vic-activation of the hydrocarbons (**Scheme 23**).



Scheme 23: (i) I_2 (1.1 equiv.), hydrocarbons (25 mL), $PhI(OAc)_2$, *tert*-BuOH, *hv*, 14 h; (ii) I_2 (1.1 equiv.), hydrocarbons (25 mL), $PhI(OAc)_2$, *t*-BuOH, 40 °C, 14 h.

The same group have used the following reagents: (i) 1-acetoxy-1,2-benziodoxole-3(1H)-

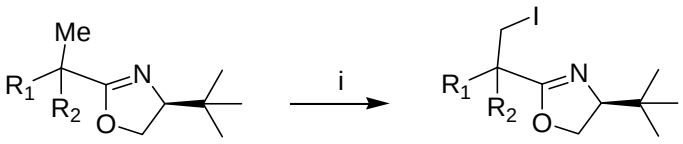
one (**42**), I_2 and $TMSN_3$; (ii) H_2O_2, I_2, and NaN_3. These reagent combinations were found to be effective for the iodination of various hydrocarbons giving the corresponding alkyl iodides in good yields (**Scheme 24**).



Scheme 24: (i) I_2 (1.1 equiv.), hydrocarbons (25 mL), $TMSN_3$, 60 °C , 15 h; (ii) I_2, H_2O_2, NaN_3, Ac_2O, H_2O, 40 °C, 13 h.

Yu's approach (2005)[41]

Yu *et al.* have reported palladium catalyzed an auxiliary approach for the chemoselective and asymmetric iodination of methyl group located at the α-position of oxazolines **43** (**Scheme 25**). The combination of $Pd(OAc)_2$, I_2, and $PhI(OAc)_2$ was shown to be a powerful protocol for the catalytic and asymmetric iodination of methyl, cyclopropyl and aryl groups under mild conditions.



43

R_1 = Me, Et
R_2 = Me, Et, *tert*-Bu

44

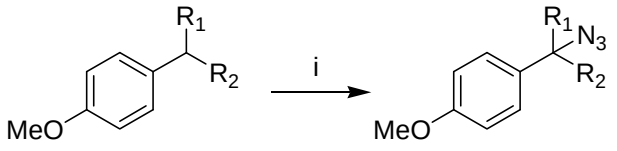
yield = 32-97%
dr = upto 9:1

Scheme 25: (i) $Pd(OAc)_2$ (10 mol%), I_2, $PhI(OAc)_2$ (1 equiv), CH_2Cl_2, 24 °C, 48-72 h.

(b) Direct benzylic azidation

Kita's approach (1994)[42]

Kita *et al*. have reported direct benzylic azidation of *p*-alkyl anisole **45** with hypervalent iodine reagent such as $PhI(OCOCF_3)_2$ and trimethylsilyl azide to give the corresponding benzyl azides **46** in 34-73% yields (**Scheme 26**).



45 **46**

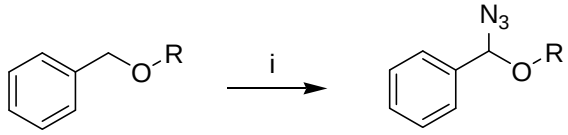
R_1 = Me, CN
R_2 = alkyl, H, S-Me

34-73%

Scheme 26: (i) *p*-alkyl anisole , $PhI(OCOCF_3)_2$, $TMSN_3$, CH_3CN, 40 °C.

Bols's approach (2001, 2005)[43, 18]

In this approach, Bols *et al.* have used iodine azide (IN_3) for the direct azidation of benzyl ether **47** to the corresponding benzyl azides **48** in high yields **(Scheme 27)**.



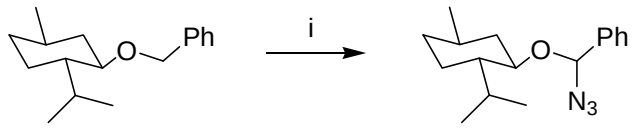
47

R = alkyl, cycloalkyl

48, 75-98%

Scheme 27: (i) ICl, NaN_3, CH_3CN, -10 °C, then benzyl ether, reflux, 3-4 h.

The same authors have also reported a direct azidation of benzyl ether **49** with polymer supported diazidoiodate to give the corresponding benzyl azides **50** in high yields **(Scheme 28)**.



49 **50,** 60%

Scheme 28: (i) polystyrene-NMe_3I, $PhI(OAc)_2$, $TMSN_3$, CH_3CN, 83 °C.

3.3.3. Present Work

3.3.3.1 Objective

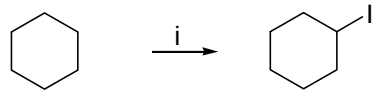
From the above discussion, it is clear that most of the reported methods for iodination of alkanes suffer from certain drawbacks like low yields and poor selectivity, molecular iodine as the iodine source and other expensive oxidants. The effective method for the 1,2-functionalization of unactivated C-H bonds in a single step represents a major challenge for chemists. Hence, a practical method for mono- and 1,2-difunctionalization of hydrocarbons which should involve less toxic and easily available reagents are desirable. This section describes the use of $NaIO_4$-KI-NaN_3 combination to selectively functionalize the C-H bonds of hydrocarbons to produce iodoalkanes **33**, 1-acetoxy- or 1-azido-2-iodocycloalkanes **51** or benzyl azides **52**, in excellent yields upon reaction with the respective hydrocarbons.

3.3.4. Results and Discussion

3.3.4.1 Direct iodination of alkanes

During the course of our study on $NaIO_4$-mediated oxidative azidoiodination, we noticed that regiospecific addition of I-N_3, generated *in situ*, onto alkenes took place in an *anti*-Markovnikov fashion, suggesting a probable radical pathway (for details, see Section I of this chapter). This prompted us to explore the effectiveness of the $NaIO_4$-KI-NaN_3

combination in the C-H activation of alkanes. We describe in this section the use of $NaIO_4$-KI-NaN_3 combination that selectively functionalizes the C-H bonds of hydrocarbons to produce iodoalkanes **33a-g**, 1-acetoxy- or 1-azido-2-iodocycloalkanes **51a-d** or benzyl azides **52a-g**, in excellent yields depending upon reaction condition with the respective hydrocarbons **32**. Thus, when cyclohexane **32a** was treated with $NaIO_4$, KI and NaN_3 (all 1 equiv.) in acetic acid at 25 °C, iodocyclohexane **32a** was isolated in 32% yield. However, the yield could be increased dramatically to 99% when 3 equiv. of NaN_3 was used (**Scheme 29**).[44]



32a **33a,** yield = 99%

Scheme29: (i) cyclohexane (excess), $NaIO_4$ (1 equiv.), KI (1 equiv.), NaN_3 (3 equiv), glacial AcOH, 25 °C.

This novel iodination process is successful for a variety of alkanes including cyclic and acyclic and its completion is readily ascertained by a distinct colour change observed in the reaction from dark brown to colourless. The presence of both $NaIO_4$ and NaN_3 was essential for obtaining high yields of iodoalkanes **33a-g**. Interestingly, for linear alkanes, an improved selectivity was observed as only the methylene positions were iodinated (**Table 4**).

Table 4: $NaIO_4$-mediated iodination of alkanes.[a]

Entry	R-H (32a-g)	t (h)	Yield of (33a-g) (%)[b]
a	Cyclohexane	8	99
b	Cyclopentane	6	98
c	Cycloheptane	8	99

d	Cyclooctane	4	99[c]
e	*n*-Pentane	9	99 (2:1)[d]
f	*n*-Hexane	6	98 (1.1:1)[e]
g	*n*-Heptane	8	97 (2.5:2.2:1)[f]

Reaction conditions: (a) alkane (5 mL), $NaIO_4$ (5 mmol), KI (5 mmol), NaN_3 (15 mmol), glacial AcOH (15 mL), 25 °C; [b] Yield was calculated based on KI; [c] 2 equiv. each of $NaIO_4$ and NaN_3 used; [d] 2-I:3-I pentane; [e] 2-I:3-I hexane; [f] 2-I:3-I:4-I heptane; (ratios determined by ^{1}H-NMR and GC).

The formation of iodoalkanes **33a-g** was confirmed by ^{1}H-NMR and ^{13}C-NMR spectroscopy. For example, the ^{1}H-NMR spectrum of iodocycloheptane (**33c**) showed a multiplet at δ 4.40-4.51 corresponding to methine proton (-CH-I). Its ^{13}C-NMR showed a typical signal at δ 35.6 for methine carbon attached to iodo group (**Fig. 5**). In the case of linear alkanes, the ratios were confirmed by GC and ^{1}H-NMR spectrum.

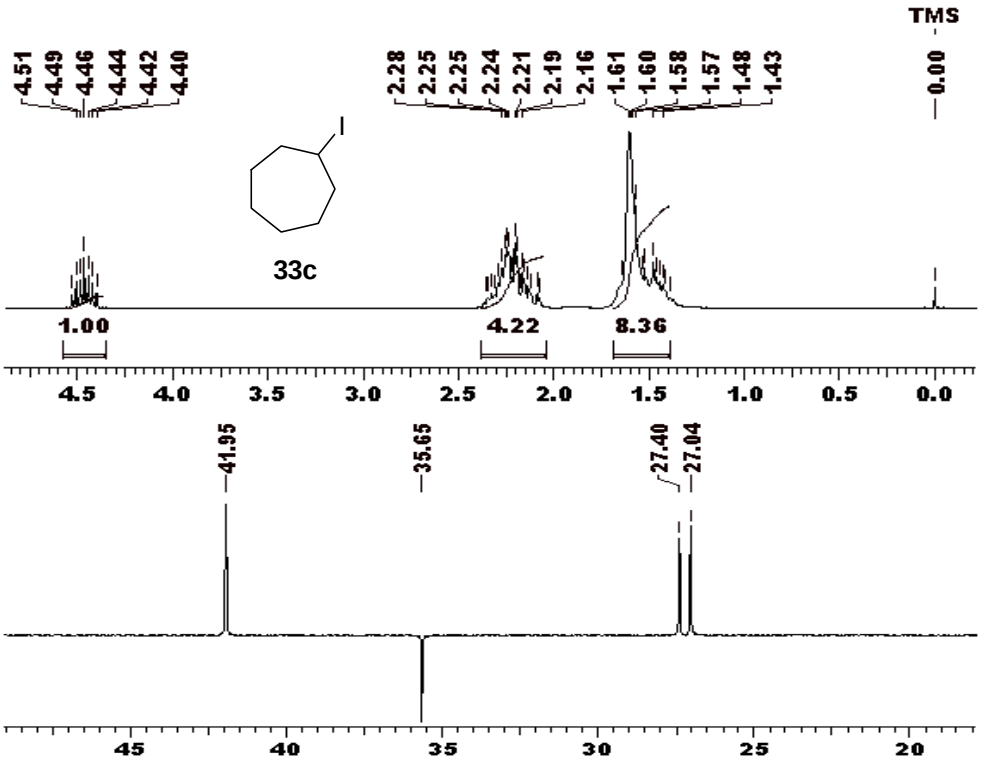
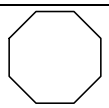
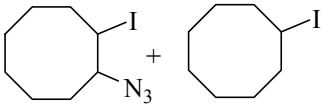
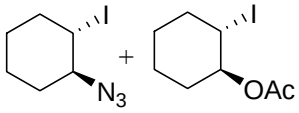
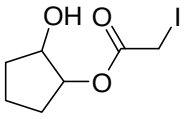


Fig. 5: ^{1}H and ^{13}C NMR spectra of **33c**

Surprisingly, for cyclooctane under the same reaction condition, the reaction took a different course to furnish **51a** in 60% yield along with **33d** in 15% yield (**Table 5**).

Table 5: $NaIO_4$-mediated 1, 2-difunctionalization of cycloalkanes with KI and NaN_3[a]

Entry	R-H (32)	NaN_3 (equiv.)	t (h)	T (°C)	Yield of 51 (%)[b]
1					 **51a** **33d**
		3	4	25	60 15
		6	4	25	85[c] -
2					 **51b** **51c**
		3	24	45	10 5[d]
		6	24	45	62 35
		3	10	75	- 70[e]
		3	10	75	- 94[f]
3					 **51d**
		3	10	45	–[g]
		6	30	45	50[h,i]

[a] Reaction conditions: cycloalkane (5 mL), $NaIO_4$ (5 mmol), KI (5 mmol), gl. AcOH (15 mL); [b]Yield was calculated based on KI; [c]*syn:anti* = 2:1 by ^{1}H NMR;
[d]**33a** was formed in 81% yield; [e]**33a** was also formed in 25% yield; [f]2 equiv. of $NaIO_4$ was used; [g]cyclopentyl acetate was formed in 95% yield; [h]cyclopentyl acetate was also formed in 46% yield; [i] Stereochemistry was not assigned.

However, with 6 molar equiv. of NaN_3, **51a** was obtained in 85% yield with *syn: anti* ratio of 2:1. It was also observed that both $NaIO_4$ and NaN_3, in appropriate concentrations, were critical in determining product selectivities. Thus, for cyclohexane, at 45 °C, with 3 molar equiv. of NaN_3, **33a** (81%) was obtained along with **51b** (10%) and **51c** (5%), while use of 6 molar equiv of NaN_3 resulted in improved product selectivity: **51b** (62%) and **51c** (35%). At 75 °C, an excellent yield of **51c** (94%) was realized with $NaIO_4$ (2 equiv.; 10 mmol). For cyclopentane, at 45 °C, only cyclopentyl monoacetate was obtained in 95% yield whereas an increase of azide concentration (6 molar equiv.) gave an unusual 1, 2-dihydroxyiodo derivative **51d** in 50% yield along with cyclopentyl monoacetate **(**46%). In the case of cycloheptane, an increase of either the temperature or azide concentration resulted in only cycloheptyl monoacetate in 96% yield. Overall, increasing the temperature facilitates oxidative elimination of the iodoalkane to furnish an alkene, thereby giving higher yields of difunctionalized products. However, in the case of cycloheptane and cyclopentane, nucleophilic substitution becomes a favorable process.[45]

The formation of 1-acetoxy- or 1-azido-2-iodocycloalkanes **51a-d** was confirmed by ^{1}H-NMR and ^{13}C-NMR spectroscopy. For example, the ^{1}H-NMR spectrum of 1-acetoxy-2-iodocyclohehanes (**51c**) showed multiplets at δ 3.98-4.11 and 4.82-4.94 corresponding to methine protons. Its ^{13}C-NMR spectrum showed a typical signal at δ169.5 for carbonyl carbon of acetoxy group (**Fig. 6)**

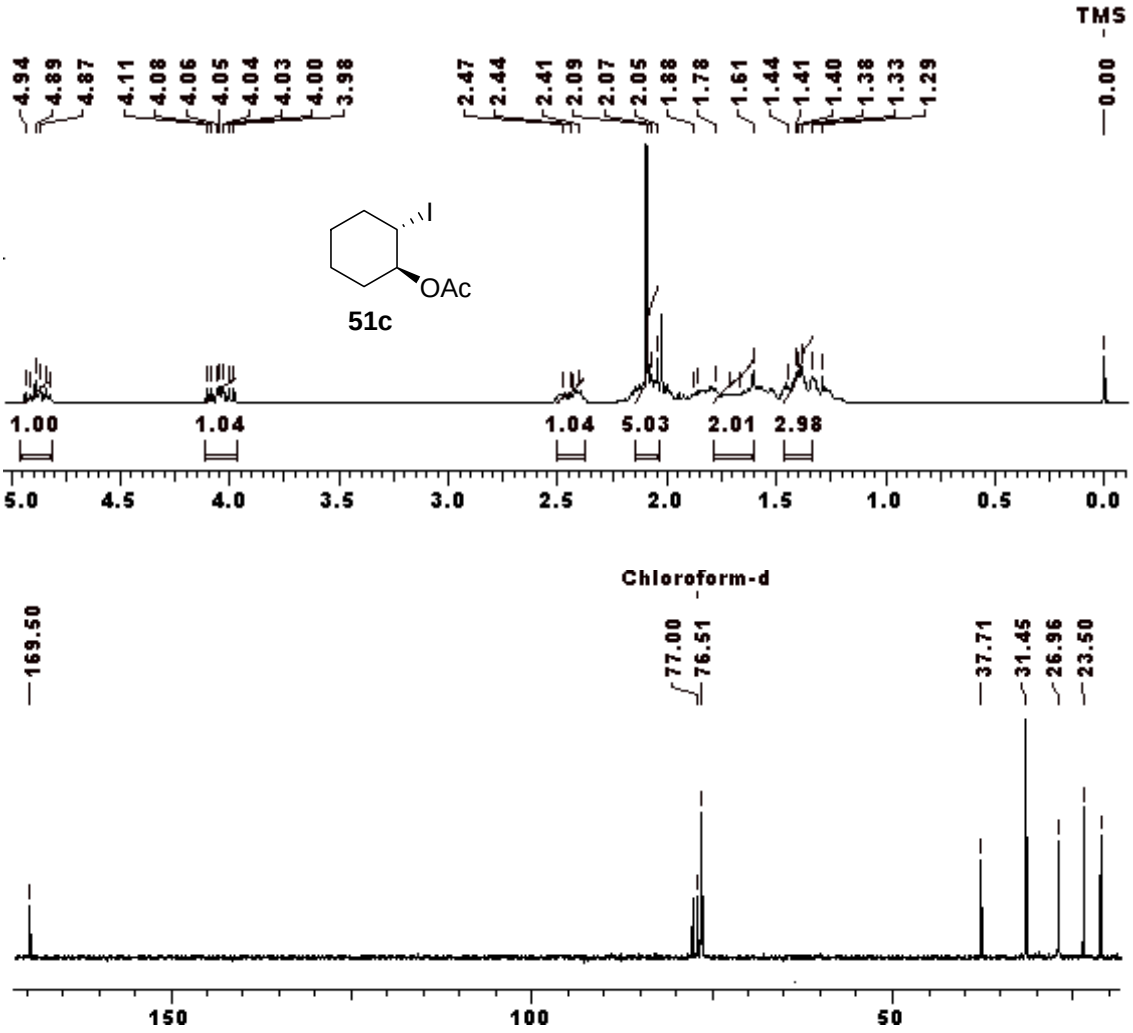
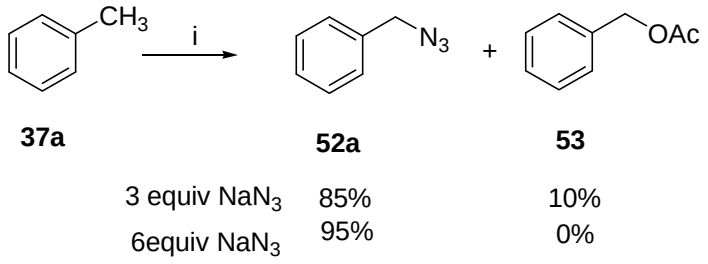


Fig. 6: ^{1}H and ^{13}C NMR spectra of **51c**

3.3.4.2 Direct azidation at benzylic position

Direct azidation *via* functionalization at Ar-C-H bonds is an atom economical route in organic synthesis.[46] A recent report on direct azidation of activated arenes using polymer-supported iodine azide has established that a certain electron-donating capacity is needed at the benzylic position for the reaction to occur. With the $NaIO_4$- KI-NaN_3 system (1:1:3 molar ratio), we found that toluene **37a** was functionalized smoothly at the benzylic position to give benzyl azide **52a** (85%) along with benzyl acetate **53** (10%). Further, on

increasing the concentration of azide (6 equiv), exclusive formation of monobenzyl azide **52a** (95%) was realized (**Scheme 30**).



Scheme30: : (i) toluene (excess), $NaIO_4$ (1 equiv.), KI (1 equiv.), NaN_3 (6 equiv.), glcial AcOH, 25 °C.

To study the generality of the reaction, a variety of toluene derivatives were subjected to azidation with $NaIO_4$-KI-NaN_3 reagent combination, and the results are presented in **Table 6**.

Table 6: $NaIO_4$-mediated azidation at the benzylic C-H bond of alkyl arenes[a]

Entry	Arene (37)	t (h)	Benzyl azide (52)	Yield (%)[b]
a	Toluene	8	benzyl azide	95
b	*o*-Xylene	8	2-methylbenzyl azide	85
c	*m*-Xylene	7	3-methylbenzyl azide	90
d	*p*-Xylene	8	4-methylbenzyl azide	93
e	mesitylene	7	3,5-dimethylbenzyl azide	89
f	Ethylbenzene	15	1-azidoethylbenzene	20[c]
g	Indane	15	1-azidoindane	50[c]

Reaction conditions: [a] arene (5 mL), $NaIO_4$ (5 mmol), KI (5 mmol), NaN_3 (30 mmol), glacial AcOH (20 mL), 25 °C;[b] Yield was calculated based on KI; [c] reaction was carried out without KI at 75 °C in DMSO-AcOH (4:1).

Notably, no polyazidation took place for other alkylarenes even if higher equivalents of NaN_3 were used (**Table 6**). In similar reaction condition, no reaction took place in the case of secondary alkyl arenes such as ethyl benzene and indane. However, when ethyl

benzene and indane were subjected to oxidative functionalization in the absence of KI, with $NaIO_4$ (1 equiv) in the presence NaN_3 (3 equiv) in AcOH: DMSO (1: 4) as solvent at 75 °C, the corresponding secondary benzyl azides could be obtained in 20% and 50% yields respectively. The formation of benzyl azides **52a-g** was confirmed by ^{1}H-NMR, ^{13}C-NMR and IR spectroscopy. The ^{1}H NMR spectrum of **52d** showed a singlet at δ 4.28 for benzylic methylene proton attached to azide group (Ar-CH_2-N_3). Its ^{13}C NMR spectrum showed a typical signal at δ 45.4 due to methylene carbon attached to azide group (**Fig. 7**).

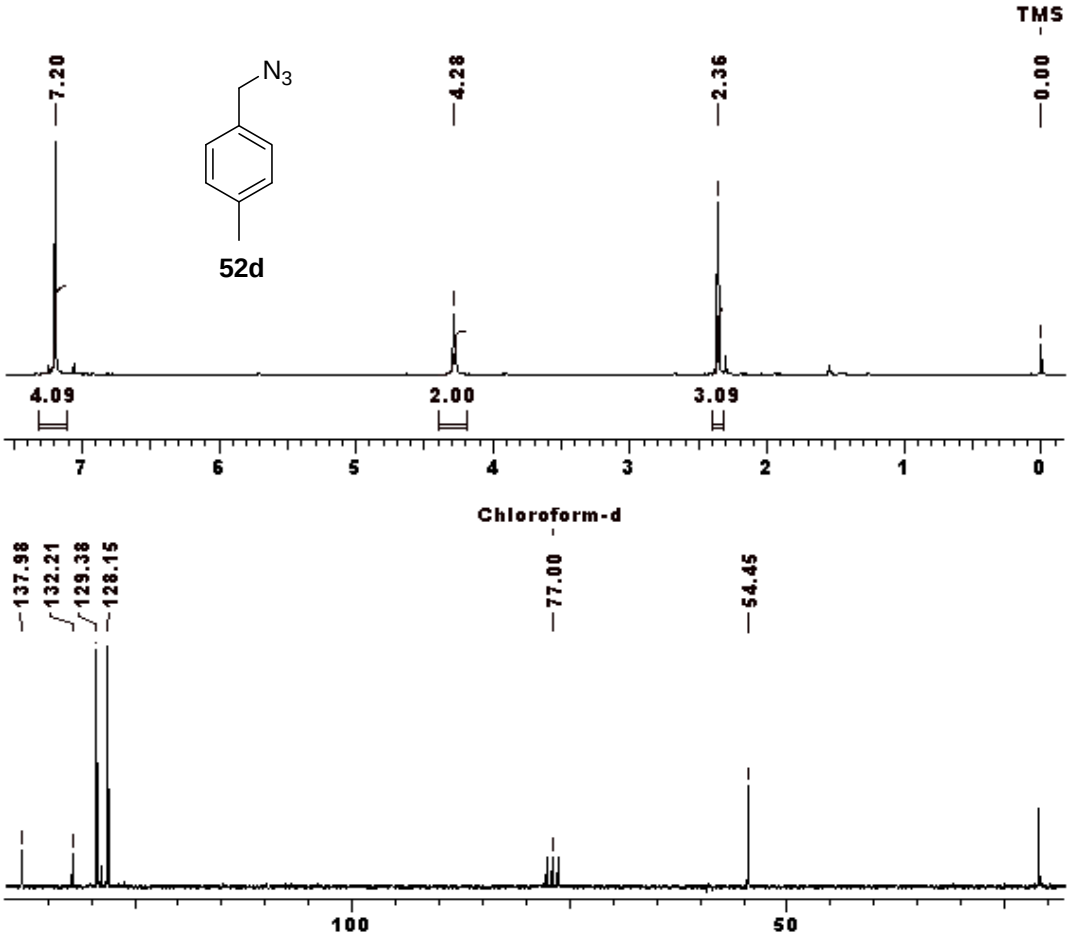


Fig. 7: ^{1}H and ^{13}C NMR spectra of **52d**

The ^{1}H NMR spectrum of **52g** showed a doublet of doublet at δ 4.85 for benzylic methine proton attached to azide group (Ph-CH.N_3). Its ^{13}C NMR spectrum showed a typical signal at δ 65.7 for methine carbon attached to azide group (**Fig. 8**).

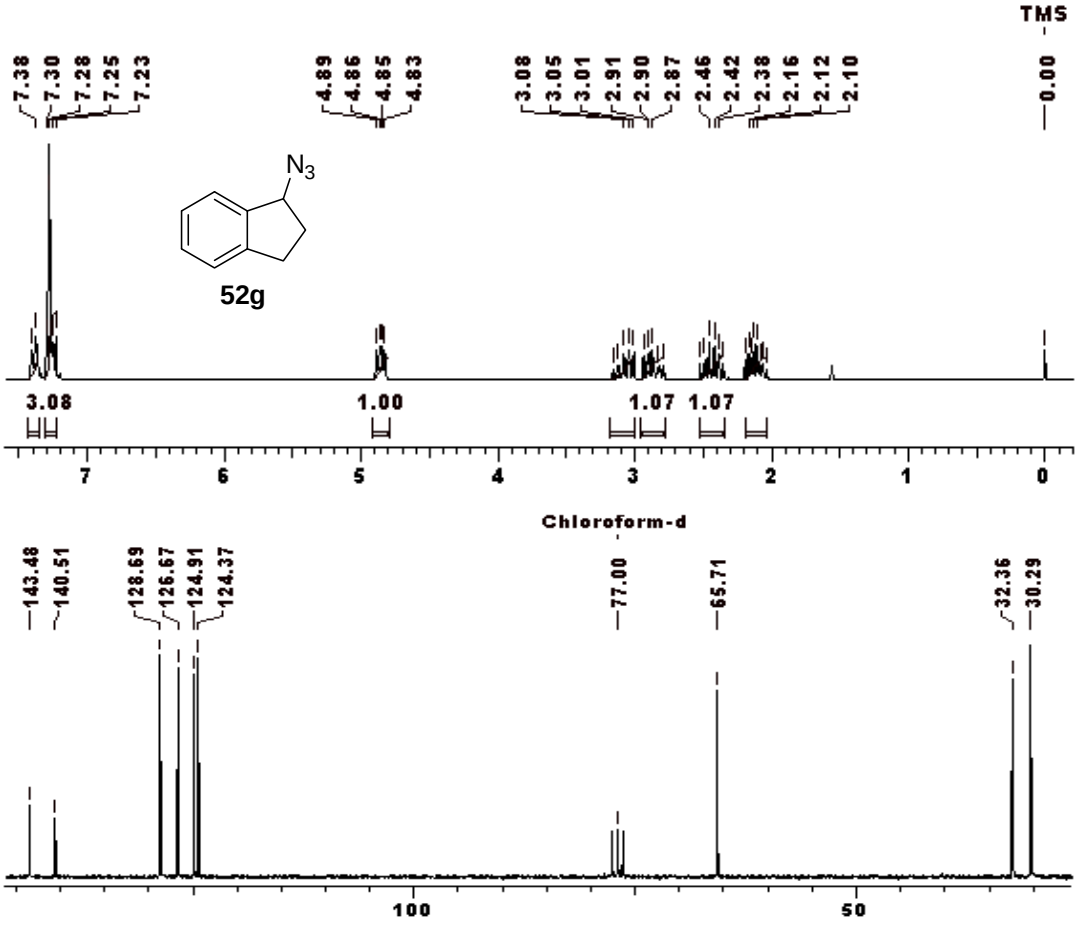
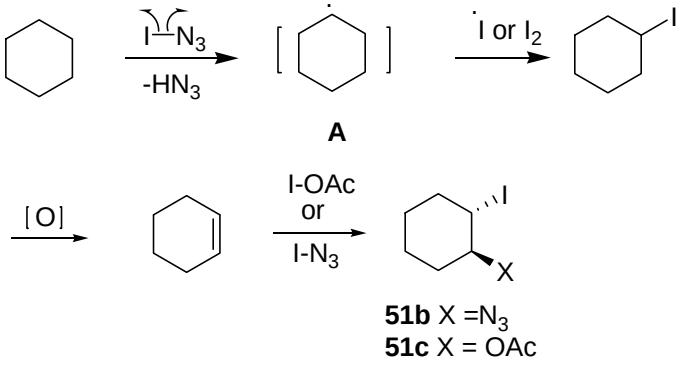


Fig. 8: ^{1}H and ^{13}C NMR spectra of **52g**

3.3.5. Mechanism for C-H activation of alkanes

Mechanistically, we have proved that $NaIO_4$ oxidizes KI as well as NaN_3 simultaneously, to liberate I_2[15] and an azide radical[16] respectively; combination of which results in the formation of I-N_3. To confirm the formation of I_2, alkane was treated with molecular iodine instead of KI. We found in this study that similar results were indeed obtained.

Homolysis of I-N_3[18] provides an azide radical, which abstracts a proton from alkane to produce alkyl radical **A**. Combination of radical **A** with I_2 followed by oxidative elimination of the resulting alkyl iodide[47] generates alkene (confirmed by GC analysis). Addition of either I-N_3 or I-OAc across the double bond produces **51b** and **51c,** respectively (**Scheme 31**). Evidence for the radical pathway is deduced from the following experiment: no reaction took place in the presence of *N-tert*-butyl-α-phenylnitrone, a radical scavenger.[18] In the case of direct azidation of alkyl arenes, the involvement of a benzyl radical followed by a benzyl cation is similarly proposed. [43]



Scheme 31: Proposed mechanistic pathway for the C-H activation of alkanes

3.3.6. Conclusion

In conclusion, we have described $NaIO_4$-KI-NaN_3 as a new efficient system suitable for mono and 1,2-difunctionalization of hydrocarbons *via* C-H bond activation. In particular, reaction invoving vicinal azido- and acetoxy iodinations of cyclic hydrocarbons in high yields and selectivity are unique and unprecedented. A high yield direct azidation at the benzylic position in less activated alkyl arenes has been demonstrated under ambient conditions.

3.3.7. Experimental section

General experimental procedure for iodination of alkane: To a suspension of NaN_3 (0.975 g, 15 mmol) and KI (0.830 g, 5 mmol) in glacial acetic acid (20 ml) at 25°C was added $NaIO_4$ (1.069 g, 5 mmol) and the reaction mixture was stirred for 5 minutes so that the dark-brown color was formed. Alkanes **32** in excess (5 mL) were then added and the colored reaction mixture was stirred at the same temperature for 8h until the dark-brown was changed to colorless. The reaction mixture was poured into water (100 mL) and extracted with CH_2Cl_2 (3×50 mL)). The combined organic layers were washed with saturated solution of $NaHCO_3$ (50 mL) and washed with aq. $Na_2S_2O_3$ (5%, 50 ml) dried over anhyd. Na_2SO_4, concentrated and unreacted alkane recovered by simple distillation under reduced pressure to give the crude product, which was then purified by column chromatography (packed with silica gel 60-120 mesh) using petroleum ether as eluents to afford the pure products **33a-g**

Iodocyclohexane (33a)

Yield: 99%; colorless oil; **IR** ($CHCl_3$, cm^{-1}): 2933, 2854, 1448, 1215, 1172, 1095, 987, 759, 669; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 1.37-1.49 (m, 3H), 1.64-1.74 (m, 3H), 1.93-2.05 (m, 2H), 2.13-2.20 (m, 2H), 4.30-4.43 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 25.1, 27.2, 32.6, 39.5; **Anal.** Calcd for $C_6H_{11}I$ requires C, 34.31; H, 5.28; found: C, 34.30; H, 5.30 %.

Iodocyclopentane (33b)

Yield: 98%; colorless oil; **IR** ($CHCl_3$, cm^{-1}): 2935, 2855, 1450, 1216, 1174, 1098, 988, 760, 670; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.56-1.73 (m, 2H), 1.76-1.94 (m, 2H), 2.03-

2.12 (m, 4H), 4.25-4.39 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 23.9, 28.1, 39.7; **Anal.** Calcd for C_5H_9I requires C, 30.63; H, 4.63; found: C, 30.62; H, 4.65 %.

Iodocycloheptane (33c)

Yield: 99%; colorless oil; **IR** ($CHCl_3$, cm^{-1}): 2925, 2854, 1446, 1215, 1184, 1120, 939, 757, 646; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.39-1.64 (m, 8H), 2.08-2.35 (m, 4H), 4.40-4.53 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 27.0, 27.3, 35.6, 41.9; **Anal.** Calcd for $C_7H_{13}I$ requires C, 37.52; H, 5.85; found: C, 37.50; H, 5.86%.

Iodocyclooctane (33d)

Yield: 99%; colorless oil; **IR** ($CHCl_3$, cm^{-1}): 2922, 2852, 1442, 1214, 1185, 1122, 935, 756, 644; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.44-1.70 (m, 10H), 2.20-2.29 (m, 4H), 4.54-4.67 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 25.0, 26.5, 27.3, 37.8, 38.2; **Anal.** Calcd for $C_8H_{15}I$ requires C, 40.35; H6.35; found: C, 40.34; H, 6.38 %.

Mixture of 2-iodopentane and 3-iodopentane ≈ 2:1 (33e)

Yield: 99%; colorless oil; **IR** ($CHCl_3$, cm^{-1}): 2928, 2847, 1461, 1216, 758, 668; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.85-1.06 (m, 4H), 1.38-1.68 (m, 2H), 1.70-1.94 (m, 4H), 3.99-4.23 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.1, 14.1, 22.9, 28.9, 29.7, 33.3, 43.9,44.9; **Anal.** Calcd for $C_5H_{11}I$ requires C, 30.32; H, 5.60; found: C, 30.34; H, 5.57 %.

Mixture of 2-iodohexane and 3-iodohexane ≈ 1:1 (33f)

Yield: 98%; colorless oil; **IR** ($CHCl_3$, cm^{-1}): 2930, 2850, 1461, 1215, 757, 669; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.81-0.99 (m, 4H), 1.22-1.33 (m, 3H), 1.48-1.59 (m, 2H), 1.69-1.89 (m, 3H), 3.99-4.15 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 13.2, 13.9, 14.0, 21.8, 22.7, 28.91, 30.6,31.8, 33.6, 42.1, 42.3, 42.6; **Anal.** Calcd for $C_6H_{13}I$ requires C, 33.98; H, 6.18; found: C, 33.95; H, 6.20 %.

Mixture of 2-iodoheptane and 3-iodoheptane and 4-iodoheptane ≈ 2.5:2.2:1 (33g)

Yield: 98%; colorless oil; **IR** ($CHCl_3$, cm^{-1}): 2931, 2873, 1461, 1216, 757, 669; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.85-1.08 (m, 4H), 1.23-1.98 (m, 10H), 4.03-4.22 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 13.3, 14.0, 14.1, 14.1, 22.0, 22.5, 22.8, 29.0, 29.4, 30.1, 30.9, 31.72, 33.7, 39.2, 40.0, 41.9, 42.7, 42.9; **Anal.** Calcd for $C_7H_{15}I$ requires C, 37.19; H, 6.69; found: C, 37.21; H, 6.70 %.

1-Azido-2-iodocyclooctane (*syn*: *anti* = 2:1) (51a)

Yield: 85%; pale yellow oil; **IR** ($CHCl_3$, cm^{-1}): 2926,2854, 2094, 1444, 1259, , 779; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 1.38-1.82 (m, 10H), 1.93-2.40 (m, 2H), 3.41-3.49 (qd, J = 3.9, 2.8, Hz, 1H), 4.54-4.64 (qd, J = 2.8, 6.2 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 23.1, 23.9, 25.1, 25.6, 26.1, 26.2, 27.1, 27.1, 31.5, 31.7, 34.2, 36.9, 38.6, 39.0, 64.1, 71.0; **Anal.** Calcd for $C_8H_{14}IN_3$ requires C, 34.42; H, 5.06, N, 15.05; found: C, 34.46; H, 5.00, N, 15.04 %.

Typical experimental procedure for 1-Azido-2-iodocyhexane (51b): To a suspension of NaN_3 (1. 950 g, 30 mmol) and KI (0.830 g, 5 mmol) in glacial acetic acid (20 ml) at 25°C was added $NaIO_4$ (1.069 g, 5 mmol) and the reaction mixture was stirred for 5 minutes so that the dark-brown color was formed, followed by the addition of cyclohexane (5 mL). The colored reaction mixture was stirred at the same temperature for 4 h followed by and at 45 °C for 24 h. During heating, the color of the reaction mixture has disappeared and again reappeared. The reaction mixture was then poured into water (100 mL) and extracted with CH_2Cl_2 (3×50 mL)). The combined organic layers were washed with saturated aq. solution of $NaHCO_3$ (50 mL), aq. $Na_2S_2O_3$ (5%, 50 mL) and dried over anhyd. Na_2SO_4, concentrated and unreacted alkanes recovered by simple

distillation under reduced pressure to give the crude product, which was then purified by column chromatography (packed with silica gel 60-120 mesh) using petroleum ether as eluent to afford the pure product **51b**.

Yield: 65%; pale yellow oil; **IR** ($CHCl_3$, cm^{-1}): 2939 2860, 2100, 1448, 1257,1217, 923, 769, 669; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.31-1.57 (m, 4H), 1.99-2.50 (m, 4H), 3.46-3.58 (m, 1H), 3.90-4.03 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 23.7, 26.9, 31.8, 33.2, 38.3, 67.1; **Anal.** Calcd for $C_6H_{10}IN_3$ requires C, 28.70; H, 4.01, N, 16.74; found: C, 28.72; H, 4.00, N, 16.73 %.

2-Iodocyclohexylacetate (51c)

Yield: 94%; pale yellow oil; **IR** ($CHCl_3$, cm^{-1}): 2939 2861, 1735, 1448, 1236,1047, 756, 667; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.25-1.52 (m, 3H), 1.57-1.85 (m, 2H), 1.98-2.16 (m, 2H), 2.09 (s, 3H), 2.40-2.51 (m, 1H), 3.98-4.11 (m, 1H), 4.82-4.94 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.1, 23.5, 27.0, 31.5, 37.7, 76.5, 169.5; **Anal.** Calcd for $C_8H_{13}IO_2$ requires C, 35.84; H, 4.89; found: C, 35.86; H, 4.86 %.

2-Hydroxycyclopentyl 2-iodoacetate (51d)

Yield: 50%; pale yellow oil; **IR** ($CHCl_3$, cm^{-1}): 3446, 2976, 1730, 1417, 1215, 923, 757, 668; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.53-2.17 (m, 8H), 1.70-1.90 (br s, 1H) 3.73-3.4 (d, J = 1.7 Hz, 2H), 4.18-4.26 (m, 1H), 4.96-5.04 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ -5.1, 19.2, 27.6, 30.6, 73.0, 78.2, 168.4; **Anal.** Calcd for $C_7H_{11}O_3$ requires C, 31.13; H, 4.11; found: C, 31.10; H, 4.12 %.

General experimental procedure for azidation of alkyl arenes: To a suspension of NaN_3 (1.950 g, 30 mmol) and KI (0.830 g, 5 mmol) in glacial acetic acid (20 ml) at 25°C was added $NaIO_4$ (1.069 g, 5 mmol) and the reaction mixture was stirred for 5 minutes so

that the dark-brown color was formed. Alkyl arenes **37** in excess (5 mL) were then added and the reaction mixture was stirred at the same temperature for 8 h. The reaction mixture was poured into water (100 mL) and extracted with CH_2Cl_2 (3×50 mL)). The combined organic layers were washed with saturated solution of $NaHCO_3$ (50 mL) followed by washed with aq. $Na_2S_2O_3$ (5%, 50 mL), dried over anhyd. Na_2SO_4, concentrated and unreacted alkane recovered by simple distillation under reduced pressure to give the crude product **52a-e**, which was then purified by column chromatography (packed with silica gel 60-120 mesh) using pet. ether as eluents to afford the pure products **52a-e**.

1-(Azidomethyl) benzene (52a)

Yield: 95%; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): 3032, 3015, 2930, 2877, 2097, 1605, 1586, 1496, 1455, 1255, 1217, 758, 699, 668; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 4.33 (s, 2H), 7.34-7.43 (m 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 54.7, 128.1, 128.2, 128.76, 135.3; **Anal.** Calcd for $C_7H_7N_3$ requires C, 63.14; H, 5.30; N, 31.56; found: C, 63.00; H, 5.40; N, 31.20%.

1-(Azidomethyl)-2-methylbenzene (52b)

Yield: 85%; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): 3019, 2974, 2934, 2105, 1553, 1456, 1215, 757, 668; **^{1}H NMR** (200 MHz, $CDCl_3$): δ2.37 (s, 3H), 4.35 (s, 2H), 7.21-7.28 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 18.8, 52.8, 126.0, 128.5, 129.2, 130.5, 133.2, 136.6; **Anal.** Calcd for $C_8H_9N_3$ requires C, 65.29; H, 6.16; N, 28.55; found: C, 65.18; H, 6.24; N, 28.45%.

1-(Azidomethyl)-3-methylbenzene (52c)

Yield: 90%; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): 3024, 2924, 2873, 2098, 1592, 1490, 1455, 1264,1237, 864, 778, 742, 702; **^{1}H NMR** (200 MHz, $CDCl_3$): δ2.37 (s, 3H), 4.29

(s, 2H), 7.09-7.16(m 3H) 7.23-7.28 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.1, 54.7, 125.1, 128.6, 128.8, 128.9, 135.2, 138.4; **Anal.** Calcd for $C_8H_9N_3$ requires C, 65.29; H, 6.16; N, 28.55; found: C, 65.22; H, 6.20; N, 28.35%.

1-(Azidomethyl)-4-methylbenzene (52d)

Yield: 93%; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): 3017, 2926, 2100, 1515, 1450, 1254, 1216, 804,757, 668; **^{1}H NMR** (200 MHz, $CDCl_3$): δ2.36 (s, 3H), 4.28 (s, 2H), 7.20 (s, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.0, 54.4, 128.1, 129.3, 132.2, 137.9; **Anal.** Calcd for $C_8H_9N_3$ requires C, 65.29; H, 6.16; N, 28.55; found: C, 65.19; H, 6.09; N, 28.44%.

1-(Azidomethyl)-3,5-dimethylbenzene (52e)

Yield: 89%; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): 3017, 2921, 2870, 2097, 1605, 1464, 1245, 841,725; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.33 (s, 6H), 4.26 (s, 2H), 6.93 (s, 2H), 6.97 (s, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 21.1, 54.7, 125.9, 129.8, 135.1, 138.3; **Anal.** Calcd for $C_9H_{11}N_3$ requires C, 67.06; H, 6.88; N, 26.07; found: C, 67.15; H, 6.92; N, 26.10%.

Typical experimental procedure for azidation of ethylbenzene and indane: To a suspension of NaN_3 (0.975 g, 15 mmol) and $NaIO_4$ (1.069 g, 5 mmol) in (20 mL) DMSO: glacial AcOH (4: 1) was added ethyl benzene or indane (**37f** or **37g)** 5 mL as the case may be, and the reaction mixture was stirred at the 75 °C for 6 h until the mixture became dark brown in color. Then the reaction mixture was poured into water (100 mL) and extracted with EtOAc (3×50 mL). The combined organic layers were washed with a saturated solution of $NaHCO_3$ (50 mL) and aq. $Na_2S_2O_3$ (5%, 50 mL), dried over anhyd. Na_2SO_4. Concentration of the organic layer gave benzyl azide, which was subjected to column purification using hexane/ethyl acetate (20:1) as eluent to obtain pure benzyl azides **52f-g**.

1-Azidoethylbenzene (52f)

Yield: 20%; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): 3040, 2960, 28880, 2106, 1607, 1494, 1250, 775, 730; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.53 (d, *J* = 6.8 Hz, 3H), 4.62 (q, *J* = 6.8, 1H), 7.30-7.38 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 23.1, 66.0, 126.1, 127.8, 128.6, 139.3; **Anal.** Calcd for $C_8H_9N_3$ requires C, 65.29; H, 6.16; N, 28.55; found: C, 65.20; H, 6.10; N, 28.63%.

1-Azidoindane (52g)

Yield: 50%; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): 3020, 2925, 2871, 2097, 1601, 1463, 1250, 843; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.03-2.19 (m, 1H), 2.36-2.52 (m,1H), 2.79-2.94 (m, 1H), 3.01-3.16 (m, 1H), 4.85 (dd, *J* = 4.7, 7.0 Hz, 1H), 7.23-7.30 (m, 3H), 7.37-7.41 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 30.2, 32.6, 65.7, 124.3, 126.6, 128.6, 140.5, 143.4; **Anal.** Calcd for $C_9H_9N_3$ requires C, 67.90; H, 5.70; N, 26.40; found: C, 67.85; H, 5.72; N, 26.44%.

3.3.8 References

1 Hassner, A.; Fowler, F. W. *J. Org. Chem.* **1968**, *33*, 2686.

2 Wasserman, H. H.; Brunner, R. K.; Buynak, J. D.; Carter, C. G.; Oku, T.; Robinson, R. P. *J. Am. Chem. Soc*. **1985**, *107*, 519.

3 (a) Van Ende, D.; Krief, A. *Angew. Chem. Int. Ed.* **1974**, *13*, 279. (b) Denis, J. N.; Krief, A. *Tetrahedron* **1979**, *35*, 2901.

4 (a) Ranganathan, S.; Ranganathan, D.; Mehrotra, A. K. *Tetrahedron Lett*. **1973**, *14*, 2265. (b) Moorthy, S. N.; Devaprabhakara, D. *Tetrahedron Lett*. **1975**, *16*, 257.

5 (a) Fowler, F. W.; Hassner, A.; Levy, A. *J. Am. Chem. Soc*. **1967**, *89*, 2077; (b) Hassner, A. *Acc. Chem. Res.* **1971**, *4*, 9.

6 Woodgate, P. D.; Lee, H. H.; Rutledge, P. S.; Cambie, R. C. *Synthesis*, **1977**, 462

7 Hassner, A.; Levy, L. A. *J. Am. Chem. Soc*. **1965**, *87*, 4203.

8 Kirschning, A.; Hashem, M. A.; Monenschein, H.; Rose, L.; Schoning, K.-U. *J. Org. Chem.* **1999**, *64*, 6522.

9 Kirschning, A.; Monenschein, H.; Schmeck, C. *Angew. Chem. Int. Ed.* **1999**, *38*, 2594.

10 Nair, V.; George, T. G.; Sheeba, V.; Augustine, A.; Balagopal, L.; Nair, L. G. *Synlett* **2000**, 1597.

11 Barluenga, J.; Alvarez-Perez, M.; Fananas, F. J.; Gonzalez, J. M. *Adv. Synth. Catal.* **2001**, *343*, 335.

12 Curini, M.; Epifano, F.; Marcotullio, M. C.; Rosati, O. *Tetrahedron Lett*. **2002**, *43*, 1201.

13 Alexander, O.; Terent'ev, I. B. K.; Vladimir, A. K.; Gennady, I. N. *Syn. Commun*. **2008**, *38*, 3797.

14 (*a*) Dewkar, G. K.; Narina S. V.; Sudalai, A. *Org. Lett.* **2003**, *5*, 4501; (*b*) Emmanuvel, L.; Shaikh T. M. A.; Sudalai, A. *Org. Lett.* **2005**, *7*, 5071.

15 Emmanuvel, L.; Shukla, R. K.; Sudalai, A.; Suryavanshi, G.; Sivaram, S. *Tetrahedron Lett*. **2006**, *47*, 4793.

16 (a) Tingoli, M.; Tiecco, M.; Chianelli, D.; Balducci, R.; Temperini, A. *J. Org. Chem.* **1991**, *56*, 6809. (b) Fontana, F.; Minisci, F.; Yan, Y. M.; Zhao, L. *Tetrahedron Lett.* **1993,** *34*, 2517.

17 Barluenga, J.; Campos-Gomez, E.; Rodriguez, D.; Gonzalez-Bobes F.; Gonzalez, J. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 5851.

18 Marinescu, L.G.; Pedersen C. M.; Bols, M. *Tetrahedron* **2005**, *61*, 123.

19 Kemp J. E. G. in *Comprehensive Organic Synthesis*, Vol. *7* (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, 469.

20 Lucet, D.; Gall, T. L.; Mioskowski, C. *Angew. Chem. Int.Ed.* **1998**, *37*, 2580.

21 Mortensen, M. S.; O_Doherty, G. A. *Chemtracts: Org. Chem.* **2005**, *18*, 555.

22 Saibabu Kotti, S. R. S.; Timmons, C.; Li, G. *Chem. Biol. Drug Des.* **2006**, *67*, 101.

23 De Figueiredo, R. M. *Angew. Chem. Int.Ed.* **2009**, *48*, 1190.

24 a) Swift, G.; Swern, D. *J. Org. Chem***. 1966**, *31*, 4226; b) Swift, G.; Swern, D. *J. Org. Chem***. 1967**, *32*, 511.

25 Skarzewski, J.; Gupta, A. *Tetrahedron Asymmetry*, **1997**, *8*, 1861.

26 Fristad, W. E.; Brandvold, T. A.; Peterson, J. R.; Thompson, S. R.; *J. Org. Chem*. **1985,** *50*, 3647.

27 Moriarty, R. M.; Khosrowshahi, J. S. *Tetrahedron Lett.* **1986**, *27*, 2809.

28 Arimoto, M.; Yamaguchi, H.; Fujita, E.; Nagao, Y.; Ochiai, M. *Chem. Pharm. Bull.* **1989**, *37*, 3221.

29 Chung, R.;Yu, E.; Incarvito, C. D.; Austin, D. J. *Org. Lett.* **2004**, *6*, 3881.

30 Suzuki,T.; Shibata, A.; Morohashi, N.; Ohba, Y. *Chem. Lett.* **2005**, *34*, 1476.

31 Pfaendler, H. R.; Klingl, A. *Helv.Chim. Act.* **2005**, *88*, 1486.

32 Moore, H. W.; Landen, G. *Tetrahedron Lett.* **1976**, *29*, 2515.

33 (a) Goldberg, K. I.; Goldman, A. S. Eds. *Activation and Functionalization of C-H Bonds*; ACS Symposium Series 885; American Chemical Society. Washington, DC, 2004. (b) Curci, R.; D'Accolti L.; Fusco, C. *Acc. Chem. Res.* **2006**, *39*, 1; (c) Godula K.; Sames, D. *Science* **2006**, *312*, 67; (d) Labinger J. A.; Bercaw, J. E. *Nature* **2002**, *417*, 507.

34 (a) Crabtree, R. H. *Chem. Rev.* **1995**, *95*, 987; (b) Mansuy, D. *Pure Appl. Chem.* **1987**, *59*, 759; (c) Sommer J.; Bukala, J. *Acc. Chem. Res.* **1993**, *26*, 370; (d) Barton, D. H. R. *NATO ASI Ser., Ser. E: Appl. Sci*. **1996**, *320*, 589; (e) Murray, R. W.; Iyanar, K.; Chen J.; Wearing, J. T. *Tetrahedron Lett.* **1995**, *36*, 6415; (f) Bales, B. C.; Brown, P.; Dehestani A.; Mayer, J. M. *J. Am. Chem. Soc*. **2005**,

127, 2832; (g) Hill, C. L. *Catal. Met. Complexes* **1992**, *9*, 253.

35 (a) Abbe, L.; Hassner, A. *Angew. Chem. Int. Ed*. **1971**, *10*, 98; (b) Workentin, M. S.; Wagner, B. D.; Lusztyk, J.; Wayner, D. D. M. *J. Am. Chem. Soc.* **1995**, *117*, 119.

36 Tanner D. D.; Gidley, G. C. *J. Am. Chem. Soc.* **1968**, *90*, 808.

37 Schreiner, P. R.; Lauenstein, O.; Butova E. D.; Fokin, A. A. *Angew. Chem. Int. Ed.* **1999**, *38*, 2786.

38 Fokin, A. A.; Lauenstein, O.; Gunchenko P. A.; Schreiner, P. R. *J. Am. Chem. Soc.* **2001**, *123*, 1842.

39 Montoro R.; Wirth, T. *Org. Lett*. **2003**, *5*, 4729.

40 Barluenga, J.; Gonzalez-Bobes F.; Gonzalez, J. M. *Angew. Chem. Int. Ed.* **2002,** *41*, 2556; (*b*)

41 Giri, R.; Chen X.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2005**, *44*, 2112.

42 Kita, Y.; Tohma, H.; Takada, T.; Mitoh, S.; Fujita, S.; Gyoten, M. *Synlett*, **1994**, 427.

43 Viuf, C.; Bols, M. *Angew. Chem. Int. Ed.* **2001**, *40*, 623.

44 Cambie, R. C.; Hayward, R. C.; Rutledge, P. S.; Smith-Plalmer, T.; Swelland, B. E.; Woodgate, P. D. *J. Chem. Soc. Perkin Trans. 1* **1979**, 180.

45 Liu, B.; Shine, H. J. *J. Phys. Org. Chem.* **2001**, *14*, 81.

46 Eric, F. V.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 297.

47 Patai, S.; Rappoport, Z. *The Chemistry of Functional Group, Supplement D*; John Wiley & Sons, 1983**,** chapt. 18, pp. 744.

CHAPTER IV

Palladium-catalyzed Hydrosilylation of Aryl Ketones and Enantioselective Rearrangement of 2-Alkyl Pyridine *N*-oxides and Synthesis of 4-Substituted Chromanes *via* Gold-catalyzed Intramolecular Friedel-Crafts Reaction

Section I

Palladium-catalyzed hydrosilylation of aryl ketones with triethylsilane

4.1.1 Introduction

Reduction of carbonyl and pseudo-carbonyl functions represents a ubiquitous protocol in organic synthesis. Transition-metal catalysis has been successfully applied to the reduction of olefins, alkynes and many carbonyl compounds *via* hydrogenation or hydrosilylation.[1] Hydrogenation reactions often proceed in good yields but only under high pressure or elevated temperature. In contrast, since the first report of metal-catalyzed hydrosilylation of ketones in the presence of Wilkinson's catalyst,[2] smooth reaction conditions have been devised and in consequence over-reduced products are rarely detected. Recently, hydrosilylation reactions using various metals such as Zn, Fe, Rh, Cu, Re, etc have been reported. Furthermore, asymmetric hydrosilylations with high enantioselectivities have also been well-documented.[3] In industry, hydrosilylation has become an appropriate method to produce organosilicon compounds, in particular with respect to the functionalization of polymers.[4] A general sequence involving hydrosilylation of carbonyl compounds followed by hydrolysis leads to the formation of alcohols, but the silyl group may also be retained as a protecting group, a process that can be of great interest in organic synthesis.[5] Moreover, a great majority of hydrosilanes employed in this reaction are easy to handle and are economical.

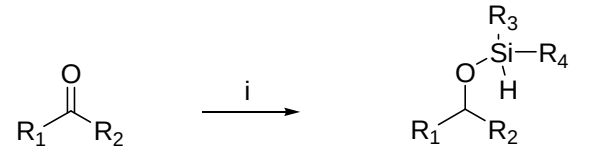
4.1.2 Review of Literature

In literature a wide variety of catalytic systems in combination with different hydrosilanes have been employed to selective reduction of carbonyl functional groups attached to aliphatic and aromatic structures. The discovery of more active catalysts and

its asymmetric version has made this process more popular. Some of the recent developments on this reaction are discussed below.

Ojima's approach (1972)[6]

Ojima et al. have reported hydrosilylation of aldehydes and ketones **1** with various hydrosilane and Rhodium(I) complex to give silyl ethers **2** in very high yields (**Scheme 1**). In case of α,β−unsaturated ketones and aldehydes the corresponding saturated derivatives were obtained in fairly high yields.



1

R_1 = alkyl, Ph

R_2 = H, Me, Ph

2

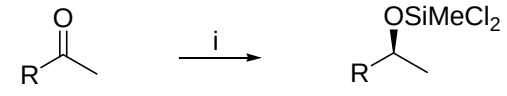
R_3 = Me, Et, Ph

R_4 = Me, Et, Ph

Scheme 1: (i) hydrosilane, $(Ph_3P)_3RhCl$ (1 mol %), n-hexane, 25 ^oC, 93-98%.

Pregosin's approach (1988)[7]

In this approach, the catalyst $PtCl_2(PhCH{=}CH_2)_2$ was shown to catalyze the hydrosilylation of various ketones **3** with dichloromethylsilane in the presence of pyridine or aniline as co-catalyst to give silyl ethers **4** in 51-98% yield (**Scheme 2**). The authors have observed that the completion of this reaction required more than 24 h.



3

R = alkyl, aryl

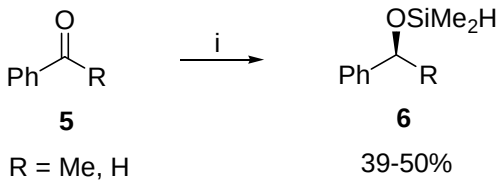
4

51-98%

Scheme 2: (i) $PtCl_2(PhCH{=}CH_2)$ (aniline), $MeCl_2SiH$, 25 ^oC, 24-41 h.

Samuel's approach (1999)[8]

Samuel et al. have reported bis (benzene) chromium as a pre-catalyst for the hydrosilylation of α-aryl carbonyl compounds to give the corresponding silyl ethers in 39-50% yield (**Scheme 3**).



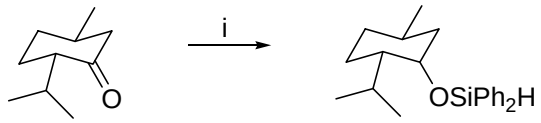
5 **6**

R = Me, H 39-50%

Scheme 3: (i) Bis(benzene)chromium (0.06 mmol), $Me_2OEtSiH$, PhH, 45 °C, 3 h.

Lee's approach (2002)[9]

Lee et al. have described a catalytic method for the synthesis of silyl ether **8** using Grubbs' I[st] generation catalyst ($Cl_2(PCy_3)_2Ru$=CHPh). Silyl ether **8** is thus obtained from the reaction of a variety of silanes by the hydrosilylation of carbonyl compound **7** under neat conditions (**Scheme 4**).

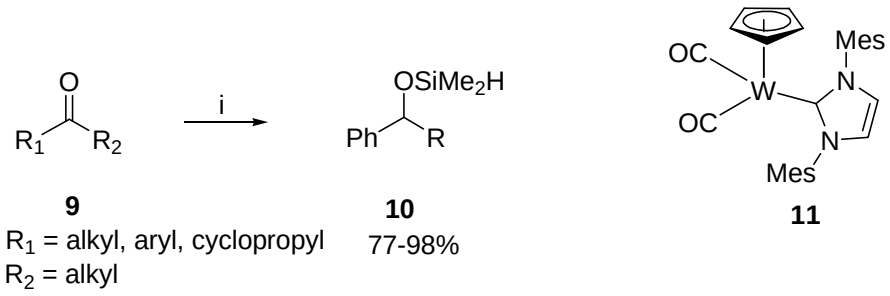


7 **8**, 80%

Scheme 4: (i) $Cl_2(PCy_3)_2Ru$=CHPh (0.5 mol%), Ph_2SiH_2, neat, 50-80 °C.

Dioumaev's approach (2003)[10]

Dioumaev et al. have reported tungsten and molybdenum N-heterocyclic carbene complexes **11** for the hydrosilylation of carbonyl compounds **9** under mild condition accompanied by precipitation of catalysts at the end of reaction. The reaction exhibits good rates, high conversion and excellent selectivity for hydrosilylation (**Scheme 5**).



9
R_1 = alkyl, aryl, cyclopropyl
R_2 = alkyl

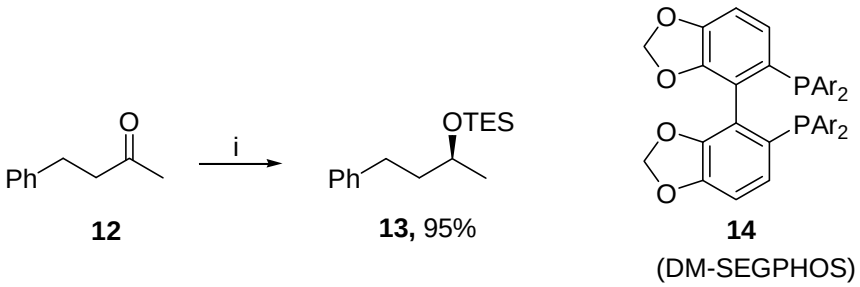
10
77-98%

11

Scheme 5: (i) ketone, cat,**11** (0.2 mol%), Et_3SiH, neat, 23 ^oC.

Lipshutz's approach (2003)[11]

Lipshutz *et al*. have developed a simple protocol for the single-flask conversion of dialkyl ketones **12** to the corresponding TES or TBS ethers **13** based on *in situ* generated catalyst i.e. hydrido copper complex (**Scheme 6**).



12

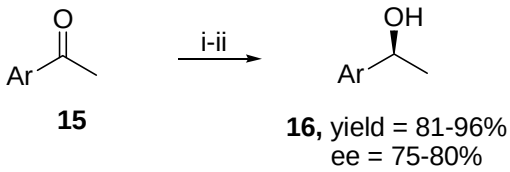
13, 95%

14
(DM-SEGPHOS)

Scheme 6: (i) CuCl (0.5 mol%), NaOMe, DM-SEGPHOS, (1 mol %), Et_3SiH, Et_2O, 25 ^oC.

Yun's approach (2004)[12]

Yun *et al.* have used air and moisture stable copper(II) salts to catalyze the hydrosilylation of aromatic ketones **15**.



15

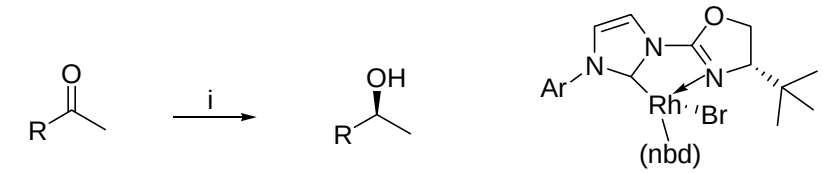
16, yield = 81-96%
ee = 75-80%

Scheme 7: (i) (i) $Cu(OAc)_2.H_2O$ (1.3 mol%), (S)-BINAP (1.3 mol %), PMHS, toluene, 0 ^oC; (ii) TBAF work up.

The combination of catalytic amounts of copper(II) acetate or copper(II) acetate monohydrate and BINAP in the presence of organosilanes as the stoichiometric reducing agent generates an active catalyst for the asymmetric hydrosilylation of ketones (**Scheme 7**).

Gade's approach (2004)[13]

Gade *et al.* have described Rh-catalyzed asymmetric hydrosilylation of ketones by using chiral *N*-heterocyclic carbene as a ligand to give the corresponding alcohol **17** up to 96% ee (**Scheme 8**).



3 R = alkyl,aryl

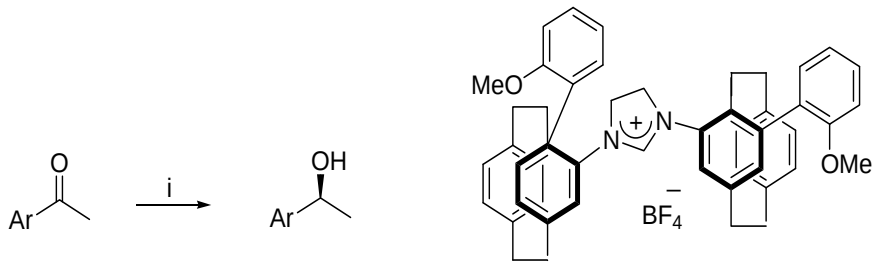
17 yield = 77 - 91%, ee = 53 - 96%

18

Scheme 8: (i) Rh-cat.**18** (1 mol%), $AgBF_4$ (1.2 mol%), Ph_2SiH_2, CH_2Cl_2, -60 ^oC. then K_2CO_3, MeOH

Andrus's approach (2005)[14]

Andrus *et al.* have reported new chiral *bis*-paracyclophane *N*-heterocyclic carbene (NHC) ligands for ruthenium catalyzed asymmetric hydrosilylation of ketones **19** using diphenyl



19

20 yield = 81 - 98%, ee = 77 - 97%

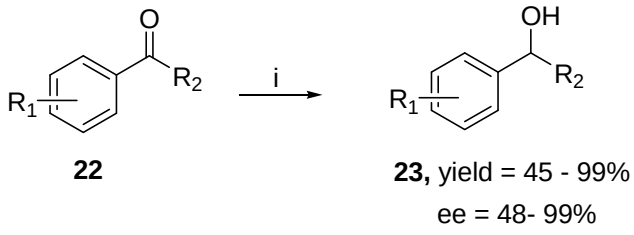
21

Scheme 9: (i) $RuCl_2(PPh_3)_3$ (0.5 mol%), ligand-**21** (1.2 mol %), $AgBF_4$, Ph_2SiH_2, THF, 25 ^oC. then HCl, H_2O.

silane to give enantioenriched alcohols **20**. These ligands provide for efficient asymmetric reduction in the presence of silver(I) triflate (1 mol %) at room temperature with high reactivity and selectivity. Acetophenone was reduced with 1 mol % catalyst in 96% isolated yield, 97% ee (**Scheme 9**).

Beller's approach (2008)[15]

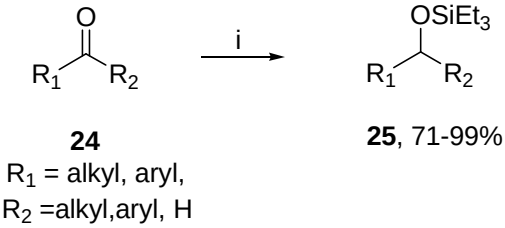
Beller *et al.* have reported Fe-catalyzed enantioselective hydrosilylation of ketones **22** with various phosphine ligands. Good to excellent enantioselectivities were obtained for electronically rich and sterically hindered aryl ketones. For example, diaryl and dialkyl ketones were converted into the corresponding alcohols **23** in good to excellent enantioselectivities (up to 99% ee) (**Scheme 10**).



Scheme 10: (i) $Fe(OAc)_2$ (5 mol%), chiral phosphenes (10 mol %), PMHS, THF, 25-100 ^oC. then NaOH, MeOH

Berke's approach (2009)[16]

Berke *et al.* have reported the easily available $[Re(CH_3CN)_3Br_2(NO)]$ rhenium(I) complex that catalyzes the homogeneous hydrosilylation of a great variety of organic carbonyl compounds (ketones and aldehydes). Various aliphatic and aromatic silanes were tested as hydride source. Excellent yields were achieved at 85 °C in chlorobenzene using triethylsilane. The reaction proceeded with TOF values of up to 495 h^{-1} (**Scheme 11**).



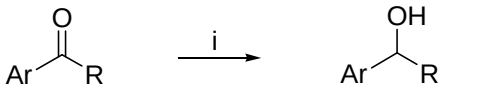
24
R_1 = alkyl, aryl,
R_2 =alkyl,aryl, H

25, 71-99%

Scheme 11: (i) $[Re(CH_3CN)_3Br_2(NO)]$ (1.0 mol%), Et_3SiH, CH_2Cl_2, 85 ^oC.

Nishiyama's approach (2009)[17]

Nishiyama *et al.* have reported zinc acetate as an efficient catalyst for hydrosilylation of ketones and aldehydes in combination with $(EtO)_2MeSiH$ to give the corresponding alcohols in 91-99% yield (**Scheme 12**).



26
R = Me, H

27, 91-99%

Scheme 12: (i) $Zn(OAc)_2$ (5 mol%), $(EtO)_2MeSiH$, THF, 65 ^oC then H_3O^+.

4.1.3 Present Work

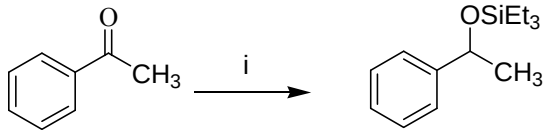
4.1.3.1 Objective

In recent years, has been made considerable progress in hydrosilylation of various organic carbonyl compounds. It has become a major tool of synthetic organic chemistry and organosilicon chemistry, thus providing an efficient and versatile access to new organo silicon compounds. There are many methods available in the literature for hydrosilylation of carbonyl compounds using a variety of metal catalysts and hydrosilanes. Moreover, metals such as palladium have not been studied extensively for the hydrosilylation of ketones.[18] In this section, we describe an efficient and selective

method for the hydrosilylation of various aryl ketones catalyzed by palladium using triethylsilane as the hydride source.

4.1.4 Results and Discussion

It has been reported in the literature that the reaction of aryl carbonyl compounds with $PdCl_2$ as catalyst and triethylsilane in ethanol led to the formation of reduction product namely alkyl arenes.[19] We found however, that when the same reaction was carried out on acetopenone **28a** using DMF as solvent, in the presence of $PdCl_2$ as catalyst, it took a different course to give the hydrosilylation product **29a** in excellent yield (**Scheme 13**).



28a **29a,** 90%

Scheme 13: (i) acetophenone (1 equiv), $PdCl_2$ (0.5 mol%) Et_3SiH (1.2 equiv.), DMF, 25 °C, 2 h.

In order to study this catalytic reaction in a systematic manner, several palladium catalysts have been screened with acetophenone as an aryl ketone and the results of such a study are shown in **Table 1**.

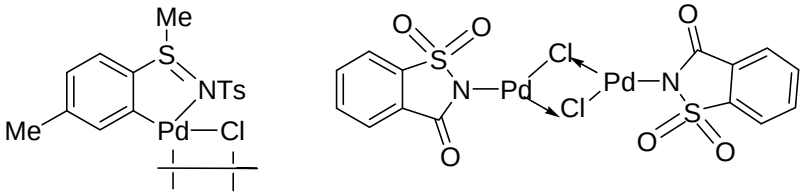
Table 1: Palladium-catalyzed hydrosilylation of acetophenone: effect of catalysts[a]

Entry	Catalyst	Yield of 29a (%)
1	$Pd(OAc)_2$	98
2	$PdCl_2$	90
3	$Pd(PhCN)_2Cl_2$	94
4	$Pd(dba)_2$	60
5	$Pd(Ph_3P)_4$	95
6	Sulfimine palladacycle (**30**)	96
7	Saccharine palladium complex	95

	(**31**)	
9	10%Pd/C	89
10	Pd [(*R, R*)-BINAP]Cl_2	80[b]
11	Pd[(-)-sparteine]$(OAc)_2$	82[b]

Reaction conditions: [a] acetophenone (1 mmol), Pd-catalyst (0.5 mol%), Et_3SiH (1.2 mmol), DMF (2 ml), 25 ^oC, 1 h; [b] no ennantiomeric excess.

All the palladium catalysts screened gave excellent yields of hydrosilylated product **29a**. The maximum yield of silyl ether obtained was with $Pd(OAc)_2$ (98%) whereas $Pd(dba)_2$ (60%) gave the lowest yield. Sulfilimine palladacycle[20] **30** and water soluble palladium saccharine compex[21] **31** (**Fig. 1**) also gave high yields of silyl ethers.



30 **31**

Fig. 1: Structures of palladium catalysts **30** and **31**

We also made an attempt to induce chirality in the molecule using different chiral palladium catalysts (entries 10 and 11); unfortunately the reaction did not give any asymmetric induction. The results in **Table 2** show that out of a variety of solvents screened, DMF was found to be more suitable for palladium-catalyzed hydrosilylation of acetophenone. However, when DMF-water (4: 1) or water was employed as solvent,[22] phenyl ethanol was obtained as the only product in good yields.

Table 2: Palladium acetate catalyzed hydrosilylation of acetophenone: effect of solvents[a]

Entry	Solvent	Time (h)	Yield of 29a (%) [b]
1	CH_2Cl_2	20	0
2	CH_3CN	6	60
3	Toluene	20	0
4	Water	6	40[c]
5	DMF- water (4:1)	1	85[c]
6	DMF	1	98
7	DMF	20[d]	0
8	DMF	20[e]	0

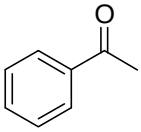
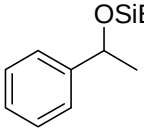
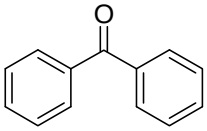
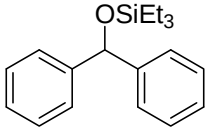
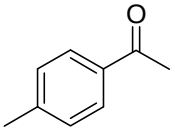
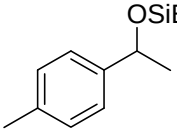
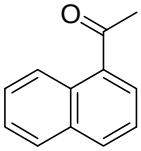
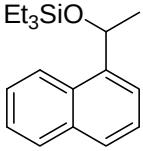
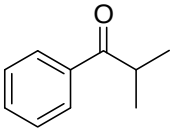
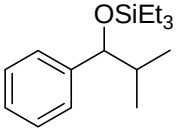
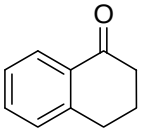
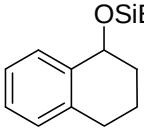
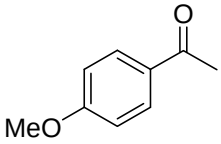
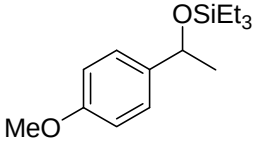
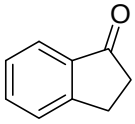
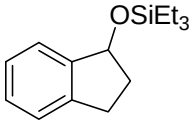
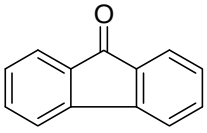
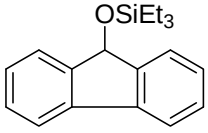
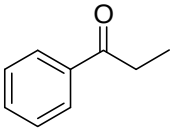
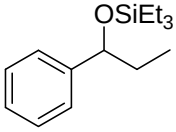
Reaction condition: [a]acetophenone (1 mmol), $Pd(OAc)_2$ (0.5 mol%), Et_3SiH (1.2 mmol), solvent (2 ml), 25 ^oC, 1 h; [b]isolated yield; [c] phenylethanol was obtained; [d] PMHS is used as as hydride source; [e] diphenyl silane is used .

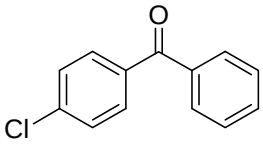
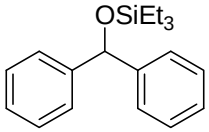
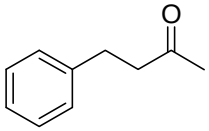
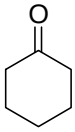
When other hydrosilanes such as Ph_2SiH_2, PMHS etc were used as a hydride sources with DMF as solvent, we observed that the reaction failed to give any product.

In order to understand the scope and generality of the reaction, a wide range of aryl ketones was subjected to hydrosilylation under this reaction condition. As can be seen, the method worked exceedingly well with all the aryl ketones employed (**Table 3**). Substrates containing bulky groups, such as tetralone, 9-fluorenone and 2, 2-dimethyl-1-phenylpropan-1-one were converted to the corresponding silyl ethers with excellent yields (entries **e, f,** and **i**). In case of chloro substituted aryl ketone (entry **k**), the corresponding dehaloganated silyl ether was obtained in 50% yield. However, we observed that the reaction failed in case of aliphatic ketones **28l-m**. This indicates that the

present catalytic system is suitable for selectively hydrosilylating aryl ketones in presence of aliphatic ketones.

Table: 3. Palladium acetate catalyzed hydrosilylation of aryl ketones.[a]

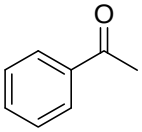
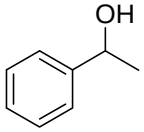
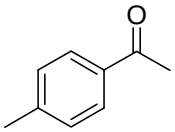
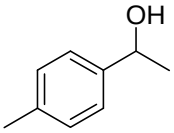
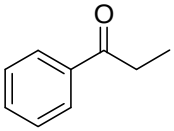
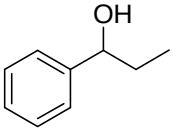
Entry	Substrates (28)	Products (29)	Yield (%)[b]
a			98
b			95
c			96
d			96
e			90
f			91
g			88
h			95
i			95
j			96

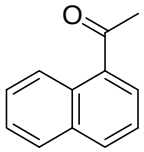
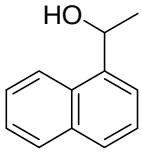
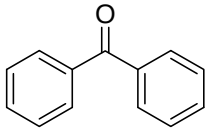
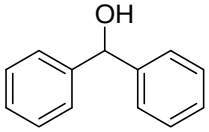
k			50
l		no reaction	0
m		no reaction	0

Reaction condition: [a] ketones (1 mmol), $Pd(OAc)_2$ (0.5mol%), Et_3SiH (1.2 mmol), DMF (2 ml), 25 ^oC, 1 h ; [b]isolated yield.

However in case of α,β-unsaturated ketones, reduction of C=C took place giving the corresponding saturated ketones in high yields. A noteworthy feature of this protocol is that when reaction was carried out in DMF-water (4:1) solvent system, the corresponding alcohols **32** were produced in high yields (**Table 4**). Thus, both hydrosilylation and deprotection of the silyl ether were achieved in a single step by using a simple modification of solvent system.

Table: 4. Pd-catalyzed hydrosilylation using DMF: H_2O as solvent system.[a]

Entry	**Substrate**	**Product (32)**	**Yield (%)[b]**	
			$Pd(OAc)_2$	**Saccharine-Pd complex**
a			85	76
b			80	75
c			79	77

d			84	78
e			86	80

Reaction condition: [a] ketones (1 mmol), Pd-catalyst (0.5 mol%), Et_3SiH (1.2 mmol), DMF: water (1.5:0.5 ml), 25 ^oC, 2 h ; [b] isolated yield.

The formation of silyl ethers **29a-j** was confirmed by ^1H and ^{13}C-NMR spectroscopy. Ex.1: The ^1H NMR spectrum of **29e** showed signals at δ 0.50 (q) and 4.30 (d) for methine (Ph-CH-OSi) and methylene (CH_3-CH_2-Si) protons respectively. Its ^{13}C-NMR spectrum showed a typical signal at δ 80.5 due to carbon attached to silyloxy group (**Fig. 2)**.

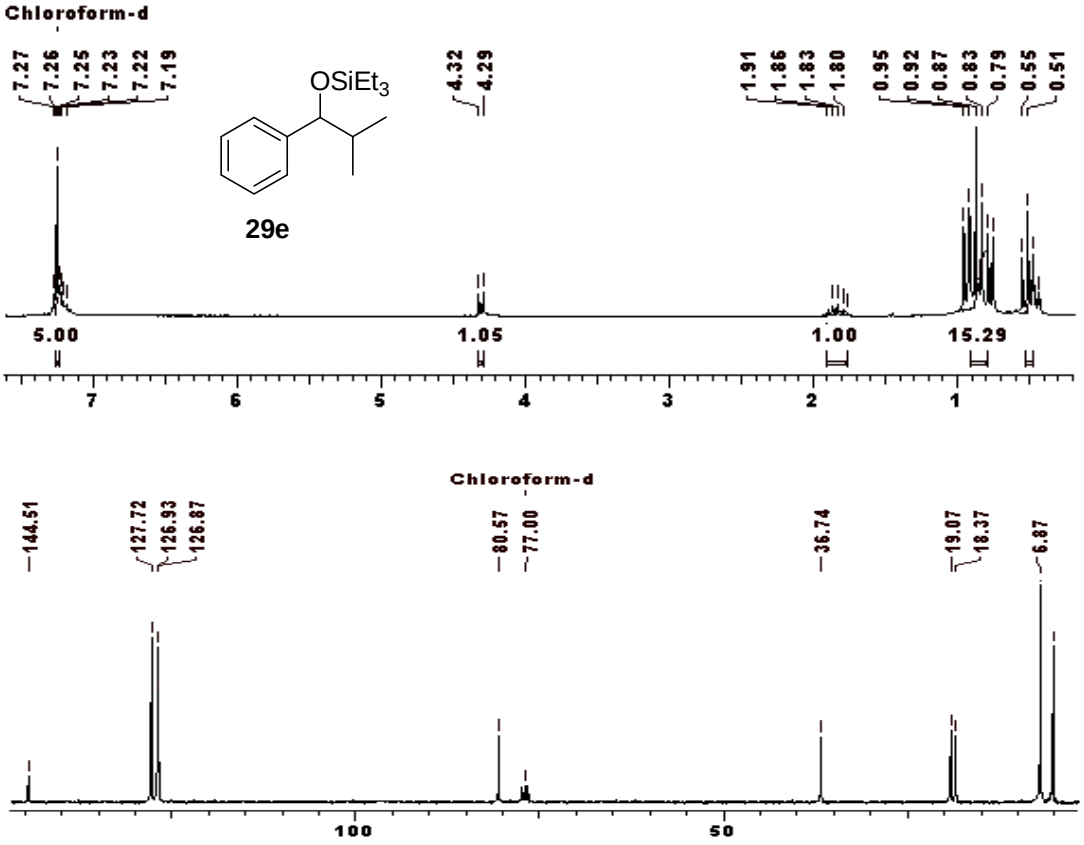


Fig. 2: ^1H and ^{13}C NMR spectra of **29e**

Example 2: The ^{1}H NMR spectrum of **29i** displayed signals at δ 0.60 (q) and 5.62 (d) for methine (Ar-CH-OSi) and methylene (CH_3-CH_2-Si) protons. Its ^{13}C-NMR spectrum showed a typical signal at δ 75.6 due to carbon attached to silyloxy group (**Fig. 3).**

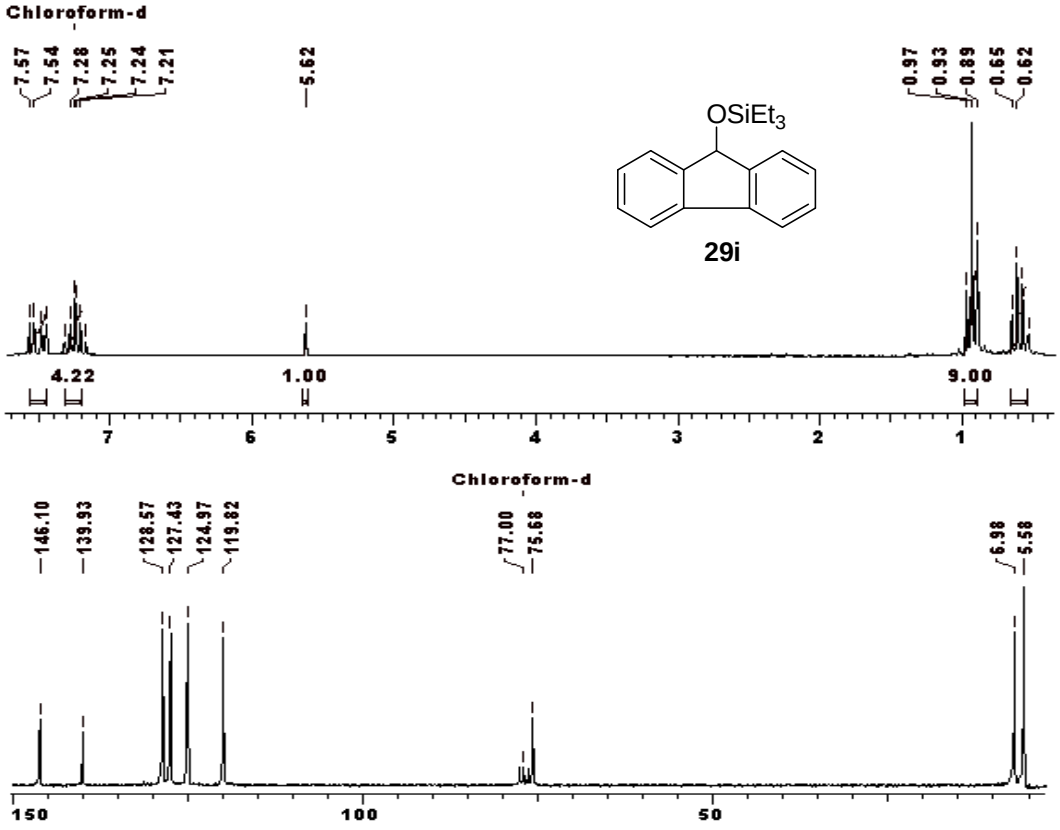
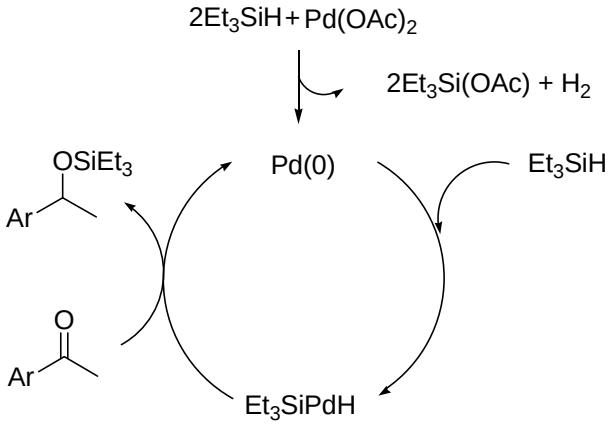


Fig. 3: ^{1}H and ^{13}C NMR spectra of **29i**

4.1.5 Mechanism

The catalytic cycle for the oxidative process is shown in **Scheme 14.** The first step corresponds to the reaction of palladium acetate with Et_3SiH leading to the formation of active metallic Pd(0) entity in the catalyzed reaction.[23] Oxidative addition of Et_3SiH to Pd(0) leads to the formation of Et_3SiPdH complex, which is co-ordinating with aryl carbonyl. Then hydride transfer to aryl carbonyl followed by reductive elimination generate the desired silylated product with liberation of Pd(0).



Scheme 14: Proposed mechanism for Pd-catalyzed hydrosilylation of ketones

4.1.6. Conclusion

In conclusion, we have demonstrated, for the first time, that palladium is a highly effective catalyst for selective hydrosilylation of aryl ketones in DMF at room temperature using triethylsilane as a hydride source. Also we found that benzyl alcohol was obtained in excellent yields, when reaction was performed in DMF: H_2O (4:1) as solvent system in a single step.

4.1.7 Experimental Section

General experimental procedure for the hydrosilylation of aryl ketones

To a 10 mL two-neck round-bottomed flask with a magnetic stir bar was added palladium catalyst (0.5 mol%) in DMF (2.0 mL). To this was added ketones (1.0 mmol) followed by triethylsilane (1.2 mmol). The resulting solution was stirred for 2 h. It was subsequently quenched with water and extracted with EtOAc (3x10 mL) and the organic layer dried over anhyd. Na_2SO_4. The solvent was concentrated under reduced pressure to give the crude product, which was purified by column chromatography (petroleum ether) as eluent to afford the pure **29a-j**.

1-Phenylethoxytriethylsilane (29a)

Yield: 98%; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): 740, 1094, 1238, 1600, 2952; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.50 (q, *J* = 8.0 Hz, 6H), 0.85 (t, *J* = 8.0 Hz, 9H), 1.36, (d, *J* = 6.6 Hz, 3H), 4.79 (q, *J* = 6.6 Hz, 1H), 7.12-7.31 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 4.8, 7.0, 27.5, 70.7, 125.2, 126.8, 128.1, 146.9; **Anal.** Calcd for $C_{14}H_{24}OSi$ requires C, 71.12; H, 10.23. Found: C, 71.18; H, 10.20%.

Benzhydryloxytriethylsilane (29b)

Yield: 95%; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): 700, 740, 1064, 1091, 1240, 1276, 1599, 2955; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.55 (q, *J* = 8.1 Hz, 6H), 0.87 (t, *J* = 8.1 Hz, 9H), 5.72 (s, 1H), 7.12-7.39 (m, 10H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 5.1, 6.84, 76.6, 126.4, 127.0, 128.1, 145.3; **Anal.** Calcd for $C_{19}H_{26}OSi$ requires C, 76.45; H, 8.78; Found: C, 76.40; H, 8.88%.

1-*p*-Tolylethoxytriethylsilane (29c)

Yield: 96%; colorless liquid; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.62 (q, *J* = 7.8 Hz, 6H), 0.89 (t, *J* = 7.8 Hz, 9H), 1.47 (d, *J* = 6.3 Hz, 3H), 2.40 (s, 3H), 4.88 (q, *J* = 6.6 Hz, 1H), 7.15 (d, *J* = 7.8 Hz, 2H), 7.27 (d, *J* = 8.1 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 4.8, 6.7, 20.9, 27.2, 70.4, 125.0, 126.6, 135.9, 143.8; **Anal.** Calcd for $C_{15}H_{26}OSi$ requires C, 71.93; H, 10.46; Found: C, 71.88; H, 10.53%.

1-Naphalene-4-ylethoxytriethylsilane (29d)

Yield: 96%; colorless liquid; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.40 (q, *J* = 7.3 Hz, 6H), 0.73 (t, *J* = 8.0 Hz, 9H), 1.40, (d, *J* = 6.6 Hz, 3H), 5.40 (q, *J* = 6.6 Hz, 1H), 7.22-7.31 (m, 3H), 7.51 (t, *J* = 7.4 Hz, 2H), 7.65 (d, *J* = 7.4 Hz, 1H), 7.88 (d, *J* = 8.3 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 4.8, 6.9, 26.7, 68.2, 122.6, 123.2, 125.1, 125.5, 127.3, 128.9,

129.8, 142.5; **Anal.** Calcd for $C_{18}H_{26}OSi$ requires C, 75.46; H, 9.15; Found: C, 75.40; H, 9.16%.

2-Methyl-1-phenylpropoxytriethylsilane (29e)

Yield: 90%; colorless liquid; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.50 (q, *J* = 7.4 Hz, 6H), 0.75-0.95 (m, 15H), 1.76 (m, 1H), 4.30 (d, *J* = 6.2 Hz, 1H), 7.19-7.28 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 5.1, 6.8, 18.3, 19.0, 36.7, 80.5, 126.8, 126.9, 127.7, 144.5; **Anal.** Calcd for $C_{16}H_{28}OSi$: C, 72.66; H, 10.67; Found: C, 72.60; H, 10.72%.

1,2,3,4-Tetrahydronaphalene-1-yloxytriethylsilane (29f)

Yield: 91%; colorless liquid; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.60 (q, *J* = 8.1 Hz, 6H), 0.93 (t, *J* = 8.0 Hz, 9H), 1.58-2.01 (m, 4H), 2.57-2.82 (m, 2H), 4.72 (t, *J* = 4.3 Hz, 1H) 6.92-7.07 (m, 3H), 7.26-7.29 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 5.4, 7.0, 19.5, 29.1, 33.1, 69.2, 125.1, 126.9, 127.9, 128.5, 136.6, 139.8; **Anal.** Calcd for $C_{16}H_{26}OSi$ C, 73.22; H, 9.98; Found: C, 73.28; H, 9.82%.

1-(4-Methoxyphenyl)ethoxytriethylsilane (29g)

Yield: 96%; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): 740, 1097, 1240, 1597, 2968; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.55 (q, *J* = 8.1 Hz, 6H), 0.91 (t, *J* = 8.1 Hz, 9H), 1.40 (d, *J* = 6.3 Hz, 3H), 3.70 (s, 3H), 4.80 (q, *J* = 6.3 Hz, 1H), 6.82 (d, *J* = 8.8 Hz, 2H), 7.22 (d, *J* = 8.8 Hz, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 5.1, 6.8, 25.0, 55.6, 69.9, 113.8, 126.6, 137.9, 158.9; **Anal.** Calcd for $C_{15}H_{26}O_2Si$ requires C, 67.61; H, 9.84; Found: C, 67.59; H, 9.90%.

2,3-Dihydro-1H-inden--3-yloxytriethylsilane (29h)

Yield: 95%; colorless liquid; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.70 (q, *J* = 8.0 Hz, 6H), 1.03 (t, *J* = 8.0 Hz, 9H), 1.83-2.02 (m, 1H), 2.33-2.48 (m, 1H), 2.67-2.79 (m, 1H), 2.94-

3.06 (m, 1H), 5.24 (t, *J* = 6.8 Hz, 1H) 7.18-7.23 (m, 3H), 7.29-7.37 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 5.4, 7.0, 19.5, 33.1, 69.3, 125.1, 126.9, 127.9, 128.5, 136.6, 139.8; **Anal.** Calcd for $C_{15}H_{24}OSi$ requires C, 72.52; H, 9.74. Found: C, 72.48; H, 9.78%.

9H-Fluoren-9-yloxytriethylsilane (29i)

Yield: 95%; colorless liquid; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.60 (q, *J* = 7.8 Hz, 6H), 0.93 (t, *J* = 8.1 Hz, 9H), 5.62 (s, 1H), 7.17-7.31 (m, 4H), 7.52 (dd, *J* = 9.7, 6.6 Hz, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 5.5, 6.9, 75.6, 119.8, 124.9, 127.4, 128.5, 139.9, 146.1; **Anal.** Calcd for $C_{19}H_{24}OSi$ requires C, 76.97; H, 8.16. Found: C, 76.90; H, 8.20%.

1-Phenylpropoxytriethylsilane (29j)

Yield: 96%; colorless liquid; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 0.55 (q, *J* = 7.4 Hz, 6H), 0.87-0.94 (m, 12H), 1.63-1.81 (m, 2H), 4.58 (t, *J* = 6.5 Hz, 1H), 7.12- 7.51 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 5.1, 6.8, 9.9, 33.7, 76.3, 126.0, 126.9, 128.0, 145.6; **Anal.** Calcd for $C_{15}H_{26}OSi$ requires C, 71.93; H, 10.46. Found: C, 71.98; H, 10.40%.

General experimental procedure for the hydrosilylation of aryl ketones in DMF-water:

To a 10 mL two-neck round-bottomed flask with a magnetic stir bar was added palladium catalyst (0.5 mol%) in DMF: water (1.5: 0.5 mL). To this was added ketones (1.0 mmol) followed by triethylsilane (1.2 mmol). The resulting solution was stirred for 2 h. It was subsequently quenched with water, extracted with EtOAc (3x10 mL) and dried over anhyd. Na_2SO_4. The solvent was concentrated under reduced pressure to give the crude product, which was purified by column chromatography (silica gel, pet. ether) as eluent to afford the pure alcohols **32a-e**.

1-Phenylethanol (32a)

Yield: 85%; colorless liquid; **IR** (Neat, cm^{-1}): 669, 761, 907, 1078, 1204, 1461, 1493, 2973, 3029, 3365; ^{1}**H-NMR** (200 MHz, CDCl3): δ 1.42 (d, *J* = 6.31 Hz, 3H); 2.55 (br s, 1H); 4.79 (q, *J* = 6.31 Hz, 1H); 7.21- 7.3 (m, 5H); ^{13}**CNMR** (50 MHz, $CDCl_3$): δ 24.9, 69.8, 125.2, 127.0, 128.1, 145.8; **Anal.** Calcd for $C_8H_{10}O$ requires C, 78.65; H, 8.25; found: C, 78.62, H, 8.38 %.

1-(4-Methylphenyl)ethanol (32b)

Yield: 80%; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): 895, 1010, 1070, 1360, 1435, 1510, 2920, 3150, 3500; ^{1}**H-NMR** (200 MHz, $CDCl_3$): δ 1.47 (d, *J* = 7.4 Hz, 3H), 2.1 (br s, 1H), 2.41 (s, 3H), 4.84 (q, *J* = 7.4 Hz, 1H), 7.15 (d, *J* = 9.2 Hz, 2H), 7.25 (d, *J* = 9.2 Hz, 2H); ^{13}**C-NMR** (50 MHz, $CDCl_3$): δ 20.9, 24.8, 69.9, 125.2, 128.94, 136.7, 142.8; **Anal.** Calcd for $C_9H_{12}O$ requires C, 79.37; H, 8.88 %; found: C, 79.32; H, 8.81%.

1-Phenylpropanol (32c)

Yield: 89%; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): 764, 975, 1014, 1097, 1454, 1494, 2877, 2934, 2966, 3030, 3339; ^{1}**H-NMR** (200 MHz, $CDCl_3$): δ 0.89 (t, *J* = 7.3 Hz, 3H), 1.64 – 1.85(m, 2H), 2.22 (br s, 1H), 4.55 (t, *J* = 6.8 Hz, 1H), 7.31 (m, 5H); ^{13}**C-NMR** (50 MHz, $CDCl_3$): δ 9.8, 31.5, 75.4, 125.8, 127.0, 128.0, 144.4; **Anal.** Calcd for $C_9H_{12}O$ requires C, 79.37; H, 8.88%; found: C, 79.47; H, 8.90%.

1-Naphthylethanol (32d)

Yield: 90%; colorless solid mp**:** 50 °C; **IR** ($CHCl_3$, cm^{-1}): 1010, 1056, 1108, 1168, 1218, 1256, 1328, 1374, 1445, 1509, 1597, 3011; ^{1}**H-NMR** (200 MHz, $CDCl_3$): δ 1.48 (d, *J* = 6.2 Hz, 3H); 3.01 (s, 1H); 5.40 (q, *J* = 6.2 Hz, 1H); 7.31- 7.90 (m, 7H); ^{13}**CNMR** (50

MHz, $CDCl_3$): δ 24.1, 66.2, 121.7, 122.9, 124.9, 125.1, 125.3, 127.2, 128.4, 129.9, 133.4, 141.2; **Anal.** Calcd for $C_{12}H_{12}O$ requires C, 83.69; H, 7.02; found: C, 83.60, H, 7.10%.

Diphenylmethanol (32e)

Yield: 86% ; **IR** ($CHCl_3$, cm^{-1}): 705, 750, 770, 1020, 1190, 1280, 1380, 1460, 3200 - 3300; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.11 (br s, 1H), 5.79 (s, 1H), 7.22-7.35 (m, 10H); **^{13}C-NMR** (50 MHz, $CDCl_3$): δ 76.0, 126.5, 127.4, 128.3, 143.8; **Anal.** Calcd for $C_{13}H_{12}O$ requires C, 84.75; H, 6.57 %; found: C, 84.70; H, 6.67%.

Section II

Enantioselective rearrangement of 2-alkyl pyridine *N*-oxides

4.2.1 Introduction

Optically active pyridyl alcohols are useful key compounds, not only as pharmaceutical intermediates,[24] but also as chiral ligands[25] and auxiliaries in asymmetric synthesis.[26] Although there have been many reports on the synthesis of this important class of compounds by means of asymmetric alkylation to pyridyl aldehydes, stoichiometric or catalytic asymmetric reduction of acetyl pyridines and enzymatic resolution of racemic pyridyl alcohols. An interesting and productive way to improve synthetic efficiency, which can give access to a multitude of Csp3 chiral compounds, is to take a new look at poorly exploited and old pioneer reactions using current knowledge of organic chemistry. In this manner, we re-investigated the so-called Boekelheide rearrangement with the aim of obtaining an asymmetric version of the reaction, and in this way expand the available tools for accessing at enantiomerically enriched 1-(2-pyridinyl) alkyl alcohol derivatives.

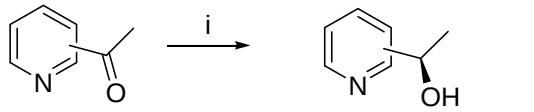
4.2.2 Review of Literature

Literature search revealed that there are various methods available for the preparation of optically active pyridyl alcohols. These methods involve the reduction of acetyl pyridines, asymmetric alkylation to pyridyl aldehydes and enzymatic resolution. Some of the important developments for the synthesis of optically active pyridyl alcohols are discussed below.

Soai's approach (1987)[27]

Soai *et al.* have reported an enantioselective reduction of acetyl pyridines using chiral lithium borohydride ($LiBH_4$) modified with *N,N'*-dibenzoylcystine and ethanol. When

2,3,4-acetylpyridine **33** was reduced with $LiBH_4$-(*R,R*)-(*N,N'*-dibenzoylcystine)-EtOH, (*R*)-1,2,3-pyridy ethanols **34** was obtained in 56-87% ee (**Scheme 15**).

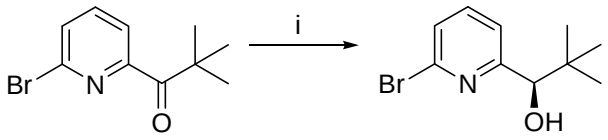


33 **34**, yield = 58-73%
ee = 56-87%

Scheme 15: (i) *N,N'*-dibenzoylcystine, $LiBH_4$, EtOH, THF, -78 ^oC.

Bolm's approach (1990)[28]

Bolm *et al* have found that (-)-β-chlorodiisopinocampheylborane as an extremely efficient reducing reagent for the conversion of pyridyl ketone **35** to the corresponding pyridyl alcohol **36** (**Scheme 16**).

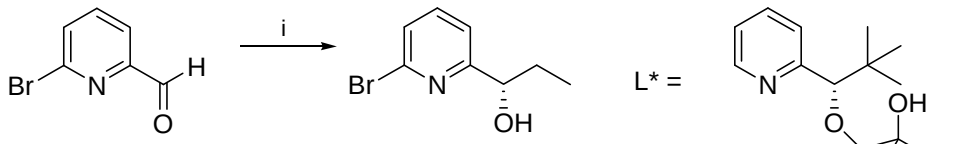


35 **36**, yield = 59%
ee = 90%

Scheme16: (i) (-)-β-chlorodiisopinocampheylborane, EtOH, THF, 25 ^oC then imino diehanol, Et2O, 3 h.

Hosino's approach (1994)[29]

Hosino *et al* have developed an asymmetric addition of dialkylzinc to pyridine-2-, 3-, and



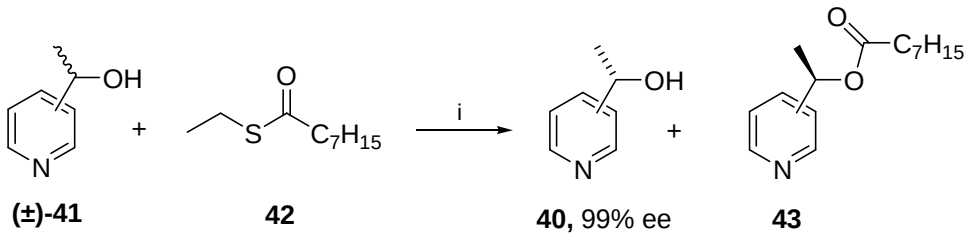
37 **39,** yield = 81%
ee = 70% **38**

Scheme 17: (i) Et_2Zn (1.5 equiv), L* **38** (5 mol%), toluene: hexane (1:1), 25 ^oC.

4-carboxaldehydes and 6-bromo-2-carboxaldehyde **37** in the presence of tridentate chiral pyridylalkanol **38.** Optically active pyridylpropanol **39** were synthesized in good to high ee (**Scheme 17**).

Norin's approach (1994)[30]

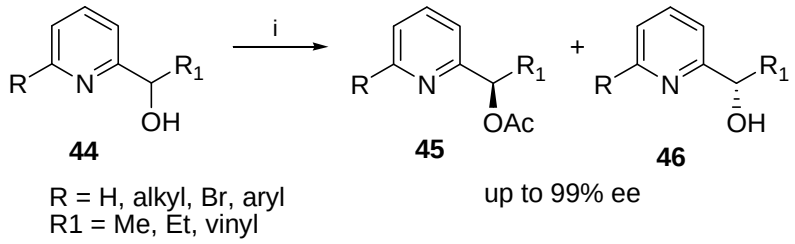
Norin *et al* have described the preparation of chiral 1,2,3-pyridinylethanols **40** with high enantiomeric purity (up to 99%) by lipase catalyzed transesterification of racemic 1, 2,3-pyridinylethanols **41** with ethylthiooctanoate **42** (**Scheme 18**).



Scheme 18:(i) ethyl thiooctanoate, lipase (component B), 39 ^{o}C.

Uenishi's approach (1998)[31]

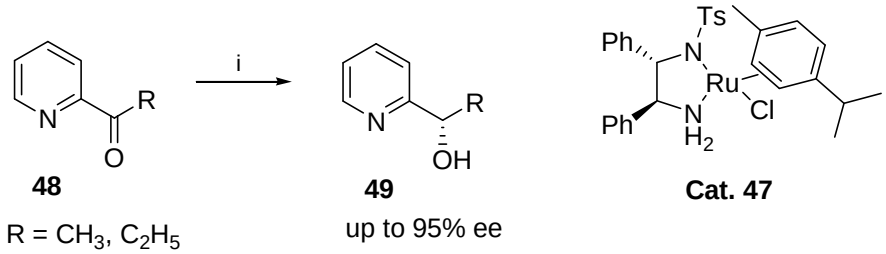
Uenishi *et al* have reported the resolution of racemic 1-(2-pyridyl)ethanols **44** by lipase-catalyzed asymmetric acetylation with vinyl acetate. The reactions were carried out in diisopropyl ether at either room temperature or 60 °C using *Candida Antarctica* lipase (CAL) to give (*R*)-acetate **45** and unreacted (*S*)-alcohol **46** with excellent enantiomeric purities in good yields (**Scheme 19**).



Scheme 19: (i) vinyl acetate, *Candida Antarctica* lipase (CAL), *i*-Pr_2O, 25 ^{o}C.

Ikariya's approach (2000)[32]

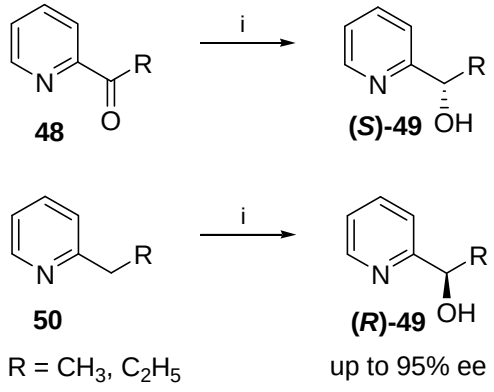
Ikariya *et al* have reported chiral Ru(II) complex, RuCl[(*S*,*S*)-*N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine](*p*-cymene), **47** serves as an efficient catalyst for asymmetric transfer hydrogenation of 2-acetylpyridine **48** with HCO_2H as a hydrogen source to give (*S*)-1-(2-pyridyl)ethanol **49** in an almost quantitative yield and with 95% ee (**Scheme 20**).



Scheme 20: (i) (*S,S*)-Ru cat (**47**), HCO_2H, Et_3N, 27 °C.

Sheldrake's approach (2002)[33]

Sheldrake *et al* have used *Pseudomonas putida* UV4 biocatalyst for the reduction of 2-, 3- and 4-acylpyridines **48** to afford the corresponding (*S*)-1-pyridyl alkanols **49**, with moderate to high ee (**Scheme 21**). In contrast, the toluene dioxygenase enzyme in the same organism catalyses the hydroxylation of 2- and 3-alkylpyridines **50** to (*R*)-1-(2-pyridyl) and (*R*)-1-(3-pyridyl)alkanols **49**.

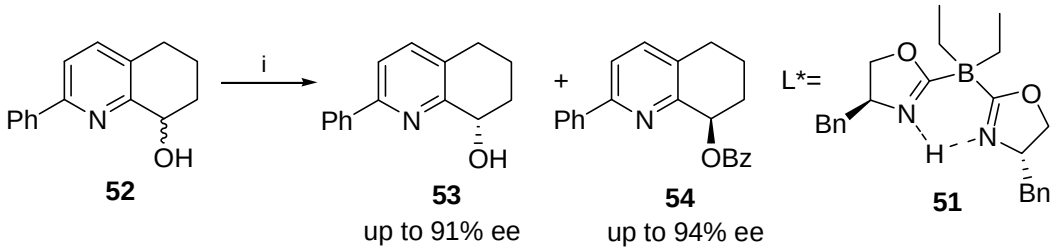


Scheme 21: (i) *Pseudomonas putida* UV4

This combination of oxidative and reductive biotransformation thus provides a method for preparing both enantiomers of chiral 1-pyridyl alkanols using one biocatalyst.

Pfaltz's approach (2006)[34]

In this approach, Cu(II)(borabox)-catalyst **51** has been used for kinetic resolution of pyridyl alcohols **52**. Both the optically active pyridyl alcohol derivative **53** and **54** were synthesized in good to high ee (**Scheme 22**).

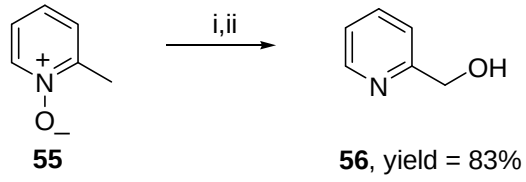


Scheme 22: (i) $CuCl_2$ (1 mol%), L* **51** (1 mol%), PhCOCl (0.51 equiv), *i*-$PrNEt_2$, CH_2Cl_2, 0 °C, 16 h.

The rearrangement of 2-alkyl pyridine *N*-oxides (Boekelheide reaction) using an acylating agent followed by saponification which gave pyridyl alcohol has also been reported in the literature as described below.

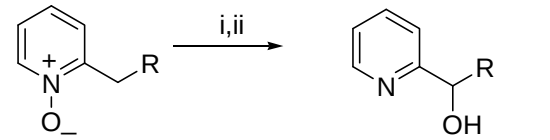
Boekelheide reaction

The modification of the Katada reaction,[35] first reported by Boekelheide,[36] is a well established and frequently used procedure in heterocyclic chemistry for the introduction of oxygen on an alkyl group α to a ring nitrogen atom (**Scheme 23**).



Scheme 23: (i) acetic anhydride, reflux; ii) con. HCl, reflux, 10 h.

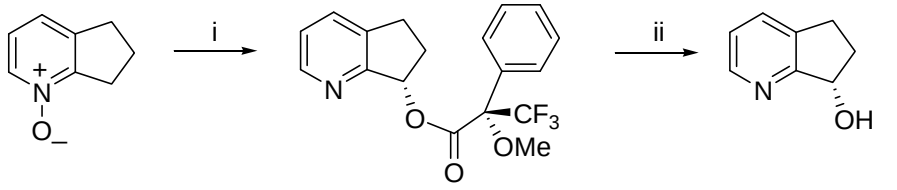
Under the classical conditions, the heterocyclic N-oxide **55** is heated with a large excess of acetic anhydride to give, after hydrolysis, the desired pyridyl alcohol **56** in good yield. In 1985, McKillop *et al*.[37] have reported a detailed study of the different parameters that control the product distribution in this reaction. They demonstrated that the use of a mixture of acetyl chloride and acetic anhydride in the Boekelheide reaction provides a convenient acylating agent. Fontenas *et al*[38] have reported Boekelheide reaction using trifluoroacetic anhydride (TFAA) as an acylating agent followed by saponification which gave pyridyl alcohol in good yield at room temperature (**Scheme 24**).



57a, R = CH_3 **58a**, yield = 98%

Scheme 24: (i) (i) trifluroacetic anhydride (2 equiv), CH_2Cl_2, 25 °C, 4 h ; ii) 2M LiOH, CH_2Cl_2, 25 °C.

Quite recently Spada et al[39] have reported the first example of asymmetric Boekelheide rearrangement applied to a set of 2-alkylpyridine N-oxide derivatives **59** using (*R*) Mosher's acyl chloride as activator of the rearrangement to give, after hydrolysis, enantiomerically enriched 1-(2-pyridinyl)alkyl alcohol **61**. Diastereoselectivity of the process was studied at low temperatures in different solvents, and was supported by a preliminary in silico modeling.



59 **60**, dr = 80:20 **61**, yield = 80%

Scheme 25: (i) (*R*)-Mosher's acyl chloride (2 equiv), ethyl acetate, -78 °C, 8 h; ii) LiOH, THF/water, 70 °C.

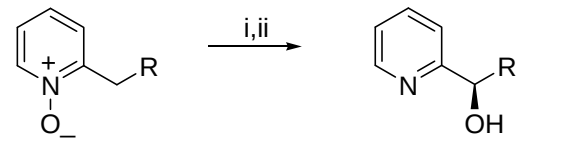
4.2.3 Present Work

4.2.3.1 Objective

From the above discussion, it is clear that most of the reported methods for the synthesis of chiral pyridyl alcohols involve enzymatic resolution and reduction of 2-acetyl pyridine with expensive metal complexes. The asymmetric version of Boekelheide reaction is an alternative method for the synthesis of chiral pyridyl alcohols. Hence, a practical rearrangement of 2-alkyl pyridine N- oxides (Boekelheide reaction), which should involve inexpensive and easily available reagents is desirable. Therefore, we have decided to explore rearrangement of 2-alkyl pyridine N-oxides (Boekelheide reaction) using acid chloride as an acylayting agent with chiral bases.

4.2.4 Results and Discussion

Initially, 2-benzylpyridine N-oxide **57b** was treated with acetyl chloride (1.0 equiv) in presence of (-)- sparteine (1.0 equiv) that produced 2-alkylpyridyl ester, which underwent in situ hydrolysis to give chiral 2-benzylpyridyl alcohol **58b**, in 80% yield with 6% ee (**Scheme 26**).



57b; R = Ph

58b, yield = 80%
ee =6%

Scheme 26: (i) CH_3COCl (1 equiv), (-)- sparteine, CH_2Cl_2, 0 ^oC, 4h ; (ii) LiOH, THF: water (4: 1), 25 ^oC.

This prompted us to explore the effectiveness of chiral bases in the rearrangement of 2-alkyl pyridine N- oxides. To increase the enantiomeric excess, we have screened a variety

of acid chlorides and chiral bases. The results of which are presented in **Table 5**.

Table 5: Rearrangement of 2-alkyl pyridine N-oxides: effect of acid chloride and base[a]

No.	R (57a-b)	Acylating agent	Base	Yield (%)[b]	ee(%)[c]
1	Ph	CH_3COCl	(-)- sparteine	80	06 (*R*)
2	Ph	$C_6H_{11}COCl$	(-)- sparteine	81	17 (*R*)
3	Ph	C_6H_5COCl	(-)- sparteine	70	16 (*R*)
4	Ph	Me_3CCOCl	(-)- sparteine	80	14 (*R*)
5	Ph	$(CH_3CO)_2O$	(-)- sparteine	75	0
6	Ph	$(CF_3CO)_2O$	(-)- sparteine	87	0
7	Ph	CH_2=CHCOCl	(-)- sparteine	80	10 (*R*)
8	CH_3	$C_6H_{11}COCl$	(-)- sparteine	70	5 (*R*)
9	Ph	$C_6H_{11}COCl$	$(DHQ)_2PYR$	50	10 (*S*)
10	Ph	$C_6H_{11}COCl$	(-) - nicotine	65	4 (*S*)
11	Ph	$C_6H_{11}COCl$	hydroquinidine	46	0
12	Ph	(R)-CH_3CH-$(OCH_2Ph)COCl$	Et_3N	70	5 (*S*) (15)[d]

Reaction condition: [a] Pyridine N-oxide (1 mmol), RCOCl (1.2 mmol), Base (1 mmol), CH_2Cl_2 (4 mL) 0 °C, (ii) LiOH (2.0 mmol) THF: water (4 :1), 25 °C, 4 h, [b] isolated yield; [c] optical rotation is compared with literature values [d] reaction was carried out at -60 °C.

The results in **Table 5** show that out of a variety of acylating reagents (entry **1-8**) screened, we have found that cyclohexylcarboxyl chloride (17%) and benzoyl chloride (16%) gave highest enantiomeric excess when carried out in presence of (-)-sparteine as a chiral base at 0 °C. With the cyclohexylcarboxyl chloride as acylating reagent, we have screened various chiral bases such as $(DHQ)_2PYR$ (10% ee), (-)-nicotine (4% ee) and hydroquinidine, (poor % ee) (entries **9-12**). Alternatively, chiral acid chloride (entry **12**)

was also studied in presence of triethyl amine as a base but low induction (5% ee only) was observed at 0 °C. Hence, in order to improve % ee, we have carried out the same reaction at -60 °C which gave % ee upto 15. Hence, we thought of lowering of the temperature of the system to see its effects on % ee (**Table 6)**.

Accordingly, 2-alkyl pyridine N- oxide was subjected to Boekelheide reaction at -78 °C by using cyclohexylcarboxyl chloride and (-)-sparteine as acylating agent and chiral base respectively. We found that a slight improvement in % ee was observed (entry **1**). Finally, in order to increase the ee, we have carried out the same reaction in presence various Lewis acids (20%) at -78 °C and the results are shown in **Table 6** (entry **3-12**). As can be seen from **Table 6,** when the Lewis acids such as $BF_3.OEt_2$ (26% ee), LiCl (27% ee), $LaCl_3$-7 H_2O (36% ee), TBSCl (25% ee) and $TiCl_4$ (34% ee), pyridyl alcohol was produced in 50-79% yield with reasonably good ee. However, when TMSCl was employed as Lewis acid (entries **4** and **7**), 2-benzyl and 2-ethyl pyridyl alcohols were obtained in 80 and 70% yields with 50% ee and 18% ee respectively.

Table 6: Rearrangement of 2-alkyl pyridine N-oxides:screening of Lewis acids at -78 °C[a]

Entry	R	Lewis Acid	Yield(%)[b]	ee(%)[c]
1	Ph	-	80	25 (R)
2	Ph	-	80	23(R)[d]
3	Ph	BF_3-OEt_2	65	26 (R)
4	Ph	TMSCl	80	50 (R)
5	Ph	TMSCl	65	34 (R)[e]
6	Ph	TMSCl	75	44 (R)[d]
7	CH_3	TMSCl	70	18(R)
8	Ph	LiCl	60	27 (R)
9	Ph	$LaCl_3$-$7H_2O$	50	36 (R)

10	Ph	TBSCl	79	25(R)
11	Ph	$B(OCH_3)_3$	60	38(R)
12	Ph	$TiCl_4$	66	34(R)

Reaction condition: [a] (i) pyridine N-oxide (1 mmol), cyclohexyl carboxyl chloride (1.2 mmol), (-)-sparteine (1 mmol), Lewis acid (20 mol%), CH_2Cl_2 (4 mL) -78 °C; (ii) LiOH (2.0 mmol) THF: water (4 :1), 25 °C, 4 h, [b] isolated yield; [c] optical rotation compared with literature; [d] benzoyl chloride was used; [e] acroyl chloride was used.

The starting materials namely 2-alkyl pyridine N-oxides **57a-b** were prepared by known procedure.[36] The formation of 2-alkyl pyridine N-oxides **57a-b** was confirmed by ^{1}H and ^{13}C-NMR spectroscopy. The ^{1}H NMR spectrum of **57b** showed a typical signal at δ 4.25 (s) for methylene (Py-CH_2-Ph) proton. Its ^{13}C-NMR showed a typical signal at δ 151.6 due to quaternary carbon attached to nitrogen atom in pyridine ring (**Fig. 4)**

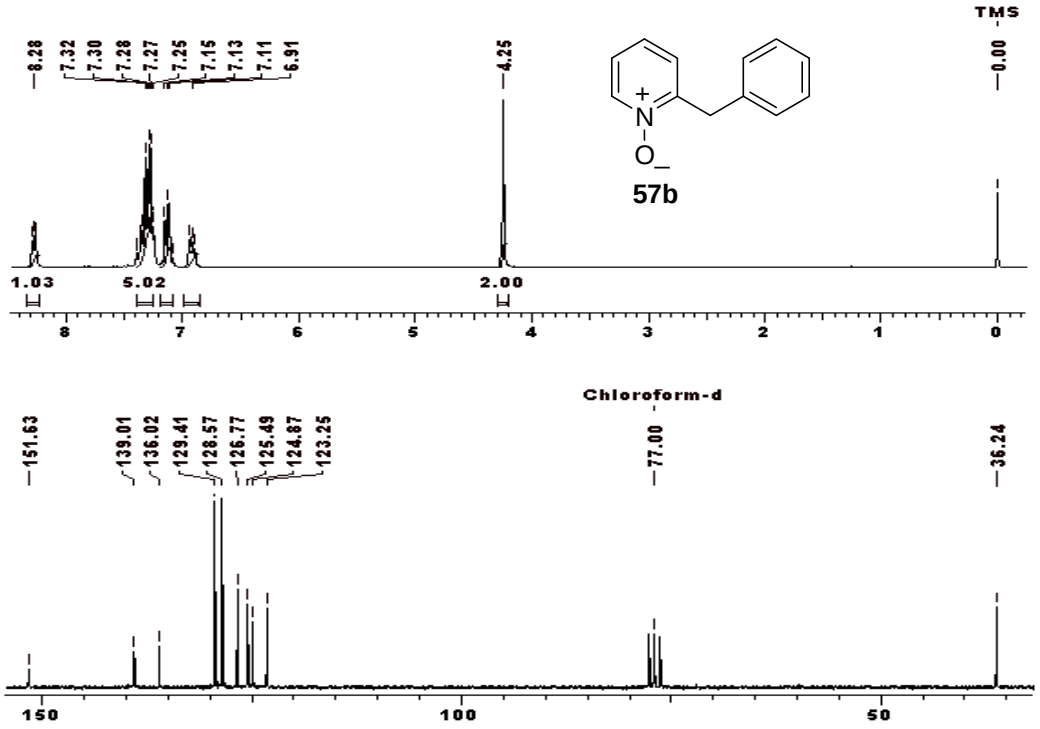


Fig. 4: ^{1}H and ^{13}C NMR spectra of N-oxide **57b**

The formation of the products namely 2-alkyl pyridyl alcohols **58a-b** was confirmed by ^{1}H and ^{13}C-NMR spectroscopy. The ^{1}H NMR spectrum of **58b** showed a signal at δ 5.72 (s) for methine (Py-CH -OH) proton. Its ^{13}C-NMR showed a typical signal at δ 74.9 due to carbon attached to hydroxyl group (**Fig. 5)**

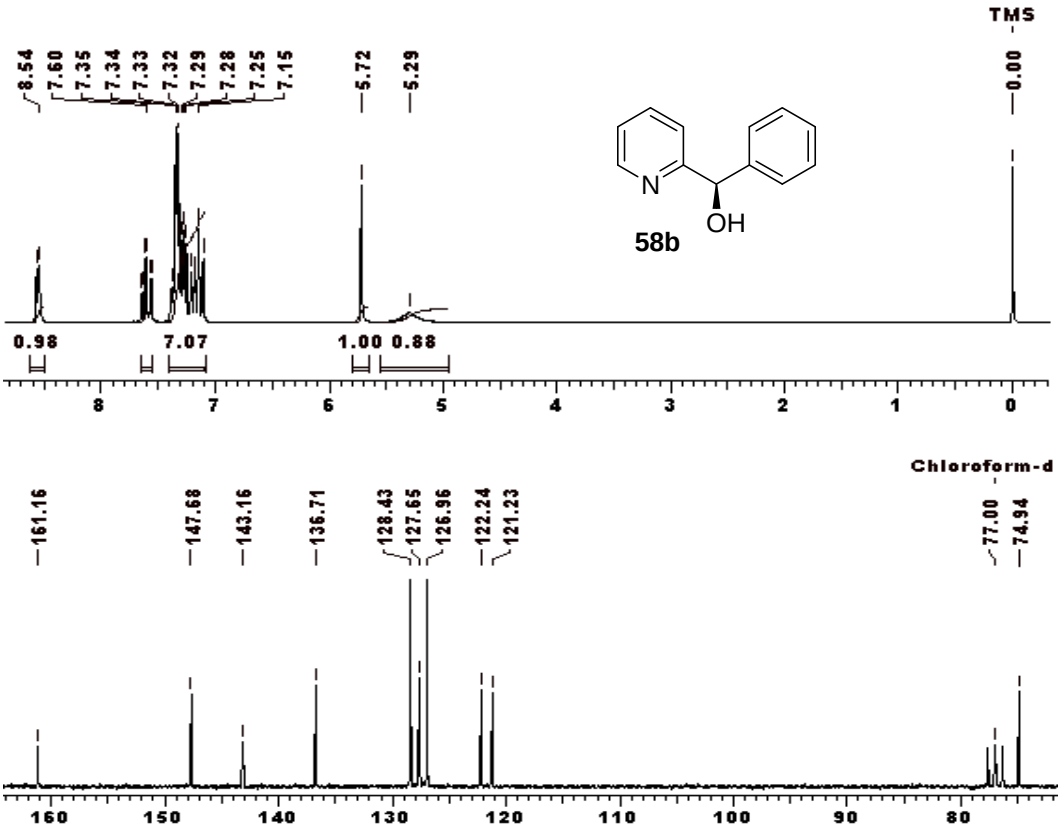
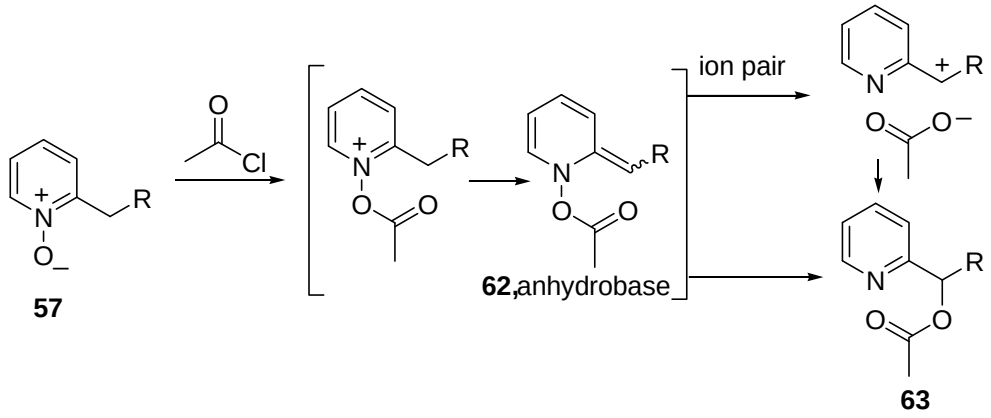


Fig. 5: ^{1}H and ^{13}C NMR spectra of pyridyl alcohol **58b**

4.2.5 mechanism

Despite much research, the mechanism of the rearrangement has not been fully understood and remains controversial.[40] The most common and accepted explanation is that of an ion-pair mechanism (**Scheme 27**) proposed by Oae[41] and Katritzky.[42] However, we cannot exclude the possibility that other mechanisms such as a hetero-Claisen

rearrangement, in relation to the nature of the substrate, could contribute to the Boekelheide rearrangement.



Scheme 27: Mechanism for rearrangement of pyridine N-oxide (Boekelheide reaction).

4.2.6. Conclusion

We have made an attempt to develop an enantioselective rearrangement of 2-alkyl pyridine N-oxide to give 2-pyridyl alcohols. However the best result obtained was up to 50% enantiomeric excess achieved using (-)-sparteine as the base in the presence of trimethyl silyl chloride as Lewis acid at -78 °C.

4.2.7 Experimental Section

General experimental procedure for synthesis of 2-alkyl pyridine *N*-oxide (57a-b):

The mixture containing 2-alkyl pyridine (0.13 mole), hydrogen peroxide (33.5 mL, 30%**)** and glacial acetic acid (90 mL) was heated at 70-80 °C for 24 h. After reaction was complete acetic acid was distilled off under reduced pressure. The residue was taken in chloroform (150 mL), washed with aq. sodium carbonate (4x100 mL) and the solvent concentrated under reduced pressure to give the crude product. It was then purified by column chromatography (packed with silica gel 60-120 mesh) using ethyl acetate/ methanol as eluents to afford the pure products **57a-b**.

2-Ethylpyridine N-oxide (57a)

Yield: 93%; yellow gum; **IR** ($CHCl_3$, cm^{-1}): 799, 1441, 1477, 1601, 2848, 2958, 3007; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 1.32 (t, *J* = 6.0 Hz, 3H), 2.95 (q, *J* = 7.0 Hz, 2H), 7.17-7.24 (m, 3H), 8.25 (d, *J* = 8.0 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 10.5, 23.65, 123.5, 124.6, 126.0, 139.3, 153.4; **Anal.** Calcd for C_7H_9NO requires C, 68.27; H, 7.37; N, 11.37; found: C, 68.30; H, 7.40; N, 11.30%.

2-Benzylpyridine N-oxide (57b)

Yield: 95%; pale yellow solid **m.p.:** 98-100 °C; **IR** ($CHCl_3$, cm^{-1}): 790, 1445, 1475, 1601, 2849, 2958, 3008; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 4.25 (s, 2H), 6.86-6.94 (m, 1H), 7.08-7.15 (m, 2H) 7.26-7.40 (m, 5H), 8.26-8.30 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 26.2, 123.2, 124.8, 125.4, 126.7, 128.5, 129.4, 136.0, 139.0, 151.6; **Anal.** Calcd for $C_{12}H_{11}NO$ requires C, 77.81; H, 5.99; N, 7.56; found C, 77.72; H, 6.01; N, 7.50%.

General experimental procedure for rrearrangement of 2-alkyl pyridine *N*-oxide:

To a solution of 2-alkyl pyridine N-oxide (1.0 mmol) and chiral base (1.0 mmol) in dry dichloromethane (4 mL) under nitrogen at -78 °C was added Lewis acid (20 mol%) followed by acyl chloride (1.0 mmol) drop-wise. The resulting reaction mix was stirred at the same temperature for 4 h. After completion of reaction (monitored by TLC), it was concentrated to dryness and the solid residue is dissolved in THF: water (8: 2 mL) and hydrolyzed with LiOH (2.0 mmol) after vigorously stirring for 4 h. Reaction mixture was subsequently extracted with ethyl acetate then dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give the crude product, which was purified by column chromatography (ethyl acetate, pet. ether) as eluent to afford the alcohols **58a-b**.

1-Pyridin-2-yl-ethanol (58a)

Yield: 93%; colorless oil; $[\alpha]^{25}_{D}$ = -5.2 (*c* 1, $CHCl_3$) {lit.[32] $[\alpha]_D^{25}$ -27.6, (*c* 0.71, $CHCl_3$)}; **IR** ($CHCl_3$, cm^{-1}): 796, 1077, 1403, 1440, 1588, 2857, 2978, 3067 3230; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 1.50 (d, *J* = 6.4 Hz, 3H), 3.97 (br s, 1H), 4.85 (q, *J* = 6.4 Hz, 1H), 7.17–7.25 (m, 1H), 7.28 (d, *J* = 8.4 Hz, 1 H), 7.63–7.71 (m, 1 H), 8.51 (d, *J* = 4.0 Hz, 1 H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 22.2, 70.8, 121.0, 122.1, 138.7, 143.8, 162.1; **Anal.** Calcd for C_7H_9NO requires C, 68.27; H, 7.37; N, 11.37; found: C, 68.30; H, 7.40; N, 11.30%.

1-Phenyl(pyridin-2-yl)methanol (58b)

Yield: 95%; white solid **m.p:** 70-73 °C; $[\alpha]^{25}_{D}$ = -80.0 (*c* 1, $CHCl_3$) {lit.[43] $[\alpha]_D^{22}$ -158.0, (*c* 0.51, $CHCl_3$)}; **IR** ($CHCl_3$, cm^{-1}): 795, 1078, 1405, 1445, 1585, 1601, 2857, 2978, 3070, 3232; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 5.29 (br s, 1H), 5.73 (s, 1H), 7.11-7.39 (m, 7H), 7.60 (td, *J* = 7.2, 1.6 Hz,1H), 8.55 (d, *J* = 5.0 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 74.9, 121.2, 122.2, 126.9, 127.6, 128.4, 136.7, 143.1, 147.6, 161.1; **Anal.** Calcd for $C_{12}H_{11}NO$ requires C, 77.81; H, 5.99; N, 7.56; found: C, 77.73; H, 6.06; N, 7.53%.

Section III

Synthesis of 4-substituted chromanes *via* gold-catalyzed intramolecular Friedel-Crafts reaction of 3-aryloxy benzyl alcohols

4.3.1 Introduction

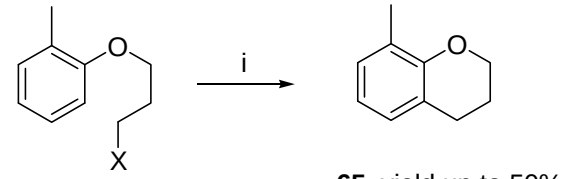
The structures of chromane and benzopyrane are abundant in natural products that possess a broad array of biological activities such as antimicrobial, antiviral, mutagenicity, antiproliferative, sex pheromone, antitumor, and central nervous system activity.[44] Organic transformations catalyzed by gold have been the focus of attention recently.[45] Generally gold(I) and gold(III) show unique activity in mediating reactions involving alkynes. In contrast, gold-catalyzed arene functionalization has been given scant attention. Such processes could provide efficient ways to construct C-C bonds from simple arene substrates. Alkylation of aromatic groups is typically achieved with Friedel-Crafts reactions.[46] In this section we have described a new method of synthesis of 4-aryl substituted chromanes by using gold (III) chloride-catalyzed intramolecular Friedel-Crafts reaction of 3-aryloxy benzyl alcohol.

4.3.2 Review of Literature

Literature search reveals that there are several reports available for the synthesis of chromane derivatives. Some of these methods are briefly discussed below.

Rindfusz's approach (1920)[47]

Rindfusz *et al*. have reported a dehydration of hydroxyl or bromo -alkyl-aryl ether **64** by using $ZnCl_2$ or P_2O_5 to give chromane **65** with 10-50% yield. This method requires high temperature and stoichiometric amount of Lewis acids (**Scheme 28**).



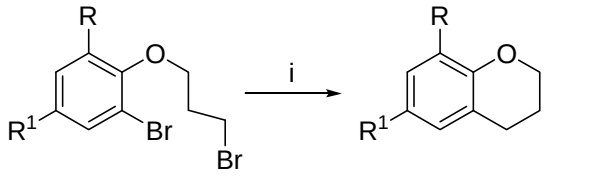
64, X= OH,Br

65, yield up to 50%

Scheme 28: (i) $ZnCl_2$ or P_2O_5, 235 °C, 10- 50%.

Bradsher's approach (1981)[48]

Bradsher *et al.* have found that the addition of butyl lithium at -100 °C to 3-(o-bromophenoxy) propyl bromides **66** led to preferential exchange of the aryl bromine at the ortho position. The resulting organolithium reagent, under suitable conditions, cyclized to afford 3,4-dihydro-2H-l-benzopyrans **67** in 79-80% yields (**Scheme 29**).



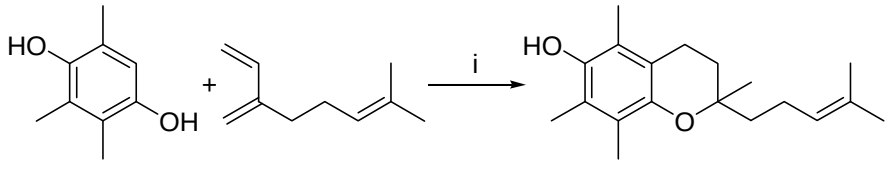
66, R = H, Br
R^1= H, Me, OMe, Cl

67, yield = 79-80%

Scheme29: (i) BuLi (2 equiv), THF, -100 °C, 2 h, 79-80%.

Yamamoto's approach (1995)[49]

Yamamoto *et al.* have reported $AlCl_3$–tetralkylammonium halide complex as a catalyst in Friedel-Crafts alkylation using trimethylhydroquinone **68** and myrcene **69** to give the



68 **69**

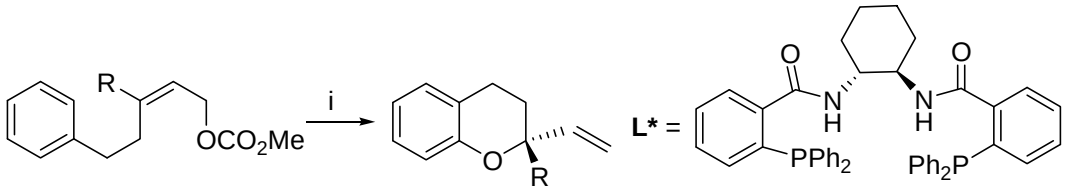
70, yield = 94%
purity = 64%

Scheme 30: (i) $AlCl_3$, Bu_4NBr, 25 °C, 94%.

chromane compound **70** as a major product (**Scheme 30**). This reagent system may expand the use of Lewis acid catalyst in a non polar solvent system and may be applicable to a wide range of reaction.

Trost's approach (2003)[50]

Trost *et al.* have described the application of Pd-catalyzed asymmetric allylic alkylation reaction of phenol allylic carbonates **71** to the synthesis of chiral chromans **72**. The authors have observed the remarkable influence on enantioselectivity by acetic acid as an additive and by the olefin geometry of the substrates (**Scheme 31**).



71, R = H, Me

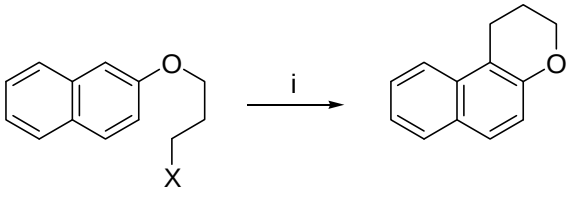
72, yield up to 99%
ee = up to 89%

73

Scheme 31:(i) Pd_2dba_3 (2 mol%), L* **73** (6 mol%), AcOH, CH_2Cl_2.

He's approach (2004)[51]

He *et al.* have found that chromanes can be synthesized in good yields with the use of gold(III)-catalyzed functionalization of aromatic C-H with primary alcohol triflate or methanesulfonate esters **74** to construct C-C bonds (**Scheme 32**).



74, X = OTf,OMs

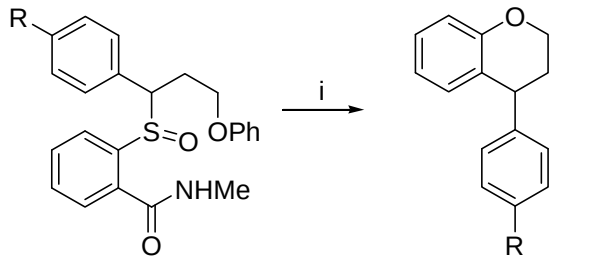
75, yield = 93%

Scheme 32: (i) $AuCl_3$/3Ag(OTf) (5 mol%), $ClCH_2CH_2Cl$, 128 ^oC, 48 h, 15-93%.

The mechanistic studies indicate the involvement of the aryl gold(III) species as the reaction intermediate. This intermediate then reacts with the sulfonate ester to give the final product.

Zanda's approach (2005)[52]

Zanda *et al.* have developed two step approach for synthesis of 4-arylbenzopyrans, **77** exploiting the synthetic potential of ortho-*N*-methylformamidophenylsulfoxides **76**. The authors have observed that the synthesis of ortho-*N*-methylformamidophenylsulfoxides requires more number of steps (**Scheme 33**).

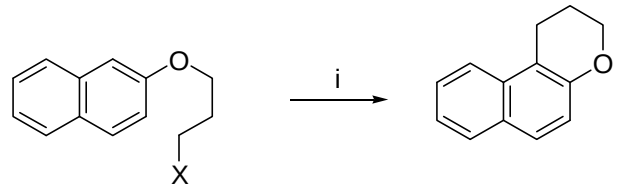


76, R = H, OMe **77,** = 63-99%

Scheme 33: (i) Tf_2O, TMP, CH_2Cl_2, -78 ^oC.

Kim's approach (2010)[53]

Kim *et a*l. have reported a novel synthetic method using ionic liquids (ILs) for a six-membered ring closure cyclization (**Scheme 34**).



74, X = OTs,OMs, I, Br **75**, upto 85%

Scheme 34: (i) [bmim][BF_4], 150 ^oC, 24-48 h.

The ring closure cyclization by nucleophilic C-alkylation was achieved with various halo and alkanesulfonyloxyalkyl aromatic compounds **74** in high yields with minimal byproducts using ILs as the reaction media in the absence of any catalyst.

4.3.3 Present Work

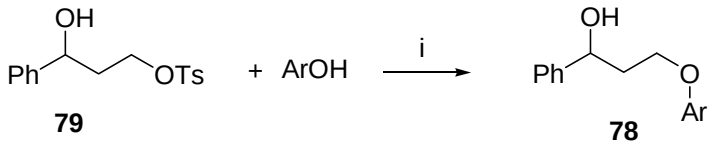
4.3.3.1 Objective

From the above discussion, it is clear that most of the reported methods are run under harsh conditions with high concentration of Lewis acids, which can hardly be tolerated by many functional groups. Given the importance of these valuable chromanes as well as the lack of efficient methods for the preparation of these important active agents, development of a new catalytic synthesis of these compounds appears to be of great importance. In this section, we describe a novel $AuCl_3$-catalyzed synthesis of 4-substituted chromanes from 3-aryloxy benzyl alcohol by the Friedel-Crafts type intramolecular cyclization of 3-aryloxy benzyl alcohols.

4.3.4. Results and Discussion

3-Aryloxy benzyl alcohols **78,** precursors for the synthesis of 4-substituted chromanes, were readily prepared by employing nucleophilic substitution of phenols on 3-hydroxy-3-phenyl propyltosylate **79** using sodium hydride as a base (**Table 7**).[54] As can be seen from **Table 7**, a variety of phenols underwent nucleophilic substitution with tosylates **79** to give the corresponding 3-aryloxy benzyl alcohols **78a-g** in excellent yields. The formation of 3-Aryloxy benzyl alcohols **78a-g** was confirmed by ^{1}H and ^{13}C-NMR spectroscopy.

Table 7: Synthesis of 3-aryloxy benzyl alcohols (**78**)[a]



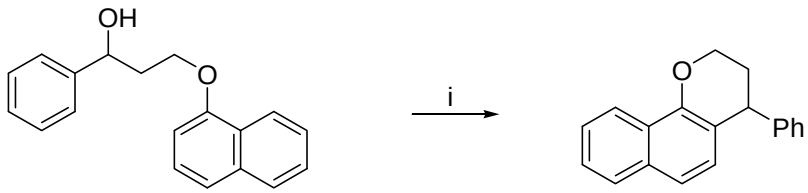
79 **78**

(i) NaH (1 mmol), DMF, 80 °C, 5h

Entry	Ar	Yield of 78 (%)[b]
a	α-Naphthyl	98
b	4-Methylphenyl	98
c	Phenyl	96
d	β-Naphthyl	97
e	4-Chlorophenyl	93
f	4-Cyanophenyl	90
g	cesamoyl	93

Reaction conditions: [a] 3-hydroxy-3-phenyl propyltosylate (1 mmol), NaH (1 mmol), phenol (1 mmol), DMF (10 mL) 80 °C, 5h; [b] yields refer to isolated yields after column chromatography.

The ^{1}H NMR spectrum of **78a** showed signals at δ 4.09-4.23 (m, 1H) and 4.28-4.39 (m, 1H), for methylene (-CH_2-OAr) proton. Its ^{13}C-NMR showed a typical signal at δ 65.1 due to carbon attached to naphthoxy group (**Fig.6**). We have then subjected 3-α-naphthoxybenzyl alcohol **78a** to gold(III)chloride-catalyzed Friedel-Crafts intramolecular cyclization in dichloromethane as a solvent at room temperature, which proceeded to give 4-aryl substituted chromanes **80a** in 98% yields (**Scheme 35**).



78a **80a**, 98%

Scheme 35: (i) 3-α-Naphthoxybenzyl alcohol (1 mmol), $AuCl_3$ (1 mol%), CH_2Cl_2, 25 °C, 6 h.

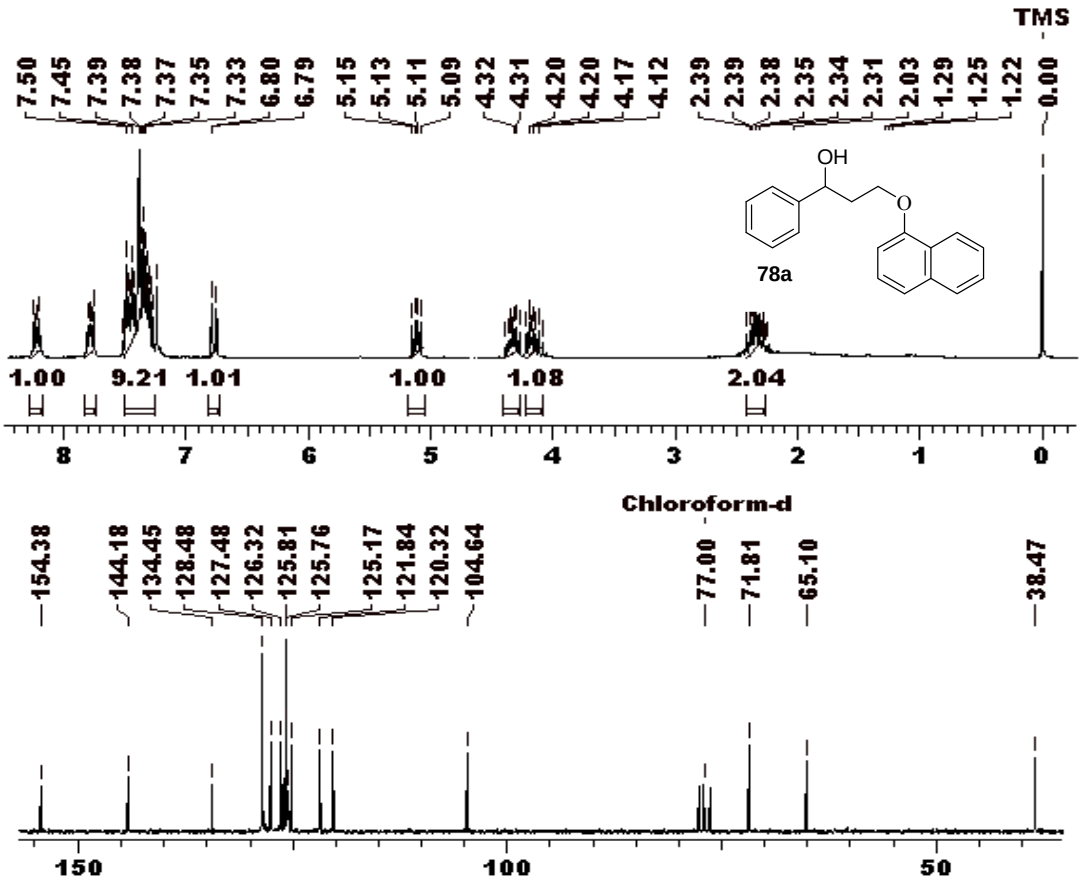
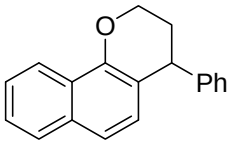
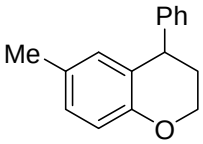
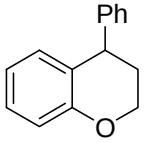
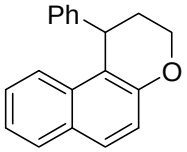
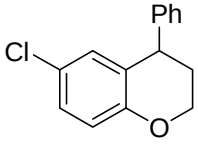
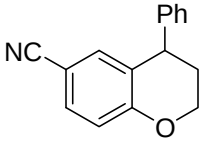
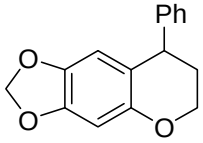


Fig. 6: ^{1}H and ^{13}C NMR spectra of **78a**

To study the generality of the reaction, several 3-aryloxy benzyl alcohols **78a-g** were subjected to $AuCl_3$-catalyzed Friedel-Crafts intramolecular cyclization the results of which are presented in **Table 8**. 3-Phenoxy benzyl alcohols as well as 3-naphthoxy benzyl alcohols gave good yields. In the case of both electron-donating (**78b)** as well as electron-withdrawing (**78f)** substituted 3-aryloxy benzylalcohols gave the corresponding chromanes in 98% and 90% yields respectively. Notably, substrate cesamoyloxy benzyl alcohol gave the corresponding cyclized product **80g** in 93% yield. However, when chiral 3-phenoxy benzyl alcohol[54] was employed as substrate, we found no optical induction.

Table 8: Synthesis of 4-phenyl substituted chromanes (**80**) [a]

Entry	Substrate (78) Ar	Product (80)	Yield (%)[b]
a	α-Naphthyl		98
b	4-Methylphenyl		98
c	Phenyl		96[c]
d	β-Naphthyl		97
e	4-Chlorophenyl		93
f	4-Cyanophenyl		90
g	Cesamoyl		93

Reaction conditions: [a] 3-aryloxy benzyl alcohols (1 mmol), $AuCl_3$ (1 mol%), CH_2Cl_2 (5 mL) 25 °C, 5h; [b] yields refer to isolated yields after column chromatography. [c] Also reaction was carried out with chiral 3-phenoxy benzyl alcohol, however no chiral induction was observed.

The formation of chromanes **80a-g** was confirmed by ^1H and ^{13}C-NMR spectroscopy. The ^1H NMR spectrum of **80b** showed signals at δ 4.08-4.16 (m, 3H) for methylene (CH_2-O-*p*-tolyl) and methine (*p*-tolyl-CH-) protons. Its ^{13}C-NMR showed a typical signal at δ 41.0 due to carbon attached to phenyl and *p*-tolyl ring (**Fig. 7).**

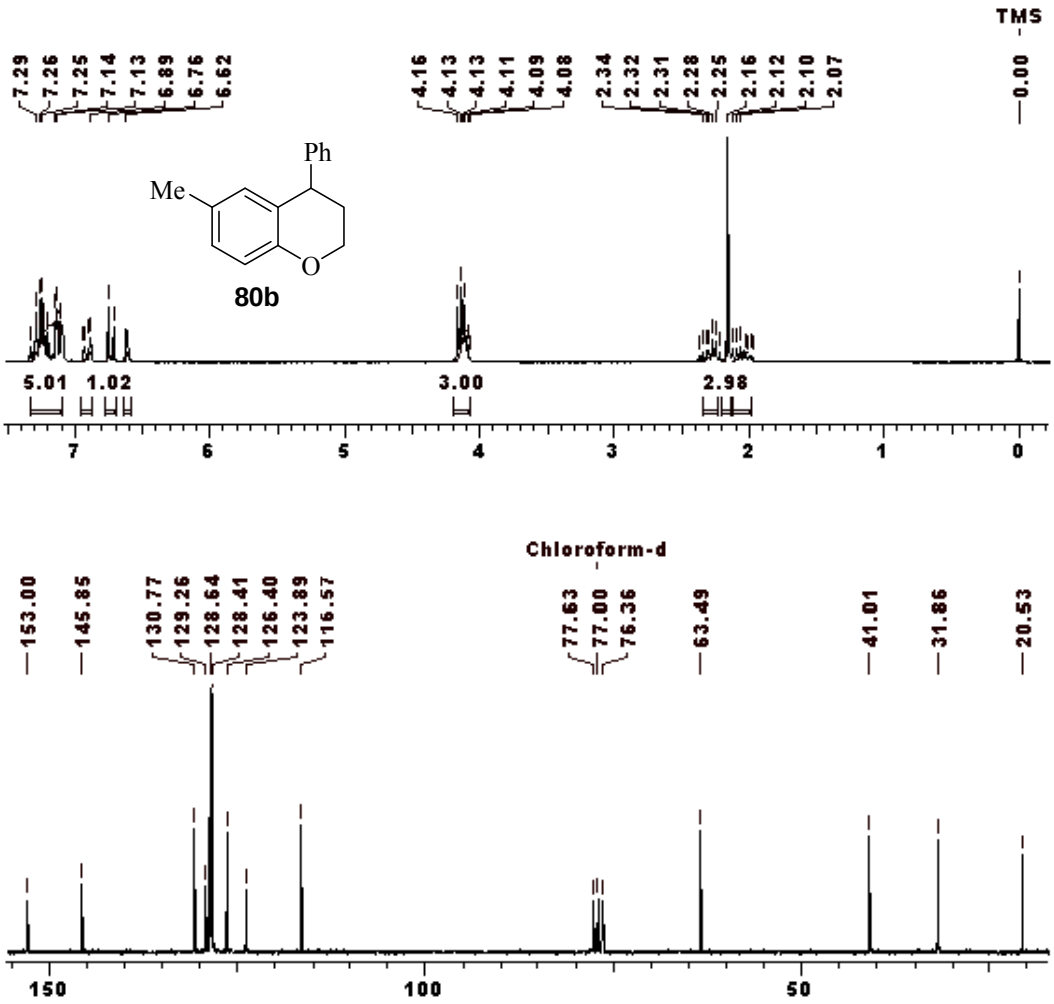
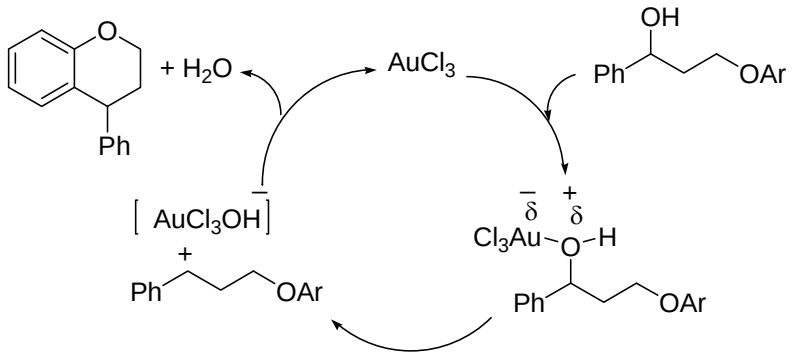


Fig. 7: ^{1}H and ^{13}C NMR spectra of **80b**

4.3.5 Mechanism

A simplified catalytic cycle shown in **Scheme 36** consists of the following three steps: (1) coordination of oxygen atom of the benzyl alcohol to Au-catalyst; (2) transfer of the hydroxyl group to the metal with concomitant generation of the intermediate carbocation;[55] (3) trapping of the carbocation by the electron-rich aryloxy ring to produce cyclized product with generation of 1 mole of water.



Scheme 36: Proposed catalytic cycle for gold (III)-catalyzed cyclization of 3-aryloxy benzylalcohols.

4.3.6 Conclusion

In conclusion we have demonstrated that gold (III) chloride is highly effective catalyst for intramolecular Friedel-Crafts reaction of 3-Aryloxy benzyl alcohols to gave 4-aryl substituted chromanes in 90-98% yields.

4.3.7 Experimental Section

General experimental procedure for the preparation of 3-aryloxy benzyl alcohols 78a-g

To a solution of phenol (1.0 mmol) in DMF (5 mL) was added 60% of sodium hydride (0.04 g, 1.0 mmol) dispersed in mineral oil at 25 °C. After five minutes of stirring, 3-hydroxy-3-phenylpropyltosylate **79** (0.309 g 1.0 mmol) in DMF (2 mL) was added via syringe. The reaction mixture was warmed to 70 °C and stirred at the same temperature for 5 h. After completion of reaction (monitored by TLC), it was quenched with aq. NH_4Cl (5 mL) and extracted with ethyl acetate (3×10 ml)). The combined organic layers were washed with saturated solution of brine (10 ml), dried over anhyd. Na_2SO_4, concentrated under reduced pressure to give the crude product, which was then purified

by column chromatography (packed with silica gel 60-120 mesh) using petroleum ether/ ethyl acetate (9:1) as eluents to afford the pure product **78a-g**.

3-Naphthalen-1-yloxy-1-phenylpropan-1-ol (78a)

Yield: 98%; colorless solid **m.p.**: 88-93 °C; **IR** ($CHCl_3$, cm^{-1}): 700, 768, 1068, 1100, 1216, 1269, 1459, 1508, 1580, 2849, 2930, 3019, 3401, 3541; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.24-2.42 (m, 2H), 2.35 (brs, 1H), 4.09-4.23 (m, 1H), 4.28-4.39 (m, 1H), 5.12 (dd, *J* = 2.6, 5.1 Hz, 1H), 6.78 (d, *J* = 1.1, 7.1 Hz 1H), 7.27-7.52 (m, 9H), 7.75-7.81 (m, 1H) 8.20-8.25 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 38.4, 65.1, 71.8, 104.6, 120.3, 121.8, 125.1, 125.5, 125.7, 125.8, 126.3, 127.4, 127.5, 128.4, 134.4, 144.1, 154.3; **Anal.** Calcd for $C_{19}H_{18}O_2$ requires C, 81.99; H, 6.52; found: C, 81.95; H, 6.60%.

3-*p*-Tolyloxy-1-phenylpropan-1-ol (78b)

Yield: 98%; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): 768, 1068, 1100, 1216, 1265, 1459, 1508, 1580, 2849, 2950, 3019, 3401, 3500; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.0-2.22 (m, 2H), 2.26 (s, 3H), 2.96 (brs, 1H), 3.85-3.95 (m, 1H), 3.99-4.10 (m, 1H), 4.86-4.93 (m 1H), 6.74 (d, *J* = 8.6 Hz, 2H), 7.02 (d, *J* = 8.6 Hz, 2H), 7.27-7.31 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 20.5, 38.5, 65.5, 72.5, 114.4, 125.7, 127.6, 128.5, 129.9, 130.0, 144.2, 156.5; **Anal.** Calcd for $C_{16}H_{18}O_2$ requires C, 79.31; H, 7.49; found: C, 79.40; H, 7.51%.

3-Phenyl-1-phenylpropan-1-ol (78c)

Yield: 96%; pale yellow liquid; **IR** ($CHCl_3$, cm^{-1}): 768, 1063, 1101, 1216, 1263, 1459, 1508, 1580, 2849, 2955, 3015, 3401; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.22-2.49 (m, 2H), 2.50 (brs, 1H), 4.0-4.17 (m, 2H), 4.95-5.03 (m, 1H), 6.87-6.94 (m, 3H), 7.27-7.36 (m, 7H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 39.0, 65.3, 72.6, 114.4, 122.4, 125.3, 127.2, 128.1,

129.3, 138.6, 156.5; **Anal.** Calcd for $C_{15}H_{16}O_2$ requires C, 78.92; H, 7.06; found: C, 78.95; H, 7.10%.

3-Naphthalen-2-yloxy-1-phenylpropan-1-ol (78d)

Yield: 95%; colorless solid **m.p**.: 90 °C; **IR** ($CHCl_3$, cm^{-1}): 700, 768, 1068, 1102, 1217, 1269, 1459, 1508, 1580, 2845, 2930, 3019, 3401, 3540; **^{1}H NM**R (200 MHz, $CDCl_3$): δ 2.11 (brs, 1H), 2.29-2.38 (m, 2H), 4.09-4.20 (m, 1H), 4.23-4.34 (m, 1H), 5.04 (dd *J* = 2.8, 5.0 Hz, 1H), 7.11-7.17 (m, 2H), 7.26-7.45 (m, 7H), 7.66-7.76 (m, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 38.3, 65.0, 71.7, 106.6, 118.7, 123.6, 125.7, 126.3, 126.7, 127.5, 127.6, 128.4, 128.9, 129.3, 134.5, 144.1, 156.5; **Anal.** Calcd for $C_{19}H_{18}O_2$ requires C, 81.99; H, 6.52; found: C, 81.90;H, 6.55%.

3-(4-Chlorophenyl)-1-phenylpropan-1-ol (78e)

Yield: 98%; yellow liquid; **IR** ($CHCl_3$, cm^{-1}): 1070, 1100, 1216, 1265, 1459, 1510, 1582, 2849, 2950, 3019, 3403, 3510; **^{1}H NM**R (200 MHz, $CDCl_3$): δ 2.12-2.25 (m, 2H), 2.38 (brs, 1H), 3.92-4.0 (m, 2H), 4.05-4.18 (m, 1H), 6.81 (d, *J* = 9.0 Hz, 2H), 7.16-7.39 (m, 7H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 38.1, 65.2, 71.5, 115.6, 116.6, 125.7, 127.6, 128.4, 129.2, 143.9, 157.2; **Anal.** Calcd for $C_{15}H_{15}ClO_2$ requires C, 68.57; H, 5.75; found: C, 68.50; H, 5.81%.

4-(3-Hydroxy-3-phenylpropoxy)benzonitrile (78f)

Yield: 90%; colorless solid **m.p.:** 82 °C; **IR** ($CHCl_3$, cm^{-1}): 1070, 1100, 1217, 1264, 1459, 1510, 1582, 2211, 2254, 2849, 2950, 3019, 3403; **^{1}H NM**R (200 MHz, $CDCl_3$): δ 2.09 (brs, 1H), 2.14-2.35 (m, 2H), 4.0-4.11 (m, 1H), 4.17-4.28 (m 1H), 4.93-5.01 (m, 1H), 6.94 (d, *J* = 8.9 Hz, 2H), 7.28-7.39 (m, 5H), 7.58 (d, *J* = 8.9 Hz, 2H); **^{13}C NMR** (50

MHz, $CDCl_3$): δ 38.0, 65.1, 70.8, 103.6, 115.0, 118.9, 125.5, 127.5, 128.4, 133.7, 143.9, 162.0; **Anal.** Calcd for $C_{16}H_{15}NO_2$ requires C, 75.87; H, 5.97; N, 5.53; found: C, 75.80; H, 6.02; N, 5.50%.

3-Benzo-1,3-dioxol-6-yloxy-1-phenylpropan-1-ol (78g)

Yield: 93%; brown colored gum; **IR** ($CHCl_3$, cm^{-1}): 768, 1070, 1100, 1216, 1265, 1455, 1508, 1580, 2849, 2950, 3019, 3430; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.03-2.19 (m, 2H), 2.47 (brs, 1H), 3.92-4.08 (m, 2H), 4.97 (dd, *J* = 2.6, 5.0 Hz 1H), 5.90 (s, 2H), 6.30 (dd, *J* = 2.6, 5.9 Hz 1H), 6.47 (d, *J* = 2.4 Hz, 1H), 6.68 (d, *J* = 8.8 Hz, 1H), 7.27-7.36 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ 38.3, 65.9, 71.6, 97.9, 100.9, 105.6, 107.8, 125.6, 127.4, 128.3, 141.6, 144.1, 148.1, 154.0; **Anal.** Calcd for $C_{16}H_{16}O_4$ requires C, 70.57; H, 5.92; found: C, 70.63; H, 5.81%.

General experimental procedure for the preparation of chromenes (80a-g)

To a solution of gold(III) chloride (3 mg, 1 mol%), in CH_2Cl_2 (5 mL) was added 3-aryloxy benzyl alcohols **78a-g** (1.0 mmol) in (2 mL, CH_2Cl_2) at room temperature. The resulting mixture was stirred for 6 h at room temperature. After starting for 5 h, 3-aryloxy benzyl alcohols were consumed. The reaction mixture was then quenched with water and extracted with CH_2Cl_2 (10 mL× 2). The organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed and the residue was purified by column chromatography (pet. ether: ethyl acetate = 9: 1) to afford the desired cyclized products in pure form (**80a-g)**.

3,4-Dihydro-4-phenyl-2*H*-benzo[*h*]chromene (80a)

Yield: 90%; colorless solid **m.p.:** 82 °C; **IR** ($CHCl_3$, cm^{-1}): 701, 768, 1023, 1105, 1216, 1262, 1403, 1404, 1491, 1507, 1576, 2882, 2954, 3019, 3057; **^{1}H NMR** (200 MHz,

$CDCl_3$): δ 2.07-2.22 (m, 1H), 2.37-2.53 (m, 1H), 4.26-4.38 (m, 3H), 6.92 (d *J* = 8.1 Hz, 1H), 7.11-7.32 (m, 6H), 7.40-7.50 (m, 2H), 7.68-7.74 (m, 1H), 8.18-8.22 (m, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): 31.8, 40.9, 63.6, 117.4, 119.7, 121.8, 125.2, 126.0, 126.4, 127.4, 128.2, 128.4, 128.7, 133.5, 145.9, 150.3; **Anal.** Calcd for $C_{19}H_{16}O$ requires C, 87.66; H, 6.19; found: C, 87.60;H, 6.25%.

3,4-Dihydro-(6-methyl-4-phenyl)-2*H*-chromene (80b)

Yield: 90%; colorless gum; **IR** ($CHCl_3$, cm^{-1}): 768, 1023, 1107, 1218, 1266, 1403, 1404, 1491, 1508, 1576, 2884, 2954, 3019, 3050; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 1.97-2.12 (m, 1H), 2.16 (s, 3H), 2.22-2.37 (m, 1H), 4.08-4.16 (m, 3H), 6.61-6.62 (m, 1H), 6.74 (d, *J* = 8.3 Hz, 1H), 6.89-6.94 (m, 1H), 7.10-7.33 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): 20.5, 31.8, 41.0, 63.4, 116.5, 123.8, 126.4, 128.4, 128.5, 128.6, 129.2, 130.7, 145.8, 153.0; **Anal.** Calcd for $C_{16}H_{16}O$ requires C, 85.68; H, 7.19; found: C, 85.70;H, 7.25%.

3,4-Dihydro-4-phenyl-2*H*-chromene (80c)

Yield: 90%; gum; **IR** ($CHCl_3$, cm^{-1}): 768, 1030, 1107, 1220, 1266, 1406, 1404, 1491, 1508, 1576, 2882, 2950, 3019, 3051; **^{1}H NMR** (200 MHz, $CDCl_3$): δ 2.04-2.14 (m, 1H), 2.27-2.36 (m, 1H), 4.13-4.20 (m, 3H), 6.73-6.86 (m, 3H), 7.07-7.33 (m, 6H); **^{13}C NMR** (50 MHz, $CDCl_3$): 20.5, 31.8, 41.0, 63.4, 116.5, 123.8, 126.4, 128.4, 128.5, 128.6, 129.2, 130.7, 145.8, 153.0; **Anal.** Calcd for $C_{15}H_{14}O$ requires C, 85.68; H, 6.71; found: C, 85.72; H, 6.67%.

3,4-Dihydro-4-phenyl-2*H*-benzo[*h*]chromene (80d)

Yield: 90%; colorless solid **m.p.**: 85 °C; **IR** ($CHCl_3$, cm^{-1}): 701, 768, 1023, 1105, 1216, 1262, 1403, 1404, 1491, 1507, 1576, 2882, 2954, 3019, 3057; **^{1}H NMR** (200 MHz,

$CDCl_3$): δ 2.10 (qd, *J* = 2.2, 6.9 Hz, 1H), 2.43-2.61 (m, 1H), 4.07 (td, *J* = 2.0, 10.4 Hz, 1H), 4.19-4.28 (m, 1H), 5.11 (d, *J* = 5.2 Hz, 1H), 7.08-7.28 (m, 8H), 7.44-7.99 (m, 1H), 7.66-7.74 (m, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$): 30.9, 36.8, 61.3, 114.1, 119.0, 123.0, 123.1, 126.3, 126.4, 128.4, 128.5, 128.8, 129.2, 133.0, 145.8, 153.0; **Anal.** Calcd for $C_{19}H_{16}O$ requires C, 87.66; H, 6.19; found: C, 87.60;H, 6.25%.

6-Chloro-3,4-dihydro-4-phenyl-2*H*-chromene (80e)

Yield: 90%; pale yellow gum; **IR** ($CHCl_3$, cm^{-1}): 766, 1030, 1100, 1218, 1260, 1403, 1404, 1491, 1508, 1576, 2884, 2952, 3010, 3045; **^{1}H NM**R (200 MHz, $CDCl_3$): δ 1.99-2.14 (m, 1H), 2.21-2.36 (m, 1H), 4.09-4.19 (m, 3H), 6.76-6.82 (m, 2H), 7.03-7.13 (m, 3H), 7.16-7.36 (m, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$): 31.3, 41.0, 63.8, 118.2, 125.1, 126.0, 127.9, 128.5, 128.6, 130.0, 144.8, 153.7; **Anal.** Calcd for $C_{15}H_{13}ClO$ requires C, 73.62; H, 5.35; found: C, 73.60; H, 5.40%.

3,4-Dihydro-4-phenyl-2*H*-chromene-6-carbonitrile (80f)

Yield: 90%; colorless gum; **IR** ($CHCl_3$, cm^{-1}): 768, 1023, 1103, 1218, 1266, 1403, 1410, 1491, 1510, 1576, 2210, 2253, 2884, 2954, 3019, 3054; **^{1}H NM**R (200 MHz, $CDCl_3$): δ 2.01-2.14 (m, 1H), 2.21-2.39 (m, 1H), 4.06-4.18 (m, 1H), 4.26 (t, *J* = 5.1 Hz, 2H), 6.90 (d, *J* = 8.3 Hz, 1H), 7.05-7.15 (m, 3H), 7.26-7.43 (m, 5H); **Anal.** Calcd for $C_{16}H_{13}NO$ requires C, 81.68; H, 5.57; N, 5.95; found: C, 81.60; H, 5.60; N, 5.91%.

7,8-Dihydro-8-phenyl-6*H*-1,3-dioxalo-4,5-chromene (80g)

Yield: 90%; colorless gum; **IR** ($CHCl_3$, cm^{-1}): 765, 1023, 1107, 1218, 1266, 1403, 1409, 1491, 15108, 1576, 2884, 2954, 3019, 3057; **^{1}H NM**R (200 MHz, $CDCl_3$): δ 1.99-2.09 (m, 1H), 2.23-2.35 (m, 1H), 4.03-4.13 (m, 3H), 5.91 (s, 2H), 6.24 (s, 1H), 6.38 (s,

1H), 7.11-7.33 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$): 38.4, 66.1, 71.7, 98.1, 101.0, 105.7, 108.0, 125.8, 127.6, 128.5, 141.7, 144.3, 148.2, 154.2; **Anal.** Calcd for $C_{16}H_{14}O_3$ requires C, 75.57; H, 5.55; found: C, 75.50;H, 5.65%.

4.3.8 References

1 (a) Ojima, I. *"The Chemistry of Organic Silicon Compounds"*, Vol. *2*, Patai, **S.;** Rappoport, Z. Wiley/Interscience, New York, **1989;** (b) **I.** Ojima, Z. Li and **J.** Zhu, *"Recent Advances in the Hydrosilylation Reaction: Chemisty of Organic Silicon Compounds"*, Vol. *2***,** Rappoport, **Z.;** Apeloig, **Y.;** John Wiley & Sons, Ltd, New York, **1998**.

2 Ojima, I.; Nihonyanagi, M.; Nagai, Y. *J. Chem. Soc., Chem. Commun.***1972**, 938.

3 (a) Han, J. W.; Tokunaga, N.; Hayashi, T. *J. Am. Chem. Soc.* **2001**, *123*, 12915; (b) Jensen, J. F.; Svendsen, B. Y.; Cour, T. V.; Pedersen, H. L.; Johannsen, M. *J. Am. Chem. Soc.* **2002**, *124*, 4558; (c) Corma, A.; Gonzalez-Arellano, C.; Iglesias, M.; Sanchez, F. *Angew. Chem. Int. Ed.* **2007**, *46*, 7820; (d) Shaikh, N. S.; Enthaler, S.; Junge, K.; Beller, M. *Angew. Chem. Int. Ed.* **2008**, *47*, 2497.

4 Sprengers, J. W.; de Greef, M.; Duin, M. A.; Elsevier, C. J. *Eur. J. Inorg. Chem.* **2003**, 3811.

5 (a) Carpentier, J.-F.; Bette, V. *Curr. Org. Chem.* **2002**, *6*, **913**; (b) Riant, O. Mostefa, N.; Courmarcel, J. *Synthesis* **2004**, 2943.

6 Ojima, I.; Kogure, T.; Nihonyanagi, M.; Nagai,Y. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 3506.

7 Caseri, W.; Pregosin, P. S. *Organometallics,* **1988**, *7*, 1373.

8 Bideau, F. L.; Henique, J.; Samuel, E.; Elschenbroich, C. *Chem. Commun.* **1999**, 1397.

9 Maifeld, S. V.; Miller, R. L.; Lee, D. *Tetrahedron Lett.* **2002**, *43*, 6363.

10 Dioumaev, V. K.; Bullock, **R.** M. *Nature,* **2003**, *424*, 530.

11 Lipshutz, B. H.; Caires, C. C.; Kuipers, P.; Chrisman, W. *Org. Lett.* **2003**, *5*, 3085.

12 Lee, D.-W.; Yun, J. *Tetrahedron Lett.* **2004,** *45*, 54 I5.

13 Gade, L. H.; Cesar, V.; Bellemin-Laponnaz, S**.** *Angew. Chem. Int. Ed.* **2004,** *43*, 1014.

14 Song, C.; Ma, C.; Ma, Y.; Feng, W.; Ma, S.; Chai, Q.; Andrus, M. B. *Tetrahedron Lett.* **2005**, *46,* 3241.

15 Shaikh, N. S.; Enthaler, S.; Junge, K.; Beller, M. *Angew. Chem. Int. Ed.* **2008**, *47*, 2497.

16 Dong, H.; Berke, H. *Adv. Synth. Catal*. **2009**, *351*, 1783.

17 Inagaki, T.; Yamada, Y.; Phong, L. T.; Furuta, A.; Ito, J-I.; Nishiyama, H. Synlett. **2009**, 253.

18 (a) Diez-Gondlez, S.; Nolan, S. P. *Organic Preparations and Procedures Int*. **2007**, *39*, 523; (b) Marciniec, B. in Hydrosilylation: A Comprehensive Review on Recent Advances (Eds.: B. Marciniec), Springer, Netherlands, **2009**, chap. 9.

19 (a) Mirza-Aghayan, M.; Boukherroub, R.; Rahimifard, M. *J. Organomet. Chem.* **2008**, *693*, 3567.

20 Thakur, V. V.; Ramesh Kumar, N. S. C.; Sudalai, A. *Tetrahedron Lett.* **2004**, *45*, 2915.

21 Ramesh Kumar, N. S. C.; Victor Paul Raj, I.; Sudalai, A. *J. Mol. Cat. A: Chemical*, **2007**, *269*, 218.

22 Mirza-Aghayan, M.; Boukherroub, R.; Bolourtchian, M. *J. Organomet. Chem.* **2005**, *690*, 2372.

23 (a) Kunai, A.; Sakurai, T.; Toyoda, E.; Ishikawa, M.; Yamamoto, Y. *Organometallics* **1994**, *13*, 3233; (b) Ferreri, C.; Costantino, C.; Chatgilialoglu, C.; Boukherroub, R.; Manuel, G. *J. Organomet. Chem.* **1998**, *554*, 135.

24 (a) Wishka, D. G.; Graber, D. R.; Seest, E. P.; Dolak, L. A.; Han, F.; Watt, W.; Morris, J. *J. Org*. *Chem*. **1998**, *63*, 7851. (b) Uenishi, J.; Takagi, T.; Ueno, T.; Hiraoka, T.; Yonemitsu, O.; Tsukube, H. *Synlett* **1999**, 41.

25 Gärtner, H.; Salz, U.; Rüchardt, C. *Angew. Chem. Int. Ed. Engl*. **1984**, *23*, 162.

26 (a) Collomb, P.; Zelewsky, A. V. *Tetrahedron*: *Asymmetry* **1998**, *9*, 3911; (b) Uenishi, J.; Ueno, T.; Hata, S.; Nishikawa, K.; Tanaka, T.; Watanabe, S.; Yonemitsu, O.; Oae, S. *Heterocycles* **1999**, 50, 341.

27 Soai, K.; Niwa, S.; Kobayashi, T. *J. Chem. SOC., Chem. Commun.* **1984**, 413.

28 Bolm, C.; Zehnder, M.**;** Bur, D. *Angew. Chem. Int. Ed*. **1990**, *29*, 205;

29 Hoschino, O.; Ishizaki, M. *Chem. Lett.* **1994**, 1337.

30 Orrenius, C.; Mattson, A.; Norin, T. *Tetrahedron Asymmetry* **1994**, *5*, 1363.

31 Uenishi, J.; Hiraoka, T.; Hata, S.; Nishiwaki, K.; Yonemitsu, O.; Nakamura K.; Tsukube, H. . *J. Org. Chem*. **1998**, *63*, 2481.

32 Okano, K.; Murata, K.; Ikariya, T. *Tetrahedron Lett*. **2000**, *41*, 9277.

33 Garrett, M. D.; Scott, R.; Sheldrake, G. N. *Tetrahedron Asymmetry* **2002**, *13*, 2201.

34 Mazet, C.; Roseblade, S.; Ko1hler,V.; Pfaltz, A. *Org. Lett.* **2006**, *8*, 1879.

35 Katada, M. *J. Pharm. Soc. Jpn.,* **1947**,*67*, 51.

36 Boekelheide, V.; Linn, W.; J. *J. Am. Chem. Soc.* **1954** , *76* , 1286.

37 McKillop, A.; Bhagrath, M.; K. *Heterocycles,* **1985**, *23*, 1697.

38 Fontenas, C.; Bejan, E.; Haddou, H. A.; Balavoine, G. G. A. *Synth. Commn.* **1995**, *25*, 629.

39 Andreotti, D.; Miserazzi, E.; Nalin, A.; Pozzan, A.; Profeta, R.; Spada, S. *Tetrahedron Lett*. **2010**, *51*, 6526.

40 Li, J. *Name Reactions in Heterocyclic Chemistry*; John Wiley & Sons: NJ, **2005**.

41 (a) Oae, S.; Kitao, Y. *J. Am. Chem. Soc*. **1962**, *84*, 3359; (b) Oae, S.; Kozuka, S. *Tetrahedron*

1964, *20*, 2671;

42 Bodalski, R.; Katritzky, A. R. *J. Chem. Soc*. (B) **1968**, 831.

43 Heller, B.; Redkin, D.; Gutnov, A.; Fischer, C.; Bonrath, W.; Karge, R.; Hapke, M. *Synthesis* **2008**, 69.

44 (a) Ellis, G. P.; Lockhart, I. M. *The Chemistry of Heterocyclic Compounds, Chromenes, Chromanones, and Chromones*; Ellis,G. P., Ed.;Wiley-VCH: New York, **2007**; Vol. *31*, pp 1. (b) Horton, D. A.; Bourne, G. T.; Smythe,M. L. *Chem. Rev*. **2003**, *103*, 893. (c) Geen, G. R.; Evans, J. M.; Vong, A. K. *Comprehensive Heterocyclic Chemistry II: Pyrans and their Benzo Derivatives: Applications*; Katritzky, A. R., Rees, C.W., Scriven, E. F. V., Eds.; Pergamon Press: Oxford, UK, **1996**; Vol. *5*, pp 469. (d) Neugebauer, R. C.; Uchiechowska, U.; Meier, R.; Hruby, H.; Valkov, V.; Verdin, E.; Sippl, W.; Jung, M. *J. Med. Chem.* **2008**, *51*, 1203–1213. (e) Posakony, J.; Hirao, M.; Stevens, S.; Simon, J. A.; Bedalov, A. *J. Med. Chem.* **2004**, *47*, 2635–2644. (f) Wilkinson, J.; Foretia, D.; Rossington, S.; Heagerty, A.; Leonard, J.; Hussain, N.; Austin, C. *Eur. J. Pharmmacol*. **2007**, *561*, 160. (g) Maloney, D. J.; Deng, J. Z.; Starck, S. R.; Gao, Z.; Hecht, S. M. *J. Am. Chem. Soc.* **2005**, *127*, 4140. (h) Kumar, S.; Malachowski, W. P.; DuHadaway, J. B.; LaLonde, J. M.; Carroll, P. J.; Jaller, D.; Metz, R.; Prendergast, G. C.; Muller, A. J. *J. Med. Chem*. **2008**, *51*, 1706.

45 (a) Hashmi, A. S. K. *Gold Bull*. **2004**, *37*, 51; (b) Arcadi, A.; Di Giuseppe, S. *Curr. Org. Chem*. **2004**, *8*, 795; (c) Zhang, L.; Sun, J.; Kozmin, S. A. *Adv. Synth. Catal.* **2006**, *348*, 2271; (d) Bond, G. C.; Louis, C.; Thompson, D. T. *Catalysis*; Gold Imperial College Press: London, **2006**; (e) Fu¨rstner, A.; Davies, P. W. *Angew. Chem., Int. Ed*. **2007**, *46*, 3410; (f) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395; (g) Hashmi, A. S. K. *Chem. Rev*. **2007**, *107*, 3180.

46 (a) Olah, G. A. *Friedel-Crafts and Related Reactions*; Wiley: New York, **1973**; (b) Bandini, M.; Melloni, A.; Umani-Ronchi, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 550.

47 Rindfusz, R. E.; Ginnings, P. M.; Harnack, V. L. *J. Am. Chem. Soc.* **1920**, *42*, 157.

48 Bradsher, C. K.; Reames, D**.** C. *J. Org. Chem.* **1981,** 46**,** 1384.

49 Matsui, M.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 2663.

50 Trost, B. M.; Shen, H. C.; Dong, L.; Surivet, J-P. *J. Am. Chem. Soc.* **2003**, *125*, 9276.

51 Shi, Z.; He, C. *J. Am. Chem. Soc.* **2004**, *126*, 13596.

52 Volonterio, A.; Zanda, M. *Tetrahedron Lett*. **2005**, *46*, 8723.

53 Hong , D. J.; Kim, D. W.; Chi, D. Y. *Tetrahedron Lett*. **2010**, *51*, 54.

54 Ali, I. S.; Sudalai, A. *Tetrahedron Letters*, **2002**, *43*, 5435.

55 Cuenca, A. B.; Mancha, G.; Asensio, G.; Medio-Sim, M. *Chem. Eur. J.* **2008**, *14*, 1518.

PUBLICATIONS

1 $NaIO_4$–KI–NaN_3 as a new reagent system for C–H functionalization in hydrocarbons. **Chouthaiwale, P. V.**; Suryavanshi, G.; Sudalai, A. *Tetrahedron Lett.* **2008**, *49*, 6401.

2 $Cu(OTf)_2$-catalyzed *α*-halogenation of ketones with 1,3-dichloro 5,5′dimethylhydantoin and *N*-bromosuccinimide. Jagdale, A. R.; **Chouthaiwale P. V**.; Sudalai, A. *Ind. J. Chem. Section B*, **2009**, *48,* 1424-1430.

3 Formal synthesis of (-)-anisomycin *via* organocatalysis. **Chouthaiwale, P. V**.; Kotkar S. P.; Sudalai, A. *ARKIVOC* **2009,** (*ii*), 88-94.

4 A concise enantioselective synthesis of (+)-decarestrictine L via proline-catalyzed sequential α-aminooxylation and Horner–Wadsworth–Emmons olefination. Rawat, V.; **Chouthaiwale, P. V.**; Suryavanshi, G.; Sudalai, A. *Tetrahedron: Asymmetry* **2009**, *20,* 2173–2177.

5 Co(III)(salen)-catalyzed HKR of two stereocentered alkoxy- and azido epoxides: a concise enantioselective synthesis of (S,S)-reboxetine and (+)-epi-cytoxazone. Reddy, R. S.; **Chouthaiwale, P. V.**; Suryavanshi, G.; Chavan, V. B.; Sudalai, A. *Chem. Commun.* **2010***, 46,* 5012–501.

6 $NaIO_4$/LiBr-mediated aziridination of olefins using chloramine-T. Karabal, P.; **Chouthaiwale, P. V.**; Shaikh, T. M. S.; Suryavanshi, G.; Sudalai, A. *Tetrahedron Lett*. **2010**, *51*, 6460-6462.

7 A facile enantioselective synthesis of (S)-N-(5-chlorothiophene-2-sulfonyl)-β,β-diethylalaninol via proline-catalyzed asymmetric α-aminooxylation and α -amination of aldehyde. Rawat, V.; **Chouthaiwale, P. V.**; Suryavanshi, G.; Chavan, V. B.; Sudalai, A. *Tetrahedron Letters* **2010,** *51,* 6565–6567.

8 Regiospecific Azidoiodination of Alkenes with Sodium Periodate, Potassium Iodide, and Sodium Azide: A High-Yield Synthesis of **β**-Iodoazides. **Chouthaiwale, P. V.**; Karabal, P.; Suryavanshi, G.; Sudalai, A. *Synthesis* **2010***, 22,* 3879–3882.

9 Cobalt-Catalyzed HKR of Alkoxy- and Azido Epoxides: Reddy, R. S.; **Chouthaiwale, P. V.**; Suryavanshi, G.; Chavan, V. B.; Sudalai, A. Highlights in current synthetic organic chemistry: ***Synfacts*** **2010**, 10, 1146.

10 Palladiun-Catalyzed Selective Hydrosilylation of Aryl ketones and Aldehyde: **Chouthaiwale, P. V.;** Rawat**,** V.; Sudalai, A. (Manuscript under preparation).

11 Enantioselective synthesis of (+) -L-733,060 *via* Hydrolytic Kinetic Resolution of Azido epoxide: **Chouthaiwale, P. V.;** Sudalai, A. (Manuscript under preparation)

12 $NaIO_4$–NaN_3–mediated 1,2-Diazidation of Olefins and α,α-Diazidation of Aryl ketones: **Chouthaiwale, P. V.;** Sudalai, A.(Manuscript under preparation).

13 Synthesis of 4-Substituted Chromanes *via* Gold-catalyzed Intramolecular Friedel-Crafts Reaction: **Chouthaiwale, P. V**.; Sudalai, A. (Manuscript under preparation).